Goodman & Gilman's

THE PHARMACOLOGICAL BASIS OF THERAPEUTICS

13TH EDITION

LAURENCE L. BRUNTON
RANDA HILAL-DANDAN
BJÖRN C. KNOLLMANN

Mc Graw Hill Education

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THIRTEENTH EDITION

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THIRTEENTH EDITION

Editor-in-chief

Laurence L. Brunton, PhD
Professor of Pharmacology and Medicine
School of Medicine, University of California, San Diego
La Jolla, California

Editors

Randa Hilal-Dandan, PhD
Lecturer in Pharmacology
School of Medicine, University of California, San Diego
La Jolla, California

Björn C. Knollmann, MD, PhD
William Stokes Professor of Medicine and Pharmacology
Director, Vanderbilt Center for Arrhythmia Research and Therapeutics
Division of Clinical Pharmacology
Vanderbilt University School of Medicine
Nashville, Tennessee

Mc Graw Hill Education

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In Memoriam

Alfred Goodman Gilman

(1941-2015)

Mentor, teacher, researcher, Nobel laureate, raconteur, mensch,
and longtime editor of this book

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Contents

Contributors

Edward P. Acosta, PharmD
Professor and Director, Division of Clinical Pharmacology
University of Alabama at Birmingham School of Medicine
Birmingham, Alabama

Susan G. Amara, PhD
Scientific Director
National Institute of Mental Health
National Institutes of Health
Bethesda, Maryland

Michael B. Atkins, MD
Professor of Oncology and Medicine
Georgetown University, School of Medicine
Washington DC

Jamil Azzi, MD, FAST
Assistant Professor of Medicine
Transplantation Research Center
Harvard Medical School
Boston, Massachusetts

Peter J. Barnes, DM, DSc, FRCP, FMedSci, FRS
Professor and Head of Respiratory Medicine
National Heart & Lung Institute
Imperial College, London

Robert R. Bies, PharmD, PhD
Associate Professor
School of Pharmacy and Pharmaceutical Sciences
University at Buffalo
The State University of New York
Buffalo, New York

Donald K. Blumenthal, PhD
Associate Professor of Pharmacology & Toxicology
College of Pharmacy
University of Utah
Salt Lake City, Utah

Katharina Brandl, PhD
Assistant Professor of Pharmacy
University of California San Diego
Skaggs School of Pharmacy and Pharmaceutical Sciences
La Jolla, California

Gregory A. Brent, MD
Professor of Medicine and Physiology
Geffen School of Medicine
University of California
Los Angeles, California

Joan Heller Brown, PhD
Professor and Chair of Pharmacology
University of California
San Diego, California

Craig N. Burkhart, MD
Associate Professor of Dermatology, School of Medicine
University of North Carolina
Chapel Hill, North Carolina

Iain L. O. Buxton, PharmD
Foundation Professor and Chair
Department of Pharmacology
University of Nevada, Reno School of Medicine
Reno, Nevada

Michael C. Byrns, PhD
Associate Professor of Environmental Health
Illinois State University
Normal, Illinois

William A. Catterall, PhD
Professor and Chair of Pharmacology
University of Washington School of Medicine
Seattle, Washington

Janet A. Clark, PhD
Director, Office of Fellowship Training
Intramural Research Program
National Institute of Mental Health
National Institutes of Health
Bethesda, Maryland

Michael W. H. Coughtrie, PhD
Professor and Dean
Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, Canada

James E. Crowe, Jr.
Professor of Pediatrics, Pathology, Microbiology and Immunology
Director, Vanderbilt Vaccine Center
Vanderbilt University Medical Center
Nashville, Tennessee

David D'Alessio, MD
Professor, Department of Medicine
Director, Division of Endocrinology
Duke University Medical Center
Durham, North Carolina

Michael David, PharmD, PhD
Professor of Biology and Moores Cancer Center
University of California, San Diego
La Jolla, California

Ankit A. Desai, MD
Assistant Professor of Medicine
University of Arizona
Tucson, Arizona

Michelle Erickson, PhD
Research Assistant Professor of Gerontology and Geriatric Medicine, School of Medicine
University of Washington
Seattle, Washington

Thomas Eschenhagen, MD
Professor of Pharmacology and Toxicology
Chair of Pharmacology
University Medical Center Hamburg Eppendorf
Hamburg, Germany

Nancy Fares-Frederickson, PhD
Division of Biology and Moores Cancer Center
University of California, San Diego
La Jolla, California

Garret A. FitzGerald, MD
Professor of Medicine, Pharmacology and Translational Medicine and Therapeutics;
Chair of Pharmacology
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Charles W. Flexner, MD
Professor of Medicine, Pharmacology and Molecular Sciences, and International Health
The Johns Hopkins University School of Medicine and Bloomberg School of Public Health
Baltimore, Maryland

Dustin R. Fraidenburg, MD
Assistant Professor of Medicine
University of Illinois at Chicago
Chicago, Illinois

R. Benjamin Free, PhD
Staff Scientist, Molecular Neuropharmacology Section
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, Maryland

Peter A. Friedman, PhD
Professor of Pharmacology and Chemical Biology, and of Structural Biology
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

John W. Funder, AC, MD, BS, PhD, FRACP
Professor of Medicine, Prince Henry's Institute
Monash Medical Centre
Clayton, Victoria, Australia

Giuseppe Giaccone, MD, PhD
Professor of Medical Oncology and Pharmacology
Georgetown University
Washington DC

Kathleen M. Giacomini, PhD
Professor of Bioengineering and Therapeutic Sciences, School of Pharmacy
University of California
San Francisco, California

Alfred G. Gilman, MD, PhD (deceased)
Professor (Emeritus) of Pharmacology
University of Texas Southwestern Medical School
Dallas, Texas

Frank J. Gonzalez, PhD
Chief, Laboratory of Metabolism
Center for Cancer Research, National Cancer Institute
Bethesda, Maryland

Tilo Grosser, MD
Research Associate Professor of Pharmacology
Institute for Translational Medicine and Therapeutics
University of Pennsylvania
Philadelphia, Pennsylvania

Tawanda Gumbo, MD
Director, Center for Infectious Diseases Research and Experimental Therapeutics
Baylor Research Institute
Baylor University Medical Center
Dallas, Texas

Holly Gurgle, PharmD, BCACP, CDE
Assistant Professor (Clinical) of Pharmacotherapy
College of Pharmacy
University of Utah
Salt Lake City, Utah

David A. Hafler, MD
William S. and Lois Stiles Edgerly Professor of Neurology and Immunobiology
Chairman, Department of Neurology
Yale School of Medicine
New Haven, Connecticut

Stephen R. Hammes, MD, PhD
Professor of Medicine, Chief of Endocrinology and Metabolism
School of Medicine and Dentistry
University of Rochester
Rochester, New York

R. Adron Harris, PhD
Professor of Neuroscience and Pharmacology
Waggoner Center for Alcohol and Addiction Research
University of Texas
Austin, Texas

Lisa A. Hazelwood, PhD
Principal Research Scientist, Liver Disease and Fibrosis, AbbVie
North Chicago, Illinois

Jeffrey D. Henderer, MD
Professor of Ophthalmology
Dr. Edward Hagop Bedrossian Chair of Ophthalmology
Lewis Katz School of Medicine at Temple University
Philadelphia, Pennsylvania

Ryan E. Hibbs, PhD
Assistant Professor of Neuroscience
University of Texas Southwestern Medical School
Dallas, Texas

Randa Hilal-Dandan, PhD
Lecturer in Pharmacology
University of California
San Diego, California

Peter J. Hotez, MD, PhD
Professor of Pediatrics and Molecular Virology & Microbiology
Texas Children's Hospital Endowed Chair in Tropical Pediatrics
Dean, National School of Tropical Medicine
Baylor College of Medicine
Houston, Texas

Claudine Isaacs, MD, FRCPC
Professor of Medicine and Oncology
Georgetown University, School of Medicine
Washington DC

Nina Isoherranen, PhD
Professor of Pharmaceutics, School of Pharmacy
University of Washington
Seattle, Washington

Edwin K. Jackson, PhD
Professor of Pharmacology and Chemical Biology
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Kenneth Kaushansky, MD
Dean, School of Medicine and Senior Vice President of Health Sciences
SUNY Stony Brook
New York, New York

Jennifer Keiser, PhD
Professor of Neglected Tropical Diseases
Swiss Tropical and Public Health Institute
Basel, Switzerland

Thomas J. Kipps, MD, PhD
Professor of Medicine, Moores Cancer Center
University of California
San Diego, California

Jennifer J. Kiser, PharmD
Associate Professor, Pharmaceutical Sciences
University of Colorado
Denver, Colorado

Ronald J. Koenig, MD, PhD
Professor of Metabolism, Endocrinology and Diabetes
Department of Internal Medicine
University of Michigan Health System
Ann Arbor, Michigan

George F. Koob, PhD
Director, National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health
Rockville, Maryland

Alan M. Krensky, MD
Vice Dean
Professor of Pediatrics and Microbiology & Immunology
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

Ellis R. Levin, MD
Professor of Medicine; Chief of Endocrinology
Diabetes and Metabolism
University of California, Irvine, and Long Beach
VA Medical Center
Long Beach, California

Heather Macarthur, PhD
Associate Professor of Pharmacology and Physiology
Saint Louis University School of Medicine
St. Louis, Missouri

Conan MacDougall, PharmD, MAS
Professor of Clinical Pharmacy
School of Pharmacy
University of California
San Francisco, California

Wallace K. MacNaughton, PhD
Professor and Head of Physiology and Pharmacology
Cumming School of Medicine,
University of Calgary
Calgary, Alberta, Canada

Kenneth P. Mackie, MD
Professor of Psychological and Brain Sciences
Indiana University
Bloomington, Indiana

Jody Mayfield, PhD
Science Writer and Editor
Waggoner Center for Alcohol and Addiction Research
University of Texas
Austin, Texas

James McCarthy, MD
Senior Scientist QIMR Berghofer Intitute of Medical Research
Department of Infectious Diseases, Royal Brisbane
and Womens Hospital
Brisbane, Queensland, Australia

James O. McNamara, MD
Professor and Chair of Neurobiology
Director of Center for Translational Neuroscience
Duke University Medical Center
Durham, North Carolina

Cameron S. Metcalf, PhD
Research Assistant Professor
Associate Director, Anticonvulsant Drug Development Program
Department of Pharmacology & Toxicology
College of Pharmacy
University of Utah
Salt Lake City, Utah

Jonathan M. Meyer, MD
Psychopharmacology Consultant
California Department of State Hospitals
Assistant Clinical Professor of Psychiatry
University of California
San Diego, California

S. John Mihic, PhD
Professor of Neuroscience
Waggoner Center for Alcohol & Addiction Research
University of Texas
Austin, Texas

Mark E. Molitch, MD
Martha Leland Sherwin Professor of Endocrinology
Northwestern University
Chicago, Illinois

Dean S. Morrell, MD
Professor of Dermatology
University of North Carolina
Chapel Hill, North Carolina

Thomas D. Nolin, PharmD, PhD
Associate Professor of Pharmacy and Therapeutics, and of Medicine
University of Pittsburgh School of Pharmacy and School of Medicine
Pittsburgh, Pennsylvania

Charles P. O'Brien, MD, PhD
Professor of Psychiatry, School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

James O'Donnell, PhD
Dean and Professor
School of Pharmacy & Pharmaceutical Sciences
University at Buffalo
The State University of New York
Buffalo, New York

Hemal H. Patel, PhD
Professor of Anesthesiology
University of California, San Diego
VA-San Diego Healthcare System
San Diego, California

Piyush M. Patel, MD, FRCPC
Professor of Anesthesiology
University of California, San Diego
VA-San Diego Healthcare System
San Diego, California

Matthew L. Pearn, MD
Associate Professor of Anesthesiology
University of California, San Diego
VA-San Diego Healthcare System
San Diego, California

Trevor M. Penning, PhD
Professor of Systems Pharmacology & Translational Therapeutics
Director, Center of Excellence in Environmental Toxicology
School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Margaret A. Phillips, PhD
Professor of Pharmacology
University of Texas Southwestern Medical School
Dallas, Texas

Alvin C. Powers, MD
Professor of Medicine, Molecular Physiology and Biophysics
Director, Vanderbilt Diabetes Center
Chief, Division of Diabetes, Endocrinology, and Metabolism
Vanderbilt University School of Medicine
Nashville, Tennessee

Christopher J. Rapuano, MD
Director, Cornea Service and Refractive Surgery
Wills Eye Hospital
Philadelphia, Pennsylvania

Anna T. Riegel, PhD
Professor of Oncology and Pharmacology
Georgetown University, School of Medicine
Washington DC

Suzanne M. Rivera, PhD, MSW
Assistant Professor of Bioethics
Case Western Reserve University
Cleveland, Ohio

Erik D. Roberson, MD, PhD
Associate Professor of Neurology and Neurobiology
Co-Director, Center for Neurodegeneration and
Experimental Therapeutics
University of Alabama at Birmingham
Birmingham, Alabama

Dan M. Roden, MD
Professor of Medicine, Pharmacology, and Biomedical Informatics
Senior Vice President for Personalized Medicine
Vanderbilt University Medical Center
Nashville, Tennessee

P. David Rogers, PharmD, PhD, FCCP
First Tennessee Endowed Chair of Excellence in Clinical Pharmacy
Vice-Chair for Research
Director, Clinical and Experimental Therapeutics
Co-Director, Center for Pediatric Pharmacokinetics and Therapeutics
Professor of Clinical Pharmacy and Pediatrics
University of Tennessee College of Pharmacy
Memphis, Tennessee

David M. Roth, MD, PhD
Professor of Anesthesiology
University of California, San Diego
VA-San Diego Healthcare System
San Diego, California

Edward A. Sausville, MD, PhD
Professor of Medicine; Adjunct Professor, Pharmacology &
Experimental Therapeutics
University of Maryland School of Medicine
Baltimore, Maryland

Matthew J. Sewell, MD
Pediatric Dermatology Fellow
Department of Dermatology
University of North Carolina
Chapel Hill, North Carolina

Bernard P. Schimmer, PhD
Professor (Emeritus) of Pharmacology and Toxicology
University of Toronto
Ontario, Canada

Keith A. Sharkey, PhD, CAGF, FCAHS
Professor of Physiology and Pharmacology
Cumming School of Medicine
University of Calgary
Calgary, Alberta, Canada

Richard C. Shelton, MD
Professor, Department of Psychiatry and Behavioral Neurobiology
The University of Alabama at Birmingham
Birmingham, Alabama

Danny Shen, PhD
Professor of Pharmaceutics, School of Pharmacy
University of Washington
Seattle, Washington

David R. Sibley, PhD
Senior Investigator, Molecular Neuropharmacology Section
National Institute of Neurological Disorders & Stroke
National Institutes of Health
Bethesda, Maryland

Randal A. Skidgel, PhD
Professor of Pharmacology
College of Medicine, University of Illinois-Chicago
Chicago, Illinois

Misty D. Smith, PhD
Research Assistant Professor, Department of Pharmacology & Toxicology;
Research Assistant Professor, School of Dentistry
Co-Investigator, Anticonvulsant Drug Development Program
University of Utah
Salt Lake City, Utah

Emer M. Smyth, PhD
Director, Cancer Research Alliances
Assistant Dean for Cancer Research
Assistant Professor, Pathology and Cell Biology
Herbert Irving Comprehensive Cancer Center
Columbia University Medical Center
New York, New York

Peter J. Snyder, MD
Professor of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Yuichi Sugiyama, PhD
Head of Sugiyama Laboratory
RIKEN Innovation Center
RIKEN Yokohama
Yokohama, Japan

Palmer Taylor, PhD
Sandra & Monroe Trout Professor of Pharmacology, School of Medicine
Dean Emeritus, Skaggs School of Pharmacy and Pharmaceutical Sciences
University of California
San Diego, California

Kenneth E. Thummel, PhD
Professor and Chair, Department of Pharmaceutics
University of Washington
Seattle, Washington

Roberto Tinoco, PhD
Research Assistant Professor
Infectious and Inflammatory Diseases Center
Sanford Burnham Prebys Medical Discovery Institute
La Jolla, California

Robert H. Tukey, PhD
Professor of Pharmacology and Chemistry/Biochemistry
University of California
San Diego, California

Joseph M. Vinetz, MD
Professor of Medicine, Division of Infectious Diseases
University of California
San Diego, California

Wendy Vitek, MD
Assistant Professor of Obstetrics and Gynecology
University of Rochester School of Medicine and Dentistry
Rochester, New York

Mark S. Wallace, MD
Professor of Clinical Anesthesiology
University of California
San Diego, California

Jeffrey I. Weitz, MD, FRCP(C), FACP
Professor of Medicine
Biochemistry and Biomedical Sciences McMaster University
Executive Director, Thrombosis & Atherosclerosis Research Institute
Hamilton, Ontario, Canada

Anton Wellstein, MD, PhD
Professor of Oncology and Pharmacology
Georgetown University, School of Medicine
Washington DC

Jürgen Wess, PhD
Chief, Molecular Signaling Section
Lab. of Bioorganic Chemistry
National Institute of Diabetes and Digestive and Kidney Diseases
Bethesda, Maryland

David P. Westfall, PhD
Professor (Emeritus) of Pharmacology
University of Nevada School of Medicine
Reno, Nevada

Thomas C. Westfall, PhD
Professor and Chair Emeritus, Department of Pharmacology and Physiology
Saint Louis University School of Medicine
St. Louis, Missouri

Dawn M. Wetzel, MD, PhD
Assistant Professor of Pediatrics (Division of Infectious Diseases) and Pharmacology
University of Texas Southwestern Medical Center
Dallas, Texas

Karen S. Wilcox, PhD
Professor and Chair, Department of Pharmacology
Director, Anticonvulsant Drug Development Program
University of Utah
Salt Lake City, Utah

Kerstin de Wit, MD
Department of Medicine
Divisions of Emergency and Haematology
McMaster University, Canada;
Thrombosis and Emergency Physician
Hamilton Health Sciences
Hamilton, Ontario, Canada

Tony L. Yaksh, PhD
Professor of Anesthesiology and Pharmacology
University of California, San Diego
La Jolla, California

Jason X.-J. Yuan, MD, PhD
Professor of Medicine and Physiology;
Chief, Division of Translational and Regenerative Medicine
University of Arizona
Tucson, Arizona

Alexander C. Zambon, PhD
Assistant Professor of Biopharmaceutical Sciences
Keck Graduate Institute
Claremont, California

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Preface

The first edition of this book appeared in 1941, the product of a collaboration between two friends and professors at Yale, Louis Goodman and Alfred Gilman. Their purpose, stated in the preface to that edition, was to correlate pharmacology with related medical sciences, to reinterpret the actions and uses of drugs in light of advances in medicine and the basic biomedical sciences, to emphasize the applications of pharmacodynamics to therapeutics, and to create a book that would be useful to students of pharmacology and to physicians. We continue to follow these principles in the 13th edition.

The 1st edition was quite successful despite its high price, $12.50, and soon became known as the "blue bible of pharmacology." The book was evidence of the deep friendship between its authors, and when the Gilmans' son was born in 1941, he was named Alfred Goodman Gilman. World War II and the relocation of both authors—Goodman to Utah, Gilman to Columbia—postponed a second edition until 1955. The experience of writing the second edition during a period of accelerating basic research and drug development persuaded the authors to become editors, relying on experts whose scholarship they trusted to contribute individual chapters, a pattern that has been followed ever since.

Alfred G. Gilman, the son, served as an associate editor for the 5th edition (1975), became the principal editor for the 6th (1980), 7th (1985), and 8th (1990) editions, and consulting editor for the 9th and 10th editions that were edited by Lee Limbird and Joel Hardman. After an absence in the 11th edition, Al Gilman agreed to co-author the introductory chapter in the 12th edition. His final contribution to G&G, a revision of that chapter, is the first chapter in this edition, which we dedicate to his memory.

A multi-authored text of this sort grows by accretion, posing challenges to editors but also offering 75 years of wisdom, memorable pearls, and flashes of wit. Portions of prior editions persist in the current edition, and we have given credit to recent former contributors at the end of each chapter. Such a text also tends to grow in length with each edition, as contributors add to existing text and as pharmacotherapy advances. To keep the length manageable and in a single volume, Dr. Randa Hilal-Dandan and I prepared a shortened version of each chapter and then invited contributors to add back old material that was essential and to add new material. We also elected to discard the use of extract (very small) type and to use more figures to explain signaling pathways and mechanisms of drug action. Not wanting to favor one company's preparation of an agent over that of another, we have ceased to use trade names except as needed to refer to drug combinations or to distinguish multiple formulations of the same agent with distinctive pharmacokinetic or pharmacodynamic properties. Counter-balancing this shortening are five new chapters that reflect advances in the therapeutic manipulation of the immune system, the treatment of viral hepatitis, and the pharmacotherapy of cardiovascular disease and pulmonary artery hypertension.

Editing such a book brings into view a number of overarching issues: Over-prescribing of antibiotics and their excessive use in agricultural animal husbandry continues to promote the development of antimicrobial resistance; the application of CRISPR/cas9 will likely provide new therapeutic avenues; global warming and the sheer size of the human population require medical scientists and practitioners to promote remedial and preventive action based on data, not ideology.

A number of people have made invaluable contributions to the preparation of this edition. My thanks to Randa Hilal-Dandan and Bjorn Knollmann for their editorial work; to Harriet Lebowitz of McGraw-Hill, who guided our work, prescribed the updated style, and kept the project moving to completion; to Vastavikta Sharma of Cenveo Publishers Services, who oversaw the copy editing, typesetting, and preparation of the artwork; to Nelda Murri, our consulting pharmacist, whose familiarity with clinical pharmacy is evident throughout the book; to James Shanahan, publisher at McGraw-Hill, for supporting the project; and to the many readers who have written to critique the book and offer suggestions.

Laurence L. Brunton
San Diego, CA
1 September 2017

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Acknowledgments

The editors appreciate the assistance of:

Harriet Lebowitz
Senior Project Development Editor
McGraw-Hill Education

Laura Libretti
Administrative Assistant
McGraw-Hill Education

Bryan Mott, PhD
Consulting Medicinal Chemist

Nelda Murri, PharmD, MBA
Consulting Pharmacist

Christie Naglieri
Senior Project Development Editor
McGraw-Hill Education

Joseph K. Prinsen, DO, PhD
Jason D. Morrow Chief Fellow in Clinical Pharmacology
Vanderbilt University School of Medicine

David Aaron Rice
Administrative Assistant
University of California, San Diego

James F. Shanahan
Publisher, Medical Textbooks
McGraw-Hill Education

Vastavikta Sharma
Lead Project Manager
Cenveo Publisher Services

Roberto Tinoco, PhD
Research Assistant Professor
Sanford-Burnham-Prebys Medical Discovery Institute

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Section I

General Principles

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Chapter 1

Drug Invention and the Pharmaceutical Industry

Suzanne M. Rivera and Alfred Goodman Gilman*

The first edition of *Goodman & Gilman*, published in 1941, helped to organize the field of pharmacology, giving it intellectual validity and an academic identity. That edition 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 that affects living protoplasm, and few substances would escape inclusion by this definition." This General Principles section provides the underpinnings for these definitions by exploring the processes of drug invention, development, and regulation, followed by the basic properties of the interactions between the drug and biological systems: *pharmacodynamics*, *pharmacokinetics* (including drug transport and metabolism), and *pharmacogenomics*, with a brief foray into *drug toxicity and poisoning*. Subsequent sections deal with the use of drugs as therapeutic agents in human subjects.

Use of the term *invention* to describe the process by which a new drug is identified and brought to medical practice, rather than the more conventional term *discovery,* is intentional. Today, useful drugs are rarely discovered hiding somewhere waiting to be found. The term *invention* emphasizes the process by which drugs are sculpted and brought into being based on experimentation and optimization of many independent properties; there is little serendipity.

From Early Experiences With Plants to Modern Chemistry

The human fascination—and sometimes infatuation—with chemicals that alter biological function is ancient and results from long experience with and dependence on plants. Because most plants are root bound, many of them produce harmful compounds for defense that animals have learned to avoid and humans to exploit (or abuse).

Earlier editions of this text described examples: the appreciation of coffee (caffeine) by the prior of an Arabian convent, who noted the behavior of goats that gamboled and frisked through the night after eating the berries of the coffee plant; the use of mushrooms and the deadly nightshade plant by professional poisoners; of belladonna ("beautiful lady") to dilate pupils; of the Chinese herb ma huang (containing ephedrine) as a circulatory stimulant; of curare by South American Indians to paralyze and kill animals hunted for food; and of poppy juice (opium) containing morphine (from the Greek *Morpheus*, the God of dreams) for pain relief and control of dysentery. Morphine, of course, has well-known addicting properties, mimicked in some ways by other problematic ("recreational") natural products—nicotine, cocaine, and ethanol.

Although terrestrial and marine organisms remain valuable sources of compounds with pharmacological activities, drug invention became more allied with synthetic organic chemistry as that discipline flourished over the past 150 years, beginning in the dye industry. Dyes are colored compounds with selective affinity for biological tissues. Study of these interactions stimulated Paul Ehrlich to postulate the existence of chemical receptors in tissues that interacted with and "fixed" the dyes. Similarly, Ehrlich thought that unique receptors on microorganisms or parasites might react specifically with certain dyes and that such selectivity could spare normal tissue. Ehrlich's work culminated in the invention of arsphenamine in 1907, which was patented as "salvarsan," suggestive of the hope that the chemical would be the salvation of humankind. This and other organic arsenicals were used for the chemotherapy of syphilis until the discovery of penicillin. The work of Gerhard Domagk demonstrated that another dye, prontosil (the first clinically useful sulfonamide), was dramatically effective in treating streptococcal infections, launching the era of antimicrobial chemotherapy.

The collaboration of pharmacology with chemistry on the one hand and with clinical medicine on the other has been a major contributor to the effective treatment of disease, especially since the middle of the 20th century.

Sources of Drugs

Small Molecules Are the Tradition

With the exception of a few naturally occurring hormones (e.g., insulin), most drugs were small organic molecules (typically <500 Da) until

*Deceased, December 23, 2015. AGG served on the Board of Directors of Regeneron Pharmaceuticals, Inc., a potential conflict of interest.

Abbreviations

ADME: absorption, distribution, metabolism, excretion
AHFS-DI: American Hospital Formulary Service-Drug Information
BLA: Biologics License Application
CDC: Centers for Disease Control and Prevention
CDER: Center for Drug Evaluation and Research
DHHS: U.S. Department of Health and Human Services
FDA: U.S. Food and Drug Administration
HCV: hepatitis C virus
HMG CoA: 3-hydroxy-3-methylglutaryl coenzyme A
IND: Investigational New Drug
LDL: low-density lipoprotein
NDA: New Drug Application
NIH: National Institutes of Health
NMEs: New Molecular Entities
NMR: nuclear magnetic resonance
PCSK9: proprotein convertase subtilisin/kexin type 9
PDUFA: Prescription Drug User Fee Act
PhRMA: Pharmaceutical Research and Manufacturers of America
R&D: research and development
SCHIP: State Children's Health Insurance Program
siRNAs: small interfering RNAs

recombinant DNA technology permitted synthesis of proteins by various organisms (bacteria, yeast) and mammalian cells. The usual approach to invention of a small-molecule drug is to screen a collection of chemicals ("library") for compounds with the desired features. An alternative is to synthesize and focus on close chemical relatives of a substance known to participate in a biological reaction of interest (e.g., congeners of a specific enzyme substrate chosen to be possible inhibitors of the enzymatic reaction), a particularly important strategy in the discovery of anticancer drugs.

Drug discovery in the past often resulted from serendipitous observations of the effects of plant extracts or individual chemicals on animals or humans; today's approach relies more on high-throughput screening of libraries containing hundreds of thousands or even millions of compounds for their capacity to interact with a specific molecular target or elicit a specific biological response. Ideally, the target molecules are of human origin, obtained by transcription and translation of the cloned human gene. The potential drugs that are identified in the screen ("hits") are thus known to react with the human protein and not just with its relative (ortholog) obtained from the mouse or another species.

Among the variables considered in screening are the "drugability" of the target and the stringency of the screen in terms of the concentrations of compounds that are tested. *Drugability* refers to the ease with which the function of a target can be altered in the desired fashion by a small organic molecule. If the protein target has a well-defined binding site for a small molecule (e.g., a catalytic or allosteric site), chances are excellent that hits will be obtained. If the goal is to employ a small molecule to mimic or disrupt the interaction between two proteins, the challenge is much greater.

From Hits to Leads

Initial hits in a screen are rarely marketable drugs, often having modest affinity for the target and lacking the desired specificity and pharmacological properties. Medicinal chemists synthesize derivatives of the hits, thereby defining the structure-activity relationship and optimizing parameters such as affinity for the target, agonist/antagonist activity, permeability across cell membranes, absorption and distribution in the body, metabolism, and unwanted effects.

This approach was driven largely by instinct and trial and error in the past; modern drug development frequently takes advantage of determination of a high-resolution structure of the putative drug bound to its target. X-ray crystallography offers the most detailed structural information if the target protein can be crystallized with the lead drug bound to it. Using techniques of molecular modeling and computational chemistry, the structure provides the chemist with information about substitutions likely to improve the "fit" of the drug with the target and thus enhance the affinity of the drug for its target. Nuclear magnetic resonance (NMR) studies of the drug-receptor complex also can provide useful information (albeit usually at lower resolution), with the advantage that the complex need not be crystallized.

The holy grail of this approach to drug invention is to achieve success entirely through computation. Imagine a database containing detailed chemical information about millions of chemicals and a second database containing detailed structural information about all human proteins. The computational approach is to "roll" all the chemicals over the protein of interest to find those with high-affinity interactions. The dream becomes bolder if we acquire the ability to roll the chemicals that bind to the target of interest over all other human proteins to discard compounds that have unwanted interactions. Finally, we also will want to predict the structural and functional consequences of a drug binding to its target (a huge challenge), as well as all relevant pharmacokinetic properties of the molecules of interest. Indeed, computational approaches have suggested new uses for old drugs and offered explanations for recent failures of drugs in the later stages of clinical development (e.g., torcetrapib; see Box 1-2) (Xie et al., 2007, 2009).

Large Molecules Are Increasingly Important

Protein therapeutics were uncommon before the advent of recombinant DNA technology. Insulin was introduced into clinical medicine for the treatment of diabetes following the experiments of Banting and Best in 1921. Insulins purified from porcine or bovine pancreas are active in humans, although antibodies to the foreign proteins are occasionally problematic. Growth hormone, used to treat pituitary dwarfism, exhibits more stringent species specificity. Only the human hormone could be used after purification from pituitary glands harvested during autopsy, and such use had its dangers—some patients who received the human hormone developed Creutzfeldt-Jakob disease (the human equivalent of mad cow disease), a fatal degenerative neurological disease caused by prion proteins that contaminated the drug preparation. Thanks to gene cloning and the production of large quantities of proteins by expressing the cloned gene in bacteria or eukaryotic cells, protein therapeutics now use highly purified preparations of human (or humanized) proteins. Rare proteins can be produced in quantity, and immunological reactions are minimized. Proteins can be designed, customized, and optimized using genetic engineering techniques. Other types of macromolecules may also be used therapeutically. For example, antisense oligonucleotides are used to block gene transcription or translation, as are siRNAs.

Proteins used therapeutically include hormones; growth factors (e.g., erythropoietin, granulocyte colony-stimulating factor); cytokines; and a number of monoclonal antibodies used in the treatment of cancer and autoimmune diseases (Chapters 34–36 and 67). Murine monoclonal antibodies can be "humanized" (by substituting human for mouse amino acid sequences). Alternatively, mice have been engineered by replacement of critical mouse genes with their human equivalents, such that they make completely human antibodies. Protein therapeutics are administered parenterally, and their receptors or targets must be accessible extracellularly.

Targets of Drug Action

Early drugs came from observation of the effects of plants after their ingestion by animals, with no knowledge of the drug's mechanism or site of action. Although this approach is still useful (e.g., in screening for the capacity of natural products to kill microorganisms or malignant cells), modern drug invention usually takes the opposite approach, starting with

a statement (or hypothesis) that a certain protein or pathway plays a critical role in the pathogenesis of a certain disease, and that altering the protein's activity would be effective against that disease. Crucial questions arise:

- Can one find a drug that will have the desired effect against its target?
- Does modulation of the target protein affect the course of disease?
- Does this project make sense economically?

The effort expended to find the desired drug will be determined by the degree of confidence in the answers to the last two questions.

Is the Target Drugable?

The drugability of a target with a low-molecular-weight organic molecule relies on the presence of a binding site for the drug that exhibits considerable affinity and selectivity.

If the target is an enzyme or a receptor for a small ligand, one is encouraged. If the target is related to another protein that is known to have, for example, a binding site for a regulatory ligand, one is hopeful. However, if the known ligands are large peptides or proteins with an extensive set of contacts with their receptor, the challenge is much greater. If the goal is to disrupt interactions between two proteins, it may be necessary to find a "hot spot" that is crucial for the protein-protein interaction, and such a region may not be detected. Accessibility of the drug to its target also is critical. Extracellular targets are intrinsically easier to approach, and, in general, only extracellular targets are accessible to macromolecular drugs.

Has the Target Been Validated?

The question of whether the target has been validated is obviously a critical one. A negative answer, frequently obtained only retrospectively, is a common cause of failure in drug invention (Box 1–1). Modern techniques of molecular biology offer powerful tools for validation of potential drug targets, to the extent that the biology of model systems resembles human biology. Genes can be inserted, disrupted, and altered in mice. One can thereby create models of disease in animals or mimic the effects of long-term disruption or activation of a given biological process. If, for example, disruption of the gene encoding a specific enzyme or receptor has a beneficial effect in a valid murine model of a human disease, one may believe that the potential drug target has been validated. Mutations in humans also can provide extraordinarily valuable information.

For example, loss-of-function mutations in the *PCSK9* gene (encoding proprotein convertase subtilisin/kexin type 9) greatly lower concentrations of LDL cholesterol in blood and reduce the risk of myocardial infarction (Horton et al., 2009; Poirier and Mayer, 2013). Based on these findings, two companies now market antibodies that inhibit the action of *PCSK9*. These antibodies lower the concentration of LDL cholesterol in blood substantially and are essentially additive to the effects of statins; long-term outcome studies are in progress to determine whether the risk of significant cardiovascular events also is reduced. Additional molecules are in the queue.

BOX 1–1 ■ Target Validation: The Lesson of Leptin

Biological systems frequently contain redundant elements or can alter expression of drug-regulated elements to compensate for the effect of the drug. *In general, the more important the function, the greater the complexity of the system.* For example, many mechanisms control feeding and appetite, and drugs to control obesity have been notoriously difficult to find. The discovery of the hormone leptin, which suppresses appetite, was based on mutations in mice that cause loss of either leptin or its receptor; either kind of mutation results in enormous obesity in both mice and people. Leptin thus appeared to be a marvelous opportunity to treat obesity. However, on investigation, it was discovered that obese individuals have high circulating concentrations of leptin and appear insensitive to its action.

Is This Drug Invention Effort Economically Viable?

Drug invention and development is expensive (see Table 1-1), and economic realities influence the direction of pharmaceutical research. For example, investor-owned companies generally cannot afford to develop products for rare diseases or for diseases that are common only in economically underdeveloped parts of the world. Funds to invent drugs targeting rare diseases or diseases primarily affecting developing countries (especially parasitic diseases) often come from taxpayers or wealthy philanthropists.

Additional Preclinical Research

Following the path just described can yield a potential drug molecule that interacts with a validated target and alters its function in the desired fashion. Now, one must consider all aspects of the molecule in question—its affinity and selectivity for interaction with the target; its pharmacokinetic properties (ADME); issues of its large-scale synthesis or purification; its pharmaceutical properties (stability, solubility, questions of formulation); and its safety. One hopes to correct, to the extent possible, any obvious deficiencies by modification of the molecule itself or by changes in the way the molecule is presented for use.

Before being administered to people, potential drugs are tested for general toxicity by long-term monitoring of the activity of various systems in two species of animals, generally one rodent (usually the mouse) and one nonrodent (often the rabbit). Compounds also are evaluated for carcinogenicity, genotoxicity, and reproductive toxicity (see Chapter 4). In vitro and ex vivo assays are used when possible, both to spare animals and to minimize cost. If an unwanted effect is observed, an obvious question is whether it is mechanism based (i.e., caused by interaction of the drug with its intended target) or caused by an off-target effect of the drug, which might be minimized by further optimization of the molecule.

Before the drug candidate can be administered to human subjects in a clinical trial, the sponsor must file an IND application, a request to the U.S. FDA (see "Clinical Trials") for permission to use the drug for human research. The IND describes the rationale and preliminary evidence for efficacy in experimental systems, as well as pharmacology, toxicology, chemistry, manufacturing, and so forth. It also describes the plan (protocol) for investigating the drug in human subjects. The FDA has 30 days to review the IND application, by which time the agency may disapprove it, ask for more data, or allow initial clinical testing to proceed.

Clinical Trials

Role of the FDA

The FDA is a federal regulatory agency within the U.S. DHHS. It is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation (FDA, 2014). The FDA also is responsible for advancing public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable and by helping people obtain the accurate, science-based information they need to use medicines and foods to improve their health.

New governmental regulations often result from tragedies. The first drug-related legislation in the U.S., the Federal Food and Drug Act of 1906, was concerned only with the interstate transport of adulterated or misbranded foods and drugs. There were no obligations to establish drug efficacy or safety. This act was amended in 1938 after the deaths of over 100 children from "elixir sulfanilamide," a solution of sulfanilamide in diethylene glycol, an excellent but highly toxic solvent and an ingredient in antifreeze. The enforcement of the amended act was entrusted to the FDA, which began requiring toxicity studies as well as approval of an NDA (see "The Conduct of Clinical Trials") before a drug could be promoted and distributed. Although a new drug's safety had to be demonstrated, no proof of efficacy was required.

In the 1960s, thalidomide, a hypnotic drug with no obvious advantages over others, was introduced in Europe. Epidemiological research eventually established that this drug, taken early in pregnancy, was responsible for an epidemic of what otherwise is a relatively rare and severe birth defect, phocomelia, in which limbs are malformed. In reaction to this catastrophe, the U.S. Congress passed the Harris-Kefauver amendments to the Food, Drug, and Cosmetic Act in 1962. These amendments established the requirement for proof of efficacy as well as documentation of relative safety in terms of the risk-to-benefit ratio for the disease entity to be treated (the more serious the disease, the greater the acceptable risk).

Today, the FDA faces an enormous challenge, especially in view of the widely held belief that its mission cannot possibly be accomplished with the resources allocated by Congress. Moreover, harm from drugs that cause unanticipated adverse effects is not the only risk of an imperfect system; harm also occurs when the approval process delays the approval of a new drug with important beneficial effects.

The Conduct of Clinical Trials

Clinical trials of drugs are designed to acquire information about the pharmacokinetic and pharmacodynamic properties of a candidate drug in humans. Efficacy must be proven and an adequate margin of safety established for a drug to be approved for sale in the U.S.

The U.S. NIH identifies seven ethical principles that must be satisfied before a clinical trial can begin:

1. Social and clinical value
2. Scientific validity
3. Fair selection of subjects
4. Informed consent
5. Favorable risk-benefit ratio
6. Independent review
7. Respect for potential and enrolled subjects (NIH, 2011).

The FDA-regulated clinical trials typically are conducted in four phases. Phases I-III are designed to establish safety and efficacy, while phase IV postmarketing trials delineate additional information regarding new indications, risks, and optimal doses and schedules. Table 1–1 and Figure 1–1 summarize the important features of each phase of clinical trials; note the attrition at each successive stage over a relatively long and costly process. When initial phase III trials are complete, the sponsor (usually a pharmaceutical company) applies to the FDA for approval to market the drug; this application is called either an NDA or a BLA. These applications contain comprehensive information, including individual case report forms from the hundreds or thousands of individuals who have received the drug during its phase III testing. Applications are reviewed by teams of specialists, and the FDA may call on the help of panels of external experts in complex cases.

Under the provisions of the PDUFA (enacted in 1992 and renewed every 5 years, most recently in 2012), pharmaceutical companies now provide a significant portion of the FDA budget via user fees, a legislative effort to expedite the drug approval review process by providing increased resources. The PDUFA also broadened the FDA's drug safety program and increased resources for review of television drug advertising. Under the PDUFA, once an NDA is submitted to the FDA, review typically takes 6–10 months. During this time, numerous review functions are usually performed, including advisory committee meetings, amendments, manufacturing facility inspections, and proprietary name reviews (FDA, 2013a). Before a drug is approved for marketing, the company and the FDA must agree on the content of the "label" (package insert)—the official prescribing information. This label describes the approved indications for use of the drug and clinical pharmacological information, including dosage, adverse reactions, and special warnings and precautions (sometimes posted in a "black box").

Promotional materials used by pharmaceutical companies cannot deviate from information contained in the package insert. Importantly, the physician is not bound by the package insert; a physician in the U.S. *may* legally prescribe a drug for any purpose that he or she deems reasonable. However, third-party payers (insurance companies, Medicare, and so on) generally will not reimburse a patient for the cost of a drug used for an "off-label" indication unless the new use is supported by a statutorily named compendium (e.g., the AHFS-DI). Furthermore, a physician may be vulnerable to litigation if untoward effects result from an unapproved use of a drug.

Determining "Safe" and "Effective"

Demonstrating efficacy to the FDA requires performing "adequate and well-controlled investigations," generally interpreted to mean two replicate clinical trials that are usually, but not always, randomized, double blind, and placebo (or otherwise) controlled.

Is a placebo the proper control? The World Medical Association's *Declaration of Helsinki* (World Medical Association 2013) discourages use of placebo controls when an alternative treatment is available for comparison because of the concern that study participants randomized to placebo in such a circumstance would, in effect, be denied treatment during the conduct of the trial.

What must be measured in the trials? In a straightforward trial, a readily quantifiable parameter (a secondary or surrogate end point), thought to be predictive of relevant clinical outcomes, is measured in matched drug- and placebo-treated groups. Examples of surrogate end points include

TABLE 1–1 ■ TYPICAL CHARACTERISTICS OF THE VARIOUS PHASES OF THE CLINICAL TRIALS REQUIRED FOR MARKETING OF NEW DRUGS

PHASE I FIRST IN HUMAN	PHASE II FIRST IN PATIENT	PHASE III MULTISITE TRIAL	PHASE IV POSTMARKETING SURVEILLANCE
10–100 participants	50–500 participants	A few hundred to a few thousand participants	Many thousands of participants
Usually healthy volunteers; occasionally patients with advanced or rare disease	Patient-subjects receiving experimental drug	Patient-subjects receiving experimental drug	Patients in treatment with approved drug
Open label	Randomized and controlled (can be placebo controlled); may be blinded	Randomized and controlled (can be placebo controlled) or uncontrolled; may be blinded	Open label
Safety and tolerability	Efficacy and dose ranging	Confirm efficacy in larger population	Adverse events, compliance, drug-drug interactions
1–2 years	2–3 years	3–5 years	No fixed duration
U.S. $10 million	U.S. $20 million	U.S. $50–100 million	—
Success rate: 50%	Success rate: 30%	Success rate: 25%–50%	—

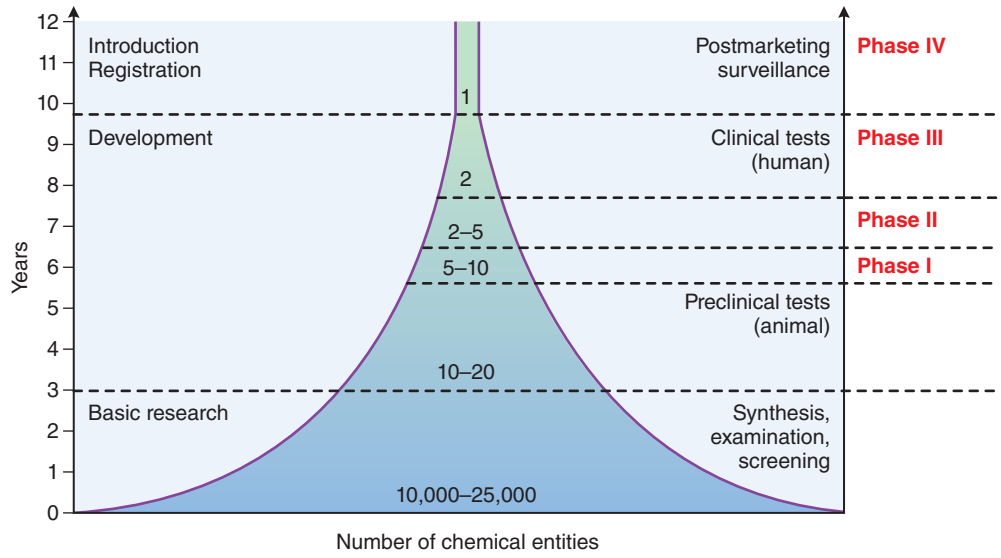

Figure 1–1 *The phases, time lines, and attrition that characterize the invention of new drugs.* See also Table 1–1.

LDL cholesterol as a predictor of myocardial infarction, bone mineral density as a predictor of fractures, or hemoglobin A_{1c} as a predictor of the complications of diabetes mellitus. More stringent trials would require demonstration of reduction of the incidence of myocardial infarction in patients taking a candidate drug in comparison with those taking an HMG CoA reductase inhibitor (statin) or other LDL cholesterol-lowering agent or reduction in the incidence of fractures in comparison with those taking a bisphosphonate. Use of surrogate end points significantly reduces cost and time required to complete trials, but there are many mitigating factors, including the significance of the surrogate end point to the disease that the candidate drug is intended to treat.

Some of the difficulties are well illustrated by experiences with ezetimibe, a drug that inhibits absorption of cholesterol from the gastrointestinal tract and lowers LDL cholesterol concentrations in blood, especially when used in combination with a statin. Lowering of LDL cholesterol was assumed to be an appropriate surrogate end point for the effectiveness of ezetimibe to reduce myocardial infarction and stroke, and the drug was approved based on such data. Surprisingly, a subsequent clinical trial (ENHANCE) demonstrated that the combination of ezetimibe and a statin did not reduce intima media thickness of carotid arteries (a more direct measure of subendothelial cholesterol accumulation) compared with the statin alone, despite the fact that the drug combination lowered LDL cholesterol concentrations substantially more than did either drug alone (Kastelein et al., 2008).

Critics of ENHANCE argued that the patients in the study had familial hypercholesterolemia, had been treated with statins for years, and did not have carotid artery thickening at the initiation of the study. Should ezetimibe have been approved? Must we return to measurement of true clinical end points (e.g., myocardial infarction) before approval of drugs that lower cholesterol by novel mechanisms? The costs involved in such extensive and expensive trials must be borne somehow (see below). A follow-up 7-year study involving over 18,000 patients (IMPROVE-IT) vindicated the decision to approve ezetimibe (Jarcho and Keaney, 2015). Taken in conjunction with a statin, the drug significantly reduced the incidence of myocardial infarction and stroke in high-risk patients (Box 1–2).

No drug is totally safe; all drugs produce unwanted effects in at least some people at some dose. Many unwanted and serious effects of drugs occur so infrequently, perhaps only once in several thousand patients, that they go undetected in the relatively small populations (a few thousand) in the standard phase III clinical trial (see Table 1–1). To detect and verify that such events are, in fact, drug-related would require administration of the drug to tens or hundreds of thousands of people during clinical trials, adding enormous expense and time to drug development and delaying access to potentially beneficial therapies. In general, the true spectrum and incidence of untoward effects become known only after a drug is released to the broader market and used by a large number of people (phase IV, postmarketing surveillance). Drug development costs and drug prices could be reduced substantially if the public were willing to accept more risk. This would require changing the way we think about a pharmaceutical company's liability for damages from an unwanted effect of a drug that was not detected in clinical trials deemed adequate by the FDA. While the concept is obvious, many lose sight of the fact that extremely severe unwanted effects of a drug, including death, may be deemed acceptable if its therapeutic effect is sufficiently unique and valuable. Such dilemmas are not simple and can become issues for great debate.

Several strategies exist to detect adverse reactions after marketing of a drug. Formal approaches for estimation of the magnitude of an adverse drug response include the follow-up or "cohort" study of patients who are receiving a particular drug; the "case-control" study, in which the frequency of drug use in cases of adverse responses is compared to controls; and meta-analysis of pre- and postmarketing studies. Voluntary reporting of adverse events has proven to be an effective way to generate an early signal that a drug may be causing an adverse reaction (Aagard and Hansen, 2009). The primary sources for the reports are responsible, alert physicians; third-party payers (pharmacy benefit managers, insurance companies) and consumers also play important roles. Other useful sources are nurses, pharmacists, and students in these disciplines. In addition, hospital-based pharmacy and therapeutics committees and quality assurance committees frequently are charged with monitoring adverse drug reactions in hospitalized patients. In 2013, the reporting system in the U.S., called *MedWatch,* celebrated its 20th anniversary and announced improvements designed to encourage reporting by consumers (FDA, 2013b). The simple forms for reporting may be obtained 24 hours a day, 7 days a week, by calling 800-FDA-1088; alternatively, adverse reactions

BOX 1–2 ■ A Late Surprise in the Development of a Blockbuster

Torcetrapib elevates high-density lipoprotein (HDL) cholesterol (the "good cholesterol"), and higher levels of HDL cholesterol are statistically associated with (are a surrogate end point for) a lower incidence of myocardial infarction. Surprisingly, clinical administration of torcetrapib caused a significant *increase* in mortality from cardiovascular events, ending a development path of 15 years and $800 million. In this case, approval of the drug based on this secondary end point would have been a mistake (Cutler, 2007). A computational systems analysis suggested a mechanistic explanation of this failure (Xie et al., 2009).

can be reported directly using the Internet (http://www.fda.gov/Safety/MedWatch/default.htm). Health professionals also may contact the pharmaceutical manufacturer, who is legally obligated to file reports with the FDA.

Personalized (Individualized, Precision) Medicine

Drug inventors strive to "fit" the drug to the individual patient. To realize the full potential of this approach, however, requires intimate knowledge of the considerable heterogeneity of both the patient population and the targeted disease process. Why does one antidepressant appear to ameliorate depression in a given patient, while another with the same or very similar presumed mechanism of action does not? Is this a difference in the patient's response to the drug; in patient susceptibility to the drug's unwanted effects; in the drug's ADME; or in the etiology of the depression? By contrast, how much of this variability is attributable to environmental factors and possibly their interactions with patient-specific genetic variability? Recent advances, especially in genetics and genomics, provide powerful tools for understanding this heterogeneity. The single most powerful tool for unraveling these myriad mysteries is the ability to sequence DNA rapidly and economically. The cost of sequencing a human genome has fallen by six orders of magnitude since the turn of the 21st century, and the speed of the process has increased correspondingly. The current focus is on the extraordinarily complex analysis of the enormous amounts of data now being obtained from many thousands of individuals, ideally in conjunction with deep knowledge of their phenotypic characteristics, especially including their medical history.

Readily measured biomarkers of disease are powerful adjuncts to DNA sequence information. Simple blood or other tests can be developed to monitor real-time progress or failure of treatment, and many such examples already exist. Similarly, chemical, radiological, or genetic tests may be useful not only to monitor therapy but also to predict success or failure, anticipate unwanted effects of treatment, or appreciate pharmacokinetic variables that may require adjustments of dosage or choice of drugs. Such tests already play a significant role in the choice of drugs for cancer chemotherapy, and the list of drugs specifically designed to "hit" a mutated target in a specific cancer is growing. Such information is also becoming increasing useful in the choice of patients for clinical trials of specific agents—thereby reducing the time required for such trials and their cost, to say nothing of better defining the patient population who may benefit from the drug. These important subjects are discussed in detail in Chapter 7, Pharmacogenetics.

Public Policy Considerations and Criticisms of the Pharmaceutical Industry

Drugs can save lives, prolong lives, and improve the quality of people's lives. However, in a free-market economy, access to drugs is not equitable. Not surprisingly, there is tension between those who treat drugs as entitlements and those who view drugs as high-tech products of a capitalistic society. Supporters of the entitlement position argue that a constitutional right to life should guarantee access to drugs and other healthcare, and they are critical of pharmaceutical companies and others who profit from the business of making and selling drugs. Free-marketers point out that, without a profit motive, it would be difficult to generate the resources and innovation required for new drug development. Given the public interest in the pharmaceutical industry, drug development is both a scientific process and a political one in which attitudes can change quickly. Two decades ago, Merck was named as America's most admired company by *Fortune* magazine 7 years in a row—a record that still stands. In the 2015 survey of the most admired companies in the U.S., no pharmaceutical company ranked in the top 10.

Critics of the pharmaceutical industry frequently begin from the position that people (and animals) need to be protected from greedy and unscrupulous companies and scientists (Kassirer, 2005). In the absence of a government-controlled drug development enterprise, our current system relies predominantly on investor-owned pharmaceutical companies that, like other companies, have a profit motive and an obligation to shareholders. The price of prescription drugs causes great consternation among consumers, especially as many health insurers seek to control costs by choosing not to cover certain "brand-name" products (discussed later). Further, a few drugs (especially for treatment of cancer) have been introduced to the market in recent years at prices that greatly exceeded the costs of development, manufacture, and marketing of the product. Many of these products were discovered in government laboratories or in university laboratories supported by federal grants.

The U.S. is the only large country that places no controls on drug prices and where price plays no role in the drug approval process. Many U.S. drugs cost much more in the U.S. than overseas; thus, U.S. consumers subsidize drug costs for the rest of the world, and they are irritated by that fact. The example of new agents for the treatment of hepatitis C infection brings many conflicting priorities into perspective (Box 1–3).

The drug development process is long, expensive, and risky (see Figure 1–1 and Table 1–1). Consequently, drugs must be priced to recover the substantial costs of invention and development and to fund the marketing efforts needed to introduce new products to physicians and patients. Nevertheless, as U.S. healthcare spending continues to rise at an alarming pace, prescription drugs account for only about 10% of total U.S. healthcare expenditures (CDC, 2013), and a significant fraction of this drug cost is for low-priced, nonproprietary medicines. Although the increase in prices is significant in certain classes of drugs (e.g., anticancer agents), the total price of prescription drugs is growing at a slower rate than other healthcare costs. Even drastic reductions in drug prices that would

BOX 1–3 ■ The Cost of Treating Hepatitis C

Infection with hepatitis C virus (HCV) is a chronic disease afflicting millions of people. Some suffer little from this condition; many others eventually develop cirrhosis or hepatocellular carcinoma. Who should be treated? The answer is unknown. Until recently, the treatment of choice for people with genotype 1 HCV involved year-long administration of an interferon (by injection) in combination with ribavirin and a protease inhibitor. Unwanted effects of this regimen are frequent and severe (some say worse than the disease); cure rates range from 50% to 75%. A newer treatment involves an oral tablet containing a combination of sofosbuvir and ledipasvir (see Chapter 63). Treatment usually requires daily ingestion of one tablet, for 8–12 weeks; cure rates exceed 95%, and side effects are minimal.

Controversy surrounds the price of the treatment, about $1000/d. Some insurers refused to reimburse this high cost, relegating many patients to less-effective, more toxic, but less-expensive treatment. However, these third-party payers have negotiated substantial discounts of the price, based on the availability of a competing product. Is the cost exorbitant? Should insurers, rather than patients and their physicians, be making such important decisions?

Continued and excessive escalation of drug and other healthcare costs will bankrupt the healthcare system. The question of appropriate cost involves complex pharmacoeconomic considerations. What are the relative costs of the two treatment regimens? What are the savings from elimination of the serious sequelae of chronic HCV infection? How does one place value to the patient on the less-toxic and more effective and convenient regimen? What are the profit margins of the company involved? Who should make decisions about costs and choices of patients to receive various treatments? How should we consider cases (unlike that for HCV) for which the benefits are quite modest, such as when a very expensive cancer drug extends life only briefly? One astute observer (and an industry critic of many drug prices) summarized the situation as follows: "great, important problem; wrong example."

severely limit new drug invention would not lower the overall healthcare budget by more than a few percent.

Are profit margins excessive among the major pharmaceutical companies? There is no objective answer to this question. Pragmatic answers come from the markets and from company survival statistics. The U.S. free-market system provides greater rewards for particularly risky and important fields of endeavor, and many people agree that the rewards should be greater for those willing to take the risk. The pharmaceutical industry is clearly one of the more risky:

- The costs to bring products to market are enormous.
- The success rate is low (accounting for much of the cost).
- Accounting for the long development time, effective patent protection for marketing a new drug is only about a decade (see Intellectual Property and Patents), requiring every company to completely reinvent itself on roughly a 10-year cycle.
- Regulation is stringent.
- Product liability is great.
- Competition is fierce.
- With mergers and acquisitions, the number of companies in the pharmaceutical world is shrinking.

Many feel that drug prices should be driven more by their therapeutic impact and their medical need, rather than by simpler free-market considerations; there is movement in this direction. Difficulties involve estimation or measurement of value, and there are many elements in this equation (Schnipper et al., 2015). There is no well-accepted approach to answer the question of value.

Who Pays?

The cost of prescription drugs is borne by consumers ("out of pocket"), private insurers, and public insurance programs such as Medicare, Medicaid, and the SCHIP. Recent initiatives by major retailers and mail-order pharmacies run by private insurers to offer consumer incentives for purchase of generic drugs have helped to contain the portion of household expenses spent on pharmaceuticals; however, more than one-third of total retail drug costs in the U.S. are paid with public funds—tax dollars.

Healthcare in the U.S. is more expensive than everywhere else, but it is not, on average, demonstrably better than everywhere else. One way in which the U.S. system falls short is with regard to healthcare access. Although the Patient Protection and Affordable Care Act of 2010 has reduced the percentage of Americans without health insurance to a historic low, practical solutions to the challenge of providing healthcare for all who need it must recognize the importance of incentivizing innovation.

Intellectual Property and Patents

Drug invention produces intellectual property eligible for patent protection, protection that is enormously important for innovation. As noted in 1859 by Abraham Lincoln, the only U.S. president to ever hold a patent (for a device to lift boats over shoals), by giving the inventor exclusive use of his or her invention for a limited time, the patent system "added the fuel of interest to the fire of genius in the discovery and production of useful things (Lincoln, 1859)." The U.S. patent protection system provides protection for 20 years from the time the patent is filed. During this period, the patent owner has exclusive rights to market and sell the drug. When the patent expires, equivalent nonproprietary products can come on the market; a generic product must be therapeutically equivalent to the original, contain equal amounts of the same active chemical ingredient, and achieve equal concentrations in blood when administered by the same routes. These generic preparations are sold much more cheaply than the original drug and without the huge development costs borne by the original patent holder.

The long time course of drug development, usually more than 10 years (see Figure 1–1), reduces the time during which patent protection functions as intended. The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417, informally called the Hatch-Waxman Act) permits a patent holder to apply for extension of a patent term to compensate for delays in marketing caused by FDA approval processes; nonetheless, the average new drug brought to market now enjoys only about 10–12 years of patent protection. Some argue that patent protection for drugs should be shortened, so that earlier generic competition will lower healthcare costs. The counterargument is that new drugs would have to bear even higher prices to provide adequate compensation to companies during a shorter period of protected time. If that is true, lengthening patent protection would actually permit lower prices. Recall that patent protection is worth little if a superior competitive product is invented and brought to market.

Bayh-Dole Act

The Bayh-Dole Act (35 U.S.C. § 200) of 1980 created strong incentives for federally funded scientists at academic medical centers to approach drug invention with an entrepreneurial spirit. The act transferred intellectual property rights to the researchers and their respective institutions (rather than to the government) to encourage partnerships with industry that would bring new products to market for the public's benefit. While the need to protect intellectual property is generally accepted, this encouragement of public-private research collaborations has given rise to concerns about conflicts of interest by scientists and universities (Kaiser, 2009).

Biosimilars

As noted previously, the path to approval of a chemically synthesized small molecule that is identical to an approved compound whose patent protection has expired is relatively straightforward. The same is not true for large molecules (usually proteins), which are generally derived from a living organism (e.g., eukaryotic cell or bacterial culture). Covalent modification of proteins (e.g., glycosylation) or conformational differences may influence pharmacokinetics, pharmacodynamics, immunogenicity, or other properties, and demonstration of therapeutic equivalence may be a complex process.

The Biologics Price Competition and Innovation Act was enacted as part of the Patient Protection and Affordable Care Act in 2010. The intent was to implement an abbreviated licensure pathway for certain "similar" biological products. *Biosimilarity* is defined to mean "that the biological product is highly similar to a reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." In general, an application for licensure of a biosimilar must provide satisfactory data from analytical studies, animal studies, and a clinical study or studies. The interpretation of this language has involved seemingly endless discussion, and hard-and-fast rules seem unlikely.

Drug Promotion

In an ideal world, physicians would learn all they need to know about drugs from the medical literature, and good drugs would thereby sell themselves. Instead, we have print advertising and visits from salespeople directed at physicians and extensive direct-to-consumer advertising aimed at the public (in print, on the radio, and especially on television). There are roughly 80,000 pharmaceutical sales representatives in the U.S. who target about 10 times that number of physicians. This figure is down from about 100,000 in 2010, and the decline is likely related to increased attention to real and actual conflicting interests caused by their practices. It has been noted that college cheerleading squads are attractive sources for recruitment of this sales force. The amount spent on promotion of drugs approximates or perhaps even exceeds that spent on research and development. Pharmaceutical companies have been especially vulnerable to criticism for some of their marketing practices.

Promotional materials used by pharmaceutical companies cannot deviate from information contained in the package insert. In addition, there must be an acceptable balance between presentation of therapeutic claims for a product and discussion of unwanted effects. Nevertheless, direct-to-consumer advertising of prescription drugs remains controversial and is permitted only in the U.S. and New Zealand. Canada allows a modified form of advertising in which either the product or the indication can be mentioned, but not both. Physicians frequently succumb with misgivings to patients' advertising-driven requests for specific medications.

The counterargument is that patients are educated by such marketing efforts and in many cases will then seek medical care, especially for conditions (e.g., depression) that they may have been denying (Avery et al., 2012).

The major criticism of drug marketing involves some of the unsavory approaches used to influence physician behavior. Gifts of value (e.g., sports tickets) are now forbidden, but dinners where drug-prescribing information is presented by non-sales representatives are widespread. Large numbers of physicians are paid as "consultants" to make presentations in such settings. The acceptance of any gift, no matter how small, from a drug company by a physician is now forbidden at many academic medical centers and by law in several states. In 2009, the board of directors of PhRMA adopted an enhanced Code on Interactions With Healthcare Professionals that prohibits the distribution of noneducational items, prohibits company sales representatives from providing restaurant meals to healthcare professionals (although exceptions are granted when a third-party speaker makes the presentation), and requires companies to ensure that their representatives are trained about laws and regulations that govern interactions with healthcare professionals.

Concerns About Global Injustice

Because development of new drugs is so expensive, private-sector investment in pharmaceutical innovation has focused on products that will have lucrative markets in wealthy countries such as the U.S., which combines patent protection with a free-market economy. Accordingly, there is concern about the degree to which U.S. and European patent protection laws have restricted access to potentially lifesaving drugs in developing countries.

To lower costs, pharmaceutical companies increasingly test their experimental drugs outside the U.S. and the E.U., in developing countries where there is less regulation and easier access to large numbers of patients. According to the U.S. DHHS, there has been a 2000% increase in foreign trials of U.S. drugs over the past 25 years. When these drugs are successful in obtaining marketing approval, consumers in the countries where the trials were conducted often cannot afford them. Some ethicists have argued that this practice violates the justice principle articulated in the Belmont Report (DHHS, 1979, p10), which states that "research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research." A counterargument is that the conduct of trials in developing nations also frequently brings needed medical attention to underserved populations. This is another controversial issue.

Product Liability

Product liability laws are intended to protect consumers from defective products. Pharmaceutical companies can be sued for faulty design or manufacturing, deceptive promotional practices, violation of regulatory requirements, or failure to warn consumers of known risks. So-called failure-to-warn claims can be made against drug makers even when the product is approved by the FDA. With greater frequency, courts are finding companies that market prescription drugs directly to consumers responsible when these advertisements fail to provide an adequate warning of potential adverse effects.

Although injured patients are entitled to pursue legal remedies, the negative effects of product liability lawsuits against pharmaceutical companies may be considerable. First, fear of liability may cause pharmaceutical companies to be overly cautious about testing, thereby delaying access to the drug. Second, the cost of drugs increases for consumers when pharmaceutical companies increase the length and number of trials they perform to identify even the smallest risks and when regulatory agencies increase the number or intensity of regulatory reviews. Third, excessive liability costs create disincentives for development of so-called orphan drugs, pharmaceuticals that benefit a small number of patients. Should pharmaceutical companies be liable for failure to warn when all of the rules were followed and the product was approved by the FDA but the unwanted effect was not detected because of its rarity or another confounding factor? The only way to find "all" of the unwanted effects that a drug may have is to market it—to conduct a phase IV "clinical trial" or observational study. This basic friction between risk to patients and the financial risk of drug development does not seem likely to be resolved except on a case-by-case basis, in the courts.

The U.S. Supreme Court added further fuel to these fiery issues in 2009 in the case *Wyeth v. Levine*. A patient (Levine) suffered gangrene of an arm following inadvertent arterial administration of the antinausea drug promethazine. She subsequently lost her hand. The healthcare provider had intended to administer the drug by so-called intravenous push. The FDA-approved label for the drug *warned against*, but did not prohibit, administration by intravenous push. The state court and then the U.S. Supreme Court held both the healthcare provider *and the company* liable for damages. Specifically, the Vermont court found that Wyeth had inadequately labeled the drug. This means that FDA approval of the label does not protect a company from liability or prevent individual states from imposing regulations more stringent than those required by the federal government.

"Me Too" Versus True Innovation: The Pace of New Drug Development

Me-too drug is a term used to describe a pharmaceutical that is usually structurally similar to a drug already on the market. Other names used are *derivative medications*, *molecular modifications*, and *follow-up drugs*. In some cases, a me-too drug is a different molecule developed deliberately by a competitor company to take market share from the company with existing drugs on the market. When the market for a class of drugs is especially large, several companies can share the market and make a profit. Other me-too drugs result coincidentally from numerous companies developing products simultaneously without knowing which drugs will be approved for sale (Box 1–4).

There are valid criticisms of me-too drugs. First, an excessive emphasis on profit may stifle true innovation. Of the 487 drugs approved by the FDA between 1998 and 2003, only 67 (14%) were considered by the FDA to be NMEs. Between 1998 and 2011, on average only 24 NMEs were approved by the FDA's CDER. Second, some me-too drugs are more expensive than the older versions they seek to replace, increasing the costs of healthcare without corresponding benefit to patients. Nevertheless, for some patients, me-too drugs may have better efficacy or fewer side effects or promote compliance with the treatment regimen. For example, the me-too that can be taken once a day rather than more frequently is convenient and promotes compliance. Some me-too drugs add great value from a business and medical point of view. Atorvastatin was the seventh statin to be introduced to market; it subsequently became the best-selling drug in the world.

Critics argue that pharmaceutical companies are not innovative and do not take risks, and, further, that medical progress is actually slowed by their excessive concentration on me-too products. Figure 1–2 summarizes a few of the facts behind this and other arguments. Clearly, only a modest number of NMEs, about two dozen a year, achieved FDA approval in the years 1980 to 2011, with the exception of the several-year spike in approvals following the introduction of PDUFA. Yet, from 1980 to 2010, the industry's annual investment in research and development grew from

BOX 1–4 ■ A Not-So-New Drug

Some me-too drugs are only slightly altered formulations of a company's own drug, packaged and promoted as if really offering something new. An example is the heartburn medication esomeprazole, marketed by the same company that makes omeprazole. Omeprazole is a mixture of two stereoisomers; esomeprazole contains only one of the isomers and is eliminated less rapidly. Development of esomeprazole created a new period of market exclusivity, although generic versions of omeprazole are marketed, as are branded congeners of omeprazole/esomeprazole. Both omeprazole and esomeprazole are now available over the counter—narrowing the previous price difference.

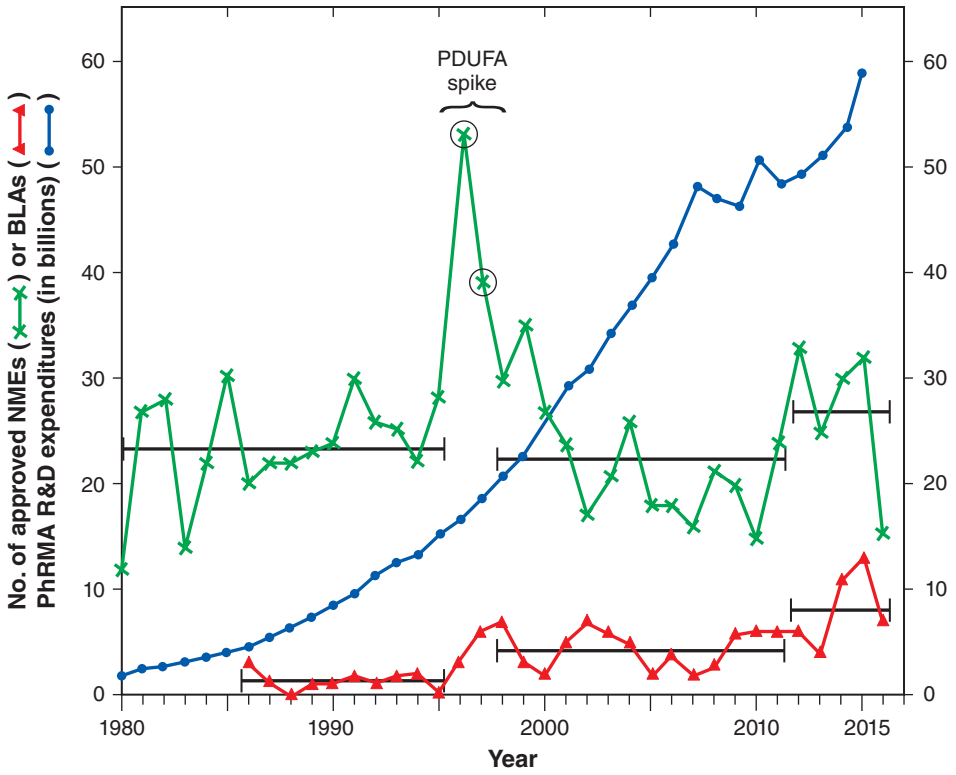

Figure 1–2 *The cost of drug invention is rising. Is productivity?* Each horizontal black line shows the average annual number of NMEs or BLAs for the time period bracketed by the line's length.

$2 billion to $50 billion. This disconnect between research and development investment and new drugs approved occurred at a time when combinatorial chemistry was blooming, the human genome was being sequenced, highly automated techniques of screening were being developed, and new techniques of molecular biology and genetics were offering novel insights into the pathophysiology of human disease.

In recent years, there has been a modest increase in approval of NMEs (inhibitors of a number of protein kinases) and new biologics (numerous therapeutic antibodies) (see Figure 1–2). A continued increase in productivity will be needed to sustain today's pharmaceutical companies as they face waves of patent expirations. There are strong arguments that development of much more targeted, individualized drugs, based on a new generation of molecular diagnostic techniques and improved understanding of disease in individual patients, will improve both medical care and the survival of pharmaceutical companies.

Finally, many of the advances in genetics and molecular biology are still new, particularly when measured in the time frame required for drug development. One can hope that modern molecular medicine will sustain the development of more efficacious and more specific pharmacological treatments for an ever-wider spectrum of human diseases.

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Chapter 2

Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination

Iain L. O. Buxton

The human body restricts access to foreign molecules; therefore, to reach its target within the body and have a therapeutic effect, a drug molecule must cross a number of restrictive barriers en route to its target site. Following administration, the drug must be absorbed and then distributed, usually via vessels of the circulatory and lymphatic systems; in addition to crossing membrane barriers, the drug must survive metabolism (primarily hepatic) and elimination (by the kidney and liver and in the feces). ADME, the absorption, distribution, metabolism, and elimination of drugs, are the processes of *pharmacokinetics* (Figure 2–1). Understanding these processes and their interplay and employing pharmacokinetic principles increase the probability of therapeutic success and reduce the occurrence of adverse drug events.

The absorption, distribution, metabolism, and excretion of a drug involve its passage across numerous cell membranes. Mechanisms by which drugs cross membranes and the physicochemical properties of molecules and membranes that influence this transfer are critical to understanding the disposition of drugs in the human body. The characteristics of a drug that predict its movement and availability at sites of action are its molecular size and structural features, degree of ionization, relative lipid solubility of its ionized and nonionized forms, and its binding to serum and tissue proteins. Although physical barriers to drug movement may be a single layer of cells (e.g., intestinal epithelium) or several layers of cells and associated extracellular protein (e.g., skin), the plasma membrane is the basic barrier.

Passage of Drugs Across Membrane Barriers

The Plasma Membrane Is Selectively Permeable

The plasma membrane consists of a bilayer of amphipathic lipids with their hydrocarbon chains oriented inward to the center of the bilayer to form a continuous hydrophobic phase, with their hydrophilic heads oriented outward. Individual lipid molecules in the bilayer vary according to the particular membrane and can move laterally and organize themselves into microdomains (e.g., regions with sphingolipids and cholesterol, forming lipid rafts), endowing the membrane with fluidity, flexibility, organization, high electrical resistance, and relative impermeability to highly polar molecules. Membrane proteins embedded in the bilayer serve as structural anchors, receptors, ion channels, or transporters to transduce electrical or chemical signaling pathways and provide selective targets for drug actions. Far from being a sea of lipids with proteins floating randomly about, membranes are ordered and compartmented (Suetsugu et al., 2014), with structural scaffolding elements linking to the cell interior. Membrane proteins may be associated with caveolin and sequestered within caveolae, be excluded from caveolae, or be organized in signaling domains rich in cholesterol and sphingolipid not containing caveolin or other scaffolding proteins.

Modes of Permeation and Transport

Passive diffusion dominates transmembrane movement of most drugs. However, carrier-mediated mechanisms (*active transport* and *facilitated diffusion*) play important roles (Figure 2–2; Figure 5–4).

Passive Diffusion

In passive transport, the drug molecule usually penetrates by 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, to the lipid:water partition coefficient of the drug, and to the membrane surface area exposed to the drug. At steady state, 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 depend on the electrochemical gradient for the ion and on differences in pH across the membrane, which will influence the state of ionization of the molecule disparately on either

Abbreviations

ABC: ATP-binding cassette
ACE: angiotensin-converting enzyme
AUC: area under the concentration-time curve of drug absorption and elimination
BBB: blood-brain barrier
CL: clearance
CNS: central nervous system
CNT1: concentrative nucleoside transporter 1
C_p: plasma concentration
CSF: cerebrospinal fluid
C_{ss}: steady-state concentration
CYP: cytochrome P450
F: bioavailability
GI: gastrointestinal
h: hours
k: a rate constant
MDR1: multidrug resistance protein
MEC: minimum effective concentration
min: minutes
SLC: solute carrier
T, t: time
$t_{1/2}$: half-life
V: volume of distribution
V_{ss}: volume of distribution at steady state

side of the membrane and can effectively trap ionized drug on one side of the membrane.

Influence of pH on Ionizable Drugs

Many drugs are weak acids or bases that are present in solution as both the lipid-soluble, diffusible nonionized form and the ionized species that is relatively lipid insoluble and poorly diffusible across a membrane. Among the common ionizable groups are carboxylic acids and amino groups (primary, secondary, and tertiary; quaternary amines hold a permanent positive charge). The transmembrane distribution of a weak electrolyte is influenced by its pK_a and the pH gradient across the membrane. The pK_a is the pH at which half the drug (weak acid or base electrolyte) is in its ionized form. The ratio of nonionized to ionized drug at any pH may be calculated from the Henderson-Hasselbalch equation:

$$\log \frac{[\text{protonated form}]}{[\text{unprotonated form}]} = pK_a - pH \qquad \text{(Equation 2–1)}$$

Equation 2–1 relates the pH of the medium around the drug and the drug's acid dissociation constant (pK_a) to the ratio of the protonated (HA or BH^+) and unprotonated (A^- or B) forms, where

$$HA \leftrightarrow A^- + H^+, \text{ where } K_a = \frac{[A^-][H^+]}{[HA]}$$

describes the dissociation of an acid, and

$$BH^+ \leftrightarrow B + H^+, \text{ where } K_a = \frac{[B][H^+]}{[BH^+]}$$

describes the dissociation of the protonated form of a base.

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. This phenomenon, known as *ion trapping*, is an important process in drug distribution with potential therapeutic benefit (Perletti et al., 2009). Figure 2–3 illustrates this effect and shows the calculated values for the distribution of a weak acid between the plasma and gastric compartments.

One can take advantage of the effect of pH on transmembrane partitioning to alter drug excretion. In the kidney tubules, urine pH can vary over a wide range, from 4.5 to 8. As urine pH drops (as $[H^+]$ increases), weak acids (A^-) and weak bases (B) will exist to a greater extent in their protonated forms (HA and BH^+); the reverse is true as pH rises, where A^- and B will be favored. Thus, alkaline urine favors excretion of weak acids; acid urine favors excretion of weak bases. Elevation of urine pH (by giving sodium bicarbonate) will promote urinary excretion of weak acids such as aspirin ($pK_a \sim 3.5$) and urate ($pK_a \sim 5.8$). Another useful consequence of a drug's being ionized at physiological pH is illustrated by the relative lack of sedative effects of second-generation histamine H_1 antagonists (e.g., loratadine): Second-generation antihistamines are ionized molecules (less lipophilic, more hydrophilic) that cross the BBB poorly compared to first-generation agents such as diphenhydramine, which are now used as sleep aids.

Carrier-Mediated Membrane Transport

Proteins in the plasma membrane mediate transmembrane movements of many physiological solutes; these proteins also mediate transmembrane movements of drugs and can be targets of drug action. Mediated transport

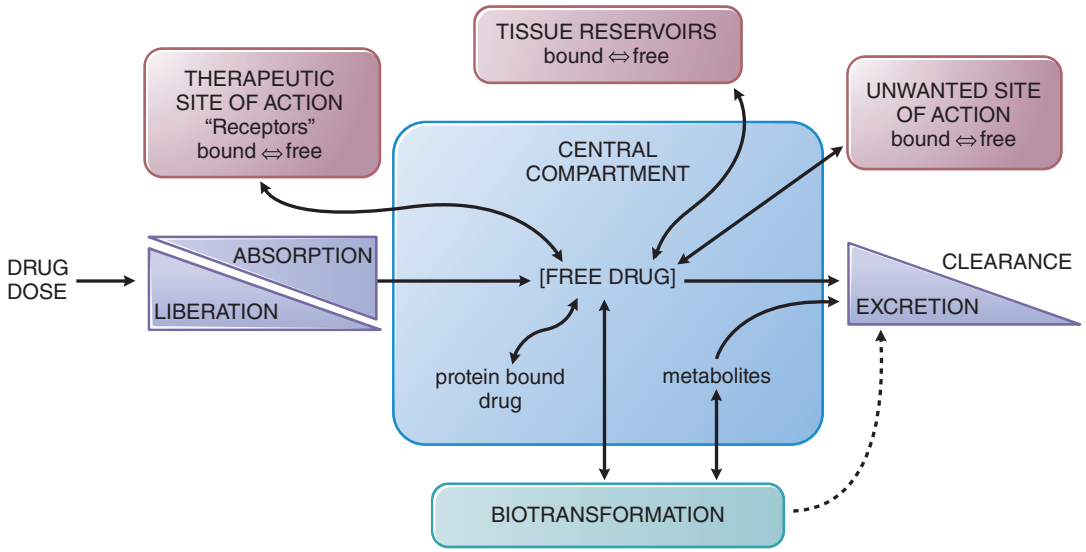

Figure 2–1 *The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its sites of action.* Possible distribution and binding of metabolites in relation to their potential actions at receptors are not depicted.

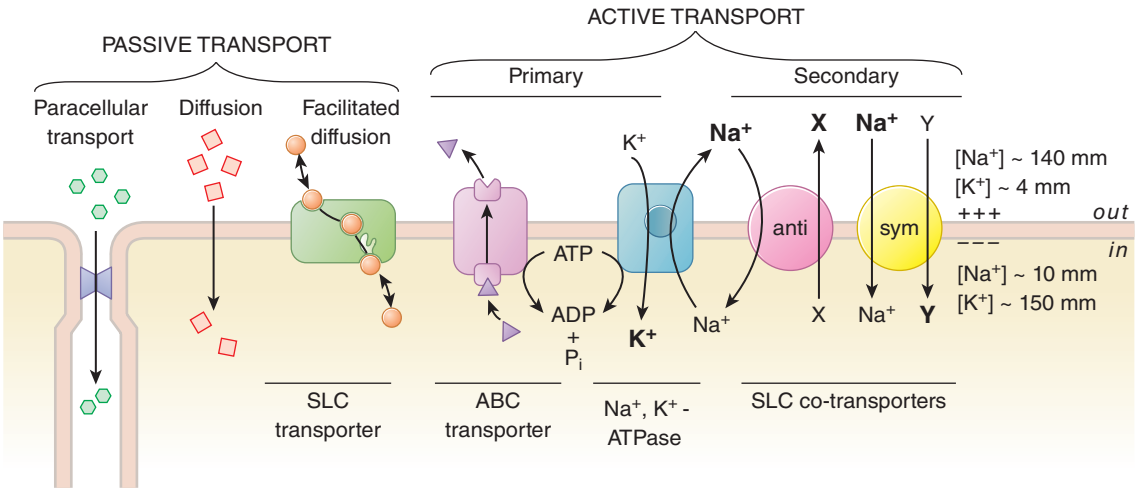

Figure 2–2 *Drugs move across membrane and cellular barriers in a variety of ways.* See details in Figures 5–1 through 5–5.

is broadly characterized as *facilitated diffusion* or *active transport* (see Figure 2–2; Figure 5–4). Membrane transporters and their roles in drug response are presented in detail in Chapter 5.

Facilitated Diffusion. *Facilitated diffusion* is a carrier-mediated transport process in which the driving force is simply the electrochemical gradient of the transported solute; thus, these carriers can facilitate solute movement either in or out of cells, depending on the direction of the electrochemical gradient. The carrier protein may be highly selective for a specific conformational structure of an endogenous solute or a drug whose rate of transport by passive diffusion through the membrane would otherwise be quite slow. For instance, the organic cation transporter OCT1 (SLC22A1) facilitates the movement of a physiologic solute, thiamine, and also of drugs, including metformin, which is used in treating type 2 diabetes. Chapter 5 describes OCT1 and other members of the human SLC superfamily of transporters.

Active Transport. *Active transport* is characterized by a direct requirement for energy, capacity to move solute against an electrochemical gradient, saturability, selectivity, and competitive inhibition by cotransported compounds. Na^+,K^+-ATPase is an important example of an active transport mechanism that is also a therapeutic target of digoxin in the treatment of heart failure (Chapter 29). A group of primary active transporters, the ABC family, hydrolyze ATP to export substrates across membranes. For example, the P-glycoprotein, also called ABCB1 and MDR1, exports bulky neutral or cationic compounds from cells; its physiologic substrates include steroid hormones such as testosterone and progesterone. MDR1 exports many drugs as well, including digoxin, and a great variety of other agents (see Table 5–4). P-glycoprotein in the enterocyte limits the absorption of some orally administered drugs by exporting compounds into the lumen of the GI tract subsequent to their absorption. ABC transporters perform a similar function in the cells of the BBB, effectively reducing net accumulation of some compounds in the brain. By the same mechanism, P-glycoprotein also can confer resistance to some cancer chemotherapeutic agents (see Chapters 65–68).

Members of the SLC superfamily can mediate secondary active transport using the electrochemical energy stored in a gradient (usually Na^+) to translocate both biological solutes and drugs across membranes. For instance, the Na^+–Ca^{2+} exchange protein (SLC8) uses the energy stored in the Na^+ gradient established by Na^+,K^+-ATPase to export cytosolic Ca^{2+} and maintain it at a low basal level, about 100 nM in most cells. SLC8 is thus an *antiporter*, using the inward flow of Na^+ to drive an outward flow of Ca^{++}; SLC8 also helps to mediate the positive inotropic effects of digoxin and other cardiac glycosides that inhibit the activity of Na^+,K^+-ATPase and thereby reduce the driving force for the extrusion of Ca^{++} from the ventricular cardiac myocyte. Other SLC cotransporters are *symporters*, in which driving force ion and solute move in the same direction. The CNT1 (SLC28A1), driven by the Na^+ gradient, moves pyrimidine nucleosides and the cancer chemotherapeutic agents gemcitabine and cytarabine into cells. DAT, NET, and SERT, transporters for the neurotransmitters dopamine, norepinephrine, and serotonin, respectively, are secondary active transporters that also rely on the energy stored in the transmembrane Na^+ gradient, symporters that coordinate movement of Na^+ and neurotransmitter in the same direction (into the neuron); they are also the targets of CNS-active agents used in therapy of depression. Members of the SLC superfamily are active in drug transport in the GI tract, liver, and kidney, among other sites.

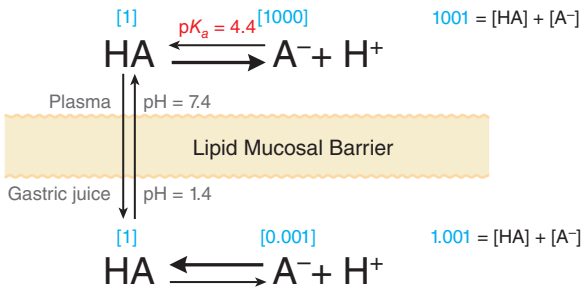

Figure 2–3 *Influence of pH on the distribution of a weak acid* (pK_a = 4.4) *between plasma and gastric juice separated by a lipid barrier.* **A weak acid dissociates to different extents** in plasma (pH 7.4) and gastric acid (pH 1.4): The higher pH facilitates dissociation; the lower pH reduces dissociation. The uncharged form, HA, equilibrates across the membrane. Blue numbers in brackets show relative equilibrium concentrations of HA and A^-, as calculated from Equation 2–1.

Paracellular Transport

In the vascular compartment, paracellular passage of solutes and fluid through intercellular gaps is sufficiently large that passive transfer across the endothelium of capillaries and postcapillary venules is generally limited by blood flow. Capillaries of the CNS and a variety of epithelial tissues have tight junctions that limit paracellular movement of drugs (Spector et al., 2015).

Drug Absorption, Bioavailability, and Routes of Administration

Absorption and Bioavailability

Absorption is the movement of a drug from its site of administration into the central compartment (see Figure 2–1). For solid dosage forms, absorption first requires dissolution of the tablet or capsule, thus liberating the drug. Except in cases of malabsorption syndromes, the clinician is concerned primarily with bioavailability rather than absorption (Tran et al., 2013).

Bioavailability describes the fractional extent to which an administered dose of drug reaches its site of action or a biological fluid (usually the systemic circulation) from which the drug has access to its site of action. A drug given orally must be absorbed first from the GI tract, but net absorption may be limited by the characteristics of the dosage form, by the drug's physicochemical properties, by metabolic attack in the intestine, and by transport across the intestinal epithelium and into the portal circulation. The absorbed drug then passes through the liver, where metabolism and biliary excretion may occur before the drug enters the systemic circulation. Accordingly, less than all of the administered dose may reach the systemic circulation and be distributed to the drug's sites of action. If the metabolic or excretory capacity of the liver and the intestine for the drug is large, bioavailability will be reduced substantially (*first-pass effect*). This decrease in availability is a function of the anatomical site from which absorption takes place; for instance, intravenous administration generally permits all of the drug to enter the systemic circulation. Other anatomical, physiological, and pathological factors can influence bioavailability (described further in this chapter), and the choice of the route of drug administration must be based on an understanding of these conditions. We can define bioavailability F as:

$$F = \frac{\text{Quantity of drug reaching systemic circulation}}{\text{Quantity of drug administered}} \quad \text{(Equation 2–2)}$$

where $0 < F \leq 1$.

Factors modifying bioavailability apply as well to prodrugs that are activated by the liver, in which case availability results from metabolism that produces the form of the active drug.

Routes of Administration

Some characteristics of the major routes employed for systemic drug effect are compared in Table 2–1.

Oral Administration

Oral ingestion is the most common method of drug administration. It also is the safest, most convenient, and most economical. Its disadvantages include limited absorption of some drugs because of their physical characteristics (e.g., low water solubility or poor membrane permeability), emesis as a result of irritation to the GI mucosa, destruction of some drugs by digestive enzymes or low gastric pH, irregularities in absorption or propulsion in the presence of food or other drugs, and the need for cooperation on the part of the patient. In addition, drugs in the GI tract may be metabolized by the enzymes of the intestinal microbiome, mucosa, or liver before they gain access to the general circulation.

Absorption from the GI tract is governed by factors such as surface area for absorption; blood flow to the site of absorption; the physical state of the drug (solution, suspension, or solid dosage form); its aqueous solubility; and the drug's concentration at the site of absorption. For drugs given in solid form, the rate of dissolution may limit their absorption. Because most drug absorption from the GI tract occurs by passive diffusion, absorption is favored when the drug is in the nonionized, more lipophilic form. Based on the pH-partition concept (see Figure 2–3), one would predict that drugs that are weak acids would be better absorbed from the stomach (pH 1–2) than from the upper intestine (pH 3–6), and vice versa for weak bases. However, the surface area of the stomach is relatively small, and a mucus layer covers the gastric epithelium. By contrast, the villi of the upper intestine provide an extremely large surface area (~200 m^2). Accordingly, the rate of absorption of a drug from the intestine will be greater than that from the stomach even if the drug is predominantly ionized in the intestine and largely nonionized in the stomach. Thus, any factor that accelerates gastric emptying (recumbent position right side) will generally increase the rate of drug absorption, whereas any factor that delays gastric emptying will have the opposite effect. The gastric emptying rate is influenced by numerous factors, including the caloric content of food; volume, osmolality, temperature, and pH of ingested fluid; diurnal and interindividual variation; metabolic state (rest or exercise); and the ambient temperature. Gastric emptying is influenced in women by the effects of estrogen (i.e., compared to men, emptying is slower for premenopausal women and those taking estrogen replacement therapy).

Drugs that are destroyed by gastric secretions and low pH or that cause gastric irritation sometimes are administered in dosage forms with an enteric coating that prevents dissolution in the acidic gastric contents. Enteric coatings are useful for drugs that can cause gastric irritation and for presenting a drug such as mesalamine to sites of action in the ileum and colon (see Figure 51–4).

TABLE 2–1 ■ SOME CHARACTERISTICS OF COMMON ROUTES OF DRUG ADMINISTRATION[a]

ROUTE AND BIOAVAILABILTY (F)	ABSORPTION PATTERN	SPECIAL UTILITY	LIMITATIONS AND PRECAUTIONS
Intravenous	Absorption circumvented	Valuable for emergency use	Increased risk of adverse effects
$F = 1$ by definition	Potentially immediate effects	Permits titration of dosage	Must inject solutions *slowly* as a rule
	Suitable for large volumes and for irritating substances, or complex mixtures, when diluted	Usually required for high-molecular-weight protein and peptide drugs	Not suitable for oily solutions or poorly soluble substances
Subcutaneous $0.75 < F < 1$	Prompt from aqueous solution	Suitable for some poorly soluble suspensions and for instillation of slow-release implants	Not suitable for large volumes
	Slow and sustained from repository preparations		Possible pain or necrosis from irritating substances
Intramuscular $0.75 < F < 1$	Prompt from aqueous solution	Suitable for moderate volumes, oily vehicles, and some irritating substances	Precluded during anticoagulant therapy
	Slow and sustained from repository preparations	Appropriate for self-administration (e.g., insulin)	May interfere with interpretation of certain diagnostic tests (e.g., creatine kinase)
Oral ingestion $.05 < F < 1$	Variable, depends on many factors (see text)	Most convenient and economical; usually safer	Requires patient compliance
			Bioavailability potentially erratic and incomplete

[a]See text for more complete discussion and for other routes.

Controlled-Release Preparations. The rate of absorption of a drug administered as a tablet or other solid oral dosage form is partly dependent on its rate of dissolution in GI fluids. This is the basis for *controlled-release, extended-release, sustained-release,* and *prolonged-action* pharmaceutical preparations that are designed to produce slow, uniform absorption of the drug for 8 h or longer. Potential advantages of such preparations are reduction in the frequency of administration compared with conventional dosage forms (often with improved compliance by the patient), maintenance of a therapeutic effect overnight, and decreased incidence and intensity of undesired effects (by dampening of the peaks in drug concentration) and nontherapeutic blood levels of the drug (by elimination of troughs in concentration) that often occur after administration of immediate-release dosage forms. Controlled-release dosage forms are most appropriate for drugs with short half-lives ($t_{1/2}$ < 4 h) or in select patient groups, such as those receiving antiepileptic or antipsychotic agents (Bera, 2014).

Sublingual Administration. Absorption from the oral mucosa has special significance for certain drugs despite the fact that the surface area available is small. Venous drainage from the mouth is to the superior vena cava, thus bypassing the portal circulation. As a consequence, a drug held sublingually and absorbed from that site is protected from rapid intestinal and hepatic first-pass metabolism. For example, sublingual nitroglycerin (see Chapter 27) is rapidly effective because it is nonionic, has high lipid solubility, and is not subject to the first-pass effect prior to reaching the heart and arterial system.

Parenteral Injection

Parenteral (i.e., not via the GI tract) injection of drugs has distinct advantages over oral administration. In some instances, parenteral administration is essential for delivery of a drug in its active form, as in the case of monoclonal antibodies. Availability usually is more rapid, extensive, and predictable when a drug is given by injection; the effective dose can be delivered more accurately to a precise dose; this route is suitable for the loading dose of medications prior to initiation of oral maintenance dosing (e.g., digoxin). In emergency therapy and when a patient is unconscious, uncooperative, or unable to retain anything given by mouth, parenteral therapy may be necessary. Parenteral administration also has disadvantages: Asepsis must be maintained, especially when drugs are given over time (e.g., intravenous or intrathecal administration); pain may accompany the injection; and it is sometimes difficult for patients to perform the injections themselves if self-medication is necessary.

The major routes of parenteral administration are intravenous, subcutaneous, and intramuscular. Absorption from subcutaneous and intramuscular sites occurs by simple diffusion along the gradient from drug depot to plasma. The rate is limited by the area of the absorbing capillary membranes and by the solubility of the substance in the interstitial fluid. Relatively large aqueous channels in the endothelial layer account for the indiscriminate diffusion of molecules regardless of their lipid solubility. Larger molecules, such as proteins, slowly gain access to the circulation by way of lymphatic channels. Drugs administered into the systemic circulation by any route, excluding the intra-arterial route, are subject to possible first-pass elimination in the lung prior to distribution to the rest of the body. The lungs also serve as a filter for particulate matter that may be given intravenously and provide a route of elimination for volatile substances.

Intravenous. Factors limiting absorption are circumvented by intravenous injection of drugs in aqueous solution because bioavailability is complete (F = 1.0) and distribution is rapid. Also, drug delivery is controlled and achieved with an accuracy and immediacy not possible by any other procedures. Certain irritating solutions can be given only in this manner because the drug, when injected slowly, is greatly diluted by the blood.

There are advantages and disadvantages to intravenous administration. Unfavorable reactions can occur because high concentrations of drug may be attained rapidly in plasma and tissues. There are therapeutic circumstances for which it is advisable to administer a drug by bolus injection (e.g., tissue plasminogen activator) and other circumstances where slower or prolonged administration of drug is advisable (e.g., antibiotics). Intravenous administration of drugs warrants careful determination of dose and close monitoring of the patient's response; once the drug is injected, there is often no retreat. Repeated intravenous injections depend on the ability to maintain a patent vein. Drugs in an oily vehicle, those that precipitate blood constituents or hemolyze erythrocytes, and drug combinations that cause precipitates to form *must not* be given intravenously.

Subcutaneous. Injection into a subcutaneous site can be done only with drugs that are not irritating to tissue; otherwise, severe pain, necrosis, and tissue sloughing may occur. The rate of absorption following subcutaneous injection of a drug often is sufficiently constant and slow to provide a sustained effect. Moreover, altering the period over which a drug is absorbed may be varied intentionally, as is accomplished with insulin for injection using particle size, protein complexation, and pH. The incorporation of a vasoconstrictor agent in a solution of a drug to be injected subcutaneously also retards absorption. Absorption of drugs implanted under the skin in a solid pellet form occurs slowly over a period of weeks or months; some hormones (e.g., contraceptives) are administered effectively in this manner.

Intramuscular. Absorption of drugs in aqueous solution after intramuscular injection depends on the rate of blood flow to the injection site and can be relatively rapid. Absorption may be modulated to some extent by local heating, massage, or exercise. Generally, the rate of absorption following injection of an aqueous preparation into the deltoid or vastus lateralis is faster than when the injection is made into the gluteus maximus. The rate is particularly slower for females after injection into the gluteus maximus, a feature attributed to the different distribution of subcutaneous fat in males and females and because fat is relatively poorly perfused. Slow, constant absorption from the intramuscular site results if the drug is injected in solution in oil or suspended in various other repository (depot) vehicles.

Intra-arterial. Occasionally, a drug is injected directly into an artery to localize its effect in a particular tissue or organ, such as in the treatment of liver tumors and head and neck cancers. Diagnostic agents sometimes are administered by this route (e.g., technetium-labeled human serum albumin). Inadvertent intra-arterial administration can cause serious complications and requires careful management (Sen et al., 2005).

Intrathecal. The BBB and the blood-CSF barrier often preclude or slow the entrance of drugs into the CNS, reflecting the activity of P-glycoprotein (MDR1) and other transporters to export xenobiotics from the CNS. Therefore, when local and rapid effects of drugs on the meninges or cerebrospinal axis are desired, as in spinal anesthesia, drugs sometimes are injected directly into the spinal subarachnoid space. Brain tumors (Calias et al., 2014) or serious CNS infections (Imberti et al., 2014) also may be treated by direct intraventricular drug administration, increasingly through the use of specialized long-term indwelling reservoir devices. Injections into the CSF and epidural space are covered in chapters on analgesia and local anesthesia (Chapters 20 and 22, respectively).

Pulmonary Absorption

Gaseous and volatile drugs may be inhaled and absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract. Access to the circulation is rapid by this route because the lung's surface area is large. In addition, solutions of drugs can be atomized and the fine droplets in air (aerosol) inhaled. Advantages are the almost instantaneous absorption of a drug into the blood, avoidance of hepatic first-pass loss, and in the case of pulmonary disease, local application of the drug at the desired site of action (see Chapters 21 and 40), as in the use of inhaled nitric oxide for pulmonary hypertension in term and near-term infants and adults (see Chapter 31).

Topical Application

Mucous Membranes. Drugs are applied to the mucous membranes of the conjunctiva, nasopharynx, oropharynx, vagina, colon, urethra, and urinary bladder primarily for their local effects. Absorption from these sites is generally excellent and may provide advantages for immunotherapy because vaccination of mucosal surfaces using mucosal vaccines

provides the basis for generating protective immunity in both the mucosal and systemic immune compartments.

Eye. Topically applied ophthalmic drugs are used primarily for their local effects (see Chapter 69). The use of drug-loaded contact lenses and ocular inserts allows drugs to be better placed where they are needed for direct delivery.

Skin: Transdermal Absorption. Absorption of drugs able to penetrate the intact skin is dependent on the surface area over which they are applied and their lipid solubility (see Chapter 70). Systemic absorption of drugs occurs much more readily through abraded, burned, or denuded skin. Toxic effects result from absorption through the skin of highly lipid-soluble substances (e.g., a lipid-soluble insecticide in an organic solvent). Absorption through the skin can be enhanced by suspending the drug in an oily vehicle and rubbing the resulting preparation into the skin. Hydration of the skin with an occlusive dressing may be used to facilitate absorption. Controlled-release topical patches are increasingly available, with nicotine for tobacco-smoking withdrawal, scopolamine for motion sickness, nitroglycerin for angina pectoris, testosterone and estrogen for replacement therapy, various estrogens and progestins for birth control, and fentanyl for pain relief.

Rectal Administration

Approximately 50% of the drug that is absorbed from the rectum will bypass the liver, thereby reducing hepatic first-pass metabolism. However, rectal absorption can be irregular and incomplete, and certain drugs can cause irritation of the rectal mucosa. Rectal administration may be desirable, as in the use of opioids in hospice care.

Novel Methods of Drug Delivery

Drug-eluting stents and other devices are being used to target drugs locally to maximize efficacy and minimize systemic exposure. Recent advances in drug delivery include the use of biocompatible polymers and nanoparticles for drug delivery (Yohan and Chithrani, 2014).

Bioequivalence

Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration. Two pharmaceutically equivalent drug products are considered to be *bioequivalent* when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable and identical test conditions. Generic versus brand name prescribing is further discussed in connection with drug nomenclature and the choice of drug name in writing prescription orders (see Appendix I). Courts have not always found generic and brand name drugs to be legally equivalent (see Chapter 1).

Distribution of Drugs

Not All Tissues Are Equal

Following absorption or systemic administration into the bloodstream, a drug distributes into interstitial and intracellular fluids as functions of the physicochemical properties of the drug, the rate of drug delivery to individual organs and compartments, and the differing capacities of those regions to interact with the drug. Cardiac output, regional blood flow, capillary permeability, and tissue volume affect the rate of delivery and amount of drug distributed into tissues (Table 2–2 and Figure 2–4). Initially, liver, kidney, brain, and other well-perfused organs receive most of the drug; delivery to muscle, most viscera, skin, and fat is slower. This second distribution phase may require minutes to several hours before the concentration of drug in tissue is in equilibrium with that in blood. The second phase also involves a far larger fraction of body mass (e.g., muscle) than does the initial phase and generally accounts for most of the extravascular distribution. With exceptions such as the brain, diffusion of drug into the interstitial fluid occurs rapidly because of the highly permeable nature of the capillary endothelium. Thus, tissue distribution is determined by the partitioning of drug between blood and the particular tissue.

Binding to Plasma Proteins

Many drugs circulate in the bloodstream bound to plasma proteins. Albumin is a major carrier for acidic drugs; α_1-acid glycoprotein binds basic drugs. Nonspecific binding to other plasma proteins generally occurs to a much smaller extent. The binding is usually reversible. In addition, certain drugs may bind to proteins that function as specific hormone carrier proteins, such as the binding of estrogen or testosterone to sex hormone–binding globulin or the binding of thyroid hormone to thyroxin-binding globulin.

The fraction of total drug in plasma that is bound is determined by the drug concentration, the affinity of binding sites for the drug, and the concentration of available binding sites. For most drugs, the therapeutic range of plasma concentrations is limited; thus, the extent of binding and the unbound fraction are relatively constant. The extent of plasma protein binding also may be affected by disease-related factors (e.g., hypoalbuminemia). Conditions resulting in the acute-phase reaction response (e.g., cancer, arthritis, myocardial infarction, Crohn's disease) lead to elevated levels of α_1-acid glycoprotein and enhanced binding of basic drugs. Changes in protein binding caused by disease states and drug-drug interactions are clinically relevant mainly for a small subset of so-called high-clearance drugs of narrow therapeutic index that are administered intravenously, such as lidocaine. When changes in plasma protein binding occur in patients, unbound drug rapidly equilibrates throughout the body and only a transient significant change in unbound plasma concentration will occur. Only drugs that show an almost-instantaneous relationship between free plasma concentration and effect (e.g., antiarrhythmics) will show a measurable effect. Thus, unbound plasma drug concentrations will exhibit significant changes only when either drug input or clearance of unbound drug occurs as a consequence of metabolism or active transport. A more common problem resulting from competition of drugs for plasma protein-binding sites is misinterpretation of measured concentrations of drugs in plasma because most assays do not distinguish free drug from bound drug. Competition for plasma protein-binding sites may cause one drug to elevate the concentration of one bound less avidly.

Binding of a drug to plasma proteins limits its concentration in tissues and at its site of action because only unbound drug is in equilibrium across membranes. Accordingly, after distribution equilibrium is achieved, the concentration of unbound drug in intracellular water is the same as that in plasma except when carrier-mediated active transport is involved. Binding of a drug to plasma protein limits the drug's glomerular filtration and may also limit drug transport and metabolism.

TABLE 2–2 ■ DISTRIBUTION OF BLOOD FLOW IN 70-KG MALE AT REST

	KIDNEYS	HEART	LIVER	BRAIN	SKELETAL MUSCLE	FAT	REMAINDER	Σ
Blood Flow (mL/min)	1100	250	1700	800	900	250	500	5500
Mass (kg)	0.3	0.3	2.6	1.3	34	10	21.5	70
Flow/Mass (mL/min/kg)	3667	833	654	615	26	25	23	
% Cardiac Output	20	4.5	31	14.5	16.4	4.5	9.1	100

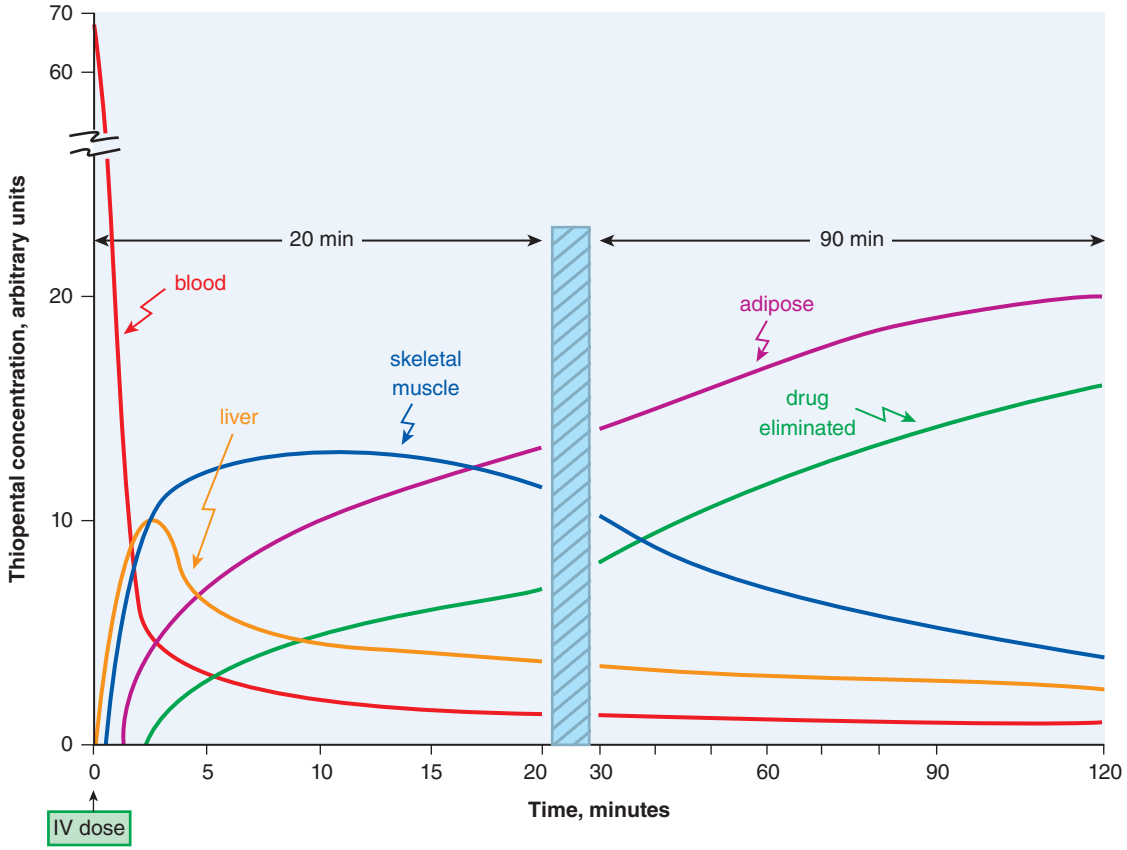

Figure 2–4 *Redistribution.* Curves depict the distribution of the barbiturate anesthetic thiopental into different body compartments following a single rapid intravenous dose. Note breaks and changes of scale on both axes. The drug level at thiopental's site of action in the brain closely mirrors the plasma level of the drug. The rate of accumulation in the various body compartments depends on regional blood flow; the extent of accumulation reflects the differing capacities of the compartments and the steady but slow effect of elimination to reduce the amount of drug available. Emergence from the anesthetic influence of this single dose of thiopental relies on redistribution, not on metabolism. The drug will partition out of tissue depots as metabolism and elimination take their course. Depletion of compartments will follow the same order as accumulation, as a function of their perfusion.

Tissue Binding

Many drugs accumulate in tissues at higher concentrations than those in the extracellular fluids and blood. Tissue binding of drugs usually occurs with cellular constituents such as proteins, phospholipids, or nuclear proteins and generally is reversible. A large fraction of drug in the body may be bound in this fashion and serve as a reservoir that prolongs drug action in that same tissue or at a distant site reached through the circulation. Such tissue binding and accumulation also can produce local toxicity (e.g., renal and ototoxicity associated with aminoglycoside antibiotics).

CNS, the BBB, and CSF

The brain capillary endothelial cells have continuous tight junctions; therefore, drug penetration into the brain depends on transcellular rather than paracellular transport. The unique characteristics of brain capillary endothelial cells and pericapillary glial cells constitute the BBB. At the choroid plexus, a similar blood-CSF barrier is present, formed by epithelial cells that are joined by tight junctions. The lipid solubility of the nonionized and unbound species of a drug is therefore an important determinant of its uptake by the brain; the more lipophilic a drug, the more likely it is to cross the BBB. In general, the BBB's function is well maintained; however, meningeal and encephalic inflammation increase local permeability. Drugs may also be imported to and exported from the CNS by specific transporters (see Chapter 5).

Bone

The tetracycline antibiotics (and other divalent metal-ion chelating agents) and heavy metals may accumulate in bone by adsorption onto the bone crystal surface and eventual incorporation into the crystal lattice. Bone can become a reservoir for the slow release of toxic agents such as lead or radium; their effects thus can persist long after exposure has ceased. Local destruction of the bone medulla also may result in reduced blood flow and prolongation of the reservoir effect as the toxic agent becomes sealed off from the circulation; this may further enhance the direct local damage to the bone. A vicious cycle results, whereby the greater the exposure to the toxic agent, the slower is its rate of elimination. The adsorption of drug onto the bone crystal surface and incorporation into the crystal lattice have therapeutic advantages for the treatment of osteoporosis.

Fat as a Reservoir

Many lipid-soluble drugs are stored by physical solution in the neutral fat. In obese persons, the fat content of the body may be as high as 50%, and even in lean individuals, fat constitutes 10% of body weight; hence, fat may serve as a reservoir for lipid-soluble drugs. Fat is a rather stable reservoir because it has a relatively low blood flow.

Redistribution

Termination of drug effect after withdrawal of a drug usually is by metabolism and excretion but also may result from redistribution of the drug from its site of action into other tissues or sites. Redistribution is a factor in terminating drug effect primarily when a highly lipid-soluble drug that acts on the brain or cardiovascular system is administered rapidly by intravenous injection or inhalation. Such is the case of the intravenous anesthetic thiopental, a lipid-soluble drug. Because blood flow to the brain is high and thiopental readily crosses the BBB, thiopental reaches its maximal concentration in brain rapidly after its intravenous injection. Subsequently, the plasma and brain concentrations decrease as thiopental redistributes to other tissues, such as muscle and, finally, adipose tissue.

This redistribution is the mechanism by which thiopental anesthesia is terminated (see Figure 2–4) because its clearance is rather slow (elimination $t_{1/2}$ after a single dose is 3–8 h). The concentration of the drug in brain follows that of the plasma because there is little binding of the drug to brain constituents. Thus, both the onset and the termination of thiopental anesthesia are relatively rapid, and both are related directly to the concentration of drug in the brain.

Placental Transfer of Drugs

The transfer of drugs across the placenta is of critical importance because drugs may cause anomalies in the developing fetus; thus, the burden for evidenced-based drug use in pregnancy is paramount (see Appendix I). Lipid solubility, extent of plasma binding, and degree of ionization of weak acids and bases are important general determinants in drug transfer across the placenta. The placenta functions as a selective barrier to protect the fetus against the harmful effects of drugs. Members of the ABC family of transporters limit the entry of drugs and other xenobiotics into the fetal circulation via vectorial efflux from the placenta to the maternal circulation (see Figure 2–2 and Chapter 5). The fetal plasma is slightly more acidic than that of the mother (pH 7.0–7.2 vs. 7.4), so that ion trapping of basic drugs occurs. The view that the placenta is an absolute barrier to drugs is inaccurate, in part because a number of influx transporters are also present. The fetus is to some extent exposed to all drugs taken by the mother. The Food and Drug Administration categorizes the relative safety of drugs that may be used in pregnant women (see Appendix I).

Metabolism of Drugs

A Few Principles of Metabolism and Elimination

The many therapeutic agents that are lipophilic do not pass readily into the aqueous environment of the urine. The metabolism of drugs and other xenobiotics into more hydrophilic metabolites is essential for their renal elimination from the body, as well as for termination of their biological and pharmacological activity.

From the point of view of pharmacokinetics, the following are the three essential aspects of drug metabolism:

- **First-order kinetics.** For most drugs in their therapeutic concentration ranges, the amount of drug metabolized per unit time is proportional to the plasma concentration of the drug (C_p) and *the fraction of drug removed by metabolism is constant (i.e., first-order kinetics).*
- **Zero-order kinetics.** For some drugs, such as ethanol and phenytoin, metabolic capacity is saturated at the concentrations usually employed, and drug metabolism becomes *zero order; that is, a constant amount of drug is metabolized per unit time.* Zero-order kinetics can also occur at high (toxic) concentrations as drug-metabolizing capacity becomes saturated.
- **Inducible biotransforming enzymes.** The major drug-metabolizing systems are inducible, broad-spectrum enzymes with some predictable genetic variations. Drugs that are substrates in common for a metabolizing enzyme may interfere with each other's metabolism, or a drug may induce or enhance metabolism of itself or other drugs.

In general, drug-metabolizing reactions generate more polar, inactive metabolites that are readily excreted from the body. However, in some cases, metabolites with potent biological activity or toxic properties are generated. Many of the enzyme systems that transform drugs to inactive metabolites also generate biologically active metabolites of endogenous compounds, as in steroid biosynthesis. The biotransformation of drugs occurs primarily in the liver and involves *phase 1 reactions* (oxidation, reduction, or hydrolytic reactions and the activities of CYPs) and *phase 2 reactions* (conjugations of the phase 1 product with a second molecule) and a few other reactions. Other organs with significant drug-metabolizing capacity include the GI tract, kidneys, and lungs. Drug-metabolizing enzymes, especially CYPs, are inducible by some drugs and inhibited by drugs and competing substrates. Chapter 6 covers drug metabolism at length. Knowing which CYP metabolizes a given drug and which other drugs may affect that metabolism is crucial to good drug therapy.

Prodrugs; Pharmacogenomics

Prodrugs are pharmacologically inactive compounds that are converted to their active forms by metabolism. This approach can maximize the amount of the active species that reaches its site of action. Inactive prodrugs are converted rapidly to biologically active metabolites, often by the hydrolysis of an ester or amide linkage. Such is the case with a number of ACE inhibitors employed in the management of high blood pressure. Enalapril, for instance, is relatively inactive until converted by esterase activity to the diacid enalaprilat (see Chapters 6 and 26).

For a number of therapeutic areas, clinical pharmacogenomics, the study of the impact of genetic variations or genotypes of individuals on their drug response or drug metabolism, allows for improved treatment of individuals or groups (Ramamoorthy et al., 2015; Zhang et al., 2015; see Chapter 7).

Excretion of Drugs

Drugs are eliminated from the body either unchanged or as metabolites. Excretory organs, the lung excluded, eliminate polar compounds more efficiently than substances with high lipid solubility. Thus, lipid-soluble drugs are not readily eliminated until they are metabolized to more polar compounds. The kidney is the most important organ for excreting drugs and their metabolites. Renal excretion of unchanged drug is a major route of elimination for 25%–30% of drugs administered to humans. Substances excreted in the feces are principally unabsorbed orally ingested drugs or drug metabolites either excreted in the bile or secreted directly into the intestinal tract and not reabsorbed. Excretion of drugs in breast milk is important not because of the amounts eliminated (which are small) but because the excreted drugs may affect the nursing infant (also small, and with poorly developed capacity to metabolize xenobiotics). Excretion from the lung is important mainly for the elimination of anesthetic gases (see Chapter 21).

Renal Excretion

Excretion of drugs and metabolites in the urine involves three distinct processes: glomerular filtration, active tubular secretion, and passive tubular reabsorption (Figure 2–5). The amount of drug entering the tubular lumen by filtration depends on the glomerular filtration rate and the extent of plasma binding of the drug; only unbound drug is filtered. In the proximal renal tubule, active, carrier-mediated tubular secretion also may add drug to the tubular fluid (see Chapters 5 and 25). Drug from the tubular lumen may be reabsorbed back into the systemic circulation. In the renal tubules, especially on the distal side, the nonionized forms of weak acids and bases undergo net passive reabsorption. Because the tubular cells are less permeable to the ionized forms of weak electrolytes, passive reabsorption of these substances depends on the pH. When the tubular urine is made more alkaline, weak acids are largely ionized and are excreted more rapidly and to a greater extent; conversely, acidification of the urine will reduce fractional ionization and excretion of weak acids. Effects of changing urine pH are opposite for weak bases. In the treatment of drug poisoning, the excretion of some drugs can be hastened by appropriate alkalinization or acidification of the urine (see Figure 2–3 and Chapter 4).

In neonates, renal function is low compared with body mass but matures rapidly within the first few months after birth. During adulthood, there is a slow decline in renal function, about 1% per year, so that in elderly patients a substantial degree of functional impairment may be present, and medication adjustments are often needed.

Biliary and Fecal Excretion

Transporters present in the canalicular membrane of the hepatocyte (see Figure 5–6) actively secrete drugs and metabolites into bile. Ultimately, drugs and metabolites present in bile are released into the GI tract during the digestive process. Subsequently, the drugs and metabolites can be reabsorbed into the body from the intestine, which, in the case of conjugated metabolites such as glucuronides, may require enzymatic hydrolysis

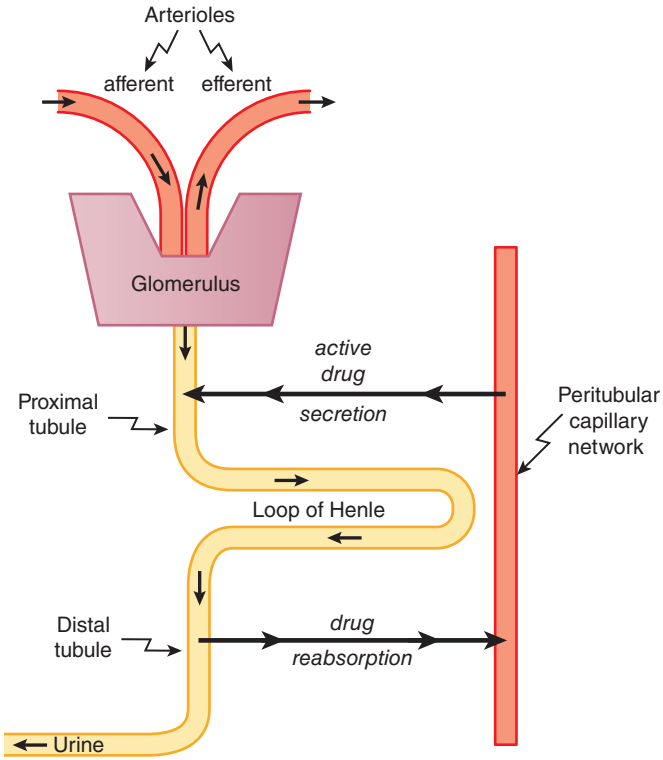

Figure 2–5 *Renal drug handling.* Drugs may be filtered from the blood in the renal glomerulus, secreted into the proximal tubule, reabsorbed from the distal tubular fluid back into the systemic circulation, and collected in the urine. Membrane transporters (OAT, OCT, MDR1, and MRP2, among others) mediate secretion into the proximal tubule (see Figures 5–12 and 5–13 for details). Reabsorption of compounds from the distal tubular fluid (generally acidic) is pH sensitive: Ionizable drugs are subject to ion trapping, and altering urinary pH to favor ionization can enhance excretion of charged species (see Figure 2–2).

by the intestinal microflora. Such *enterohepatic recycling*, if extensive, may prolong significantly the presence of a drug (or toxin) and its effects within the body prior to elimination by other pathways. To interrupt enterohepatic cycling, substances may be given orally to bind metabolites excreted in the bile (for instance, see bile acid sequestrants and ezetimibe, Chapter 33). Biliary excretions and unabsorbed drug are excreted in the feces.

Excretion by Other Routes

Excretion of drugs into sweat, saliva, and tears is quantitatively unimportant. Because milk is more acidic than plasma, basic compounds may be slightly concentrated in this fluid; conversely, the concentration of acidic compounds in the milk is lower than in plasma. Nonelectrolytes (e.g., ethanol and urea) readily enter breast milk and reach the same concentration as in plasma, independent of the pH of the milk (Rowe et al., 2015). Breast milk can also contain heavy metals from environmental exposures. The administration of drugs to breastfeeding women carries the general caution that the suckling infant will be exposed to some extent to the medication or its metabolites. Although excretion into hair and skin is quantitatively unimportant, sensitive methods of detection of drugs in these tissues have forensic significance.

Clinical Pharmacokinetics

Clinical pharmacokinetics relate the pharmacological effects of a drug and concentration of the drug in an accessible body compartment (e.g., in blood or plasma) as these change in time. In most cases, the concentration of drug at its sites of action will be related to the concentration of drug in the systemic circulation (see Figure 2–1). The pharmacological effect that results may be the clinical effect desired or an adverse or toxic effect. Clinical pharmacokinetics attempts to provide

- a quantitative relationship between dose and effect, and
- a framework within which to interpret measurements of drug concentration in biological fluids and their adjustment through changes in dosing for the benefit of the patient.

The importance of pharmacokinetics in patient care is based on the improvement in therapeutic efficacy and the avoidance of unwanted effects that can be attained by application of its principles when dosage regimens are chosen and modified.

The following are the four most important parameters governing drug disposition:

1. *Bioavailability,* the fraction of drug absorbed as such into the systemic circulation.
2. *Volume of distribution,* a measure of the apparent space in the body available to contain the drug based on how much is given versus what is found in the systemic circulation.
3. *Clearance,* a measure of the body's efficiency in eliminating drug from the systemic circulation.
4. *Elimination* $t_{1/2}$, a measure of the rate of removal of drug from the systemic circulation.

Clearance

Clearance is the most important concept to consider when designing a rational regimen for long-term drug administration. The clinician usually wants to maintain steady-state concentrations of a drug within a *therapeutic window* or range associated with therapeutic efficacy and a minimum of toxicity for a given agent. Assuming complete bioavailability, the steady-state concentration of drug in the body will be achieved when the rate of drug elimination equals the rate of drug administration. Thus,

$$\text{Dosing rate} = CL \cdot C_{ss} \qquad \text{(Equation 2–3)}$$

where CL is clearance of drug from the systemic circulation, and C_{ss} is the steady-state concentration of drug. When the desired steady-state concentration of drug in plasma or blood is known, the rate of clearance of drug will dictate the rate at which the drug should be administered.

Knowing the clearance of a drug is useful because its value for a particular drug usually is constant over the range of concentrations encountered clinically. This is true because metabolizing enzymes and transporters usually are not saturated; thus, the absolute rate of elimination of the drug is essentially a linear function of its concentration in plasma (first-order kinetics), where a *constant fraction* of drug in the body is eliminated per unit of time. If mechanisms for elimination of a given drug become saturated, the kinetics approach zero order (the case for ethanol and high doses of phenytoin), in which case a *constant amount* of drug is eliminated per unit of time.

With first-order kinetics, clearance CL will vary with the concentration of drug (C), often according to Equation 2–4:

$$CL = \frac{v_m}{(K_m + C)} \qquad \text{(Equation 2–4)}$$

where K_m represents the concentration at which half the maximal rate of elimination is reached (in units of mass/volume), and v_m is equal to the maximal rate of elimination (in units of mass/time). Thus, clearance is derived in units of volume cleared of drug/time. This equation is analogous to the Michaelis-Menten equation for enzyme kinetics.

Clearance of a drug is its rate of elimination by all routes normalized to the concentration of drug C in some biological fluid where measurement can be made:

$$CL = \text{Rate of elimination}/C \qquad \text{(Equation 2–5)}$$

Thus, when clearance is constant, the rate of drug elimination is directly proportional to drug concentration. Clearance indicates the volume of

biological fluid such as blood or plasma from which drug would have to be completely removed to account for the clearance per unit of body weight (e.g., mL/min per kg). Clearance can be defined further as blood clearance CL_b, plasma clearance CL_p, or clearance based on the concentration of unbound drug CL_u, depending on the measurement made (C_b, C_p, or C_u). Clearance of drug by several organs is additive. Elimination of drug from the systemic circulation may occur as a result of processes that occur in the kidney, liver, and other organs. Division of the rate of elimination by each organ by a concentration of drug (e.g., plasma concentration) will yield the respective clearance by that organ. Added together, these separate clearances will equal systemic clearance:

$$CL_{renal} + CL_{hepatic} + CL_{other} = CL \qquad \text{(Equation 2–6)}$$

Any significant alteration in renal or hepatic function can result in decreased clearance for those drugs with high renal or hepatic clearance. Systemic clearance may be determined at steady state by using Equation 2–3. For a single dose of a drug with complete bioavailability and first-order kinetics of elimination, systemic clearance may be determined from mass balance and the integration of Equation 2–5 over time:

$$CL = \text{Dose}/AUC \qquad \text{(Equation 2–7)}$$

AUC is the total area under the curve that describes the measured concentration of drug in the systemic circulation as a function of time (from zero to infinity), as in Figure 2–9.

Examples of Clearance

The plasma clearance for the antibiotic cephalexin is 4.3 mL/min/kg, with 90% of the drug excreted unchanged in the urine. For a 70-kg man, the clearance from plasma would be 301 mL/min, with renal clearance accounting for 90% of this elimination. In other words, the kidney is able to excrete cephalexin at a rate such that the drug is completely removed (cleared) from about 270 mL of plasma every minute (renal clearance = 90% of total clearance). Because clearance usually is assumed to remain constant in a medically stable patient (e.g., no acute decline in kidney function), the rate of elimination of cephalexin will depend on the concentration of drug in the plasma (see Equation 2–5).

The β adrenergic receptor antagonist propranolol is cleared from the blood at a rate of 16 mL/min/kg (or 1600 mL/min in a 100-kg man), almost exclusively by the liver. Thus, the liver is able to remove the amount of propranolol contained in 1600 mL of blood in 1 min, roughly equal to total hepatic blood (see Table 2–2). In fact, the plasma clearance of some drugs exceeds the rate of blood flow to this organ. Often, this is so because the drug partitions readily into and out of red blood cells (rbc), and the rate of drug delivered to the eliminating organ is considerably higher than expected from measurement of its concentration in plasma. The relationship between plasma clearance (subscript p) and blood clearance (subscript b; all components of blood) at steady state is given by

$$\frac{CL_p}{CL_b} = \frac{C_b}{C_p} = 1 + H\left[\frac{C_{rbc}}{C_p} - 1\right] \qquad \text{(Equation 2–8)}$$

Clearance from the blood therefore may be estimated by dividing the plasma clearance by the drug's blood-to-plasma concentration ratio, obtained from knowledge of the hematocrit (H = 0.45) and concentration ratio of red cells to plasma. In most instances, the blood clearance will be less than liver blood flow (1.5–1.7 L/min) or, if renal excretion also is involved, the sum of the blood flows to each eliminating organ. For example, the plasma clearance of the immunomodulator tacrolimus, about 2 L/min, is more than twice the hepatic plasma flow rate and even exceeds the organ's blood flow despite the fact that the liver is the predominant site of this drug's extensive metabolism. However, after taking into account the extensive distribution of tacrolimus into red cells, its clearance from the blood is only about 63 mL/min, and it is actually a drug with a rather low clearance, not a high-clearance agent as might be expected from the plasma clearance value alone. Clearance from the blood by metabolism can exceed liver blood flow, and this indicates extrahepatic metabolism. In the case of the β_1 receptor antagonist esmolol, the blood clearance value (11.9 L/min) is greater than cardiac output (~5.5 L/min) because the drug is metabolized efficiently by esterases present in red blood cells.

A further definition of clearance is useful for understanding the effects of pathological and physiological variables on drug elimination, particularly with respect to an individual organ. The rate of presentation of drug to the organ is the product of blood flow Q and the arterial drug concentration C_A, and the rate of exit of drug from the organ is the product of blood flow and the venous drug concentration C_V. The difference between these rates at steady state is the rate of drug elimination by that organ:

$$\begin{aligned}\text{Rate of elimination} &= Q \cdot C_A - Q \cdot C_V \\ &= Q(C_A - C_V)\end{aligned} \qquad \text{(Equation 2–9)}$$

Dividing Equation 2–8 by the concentration of drug entering the organ of elimination, C_A, yields an expression for clearance of the drug by the organ in question:

$$CL_{organ} = Q\left[\frac{C_A - C_V}{C_A}\right] = Q \cdot E \qquad \text{(Equation 2–10)}$$

The expression $(C_A - C_V)/C_A$ in Equation 2–10 can be referred to as the extraction ratio E of the drug. While not employed in general medical practice, calculations of a drug's extraction ratio(s) are useful for modeling the effects of disease of a given metabolizing organ on clearance and in the design of ideal therapeutic properties of drugs in development.

Hepatic Clearance

For a drug that is removed efficiently from the blood by hepatic processes (metabolism or excretion of drug into the bile), the concentration of drug in the blood leaving the liver will be low, the extraction ratio will approach unity, and the clearance of the drug from blood will become limited by hepatic blood flow. Drugs that are cleared efficiently by the liver (e.g., drugs with systemic clearances > 6 mL/min/kg, such as diltiazem, imipramine, lidocaine, morphine, and propranolol) are restricted in their rate of elimination not by intrahepatic processes but by the rate at which they can be transported in the blood to the liver.

Pharmacokinetic models indicate that when the capacity of the eliminating organ to metabolize the drug is large in comparison with the rate of presentation of drug to the organ, clearance will approximate the organ's blood flow. By contrast, when the drug-metabolizing capacity is small in comparison with the rate of drug presentation, clearance will be proportional to the unbound fraction of drug in blood and the drug's intrinsic clearance, where intrinsic clearance represents drug binding to components of blood and tissues or the intrinsic capacity of the liver to eliminate a drug in the absence of limitations imposed by blood flow (Guner and Bowen, 2013).

Renal Clearance

Renal clearance of a drug results in its appearance in the urine. In considering the clearance of a drug from the body by the kidney, glomerular filtration, secretion, reabsorption, and glomerular blood flow must be considered (see Figure 2–5). The rate of filtration of a drug depends on the volume of fluid that is filtered in the glomerulus and the concentration of unbound drug in plasma (because drug bound to protein is not filtered). The rate of secretion of drug into the tubular fluid will depend on the drug's intrinsic clearance by the transporters involved in active secretion as affected by the drug's binding to plasma proteins, the degree of saturation of these transporters, the rate of delivery of the drug to the secretory site, and the presence of drugs that can compete for these transporters. In addition, one must consider processes of drug reabsorption from the tubular fluid back into the bloodstream. The influences of changes in protein binding, blood flow, and the functional state of nephrons will affect renal clearance.

Aspirin demonstrates the interplay among these processes. Aspirin has a bimodal effect on the renal handling of uric acid: High doses of aspirin (>3 g/d) are uricosuric (probably by blocking urate reabsorption), while low dosages (1–2 g/d) cause uric acid retention (probably via inhibiting urate secretion). Low-dose aspirin, indicated for the prophylaxis of cardiovascular events, can cause changes in renal function and uric acid handling in elderly patients.

Distribution

Volume of Distribution

The volume of distribution V relates the amount of drug in the body to the concentration of drug C in the blood or plasma, depending on the fluid measured. This volume does not necessarily refer to an identifiable physiological volume but rather to the fluid volume that would be required to contain all of the drug in the body at the same concentration measured in the blood or plasma:

$$\text{Amount of drug in body}/V = C$$

or

$$V = \text{Amount of drug in body}/C \qquad \text{(Equation 2–11)}$$

View V as an imaginary volume because for many drugs V exceeds the known volume of any and all body compartments (Box 2–1). For example, the value of V for the highly lipophilic antimalarial chloroquine is some 15,000 L, whereas the volume of total-body water is about 42 L in a 70-kg male.

For drugs that are bound extensively to plasma proteins but are not bound to tissue components, the volume of distribution will approach that of the plasma volume because drug bound to plasma protein is measurable in the assay of most drugs. In contrast, certain drugs have high volumes of distribution even though most of the drug in the circulation is bound to albumin because these drugs are also sequestered elsewhere.

The volume of distribution defined in Equation 2–11 considers the body as a single homogeneous compartment. In this one-compartment model, all drug administration occurs directly into the central compartment, and distribution of drug is instantaneous throughout the volume V. Clearance of drug from this compartment occurs in a first-order fashion, as defined in Equation 2–5; that is, the amount of drug eliminated per unit of time depends on the amount (concentration) of drug in the body compartment at that time. Figure 2–6A and Equation 2–9 describe the decline of plasma concentration with time for a drug introduced into this central compartment:

$$C = \left[\frac{\text{Dose}}{V}\right][e^{-kt}] \qquad \text{(Equation 2–12)}$$

where k is the rate constant for elimination that reflects the fraction of drug removed from the compartment per unit of time. This rate constant is inversely related to the $t_{1/2}$ of the drug [$kt_{1/2} = \ln 2 = 0.693$]. The idealized one-compartment model does not describe the entire time course of the plasma concentration. Certain tissue reservoirs can be distinguished from the central compartment, and the drug concentration appears to decay in a manner that can be described by multiple exponential terms (Figure 2–6B).

Rates of Distribution

In many cases, groups of tissues with similar perfusion-to-partition ratios all equilibrate at essentially the same rate such that only one apparent phase of distribution is seen (rapid initial decrease in concentration of intravenously injected drug, as in Figure 2–6B). It is as though the drug starts in a "central" volume (see Figure 2–1), which consists of plasma and tissue reservoirs that are in rapid equilibrium, and distributes to a "final" volume, at which point concentrations in plasma decrease in a log-linear fashion with a rate constant of k (see Figure 2–6B). The multicompartment model of drug disposition can be viewed as though the blood and highly perfused lean organs such as heart, brain, liver, lung, and kidneys cluster as a single central compartment, whereas more slowly perfused tissues such as muscle, skin, fat, and bone behave as the final compartment (the tissue compartment).

If blood flow to certain tissues changes within an individual, rates of drug distribution to these tissues also will change. Changes in blood flow may cause some tissues that were originally in the "central" volume to equilibrate sufficiently more slowly so they appear only in the "final" volume. This means that central volumes will appear to vary with disease states that cause altered regional blood flow (such as would be seen in cirrhosis of the liver). After an intravenous bolus dose, drug concentrations in plasma may be higher in individuals with poor perfusion (e.g., shock) than they would be if perfusion were better. These higher systemic concentrations may in turn cause higher concentrations (and greater effects) in tissues such as brain and heart, whose usually high perfusion has not been reduced. Thus, the effect of a drug at various sites of action can vary depending on perfusion of these sites.

Multicompartment Volumes

In multicompartment kinetics, a volume of distribution term is useful especially when the effect of disease states on pharmacokinetics is to be determined. The volume of distribution at steady state V_{ss} represents the volume in which a drug would appear to be distributed during steady state if the drug existed throughout that volume at the same concentration as that in the measured fluid (plasma or blood). V_{ss} also may be appreciated as shown in Equation 2–13, where V_C is the volume of distribution of drug in the central compartment and V_T is the volume term for drug in the tissue compartment:

$$V_{ss} = V_C + V_T \qquad \text{(Equation 2–13)}$$

Steady-State Concentration

Equation 2–3 (Dosing rate = $CL \cdot C_{ss}$) indicates that a steady-state concentration eventually will be achieved when a drug is administered at a constant rate. At this point, drug elimination (the product of clearance and concentration; Equation 2–5) will equal the rate of drug availability. This concept also extends to regular intermittent dosage (e.g., 250 mg of drug every 8 h). During each interdose interval, the concentration of drug rises with absorption and falls by elimination. At steady state, the entire cycle is repeated identically in each interval (Figure 2–7). Equation 2–3 still applies for intermittent dosing, but it now describes the average

BOX 2–1 ■ *V* Values May Exceed Any Physiological Volume

For many drugs, Equation 2–11 will give V values that exceed any physiological volume. For example, if 500 μg of the cardiac glycoside digoxin were added into the body of a 70-kg subject, a plasma concentration of about 0.75 ng/mL would be observed. Dividing the amount of drug in the body by the plasma concentration yields a volume of distribution for digoxin of about 667 L, or a value about 15 times greater than the total-body volume of a 70-kg man. In fact, digoxin distributes preferentially to muscle and adipose tissue and binds to its specific receptors, the Na^+,K^+-ATPase, leaving a very small amount of drug in the plasma to be measured. A drug's volume of distribution therefore can reflect the extent to which it is present in extravascular tissues and not in the plasma.

Thus, V may vary widely depending on the relative degrees of binding to high-affinity receptor sites, plasma and tissue proteins, the partition coefficient of the drug in fat, and accumulation in poorly perfused tissues. The volume of distribution for a given drug can differ according to a patient's age, gender, body composition, and presence of disease. Total-body water of infants younger than 1 year of age, for example, is 75%–80% of body weight, whereas that of adult males is 60% and that of females is 55%.

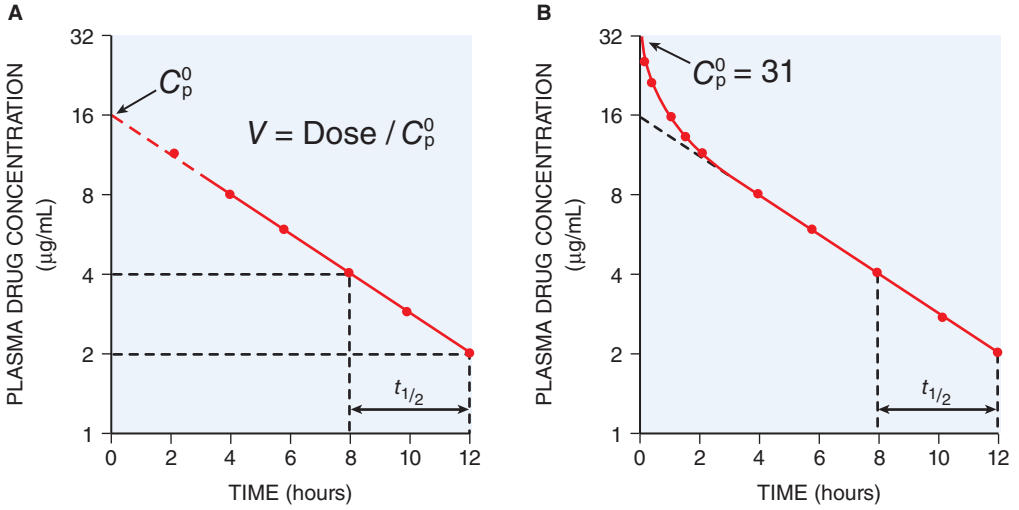

Figure 2–6 *Plasma concentration-time curves following intravenous administration of a drug (500 mg) to a 70-kg patient.* **A.** Drug concentrations are measured in plasma at 2-hour intervals following drug administration. The semilogarithmic plot of plasma concentration C_p versus time suggests that the drug is eliminated from a single compartment by a first-order process (see Equation 2–12) with a $t_{1/2}$ of 4 h ($k = 0.693/t_{1/2} = 0.173\ h^{-1}$). The volume of distribution V may be determined from the value of C_p obtained by extrapolation to zero-time. Volume of distribution (see Equation 2–11) for the one-compartment model is 31.3 L, or 0.45 L/kg (V = dose/C_p^0). The clearance for this drug is 90 mL/min; for a one-compartment model, $CL = kV$.
B. Sampling before 2 h indicates that the drug follows multiexponential kinetics. The terminal disposition $t_{1/2}$ is 4 h, clearance is 84 mL/min (see Equation 2–7), and V_{ss} is 26.8 L (see Equation 2–13). The initial or "central" distribution volume for the drug (V = dose/C0p) is 16.1 L. The example indicates that multicompartment kinetics may be overlooked when sampling at early times is neglected. In this particular case, there is only a 10% error in the estimate of clearance when the multicompartment characteristics are ignored. For many drugs, multicompartment kinetics may be observed for significant periods of time, and failure to consider the distribution phase can lead to significant errors in estimates of clearance and in predictions of appropriate dosage.

steady-state drug concentration during an interdose interval. Note the extension of this idea to derive $\bar{C}_{ss}$ during continuous intravenous drug infusion, as explained in the legend to Figure 2–7.

Half-Life

The $t_{1/2}$ is the time it takes for the plasma concentration to be reduced by 50%. For the one-compartment model of Figure 2–6A, $t_{1/2}$ may be determined readily by inspection of the data and used to make decisions about drug dosage. However, as indicated in Figure 2–6B, drug concentrations in plasma often follow a multicomponent pattern of decline.

Half-Life, Volume of Distribution, and Clearance

When using pharmacokinetics to calculate drug dosing in disease, note that $t_{1/2}$ changes as a function of both clearance and volume of distribution:

$$t_{1/2} \cong 0.693 \cdot V_{ss}/CL \qquad \text{(Equation 2–14)}$$

This $t_{1/2}$ reflects the decline of systemic drug concentrations during a dosing interval at steady state as depicted in Figure 2–7.

Terminal Half-Life

With prolonged dosing (or with high drug concentrations), a drug may penetrate beyond the central compartment into "deep" or secondary body compartments that equilibrate only slowly with the plasma. When the infusion or dosing stops, the drug will be initially cleared from plasma as expected but will eventually drop to a point at which net diffusion from the secondary compartments begins, and this slow equilibration will produce a prolongation of the half-life of the drug, referred to as the terminal half-life.

Steady-State $t_{1/2}$ and Terminal $t_{1/2}$ Compared

Examples of drugs with marked differences in terminal $t_{1/2}$ versus steady-state $t_{1/2}$ are gentamicin and indomethacin. Gentamicin has a $t_{1/2}$ of 2–3 h following a single administration, but a terminal $t_{1/2}$ of 53 h because drug accumulates in spaces such as kidney parenchyma (where this accumulation can result in toxicity). Biliary cycling probably is responsible for the 120-h terminal value for indomethacin (compared to the steady-state value of 2.4 h). Intravenous anesthetics provide a good example; many have *context-sensitive* half-times; these agents, with short half-times after single intravenous doses, exhibit longer half-times in proportion to the duration of exposure when used in maintenance anesthesia (see Figure 21–2).

Clearance is the measure of the body's capacity to eliminate a drug; thus, as clearance decreases, owing to a disease process, for example, $t_{1/2}$ will increase as long as the volume of distribution remains unchanged; alternately, the volume of distribution may change but *CL* remains constant or a combination of the two changes. For example, the $t_{1/2}$ of diazepam increases with increasing age; however, this does not reflect a change in clearance but rather a change in the volume of distribution. Similarly, changes in protein binding of a drug (e.g., hypoalbuminemia) may affect its clearance as well as its volume of distribution, leading to unpredictable changes in $t_{1/2}$ as a function of disease. The $t_{1/2}$ defined in Equation 2–14 provides an approximation of the time required to reach steady state after a dosage regimen is initiated or changed (e.g., four half-lives to reach ~ 94% of a new steady state).

Extent and Rate of Absorption

Bioavailability

It is important to distinguish between the amount of drug that is administered and the quantity of drug that ultimately reaches the systemic circulation. Dissolution and absorption of drug may be incomplete; some drug may be destroyed prior to entering the systemic circulation, especially by hepatic first-pass metabolism. The first-pass effect is extensive for many oral medications that enter the portal vein and pass directly to the liver. The fraction of a dose F that is absorbed and escapes first-pass elimination measures the drug's *bioavailability*; thus, $0 < F \leq 1$ (see Equation 2–2).

For some drugs, extensive first-pass metabolism greatly reduces their effectiveness or precludes their use as oral agents (e.g., lidocaine, propranolol, naloxone, and glyceryl trinitrate). For other agents, the extent of absorption may be very low, thereby reducing bioavailability. When drugs are administered by a route that is subject to significant first-pass loss or incomplete absorption, the equations presented previously that contain

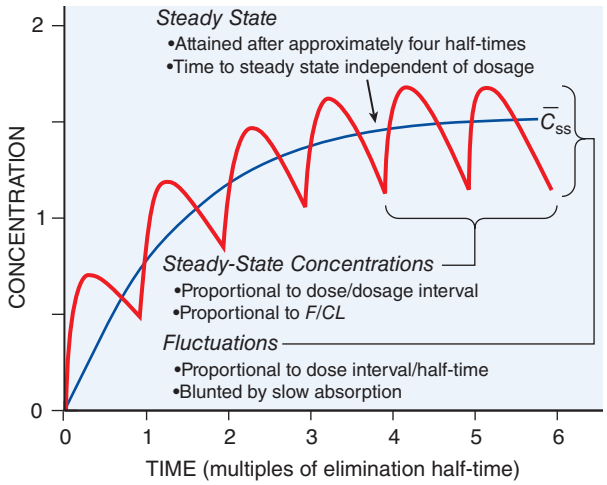

Figure 2–7 *Fundamental pharmacokinetic relationships for repeated administration of drugs.* The red line is the pattern of drug accumulation during repeated administration of a drug at intervals equal to its elimination half-time. With instantaneous absorption, each dose would add 1 concentration unit to C_p at the time of administration, and then half of that would be eliminated prior to administration of the next dose, resulting in the oscillation of C_p between 1 and 2 after four or five elimination half-times. However, this more realistic simulation uses a rate of drug absorption that is not instantaneous but is 10 times as rapid as elimination; drug is eliminated throughout the absorption process, blunting the maximal blood level achieved after each dose. With repeated administration, C_p achieves steady state, oscillating around the blue line at 1.5 units. The blue line depicts the pattern during administration of equivalent dosage by continuous intravenous infusion. Curves are based on the one-compartment model. Average drug concentration at steady state $\bar{C}_{ss}$ is:

$$C_{ss} = \frac{F \cdot \text{dose}}{CL \cdot T} = \frac{F \cdot \text{dosing rate}}{CL}$$

where the dosing rate is the dose per time interval and is dose/T, F is the fractional bioavailability, and CL is clearance. Note that substitution of infusion rate for [$F \cdot$ dose/T] provides the concentration maintained at steady state during continuous intravenous infusion ($F = 1$ with intravenous administration).

the terms *dose* or *dosing rate* (see Equations 2–3, 2–7, and 2–12) also must include the bioavailability term F such that the available dose or dosing rate is used (Box 2–2). For example, Equation 2–2 is modified to

$$F \cdot \text{Dosing rate} = CL \cdot C_{ss} \qquad \text{(Equation 2–15)}$$

where the value of F is between 0 and 1.

Rate of Absorption

The rate of absorption can be important with a drug given as a single dose, such as a sleep-inducing medication that must act in a reasonable time frame and achieve an effective blood level that is maintained for an appropriate duration. However, with periodic and repeated dosing, the rate of drug absorption does not, in general, influence the average steady-state concentration of the drug in plasma, provided the drug is stable before it is absorbed; the rate of absorption may, however, still influence drug therapy. If a drug is absorbed rapidly (e.g., a dose given as an intravenous bolus) and has a small "central" volume, the concentration of drug initially will be high. It will then fall as the drug is distributed to its "final" (larger) volume (see Figure 2–6B). If the same drug is absorbed more slowly (e.g., by slow infusion), a significant amount of the drug will be distributed while it is being administered, and peak concentrations will be lower and will occur later. Controlled-release oral preparations are designed to provide a slow and sustained rate of absorption to produce smaller fluctuations in the plasma concentration-time profile during the dosage interval compared with more immediate-release formulations. Because the beneficial, nontoxic effects of drugs are based on knowledge of an ideal or desired plasma concentration range, maintaining that range while avoiding large swings between peak and trough concentrations can improve therapeutic outcome.

BOX 2–2 ■ Poor Absorption Notwithstanding, Some Agents With Low Bioavailability Are Effective Orally

The value of F varies widely for drugs administered by mouth, and successful therapy can still be achieved for some drugs with F values as low as 0.03 (e.g., etidronate and aliskiren). Aliskiren is the first orally applicable direct renin inhibitor approved for treatment of hypertension; its bioavailability is 2.6%. Etidronate, a bisphosphonate used to stabilize bone matrix in the treatment of Paget's disease and osteoporosis, has a similarly low bioavailability of 0.03, meaning that only 3% of the drug appears in the bloodstream following oral dosing. In these cases, therapy using oral administration is still useful, although the administered dose of the drug per kilogram is larger than would be given by injection.

Nonlinear Pharmacokinetics

Nonlinearity in pharmacokinetics (i.e., changes in such parameters as clearance, volume of distribution, and $t_{1/2}$ as a function of dose or concentration of drug) is usually caused by saturation of protein binding, hepatic metabolism, or active renal transport of the drug.

Saturable Protein Binding

As the molar concentration of small drug molecules increases, the unbound fraction eventually also must increase (as all binding sites become saturated when drug concentrations in plasma are in the range of tens to hundreds of micrograms per milliliter). For a drug that is metabolized by the liver with a low intrinsic clearance-extraction ratio, saturation of plasma-protein binding will cause both V and CL to increase as drug concentrations increase; $t_{1/2}$ thus may remain constant (see Equation 2–14). For such a drug, C_{ss} will not increase linearly as the rate of drug administration is increased. For drugs that are cleared with high intrinsic clearance-extraction ratios, C_{ss} can remain linearly proportional to the rate of drug administration. In this case, hepatic clearance will not change, and the increase in V will increase the half-time of disappearance by reducing the fraction of the total drug in the body that is delivered to the liver per unit of time. Most drugs fall between these two extremes.

Saturable Elimination

In the case of saturable elimination, the Michaelis-Menten equation (see Equation 2–4) usually describes the nonlinearity. All active processes are undoubtedly saturable, but they will appear to be linear if values of drug concentrations encountered in practice are much less than K_m for that process (Box 2–3). When drug concentrations exceeds K_m, nonlinear kinetics are observed. Saturable metabolism causes oral first-pass metabolism to be less than expected (higher *fractional bioavailability*), resulting in a greater fractional increase in C_{ss} than the corresponding fractional increase in the rate of drug administration; basically, the rate of drug entry into the systemic circulation exceeds the maximum possible rate of drug metabolism, and elimination becomes zero order. The major consequences of saturation of metabolism or transport are the opposite of those for saturation of protein binding. Saturation of protein binding will lead to increased CL because CL increases as drug concentration increases, whereas saturation of metabolism or transport may decrease CL.

C_{ss} can be computed by substituting Equation 2–4 (with $C = C_{ss}$) into Equation 2–3 and solving for the steady-state concentration:

$$C_{ss} = \frac{\text{Dosing rate} \cdot K_m}{v_m - \text{dosing rate}} \qquad \text{(Equation 2–16)}$$

As the dosing rate approaches the maximal elimination rate v_m, the denominator of Equation 2–16 approaches zero, and C_{ss} increases disproportionately. Because saturation of metabolism should have no effect on

BOX 2–3 ■ Saturable Metabolism: Phenytoin

The antiseizure medication phenytoin is a drug for which metabolism can become saturated by levels of the drug in the therapeutic range. Factors contributing to this are phenytoin's variable half-life and clearance and an effective concentration that varies and can saturate clearance mechanisms, such that the C_{ss} may be saturating clearance mechanisms or be well above or below that value. The $t_{1/2}$ of phenytoin is 6–24 h. For clearance, K_m (5–10 mg/L) is typically near the lower end of the therapeutic range (10–20 mg/L). For some individuals, especially young children and newborns being treated for emergent seizures, K_m may be as low as 1 mg/L. Consider an extreme case of a 70kg adult in whom the target concentration (C_{ss}) is 15 mg/L, K_m = 1 mg/L, and the maximal elimination rate, v_m, (from Appendix II) is 5.9 mg/kg/day, or 413 mg/day/70kg. Substituting into Equation 2–16:

$$15\text{mg/L} = (\text{dosing rate})(1\text{mg/L})/(413\text{mg/day} - \text{dosing rate})$$
$$\text{dosing rate} = 387\ \text{mg/day}$$

In this case, the dosing rate is just below the elimination capacity. If the dosing rate were to vary upward by 10% (to 387 + 38.7 or ~426 mg/day), the dosing rate would exceed the elimination capacity by 13 mg/day and the C_p of phenytoin would begin a slow climb to toxic levels. Conversely, if the dosing rate were to vary downward by 10% (to 387-38.7 or ~348 mg/day), the C_{ss} achieved would be 5.4 mg/L, a drastic reduction to a level below the therapeutic range.

Consider a more common K_m, 8 mg/L, such that the desired C_{ss} of 15mg/L is farther from saturating the elimination capacity. In a 70 kg subject (v_m = 413 mg/day), these data require a dosing rate of only 269 mg/day. An increase in this rate by 10% (to 296 mg/day) would not saturate the elimination capacity but would lead to a C_{ss} = 20.2 mg/L. A 10% downward variance in the dosing rate (to 242 mg/day) will produce a C_{ss} = 11.3 mg/L, a much less drastic decrease than above and still in the therapeutic range.

Factoring in all the variables, predicting and controlling dosage so precisely (<10% error) can be difficult. Therefore, for patients in whom the target concentration for phenytoin is ≥10 times the K_m, alternating between inefficacious therapy and toxicity is common, careful monitoring is essential, and a pharmacokinetic consult to establish or revise dosing may be appropriate.

Other agents exhibiting saturated metabolism at or near the commonly employed concentrations include aspirin, fluoxetine, verapamil, and ethanol.

the volume of distribution, clearance and the relative rate of drug elimination decrease as the concentration increases; therefore, the log C_p time curve is concave-downward until metabolism becomes sufficiently desaturated such that first-order elimination is observed (Figure 2–8).

Thus, in the region of saturation of metabolism, the concept of a constant $t_{1/2}$ is not applicable. Consequently, changing the dosing rate for a drug with nonlinear metabolism is difficult and unpredictable because the resulting steady state is reached more slowly, and importantly, the effect is disproportionate to the alteration in the dosing rate.

Figure 2–8 compares the effects of first-order and zero-order elimination kinetics on important pharmacokinetic parameters.

Design and Optimization of Dosage Regimens

The Therapeutic Window

The intensity of a drug's effect is related to its concentration (usually C_p) above a minimum effective concentration, whereas the duration of the drug's effect reflects the length of time the drug level is above this value (Figure 2–9). These considerations, in general, apply to both desired and undesired (adverse) drug effects; as a result, a *therapeutic window* exists that reflects a concentration range that provides efficacy without unacceptable toxicity. Following administration of a single dose, a lag period precedes the onset of the drug effect, after which the magnitude of the effect increases to a maximum and then declines; if a subsequent dose is not administered, the effect eventually disappears as the drug is eliminated. This time course reflects changes in the drug's concentration as determined by the pharmacokinetics of its absorption, distribution, and elimination.

Similar considerations apply after multiple dosing associated with long-term therapy, and they determine the amount and frequency of drug administration to achieve an optimal therapeutic effect. *In general, the lower limit of a drug's therapeutic range is approximately equal to the drug concentration that produces about half the greatest possible therapeutic effect, and the upper limit of the therapeutic range is such that no more than 5%–10% of patients will experience a toxic effect.* For some drugs, this may mean that the upper limit of the range is no more than twice the lower limit. Of course, these figures can be highly variable, and some patients may benefit greatly from drug concentrations that exceed the therapeutic range, whereas others may suffer significant toxicity at much lower values (e.g., with digoxin).

For a limited number of drugs, some effect of the drug is easily measured (e.g., blood pressure, blood glucose) and can be used to optimize dosage using a trial-and-error approach. Even in an ideal case, certain

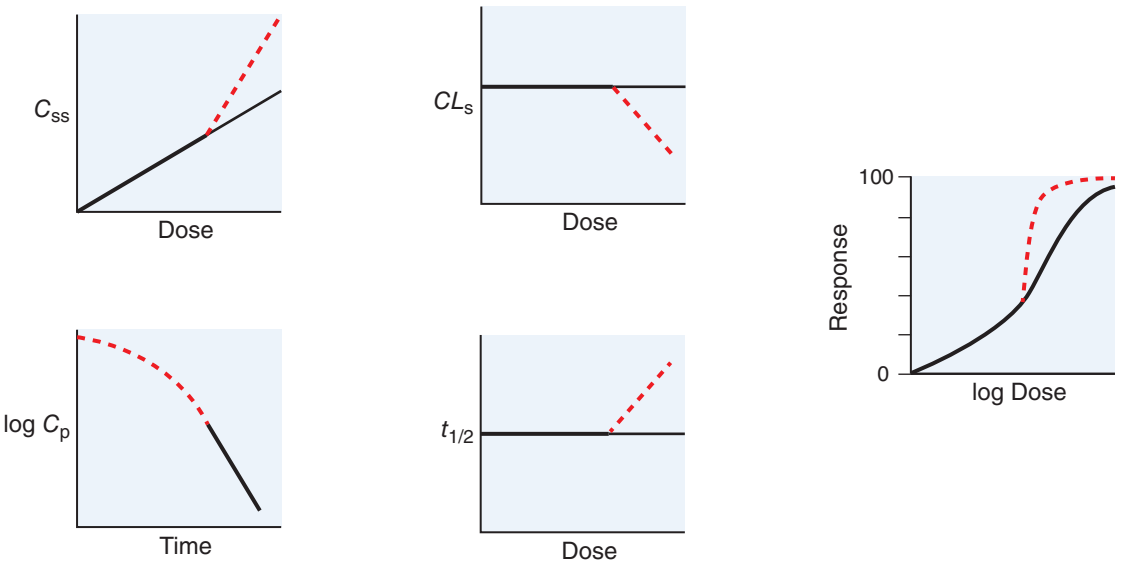

Figure 2–8 *Comparative pharmacokinetic parameters with first-order and zero-order elimination.* Black lines represent the relationships under first-order kinetics of elimination. Dashed red lines indicate the effects of transitioning to a region of saturated elimination (zero-order kinetics).

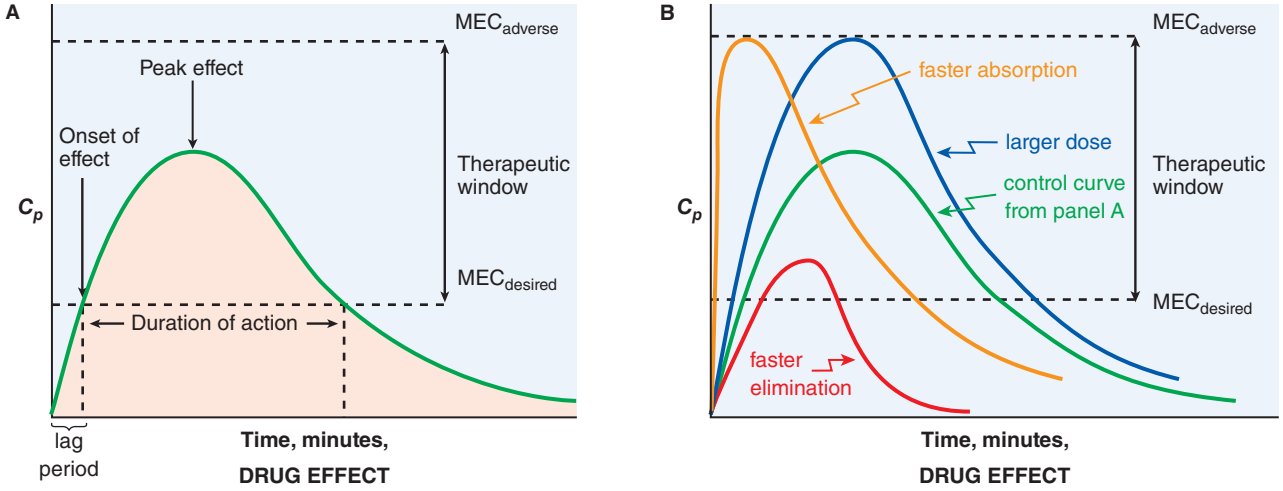

Figure 2–9 **A.** *Temporal characteristics of drug effect and relationship to the therapeutic window (e.g., single dose, oral administration).* A lag period is present before the plasma drug concentration C_p exceeds the MEC for the desired effect $MEC_{desired}$. Following onset of the response, the intensity of the effect increases as the drug continues to be absorbed and distributed. This reaches a peak, after which drug elimination results in a decline in C_p and in the effect's intensity. Effect disappears when the drug concentration falls below the $MEC_{desired}$. The duration of a drug's action is determined by the time period over which concentrations exceed the $MEC_{desired}$. An MEC also exists for each adverse response ($MEC_{adverse}$), and if the drug concentration exceeds this, toxicity will result. The therapeutic goal is to obtain and maintain concentrations within the therapeutic window for the desired response with a minimum of toxicity. Drug response *below* the $MEC_{desired}$ will be subtherapeutic; *above* the $MEC_{adverse}$, the probability of toxicity will increase. The AUC (pale red) can be used to calculate the clearance (see Equation 2–7) for first-order elimination. The AUC is also used as a measure of bioavailability (defined as 100% for an intravenously administered drug). Bioavailability is less than 100% for orally administered drugs, due mainly to incomplete absorption and first-pass metabolism and elimination. Changing drug dosage shifts the curve up or down the C_p scale and is used to modulate the drug's effect, as shown in panel B.
B. *Effects of altered absorption, elimination, and dosage and the temporal profile of a single dose administered orally.* The bold green curve is the same as that shown in panel A. Increasing the dose (blue line) decreases the lag period and prolongs the drug's duration of effectivess but at the risk of increasing the likelihood of adverse effects. Unless the drug is nontoxic (e.g., penicillins), increasing the dose is not a useful strategy for extending the duration of action if the increase puts the drug level near $MEC_{adverse}$. Instead, another dose of drug should be given, timed to maintain concentrations within the therapeutic window (see Figure 2–7). An increased rate of absorption of the dose (orange line) reduces the lag period, leads to a higher maximum C_p at an earlier time, but results in a shorter duration of action (time above $MEC_{desired}$). Increasing the rate of elimination of the dose decreases the maximum C_p and reduces the time of $C_p > MEC_{desired}$.

quantitative issues arise, such as how often to change dosage and by how much. These usually can be settled with simple rules of thumb based on the principles presented (e.g., change dosage by no more than 50% and no more often than every three or four half-lives). Alternatively, some drugs have little dose-related toxicity, and maximum efficacy usually is desired. In such cases, doses well in excess of the average required will ensure efficacy (if this is possible) and prolong drug action. Such a "maximal dose" strategy typically is used for penicillins. For many drugs, however, the effects are difficult to measure (or the drug is given for prophylaxis), toxicity and lack of efficacy are both potential dangers, or the therapeutic index is narrow. In these circumstances, doses must be titrated carefully, and drug dosage is limited by toxicity rather than efficacy.

Thus, the therapeutic goal is to maintain steady-state drug levels within the therapeutic window. When the concentrations associated with this desired range are not known, it is sufficient to understand that efficacy and toxicity depend on concentration and how drug dosage and frequency of administration affect the drug level. However, for a small number of drugs for which there is a small (2- to 3-fold) difference between concentrations resulting in efficacy and toxicity (e.g., digoxin, theophylline, lidocaine, aminoglycosides, cyclosporine, tacrolimus, sirolimus, warfarin, and some anticonvulsants), a plasma concentration range associated with effective therapy has been defined. In these cases, a desired (target) steady-state concentration of the drug (usually in plasma) associated with efficacy and minimal toxicity is chosen, and a dosage is computed that is expected to achieve this value. Drug concentrations are subsequently measured, and dosage is adjusted if necessary (described further in the chapter).

Maintenance Dose

In most clinical situations, drugs are administered in a series of repetitive doses or as a continuous infusion to maintain a steady-state concentration of drug associated with the therapeutic window. Calculation of the appropriate maintenance dosage is a primary goal. To maintain the chosen steady-state or target concentration, the rate of drug administration is adjusted such that the rate of input equals the rate of loss. This relationship is expressed here in terms of the desired target concentration:

$$\text{Dosing rate} = \text{Target } C_p \cdot CL/F \qquad \text{(Equation 2–17)}$$

If the clinician chooses the desired concentration of drug in plasma and knows the clearance and bioavailability for that drug in a particular patient, the appropriate dose and dosing interval can be calculated (Box 2–4).

Dosing Interval for Intermittent Dosage

In general, marked fluctuations in drug concentrations between doses are not desirable. If absorption and distribution were instantaneous, fluctuations in drug concentrations between doses would be governed entirely by the drug's elimination $t_{1/2}$. If the dosing interval t were chosen to be equal to the $t_{1/2}$, then the total fluctuation would be 2-fold; this is often a tolerable variation. Pharmacodynamic considerations modify this. If a drug is relatively nontoxic such that a concentration many times that necessary for therapy can be tolerated easily, the maximal dose strategy can be used, and the dosing interval can be much longer than the elimination $t_{1/2}$ (for convenience). The $t_{1/2}$ of amoxicillin is about 2 h, but dosing every 2 h would be impractical. Instead, amoxicillin often is given in large doses every 8 or 12 h.

For some drugs with a narrow therapeutic range, it may be important to estimate the maximal and minimal concentrations that will occur for a particular dosing interval. The minimal steady-state concentration $C_{ss,\,min}$ may be reasonably determined by:

$$C_{ss,\,min} = \frac{F \cdot \text{dose}/V_{ss}}{1 - e^{-kT}} \cdot e^{-kT} \qquad \text{(Equation 2–18)}$$

where k equals 0.693 divided by the clinically relevant plasma $t_{1/2}$, and T is the dosing interval. The term e^{-kT} is the fraction of the last dose (corrected for bioavailability) that remains in the body at the end of a dosing interval.

BOX 2–4 ■ Calculating Dosage of Digoxin in Heart Failure

Oral digoxin is to be used as a maintenance dose to gradually "digitalize" a 63-year-old, 84-kg patient with congestive heart failure. A steady-state plasma concentration of 0.7–0.9 ng/mL is selected as a conservative target based on prior knowledge of the action of the drug in patients with heart failure to maintain levels at or below the 0.5- to 1.0-ng/mL range (Bauman et al., 2006). This patient's creatinine clearance CL_{Cr} is given as 56 mL/min/84 kg; knowing that digoxin's clearance may be estimated by consulting the entry for digoxin in Appendix II: $CL = 0.88\ CL_{Cr} + 0.33$ mL/min/kg. Thus,

$$\begin{aligned} CL &= 0.88\ CL_{Cr} + 0.33\ \text{mL/min/kg} \\ &= 0.88 \times 56/84 + 0.33\ \text{mL/min/kg} \\ &= 0.92\ \text{mL/min/kg} \end{aligned}$$

For this 84-kg patient:

$$CL = (84\ \text{kg})(0.92\ \text{mL/min/kg}) = 77\ \text{mL/min} = 4.6\ \text{L/h}$$

Knowing that the oral bioavailability of digoxin is 70% ($F = 0.7$) and with a target C_p of 0.75 ng/mL, one can use Equation 2–17 to calculate an appropriate dose rate for this 84-kg patient:

$$\begin{aligned} &\text{Dosing rate} = \text{Target } C_p \cdot CL/F \\ &= [0.75\ \text{ng/mL} \times 77\ \text{mL/min}] \div [0.7] = 82.5\ \text{ng/min} \\ &\text{or } 82.5\ \text{ng/min} \times 60\ \text{min/h} \times 24\ \text{h/d} = 119\ \mu\text{g/d} \end{aligned}$$

In practice, the dosing rate is rounded to the closest oral dosage size, 0.125 mg/d, which would result in a C_{ss} of 0.79 ng/mL (0.75 × 125/119, or using Equation 2–15). Digoxin is a well-characterized example of a drug that is difficult to dose, has a low therapeutic index (~2–3), and has a large coefficient of variation for the clearance equation in patients with heart failure (52%); the effective blood level in one patient may be toxic or ineffective in another. Thus, monitoring the clinical status of patients (new or increased ankle edema, inability to sleep in a recumbent position, decreased exercise tolerance), whether accomplished by home health follow-up or regular visits to the clinician, is essential to avoid untoward results (see Chapter 29).

BOX 2–5 ■ Estimating Maximal and Minimal Blood Levels of Digoxin

In the 84-kg patient with congestive heart failure discussed in Box 2–4, an oral maintenance dose of 0.125 mg digoxin per 24 h was calculated to achieve an average plasma concentration of 0.79 ng/mL during the dosage interval. Digoxin has a narrow therapeutic index, and plasma levels ≤ 1.0 ng/mL usually are associated with efficacy and minimal toxicity. What are the maximum and minimum plasma concentrations associated with this regimen? This first requires estimation of digoxin's volume of distribution based on pharmacokinetic data (Appendix II).

$$\begin{aligned} V_{ss} &= 3.12\ CL_{Cr} + 3.84\ \text{L} \cdot \text{kg}^{-1} \\ &= 3.12 \times (56/84) + 3.84\ \text{L} \cdot \text{kg}^{-1} \\ &= 5.92\ \text{L/kg} \end{aligned}$$

or 497 L in this 84-kg patient.

Combining this value with that of digoxin's clearance provides an estimate of digoxin's elimination $t_{1/2}$ in the patient (Equation 2–14).

$$\begin{aligned} t_{1/2} &= 0.693\ V_{ss}/CL \\ &= \frac{0.693 \times 497\ \text{L}}{4.6\ \text{L/h}} = 75\ \text{h} = 3.1\ \text{days} \end{aligned}$$

Accordingly, the fractional rate constant of elimination k is equal to 0.22 day^{-1} (0.693/3.1 days). Maximum and minimum digoxin plasma concentrations then may be predicted depending on the dosage interval. With $T = 1$ day (i.e., 0.125 mg given every day),

$$\begin{aligned} C_{ss,max} &= \frac{F \cdot \text{dose}/V_{ss}}{1 - e^{-kT}} \qquad \text{(Equation 2–19)} \\ &= \frac{0.7 \times 0.125\ \text{mg/497 L}}{0.2} \\ &= 0.88\ \text{ng/mL (~0.9 ng/mL)} \end{aligned}$$

$$\begin{aligned} C_{ss,min} &= C_{ss,max} \cdot e^{-kt} \qquad \text{(Equation 2–20)} \\ &= (0.88\ \text{ng/mL})(0.8) = 0.7\ \text{ng/mL} \end{aligned}$$

Thus, the plasma concentrations would fluctuate minimally about the steady-state concentration of 0.79 ng/mL, well within the recommended therapeutic range of 0.5–1.0 ng/mL.

For drugs that follow multiexponential kinetics (administered orally), estimation of the maximal steady-state concentration $C_{ss,max}$ involves a set of parameters for distribution and absorption (Box 2–5). If these terms are ignored for multiple oral dosing, one easily may estimate a maximal steady-state concentration by omitting the e^{-kT} term in the numerator of Equation 2–18 (see Equation 2–19 in Box 2–5). Because of the approximation, the predicted maximal concentration from Equation 2–19 will be greater than that actually observed.

Loading Dose

As noted, repeated administration of a drug more frequently than its complete elimination will result in accumulation of the drug to or around a steady-state level (see Figure 2–7). When a constant dosage is given, reaching a steady-state drug level (the desired therapeutic concentration) will take four to five elimination half-times. This period can be too long when treatment demands a more immediate therapeutic response. In such a case, one can employ a *loading dose*, one or a series of doses given at the onset of therapy with the aim of achieving the target concentration rapidly. The loading dose is calculated as

$$\text{Loading dose} = \text{Target } C_p \cdot V_{ss}/F \qquad \text{(Equation 2–21)}$$

Consider the case for treatment of arrhythmias with lidocaine, for example. The $t_{1/2}$ of lidocaine is usually 1–2 h. Arrhythmias encountered after myocardial infarction may be life threatening, and one cannot wait four half-times (4–8 h) to achieve a therapeutic concentration of lidocaine by infusion of the drug at the rate required to attain this concentration. Hence, use of a loading dose of lidocaine in the coronary care unit is standard.

The use of a loading dose also has significant disadvantages. First, the particularly sensitive individual may be exposed abruptly to a toxic concentration of a drug that may take a long time to decrease (i.e., long $t_{1/2}$). Loading doses tend to be large, and they are often given parenterally and rapidly; this can be particularly dangerous if toxic effects occur as a result of actions of the drug at sites that are in rapid equilibrium with plasma. This occurs because the loading dose calculated on the basis of V_{ss} subsequent to drug distribution is at first constrained within the initial and smaller "central" volume of distribution. It is therefore usually advisable to divide the loading dose into a number of smaller fractional doses that are administered over a period of time (Box 2–6). Alternatively, the loading dose should be administered as a continuous intravenous infusion over a period of time using computerized infusion pumps.

BOX 2–6 ■ A Loading Dose of Digoxin

In the 84-kg patient described previously, accumulation of digoxin to an effective steady-state level was gradual when a daily maintenance dose of 0.125 mg was administered (for at least 12.4 days, based on $t_{1/2}$ = 3.1 days). A more rapid response could be obtained (if deemed necessary) by using a loading dose strategy and Equation 2–21. Choosing a target C_p of 0.9 ng/mL (the $C_{ss,\,max}$ calculated in Box 2–5 and below the recommended maximum of 1.0 ng/mL):

$$\text{Loading dose} = 0.9\ \text{ng} \cdot \text{mL}^{-1} \times 497\ \text{L}/0.7 = 639\ \mu\text{g}$$

Using standard dosage sizes, one would use a loading dose of 0.625 mg given in divided doses. To avoid toxicity, this oral loading dose would be given as an initial 0.25-mg dose followed by a 0.25-mg dose 6–8 h later, with careful monitoring of the patient, and the final 0.125-mg dose given another 6–8 h later.

Therapeutic Drug Monitoring

The major use of measured concentrations of drugs (at steady state) is to refine the estimate of *CL*/*F* for the patient being treated, using Equation 2–15 as rearranged:

$$CL/F_{\text{patient}} = \text{Dosing rate}/C_{ss}(\text{measured}) \qquad \text{(Equation 2–22)}$$

The new estimate of *CL*/*F* can be used in Equation 2–17 to adjust the maintenance dose to achieve the desired target concentration (Box 2–7).

Practical details associated with therapeutic drug monitoring should be kept in mind. The first of these relates to the time of sampling for measurement of the drug concentration.

The purpose of sampling during supposed steady state is to modify the estimate of *CL*/*F* and thus the choice of dosage. Early postabsorptive concentrations do not reflect clearance; they are determined primarily by the rate of absorption, the "central" (rather than the steady-state) volume of distribution, and the rate of distribution, all of which are pharmacokinetic features of virtually no relevance in choosing the long-term maintenance dosage. When the goal of measurement is adjustment of dosage, the sample should be taken just before the next planned dose, when the concentration is at its minimum.

If it is unclear whether efficacious concentrations of drug are being achieved, a sample taken shortly after a dose may be helpful. On the other hand, if a concern is whether low clearance (as in renal failure) may cause accumulation of drug, concentrations measured just before the next dose will reveal such accumulation and are considerably more useful for this purpose than is knowledge of the maximal concentration.

Determination of both maximal and minimal concentrations is recommended. These two values can offer a more complete picture of the behavior of the drug in a specific patient (particularly if obtained over more than one dosing period) and can better support pharmacokinetic modeling to adjust treatment.

When constant dosage is given, steady state is reached after four to five elimination half-times. If a sample is obtained too soon after dosage is begun, it will not reflect this state and the drug's clearance accurately. Yet, for toxic drugs, if sampling is delayed until steady state, the damage may have been done. In such cases, the first sample should be taken after two $t_{1/2}$ assuming that no loading dose has been given. If the concentration already exceeds 90% of the eventual expected mean steady-state concentration, the dosage rate should be halved, another sample obtained in another two (supposed) $t_{1/2}$, and the dosage halved again if this sample exceeds the target. If the first concentration is not too high, the initial rate of dosage is continued; even if the concentration is lower than expected, it is usually reasonable to await the attainment of steady state in another two estimated $t_{1/2}$ and then to proceed to adjust dosage as described in Box 2–7.

BOX 2–7 ■ Adjusting the Dose at Steady State

If a drug follows first-order kinetics, the average, minimum, and maximum concentrations at steady state are linearly related to dose and dosing rate (see Equations 2–15, 2–18, and 2–19). Therefore, the ratio between the measured and desired concentrations can be used to adjust the dose, consistent with available dosage sizes:

$$\frac{C_{ss}(\text{measured})}{C_{ss}(\text{predicted})} = \frac{\text{Dose (previous)}}{\text{Dose (new)}} \qquad \text{(Equation 2–23)}$$

Consider the previously described patient given 0.125 mg digoxin every 24 h, for example. If the measured minimum (trough) steady-state concentration were found to be 0.35 ng/mL rather than the predicted level of 0.7 ng/mL, an appropriate, practical change in the dosage regimen would be to increase the daily dose by 0.125 mg to 0.25 mg digoxin daily.

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Chapter 3

Pharmacodynamics: Molecular Mechanisms of Drug Action

Donald K. Blumenthal

Pharmacodynamic Concepts

Pharmacodynamics is the study of the biochemical, cellular, and physiological effects of drugs and their mechanisms of action. The effects of most drugs result from their interaction with macromolecular components of the organism. The term drug *receptor* or drug *target* denotes the cellular macromolecule or macromolecular complex with which the drug interacts to elicit a cellular or systemic response. Drugs commonly alter the rate or magnitude of an intrinsic cellular or physiological response rather than create new responses. Drug receptors are often located on the surface of cells but may also be located in specific intracellular compartments, such as the nucleus, or in the extracellular compartment, as in the case of drugs that target coagulation factors and inflammatory mediators. Many drugs also interact with *acceptors* (e.g., serum albumin), which are entities that do not directly cause any change in biochemical or physiological response but can alter the pharmacokinetics of a drug's actions.

A large percentage of the new drugs approved in recent years are *therapeutic biologics*, including genetically engineered enzymes and monoclonal antibodies. Going far beyond the traditional concept of a drug are genetically modified viruses and microbes. One recently approved agent for treating melanoma is a genetically modified live oncolytic herpes virus that is injected into tumors that cannot be removed completely by surgery. *Gene therapy products* using viruses as vectors to replace genetic mutations that give rise to lethal and debilitating diseases have already been approved in China and Europe. The next generation of gene therapy products will be those capable of targeted genome editing using antisense oligonucleotides and RNAi and by delivering the CRISPR/Cas9 genome-editing system using viruses or genetically modified microorganisms. These new agents will have pharmacological properties that are distinctly different from traditional small-molecule drugs.

Physiological Receptors

Many drug receptors are proteins that normally serve as receptors for endogenous regulatory ligands. These drug targets are termed *physiological receptors*. Drugs that bind to physiological receptors and mimic the regulatory effects of the endogenous signaling compounds are termed *agonists*. If the drug binds to the same *recognition site* as the endogenous agonist, the drug is said to be a *primary agonist*. *Allosteric* (or *allotopic*) *agonists* bind to a different region on the receptor, referred to as an allosteric or allotopic site. Drugs that block or reduce the action of an agonist are termed *antagonists*. Antagonism generally results from competition with an agonist for the same or overlapping site on the receptor (a *syntopic interaction*), but can also occur by interacting with other sites on the receptor (*allosteric antagonism*), by combining with the agonist (*chemical antagonism*), or by *functional antagonism* by indirectly inhibiting the cellular or physiological effects of the agonist. Agents that are only partially as effective as agonists are termed *partial agonists*. Many receptors exhibit some constitutive activity in the absence of a regulatory ligand; drugs that stabilize such receptors in an inactive conformation are termed *inverse agonists* (Figure 3–1) (Kenakin, 2004; Milligan, 2003). In the presence of a full agonist, partial and inverse agonists will behave as competitive antagonists.

Specificity of Drug Responses

The strength of the reversible interaction between a drug and its receptor, as measured by the **dissociation constant**, is defined as the *affinity* of one for the other. (By tradition, only rarely will the inverse of the dissociation constant, the association constant, be used, even though both carry the same information.) Both the *affinity* of a drug for its receptor and its *intrinsic activity* are determined by its *chemical structure*. The chemical structure of a drug also contributes to the drug's *specificity*. A drug that interacts with a single type of receptor that is expressed on only a limited number of differentiated cells will exhibit high specificity. Conversely, a drug acting on a receptor expressed ubiquitously throughout the body will exhibit widespread effects.

Many clinically important drugs exhibit a broad (low) specificity because they interact with multiple receptors in different tissues. Such broad specificity might not only enhance the clinical utility of a drug but also contribute to a spectrum of adverse side effects because of off-target interactions. One example of a drug that interacts with multiple receptors is *amiodarone*, an agent used to treat cardiac arrhythmias. Amiodarone also has a number of serious toxicities, some of which are caused by the drug's structural similarity to thyroid hormone and, as a result, its capacity to interact with nuclear thyroid receptors. Amiodarone's salutary effects and toxicities may also be mediated through interactions with receptors that are poorly characterized or unknown.

Some drugs are administered as racemic mixtures of stereoisomers. The stereoisomers can exhibit different pharmacodynamic as well as pharmacokinetic properties. For example, the antiarrhythmic drug *sotalol* is prescribed as a racemic mixture; the D- and L-enantiomers are equipotent as K^+ channel blockers, but the L-enantiomer is a much more potent β adrenergic antagonist (see Chapter 30). A drug may have

Abbreviations

AAV: adeno-associated virus
AC: adenylyl cyclase
ACE: angiotensin-converting enzyme
ACh: acetylcholine
AChE: acetylcholinesterase
AKAP: A-kinase anchoring protein
AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
AngII: angiotensin II
ANP: atrial natriuretic peptide
Apaf-1: apoptotic activating protease factor 1
ASO: antisense oligonucleotide
***ATG*:** autophagy gene
AT_1R: AT_1 receptor
BNP: brain natriuretic peptide
cAMP: cyclic adenosine monophosphate
cAMP-GEF: cAMP-guanine exchange factor
cGMP: cyclic guanosine monophosphate
CNG: cyclic nucleotide–gated channel
CNP: C-type natriuretic peptide
CREB: cAMP response element–binding protein
CRISPR/Cas9: clustered regularly interspersed short palindromic repeats/CRISPR-associated protein 9
DA: dopamine
DAG: diacylglycerol
DMD: Duchenne muscular dystrophy
DRAM: damage-regulated autophagy modulator
4EBP: eukaryotic initiation factor 4e (eif-4E)–binding protein
EC_{50}: half-maximally effective concentration
EGF: epidermal growth factor
eNOS: endothelial NOS (NOS3)
EPAC: exchange protein activated by cAMP
FADD: Fas-associated death domain
FGF: fibroblast growth factor
FKBP12: immunophilin target (binding protein) for tacrolimus (FK506)
FXR: farnesoid X receptor
GABA: γ-aminobutyric acid
GAP: GTPase-activating protein
GC: guanylyl cyclase
GEF: guanine nucleotide exchange factor
GI: gastrointestinal
GPCR: G protein–coupled receptor
GRK: GPCR kinase
HCN: hyperpolarization-activated, cyclic nucleotide–gated channel
HRE: hormone response element
5HT: serotonin
IGF1R: insulinlike growth factor 1 receptor
IKK: IκB kinase
iNOS: inducible NOS (NOS2)
IP_3: inositol 1,4,5-trisphosphate
IRAK: interleukin-1 receptor-associated kinase
Jak: Janus kinase
JNK: c-Jun N-terminal kinase
K_{ATP}: ATP-dependent K^+ channel
K_i: affinity of a competitive antagonist
LBD: ligand-binding domain
LDLR: low-density lipoprotein receptor
LXR: liver X receptor
MAO: monoamine oxidase
MAPK: mitogen-activated protein kinase
MHC: major histocompatibility complex
MLCK: myosin light chain kinase
mTOR: mammalian target of rapamycin
MyD88: myeloid differentiation protein 88
NE: norepinephrine
NF-κB: nuclear factor kappa B
NGF: nerve growth factor
NGG: 5′-(any Nucleotide)-Guanosine-Guanosine-3′
NMDA: *N*-methyl-D-aspartate
nmDMD: nonsense mutation Duchenne muscular dystrophy
nNOS: neuronal NOS (NOS1)
NO: nitric oxide
NOS: NO synthase
NPR-A: ANP receptor
NPR-B: natriuretic peptide B receptor
NPR-C: natriuretic peptide C receptor
NSAID: nonsteroidal anti-inflammatory drug
PDE: cyclic nucleotide phosphodiesterase
PAM: protospacer-adjacent motif
PDGF: platelet-derived growth factor
PDGF-R: PDGR receptor
PI3K: phosphatidylinositol 3-kinase
PIP_3: phosphatidylinositol 3,4,5-trisphosphate
PK_: protein kinase _ (e.g., PKA)
PKB: protein kinase B (also known as Akt)
PLC: phospholipase C
PPAR: peroxisome proliferator-activated receptor
RGS: regulator of G protein signaling
RIP1: receptor interacting protein 1
RISC: RNA-induced silencing complex
RNAi: RNA interference
RXR: retinoic acid receptor
SERCA: SR Ca^{2+}-ATPase
sGC: soluble guanylyl cyclase
sgRNA: single "guide" RNA
siRNA: small interfering RNA
S6K: S6 kinase
SMAC: second mitochondria-derived activator of caspase
SMC: smooth muscle cell
SR: sarcoplasmic reticulum
STAT: signal transducer and activator of transcription
TAK1: transforming growth factor β–activated kinase 1
TCR: T cell receptor
TGF-β: transforming growth factor β
TLR: Toll-like receptor
TNF-α: tumor necrosis factor α
TRADD: TNF receptor–associated death domain
TRAF: TNF receptor–associated factor
TRAIL: TNF-related apoptosis-inducing ligand
TRP: transient receptor potential
VEGF: vascular endothelial growth factor

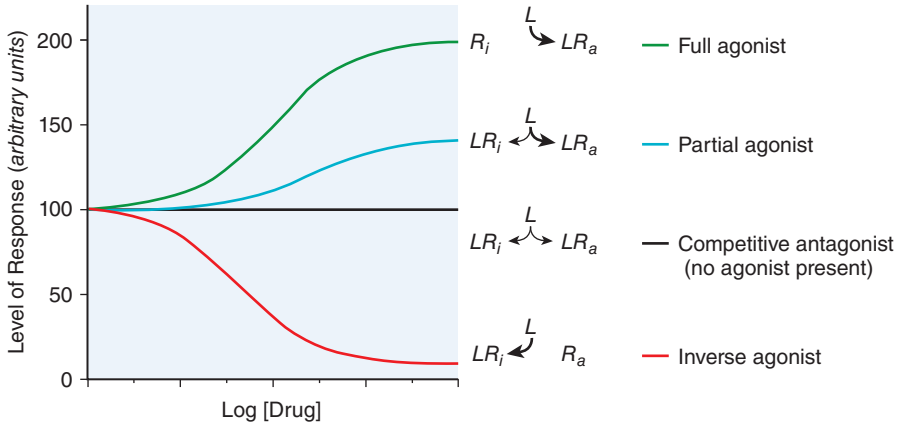

Figure 3–1 *Regulation of the activity of a receptor with conformation-selective drugs.* In this model, receptor R can exist in active (R_a) and inactive (R_i) conformations, and drugs binding to one, the other, or both states of *R* can influence the balance of the two forms of *R* and the net effect of receptor-controlled events. The ordinate is the activity of the receptor produced by R_a, the active receptor conformation (e.g., stimulation of AC by an activated β adrenergic receptor). If a drug *L* selectively binds to R_a, it will produce a maximal response. If *L* has equal affinity for R_i and R_a, it will not perturb the equilibrium between them and will have no effect on net activity; *L* would appear as a competitive antagonist if it blocks an agonist binding site (see Figure 3–4). If the drug selectively binds to R_i, then the net influence and amount of R_a will be diminished. If *L* can bind to receptor in an active conformation R_a but also bind to inactive receptor R_i with lower affinity, the drug will produce a partial response; *L* will be a partial agonist. If there is sufficient R_a to produce an elevated basal response in the absence of ligand (agonist-independent constitutive activity), and *L* binds to R_i, then that basal activity will be inhibited; *L* will then be an inverse agonist. Inverse agonists selectively bind to the inactive form of the receptor and shift the conformational equilibrium toward the inactive state. In systems that are not constitutively active, inverse agonists will behave like competitive antagonists, which helps explain that the properties of inverse agonists and the number of such agents previously described as competitive antagonists were only recently appreciated. Receptors that have constitutive activity and are sensitive to inverse agonists include benzodiazepine, histamine, opioid, cannabinoid, dopamine, bradykinin, and adenosine receptors.

multiple mechanisms of action that depend on receptor specificity, the tissue-specific expression of the receptor(s), drug access to target tissues, different drug concentrations in different tissues, pharmacogenetics, and interactions with other drugs.

Chronic administration of a drug may cause a *downregulation* of receptors or *desensitization* of response that can require dose adjustments to maintain adequate therapy. Chronic administration of nitrovasodilators to treat angina results in the rapid development of *complete tolerance*, a process known as *tachyphylaxis*. *Drug resistance* may also develop because of pharmacokinetic mechanisms (i.e., the drug is metabolized more rapidly with chronic exposure), the development of mechanisms that prevent the drug from reaching its receptor (i.e., increased expression of the multidrug resistance transporter in drug-resistant cancer cells; see Chapter 5), or the clonal expansion of cancer cells containing drug-resistant mutations in the drug receptor.

Some drug effects do not occur by means of macromolecular receptors. For instance, aluminum and magnesium hydroxides [$Al(OH)_3$ and $Mg(OH)_2$] reduce gastric acid chemically, neutralizing H^+ with OH^+ and raising gastric pH. Mannitol acts osmotically to cause changes in the distribution of water to promote diuresis, catharsis, expansion of circulating volume in the vascular compartment, or reduction of cerebral edema (see Chapter 25). Anti-infective drugs such as antibiotics, antivirals, and antiparasitics achieve specificity by targeting receptors or cell processes that are critical for the growth or survival of the infective agent but are nonessential or lacking in the host organism. Resistance to antibiotics, antivirals, and other drugs can occur through a variety of mechanisms, including mutation of the target receptor, increased expression of enzymes that degrade or increase efflux of the drug from the infective agent, and development of alternative biochemical pathways that circumvent the drug's effects on the infective agent.

Structure-Activity Relationships and Drug Design

The receptors responsible for the clinical effects of many drugs have yet to be identified. Conversely, sequencing of the entire human genome has identified novel genes related by sequence to known receptors, for which endogenous and exogenous ligands are unknown; these are called *orphan receptors*.

Both the affinity of a drug for its receptor and its intrinsic activity are determined by its chemical structure. This relationship frequently is stringent. Relatively minor modifications in the drug molecule may result in major changes in its pharmacological properties based on altered affinity for one or more receptors. Exploitation of structure-activity relationships has frequently led to the synthesis of valuable therapeutic agents. Because changes in molecular configuration need not alter all actions and effects of a drug equally, it is sometimes possible to develop a congener with a more favorable ratio of therapeutic to adverse effects, enhanced selectivity amongst different cells or tissues, or more acceptable secondary characteristics than those of the parent drug. Therapeutically useful antagonists of hormones or neurotransmitters have been developed by chemical modification of the structure of the physiological agonist.

With information about the molecular structures and pharmacological activities of a relatively large group of congeners, it is possible to use computer analysis to identify the chemical properties (i.e., the *pharmacophore*) required for optimal action at the receptor: size, shape, position, and orientation of charged groups or hydrogen bond donors, and so on. Advances in molecular modeling of organic compounds and the methods for drug target (receptor) discovery and biochemical measurement of the primary actions of drugs at their receptors have enriched the quantitation of structure-activity relationships and its use in drug design (Carlson and McCammon, 2000). Such information increasingly is allowing the optimization or design of chemicals that can bind to a receptor with improved affinity, selectivity, or regulatory effect. Similar structure-based approaches also are used to improve pharmacokinetic properties of drugs, particularly if knowledge of their metabolism is known. Knowledge of the structures of receptors and of drug-receptor complexes, determined at atomic resolution by X-ray crystallography, is even more helpful in the design of ligands and in understanding the molecular basis of drug resistance and circumventing it. Emerging technology in the field of pharmacogenetics (see Chapter 7) is improving our understanding of the nature of and variation in receptors and their impact on pharmacotherapy (Jain, 2004).

Quantitative Aspects of Drug Interactions With Receptors

Receptor occupancy theory assumes that a drug's response emanates from a receptor occupied by the drug, a concept that has its basis in the law of mass action. The *dose-response curve* depicts the observed effect of a drug

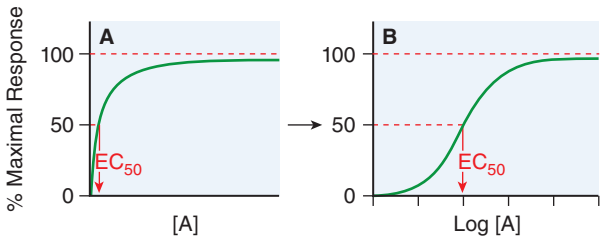

Figure 3–2 *Graded responses. On the* y *axis, the response is expressed as a percentage of maximal response plotted as a function of the concentration of drug A present at the receptor (x axis).* The hyperbolic shape of the curve in panel **A** becomes sigmoid when plotted semilogarithmically, as in panel **B**. The concentration of drug that produces 50% of the maximal response quantifies drug activity and is referred to as the EC_{50} (effective concentration of agonist for 50% response). The range of concentrations needed to fully depict the dose-response relationship (~3 $\log_{10}$ [10] units) is too wide to be useful in the linear format of Figure 3–2A; thus, most dose-response curves use *log [Drug]* on the *x* axis, as in Figure 3–2B. Dose-response curves presented in this way are sigmoidal in shape and have three noteworthy properties: threshold, slope, and maximal asymptote. These three parameters quantitate the activity of the drug.

as a function of its concentration in the receptor compartment. Figure 3–2 shows a typical dose-response curve, usually plotted as in Figure 3-2B.

Some drugs cause low-dose stimulation and high-dose inhibition. Such U-shaped relationships are said to display *hormesis*. Several drug-receptor systems can display this property (e.g., prostaglandins, endothelin, and purinergic and serotonergic agonists), which may be at the root of some drug toxicities (Calabrese and Baldwin, 2003).

Affinity, Efficacy, and Potency

In general, the drug-receptor interaction is characterized by (1) binding of drug to receptor and (2) generation of a response in a biological system, as illustrated in Equation 3–1, where the drug or ligand is denoted as *L* and the inactive receptor as *R*. The first reaction, the reversible formation of the ligand-receptor complex *LR*, is governed by the chemical property of *affinity*.

$$L + R \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} LR \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} LR^* \qquad \text{(Equation 3–1)}$$

LR^* is produced in proportion to $[LR]$ and leads to a *response*. This simple relationship illustrates the reliance of the affinity of the ligand (L) with receptor (R) on both the forward or *association rate* k_{+1} and the reverse or *dissociation rate* k_{-1}. At any given time, the concentration of ligand-receptor complex $[LR]$ is equal to the product of $k_{+1}[L][R]$, the rate of formation of the bimolecular complex *LR*, minus the product $k_{-1}[LR]$, the rate of dissociation of *LR* into *L* and *R*. At equilibrium (i.e., when $\delta[LR]/\delta t = 0$), $k_{+1}[L][R] = k_{-1}[LR]$. The *equilibrium dissociation constant* K_D is then described by ratio of the off and on rate constants, k_{-1}/k_{+1}.

Thus, at equilibrium,

$$K_D = \frac{[L][R]}{[LR]} = \frac{k_{-1}}{k_{+1}} \qquad \text{(Equation 3–2)}$$

The *affinity constant* or *equilibrium association constant* K_A is the reciprocal of the equilibrium dissociation constant (i.e., $K_A = 1/K_D$); thus, *a high-affinity drug has a low* K_D *and will bind a greater number of a particular receptor at a low concentration than a low-affinity drug.* As a practical matter, the affinity of a drug is influenced most often by changes in its off rate (k_{-1}) rather than its on rate (k_{+1}).

Equation 3–2 permits us to describe the *fractional occupancy f* of receptors by agonist *L* as a function of $[R]$ and $[LR]$:

$$f = \frac{[\text{ligand-receptor complexes}]}{[\text{total receptors}]} = \frac{[LR]}{[R]+[LR]} \qquad \text{(Equation 3–3)}$$

f can also be expressed in terms of K_A (or K_D) and $[L]$:

$$f = \frac{K_A[L]}{1+K_A[L]} = \frac{[L]}{1/K_A+[L]} = \frac{[L]}{K_D+[L]} \qquad \text{(Equation 3–4)}$$

From Equation 3–4, it follows that *when the concentration of drug equals the* K_D (or $1/K_A$), $f = 0.5$, *that is, the drug will occupy 50% of the receptors.* When $[L] = K_D$:

$$f = \frac{K_D}{K_D+K_D} = \frac{1}{2} \qquad \text{(Equation 3–4A)}$$

Equation 3–4 describes only receptor occupancy, not the eventual response that may be amplified by the cell. Because of downstream amplification, many signaling systems can reach a full biological response with only a fraction of receptors occupied.

Potency is defined by example in Figure 3–3. Basically, when two drugs produce equivalent responses, the drug whose dose-response curve (plotted as in Figure 3–3A) lies to the left of the other (i.e., the concentration producing a half-maximal effect [EC50] is smaller) is said to be the more potent.

Efficacy reflects the capacity of a drug to activate a receptor and generate a cellular response. Thus, a drug with high efficacy may be a full agonist, eliciting, at some concentration, a full response. A drug with a lower efficacy at the same receptor may not elicit a full response at any dose (see Figure 3–1). A drug with a low intrinsic efficacy will be a partial agonist. A drug that binds to a receptor and exhibits zero efficacy is an antagonist.

Quantifying Agonism

When the relative potency of two agonists of equal efficacy is measured in the same biological system and downstream signaling events are the same for both drugs, the comparison yields a relative measure of the affinity and efficacy of the two agonists (see Figure 3–3). We often describe agonist response by determining the *half-maximally effective concentration* (EC_{50}) for producing a given effect. We can also compare maximal

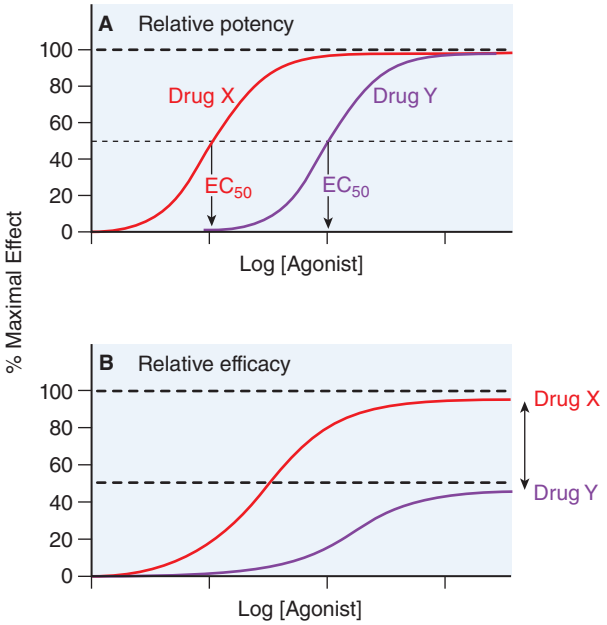

Figure 3–3 *Two ways of quantifying agonism.* **A.** The relative potency of two agonists (drug X, ——; *drug Y*, ——) obtained in the same tissue is a function of their relative affinities and intrinsic efficacies. The EC_{50} of drug X occurs at a concentration that is one-tenth the EC_{50} of drug Y. Thus, drug X is more potent than drug Y. **B.** In systems where the two drugs do not both produce the maximal response characteristic of the tissue, the observed maximal response is a nonlinear function of their relative intrinsic efficacies. Drug X is more efficacious than drug Y; their asymptotic fractional responses are 100% for drug X and 50% for drug Y.

asymptotes in systems where the agonists do not produce maximal response (Figure 3–3B). The advantage of using maxima is that this property depends solely on efficacy, whereas drug *potency* is a mixed function of both affinity and efficacy.

Quantifying Antagonism

Characteristic patterns of antagonism are associated with certain mechanisms of receptor blockade. One is straightforward *competitive antagonism*, whereby a drug with affinity for a receptor but lacking intrinsic efficacy (i.e., an antagonist) competes with the agonist for the primary binding site on the receptor (Ariens, 1954; Gaddum, 1957). *The characteristic pattern of such antagonism is the concentration-dependent production of a parallel shift to the right of the agonist dose-response curve with no change in the maximal response* (Figure 3–4A). The magnitude of the rightward shift of the curve depends on the concentration of the antagonist and its affinity for the receptor (Schild, 1957). *A competitive antagonist will reduce the response to zero.*

A *partial agonist* similarly can compete with a "full" agonist for binding to the receptor. *However, increasing concentrations of a partial agonist will inhibit response to a finite level characteristic of the intrinsic efficacy of the partial agonist.* Partial agonists may be used therapeutically to buffer a response by inhibiting excessive receptor stimulation without totally abolishing receptor stimulation. For example, varenicline is a nicotinic receptor partial agonist used in smoking cessation therapy. Its utility

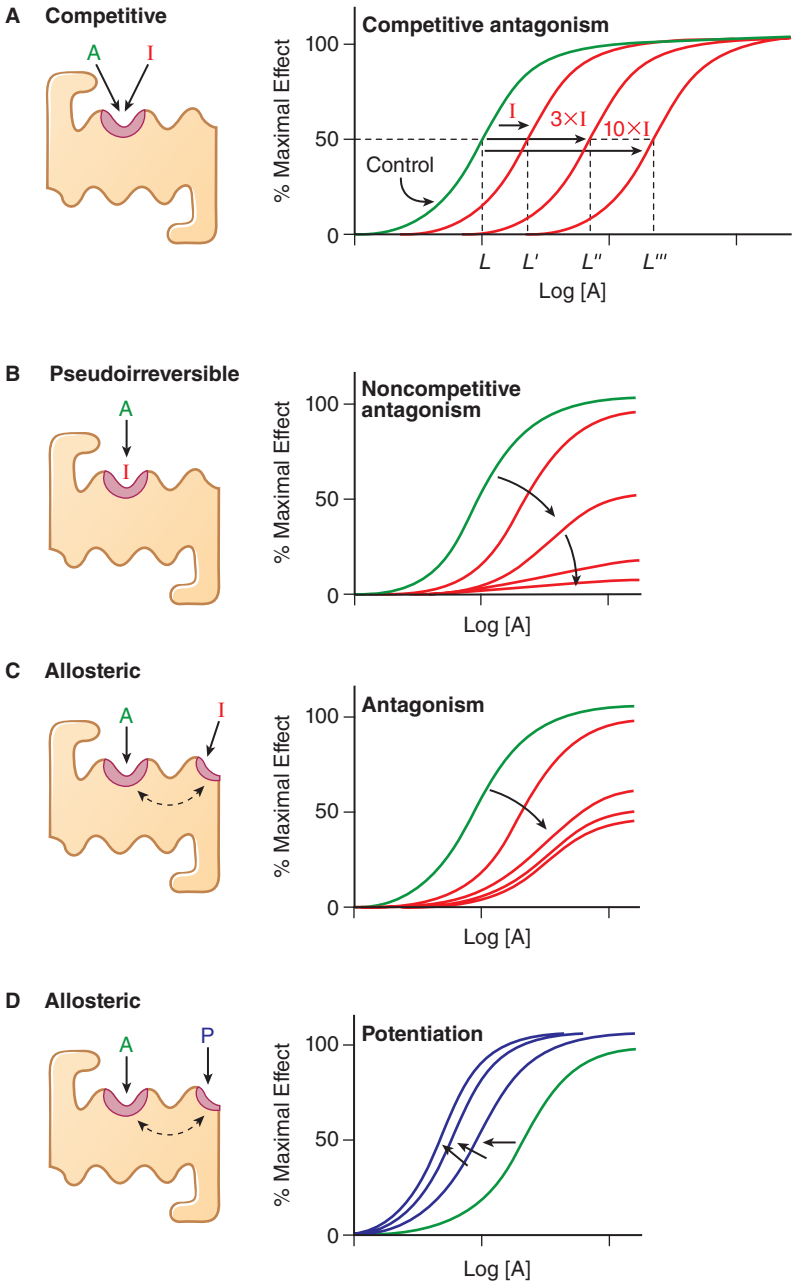

Figure 3–4 *Mechanisms of receptor antagonism.* In each set of curves, the green curve represents the effect of orthosteric agonist, unmodulated by any antagonist or potentiator. **A.** Competitive antagonism occurs when the agonist **A** and antagonist **I** compete for the same binding site on the receptor. Response curves for the agonist are shifted to the right in a concentration-related manner by the antagonist such that the EC_{50} for the agonist increases (e.g., *L* versus *L′*, *L″*, and *L‴*) with the concentration of the antagonist. **B.** If the antagonist binds to the same site as the agonist but does so irreversibly or pseudoirreversibly (slow dissociation but no covalent bond), it causes a shift of the dose-response curve to the right, with progressive depression of the maximal response as [**I**] increases. Allosteric effects occur when an allosteric ligand **I** or **P** binds to a different site on the receptor to either inhibit (I) the response (panel **C**. Increasing concentrations of I shift the curves progressively to right and downward.) or potentiate (**P**) the response (panel **D**. Increasing concentrations of P shift the curves progressively to left.). This allosteric effect is saturable; inhibition or potentiation reaches a limiting value when the allosteric site is fully occupied.

derives from the fact that it activates brain nicotinic receptors sufficiently to prevent craving, but blocks the effects of high-dose nicotine delivered by smoking a cigarette.

An antagonist may dissociate so slowly from the receptor that its action is exceedingly prolonged. In the presence of a slowly dissociating antagonist, the maximal response to the agonist will be depressed at some antagonist concentrations (Figure 3–4B). Operationally, this is referred to as *noncompetitive antagonism*, although the molecular mechanism of action cannot be inferred unequivocally from the effect on the dose-response curve. An *irreversible antagonist* competing for the same binding site as the agonist can produce the same pattern of antagonism shown in Figure 3–4B. Noncompetitive antagonism can be produced by an *allosteric* or *allotopic antagonist*, which binds to a site on the receptor distinct from that of the primary agonist, thereby changing the affinity of the receptor for the agonist. *In the case of an allosteric antagonist, the affinity of the receptor for the agonist is decreased by the antagonist* (Figure 3–4C). In contrast, a drug binding at an allosteric site could potentiate the effects of primary agonists (Figure 3–4D); such a drug would be referred to as an *allosteric agonist* or *coagonist* (May et al., 2007).

The affinity of a competitive antagonist (K_i) for its receptor can be determined in radioligand binding assays or by measuring the functional response of a system to a drug in the presence of the antagonist (Cheng, 2004; Cheng and Prusoff, 1973; Limbird, 2005). Measuring a functional response, concentration curves are run with the agonist alone and with the agonist plus an effective concentration of the antagonist (see Figure 3–4A). As more antagonist (I) is added, a higher concentration of the agonist is needed to produce an equivalent response (the half-maximal, or 50%, response is a convenient and accurately determined level of response). *The extent of the rightward shift of the concentration-dependence curve is a measure of the affinity of the inhibitor, and a high-affinity inhibitor will cause a greater rightward shift than a low-affinity inhibitor at the same inhibitor concentration.*

Using Equations 3–3 and 3–4, one may write mathematical expressions of *fractional occupancy* $\boldsymbol{f}$ of the receptor R by an agonist ligand (L) for the agonist alone [$\boldsymbol{f}_{control}$] and agonist in the presence of inhibitor [$\boldsymbol{f}_{+I}$].

For the agonist drug alone, the fractional occupancy is given by Equations 3–3 and 3–4:

$$\boldsymbol{f}_{control} = \frac{[L]}{[L]+K_D} \qquad \text{(Equation 3–5)}$$

For the case of agonist plus antagonist, the problem involves two equilibria:

$$R + L \rightleftharpoons RL \text{ (fractional occupancy is expressed by Eq 3–5)}$$

$$R + I \rightleftharpoons RI;\ K_i = \frac{[R][I]}{[RI]} \text{ or } [RI] = \frac{[R][I]}{K_i} \qquad \text{(Equation 3–6)}$$

Fractional occupancy by the agonist L in the presence of I is:

$$\boldsymbol{f}_{+I} = \frac{[RL]}{[RL]+[RI]+[R]} \qquad \text{(Equation 3–7)}$$

Equal fractional occupancies can occur in the absence and presence of a competitive inhibitor, but at different concentrations of agonist. The concentration of agonist needed to achieve a designated fractional occupancy in the presence of antagonist ([**L′**]) will be greater than the concentration of agonist needed in the inhibitor's absence ([**L**]). Using the expressions for dissociation constants for the agonist and antagonist ligands (Equations 3-2 and 3-6) and applying a little algebraic tinkering to the righthand side of Equation 3-7, the fractional occupancy in the presence of the competitive inhibitor [$\boldsymbol{f}_{+I}$] can be expressed in terms of L′, K_D, K_i, and I:

$$\boldsymbol{f}_{+I} = \frac{[L']}{[L']+K_D\left(1+\frac{[I]}{K_i}\right)} \qquad \text{(Equation 3–8)}$$

Assuming that equal responses result from equal fractional receptor occupancies in both the absence and presence of antagonist, one can set the fractional occupancies equal at experimentally determined agonist concentrations ([**L**] and [**L′**]) that generate equivalent responses, as depicted in Figure 3–4A. Thus,

$$\boldsymbol{f}_{control} = \boldsymbol{f}_{+I} \qquad \text{(Equation 3–9)}$$

$$\frac{[L]}{[L]+K_D} = \frac{[L']}{[L']+K_D\left(1+\frac{[I]}{K_i}\right)} \qquad \text{(Equation 3–10)}$$

Simplifying, one obtains

$$\frac{[L']}{[L]} - 1 = \frac{[I]}{K_i} \qquad \text{(Equation 3–11)}$$

where all values are known except K_i. *Thus, one can determine the* K_i *for a reversible, competitive antagonist without knowing the* K_D *for the agonist and without needing to define the precise relationship between receptor and response*.

Additivity and Synergism: Isobolograms

Drugs with different mechanisms of action are often used in combination to achieve *additive* and *positive synergistic* effects (Figure 3–5). Such positive interactions of two agents may permit use of reduced concentrations of each drug, thereby reducing concentration-dependent adverse effects. *Positive synergism* refers to the *superadditive* effects of drugs used in combination. Drugs used in combination can also demonstrate *negative synergism* or *subadditive effects*, where the efficacy of the drug combination is less than would be expected if the effects were additive. Figure 3–5 is a plot known as an *isobologram*, which shows that a line connecting the EC_{50} values of two drugs, A and B, describes the relative concentrations of each drug that will achieve a half-maximal response *when A and B are used in combination, if the effects of A and B are additive*. Similar lines drawn parallel to the 50% additive line can be used to determine the relative concentrations of A and B required to achieve other responses (e.g., 10%, 20%, 80%, 90%, etc.). If A and B are superadditive (positive synergism), the relative concentrations of A and B needed to achieve a given response will fall below the additive response line. Conversely, if A and B are subadditive (negative synergism), their relative concentrations will lie above the additive response line. The basis for the use of isobolograms in characterizing the effects of drug combinations has been developed and reviewed by Tallarida (2006, 2012).

Pharmacodynamic Variability: Individual and Population Pharmacodynamics

Individuals vary in the magnitude of their response to the same concentration of a single drug, and a given individual may not always respond in the same way to the same drug concentration. Drug responsiveness may change because of disease, age, or previous drug administration. Receptors are dynamic, and their concentrations and functions may be up- or downregulated by endogenous and exogenous factors.

Data on the correlation of drug levels with efficacy and toxicity must be interpreted in the context of the pharmacodynamic variability in the population (e.g., genetics, age, disease, and the presence of coadministered drugs). The variability in pharmacodynamic response in the population may be analyzed by constructing a *quantal concentration-effect curve* (Figure 3–6A). The dose of a drug required to produce a specified effect in 50% of the population is the *median effective dose* (ED_{50}; see Figure 3–6A). In preclinical studies of drugs, the *median lethal dose* (LD_{50}) is determined in experimental animals (Figure 3–6B). The LD_{50}/ED_{50} ratio is an indication of the *therapeutic index*, a term that reflects how selective the drug is in producing its desired effects versus its adverse effects. A similar term, the *therapeutic window*, is the range of steady-state concentrations of drug that provides therapeutic efficacy with minimal toxicity (Figures 2–9 and 3–7). In clinical studies, the dose, or preferably the concentration, of a drug required to produce toxic effects can be compared with