

## CONSUMER CHOICES: PHARMACEUTICALS

### Aspirin: Story of a Wonder Drug

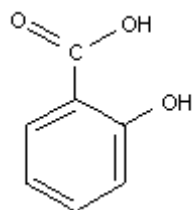
No drug is more common and familiar than an aspirin tablet. Yet before taking an aspirin, you should be aware of a number of important facts about this commonplace yet potent medicine. Some people, like children and pregnant women, should never take aspirin at all because of the potential dangers of its effects. Others, like arthritics, are advised to take aspirin daily. Aspirin is a chemical derivative of a folk medicine that has been known for centuries; native Americans and Europeans both knew that chewing the bark of the willow tree could cure a fever. Yet aspirin is produced from fossil fuel starting materials in the giant vats of chemical factories. We shall look at aspirin, its origins and its actions, what we know about it and don't know, in some detail. By gaining an understanding about this commonplace drug, we will gain insights about all the drugs that crowd the marketplace today. How are drugs discovered, and how are they tested? What is a therapeutic dose, and what is a toxic dose? How do drugs act on the complex biochemistry of our bodies? And how much do we really understand about these actions? What side effects does a drug have? How can we find out what side effects to expect? Decisions about drugs are among the most important consumer decisions we must make, and understanding the issues involved in these decisions requires knowledge of chemical principles and facts.

### Aspirin: a Brief History

Though willow bark is a very old folk medicine, the first person to record its effects was probably the English physician and clergyman Edward Stone, who dissolved powdered willow bark in water, and observed that the mixture relieved pain and reduced the fever of malaria. In 1860 the active ingredient was found by chemists to be **salicylic acid** (Fig. 18-1), and by the late 1800's salicylic acid was a widely used drug.

*In this chapter, concepts about the chemistry and action of drugs that we learn from specific examples like aspirin appear in italicized paragraphs for emphasis.*

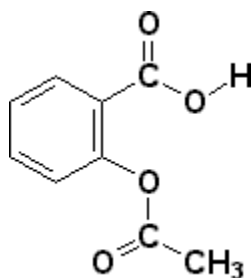
Fig. 19-1. *Chemical structure of salicylic acid.*



Though effective against pain and fever, salicylic acid had its drawbacks: it was highly irritating to the mouth, esophagus, and stomach. Looking at the chemical structure of salicylic acid, we can see why this is so. Not only does salicylic acid have a carboxylic acid group attached to the benzene ring, it has an -OH group as well. Though the -OH or alcohol group is not usually acidic, when an -OH group is attached to a benzene ring, the hydrogen becomes acidic, and the -OH group is called a **phenol**. Moreover, the acidic character of a phenol is greatly enhanced when it is adjacent to another electronegative group on the benzene ring. The corrosive nature of salicylic acid, then, is caused by the  $H^+$  generated in aqueous solution by these two acidic functional groups, the carboxylic acid group and the phenol group.

A young German chemist named Felix Hoffman had a father who suffered from severe rheumatoid arthritis, yet found salicylic acid very irritating to his stomach. Looking for a way to modify the aspirin so his father could tolerate it, Hoffman reacted the -OH group to form an ester group instead, forming the compound called **acetylsalicylic acid** (Fig. 18-2).

Fig. 19-2. *Chemical structure of acetylsalicylic acid.*



Hoffman's new compound worked successfully for his father; it retained the therapeutic properties of its parent compound, salicylic acid, without having its corrosive side effects. When Hoffman brought his discovery to the director of pharmacological research at the Bayer Company where he worked, the new drug became a great commercial success as well, becoming the best-selling drug in the world. Worldwide, over 100,000 tons of aspirin are consumed each year. In the United States alone, over 30

million pounds of aspirin are taken annually.

If we were to rely on willow trees for our aspirin supply, the willow tree would long ago have been driven to extinction; alternatively, large areas of land would have to be given over to its cultivation. However, since its first manufacture by the Bayer Company in 1899, aspirin has been made in a multi-step chemical synthesis with benzene, derived from coal tar, as a starting point. Fig. 18-3 shows the steps in this synthesis, starting with benzene, then chlorobenzene, then phenol. The acidic phenol is reacted with sodium hydroxide to form its sodium salt, then reacted with carbon dioxide to form the sodium salt of salicylic acid. Finally the salt is acidified to form salicylic acid, which is reacted to form the ester acetylsalicylic acid. If methanol is used instead of acetic anhydride to react with the salicylic acid, the ester methyl salicylate, or oil of wintergreen, is formed. Oil of wintergreen is a familiar flavoring agent, and it is used in some muscle rub formulations as well.



How do the different brands of aspirin differ from one another? Since they are all the same chemical compound, made in the same way, they cannot differ at all. All of them must conform to government standards of purity, though all contain some starch added as a binder to help hold the tablet together. In fact, nearly all the aspirin produced in the U.S. is manufactured by two chemical companies, Monsanto and Dow Chemical. Norwich-Eaton and Sterling Drug (which makes the Bayer aspirin produced in the U.S.) also manufacture aspirin. Since prices among aspirin brands can differ considerably, the consumer should feel free to choose the lowest-cost aspirin.



*This principle applies whenever a choice is to be made between **generic drugs**, those purchased by their chemical names, and higher-priced brand names. Generally, a drug is a specific chemical compound manufactured in a standard way to government-approved purity standards, so that there is no detectable difference among brands.*

### Effects of Aspirin on the Body

Drugs, like aspirin, which reduce fever are called **antipyretics**. Because of its ability to relieve pain, aspirin is also an **analgesic**. In addition to these effects, aspirin reduces inflammation; such a drug

is called an **antiinflammatory**. It has been found that aspirin also reduces the tendency for blood to clot; hence aspirin is also an **anticoagulant**. Because the use of aspirin as a drug has its origins in the use of salicylic acid as a folk medicine, its action as an antipyretic, analgesic, and antiinflammatory predates any knowledge of its action on the biochemistry of the body. Research on the function of prostaglandins in the body, begun after World War II, eventually shed some light on the action of aspirin when it was found that aspirin affected the levels of **prostaglandins** in the body. Now after extensive research it is known that aspirin deactivates the enzyme cyclooxygenase which is required for the production of prostaglandins and thromboxane.

Prostaglandins are potent biochemicals with wide-ranging effects throughout the body. They regulate hormone levels, and they affect blood pressure, smooth muscle contraction, body temperature, gastric secretions and blood platelet aggregations.

Now that the structure of prostaglandins is known, chemists have been able to produce them synthetically, and the use of these natural body substances as drugs is considered to have vast potential. The first clinical use of a prostaglandin (prostaglandin  $F_{2\alpha}$ ) was to induce labor in childbirth in 1968. Prostaglandin  $F_{2\alpha}$  is used extensively today in cattle breeding. Prostaglandin  $E_1$  is used to induce labor to terminate pregnancy. Prostaglandins have also been used clinically to lower or raise blood pressure and are being tested for a wide variety of therapeutic uses. Body areas which are inflamed and swollen are found to have greatly increased levels of prostaglandins. Since prostaglandins regulate body temperature, excessive prostaglandin formation can cause fever. Thus it makes sense that a compound which can lower prostaglandin levels would be able to act as an antiinflammatory, as in the case of arthritis or a swollen ankle, and as an antipyretic to reduce fever. This is how aspirin has been found to act, by regulating the biosynthesis of prostaglandins in the body. Additionally, by inhibiting the formation of thromboxane which causes blood platelets to aggregate causing blood clots.

In Chapter 15 we learned how prostaglandins are synthesized in the body in a multistep process starting from the polyunsaturated fatty acid arachidonic acid. Aspirin is thought to inhibit the enzyme cyclooxygenase which catalyzes the reaction of oxygen with the polyunsaturated acid in one step of this synthesis, preventing the formation of prostaglandins. Thus, aspirin acts as a prostaglandin inhibitor. Today, aspirin is only one of this new class of drugs, the prostaglandin inhibitors. These include naproxen (marketed as Naprosyn), naproxyn sodium (marketed as Anaprox), and ibuprofen (now sold over-the counter in numerous brands including Motrin, Nuprin, and Advil, as well as generically). Some of the other prostaglandin inhibitors are as much as thirty times more effective than aspirin in inhibiting prostaglandin synthesis.

### **Side Effects of Aspirin and Other Salicylates**

Though aspirin is the most common of all over-the-counter medicines, no medication is free of side-effects, and aspirin is no exception.

*With any medication it is important to realize that the effect may vary with the individual. Allergies to a particular substance may make a patient violently ill. The number of possible side effects for a given medication may be large, even though most patients experience little or no negative reaction.*

In allergic individuals, hives or severe asthma can result from aspirin ingestion. Those who are allergic to aspirin are likely to have allergies to other salicylates like methyl salicylate (oil of wintergreen), found in breath mints or muscle rubs, or even to other antiinflammatory agents like ibuprofen.

Aspirin is an acidic compound. Changing the phenol group of salicylic acid to the ester group in aspirin still leaves a carboxylic acid group on the compound. Moreover, in the acidic solution in the stomach, aspirin can be hydrolyzed to form the even more irritating compound, salicylic acid. Irritation to the stomach is therefore a common side effect of aspirin. To lessen problems with irritation, it is best to take aspirin with a full glass of water, and either with a meal or on a full stomach. Placing an aspirin tablet directly on a gum surface in the mouth can cause so much irritation as to lead to a chemical burn. Patients with a history of stomach ulcers should consult a physician before taking aspirin.

Aspirin is an anticoagulant, inhibiting the tendency of the blood to clot. Some patients with a susceptibility to stroke or with heart ailments are being advised to take very small amounts of aspirin daily, as recent research seems to show some statistical benefits in preventing a stroke or heart attack, which are probably related to aspirin's anticoagulant effect. Anticoagulant action can be dangerous in some cases, however. Use of salicylates, especially aspirin, during the last two weeks of pregnancy can cause bleeding problems in the fetus before or during delivery or in the newborn infant. Also, too much use of salicylates during the last three months of pregnancy may increase the length of pregnancy, prolong labor, cause other problems during delivery, or cause severe bleeding in the mother before, during, or after delivery. Aspirin should not be taken for 5 days before any surgery, including dental surgery, unless otherwise directed by your medical doctor or dentist; otherwise, bleeding problems may occur during or after surgery.

The list of possible side effects of aspirin is very long. They include ringing noises in the ears, loss of hearing, confusion, convulsions, diarrhea, dizziness, nervousness, hallucinations, nausea, shortness of breath, and vision problems. Given the very large quantities ingested regularly by a wide segment of the population, most of these occur rarely.

*Nevertheless, it is important for anyone taking a medication to be aware of the possibility of side effects. These are listed in reference publications like the Physician's Desk Reference (PDR) and the Consumer's Reports publication Drug Information for the Consumer. You should check with your doctor if you think a drug may be causing side effects.*

Salicylic acid is an active ingredient in over-the counter pharmaceuticals used to treat skin problems. Some commonly used brand names of salicylic acid medications include: Clearasil, Noxema Clear-Ups, Oxy Clean Medicated Cleanser, Stri-Dex, Propa-P.H., and the wart removal products Compound W and Wart-Off. In all of these medications the irritating effect of salicylic acid is observed. Because the salicylic acid can be absorbed through the skin, side effects observed for salicylates can be observed in these compounds as well as those taken by mouth. Salicylate overdose is a possibility if these products are used on children, or if they are used in combination with aspirin taken as an analgesic, antipyretic, or antiinflammatory.

Aspirin has been linked with a serious side effect in children. Reye's syndrome is a childhood disease that can cause brain damage and degeneration of the liver and other organs. It can occur during

recovery from the flu or chicken pox, first causing confused or irritable behavior, then in serious cases progressing to coma and death. Of the 250 to 650 cases of Reye's syndrome in the United States each year, about one quarter are fatal. In 1982 a study by physician Ronald J. Waldman and coworkers at the Center for Disease Control, Atlanta, linked the occurrence of Reye's syndrome with the use of aspirin to treat children for chicken pox or flu. Soon afterward, the Food and Drug administration required a warning label on aspirin-containing products warning of the link between aspirin use for childhood diseases and Reye's syndrome. For this reason, aspirin is not recommended as the analgesic or antipyretic of choice for children or teenagers, and is particularly to be avoided for flu and chickenpox.

*Knowing chemical structures is a useful aid to choosing and understanding drugs. Because of its functional groups, salicylic acid is a more acidic compound than aspirin and hence is more irritating. Salicylic acid, aspirin, and methyl salicylate, or oil of wintergreen, are all closely related chemically, so a person allergic to one of these is likely to be allergic to all of them. Since all are salicylates, their chemical action on the body can be cumulative.*

### Combination Drugs Containing Aspirin



Many of the headache remedies sold over-the-counter are a combination of ingredients including aspirin. Anacin, the most heavily promoted product in the OTC market, is simply a formulation of aspirin and caffeine. It has been advertised, and probably correctly, as containing "the pain reliever doctors recommend most for headaches." The amount of caffeine in Anacin is about the same as a quarter-cup of coffee. According to the *AMA Drug Evaluations*, there is no evidence that this amount of caffeine "has an analgesic effect or that it affects the activity of the analgesic components." Excedrin is a mixture of aspirin, caffeine, and another analgesic-antipyretic called acetaminophen. Excedrin contains about twice the amount of caffeine in Anacin, so that a person taking eight Excedrin tablets in a day would have consumed the equivalent of four cups of coffee in the Excedrin alone, in addition to any caffeine consumed in coffee, tea, or cola drinks. This amount of caffeine for most people will cause nervousness and sleeplessness, and certainly should not be consumed unknowingly. The active ingredients in Alka-Seltzer, recommended for headache and upset

stomach, are sodium bicarbonate (acting as an antacid) and aspirin. As we have seen, ulcer patients are advised to avoid using aspirin, yet these may well fall into the category of those looking for relief from "upset stomach."



*These combination products containing aspirin are but examples of over-the-counter combination medications, and of OTC products in general. Advertisements, though they may not be false, can be misleading, and are no substitutes for substantive information about the ingredients in a product, their effects, and their side effects.*

## Substitutes for Aspirin

Aspirin is an inexpensive and effective drug. Given what we have learned about its effects and side effects, however, it is not appropriate for all people or in all circumstances. What are the alternatives to aspirin? Of the over-the-counter drugs, by far the most popular and effective alternatives are acetaminophen and ibuprofen (Fig. 19-5).

Fig. 19-5. Chemical structures of acetaminophen and ibuprofen.



Acetaminophen, available generically as well as under numerous brand names like Tylenol, Datril, and Panadol, is often used as a substitute for aspirin.





It does not have the anticoagulant effect of aspirin, nor is it as irritating to the stomach. Because of the fear of Reye's syndrome, it has effectively replaced children's aspirin in analgesic-antipyretic products for children like Liquiprin. For ulcer patients and surgical patients it is a logical choice over aspirin. Before choosing a drug, however, it is necessary to consider both the effects and the side effects that are important in an individual case, and acetaminophen is not always an appropriate choice. When inflammation is the problem, acetaminophen is not an effective choice, as it is not a prostaglandin regulator like aspirin.

Especially since it has become available in over-the-counter doses as well as in prescription form, ibuprofen has become popular as an aspirin alternative, in generic form or in brands like Nuprin and Advil. Ibuprofen is a highly effective prostaglandin inhibitor, so it is an effective aspirin substitute as analgesic, an antipyretic, and an antiinflammatory. It does not have the anticoagulant properties of aspirin. Less irritating to the stomach than aspirin, it is still not easily tolerated by some people. Since its mode of action is similar to aspirin, it is possible though not certain that a person who is allergic to aspirin may have an allergic reaction to ibuprofen.



Menstrual pain and accompanying discomforts like headache and nausea have been found to be the result of excess prostaglandin concentrations. Studies conducted in 1979 showed that menstrual fluid of women with these symptoms has been found to be high in prostaglandins, and, when prostaglandin inhibitors are ingested, prostaglandin levels decrease and symptoms disappear. Since the discovery of the biochemical basis of dysmenorrhea, rational therapy using readily available medications has been possible. Clearly, any product in which acetaminophen is the active ingredient will be ineffective in this case, since acetaminophen is not a prostaglandin inhibitor. Aspirin is not very effective in most cases either, as it is a weak prostaglandin inhibitor compared to more recently developed drugs. Ibuprofen is the only non-prescription choice, and other appropriate prostaglandin inhibitors are available by prescription.

Finally, it should be pointed out that the appropriate alternative to aspirin may not be another drug at all. A muscle therapist has wryly observed that "most Americans believe that a headache is a sign of an aspirin deficiency." Perhaps one really needs a brisk walk in the fresh air to relieve tension and the effects of a stuffy, underventilated room. Given the fact that we know that no drug is free of side effects, some of which, like Reye's syndrome, are not understood for many years, it makes sense to explore non-drug alternatives instead of automatically taking a pill. Massage can be effective in relieving some kinds of pain, and physical therapy can be effective in helping to correct some pain-producing conditions, as in some types of back pain.

*When choosing an appropriate over-the-counter remedy, first determine as specifically as possible what the desired effect of the drug is to be. Then, considering all possible factors, including age, possible pregnancy, and any other existing physical conditions, the effects and the side effects of the available drugs should be weighed. If there is any question about these, a doctor or appropriate reference source should be consulted. If there are no contraindications, the least expensive alternative can be chosen. Consider the possibility that the appropriate remedy is not a drug, but simply appropriate rest, exercise, fresh air, or diet.*

## **Nature's Pharmacy**

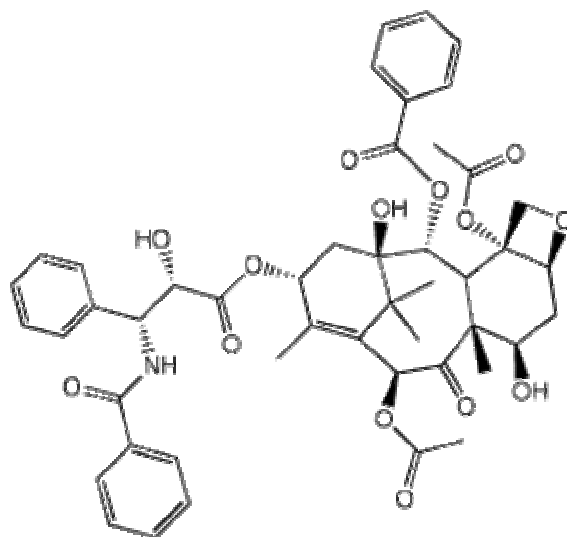
We have seen that aspirin, one of our most powerful and popular drugs, originated as a folk medicine found in willow bark. Aspirin is not unusual in that respect. Many pharmaceuticals have their origins in natural materials that may first have been discovered as folk medicines, and scientists believe that the most useful natural products, perhaps the cures for cancer and AIDS, await discovery in the form of natural products like those found in forest plants. A recent, dramatic example of a potent natural product is the cancer-fighting drug, taxol, found in the bark of the Pacific yew.

In December of 1991 researchers reported that taxol had eliminated or shrunk tumors in more than half of cases of advanced breast cancer which had relapsed after other forms of treatment. Previous studies had also shown its effectiveness against ovarian cancer and suggested its possible use against lung cancer. Though these experimental results have caused excitement among cancer researchers and among the victims of the disease, the supply of the drug is limited. The yew is a slow-growing tree, and the isolation procedure for obtaining taxol from the bark is difficult and low-yielding. The yew grows in old-growth forests in the Pacific Northwest, where clear-cutting of the forest by loggers has already created controversy. In order to cut large, old trees more efficiently, the entire forest growth is razed, and smaller species left dead but unharvested. Environmentalists object to the destruction of the old-growth forest, with trees hundreds of years old, for commercial logging. Cancer victims object to the destruction of potentially life-saving Pacific yews. And scientists point out that other, as yet undiscovered, compounds of equal or greater value may be present in these forests, and will be lost forever if the forests are destroyed. Cutting of the Pacific yew on Federal land is now

government-regulated, and nurseries of the yews are being started in an attempt to accelerate the availability of the plants for harvesting taxol, from both the needles and the bark.

Will chemists be able to develop a way to make taxol in the laboratory, as was done with aspirin? The synthesis of taxol will be much more difficult than that of aspirin, because the structure is much more complex (Fig. 18-6).

Fig. 19-6. *The chemical structure of taxol.*



The synthesis of taxol is one of the most important synthetic problems facing organic chemists today, and at least thirty groups have worked on the problem of putting together the many rings in taxol in just the correct way. The stereochemistry of the molecule, or the arrangement of the atoms in space, is as important as having the correct number of bonds. In Fig. 18-6, the dark-shaded bonds project forward from the plane of the page, and the bonds represented by dashed lines project backward from the plane of the page; synthesis of taxol involves making the bonds in just this way. Chemists would like to be able to synthesize taxol, and also to make similar compounds that might even be more desirable as therapeutic agents. Taxol, for example, is not water soluble, and a similar compound with solubility in water might be more easily incorporated into the body.

*More than a quarter of all prescription drugs now in use have come from plants, yet these represent only a tiny fraction of the natural products yet to be discovered and analyzed.*

One famous success story tells how biochemist Russell Marker coaxed some Indian women in Mexico into telling him about a wild yam they ate to keep from becoming pregnant. The discovery of *Dioscorea* in those yams led to the synthesis of steroids, the birth control pill, and cortisone. Other chemists and ethnobiologists are trying to learn the vanishing arts of the shamans, or medicine men, who have been treating native peoples for centuries for medicines from the forests. The World Health Organization estimates that 80% of the world's population relies on traditional preparations administered by native healers, or medicine men and women. In many parts of the world, however, this knowledge is being lost as native habitats and native cultures disappear.

The rain forest is both the most threatened and the most promising of the earth's habitats as a source of new medicines. Rich in biological diversity, these forests are home to half of all known species. These forests, according to a 1990-91 report on world resources sponsored by the United Nations, are disappearing at the rate of one and one-half acres per second as they are cleared for agriculture and development. It has been estimated that the current rate of destruction causes 100 species a day to become extinct.

Of the 3,000 plant species known to possess anti-cancer properties, 70% originated in the rain forests. The National Cancer Institute is currently screening large numbers of rain forest plants to test for activity against cancer and AIDS. So far, about 5% of the plant extracts have shown promise as drugs for AIDS treatment. Less than 1% of promising substances reaches the trial stage, however, and then it may take as much as 15 years for a drug to be fully tested and reach the market. This painstaking process, called random screening, has yielded most of the drugs we now have against cancer and AIDS.

Name \_\_\_\_\_

Date \_\_\_\_\_

**CHAPTER 19 PROBLEMS**

1. Fill in the following table by placing an X in each blank that describes a property of the compound at the beginning of the row.

Compound	Analgesic	Anti-pyretic	Anti-inflamma-tory	Anti-coagulant	Prosta-glandin inhibit.
Acetyl-sali-cyclic acid					
Acetamin-ophen					
Ibu-profen					
Taxol					

2. Draw the chemical structure of salicylic acid. Circle the acidic hydrogens.

3. Draw the chemical structure of acetylsalicylic acid. Circle the acidic hydrogen.

4. Name a medicinal use for each of these salicyates.

a. Acetylsalicylic acid

b. Salicylic acid

c. Methyl salicylate

5. What do prostaglandins do in the body?

6. How does aspirin act biochemically to relieve fever, pain, and swelling?

7. Match the chemical name with the brand name.

Acetylsalicylic acid

A. Tylenol

Salicylic acid

B. Bayer aspirin

Methyl salicylate

C. Advil

Acetylsalicylic acid/sodium bicarbonate D. Clearasil

Ibuprofen

E. Bengay (Muscle rub)

Acetaminophen

F. Alka-Seltzer

Acetaminophen/aspirin/caffeine

G. Excedrin

8. Explain how destruction of the rain forest can affect the outcome of the search for an effective cancer drug.

9. Name three drugs that come from natural products from forests.

10. Why are scientists concentrating their search for new chemical substances in the rain forest areas?

11. Name three groups of people who should not take aspirin. Explain why.