Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry

Twelfth Edition

John M. Beale, Jr. • John H. Block

Wolters Kluwer Health | Lippincott Williams & Wilkins

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Wilson and Gisvold's
Textbook of

ORGANIC MEDICINAL AND PHARMACEUTICAL CHEMISTRY

TWELFTH EDITION

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The 12th Edition of Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry *is dedicated to the memory of Robert F. Doerge.*

Robert F. Doerge
1915–2006

Robert Doerge—pharmacist, medicinal chemist, and educator—experienced the Depression and served in the Civilian Conservation Corp in Sheridan, AR. Dr. Doerge received his B.S. in pharmacy in 1943 and his PhD in pharmaceutical chemistry, both from the University of Minnesota in 1949. The latter was under the direction of Dr. Charles O. Wilson, who, with Dr. Ole Gisvold, started this well-respected medicinal chemistry textbook. Dr. Doerge began his professional career as an assistant professor in the University of Texas-Austin School of Pharmacy before becoming a research chemist with the former Smith Kline and French Laboratories in Philadelphia. Beginning in 1960, he returned to academia as professor and chair of the pharmaceutical chemistry department in Oregon State University's College of Pharmacy. Prior to his retirement as professor emeritus in 1981, he was the assistant dean.

Dr. Doerge's initial publications were on the topic of synthesis of anticonvulsants. At Smith Kline and French, his work included publications on vitamin stability, and at Oregon State University, his papers focused on the heterocyclic phenylindolizines. Dr. Doerge was a volunteer abstractor for *Chemical Abstracts*. As an educator, Dr. Doerge was an author of chapters in *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, coeditor of the 6th and 7th editions, and editor of the 8th edition. His skill and dedication in the classroom were recognized by the students and university with several teaching awards.

We certainly miss this fine gentleman who put the students first and advanced the teaching of medicinal chemistry as a chapter author, coeditor, and editor of the Wilson and Gisvold textbook series.

John H. Block

PREFACE

For 6 decades, *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry* has been a standard in the literature of medicinal chemistry. Generations of students and faculty have depended on this textbook not only for undergraduate courses in medicinal chemistry but also as a supplement for graduate studies. Moreover, students in other health sciences have found certain chapters useful. The current editors and authors worked on the 12th edition with the objective of continuing the tradition of a modern textbook for undergraduate students and also for graduate students who need a general review of medicinal chemistry. Because the chapters include a blend of chemical and pharmacological principles necessary for understanding structure–activity relationships and molecular mechanisms of drug action, the book should be useful in supporting courses in medicinal chemistry and in complementing pharmacology courses.

ABOUT THE 12TH EDITION

The 12th edition follows in the footsteps of the 11th edition by reflecting the dynamic changes occurring in medicinal chemistry. With increased knowledge of the disease process and the identification of the key steps in the biochemical process, the chapters have been updated, expanded, and reorganized. At the same time, to streamline the presentation of the content, some topics were combined into existing chapters. For example, Chapter 2, "Drug Design Strategies," incorporates material from 11th edition Chapters 2, 3, and 28, and Chapter 3, "Metabolic Changes of Drugs and Related Organic Compounds," includes the content from 11th edition Chapter 5, "Prodrugs and Drug Latentiation." In addition, with the newer drugs that have entered the pharmaceutical armamentarium since publication of the 11th edition, coverage of the following topics has been expanded in the 12th edition: Central Dopaminergic Signaling Agents (Chapter 13), Anticonvulsants (Chapter 14), Hormone-Related Disorders: Nonsteroidal Therapies (Chapter 20), Agents Treating Bone Disorders (Chapter 21), and Anesthetics (Chapter 22).

New features of the 12th edition include a chapter overview at the beginning of each chapter to introduce material to be covered in the chapter and review questions at the end of each chapter to reinforce concepts learned in the chapter (answers to these questions are available to students on the book's companion Web site; see next section).

ADDITIONAL RESOURCES

Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 12th Edition, includes additional resources for both instructors and students that are available on the book's companion Web site at http://www.thePoint.lww.com/Beale12e.

Instructors

Approved adopting instructors will be given access to the following additional resources:

- Image bank of all the figures and tables in the book

Students

Students who have purchased *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 12th Edition, have access to the following additional resources:

- The answers to the review questions found in the book

In addition, purchasers of the text can access the searchable Full Text On-line by going to the *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 12th Edition, Web site at http://www.thePoint.lww.com/Beale12e. See the inside front cover of this text for more details, including the passcode you will need to gain access to the Web site.

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The editors welcome the new contributors to the 12th edition: Jeffrey J. Christoff, A. Michael Crider, Carolyn J. Friel, Ronald A. Hill, Shengquan Liu, Matthias C. Lu, Marcello J. Nieto, and Kenneth A. Witt. The editors extend thanks to all of the authors who have cooperated in the preparation of the current edition. Collectively, the authors represent many years of teaching and research experience in medicinal chemistry. Their chapters include summaries of current research trends that lead the reader to the original literature. Documentation and references continue to be an important feature of the book.

We continue to be indebted to Professors Charles O. Wilson and Ole Gisvold, the originators of the book and editors of five editions, Professor Robert Doerge, who joined Professors Wilson and Gisvold for the 6th and 7th editions and single-handedly edited the 8th edition, and Professors Jaime Delgado and William Remers, who edited the 9th and 10th editions. They and the authors have contributed significantly to the education of countless pharmacists, medicinal chemists, and other pharmaceutical scientists.

John M. Beale, Jr.
John H. Block

1st	1949	Wilson and Gisvold (*Organic Chemistry in Pharmacy*)	6th	1971	Wilson, Gisvold, and Doerge
			7th	1977	Wilson, Gisvold, and Doerge
2nd	1954	Wilson and Gisvold	8th	1982	Doerge
3rd	1956	Wilson	9th	1991	Delgado and Remers
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CHAPTER 1

Introduction

JOHN M. BEALE, JR. AND JOHN H. BLOCK

The discipline of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. Most of this activity is directed to new natural or synthetic organic compounds. Paralleling the development of medicinal agents has come a better understanding of the chemistry of the receptor. The latter has been greatly facilitated by low-cost computers running software that calculates molecular properties and structure and pictures it using high-resolution graphics. Development of organic compounds has grown beyond traditional synthetic methods. It now includes the exciting field of biotechnology using the cell's biochemistry to synthesize new compounds. Techniques ranging from recombinant DNA and site-directed mutagenesis to fusion of cell lines have greatly broadened the possibilities for new entities that treat disease. The pharmacist now dispenses modified human insulins that provide more convenient dosing schedules, cell-stimulating factors that have changed the dosing regimens for chemotherapy, humanized monoclonal antibodies that target specific tissues, and fused receptors that intercept immune cell–generated cytokines.

This 12th edition of *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry* continues the philosophy of presenting the scientific basis of medicinal chemistry originally established by Professors Charles Wilson and Ole Gisvold, describing the many aspects of organic medicinals: how they are discovered, how they act, and how they developed into clinical agents. The process of establishing a new pharmaceutical is exceedingly complex and involves the talents of people from various disciplines, including chemistry, biochemistry, molecular biology, physiology, pharmacology, pharmaceutics, and medicine. Medicinal chemistry, itself, is concerned mainly with the organic, analytical, and biochemical aspects of this process, but the chemist must interact productively with those in other disciplines. Thus, medicinal chemistry occupies a strategic position at the interface of chemistry and biology. All of the principles discussed in this book are based on fundamental organic chemistry, physical chemistry, and biochemistry. To provide an understanding of the principles of medicinal chemistry, it is necessary to consider the physicochemical properties used to develop new pharmacologically active compounds and their mechanisms of action, the drug's metabolism, including possible biological activities of the metabolites, the importance of stereochemistry in drug design, and the methods used to determine what "space" a drug occupies.

The earliest drug discoveries were made by random sampling of higher plants. Some of this sampling, although based on anecdotal evidence, led to the use of such crude plant drugs as opium, belladonna, and ephedrine that have been important for centuries. With the accidental discovery of penicillin came the screening of microorganisms and the large number of antibiotics from bacterial and fungal sources. Many of these antibiotics provided the prototypical structure that the medicinal chemist modified to obtain antibacterial drugs with better therapeutic profiles. With the changes in federal legislation reducing the efficacy requirement for "nutriceutical," the public increasingly is using so-called nontraditional or alternative medicinals that are sold over the counter, many outside of traditional pharmacy distribution channels. It is important for the pharmacist and the public to understand the rigor that is required for prescription-only and Food and Drug Administration (FDA)-approved nonprescription products to be approved relative to the nontraditional products. It is also important for all people in the healthcare field and the public to realize that whether these nontraditional products are effective as claimed or not, many of the alternate medicines contain pharmacologically active agents that can potentiate or interfere with physician-prescribed therapy.

Hundreds of thousands of new organic chemicals are prepared annually throughout the world, and many of them are entered into pharmacological screens to determine whether they have useful biological activity. This process of random screening has been considered inefficient, but it has resulted in the identification of new lead compounds whose structures have been optimized to produce clinical agents. Sometimes, a lead develops by careful observation of the pharmacological behavior of an existing drug. The discovery that amantadine protects and treats early influenza A came from a general screen for antiviral agents. The use of amantadine in long-term care facilities showed that it also could be used to treat parkinsonian disorders. More recently, automated high-throughput screening systems utilizing cell culture systems with linked enzyme assays and receptor molecules derived from gene cloning have greatly increased the efficiency of random screening. It is now practical to screen enormous libraries of peptides and nucleic acids obtained from combinatorial chemistry procedures.

Rational design, the opposite approach to high-volume screening, is also flourishing. Statistical methods based on the correlation of physicochemical properties with biological potency are used to explain and optimize biological activity. Significant advances in x-ray crystallography and nuclear magnetic resonance have made it possible to obtain detailed representations of enzymes and other drug receptors. The techniques of molecular graphics and computational

chemistry have provided novel chemical structures that have led to new drugs with potent medicinal activities. Development of human immunodeficiency virus (HIV) protease inhibitors and angiotensin-converting enzyme (ACE) inhibitors came from an understanding of the geometry and chemical character of the respective enzyme's active site. Even if the receptor structure is not known in detail, rational approaches based on the physicochemical properties of lead compounds can provide new drugs. For example, the development of cimetidine involved a careful study of the changes in antagonism of H_2-histamine receptors induced by varying the physical properties of structures based on histamine.

As you proceed through the chapters, think of what problem the medicinal chemist is trying to solve. Why were certain structures selected? What modifications were made to produce more focused activity or reduce adverse reactions or produce better pharmaceutical properties? Was the prototypical molecule discovered from random screens, or did the medicinal chemist have a structural concept of the receptor or an understanding of the disease process that must be interrupted?

CHAPTER 2

Drug Design Strategies

JOHN H. BLOCK

CHAPTER OVERVIEW

Modern drug design as compared with the classical approach—*let's make a change on an existing compound or synthesize a new structure and see what happens*—continues to evolve rapidly as an approach to solving a drug design problem. The combination of increasing power and decreasing cost of desktop computing has had a major impact on solving drug design problems. Although drug design increasingly is based on modern computational chemical techniques, it also uses sophisticated knowledge of disease mechanisms and receptor properties. A good understanding of how the drug is transported into the body, distributed throughout the body compartments, metabolically altered by the liver and other organs, and excreted from the patient is required, along with the structural characteristics of the receptor. Acid–base chemistry is used to aid in formulation and biodistribution. Structural attributes and substituent patterns responsible for optimum pharmacological activity can often be predicted by statistical techniques such as regression analysis. Computerized conformational analysis permits the medicinal chemist to predict the drug's three-dimensional (3D) shape that is *seen* by the receptor. With the isolation and structural determination of specific receptors and the availability of computer software that can estimate the 3D shape of the receptor, it is possible to design molecules that will show an optimum fit to the receptor.

DRUG DISTRIBUTION

A drug is a chemical molecule. Following introduction into the body, a drug must pass through many barriers, survive alternate sites of attachment and storage, and avoid significant metabolic destruction before it reaches the site of action, usually a receptor on or in a cell (Fig. 2.1). At the receptor, the following equilibrium (Rx. 2.1) usually holds:

$$\text{Drug} + \text{Receptor} \rightleftharpoons \text{Drug-Receptor Complex} \downarrow \text{Pharmacologic Response} \qquad \text{(Rx. 2.1)}$$

The ideal drug molecule will show favorable binding characteristics to the receptor, and the equilibrium will lie to the right. At the same time, the drug will be expected to dissociate from the receptor and reenter the systemic circulation to be excreted. Major exceptions include the alkylating agents used in cancer chemotherapy (see Chapter 10), a few inhibitors of the enzyme acetylcholinesterase (see Chapter 17), suicide inhibitors of monoamine oxidase (see Chapter 16), and the aromatase inhibitors 4-hydroxyandrostenedione and exemestane (see Chapter 25). These pharmacological agents form covalent bonds with the receptor, usually an enzyme's active site. In these cases, the cell must destroy the receptor or enzyme, or, in the case of the alkylating agents, the cell would be replaced, ideally with a normal cell. In other words, the usual use of drugs in medical treatment calls for the drug's effect to last for a finite period of time. Then, if it is to be repeated, the drug will be administered again. If the patient does not tolerate the drug well, it is even more important that the agent dissociate from the receptor and be excreted from the body.

Oral Administration

An examination of the *obstacle course* (Fig. 2.1) faced by the drug will give a better understanding of what is involved in developing a commercially feasible product. Assume that the drug is administered orally. The drug must go into solution to pass through the gastrointestinal mucosa. Even drugs administered as true solutions may not remain in solution as they enter the acidic stomach and then pass into the alkaline intestinal tract. (This is explained further in the discussion on acid–base chemistry.) The ability of the drug to dissolve is governed by several factors, including its chemical structure, variation in particle size and particle surface area, nature of the crystal form, type of tablet coating, and type of tablet matrix. By varying the dosage form and physical characteristics of the drug, it is possible to have a drug dissolve quickly or slowly, with the latter being the situation for many of the sustained-action products. An example is orally administered sodium phenytoin, with which variation of both the crystal form and tablet adjuvants can significantly alter the bioavailability of this drug widely used in the treatment of epilepsy.

Chemical modification is also used to a limited extent to facilitate a drug reaching its desired target (see Chapter 3). An example is olsalazine, used in the treatment of ulcerative colitis. This drug is a dimer of the pharmacologically active mesalamine (5-aminosalicylic acid). The latter is not effective orally because it is metabolized to inactive forms before reaching the colon. The dimeric form passes

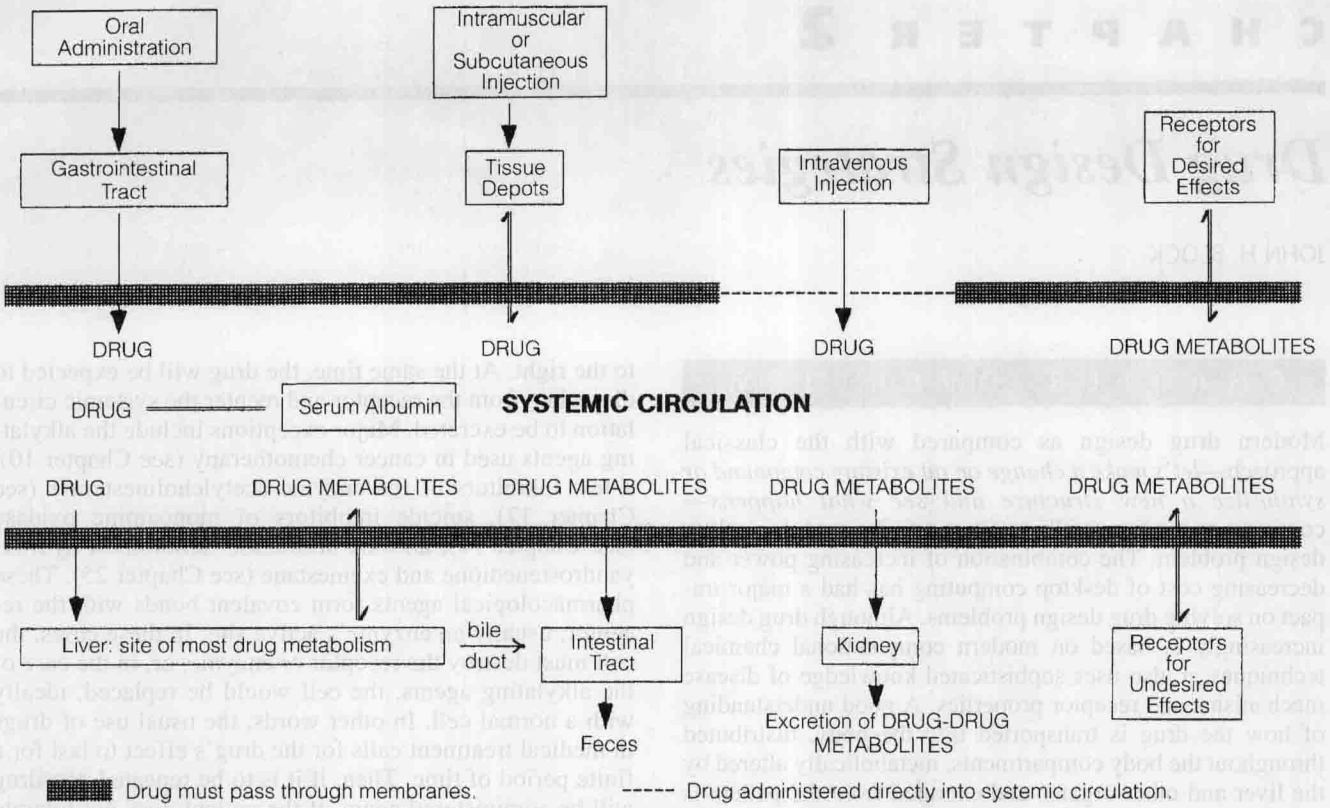
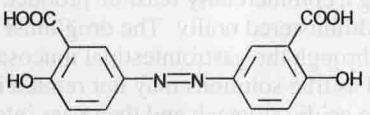
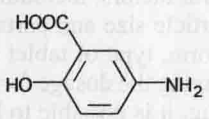


Figure 2.1 • Summary of drug distribution.

through a significant portion of the intestinal tract before being cleaved by the intestinal bacteria to two equivalents of mesalamine.



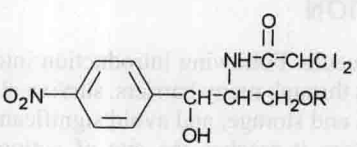
Olsalazine



Mesalamine

As illustrated by olsalazine, any compound passing through the gastrointestinal tract will encounter a large number and variety of digestive and bacterial enzymes, which, in theory, can degrade the drug molecule. In practice, a new drug entity under investigation will likely be dropped from further consideration if it cannot survive in the intestinal tract or its oral bioavailability is low, necessitating parenteral dosage forms only. An exception would be a drug for which there is no effective alternative or which is more effective than existing products and can be administered by an alternate route, including parenteral, buccal, or transdermal.

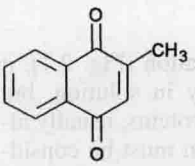
In contrast, these same digestive enzymes can be used to advantage. Chloramphenicol is water soluble enough (2.5 mg/mL) to come in contact with the taste receptors on the tongue, producing an unpalatable bitterness. To mask this intense bitter taste, the palmitic acid moiety is added as an ester of chloramphenicol's primary alcohol. This reduces the parent drug's water solubility (1.05 mg/mL), enough so that it can be formulated as a suspension that passes over the bitter taste receptors on the tongue. Once in the intestinal tract, the ester linkage is hydrolyzed by the digestive esterases to the active antibiotic chloramphenicol and the very common dietary fatty acid palmitic acid.



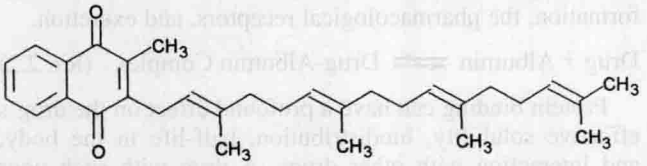
Chloramphenicol: R = H

Chloramphenicol Palmitate: R = $CO(CH_2)_{14}CH_3$

Olsalazine and chloramphenicol palmitate are examples of *prodrugs*. Most prodrugs are compounds that are inactive in their native form but are easily metabolized to the active agent. Olsalazine and chloramphenicol palmitate are examples of prodrugs that are cleaved to smaller compounds, one of which is the active drug. Others are metabolic precursors to the active form. An example of this type of prodrug is menadione, a simple naphthoquinone that is converted in the liver to phytonadione (vitamin $K_{2(20)}$).

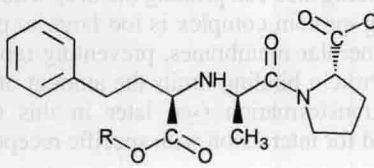


Menadione



Phytonadione (Vitamin $K_{2(20)}$)

Occasionally, the prodrug approach is used to enhance the absorption of a drug that is poorly absorbed from the gastrointestinal tract. Enalapril is the ethyl ester of enalaprilic acid, an active inhibitor of angiotensin-converting enzyme (ACE). The ester prodrug is much more readily absorbed orally than the pharmacologically active carboxylic acid.



Enalapril: R = C_2H_5

Enalaprilic Acid: R = H

Unless the drug is intended to act locally in the gastrointestinal tract, it will have to pass through the gastrointestinal mucosal barrier into venous circulation to reach the site of the receptor. The drug's route involves distribution or partitioning between the aqueous environment of the gastrointestinal tract, the lipid bilayer cell membrane of the mucosal cells, possibly the aqueous interior of the mucosal cells, the lipid bilayer membranes on the venous side of the gastrointestinal tract, and the aqueous environment of venous circulation. Some very lipid-soluble drugs may follow the route of dietary lipids by becoming part of the mixed micelles, incorporating into the chylomicrons in the mucosal cells into the lymph ducts, servicing the intestines, and finally entering venous circulation via the thoracic duct.

The drug's passage through the mucosal cells can be passive or active. As is discussed later in this chapter, the lipid membranes are very complex with a highly ordered structure. Part of this membrane is a series of channels or tunnels that form, disappear, and reform. There are receptors that move compounds into the cell by a process called *pinocytosis*. Drugs that resemble a normal metabolic precursor or intermediate may be actively transported into the cell by the same system that transports the endogenous compound. On the other hand, most drug molecules are too large to enter the cell by an active transport mechanism through the passages. The latter, many times, pass into the patient's circulatory system by passive diffusion.

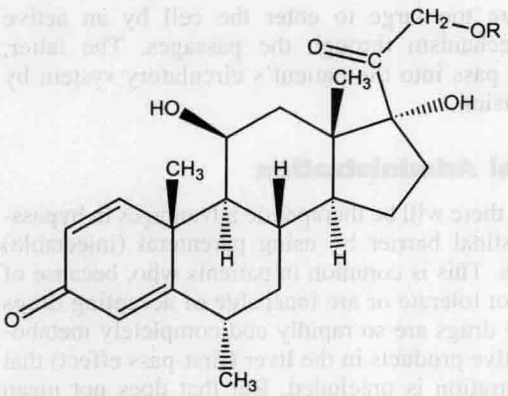
Parenteral Administration

Many times, there will be therapeutic advantages in bypassing the intestinal barrier by using parenteral (injectable) dosage forms. This is common in patients who, because of illness, cannot tolerate or are incapable of accepting drugs orally. Some drugs are so rapidly and completely metabolized to inactive products in the liver (first-pass effect) that oral administration is precluded. But that does not mean that the drug administered by injection is not confronted by obstacles (Fig. 2.1). Intravenous administration places the drug directly into the circulatory system, where it will be rapidly distributed throughout the body, including tissue depots and the liver, where most biotransformations occur (see later in this chapter), in addition to the receptors. Subcutaneous and intramuscular injections slow distribution of the drug, because it must diffuse from the site of injection into systemic circulation.

It is possible to inject the drug directly into specific organs or areas of the body. Intraspinal and intracerebral routes will place the drug directly into the spinal fluid or brain, respectively. This bypasses a specialized epithelial tissue, the blood-brain barrier, which protects the brain from exposure to a large number of metabolites and chemicals. The blood-brain barrier is composed of membranes of tightly joined epithelial cells lining the cerebral capillaries. The net result is that the brain is not exposed to the same variety of compounds that other organs are. Local anesthetics are examples of administration of a drug directly onto the desired nerve. A spinal block is a form of anesthesia performed by injecting a local anesthetic directly into the spinal cord at a specific location to block transmission along specific neurons.

Most of the injections a patient will experience in a lifetime will be subcutaneous or intramuscular. These parenteral routes produce a depot in the tissues (Fig. 2.1), from which the drug must reach the blood or lymph. Once in systemic circulation, the drug will undergo the same distributive phenomena as orally and intravenously administered agents before reaching the target receptor. In general, the same factors that control the drug's passage through the gastrointestinal mucosa will also determine the rate of movement out of the tissue depot.

The prodrug approach described previously can also be used to alter the solubility characteristics, which, in turn, can increase the flexibility in formulating dosage forms. The solubility of methylprednisolone can be altered from essentially water-insoluble methylprednisolone acetate to slightly water-insoluble methylprednisolone to water-soluble methylprednisolone sodium succinate. The water-soluble sodium hemisuccinate salt is used in oral, intravenous, and intramuscular dosage forms. Methylprednisolone itself is normally found in tablets. The acetate ester is found in topical ointments and sterile aqueous suspensions for intramuscular injection. Both the succinate and acetate esters are hydrolyzed to the active methylprednisolone by the patient's own systemic hydrolytic enzymes (esterases).



Methylprednisolone: R = H
Methylprednisolone Acetate: R = $C(=O)CH_3$
Methylprednisolone Sodium Succinate: R = $C(=O)CH_2CH_2COO^-$ Na^+

Another example of how prodrug design can significantly alter biodistribution and biological half-life is illustrated by two drugs based on the retinoic acid structure used systemically to treat psoriasis, a nonmalignant hyperplasia. Etretinate has a 120-day *terminal* half-life after 6 months of therapy. In contrast, the active metabolite, acitretin, has a 33- to 96-hour *terminal* half-life. Both drugs are potentially teratogenic. Women of childbearing age must sign statements that they are aware of the risks and usually are administered a pregnancy test before a prescription is issued. Acitretin, with its shorter half-life, is recommended for a woman who would like to become pregnant, because it can clear her body within a reasonable time frame. When effective, etretinate can keep a patient clear of psoriasis lesions for several months.

Protein Binding

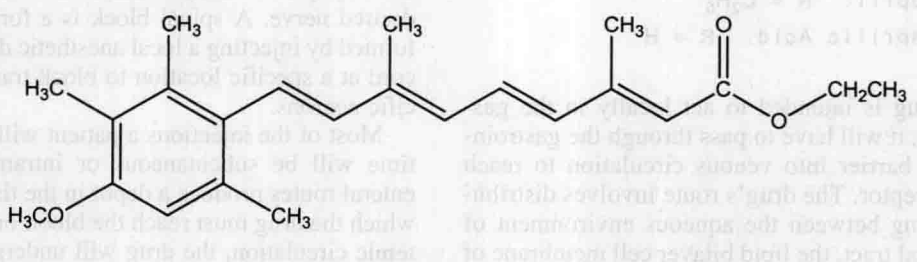
Once the drug enters the systemic circulation (Fig. 2.1), it can undergo several events. It may stay in solution, but many drugs will be bound to the serum proteins, usually albumin (Rx. 2.2). Thus, a new equilibrium must be considered. Depending on the equilibrium constant, the drug can remain in systemic circulation bound to albumin for a considerable period and not be available to the sites of biotransformation, the pharmacological receptors, and excretion.

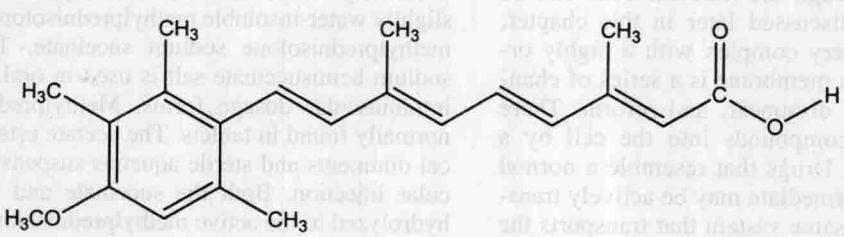
Drug + Albumin $\rightleftharpoons$ Drug-Albumin Complex (Rx. 2.2)

Protein binding can have a profound effect on the drug's effective solubility, biodistribution, half-life in the body, and interaction with other drugs. A drug with such poor water solubility that therapeutic concentrations of the unbound (active) drug normally cannot be maintained still can be a very effective agent. The albumin–drug complex acts as a reservoir by providing large enough concentrations of free drug to cause a pharmacological response at the receptor.

Protein binding may also limit access to certain body compartments. The placenta is able to block passage of proteins from maternal to fetal circulation. Thus, drugs that normally would be expected to cross the placental barrier and possibly harm the fetus are retained in the maternal circulation, bound to the mother's serum proteins.

Protein binding also can prolong the drug's duration of action. The drug–protein complex is too large to pass through the renal glomerular membranes, preventing rapid excretion of the drug. Protein binding limits the amount of drug available for biotransformation (see later in this chapter and Chapter 3) and for interaction with specific receptor sites. For





Acitretin