Scene One. The year is 1614; the place is eastern Massachusetts. Four members of the Wampanoag tribe of American Indians have developed high fevers. The shaman ventures out into the forest, where he carefully collects some leaves, roots, and bark from a willow tree. He returns home, grinds up the plant material, and brews it in water. The patients drink the hot herbal tea, and bathe in a cooled solution of the ground bark. Within hours, the fevers are lower, and the sick people are resting comfortably.

Scene Two. The year is 1846; the place is London, England. On the day of the Prince's annual ball, the Grand Duchess is suffering from severe joint pain due to arthritis. She sends for her doctor, and is given oil of wintergreen to swallow. In a short time the inflammation in her joints lessens, and she can move without pain. The duchess attends the ball, and fulfills her social obligations.

Scene Three. The year is 1992. A high school student, diligently studying for an exam, develops a headache after several hours of intense concentration. She goes to the medicine cabinet, takes out a bottle marked “aspirin,” and swallows two pills with a glass of water. In less than an hour, her headache is gone.

Taking medicine to relieve pain, fever, and inflammation is a ritual that has been repeated through most of recorded history. Willow tree bark extract, oil of wintergreen, and aspirin are similar in molecular structure and metabolic effect. All three belong to a group of chemicals called salicylates, and are some of the oldest and most frequently used drugs. Willow trees contain salicin, oil of wintergreen is methyl salicylate, and aspirin is acetylsalicylic acid (see Figure 1).

Painful discoveries
At some time in the remote past, a primitive physician may have tried using the bark from a willow tree to relieve a patient's pain or fever. Unlike so many other plant remedies that were tried, this one worked! Many cultures have a history of herbal medicine, so the same discovery was probably made hundreds of times, beginning with very early humans.

These first investigations were mostly “trial and error” (much to the dismay of the suffering patient). Studying the actual chemistry of medicinal plants began only in the 1800s. Imagine the difficulties the early chemists faced! Identifying the active ingredient in a mound of willow tree bark was a formidable task. From the hundreds of chemicals contained in
When acetylsalicylic acid ages, it may decompose and return to salicylic acid and acetic acid. If you have a very old bottle of aspirin around the house, open it and take a sniff. It may smell like vinegar, because vinegar is dilute acetic acid.

**Something for everyone**

Researchers have been puzzled by the many and varied actions of aspirin. This one drug not only can relieve pain and fever, especially when the chemist was working without the computers and analytical equipment we routinely use today.

In the mid-1800s the German chemist Hermann Kolbe synthesized salicylic acid (so named because the scientific name for willow is Salix) in his laboratory by heating phenol with carbon dioxide. Although several different plants are able to relieve fever and pain, the active chemical part of all of them is salicylic acid. Unfortunately, salicylic acid is very irritating to the stomach—so much so that many patients preferred their aches and fever to the severe heartburn caused by the remedy. So the search was on for a chemical that was similar to salicylic acid—but without the side-effects.

In 1899, a German scientist named Felix Hoffman suggested acetylsalicylic acid as a good alternative to salicylic acid. He had been searching for a drug that would give his elderly father relief from severe arthritis, and he stumbled upon acetylsalicylic acid after trying phenyl salicylate and sodium salicylate without success. The new drug was named aspirin—a from acetyl, and spirin from spiraea (meadowsweet flower), one of the natural plant sources of salicylic acid. Hoffman worked at the Bayer Company, which marketed the new remedy with great success. Aspirin became a mainstay of the home medicine cabinet; today, Americans swallow nearly 50 million tablets a day.

**Take a"BAYER BREAK"!**

1. Take 2 Bayer Aspirin for your headache.
2. Sit down and relax.
3. With Bayer Aspirin and a few minutes' rest, you'll feel fine in practically no time. Try it.

When the hot weather and high humidity get you down—when you feel tense, irritable, headachy, all worn out—just take a "Bayer Break!" Thanks to Bayer's feeling good, Bayer brings the relaxed, quiet relief you can get from hot-weather aches and pains. Ask your doctor to take down, take a Bayer Break, the promise you feel better now!

This aspirin advertisement from 1961 looks out of date, but modern ads promote the same benefits.
relieves fever, pain, and inflammation, but also inhibits blood clotting. Some new evidence indicates that it may help prevent some types of heart attacks if taken regularly. None of these effects seems to be very closely related. Despite its many years of use, aspirin's mode of action is only partly understood.

Unlike many painkillers (such as narcotics) that act directly on the nervous system, aspirin seems to relieve pain primarily by stopping the production of hormone-like chemical messengers called prostaglandins. Hormones are messengers that are produced in one part of the body and act on another. Prostaglandins, in contrast, are produced by the same tissue as the one they act upon. They are produced in very tiny amounts and are degraded within a few minutes, but in their short lifetime they exert a powerful influence on the body. Prostaglandins regulate digestion, kidney output, reproduction, blood circulation, and some nervous system functions.

Aspirin interferes with the action of one particular enzyme, cyclooxygenase, which acts at the beginning of a chain of prostaglandin synthesis. As a result, all the prostaglandins produced by this chain of reactions are suppressed. All of aspirin's numerous effects—reducing fever, enlarging blood vessels, reducing clotting of the blood—come from altering the balance of prostaglandins, even though aspirin itself disturbs only a single reaction.

Too much of a good thing

If a person takes an overdose of aspirin, the salicylic acid absorbed by the stomach and intestine lowers the pH of the blood. The body responds by breathing more rapidly to get rid of some carbon dioxide, in an attempt to reduce the blood acidity. Then the kidneys start to work overtime to excrete the excess acid from the blood, and the person may become dehydrated. If the dose of aspirin is extremely large, the body cannot compensate, and the extra acid in the blood starts to damage the brain.

Reye's syndrome is a rare, potentially fatal illness that can strike people who have used aspirin to treat symptoms of a viral infection, such as flu or chicken pox. No age group is immune, but Reye's syndrome most commonly strikes young people from infants to age 19. Early symptoms include severe vomiting and drowsiness; later symptoms may include confusion, irrational behavior, delirium, convulsions, and coma. There is no cure for Reye's syndrome, but early treatment can improve the chances of recovery. The disease affects all organs of the body but especially the liver (where it causes accumulation of fat) and the brain (where it increases pressure). Exactly how aspirin interacts with the viral infection is still unclear.

Since 1986, all aspirin labels carry the warning, "Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness." Read labels carefully; confusion can arise when the product is not called aspirin, but contains aspirin as one of its ingredients (such as Alka-Seltzer, Anacin, Ecotrin).

In 1991, 57% of people diagnosed with Reye's syndrome died, though the fatality rate was only 10% when the disease was diagnosed early.
Ibuprofen (~ Advil, Motrin) is another non-aspirin painkiller and fever reducer, but it has no value to the rest of us.

Liver, and other tissues. This acid-base imbalance is called acidosis, and is potentially fatal. (See box, Acidosis, in "Mystery Matters, Poisoned Milk," in the December 1992 issue of Chem Matters.) What should you do if you find your little brother or sister has swallowed a lot of aspirin? Or eaten a whole tube of Ben-Gay, which contains methyl salicylate? First—and most important—call your local poison control center and ask for instructions (the telephone operator will give you the number). Salicylate poisoning causes ringing in the ears, extremely rapid breathing, nausea, and, surprisingly, fever. Once these symptoms appear, the situation is very serious, and the patient needs medical treatment immediately.

Stomach upset

"Over-the-counter" drugs do not require a doctor's prescription—but that doesn't mean they're not potent medicines. Aspirin is a very effective painkiller and fever reducer, but it causes side-effects in some people. Most common is the problem of stomach upset. Though aspirin is much less irritating than plain salicylic acid, it causes stomach upset in a very small percentage of people. One strategy for reducing stomach irritation is to combine the aspirin with an acid buffer—a combination of chemicals that reduces acidity. The resulting product, buffered aspirin, is a genuine help for this group of people. However, the drug manufacturers used buffers as a way to distinguish their brand of aspirin from others and produced a blitz of TV advertisements claiming, "Our aspirin won't upset your stomach." The claim is both correct and misleading. Buffered aspirin is a genuine improvement for the small percentage of people who are susceptible to this kind of stomach irritation, but it has no value to the rest of us.

For people who are under a doctor's orders to take aspirin around the clock every day (arthritis sufferers, for example), stomach irritation can become a serious issue. For these patients, the drug companies introduced specially coated aspirin tablets that pass through the stomach without dissolving. The coating resists the acid juices of the stomach, but dissolves quickly in the basic environment of the small intestine. Called "enteric" aspirin, these tablets effectively eliminate stomach irritation, but they cannot work until the contents of the stomach are passed to the intestine, which may not happen until several hours after the tablet is ingested.

People who need a constant dose of analgesic, or who are treating symptoms of flu or other viral illness, frequently turn to the aspirin-free alternatives. The most common is acetaminophen, marketed under the familiar name "Tylenol" as well as other brands. Like aspirin, acetaminophen reduces fever and relieves pain, but it has no effect on inflammation or blood clotting. Ibuprofen (sold under the brand names Motrin and Advil) is another non-aspirin painkiller.

The discovery that aspirin works by inhibiting prostaglandins opened new avenues of medical research. A specific prostaglandin that promotes coagulation of the blood and another that inhibits coagulation have been identified. A new group of prostaglandins was discovered by following the clue that aspirin reduces most forms of inflammation but not the inflammation of asthma. Researchers have learned a lot from the once-mysterious ingredient of the bark of the willow tree.

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References

