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Editor's Note—*It's been called a wonder drug. If any drug could fit that bill, it's aspirin. It's easily the most cost-effective pharmacological agent in the history of medicine and its indications keep expanding. The latest news is that less may be better. A recent investigation demonstrated that ASA given at 81 mg/d resulted in superior clinical outcomes compared to a high dose of 650 mg/d in patients awaiting carotid enarterectomy. Drs Weisman and Rabe review the fascinating history of aspirin and its expanding clinical roles as we move into the next millennium.*

Aspirin: New Tricks for an Old Drug

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Aspirin's Beginnings

Aspirin is an old drug. It has been commercially available for more than 100 years and its precursor, salicylic acid (present in a number of common plants) has been therapeutically used since ancient times.[1] Accounts of the use of extracts of the leaves, bark, and roots of plants, such as the willow, myrtle, and meadowsweet, are described in folklore and traditional herbal therapies of ancient cultures. Hippocrates recommended the use of willow extract to treat fever and ease the pain of childbirth, ancient Egyptians used extracts of myrtle leaves to treat pain, and explorers observed that Native American Indians chewed willow bark for medicinal purposes.

It wasn't until the1700s that the medicinal properties of these herbal therapies were scientifically investigated. At that time, medicine and religion were intertwined; the scientists at that time were clergymen who held the responsibility for both physical and spiritual health. A popular doctrine embraced by these clergymen was the Doctrine of Signatures. This doctrine suggested that the cause of a disease offers clues to its treatment. A vicar named Edward Stone reasoned that since the willow thrives in moist environs, where fever is a common complaint, the willow might contain some cure for fever. He pulverized the bark of the willow, brewed a tea from it, and found that it reduced fever.

Another 70 years passed before the active ingredient in willow was extracted and identified. The constituent responsible for the reduction of pain and fever was identified and named "salicin" or "salicylic acid" based on its origin in the

willow, *Salix alba*. Salicylic acid, although widely used to treat pain and fever at the time, was bitter and irritating to the stomach, and many patients were unable to tolerate it.[1] In the mid-to-late 1800s, chemists throughout Europe were attempting to synthesize less acidic forms of salicylic acid. In 1898, Felix Hoffmann, an industrial chemist working at the Friedrich Bayer Company in Elberfeld, Germany, succeeded in synthesizing a pure and stable form of the acetate derivative of salicylic acid, acetylsalicylic acid. Approximately one year later, acetylsalicylic acid was given the name, Aspirin—A to denote the important acetyl group and spirin to refer to the meadowsweet, *Spiraea ulmaria*, from which salicylic acid may be isolated. Although Hoffman's superiors were initially skeptical about the value of this new drug, tests soon showed that aspirin had anti-inflammatory and analgesic properties and was much better tolerated than salicylic acid. In the first mass marketing effort to be undertaken for a drug substance, Bayer set out to spread the word on aspirin, and it was not long before this product contributed substantially to Bayer's profits.

Today, aspirin is the most popular over-the-counter medication sold in the United States and around the world. In the United States alone, in one day, on average, 220 million tablets are consumed—the equivalent of 9 million tablets per hour. The remarkable success of aspirin relates to its recognized effectiveness in the relief of pain and inflammation as well as its use in cardiovascular disease prevention.

How Does It Work?

Aspirin was used throughout the world for approximately 70 years with little knowledge of the mechanism by which this drug conferred its health benefits. Then, in 1971, John Vane, a scientist at the Royal College of Surgeons in London, discovered that aspirin suppresses the production of a family of biologically active compounds called prostaglandins.[2] Aspirin does this by transferring its acetyl group to the serine residues present on the enzyme responsible for prostaglandin synthesis, cyclooxygenase, also known as prostaglandin synthetase.[3] The irreversible acetylation of the active site of the enzyme blocks the interaction between the primary prostaglandin precursor, arachidonic acid, and the active site of this enzyme. This, in turn, blocks the conversion of arachidonic acid to the cyclic endoperoxide that is subsequently metabolized by other enzymes to a variety of prostaglandins. This inhibition of prostaglandin synthesis is believed to underlie many of aspirin's effects.

Prostaglandins are local hormone-like mediators that have a broad spectrum of effects.[4] They have a major role in protecting the gastrointestinal tract, inducing uterine contractions during labor, and maintaining renal blood flow in individuals for whom disease has rendered renal blood flow dependent on the vasodilatory effects of prostaglandins. Prostaglandins are also responsible for mediating a variety of pathological processes including pain, inflammation, fever, and the formation of occlusive blood clots. It is the ability of aspirin to inhibit prostaglandins that accounts for its diversity of effects, both advantageous and disadvantageous. For example, during tissue injury, the release of prostaglandins by damaged tissues causes local vasodilation and sensitization of nerve endings, accounting, in part, for the redness, swelling, and tenderness that accompanies such injury. It is the inhibition of the synthesis of prostaglandins that explains the effectiveness of aspirin in reducing inflammation and relieving pain.

Prostaglandins also play an important role in platelet aggregation.[5,6] When activated, platelets release a variety of substances that precipitate the aggregation of platelets with one another and the formation of a platelet thrombus. Thomboxane A_2, a cyclooxygenase product, is one such substance. Inhibition of its formation by aspirin-mediated inhibition of cyclooxygenase reduces the ability of platelets to form a clot.

Aspirin's ability to inhibit prostaglandin synthesis accounts for its beneficial effects in reducing pain, inflammation, and fever, and the tendency of platelets to form clots. However, the inhibition of prostaglandin synthesis also accounts for several detrimental effects that are known to occur with aspirin usage. For example, the inhibition of prostaglandin synthesis in the gastrointestinal system blocks the anti-ulcerogenic effects of the prostaglandins (e.g., vasodilation, stimulation of gastric mucus and duodenal bicarbonate secretion, and inhibition of gastric acid secretion), which lead to gastrointestinal adverse effects, including, in rare cases, erosion of the gastric mucosa. A direct toxic effect of aspirin on the gastric mucosa is also thought to contribute to gastrointestinal toxicity. However, the prevalence of gastrointestinal effects decreases with the dose

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of aspirin that is used. A direct comparison of the prevalence of gastrointestinal toxicity among patients using 300 mg per day and 1200 mg per day showed significantly less toxicity at 300 mg per day.[7] Furthermore, the prevalence of gastrointestinal toxicity at 300 mg per day was similar to that observed in the placebo group. Reducing the dose of aspirin used to 81 mg per day, using enteric-coated or highly buffered aspirin, or using aspirin in conjunction with products that protect the gastric lining may eliminate aspirin-induced gastric toxicity.[8] Generally, when used on an episodic basis as an over-the-counter remedy for the symptomatic relief of pain, fever, and inflammation, the adverse effects of aspirin are remarkably few. Complaints of dyspepsia are most common and preclude some from taking aspirin. In fact, only 2-6% of patients cannot take aspirin due to gastric intolerance. The vast majority of patients can take aspirin without unwanted effects.

Figure 1. Felix Hoffman

Bayer chemist Felix Hoffman discovered a stable form of acetylsalicyclic acid (ASA), the active ingredient in aspirin. Hoffman discovered ASA in his search for a more effective, safe treatment for his father who was crippled by rheumatism. Reprinted with permission from Bayer Corporation.

Research into ways to separate the beneficial and adverse effects of aspirin has led to the discovery that two forms of the cyclooxygenase enzyme exist, COX-1 and COX-2.[9] While these isoforms act on the identical substrate and produce identical products, there are important differences between them. COX-1 and COX-2 predominate in different types of cells and differ in their ability to be induced. For example, COX-1 is found in platelets, the cells of the gastrointestinal tract, the kidney, and other organ systems, and is maintained at a relatively constant level in these tissues. The prostaglandins produced by this form of cyclooxygenase are involved in normal housekeeping functions, such as maintaining renal blood flow, protecting the integrity of the gastrointestinal mucosa, and contributing to platelet aggregation. By contrast, COX-2 is found primarily in immune system cells and is normally found at low levels. However, when the immune cell is exposed to inflammatory stimuli, rapid and dramatic increases in COX-2 expression occur. This results in a local and rapid release of prostaglandins and an inflammatory reaction.

Aspirin, while able to inhibit both COX-1 and COX-2, has a greater affinity for the COX-1 enzyme. As such, its effects on tissues expressing COX-1 can be observed at lower doses than on those expressing COX-2. More selective COX-2 inhibitors, by contrast, preferentially inhibit those effects mediated by prostaglandins produced in response to inflammatory stimuli, leaving those effects mediated by COX-1 activity relatively unaffected. This differential inactivity of various nonsteroidal anti-inflammatory drugs (NSAIDs) allows selective use in different pathological situations (e.g., thrombosis vs inflammation). Selective COX-2 inhibitors are now in development that may possess beneficial analgesic, anti-inflammatory, and antipyretic effects, with a lower degree of the side effects associated with the currently available mixed COX-1/COX-2 inhibitors.[9]

It is the effects of aspirin on COX-1, however, that account for what has become acknowledged to be its most beneficial effect. The use of aspirin for inhibition of prostaglandin-mediated platelet aggregation is widely accepted as beneficial in preventing the morbidity and mortality associated with atherothrombotic cardiovascular events. Although inhibition of platelet aggregation can, in some individuals, result in increased bleeding, most aspirin-associated bleeding is relatively minor (e.g., epistaxis, purpura). Severe gastrointestinal or cerebral hemorrhages are infrequent at the low doses of aspirin required for prevention of heart attack or stroke.

Aspirin, Heart Attack, and Stroke Prevention

Today, the effectiveness of aspirin in the prevention of cardiovascular events is well known. It may be surprising, however, that the initial advertisements that appeared at the beginning of this century promoted the fact that "aspirin does not affect the heart." Such promotion was felt to be necessary at the time to distinguish the effects of aspirin from those of the salicylates, since the salicylates were thought to have "enfeebling" effects on the heart.

It wasn't until the 1950s that aspirin was first found to be beneficial in treating patients with cardiovascular disease. Lawrence Craven, an otolaryngologist from California, noted that patients for whom he had been prescribing a chewable

form of aspirin for pain relief after tonsillectomies had an unusually high incidence of bleeding problems. He reasoned that the effect of aspirin on bleeding might be beneficial in preventing the formation of blood clots that caused heart attacks and stroke. To test his hypothesis, he prescribed aspirin to thousands of middle-aged patients for long-term use and found that the incidence of heart and stroke in these patients was reduced to zero. Unfortunately, Craven failed to use an adequate control group, and scientists of the day found Craven's claims to be unbelievable. Craven's findings were largely ignored at the time, and it took more than 20 years for his initial hypothesis to find firm scientific support.

It is now known that the blood clots that obstruct blood vessels and give rise to heart attacks and stroke form when atherosclerotic plaques rupture and platelets come in contact with the subendothelial layers of blood vessels.[10] This contact leads to adhesion of platelets to the rupture site, activation, aggregation, the recruitment of other platelets, and fibrin formation. In healthy blood vessels, platelet clot formation provides a beneficial effect—the prevention of blood loss when the vessel is injured. However, when the clot forms within a blood vessel leading to the heart or the brain that is already narrowed by the build-up of atherosclerotic plaque, obstruction of blood flow may occur and ischemic damage to the tissue distal to the obstruction can occur. Aspirin administration, by inhibiting the ability of platelets to aggregate, can limit the development of a heart attack or stroke.

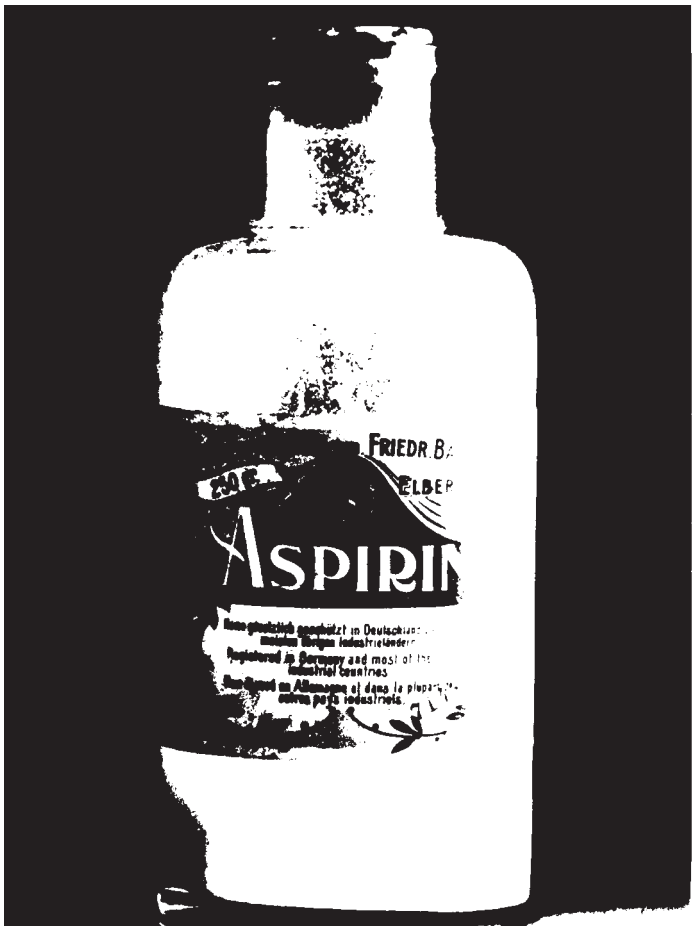
Aspirin's ability to inhibit platelet clot formation is a result of its ability to block the activity of the enzyme cyclooxygenase. When platelets adhere to the subendothelium, they become activated. Synthesis of thromboxane A_2 is stimulated, and the platelets release this along with the contents of their secretory granules adenosine diphosphate (ADP) and serotonin. Each of these substances contributes to aggregation and recruitment of additional platelets to the site of injury. Platelet thromboxane A_2 also causes local vasoconstriction, an important factor in hemostasis. When cyclooxygenase activity is blocked by aspirin, thromboxane A_2 synthesis is impaired and the rapid formation of the clot is impeded. The contribution of ADP and serotonin to the formation of a clot is not affected by aspirin, since cyclooxygenase plays no role in either the formation or effects of these substances. Other antiplatelet drugs, such as clopidogrel and ticlopidine,[11] block the effects of released ADP, suggesting a potential synergy between aspirin and these compounds.

Aspirin is unique among the NSAIDs in that it irreversibly inhibits platelet thromboxane production.[11] Other NSAIDs competitively block cyclooxygenase activity, but their effects are reversible. The ability of aspirin to irreversibly inhibit cyclooxygenase and the inability of platelets to synthesize new enzymes combine to allow maximal effects with intermittent dosing with low doses of aspirin. Optimal effects with other NSAIDs would require dosing throughout the day to maintain levels sufficient to provide a constant level of cyclooxygenase inhibition. Acetaminophen, the active ingredient in analgesics such as Tylenol,® has no effect on the cyclooxygenase enzyme and, as such, is not of value in cardiovascular disease prevention.

The clinical benefits of aspirin have been observed in three categories of patients: individuals with an evolving acute myocardial infarction, individuals with a past history of atherothrombotic events, and individuals with no history of ischemic cardiovascular disease. Each of these patients has different degrees of underlying risk, and the absolute benefit observed in terms of reduced atherothrombotic morbidity and mortality increases with higher levels of risk. The most important clinical benefit thus far observed occurs in patients presenting with an evolving acute myocardial infarction. Patients experiencing an acute myocardial infarction are at risk not only from the event but also from further occlusion from ongoing thrombus formation. Aspirin administered during the early stages of an acute myocardial infarction is hypothesized to reduce the development of these later-formed clots. The landmark trial of infarct survival, ISIS-2 (International Study of Infarct Survival-2 Collaborative Group[12]), demonstrated that administering as little as 160 mg of aspirin (half a regular tablet) within 24 hours of the onset of symptoms resulted within five weeks in a 49% decrease in nonfatal myocardial infarction, a 46% decrease in nonfatal stroke, and a 23% decrease in the risk of vascular death when compared to patients randomized to placebo. In 1998, the FDA approved the use of aspirin in acute myocardial infarction, and the American Heart Association now recommends the routine use of aspirin to virtually all patients presenting with symptoms of an acute evolving myocardial infarction, based on the results of this trial.[13]

Controlled clinical trials of the efficacy of aspirin in secondary prevention have also demonstrated reduced atherothrombotic morbidity and mortality, although the risk of these events is somewhat lower than in patients suffering an evolving acute myocardial infarction. These benefits have been observed in patients with prior myocardial infarction,[14] unstable angina,[15] or prior transient ischemic attack (TIA) or stroke.[7,16] The reduction in the combined end point of nonfatal myocardial infarction, nonfatal stroke, or vascular death observed in patients with a prior myocardial infarction was approximately 25%.[14] This was slightly higher than that observed in patients with a prior stroke or TIA (approximately 16%;[7,16] and lower than that observed in patients with a history of unstable angina (approximately 50%;[15]). The overall benefit determined in a meta-analysis of 46 clinical trials in which event rates in more than 22,000 aspirin-treated individuals with a history of thrombotic ischemic events were compared to those in patients receiving placebo was a 25% reduction in the incidence of subsequent myocardial infarction, stroke, or vascular death.[17] The magnitude of this effect was the same whether patients had been treated with high-dose (500-1500 mg) or low-dose (75-325 mg) aspirin. This is important because studies have demonstrated that the use of low-dose aspirin is associated with fewer side effects (e.g., gastrointestinal symptoms and inappropriate bleeding) than high-dose regimens. The benefit of aspirin in terms of reduced atherothrombotic morbidity and mortality has been recognized by the FDA, and aspirin is currently approved for use in patients with a prior TIA, myocardial infarction, or unstable angina.[18] On Oct. 23 of this year, the FDA extended the approved uses to include patients with an evolving MI, prior completed stroke, or stable angina as well as those with rheumatological disorders.[18]

Figure 2. First Bottle of Aspirin, Manufactured by Bayer in 1899



First bottle of aspirin manufactured and distributed in powder form by Bayer in Germany beginning in 1899. Reprinted with permission from Bayer Corporation.

Thus far, no other antiplatelet drug has been demonstrated to be clearly superior to aspirin in secondary prevention of cardiovascular disease. A recent trial including more than 19,000 patients and 35,000 person-years of exposure data found only a marginal advantage of another antiplatelet drug (i.e., clopidogrel) over aspirin.[19] When the combined end point of nonfatal myocardial infarction, nonfatal stroke, and vascular death was evaluated, the event rate was 5.32% in the clopidogrel group and 5.83% in the aspirin group (P = 0.043). This response was not, however, homogeneous in the three populations of patients recruited for the trial. The majority of the response was accounted for by reduced morbidity and mortality in patients with peripheral arterial disease; no significant advantage of clopidogrel over aspirin was seen in patients recruited for the trial on the basis of either a prior stroke or a prior MI. Furthermore, both drugs were tolerated to essentially the same extent (i.e., 11.4% of the subjects in both groups discontinuing because of side effects) although the distribution of findings differed slightly between treatment groups (i.e., slightly more gastrointestinal discomfort, gastrointestinal hemorrhage, peptic ulcer, and liver effects in the aspirin group and slightly more rash and diarrhea in the clopidogrel group). If the heterogeneity of the response between groups is ignored, the reduction in relative risk shown in this study, if substantiated in future trials, is of questionable clinical significance and is unlikely to support the substantial differential in costs between these drugs.

Decisions about the use of aspirin for the prevention of atherothrombotic events in individuals with no history of prior manifestations of this disease is more problematic since this group has a much lower incidence of atherothrombotic events. Although several large trials in which aspirin use has been tested in apparently healthy individuals have been conducted (Physicians' Health Study, British Doctor's Study, Thrombosis Prevention Trial, and Hypertension Optimal Treatment Trial), the majority of which have shown a clear reduction in the incidence of myocardial infarctions in aspirin-treated patients, there is a reluctance to recommend widespread use of aspirin by healthy individuals. This reluctance is based on concerns that the occurrence of serious rare adverse events (e.g., hemorrhagic stroke) that accompany the use of aspirin may outweigh any benefit in terms of reduced incidence of myocardial infarction in many of these patients.

It is clear, however, that not all apparently healthy individuals have the same risk of experiencing a first myocardial infarction in the absence of aspirin use. Differences in lifestyle, age, or genetic predisposition may put some individuals at greater risk than others. The challenge for the future will be to identify tools to assist physicians in selecting those individuals at greatest risk of experiencing an acute myocardial infarction and treat those individuals for whom the benefit will outweigh the potential risk. In the interim, this decision must be made based on good clinical judgment and a discussion between the physician and patient about the balance between benefit and risk. It should be recognized, however, that the use of aspirin for reducing the risk of atherothrombotic events should not replace good health habits. Aspirin should be considered only as an adjunct to lifestyle management. The cardiovascular benefits accrued through the use of aspirin cannot outweigh the damage resulting from an unhealthy lifestyle.

Other Uses on the Horizon for Aspirin

In addition to its long-recognized benefits as an anti-inflammatory, anti-pyretic, and analgesic, and its more recent acceptance as a prophylactic agent against atherothrombotic events, several new uses are being investigated for aspirin.

Prevention of Colorectal Cancer and Other Cancers

Among the most promising uses for aspirin is the prevention of colorectal cancer. Observational studies suggest that there may be a 40-50% reduction in mortality from colorectal cancer in individuals who regularly consume aspirin or other NSAIDs. For example, the American Cancer Society Cancer Prevention Study II,[20] a prospective study of more than 660,000 patients, showed an approximate 40% reduction in the risk of dying from colon cancer in both men and women who used aspirin 16 or more times per month for at

Figure 3. 'Demand Bayer Aspirin' 1920s

In the 1920s, aspirin continued to be promoted for treatment of pain, as well as for symptoms related to rheumatism, lumbago, and neuralgia. Ironically, aspirin was also thought to "not affect the heart," although research decades later pointed to a positive effect on the heart—in helping to prevent cardiovascular disease. Reprinted with permission from Bayer Corporation.

least one year. Although the Physicians' Health Study failed to observe a protective effect of aspirin on the development of colorectal cancer,[21] this study was not specifically designed to assess the effects of aspirin on colon cancer, and it has been suggested that potential confounders (diet, etc.) or the dose used may have obscured any effect. Studies such as the Nurses Health Study suggest that the protective effects of aspirin increase with duration of use.[22] Data further suggest that the benefit may be accrued not only in those with familial adenomatous polyposis, a rare disease in which NSAID use causes regression of rectal adenomas,[23] but also in the more common sporadic adenomas of the colon and rectum and in other types of cancer as well. Review of the National Health and Nutrition Examination Survey (NHANES I) and NHANES I epidemiologic follow-up studies indicate that aspirin use may be associated with reductions in cancer at sites such as the lung and breast.[24] Randomized controlled clinical trials are currently underway to verify efficacy and to determine the optimal dose and duration of exposure necessary to convey beneficial effects.

Although the precise mechanism by which aspirin confers its beneficial effects are unknown, the potential preventive action of aspirin and other NSAIDs is believed to be due, at least in part, to effects of these drugs on COX-2 activity.[25] COX-2 levels increase in intestinal tumors, and it is thought that COX-2 may act as a tumor promoter in the intestine. However, cyclooxygenase-independent mechanisms may also exist for the effects of aspirin and other NSAIDs on colorectal cancer. It has been demonstrated that NSAIDs stimulate apoptosis in colon tumor cells independent of cyclooxygenase inhibition.[26]

Alzheimer's Disease Treatment and Prevention

There is also emerging evidence that the risk of developing Alzheimer's disease is lessened with chronic ingestion of aspirin (Breitner 1996). Numerous observational studies suggest that patients who take inflammatory drugs or suffer from inflammatory diseases have both a reduced risk of developing Alzheimer's disease and a delayed onset and a slower progression of disease if it occurs. Inflammatory processes have been proposed to play a role in Alzheimer's disease,[27] and it has been hypothesized that high doses of aspirin (i.e., those necessary to achieve COX-2 inhibition) may be required in order to observe aspirin's beneficial effects on Alzheimer's disease.[9] Randomized controlled clinical trials will ultimately be necessary to assess the potential benefits vs. the potential risks of high-dose aspirin in preventing Alzheimer's disease.

Migraine Prophylaxis

Aspirin is well recognized for its ability to relieve migraine headaches, and aspirin remains the most commonly used drug for mild or moderate migraine attacks. Its use in preventing migraine headaches, however, remains relatively unstudied. Initial reports suggest that low doses of aspirin, such as those

associated with inhibition of platelet aggregation, may be effective in preventing migraine headaches. For example, migraine headache incidence was significantly decreased in those randomized to low-dose aspirin in the Physicians' Health Study,[28] and reductions have been reported in the frequency, severity, and duration of migraine in other studies in which it has been used prophylactically at doses of 80 mg per day and greater.[29] However, the use of low-dose aspirin in preventing migraine headaches awaits testing in controlled clinical trials specifically designed to evaluate this effect.

Summary

Although originally developed for its anti-inflammatory, anti-pyretic, and analgesic properties, aspirin has become recognized as a highly beneficial drug for preventing cardiovascular morbidity and mortality. Unfortunately, because of its low cost and ubiquity in people's medicine cabinets, patients and physicians tend to diminish aspirin's potential. Nonetheless, it continues to this day as a highly effective pain, fever, and inflammation reliever, providing benefits comparable to those achieved with many much higher priced drugs. In terms of fatal and nonfatal ischemic events avoided, these benefits accrue in individuals with an evolving acute myocardial infarction, in individuals with a history of ischemic disease and who are at risk of recurrent events, and in apparently healthy individuals. Research further suggests that low-dose aspirin may be effective in reducing the occurrence of migraine headaches, and that chronic use of aspirin may prevent colon cancer and limit the development of Alzheimer's disease. Verification of its use of this remarkable, simple and inexpensive drug for these latter indications awaits the results of controlled clinical trials.

References

1. Vane JR, Botting RM. The history of aspirin. In: Vane JR and Botting RM (eds.) *Aspirin and Other Salicylates*. New York: Chapman & Hall Medical; 1992:3-16.
2. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature* 1971; 231:232-235.
3. Roth GJ, Stanford N, Majerus PW. Acetylation of prostaglandin synthase by aspirin. *Proc Natl Acad Sci USA* 1975;72:3073-3076.
4. Vane JR, Botting RM. The prostaglandins. In: Vane JR and Botting RM (eds.) *Aspirin and Other Salicylates*. New York: Chapman & Hall Medical; 1992:17-34.
5. Botting RM, Gryglewski RJ, Vane JR. The anti-thrombotic and fibrinolytic actions of aspirin. In: Vane JR and Botting RM (eds.) *Aspirin and Other Salicylates*. New York: Chapman & Hall Medical; 1992:245-291.
6. Patrono C. Aspirin as an antiplatelet drug. *N Engl J Med* 1994;330:1287-1294.
7. UK-TIA Study Group. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: Final results. *J Neurol Neurosurg Psychiatry* 1991;54:1044-1054.
8. Hirsh J, et al. Aspirin and other platelet-active drugs. *Chest* 1995;108:247S-257S.
9. Vane JR, Botting RM. Mechanism of action of non-steroidal anti-inflamatory drugs. *Am J Med* 1998;104: 2S-8S.
10. Fuster V, Cohen M, Chesebro JH. Usefulness of aspirin for coronary artery disease. *Am J Cardiol* 1988;61:637-640.
11. Schafer AI. Antiplatelet therapy. *Am J Med* 1996;101: 199-209.
12. International Study of Infarct Survival-2 Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349-359.
13. Hennekens CH, Dyken ML, Fuster V. Aspirin as a therapeutic agent in cardiovascular disease. *Circulation* 1997;96:2751-2753.
14. Peto R. Aspirin after myocardial infarction (editorial). *Lancet* 1980;1:1172-1173.
15. Lewis HD, 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.
16. SALT Collaborative Group. Swedish Aspirin Low-dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. *Lancet* 1991;338:1345-1349.
17. 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.
18. Food and Drug Administration (FDA). Internal analgesic, antipyretic, and antirheumatic drug products for over-the-counter human use; tentative final monograph. *Fed Reg* 1988;53:46204-46260.
19. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of

ischaemic events (CAPRIE). *Lancet* 1996;348:1329-1339.
20. Thun MJ, et al. Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med* 1991;325:1593-1596.
21. Gann PH, et al. Low-dose aspirin and the incidence of colorectal tumors in a randomized trial. *J Natl Cancer Inst* 1993;85:1220-1224.
22. Giovannucci E, et al. Aspirin and the risk of colorectal cancer in women. *N Engl J Med* 1995;333:609-614.
23. Waddell WR, Loughry RW. Sulindac for polyposis of the colon. *J Surg Oncol* 1983;24:83-87.
24. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. *Epidemiol* 1994;5:138-146.
25. Williams CS, et al. Aspirin use and potential mechanisms for colorectal cancer prevention. *J Clin Invest* 1997 100:1325-1329.
26. Waddell WR. Stimulation of apoptosis by sulindac and piroxicam. *Clin Sci* 1998;95:385-388.
27. Breitner JCS. The role of anti-inflammatory drugs in the prevention and treatment of Alzheimer's disease. *Ann Rev Med* 1996;47:401-411.
28. Buring JE, et al. Low-dose aspirin for migraine prophylaxis. *J Am Med Assoc* 1990;264:1711-1713.
29. Nelson-Piercy C, De Swiet M. Diagnosis and management of migraine. Low dose aspirin may be used for prophylaxis [letter]. *Br Med J* 1996;313:691-692.

Physician CME Questions

56. Aspirin's ability to inhibit prostaglandin synthesis accounts for which of the following effects?
    a. Reducing pain, inhibiting platelet aggregation, and increasing cardiac contractility
    b. Reducing pain, improving gastric blood flow, and inhibiting inflammation
    c. Reducing pain, inhibiting inflammation, and reducing platelet aggregation
    d. Inhibiting platelet aggregation, improving gastric blood flow, and reducing pain

57. The dose of aspirin required for its cardiovascular benefits is:
    a. higher than that required for its anti-inflammatory effects.
    b. lower than that required for its anti-inflammatory effects.
    c the same as that required for its anti-inflammatory effects.
    d. lower, but more frequent dosing is required to achieve constant inhibition of platelet aggregation.

58. The COX-2 inhibitors under development lack aspirin's beneficial effects on:
    a. fever.
    b. inflammation.
    c. cardiac contractility.
    d. platelet aggregation.

59. As a result of aspirin's ability to inhibit platelet aggregation, patients might experience the following:
    a. Liver failure
    b. Increased urine output
    c. Visual disturbances
    d. Purpura, epistaxis, gastric disturbance

60. Which of the following statements describes the use of aspirin for its cardiovascular benefits?
    a. Aspirin is not as effective but costs less than other antiplatelet agents.
    b. Aspirin is as effective as alternative antiplatelet drugs but costs less.
    c. Aspirin has always been recognized for its cardiovascular benefits.
    d. Aspirin is of no use in cardiovascular disease management.

61. Research is ongoing to assess the potential benefits of aspirin in:
    a. preventing cancer.
    b. preventing Alzheimer's disease.
    c. preventing migraines.
    d. All of the above

Readers are Invited . . .

Readers are invited to submit questions or comments on material seen in or relevant to *Primary Care Reports*. Send your questions to: Robin Mason—Reader Questions, *Primary Care Reports*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. Or, you can reach the editors and customer service personnel for *Primary Care Reports* via the Internet by sending e-mail to robin.mason@medec.com. You can also visit our home page at http://www.ahcpub.com. We look forward to hearing from you.

In Future Issues:

Eye Emergencies
—David D. Markoff, MD, FACS, and David Chako, MD, PhD