CHAPTER

1

Some Basic Pharmacology

WHAT IS A DRUG?

Most people understand what is meant by the term *drug*, but, surprisingly, coming up with a precise definition is not all that easy. The traditional way is to define a drug as any substance that alters the physiology of the body. This definition, however, includes food and nutrients, which are not usually thought of as drugs. Consequently, a drug is sometimes defined as a substance that alters the physiology of the body but is not a food or nutrient. This definition usually works, but it still leaves a lot to be desired. To begin with, the distinction between a drug and a nutrient is not at all clear. Vitamin C, for example, alters physiology, but is it a drug? If it is consumed in the form of an orange, it is clearly food, but if taken as a tablet to remedy a cold, it could be thought of as a drug.

Similarly, some substances that alter the physiology of the body may best be thought of as toxins or poisons rather than as drugs and may not be deliberately consumed. Gasoline and solvent vapors are examples. If they are consumed deliberately to get high, they might be drugs, but when inhaled unintentionally in the workplace, they may be called environmental toxins. The exact distinction between a toxin and a drug is not clear.

One element that complicates the definition appears to be the intention of the drug user. If a substance is consumed to get high or to treat a disorder, it is clearly best to think of it as a drug, but if it is consumed for taste or sustenance, it may not be useful to think of it as a drug. Such a debate has been waged about caffeine. As you will see in Chapter 9, caffeine clearly alters human physiology, but it also has been used as a flavoring agent in products such as soft drinks. If consumers prefer a soft drink that contains caffeine because they like the drink's taste, perhaps caffeine should not be thought of as a drug in that context. If the soft drink is consumed because of the effect caffeine has on the nervous system, then it is appropriate to think of it as a drug. A similar debate has been waged about the role of nicotine in tobacco (see Chapter 8). In these cases, the consequences are important to government regulatory agencies and various manufacturers. Fortunately, it is not necessary for us to form a precise definition of the term *drug*. An intuitive definition will serve our purposes. However, we should never lose sight of the fact that any one definition may not be appropriate in all circumstances.

NAMES OF DRUGS

One of the more confusing things about studying drugs is their names. Most drugs have at least three names—a chemical name, a generic name, and a trade name—and it may not always be apparent which name is being used at any given time. In addition, recreational drugs have an assortment of street names.

Chemical Name

All drugs have a *chemical name* stated in formal chemical jargon. A chemist can usually tell by looking at the name what the molecule of the drug looks like. Here is the chemical name of a drug:

7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

As you can see, it is full of chemical terminology, letters, and numbers. The numbers refer to places where different parts of the drug molecule are joined. To make things more complicated, there are different conventions for numbering these parts of molecules. As a result, the same drug will have different chemical names if different conventions are used.

Generic Name

When a drug becomes established, its chemical name is too clumsy to be useful, so a new, shorter name is made up for it—a *generic name* or *nonproprietary name*. The generic name for the drug whose chemical name we just struggled through is *diazepam*. A drug's generic name bears some resemblance to its chemical name. The conventions for making up generic names are handy to know because they are clues to the nature of the drug. Initially, the generic name was derived by combining parts of the chemical name, and these names are still in use, but more recently, a system has been adopted that uses a *stem* to indicate the class or function of the drug. The stem is usually the last part of the generic name, although it could be at the beginning or in the middle. For example, *oxetine* is a stem that indicates an antidepressant drug. Thus, if you see the name *fluoxetine* or *duloxetine*, you know what type of drug it is, even though you may never have heard of it before. Table 1-1 shows stems for some behaviorally active drugs you may come across.

Generic names are established in the United States by the United States Adopted Names Council (USANC) and are called United States Adopted Names (USAN). Similarly, the British Approved Name (BAN) is established by the British Pharmacopoeia (2012). Internationally, the World Health Organization establishes the International Nonproprietary Name (INN). Attempts are made to harmonize all these names so that the same generic name is used throughout the world. In spite of these attempts, there are still a few cases where different names are used for the same drug. For example, the USAN *amphetamine* is still widely used in Britain and the United States, but many other parts of the world are now using *amfetamine*, the INN. Most scientific journals and textbooks published in North America (including this book) use USANC generic names.

There is a type of unofficial generic name you might also encounter. Because establishing a generic name is a costly and time-consuming process, new drugs created by drug companies may be used extensively before generic names are officially awarded by the official naming agencies. But instead of using their clumsy chemical names, these drugs are sometimes referred to by a code using letters and numbers established by the company. For example, you may see a name like *SKF 10,047*. The letters refer to the drug company (in this case, Smith, Kline, and French), and the numbers are a unique code for the drug. SKF 10,047 has now been assigned the generic name *alazocine*.

Trade Name

When a drug company discovers and develops a new drug, often at a cost of millions of dollars, it can patent the drug for a number of years so that no other company can sell it. Even though it must use the generic name somewhere in its advertising and documentation, the drug company does not sell the drug under its generic name. Instead, it makes up a new name called the *trade name*, *proprietary name*, or *brand name*. The trade name is the property of the company that sells the drug, and no other company can use that name (hence, the name is proprietary). Generic names, on the other hand, are nonproprietary and can be used by anyone. The trade name for diazepam is Valium. After the patent expires, which typically occurs in 5 to 7 years, other companies can sell the drug or they can make it under license from the owner of the patent, but they frequently sell it under a different trade name. Therefore, one drug can have many different trade names.

Because drug companies sell their products under trade names, people in the medical profession are most familiar with trade names and are most likely to use those names. If a physician gives you a prescription for a drug and you are told the name of the drug, you may not

TABLE 1-1 Generic Name Stems of Behaviorally Active Drugs

Generic Drug Name Stem	Definition	Examples
-adol or -adol-	Analgesics (mixed opiate receptor agonists/antagonists)	taz***adol***ene; spir***adol***ene; levonantr***adol***
-anserin	Serotonin 5-HT2 receptor antagonists	alt***anserin***; trop***anserin***; adat***anserin***
-axine	Antianxiety, antidepressant inhibitor of norepinephrine and dopamine reuptake	radaf***axine***
-azenil	Benzodiazepine receptor agonists/antagonists	bret***azenil***; flum***azenil***
-azepam	Antianxiety agents (diazepam type)	lor***azepam***
-azocine	Narcotic antagonists/agonists (6,7-benzomorphan derivatives)	quad***azocine***; ket***azocine***
-barb or -barb-	Barbituric acid derivatives	pheno***barb***ital; seco***barb***ital; etero***barb***
-caine	Local anaesthetics	dibu***caine***
-caserin	Serotonin receptor agonists, primarily 5-HT2	lor***caserin***; vabi***caserin***
-clone	Hypnotics/tranquilizers (zopiclone type)	pago***clone***
-dopa	Dopamine receptor agonists	levo***dopa***
-erg-	Ergot alkaloid derivatives	p***erg***olide
-fenine	Analgesics (fenamic acid subgroup)	flocta***fenine***
-fylline	Theophylline derivatives	enpro***fylline***; bami***fylline***; cipam***fylline***
nab- or -nab-	Cannabinol derivatives	***nab***azenil; dro***nab***inol
nal-	Narcotic agonists/antagonists (normorphine type)	***nal***mefene
-nicline	Nicotinic acetylcholine receptor partial agonists/agonists	alti***nicline***
-orphan	Narcotic antagonists/agonists (morphinan derivatives)	dextro-meth***orphan***; dextr***orphan***
-peridol	Antipsychotics (haloperidol type)	halo***peridol***
-peridone	Antipsychotics (risperidone type)	ris***peridone***; ilo***peridone***; oca***peridone***
-perone	Antianxiety agents/neuroleptics (4′-fluoro-4-piperidinobutyrophenone derivatives)	duo***perone***
-serod	Serotonin receptor antagonists and partial agonists	pibo***serod***
-spirone	Anxiolytics (buspirone type)	zalo***spirone***; tio***spirone***
-stigmine	Cholinesterase inhibitors (physostigmine type)	quilo***stigmine***; teser***stigmine***

Prefixes are shown as "stem-," middle syllable as "-stem-," and suffixes as "-stem."

Source: Adapted from United States National Library of Medicine, National Institutes of Health (2011), http://druginfo.nlm.nih.gov/drugportal/jsp/drugportal/DrugNameGenericStems.jsp, accessed December 7, 2011.

be able to find it listed in this or any other text that uses generic names. Trade names can be distinguished from generic names because the first letter is capitalized.

Strictly speaking, the trade name refers to more than just the active ingredient in the medicine; it refers to the drug's *formulation*. The active ingredient is marketed in the form of a pill, tablet, capsule, or liquid that may contain a number of other ingredients—fillers, coloring agents, binding agents, and coatings, collectively referred to as *excipients*. The excipients and the active ingredient are combined in a particular way, and this is known as the formulation. Different pharmaceutical companies may market the same drug but in different formulations that are given different trade names. It cannot be assumed that all formulations with the same active ingredient are equal. For example, different formulations may dissolve at different rates in different parts of the digestive system and, consequently, may not be equally effective.

Street Name

Drugs that are sold on the street for recreational purposes usually have a street name, which can change with time and differ geographically; however, a particular drug usually has one street name that is widely recognized. For example, the club drug MDMA (3,4-methylenedioxymethamphetamine) is widely known by most people by the street name *ecstasy*, even though it has had many other names at different times and in different places. A quick search of the Internet can turn up names such as X, E, XTC, Disco Biscuit, Go, Crystal, Adam, Hug Drug, Love Drug, Lover's Speed, Clarity, and Speed. Some street names for Valium include Downers, Tranks, Vs, Foofoo, Dead Flower Powers, and Sleep Away.

DESCRIBING DOSAGES

All of modern science uses the metric system, and drug doses are nearly always stated in *milligrams* (mg). A milligram is 1/1,000 of a gram (there are a little over 28 grams in an ounce).

It is generally true that the behavioral and physiological effects of a drug are related to its concentration in the body rather than the absolute amount of drug administered. If the same amount of a drug is given to individuals of different sizes, the drug will reach a different concentration in the body of each individual. To ensure that the drug is present in the same concentration in the brains of all experimental participants or patients, different doses are frequently given according to body weight. For this reason, in research papers, doses are usually reported in terms of milligrams per kilogram (kg) of body weight—for example, 6.5 mg/kg (a kilogram is equal to 2.2 pounds).

Reporting doses in this manner also helps when comparing research on different species. If you account for such other factors as metabolic rate and body composition, a dose of 1 mg/kg in a monkey will be roughly comparable to a dose of 1 mg/kg in a human. Interspecies comparisons, however, can be tricky. Generally, smaller organisms have higher metabolic rates than larger animals. As we shall see later, many drugs are destroyed by the body's metabolism. What this means is that drugs are metabolized faster in smaller animals, and so it is often necessary to give them a higher dose if they are to reach an exposure equivalent to that of a human. Thus, a dose of 1.0 mg/kg in a human may be equivalent to a dose of 10.0 mg/kg in a mouse or a rat. For this reason, research done on rats and mice often uses doses that seem ridiculously high in human terms.

Dose–Response Curves

To establish a true picture of the physiological and behavioral effects of a drug, it is usually necessary to give a wide range of drug doses. The range should include a dose so low that there is no detectable effect, a dose so high that increases in dose have no further effect, and a number of doses in between. It is usual to plot the effect of this range of doses on a graph, with the dose indicated on the horizontal axis and the effect on the vertical axis. This type of figure is called a *dose–response curve* or a *dose–effect curve*. Some make a distinction between these terms, but such distinctions are not widely used and these terms are often used interchangeably. The term *dose–response curve* (*DRC*) will be used here.

Figure 1-1 shows a typical DRC. It indicates the effect of caffeine on a mouse's rate of pressing a lever on an FI (fixed interval) schedule (schedules will be explained in Chapter 2). Note that the scale on the horizontal axis is graduated logarithmically. It is generally found that a small change in low doses can have a big effect, but an equally small change in a large dose has no effect. Plotting doses on a log scale allows a wide range of doses

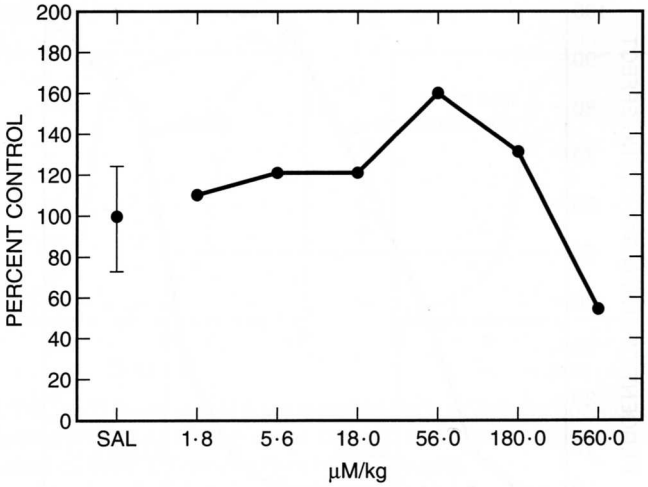

FIGURE 1-1 The dose–response curve for the effect of caffeine on the rate of responding of a mouse on an FI schedule with food reinforcement. Note that the dose is given in S.I. units. (Adapted from McKim, 1980)

to be reported and permits greater precision at the low end of the dosage range.

In the example just used, the drug effect was a measure of response rate, but there are other types of DRCs in which the effect is a discrete binary variable rather than a continuous one. For example, we could not use this type of curve if we wanted to report a DRC for the effectiveness of a drug as an anesthetic. Either subjects are anesthetized or they are not. If the vertical axis simply read *Yes* or *No*, we would not have any sort of a curve. When a binary variable is used, DRCs are constructed differently.

Binary drug effects are handled by working with groups of subjects. Each group is given a different dose of the drug, and the percentage of subjects in each group that shows the effect is then plotted. An example of this type of DRC is given in Figure 1-2. This hypothetical experiment is designed to establish the DRC for loss of consciousness and the lethal effects (another clearly binary variable) of a fictitious new drug Endital. In this experiment, there are 12 groups of rats. Each group is given a different dose of endital—from 0 mg/kg, a placebo, to 110 mg/kg. The vertical axis of the graph shows the percentage of rats in each group that showed the effect. The curve on the left shows how many rats lost consciousness, and the curve on the right shows the percentage of rats in each group that died.

ED_{50} AND LD_{50}. A common way of describing these curves and comparing the effectiveness of different drugs is by using the *ED_{50}, the median effective dose*, or the dose that is effective in 50% of the individuals tested. The ED_{50} for losing consciousness from endital in Figure 1-2 is 35 mg/kg. By checking the next curve, you can see that the dose of endital that killed 50% of the rats was 84 mg/kg. This is known as the *median lethal dose*, or the *LD_{50}*.

It is also common to use this shorthand to refer to lethal and effective doses that are not at the median. For example, the LD_{50} is the dose at which 50% of subjects die, the LD_1 is the dose that kills 1% of subjects, and the ED_{99} is the dose that is effective in 99% of all cases.

In DRCs constructed from continuous rather than binary measures, the ED_{50} is also used, but in this case, it refers to a dose that produces an effect that is 50% of the maximum effect that the drug causes at its most effective dose.

Drug Safety

When new drugs are being developed and tested, it is common to establish the LD_{50} and the ED_{50} to give an idea of the safety of a drug. Obviously, the farther the lethal dose is from the effective dose, the safer the drug. The *therapeutic index* (TI; also known as

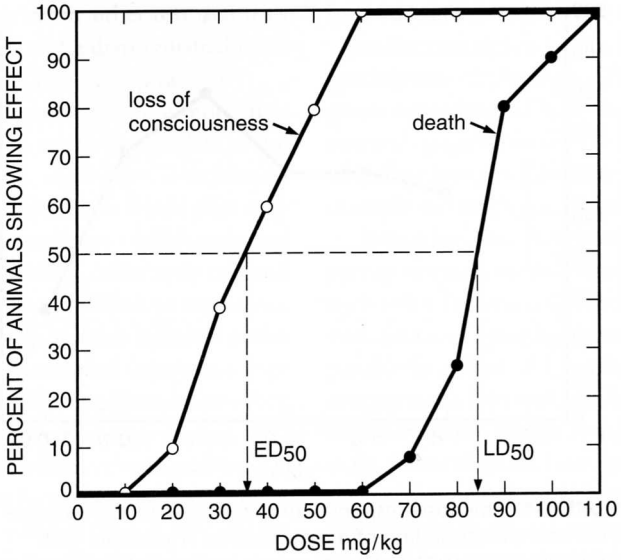

FIGURE 1-2 Results of a hypothetical experiment using 12 groups of rats. Each group was given a different dose of enditol, ranging from 0.0 (a placebo) to 110 mg/kg. One curve shows the percentage of animals in each group that lost consciousness; the other curve shows the percentage that died at each dose. The ED_{50} and the LD_{50} are also indicated.

the *therapeutic ratio*) is sometimes used to describe the safety of a drug. This is the ratio of the LD_{50} to the ED_{50}; TI = LD_{50}/ED_{50}. The higher the TI, the safer the drug. The TI of endital calculated from Figure 1-2 would be 84/35 = 2.4.

Drug safety may also be described as a ratio of the ED_{99} and the LD_1.

POTENCY AND EFFECTIVENESS

Potency and *effectiveness* (or *efficacy*) are terms that are sometimes used to describe the extent of a drug's effect. The two terms do not mean the same thing. When you are comparing two drugs that have the same effect, *potency* refers to differences in the ED_{50} of the two drugs. The drug with the lower ED_{50} is more potent. For example, if you constructed two DRCs for LSD and lysergic acid amide (a related hallucinogen found in morning glory seeds) for the ability to cause hallucinations, you would find that the ED_{50} of lysergic acid amide is 10 times higher than that of LSD. In other words, the nature and extent of the effect of lysergic acid amide would be the same as that of LSD if you increased the dose of lysergic acid amide by a factor of 10—LSD is 10 times more potent than lysergic acid amide.

Effectiveness refers to differences in the maximum effect that drugs will produce at any dose. Both aspirin and morphine are analgesics or painkillers. When dealing with severe pain, aspirin at its most effective dose is not as effective as morphine. To compare these two drugs in terms of potency would not be appropriate. They both might produce analgesia at the same dose and, thus, be equally potent, but the extent of the analgesia would be vastly different. The difference between potency and effectiveness is shown in Figure 1-3.

PRIMARY EFFECTS AND SIDE EFFECTS

It is generally accepted that no drug has only one effect. In most cases, however, only one effect of a drug is wanted, and other effects are not wanted. It is common to call the effect for which a drug is taken the *primary* or *main effect* and any other effect a *side effect*. If a drug is taken to treat a disease symptom, that is its primary

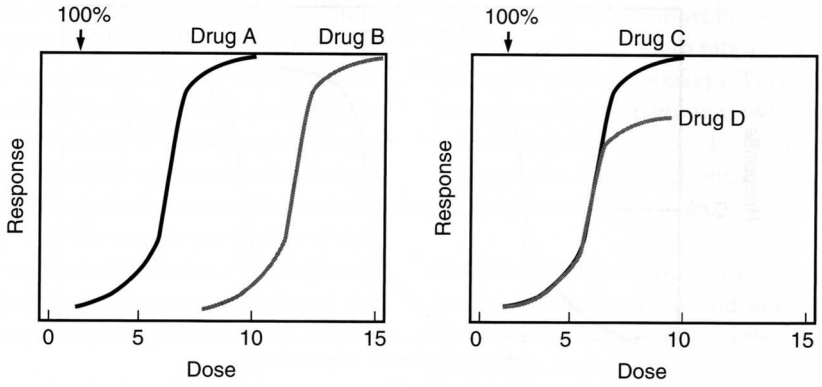

FIGURE 1-3 *Left*: Drugs A and B are equally effective, but the potency of Drug A is greater than that of Drug B. *Right*: Drugs C and D are equally potent, but the effectiveness of Drug C is greater than that of Drug D.

effect. Anything else it might do, harmful or otherwise, is a side effect.

Very often, the distinction between the two is arbitrary. Aspirin, for example, has several physiological effects: It brings down fever, it reduces swelling and inflammation, and it slows the blood's ability to clot. If you take aspirin because you have a high temperature, the temperature-reducing effect is the primary effect, and the other two are side effects. The inhibition of blood clotting is a potentially harmful effect because it can cause bleeding into the stomach, which can have serious consequences for some people. But this anticlotting effect can be useful. Strokes are caused by a clot of blood getting caught in the brain. It has been shown that taking low-dose aspirin every day can reduce the chances of stroke in people at risk. In this case, the anticlotting effect would be the primary effect, and any other effects that the aspirin might be having would be the side effects.

When new behaviorally active drugs are developed to treat diseases, the ability of a drug to be abused or to create an addiction is considered a dangerous side effect. To a drug user, however, this psychological effect of the drug is vitally important, and any other effects the drug may have on the body are considered unimportant or undesirable side effects.

DRUG INTERACTIONS

When two drugs are mixed together, their effects can interact in several ways. If one drug diminishes the effect of another, this interaction is called *antagonism*. Drug antagonism is established by plotting two DRCs: one DRC for the drug alone and a second DRC for the drug in the presence of the other drug. If the DRC for the first drug is shifted to the right (i.e., the ED_{50} increases) by adding the new drug, this result indicates antagonism between the drugs.

If adding the new drug shifts the DRC to the left (i.e., the ED_{50} decreases), the drugs are said to have an *additive effect*. If drugs have an effect together that is greater than might be expected simply by combining their effects, a *superadditive effect*, or *potentiation*, exists. This can be particularly dangerous if the drugs' effects include respiratory depression, as is the case with alcohol and tranquilizing drugs (barbiturates). It is not always obvious whether a drug interaction is additive or superadditive, but in one situation the distinction is clear: If one drug has no effect alone but increases the effect of a second drug, potentiation is clearly occurring.

In these examples, drug interaction is defined in terms of shifts in the DRC indicated by changes in the ED_{50}, that is, changes in potency, but interactions may also change the effectiveness of drugs. That is, the ED_{50} may not change, but the maximum effect may increase or decrease (see Figure 1-4).

PHARMACOKINETICS

The study of how drugs move into, get around in, and are eliminated from the body is called *pharmacokinetics*. The pharmacokinetics of a drug can be described in three processes: *absorption*, how a drug gets into

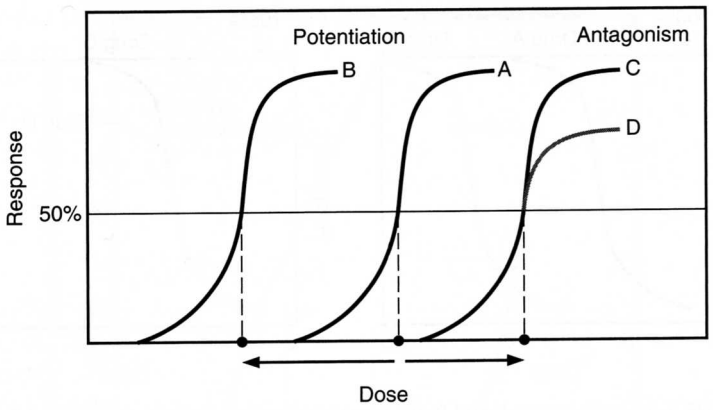

FIGURE 1-4 Drug interactions. The curve labeled A is the dose–response curve (DRC) for a drug, against which the effects of the addition of other drugs will be compared. The curve labeled B shows the DRC after the administration of a second drug. Note that the DRC has been shifted to the left and the ED_{50} has decreased. This indicates potentiation or an additive effect. Curve C is the DRC after another drug has been given. This drug has shifted the DRC to the right, increasing the ED_{50}. This indicates antagonism. Curve D shows the effect of another drug on the DRC. In this case the DRC has been shifted to the right, showing a decrease of potency, and the maximum effect has also been reduced showing a decrease in effectiveness.

the blood; *distribution*, where it goes in the body; and *elimination*, how the drug leaves the body.

Drugs do not have an effect on all body tissues. As a matter of fact, most drugs influence the operation of the body only at specific and limited places, called *sites of action*. A drug may get into the body, but it will have no effect unless it gets to its site of action where it will interact with the cell to change the cell's biochemical processes. It is, therefore, important to understand how drugs get from their place of administration to the place where they act (i.e., pharmacokinetics).

ROUTES OF ADMINISTRATION

Some foods and medications may contain large amounts of valuable nourishment and medicine, but simply swallowing them or otherwise putting them into the body is no guarantee that they will get to their site of action and have the desired effect. It is also true that the way a substance is administered can determine not only whether it gets to its site of action but also how fast it gets there and how much of it gets there.

A route of administration refers to the method used to get a drug from outside the body to some place under the skin. Some substances can be directly absorbed through the skin, but most are not. Getting drugs into the body can be accomplished by taking advantage of the body's natural mechanisms for taking substances inside itself (such as digestion, breathing, or absorption through mucous membranes), or the drug can be artificially placed under the skin by means of injection.

Parenteral Routes of Administration

Parenteral routes of administration involve injection through the skin into various parts of the body, using a hollow needle and syringe. Parenteral routes are further subdivided, depending on the specific point in the body where the drug is to be left by the needle.

VEHICLE. Before a drug can be injected, it must be in a form that can pass through a syringe and needle—that is, it must be liquid. Because most drugs are in a dry powder or crystalline form (the word *drug* is derived from the French *drogue*, meaning *dry powder*), it is

necessary to dissolve or suspend a drug in some liquid before it can be injected. This liquid is called a *vehicle*. Most behaviorally active drugs tend to dissolve well in water and remain stable for long periods of time in water solution. Pure water is not totally inert with respect to the physiology of the body, so a weak salt solution is used instead. Because body fluids contain dissolved salts, the most common vehicle is *normal* or *physiological saline*, a solution of 0.9% sodium chloride (ordinary table salt), which matches body fluids in concentration and does not irritate the tissues when it is injected as pure water would.

In some cases, the drug to be injected does not dissolve in water. The primary active ingredient in marijuana, tetrahydrocannabinol (THC), is an example of such a drug; it requires a different vehicle, such as vegetable oil (see Chapter 14). Administering lipid-soluble drugs in an oil vehicle slows the rate of absorption, prolonging the drug's effects over several days.

When a drug is in liquid form and the syringe is filled, the needle can be inserted into various places in the body, and the drug and vehicle are then injected to form a small bubble, or *bolus*. There are four common parenteral routes, depending on the site where the bolus containing the drug is to be placed: (a) *subcutaneous*, (b) *intramuscular*, (c) *intraperitoneal*, and (d) *intravenous*.

SUBCUTANEOUS. In published material, the term *subcutaneous* is frequently abbreviated *s.c.* In jargon, it is called *sub-q*. As the name suggests, in this route of administration, the drug is injected to form a bolus just under the skin or cutaneous tissue. In most laboratory animals, the injection is usually made into the loose skin on the back, between the shoulders. For medical purposes in humans, s.c. injections are usually done under the skin of the arm or thigh, but the hand or wrist is sometimes used to self-administer recreational drugs such as heroin, a procedure referred to as *skin popping*. Some drugs, including contraceptives, may be manufactured as pellets for s.c. implantation, which prolongs absorption, sometimes for years.

INTRAMUSCULAR. In the *intramuscular* (*i.m.*) route, the needle is inserted into a muscle, and a bolus is left there. In humans, the most common muscle used for this purpose is the *deltoid* muscle of the upper arm or the *gluteus maximus* muscle of the buttock. To receive such an injection, the muscle must be fairly large, so i.m. injections are seldom given to rats and mice. They are more frequently given to monkeys. This route of administration is common for pigeons as well; the injection is given into the large breast muscle. Drugs administered i.m. are typically absorbed through the muscle's capillaries within about an hour.

INTRAPERITONEAL. The abbreviation for the *intraperitoneal* route is *i.p.*, and, as the name suggests, the needle is inserted directly into the peritoneal cavity. The *peritoneum* is the sack containing the visceral organs, such as the intestines, liver, and spleen. The aim of an i.p. injection is to insert the needle through the stomach muscle and inject the drug into the cavity that surrounds the viscera. It is not desirable to inject the drug directly into the stomach or any of the other organs. Doing so could be harmful and cause hemorrhaging and death. At the very least, injection into an organ is likely to alter the reaction to the drug.

Intraperitoneal injections are commonly used with rats and mice because they are easy and safe and cause the animals very little discomfort. They are much less convenient in larger animals and are almost never given to humans. At one time, rabies vaccine was commonly given to humans via this route, but this is no longer the case.

INTRAVENOUS. In an *intravenous* (i.v.) injection, the needle is inserted into a vein, and the drug is injected directly into the bloodstream. This procedure is more popularly known as *mainlining*. Before an i.v. injection can be given, it is necessary to find a vein that comes close enough to the surface of the skin that it can be pierced with a needle. In humans, this is usually the vein on the inside of the elbow. The most common procedure is to wrap a tourniquet around the upper arm between the injection site and the heart. Because veins carry blood toward the heart, the tourniquet will dilate or enlarge the vein at the injection site and make injection easier.

When the end of the needle is inserted into the vein, the tourniquet is removed, and the drug is injected when normal blood flow has resumed. This is essentially the reverse of the procedure used when blood is removed for a blood test. When a drug is administered i.v., it gets distributed throughout the body very quickly, reaching the brain in a matter of seconds and producing rapid effects. One difficulty with i.v. injections, however, is that a vein

cannot be used too frequently or it will collapse and simply stop carrying blood. When veins have collapsed in the arms, other veins in the wrists, hands, and feet may be used, but they are more difficult to strike accurately with a needle. Another problem is that recreational drugs may contain contaminants that are insoluble (do not dissolve) and, once in the bloodstream, become lodged in and cause damage to small blood vessels in organs such as the lungs or eyes.

In laboratory animals, i.v. injections are not commonly used by behavioral pharmacologists because veins close to the surface of the skin are unusual in rats, mice, and pigeons, and the procedure is not easy in unrestrained animals. Fur and feathers also make the location of such veins difficult to find. When i.v. injections are necessary, they are usually accomplished by means of a permanently implanted catheter. A *catheter* is a tube that is surgically implanted into the body. One end of the tube is at a site inside the body, and the other end is outside. In rodents and monkeys, venous (in a vein) catheters are usually inserted in the jugular vein in the neck, and the free end of the tube emerges from the animal's back. When an intravenous injection is required, the syringe is attached to the end of the catheter outside the body, and the drug is injected. Researchers frequently use this type of preparation to study self-administration of drugs by animals (the catheter may be attached to a motor-driven pump that the animal can control by pressing a lever; see Chapter 5). Intravenous catheters are fairly permanent and may last for months before they have to be replaced.

OTHER PARENTERAL ROUTES. Experimental research with laboratory animals sometimes involves injections directly into the central nervous system (the brain and spinal cord; see Chapter 4). In *intrathecal* injections, for example, the needle is inserted into the nervous system between the base of the skull and the first vertebra. The drug is left in the *cerebrospinal fluid* (CSF; the fluid that bathes the nervous system) and quickly diffuses throughout the nervous system. A drug may also reach the CSF through an *intracerebroventricular* injection directly into one of the brain's *ventricles*, which are chambers filled with CSF. To more precisely determine drug effects on specific areas of the brain, *intracerebral* injections may be used in which a drug is administered directly into brain tissue. These forms of drug administration are often done through a *cannula*. A cannula is like a catheter, except it is a rigid tube resembling a hypodermic needle. Cannulae are often attached to the animal's skull using dental cement and can remain permanently implanted.

ABSORPTION FROM PARENTERAL SITES

With intravenous injections, the drug is put directly into the blood, but when other sites are used, the drug must be absorbed into the circulatory system. The rate at which a drug gets into the blood from an injection site is determined by a number of factors associated with blood flow to the area. Generally, the volume of blood flow is greater to the peritoneal cavity than to the muscles, and it is greater to the muscles than under the skin. As a result, absorption is fastest from an i.p. injection and slowest from an s.c. injection.

Heat and exercise can speed absorption from i.m. and s.c. sites because such factors increase blood flow to muscles and skin. Thus, an i.m. injection will be absorbed faster if the muscle is exercised after the injection, and the drug from a subcutaneous site will get into the blood faster if heat is applied to the area and more slowly if the area is chilled.

To be absorbed into the bloodstream, a drug must pass through the walls of the capillaries. A *capillary* is a tiny vessel through which blood flows. Capillaries permeate most body tissues. They are so small in diameter that red blood cells can barely pass through. It is through the walls of capillaries that nutrients and oxygen pass out of the blood into body tissues, and it is also through these capillary walls that waste products and carbon dioxide pass into the blood and are removed. Blood leaves the heart and is distributed around the body in *arteries*. The arteries divide into smaller and smaller branches until they become capillaries. The blood in capillaries is eventually collected in *veins*, which carry the blood back to the heart and the lungs (see Figure 1-5).

The walls of the capillaries are made up of a single layer of cells. Between these cells are small openings, or *pores*, through which nutrients, waste products, and drugs may pass freely. The only substances in the blood that cannot move in and out of the capillaries through these pores are red blood cells and large protein molecules, which are trapped inside because they are larger than the pores.

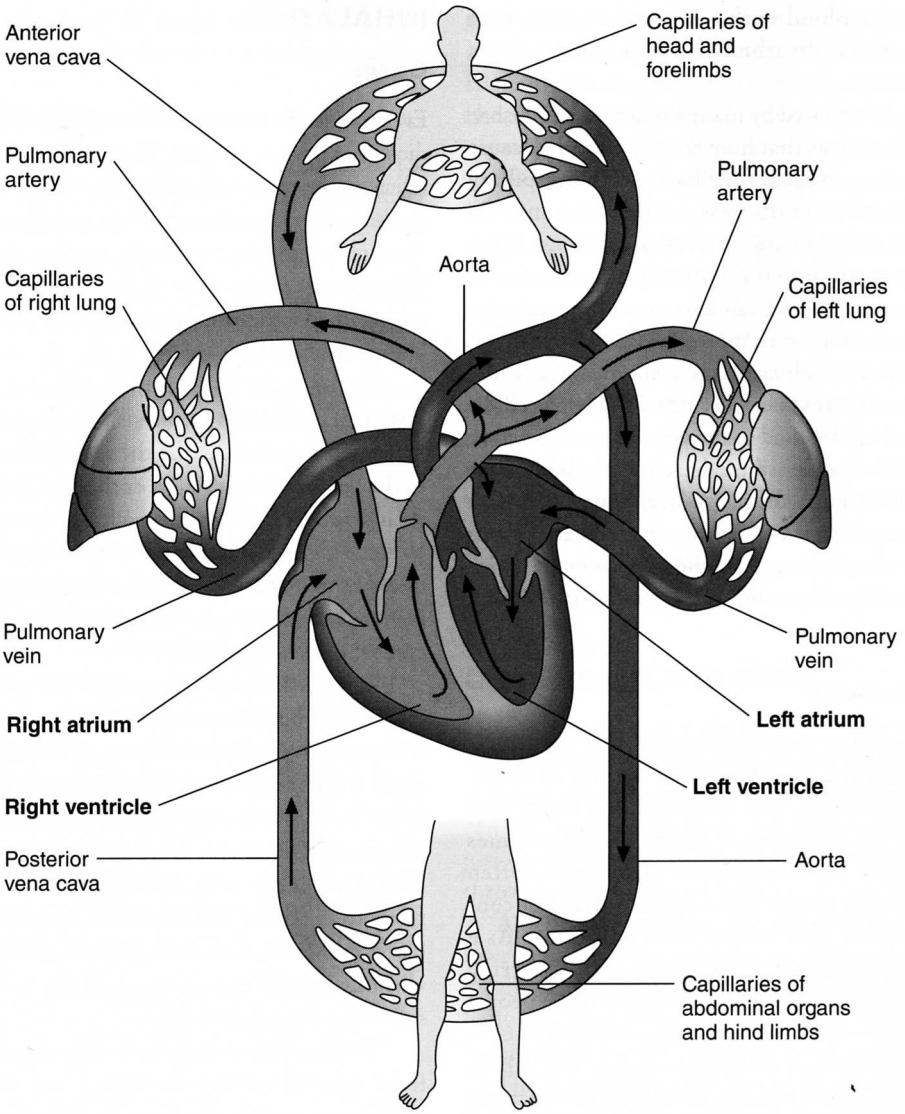

FIGURE 1-5 Circulatory system.

Injected drugs pass into capillaries and the bloodstream through these pores by simple *diffusion*. Diffusion is the process by which a substance tends to move from an area of high concentration to an area of low concentration until the concentrations are equal in both areas. If a drop of food coloring is placed in the corner of a tub of still water, it will remain as a highly colored drop for only a short period of time. The force of diffusion will soon distribute the coloring evenly throughout the tub of water. The same principle determines that a drug injected into a muscle or under the skin will move from the area of high concentration (the bolus at the site of the injection) into the blood, an area of low concentration, until the concentrations in the two places are equal. The drug from an injection site will move through the pores into the blood in the capillaries surrounding the injection site. Because this blood is constantly circulating and being

replaced by new blood with a low concentration of drug, more will be absorbed as the blood circulates through the area.

Areas that are serviced by many capillaries will absorb drugs faster than areas that have few capillaries. Because muscles use more oxygen, they have a richer capillary supply than the skin; for this reason, absorption into the blood is faster from i.m. injections than from s.c. injections. Drugs injected into the peritoneum have access to an even greater number of capillaries; consequently, i.p. injections are absorbed even more rapidly.

Absorption through capillary walls is not a factor in intravenous injections because the drug is placed directly into the blood. Blood in the veins is transported to the heart and then redistributed around the body after a short detour through the lungs (see Figure 1-5). The body has about 6 liters of blood, and the heart pumps these 6 liters once a minute, so the drug in most i.v. injections is distributed around the body about a minute after injection.

Depot Injections

Some drugs need to be taken continuously or chronically to prevent the symptoms of a disease or disorder from reappearing. The antipsychotic drugs (see Chapter 12) are examples of drugs that sometimes need to be taken continuously for many years. Often people do not like to take these drugs and do not continue to use them after release from a hospital. As a result, they are readmitted regularly with recurring psychotic symptoms. It is possible to give these people *depot injections*—the drug is dissolved in a high concentration in a viscous oil (often sesame oil), which is then injected into a muscle, usually in the buttock. The drug then slowly diffuses from the oil into the body fluids over a long period of time. A single depot injection of an antipsychotic drug can be effective as long as 4 weeks. This technique usually works only with drugs that are highly lipid soluble (to be discussed shortly); otherwise, they would be released too quickly. Fortunately, antipsychotic drugs have this property (Lemberger, Schildcrout, & Cuff, 1987). Newer formulations use more advanced techniques to generate synthetic polymer beads that have no physiological effect, but degrade slowly in the body and release constant levels of a drug over an extended period of time (Fleischhacker, 2009).

INHALATION

Gases

Every cell in the body requires oxygen and gives off carbon dioxide as a waste product. The body has developed a very efficient system for absorbing gases from the air (that is, the lungs) and distributing them quickly and completely throughout the body (that is, the circulatory system). When drugs in the form of gases, vapors, or fine mists are breathed into the lungs, this system gets them into the blood very rapidly.

The lungs are an extremely efficient gas exchange system. Their inside surface is convoluted and contains many pockets of air so that the total surface area exposed to the air is very large. This entire area is richly supplied with blood by capillaries, which are close to the surface. When a gas or fumes of volatile substances (substances that evaporate rapidly, such as solvents) are inhaled, they are very quickly absorbed through the capillary walls and enter the circulating blood.

Figure 1-5 shows the circulation to and from the lungs. After blood returns to the heart through the veins, it is pumped directly to the lungs. Here the carbon dioxide is released from the blood into the air, and oxygen in the lungs is absorbed into the blood. The blood then returns directly to the heart and is pumped around the body. One of the main arteries from the heart goes directly to the brain. Consequently, drugs dissolved in the blood in the lungs are delivered very quickly to the brain without having to pass through the liver first, where some metabolism takes place.

The principle that governs the movement of gases from inhaled air into the blood and from the blood into the air within the lungs is diffusion. Gases move from areas of high concentration to areas of low concentration. If the concentration of drug in the inhaled air is higher than that in the blood, the drug will move from the air into the blood, but the reverse is also true; the drug passes out of the blood into the air and is exhaled so that the concentration of the gas in the blood reflects the concentration in the gas that is breathed. Thus, the inhalation of gases provides a means of controlling drug levels in the blood with considerable precision. This ability is one reason gases are used widely as general anesthetics, and inhalation is the favored route of administration for anesthesia. Volatile substances

can also be exhaled from the lungs, although the rate is determined by how rapidly the substance evaporates.

Smoke and Solids

Gases and solvent vapors are not the only substances administered through the lungs. Drugs that occur naturally in some plants may be administered by burning the dried plant material and inhaling the smoke. Tobacco, opium, and marijuana are traditionally ingested in this manner. When the dried plant material is burned, the active ingredient remains either in the smoke as a vapor or in tiny particles of ash that are inhaled into the lungs. When contact is made with the moist surface of the lungs, the drug dissolves and diffuses into the blood. The major difference between smoke and gases is that the drug in the smoke particles will not revaporize after it is dissolved in the blood, and, consequently, it cannot be exhaled. These drugs must stay in the body until they are eliminated by other means.

The problem with administration of solids and smoke by inhalation is the susceptibility to damage of all the tissues in the respiratory system. Smoke from burning marijuana and tobacco contains many substances in addition to the active drug; there are tars, hydrocarbons, and other chemicals created by the burning process. In time, these substances may cause respiratory diseases such as emphysema, asthma, and lung cancer, and they may decrease the ability of the lungs to absorb oxygen and eliminate carbon dioxide from the blood. Other forms of the drug with unknown toxicity may also be created by the burning process. In addition, when most substances burn in air, carbon monoxide gas is given off. Carbon monoxide is a very toxic gas because it blocks the ability of the blood to carry oxygen.

Sometimes, refined drugs like cocaine, heroin, methamphetamine, and oxycodone are administered by heating them till they vaporize and inhaling the vapors. This works the same way as inhaling smoke, but has the advantage that there is no smoke involved and consequently no hydrocarbons or carbon monoxide.

In the experimental laboratory, drugs are seldom administered by inhalation to laboratory animals. This is unfortunate because inhalation is a common method used by humans to administer abused drugs. The major difficulty is that in order to make an animal inhale a gas or smoke, it is usually necessary to confine it in a closed environment filled with gas or smoke, or the experimenter must make it wear some kind of helmet or face mask. The uncertainty about total dose and the technical problems of administration make this a cumbersome and unpopular route of administration in behavioral pharmacology. However, some researchers have had some success in training monkeys to suck smoke or vaporized drugs from a spout inserted into their cage.

Powdered drugs such as cocaine, heroin, and tobacco snuff are sometimes sniffed into the nostrils. This practice is known as *intranasal administration* or *insufflation*. On the street it is called *snorting*. What happens to the drug when given in this manner is unclear. It appears that most of the drug sniffed in the nose is dissolved in the moist mucous membranes of the nasal cavities and is absorbed into the blood from there. Some drug enters the lungs, while more runs down the throat into the stomach and digestive system and may be absorbed there. Although the nasal cavity is not as richly supplied with blood as the lungs and although the area is not designed to transport substances into the blood, it is a reasonably efficient system for getting drugs into the blood.

ORAL ADMINISTRATION

Drugs absorbed into the body through the digestive system are taken into the mouth and swallowed—hence the term *per oral* or *per os* (*p.o.*). Sometimes substances can get into the digestive system by other means. As just explained, snuff from the nostrils can get down the throat and be swallowed.

A drug may be taken into the mouth and not swallowed, as with chewing tobacco. Although this is technically an oral administration, the absorption into the body is through the *buccal membranes*, or mucous membranes of the mouth, not the digestive system.

The digestive system may also be entered via its other end (*intrarectal* administration). Suppositories placed in the rectum also cause the drug to be absorbed into the blood. Such absorption is not as reliable as oral administration, but it can be a useful method of administering a medication when it is impossible to give it orally (e.g., when a patient or animal is unconscious or vomiting).

The Digestive System

After a drug is swallowed, it goes directly to the stomach. The stomach churns and secretes strong acids and digestive enzymes to break down food pieces and turn them into a liquid that is then released slowly into the intestines, where nutrients are absorbed. Drugs that are

soluble in gastric fluids and resistant to destruction by digestive enzymes may be absorbed from the stomach, but absorption is most efficient in the intestines. The rate at which a swallowed drug will be absorbed may be determined by the speed with which it gets through the stomach to the intestines. Because solid food tends to be held in the stomach, taking a drug with a meal generally slows its absorption. When a drug is taken on an empty stomach, it passes quickly into the intestines and is absorbed rapidly.

The walls of the intestines are lined with capillaries to absorb nutrients from food, and these capillaries also absorb drugs. To get to the capillaries and be absorbed into the blood through the pores in the capillary walls, the drug must first pass through the membrane of the intestinal wall, which does not have any pores.

All body tissue is made of cells that form membranes. Figure 1-6 shows the cross section of a typical membrane in the body, made up primarily of what is called a *lipid bilayer*. *Lipid* is another name for fat, and the membrane consists of two layers of fat molecules held tightly together. Each lipid molecule has a clump of atoms at one end (the head region) and two chains of atoms at the other (the tail region). The lipid molecules in a membrane are organized so that, in each of the two layers, the heads point outward, toward the intracellular fluid for one layer and toward the extracellular fluid for the other, and the tails of each layer point inward, toward each other. The heads are *hydrophilic* (water loving) whereas the tails are *hydrophobic* (water repelling), thereby preventing the passage of water-soluble substances through the membrane. Therefore, the extent to which a drug can get through the lining of the intestine to the blood will depend on its ability to dissolve in lipids.

Large molecules of protein are embedded in the lipid bilayer, and they have specific functions that will be described in this chapter and in Chapter 4.

Lipid Solubility

Different drugs have different degrees of lipid solubility that are usually expressed in terms of the *olive oil partition coefficient*. To test lipid solubility, equal amounts of olive oil and water are placed in a beaker, and a fixed amount of drug is mixed in. Later the oil and water are separated, and the amount of drug dissolved in each one is measured. Drugs that are highly lipid soluble are more highly concentrated in the oil. Poorly lipid-soluble drugs mostly end up in the water. This test, although not perfectly accurate, predicts reasonably well the degree to which a drug will dissolve in fat tissue in the body.

All drug molecules vary in their degree of lipid solubility in their normal state, but when a molecule of a drug carries an electric charge, it loses its ability to dissolve in lipids. Such a charged molecule is called an *ion*. Ions are unable to pass through membranes. When a drug is dissolved in a liquid, some or all of its molecules become ionized. The percentage of ionized molecules in a solution is determined by (a) whether the drug is a weak acid or a weak base, (b) whether it is dissolved in

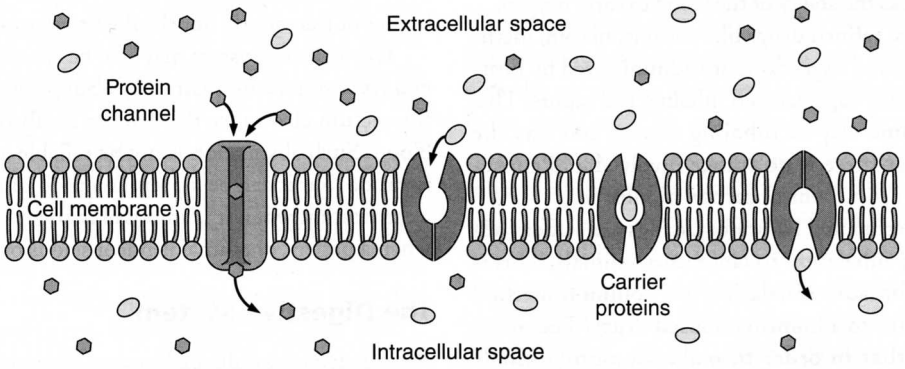

FIGURE 1-6 A cross section of a typical membrane. It is made up of two layers of lipid molecules with their hydrophilic heads pointing out and their lipophilic tails pointing inward. Embedded in this lipid bilayer are large molecules of protein that serve special functions such as protein channels, ion pumps, and transporters.

an acid or a base, and (c) its *pKa*. The pKa of a drug is the *pH* at which half its molecules are ionized.

The easiest way to understand pKa is to imagine the following experiment with a fictional drug called *damital*. A fixed amount of damital is dissolved in each of 15 bottles; each bottle contains a liquid with a different pH, ranging from 0 to 14. A solution's pH is a number that describes the degree to which it is either an acid or a base. On this scale, 7 is completely neutral. Numbers less than 7 indicate increasing acidity, and numbers greater than 7 indicate increasing alkalinity.

After we dissolve the damital in each bottle, we determine the percentage of damital molecules that are ionized and plot the results. As shown in Figure 1-7, the pH at which half the damital molecules are ionized is 5.

Most drugs are either weak acids or weak bases. Damital is a weak acid. If we do this experiment again with a drug that is a weak base, we see something different. One line in Figure 1-7 is a plot for an imaginary base, *endital*. The curve for the acid damital starts with 0% ionization at the acid end of the scale, and ionization increases as it moves toward the base end. Just the opposite is true for endital, the base. It starts with 100% ionization in the acids, but its percentage of ionization decreases as the solution gets more basic. The pKa for endital is calculated in the same way as that for damital. In this case, the pKa for endital is 8. By knowing whether a drug is an acid or a base and by knowing its pKa, it is possible to predict the degree to which it is likely to be ionized in a solution of known pH. The pH at the lining of the intestine is about 3.5. In Figure 1-7, we can see that damital is about 5% ionized at this pH, and endital is completely ionized. Because ionized molecules are not lipid soluble and do not pass through membranes, we can conclude that endital will not be very effective when taken orally, whereas damital will be readily absorbed.

Morphine is a base; its pKa is about 8. Bases are highly ionized in solutions with a low pH (acids), and the curve drops in solutions with higher pHs, so we can predict (correctly) that morphine will be poorly absorbed from the digestive system.

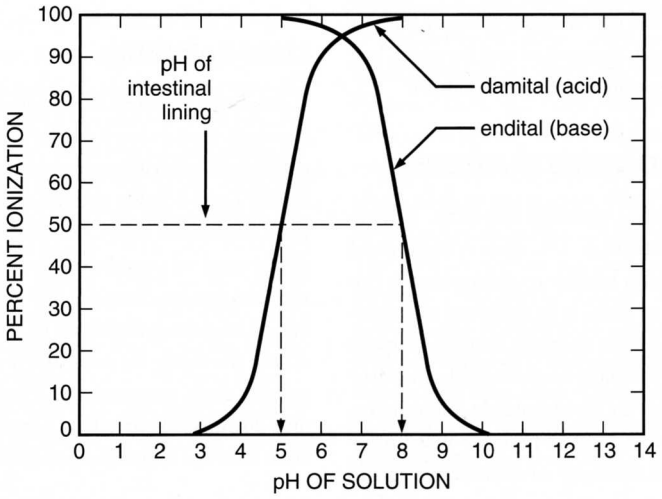

FIGURE 1-7 The percentage of ionized molecules in two fictional drugs dissolved in solutions with different pHs. Damital, a weak acid, becomes more highly ionized as the pH becomes more basic (higher numbers). Endital is a weak base, and it becomes more highly ionized at acid pHs. By drawing a horizontal line at the 50% ionization level, we can determine the pKa of each drug: damital, 5.0, and endital, 8.0. Caffeine is a weak base with a pKa of 0.5. Try to envision what its curve would look like on the graph. There is no significant ionization of caffeine at any of the physiological pHs in the body.

In general, most bases like morphine are poorly absorbed when taken orally, but their absorption depends on their pKa. For example, caffeine is a base, but it has a pKa of 0.5. Its ionization curve drops off quickly at very low pHs; consequently, it is almost entirely nonionized at pHs encountered in the digestive system. Caffeine, therefore, is readily absorbed when taken orally.

It should be pointed out that significant absorption will take place even if only a small percentage of molecules is not ionized. For example, if 97% of a drug is ionized at digestive system pHs, only 3% will be lipid soluble, but as soon as that percentage diffuses through the membrane and is removed by the blood, 3% of the remaining drug loses its charge, so the 97% ionization figure will stay constant for the drug remaining in the digestive system. The newly nonionized 3% now diffuses into the blood, and 3% more can lose its ionization. This process will continue until equilibrium is reached—that is, the concentration of nonionized molecules is the same on either side of the membrane. For this reason, it is not appropriate to think that the percentage of nonionized drug is all that is absorbed. Rather, the percentage of nonionized molecules determines the number of molecules available for absorption at any period of time and, therefore, determines the rate of absorption. If 50% of the molecules are not ionized, absorption will be rapid, but if 3% are not ionized, absorption will be much slower.

TRANSDERMAL ADMINISTRATION

Some drugs can be absorbed through the skin. This is called *transdermal administration*. The skin is composed of several layers, but the main barrier to absorption is the *epidermis*, the outer layer of skin. It is made up of a continuous sheet of flattened cells that are densely packed with *keratin*. This layer is virtually impermeable to water and can be penetrated only by lipid-soluble substances. Even then, absorption is very slow. The layer just under the epidermis, however, is made up of connective tissue and serviced by capillaries; therefore, drugs applied to areas where there is a break in the epidermis (as occurs when there is a cut or a wound) can be absorbed.

Considerable research has been aimed at developing ways to make transdermal administration more effective. Traditionally, a drug has been applied in ointments or salves. In this form, absorption of the drug is determined entirely by the lipid solubility of the drug. In some cases, an absorption enhancer may be added to increase the rate of absorption, or the drug may be fixed in a special substance that releases it slowly for absorption.

The technology of transdermal administration has greatly improved with the development of the patch technology where the drug is separated from the skin by a special membrane that limits the rate of absorption. Using systems such as this, it is possible to administer a drug at a constant rate and maintain a constant blood level for an extended period of time. Nicotine patches were first developed in the 1980s for the treatment of tobacco addiction (see Chapter 8), but now skin patches are used for the controlled delivery of many drugs including opioid analgesics such as fentanyl (see Chapter 11), methylphenidate for treating symptoms of Attention Deficit Hyperactivity Disorder (ADHD; see Chapter 10), and hormones including the contraceptive patch Ortho Evra.

DISTRIBUTION OF DRUGS

Even though most drugs get transported widely around the body by the blood, they tend to become concentrated in particular places and segregated from others. This process is called the *distribution* of a drug.

Lipid Solubility

It has been stressed that lipid-soluble substances can get through membranes easily, but as the olive oil partition coefficient experiment shows, this capacity also means that highly lipid-soluble drugs tend to stay in lipids wherever they encounter them. Consequently, highly lipid-soluble drugs tend to concentrate in body fat outside the central nervous system. Because few drugs have any effect in body fat, all of a drug dissolved in fat is, in effect, inactive. Very often, the body fat acts like a sponge, absorbing a lipid-soluble drug, preventing it from reaching its site of action, and diminishing its effect. Later, the drug is slowly released back into the blood from the fat over a long period of time.

Ion Trapping

The pKa of a drug can also influence where a drug ends up in the body. As pointed out earlier, drugs that are weak bases tend to ionize in acidic solutions, and drugs that are weak acids tend to ionize in basic solutions. Since ionized molecules are not lipid soluble, the pKa of a drug can hasten or retard its absorption and excretion. This process was described earlier in the discussion of

lipid solubility and absorption of basic and acidic drugs from the digestive system.

The same process operates anywhere in the body where body fluids with different pHs are separated by a membrane; drugs can get *trapped* on one side of the membrane. Drugs that are weak bases will be concentrated in the fluid on the side of a membrane that is more basic, and weak bases will be concentrated in the fluids on the more acidic side of a membrane. The imbalance can be quite dramatic because a difference in pH of 1.0 on either side of a membrane can cause a drug to be 10 times more concentrated on one side than the other. The change in concentration is logarithmically related to the concentration difference so that a difference in pH of 2.0 means that there will be a 100-fold difference in concentration, and a difference of 3.0 will create a 1,000-fold difference in concentration.

Distribution to the Central Nervous System

Many years ago, it was discovered that when certain types of dyes were injected into the blood, they would be distributed to all extracellular fluids except those in the brain and the spinal cord. At that time, it was hypothesized that a special barrier between the blood and the brain protected the central nervous system from free diffusion of many materials out of the blood. This became known as the *blood–brain barrier*. It has now been established that the blood–brain barrier is a result of special cells in the central nervous system that wrap themselves around the capillaries and block the pores through which substances normally diffuse. These cells provide a solid lipid barrier so that non-lipid-soluble substances have great difficulty getting into the brain. If not for the blood–brain barrier, the delicate balance of chemicals inside and outside brain cells would be disrupted, even by the food we eat, altering the ability of the cells to communicate one with another.

The blood–brain barrier is incomplete or weak in some areas of the brain and will permit some non-lipid-soluble molecules to enter. For example, the *area postrema* of the *medulla oblongata* (see Chapter 4) contains specialized cells that play an important role in detecting impurities or toxins in the blood and elicits vomiting by stimulating the vomiting center in an attempt to rid the body of these substances. When opioid drugs such as heroin are first used, they activate the vomiting center this way. Also, the *subfornical organ* in the brain plays an important role in detecting hormone levels in the blood, especially those hormones involved in regulating the balance of bodily fluids.

Active and Passive Transport Across Membranes

It is important for the body to get some non-lipid-soluble substances across membranes, so special *transport mechanisms* exist. This process is carried out by large protein molecules that span the cell membrane (visible in Figure 1-6) and may involve either active or passive mechanisms.

In the *passive transport mechanism*, the large protein molecule may create a channel that allows the non-lipid-soluble molecule to pass through in response to diffusion. In another variation it appears that the non-lipid-soluble molecule attaches itself to a *carrier protein* or specialized molecule that permits it to diffuse across the membrane and releases it on the other side. In this way, a substance can move from areas of high to low concentration on either side of a membrane as though it were lipid soluble without the expenditure of energy. The protein molecules illustrated in Figure 1-6 are examples of passive transport mechanisms.

An *active transport mechanism* is similar to a passive mechanism except that it can work against normal diffusion by concentrating a substance on one side of a membrane. This is an active process that requires an expenditure of energy and takes place only in living membranes. Mechanisms such as ion pumps, which maintain electrical potentials of nerve cells, are examples of active transport systems. The sodium–potassium transporter protein, illustrated in Figure 4-2 of Chapter 4, is one example of an active transport system. The blood–brain barrier has a number of such systems, many of which actively remove undesirable substances, like toxic waste products, from the brain and some of which selectively concentrate substances, like glucose (blood sugar) and some amino acids, in the brain.

Protein Binding

The blood contains a number of large protein molecules that cannot diffuse out of the pores in the capillaries because of their size. Some drugs attach, or bind, themselves to these protein molecules so strongly that they remain attached until metabolized. Consequently, they never get to their site of action. Other times, protein-bound drug molecules may act like depot injections,

becoming slowly released as the blood concentration of the drug declines so that they reach their sites of action and are eventually metabolized and excreted.

The Placental Barrier

The blood of the fetus and the blood of the mother are not continuous. Nutrients are transferred to (and waste products are transferred from) the blood of the unborn child through a membrane similar to the blood–brain barrier. This transfer takes place in the *placenta*, the intermediary organ between the fetus and the wall of the uterus. Most behaviorally active drugs can be transferred from the mother's blood through the placenta to the fetus. Highly lipid-soluble substances cross more easily than drugs with low lipid solubility. Drug concentration in the blood of the fetus usually reaches 75% to 100% of that of the mother within 5 minutes of administration. Thus, the fetus appears to have very little protection from any drug the mother takes.

ELIMINATION

Metabolism and Excretion

There are some substances—for example, heavy metals such as lead and mercury—that the body is not very good at getting rid of. Levels of these substances can build up over time and accumulate to high and toxic concentrations. However, the body has fairly efficient systems to rid itself of most unwanted substances, including drugs, which would continue to exert their effects if not metabolized and excreted. It has already been described how gases and volatile solvent vapors can be eliminated in exhaled breath. Small amounts of many drugs are eliminated in sweat, saliva, and feces, but the major job of elimination is done by the liver and the kidneys, the *dynamic duo* of excretion (the location of these organs can be seen in Figure 1-8).

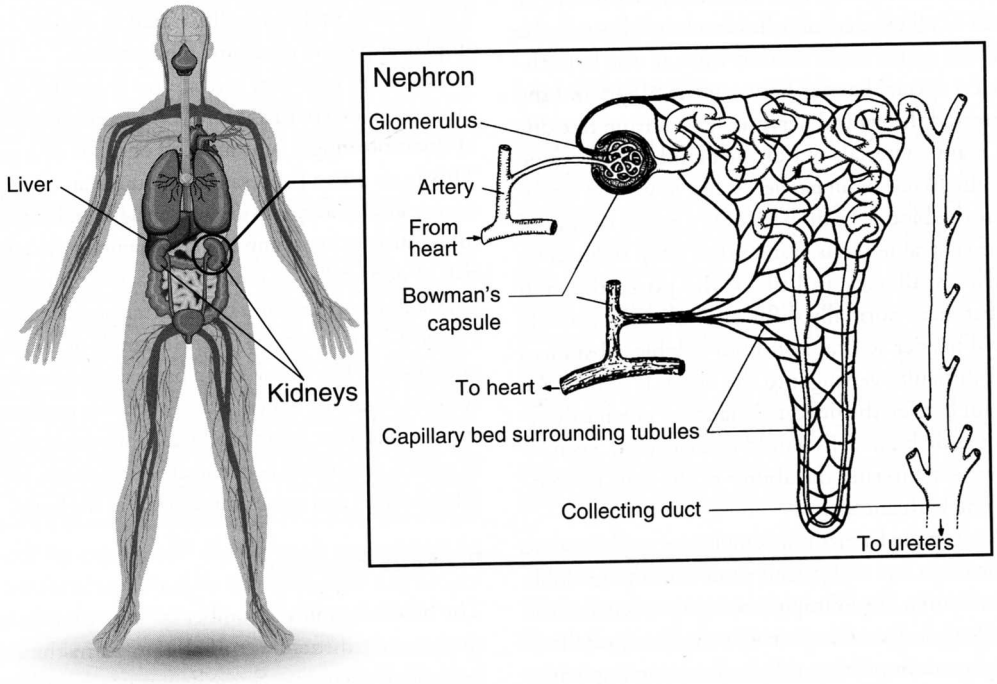

FIGURE 1-8 The location of the liver and kidneys within the body. The close-up is of a nephron, showing the capillaries of the glomerulus that filter fluid out of the blood into the nephron, and the capillary bed that reabsorbs water, nutrients, and lipid-soluble drugs into the blood. All material that is not reabsorbed is excreted in the urine.

The Liver

The *liver* is a large organ located high in the abdomen, under the diaphragm. Its function may best be compared to that of a chemical factory where molecules are modified to form new substances useful to the body, and where toxic molecules are changed into less harmful substances to be filtered out of the blood by the kidneys. These molecular changes are achieved by molecules called *enzymes*. An enzyme is a catalyst, a substance that controls a certain chemical reaction. The enzyme takes part in the reaction, but when the reaction is finished, the enzyme is released unchanged and is free to participate in another reaction in the same way. Without the presence of the enzyme, the reaction would proceed very slowly or would not take place at all. The body controls chemical reactions by controlling the amount of enzyme available to act as a catalyst. Not all enzymes that metabolize drugs are located in the liver. Some may be found in the blood and brain, or as we will see soon, in the digestive system.

An example of an enzyme is *alcohol dehydrogenase*. Someone with a background in chemistry can usually tell from its name what an enzyme does. Most enzymes end in the suffix *-ase*. The enzyme alcohol dehydrogenase removes hydrogen from a molecule of alcohol and makes it into acetaldehyde.

The process of restructuring molecules is referred to as *metabolism*, and the products of metabolism are called *metabolites*. In general, metabolites are either more useful to the body or less toxic than the original substance. Where drugs are concerned, the metabolic process is sometimes called *detoxification*. Although this term is appropriate some of the time, metabolites are not always less active or less toxic than the original drug. Chloral hydrate, psilocybin, and THC, are good examples of substances whose metabolites can be more active than the original drugs from which they are formed. Drugs with active metabolites typically show a prolonged action in the body, but these metabolites are eventually changed into inactive water-soluble substances and excreted from the body by the kidneys.

Another general rule is that metabolites are usually more likely to ionize. This tendency is very important for the functioning of the kidneys because ionized molecules cannot be reabsorbed into the blood through the nephron wall and, consequently, can be excreted more easily. In this way, the liver and kidneys work together to rid the body of unwanted substances (see the next section).

First-Pass Metabolism

Not all metabolism of drugs takes place after absorption and distribution have occurred. Drugs that are absorbed from the digestive system are absorbed into blood that goes to the liver before it returns to the heart. This means that any drug absorbed from the digestive system will pass through the liver before going anywhere else in the body and will be subjected to a certain amount of metabolism by liver enzymes. This is known as *first-pass metabolism*, and it may be responsible for a significant amount of the metabolism of some drugs. Drugs administered by other routes of administration, including drugs absorbed from the nasal cavities and the membranes of the mouth and rectum, are not subjected to first-pass metabolism by the liver and may reach higher levels in the body. For a drug such as alcohol, some metabolism takes place in the stomach and intestines even before it is absorbed. This is also referred to as first-pass metabolism.

The Kidneys

The *kidneys* are two organs, each about the size of a fist, located on either side of the spine. Their primary function is to maintain the correct balance between water and salt in body fluids. Along with the excretion of excess water in the form of urine, the kidneys can also excrete molecules of unwanted substances, the by-products of metabolism by liver enzymes. They function as a complex filtering system that physically removes certain substances from the blood. The close-up portion of Figure 1-8 shows the nephron, the functional unit of the kidney. Each kidney has millions of nephrons, all of which work in more or less the same way.

The *nephron* is essentially a long tube. At one end of the tube is a cuplike structure called *Bowman's capsule*, and inside Bowman's capsule is a clump of capillaries called the *glomerulus*. The other end of the nephron empties into collecting tubes, which, in turn, empty into the urinary bladder. The capillaries in the glomerulus have pores in their membranes, and most of the fluid in the blood that flows through these capillaries

passes into Bowman's capsule and down the nephron. The remaining blood, which contains red and white cells and large protein molecules that are too large to pass out of the pores, continues out of the glomerulus and then moves through another bed of capillaries that surround the nephron along most of its length. At this point, most of the fluid and other substances are absorbed through the nephron wall back into the blood. Whatever is not reabsorbed passes through the length of the nephron and is excreted from the body in the urine.

The kidney works not by filtering impurities out of the blood but by filtering everything out of the blood and then selectively reabsorbing what is required. Reabsorption in the nephron is accomplished by the mechanisms just described: diffusion, lipid solubility, and active and passive transport. All lipid-soluble substances diffuse through the nephron wall into the blood, unless a selective transport mechanism is working against this diffusion. Desirable substances that are not lipid soluble, such as glucose, have a transport mechanism that successfully reclaims them into the blood. Unless they are reabsorbed by special transport systems, ionized or non-lipid-soluble substances will be excreted.

As with the digestive system, pH influences the degree of ionization and, as a consequence, can influence reabsorption. Urine tends to be acidic (pH = 6.0), and blood is basic (pH = 7.5), so, much like in the digestive system, acids tend to pass through and to concentrate on the blood side of the nephron wall, and bases tend to be retained in the urine and are excreted more easily.

Rate of Elimination

In most cases there are more than enough enzymes in the liver to handle a drug so that when the drug arrives in the liver in high concentrations, a lot of the drug will be metabolized at once. At low concentrations, the rate of metabolism will be lower. Thus, as drug levels fall, the rate of metabolism slows. The curve that plots the level of a drug in the blood over time is, therefore, not a straight line but tends to level off to an asymptote. Because of this trailing off, the rate of excretion for most drugs can be described in terms of a *half-life*. This is the time taken for the body to eliminate half of a given blood level of a drug. In the example given in the top (A) panel of Figure 1-9, half of the original blood level is eliminated in 30 minutes. Thirty minutes later, the level has fallen to 25% of the original level, and 30 minutes after that, it is down to 12.5%. Every 30 minutes, the body gets rid of half of the drug circulating in the blood, so the half-life of the drug is 30 minutes. When the elimination of a drug changes with concentration in this manner, it is said to have *first order kinetics*.

The excretion of most drugs can be described in terms of half-life, but there is one important exception: alcohol. The excretion curve for alcohol is a straight line, as shown in the bottom (B) panel of Figure 1-9. It is not appropriate therefore to describe the excretion of alcohol in terms of half-life; an absolute rate of excretion is usually given, that is, about 15 mg of alcohol/100 ml blood/hour. When the rate of elimination of a drug is a straight line, it is said to have *zero order kinetics*.

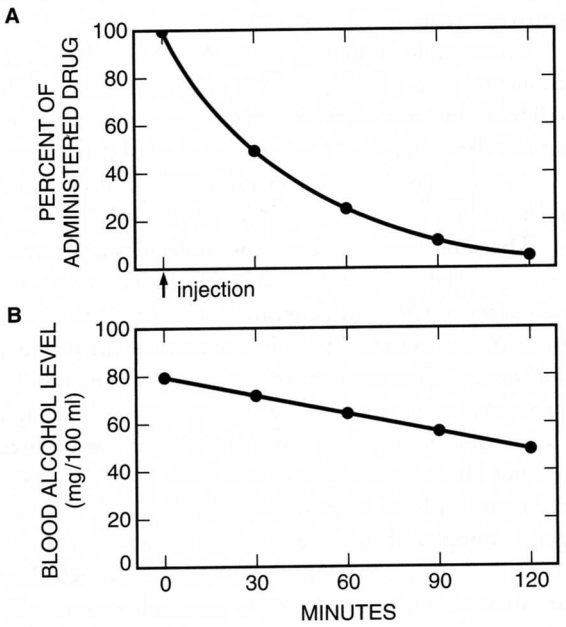

FIGURE 1-9 The top panel (A) shows a typical elimination curve for a drug like nicotine, which has a half-life of about 30 minutes. This is an example of first-order kinetics. The bottom panel (B) shows the elimination function for alcohol, which is metabolized at a constant rate (about 15 mg of alcohol/100 ml of blood/hour). Because the elimination function for alcohol is a straight line, the concept of half-life does not apply. This is an example of zero-order kinetics.

FACTORS THAT ALTER DRUG METABOLISM

A number of factors can influence the rate of metabolism of drugs in the liver and, consequently, the intensity and duration of a drug's effect. A great many individual differences in response to drugs can be explained in terms of variations in drug metabolism and enzyme systems that change according to such factors as age, gender, species, past experience with drugs, and genetics.

Stimulation of Enzyme Systems

To illustrate how enzymes work, we will use the metabolism of alcohol as an example. The steps in alcohol metabolism are shown in Figure 1-10. In the first two steps, alcohol is converted to *acetaldehyde* by the enzyme mentioned earlier: *alcohol dehydrogenase*. Then the acetaldehyde is converted to *acetyl coenzyme A* by another enzyme called *aldehyde dehydrogenase*.

Levels of a given enzyme can be increased by previous exposure to a specific drug that uses that enzyme or some other enzyme system. This process, known as *enzyme induction*, is responsible for the development of metabolic tolerance (discussed in Chapter 3). A good example of such a process is an increase in levels of alcohol dehydrogenase in the livers of heavy drinkers. Those who drink a great deal are able to metabolize alcohol slightly faster than nondrinkers, and this is one reason why they are more resistant to its effects. Box 1-1 gives another example of enzyme induction caused by the herbal antidepressant St. John's wort.

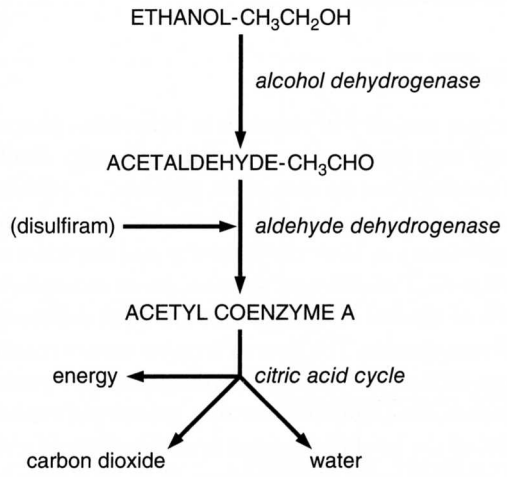

FIGURE 1-10 Steps in the metabolism of alcohol. The enzyme that controls each step is shown to the right of each arrow. Note that disulfiram (Antabuse) blocks the enzyme aldehyde dehygenase. This stops the process at a point that causes a buildup of acetaldehyde.

Depression of Enzyme Systems

When two drugs that use the same enzyme are introduced into the body at the same time, the metabolism of each will be depressed because both will be competing for the enzyme. In other cases, the activity of an enzyme can be blocked by another drug.

Again, we turn to the metabolism of alcohol as an example. Acetaldehyde is converted into acetyl coenzyme A by *aldehyde dehydrogenase*. *Disulfiram* (*Antabuse*) is a drug that blocks aldehyde dehydrogenase. Acetaldehyde levels then increase in the body because the enzyme is not readily available to metabolize it (refer back to Figure 1-10). Acetaldehyde is toxic and causes sickness and discomfort, so people who take disulfiram and then drink alcohol will get sick because of the buildup of high acetaldehyde levels. Disulfiram is sometimes used to discourage alcoholics from drinking; alcoholics will feel well and stay that way if they refrain from ingesting alcohol, but as soon as they take a drink, they will feel ill.

Even foods can alter drug metabolism. It was shown in the late 1990s that there are substances in grapefruit juice that can block *cytochrome P4503A4*, an enzyme located in the intestine. This important enzyme is responsible for the significant first-pass metabolism of many drugs. It has been shown that drinking grapefruit juice can significantly increase blood levels of many drugs. As a result, people should avoid drinking grapefruit juice if they are taking any of a number of drugs. These include the antianxiety drug *buspirone* (*Buspar*), the cholesterol-lowering drugs *lovastatin* (*Mevacor*) and *simvastatin* (*Zocor*), and the erectile dysfunction drug *sildenafil* (*Viagra*).

Age

Enzyme systems are not fully functional at birth and may take time to develop completely. For this reason, immature members of a species may metabolize drugs differently from adults or may not metabolize them at all. For example, the liver of a newborn human first converts theophylline to caffeine and then metabolizes

BOX 1-1 Enzyme Induction Caused by St. John's Wort

St. John's wort is a plant that is widely used as an alternative medicine for treating depression (see Chapter 13). St. John's wort appears to be about as effective as standard antidepressant drugs. It is one of the top 10 natural products sold in the United States, used by about 12% of the population. Many believe that it has fewer unwanted sleep, sexual, and cognitive side effects compared to pharmaceutical antidepressant drugs, but it turns out that St. John's wort has some potentially serious side effects that may not be readily apparent. It can reduce the effectiveness of many other drugs because it induces production of the enzyme that destroys them.

St. John's wort has many potentially active ingredients, including *hyperfortin*, which is a potent activator of something called *PXR* (*pregnane X receptor*). PXR is a protein that can be activated by a variety of chemicals and toxins, including hyperfortin. Its activation is the first step in an elaborate defense mechanism against being poisoned by an array of chemicals and toxins. PXR is a transcription factor that stimulates genes to produce a large number of enzymes responsible for the destruction of many drugs and toxins. One such enzyme stimulated by PXR is *cytochrome P4503A4*, which alone metabolizes about 60% of all clinically relevant drugs.

By taking St. John's wort in the recommended doses, you can stimulate the enzymes that destroy many important drugs that you may be taking concurrently. One such drug is the immunosuppressant *cyclosporine*, which is taken widely by organ transplant patients to prevent tissue rejection. Other drugs include *atorvastatin*, a cholesterol-lowering drug; *indinavir*, a drug used in the treatment of HIV; *amitriptyline*, an antidepressant; *theophylline*, a respiratory stimulant; and the tranquilizer *alprazolam*. St. John's wort can also increase the likelihood of unplanned pregnancy by reducing the effectiveness of oral contraceptives.

Thus, while it may appear that St. John's wort is an effective antidepressant with few side effects, the picture may not be that simple. This is an example of how use of a "natural" medicine can have significant unforeseen health consequences (Choudhri and Valerio (2005).

caffeine very slowly. In adults, theophylline is metabolized directly without this intermediate stage. Theophylline is similar to caffeine and is found in tea but is sometimes given to newborn babies to stimulate breathing. In infants, the effects of theophylline are greatly enhanced because of the intermediate stage of metabolism involving caffeine. For this reason, doses must be small and closely monitored to avoid overdose. A similar problem is encountered when drugs are given to a woman immediately before she gives birth. Drugs given at this time cross the placental barrier and circulate in the blood of the fetus. As long as the child's circulatory system is connected to the mother, the mother's liver can handle the drug, but if the baby is born and the umbilical cord is cut before all the drug is metabolized, the drug remains in the infant's body and is dependent solely on the baby's immature liver for metabolism, a process that may take many days.

There can also be impairments in metabolism at the other end of the life span. Liver functioning is less efficient in elderly people, so physicians prescribing for elderly patients often reduce drug doses accordingly.

Species

The vast majority of research in behavioral pharmacology uses species other than human beings. Studies are usually done on rats, mice, pigeons, or primates. It is important to understand how differences in drug metabolism can alter the intensity and duration of a similar dose in different species. As an example, the levels of alcohol dehydrogenase are quite different in different species. The liver of a rat or mouse contains about 60% of the alcohol dehydrogenase per gram in a human liver, but the liver of a guinea pig contains 160% of the level in a human liver. The liver of a rhesus monkey has a concentration of alcohol dehydrogenase similar to that of a human liver. As you can see, the same experiment, if performed on a guinea pig, a rat, or a human, might reach quite different conclusions.

COMBINING ABSORPTION AND EXCRETION FUNCTIONS

The effects of a drug change over time during a single administration. This change reflects increasing and decreasing drug levels after administration. When these varying effects are plotted on a graph, the result is usually called a *time course* (the drug effect is usually represented on the vertical axis, and time is on the horizontal axis). Figure 1-11 is a time course for the concentration of a drug in the blood after administration. Note that there are three curves. One shows the time course of absorption of a drug from the site of administration. This curve is hypothetical because it assumes that while the drug is being absorbed, the liver and kidneys are not working and no excretion is going on. The second curve is a hypothetical elimination curve; it shows the rate of elimination of a drug, but assumes instantaneous absorption. In reality, neither of these curves could exist. What is usually seen is a combination of the first two curves, shown here as a third curve that has both an ascending phase corresponding to the time when absorption is more rapid than elimination and a descending phase when elimination is more rapid than absorption.

The rate of excretion of any drug (i.e., its half-life) remains constant, but the absorption rate of any given drug can change, depending on the route of administration. Thus, the shape of this curve will vary depending on route of administration.

Figure 1-12 shows typical curves for various routes of administration. When drugs are given intravenously, the absorption phase is very steep; the drug achieves high levels and is metabolized and excreted quickly. When drugs are given orally, the absorption is slow, and blood levels do not reach the same high concentrations seen after i.v. administration, but the drug lasts much longer in the body. Intramuscular and subcutaneous routes are intermediate between i.v. and oral routes. The route of administration can determine whether a drug reaches high levels for a short period or lasts a long time at low levels. If the function of a drug depends on maintaining constant blood levels, as with antibiotics, oral administration is preferred. If it is necessary to achieve very high levels for brief periods, the drug is best given intravenously.

THE THERAPEUTIC WINDOW

When drugs are administered for therapeutic purposes, it is often important that the right level of the drug be maintained in the blood for an extended period of time. If the drug reaches too high a level, there will be an increase in unwanted side effects and no increase in the therapeutic effect. If the drug falls below a certain level, it will not have a therapeutic effect at all. This range, called the *therapeutic window*, is illustrated in Figure 1-13.

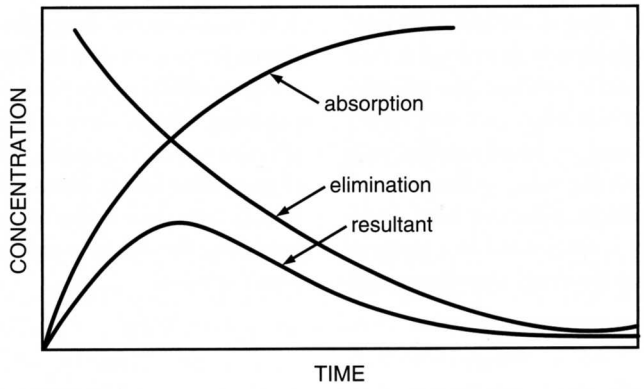

FIGURE 1-11 Shown is a theoretical absorption curve, assuming no elimination; a theoretical elimination curve, assuming instantaneous absorption and distribution; and a third line showing the resultant of these two theoretical processes. The resultant curve is typical of the time course for blood level of most drugs.

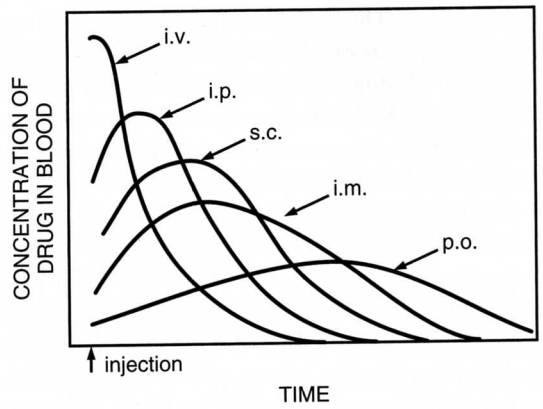

FIGURE 1-12 The time courses for blood levels of a drug typically seen after different routes of administration. After i.v administration, absorption is very rapid with a high peak and the drug leaves the body relatively quickly. When the drug is given orally, absorption is slow; the peak level is relatively low; and the drug stays in the body a longer time. The other routes have the same shape curve between these two. The faster the absorption, the higher the peak and the shorter the duration of action.

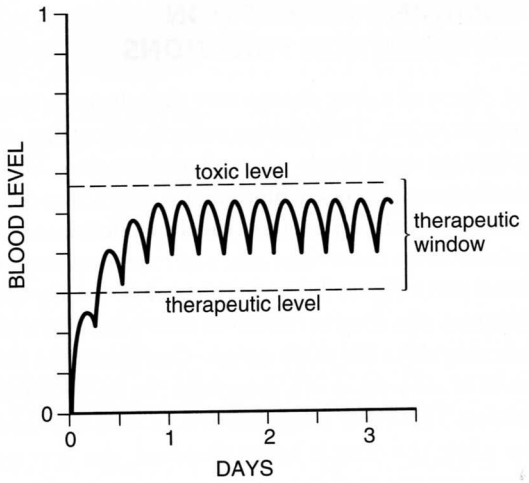

FIGURE 1-13 The therapeutic window is the range of blood concentrations of a medicine between a level that is ineffective (therapeutic level) and a level that has toxic side effects (toxic level). When drugs are taken chronically, it is important that the drug be given in the right dose and at the right frequency so that blood levels remain within the therapeutic window.

To keep its concentration within this range, a drug must be taken at the correct dose at regular intervals.

For drugs that are absorbed and excreted slowly, it is usually not difficult to achieve a dosing regimen that keeps the blood level within this window, but the task is more complicated for drugs that are absorbed and excreted rapidly. One such drug is *lithium carbonate*, which is given to people with bipolar disorder. Lithium has a rather narrow therapeutic window (the effective dose and a dose that causes side effects are very close). Lithium is also absorbed and excreted rapidly, so it must be given in small doses (as many as four times a day). To help solve this problem, pills have been developed in which the lithium is embedded in a material that dissolves slowly to delay the drug's absorption and, hence, its peak blood level. Using this type of medication makes it easier to keep the blood level within the therapeutic window and reduce the number of doses to two a day.

With repeated use, individuals may build tolerance to some drugs (this will be discussed further in Chapter 3). Tolerance for some drug effects may build more quickly than tolerance for others. For example, tolerance to the analgesic effects of opioids like morphine builds rapidly, requiring a larger dose of the drug in order for it to be effective in relieving pain. Tolerance to the toxic effects of morphine builds more slowly, moving the curve for the effective dose closer to the curve for the toxic dose, increasing the risk of overdose and narrowing the therapeutic window.