AMA DRUG EVALUATIONS

SECOND EDITION

Prepared by the
AMA DEPARTMENT OF DRUGS

PUBLISHING SCIENCES GROUP, INC.
ACTON, MASSACHUSETTS

Copyright © 1973 by The American Medical Association.
Previous Edition © 1971 by The American Medical Association.

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage or retrieval system, without permission in writing from Publishing Sciences Group, Inc., the publisher.

Printed in the United States of America.

International Standard Book Number: 0-88416-003-3

Library of Congress Catalog Number: 75-147249

PREFACE

The second edition of *AMA Drug Evaluations (AMA-DE)* was compiled by the AMA Department of Drugs under the direction of the former AMA Council on Drugs. It provides reliable and current scientific information for those who prescribe, dispense, and administer drugs.

Readers familiar with the first edition will detect significant new features and changes in format. Among these are (1) a smaller, more convenient size, (2) a hard cover, (3) indexing by trade name as well as generic name, (4) inclusion of structural formulas, (5) use of conventional prose instead of telegraphic style in the individual evaluations, and (6) expanded coverage of information on drug interactions. The New Drugs Section and the Indications Index have been eliminated.

AMA-DE describes uses, routes of administration, or dosages that may not be found in the "package insert." FDA-approved labeling limits the use of drugs for purposes of marketing and advertising but does not rigidly constrain a physician's use of the drug for individual patients. Accordingly, *AMA-DE* describes all scientific, recognized uses of drugs irrespective of their status in approved labeling in the "package insert."

In the 2½ years since the first edition, many drug products have been removed from the market by the FDA as the result of the Drug Efficacy Study by the National Academy of Sciences-National Research Council. Every effort has been made to delete these products from the text. Because of the time lag between preparation of final copy and publication, however, some drugs are described that are no longer available.

The American Medical Association hopes that the second edition of *AMA-DE* will be a valuable and useful service to the medical profession and to others working in the field of medical care.

ERNEST B. HOWARD, M.D.
Executive Vice President

ACKNOWLEDGMENTS

Appreciation is expressed for the assistance of the following members of the professional staff of the Department of Drugs:

John D. Archer, M.D.
Morton S. Comer, Ph.D.
Michael H. M. Dykes, M.D.
Howard G. Glass, M.D., Ph.D.
Kathryn S. Huss, M.D.
Joseph B. Jerome, Ph.D.
Mary Ellen Kosman, Ph.D.
Roland E. Lapointe, M.D.
John Reed Lewis, Ph.D.
Karl Mayer, D.V.M.
Russell R. Miller, Ph.D.
Barbara F. Murphy, M.S.
Edward L. Platcow, Ph.D.
Donald O. Schiffman, Ph.D.
Philip G. Seitner, Ph.D.
Leon H. Warren, M.D.

The editorial, technical, and administrative aid furnished by the following Department staff is also acknowledged and appreciated:

Joquain Chang
Susan Connors
Barbara M. Eckel
Helena Suen Fu
Medina Gross
Sandra Kodani
Marilyn Krause
John W. Richardson
Beverly J. Rodgers
Linda A. Schoen
Jill Senrick
Marjorie Spence
Karen Steffensen

The valuable help of the following secretarial staff is recognized:

Lerinee Allen
Barbara Bates
Beverly Blumenshine
Nancy Jo Carpenter
Bonnie Christiansen
Patricia L. Danzinger
Rhonda Dobbs
Barbara J. Fisher
Jeanne M. Kelso
Hei Sung Kim
Melenie Lester
Jean Rawn
Rhonda A. Reese
Offie Robinson
Wanda Ryska
Barbara Schweisheimer
Ellen Skalnik
Carol Strauss
Christine Swiatek
Patricia Washington

The contributions of those pharmaceutical companies that supplied information on products of their manufacture to assist in the preparation of the evaluative statements in this volume are gratefully acknowledged.

JOHN C. BALLIN, PH.D.
Director
Department of Drugs

此为试读,需要完整PDF请访问: www.ertongbook.com

Consultants for AMA Drug Evaluations

The staff of the Department of Drugs expresses its appreciation to the following consultants for their cooperation and assistance in reviewing the content of this edition of *AMA Drug Evaluations*:

Robert Abel, M.D.
Robert S. Abernathy, M.D.
Charles F. Abildgaard, M.D.
F.S. Abuzzahab, M.D., Ph.D.
*John Adriani, M.D.
Edward H. Ahrens, Jr., M.D.
Thomas P. Almy, M.D.
Joel J. Alpert, M.D.
Thomas T. Amatruda, Jr., M.D.
William W. Anderson, M.D.
Vincent T. Andriole, M.D.
Leonard Apt, M.D.
Jay M. Arena, M.D.
Charles D. Aring, M.D.
Leslie R. Arnett, D.D.S.
Harry L. Arnold, Jr., M.D.
Malcolm Artenstein, M.D.
Joseph F. Artusio, Jr., M.D.
*Daniel L. Azarnoff, M.D.

William Bageant, M.D.
Irving W. Bailit, M.D.
Charles L. Baird, Jr., M.D.
Andre Barbeau, M.D.
Charles F. Barlow, M.D.
*Allan D. Bass, M.D.
Joseph Bateman, M.D.
William T. Beaver, M.D.
J. Weldon Bellville, M.D.
John Benson, Jr., M.D.
Leonard B. Berman, M.D.
Jerrold G. Bernstein, M.D.
Ernest Beutler, M.D.
Edwin Bierman, M.D.
Hugh Biller, M.D.
Harvey Blank, M.D.
Morton D. Bogdonoff, M.D.
Herbert Borison, Ph.D.
Kenneth M. Brinkhous, M.D.
Harold W. Brown, M.D.
Heinrich G. Brugsch, M.D.
Gerald Burke, M.D.
Philip J. Burke, M.D.
Robert P. Burns, M.D.

John R. Calverley, M.D.
John Canary, M.D.
Craig J. Canfield, M.D.
Paul P. Carbone, M.D.
Denis Cavanagh, M.D.
M.H. Charlton, M.D.
Maynard B. Chenoweth, M.D.
Nicholas L. Christy, M.D.
Harold O. Closson, M.D.
David F. Clyde, M.D., Ph.D.
Jay D. Coffman, M.D.
Irvin M. Cohen, M.D.
Jonathan O. Cole, M.D.
Jerome W. Conn, M.D.
Julius M. Coon, M.D., Ph.D.
Herbert L. Cooper, M.D.
George C. Cotzias, M.D.
Henry G. Cramblett, M.D.
William H. Crosby, M.D.
J. Richard Crout, M.D.
*John J. Curry, M.D.

Donald J. Dalessio, M.D.
Willy H. Dam, M.D.
*Norman A. David, M.D.
Paul T. Davidson, M.D.
Edward H. Davis, M.D.
John M. Davis, M.D.
Russell DeJong, M.D.
Thomas J. DeKornfeld, M.D.
Francesco del Greco, M.D.
Herman C.B. Denber, M.D.
Daniel Deykin, M.D.
Seymour Diamond, M.D.
Alberto Di Mascio, Ph.D.
Joseph F. Dingman, M.D.
John W. Ditzler, M.D.
Malin R. Dollinger, M.D.
David A. Dolowitz, M.D.
Edward F. Domino, M.D.
Alan K. Done, M.D.
*Harry F. Dowling, M.D.
Leonard S. Dreifus, M.D.
Harriet Dustan, M.D.

Charles E. Edwards, M.D.
Joel Elkes, M.D.
Philip P. Ellis, M.D.
Rose Ruth Ellison, M.D.
Mark Entman, M.D.
Stephen E. Epstein, M.D.

*Former member of Council on Drugs

William L. Epstein, M.D.
Audrey E. Evans, M.D.

Paul Fasal, M.D.
Samuel Feinberg, M.D.
Harry A. Feldman, M.D.
Gerald Fenichel, M.D.
L.S. Filer, Jr., M.D.
S.K. Fineberg, M.D.
Max Fink, M.D.
Maxwell Finland, M.D.
Frank A. Finnerty, Jr., M.D.
Delbert A. Fisher, M.D.
Thomas B. Fitzpatrick, M.D.
Anthony P. Fletcher, M.D.
Francis F. Foldes, M.D.
Noble O. Fowler, M.D.
Daniel X. Freedman, M.D.
*Edward D. Freis, M.D.
Walter J. Friedlander, M.D.
Arnold P. Friedman, M.D.
Dale G. Friend, M.D.

Donald M. Gallant, M.D.
Ronald B. George, M.D.
Samuel Gershon, M.D.
Ray W. Gifford, Jr., M.D.
Aaron J. Gissen, M.D.
Gilbert H. Glaser, M.D.
Louis Gluck, M.D.
Marian Goble, M.D.
Leon I. Goldberg, M.D., Ph.D.
Douglas Goldman, M.D.
Joseph Goldman, M.D.
Grace A. Goldsmith, M.D.
Franz Goldstein, M.D.
Raymond H. Goodale, M.D.
David J. Goode, M.D.
Edgar S. Gordon, M.D.
W. Morton Grant, M.D.
Jared Grantham, M.D.
*William C. Grater, M.D.
J.S. Gravenstein, M.D.
Norton J. Greenberger, M.D.
*Theodore H. Greiner, M.D.
Raymond F. Grenfell, M.D.
David Grob, M.D.
Morton Grossman, M.D.

Philip D. Hansten, Ph.D.
Paul V. Harper, M.D.
John Harris, M.D.
M. Coleman Harris, M.D.
Donald C. Harrison, M.D.
James B. Hartney, M.D.
William H. Havener, M.D.
Henry O. Heinemann, M.D.
H.F. Henderson, M.D.
Lowell L. Henderson, M.D.
James Henry, M.D.
Victor Herbert, M.D.
Paul Hoeprich, M.D.
Leo E. Hollister, M.D.
*William J. Hossley, M.D.
Frank M. Howard, Jr., M.D.
*John M. Howard, M.D.
Charles Huguley, Jr., M.D.
Daniel A. Hussar, Ph.D.

Sidney H. Ingbar, M.D.
Franz J. Ingelfinger, M.D.

Jay Jacoby, M.D.
Ralph F. Jacox, M.D.
Murray E. Jarvik, M.D., Ph.D.
Ernest Jawetz, M.D., Ph.D.
J.E. Jelinek, M.D.
Hershel Jick, M.D.
Richard J. Johns, M.D.
Joseph E. Johnson, III, M.D.

Sherwin A. Kabins, M.D.
Werner Kalow, M.D.
Naomi M. Kanof, M.D.
Kenneth Kaplan, M.D.
Samuel Kaplan, M.D.
John E. Kasik, M.D., Ph.D.
Irving Kass, M.D.
Donald G. Kassebaum, M.D.
Harry Irving Katz, M.D.
Ronald L. Katz, M.D.
Sol Katz, M.D.
Arthur S. Keats, M.D.
John H. Killough, M.D., Ph.D.
William M. M. Kirby, M.D.
*Joseph B. Kirsner, M.D., Ph.D.
Harold L. Klawans, Jr., M.D.
Stuart A. Kleit, M.D.
Albert M. Kligman, M.D., Ph.D.
George Koelle, M.D., Ph.D.
M. Glenn Koenig, M.D.
David Kritchevsky, Ph.D.
Donald Krogstad, M.D.
Leslie A. Kuhn, M.D.
Calvin M. Kunin, M.D.

Bert N. La Du, M.D., Ph.D.
Richard Landau, M.D.
Elliot C. Lasser, M.D.
Robert S. Lees, M.D.
Carroll M. Leevy, M.D.
Louis Leiter, M.D.

John M. Leonard, M.D.
*Irving H. Leopold, M.D.
Simmons Lessell, M.D.
William Lester, M.D.
Irving M. Levine, M.D.
Samuel A. Levinson, M.D., Ph.D.
Robert I. Levy, M.D.
George B. Lewis, Jr., M.D.
Richard Lewis, M.D.
Theodore W. Lieberman, M.D.
Harry W. Linde, Ph.D.
J.P. Long, Ph.D.
Francis C. Lowell, M.D.
Peere C. Lund, M.D.

Howard I. Maibach, M.D.
Gerald L. Mandell, M.D.
Leslie B. Mann, M.D.
Alexander Marble, M.D.
Frank I. Marcus, M.D.
Lester C. Mark, M.D.
William R. Martin, M.D.
Richard L. Masland, M.D.
Dean T. Mason, M.D.
J. Kenneth McClatch, Ph.D.
Fletcher McDowell, M.D.
James C. Melby, M.D.
Albert I. Mendeloff, M.D.
Sidney Merlis, M.D.
L.H. Miller, M.D.
Russell R. Miller, Ph.D.
William F. Miller, M.D.
J. Gordon Millichap, M.D.
Daniel R. Mishell, Jr., M.D.
Roger S. Mitchell, M.D.
James Monroe, M.D.
Max M. Montgomery, M.D.
Daniel C. Moore, M.D.
Neil C. Moran, M.D.
Karl M. Morgenstein, M.D.
Howard F. Morrelli, M.D.
J.D. Morrison, M.D.
*John G. Morrison, M.D.
*Robert H. Moser, M.D.
James W. Mosley, M.D.
Harry Most, M.D.
John H. Moyer, M.D.
John F. Mueller, M.D.
Sheila M. Muldoon, M.D.

Alexander S. Nadas, M.D.
Franklin A. Neva, M.D.
S.H. Ngai, M.D.
Mark Nickerson, M.D., Ph.D.
Albert Norris, M.D.

Robert A. O'Reilly, M.D.

Ernest W. Page, M.D.
Frank Parker, M.D.
Madhukar A. Pathak, Ph.D.
*C. Alvin Paulsen, M.D.
James Paximos, R.Ph.
Eugene S. Paykel, M.D.
Rufus F. Payne, M.D.
Gustavus A. Peters, M.D.
Donald Pinkel, M.D.
Carl Pochedly, M.D.
Edwin O. Polish, M.D.
Judith G. Pool, Ph.D.
E.L. Posey, Jr., M.D.
Robin D. Powell, M.D.
Phillip Pratt, M.D.
Edward Press, M.D.
Thaddeus Prout, M.D.
Majorie M. Pyle, M.D.

Armand J. Quick, M.D.

Morton I. Rapoport, M.D.
Richard J. Reitemeier, M.D.
Clayton Rich, M.D.
Karl Rickels, M.D.
J. Alfred Rider, M.D., Ph.D.
John F. Roach, M.D.
Laurence L. Robbins, M.D.
Donald S. Robinson, M.D.
*Daniel M. Rogers, M.D.
Edward C. Rosenow, III, M.D.
Thomas G. Rudd, M.D.
Richard Rudders, M.D.
John Ruedy, M.D.

Max S. Sadove, M.D.
Jay Sanford, M.D.
Howerde E. Sauberlich, Ph.D.
Irwin J. Schatz, M.D.
Maurice Schiff, M.D.
Joseph J. Schildkraut, M.D.
Robert F. Schilling, M.D
Frank R. Schmid, M.D.
Paul H. Schreibman, M.D.
Myron G. Schultz, M.D., D.V.M.
George A. Schumacher, M.D.
Robert S. Schwab, M.D.
John H. Seabury, M.D.
Marvin L. Sears, M.D.
William H. Sebrell, Jr., M.D.
Paul M. Seebohm, M.D.
Harry L. Segal, M.D.
Sarah H. Sell, M.D.

W705088

Seth K. Sharpless, Ph.D.
Edward B. Shaw, M.D.
C. Norman Shealy, M.D.
Charles C. Shepard, M.D.
Lawrence Sherman, M.D.
William B. Sherman, M.D.
*Sol Sherry, M.D.
Maurice E. Shils, M.D.
*Harry C. Shirkey, M.D.
David Shoch, M.D.
Howard B. Shookhoff, M.D.
Jonas A. Shulman, M.D.
*F.A. Simeone, M.D.
Stanley Slater, M.D.
Robert E. Slayton, M.D.
David E. Smith, M.D.
*Donn L. Smith, M.D., Ph.D.
Edgar B. Smith, M.D.
J. Ned Smith, M.D.
Morton Smith, M.D.
N. Ty Smith, M.D.
Konrad H. Soergel, M.D.
J. Kenneth Sokol, M.D.
Lawrence M. Solomon, M.D.
William N. Spellacy, M.D.
Herta Spencer, M.D.
Bertram Sprofkin, M.D.
Harold C. Standiford, M.D.
John E. Steinhaus, M.D.
Robert K. Stoelting, M.D.
Marion B. Sulzberger, M.D.
Abraham Sunshine, M.D.

Robert W. Talley, M.D.
Peter A. Theodos, M.D.
Richard A. Theye, M.D.
Jared R. Tinklenberg, M.D.
Donald P. Todd, M.D.
Ross M. Tucker, M.D.
John P. Utz, M.D.

Parker Vanamee, M.D.
Leroy D. Vandam, M.D.
Eugene Van Scott, M.D.
Robert W. Virtue, M.D., Ph.D.
Perry P. Volpitto, M.D.

Burton A. Waisbren, M.D.
Alfred J. Wall, M.D.
Shik-Chun Wang, M.D.
Albert J. Wasserman, M.D.
Irwin M. Weiner, M.D.
Ira Weinstein, Ph.D.
Louis Weinstein, M.D., Ph.D.
Sidney C. Werner, M.D.
Stanford Wessler, M.D.
Frederic B. Westervelt, Jr., M.D.
Jean K. Weston, M.D.
June M. Whaun, M.D.
Frances K. Widmann, M.D.
Joseph A. Wilber, M.D.
Park W. Willis, III, M.D.
Charles S. Winans, M.D.
*Maxwell M. Wintrobe, M.D., Ph.D.
Heinz J. Wittig, M.D.
Robert L. Wolf, M.D.
Donald E. Wood, M.D.
Francis Wood, Jr., M.D.
J. Edwin Wood, M.D.
*Lauren A. Woods, M.D., Ph.D.
Theodore E. Woodward, M.D.
Irving S. Wright, M.D.
James B. Wyngaarden, M.D.

Sumner J. Yaffe, M.D.
Melvin D. Yahr, M.D.

Hyman J. Zimmerman, M.D.
Morton Ziskind, M.D.

GENERAL INFORMATION

SCOPE AND ORGANIZATION OF EVALUATIONS

As with the first (1971) edition of *AMA Drug Evaluations*, this second edition has been organized into chapters and sections that are based, insofar as possible, on therapeutic classifications. Each chapter contains an introductory statement that discusses the overall therapeutic category, followed by brief evaluative monographs for individual drugs in the class. Drugs selected for individual evaluations include virtually all therapeutic agents in the official compendia, *United States Pharmacopeia* (U.S.P.) and *National Formulary* (N.F.); the drugs, including mixtures, most commonly prescribed or administered by physicians in the United States; and single-entity preparations introduced during the past ten years. In addition, other drugs have been selected for evaluative statements if they were judged to be of particular importance to complete a discussion of a therapeutic category. Other nationally distributed preparations that are not individually evaluated are listed and indexed to give information about their therapeutic category and availability.

All chapters have been revised and updated from the first edition, and some of them have also been reorganized (and occasionally renamed). Further, several changes in style have been made. For example, more conventional prose has replaced the telegraphic style in the bodies of the evaluations.

To reduce redundancy, the New Drugs Section has been omitted. Necessary information that would have appeared in this section has been incorporated into appropriate chapters.

In the previous edition, some combinations were singled out for discussion on the basis of frequent use, followed by a listing of similar preparations. In this edition, when several mixtures of analogous composition are considered, usually one evaluative discussion applicable to the group precedes the list and specific dosage information may be omitted. In these instances, the prescriber should usually be able to extrapolate a dose from information given elsewhere for the individual ingredients. To facilitate the latter procedure, the quantitative formulas of active ingredients are customarily given for all mixtures in a list.

Finally, structural formulas are provided for most single-entity drugs. In the previous edition, these were given only for drugs in the New Drugs Section.

The evaluative or interpretive information in the book, particularly on controversial matters, may disagree with opinions from other sources. Statements are based on the convergent trend of information available from scientific literature, unpublished data, and the advice of consultants and review committees of the former Council on Drugs. Reportorial information has been condensed and represents that considered most essential to the physician in his choice and use of the drugs. Accordingly, such information as rare, minor, or unconfirmed reactions, precautions that relate to obvious or remote situations, and unusual or speculative uses of a drug are sometimes omitted. For other details, for basic data, and even for varying points of view, the physician is encouraged to consult and compare the many other sources of information on drugs: journal articles, standard textbooks, official compendia, manufacturers' labeling, prominent bulletins and periodicals on drugs and therpeutics, and symposia.

The mere inclusion of a particular drug in *AMA Drug Evaluations* does not imply endorsement by the American Medical Association, nor should it be a criterion for approving the use of that drug in any institution or for any other purpose. The principal purpose of this volume is to provide the medical profession with an evaluation of selected drugs based on the available evidence. Since an evaluation may be favorable, unfavorable, or a combination of both, depending upon the merits

of the preparation, the physician should determine in each individual case the relevancy of the limitations, adverse reactions, contraindications, or precautions given in the text.

An effort has been made to list all nationally distributed products that are dispensed exclusively or principally by prescription. Many drugs are listed or described, of course, that *can* be sold without prescription, but ordinarily their brands are not listed if these are principally advertised for over-the-counter sale.

Inclusion of drugs has been based upon the most recent information available, and in a project of this scope, it is inevitable that some preparations have been inadvertently omitted; such omissions are regretted. In part because of the current regulatory activities of the Food and Drug Administration, some preparations probably will no longer be marketed when this book appears in print. Deletion of products and updating of other information has continued as near as possible to the time of publication. In addition, efforts have been made to include drugs newly introduced to the market as near the publication date as practicable.

Published research and reports of clinical experience often are limited to the products of one or only a few manufacturers. Fully adequate clinical comparisons of all brands of the same drug are rarely available. For this reason a valid comparison of brands has rarely been possible and seldom attempted. However, the reader should bear in mind that not all brands and generically labeled forms of the same drug are necessarily therapeutically equivalent. Differences in coatings, binders, particle size, ease of dissolution, purity of ingredients, and other factors can lead to variations in absorption and biological availability of a drug. Also, the degree of consistency from batch to batch will depend upon the manufacturer's quality control procedures. How frequently really significant differences occur in various brands of alleged equivalent products is difficult to estimate. Nevertheless, the fact that they sometimes do occur should be recognized by the prescribing physician in appraising the information in this book and in writing prescriptions that may be filled with the product of any of several manufacturers.

DOSAGE RECOMMENDATIONS

Usual Doses: The dosage information presented falls within the ranges given in official compendia, those suggested by one or more manufacturers, or those considered appropriate by other authorities. For many drugs, however, the correct dose will depend upon the size, age, and condition of the patient; his response to treatment; his sensitivity or tolerance; and the possible synergistic or antagonistic effect of concomitant medication. The epitome of dosage is to weigh expected benefits against risks. If an illness can be tolerated for a while, establishment of the dose should be cautious and exploratory unless a wide margin of safety prevails. However, if immediate disaster threatens from therapeutic failure, treatment should be aggressive. In either situation the physician should remember that improper dosage with the proper drug is probably as common a cause of failure in therapy as the use of an improper drug.

Accordingly, many usual doses are given as ranges. Even the limits of these ranges are seldom inviolable. The upper limits stated for most ranges, however, do suggest that larger amounts either may increase the risks of toxicity beyond what is ordinarily acceptable or may fail to provide additional therapeutic effect in significant degree; similarly, the lower limits often indicate that smaller doses could not be expected to provide full therapeutic effects for most patients.

In the first edition, dosage information was frequently excluded for some drugs when their use was questioned or not recommended; this practice has largely been discontinued. Although a collateral statement may make it clear that no dosage is suggested on the basis of the evaluation of a particular drug, the dose given in the manufacturer's labeling or that usually employed will ordinarily be included as an item of information.

Dosage in Children and Infants: Many problems attend the choice of drugs and determination of doses in pediatric patients. Whether children and infants will respond to a particular drug in the same manner as adults can only be determined through research and experience, and their responses to many drugs are known to be different. Many of the metabolic mechanisms of premature and newborn infants are not fully developed, and a lethal blood concentration of a drug may accumulate if a dosage regimen is based upon the common criteria for conversion from the adult regimen. In fact, the infant's response to drugs during the first weeks of life probably varies more, overall, from that of a one-year-old

此为试读,需要完整PDF请访问: www.ertongbook.com

than the response of a one-year-old varies from that of an adult. This consideration should be borne in mind not only in treating the newborn but also in treating an expectant mother near the time of delivery.

A common practice in the determination of a child's dose has been to give some fraction of an adult dose, using the age of the patient as a rough guide. Because of the great variation in size among children of the same age, this method can be satisfactory only if there is a wide margin of safety. Usually it is better to consider the dose for *all* patients in terms of mg/kg of body weight or to establish the pediatric dose as a fraction proportionate to the weight of the child in comparison with that of an average adult. However, when it is valid to assume that a child will respond to a drug in the same way as an adult will, the best conversion of dosage is one based on body surface area.

Statements of pediatric doses for individual drugs in this book follow the method of conversion which has been developed generally for that particular drug. Thus, some conversions are based upon age, some upon weight, and some upon body surface area. If adequate dosage information based on actual pediatric use is either nonexistent or not readily available, suggested dosage guidelines sometimes are furnished even though it is recognized that more data would be desirable; at times, lack of data has been specifically acknowledged. When dosage information is inadequate, it is suggested that the body surface area be taken as the criterion—*provided no evidence indicates that a child will react to the drug differently from an adult.* In the clinic or office, repeated calculations of these conversions may be too forbidding to be practical. For convenience, a simple table is provided on the inside back cover of this book.

TIMED-RELEASE PREPARATIONS

Drugs that are rapidly metabolized or excreted, but whose effects must be maintained steadily for prolonged periods, can present serious inconveniences because of the need for repeated administration at short intervals; this is especially true with injectable drugs. Accordingly, pharmaceutical formulations have been developed to provide the release of active ingredients for relatively long periods.

In parenteral preparations, sustained release is achieved by using relatively insoluble salts or esters of the active drug or a special vehicle from which the drug is slowly absorbed. It is doubtful that such techniques can ever deliver a dosage that is as precisely controlled as that with intravenous infusion. Nevertheless, when some latitude is permissible in the range of the safe and effective blood level, substitution of sustained-release preparations for repeated injections may provide a somewhat more uniform blood concentration, and this type of preparation is certainly more convenient. Depot preparations of penicillin provide an outstanding example of a useful sustained-release formulation. In some serious infections, of course, continuous intravenous infusion is still needed. Insulin is another excellent example of a drug which, even though dosage requirements are critical, has been prepared in sustained-release forms that have greatly simplified the management of diabetes. Reasonably satisfactory formulations also are available for various corticosteroids, androgens, estrogens, and a few other agents.

The need for sustained-release formulations for oral medications is less apparent. Nevertheless, many have been prepared, and some can provide a certain convenience over more frequent administration—provided they actually deliver the medication in the even, measured manner that is intended. The general term "timed-release" is the one adopted by the *National Formulary* to describe these oral preparations, and the practice is followed in this text. The term includes formulations variously known as "delayed-action," "extended-release," "prolonged-action," "sustained-action," or "repeat-action," but does not include tablets specifically identified as "enteric-coated."

When a physician chooses a timed-release preparation for the convenience of his patient, he should bear in mind that he is introducing one more potential variable into the predictable physiologic availability of the drug. These preparations are listed in this book to provide information on their availability; such listing does not imply endorsement. Actually, only a few have been evaluated for effectiveness, since data on which to base an evaluation of effectiveness are inadequate or are not available for most timed-release forms. In vitro tests designed to demonstrate product uniformity do not assure in vivo effectiveness. No precise product specifications have been established by the official compendia for timed-release preparations.

One type of timed-release preparation clearly to be condemned is that for drugs with a long

half-life after absorption. The half-lives of an increasing number of drugs are now being determined, and, when known, this property should be considered in ascertaining the dosage regimen of a drug. For example, results of recent studies have demonstrated that some drugs (eg, diphenylhydantoin) are equally effective whether the total daily amount is given in a single dose or in divided doses. Little logic can be seen for use of a timed-release form of a phenothiazine, phenobarbital, or diphenylhydantoin. And timed-release preparations have actually been formulated for such drugs as digitalis and thyroid. Such practice represents pure nonsense.

"LABEL AS SUCH" AND RELATED MATTERS

In traditional pharmaceutic practice, the name of a prescription drug does not appear on the label of the package that the pharmacist furnishes the patient. However, the physician may instruct the pharmacist to put information on the label by including on the prescription the direction, "Label as such," "L.A.S.," or merely "Label." For several years, the American Medical Association has encouraged physicians to follow this practice and to make an exception only when such disclosure would be detrimental to the welfare of the patient. The reasons for believing prescription drugs should be labeled with their names and strength have been set forth repeatedly: (1) The patient has the right to be informed about his illness and the medications prescribed. (2) In emergency situations, such as accidental poisoning, overdosage, or attempted suicide, immediate identification of a prescription drug from the label may be lifesaving. (3) The information is valuable when the patient changes physicians, moves to another locality, or contacts the prescribing physician at a time when his records are not readily available. (4) The information on the label is of value in group practices in which the patient may not always have the same attending physician. (5) It is advisable that patients with allergies know what is being prescribed. (6) This specific information on the label helps to prevent mix-ups between two or more drugs being taken concurrently, or between medications being taken by different members of the family. (7) If it becomes necessary to issue a warning against the use of a particular drug, the name on the label serves as a danger signal to those who have been given prescriptions for the product.

The reasons that have been advanced opposing the labeling of prescription drugs with the name and strength are far less persuasive than those just given for labeling. There are, of course, some occasions when such labeling is inadvisable for psychological or other reasons, but in these circumstances, the instruction can be omitted from the prescription.

A related matter involves that of refills. Restrictions on refills are controlled by law for certain narcotics and drugs subject to abuse (see the discussion on Department of Justice in the section on Official and Regulatory Agencies). However, it is advisable for the physician to designate the number of refills, if any, he wishes the patient to have and to prescribe only the number of doses usually required in any specific condition, since adjustments in dosage are often necessary to obtain the desired result in individual patients. Prescriptions may not legally be refilled without the physician's authorization. When this authorization is given in advance (on the prescription at the time of writing) the physician would be well advised to place some time limit on the authorization. The very fact that a drug is dispensed by prescription implies the need for professional control. Yet prescriptions with open-end authorization for refills, especially if marked "refill p.r.n." or "ad lib," remain valid indefinitely. It is not unusual for prescriptions to be refilled repeatedly for years after the prescriber has retired, moved away, or even has long been dead. However, in some circumstances a large-quantity prescription *is* appropriate. If a patient is expected to take a drug for a prolonged period, if his correct dosage has been established, and if he can be trusted to follow instructions properly, a prescription for a large quantity will often be more economical than repeated prescriptions or refills for small quantities.

USE OF LABORATORY STUDIES TO MONITOR ADVERSE REACTIONS

Although nearly all drugs have known and reasonably predictable toxicity in excessive dosage, most are given in doses calculated to be in the safe range. In order to achieve therapeutic effects, however, some drugs must be given in amounts that approach the toxic range or that may even reach it for some patients. Accordingly, appropriate observations are needed to detect the approach or onset of toxicity and to reverse it or at least avoid its

progression to intolerable proportions.

Numerous vital organs, such as the hematopoietic system, the liver, and the kidneys, can be adversely affected by drugs. When toxic reactions occur gradually, or when their overt manifestations appear slowly, appropriate laboratory testing may reveal their presence earlier than would be detected by the appearance of symptoms. On the other hand, much routine laboratory testing that is done in the absence of symptoms of a reaction is essentially wasteful and may lead to a false sense of security. This condition prevails when efforts are made to anticipate types of reactions that occur precipitously and cause overt signs and symptoms.

The problem is to know what possible reactions to what drugs are likely to be detected by laboratory tests in asymptomatic patients. When test results are abnormal, especially if only to a mild degree, their interpretation can be difficult.

If a drug must be given that is known to cause such effects as leukopenia, anemia, cholestasis, hepatocellular damage, or nephropathy in a substantial number of recipients, it usually is wise to perform some appropriate baseline tests initially for later comparison should the need arise. Tests should be repeated, of course, if signs or symptoms of the disorder occur during treatment. The need to repeat them at intervals during treatment in the absence of symptoms largely depends upon the likelihood that a serious reaction may develop without overt manifestations.

Clearly, an antileukemic drug requires frequent blood cell counts for safe administration; it will cause marrow depression in all patients and this will reach toxic proportions if too much is given. Periodic counts at arbitrarily chosen intervals is less beneficial with agents that occasionally cause a precipitous agranulocytosis as a hypersensitivity reaction. It is true that the prognosis is improved if one is so lucky as to make the diagnosis by laboratory means before any infection begins. However, in view of the prodigious number of routine hemograms that are performed and the rarity of the diagnosis by such means, the chance of benefiting any given patient is remote. There is no intent in this discussion to advise *against* such tests when a drug that can cause allergic agranulocytosis is given. However, performing them is more a matter of discretion than compulsion, and it is proper to consider the patient's convenience and economic status in making the decision. One thing can be said with confidence: careful observation for signs of sudden infection is a far more important precaution. If such infection occurs, immediate laboratory evaluation is then indicated.

Drugs that cause megaloblastic anemia with prolonged use, such as some anticonvulsants, also warrant monitoring with occasional routine blood studies. The reaction progresses gradually, may be detected well in advance of symptoms, and can be controlled by proper management. This precaution is particularly significant during pregnancy, because megaloblastic anemia may damage the fetus if allowed to progress.

Drug-induced liver disease of an allergic or hypersensitivity type also presents problems regarding the best means of early detection. Monitoring treatment with laboratory tests would be valuable with any drug known to produce gradual, subtle, and serious hepatotoxic injury. Fortunately, however, few modern drugs have such potentiality. Nevertheless, many can produce liver damage, without apparent relation to dosage, in hypersensitive patients. Cholestatic reactions are typically less dangerous than the hepatocellular type, but either must be regarded as potentially serious. (A possible exception is the mild and apparently benign cholestasis that seems to be a direct, dose-related effect of various synthetic androgens.)

It would be advantageous if a hepatic reaction could be detected at its earliest development so that administration of the drug could be stopped. Unfortunately, the serious hypersensitivity reactions tend to develop precipitously. Documentation that such reactions can be diagnosed in any substantial number of patients with routine liver function tests before symptoms develop is scanty. Although such diagnoses might occasionally be made, minor abnormalities are often difficult to assess in terms of cause or importance, and striking ones would seldom precede some symptoms by a significant length of time. By far the most important precaution is to observe the patient for such symptoms as malaise, abdominal discomfort, anorexia, dark urine, and jaundice and to perform proper laboratory studies if these reactions occur.

Occasionally, nephrotoxicity from a drug can occur with dramatic suddenness. Usually, however, drugs that can cause kidney damage are more likely to produce it subtly and well in advance of symptoms than are most of those that cause blood, marrow, or liver damage that is detectable in advance. When such a drug is given

for prolonged periods, occasional routine laboratory tests, especially urinalyses, may provide a useful means of early detection.

In preparing this book, the usual custom has been to warn of reactions known or thought to be possible, but not to attempt too detailed advice in how to observe for them. Suggestions for routine, periodic laboratory testing are ordinarily reserved for situations when the tests seem to provide clear-cut value. More commonly, the discussions rely upon the physician's discretion and judgment in determining the details of monitoring a patient's treatment with a drug. Even when advice to perform laboratory tests has been indicated, it seldom has been practical to specify frequency. It is unlikely that a precise routine could be outlined that would be ideal for all patients in all situations.

The most important information that a physician can have about adverse reactions to drugs is advice about which ones to expect, either commonly or uncommonly. It is worth repeating, however, that when damage to an important organ is within the spectrum of known reactions to a drug, appropriate baseline observations before treatment may later prove valuable for comparison.

USE OF DRUGS DURING PREGNANCY

In view of the ease with which substances in the mother's bloodstream pass into the fetus, what was once thought of as the placental barrier would more appropriately be called the "placental sieve." In giving a drug to a pregnant woman, the physician must be aware that he may be simultaneously exposing the developing fetus to a potentially toxic substance. Accordingly, special caution and judgment are mandatory during pregnancy. Of course, it is sometimes necessary to administer drugs to pregnant women, since complications of pregnancy must often be treated with drugs, and serious illness can occur coincidentally with pregnancy.

The fact that a drug has been given during pregnancy without recognized untoward effects is not necessarily proof that it will be safe in all cases. Nevertheless, the fact that a drug has a long history of use without reported fetal damage at least *tends* to place it in higher favor for use in pregnant women than a newer similar drug or one that has been associated with reported injury.

Although studies to determine fetal toxicity in animals are now routinely included in the investigation of new drugs, no technique has been developed that can be translated reliably into expected experience in humans.

In preparing this book, an effort has been made to include information on known or reasonably assumed hazards if the drugs are given during pregnancy. With many drugs, however, and particularly with most new ones, little or no information is available on use in humans. Accordingly, it often has been necessary to resort to some form of warning that a drug should be given only if the expected benefits exceed the risks. This warning admittedly is not too helpful when inadequate data exist to know that risks, if any, are present. It merely can serve as a reminder that unless a systemically absorbed drug has been clearly proved safe for use during pregnancy, it should be given only if an overwhelming need exists, and then the possibility of fetal toxicity should be acknowledged.

CAUTION IN USE OF "POTENT" DRUGS

The administration of virtually all effective drugs is attended by at least some degree of risk that must be weighed against the expected benefits. With drugs of certain classes, however, at least three dangers are involved that can be partly minimized if they are given sufficient consideration. These are the dangers of physical dependence, suicidal ingestion, and impairment of mental or physical performance. A fourth danger might be added, but it pertains to practically any potent drug that may be prescribed for administration at home: the possibility of accidental poisoning. Although the physician's control over this hazard is often limited, he can at least caution patients, when appropriate, against improvising in their dosage, against carelessness in reading labels, and against leaving medicines accessible to small children.

Physical Dependence and Related Problems: The potential for physical dependence, including characteristic tolerance and liability to produce withdrawal symptoms, with use of narcotic analgesics is probably the most widely understood. On the other hand, although dependence on sedative-hypnotic agents is by no means a recently discovered phenomenon, its distinctive features are less commonly understood. Usual hypnotic doses do not produce significant physical dependence although some psychic habituation may occur.

However, when daily intake is gradually increased, marked physical dependence and tolerance to the hypnotic effect develop, and the individual is intoxicated by the drug. In contrast to the narcotics, the tolerance is not complete; it develops to the hypnotic effect but not to the lethal toxic effect. Thus, accidental fatal overdosage is common. Abrupt withdrawal of the drug results in a severe withdrawal illness that progresses to psychosis after a few days and often includes dangerous convulsions resembling grand mal. The illness is similar to alcoholic delirium tremens, which also is a withdrawal illness, but convulsions are even more common after barbiturates. This abstinence syndrome is much more dangerous to life than the one from narcotics.

Virtually any agent whose primary pharmacologic action is hypnotic or sedative, including antianxiety agents, is potentially capable of producing physical dependence similar to that with the barbiturates if daily intake is substantially above ordinary therapeutic doses.

Various central nervous system stimulants are also abused because of their euphoriant action (eg, cocaine, amphetamine and related agents, particularly methamphetamine). The amphetamines can cause prolonged wakefulness, bizarre ideation and behavior, and even hallucinations with large doses. Withdrawal from a regimen of abuse does not cause a syndrome resembling that from either narcotics or hypnotics. Without question, however, withdrawal after prolonged high dosage can leave the individual fatigued and depressed.

Discussion of the management of drug-dependent individuals is beyond the scope of this book. For current medical opinion related to treating withdrawal syndromes, care of the drug-dependent patient, types of patients who abuse drugs, and prevention of drug abuse, the reader is referred to *Drug Dependence—A Guide for Physicians*, published by the AMA, as well as the following articles: Narcotics and medical practice: Medical use of morphine and morphine-like drugs and management of persons dependent on them, AMA Council on Mental Health (*JAMA* 218:578-583, 1971); Treatment of morphine-type dependence by withdrawal methods, AMA Council on Mental Health (*JAMA* 219:1611-1615, 1972); and Oral methadone maintenance techniques in the management of morphine-type dependence, AMA Council on Mental Health (*JAMA* 219:1618-1619, 1972).

Suicide With Prescribed Drugs: Efforts at suicide have been made with most common agents. However, because of the patient population involved, psychotropic drugs tend to be especially popular for suicidal attempts, particularly if the term is used broadly to include hypnotics. Suicidal inclination is a common symptom of psychiatric depression and often is greatest when the depression has partly but incompletely subsided. Moreover, antidepressant drugs themselves can be used for suicidal purposes.

Although the physician faces practical and legal limits in his ability to preclude suicide, he can, as circumstances warrant, limit the size of prescriptions, select a relatively nontoxic drug if possible, recommend hospitalization, and advise family members about needed precautions.

Drugs and Accidents: An array of drug effects can diminish the patient's ability to perform his customary tasks, for example, drowsiness, impaired judgment, decreased coordination, blurred vision, as well as more precipitous reactions like hypoglycemia, postural hypotension, and lowered convulsive threshold. In prescribing drugs that may impair such functions as alertness, judgment, or coordination, a physician is wise to caution patients about the manner in which their activities may be affected. Drugs and circumstances vary too greatly to attempt to make any comprehensive statement on which activities should be forbidden, which should be approached with caution, and which perhaps should be temporarily avoided pending a trial with the drug. A physician must evaluate the individual situation and should advise his patients appropriately of possible hazards. Medicolegal considerations may make it prudent to record the advice in his records.

DRUG INTERACTIONS

Many patients require multiple drug therapy, and in recent years there has been an increasing awareness of the importance of drug interactions. Studies in laboratory animals have shown that many drugs may increase or decrease the efficacy or toxicity of other agents, but considerably less is known about drug interactions in man.

Following is a brief review of the mechanisms of some interactions that are probably of clinical significance. Not included in this review are direct in vitro physicochemical interactions or

familiar additive, synergistic, or antagonistic effects. Since there are some important interactions for which the mechanism is at present unknown, this discussion cannot be comprehensive.

Interactions Involving Gastrointestinal Absorption of Drugs and Other Agents

Binding: Drug absorption may be decreased by the formation of inactive or insoluble complexes in the intestinal tract. Antacids containing calcium, magnesium, or aluminum interfere with the absorption of tetracyclines due to the chelating action of the antibiotic. Ferrous sulfate also interferes with the absorption of tetracyclines, but the mechanism is not clearly understood. Formation of insoluble complexes may explain the decreased response to iron therapy that has been observed in patients receiving magnesium trisilicate. Cholestyramine resin interferes with the absorption of levothyroxine sodium, liothyronine sodium, and warfarin by intestinal binding. This ion exchange resin also may form complexes with other agents (thiazide diuretics, phenylbutazone) but this has not been clearly established. The absorption of lincomycin is reduced if kaolin-pectin combinations are administered concomitantly or up to two hours after the antibiotic; this interaction may be caused by the adsorbent effect of the antidiarrheal agents.

pH: Most orally administered drugs cross the membranes of the stomach and small intestine by passive diffusion. Since these cell membranes consist of a lipid-protein structure, drugs are more readily absorbed in their nonionized (lipid-soluble) state. Theoretically, changes in the gastric pH could alter the ionization of drugs, thus affecting their absorption. For example, it has been suggested that antacids may interfere with the absorption of acidic agents by increasing the proportion of ionized drug. The clinical significance of this potential interaction has not been established, and, in view of the large surface area involved in drug absorption, it is unlikely that gastric pH is an important factor in the rate of absorption of most drugs. However, results of one study have demonstrated that a low gastric pH is necessary for complete dissolution of tetracycline capsules; sodium bicarbonate decreases dissolution and, therefore, reduces absorption of this antibiotic.

Motility: It has been suggested that anticholinergic drugs and ganglionic blocking agents may delay drug absorption by reducing gastrointestinal motility. Despite the widespread use of drugs with anticholinergic properties, this theoretical interaction has apparently not been studied in man.

Phenobarbital reduces plasma levels (and possibly the therapeutic effect) of griseofulvin by impairing its absorption from the gastrointestinal tract. One proposed explanation for this effect is that phenobarbital stimulates the secretion of bile which, in turn, stimulates peristalsis. The increase in motility would decrease the transit time in the upper portion of the intestinal tract where griseofulvin is absorbed most efficiently.

Inhibition of Gastrointestinal Enzymes: Diphenylhydantoin inhibits the activity of the intestinal conjugase enzyme involved in the conversion of polyglutamates to readily absorbed monoglutamates. This agent can, therefore, reduce the absorption of folic acid and may cause mild megaloblastic anemia in some patients.

Alterations in Intestinal Flora: The prothrombin time after administration of coumarin anticoagulants is increased by chloramphenicol, neomycin, tetracycline, and possibly by other antibiotics. The mechanism of this interaction has not been established but may involve inhibition of vitamin K synthesis by intestinal bacteria. Other suggested mechanisms include inhibition of hepatic microsomal enzymes (chloramphenicol) and impairment of prothrombin utilization (tetracycline).

Interactions involving gastrointestinal absorption are summarized in Table 1.

Interactions Affecting Distribution of Drugs (Protein Binding)

After absorption, most drugs become reversibly bound to plasma proteins, usually albumin. The extent of protein binding varies considerably. Some agents show a high affinity for albumin (eg, phenylbutazone, coumarin anticoagulants, and the highly bound sulfonamides: sulfadimethoxine [Madribon], sulfamethoxypyridazine [Midicel], sulfamoxole, and sulfisoxazole), whereas others are present largely in the free state (eg, antipyrine). The bound portion of the drug is biologically inactive, while the unbound portion is free to diffuse to receptor sites. Since the number of available binding sites is limited, the

此为试读,需要完整PDF请访问: www.ertongbook.com