PRODUCT MONOGRAPH

ASA SUPPOSITORIES
(Acetylsalicylic Acid Suppositories, USP)

150 mg and 650 mg

PMS-ASA 325 mg Tablets, PMS-ASA 80 mg Tablets, PMS-ASA 81 mg Tablets
(Acetylsalicylic Acid Tablets, USP)

PMS-ASA EC 80 mg Tablets, PMS-ASA EC 81 mg Tablets, ASAPHEN EC 162 mg Tablets
(Acetylsalicylic Acid Delayed-release Tablets, USP)

Analgesic, anti-inflammatory, antipyretic and
platelet aggregation inhibitor

Pharmascience Inc
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H4P 2T4

Date of Preparation
July 18, 2006

Control # 107111, 107112

PRODUCT MONOGRAPH

ASA Suppositories

(Acetylsalicylic acid suppositories USP)

pms-ASA 325 mg Tablets, pms-ASA 80 mg Tablets, pms-ASA 81 mg Tablets

(Acetylsalicylic acid tablets, USP)

pms-ASA EC 80 mg Tablets, pms-ASA EC 81 mg Tablets, ASAPHEN EC 162 mg Tablets

(Acetylsalicylic acid delayed release tablets, USP)

THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

Analgesic, anti-inflammatory, anti-pyretic and platelet aggregation inhibitor.

ACTION AND CLINICAL PHARMACOLOGY

ASA interferes with the production of prostaglandins in various organs and tissues through acetylation of the enzyme cyclo-oxygenase. Prostaglandins are themselves powerful irritants and produce headaches and pain on injection in man. Prostaglandins also appear to sensitize pain receptors to other noxious substances such as histamine and bradykinin. By preventing the synthesis and release of prostaglandins in inflammation, ASA may avert the sensitization of pain receptors.

The antipyretic activity of ASA is due to its ability to interfere with the production of prostaglandin E_1 in the brain. Prostaglandin E_1 is one of the most powerful pyretic agents known.

The inhibition of platelet aggregation by ASA is due to its ability to interfere with the production of thromboxane A_2 within the platelet. Thromboxane A_2 is largely responsible for the aggregating properties of platelets.

INDICATIONS AND CLINICAL USE

Acetylsalicylic acid (ASA) is indicated for the relief of pain, fever and inflammation of a variety of conditions such as influenza, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, fractures, myositis, neuralgia, synovitis, arthritis, bursitis, burns, injuries, following surgical and dental procedures.

pms-ASA 81 mg and pms-ASA EC 81 mg and ASAPHEN E.C. 162 mg are also indicated for the following uses, based on its platelet aggregation inhibitory properties:

-For reducing the risk of morbidity and death in patients with unstable angina and in those with previous myocardial infarction.

-For reducing the risk of transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction;

-For prophylaxis of venous thromboembolism after total hip replacement;

-For reduction of adhesive properties of platelets in patients following carotid endarterectomy to prevent recurrence of TIA and in hemodialysis patients with a silicone rubber arteriovenous cannula.

In addition, pms-ASA EC 81 mg and ASAPHEN E.C. 162 mg is also indicated for the following uses, based on its platelet aggregation inhibitory properties:

-For reducing the risk of vascular mortality in patients with a suspected acute myocardial infarction.

-For reducing the risk of a **first** non-fatal myocardial infarction in individuals deemed to be at sufficient risk of such an event by their physician. There is no evidence for a reduction in the risk of **first** fatal myocardial infarction. ASA does not reduce the risk of either cardiovascular mortality or **first** strokes, fatal or non-fatal . The decrease in the risk of **first** non-fatal myocardial infarction must be assessed against a much smaller but not insignificant increase in the risk of haemorrhagic stroke as well as gastrointestinal bleeding.

CONTRAINDICATIONS

Salicylate sensitivity, active peptic ulcer.

WARNINGS

ASA is one of the most frequent causes of accidental poisonings in toddlers and infants. Tablets should be kept well out of the reach of children.

A possible association between Reye's syndrome and the use of salicylates has been suggested but not established. Reye's syndrome has also occurred in many patients not exposed to salicylates. However, caution is advised when prescribing salicylate-containing medications for children and teenagers with influenza or chickenpox.

PRECAUTIONS

Salicylates should be administered cautiously to patients with asthma and other allergic conditions, a history of gastrointestinal ulcerations; bleeding tendencies; significant anemia or hypoprothrombinemia.

Patients taking ASA daily are at an increased risk of developing gastrointestinal bleeding following the ingestion of alcohol.

Caution is necessary when salicylates and anticoagulants are prescribed concurrently, as salicylates can depress the concentration of prothrombin in the plasma.

Diabetics receiving concurrent salicylate and hypoglycemic therapy should be monitored closely; reduction of the sulfonylurea hypoglycemic drug dosage may be necessary; insulin requirements may change.

High doses (3g daily) of ASA during pregnancy may lengthen the gestation and parturition time.

Salicylates can produce changes in thyroid function tests.

Sodium excretion produced by spironolactone may be decreased by salicylate administration.

Salicylates in large doses are uricosuric agents; smaller amounts may depress uric acid clearance and thus decrease the uricosuric effects of other drugs.

Salicylates retard the renal elimination of methotrexate.

Salicylates may alter valproic acid (VPA) metabolism and may displace VPA from protein binding sites, possibly intensifying the effects of VPA. Caution is recommended when VPA is administered concomitantly with salicylates.

The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant

administration of ASA due to its indirect effect on the renin-angiotensin conversion pathway. The potential interaction may be related to the dose of ASA.

ADVERSE REACTIONS

Gastrointestinal: (the frequency and severity of these adverse effects are dose-related): nausea, vomiting, diarrhea, gastrointestinal bleeding and/or ulceration, dyspepsia, heartburn.

Ear: tinnitus, vertigo, hearing loss.

Hematologic: leukopenia, thrombocytopenia, purpura, anemia.

Dermatologic and hypersensitivity: urticaria, angioedema, pruritus, skin eruptions, asthma, anaphylaxis.

Miscellaneous: mental confusion, drowsiness, sweating, thirst.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: in mild overdosage these may include rapid and deep breathing, nausea, vomiting, vertigo, tinnitus, flushing, sweating, thirst, arid tachycardia. In more severe cases, acid-base disturbances including respiratory alkalosis and metabolic acidosis can occur. Severe cases may show fever, hemorrhage, excitement, confusion, convulsions or coma and respiratory failure.

Treatment consists of prevention and management of acid-base and fluid and electrolyte disturbances. Renal clearance is increased by increasing urine flow and by alkaline diuresis but care must be taken in this approach to not aggravate further the metabolic acidosis that develops and the hypokalemia. Acidemia should be prevented by administration of adequate sodium containing fluids and sodium bicarbonate. Hypoglycemia is an occasional accompaniment of salicylate overdosage and can be managed by glucose solutions. If a hemorrhagic diathesis is evident, give vitamin K. Hemodialysis may be useful in complex acid base disturbances particularly in the presence of abnormal renal funtion.

DOSAGE AND ADMINISTRATION

Analgesic and antipyretic:

Adults: 1-2 tablets (325 mg to 650 mg) orally every 4 hours.

Children under 12: 10 to 15 mg/kg every 6 hours, not to exceed a total daily dose of 2.4 g.

Anti-inflammatory:

Adults: 3 tablets (975 mg) 4 to 6 times a day, up to 30 tablets daily, may be required for optimal anti-inflammatory effect. A blood level between 15 and 30 mg per 100 mL is in the desirable therapeutic range.

Children: 60 to 125 mg/kg daily in 4 to 6 divided doses.

Platelet aggregation inhibitor:

- For suspected acute myocardial infarction: An initial dose of at least 160 -162.5 mg chewed or crushed to ensure rapid absorption as soon as a myocardial infarction is suspected. The same dose should be given as maintenance over the next 30 days. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI (see Prior Myocardial Infarction). **pms-ASA EC 81 mg and ASAPHEN EC 162 mg (Acetylsalicylic acid delayed release tablets) is specifically indicated for these uses.**

- For the prevention of a first myocardial infarction: 80 - 325 mg daily according to the individual needs of the patient, as determined by the physician. **pms-ASA EC 81 mg and ASAPHEN E.C. 162 mg (Acetylsalicylic acid delayed release tablets) is specifically indicated for these uses.**

- For reducing the risk of morbidity and death in patients with unstable angina and in those with previous myocardial infarction: 80 - 325 mg daily according to the individual needs of the patient, as determined by the physician. **pms-ASA 81 mg (Acetylsalicylic acid tablets), pms-ASA EC 81 mg and ASAPHEN E.C. 162 mg (Acetylsalicylic acid delayed release tablets) is specifically indicated for these uses.**

- For reducing the risk of transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction: 80 - 325 mg daily according to the individual needs of the patient, as determined by the physician. **pms-ASA 81 mg (Acetylsalicylic acid tablets), pms-ASA EC 81 mg and ASAPHEN E.C. 162 mg (Acetylsalicylic acid delayed release tablets) is specifically indicated for these uses.**

- For prophylaxis of venous thromboembolism after total hip replacement: 650 mg twice a day (1,300 mg daily), started 1 day before surgery and continued for 14 days. **pms-ASA 81 mg (Acetylsalicylic acid tablets), pms-ASA EC 81 mg and ASAPHEN E.C. 162 mg (Acetylsalicylic acid delayed release tablets) is specifically indicated for these uses.**

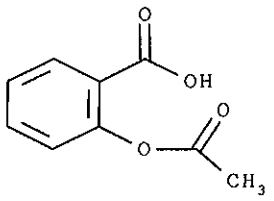
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Acetylsalicylic acid

Chemical Names: 2-(Acetyloxy) benzoic acid;
Salicylic acid acetate.

Structure:



Molecular Formula: $C_9H_8O_4$

Molecular Weight: 180.16

Description: White granules, commonly tabular or needle-like, or white crystalline powder. Odorless or having a faint odor.

Solubility: Slightly soluble in water; freely soluble in alcohol; soluble in chloroform and ether; sparingly soluble in absolute ether.

pK value (25°C): 3.49

Melting Point: 135°C (rapid heating)

COMPOSITION

ASA Suppositories: Each suppository contains 150 mg or 650 mg acetylsalicylic acid as active ingredient.
Non-medicinal ingredients: Novata 299.

pms-ASA Tablets: Each tablet contains 325 mg acetylsalicylic acid as active ingredient.
Non-medicinal ingredients: Croscarmellose sodium, microcrystalline cellulose.

pms-ASA : Each chewable tablet contains 80 mg or 81 mg acetylsalicylic acid as active ingredient.
Non-medicinal ingredients: DC Yellow #10, FDC Red #40, mannitol, orange flavor, pregelatinized starch, sodium saccharin, stearic acid.

pms-ASA EC: Each tablet contains 80 mg or 81 mg acetylsalicylic acid as active ingredient.
(80 & 81 mg) Non-medicinal ingredients: Hydrogenated soya bean oil, hydroxypropyl methylcellulose, lactose, polyethylene glycol, pregelatinized starch, stearic acid.

Asaphen E.C.: Each caplet contains 162 mg acetylsalicylic acid as active ingredient.
(162 mg) Non-medicinal ingredients: carnauba Wax, colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, methylated silica, methylcellulose, polydextrose, polydimethylsiloxane, polyethylene glycol, polyethylene glycol sorbitan tristearate, polyvinyl acetate phthalate, pregelatinized starch, sodium alginate, sodium bicarbonate, stearic acid, Talc, titanium dioxide, triethyl citrate.

AVAILABILITY OF DOSAGE FORM

ASA Suppositories: White, cone-shaped suppositories. Available in strengths of 150 mg and 650 mg. In package of 10.

pms-ASA Tablets: Each round, biconvex, compressed white tablet contains 325 mg acetylsalicylic acid. In packages of 100, 500 and 1000 tablets.

pms-ASA 80mg: Each chewable, orange, round, biconvex, scored tablet, embossed "ASAPHEN 80" contains 80 mg acetylsalicylic acid. In packages of 24, 30, 100 and 500 tablets.

pms-ASA 81 mg: Each chewable, salmon coloured, round, biconvex tablet, embossed "ASAPHEN 81" contains 81 mg acetylsalicylic acid. In packages of 30 and 120 tablets.

pms-ASA EC 80mg: Each round, white enteric-coated tablet contains 80 mg acetylsalicylic acid. In packages of 24, 30, 120 and 500 tablets and in blister packs of 7 tablets.

pms-ASA EC 81mg: Each round, white enteric-coated tablet contains 81 mg acetylsalicylic acid. In packages of 24, 30, 100,120, 180, 200, 225, 250 and 255 tablets and in blister packs of 7 tablets.

Asaphen E.C. 162mg: Each caplet shaped, white enteric-coated tablet contains 162 mg acetylsalicylic acid. In packages of 30, 60, 90 and 120 tablets and in blister packs of 12 tablets.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15°-30°C).

PATIENT INFORMATION TO BE DISTRIBUTED ONLY BY PHYSICIANS/PHARMACISTS

pms-ASA 81 mg,

pms-ASA EC 81 mg

and ASAPHEN E.C. 162 mg

This section provides you with information about **pms-ASA 81 mg** acetylsalicylic acid (chewable) tablets, **pms-ASA EC 81 mg** acetylsalicylic acid (enteric coated) and **ASAPHEN E.C. 162 mg** acetylsalicylic acid (enteric coated) tablets and how to take this medication. ***Please read carefully before you take this medication.***

Your physician has recommended **pms-ASA 81 mg** or **pms-ASA EC 81 mg** or **ASAPHEN E.C. 162 mg** for supervised adult long-term preventative therapy.

Follow your physician's instructions concerning the use of **pms-ASA 81 mg** or **pms-ASA EC 81 mg** or **ASAPHEN E.C. 162 mg** as well as any lifestyle changes, e.g. diet and/or exercise, that he/she may have recommended. Always contact your physician if you experience any difficulties while taking this product.

pms-ASA 81 mg, pms-ASA EC 81 mg and **ASAPHEN E.C. 162 mg** contains acetylsalicylic acid, commonly referred to as ASA, as its active ingredient. Plain (uncoated) ASA, particularly when taken regularly, may cause stomach upset in some people. The special enteric coating of **pms-ASA EC 81 mg** and **ASAPHEN E.C. 162 mg** tablets allows them to pass intact through the stomach and on into the intestine before they dissolve which may reduce the risk of stomach upset.

Your physician has specifically recommended **pms-ASA EC 81 mg** and **ASAPHEN E.C. 162 mg** because it contains a special, low-dose, enteric-coated, formulation of ASA. Other medications such as acetaminophen or ibuprofen that are meant to relieve pain do not have the same preventative action as **pms-ASA EC 81 mg** and **ASAPHEN E.C. 162 mg** which has been specifically formulated for your condition.

DIRECTIONS FOR USE

It is very important that you take this medication as directed by your physician. If you have not seen a physician, do not take this medication until you have done so.

Dosage:

1 to 4 tablets daily of **pms-ASA EC 81 mg** or 1 to 2 tablets of **ASAPHEN E.C. 162 mg**, depending on your doctor's instructions. Your doctor may tell you to take or with other medications. He/she may also advise you to make certain lifestyle changes, (e.g. diet, exercise, smoking cessation), to safeguard your health. You should take this medication at the same time every day to help you to remember to take it. For maximum

effectiveness, it is very important to take **pms-ASA EC 81 mg** or **ASAPHEN E.C. 162 mg** every day, as directed by your physician. Do not take more tablets than your physician recommends.

pms-ASA EC 81 mg tablets and ASAPHEN E.C. 162 mg tablets must be swallowed whole for the medication to work properly. pms-ASA EC 81 mg tablets and ASAPHEN E.C. 162 mg tablets have a special enteric coating designed to help prevent stomach upset. To benefit from this protection, the tablets should not be crushed or broken. pms-ASA 81 mg tablets are chewable and therefore must be chewed well and swallowed.

ANSWERS TO COMMONLY ASKED QUESTIONS

WHY WAS ASAPHEN RECOMMENDED BY MY DOCTOR?

FOR PREVENTION OF A SECOND HEART ATTACK OR STROKE (DAILY THERAPY)

It can be used to prevent a second stroke or heart attack. If you have experienced either a stroke or a heart attack you may be at risk for a second one. There are certain risk factors that can place you at an increased risk:

-Overweight
-Smoking
-Inactive (sedentary) lifestyle
-Stress
-High blood cholesterol
-High blood pressure

These can be discussed with your physician in order to complement the effectiveness of pms-ASA 81 mg or pms-ASA EC 81mg or ASAPHEN EC 162 mg.

Your doctor may recommend changes in diet, exercise and lifestyle for your benefit in avoiding a second heart attack or stroke.

If you experience any difficulties with your treatment always discuss with your doctor or pharmacist.

USE DURING A HEART ATTACK

If you think you are having a heart attack, you should immediately chew or crush 2 - 81mg pms-ASA EC tablets or 1-162 mg pms-ASA EC tablets and call an ambulance. It is important to chew or crush the product, to ensure this medicine quickly works. Then get to a hospital immediately for medical attention. Taking pms-ASA EC at the first signs and symptoms can reduce your risk of dying from the heart attack.

The signs and symptoms of a heart attack include:

1. uncomfortable pressure, fullness, squeezing or pain in the center of the chest that lasts more than a few minutes, or goes away quickly and comes back,
2. pain that spreads to the shoulders, neck or arms,
3. chest discomfort with lightheadedness, fainting, sweating, nausea or shortness of breath.

At the hospital, the doctor will then recommend appropriate therapy

WHAT IF I FORGET TO TAKE MY MEDICATION?

If you forget to take your medication at the usual time, take it when you remember. Do not take extra medication to compensate for a missed dosage unless instructed by your physician.

WILL I EXPERIENCE ANY SIDE EFFECTS WITH THIS MEDICINE?

Like any medication, ASA may occasionally produce unwanted side effects. You should call your physician if you experience any of the following: nausea, vomiting, bleeding or stomach irritation, dizziness, weakness, fainting spells, any loss of hearing, including ringing or buzzing in the ears or pain; skin rashes, hives or itching and breathing difficulties. Regular use of alcohol while on ASA daily therapy may increase your risk of developing gastrointestinal bleeding.

WHAT ELSE SHOULD I KNOW BEFORE TAKING THIS MEDICINE?

Your doctor will have asked you many questions about your health, lifestyle, and medications before recommending **pms-ASA 81 mg** or **pms-ASA EC 81 mg or ASAPHEN E.C. 162 mg.** This is why it is very important that you tell your doctor all such information. If you have forgotten to tell your doctor about any of the following, call your doctor or pharmacist before you take this medicine.

- Allergy to salicylates
- Asthma
- Stomach problems
- Peptic ulcer
- Severe liver disease
- Severe anemia
- Are pregnant or breast-feeding
- Will be having surgery in five to seven days
- Are taking other medications containing salicylates or acetaminophen
- Are taking anti-inflammatory drugs, anticonvulsants, anti-diabetics or gout medication
- Are taking or planning to take this medication while consuming alcohol
- History of blood clotting defects or receiving blood thinners

CAUTION

This product is not recommended for children or teenagers. This package contains enough drug to seriously harm a child. Keep out of children's reach. Do not administer to children and teenagers for chicken pox or flu symptoms before a doctor is consulted. Reye's Syndrome, which can occur in children or teenagers, is a rare but serious illness reported to be associated with ASA.

It is especially important not to use this medication during the last 3 months of pregnancy unless specifically directed to do so by your physician because it may cause problems in the unborn child or complications during delivery.

Call your doctor before taking this drug when nursing.

In case of accidental overdose call a doctor or hospital immediately, even if there are no symptoms.

Product Monograph is available to health professionals on request.

For further information or questions about this product, contact Pharmascience Inc., Montreal, Canada at their Medical Information Hotline between 8:30am and 4:30pm, Eastern Standard Time, Monday to Friday. Call toll-free at 1-888-550-6060.

PHARMACOLOGY

Absorption, distribution, metabolism and excretion:

When ASA is taken orally, it is rapidly absorbed from the stomach and proximal small intestine. The gastric mucosa is permeable to the non-ionized form of acetylsalicylic acid, which passes through the stomach wall by a passive diffusion process.

Optimum absorption of salicylate in the human stomach occurs in the pH range of 2.15 to 4.10. Absorption in the small intestine occurs at a significantly faster rate than in the stomach. After an oral dose of 0.65 g ASA, the plasma acetylsalicylate concentration in man usually reaches a level between 0.6 and 1.0 mg% in 20 minutes after ingestion and drops to 0.2 mg% within an hour. Within the same period of time, half or more of the ingested dose is hydrolyzed to salicylic acid by esterases in the gastrointestinal mucosa and the liver, the total plasma salicylate concentration reaching a peak between one or two hours after ingestion, averaging between 3 and 7 mg%. Many factors influence the speed of absorption of ASA in a particular individual at a given time; tablet disintegration, solubility, particle size, gastric emptying time, psychological state, physical condition, nature and quantity of gastric contents, etc., all affect absorption.

Distribution of salicylate throughout most body fluids and tissues proceeds at a rapid rate after absorption. Aside from the plasma itself, fluids which have been found to contain substantial amounts of salicylate after oral ingestion include spinal, peritoneal and synovial fluids, saliva and milk. Tissues containing high concentrations of the drug are the kidney, liver, heart and lungs. Concentrations in the brain are usually low, and are minimal in feces, bile and sweat.

The drug readily crosses the placental barrier. At clinical concentrations, from 50% to 90% of the salicylate is bound to plasma proteins especially albumin, while acetylsalicylic acid itself is bound to only a very limited extent. However, ASA has the capacity of acetylating various proteins, hormones, DNA, platelets and hemoglobin, which at least partly explains its wide-ranging pharmacological actions.

The liver appears to be the principal site for salicylate metabolism, although other tissues may also be involved. The three chief metabolic products of ASA or salicylic acid are salicyluric acid, the ether or phenolic glucuronide and the ester or acyl glucuronide. A small fraction is also converted to gentisic acid and other hydroxybenzoic acids. The half-life of ASA in the circulation is from 13 to 19 minutes so that the blood level drops quickly after absorption is complete. However, the half-life of the salicylate ranges between 3.5 and 4.5 hours, which means that 50% of the ingested dose leaves the circulation within that time.

Excretion of salicylates occurs principally via the kidney, through a combination of glomerular filtration and tubular excretion, in the form of free salicylic acid, salicyluric acid, as well as phenolic and acyl glucuronides. Salicylate can be detected in the urine shortly after its ingestion but the full dose requires up to 48 hours for complete elimination. The rate of excretion of free salicylate is extremely variable, reported recovery rates in human urine ranging from 10% to 85%, depending largely on urinary pH. In general, it can be stated that acid urine facilitates reabsorption of salicylate by renal tubules, while alkaline urine promotes excretion of the drug.

Analgesia:

The analgesic effect of ASA has been recognized and utilized clinically for more than half a century. The degree of analgesia attained with ASA is moderate but it has proved highly suitable in the management of pathological pain of mild to moderate severity. As regards site of action, both peripheral and CNS factors appear to contribute significantly to the pain relief afforded by ASA. As for mechanism of action, the accumulated evidence of recent years indicates that ASA acts by interfering with the synthesis and release of prostaglandins, thereby averting the sensitization of pain receptors to mechanical stimulation or to other mediators.

Antipyresis:

Interference with the synthesis and release of prostaglandins is also involved in ASA's antipyretic activity. ASA effects a significant reduction in elevated body temperature, but has little effect on normal body temperature. This latter is maintained by a delicate balance between heat production and heat loss, with the hypothalamus regulating the set point at which body temperature is maintained. Fever is induced by synthesis and release of prostaglandins in this temperature-regulating area and ASA acts by interfering with this process. Heat production is not inhibited but dissipation of heat is augmented by increased peripheral blood flow and by sweating.

Anti-inflammatory effect:

Components of the anti-inflammatory action of the salicylates are increased capillary resistance, thus reducing capillary leakage in response to local toxins, interference with the production of tissue-destructive lysosomal enzymes and inhibition of the synthesis of prostaglandin E compounds which have been shown to be potent mediators of the inflammatory process. Besides interfering with the synthesis of prostaglandins ASA also acts by interfering with lymphocyte activation and lymphokine production. Lymphokines are produced by activated thymus lymphocytes, which are abundant in the inflammatory tissues of patients suffering from rheumatoid arthritis. They cause increased vascular permeability and white blood cell chemotaxis, activate macrophages and stimulate lymphocyte DNA synthesis. They also induce release of tissue-destructive lysosomal enzymes as well as prostaglandins. The prostaglandins themselves, beside causing many manifestations of inflammation also act as a potent negative feedback mechanism by inhibiting lymphokine production. An indepth review of the effects of ASA on the lymphocyte-macrophage axis in inflammation has recently been published.

Effects on platelets: relation to hemostasis and thrombosis.

Platelets play an important role in normal hemostasis and clinical pathologic and experimental evidence indicates that their aggregation may play an equally important role in the evolution of a variety of disease states including cerebrovascular disease, ischemic heart disease and myocardial infarction. pms-ASA EC 81mg and ASAPHEN E.C. 162 mg inhibits platelet aggregation by irreversibly acetylating platelet cyclo-oxygenase, thereby blocking the production of prostaglandin endoperoxides PGG_2 and PGH_2 which are precursors of the major platelet-aggregating material, thromboxane A_2, which is also a powerful vasoconstrictor. However, pms-ASA EC 81mg and ASAPHEN E.C. 162 mg does not prevent the adherence of platelets to damaged vessel walls or the release of granule contents from these adherent platelets. As the anuclear platelets are unable to synthesize new enzyme molecules to replace those that have been inactivated, inhibition of platelet aggregation by pms-ASA EC 81mg and ASAPHEN E.C. 162 mg thus persist for the life of the platelets.

Daily administration of 20 to 40 mg of ASA to healthy volunteers reduced platelet thromboxane production but inhibited platelet aggregation only partially. When administered to patients recovering from myocardial infarction, 50 mg ASA daily had the same effects on thromboxane production, platelet aggregation and bleeding times as 324 mg daily. Other studies show that ASA doses of 40 to 325 mg daily suppressed thromboxane production by at least 80 %, but 80 mg ASA daily was the lowest dose required for maximum cumulative thrombocyte function inhibition. The protective effect of ASA against experimentally induced thrombosis or atherosclerosis has been demonstrated in several animal models.

Besides inhibiting the biosynthesis of thromboxane A_2 by platelets, ASA also interferes with the production of prostacyclin (PGI_2) by vascular endothelial cells, the above-mentioned prostaglandin endoperoxides being common precursors of both thromboxane A_2 and prostacyclin. This latter compound is one of the most powerfully acting platelet deaggregators and vasodilators and thus it would appear that the interference with the hemostatic processes by ASA depends on the thromboxane-prostacyclin balance. In fact, it has been suggested that under some conditions, high doses of ASA may be thrombogenic. However, in contrast to platelets, the vascular endothelial cells are able to regenerate cyclo-oxygenase in a relatively short time and therefore therapeutic doses of ASA are likely to produce a lesser inhibition of the vascular prostacyclin system than of the platelet thromboxane-forming mechanism. In fact, there is no clinical evidence to indicate that high doses of ASA would result in an increased risk of thromboembolism. Indeed, quite the contrary was observed and , in a controlled study, paradoxical shortening of the bleeding time was not observed at a daily ASA dose 3.6 g. Lower dosages of ASA make selective blocking of the TxA_2-synthesis without a simultaneous blocking of PGI_2-production possible.

The use of ASA in patients with a suspected acute myocardial infarction was investigated in a large multicenter trial involving over 17,000 patients. Treatment with ASA resulted in a 23% reduction in the risk of vascular

mortality versus placebo at 5 weeks. This use translates to a reduction of 24 deaths and 14 non-vascular events per 1000 patients treated.

The effect of time to therapy revealed that patients treated with ASA "early" (0 to 4 hours) versus "late" (5 to 24 hours) after symptom onset experienced reductions in the odds of vascular death of 25% versus 21%, versus placebo at 5 weeks. 'Early' treatment with ASA resulted in the saving of 4 additional lives per 1000 patients versus 'late' treatment.

Long term follow-up (up to 10 years) of patients in this study established that the early survival advantage to ASA persisted long term, and that this prolonged benefit was additive to that of fibrinolytic therapy.

The use of ASA for secondary prevention of thrombotic events is supported by a comprehensive overview of a number of clinical trials involving patients who already had some type of vascular disease (myocardial infarction, unstable angina, stroke or transient cerebral ischemia). Overall, these studies point to a 26-28% reduction of the combined endpoints of MI, stroke, or vascular deaths by treatment with ASA alone at doses of 75 to 325 mg daily. Studies which directly compared low doses with higher doses (30-1200 mg/day), indicated that the incidence of gastrointestinal adverse effects were significantly less common with the lower doses.

Recent discussions have focused on the efficacy of ASA for the primary prevention of myocardial infarction and stroke. Two large scale randomized trials, aimed at evaluating prophylactic use of ASA, were conducted among apparently healthy male physicians (22,000 in the United States and 5,000 in the United Kingdom respectively and their results have been published. In the summary overview of the combined results presented by the principal investigators, the authors state that:

".....Taken together, these two primary-prevention studies demonstrate a significant ($P<0.0001$) reduction in nonfatal myocardial infarction of about one third."

On the other hand, the same two studies have not indicated any reduction in overall vascular mortality and also suggested a slight increase in the risk of non-fatal disabling stroke. Current controversy exists about the applicability of these findings, obtained in a selected population, to the general public. As well, the optimum dosage regimen still remains an open question in this regard. Thus, the use of ASA for primary prevention should remain, in the words of the principal investigators:

"A matter of judgment in which the physician considers the cardiovascular risk profile of the patient and balances the known hazards of aspirin...against the clearly established reduction in the incidence of a first myocardial infarction."

TOXICOLOGY

The clinical and pathological signs of poisoning from toxic and lethal oral doses of ASA have been extensively described for man, much less extensively for other species.

The acute toxicity of ASA in animals has been studied and reviewed in detail by Boyd. The signs of poisoning in rats from doses in the lethal range are due to varying degrees of gastroenteritis, hepatitis, nephritis, pulmonary edema, encephalopathy, shock and minor toxic effects on other organs and tissues. Death is due to convulsions or cardiovascular shock. The major difference between species appears to be the ability to vomit toxic doses seen in man, cats and dogs, but not in mice, rats and rabbits. Otherwise, the pathological reaction to toxic doses of ASA is similar in all species in which such studies have been reported. The acute oral LD_{50} values have been reported as being over 1.0 g/kg in man, cat and dog, 0.92 g/kg in female and 1.48 g/kg in male albino rats, 1.19 g/kg in guinea pig, 1.1 g/kg in mouse and 1.8 g/kg in rabbit.

Chronic toxicity studies were reported in mice and rats. When ASA was administered at 2 to 20 times the maximum tolerated clinical dose to mice for up to one year, a dose-related deleterious effect was observed on mean survival time, number of young born and number of young raised to wearing age, no evidence of carcinogenic effect was found.

The chronic oral LD_{50} in male albino rats has been reported as 0.24g/kg/day when given for 100 days. At these daily doses ASA produced no anorexia and no loss of body weight. It did produce polydipsia, aciduria, diuresis, drowsiness, hyperreflexia, piloeraction, rapid and deep respiration, tachycardia, and during the second month, soft stools, epistaxis, sialorrhea, dacryorrhea and death in hypothermic coma. Autopsy disclosed the presence of a hypertrophied stomach, renal congestion, mild hepatitis and pneumonitis. While teratogenic effects were noted in animals at near lethal doses, there is no evidence to indicate that ASA is teratogenic in man.

BIBLIOGRAPHY

1. Abbott F, Kassam J, Orr J, and K. Farrell, The effects of aspirin on valproic acid metabolism. Clin. Pharmacol. Ther. 1986;40:94-100.

2. Altman R, Boullon F, Rouvier J, Raca R, de la Fuente, Favaloro R. Aspirin and prophylaxis of thromboembolic complications in patients with substitute heart valves. J Thorac Cardiovasc Surg 1976; 72: 127-9.

3. Amrein PC, Ellman L, Harris WH. ASPIRIN prolongation of bleeding time and perioperative blood loss. JAMA 1981; 245: 1825-8.

4. Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. Br Med J 1988; 296: 320-1.

5a Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Br Med J 1994; 308: 81-106.

5b Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. Br Med J 1994; 308: 158-68.

5c Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Br Med J 1994; 308: 235-46.

6. Aspirin Myocardial Infarction Study Research Group. A randomized controlled trial of aspirin in persons recovered from myocardial infarction. JAMA 1980; 243: 661-9.

7. Aspirin Myocardial Infarction Study Research Group: The aspirin myocardial infarction study: final results. Circulation 1980; 62 (Suppl V): V79-V84.

8. Bailey JM. Prostacyclins, thromboxane and cardiovascular disease. Tr Biochem Sci 1979; 4: 68-71.

9. Boston Collaborative Drug Surveillance Group. Regular aspirin intake and acute myocardial infarction. Br Med J 1974; 1: 440-3.

10. Bousser MG, Eschwege E, Haguenau M, Lefaucconnier JM, Thibult N, et al. "AICLA" controlled trial of aspirin and dipyridamole in the secondary prevention of athero-thrombotic cerebral ischema. Stroke 1983; 14:5-14.

11. Boyd EM. Analgesic abuse. Maximal tolerated daily doses of acetylsalicylic acid. Can Med Ass J 1968; 99: 790-8.

12. Boyd EM. The acute oral toxicity of acetylsalicylic acid. Toxic Appl Pharmac 1959; 1: 229-39.

13. Breddin K, Loew D, Lechner K, Uberla K, Walter E. Secondary prevention of myocardial infarction: Comparison of treatment with acetylsalicylic acid, phenprocoumon or placebo. A multicentre 2 year prospective study. Int Congr Ser 1979; 470: 263-8.

14. Breddin K, Loew D, Lechner K, Oberla K, Walter E. The German-Austrian trial. A comparison of acetylsalicylic acid, placebo and phenprocoumon in secondary prevention of myocardial infarction. Circulation 1980; 62 (Suppl V): V63-V72.

15. Hirsh J, Dalen JE, Fuster V, Harker LB, Salzman EW. Aspirin and other platelet-active drugs. The relationship between dose, effectiveness and side effects. Chest 1992; 102: 327S-36S.

16. Cairns JA, Gent M, Singer J, Finnie KJ, Froggatt GM, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. N Engl J Med 1985; 313: 1369-75.

17. Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. N Engl J Med 1978; 299: 53-9.

18. Clopath P. The effect of acetylsalicylic acid (ASA) on the development of atherosclerotic lesions in miniature swine. Br J Exp Path 1980; 61: 440-3.

19. Coronary Drug Project Research Group. Aspirin in coronary heart disease. J Chron Dis 1976; 29: 625-42.

20. Coronary Drug Project Research Group. Aspirin in coronary heart disease. Circulation 1980; 62 (Suppl V): V59-V62.

21. Craven LL. Acetylsalicylic acid, Possible preventive coronary thrombosis. Ann West Med Surg 1950; 4: 95-9.

22. Craven LL. Prevention of coronary and cerebral thrombosis. Miss Valley Med J 1956; 78: 213-5.

23. Czaplicki S, Gietka J, Suzek K. The frequency of coronary heart disease and myocardial infarction in rheumatoid arthritis patients. Cor Vasa 1978; 20: 249-54.

24. Danese CA, Voletti CD, Weiss HJ. Protection by aspirin against experimentally induced arterial thrombosis in dogs. Thrombos Diathes Haemorrh 1971; 25: 288-96.

25. De Caterina R, Giannessi D, Boem A, Bernini W, Battaglia D, Michelassi C, Dell'Amico F, L'Abbate A, Patrignani P, Patrono C. Equal antiplatelet effects of aspirin 50 or 324 mg/day in patients after acute myocardial infarction. Thromb Haemostas 1985; 54: 528-32.

26. De Gaetano G. Primary prevention of vascular disease by aspirin. Lancet 1988; 1: 1093-1094.

27. Editorial. Aspirin after myocardial infarction. Lancet 1980; 1: 1172-3.

28. Editorial. Trials of drugs for prevention of 'secondary' MIs indecisive. Hosp Prac (April) 1980: 53-4.

29. The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med 1991; 325: 1261-6.

30. EDTRS Investigators. Aspirin Effects on Mortality and Morbidity in Patients with Diabetes Mellitus. JAMA 1992; 268(10); 1292-1300.

31. Elwood PC, Sweetnam PM. Aspirin and secondary mortality after myocardial infarction. Lancet 1979; 2: 1313-5.

32. Farah AE, Rosenberg F. Potential therapeutic application of aspirin and other cyclo-oxygenase inhibitors. Br J Clin Pharmac 1980; 10: 261S-78S.

33. Fields WS, Lemak NA, Frankowski RF, Hardy RJ. Controlled trial of aspirin in cerebral ischemia. Stroke 1977; 8: 301-16.

34. Fitzgerald GA, Oates JA, Hawiger J, Maas RL, Jackson R, et al. Endogenous biosynthesis of prostacyclin and thromboxane and platelet function during chronic administration of aspirin in man. Clin Invest 1983; 71: 676-88.

35. Flower RJ, Moncada S, Vane JR. Analgesic - antipyretics and anti-inflammatory agents; drugs employed in the treatment of gout. *In:* The Pharmacological Basis of Therapeutics, Chapter 29, 1980, 682-692.

36. Genton E. A perspective on platelet - suppressant drug treatment in coronary artery and cerebrovascular disease. Circulation 1980; 62: V111-V121.

37. Analgesic-antipyretic and anti-inflammatory agents: the salicylates. *In:* Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 9th Edition, Hardman JG, Limbird LE, Gilman (eds), McGraw-Hill, USA, 1996.

38. Green LH, Seroppian E, Handin RI. Platelet activation during exercise-induced myocardial ischemia. N Engl J Med 1980; 302: 193-7.

39. Guslandi M. Gastric toxicity of antiplatelet therapy with low-dose aspirin. Drugs 1997; 53: 1-5.

40. Haft JI. Platelets and coronary artery disease. Prim Card 1979; June: 97-104.

41. Hansson L, Zanchetti A, Carruthers GS, Dahlof B, Eimfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerlin S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trail. Lancet 1998:351: 1755-1762.

42. Harker LA, Slichter SJ. Studies of platelet and fibrinogen kinetics in patients with prosthetic heart valves. N Engl J Med 1970; 283: 1302-5.

43. Harris WH, Salzman EW, Athanasoulis CA, Waltman AC, Baum S, De Sanctis RW. Aspirin prophylaxis of venous thromboembolism after total hip replacement. N Engl J Med 1977: 297: 1246-9.

44. Harris WH, Salzman EW, Athanasoulis CA, Waltman AC, Baum S, De Sanctis RW. Comparison of warfarin, low molecular-weight dextran, aspirin and subcutaneous heparin in prevention of venous thromboembolism following total hip replacement. J Bone Joint Surg 1974; 56: 1552-62.

45. Harrison MJG, Marshall J, Meadows JC, Russell RWR. Effect of aspirin in Amaurosis Fugax. Lancet 1971; 2: 743-4.

46. Hennekens CH, Peto R, Hutchison GB, Doll R. An overview of the British and American aspirin studies. N Engl J Med 1988; 318: 923-4.

47. Hoffman W, Forster W. Two year Cottbus reinfarction study with 30 mg aspirin per day. Prostaglandins, Leukotrienes and Essential Fatty Acid 1991; 44: 159-69.

48. Hoffman W, Nitschke M, Muche J, Kampe W, Handreg W, Forster W. Reevaluation of the Cottbus reinfarction study with 30 mg aspirin per day 4 years after the end of the study. Prostaglandins, Leukotrienes and Essential Fatty Acids 1991; 42: 137-9.

49. Hogben AMC, Tocco DJ, Brodie BB, Schanker LS. On the mechanism of intestinal absorption of drugs. J Pharm Ther 1959; 125: 275-82.

50. Hsia J, Hamilton WP, Kleiman N, Roberts R, Chaitman BR, Ross AM for the Heparin-Aspirin Reperfusion Trial (HART) Investigators. A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1990; 323: 1433-7.

51. Hume M, Bierbaum B, Kurlakose TX, Surprenant J. Prevention of post-operative thrombosis by aspirin. Amer J Surg 1977; 133: 420-2.

52. Jakubowski JA, Stampfer MJ, Vaillancourt R, Deykin D. Cumulative antiplatelet effect of low-dose enteric coated aspirin. Br J Haematolo 1985; 60: 635-42.

53. Jennings JJ, Harris WH, Sarmiento A. A clinical evaluation of aspirin prophylaxis of thromboembolic disease after total hip arthroplasty. J Bone Joint Surg 1976; 58: 926-8.

54. Juul-Moller S, Edvardsson N, Jahnmatz B, Rosen A, Sorensen S, Omblus R, for the Swedish Angina Pectoris Aspirin Trial (SAPAT) Group: Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. Lancet 1992; 340: 1421-5.

55. Kumpuris AG, Luchi RJ, Waddell CC, Miller RR. Production of circulating platelet aggregates by exercise in coronary patients. Circulation 1980; 61: 62-5.

56. Lewis HD Jr, Davis JW, Archibald DG, Steinke WE, Smitherman TC, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a veterans administration cooperative study. N Engl J Med 1983; 309: 396-403.

57. Lindblad B, et al. Does low-dose acetylsalicylic acid prevent stroke after carotid surgery? A double-blind, placebo-controlled randomized trial. Stroke 1993; 24:1125-8.

58. Malseed R, Malseed Z. Aspirin: a pharmacologic profile. Amer J Pharm 1978; July-Aug: 99-106.

59. McCann RL, Hagen P, Fuchs JCA. Aspirin and dipyridamole decrease intimal hyperplasia in experimental vein grafts. Ann Surg 1980; 191: 238-43.

60. McKenna R, Bachmann F, Kaushal SP, Galante JO. Thromboembolic disease in patients undergoing total knee replacement. J Bone Joint Surg 1976; 58: 928-32.

61. Medical Research Council's General Practice Research Framework. Thrombosis prevention trial:randomized trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet 1998:351:233-41

62. Mehta J, Mehta P, Burger C, Pepine CJ. Platelet aggregation studies in coronary heart disease. IV. Effect of aspirin. Atherosclerosis 1978; 31: 169-75.

63. Mehta P, Mehta J. Platelet function studies in coronary heart disease. V. Evidence for enhanced platelet microthrombus formation activity in acute myocardial infarction. Am J Cardiol 1979; 43: 757-60.

64. Mehta J, Mehta P, Pepine CJ, Contic R. Platelet aggregation studies in coronary heart disease. VII. Effect of aspirin and tachycardia stress on aortic and coronary venous blood. Am J Cardiol 1980; 45: 945-51.

65. Morley J. Mechanism of action of aspirin in inflammation. Proc Roy Soc Med 1977; 70: 32-6.

66. Moschos CB, Haider B, De La Cruz C, Lyons MM, Regan TJ. Antiarrhythmic effects of aspirin during non-thrombotic coronary occlusion. Circulation 1978; 57:681-4.

67. Mundall J, Quintero P, Von Kaulla KN, Harmon R, Austin J. Transient monocular blindness and increased platelet aggregability treated with aspirin. Neurology 1972; 22: 280-5.

68. Orme M. Aspirin all round? Br Med J 1988; 296: 307-8.

69. Orr J, Abbott F, Farrell K, Ferguson S, Sheppard I, and W Godolphin, Interaction between valproic acid and aspirin in epileptic children: Serum protein binding and metabolic effects. Clin. Pharmacol.Ther. 1982:31:642-649.

70. Packham MA, Mustard JF. Pharmacology of platelet affecting drugs. Circulation 1980; 62: V26-V41.

71. Patrignani P, Filabozzi P, Patrono C. Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. J Clin Invest 1982; 69: 1366-72.

72. Persantine-Aspirin Reinfarction Study (PARIS) Research Group: The persantine-aspirin reinfarction study. Circulation 1980; 62 (Suppl V): V85-V88.

73. Peto R, Gray R, Collins R, et al. Randomized trial of prophylactic daily aspirin in British male doctors. Br Med J 1988; 296: 313-6.

74. Pick R, Chedlak J, Glick G. Aspirin inhibits development of coronary atherosclerosis in cynomolgus monkeys (Macaca Fascicularis) fed on atherogenic diet. J Clin Invest 1970; 63: 158-62.

75. Relman AS. Aspirin for the primary prevention of myocardial infarction. N Engl J Med 1988; 318: 245-6.

76. Renaud S, Godu J. Thrombosis prevention by acetylsalicylic acid in hyperlipemic rats. CMAJ 1970: 103; 1037-40.

77. RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. Lancet 1990; 336: 827-30.

78. Roberts MS, Joyce RM, McLeod LJ, Vial JH, Seville PR. Slow-release aspirin and prostaglandin inhibition. Lancet 1986; 1(8490): 1153-4.

79. Ross R, Glomset JA. Pathogenesis of atherosclerosis. N Engl J Med 1976; 295: 369-377, 420-5.

80. Roth GJ, Stanford N, Majenus PW. Acetylation of prostaglandin synthase by aspirin. Proc Nat Acad Sci 1975; 72: 3073-6.

81. Rowland M, Riegelman S. Pharmacokinetics of acetylsalicylic acid and salicylic acid after intravenous administration in man. J Pharm Sci 1968; 57: 1313-9.

82. SALT Collaborative Group. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. Lancet 1991; 338: 1345-9.

83. Salzman EW, Harris WH, De Sanctis RW. Reduction in venous thromboembolism by agents affecting platelet function. N Engl J Med 1971; 284: 1287-92.

84. Schafer A, Handin R. The role of platelets in thrombotic and vascular disease. Proj Cardio Dis 1979; 22: 31-52.

85. Smith MJH. Plasma-salicylate concentrations after small doses of acetylsalicylic acid. J Pharm Pharmacol 1951; 3: 409-14.

86. Soreff J, Johnson H, Diener L. Acetylsalicylic acid in a trial to diminish thromboembolic complications after elective hip surgery. Acta Orthop Scand 1975; 46: 246-55.

87. Steering Committee of the Physicians' Health Study Research Group. Preliminary report: findings from the aspirin component of the ongoing Physicians' Health study. N Engl J Med 1988; 318: 262-4.

88. UK-TIA Study Group. United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results. Br Med J 1988; 296: 316-20.

89. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature New Biol 1971; 231: 232-5.

90. Verheugt FWA, van der Loarse A, Funke-Kupper AJ, Sterkman LGW, Galema TW, Roos JP. Effects of early intervention with low-dose aspirin (100 mg) on infarct size, reinfarction and mortality in anterior wall acute myocardial infarction. Am J Cardiol 1990; 66: 267-70.

91. Wallentin LC and The Research Group on Instability in Coronary Artery Disease in Southeast Sweden. Aspirin (75 mg/day) after an episode of unstable coronary artery disease: Long-term effects on the risk for myocardial infarction, occurrence of severe angina and the need for revascularization. J Am Coll Cardiol 1991; 18: 1587-93.

92. Weiss HJ, Aledort LM, Kochwa S. The effect of salicylates on the hemostatic properties of platelets in man. J Clin Invest 1968; 47: 2169-80.

93. Weiss HJ. Antiplatelet therapy (second of two parts). N Engl J Med 1978; 298: 1403-6.

94. Wilson PF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel W. Predictions of Coronary Heart Disease Using Risk Factor Categories. Circulation 1998; 97: 1837-1847.

95. Wright HN. Chronic toxicity studies of analgesic and anti-pyretic drugs and congeners. Toxicol Appl Pharmacol 1967; 11: 280-92.

96. Wolinsky H. Atherosclerosis. Textbook of Medicine 15th Edition. Philadelphia. W.B. Saunders Co. Vol. 1: Chapter 362, pg. 1218 (1979).

97. Wood MD, Alastair J.J, Aspirin as an antiplatelet drug.
N Engl J Med. 1994. 330: 1287-1294.

98. Young VP, Giles AR, Pater J, Corbett WEN. Sex differences in bleeding time and blood loss in normal subjects following aspirin ingestion. Thromb Research 1980; 20: 705-9.

99. Zekert F, Kohn P, Vormittag E, Poigenfurst J, Thien M.Thromboembolie-prophylaxe mit Acetylsalicylsaure bei Operationen wegen huftgelenksnaher Frakturen Mschr Unfallheilk 1974; 77: 97-11.