Antiepileptic Drugs

Second Edition

Editors

Dixon M. Woodbury • J. Kiffin Penry • C. E. Pippenger

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Editors

Dixon M. Woodbury, Ph.D.
Professor of Pharmacology
Division of Neuropharmacology and Epileptology
University of Utah College of Medicine
Salt Lake City, Utah

J. Kiffin Penry, M.D.
Professor of Neurology
Bowman Gray School of Medicine
of Wake Forest University
Winston-Salem, North Carolina

C. E. Pippenger, Ph.D.
Associate Professor of Neuropharmacology
Columbia University College
of Physicians and Surgeons
New York, New York

Assistant Editor

B. J. Hessie
Rockville, Maryland

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Preface

When *Antiepileptic Drugs* was first published a decade ago, as a compilation of the available information concerning all aspects of drug therapy for the epilepsies, it was obvious that our knowledge of the mechanisms of action of antiepileptic drugs was incomplete and that the therapeutic application of the existing information was inadequate.

During the past 10 years, however, many of the gaps in our knowledge of the antiepileptic drugs have been filled and the clinical management of the epilepsies has improved. Many factors are responsible for these advances. Improved techniques of video monitoring and telemetered electroencephalography allowed better determination of the seizure type. Rapid technological developments in the quantification of antiepileptic drugs in biological fluids by gas-liquid chromatography, high-pressure liquid chromatography, and homogeneous enzyme immunoassay permitted the correlation of drug concentration with clinical response. With this information, it was then possible to establish the pharmacokinetic profiles of individual patients in various clinical situations.

Simultaneously with the clinical studies, basic research on the epilepsies provided new insights into the mechanisms that cause and regulate seizure activity in the central nervous system and into the ways that antiepileptic drugs alter these mechanisms. Such basic studies are exemplified by exploration of the role of neurotransmitters in the regulation of neuronal activity and investigation of ionic channels, the gating process, and ion transport across neuronal membranes.

Without a doubt, however, the key factor in the advances in our knowledge and use of the antiepileptic drugs is the dedicated efforts of investigators throughout the world to provide better care for patients with epilepsy. It is impossible to cite each individual who has contributed to these advances, but special recognition should be given to the National Institute of Neurological and Communicative Disorders and Stroke, the Epilepsy Foundation of America, the International League Against Epilepsy, and the organizers of the Workshops on the Determination of Antiepileptic Drugs in Body Fluids.

The aim of this second edition duplicates that of the original work, namely, to "present in a single source all of the recent advances in knowledge concerning the antiepileptic drugs as well as an in-depth review of basic pharmacologic data from both animals and man." With an up-to-date presentation of this information on both old and new drugs and the addition of current findings on the mechanisms of action of antiepileptic drugs, this new volume offers a thorough treatment of the pharmacological approach to the epilepsies.

Notwithstanding the recent advances mentioned above, the drug therapy of epilepsy is still wanting. It is our hope that this book will enhance our basic and clinical understanding of the antiepileptic drugs for the good of patients with epilepsy. We hope, too, that it will serve to stimulate future investigations in this field.

The Editors

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Contributors

AGOSTINO BARUZZI, M.D.
Neurological Clinic, University of Bologna School of Medicine, 40123 Bologna, Italy

DANIEL L. BIUS
Department of Pharmacology, Epilepsy and Anticonvulsant Drug Research Laboratory, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27514

HAROLD E. BOOKER, M.D.
Director, Neurology Service, Veterans Administration Central Office, Washington, D.C. 20420

LAURA BOSSI, M.D.
Department of Clinical Research, Synthelabo—L.E.R.S., 75013 Paris, France

JAMES J. CEREGHINO, M.D.
Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland 20205

TSUN CHANG, M.S.
Research Associate, Warner-Lambert/Parke-Davis, Pharmaceutical Research, Ann Arbor, Michigan 48105

JAMES C. CLOYD, PHARM.D.
Assistant Professor, University of Minnesota College of Pharmacy, St. Paul–Ramsey Medical Center, St. Paul, Minnesota 55101

JOYCE A. CRAMER
Epilepsy Center, Veterans Administration Medical Center, West Haven, Connecticut 06516

MOGENS DAM, M.D.
Consultant Neurologist, University Clinic of Neurology, Hvidovre Hospital, DK-2650 Hvidovre, Denmark

F. E. DREIFUSS, M.B., M.R.C.P., F.R.A.C.P.
Professor of Neurology, University of Virginia Medical Center, Charlottesville, Virginia 22901

KENNETH H. DUDLEY, PH.D.
Department of Pharmacology, Epilepsy and Anticonvulsant Drug Research Laboratory, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27514

MERVYN J. EADIE, M.D., PH.D., F.R.A.C.P.
Professor of Clinical Neurology and Neuropharmacology, University of Queensland; and Department of Medicine, Royal Brisbane Hospital, Brisbane, Australia 4029

J. W. FAIGLE, PH.D.
Senior Research Associate, Research Department, Pharmaceuticals Division, CIBA-GEIGY Limited, CH-4002 Basle, Switzerland

K. F. FELDMANN, PH.D.
Senior Staff Scientist, Research Department, Pharmaceuticals Division, CIBA-GEIGY Limited, CH-4002 Basle, Switzerland

JAMES A. FERRENDELLI, M.D.
Professor of Pharmacology and Neurology, Washington University School of Medicine, St. Louis, Missouri 63110

R. W. FINCHAM, M.D.
Department of Neurology, University of Iowa College of Medicine, Iowa City, Iowa 52242

ANTHONY J. GLAZKO, PH.D.
Director, Drug Metabolism, Warner-Lambert/Parke-Davis, Pharmaceutical Research, Ann Arbor, Michigan 48105

MARK A. GOLDBERG, PH.D., M.D.
Professor of Neurology and Pharmacology, University of California, Los Angeles, School of Medicine, Harbor–UCLA Medical Center, Torrance, California 90509

PIETER J. M. GUELEN
ABL Drug Studies Unit, Applied Bioresearch Laboratories, Assen, The Netherlands

PETER M. JEAVONS, M.A., F.R.C.P., F.R.C.PSYCH.
Honorary Visiting Professor, The University of Aston in Birmingham, Birmingham B4 7ET, England

SVEIN I. JOHANNESSEN, PH.D.
Head, Department of Clinical Chemistry, The National Center for Epilepsy, N-1301 Sandvika, Norway

DANIEL JOHNSTON, PH.D.
Department of Neurology, Baylor College of Medicine, Houston, Texas 77030

GARY L. JONES, PH.D.
Department of Pharmacology, Texas College of Osteopathic Medicine, Fort Worth, Texas 76107

ROBERT M. JULIEN, M.D., PH.D.
University of Oregon Health Sciences Center, Portland, Oregon 97201

BARRY J. KARAS, PHARM.D.
Postdoctoral Fellow, Neurology Service, Veterans Administration Medical Center, Gainesville, Florida 32602

JOHN W. KEMP, PH.D.
Division of Neuropharmacology and Epileptology, University of Utah College of Medicine, Salt Lake City, Utah 84132

BETSY T. KING
Department of Pharmacology, Epilepsy and Anticonvulsant Drug Research Laboratory, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27514

WILLIAM E. KLUNK
Department of Pharmacology, Washington University School of Medicine, St. Louis, Missouri 63110

HARVEY J. KUPFERBERG, PH.D.
Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland 20205

HENN KUTT, M.D.
Associate Professor of Neurology and Pharmacology, The New York Hospital—Cornell Medical Center, New York, New York 10021

ALLEN A. LAI, PH.D.
Department of Clinical Research, Medical Division, Burroughs Wellcome Company, Research Triangle Park, North Carolina 27709

ILO E. LEPPIK, M.D.
Assistant Professor of Neurology, University of Minnesota, St. Paul–Ramsey Medical Center, St. Paul, Minnesota 55101

RENÉ H. LEVY, PH.D.
Professor and Chairman, Department of Pharmaceutics, University of Washington School of Pharmacy, Seattle, Washington 98195

KENNETH G. LLOYD, PH.D.
Department of Clinical Research, Synthelabo—L.E.R.S., 75013 Paris, France

JOAN S. LOCKARD, PH.D.
Professor, Department of Neurological Surgery, University of Washington School of Medicine, Seattle, Washington 98195

RICHARD L. MASLAND, M.D.
Emeritus Professor of Neurology, Columbia University College of Physicians and Surgeons, New York, New York 10032

RICHARD H. MATTSON, M.D.
Clinical Professor of Neurology, Yale University School of Medicine, New Haven, Connecticut 06510; and Director, Epilepsy Center, Veterans Administration Medical Center, West Haven, Connecticut 06516

E. W. MAYNERT, M.D., PH.D.
Professor of Pharmacology, University of Illinois College of Medicine, Chicago, Illinois 60680

ROBERTO MICHELUCCI, M.D.
Neurological Clinic, University of Bologna School of Medicine, 40123 Bologna, Italy

PAOLO L. MORSELLI, M.D.
Director of Clinical Research, Synthelabo—L.E.R.S., 75013 Paris, France

HELGA PARIS-KUTT, M.D.
Staff Associate in Neurology, Columbia University College of Physicians and Surgeons, New York, New York 10032

J. KIFFIN PENRY, M.D.
Professor of Neurology and Associate Dean for Neurosciences Development, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina 27103

ROBERT J. PERCHALSKI, M.S.
Research Chemist, Medical Research Service, Veterans Administration Medical Center, and Adjunct Assistant Professor, University of Florida College of Pharmacy, Gainesville, Florida 32602

E. PERUCCA, PH.D.
Department of Pharmacology, Unit of Clinical Pharmacology, Piazza Botta, 10, Pavia, Italy

C. E. PIPPENGER, PH.D.
Associate Professor of Neuropharmacology, Columbia University College of Physicians and Surgeons, New York, New York 10032

ANTHONY V. PISCIOTTA, M.D.
Professor of Medicine, Blood Research Laboratory, Department of Medicine, The Medical College of Wisconsin, Milwaukee County Medical Complex, Milwaukee, Wisconsin 53226

WILLIAM H. PITLICK, PH.D.
Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland 20205

GABRIEL L. PLAA, PH.D.
Professor and Chairman, Department of Pharmacology, University of Montreal Faculty of Medicine, Montreal, P.Q. H3C 3J7, Canada

ROGER J. PORTER, M.D.
Chief, Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland 20205

JAMES W. PRICHARD, M.D.
Professor of Neurology, Yale University School of Medicine, New Haven, Connecticut 06510

A. RICHENS, PH.D., F.R.C.P.
Clinical Pharmacology Unit, Department of Clinical Neurology, Institute of Neurology, The National Hospital, Queen Square, London WC1N 3BG, England

SUSUMU SATO, M.D.
Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland 20205

DR. RER. NAT. HELMUT R. SCHÄFER
Research Department, Desitin-Werk Carl Klinke GmbH, 2000 Hamburg 63, Federal Republic of Germany

ASST. PROF. DR. DIETER SCHMIDT
Free University of Berlin, University Clinic Charlottenburg, 1000 Berlin 19, Federal Republic of Germany

FRED SCHOBBEN, PH.D.
Apotheek Academisch Ziekenhuis Utrecht, 3500 CG Utrecht, The Netherlands

DOROTHY D. SCHOTTELIUS, PH.D.
Department of Neurology, University of Iowa College of Medicine, Iowa City, Iowa 52242

ALLAN L. SHERWIN, M.D., PH.D.
Professor of Neurology, Montreal Neurological Institute, Montreal, P.Q. H3A 2B4, Canada

GERALD E. SLATER, M.D.
Departments of Neurology and Pediatrics, Hennepin County Medical Center, University of Minnesota, Minneapolis, Minnesota 55415

EWART A. SWINYARD, PH.D.
Emeritus Professor of Pharmacology and Former Dean, College of Pharmacy, University of Utah Colleges of Medicine and Pharmacy, Salt Lake City, Utah 84112

CARLO ALBERTO TASSINARI, M.D.
Professor, Neurological Clinic, University of Bologna School of Medicine, 40123 Bologna, Italy

EPPO VAN DER KLEIJN, PH.D.
Department of Clinical Pharmacy, St. Radboud Hospital, University of Nijmegen, 6525 GA Nijmegen, The Netherlands

B. G. WHITE, PH.D.
Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland 20205

B. J. WILDER, M.D.
Chief, Neurology Service, Veterans Administration Medical Center, and Professor of Neurology and Neuroscience, University of Florida College of Medicine, Gainesville, Florida 32602

C. D. WITHROW, PH.D.
Associate Professor of Pharmacology, University of Utah College of Medicine, Salt Lake City, Utah 84132

DIXON M. WOODBURY, PH.D.
Professor of Pharmacology, Division of Neuropharmacology and Epileptology, University of Utah College of Medicine, Salt Lake City, Utah 84132

JOSE H. WOODHEAD
Research Specialist, Department of Biochemical Pharmacology and Toxicology, University of Utah College of Pharmacy, Salt Lake City, Utah 84112

Contents

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Introduction

Ewart A. Swinyard

Contemporary antiepileptic drug therapy emerged only after millennia of treatment based on ignorance, superstition, and antique remedies. The first effective anticonvulsant drugs were the direct result of advances in synthetic chemistry, neuropathology, and experimental pharmacology. The discovery of bromine in the waters of the Mediterranean Sea by A. J. Balard in 1826 and the synthesis of urea by F. Wöhler in 1828 marked the beginning of synthetic chemistry and led to the laboratory synthesis of the first drugs demonstrated to be useful in the treatment of epilepsy. As a consequence of the isolation of bromine, potassium bromide was synthesized and soon widely used as a sedative. This prompted Sir Charles Locock in 1857 (42) to use potassium bromide in the treatment of hysterical and menstrual epilepsies in women; all but one of 14 such cases responded favorably to therapy. As a result of the synthesis of urea, phenobarbital was synthesized in 1911 and introduced by Hauptmann in 1912 (29) for the treatment of epilepsy. The barbituric acid moiety was easily modified in the chemical laboratory, and numerous synthetic congeners appeared during the next 25 years. One of these, mephobarbital, was reported by Weese in 1932 (68) to be clinically useful in epilepsy.

Meanwhile, John Hughlings Jackson (1825–1911), often referred to as the "father of the modern concepts of epilepsy," proposed that seizures are caused by "occasional, sudden, excessive, rapid and local discharges of gray matter in the brain"; this established a neuropathological basis for the disease. Within this same time frame, several workers demonstrated that the obvious symptom of epilepsy, the seizure, could be replicated in laboratory animals by electroshock and a variety of naturally occurring chemicals. In 1864, Marcé (44) induced convulsions in dogs and rabbits by the administration of absinthe; in 1870, Fritsch and Hitzig (18) evoked seizures in animals by the excessive electrical stimulation of the brain; in 1875, Browne (4) described the convulsive effects induced in animals by the administration of picrotoxin. These early studies in experimental pharmacology prompted Albertoni, in 1882, to test bromides, atropine, and cinchona alkaloids against electrically induced seizures in dogs (1). Pentylenetetrazol was synthesized in 1924, and its convulsant action was demonstrated by Hildebrant (30) in 1926. Although it soon replaced other chemical convulsants, its use for evaluating potential antiepileptic drugs was not considered reliable (46,58).

If any of the above-mentioned areas of investigation had not been pursued, the most significant antiepileptic drug discovery of this century could have been delayed by many years.

In 1937, Putnam and Merritt (56) described a technique in which seizures were induced in cats by interrupted (80/sec) direct current delivered to the brain for 10 sec through mouth–occipital electrodes. By means of this procedure, Putnam and Merritt discovered diphenylhydantoin (now known as phenytoin) and reported that in cats, doses minimally depressive to spontaneous