

# Antiepileptic Drugs

*Second Edition*

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Editors

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

# ANTIEPILEPTIC DRUGS

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Raven Press ■ New York

**Raven Press, 1140 Avenue of the Americas, New York, New York 10036**

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Made in the United States of America

International Standard Book Number 0-89004-498-8

Library of Congress Catalog Card Number 79-5501

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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*

# Acknowledgments

We are grateful, first of all, to the many contributors, whose cooperation, enthusiasm, and patience made this work possible. Special thanks and gratitude are extended to B. J. Hessie, without whose devotion and sustained effort this new edition would not have been prepared. Finally, we thank Raven Press, and particularly Ann Berlin and Virginia B. Martin, for the careful production of this book.

During the past 10 years, however, many of the gaps in our knowledge 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 determined electroencephalography allowed better determination of the seizure type. Rapid technological developments in the quantitation of antiepileptic drugs in biological fluids by gas-liquid chromatography, high-pressure liquid chromatography, and homogeneous enzyme immunoassays 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.

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Now, having 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.

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# 1

## 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 neuropath-

ological 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 Hildebrandt (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