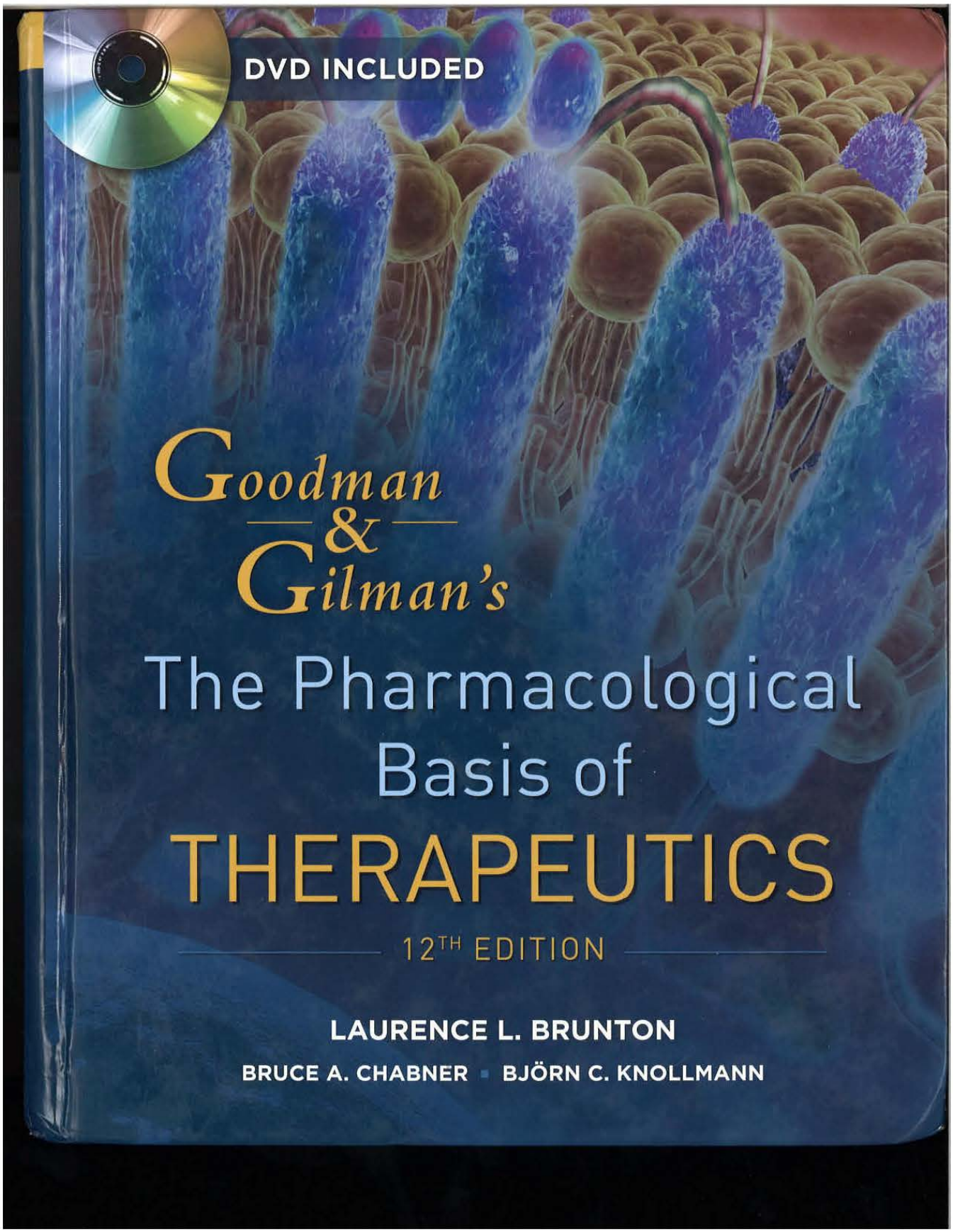

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Goodman & Gilman's The Pharmacological Basis of THERAPEUTICS

twelfth edition

editor

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

associate editors

Bruce A. Chabner, MD
Professor of Medicine
Harvard Medical School
Director of Clinical Research
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

Björn C. Knollmann, MD, PhD
Professor of Medicine and Pharmacology
Oates Institute for Experimental Therapeutics
Division of Clinical Pharmacology
Vanderbilt University School of Medicine
Nashville, Tennessee

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In Memoriam
Keith L. Parker
(1954-2008)

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Contributors

Edward P. Acosta, PharmD
Professor of Clinical Pharmacology
University of Alabama, Birmingham

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

Jeffrey A. Barnes, MD, PhD
Fellow in Hematology-Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Leslie Z. Benet, PhD
Professor of Bioengineering and Therapeutic Sciences
Schools of Pharmacy and Medicine
University of California, San Francisco

John E. Bennett, MD
Chief of Clinical Mycology
National Institute of Allergy and Infectious Diseases
Bethesda, Maryland

William Bennett, MD
Professor (Emeritus) of Medicine and Pharmacology
Oregon Health & Science University, Portland

Thomas P. Bersot, MD, PhD
Professor of Medicine; Associate Investigator
Gladstone Institute of Cardiovascular Disease
University of California, San Francisco

Joseph R. Bertino, MD
Professor of Medicine and Pharmacology
Robert Wood Johnson Medical School
University of Medicine & Dentistry of New Jersey
New Brunswick

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

Viengngeun Bounkeua, PhD
Medical Scientist Training Program, School of Medicine
University of California, San Diego

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

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

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

Iain L. O. Buxton, PharmD
Professor of Pharmacology
University of Nevada School of Medicine, Reno

Michael C. Byrns, PhD
Fellow in Pharmacology
University of Pennsylvania School of Medicine,
Philadelphia

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

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Page 4

Bruce A. Chabner, MD
Professor of Medicine, Harvard Medical School
Director of Clinical Research, Massachusetts General Hospital Cancer Center
Boston, Massachusetts

Henry F. Chambers, MD
Professor of Medicine and Chief of Infectious Diseases
San Francisco General Hospital
University of California, San Francisco

Jérôme Clain, PharmD, PhD
Research Fellow in Microbiology and Immunology
College of Physicians and Surgeons
Columbia University, New York

James M. Cleary MD, PhD
Attending Physician
Dana-Farber Cancer Institute
Boston, Massachusetts

Michael W.H. Coughtrie, PhD
Professor of Biochemical Pharmacology
Division of Medical Sciences
University of Dundee, Scotland

David D'Alessio, MD
Professor of Endocrinology and Medicine
University of Cincinnati, Ohio

Richard T. Eastman, PhD
Fellow in Microbiology
Columbia University, New York

Ervin G. Erdös, MD
Professor (Emeritus) of Pharmacology
University of Illinois-Chicago

David A. Fidock, PhD
Associate Professor of Microbiology and Medicine
College of Physicians and Surgeons
Columbia University, New York

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

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

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

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

James C. Garrison, PhD
Professor of Pharmacology, School of Medicine
University of Virginia, Charlottesville

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

Alfred G. Gilman, MD, PhD
Professor (Emeritus) of Pharmacology
University of Texas Southwestern Medical School
Chief Scientific Officer, Cancer Prevention and Research Institute of Texas, Dallas

Lowell A. Goldsmith, MD, MPH
Professor of Dermatology, School of Medicine
University of North Carolina, Chapel Hill, North Carolina

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

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

Tawanda Gumbo, MD
Associate Professor of Internal Medicine
University of Texas Southwestern Medical School, Dallas

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

R. Adron Harris, PhD
Professor of Molecular Biology; Director, Waggoner Center for Alcohol and Addiction Research
University of Texas, Austin

Lisa A. Hazelwood, PhD
Research Fellow, Molecular Neuropharmacology Section
National Institute of Neurological Disorders and Stroke
Bethesda, Maryland

Jeffrey D. Henderer, MD
Professor and Chair of Ophthalmology
Temple University School of Medicine
Philadelphia, Pennsylvania

Ryan E. Hibbs, PhD
Research Fellow, Vollum Institute
Oregon Health & Science University, Portland

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

Brian B. Hoffman, MD
Professor of Medicine, Harvard Medical School
Physician, VA-Boston Health Care System
Boston, Massachusetts

Peter J. Hotez, MD, PhD
Professor and Chair of Microbiology, Immunology, and Tropical Medicine
George Washington University Washington, DC

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

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

Allen P. Kaplan, MD
Clinical Professor of Medicine
Medical University of South Carolina, Charleston

Robert S. Kass, PhD
Professor and Chair of Pharmacology
Vice Dean for Research
College of Physicians and Surgeons
Columbia University, New York

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

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

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

Alan M. Krensky, MD
Senior Investigator, National Cancer Institute, Bethesda, Maryland

Nora Laiken, PhD
Lecturer in Pharmacology and Medicine
University of California, San Diego

Andrew A. Lane, MD, PhD
Fellow, Dana-Farber Cancer Institute
Massachusetts General Hospital Cancer Center, Boston

Richard J. Lee, MD, PhD
Professor of Medicine, Harvard Medical School
Physician, Massachusetts General Hospital
Boston, Massachusetts

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

Dan L. Longo, MD
Scientific Director, National Institute on Aging
National Institutes of Health, Bethesda, Maryland

Alex Loukas, PhD
Professor of Public Health, Tropical Medicine and Rehabilitation Sciences
James Cook University, Cairns, Australia

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

Kenneth P. Mackie, MD
Professor of Neuroscience
Indiana University, Bloomington

Bradley A. Maron, MD
Fellow in Cardiovascular Medicine
Harvard Medical School and Brigham and Women's Hospital
Boston, Massachusetts

James McCarthy, MD
Associate Professor of Clinical Tropical Medicine
University of Queensland
Brisbane, Australia

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

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Jonathan M. Meyer, MD
Assistant Adjunct Professor of Psychiatry
University of California, San Diego

Thomas Michel, MD, PhD
Professor of Medicine and Biochemistry
Harvard Medical School
Senior Physician in Cardiovascular Medicine
Brigham and Women's Hospital
Boston, Massachusetts

S. John Mihic, PhD
Professor of Neurobiology
Waggoner Center for Alcohol & Addiction Research
Institute for Neuroscience and Cell & Molecular Biology
University of Texas, Austin

Constantine S. Mitsiades, MD, PhD
Professor of Medical Oncology
Dana-Farber Cancer Institute, Harvard Medical School
Boston, Massachusetts

Perry Molinoff, MD
Professor of Pharmacology, School of Medicine
University of Pennsylvania, Philadelphia

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

Beverly Moy, MD, MPH
Assistant Professor of Medicine
Harvard Medical School
Massachusetts General Hospital, Needham

Hamza Mujagic, MD, MR. SCI, DR. SCI
Visiting Professor of Hematology and Oncology
Harvard Medical School
Massachusetts General Hospital, Needham

Joel W. Neal, MD, PhD
Assistant Professor of Medicine-Oncology,
Stanford University School of Medicine,
Palo Alto, California

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

James O'Donnell, PhD
Professor of Behavioral Medicine and Psychiatry
School of Medicine
West Virginia University, Morgantown

Erin M. Olson, MD
Fellow in Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Taylor M. Ortiz, MD
Clinical Fellow in Medical Oncology
Dana-Farber Cancer Institute
General Hospital Cancer Center
Boston, Massachusetts

Kevin Osterhoudt, MD, MSCE, FAAP, FACMT
Associate Professor of Pediatrics
School of Medicine, University of Pennsylvania;
Medical Director, Poison Control Center, Children's Hospital
of Philadelphia, Pennsylvania

Keith L. Parker, MD, PhD (deceased)
Professor of Internal Medicine and Pharmacology
Chief of Endocrinology and Metabolism
University of Texas Southwestern Medical School, Dallas

Hemal H. Patel, PhD
Associate Professor of Anesthesiology
University of California, San Diego Dean, School of Medicine
and Senior Vice President of Health Sciences
SUNY Stony Brook, New York

Piyush M. Patel, MD, FRCPC
Professor of Anesthesiology
University of California, San Diego

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

William A. Petri, Jr, MD, PhD
Professor of Medicine; Chief, Division of Infectious Diseases
University of Virginia, Charlottesville

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

Alvin C. Powers, MD
Professor of Medicine, Molecular Physiology and Biophysics
Vanderbilt University Medical Center
Nashville, Tennessee

Christopher Rapuano, MD
Director, Cornea Service and Refractive Surgery
Department, Wills Eye Institute
Philadelphia, Pennsylvania

Robert F. Reilly, Jr, MD
Professor of Internal Medicine
University of Texas Southwestern Medical School, Dallas
Chief of Nephrology
VA-North Texas Health Care System, Dallas

Mary V. Relling, PharmD
Chair of Pharmaceutical Sciences
St. Jude Childrens' Research Hospital
Memphis, Tennessee

Paul G. Richardson, MD
Associate Professor of Medicine, Harvard Medical School
Clinical Director, Lipper Center for Multiple Myeloma
Dana-Farber Cancer Institute
Boston, Massachusetts

Suzanne M. Rivera, PhD, MSW
Assistant Professor of Clinical Sciences
University of Texas Southwestern Medical Center, Dallas

Erik Roberson, MD, PhD
Assistant Professor of Neurology and Neurobiology
University of Alabama, Birmingham

Thomas P. Rocco, MD
Associate Professor of Medicine
Harvard Medical School
VA-Boston Healthcare System
Boston, Massachusetts

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

David P. Ryan, MD
Associate Professor of Medicine
Harvard Medical School
Massachusetts General Hospital Cancer Center, Boston

Kevin J. Sampson, PhD
Postdoctoral Research Scientist in Pharmacology
Columbia University, New York

Elaine Sanders-Bush, PhD
Professor (Emerita) of Pharmacology
School of Medicine, Vanderbilt University
Nashville, Tennessee

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

Marc A. Schuckit, MD
Distinguished Professor of Psychiatry
University of California, San Diego
Director, Alcohol Research Center
VA-San Diego Healthcare System

Lecia Sequist, MD, MPH
Assistant Professor of Medicine
Harvard Medical School, Massachusetts General
Hospital Cancer Center, Boston

Keith A. Sharkey, PhD
Professor of Physiology & Pharmacology and Medicine
University of Calgary, Alberta

Richard C. Shelton, MD
Professor of Psychiatry and Pharmacology
School of Medicine, Vanderbilt University
Nashville, Tennessee

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

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

Matthew R. Smith, MD, PhD
Associate Professor of Medicine, Harvard Medical School
Physician, Massachusetts General Hospital, Boston

Emer M. Smyth, PhD
Research Assistant, Professor of Pharmacology
University of Pennsylvania, Philadelphia

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

David Standaert, MD, PhD
Professor of Neurology
Director, Center for Neurodegeneration and Experimental
Therapeutics
University of Alabama, Birmingham

Samuel L. Stanley, Jr, MD
Professor of Medicine and President
SUNY Stony Brook, New York

Yuichi Sugiyama, PhD
Professor and Chair of Molecular Pharmacokinetics
University of Tokyo, Japan

Jeffrey G. Supko, PhD
Associate Professor of Medicine, Harvard Medical School
Massachusetts General Hospital, Boston

Palmer W. Taylor, PhD
Professor of Pharmacology, School of Medicine
Dean, Skaggs School of Pharmacy and Pharmaceutical
Sciences
University of California, San Diego

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

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

Flavio Vincenti, MD
Professor of Clinical Medicine
Medical Director, Pancreas Transplant Program
University of California, San Francisco

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

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

John L. Wallace, PhD, MBA, FRSC
Professor and Director, Farncombe Family Digestive Health Research Institute
McMaster University, Hamilton, Ontario

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

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

Thomas C. Westfall, PhD
Professor and Chair of Pharmacological and Physiological Science
St. Louis University School of Medicine, Missouri

Wyndham Wilson, MD, PhD
Senior Investigator and Chief of Lymphoid Therapeutics Section,
Center for Cancer Research, National Cancer Institute
Bethesda Maryland

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

Alexander C. Zambon, PhD
Assistant Professor of Pharmacology
University of California, San Diego

Preface

The publication of the twelfth edition of this book is a testament to the vision and ideals of the original authors, Alfred Gilman and Louis Goodman, who, in 1941 set forth the principles that have guided the book through eleven editions: 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 will be useful to students of pharmacology and to physicians. These precepts continue to guide the current edition.

As with editions since the second, expert scholars have contributed individual chapters. A multiauthored book of this sort grows by accretion, posing challenges to editors but also offering memorable pearls to the reader. Thus, portions of prior editions persist in the current edition, and I hasten to acknowledge the contributions of previous editors and authors, many of whom will see text that looks familiar. However, this edition differs noticeably from its immediate predecessors. Fifty new scientists, including a number from outside the U.S., have joined as contributors, and all chapters have been extensively updated. The focus on basic principles continues, with new chapters on drug invention, molecular mechanisms of drug action, drug toxicity and poisoning, principles of antimicrobial therapy, and pharmacotherapy of obstetrical and gynecological disorders. Figures are in full color. The editors have continued to standardize the organization of chapters; thus, students should easily find the basic physiology, biochemistry, and pharmacology set forth in regular type; bullet points highlight important lists within the text; the clinician and expert will find details in extract type under clear headings.

Online features now supplement the printed edition. The entire text, updates, reviews of newly approved drugs, animations of drug action, and hyperlinks to relevant text in the prior edition are available on the Goodman & Gilman section of McGraw-Hill's websites, *AccessMedicine.com* and *AccessPharmacy.com*. An Image Bank CD accompanies the book and makes all tables and figures available for use in presentations.

The process of editing brings into view many remarkable facts, theories, and realizations. Three stand out: the invention of new classes of drugs has slowed to a trickle; therapeutics has barely begun to capitalize on the information from the human genome project; and, the development of resistance to antimicrobial agents, mainly through their overuse in medicine and agriculture, threatens to return us to the pre-antibiotic era. We have the capacity and ingenuity to correct these shortcomings.

Many, in addition to the contributors, deserve thanks for their work on this edition; they are acknowledged on an accompanying page. In addition, I am grateful to Professors Bruce Chabner (Harvard Medical School/Massachusetts General Hospital) and Björn Knollmann (Vanderbilt University Medical School) for agreeing to be associate editors of this edition at a late date, necessitated by the death of my colleague and friend Keith Parker in late 2008. Keith and I worked together on the eleventh edition and on planning this edition. In anticipation of the editorial work ahead, Keith submitted his chapters before anyone else and just a few weeks before his death; thus, he is well represented in this volume, which we dedicate to his memory.

Laurence L. Brunton
San Diego, California
December 1, 2010

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chapter 4

Drug Toxicity and Poisoning

Kevin C. Osterhoudt
and Trevor M. Penning

Pharmacology deals with drugs and their chemical properties or characteristics, their mode of action, the physiological response to drugs, and the clinical uses of drugs. Pharmacology intersects with *toxicology* when the physiological response to a drug is an *adverse effect*. Toxicology is often regarded as the science of poisons or poisoning, but developing a strict definition for poison is problematic. A *poison* is any substance, including any drug, that has the capacity to harm a living organism. The Renaissance physician Paracelsus (1493-1541) is famously credited with offering the philosophical definition of poisons: "What is there that is not poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison." However, *poisoning* inherently implies that damaging physiological effects result from exposure to pharmaceuticals, illicit drugs, or chemicals. So each drug in the pharmacopeia is a potential poison, and individual dose-, situation-, environment-, and gene-related factors contribute to a drug's ability to achieve its adverse potential.

Some chemicals may inherently be poisons, such as lead, which has no known necessary physiological role in the human body, and which is known to cause neuronal injury even at very low exposure levels. Most pharmaceuticals are threshold poisons; at therapeutic dosing the drug is used to confer a health advantage, but at higher doses the drug may produce a toxic effect. For instance, iron is a nutrient essential for heme synthesis and numerous physiological enzyme functions, but overdose of ferrous sulfate can lead to life-threatening multi-organ dysfunction.

DOSE-RESPONSE

Evaluation of the dose-response or the dose-effect relationship is crucially important to toxicologists. There is a graded dose-response relationship in an *individual* and a quantal dose-response relationship in the *population* (see Chapters 2 and 3). Graded doses of a drug given to an individual usually result in a greater magnitude of response as the dose is increased. In a quantal dose-response relationship, the percentage of the population affected increases as the dose is raised; the relationship is quantal in that the effect is specified to be either present or absent in a given individual (Figure 4–1). This quantal dose-response phenomenon is extremely important in toxicology and is used to determine the *median lethal dose* (LD_{50}) of drugs and other chemicals.

The LD_{50} of a compound is determined experimentally, usually by administration of the chemical to mice or rats (orally or intraperitoneally) at several doses in the lethal range (Figure 4–1A).

To linearize such data, the response (death) can be converted to units of *deviation from the mean,* or *probits* (*probability units*). The probit designates the deviation from the median; a probit of 5 corresponds to a 50% response, and because each probit equals one standard deviation, a probit of 4 equals 16% and a probit of 6 equals 84%. A plot of the percentage of the population responding, in probit units, against log dose yields a straight line (Figure 4–1B). The LD_{50} is determined by drawing a vertical line from the point on the line where the probit unit equals 5 (50% mortality). The slope of the dose-effect curve also is important. The LD_{50} for both compounds depicted in Figure 4–1 is the same (~10 mg/kg); however, the slopes of the dose-response curves are quite different. At a dose equal to one-half the LD_{50} (5 mg/kg), less than 5% of the animals exposed to compound **B** would die, but 30% of the animals given compound **A** would die.

Figure 4–2 illustrates the relationship between a quantal dose-response curve for the therapeutic effect of a drug to generate a median effective dose (ED_{50}), the concentration of drug at which 50% of the population will have the desired response, and a quantal dose-response curve for lethality by the same agent. These two curves can be used to generate a therapeutic index (TI), which quantifies the relative safety of a drug. Clearly, the higher the ratio, the safer the drug.

$$TI = LD_{50}/ED_{50}$$

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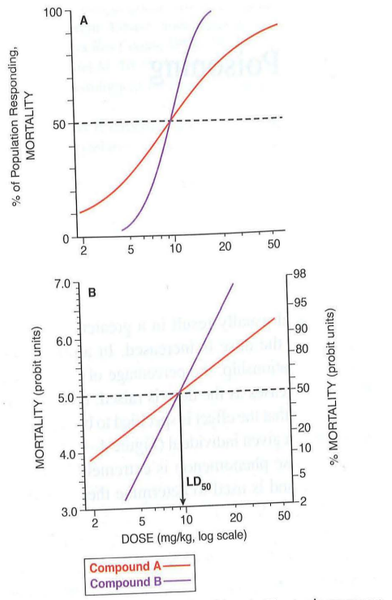

Figure 4–1. *Dose-response relationships.* ***A.*** The toxic response to a chemical is evaluated at several doses in the toxic or lethal range. The midpoint of the curve representing percent of population responding (response here is death) versus dose (log scale) represents the LD_{50}, or the concentration of drug that is lethal in 50% of the population. ***B.*** A linear transformation of the data in panel A, obtained by plotting the log of the dose administered versus the percent of the population killed, in probit units.

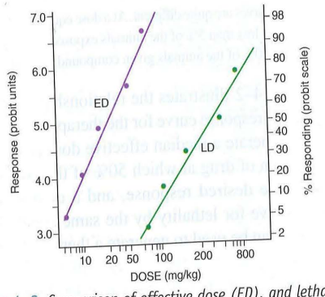

Figure 4–2. *Comparison of effective dose (ED), and lethal dose (LD).* See text for explanation of probit units. Note that abscissa is a logarithmic scale.

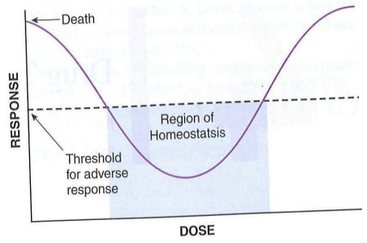

Figure 4–3. *U-Shaped dose-response curve for essential metals and vitamins.* Vitamins and essential metals are essential for life and their lack can cause adverse responses (plotted on the vertical axis), as can their excess, giving rise to a U-shaped concentration-dependence curve.

Drugs show a wide range of TI, from 1-2 to >100. Drugs with a low TI must be administered with caution. Agents that fall into this category include the cardiac glycoside digitalis and cancer chemotherapeutic agents. Agents with very high TI are extremely safe and include some antibiotics (e.g., penicillin), unless there is a known allergic response.

The use of median effective and median lethal doses is not without disadvantages, because median doses do not consider that the slopes of the dose-response curves for therapeutic and lethal (toxic) effects may differ. As an alternative the ED_{99} for the therapeutic effect can be compared to the LD_1 for lethality (toxic effect), to yield a margin of safety.

$$\text{Margin of safety} = LD_1/ED_{99}$$

The quantal dose-response curves described thus far represent linearization of sigmoidal dose-response curves (Figure 4–1). However, not all dose-response curves follow this shape. "U"-shaped dose-response curves can be observed for essential metals and vitamins (Figure 4–3). At low dose, adverse effects are observed since there is a deficiency of these nutrients to maintain homeostasis. As dose increases, homeostasis is achieved, and the bottom of the "U"-shaped dose-response curve is reached. As dose increases to surpass the amount required to maintain homeostasis, overdose toxicity can ensue. Thus, adverse effects are seen at both low and high dose.

PHARMACOKINETICS VERSUS TOXICOKINETICS

The principles of pharmacokinetics (absorption, distribution, metabolism, and elimination) are described in Chapters 2, 5, and 6, and specific details are provided throughout this text. *Toxicokinetics* (the pharmacokinetics of a drug under circumstances that produce toxicity or excessive exposure) may differ significantly after poisoning, and these differences may profoundly alter treatment decisions and prognosis. Ingesting larger than therapeutic doses of a pharmaceutical may prolong its absorption, alter its protein binding and apparent volume of distribution, and change its metabolic fate. When confronted with a potential poisoning, two questions are foremost in the clinician's mind:

1. How long does an asymptomatic patient need to be monitored (drug absorption and dynamics)?
2. How long will it take an intoxicated patient to get better (drug elimination and dynamics)?

Drug Absorption. Aspirin poisoning is a leading cause of overdose morbidity and mortality as reported to U.S. poison control centers (Bronstein et al., 2008). In therapeutic dosing, aspirin reaches peak plasma concentrations in ~1 hour (Chapter 34). However, after overdose, several drug-related and physiology-related factors change. Aspirin overdose may cause spasm of the pyloric valve, delaying entry of the drug into the small intestine. Aspirin, especially enteric coated forms, may coalesce into bezoars, reducing the effective surface area for absorption. Peak plasma salicylate concentrations from aspirin overdose may not be reached for 4-35 hours after ingestion (Rivera et al., 2004).

Drug Elimination. After therapeutic dosing, valproic acid has an elimination half-life ($t_{1/2}$) of ~14 hours (see Appendix II). Valproic acid poisoning may lead to coma. In predicting the duration of coma, it is important to consider that, after overdose, first-order metabolic processes appear to become saturated and the apparent elimination $t_{1/2}$ may exceed 30-45 hours (Sztajnkrycer, 2002). Such consideration has important clinical ramifications pertaining to prognosis, resource utilization, and therapy.

Table 4–1 lists some pharmaceuticals notorious for their predilection to have initial symptoms develop after a typical 4-6 hour emergency medical observation period for a suspected drug overdose.

Table 4–1

Drugs That Commonly Manifest Initial Symptoms More Than 4-6 Hours after Oral Overdose[a]

Acetaminophen
Aspirin
Illicit drugs in rubber or plastic packages
Monoamine oxidase inhibitors
Sulfonylureas
Sustained-release formulation drugs
Thyroid hormones
Valproic acid
Warfarin-like anticoagulants

[a]Drugs co-ingested with agents having anticholinergic activity, manifest by diminished GI motility, may also exhibit delayed onset of action.

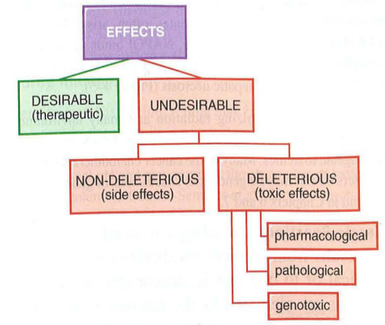

Figure 4–4. *Spectrum of the effects of pharmaceuticals.*

Types of Therapeutic Drug Toxicity

In therapeutics, a drug typically produces numerous effects, but usually only one is sought as the primary goal of treatment; most of the other effects are undesirable effects of that drug for that therapeutic indication (Figure 4–4). *Side effects* of drugs usually are bothersome but not deleterious; they include effects such as dry mouth occurring with tricyclic antidepressant therapy. Other undesirable effects may be characterized as toxic effects.

Dose-Dependent Reactions. Toxic effects of drugs may be classified as pharmacological, pathological, or genotoxic. Typically, the incidence and seriousness of the toxicity is proportionately related to the concentration of the drug in the body and to the duration of the exposure. Drug overdose provides a dramatic example of dose-dependent toxicities.

Pharmacological Toxicity. The CNS depression produced by barbiturates is largely predictable in a dose-dependent fashion. The progression of clinical effects goes from anxiolysis to sedation to somnolence to coma. Similarly, the degree of hypotension produced by nifedipine is related to the dose of the drug administered. Tardive dyskinesia (Chapter 16), an extrapyramidal motor disorder associated with use of antipsychotic medications, seems to be dependent upon duration of exposure. Pharmacological toxicity can also occur when the correct dose is given: there is phototoxicity associated with exposure to sunlight in patients treated with tetracyclines, sulfonamides, chlorpromazine, and nalidixic acid.

Pathological Toxicity. Acetaminophen is metabolized to non-toxic glucuronide and sulfate conjugates, and to a highly reactive metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI) via CYP

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isoforms. NAPQI is referred to as a biologically reactive intermediate, and such intermediates often arise due to drug metabolism. At therapeutic dosing, NAPQI binds to nucleophilic glutathione; but, in overdose, glutathione depletion may lead to the pathological finding of hepatic necrosis (Figure 4–5).

Genotoxic Effects. Ionizing radiation and many environmental chemicals are known to injure DNA, and may lead to mutagenic or carcinogenic toxicities. Many of the cancer chemotherapeutic agents (Chapters 60-63) may be genotoxic. Discussions of genotoxicity can be found in Chapters 6 and 7.

Allergic Reactions. An *allergy* is an adverse reaction that results from previous sensitization to a particular chemical or to one that is structurally similar. Such reactions are mediated by the immune system. For a low-molecular-weight chemical to cause an allergic reaction, it or its metabolic product usually acts as a hapten, combining with an endogenous protein to form an antigenic complex. Such antigens induce the synthesis of antibodies, usually after a latent period of at least 1-2 weeks. Subsequent exposure to the chemical results in an antigen-antibody interaction that provokes the typical manifestations of allergy. Dose-response relationships usually are not apparent for the provocation of allergic reactions. Allergic responses have been divided into four general categories based on the mechanism of immunological involvement.

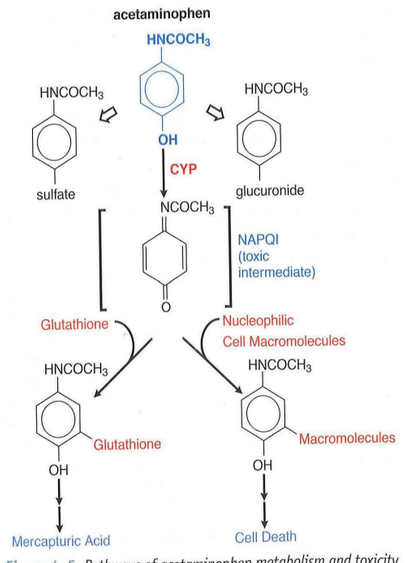

Figure 4–5. *Pathways of acetaminophen metabolism and toxicity.* The toxic intermediate NAPQI is *N*-acetyl-*p*-benzoquinoneimine.

Type I: Anaphylactic Reactions. Anaphylaxis is mediated by IgE antibodies. The Fc portion of IgE can bind to receptors on mast cells and basophils. If the Fab portion of the antibody molecule then binds antigen, various mediators (e.g., histamine, leukotrienes, and prostaglandins) are released and cause vasodilation, edema, and an inflammatory response. The main targets of this type of reaction are the gastrointestinal (GI) tract (food allergies), the skin (urticaria and atopic dermatitis), the respiratory system (rhinitis and asthma), and the vasculature (anaphylactic shock). These responses tend to occur quickly after challenge with an antigen to which the individual has been sensitized and are termed *immediate hypersensitivity reactions*.

Type II: Cytolytic Reactions. Type II allergies are mediated by both IgG and IgM antibodies and usually are attributed to their capacity to activate the complement system. The major target tissues for cytolytic reactions are the cells in the circulatory system. Examples of type II allergic responses include penicillin-induced hemolytic anemia, quinidine-induced thrombocytopenic purpura, and sulfonamide-induced granulocytopenia. Fortunately, these autoimmune reactions to drugs usually subside within several months after removal of the offending agent.

Type III: Arthrus Reactions. Type III allergic reactions are mediated predominantly by IgG; the mechanism involves the generation of antigen-antibody complexes that subsequently fix complement. The complexes are deposited in the vascular endothelium, where a destructive inflammatory response called *serum sickness* occurs. This phenomenon contrasts with the type II reaction, in which the inflammatory response is induced by antibodies directed against tissue antigens. The clinical symptoms of serum sickness include urticarial skin eruptions, arthralgia or arthritis, lymphadenopathy, and fever. Several drugs, including commonly used antibiotics, can induce serum sickness-like reactions. These reactions usually last 6-12 days and then subside after the offending agent is eliminated.

Type IV: Delayed Hypersensitivity Reactions. These reactions are mediated by sensitized T-lymphocytes and macrophages. When sensitized cells come in contact with antigen, an inflammatory reaction is generated by the production of lymphokines and the subsequent influx of neutrophils and macrophages. An example of type IV or delayed hypersensitivity is the contact dermatitis caused by poison ivy.

Idiosyncratic Reactions. *Idiosyncrasy* is an abnormal reactivity to a chemical that is peculiar to a given individual. The idiosyncratic response may take the form of extreme sensitivity to low doses or extreme insensitivity to high doses of drugs. Idiosyncratic reactions can result from genetic polymorphisms that cause individual differences in drug pharmacokinetics, from pharmacodynamic factors such as drug-receptor interactions (Evans and Rolling, 1999), or from variability in expression of enzyme activity. The use of genetic information to explain interindividual differences in drug responses or to individualize dosages of drugs for patients with known genetic polymorphisms is referred to as pharmacogenetics (Chapter 7).

An increased incidence of peripheral neuropathy is seen in patients with inherited deficiencies in acetylation when isoniazid is used to treat tuberculosis, e.g., slow and fast acetylators exist due to polymorphisms in *N*-acetyl transferase. Many black males (~10%) develop a serious hemolytic anemia when they receive primaquine as an antimalarial therapy. Such individuals have a deficiency of erythrocyte glucose-6-phosphate dehydrogenase. Genetically determined resistance to the anticoagulant action of warfarin is due to an alteration in the vitamin K epoxide reductase.

Drug–Drug Interactions. Patients are commonly treated with more than one drug, have individual dietary choices, and may also be using over-the-counter (OTC) medications, vitamins, and other "natural" supplements. This polypharmaceutical nature of healthcare requires consideration of potential drug interactions (Figure 4–6). Similar to changes in pharmacokinetics and pharmacodynamics seen after drug overdose, drug interactions may lead to altered rates of absorption, altered protein binding, or different rates of biotransformation or excretion of one or both interacting compounds. The pharmacodynamics of a drug can be altered by competition at receptors, and nonreceptor pharmacodynamic interactions can occur when two drugs have similar actions through different cellular mechanisms. Induction or inhibition of drug metabolism by CYPs (Chapter 6) are among the most clinically challenging of drug interactions.

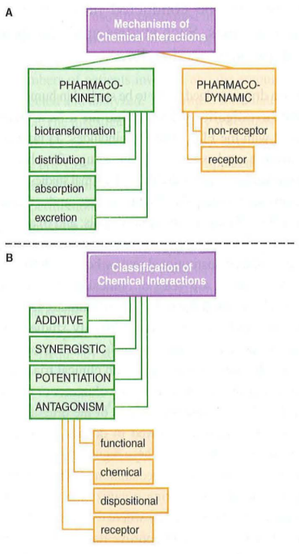

Figure 4–6. *Mechanisms and classification of drug interactions.*

Interaction of Absorption. A drug may cause either an increase or a decrease in the absorption of another drug from the intestinal lumen. Ranitidine, an antagonist of histamine H_2 receptors, raises gastrointestinal pH and may increase the absorption of basic drugs such as triazolam (O'Connor-Semmes et al., 2001). Conversely, the bile-acid sequestrant cholestyramine leads to significantly reduced serum concentrations of propranolol, and may diminish its effect for a given dosage (Hibbard et al., 1984).

Interaction of Protein Binding. Many drugs, such as aspirin, barbiturates, phenytoin, sulfonamides, valproic acid, and warfarin, are highly protein-bound in the plasma, and it is the free (unbound) drug that produces the clinical effects. These drugs may have enhanced toxicity in overdose if protein binding sites become saturated, in physiological states that lead to hypoalbuminemia, or when displaced from plasma proteins by other drugs. The anticoagulant effects of warfarin may be enhanced by displacement from plasma proteins by simultaneous valproic acid therapy (Guthrie et al., 1995).

Interaction of Metabolism. A drug can frequently influence the metabolism of one or several other drugs (Chapter 6), and this is especially notable within hepatic CYPs. Acetaminophen is partially transformed by CYP2E1 to the toxic metabolite NAPQI (Figure 4–5). Intake of ethanol, a potent inducer of the 2E1 isoenzyme, may lead to increased susceptibility to acetaminophen poisoning after overdose (Dart et al., 2006). Similarly, a number of second-generation piperidine antihistamines (terfenadine, astemizole) were removed from the market when they were noted to lead to QT interval prolongation and tachydysrhythmias when co-administered with macrolide antibiotics.

Interaction of Receptor Binding. Buprenorphine is an opioid with partial agonist and antagonist receptor activities. It can be used as an analgesic but is more commonly used to treat opioid addiction. The drug binds opioid receptors with high affinity, and can prevent euphoria from concomitant use of narcotic drugs of abuse.

Interaction of Therapeutic Action. Aspirin is an inhibitor of platelet aggregation and heparin is an anticoagulant; given together they may increase risk for bleeding. Sulfonylureas cause hypoglycemia by stimulating pancreatic insulin release, whereas biguanide drugs (metformin) lead to decreased hepatic glucose production, and these drugs can be used together to control diabetic hyperglycemia.

A drug interaction is said to be *additive* when the combined effect of two drugs equals the sum of the effect of each agent given alone. A *synergistic* effect is one in which the combined effect exceeds the sum of the effects of each drug given alone. *Potentiation* describes the creation of a toxic effect from one drug due to the presence of another drug. *Antagonism* is the interference of one drug with the action of another. Drug antagonism may confer a therapeutic advantage when one drug is to be used as an antidote for the toxicity of another drug. *Functional* or *physiological*

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antagonism occurs when two chemicals produce opposite effects on the same physiological function; this is the basis for most supportive care provided to patients treated for drug overdose poisoning. *Chemical* antagonism, or *inactivation*, is a reaction between two chemicals to neutralize their effects, such as is seen with chelation therapy. *Dispositional* antagonism is the alteration of the disposition of a substance (its absorption, biotransformation, distribution, or excretion) so that less of the agent reaches the target organ or its persistence in the target organ is reduced. *Receptor* antagonism entails the blockade of the effect of a drug with another drug that competes at the receptor site.

DESCRIPTIVE TOXICITY TESTING IN ANIMALS

Two main principles underlie all descriptive toxicity tests performed in animals. First, those effects of chemicals produced in laboratory animals, when properly qualified, apply to human toxicity. When calculated on the basis of dose per unit of body surface, toxic effects in human beings usually are encountered in the same range of concentrations as those in experimental animals. On the basis of body weight, human beings generally are more vulnerable than experimental animals. Such information is used to select dosages for clinical trials of candidate therapeutic agents and to attempt to set limits on permissible exposure to environmental toxicants.

Second, exposure of experimental animals to toxic agents in high doses is a necessary and valid method to discover possible hazards to human beings who are exposed to much lower doses. This principle is based on the quantal dose-response concept. As a matter of practicality, the number of animals used in experiments on toxic materials usually will be small compared with the size of human populations potentially at risk. For example, 0.01% incidence of a serious toxic effect (such as cancer) represents 25,000 people in a population of 250 million. Such an incidence is unacceptably high. Yet, detecting an incidence of 0.01% experimentally probably would require a minimum of 30,000 animals. To estimate risk at low dosage, large doses must be given to relatively small groups. The validity of the necessary extrapolation is clearly a crucial question.

Chemicals are first tested for toxicity by estimation of the LD_{50} in two animal species by two routes of administration; one of these is the expected route of exposure of human beings to the chemical being tested. The number of animals that die in a 14-day period after a single dose is recorded. The animals also are examined for signs of intoxication, lethargy, behavioral modification, and morbidity. The chemical is next tested for toxicity by repeat exposure, usually for 90 days. This study is performed most often in two species by the route of intended use or exposure with at least three doses. A number of parameters are monitored during this period, and at the end of the study, organs and tissues are examined by a pathologist.

Long-term or chronic studies are carried out in animals at the same time that clinical trials are undertaken. For drugs, the length of exposure depends somewhat on the intended clinical use. If the drug normally would be used for short periods under medical supervision, as would an antimicrobial agent, a chronic exposure of animals for 6 months might suffice. If the drug would be used in human beings for longer periods, a study of chronic use for 2 years may be required.

Studies of chronic exposure often are used to determine the carcinogenic potential of chemicals. These studies usually are performed in rats and mice for the average lifetime of the species. Other tests are designed to evaluate teratogenicity (congenital malformations), perinatal and postnatal toxicity, and effects on fertility. Teratogenicity studies usually are performed by administering drugs to pregnant rats and rabbits during the period of organogenesis. As noted in Chapter 6, *in silico* computational methods of chemical biology systems may soon contribute to such studies.

TOXICOLOGY, SAFETY TESTING, AND CLINICAL TRIALS

Fewer than one-third of the drugs tested in clinical trials reach the marketplace. Federal law in the U.S. and ethical considerations require that the study of new drugs in humans be conducted in accordance with stringent guidelines. Such studies apply the principles of toxicology mentioned earlier.

Once a drug is judged ready to be studied in humans, a **Notice of Claimed Investigational Exemption for a New Drug (IND)** must be filed with the FDA. The IND includes: 1) information on the composition and source of the drug; 2) chemical and manufacturing information; 3) all data from animal studies; 4) proposed clinical plans and protocols; 5) the names and credentials of physicians who will conduct the clinical trials; and 6) a compilation of the key data relevant to study the drug in man made available to investigators and their institutional review boards (IRBs).

It often requires 4-6 years of clinical testing to accumulate and analyze all required data. Testing in humans is begun after sufficient acute and subacute animal toxicity studies have been completed. Chronic safety testing in animals, including carcinogenicity studies, is usually done concurrently with clinical trials. In each of the three formal phases of clinical trials, volunteers or patients must be informed of the investigational status of the drug as well as the possible risks and must be allowed to decline or to consent to participate and receive the drug. These regulations are based on the ethical principles set forth in the Declaration of Helsinki. In addition to the approval of the sponsoring organization and the FDA, an interdisciplinary IRB at the facility where the clinical drug trial will be conducted must review and approve the scientific and ethical plans for testing in humans.

In **phase 1**, the effects of the drug as a function of dosage are established in a small number (20–100) of healthy volunteers. Although a goal is to find the maximum tolerated dose, the study is designed to prevent severe toxicity. If the drug is *expected* to have significant toxicity, as may be the case in cancer and AIDS therapy, volunteer patients with the disease rather than disease-free volunteers are used in phase 1. Phase 1 trials are designed to determine the probable limits of the safe clinical dosage range. These trials may be non-blind or "open"; i.e., both the investigators and the subjects know what is being given. Alternatively, they may be "blinded" and/or placebo-controlled. The choice of design depends on the drug, disease, goals of investigators, and ethical considerations. Many predictable toxicities are detected in this phase. Pharmacokinetic measurements of absorption, $t_{1/2}$, and metabolism are often conducted. Phase 1 studies are usually performed in research centers by clinical pharmacologists.

In **phase 2**, the drug is studied *in patients with the target disease* to determine its efficacy ("proof of concept"), and the doses to be used in any follow-on trials. A modest number of patients (100–200) are studied in detail. A single-blind design may be used, with an inert placebo medication and an established active drug (positive control) in addition to the investigational agent. Phase 2 trials are usually done in special clinical centers (e.g., university hospitals). A broader range of toxicities may be detected in this phase. Phase 2 trials have the highest rate of drug failures, and only ~25% of drug candidates move on to phase 3.

In **phase 3**, the drug is evaluated in much larger numbers of patients with the target disease—usually thousands—to further establish and confirm safety and efficacy. Using information gathered in phases 1 and 2, phase 3 trials are designed to minimize errors caused by placebo effects, variable course of the disease, etc. Therefore, double-blind and crossover techniques are frequently used. Phase 3 trials are usually performed in settings similar to those anticipated for the ultimate use of the drug. Phase 3 studies can be difficult to design and execute and are usually expensive because of the large numbers of patients involved and the amount of data that must be collected and analyzed. The drug is formulated as intended for the market. The investigators are usually specialists in the disease being treated. Certain toxic effects, especially those caused by immunologic processes, may first become apparent in phase 3 trials.

If phase 3 results meet expectations, application is made to the FDA for permission to market the new agent. Marketing approval requires submission of a **New Drug Application (NDA)** (or for biologicals, a **Biological License Application [BLA]**) to the FDA. Note that even at this point in the process, experience with the new drug is limited to information gathered from a few thousand patients. Thus, post-marketing surveillance is crucial in determining the actual toxicity of the drug as it is administered to a much larger population in which low-frequency adverse reactions will be noticeable.

Table 4–2
Potential Scenarios for the Occurrence of Poisoning

Therapeutic drug toxicity
Exploratory exposure by young children
Environmental exposure
Occupational exposure
Recreational abuse
Medication error
Prescribing error
Dispensing error
Administration error
Purposeful administration for self-harm
Purposeful administration to harm another

EPIDEMIOLOGY OF ADVERSE DRUG RESPONSES AND PHARMACEUTICAL POISONING

Poisoning can occur in many ways following both therapeutic and nontherapeutic drug or chemical exposures (Table 4–2). The incidence of serious and fatal adverse drug reactions in U.S. hospitals is extremely high (Institute of Medicine, 1999; Lazarou et al., 1998). It is estimated that ~2 million hospitalized patients have serious adverse drug reactions each year, and ~100,000 have fatal adverse drug reactions. Use of good principles of prescribing, as described in Appendix I and Table 4–6, can aid in avoiding such adverse outcomes.

Some toxicities of pharmaceuticals can be predicted based upon their known pharmacological mechanism; however, it is often not until the post-marketing period that the therapeutic toxicity profile of a drug becomes fully appreciated. In the U.S., the approval system for new drugs typically uses only 500 to 3000 exposed subjects. Such a system is likely to identify toxicities occurring in 1% or more of patients receiving a drug (Strom, 2004). The Adverse Event Reporting System of the FDA relies upon two signals to detect rarer adverse drug events. *First*, the FDA requires (Code of Federal Regulations, Title 21, Volume 5, Section 314.80) drug manufacturers to perform post-marketing surveillance of prescription drugs, and similar regulations exist for nonprescription products. *Second*, the FDA operates a voluntary reporting system (MedWatch, online at http://www.fda.gov/Safety/MedWatch/default.htm) available to both health professionals and consumers. Hospitals may also support adverse drug event committees to investigate potential adverse drug events, and these investigations may be made available to industry and the government. Unfortunately, any national dataset will significantly underestimate the morbidity and mortality attributable to adverse drug events because of under-reporting and because it is difficult to estimate the denominator of total patient exposures for each event reported once a drug is available on the open market.

As an example, post-marketing surveillance identified the toxicity associated with the serotonin receptor-modulating drug cisapride. This drug was known to enhance GI motility and was marketed in the U.S. as a treatment for gastroesophageal reflux. Post-marketing surveillance revealed that cisapride was associated with prolongation of the QT interval and predisposition to ventricular

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arrhythmia. It was withdrawn from the market, and subsequent case-control studies demonstrated increased risk of arrhythmia (Hennessy et al., 2008). Cisapride is now limited in its distribution through an investigational access program managed by the manufacturer. In another instance, selective serotonin reuptake inhibitors (SSRIs, Chapter 15) are believed to be safer than monoamine oxidase inhibitors and tricyclic antidepressants, and are popularly prescribed for treatment of depression; however, current post-marketing studies are looking to see if the use of SSRIs may predispose adolescent and young adult patients to suicidality (Barbui et al., 2009). Thus, the determination of drug toxicity carries beyond the stages of drug development.

Therapeutic drug toxicity is only a subset of poisoning, as noted in Table 4–2. Misuse and abuse of both prescription and illicit drugs is a major public health problem. The incidence of unintentional, non-iatrogenic poisoning is bimodal, primarily affecting exploratory young children, ages 1-5 years, and the elderly. *Intentional* overdose with pharmaceuticals is most common in adolescence and through adulthood. Fifty-one percent of poison exposures reported to the American Association of Poison Control Centers (AAPCC) involve children ≤5 years, but this group accounts for <3% of reported fatalities, demonstrating that intentional poisonings are inherently more dangerous than exploratory or inadvertent exposures (Bronstein et al., 2008).

Exact quantification of nontherapeutic poisoning occurrences remains elusive. The National Institute of Drug Abuse (NIDA) commissioned the University of Michigan to perform the "Monitoring the Future" survey of U.S. high school children regarding drug use patterns (NIDA, 2009). In 2008, 47% of surveyed high school seniors reported that they had previously used an illicit drug. Among pharmaceutical abuse, 13% reported having abused a non-heroin narcotic, 10% an amphetamine drug, 8.9% a benzodiazepine, antidepressant, or antipsychotic medicine, and 8.5% a barbiturate. NIDA also monitors emergency department (ED) visits through its Drug Abuse Warning Network (DAWN). In 2006, ~250 ED visits per 100,000 population were related to drug toxicity and 49% of these visits were related to the nonmedical use and abuse of pharmaceutical agents (U.S. DHHS). The top five drugs involved in drug-related deaths reported to DAWN-participating medical examiners' offices in 2005 are presented in Table 4–3.

The AAPCC (www.aapcc.org) offers a toll-free poisoning information phone hotline throughout the U.S., and has been collecting voluntary reports of potential poison exposures for over 25 years. It currently has over 46 million human exposure case records in its database. In 2007, nearly 2.5 million cases, including 1239 fatal poisonings, were voluntarily reported to the AAPCC's National Poison Data System (NPDS). Eighty-three percent of human poison exposures reported to the NPDS were unintentional, 13% were intentional, and 2.5% were adverse drug reactions (Bronstein et al., 2008). The substances most frequently involved in human exposures and fatalities are presented in Tables 4–4 and 4–5.

Table 4–3
Top Five Agents Involved in Drug-Related Deaths

Cocaine
Opioids
Benzodiazepines
Alcohol
Antidepressants

Source: U.S. DHHS.

Table 4–4
Substances Most Frequently Involved in Human Poisoning Exposures

Substance	%
Analgesics	12.5
Personal care products	9.1
Cleaning substances	8.7
Sedatives/hypnotics/antipsychotics	6.2
Foreign bodies	5.1
Topical preparations	4.5
Cold and cough medications	4.5
Antidepressants	4.0

Source: Data From Bronstein et al., 2008.

Table 4–5
Poisons Associated with the Largest Number of Human Fatalities

Sedatives/hypnotics/antipsychotics
Acetaminophen
Opioids
Antidepressants
Cardiovascular drugs
Stimulants and street drugs
Alcohols

Source: Bronstein et al., 2008.

PREVENTION OF POISONING

Reduction of Medication Errors. Over the past decade considerable attention has been given to the reduction of medication errors and adverse drug events (ADEs). Medication errors can occur in any part of the medication prescribing or use process, while ADEs are injuries related to the use or nonuse of medications. It is believed that medication errors are 50-100 times more common than ADEs (Bates et al., 1995). Some ADEs, such as previously unknown allergies, are unpreventable, but most ADEs can be prevented. Traditionally, the "5 Rights" of safe medication administration have been taught on hospital wards:

Right drug, right patient, right dose, right route, right time.

However, accomplishing a reduction in medication errors involves scrutiny of the systems involved in prescribing, documenting, transcribing, dispensing, administering, and monitoring a therapy, as presented in Appendix I. Good medication use practices have mandatory and redundant checkpoints, such as having a pharmacist, a doctor, and a nurse all review and confirm that an ordered dose of a medication is appropriate for a patient prior to the drug's administration. In such a system, medication errors occur only when several "holes" in the medication administration safeguards exist and are simultaneously aligned (Figure 4–7). Several practical strategies have been suggested to reduce medication errors within hospitals and other healthcare settings (Table 4–6), and these strategies are being constantly revised.

Poisoning Prevention in the Home. Table 4–2 demonstrates that there are several contexts into which poisoning prevention can be directed. Depression and suicidal ideation need to be identified and treated. Exposure to hazards in the home, outdoor, and work environments need to be reduced to reasonably achievable levels.

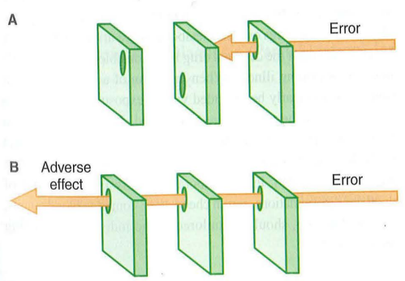

Figure 4–7. The "Swiss cheese" model of medication error. Several checkpoints typically exist to identify and prevent an adverse drug event, and that adverse event can only occur if holes in several systems align. ***A.*** One systematic error does not lead to an adverse event, because it is prevented by another check in the system. ***B.*** Several systematic errors align to allow an adverse event to occur. (Adapted from Reason, 2000.)

Table 4–6
Best Practice Recommendations to Reduce Medication Administration Errors[a]

Short Term
- Maintain unit-dose distribution systems for non-emergency medications
- Have pharmacies prepare intravenous solutions
- Remove inherently dangerous medications (e.g., concentrated KCl) from patient care areas
- Develop special procedures for high-risk drugs
- Improve drug-related clinical information resources
- Improve medication administration education for clinicians
- Educate patients about the safe and accurate use of medications
- Improve access of bedside clinicians to pharmacists

Long Term

Implement technology-based safeguards:
- Computerized order entry
- Computerized dose and allergy checking
- Computerized medication tracking
- Use of bar codes or electronic readers for medication preparation and administration

[a]See Massachusetts Hospital Association.

Poisoning prevention strategies may be categorized as being *passive*, requiring no behavior change on the part of the individual, or *active*, requiring sustained adaptation to be successful. Passive prevention strategies are the most effective, and several types of passive poisoning prevention are described in Table 4–7.

Table 4–7
Passive Poisoning Prevention Strategies and Examples

Reduce manufacture/sale of poisons
Withdrawal of phenformin from U.S. pharmaceutical market
Decrease amount of poison in a consumer product
Limiting number of pills in a single bottle of baby aspirin
Prevent access to poison
The use of child-resistant packaging
Change product formulation
Removing ethanol from mouthwash

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The incidence of poisoning in children has decreased dramatically over the past four decades. This favorable trend is largely due to improved safety packaging of drugs, drain cleaners, turpentine, and other household chemicals; improved medical training and care; and increased public awareness of potential poisons.

From 1958-1973, aspirin ingestion was a common cause of childhood poisoning death. In 1973, regulations were instituted requiring child-resistant packaging for aspirin consumer products, and this change in packaging was associated with a 34% reduction in the aspirin-related child mortality rate (Rodgers, 2002). In 2007, no aspirin deaths among children aged less than 6 years were reported to the AAPCC (Bronstein et al., 2008). From 1983-1990, iron was the single most frequent cause of unintentional pharmaceutical ingestion fatality in children younger than 6 years, and accounted for almost one-third of such deaths. In 1997, drug products with 30 mg or more of elemental iron per dosage unit were required to be placed into unit-dose packaging. This packaging change was associated with a decrease in mortality (odds ratio of 0.07; 95% confidence interval, 0.52–0.01) (Tenenbein, 2005).

PRINCIPLES OF TREATMENT OF POISONING

The majority of poisoning exposures reported to U.S. poison control centers are judged to be nontoxic or only minimally toxic (Bronstein et al., 2008). When toxicity is expected, or does occur, the priority of poisoning treatment is to support vital functions until the drug or chemical is eliminated from the body. Because of the acute onset of action and finite duration of action of most drugs, the treatment of poisoning must be prompt and goal-directed. The first goal is to maintain vital physiological functions from impairment. The second goal is to keep the concentration of poison in tissues as low as possible by preventing absorption and enhancing elimination. The third goal is to combat the toxicological effects of the poison at the effector sites.

Initial Stabilization of the Poisoned Patient. The "ABC" mnemonic of emergency care is popularly taught and applies to the treatment of acute poisoning (Table 4–8). In severe cases, endotracheal intubation, mechanical ventilation, pharmacological blood pressure support, and/or extracorporeal circulatory support may be necessary and appropriate.

Identification of Clinical Patterns of Toxicity. A carefully obtained medical history may allow for the creation of a list of available medications or chemicals that might be implicated in a poisoning event. Often, an observation of physical symptoms and signs may be the only additional clues to a poisoning diagnosis.

Table 4–8

ABCDE: Initial Treatment Approach for Acute Poisoning

Airway	Maintain patency
Breathing	Maintain adequate oxygenation and ventilation
Circulation	Maintain perfusion of vital organs
Disability	Assess for central nervous system dysfunction *If neurological disability is noted, consider:* • *Oxygen administration (check pulse oximetry)* • *Dextrose administration (check blood glucose concentration)* • *Naloxone administration (consider empiric trial)* • *Thiamine (for adult patients receiving dextrose)*
Exposure	Assess "toxidrome" (see Table 4–9)

Groups of physical signs and symptoms associated with specific poisoning syndromes are known as *toxidromes* (Erickson, 2007; Osterhoudt, 2004). Table 4–9 describes commonly encountered toxidromes.

The most typically available urine drug toxicology test is an immunoassay designed to detect common drugs of abuse such as amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, and opiates. Acute poisoning with these substances can usually be determined on clinical grounds, and the results of these assays are infrequently available fast enough to guide stabilization. Additionally, detection of drugs or their metabolites on a urine immunoassay does not mean that the detected drug is responsible for the currently observed poisoning illness. When ingestion of acetaminophen or aspirin cannot clearly be excluded via the exposure history, serum quantification of these drugs is recommended. An electrocardiogram (ECG) may be useful at detecting heart blocks, Na^+ channel blockade, or K^+ channel blockade associated with specific medication classes (Table 4–10). Further laboratory analysis, such as use of blood gas determinations, serum chemistries, complete blood counts, and other testing, should be tailored to the individual poisoning circumstance.

Decontamination of the Poisoned Patient. Poisoning exposures may be by inhalation, by dermal or mucosal absorption, by injection, or by ingestion. The first step in preventing absorption of poison is to stop any ongoing exposure. If necessary, eyes and skin should be washed copiously. Gastrointestinal decontamination is the process of preventing or reducing absorption of a substance after it has been ingested. The primary strategies for GI decontamination are gastric emptying, adsorption of poison, and catharsis. Minimal indications for considering GI decontamination include: 1) the poison must be potentially dangerous; 2) the poison must still be unabsorbed in the stomach or intestine, so it must be soon after ingestion; and 3) the procedure must be able to be performed safely and with proper technique. Gastric emptying is rarely recommended anymore, but the administration of activated charcoal and the performance of whole bowel irrigation remain therapeutic options.

Table 4–9

Common Toxidromes

DRUG CLASS	EXAMPLE(S)	MENTAL STATUS	HR	BP	RR	T	PUPIL SIZE	OTHER
Sympathomimetic	Cocaine Amphetamine	Agitation	↑	↑		↑	↑	Tremor, diaphoresis
Anticholinergic	Diphenhydramine *Belladonna atropa*	Delirium	↑	↑		↑	↑	Ileus, flushing
Cholinergic	Organophosphates	Somnolence/coma			↑		↓	SLUDGE[a], fasciculation
Opioid	Heroin Oxycodone	Somnolence/coma	↓		↓		↓	
Sedative-hypnotic	Benzodiazepines Barbiturates	Somnolence/coma		↓	↓			
Salicylate	Aspirin	Confusion	↑		↑	↑		Diaphoresis, vomiting
Ca^{2+} channel blocker	Verapamil		↓	↓				

HR, heart rate; BP, blood pressure; RR, respiratory rate; T, temperature. [a]SLUDGE, muscarinic effects of Salivation, Lacrimation, Urination, Defecation, Gastric cramping, and Emesis.

Table 4–10

Differential Poisoning Diagnosis (Partial Listing) for Electrocardiographic Manifestations of Toxicity

BRADYCARDIA/HEART BLOCK	QRS INTERVAL PROLONGATION	QTC INTERVAL PROLONGATION
Cholinergic agents Physostigmine Neostigmine Organophosphates, carbamates *Sympatholytic agents* β receptor antagonists Clonidine Opioids *Other* Digoxin Ca^{2+} channel blockers Lithium	Antiarrhythmia drugs Bupropion Chloroquine Diphenhydramine Lamotrigine Phenothiazines Propranolol Tricyclic antidepressants	(See Arizona Center for Education and Research on Therapeutics website, http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm)

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Gastric emptying may be attempted by induced vomiting or by gastric lavage. Historically, pharmaceutical methods to stimulate vomiting included administration of potentially toxic doses of copper sulfate or apomorphine; more recently, syrup of ipecac took their place as the favored drug to induce emesis. Gastric emptying has been shown in volunteer studies to reduce drug absorption by ~ one-third under optimal conditions (Tenenbein, 1987). A randomized trial of gastric emptying for poisoned patients did not show improvement in clinical outcome (Pond et al., 1995), but the selection of subjects and timing of therapy may have biased the study toward the null hypothesis. *Based upon review of existing evidence, the American Academy of Pediatrics no longer recommends syrup of ipecac as part of its childhood injury prevention program (AAP, 2003), and the American Academy of Clinical Toxicology dissuades routine use of gastric emptying in the poisoned patient (AACT, 2004; Manoguerra and Cobaugh, 2005).* The declining role of syrup of ipecac in the treatment of poisoning is evident by its use in <0.1% of cases reported to the AAPCC in 2007, compared to ~10% in 1987 (Bronstein et al., 2008).

Syrup of Ipecac. The U.S. FDA approved syrup of ipecac for sale without a prescription in 1965. The alkaloids cephaeline and emetine within syrup of ipecac act as emetics because of both a local irritant effect on the enteric tract and a central effect on the chemoreceptor trigger zone in the area postrema of the medulla. Syrup of ipecac is available in 0.5- and 1-fluid ounce containers. Ipecac is given orally at a dose of 15 mL for children up to 12 years, and 30 mL for older children and adults. Administration of ipecac is typically followed by a drink of water, and reliably produces emesis in 15-30 minutes. Contraindications for syrup of ipecac administration include existing or impending CNS depression, ingestion of a corrosive or hydrocarbon drug (due to the emergence of chemical pneumonia), or presence of a medical condition that might be exacerbated by vomiting. Ipecac has been misused by bulimic patients; in cases of Munchausen syndrome by proxy and with chronic abuse, ipecac may cause serum electrolyte abnormalities, cardiomyopathy, ventricular arrhythmia, and death.

Gastric Lavage. The procedure for gastric lavage involves passing an orogastric tube (24-French for small children, up to 40-French for adults) into the stomach with the patient in the left-lateral decubitus position with head lower than feet. Preferably, the tube will have been designed for lavage purposes, and will have sizable side holes in the tubing. After withdrawing stomach contents, 10 to 15 mL/kg (up to 250 mL) of saline lavage fluid is administered and withdrawn. This process continues until the lavage fluid returns clear. Complications of the procedure include mechanical trauma to the stomach or esophagus, pulmonary aspiration of stomach contents, and vagus nerve stimulation.

Adsorption of a poison refers to the binding of a poison to the surface of another substance. An adsorbed poison may be less available for absorption into the body. It is well known that the fullness of the stomach from a meal affects a drug's absorption kinetics. Fuller's earth has been suggested as an adsorbent for paraquat, Prussian blue binds thallium and cesium, and sodium polystyrene can adsorb lithium. The most common adsorbent used in the treatment of acute drug overdose is activated charcoal.

Volunteer studies suggest that activated charcoal is more effective at reducing drug absorption than either induced emesis or gastric lavage (Tenebein, 1987). In a position paper of the American Academy of Clinical Toxicology on the use of single-dose activated charcoal, the opinion is given that single-dose charcoal should not be administered routinely in the management of poisoned patients, and that it should only be considered if a patient has ingested a potentially toxic amount of poison up to 1 hour before charcoal administration (AACT, 2005). In 2007, charcoal was used in 4.3% of cases reported to American poison control centers (Bronstein et al., 2008). Clinical evidence of improved patient parameters from treatment with activated charcoal are slowly emerging (Buckley et al., 1999; Isbister et al., 2007; Page et al., 2009), but good outcome data from clinical trials are still lacking.

Activated Charcoal. Charcoal is created through controlled pyrolysis of organic matter, and is *activated* through steam or chemical treatment that increases its internal pore structure and adsorptive surface capacity. The surface of activated charcoal contains carbon moieties, such as carbonyl and hydroxyl groups, that are capable of binding poisons. The recommended dose is typically 0.5-2 g/kg of body weight, up to a maximum tolerated dose of ~75-100 g. As a rough estimate, 10 g of activated charcoal is expected to bind ~1 g of drug. The efficacy of activated charcoal at adsorbing ingested drug diminishes over time. Alcohols, corrosives, hydrocarbons, and metals are not believed to be well adsorbed by charcoal.

Complications of activated charcoal therapy include vomiting, constipation, pulmonary aspiration, and death. Charcoal slurries are black and gritty; in a series of children offered charcoal in a pediatric emergency department, only 44% of the children <6 years accepted the agent orally (Osterhoudt et al., 2004a). Nasogastric administration of charcoal increases the incidence of vomiting (Osterhoudt et al., 2004b), and may increase the risk for pulmonary aspiration. Charcoal should not be given to patients with suspected GI perforation, or to patients who may be candidates for endoscopy.

Whole Bowel Irrigation. Whole bowel irrigation (WBI) involves the enteral administration of large amounts of a high molecular weight, iso-osmotic polyethylene glycol electrolyte solution with the goal of passing poison by the rectum before it can be absorbed. Potential candidates for WBI include: 1) "body-packers" with intestinal packets of illicit drugs; 2) patients with iron overdose; 3) patients who have ingested patch pharmaceuticals; and 4) patients with overdoses of sustained-release or bezoar-forming drugs.

Polyethylene glycol electrolyte solution is typically administered at a rate of 25 to 40 mL/kg/h until the rectal effluent is clear and no more drug is being passed. To achieve these high administration rates a nasogastric tube may be used. Large doses have been administered without adversely affecting serum electrolyte concentrations. WBI is contraindicated in the presence of bowel obstruction or perforation, and may be complicated by abdominal distention or pulmonary aspiration.

Cathartics. The two most common categories of simple cathartics are the magnesium salts, such as magnesium citrate and magnesium sulfate, and the nondigestible carbohydrates, such as sorbitol. The use of simple cathartics has been abandoned as a GI decontamination strategy, although sorbitol is sometimes administered with single-dose activated charcoal in an effort to add sweetness and reduce its predilection toward constipation.

Enhancing the Elimination of Poisons. Once absorbed, the deleterious toxicodynamic effects of some drugs may be reduced by methods that hasten their elimination from the body. Urinary excretion of some drugs may be enhanced by the process of ion-trapping in alkaline urine. Gastrointestinal excretion of some drugs may be enhanced through use of multiple doses of activated charcoal. Some drugs may be removed from the body by extracorporeal techniques such as peritoneal dialysis, hemodialysis, or hemoperfusion.

Manipulating Urinary pH: Urinary Alkalinization. Drugs subject to renal clearance are excreted into the urine by glomerular filtration and active tubular secretion (Chapter 2); non-ionized compounds may be reabsorbed far more rapidly than ionized polar molecules. Weakly acidic drugs are susceptible to "ion-trapping" in the urine. Aspirin is a weak acid with a $pK_a = 3.0$. As the pH of the urine increases, more salicylate is in its ionized form at equilibrium, and more salicylic acid is diffused into the tubular lumen of the kidney. Urinary alkalinization is also believed to speed clearance of phenobarbital, chlorpropamide, methotrexate, and chlorphenoxy herbicides. The American Academy of Clinical Toxicologists recommends urine alkalinization as first-line treatment only for moderately severe salicylate poisoning that does not meet criteria for hemodialysis (Proudfoot et al., 2004). To achieve alkalinization of the urine, 100-150 mEq of sodium bicarbonate in 1L of D5W is infused intravenously at twice the maintenance fluid requirements and then titrated to effect. Hypokalemia should be treated since it will hamper efforts to alkalinize the urine due to H^+-K^+ exchange in the kidney. Urine alkalinization is contraindicated in the presence of renal failure, or when the fluid administration may worsen pulmonary edema or congestive heart failure. Acetazolamide is not used to alkalinize urine as it promotes acidemia.

Multiple-Dose Activated Charcoal. Activated charcoal adsorbs drug to its surface and promotes enteral elimination. Multiple doses of activated charcoal can speed elimination of absorbed drug by two mechanisms. Charcoal may interrupt enterohepatic circulation of hepatically metabolized drug excreted in the bile, and charcoal may create a diffusion gradient across the GI mucosa and promote movement of drug from the bloodstream onto the charcoal in the intestinal lumen. Activated charcoal may be administered in multiple doses, 12.5 g/h every 1, 2, or 4 hours (smaller doses may be used for children). Complications of therapy are similar to those listed for single-dose activated charcoal. Charcoal enhances the clearance of many drugs of low molecular weight, small volume of distribution, and long elimination $t_{1/2}$. In the absence of good clinical outcomes data, multiple-dose activated charcoal is believed to have the most potential utility in overdoses of carbamazepine, dapsone, phenobarbital, quinine, theophylline, and yellow oleander (AACT, 1999; de Silva et al., 2003).

Extracorporeal Drug Removal. The ideal drug amenable to removal by hemodialysis has a low molecular weight, a low volume of distribution, high solubility in water, and minimal protein binding. Hemoperfusion involves passing blood through a cartridge containing adsorbent particles. The most common poisonings for which hemodialysis is sometimes used include salicylate, methanol, ethylene glycol, lithium, carbamazepine, and valproic acid. For a more exhaustive list of drugs amenable to hemodialyis or hemoperfusion, see Winchester (2002).

Antidotal Therapies. Antidotal therapy involves antagonism or chemical inactivation of an absorbed poison. The pharmacodyamics of a poison can be altered by competition at a receptor, as in the antagonism provided by naloxone therapy in the setting of heroin overdose. A physiological antidote may use a different cellular mechanism to overcome the effects of a poison, as in the use of glucagon to stimulate an alternative to the blocked β adrenergic receptor and increase cellular cyclic AMP in the setting of propranolol overdose. Antivenoms and chelating agents bind and directly inactivate poisons. The biotransformation of a drug can also be altered by an antidote; for instance, fomepizole will inhibit alcohol dehydrogenase and stop the formation of toxic acid metabolites from ethylene glycol and methanol. Many drugs used in the supportive care of a poisoned patient (anticonvulsants, vasoconstricting agents, etc.) may be considered nonspecific functional antidotes.

The mainstay of therapy for poisoning is good support of the airway, breathing, circulation, and vital metabolic processes of the poisoned patient until the poison is eliminated from the body; specific antidotes are uncommonly needed. Among the most common specific antidotes used are *N*-acetyl-*L*-cysteine for acetaminophen poisoning, opioid antagonists for opioid overdose, and chelating agents for poisoning from certain metal ions. A listing of other commonly used antidotes is presented in Table 4–11.

IMPORTANT RESOURCES FOR INFORMATION RELATED TO DRUG TOXICITY AND POISONING

Pharmacology textbooks offer important information pertaining to the toxic nature of drugs, but they may lack

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Table 4–11

Some Common Antidotes and Their Indications

ANTIDOTE	POISONING INDICATION(S)
Acetylcysteine	Acetaminophen
Atropine sulfate	Organophosporus and carbamate pesticides
Benztropine	Drug-induced dystonia
Bicarbonate, sodium	Na^+ channel blocking drugs
Bromocriptine	Neuroleptic malignant syndrome
Calcium gluconate or chloride	Ca^{2+} channel blocking drugs, Fluoride
Carnitine	Valproate hyperammonemia
Crotalidae polyvalent immune Fab	North American crotaline snake envenomation
Dantrolene	Malignant hyperthermia
Deferoxamine	Iron
Digoxin immune Fab	Cardiac glycosides
Diphenhydramine	Drug-induced dystonia
Dimercaprol (BAL)	Lead, mercury, arsenic
EDTA, $CaNa_2$	Lead
Ethanol	Methanol, ethylene glycol
Fomepizole	Methanol, ethylene glycol
Flumazenil	Benzodiazepines
Glucagon hydrochloride	β adrenergic antagonists
Hydroxocobalamin hydrochloride	Cyanide
Insulin (high dose)	Ca^{2+} channel blockers
Leucovorin calcium	Methotrexate
Methylene blue	Methemoglobinemia
Naloxone hydrochloride	Opioids
Octreotide acetate	Sulfonylurea-induced hypoglycemia
Oxygen, hyperbaric	Carbon monoxide
Penicillamine	Lead, mercury, copper
Physostigmine salicylate	Anticholinergic syndrome
Pralidoxime chloride (2-PAM)	Organophosphorus pesticides
Pyridoxine hydrochloride	Isoniazid seizures
Succimer (DMSA)	Lead, mercury, arsenic
Thiosulfate, sodium	Cyanide
Vitamin K_1 (phytonadione)	Coumarin, indanedione

discussion of household, industrial, or environmental chemicals, and they may lack detailed discourse of prevention, identification, and treatment of overdose. Additional information on poisoning from drugs and chemicals can be found in many dedicated books of toxicology (Flomenbaum, 2006; Klaassen, 2007; Olson, 2007; Shannon et al., 2007). A popular computer database for information on toxic substances is POISINDEX (Micromedex, Inc., Denver, CO).

The National Library of Medicine offers information on toxicology and environmental health (http://sis.nlm.nih.gov/enviro.html), including a link to ToxNet (http://toxnet.nlm.nih.gov/), a cluster of full-text and bibliographic databases on toxicology, hazardous chemicals, and related areas.

Regional poison control centers are a resource for valuable poisoning information, and can be reached from anywhere within the U.S. through a national PoisonHelp hotline: 1-800-222-1222. Poison centers also collect epidemiological data regarding poisoning, perform all hazards surveillance, provide education, and work collaboratively with other agencies to effect poisoning prevention.

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