In the fourth century B.C., Hippocrates, perhaps the most famous physician of all time, described a “tea” made by boiling willow bark in water. The concoction was said to be effective against fevers. Over the centuries, that improbable folk remedy ultimately led to the synthesis of a true “wonder drug”—one that has aided millions of people. Indeed, the name of the drug is so familiar that we have intentionally tried to hide its identity in the brief history that follows.

**The Origin of a Miracle Drug**

One of the first modern investigators of willow bark tea was Edmund Stone, an English clergyman. His report to the Royal Society set the stage for a series of further chemical and medical investigations. Chemists were subsequently able to isolate small amounts of yellow needle-shaped crystals of a pure compound from the willow bark extract. Because the tree species was *Salix alba*, this new compound was named *salicin*. Experiments showed that salicin could be chemically separated into two compounds. Clinical tests provided evidence that only one of these components reduced fevers and inflammation. It was also demonstrated that the active component was converted to an acid in the body. Unfortunately, the clinical testing revealed some troubling side effects. The active component not only had a very unpleasant taste, its acidity also led to acute stomach irritation.

Although the active acid was used as a treatment for pain, fever, and inflammation, chemists set out to modify its structure in order to form a related compound that still had the desired medicinal properties, but without the undesirable taste or stomach distress. Because the active ingredient was known to be an acid, the first modification attempt took a very simple approach. The acid was reacted with a base to produce a salt.

A number of simple salts were made with bases such as sodium hydroxide or calcium hydroxide.

\[
2 \text{RCOO}^- + \text{Ca(OH)}_2 \rightarrow \text{Ca(OOCR)}_2 + 2 \text{H}_2\text{O}
\]

The $\text{RCOO}^-$ is the acidic portion of the molecule; the $R$ represents a group of carbon and hydrogen atoms that are not directly involved in the acid-base reaction. The derivatives (salts) had less pronounced side effects than the parent compound. Thus, chemists correctly concluded that the acidic part of the molecule was responsible for these effects. The next step was to seek a structural modification that would lessen the acid strength of the compound without destroying its medicinal effectiveness.

One of the chemists working on the problem was Felix Hoffman, an employee of a major German chemical firm. Hoffman’s motivation was more than just scientific curiosity or assigned work. His father suffered nausea from the acidic compound he took for his arthritis. The molecular modification achieved by the younger Hofmann greatly reduced the nausea and other adverse reactions. The resulting compound was a stable solid that reverted to the active acid form once in the body.

Extensive hospital testing of Hoffman’s compound began along with a simultaneous development for its large-scale manufacture by a well-known pharmaceutical company. The new drug itself could not be patented because it was already in the chemical literature. However, the company hoped to recoup its investment by patenting the manufacturing process. Clinical trials showed the drug to be nonaddicting and relatively nontoxic. Its toxicity is classed as low by ingestion, but 20–30 grams ingested at one time may be lethal. At the suggested dose of 325–650 mg (0.325–0.650 g) every 4 hours, it is a remarkably effective antipyretic (fever reducing), analgesic (anti-pain), and anti-inflammatory agent. Data from clinical tests uncovered the side effects noted in Table 11.1. The drug was also found to increase blood clotting time and to cause at least some small, almost always medically insignificant, amounts of stomach bleeding in about 70% of users.
Table 11.1  Side Effects of the "Wonder Drug"

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>rare</td>
<td>4</td>
</tr>
<tr>
<td>Rash, hives, itch</td>
<td>rare</td>
<td>3</td>
</tr>
<tr>
<td>Diminished vision</td>
<td>rare</td>
<td>3</td>
</tr>
<tr>
<td>Ringing in the ears</td>
<td>common</td>
<td>5</td>
</tr>
<tr>
<td>Nausea, vomiting, abdominal pain</td>
<td>common</td>
<td>2</td>
</tr>
<tr>
<td>Heartburn</td>
<td>common</td>
<td>4</td>
</tr>
<tr>
<td>Black or bloody vomit</td>
<td>rare</td>
<td>1</td>
</tr>
<tr>
<td>Black stool</td>
<td>rare</td>
<td>2</td>
</tr>
<tr>
<td>Blood in the urine</td>
<td>rare</td>
<td>1</td>
</tr>
<tr>
<td>Jaundice</td>
<td>rare</td>
<td>3</td>
</tr>
<tr>
<td>Anaphylaxis (severe allergic reaction)</td>
<td>rare</td>
<td>1</td>
</tr>
<tr>
<td>Unexplained fever</td>
<td>rare</td>
<td>2</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>rare</td>
<td>3</td>
</tr>
</tbody>
</table>


11.1  Consider This

In the United States, the final step for approval of a drug is the submission of all clinical test results to the Food and Drug Administration (FDA) for a license to market the product. Suppose you were part of an FDA panel that had to rule on the safety of the drug described in Table 11.1. Should it be allowed on the market as an over-the-counter drug or a prescription drug, or should approval be withheld? What further information might you require before making a ruling?

The World's Most Used Drug

Perhaps you have already guessed the identity of the miracle drug related to willow bark tea. Its chemical names, 2-(acetyloxy)-benzoic acid or (more commonly) acetyl salicylic acid, may not help much. But the power of advertising is such that, had we revealed that the firm that originally marketed the drug was the Bayer division of I. G. Farben, we would have let the tablet out of the bottle. The compound in question is aspirin, the world’s most widely used drug.

Admittedly, we have compressed the time somewhat. Most of the development, testing, and design of aspirin occurred in the eighteenth and nineteenth centuries. Stone’s letter to the Royal Society was written in 1763, and Felix Hoffman’s modification of salicylic acid to yield aspirin was done in 1898. Furthermore, the clinical testing of aspirin was somewhat less systematic than our account implies. But the basic facts and the steps that led to aspirin’s full development are essentially correct. We must also add one more very important fact: aspirin did not have to receive drug approval before being put on the market; no such certifying process was in place at that time. Had such approval based on clinical test results been necessary, it is quite likely that aspirin might only be available on a prescription basis.
11.2 Consider This

The price of aspirin tablets varies considerably, though the compound itself is a pure substance. The heavily-marketed brands can cost five to ten times as much as less well-known or no-name brands. Suppose the FDA proposed to establish a standard price for all aspirin tablets. Speculate on who might favor such a ruling and who might be opposed. Cite arguments on both sides and state your own opinion.

Chapter Overview

Drugs or pharmaceuticals are substances that prevent, moderate, or cure illnesses. We began the chapter with a drug that has probably been used by all readers of this book. We chose aspirin not only because of its familiarity, but because its discovery and development demonstrate how a new drug often comes into existence. The section that follows the overview generalizes this process and cites several other examples. All of the drugs mentioned (indeed, most of the drugs used today) contain the element carbon. Therefore, we embark on an excursion into the realm of carbon compounds—organic chemistry. Although the principles involved should be familiar, you will encounter new features such as isomers and functional groups. Both are of great importance in linking molecular structure to drug function. An example of characteristic drug activity is again provided by aspirin, but a more general treatment of the topic introduces the concept of the fit between the drug and the biochemical site at which it acts. Sometimes, activity depends on the subtle property of optical isomerism.

We next turn to the steroids, one of the most interesting and important families of biologically active compounds. Members of the family that are treated in some depth are cholesterol, sex hormones, contraceptives, aborting agents, and anabolic steroids. These compounds, or at least their uses, are familiar to almost everyone because they have often been steeped in controversy. By setting the steroids in their social context we explore a number of these issues. Finally, we turn to the topic of drug testing, and survey the lengthy and demanding process that is necessary in order to obtain approval to sell, distribute, and use a new drug. Here again, we will find that risks and benefits contend.

Drug Discovery and Development

The curative powers of certain chemicals have been discovered by various means, from lucky accidents to systematic investigation and from folk remedies to targeted research. However, the development of drugs, particularly in modern societies, generally follows a common set of steps. Both discovery and development are summarized in Table 11.2, but more detailed commentary follows.

Folk Remedies

In aspirin you have already encountered an example of a drug derived from a folk remedy. Throughout recorded history and in all societies, the study of substances effective against illness and disease has been an important activity. Traditional healers, from Greek philosophers to tribal shamans, have been keen observers of the effects of plant extracts on their patients. Some of these extracts have proven useful in modern medicine. In addition to aspirin, the best known are probably quinine, morphine, and mind-altering drugs. One argument for the preservation of tropical rain forests is that they may contain plant species with still undiscovered medicinal properties.
Table 11.2 Drug Discovery and Development

1. Discovery
   a. From folk remedies or traditional remedies. Examples: aspirin, quinine, digitalis.
   d. Specified, targeted drug design and modification, planned screening. Examples: analgesics, steroids, modern narcotics, antihistamines, and most derivative drugs of all kinds.
2. Development
   a. In vitro testing (literally "in glass," testing outside the body), often coupled with screening, drug modification, and research on the mode of drug action.
   b. Chemical modification of existing drug to improve efficacy.
   c. In vivo testing (testing in living organisms, primarily in animals).
   d. After suitable approvals, carefully controlled human trials.
   e. Various levels of drug approvals and reviews from clinical trials to acceptance for general use.

On the other hand, curative powers have been attributed to many more folk remedies than the number from which actual healing results. The spectacular medical and rejuvenative properties attributed to powdered rhinoceros horn or dried bear spleen are without medicinal validity and pose serious threats to endangered species. Moreover, natural folk remedies can do considerably more harm than good. For example, tea made from sassafras contains saffrole, a known carcinogen.

11.3 Consider This

Look up the story of the discovery of quinine and determine how it fits the pattern described in Table 11.2.

Accidental Discovery

Some drugs have been discovered accidentally, through the correct interpretation of a lucky observation or curiosity about an unusual occurrence. The most famous, and perhaps luckiest, discovery of this type was that of penicillin by Alexander Fleming. Fleming's curiosity was aroused by the chance observation that in a container of bacterial colonies (a petri dish), the area contaminated by the mold Penicillium notatum was free of bacteria. He correctly concluded that the mold gave off a substance that inhibited the growth of the bacteria. That substance turned out to be penicillin. A careful reconstruction has indicated that at least six critical, but lucky, events had to occur sequentially in order for the discovery to be made. They are summarized below.

1. In a laboratory one floor below Fleming's, a colleague worked on molds used to make vaccines in the treatment of allergies. Mold spores from that laboratory were carried through the air, entered Fleming's laboratory, and settled on a dish of staphylococci bacteria, an organism sensitive to penicillin.
2. The mold was a rare strain of Penicillium notatum that produced relatively large amounts of penicillin.
3. The dish was left at room temperature rather than put into an incubator.
4. The dish was left in the unheated laboratory during Fleming's vacation, a period of unusually cool weather that retarded bacterial growth, but not mold growth.
5. The weather subsequently changed and the temperature increased, allowing the bacteria to grow. By this time, however, the mold had produced enough penicillin to kill any bacteria near it, thus generating a bacteria-free region or zone of inhibition around it.
6. The sixth lucky accident had to do with poor housekeeping by an overworked laboratory staff. On September 3, 1928, Fleming was being visited by D. M. Pryce, a former colleague. A pile of unwashed petri dishes became the focus of their attention. This is an account of what happened:

The dishes on top of the pile had not yet been soaked in the disinfectant, and it was these that Fleming showed Pryce to illustrate the work he had done with *staphylococci* before departing on holiday. Most of them were contaminated by yeasts and molds, which was hardly surprising since they had been lying in the pile for several weeks. Fleming, however, spotted something unusual on one of them, namely a zone of inhibition of *staphylococcal* growth around a mold.¹

Fleming’s insightful response to the unexpected illustrates the often misquoted maxim of the great French scientist, Louis Pasteur: “In the fields of observation, chance favors only the prepared mind.” Most versions of this famous aphorism neglect the “only.” But it was only because Fleming’s mind was prepared that he was able to capitalize on this chain of unlikely events.

**Drugs through Planning and Design**

More recently, new drugs have come about through careful planning and designed syntheses. Typically, a researcher considers a group of compounds that, because of some shared properties, hold some promise as a drug against a particular condition or infectious agent. The researcher then plans a series of systematic investigations to further study the chemical nature of the compound and its potential as a drug. For example, after it became clear that molds produce antibiotic compounds, several pharmaceutical companies began programs to collect mold samples from all over the world and screen them for antibacterial activity. Though costly and time consuming, the approach proved fruitful by producing a number of potent antibiotics and other pharmaceuticals. Cyclosporin, a major anti-tissue rejection drug that has revolutionized organ transplant surgery, was discovered in this way.

Medicinal chemists, specifically trained in the nature and actions of drugs, have developed methods to synthesize molecules for specific applications. These scientists have become adept at creating new compounds having novel structures that may be active drugs, or making small, but intentional changes in rather complex molecules in order to convey or enhance biological activity. In a sense, medicinal chemists are molecular architects who “customize” molecules for use against a particular medical problem. To better understand this design process, we must first make a brief excursion into organic chemistry.

**A Brief Excursion into Organic Chemistry**

**Organic chemistry**

About 10 million organic compounds have been identified, but we will concentrate on particular portions of only a few molecules and stress their important role in interactions with living systems. Molecular shape will prove to be of special significance.

Chemists name organic compounds using a formal, stylized set of nomenclature rules set down by an international committee. However, many organic compounds have been known for a long time by common names such as alcohol, sugar, morphine, and aspirin. When a headache strikes, even chemists do not call out for 2-(acetyloxy)benzoic acid; they simply say “give me some aspirin!” Likewise, prescriptions specify

penicillin-N rather than 6[(5-amino-5-carboxy-1-oxopentyl)amino]-3,3-dimethyl-7-oxopentyl-4-thia-1-azabicyclo[3,2,0.]heptane-2-carboxylic acid. Mouthfuls like this are the cause of great merriment to those who like to satirize chemists, but they are important and unambiguous to those who know the system. You can rest easy because in this chapter we will use common names in almost all cases.

The incredible variety of organic compounds exists because of the remarkable ability of carbon atoms to bond in multiple ways. They can bond with other carbon atoms or with atoms of other elements. To better understand such possibilities, we need a few basic "ground rules" for bonding in organic molecules. The most fundamental generalization is one you used as early as Chapter 2—the octet rule. These electrons are paired to form covalent bonds and can be grouped in four different bonding patterns: (a) four single bonds, (b) two single bonds and one double bond, (c) one single bond and one triple bond, or (d) two double bonds. These arrangements are illustrated in Figure 11.1. Other elements exhibit different bonding behavior. A hydrogen atom is always attached to a molecule with a single covalent bond. An oxygen atom in a molecule typically has two pairs of bonding electrons, either in the form of two single bonds or one double bond. A nitrogen atom shares in three pairs of bonding electrons and hence can form three single bonds, one triple bond, or one single and one double bond.

\[
\begin{align*}
\text{(a)} & \quad \text{(b)} & \quad \text{(c)} & \quad \text{(d)} \\
\text{C} & \quad \text{O} & \quad \text{N} & \quad \text{C} \\
\text{C} & \quad \text{C} & \quad \text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\end{align*}
\]

Molecular formulas, such as \( \text{C}_4\text{H}_{10} \), indicate the kinds and numbers of atoms present in a molecule, but do not show how the atoms are arranged. In order to get that higher level of detail, structural formulas are used. These representations show the atoms and their arrangement with respect to each other in a molecule. In the case of \( \text{C}_4\text{H}_{10} \) (butane, a hydrocarbon used in cigarette lighters and camp stoves) a structural formula can be written as follows.

\[
\begin{align*}
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\text{H} & \quad \text{C} & \quad \text{C} & \quad \text{C} & \quad \text{C} & \quad \text{H} \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\end{align*}
\]

Notice that in this representation, the bonding and position of each atom relative to all others is specified. But a drawback to writing structural formulas, at least in a textbook, is that they take up considerable space. Instead, modified or condensed structural formulas can be used to convey the same information. In these, carbon-to-hydrogen bonds are not drawn out explicitly, but simply understood to be single bonds. Condensed structural formulas for \( \text{C}_4\text{H}_{10} \) are given below.

\[
\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_3 \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3
\]

This representation implies that carbon atoms are bonded directly to other carbon atoms in a straight chain. The hydrogen atoms do not intervene in the chain. Rather, two or three are attached to each carbon atom, depending upon its position in the molecule.

One reason why there are so many different organic molecules is because the same number and kinds of atoms can be arranged in unique ways called isomers.
You have already encountered isomers in Chapter 4 in the discussion of various components of petroleum. We will illustrate the idea with \( \text{C}_4\text{H}_{10} \). One way the atoms can be arranged is given above, the linear isomer called normal-butane or n-butane. However, another arrangement is possible in which the four carbon atoms are not in a “straight” line. This other isomer is represented by the following structural formula.

\[
\begin{array}{c}
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{C} \\
\text{C} \\
\text{H} \\
\text{H} \\
\end{array}
\]

This isomer is known as iso-butane, and its formula can also be written in condensed form.

\[
\text{CH}_3\text{CH} \longrightarrow \text{CH}_3 \quad \text{CH}_3\text{CH}\text{(CH}_3\text{)}\text{CH}_3
\]

The parentheses around the \( \text{CH}_3 \) indicate that its carbon is attached to the carbon to its left. It introduces a “branch” into the molecule.

These are the only isomers of \( \text{C}_4\text{H}_{10} \). It might be tempting to draw another structural formula that looks something like the following.

\[
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3 \text{CH} \longrightarrow \text{CH}_3 \\
\text{CH}_3
\end{array}
\]

However, a bit of inspection should reveal that this is simply the previous structure for iso-butane written upside down, and not a different compound. Molecular models of both isomers of \( \text{C}_4\text{H}_{10} \) are pictured in Figure 11.2. As the number of atoms in a hydrocarbon increases, so do the number of possible isomers. Thus, there are 18 isomers of \( \text{C}_8\text{H}_{18} \) and 75 isomers of \( \text{C}_{10}\text{H}_{22} \).

### 11.4 Your Turn

Pentane, \( \text{C}_5\text{H}_{12} \) exists in three isomers. Draw structural formulas for each of them.

---

**Figure 11.2**
Photographs of molecular models of the two isomers of butane, \( \text{C}_4\text{H}_{10} \): normal-butane (left) and iso-butane (right).
Carbon atoms are not limited to being bonded in a linear or branched fashion. In many molecules, including aspirin, carbon atoms are arranged in a ring. Such rings most commonly contain five or six carbon atoms. In aspirin, the carbon atoms are joined in a six-member hexagonal ring called a benzene ring after the compound with the formula $C_6H_6$. The Lewis octet rule applied to $C_6H_6$ predicts alternating single and double bonds between adjacent carbon atoms. The complete representation of this structure appears on the left of Figure 11.3. But the benzene ring is so widely distributed in organic molecules that symbols for individual carbon and hydrogen atoms are generally not written. The form in the center indicates the individual bonds, but is a bit misleading. Experiment shows that the bonding electrons in benzene are uniformly distributed around the ring and shared equally by all six carbon atoms. This is conveyed by the circle within the hexagon in the representation on the right.

## Functional Groups

Another very important concept in the properties of drugs and in the subdiscipline of organic chemistry is the idea of **functional groups**. These are certain arrangements of atoms that appear over and over again in carbon-containing molecules. Functional groups convey characteristic properties to the molecules that contain them. Indeed, these groups are so important that we often focus our formulas on them and symbolize the remainder of the molecule with an $R$. The $R$ is generally assumed to include at least one carbon atom that is connected to the functional group, but it can be practically anything. You already encountered some functional groups in Chapter 10. An alcohol is ROH, as in methyl (wood) alcohol, $CH_3OH$, and ethyl (grain) alcohol, $CH_3CH_2OH$. The presence of the $-OH$ group makes the compound an alcohol.

Similarly, acidic properties are conveyed by a carboxylic acid group,

$$\text{O}\Bigg|\hspace{1cm}\text{C}\hspace{1cm}\text{OH},$$

commonly written as $-COOH$. The hydrogen is released in solution as an $H^+$ ion. Thus, we represent an organic acid with the general formula, $RCOOH$. In acetic acid, the acid in vinegar, $R$ is $CH_3$, a methyl group. There are a dozen or so common functional groups, and you will meet a few of them on a “need to know” basis.

The presence and properties of functional groups are responsible for the action of all drugs. Aspirin has three such subunits, boxed and numbered in Figure 11.4.

You will recognize that box 1 encloses a benzene ring. Its presence makes aspirin soluble in lipids, which are fatty compounds that are important cell membrane components. The other two portions, boxes 2 and 3, are responsible for the drug activity. You have just been reminded that the $-COOH$ group indicates an organic acid. The other functional group (box 3) is an ester. You will recall from our discussion of polyethylene terephthalate in Chapter 10 that an ester is formed by the reaction of an alcohol and an acid. Water is eliminated in the process.

Felix Hofmann prepared aspirin by modifying the structure of salicylic acid. But note that he did not modify the carboxylic acid group on the molecule. Salicylic acid
also contains an alcoholic OH group, and it was this part of the molecule that Hofmann reacted with acetic acid via equation 11.2. The product was an ester of acetic acid and salicylic acid, which accounts for one of aspirin’s names—acetyl salicylic acid.

\[
\begin{align*}
\text{CH}_3\text{C} &= \text{OH} + \text{O} & \text{O} \quad \text{COOH} & \quad \text{C} &= \text{OH} + \text{H}_2\text{O} \\
\text{Acetic acid} & & \text{Salicylic acid} & & \text{Aspirin}
\end{align*}
\]

Because aspirin retains the \(-\text{COOH}\) group of the original salicylic acid, it still has some of the undesirable acidic properties of the parent compound. However, the presence of the ester group reduces the strength of the acid group and makes the compound more palatable and less irritating to the stomach lining. Once aspirin is ingested and reaches the site of its action, reaction 11.2 is reversed. The ester splits into acetic acid and salicylic acid, and the latter compound exerts its antipyretic and analgesic properties.

Functional groups sometimes play a role in the solubility of a compound, an important consideration in the uptake, rate of reaction, and residence time of drugs in the body. The general solubility rule, “like likes like” applies in the body as well as in the test tube. Functional groups containing oxygen and nitrogen atoms usually increase the polarity of the molecule and enhance its solubility in a polar substance such as water. Those compounds whose molecules do not contain such groups, but consist primarily or exclusively of carbon and hydrogen atoms, are more likely to dissolve in nonpolar solvents. Therefore, drugs with significant nonpolar character tend to accumulate in cell membranes and fatty tissues, which are themselves largely hydrocarbon.

Research has produced about 40 other aspirin-like compounds. Two of these, ibuprofen and acetaminophen (Tylenol\textsuperscript{®}), are more specific in their mode of action than is aspirin. Their structural formulas are given in Figure 11.5.

**Figure 11.5**
Structural formulas of analgesics.

\[
\begin{align*}
\text{Aspirin} & & \text{Ibuprofen} \\
\text{Acetaminophen} & & (\text{Tylenol}\textsuperscript{®})
\end{align*}
\]

**11.5 Your Turn**
Look at the structural formulas given in Figure 11.5. Identify the structural features and functional groups that aspirin, ibuprofen, and acetaminophen have in common.
How Aspirin Works

A complex internal means of communication is essential for higher-order living systems such as human beings. You may think of your body’s communication system as made up almost entirely of electrical impulses traveling along nerves. This is certainly true for activities such as movement, reflex actions, breathing, and heartbeats. However, most of the body’s internal “messages” occur not by electrical impulses, but through chemical processes. In fact, your very first communication with your mother was a chemical signal saying “I’m here; better get your body ready for me.” It is much more efficient to release chemical messengers into the bloodstream, which then circulates them to appropriate body cells, than to “hardwire” each individual cell with nerve endings. Figure 11.6 is a representation of such chemical communication.

These chemical messengers are called hormones and they are produced by the body’s endocrine glands. Hormones encompass a wide range of functions and a similarly wide range of chemical composition and structure. Thyroxine, an iodine-containing amino acid, is one of the simpler ones, but is essential for regulating metabolism. The chemical breakdown of “blood sugar” or glucose requires insulin. This hormone, a small protein of only 51 amino acids, is secreted by the pancreas. Persons who suffer from diabetes are often required to take daily injections of insulin. Yet another well-known hormone is adrenaline or epinephrine, a small molecule that prepares
the body to “fight or flee” in the face of danger. And the hormonal messages that are so compelling in adolescents are carried by steroids, a sexy set of molecules that we will revisit in a few pages.

Aspirin and other drugs that are physiologically active but not anti-infective agents are almost always involved in altering the chemical communication system of the body. A significant problem is that this system is very complex, allowing many compounds to be used to send more than one message simultaneously. The wide range of aspirin’s therapeutic properties, as well as its side effects, are clear evidence that the drug is involved in several chemical communication systems. It works in the brain to reduce fever, it relieves inflammation in muscles and joints, it apparently lowers the chances of stroke, and it seems to reduce the likelihood of heart attack. As we have seen, it also can cause stomach irritation.

In large measure, the versatility of aspirin and similar nonsteroidal anti-inflammatory drugs is related to their remarkable ability to block the actions of other molecules. Research on the activity of aspirin indicates that one of its modes of action involves blocking a particular enzyme, prostaglandin synthase. This enzyme causes the formation of products, prostaglandins, prostaglandins cause a variety of effects. They produce fever, swelling, increase sensitivity of pain receptors, inhibit blood vessel dilation, and regulate the production of acid and mucus in the stomach. By preventing prostaglandin production, aspirin reduces fever and swelling. It also suppresses pain receptors and functions as a painkiller. Because the benzene ring conveys high fat solubility, aspirin is also taken up into cell membranes. In certain specialized cells, the drug blocks the transmission of chemical signals that trigger inflammation. This process also appears to be related to aspirin’s effectiveness as a pain reliever.

The aspirin substitutes exhibit these same properties in varying degrees. For example, because acetaminophen blocks prostaglandin synthase, but does not affect specialized cells, it reduces fever but has little anti-inflammatory action. On the other hand, ibuprofen is a better enzyme blocker and specialized cell inhibitor. Consequently, it is both a better pain reliever and fever reducer than aspirin. Ibuprofen has fewer functional groups than aspirin, which may be the reason why ibuprofen has fewer side effects. Fewer functional groups also makes it less polar and more lipid soluble than aspirin. Its anti-inflammatory activity is five to fifty times that of aspirin.

All of these related anti-inflammatory drugs appear to affect the way cell membranes respond to stimuli. Research has shown that this is yet another possible mode of action for aspirin and its chemical relatives. On the other hand, aspirin is unique among these three compounds in its ability to inhibit blood clotting. This property led to the suggestion that low regular doses of aspirin can help prevent strokes or heart attacks. Of course, these anticoagulation characteristics also mean that aspirin is not the painkiller of choice for surgical patients or those suffering from ulcers. That is why “more hospitals use Tylenol®.”

## Drug Function and Drug Design

The modern approach to chemotherapy and drug design probably began early in the last century with Paul Ehrlich’s search for an arsenic compound that would cure syphilis without doing serious damage to the patient. His quest was for a “magic bullet” that would affect only the diseased site and nothing else. He systematically varied the structure of many arsenic compounds, simultaneously testing each new compound for activity and toxicity using experimental animals. He finally achieved success with Salvarsan 606, so named because it was the 606th compound investigated. Since the
medicinal chemists have adopted Ehrlich's strategy of carefully relating chemical structure and drug activity. The goal remains to produce a drug that meets the desired therapeutic need while exhibiting minimum side effects.

Drugs can be broadly classified into two groups: those that produce a physiological response in the body and those that kill or inhibit the growth of substances that cause infections. You have already learned that aspirin falls in the first group. So do synthetic hormones and psychologically active drugs. These drugs typically initiate or block a chemical action that generates a cellular response, such as a nerve impulse or the synthesis of a protein. Antibiotics exemplify drugs that kill foreign invaders. They do so by inhibiting an essential chemical process in the infecting organism. Thus, they are particularly effective against bacteria.

Although drugs vary in their versatility, many of them act only against particular diseases or infections. This specificity is consistent with the relationship that exists between the chemical structure of a drug and its therapeutic properties. Both the general shape of the molecule and the identity and location of its functional groups are important factors in determining its physiological efficacy. This correlation between form and function can be explained in terms of the interaction between biologically important molecules. Although many of these molecules are very large, they often contain a relatively small active site or receptor site. For example, the

is the one of the enzymes that breaks down proteins as part of the digestive process. The enzyme forms a temporary chemical bond with the protein molecule. The protein is called the substrate, In this particular geometrical arrangement, the functional groups in the active site of the enzyme facilitate the breaking of the protein chain. Similarly, many hormones trigger chemical reactions by specific interactions with receptor sites on cell membranes.

These interactions have been likened to the relationship of a key to a lock. Just as specific keys fit only specific locks, a molecular match between substrate and receptor site is required for physiological function. The process is illustrated in Figure 11.7.

If a perfect lock-and-key match were required in the body, it would mean that each of the millions of physiological functions would have a unique receptor site and a specific molecular segment to fit it. Simple logic suggests that such rigid demands would not promote cellular efficiency. Consequently, the lock-and-key model, although a good starting point that works in a limited number of cases, must be modified.

Using another analogy, a receptor site is like a size 9 right footprint in the sand. Only one foot would fit it exactly, and many feet (all left feet and all right feet larger than size 9) would not fit it at all. But many other right feet could fit into the print reasonably well. So it is with receptor sites and the molecules or functional groups that bind to them. Some active sites can accommodate a variety of substrates—including drugs. Indeed, the way most drugs function is by replacing a normal protein, hormone, or other substrate in the invading organism. The presence of the drug molecule thus prevents the enzyme, cell membrane, or other biological unit from carrying out its chemistry. As a result, the growth of an invading bacterium is inhibited, or the synthesis of a particular molecule is turned off.

Generally speaking, the drug that best fits the receptor site has the highest therapeutic activity. In some cases, however, a drug molecule does not need to fit the receptor site particularly well. The bonding of functional groups of the drug to the receptor site may even alter the shape of the drug, the site, or both. Often what counts is for the drug to have functional groups of the proper polarity in the right places. Thus, one important strategy used by medicinal chemists in designing drugs is to determine the specific part of the molecule that gives the compound its activity. Chemists then synthesize a molecule having that specific active portion, but with a much simpler non-active remainder. In effect, chemists custom design the molecule to meet the requirements of the receptor site.
An outstanding example of this approach is provided by opiate drugs such as morphine. Morphine, a very complex molecule, is difficult to synthesize. However, the particular portion of the molecule responsible for opiate activity has been identified and is highlighted in Figure 11.8. The flat benzene ring fits into a corresponding flat area of the receptor, and the nitrogen atom binds the drug molecule to the site. Incorporating this particular portion into other less complex molecules, such as demerol, conveys opiate activity.

The discovery that only certain functional groups are responsible for the therapeutic properties of pharmaceutical molecules has been an important breakthrough. Sophisticated computer graphics are now used to model potential drugs and receptor sites. Thanks to these drawings, with their three-dimensional character, medicinal chemists can "see" how drugs interact with a receptor site. Computers can then be used to search for compounds that have structures similar to that of an active drug. Chemists can also modify structure in the computer models and visualize how the new compounds will function. These revolutionary techniques hold great promise for speeding up drug design and development.

**Consider This**

Aspirin and other drugs have a large and profitable market around the world. But development and marketing of critical drugs needed by a small number of people suffering from rare diseases can be an enormous drain on a pharmaceutical company. Should the government step in and require successful drug companies to contribute a percentage of their profits to a fund for research on these "orphan drugs"? As president of a pharmaceutical company, draft a letter to your senator, stating your position on this issue.

- **Left- and Right-handed Molecules**

Drug design is complicated when drug-receptor interaction involves optical isomerism, hence the name. Although the nature of that interaction is rather complex, it is related to a familiar consumer product. Yet may even own a pair of Polaroid® sunglasses. The lenses of these glasses permit only the passage of light waves vibrating in a single plane. All other waves are filtered out (Figure 11.9). When a beam of this plane-polarized light is passed through a solution of an optically active compound, the plane of vibration is rotated.

```
  dextrorotary
```

Conversely the

```
  levorotary
```

Research has shown that optical isomerism most frequently arises when four different atoms or groups of atoms are attached to a central carbon atom. A compound having such a carbon atom can exist in two different molecular forms that are mirror.
images of each other. These are the optical isomers, and they rotate light in opposite directions—one isomer to the right and the other to the left. Mirror images should not be completely unfamiliar to you because you carry two around with you all the time—your hands. If you hold them so that the palms face each other, you can recognize them as being mirror images; what is on the left side of one is on the right side of the other. Your left hand looks like the reflection of your right hand in a mirror; they are not identical. Figure 11.10 illustrates this for both a hand and a molecule. Note that the
four atoms or groups of atoms bonded to the central carbon atom are in a tetrahedral arrangement. Their positions correspond to the corners of a three-dimensional solid figure with equal triangular faces.

It turns out that many biologically important molecules, including sugars and amino acids, exhibit optical isomerism. This is significant because, although most chemical and physical properties of a pair of optical isomers are very nearly identical, their biological behavior can be profoundly different. You can illustrate this relationship between optical isomerism and biological activity by taking things into your own hands. Your left hand will represent an optically active drug molecule. Start by folding the middle two fingers down onto the palm. Then, put your thumb, your index finger, and your little finger down on a sheet of paper in a triangular arrangement. Your palm represents the central carbon atom and the three fingers and the wrist represent the four different substituents. Mark the location of your three fingers and your wrist on the paper, specifically noting where the index finger, little finger, and thumb touch. The marked paper represents a receptor site for a left-handed molecule. Now, fold your right hand in a similar position and try to fit the index and little finger and thumb onto this receptor site. You will soon find that, no matter how hard you try, your right hand cannot fit into the pattern that is appropriate for your left hand. For example, if your index finger is in the correct position, your thumb and little finger will be interchanged. Similarly, right-handed optical isomers will not fit into receptor sites for left-handed molecules (Figure 11.11). It follows that any drug containing a central carbon atom with four different atoms or groups attached to it will be optically active and have optical isomers, only one of which will usually fit into a particular receptor site.

**Figure 11.11**
Mode representation of an optically active molecule binding to an asymmetric site.

The extreme molecular specificity created by optical isomerism makes the medicinal chemist’s job more complex. A drug molecule must include the appropriate functional groups, and these groups must be arranged in the biologically active configuration. Often the “right” and “left” isomers are made together, but only one isomer is pharmaceutically active. For example, many opiate drugs exist in optical isomers, only one of which may have opiate activity. Levomethorphan, the sinister, left-handed isomer of methorphan, is an addictive opiate. On the other hand, its dexteroius mirror image is a non-addictive cough suppressant. This permits the use of dextromethorphan in many over-the-counter cough remedies.

**11.7 Consider This**
The discussion of the complications of optical isomerism probably sounds familiar to left-handed people. Southpaws often encounter difficulties living in a right-handed world. List five ways in which our society favors the right-handed.
**Steroids: Cholesterol, Sex Hormones, and More**

Sometimes a single structural feature appears, with modification, in a wide variety of biomolecules and related drugs. This structural ubiquity is beautifully illustrated by one of the most important biochemical families—the **steroids**. These compounds cover an amazingly broad range of form and function—from cholesterol to sex hormones. Moreover, as we will soon see, some steroids have been associated with a good deal of controversy.

The common molecular basis of these compounds is a marvelous example of the economy with which living systems use certain structures for many different purposes. Cells operate rather efficiently by combining small molecular fragments in controlled ways to synthesize large molecules. Once such a molecular process is established, a cell continues to use it, incorporating molecular fragments into a variety of compounds. The process is rather like having a standardized house plan that can be reproduced readily—a unit that gains individuality by changes in the types of windows and doors or by the interior decorations. The common characteristic of the steroids is a molecular framework consisting of 17 carbon atoms arranged in four rings—"three rooms and a garage" if you like. This steroid nucleus is illustrated below. Recall that in such a representation, carbon atoms are assumed to occupy the corners of the rings, but they are not explicitly drawn.

![The steroid nucleus](image)

It is evident from the structural formula that the steroid nucleus has three 6-carbon rings and one 5-carbon ring, designated as A, B, C, and D. This framework serves as the basic unit for many physiologically active molecules that differ in the functional groups attached to certain locations on the four rings. Adding extra carbon atoms and/or functional groups at a critical position on the ring can cause enormous differences in physiological effects. The range of these physiological effects is indicated in Table 11.3.

Figure 11.12 shows some of the molecular structures responsible for this variety of function. The system used to represent these structures concentrates on the carbon backbone of the molecule. A carbon atom is assumed to occupy each bend in a sequence of line segments, and a line protruding from a molecule also represents a carbon atom unless the symbol for another atom is attached to it. Hydrogen atoms, which

<table>
<thead>
<tr>
<th>Function</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulation of secondary sexual characteristics</td>
<td>Estradiol and testosterone (an estrogen and an androgen)</td>
</tr>
<tr>
<td>Reproduction and the control of the reproductive cycle</td>
<td>Progesterone and other gestagens</td>
</tr>
<tr>
<td>Regulation of metabolism</td>
<td>Cortisol and cortisone derivatives</td>
</tr>
<tr>
<td>Digestion of fat</td>
<td>Cholic acid and bile salts</td>
</tr>
<tr>
<td>Cell membrane component</td>
<td>Cholesterol</td>
</tr>
</tbody>
</table>
Figure 11.12
Molecular structures of some important steroids.

Female sex hormone
Estradiol

Male sex hormone
Testosterone

Metabolic regulator
Cortisone

Pregnancy hormone
Progesterone

Bile salt for fat digestion
Cholic Acid

Cell membrane component
Cholesterol

are not specified, are bonded to the carbon atoms as is necessary to satisfy the octet rule. This method is illustrated below with estradiol, a female sex hormone. The figure on the left includes all the atoms in the molecule, the one on the right gives the skeletal representation.

The structures in Figure 11.12 indicate that some very subtle molecular differences can result in profoundly altered properties. For example, maleness and femaleness rest on just a few carefully-placed atoms on a steroid nucleus!
11.8 Your Turn

Carefully examine the structural formulas given in Figure 11.12. Identify the similarities and differences in the structures of the following:

a. the male and female sex hormones
b. cholesterol and cholic acid

In this chapter we will concentrate on only a small number of the many steroid compounds. We begin with cholesterol, the most abundant steroid in the body and probably the best known. The average-sized adult has about half a pound of cholesterol in his or her body! Cholesterol is a starting point for the production of steroid-related hormones and a major component of cell membranes. Because their shape is relatively long, flat, and rigid, cholesterol molecules help to enhance the firmness of cell membranes. Although cholesterol is essential for human life, there are concerns that too much of the compound in the blood can lead to the build-up of plaque, fatty deposits in the blood vessels. This plaque restricts blood flow and can lead to strokes or heart attacks. Therefore, people are advised to regulate their dietary intake of cholesterol, which is found in milk, butter, cheese, egg yolks, and other foods rich in animal fats. But one must keep in mind that some “cholesterol-free” foods can nevertheless contribute to the build-up of cholesterol in the body. It is synthesized there from fatty acids of animal or vegetable origin. A diet rich in “saturated fats” (those without double bonds between carbon atoms) is particularly likely to lead to elevated serum cholesterol.

The role of cholesterol in the body is relatively passive, but steroid hormones are involved in a tremendous range of physiologically vital processes, including such popular pastimes as digestion and reproduction. Because of the importance of these functions, medicinal chemists have, over the past 50 years, synthesized many derivatives of naturally occurring steroid hormones. These drugs, developed to mimic or inhibit the activities of the hormones in the body, have been variously described as “miracle drugs,” “killer compounds,” or “sleazy therapeutic agents.” Perhaps more than any other type of pharmaceutical, steroid-related drugs are involved with social and ethical issues. These issues include birth control, abortion, diet, body-building, drug abuse, and drug testing. We begin by looking at drugs related to sex hormones.

“The Pill”

Sex hormones are the chemical agents that determine the secondary sex characteristics of individuals. Female sex hormones are classified as estrogens; male sex hormones as androgens. You may be surprised to learn that males have female sex hormones, and there are male sex hormones in females. However, androgens predominate in males and estrogens in females.

Because of their importance, androgens and estrogens were the first steroidal hormones studied in great detail. When this work was just beginning, techniques for determining molecular structure were in their infancy. A sample of several milligrams of the pure substance was required—much more than is needed today. Because sex hormones occur only in very small quantities, heroic efforts were required to obtain sufficient amounts for the early chemical studies. For example, one ton of bull testicles was processed to yield just 5 milligrams of testosterone, and four tons of pig ovaries provided only 12 mg of estrone. Fortunately, improved technology and instrumentation allow modern chemists to determine molecular structures with samples weighing only a fraction of a milligram.

After the molecular structures of the sex hormones were determined in the 1930s, work could proceed on the synthesis of drugs of similar structure. These efforts ultimately led to the creation of “the Pill”—the oral contraceptive that has had such a
Figure 11.13
Molecular structures of progesterone and norethynodrel.

A profound effect on modern society by launching the so-called “sexual revolution.” As with aspirin, birth control drugs came about through molecular modifications, in this case, changing substituents on the steroid nucleus. The aim was to develop a drug that would mimic the action of progesterone on the complex female reproductive cycle. Interestingly, the initial motivation of the research was to improve fertility in women who found it difficult to conceive. Gregory Pincus and John Rock injected progesterone into patients in order to block ovulation and stimulate body changes related to pregnancy. Their hope was that when the therapy was discontinued, a kind of rebound would occur and fertility would increase. Such a response, now known as the “Rock rebound,” does in fact take place.

Unfortunately, progesterone was expensive and not very effective when administered orally. It also caused some serious side effects in a small percentage of patients. Therefore, chemists working in a number of pharmaceutical firms set out to develop a synthetic analog for progesterone that could be taken orally, would reversibly suppress ovulation, and would have few side effects. The ultimate goal of these efforts soon became the inhibition of fertility, not its enhancement. In the mid-1950s, Frank Colton, a chemist at G. D. Searle, synthesized norethynodrel. The molecular structure of this compound (Figure 11.13) shows some subtle but significant differences from progesterone, notably the replacement of $\text{–COCH}_3$ on the D ring with $\text{–OH}$ and $\text{–C=CH}$. As a consequence of these changes, the norethynodrel molecule is tightly held on a receptor site, which prevents its rapid breakdown by the liver and permits its oral administration. Norethynodrel became the active ingredient in Enovid, the first commercially available oral contraceptive, which was approved for sale in 1960.

Since the development of the original birth control pill, further molecular modifications (many of them minor) have led to decreased dosage and minimized side effects. A major contributor to these innovations has been Carl Djerassi, currently professor of chemistry at Stanford University and president of Zoeticon Corporation. Djerassi, the author of hundreds of scientific papers and the holder of many patents for modified steroids, is also a novelist and poet. Recent research into an alternative birth control delivery system culminated in a plastic implant that releases a progesterone analog so slowly so that it can be effective for several years.

The mechanism for the action of steroid-based contraceptives is diagrammed in the simple schematic of Figure 11.14. In effect, the drug “fools” the female reproductive system by mimicking the action of progesterone in true pregnancy. When fertilization occurs, progesterone is released, carrying a number of chemical messages. Some of these help prepare the uterus for the implantation of the embryo. Others block the release of pituitary hormones that stimulate ovulation. The reason for this is clear: ovulation during pregnancy could lead to very serious complications. Birth control steroids, being progesterone-like molecules, send a chemical message much like progesterone. By thus simulating pregnancy, ovulation is inhibited. In effect, the message this time is not “Hey, Mom, I’m here!” but rather “Hey, you think I’m here, but I’m not!”
Consider This

Oral contraceptives put control of fertility into the hands of women. What are the social and political implications of this development? What scientific and/or social reasons lie behind the fact that chemical control of reproduction was developed first for the female rather than the male reproductive system?

RU-486: The “Morning-after Pill”

Some controversy still surrounds the synthetic steroidal hormones that control fertility by inhibiting ovulation. But a far more controversial approach to birth control is a drug that can induce abortion with relative ease and safety—a “morning-after pill.” The drug, currently available in France, Sweden, and the United Kingdom, is mifepristone. It is better known as RU-486, after its manufacturer, Roussel-Uclaf. Its invention was announced in 1982 by Etienne-Emil Baulieu, a French physician and researcher.

Comparison of the structural formula for RU-486 with that of progesterone shows that they are very similar, each having a steroid nucleus. The critical difference is the bulky benzene ring attached to the C steroid ring in RU-486. This bulky ring prevents changes that occur at the receptor site when progesterone is present. As noted above, when progesterone binds to the receptor, it initiates a chain of chemical events signaling the body to produce proteins needed in pregnancy. RU-486 is an antagonist for progesterone—it occupies the progesterone binding site, but it shows no activity. Thus, no pregnancy protein production signal is sent. Because progesterone activity is essential for implantation of the embryo in uterine cells, the developing embryo is spontaneously aborted.
RU–486 has been extensively tested and found to be 96% reliable. Moreover, it appears to have a relatively low incidence of serious side effects. Risk assessment studies suggest that the drug is probably the safest method to terminate a very early pregnancy. Nevertheless, initial opposition to the distribution and use of RU–486 was so strong that Roussel-Uclaf originally sought to suspend marketing the drug. But the announcement of that decision was opposed by a petition signed by 1000 leading physicians attending a world congress of gynecology and obstetrics. Claude Evin, the French Minister of Health, called the drug “the moral property of women, not just the property of the drug company” and ordered RU–486 to be put back on the market. Since then, over 100,000 French women have used the drug successfully.

The company has established five criteria, given below, that a country must meet before the company will seek approval of RU–486 in that country.

1. Abortion must be legal.
2. Abortion must be accepted by the public and the medical community.
3. A suitable synthetic prostaglandin must be available for use in the country. (RU–486 is given in conjunction with the prostaglandin for maximum efficacy and safety.)
4. Distribution must be strictly controlled.
5. A patient must agree in writing that if induced abortion fails, she will proceed with a surgical abortion.

As this book went to press, plans were being made to test RU–486 in the United States, and antiabortion forces were organizing their opposition to the testing.

11.10 Consider This
The development of RU–486 is a scientific fact. The company’s decision whether or not to market it in a specific country has an ethical dimension. Your own response to this issue will undoubtedly involve all facets of the argument—moral, ethical, cultural, religious, and scientific. Develop your personal position on the question of whether RU–486 should be available in this country and draft a letter explaining your conclusion to a close friend of the opposite opinion.

**Anabolic Steroids: What Price Glory?**

Like birth control drugs, anabolic ("building up") steroids are controversial. Moreover, again like their contraceptive chemical cousins, anabolic steroids were created for quite a different purpose than their ultimate use. These steroids were developed initially to help patients suffering from wasting illnesses to regain muscle tissue. Ironically, their use has now become perverted by the strong who seek to become even stronger.

It has long been known that testosterone promotes muscle growth as well as the development of male secondary sexual characteristics. Drug companies sought to pursue this avenue to produce a testosterone-like drug that would stimulate muscle growth in debilitated patients, such as those recovering from long-term illness. The intent was to modify the testosterone molecule in such a way that its analog would have the desired effects on muscle development without serious negative side effects. Anabolic steroids were the result.
This research project, as any involving sex hormones, required the use of a suitable animal model to evaluate the effectiveness and safety of the drugs. Ethical considerations and public opinion preclude the use of human subjects for testing in such unpredictable circumstances. Therefore, castrated rats were used to test anabolic steroids. Various trials compared prostate gland weight with the weight of an isolated abdominal muscle. The idea was to develop a drug that increased muscle mass (an anabolic effect) without increasing prostate mass (an undesirable side effect). Side effects such as this are said to be androgenic. They result from changes in the level of sex hormones, and they often accentuate female characteristics in males and male characteristics in females.

Several drug companies eventually succeeded in greatly reducing the androgenic effects of synthetic steroids, while not affecting their desired anabolic effects. The structural formulas of the two most potent anabolic steroids, norethandrolone and ethylestrenol, are given in Figure 11.15, along with that of testosterone for comparison. Note their very close similarities.

In other synthetic anabolic steroids, the molecular shape has been altered by adding substituents to the A ring. These substituents interfere with the fit of the molecule on the androgen activity receptor, but they do not impair anabolic activity. Two examples are stanozolol and oxymetholone.

Research efforts to properly balance anabolic and androgenic effects in synthetic anabolic steroids have not been completely successful. Unfortunately, this serious drawback has not precluded the widespread use of these drugs. A vast new market has sprung up on the world’s playing fields and athletic training facilities, even though the drugs can be obtained legally only by prescription. Because anabolic steroids increase muscle mass, they appeal to some athletes who compete in strength-related sports such as football, weight lifting, and certain track and field events. The desire to win has led athletes to take anabolic steroids in order to gain a purported competitive edge. And the problem seems to be pervasive. It has been estimated that half of recent Olympic athletes, in sports ranging from weight lifting to figure skating, have used steroids at some time in their careers. Annual sales of illegal steroids to athletes are estimated to
be in excess of 200 million dollars—in spite of the fact that legitimate experts in exercise physiology and related fields hold opposing opinions about the merits of steroid use to enhance athletic performance.

On the other hand, it is well established that using large doses of anabolic steroids over time can cause a variety of undesirable side effects. In males, these include shrinking testes, difficulty in urination, impotence, fluid retention, baldness, high blood pressure, and heart attack. Women suffer from masculinization in which female secondary characteristics are lost. Both sexes show increased aggressiveness, unpredictable periods of violent mood changes, and other behavior disorders. Heavy users often compound the problem of drug abuse by using more than one anabolic steroid at a time—sometimes in untested combinations. Many abusers seem to be convinced that “more is better.” For example, steroids that are prescribed in legitimate therapeutic doses of a few milligrams have been taken in doses twenty times larger. In spite of the fact that such a large overdose may be lethal, Lyle Alzado, the NFL football star who died in May 1992, attributed his brain cancer to consuming $20,000–$30,000 worth of steroids per year. Although Alzado championed a national campaign against steroid abuse, physicians have concluded that there is no evidence linking his use of these drugs and his cancer. Even without this connection, the physiological effects of anabolic steroid abuse are bad enough.

One of the most challenging competitions in sports is that between athletes who use performance-enhancing illegal drugs and the chemists who test for them. Very sophisticated chemical separation and analytical techniques have been developed to detect banned substances in blood and urine samples at the level of parts per billion. Detection of synthetic steroids is difficult because they are generally used in relatively small amounts. But the real detection problem arises because they are chemically very similar to compounds that occur normally in the body. The success of synthetic chemists now becomes the analytical chemists’ burden.

Athletes who use illegal steroids have resorted to many strategies in order to avoid detection. These range from simple substitution of a “clean” urine sample for their own, to the rather extreme practice of draining their bladder and then using a catheter to fill the bladder with a sample of “pure” urine just before the drug test. Methods for steroid testing must take into consideration the fact that the fat-soluble steroids take some time to completely clear the body. Because of this time lag, elaborate schemes have been developed for tapering off illegal drugs in order to get below allowable limits just before competitions. Not surprisingly, some coaches and athletes with very little previous curiosity of medicinal chemistry now make it a significant area of interest—at least the part that applies to steroids.

### Consider This

**11.11**

In a recent survey of world-class athletes, 50% said they would take a drug that would enable them to win an Olympic gold medal, even though it would probably cause their death within ten years. Assume you are the editor of a sports magazine for teenage readers and write an editorial on this subject.

### Consider This

**11.12**

Before the unification of Germany, trainers in the East German Olympic program administered carefully monitored doses of anabolic steroids to athletes. It appears that under such controlled conditions, many of these drugs can be used quite safely. Should such a program be permitted and/or established for all Olympic athletes? As an Olympic judge, make a case either supporting or opposing a carefully monitored steroid supplement program.
The Thalidomide Story

The type of drug testing mentioned in the previous paragraph refers to determining the presence or absence of an illegal drug in a biological fluid and, if it is present, measuring its concentration. Another very different and far broader testing program is required of all new drugs. In accordance with the prevailing laws and regulations, drugs are subjected to an intensive, extensive, and expensive screening process before they can be approved for sale and public use. Ultimately, the question to be answered is, “Is the drug safe to use?” Considering the variability within target populations and the need to minimize unwanted side effects, it is somewhat remarkable that any drug ever receives approval. However, if an error must be made, it seems preferable that it be made on the side of rejecting rather than approving a drug that does not fully meet requirements after a thorough program of testing. Such was not the case for the drug thalidomide.

In 1956, thalidomide was put on the European market without sufficient screening because of an erroneous conclusion reached on the basis of incomplete testing data. The results were tragic. Discovered and developed by a small German drug company, Chemie Grunenthal, thalidomide was a by-product of research aimed at developing new antibiotics. A medicinal chemist at Chemie Grunenthal recognized thalidomide as an analog of a drug that had recently been put into use as a sedative. Testing of thalidomide on four species—mice, rats, guinea pigs, and rabbits—led to the conclusion that the drug was a remarkably safe sedative. Unfortunately, testing was not done to determine if thalidomide was a teratogen, that is, whether it could damage a developing embryo sufficiently to cause birth defects. Assuming the new drug to be safe, Chemie Grunenthal approached several companies who were interested in gaining a greater share of the sedative market. At least one United States drug company rejected the compound as worthless and possibly unsafe after carrying out its own testing of the drug. However, several pharmaceutical firms accepted Chemie Grunenthal’s offer and marketed thalidomide in different parts of the world.

Soon after thalidomide was introduced, several physicians reported cases of nerve damage in patients who had taken the drug, but these reports were largely ignored. Five years later, a German pediatrician reported a large increase in the number of infants suffering from phocomelia. In this condition, the development of the bones in the arms and legs is severely arrested, producing flipper-like limbs, badly deformed limbs, or no limbs at all. Because phocomelia is one of the rarest birth defects known, the sudden increase in its occurrence caused alarm. Subsequently, the outbreak of phocomelia was traced to thalidomide taken during the first three months of pregnancy by mothers who used the drug to control morning sickness and nausea. All together, some 9000 deformed infants, known as “thalidomide babies,” were born worldwide.

News of the thalidomide debacle brought expressions of grief and outrage from people around the world. Investigations indicated that greed plus inept, inadequate, and fraudulent testing were responsible for the disaster. Exceptional bad luck was also involved in that humans are more sensitive to the drug’s teratogenic effects than are most test animals.

Thalidomide was not sold in the United States because Dr. Frances Kelsey, a pharmacologist with the Food and Drug Administration, had been unconvinced by the limited safety data supplied by the manufacturers. Thus, because of scientific integrity and the insistence on good testing procedures, relatively few thalidomide babies were born in the United States. Although the thalidomide story is probably the darkest chapter in the history of drug design, it was responsible for the establishment of greatly improved drug testing procedures throughout the world. Teratogenicity testing is now a standard part of new drug approval procedures in most western countries. The FDA testing procedures, considered slow and overly methodical by some, have been widely adopted.
Figure 11.16
Schematic of the drug approval process in the United States.

- **Drug Testing and Approval**

All proposed new drugs, be they extracted from natural materials or synthesized in the laboratory, are subjected to exacting series of tests before they obtain FDA approval. These steps are summarized in Figure 11.16.

From discovery to approval, the development of a new drug takes, on average, nearly twelve years and more than 200 million dollars—over twice the cost of a decade ago. The expenses are principally for the various stages of drug testing, probably the most complicated and thorough pre-marketing process ever developed for any product. Although the number of pills getting through the funnel of Figure 11.16 gets progressively smaller with time, the diagram does not begin to convey the high mortality rate of proposed drugs. Currently, the odds of getting a candidate drug from identification to approval are 1 in 10,000. For every 10,000 trial compounds that begin the process, 20 make it to the level of animal studies, half that many get clearance for use in clinical testing with humans, and finally only one gets FDA approval.

Examples already encountered in this chapter have suggested the long process of chemical hide-and-seek that often precedes the identification of a compound as possibly having therapeutic properties. Once the promising candidates have been identified, they are subjected to *in vitro* studies. Simultaneously, a wide range of activity is undertaken by the pharmaceutical company. Chemists and chemical engineers investigate whether the compound can be produced in high volume with consistent quality control. Pharmacists carry out studies of the most effective way to formulate the drug for administration—as capsules, pills, injection, syrup, or perhaps something more unusual such as a nasal spray, skin patch, or implant. Stability and shelf-life are investigated. Economists, accountants, patent attorneys, and market analysts conduct research on the likelihood of deriving a profit from the product. A fair, responsible price must be established that allows the corporation to recapture the extensive development costs while keeping the drug affordable.

Only a small fraction of compounds survive this scrutiny to move on to animal testing. These *in vivo* tests are designed to determine the drug's efficacy, safety, dosage, and side effects. It is typically at this stage that pharmacologists determine the drug’s mode of action, its metabolic fate in the test animals, and its rate of absorption and excretion. The tests are carefully controlled, requiring the collection of very specific
kinds of data. For example, drugs are evaluated for their short- and long-term effects on particular organs (such as the liver or kidneys) and on more general systems (such as the nervous or reproductive system). Perhaps the most controversial toxicity testing involves the determination of \( \text{LD}_{50} \), the lethal dose for 50% of the test animals.

**11.13 Consider This**

Animal rights groups often target the \( \text{LD}_{50} \) requirement as an example of callous indifference to animal welfare. Others argue that such tests are essential to ensure drug safety and effectiveness. Take one of these positions and defend it in a statement that could be used in a public information campaign.

Results of animal tests must be submitted to the FDA for evaluation before permission is granted to proceed to the next stage—clinical testing of the drug on humans. In addition, approval must be obtained from local agencies and authorities such as a hospital’s ethics panel or medical board. Typically, clinical studies involve the three phases identified in Figure 11.16: developing a pharmacological profile, testing the efficacy of the drug, and carrying out the actual clinical tests. The entire process often requires six years or more.

The clinical trials may involve only a few patients or several hundred. A large pool will more likely include a wide range of subjects. This is desirable because the drug in question may have markedly different effects on the young and the old; men and women; pregnant or lactating women; infants, nursing infants, and unborn infants; and persons suffering from diabetes, poor circulation, kidney problems, high blood pressure, heart conditions, and a host of other disabilities. Typically, double blind studies are carried out in order to obtain unbiased results. In this methodology, neither the patient nor the physician knows which patients are receiving the drug and which are receiving a placebo, an inactive imitation made to look like the “real thing.”

**11.14 Consider This**

A friend of yours is dying from AIDS. He is in a hospital where a double blind study of a new anti-AIDS drug is being tested. By the nature of the test, he may or may not get the drug. Draft a letter to the director of the hospital in which you express your opinion on the research methodology involved.

Once clinical trials have been completed successfully—typically by only 10 drugs out of an original pool of 10,000 compounds—the test data are submitted to the FDA. Upon review, the Agency may require the repetition of experiments or the inclusion of new ones, thus adding years to the approval process. Of the drugs submitted to clinical testing, only about one in ten is finally approved. Once approval is granted, the drug can be sold in the United States. Nevertheless, it still remains under scrutiny, monitored through reports from physicians. Drugs are removed from the market if serious problems occur. Some side effects show up only when large numbers of users are involved. For example, benoxaprofen, an anti-arthritis drug, was withdrawn from the market because of severe side effects that occurred with an incidence of 1 in 8400 patients (0.012%). It is estimated that to ensure detection of side effects at this level of incidence, nearly 30,000 people would have had to receive the drug.
## Conclusion

The molecular manipulations of chemists have created a vast new pharmacopoeia of wonder drugs that have significantly increased the number and quality of cures of the future. Today, the great majority of bacterial infections are quite easily controlled, and once a dread killers such as typhoid, cholera, tuberculosis, and pneumonia have been largely eliminated—at least in wealthy, industrialized societies. But after reading this chapter, you should be well aware that no drug can be completely safe and that almost any drug can be misused. Taking a medication is making a conscious choice between the benefits derived from the drug and the risks associated with its side effects and limits of safety. Because most drugs have very wide, carefully established margins of safety, their benefits far outweigh the risks. For some drugs, however, the trade-off between effectiveness and safety involves a different balance. A drug with severe side effects may be the only treatment available for a life-threatening disease. Someone suffering from AIDS or an inoperable cancer will understandably have a different perspective on the risks and benefits than a person with a serious cold. When there is nothing to lose, one is willing to take great chances, including an imperfectly tested drug. Even the most impersonal anonymity of averages take on new meaning at the bedside of a loved one. When chemistry is applied to medicine, science must be guided by morality and reason must be tempered with compassion.

## References and Resources


## Experiments and Investigations

14. Properties of Analgesic Drugs

15. Synthesis of Aspirin
Exercises

1. The recommended dose of the miracle drug described early in the chapter is 0.650 grams (2 tablets), whereas the lethal dose is 20–30 grams. Calculate the number of tablets that would have to be taken at one time to reach the estimated lethal limit.

2. Draw Lewis structures and determine the number and type of bonds (single, double, triple) used by each carbon in the following molecules.
   a. \( \text{H}_2\text{CCN} \) (acetonitrile)
   b. \( \text{H}_2\text{NC(O)NH}_2 \) (urea)
   c. \( \text{C}_6\text{H}_5\text{COOH} \) (benzoic acid)
   (See Chapter 2 if you have forgotten how to write Lewis structures.)

3. Write condensed structural formulas for the three isomers of pentane you drew in 11.4 Your Turn.

4. Before the structure of benzene (shown in Figure 11.3) was determined, there was a great deal of controversy about how the atoms in a compound with this formula could be arranged. Draw three possible isomers.

5. Using equation 11.2, calculate the minimum number of grams of salicylic acid needed to yield the aspirin in 100 aspirin tablets, each containing 0.325 g of the drug.

6. If aspirin is a specific chemical compound, what, if anything, justifies claims for the superiority of one brand of aspirin tablets over another, and differences in price?

7. Consider the formulas given for the analgesics in Figure 11.5. Identify the portions of each molecule you would expect to promote solubility in polar solvents and in nonpolar solvents.

8. From the differences in the molecular structures of the analgesics in Figure 11.5 and the differences in their physiological activity, speculate on the possible relationships between their modes of activity and the presence of specific functional groups.

9. From the molecular structure of acetaminophen given in Figure 11.5, propose a possible equation representing its synthesis. (Hint: See the synthesis of nylon in Chapter 10.)

10. Sulfanilamide is the simplest of the class of antibiotics known as sulfa drugs. It appears to against bacteria by replacing para-aminobenz an essential nutrient for bacteria. Account for substitution of the drug for the nutrient on the of their molecular structures.

   
   ![Sulfanilamide](image)

   Para-aminobenzoic acid

11. Which of the compounds below can exist in active isomers?

    a. \( \text{H}_2\text{C} - \text{C} - \text{CH}_3 \)
    b. \( \text{H}_2\text{C} - \text{C} - \text{C}_6\text{H}_5 \)
    c. \( \text{H}_2\text{C} - \text{C} - \text{COOH} \)

12. As mentioned in the text, testosterone and estrogens were first isolated from animal tissue. One to bulls’ testicles were needed to obtain 5 mg of testosterone and four tons of pig ovaries were processed to yield 12 mg of estrone. Assume complete isolation of the hormones was achieved. Calculate the mass percentage of the two steroids in the original tissue. Explain why the calculation is very likely incorrect.
13. In 1973 diethylstilbestrol (DES) was approved to induce abortions. Identify the similarities and differences between the structure of the DES molecule, shown below, and estradiol.

14. A new synthesis of ibuprofen has been reported (Chemical & Engineering News, Feb. 8, 1993) that involves three steps rather than the six steps used previously. If each step in these two syntheses gives a 75% yield, compare overall percentage yield of ibuprofen from each of the two processes.

15. A new development in contraception, called Norplant®, involves surgically implanting six matchstick-size capsules in a woman’s arm. These capsules slowly release a low dosage of levonorgestrel, a synthetic hormone, that can prevent pregnancy for up to five years. Make lists of the advantages and disadvantages of such a contraception option.

16. Identify the molecular similarities and differences between testosterone and the two anabolic steroids depicted in Figure 11.15.

17. Estrogens, along with other drugs, are often given to men suffering from testicular cancer. On the basis of your knowledge of the effects of estrogen, speculate on why this therapy is effective.

18. Why might the teratogenic effects of thalidomide not have shown up in the test animals used even if they had been sought? What implications does this have for drug testing in general?

19. Potential treatments for fatal diseases such as AIDS and cancer have often been denied to people suffering from these diseases if they are not part of controlled studies. Discuss the possible reasons for such action and the pros and cons of such regulations.

20. The drug-testing laws in some other nations are not as stringent as those in the United States. As a result, some American citizens purchase drugs that are illegally imported from countries where they are approved for use. Under what circumstances, if any, would you resort to this practice?