PRODUCT MONOGRAPH

ASPIRIN*
(acetylsalicylic acid tablets, USP)
(325mg, 500mg)

ASPIRIN*
(acetylsalicylic acid delayed release tablets, USP)
(81mg, 325mg, 500mg, 650mg)

Analgesic, anti-inflammatory, antipyretic and
platelet aggregation inhibitor

BAYER INC.
Toronto, Ontario

Control# 092023

DATE OF REVISION:
July 26, 2004

NAME OF DRUG

ASPIRIN*

(acetylsalicylic acid tablets, USP)

THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

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

ACTIONS

Acetylsalicylic acid (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, ASPIRIN* 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

ASPIRIN* (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. ASPIRIN® Extra Strength is also indicated for relief of migraines including pain and the associated symptoms of photophobia (sensitivity to light) and phonophobia (sensitivity to sound), and improves overall quality of life.

ASPIRIN* 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;	Aspirin 81mg DIN 02237726; Aspirin Tablets 325mg DIN02150328
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. Aspirin 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.	Aspirin 81mg DIN 02237726; Aspirin Tablets 325mg DIN02150328;
for reducing the risk of morbidity and death in patients with unstable angina and in those with previous myocardial infarction	Aspirin 81mg DIN 02237726; Aspirin Tablets 325mg DIN02150328;

for reducing the risk of transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction;	Aspirin 81mg DIN 02237726; Aspirin Tablets 325mg DIN02150328;
for prophylaxis of venous thromboembolism after total hip replacement;	Aspirin Tablets 325mg DIN02150328;
for reducing the adhesive properties of platelets in patients following carotid endarterectomy to prevent recurrence of TIA and in hemodialysis patients with a silicone rubber arteriovenous cannula.	Aspirin Tablets 325mg DIN02150328;

CONTRAINDICATIONS

• Hypersensitivity to acetylsalicylic acid, to other salicylates, or to any other components of the product; 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, 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 (3 g 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 (3g/day or more).

ADVERSE EFFECTS

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 and 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 function.

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.

Migraine pain and associated symptoms:

Adults: 1000 mg (2 x 500mg tablets) at onset of pain or symptoms.

Children: Clinical studies to support migraine relief in children have not been conducted with acetylsalicylic acid.

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:

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).

Prevention of a first non-fatal myocardial infarction: 80 - 325 mg once daily, according to the individual needs of the patient, as determined by the physician.
Prior Myocardial Infarction or Unstable Angina Pectoris: 80 - 325 mg daily according to the individual needs of the patient, as determined by the physician.

Transient Ischemic Attack and Secondary Prevention of Atherothrombotic Cerebral Infarction: 80 - 325 mg daily according to the individual needs of the patient, as determined by the physician.

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.

AVAILABILITY

ASPIRIN* Tablets: Each round, white tablet with the Bayer Cross* on both sides contains 325 mg acetylsalicylic acid. In packages of 12, 24, 50, 100, 115, 200 and 400.

ASPIRIN* Tablets Extra-Strength: Each round, white tablet, with the Bayer Cross* on one side and 500 on the other, contains 500 mg acetylsalicylic acid. In packages of 30, 60 and 100 in a formula containing carnauba wax, corn starch, D&C Red #7, FD&C Blue #2, FD&C Red #40, hydroxypropyl methylcellulose, powdered cellulose, propylene glycol, shellac, titanium dioxide, triacetin. Store between 15-25°C.

ASPIRIN* Caplets: Each white capsule-shaped tablet (caplet), with BAYER on one side and score on the other, contains 325 mg acetylsalicylic acid. In packages of 50 and 100.

Coated ASPIRIN* Caplets: Each pale yellow enteric coated caplet, with BAYER 325 in brown ink on one side and blank on the other, contains 325 mg of acetylsalicylic acid. In packages of 50, 100 and 200.

Coated ASPIRIN* Extra Strength Caplet: Each pale yellow enteric coated caplet, with BAYER 500 in brown ink on one side and blank on the other, contains 500 mg of acetylsalicylic acid. In packages of 50 and 100.

Coated ASPIRIN* Arthritis Pain Relief Caplets: Each orange enteric coated caplet, with B embossed on one side and blank on the other, contains 650mg of acetylsalicylic acid. In packages of 100.

ASPIRIN* With Stomach Guard Tablets: Each round, white, film-coated tablet with BAYER PLUS in blue ink on one side contains 325 mg acetylsalicylic acid, 160 mg calcium carbonate, 34 mg magnesium carbonate, 63 mg magnesium oxide. In packages of 36.

ASPIRIN* With Stomach Guard Extra Strength Tablets: Each white, film-coated caplet, with BAYER PLUS over 500 on one side in blue ink, contains 500 mg acetylsalicylic acid, 245.2 mg calcium carbonate, 52.5 mg magnesium carbonate and 96.9 mg magnesium oxide. In packages of 30 and 60.

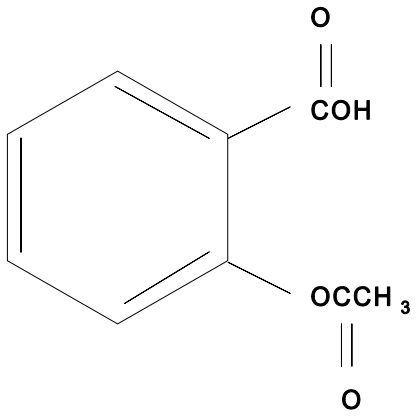
Flavoured Children's Size ASPIRIN*: Each peach coloured tablet, with pleasant orange taste and the Bayer Cross* on one side, with ASPIRIN on the other contains 80 mg (1-1/4 gr) acetylsalicylic acid. In bottles of 24, 60 and 90.

ASPIRIN* 81 mg: Each pale blue coloured enteric coated tablet, with 81 in dark blue ink on one side contains 81 mg (1-1/4 gr) acetylsalicylic acid. In bottles of 24, 120 and 180 tablets.

All Bayer ASA preparations are tartrazine-free.

CHEMISTRY

Structural Formula:



Molecular Formula: $C_9H_8O_4$

Molecular Weight: 180.16

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

INFORMATION FOR THE CONSUMER

ASPIRIN* 81 mg

Patient Information Leaflet -Provided by the Physician or Pharmacist

This leaflet provides you with information about ASPIRIN 81 mg and how to take this medication. ***Please read carefully before using this medicine***. Also see package insert for additional information.

WHEN AND HOW SHOULD I TAKE THIS MEDICINE?

ASPIRIN 81 mg can help save your life in the following situations:

• to help prevent a first heart attack in those who are at increased risk, or

• to help prevent a second heart attack or stroke in those who have already had such an event, or

•when you suspect you are having a heart attack.

FOR PREVENTION OF A FIRST NON-FATAL HEART ATTACK (DAILY THERAPY):

Your doctor may recommend you take ASPIRIN 81 mg to help reduce the risk of a first non-fatal heart attack because you are at risk of having a heart attack. There is no evidence that this product reduces the risk of a first fatal heart attack, nor first strokes (fatal and non-fatal), nor death due to any cardiovascular problems. Your doctor will assess the appropriate balance of possible benefit of this product against the potential risk of stomach bleeding and stroke. Factors that increase your risk include high blood pressure, high cholesterol, diabetes, family history of heart disease, increased age, overweight and smoking. You should follow your doctor’s instructions carefully. Please notify your doctor if you intend to stop taking this medication.

USE DURING A HEART ATTACK

If you think you are having a heart attack, you should immediately chew or crush 2 - ASPIRIN 81 mg 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 ASPIRIN 81 mg 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:

- 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,
- pain that spreads to the shoulders, neck or arms,
- chest discomfort with lightheadedness, fainting, sweating, nausea or shortness of breath.

At the hospital, the doctor will then recommend appropriate therapy

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

Your doctor may recommend you take ASPIRIN 81 mg daily to help prevent a second heart attack or stroke. After having experienced a first heart attack or stroke, you can be at increased risk of experiencing a second one. You may also be at risk for heart disease and stroke because you may be overweight, a smoker, have an inactive lifestyle, high blood pressure, are under stress or have high blood cholesterol.

Following your doctor’s instructions concerning the use of ASPIRIN 81 mg and the changes in diet, exercise and lifestyle he/she may have prescribed, will provide you with your best opportunity to avoid experiencing a second heart attack or stroke. Always contact your doctor if you experience any difficulties.

WHEN SHOULD I TAKE THIS MEDICINE?

During a heart attack: Immediately chew or crush 2 ASPIRIN 81mg tablets and call an ambulance.

For prevention of a first heart attack or for the prevention of a second heart attack or stroke: Take 1 to 4 tablets daily, depending on your doctor's instructions. You should take this medicine at the same time every day. This will help you to remember to take your medication. For maximum effectiveness, it is very important to take ASPIRIN 81 mg *every day* as directed by your doctor. Do not take more tablets than your doctor recommends. Your doctor may tell you to take ASPIRIN 81 mg with other medications; he or she may also tell you to eat special foods, exercise or take other steps to safeguard your health.

WHAT IF I FORGET TO TAKE MY MEDICATION?

If you forget to take your medication, take it when you remember. But do not take *extra* medication to compensate for a missed dosage unless instructed by your doctor.

WHY SHOULD I USE ASPIRIN 81 mg?

ASPIRIN 81 mg is unlike other pain reliever products such as acetaminophen (Tylenol®) or ibuprofen (Advil®), it is specially formulated and has a different use to help prevent damage to the heart during a heart attack, to help prevent a first heart attack in those who are at increased risk and to help prevent a second heart attack or stroke. ASPIRIN 81 mg is specially formulated for your condition.

ASPIRIN 81 mg also has a special coating, *enteric coating*, which allows the tablet to pass, undissolved, through the stomach and on into the intestine. By using ASPIRIN 81 mg, the risk of stomach upset is reduced in those people with sensitive stomachs.

CAN I CRUSH OR BREAK THE TABLETS?

If you are having a heart attack, immediately chew or crush 2 ASPIRIN 81 mg tablets and call an ambulance. However, for daily therapy, ASPIRIN 81 mg tablets should be swallowed whole for the medicine to work properly. ASPIRIN 81 mg tablets have a special coating, *enteric coating*, which allows the tablets to pass undissolved through the stomach and on into the intestine. By dissolving in the intestine rather than the stomach, the risk of

stomach upset is reduced. Therefore, to maintain this protection, the tablets should not be crushed or broken.

CAN I CONTINUE TO TAKE ASPIRIN FOR RELIEF OF HEADACHE, FEVER OR ARTHRITIC PAIN?

ASPIRIN 81 mg is specially designed to reduce your risk of dying during a heart attack, to help prevent a first heart attack in those who are at increased risk and to help prevent a second heart attack or stroke. It is a smaller dose than you would need to take for a headache or other types of pain. Ask your doctor or pharmacist about other ASPIRIN products available (or other pain relievers such as acetaminophen or ibuprofen) and the correct dosage for the relief of your headache, fever or arthritic pain.

Always consult with your physician or pharmacist before taking other medications.

WILL I EXPERIENCE ANY SIDE EFFECTS WITH THIS MEDICINE?

Like all medicines, ASA may occasionally produce unwanted side effects. You should call your doctor if you experience any of the following: nausea, vomiting; bleeding or stomach irritation, any loss of hearing, including ringing or buzzing in the ears or pain; if you notice that you are 'bruising' more easily than you were before starting a daily dose of ASPIRIN**,** skin rashes, hives or itching and breathing difficulties.

Regular daily 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 ASPIRIN 81 mg. That 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 (or any medicine): allergy to salicylates; asthma; stomach problems; peptic ulcer; severe liver disease, history of blood clotting defects or receiving blood thinners; have severe anemia; are pregnant or breast-feeding; will be having surgery in five to seven days; are taking

simultaneously while consuming alcohol; are taking anti-inflammatory drugs, anticonvulsants, anti-diabetic or gout medicine; or are taking other medications containing salicylates or acetaminophen.

REMEMBER:

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 drug during the last 3 months of pregnancy unless specifically directed to do so by your doctor 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.

PHARMACOLOGY

Absorption, distribution, metabolism and excretion:

When ASPIRIN* 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 ASPIRIN*, 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 ASPIRIN* 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 ASPIRIN* 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 analgetic effect of ASPIRIN* has been recognized and utilized clinically for more than half a century. The degree of analgesia attained with ASPIRIN* 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 ASPIRIN*. As for mechanism of action, the accumulated evidence of recent years indicates that ASPIRIN* acts by interfering with the synthesis and release of prostaglandins, thereby averting the sensitization of pain receptors to mechanical stimulation or to other mediators.

Migraine:

Migraines are reoccurring headaches that last 4-72 hours and are characterized by lateralized throbbing, moderate to severe pain intensity and at least one other of the following symptoms: nausea, photophobia, phonophobia. Routine physical activity aggravates the symptoms. Some individuals also experience neurological aura such as blurring of vision before the pain and associated symptoms occur.

Evidence suggests that there are at least three mechanisms involved in the pathophysiology of migraines: extracranial arterial vasodilatation, extracranial neurogenic inflammation and decrease inhibition of central pain transmission. It has been shown that the degree of inflammatory activity is proportional to the intensity of the pain felt and as the blood pulses, the characteristic throbbing emerges.

An estimated two million Canadians have been diagnosed with migraines but many migraineurs never receive a clinical diagnosis; therefore, the actual numbers of Canadians who suffer from migraines could be over 3 million. Over 70% of migraine suffers are women and the majority are aged between 20 and 50 years. This prevalence is based in part due to hormonal fluctuations that women experience related to menstruation, oral contraceptive use, pregnancy, menopause and hormone replacement therapy.

The use of a single dose of ASPIRIN* (2 x 500mg tablets) in patients with a migraine attack was investigated in two placebo-controlled clinical studies conducted by Bayer. Treatment with ASPIRIN* resulted in a statistically significant relief of migraine pain and in the associated symptoms of photophobia and phonophobia that continued throughout the 6 hour post-dose observation. The results also showed a significant improvement in overall quality of life for migraine sufferers but there was no difference between ASPIRIN* and placebo groups in headache recurrence.

Antipyresis:

Interference with the synthesis and release of prostaglandins is also involved in the antipyretic activity of ASPIRIN*. ASPIRIN* 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 ASPIRIN* 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 ASPIRIN* 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 ASPIRIN* 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. ASPIRIN* 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, ASPIRIN* 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 ASPIRIN* thus persists 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

ASPIRIN* against experimentally induced thrombosis or atherosclerosis has been demonstrated in several animal models.

Besides inhibiting the biosynthesis of thromboxane A_2 by platelets, ASPIRIN* 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 ASPIRIN* depends on the thromboxane-prostacyclin balance. In fact, it has been suggested that under some conditions, high doses of ASPIRIN* 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 ASPIRIN* 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 ASPIRIN* 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 of 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 ASPIRIN* in patients with a suspected acute myocardial infarction was investigated in a large multi-centre trial involving over 17,000 patients. Treatment with ASPIRIN* 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 ASPIRIN* “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 ASPIRIN* 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 ASPIRIN* persisted long term, and that this prolonged benefit was

additive to that of fibrinolytic therapy.

The use of ASPIRIN* 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.

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 weaning age. No evidence of carcinogenic effect was found.

The chronic oral LD_{50} in male albino rats has been reported as 0.24 g/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, piloerection, 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.

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