Brenner and Stevens'

PHARMACOLOGY

FIFTH EDITION

George M. Brenner
Craig W. Stevens

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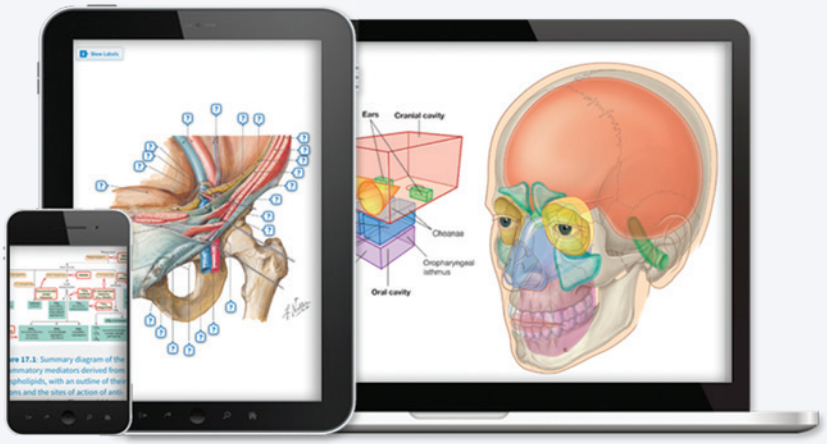

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Preface

Medical pharmacology is primarily concerned with the mechanisms by which drugs treat disease processes, relieve symptoms, and counteract the molecular manifestations of disease. Pharmacology is also concerned with the factors that determine the time course of drug action, including drug absorption, distribution, metabolism, and excretion. Students are often overwhelmed by the vast amount of pharmacological information available today. This textbook provides the essential concepts and information that students need to be successful in their courses without an overwhelming amount of detail.

This text is primarily intended for students who are taking their first course in pharmacology, but it will also be useful for those who are preparing to take medical board or licensing examinations. Because of the large number of drugs available today, this text emphasizes the general properties of drug categories and prototypical drugs. Chapters begin with a drug classification box to familiarize students with drug categories, subcategories, and specific drugs to be discussed in the chapter.

In the four years since the publication of the previous edition of *Pharmacology* by Brenner and Stevens, major trends in the development and marketing of new medications and new formulations were apparent. First, there was an explosion of combination drugs released onto the market in recent years. This is a good thing, as there is often pharmacological synergy between combined agents, but also because patient compliance is improved. It is easier to take one pill than two, or three, or four. The usual product combines two successful and effective single agents for the treatment of a disorder. These newly approved combination drugs are included in this 5th edition of Brenner & Stevens' *Pharmacology*.

Second, the market is flush with a number of new immunopharmacology products. Immunopharmacology is now a well-ripened field and the fruits of this discipline are apparent to both the physician and consumer by the new immunopharmacology drugs touted in TV commercials. Pharmaceutical manufacturing of monoclonal antibodies that target receptors or other proteins is a rapidly growing sector of biologics. Many therapeutic classes of pharmacological agents now have one or two drugs that work via antibodies or that target immune system factors. This edition contains a number of such new immunopharmacology drugs. However, the FDA approval of monoclonal antibody drugs and other biologics often comes with a number of serious warnings and adverse outcomes.

Third, during the last four years, the rampant use of prescription opioids and the resultant opioid overdose epidemic were fully recognized. The appropriate response from the pharmaceutical manufacturers was to develop new agents and formulations for the treatment of opioid dependence. The expanded class of these opioid medications is fully described in Chapter 23, "Opioid Analgesic and Antagonists."

Fourth, the epidemic of type 2 diabetes across the USA, and the tremendous market for product, brought drug developers back into the lab to work on antidiabetes medications. There were eight FDA-approved antidiabetes medications released into the market in the last two years. Many of these new medications target recently discovered mechanisms of action, like blocking sugar uptake at the kidneys. These new drugs and mechanisms of action for treating diabetes are updated in Chapter 35, "Drugs for Diabetes."

The book now in your hands was extensively revised for the 5th edition to include all the new drugs on the market, and to exclude older drugs that were withdrawn from the market since the last edition of this textbook. The figures that were retained were updated and new figures added, with an emphasis on illustrating drug mechanisms of action. A modern graphic style was developed for the figures to improve understanding and to entice the eye.

The reader of this book will know some drugs better by their trade names. With the incessant marketing of new pharmaceuticals, many trade names of new drugs become common. As all medications are indexed under both their generic and brand name, this book is also a valuable reference for a quick review of drugs encountered in the reader's personal or professional life.

We thank our spouses and offspring for their encouragement and patience while we worked on this book. Much appreciation goes to our "significant others" ($P < 0.05$) who both assisted with discussions of new drugs in their areas of expertise. However, any errors or typos are solely the responsibility of the authors. We also appreciate the fine people at Elsevier, who bring it all together to produce the nicely designed textbook now in your hands. The interactions with Lauren Willis (no relation to Bruce) and Rebecca Gruliow were especially professional and pleasant. They both seem to really know what they are doing.

Finally, we are pharmacologists who spent most of our careers at a university medical school. We are not physicians or medical consultants. Therefore none of the following text should be taken as medical advice.

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PRINCIPLES OF PHARMACOLOGY

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CHAPTER 1

Introduction to Pharmacology

PHARMACOLOGY AND RELATED SCIENCES

Pharmacology is the **study of drugs and their effects** on life processes. It is a fundamental science that sprang to the forefront of modern medicine with demonstrated success in treating disease and saving lives. Pharmacology is also a science that drives the international pharmaceutical industry to billion-dollar sales. This chapter reviews the history and subdivisions of pharmacology and discusses, in detail, the types of drugs, formulations, and routes of administration.

History and Definition of Pharmacology

Since the beginning of the species, people have treated pain and disease with substances derived from plants, animals, and minerals. However, the **science of pharmacology** is less than 150 years old, ushered in by the ability to isolate pure compounds and the establishment of the scientific method.

In the earliest phases of drug use, noxious plant and animal preparations were administered to a sick person to rid the body of the evil spirits believed to cause illness. The Greek word ***pharmakon,*** from which the term *pharmacology* is derived, originally meant a magic charm for treating disease. Later, *pharmakon* came to mean a remedy or drug.

In the second phase of drug use, generations of folk knowledge enabled people to correlate natural substances with treatment of particular diseases or symptoms. The **first effective drugs** were probably simple external preparations, such as cool mud or a soothing leaf. The earliest known prescriptions, dating from 2100 BCE, included salves containing the spice thyme. Over many centuries, people learned the **therapeutic value of natural products** through trial and error. By 1500 BCE, Egyptian prescriptions called for **castor oil, opium,** and other drugs still used today. In China, ancient scrolls from that time listed prescriptions for **herbal medicines** for more than 50 diseases. Dioscorides, a Greek army surgeon who lived in the 1st century, described more than 600 medicinal plants that he collected and studied as he traveled with the Roman army. Susruta, a Hindu physician, described the principles of Ayurvedic medicine in the 5th century. During the Middle Ages, Islamic physicians (most famously Avicenna) and Christian monks cultivated and studied the use of herbal medicines.

The present phase of drug use gradually evolved with important advances in chemistry and physiology that gave rise to the new science of pharmacology. At the same time, a more rational understanding of disease mechanisms provided a scientific basis for using drugs whose physiologic actions and effects were understood.

The advent of pharmacology was particularly dependent on the isolation of pure drug compounds from natural sources and on the development of experimental physiology methods to study these compounds. The **isolation of morphine** from opium in 1804 was rapidly followed by the extraction of many other drugs from plant sources, providing a diverse array of pure drugs for **pharmacologic experimentation.** Advances in physiology allowed pioneers, such as François Magendie and Claude Bernard, to conduct some of the earliest pharmacologic investigations, including studies that localized the site of action of curare to the neuromuscular junction. The first medical school pharmacology laboratory was started by Rudolf Buchheim in Estonia. Buchheim and one of his students, Oswald Schmiedeberg, trained many other pharmacologists, including John Jacob Abel, who established the first pharmacology department at the University of Michigan in 1891 and is considered the father of American pharmacology.

The goal of pharmacology is to **understand the mechanisms by which drugs interact** with biologic systems to enable the rational use of effective agents in the diagnosis and treatment of disease. The success of pharmacology in this task has led to an explosion of new drug development, particularly in the past 50 years. Twentieth-century developments include the isolation and use of insulin for diabetes, the discovery of antimicrobial and antineoplastic drugs, and the advent of modern psychopharmacology. Recent advances in molecular biology, genetics, and drug design suggest that new drug development and pharmacologic innovations will provide even greater advances in the treatment of medical disorders in this century.

The history of many significant events in pharmacology, as highlighted by selected Nobel Prize recipients, is presented in Table 1.1.

Pharmacology and Its Subdivisions

Pharmacology is the biomedical science concerned with the interaction of chemical substances with living cells, tissues, and organisms. It is particularly concerned with the mechanisms by which drugs counteract the manifestations of disease and affect fertility. Pharmacology is not primarily focused on the methods of synthesis, isolation of drugs, or with the preparation of pharmaceutical products. The disciplines that deal with these subjects are described later.

Pharmacology is divided into two main subdivisions, **pharmacokinetics** and **pharmacodynamics.** The relationship between these subdivisions is shown in Fig. 1.1. Pharmacokinetics is concerned with the processes that determine the concentration of drugs in body fluids and tissues over time, including drug **absorption, distribution, metabolism,** and **excretion (ADME).** Pharmacodynamics is the study of the actions of drugs on target receptors and tissues. A shorthand way of thinking about it is that pharmacodynamics is what the drug does to the body, and pharmacokinetics is what the body does to the drug. Modern pharmacology is focused on the biochemical and molecular mechanisms by which drugs produce their physiologic effects and with

TABLE 1.1 The Nobel Prize and the History of Pharmacology*

PERSON(S) AND YEAR AWARDED	SIGNIFICANT DISCOVERY IN PHARMACOLOGY
Ilya Metchnikoff, Paul Ehrlich (1908)	First antimicrobial drugs *(magic bullet)*
Frederick Banting, John Macleod (1923)	Isolation and discovery of insulin and its application in the treatment of diabetes
Sir Henry Dale, Otto Loewi (1936)	Chemical transmission of nerve impulses
Sir Alexander Fleming, Ernst Chain, Sir Howard Florey (1945)	Discovery of penicillin and its curative effect in various infectious diseases
Daniel Bovet (1957)	Antagonists that block biologically active amines, including the first antihistamine
Sir Bernard Katz, Ulf von Euler, Julius Axelrod (1970)	Transmitters in the nerve terminals and the mechanism for storage, release, and inactivation
Sune Bergström, Bengt Samuelsson, John Vane (1982)	Discovery of prostaglandins and the mechanism of action of aspirin that inhibits prostaglandin synthesis
Sir James Black, Gertrude Elion, George Hitchings (1988)	Development of the first β-blocker, propranolol, and anticancer agents that block nucleic acid synthesis
Alfred Gilman, Martin Rodbell (1994)	Discovery of G proteins and the role of these proteins in signal transduction in cells
Robert Furchgott, Louis Ignarro, Ferid Murad (1998)	Recognition of nitric oxide as a signaling molecule in the cardiovascular system
Arvid Carlsson, Paul Greengard, Eric Kandel (2000)	Role of dopamine in schizophrenia and signal transduction in the nervous system leading to long-term potentiation
Robert J. Lefkowitz and Brian K. Kobilka (2012)	The structural basis of G protein-coupled receptor signaling

*Selected from the list of recipients of the Nobel Prize for Physiology or Medicine, or the Nobel Prize for Chemistry; note that many other discoveries pertinent to pharmacology have been made by other Nobel Prize winners and that the original discovery was often made many years before the Nobel Prize was awarded.

the **dose-response relationship,** defined as the relationship between the concentration of a drug in a tissue and the magnitude of the tissue's response to that drug. Most drugs produce their effects by binding to protein **receptors** in target tissues, a process that activates a cascade of events known as **signal transduction.** Pharmacokinetics and pharmacodynamics are discussed in greater detail in Chapters 2 and 3, respectively.

Toxicology

Toxicology is the study of **poisons** and **organ toxicity.** It focuses on the **harmful effects of drugs** and other chemicals and on the mechanisms by which these agents produce pathologic changes, disease, and death. As with pharmacology, toxicology is concerned with the relationship between the dose of an agent and the resulting tissue concentration and biologic effects that the agent produces. Most drugs have **toxic effects** at high enough doses and may have **adverse effects** related to toxicity at therapeutic doses.

Pharmacotherapeutics

Pharmacotherapeutics is the medical science concerned with the **use of drugs in the treatment of disease.** Pharmacology provides a rational basis for pharmacotherapeutics by explaining the mechanisms and effects of drugs on the body and the relationship between dose and drug response. A cadre of research pharmacologists around the world does much preclinical research before drug candidates emerge. Human studies known as **clinical trials** are then used to determine the efficacy and safety of drug therapy in human subjects. The purpose, design, and evaluation of human drug studies are discussed in Chapter 4.

Pharmacy and Related Sciences

Pharmacy is the science and profession concerned with the **preparation, storage, dispensing,** and **proper use** of drug products. Related sciences include pharmacognosy, medicinal chemistry, and pharmaceutical chemistry. **Pharmacognosy** is the study of drugs isolated from natural sources, including plants, microbes, animal tissues, and minerals. **Medicinal chemistry** is a branch of organic chemistry that specializes in the design and chemical synthesis of drugs used in medicine. **Pharmaceutical chemistry,** or **pharmaceutics,** is concerned with the formulation and chemical properties of pharmaceutical products, such as tablets, liquid solutions and suspensions, and aerosols.

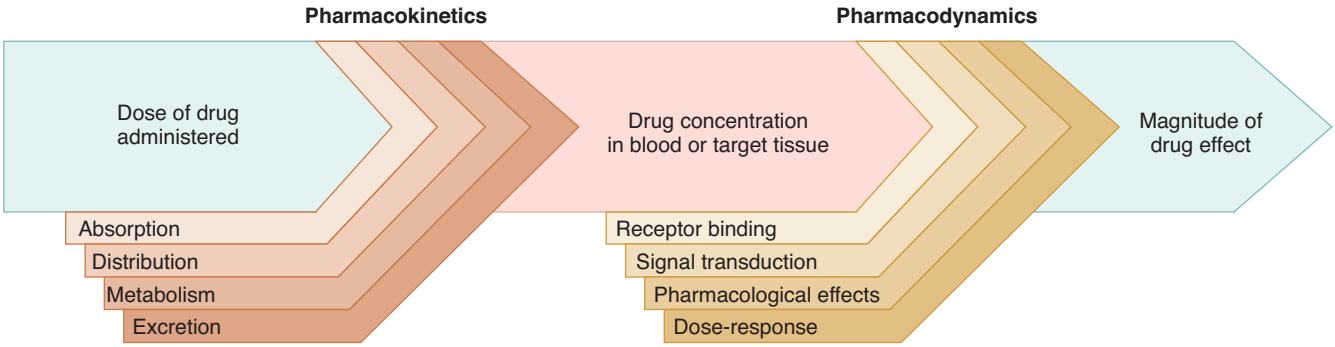

FIGURE 1.1. Relationship between pharmacokinetics and pharmacodynamics.

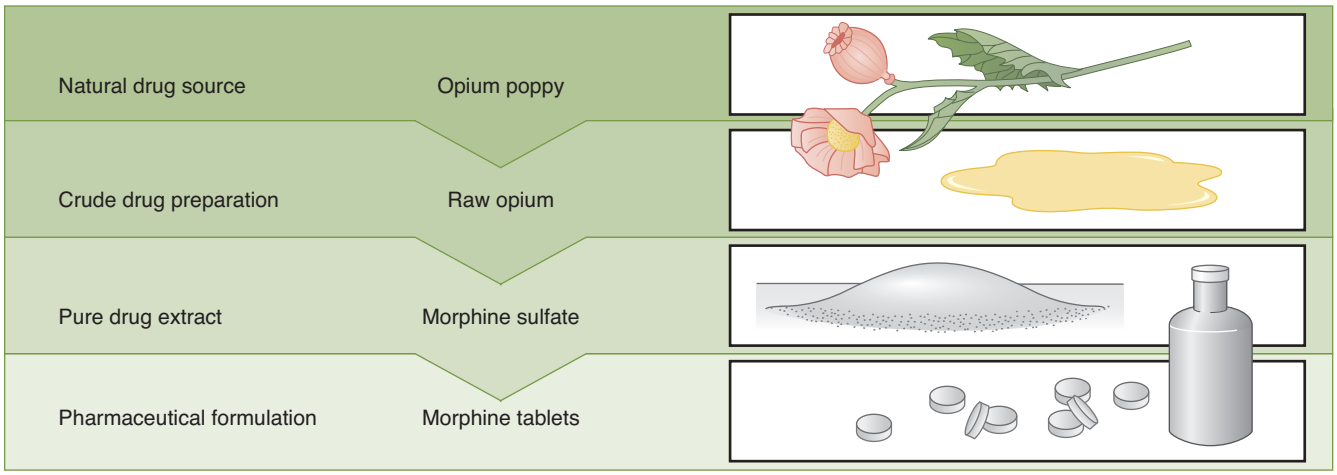

FIGURE 1.2. Types of drug preparations. A crude drug preparation retains most or all of the active and inactive compounds contained in the natural source from which it was derived. After a pure drug compound (e.g., morphine) is extracted from a crude drug preparation (in this case, opium), it is possible to manufacture pharmaceutical preparations that are suitable for administration of a particular dose to the patient.

DRUG SOURCES AND PREPARATIONS

A **drug** can be defined as a natural product, chemical substance, or pharmaceutical preparation intended for administration to a human or animal to diagnose or treat a disease. A drug can also be a *biologic*, for example, a preparation of monoclonal antibodies. The word *drug* is derived from the French *drogue*, which originally meant dried herbs and was applied to herbs in the marketplace used for cooking rather than for any medicinal reason. Ironically, the medical use of the drug **marijuana,** a dried herb, is hotly debated in many societies today. Drugs may be **hormones, neurotransmitters,** or **peptides** produced by the body; conversely, a **xenobiotic** is a drug produced outside the body, either synthetic or natural. A **poison** is a drug that can kill, whereas a **toxin** is a drug that can kill and is produced by a living organism. The terms **medication** and, used less frequently, **medicament** are synonymous with the word *drug*.

Natural Sources of Drugs

Drugs have been obtained from plants, microbes, animal tissues, and minerals. Among the various types of drugs derived from plants are **alkaloids,** which are substances that contain nitrogen groups and produce an alkaline reaction in aqueous solution. Examples of alkaloids include morphine, cocaine, atropine, and quinine. **Antibiotics** have been isolated from numerous microorganisms, including *Penicillium* and *Streptomyces* species. **Hormones** are the most common type of drug obtained from animals, whereas **minerals** have yielded a few useful therapeutic agents, including the lithium compounds used to treat bipolar mental illness.

Synthetic Drugs

Modern chemistry in the 19th century enabled scientists to synthesize new compounds and to modify naturally occurring drugs. Aspirin, barbiturates, and local anesthetics (e.g., **procaine**) were among the first drugs to be synthesized in the laboratory. Semisynthetic derivatives of naturally occurring compounds have led to new drugs with different properties, such as the morphine derivative **oxycodone.**

In some cases, new drug uses were discovered by accident when drugs were used for another purpose, or by actively screening a huge number of related molecules for a specific pharmacologic activity. Medicinal chemists now use molecular modeling software to discern the **structure-activity relationship,** which is the relationship among the drug molecule, its target receptor, and the resulting pharmacologic activity. In this way a virtual model for the receptor of a particular drug is created, and drug molecules that best fit the three-dimensional conformation of the receptor are synthesized. This approach has been used, for example, to design agents that inhibit angiotensin synthesis, treat hypertension, and inhibit the maturation of the human immunodeficiency virus (HIV).

Drug Preparations

Drug preparations include **crude drug** preparations obtained from natural sources, **pure drug** compounds isolated from natural sources or synthesized in the laboratory, and **pharmaceutical preparations** of drugs intended for administration to patients. The relationship among these types of drug preparations is illustrated in Fig. 1.2.

Natural Sources of Drugs

The natural source of drugs is often a plant well-known for its medicinal use and taken as is. Nicotine and marijuana plants are usually administered as drugs in their raw form as dried leaves. Other natural sources of drugs include *Amanita* mushrooms, which yield the plant alkaloid muscarine, and peyote cacti with the active ingredient of mescaline.

Crude Drug Preparations

Some **crude drug preparations** are made by drying or pulverizing a plant or animal tissue. Others are made by extracting substances from a natural product with the aid of hot water or a solvent such as alcohol. Familiar examples of crude drug preparations are **coffee** and **tea,** made from distillates of the beans and leaves of *Coffea arabica* and *Camellia sinensis* plants, and **opium,** which is the dried juice of the unripe poppy capsule of the plant *Papaver somniferum*.

Pure Drug Compounds

It is difficult to identify and quantify the pharmacologic effects of crude drug preparations because these products

contain multiple ingredients with varying amounts from batch to batch. Therefore, the development of methods to isolate **pure drug compounds from natural sources** was an important step in the growth of pharmacology and rational therapeutics. Frederick Sertürner, a German pharmacist, isolated the first pure drug from a natural source in 1804. He extracted and tested a potent **analgesic** agent from opium and named it **morphine,** from Morpheus, the Greek god of dreams. The subsequent isolation of many other drugs from natural sources provided pharmacologists with a number of pure compounds for study and characterization. One of the greatest medical achievements of the early 20th century was the isolation of insulin from the pancreas. This achievement led to the development of **insulin** preparations for treating **diabetes mellitus.**

Pharmaceutical Preparations

Pharmaceutical preparations or dosage forms are drug products suitable for administration of a specific dose of a drug to a patient by a **particular route of administration.** Most of these preparations are made from pure drug compounds, but a few are made from crude drug preparations and sold as herbal remedies. By far, the most common formulation of drugs is for the **oral route** of administration, followed by formulations used for **injections.**

Tablets and Capsules. Tablets and capsules are the most common preparations for oral administration because they are suitable for mass production, are stable and convenient to use, and can be formulated to release the drug immediately after ingestion or to release it over a period of hours.

In the manufacture of tablets, a machine with a punch and die mechanism compresses a mixture of powdered drug and inert ingredients into a hard pill. The **inert ingredients** include specific components that provide bulk, prevent sticking to the punch and die during manufacture, maintain tablet stability in the bottle, and facilitate solubilization of the tablet when it reaches gastrointestinal fluids. These ingredients are called **fillers, lubricants, adhesives,** and **disintegrants,** respectively.

A tablet must disintegrate after it has been ingested, and then the drug must **dissolve in gastrointestinal fluids** before it can be absorbed into the circulation. Variations in the rate and extent of tablet disintegration and drug dissolution can give rise to differences in *bioavailability* of drugs from different tablet formulations (see Chapter 2).

Tablets may have various types of coatings. **Enteric coatings** consist of polymers that will not disintegrate in gastric acid but will break down in the more basic pH of the intestines. Enteric coatings are used to protect drugs that would otherwise be destroyed by gastric acid and to slow the release and absorption of a drug when a large dose is given at one time, for example, in the formulation of the antidepressant **fluoxetine,** called Prozac Weekly.

Sustained-release products, or **extended-release products,** release the drug from the preparation over many hours. The two methods used to extend the release of a drug are **controlled diffusion** and **controlled dissolution.** With controlled diffusion, a rate-controlling membrane regulates release of the drug from the pharmaceutical product. Inert polymers gradually break down in body fluids creating a controlled dissolution. These polymers may be part of the tablet matrix, or they may be used as coatings over small pellets of drug enclosed in a capsule. In either case, the drug is gradually released into the gastrointestinal tract as the polymers dissolve.

Some products use **osmotic pressure** to provide a sustained release of a drug. These products contain an osmotic agent that attracts gastrointestinal fluid at a constant rate. The attracted fluid then forces the drug out of the tablet through a small laser-drilled hole (Fig. 1.3A).

Capsules are hard or soft gelatin shells enclosing a powdered or liquid medication. **Hard capsules** are used to enclose powdered drugs, whereas **soft capsules** enclose a drug in solution. The gelatin shell quickly dissolves in gastrointestinal fluids to release the drug for absorption into the circulation.

Solutions and Suspensions. Drug solutions and particle suspensions, the most common liquid pharmaceutical preparations, can be formulated for oral, parenteral, or other routes of administration. Solutions and suspensions provide a convenient method for administering drugs to pediatric and other patients who cannot easily swallow pills or tablets. They are less convenient than solid dosage forms, however, because the liquid must be measured each time a dose is given.

Solutions and suspensions for oral administration are often sweetened and flavored to increase palatability. Sweetened aqueous solutions are called **syrups,** whereas sweetened aqueous-alcoholic solutions are known as **elixirs.** Alcohol is included in elixirs as a solvent for drugs that are not sufficiently soluble in water alone.

Sterile solutions and suspensions are available for **parenteral** administration with a needle and syringe, or with an intravenous infusion pump. Many drugs are formulated as sterile powders for reconstitution with sterile liquids at the time the drug is to be injected, because the drug is not stable for long periods of time in solution. Sterile ophthalmic solutions and suspensions are suitable for administration with an eyedropper into the conjunctival sac.

Skin Patches. Transdermal skin patches are drug preparations in which the drug is slowly released from the patch for absorption through the skin into the circulation. Most skin patches use a **rate-controlling membrane** to regulate the diffusion of the drug from the patch (Fig. 1.3B). Such devices are most suitable for potent drugs, which are therefore effective at relatively low doses and that have **sufficient lipid solubility** to enable skin penetration.

Aerosols. Aerosols are a type of drug preparation administered by inhalation through the **nose or mouth.** They are particularly useful for treating respiratory disorders because they deliver the drug directly to the site of action and may thereby minimize the risk of systemic side effects. Some aerosol devices contain the drug dispersed in a pressurized gas and are designed to deliver a precise dose each time they are activated by the patient. **Nasal sprays,** another type of aerosol preparation, can be used either to deliver drugs that have a localized effect on the nasal mucosa or to deliver drugs that are absorbed through the mucosa and exert an effect on another organ. For example, **butorphanol,** an opioid analgesic, is available as a nasal spray (Stadol NS) for the treatment of pain.

Ointments, Creams, Lotions, and Suppositories. Ointments and creams are semisolid preparations intended for **topical application** of a drug to the skin or mucous membranes. These products contain an active drug incorporated into a

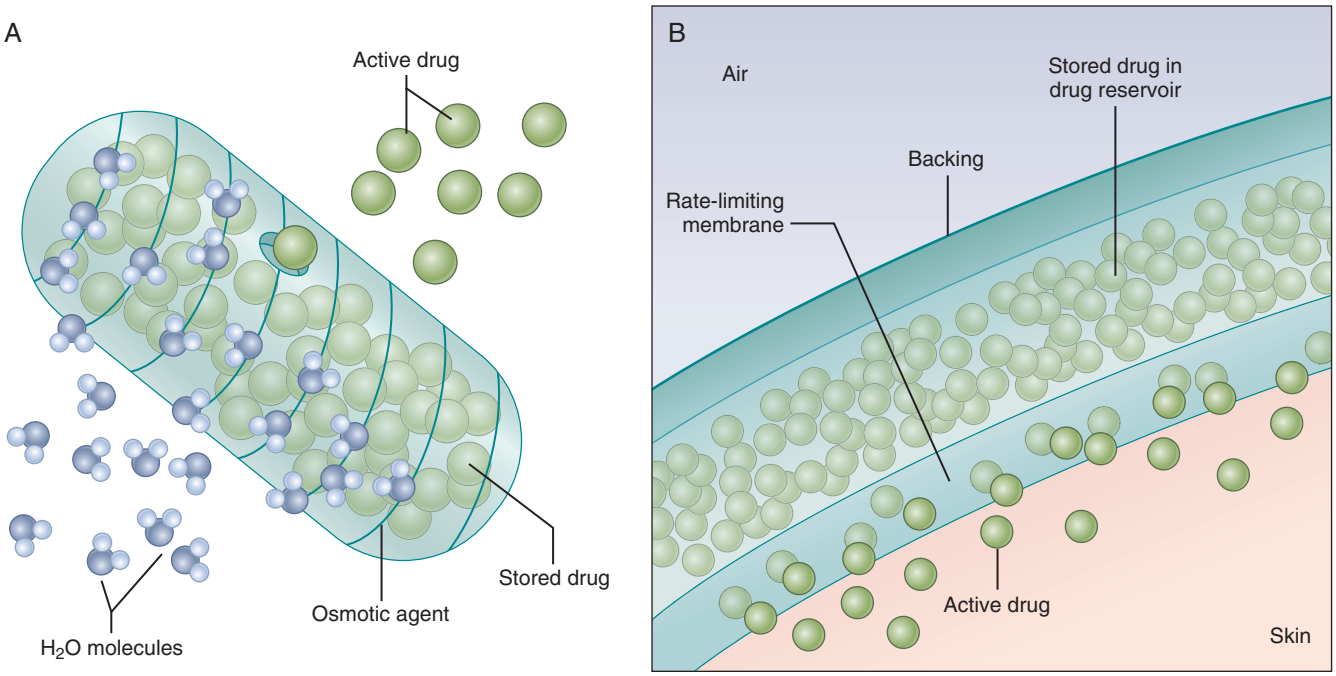

FIGURE 1.3. Mechanisms of sustained-release drug products. In the sustained-release tablet **A,** water is attracted by an osmotic agent in the tablet, and this forces the drug out through a small orifice. In the transdermal skin patch **B,** the drug diffuses through a rate-controlling membrane and is absorbed through the skin into the circulation.

vehicle (e.g., polyethylene glycol or petrolatum), which enables the drug to adhere to the tissue for a sufficient length of time to exert its effect. Lotions are liquid preparations often formulated as oil-in-water emulsions and are used to treat dermatologic conditions. Suppositories are products in which the drug is incorporated into a solid base that melts or dissolves at body temperature. Suppositories are used for **rectal, vaginal,** or **urethral administration** and may provide either localized or systemic drug therapy.

ROUTES OF DRUG ADMINISTRATION

Some routes of drug administration, such as the **enteral** and common **parenteral** routes compared in Table 1.2, are intended to elicit systemic effects and are therefore called **systemic routes.** Other routes of administration, such as the inhalational route, can elicit either localized effects or systemic effects, depending on the drug being administered.

Enteral Administration

The enteral routes of administration are those in which the drug is absorbed from the gastrointestinal tract. These include the **sublingual, buccal, oral,** and **rectal** routes.

In **sublingual administration,** a drug product is placed under the tongue. In **buccal administration,** the drug is placed between the cheek and the gum. Both the sublingual and the buccal routes of administration enable the rapid absorption of certain drugs and are not affected by first-pass drug metabolism in the liver. Drugs for sublingual and buccal administration are given in a relatively low dose and must have good solubility in water and lipid membranes. Larger doses might be irritating to the tissue and would likely be washed away by saliva before the drug could be absorbed. Two examples of drugs available for sublingual administration are **nitroglycerin** for treating ischemic heart disease and **hyoscyamine** for treating bowel cramps. **Fentanyl,** a potent opioid analgesic, is available in an oral transmucosal formulation (ACTIQ) with a lozenge on a stick ("lollypop") for rapid absorption from the buccal mucosa in the treatment of breakthrough cancer pain.

TABLE 1.2 Advantages and Disadvantages of Four Common Routes of Drug Administration

ROUTE	ADVANTAGES	DISADVANTAGES
Oral	Convenient, relatively safe, and economical.	Cannot be used for drugs inactivated by gastric acid, for drugs with a large first-pass effect, or for drugs that irritate the gut.
Intramuscular	Suitable for suspensions and oily vehicles. Absorption is rapid from solutions and is slow and sustained from suspensions.	May be painful. Can cause bleeding if the patient is receiving an anticoagulant.
Subcutaneous	Suitable for suspensions and pellets. Absorption is similar to that in the intramuscular route but is usually somewhat slower.	Cannot be used for drugs that irritate cutaneous tissues or for drugs that must be given in large volumes.
Intravenous	Bypasses absorption to give an immediate effect. Allows for rapid titration of drug. Achieves 100% bioavailability.	Poses more risks for toxicity and tends to be more expensive than other routes.

In medical orders and prescriptions, **oral administration** is designated as *per os* (PO), which means to administer "by mouth." The medication is swallowed, and the drug is absorbed from the stomach and small intestine. The oral route of administration is convenient, relatively safe, and the most economical. It does have some disadvantages, however. Absorption of orally administered drugs can vary widely because of the interaction of drugs with food and gastric acid and the varying rates of gastric emptying, intestinal transit, and tablet disintegration and dissolution. Moreover, some drugs are inactivated by the liver after their absorption from the gut, called **first-pass metabolism** (see Chapter 2), and oral administration is not suitable for use by patients who are sedated, comatose, or experiencing nausea and vomiting.

Rectal administration of drugs in suppository form can result in either a localized effect or a systemic effect. Suppositories are useful when patients cannot take medications by mouth, as in the treatment of nausea and vomiting. They can also be administered for localized conditions such as hemorrhoids. Drugs absorbed from the lower rectum undergo relatively little first-pass metabolism in the liver.

Parenteral Administration

Parenteral administration refers to drug administration with a needle and syringe or with an intravenous infusion pump. The most commonly used parenteral routes are the **intravenous, intramuscular,** and **subcutaneous** routes.

Intravenous administration bypasses the process of drug absorption and provides the greatest reliability and control over the dose of drug reaching the systemic circulation. Because the drug is delivered directly into the blood, it has 100% **bioavailability** (see Chapter 2). The route is often preferred for administration of drugs with short half-lives and drugs whose dose must be carefully titrated to the physiologic response, such as agents used to treat hypotension, shock, and acute heart failure. The intravenous route is widely used to administer antibiotics and antineoplastic drugs to critically ill patients, as well as to treat various types of medical emergencies. The intravenous route is potentially the **most dangerous,** because rapid administration of drugs by this route can cause serious toxicity.

Intramuscular administration and **subcutaneous administration** are suitable for treatment with drug solutions and particle suspensions. Solutions are absorbed more rapidly than particle suspensions, so suspensions are often used to extend the duration of action of a drug over many hours or days. Most drugs are absorbed more rapidly after intramuscular than after subcutaneous administration because of the greater circulation of blood to the muscle.

Intrathecal administration refers to injection of a drug through the thecal covering of the spinal cord and into the subarachnoid space. In cases of meningitis, the intrathecal route is useful in administering antibiotics that do not cross the blood-brain barrier. **Epidural administration,** common in labor and delivery, targets analgesics into the space above the dural membranes of the spinal cord.

Other, less common parenteral routes include **intraarticular administration** of drugs used to treat arthritis, **intradermal administration** for allergy tests, and **insufflation (intranasal administration)** for sinus medications.

Transdermal Administration

Transdermal administration is the application of drugs to the skin for absorption into the circulation. Application can be via a **skin patch** or, less commonly, via an ointment. Transdermal administration, which bypasses first-pass metabolism, is a reliable route of administration for drugs that are effective when given at a relatively low dosage and that are highly soluble in lipid membranes. Transdermal skin patches slowly release medication for periods of time that typically range from 1 to 7 days. Two examples of transdermal preparations are the skin patches called **fentanyl transdermal** (Duragesic), used to treat severe chronic pain, and **nitroglycerin** ointment, used to treat heart failure and angina pectoris.

Inhalational Administration

Inhalational administration can be used to produce either a localized or a systemic drug effect. A localized effect on the respiratory tract is achieved with drugs used to treat **asthma** or **rhinitis,** whereas a systemic effect is observed when a general anesthetic such as **sevoflurane** is inhaled.

Topical Administration

Topical administration refers to the application of drugs to the **surface** of the body to produce a localized effect. It is often used to treat disease and trauma of the skin, eyes, nose, mouth, throat, rectum, and vagina.

DRUG NAMES

A drug often has several names, including a **chemical** name, a **nonproprietary (generic)** name, and a **proprietary** name (or **trade** or **brand** name).

The **chemical name,** which specifies the chemical structure of the drug, uses standard chemical nomenclature. Some chemical names are short and easily pronounceable—for example, the chemical name of aspirin is acetylsalicylic acid. Others are long and hard to pronounce owing to the size and complexity of the drug molecule. For most drugs, medicinal chemists primarily use the chemical name.

The **generic name** (nonproprietary name) is the type of drug name **most suitable for use by health care professionals.** In the United States, the generic names of drugs are the **United States Adopted Name** (USAN) designations. These designations, which are often derived from the chemical names of drugs, provide some indication of the class to which a particular drug belongs. For example, oxacillin can be easily recognized as a type of penicillin. The designations are selected by the USAN Council, which is a nomenclature committee representing the medical and pharmacy professions and the *United States Pharmacopeial Convention* (see Chapter 4). Students taking various board examinations including pharmacology (e.g., nursing boards, medical boards) will also be **most attentive to the generic** names of drugs.

The **brand name** (proprietary name, trade name) for a drug is the registered trademark belonging to a particular drug manufacturer and is used to designate a drug product marketed by that manufacturer. Heavily marketed brand names become common knowledge to patients, such as Prozac and Viagra. Many drugs are marketed under two or more brand names, especially after the manufacturer loses patent exclusivity. For example, ibuprofen (generic name) is marketed in the United States with the brand names of Advil, Motrin, and Midol. Drugs can also be marketed under their USAN

designation. For these reasons, it is often less confusing and more precise to use the USAN rather than a brand name for a drug. However, the brand name may provide a better indication of the drug's pharmacologic or therapeutic effect. For example, DIURIL is a brand name for **chlorothiazide,** a diuretic; FLOMAX for **tamsulosin,** a drug used to increase urine flow; and MAXAIR for **pirbuterol,** a drug used to treat asthma.

Generic Drug Substitution for Branded Drugs

When a new drug is developed and brought to market by a pharmaceutical manufacturer, the Food and Drug Administration (FDA) approval comes with an exclusivity patent for the next 17 to 20 years. During this time, no other company can manufacture or sell the same drug. When the original drug loses exclusivity, generic drug manufacturers can file for a brief form of drug approval, limited to showing that the generic formulation exhibits the same **absorption** and **bioavailability** as the original, branded drug. Generic drugs are much cheaper as the second manufacturer does not have to recoup the costs of drug discovery, development, clinical trials, and FDA new drug application.

Although the FDA does not regulate when to use generic drugs, most states have passed laws on **generic substitution.** Because use of generic medications instead of branded drugs can save millions of dollars in health care costs, some states mandate generic substitution without patient or physician approval, although physicians can override generic substitutions in some cases. Other states need the approval of the patient or physician to switch from a branded drug prescription to a generic substitute.

Both patient and physician misconceptions affect the underutilization of generic drugs. Scientific studies show that the overwhelming majority of generic medicines are **bioequivalent** to the branded, originator drug. The FDA has identified certain drugs that may be more dangerous to switch, called **narrow therapeutic index** (NTI) drugs, which may warrant further drug blood monitoring after a generic to branded drug substitution.

In this textbook, the generic name of a drug is given in the normal-sized font and its brand name in SMALL CAPS font. Note that not all generic drugs have a brand name counterpart.

SUMMARY OF IMPORTANT POINTS

- The development of pharmacology was made possible by important advances in chemistry and physiology that enabled scientists to isolate and synthesize pure chemical compounds (drugs) and to design methods for identifying and quantifying the physiologic actions of the compounds.
- Pharmacology has two main subdivisions. Pharmacodynamics is concerned with the mechanisms of drug action and the dose-response relationship, whereas pharmacokinetics is concerned with the relationship between the drug dose and the plasma drug concentration over time.
- The sources of drugs are natural products (including plants, microbes, animal tissues, and minerals) and chemical synthesis. Drugs can exist as crude drug preparations, pure drug compounds, or pharmaceutical preparations used to administer a specific dose to a patient.
- The primary routes of administration are enteral (e.g., oral ingestion), parenteral (e.g., intravenous, intramuscular, and subcutaneous injection), transdermal, inhalational, and topical. Most routes produce systemic effects. Topical administration produces a localized effect at the site of administration.
- All drugs (pure compounds) have a nonproprietary name (or generic name, such as a USAN designation) as well as a chemical name. Some drugs also have one or more proprietary names (trade names or brand names) under which they are marketed by their manufacturer.

Review Questions

1. Which route of drug administration is used with potent and lipophilic drugs in a patch formulation and avoids first-pass metabolism?
   (A) topical
   (B) sublingual
   (C) rectal
   (D) oral
   (E) transdermal
2. Which one of the following routes of administration does not have an absorption phase?
   (A) subcutaneous
   (B) intramuscular
   (C) intravenous
   (D) sublingual
   (E) inhalation
3. Which of the following correctly describes the intramuscular route of parenteral drug administration?
   (A) drug absorption is erratic and unpredictable
   (B) used to administer drug suspensions that are slowly absorbed
   (C) bypasses the process of drug absorption to achieve an immediate effect
   (D) cannot be used for drugs that undergo a high degree of first-pass metabolism
   (E) poses more risks than intravenous administration
4. An elderly patient has problems remembering to take her medication three times a day. Which one of the drug formulations might be particularly useful in this case?
   (A) extended-release
   (B) suspension
   (C) suppository
   (D) skin patch
   (E) enteric-coated
5. Which form of a drug name is most likely known by patients from exposure to drug advertisements?
   (A) nonproprietary name
   (B) British Approved Name
   (C) chemical name
   (D) generic name
   (E) trade name