CONTRIBUTORS

E. JACK BENNER, M.D.
Associate Professor of Internal Medicine, University of California School of Medicine, Davis; Director of Department of Internal Medicine and Consultant in Infectious Diseases, Sacramento Medical Center, Sacramento, California.

BARBARA C. BREGER, M.D.
Assistant in Ophthalmology, Mount Sinai School of Medicine, New York, New York.

DONALD L. BRUMMER, M.D.
Associate Professor of Medicine, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University, Richmond, Virginia.

LEIGHTON E. CLUFF, M.D.
Professor and Chairman of Department of Medicine, University of Florida College of Medicine; Chief, Medical Service, W. A. Shands Teaching Hospital and Clinics, University of Florida; Consultant, Veterans Administration Hospital, Gainesville, Florida.

ISIDORE COHN, Jr., M.D., D.Sc.(Med.), F.A.C.S.
Professor of Surgery and Chairman of Department of Surgery, Louisiana State University School of Medicine, New Orleans; Senior Visiting Surgeon and Surgeon-in-Chief, L.S.U. Surgical Service, Charity Hospital of Louisiana at New Orleans, New Orleans, Louisiana.

ALVIN M. COTLAR, M.D.
Clinical Assistant Professor of Surgery, Louisiana State University School of Medicine; Visiting Surgeon, L.S.U. Surgical Service, Charity Hospital of

Louisiana at New Orleans; Clinical Assistant, Division of General Surgery, Touro Infirmary, New Orleans; Member Courtesy Staff, Department of General Surgery, West Jefferson General Hospital, Marrero, Louisiana.

FRANK COX, M.D.
Associate Physician, Division of Infectious Diseases, Department of Medicine, Henry Ford Hospital, Detroit, Michigan.

C. WILLIAM DAESCHNER, Jr., M.D.
Professor and Chairman of Department of Pediatrics, University of Texas Medical Branch; Chief of Pediatrics, The University of Texas Medical Branch Hospitals, Galveston, Texas.

IAN DONALD, M.B.E., M.D., F.R.C.S. (Glasg.), F.R.C.O.G., F.C.O.G. (S.A.)
Regius Professor of Midwifery, University of Glasgow; Obstetrician-in-Chief, The Queen Mother's Hospital; Gynaecologist-in-Chief, Western Infirmary, Glasgow, Scotland.

SYDNEY M. FINEGOLD, M.D., F.A.C.P.
Professor of Medicine, Department of Medicine, The UCLA School of Medicine, Los Angeles; Chief, Infectious Disease Section, Veterans Administration Center, Wadsworth Hospital, Los Angeles, California.

JOHN J. GARTLAND M.D.
Associate Professor of Orthopaedic Surgery, Jefferson Medical College; Chief, Department of Orthopaedic Surgery, Lankenau Hospital, Philadelphia, Pennsylvania.

MOSES GROSSMAN, M.D.
Professor of Pediatrics, University of California San Francisco Medical Center School of Medicine, San Francisco; Chief of Pediatrics, San Francisco General Hospital, San Francisco, California.

PETER HACKER, M.D.
Research Fellow, University of California San Francisco Medical Center School of Medicine, San Francisco, California.

J. ALEX HALLER, Jr. M.D.
Robert Garrett Professor of Pediatric Surgery, Johns Hopkins University School of Medicine; Children's Surgeon-in-Charge, Johns Hopkins Hospital, Baltimore, Maryland.

GAVIN HILDICK-SMITH, M.D., M.R.C.P., C.R.C.P.(C.), F.A.A.P.
Instructor in Pediatrics, University of Pennsylvania School of Medicine; Attending Physician, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

DAVID INGALL, M.D.
Associate Professor of Pediatrics, Obstetrics and Gynecology, Boston University School of Medicine; Director of Newborn Nurseries, Boston City Hospital Boston, Massachusetts.

ERNEST JAWETZ, M.D., Ph.D.
Professor of Microbiology and Professor of Medicine, University of California San Francisco Medical Center School of Medicine, San Francisco, California.

BENJAMIN M. KAGAN, M.D., F.A.A.P., F.A.C.P.
Professor of Pediatrics, University of California at Los Angeles School of Medicine; Director, Department of Pediatrics, and Consultant, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California.

KENNETH KAPLAN, M.D.
Instructor, Tufts University School of Medicine, Boston, Massachusetts.

RALPH J. KAPLAN, M.D.
Assistant Professor, The University of New Mexico School of Medicine; Chief, Neurosurgical Division, Albuquerque Veterans Administration Hospital; Attending Neurosurgeon, Bernalillo County Medical Center, Albuquerque, New Mexico.

EDWIN L. KENDIG, Jr., M.D.
Professor of Pediatrics, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University; Director, Child Chest Clinic, Medical College of Virginia Hospitals, Richmond, Virginia.

CALVIN M. KUNIN, M.D.
Professor of Preventive Medicine and Medicine, University of Virginia; Attending Physician, University of Virginia Hospital, Charlottesville, Virginia.

IRVING H. LEOPOLD, M.D.
Professor and Chairman of Department of Ophthalmology, Mount Sinai School of Medicine, New York, New York.

HERBERT S. LEVIN, M.D.
Attending Physician, Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, California.

KATHRYN HUXTABLE LEWIS, M.D., M.P.H.
Clinical Assistant Professor, Department of Pediatrics and Department of Preventive Medicine, University of Pittsburgh School of Medicine; Assistant Director, Out-Patient Department, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania.

E. LISKE, M.D.
Associate Professor in Neurology, University of New Mexico School of Medicine; Consultant in Neurology and Electroencephalography, Veterans Administration Hospital, Albuquerque, New Mexico.

THOMAS A. McALLISTER, M.B., Ch.B.
Bacteriologist-in-Chief, Royal Hospital for Sick Children and The Queen Mother's Hospital, Glasgow, Scotland.

HOWARD I. MAIBACH, M.D.
Associate Professor of Dermatology, University of California San Francisco Medical Center School of Medicine, San Francisco, California.

MICHAEL A. MANKO, M.D.
Associate in Medicine, Jefferson Medical College; Head, Infectious Disease Section, Lankenau Hospital, Philadelphia, Pennsylvania.

ALLEN W. MATHIES, Jr., M.D., Ph.D.
Associate Professor of Pediatrics, University of Southern California School of Medicine; Head Physician, Communicable Disease Service, Los Angeles County –University of Southern California Medical Center, Los Angeles, California.

WILLIAM F. MILLER, M.D.
Professor of Internal Medicine, University of Texas Medical School at Dallas; Director, Pulmonary Section, Cardiopulmonary Institute, Methodist Hospital of Dallas, Dallas, Texas.

JOHN ARTHUR MONCRIEF, M.D.
Professor of Surgery, Medical University of South Carolina, Charleston, South Carolina.

EDWARD A. MORTIMER, Jr., M.D.
Professor and Chairman of Department of Pediatrics, University of New Mexico School of Medicine; Chief of Pediatrics, Bernalillo County Medical Center, Albuquerque, New Mexico.

CHARLES V. PRYLES, M.D.
Professor of Pediatrics, State University of New York Downstate Medical Center; Chairman, Department of Pediatrics, The Jewish Hospital and Medical Center, Brooklyn, New York.

EDWARD L. QUINN, M.D.
Chairman, Division of Infectious Diseases, Department of Medicine, Henry Ford Hospital, Detroit, Michigan.

WILLIAM A. REED
Associate Professor of Surgery, University of Kansas Medical Center; Consultant in Thoracic Surgery, Veterans Administration Hospitals and Menorah Medical Center, Kansas City, Kansas.

HARRIS D. RILEY, Jr., M.D.
Professor and Head of Department of Pediatrics, University of Oklahoma School of Medicine; Pediatrician-in-Chief, Children's Memorial Hospital, University of Oklahoma Medical Center, Oklahoma City, Oklahoma.

SYDNEY ROSS, M.D.
Clinical Professor of Pediatrics, George Washington University School of Medicine; Senior Attending Physician, Children's Hospital of the District of Columbia. Chief of Microbiology Section, Research Foundation, Children's Hospital of the District of Columbia, Washington, D.C.

EUGENE SANDERS, M.D.
Associate Professor of Medicine and Microbiology, University of Florida College of Medicine; Attending Physician, W. A. Shands Teaching Hospital and Clinics and Gainesville Veterans Administration Hospital, Gainesville, Florida; Consultant, W. T. Edwards Hospital, Tampa, Florida.

DEXTER S. Y. SETO, M.D.
Assistant Professor of Pediatrics and Microbiology, Johns Hopkins University School of Medicine; Head, Pediatric Chest Clinic, Johns Hopkins Hospital, Baltimore, Maryland.

JOSEPH D. SHERMAN, M.D., Ph.D.
Assistant Clinical Professor of Internal Medicine, Boston University School of Medicine, Boston; Chief of Hematology, Framingham Union Hospital, Framingham, Massachusetts.

HAROLD J. SIMON, M.D., Ph.D.
Associate Professor of Community Medicine and Associate Dean, School of Medicine, University of California, San Diego, California.

GORDON T. STEWART, M.D.
Watkins Professor and Chairman of Department of Epidemiology, School of Public Health; Professor of Medicine, School of Medicine, Tulane University, New Orleans, Louisiana.

PAUL F. WEHRLE, M.D.
Hastings Professor of Pediatrics, University of Southern California School of Medicine; Chief Physician, Children's Division, Departments of Pediatrics and Communicable Disease, Los Angeles County–University of Southern California Medical Center, Los Angeles, California.

LOUIS WEINSTEIN, M.D., Ph.D.
Professor of Medicine, Tufts University School of Medicine; Lecturer on Infectious Diseases, Harvard Medical School; Associate Physician-in-Chief and Chief of the Infectious Disease Service, New England Medical Center Hospitals; Associate Physician, Medical Service of the Massachusetts General Hospital, Boston, Massachusetts.

IRWIN ZIMENT, M.B. M.R.C.P.
Assistant Professor of Medicine, Department of Medicine, The UCLA School of Medicine, Los Angeles; Full-time Staff Physician, Medical Service, Harbor General Hospital, Torrance, California.

PREFACE

There has long been a clear need for a comprehensive text on antimicrobial therapy. It is hoped that this book will fulfill that need. In spite of the publication of a wealth of isolated data, no single text exists in which all the essential areas have been covered.

Today, in every field of clinical practice, antimicrobial agents are being widely used. It is therefore of the utmost importance that physicians be thoroughly acquainted with them. This book provides necessary information about the nature of these agents and about their use. The first portion is devoted to basic pharmacologic principles of importance to the clinician; the second to clinical application. In order to avoid duplication, the dosages, routes of administration, and preparation procedures are outlined in the last chapter. However, where individual authors differ from one another in any way, they have included their specific recommendations, each in his own chapter.

The authors of the various sections of this book have been chosen because of their leadership and advanced knowledge in the specific fields about which they are writing. The editor is most grateful to these authors who have made this text so thorough and comprehensive.

BENJAMIN M. KAGAN, M.D.

CONTENTS

part one

APPLIED PHARMACOLOGY

chapter 1

Antimicrobial Drugs: Mechanisms and Factors Influencing Their Action

EUGENE SANDERS and LEIGHTON E. CLUFF

The mechanisms of action of antimicrobial agents may be discussed within three frames of reference: molecular or subcellular, cellular, and biological. Mechanisms on the cellular or subcellular level involve interactions of drug and parasite exclusively; those on the biological level, the triad of host, drug, and parasite. Application of advances in our understanding on any of these levels is frequently of value to the physician involved in care of patients with infectious diseases. The purpose of the present discussion is twofold: to review briefly the current status of our knowledge of the molecular mechanisms of antimicrobial action, and to describe those interactions of host, microorganism, and drug that may modify or impair the anticipated action of antimicrobial drugs in vivo.

MOLECULAR AND CELLULAR MECHANISMS OF ANTIMICROBIAL ACTION

Knowledge of the molecular mechanisms of action of the antimicrobial drugs has increased exponentially during the past several years. This advance

Supported in part by a Training Grant from the National Institutes of Allergy and Infectious Diseases.

Table 1–1. *Classification of Antimicrobial Agents in Current Use According to Molecular Mechanism of Action*

Agents that impede replication of genetic information
Nalidixic acid
Griseofulvin
Agents that impair translation of genetic information into protein synthesis
Chloramphenicol
The tetracyclines
Erythromycin
Lincomycin
Kanamycin
Neomycin
Streptomycin
Agents that alter structure and function of the cell wall
Cycloserine
Vancomycin
Ristocetin
Bacitracin
The penicillins
Cephalothin and analogues
Agents that restrict function of the cell membrane
Gramicidin
Tyrocidin
Polymyxin B
Colistin
Amphotericin B
Nystatin

has paralleled, and was in large part a by-product of, increased understanding of the replication of genetic information and its translation into synthesis of specific proteins. Description of this association is beyond the scope of this discussion; the reader may consult the excellent review by Carter and McCarty for details.[2] The antimicrobial agents in current clinical use may be classified into four major categories, for they may either (1) impede replication of genetic information, (2) impair translation of genetic information into protein synthesis, (3) alter structure and function of cell walls, or (4) restrict function of cell membranes. Drugs constituting each of these groups are listed in Table 1–1. Drugs that impair intermediary metabolism, such as the sulfonamides, as well as most of the antituberculous agents, will not be included in this discussion.

Agents That Impede Replication of Genetic Information

Nalidixic acid and griseofulvin are structurally related to the purine nucleotides. Both have been shown to block DNA synthesis in sensitive microorganisms.[8,19] Although their precise locus of action is unknown, their structural similarity to purines suggests that they may inhibit DNA replication at the level of assembly of the purine nucleotides.

Agents That Impair Translation of Genetic Information

These drugs either inhibit protein synthesis (chloramphenicol, the tetracyclines, erythromycin, and lincomycin) or induce formation of defective protein molecules (kanamycin, neomycin, and streptomycin). The former are bacteriostatic, the latter bactericidal.

Chloramphenicol has been known for over a decade to abolish protein synthesis in bacterial cells.[6,7] That this effect is not limited to microorganisms has also been well recognized. The universality of inhibition of protein synthesis by chloramphenicol readily accounts for its major toxicity in man—impairment of hemoglobin synthesis. Chloramphenicol has no effect upon cell synthesis of mucopeptides, respiration, or permeability.[6,7] It has recently been shown to inhibit protein synthesis by preventing attachment of messenger RNA (mRNA) to ribosomes.[12] This activity may be antagonized by synthetic mRNA[11] or phenylalanine.[10]

The tetracyclines and lincomycin abolish bacterial protein synthesis by inhibition of the binding of amino acid–activated transfer RNA (tRNA) to ribosomes.[3,28] Because of the differences in antibacterial spectrum of these two drugs, one may anticipate that they inhibit tRNA binding through dissimilar mechanisms. Erythromycin, on the other hand, shares the antibacterial spectrum of lincomycin. It may thus restrict protein synthesis by a mechanism closely related or identical to that of lincomycin.

The aminoglycoside antibiotics, streptomycin, kanamycin, and neomycin, appear to act by similar mechanisms. These drugs produce specific misreadings in the genetic code at the level of the ribosome.[5] After their attachment to the ribosome, they appear to permit incorporation of one or more incorrect amino acids into a growing peptide chain, resulting in synthesis of defective proteins. Since these drugs are bactericidal, it may be reasoned either that these defective proteins are lethal to the cell or that the deficiency in normal proteins created by their synthesis leads to failure of one or more vital metabolic functions of the cell. Convincing evidence in support of either of these hypotheses has not been presented.

Agents That Alter Structure and Function of the Bacterial Cell Wall

Knowledge of the chemical structure and biosynthesis of bacterial cell walls has been reviewed by Perkins.[22] The antimicrobial agents known to affect bacterial cell walls adversely are vancomycin, ristocetin, bacitracin, cycloserine, the penicillins, and cephalothin and its analogues. These drugs are bactericidal for sensitive cells.

Cycloserine is a structural analogue of D-alanine, one of the substrates for the pentapeptide side chain within the cell wall.[27] This drug appears to prevent assembly of the side chain containing D-alanine by competitively inhibiting one or both of the enzymes, alanine racemase or D-alanyl-D-alanine synthetase.[20,26] Vancomycin, ristocetin, and bacitracin appear to inhibit the