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GOODMAN &GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS

古德曼 吉尔曼

治疗学的药理学基础

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ALFRED GOODMAN GILMAN

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NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Preface

The tenth edition of *Goodman and Gilman's The Pharmacological Basis of Therapeutics* marks the sixtieth anniversary of this book. The objectives that guided the two original authors in writing the first edition have continued to guide authors and editors of subsequent editions, including this one. These objectives—stated in the preface to the first edition, which is reprinted herein—are: correlation of pharmacology with related medical sciences, reinterpretation of the actions and uses of drugs from the viewpoint of important advances in medicine, and placing of emphasis on the application of pharmacodynamics to therapeutics.

We are indebted to the new and returning contributors to this edition, who worked diligently to revise and update their chapters in a field that is undergoing change at a remarkable pace, and we are grateful to our consultants, who reviewed and made suggestions for improving many chapters. We also are pleased to acknowledge three other individuals who played indispensable roles in the preparation of this edition. Lauralea Edwards, D.Ph., provided thorough and well-researched reviews of the text for accuracy of pharmaceutical information and in addition assisted the editors in the early planning of the edition. Tracy Shields as editorial assistant worked tenaciously and efficiently and with much initiative in preparing the final chapter manuscripts submitted to the publisher and in documenting the accuracy of references. Lynne Hutchison served as managing editor for this edition. Her superb organization and management of the editorial office, effective and diplomatic interactions with contributors and the publisher, well-developed literary skills, and enthusiasm for the project made the many pieces of the book come together in a timely and accurate fashion. The completion of this edition would not have been possible, much less pleasurable, without the dedicated work of these talented women. We also appreciate the help of John Morriss and Kathleen McCullough of McGraw-Hill.

The timing of the publication of the tenth edition of this book, the first edition of the new millennium, is significant. We witness a spectacular revolution in biology and biomedical science that is coupled inexorably with unparalleled access to information. We are struck by a profound tension between knowledge and wisdom. We earnestly seek both. But they fight with each other, particularly when we teach, write, and reason. How do we transmit our intellectual heritage while sustaining the necessary context of insight and applicability? What is the next-generation biomedical textbook to be? Certainly not just a database; print pages will retain their place as a necessary medium of analysis and reason.

Our history provides guidance to meet this challenge. The first edition of this book often is credited with establishing pharmacology as a discipline. This accolade was not earned because of organized exposition of facts, but rather because of synthesis of pharmacological information and application of this synthesis to clinical science. The original authors of this book, Louis S. Goodman and Alfred Gilman, made many contributions as rescarchers, teachers, and sage advisors, but commentators note the creation of this work as their most notable accomplishment. This opinion is borne out by the continuation of the book through ten editions. The careful reader can find many scholarly passages in this edition that appeared in the first and second editions of this book. The seventh edition of this book (1985) was dedicated to Alfred Gilman shortly after his death. The eighth edition (1990) was dedicated to Louis Goodman as he retired from an active editorial role. Louis Goodman, the founder of this book, died on November 19, 2000. He is remembered fondly for his wisdom, scholarship, gruff sense of humor, impeccable sense of perfection, and infuriatingly successful motivational orations for those who would rise to the challenge.

We rededicate this edition to Louis S. Goodman and Alfred Gilman in recognition of their vision and many contributions and with the hope that the need met by the first edition of this book will be met by this and subsequent editions. A book such as this will remain extraordinarily valuable if its heritors adhere to its founding precepts envisioned by these two men.

ALFRED GOODMAN GILMAN
JOEL G. HARDMAN
LEE E. LIMBIRD

June 5, 2001

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SECTION I

GENERAL PRINCIPLES

INTRODUCTION

Alfred Goodman Gilman

Publication of the tenth edition of *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* the first new-millennium edition of a textbook that has documented six decades of spectacular progress in both the basic and applied aspects of pharmacology, provokes both retrospection and thoughts of the future.

Some things do not change. The first (1941) edition of this textbook began: "The subject of pharmacology is a broad one and embraces the knowledge of the source, physical and chemical properties, compounding, physiological actions, absorption, fate, and excretion, and therapeutic uses of drugs. A *drug* may be broadly defined as any chemical agent which affects living protoplasm, and few substances would escape inclusion by this definition." It is a tribute to both the original authors and to the validity of their definition of the discipline that this paragraph has appeared virtually unchanged in every subsequent edition of this work.

Most things do change. Comparison of the table of contents of the first and current edition of this textbook offers a concise but amazing view of progress during a single lifetime. For example, in the first edition, the section entitled *Chemotherapy of Infectious Diseases* spans 182 pages, but there is no mention of an antibiotic; instead there are four chapters on syphilotherapy and four more on the sulfonamides. *Cancer* is not found in the index, and *carcinoma* provides only cursory references to pain relief. Antihypertensives, antipsychotics, and antidepressants are not present in 1941, and the list goes on and on.

This progress, so evident, has many mothers, particularly chemistry, all of the basic biomedical disciplines, and all of the clinical specialties. Techniques of chemical synthesis have improved enormously and now include the powerful approach of combinatorial chemistry; these provide the raw materials for the pharmacopoeia. Detailed understanding of both normal and pathological physiology and biochemistry bring mechanistic insight into disease. Molecular biology and genetics offer powerful DNA-based technologies for decoding the blueprints for all organisms, assigning functions to unknown genes, identifying inherited contributions to disease, and synthesizing human proteins in cultured microbes or mammalian cells for use as therapeutic agents. Equally critical are appropriate experimental and statistical approaches to therapy; the double-blind, placebo-controlled clinical trial is the *sine qua non.* Pharmacology draws on all of these disciplines and their techniques to identify disease-relevant targets (receptors) for drug actions, select the chemicals best suited to manipulate each target, understand in detail the consequences of the drug–receptor interaction, maximize the specificity of drug interaction, minimize toxicity, optimize and vary the pharmacokinetic profiles of drugs, and prove that the agents identified are in fact appropriate for clinical use.

The chapters included in Section I of this book provide understanding of the basic principles that underlie both current therapy and the advances that will be witnessed by all interested in pharmacology and medicine. In brief, *pharmacokinetics* (Chapter 1) explores the factors that determine the relationship between drug dosage and the time-varying concentration of drug at its site(s) of action. The practical importance of these

C H A P T E R 1

PHARMACOKINETICS

The Dynamics of Drug Absorption, Distribution, and Elimination

Grant R. Wilkinson

To produce its characteristic effects, a drug must be present in appropriate concentrations at its sites of action. Although obviously a function of the amount of drug administered, the concentrations of active, unbound (free) drug attained also depend upon the extent and rate of its absorption, distribution (which mainly reflects relative binding to plasma and tissue proteins), metabolism (biotransformation), and excretion. These disposition factors are depicted in Figure 1–1 and are described in this chapter.

PHYSICOCHEMICAL FACTORS IN TRANSFER OF DRUGS ACROSS MEMBRANES

The absorption, distribution, metabolism, and excretion of a drug all involve its passage across cell membranes. Mechanisms by which drugs cross membranes and the physicochemical properties of molecules and membranes that influence this transfer are, therefore, important. The determining characteristics of a drug are its molecular size and shape, degree of ionization, relative lipid solubility of its ionized and nonionized forms, and its binding to tissue proteins.

When a drug permeates a cell, it obviously must traverse the cellular plasma membrane. Other barriers to drug movement may be a single layer of cells (intestinal epithelium) or several layers of cells (skin). Despite such structural differences, the diffusion and transport of drugs across these various boundaries have many common characteristics, since drugs in general pass through cells rather than between them. The plasma membrane thus represents the common barrier.

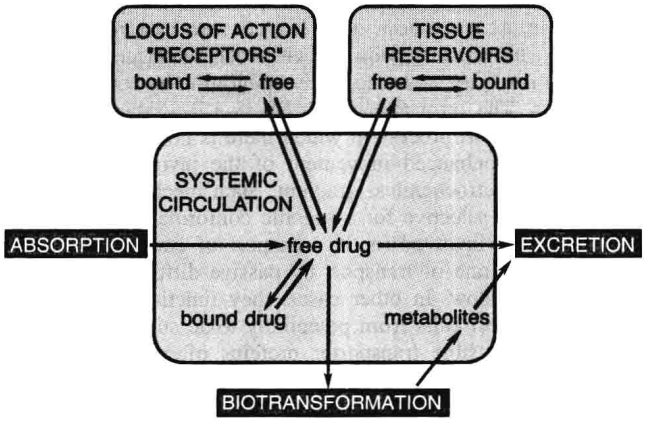

Figure 1–1. Schematic representation of the interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its locus of action.

Possible distribution and binding of metabolites are not depicted.

Cell Membranes. The plasma membrane consists of a bilayer of amphipathic lipids, with their hydrocarbon chains oriented inward to form a continuous hydrophobic phase and their hydrophilic heads oriented outward. Individual lipid molecules in the bilayer vary according to the particular membrane and can move laterally, endowing the membrane with fluidity, flexibility, high electrical resistance, and relative impermeability to highly polar molecules. Membrane proteins embedded in the bilayer serve as receptors, ion channels, or transporters to elicit electrical or chemical signaling pathways and provide selective targets for drug actions.

Most cell membranes are relatively permeable to water either by diffusion or by flow resulting from hydrostatic or osmotic differences across the membrane, and bulk flow of water can carry with it drug molecules. Such transport is the major mechanism by which drugs pass across most capillary endothelial membranes. However, proteins and drug molecules bound to them are too large and polar for this type of transport to occur; thus, transcapillary movement is limited to unbound drug. Paracellular transport through intercellular gaps is sufficiently large that passage across most capillaries is limited by blood flow and not by other factors (*see* below). As described later, this type of transport is an important factor in filtration across

glomerular membranes in the kidney. Important exceptions exist in such capillary diffusion, however, since "tight" intercellular junctions are present in specific tissues and paracellular transport in them is limited. Capillaries of the central nervous system (CNS) and a variety of epithelial tissues have tight junctions (*see* below). Although bulk flow of water can carry with it small, water-soluble substances, if the molecular mass of these compounds is greater than 100 to 200 daltons, such transport is limited. Accordingly, most large lipophilic drugs must pass through the cell membrane itself by one or more processes.

Passive Membrane Transport. Drugs cross membranes either by passive processes or by mechanisms involving the active participation of components of the membrane. In the former, the drug molecule usually penetrates by passive diffusion along a concentration gradient by virtue of its solubility in the lipid bilayer. Such transfer is directly proportional to the magnitude of the concentration gradient across the membrane, the lipid:water partition coefficient of the drug, and the cell surface area. The greater the partition coefficient, the higher is the concentration of drug in the membrane and the faster is its diffusion. After a steady state is attained, the concentration of the unbound drug is the same on both sides of the membrane if the drug is a nonelectrolyte. For ionic compounds, the steady-state concentrations will be dependent on differences in pH across the membrane, which may influence the state of ionization of the molecule on each side of the membrane and on the electrochemical gradient for the ion.

Weak Electrolytes and Influence of pH. Most drugs are weak acids or bases that are present in solution as both the nonionized and ionized species. The nonionized molecules are usually lipid-soluble and can diffuse across the cell membrane. In contrast, the ionized molecules are usually unable to penetrate the lipid membrane because of their low lipid solubility.

Therefore, the transmembrane distribution of a weak electrolyte usually is determined by its pK_a and the pH gradient across the membrane. The pK_a is the pH at which half of the drug (weak electrolyte) is in its ionized form. To illustrate the effect of pH on distribution of drugs, the partitioning of a weak acid ($pK_a = 4.4$) between plasma (pH = 7.4) and gastric juice (pH = 1.4) is depicted in Figure 1–2. It is assumed that the gastric mucosal membrane behaves as a simple lipid barrier that is permeable only to the lipid-soluble, nonionized form of the acid. The ratio of nonionized to ionized drug at each pH is readily calculated from the Henderson–Hasselbalch equation. Thus, in plasma, the ratio of nonionized to ionized drug is 1:1000; in gastric juice, the ratio is 1:0.001. These values are given in brackets in Figure 1–2. The total concentration ratio between the plasma and the gastric juice would therefore be 1000:1 if such a system came to a steady state. For a weak base with a pK_a of 4.4, the ratio would be reversed, as would the thick horizontal arrows in Figure 1–2, which indicate the predominant species at

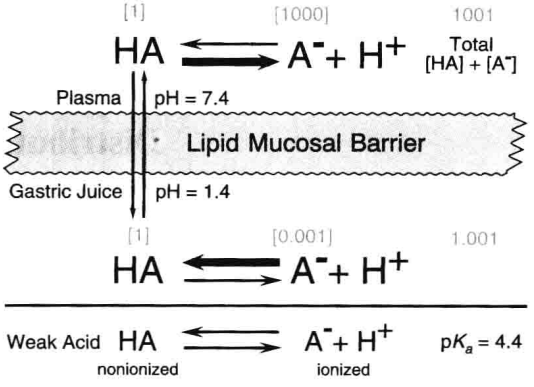

Figure 1–2. Influence of pH on the distribution of a weak acid between plasma and gastric juice, separated by a lipid barrier.

each pH. Accordingly, at steady state, an acidic drug will accumulate on the more basic side of the membrane and a basic drug on the more acidic side—a phenomenon termed *ion trapping*. These considerations have obvious implications for the absorption and excretion of drugs, as discussed more specifically below. The establishment of concentration gradients of weak electrolytes across membranes with a pH gradient is a purely physical process and does not require an active transport system. All that is necessary is a membrane preferentially permeable to one form of the weak electrolyte and a pH gradient across the membrane. The establishment of the pH gradient is, however, an active process.

Carrier-Mediated Membrane Transport. While passive diffusion through the bilayer is dominant in the disposition of most drugs, carrier-mediated mechanisms also can play an important role. *Active transport* is characterized by a requirement for energy, movement against an electrochemical gradient, saturability, selectivity, and competitive inhibition by cotransported compounds. The term *facilitated diffusion* describes a carrier-mediated transport process in which there is no input of energy and therefore enhanced movement of the involved substance is down an electrochemical gradient. Such mechanisms, which may be highly selective for a specific conformational structure of a drug, are involved in the transport of endogenous compounds whose rate of transport by passive diffusion otherwise would be too slow. In other cases, they function as a barrier system to protect cells from potentially toxic substances.

The responsible transporter proteins often are expressed within cell membranes in a domain-specific fashion such that they mediate either drug uptake or efflux, and often such an arrangement facilitates vectorial transport across cells. Thus, in the liver, a number of basolaterally localized transporters with different substrate specificities are involved in the uptake of bile acids and amphipathic organic anions and cations into the hepatocyte, and a similar variety of ATP-dependent transporters in the canalicular membrane export such compounds into the bile. Analogous situations also are present in intestinal and renal tubular membranes. An important efflux transporter present at