
**Library of Congress Cataloging-in-Publication Data**
A catalog record for this book is available from the Library of Congress

**ISBN:** 0-8247-4242-7

This book is printed on acid-free paper

**Headquarters**
Marcel Dekker, Inc
270 Madison Avenue, New York, NY 10016, U.S.A
tel 212-696-9000, fax 212-685-4540

**Distribution and Customer Service**
Marcel Dekker, Inc
Cimarron Road, Monticello, New York 12701, U.S.A
tel 800-228-1160, fax 845-796-1772

**Eastern Hemisphere Distribution**
Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel 41-61-260-6300, fax 41-61-260-6333

**World Wide Web**
http://www.dekker.com

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above

Copyright © 2003 by Marcel Dekker, Inc. All Rights Reserved.

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher

Current printing (last digit)

10 9 8 7 6 5 4 3 2 1

**PRINTED IN THE UNITED STATES OF AMERICA**
NEUROLOGICAL DISEASE AND THERAPY

Advisory Board

Louis R. Caplan, M.D.
Professor of Neurology
Harvard University School of Medicine
Beth Israel Deaconess Medical Center
Boston, Massachusetts

John C. Morris, M.D.
Friedman Professor of Neurology
Co-Director, Alzheimer's Disease Research Center
Washington University School of Medicine
St Louis, Missouri

Kapil Sethi, M.D.
Professor of Neurology
Director, Movement Disorders Program
Medical College of Georgia
Augusta, Georgia

William C. Koller, M.D.
Mount Sinai School of Medicine
New York, New York

Bruce Ransom, M.D., Ph.D.
Warren Magnuson Professor
Chair, Department of Neurology
University of Washington School of Medicine
Seattle, Washington

Mark Tuszynski, M.D., Ph.D.
Associate Professor of Neurosciences
Director, Center for Neural Repair
University of California–San Diego
La Jolla, California

1. Handbook of Parkinson's Disease, edited by William C. Koller
2. Medical Therapy of Acute Stroke, edited by Mark Fisher
4. Alzheimer's Disease: Treatment and Long-Term Management, edited by Jeffrey L. Cummings and Bruce L. Miller
5. Therapy of Parkinson's Disease, edited by William C. Koller and George Paulson
6. Handbook of Sleep Disorders, edited by Michael J. Thorpy
7. Epilepsy and Sudden Death, edited by Claire M. Lathers and Paul L. Schraeder
8. Handbook of Multiple Sclerosis, edited by Stuart D. Cook
9. Memory Disorders. Research and Clinical Practice, edited by Takehiko Yanagihara and Ronald C. Petersen
10. The Medical Treatment of Epilepsy, edited by Stanley R. Resor, Jr., and Henn Kutt
12. Handbook of Amyotrophic Lateral Sclerosis, edited by Richard Alan Smith

Copyright 2003 by Marcel Dekker, Inc. All Rights Reserved.
14. Handbook of Pediatric Epilepsy, edited by Jerome V. Murphy and Fereydoun Dehkharghani
15. Handbook of Tourette's Syndrome and Related Tic and Behavioral Disorders, edited by Roger Kurlan
17. Handbook of Cerebrovascular Diseases, edited by Harold P. Adams, Jr.
18. Parkinsonian Syndromes, edited by Matthew B. Stern and William C. Koller
19. Handbook of Head and Spine Trauma, edited by Jonathan Greenberg
20. Brain Tumors: A Comprehensive Text, edited by Robert A. Morantz and John W. Walsh
22. Handbook of Dementing Illnesses, edited by John C. Morris
24. Handbook of Neurorehabilitation, edited by David C. Good and James R. Couch, Jr.
25. Therapy with Botulinum Toxin, edited by Joseph Jankovic and Mark Hallett
29. Handbook of Neuroepidemiology, edited by Philip B. Gorelick and Milton Alter
30. Handbook of Tremor Disorders, edited by Leslie J. Findley and William C. Koller
32. Handbook of Olfaction and Gustation, edited by Richard L. Doty
33. Handbook of Neurological Speech and Language Disorders, edited by Howard S. Kirshner
35. Evaluation and Management of Gait Disorders, edited by Barney S. Spivack
37. Neurological Complications of Cancer, edited by Ronald G. Wiley
39. Handbook of Dystonia, edited by Joseph King Ching Tsui and Donald B. Calne
40. Etiology of Parkinson's Disease, edited by Jonas H. Ellenberg, William C. Koller, and J. William Langston
41. Practical Neurology of the Elderly, edited by Jacob I. Sage and Margery H. Mark
42. Handbook of Muscle Disease, edited by Russell J. M. Lane
44. Central Nervous System Infectious Diseases and Therapy, edited by Karen L. Roos
46. Neurology Practice Guidelines, edited by Richard Lechtenberg and Henry S. Schutta
47. Spinal Cord Diseases: Diagnosis and Treatment, edited by Gordon L. Engler, Jonathan Cole, and W. Louis Merton
49. Sleep Disorders and Neurological Disease, edited by Antonio Culebras
50. Handbook of Ataxia Disorders, edited by Thomas Klockgether
51. The Autonomic Nervous System in Health and Disease, David S. Goldstein
52. Axonal Regeneration in the Central Nervous System, edited by Nicholas A. Ingoglia and Manon Murray
54. Long-Term Effects of Stroke, edited by Julien Bogousslavsky

Additional Volumes in Preparation

Clinical Neurovirology, edited by Avi Nath and Joseph R. Berger
We would like to thank our parents, Vidya and Badrinath Pahwa and Thomas and Elaine Lyons, for their many years of continued encouragement, understanding and support throughout our careers.
Parkinson’s disease is a common neurological condition that is becoming more common as the population ages. It is a chronic condition and can be a source of significant disability. Fortunately, for many decades there has been some understanding of the pathophysiology of Parkinson’s disease, and useful therapies have been available. Better therapies and definitive curative therapies, however, are yet to come. For these reasons, Parkinson's disease has been the focus of considerable research effort, and we have seen a virtual explosion of progress in recent years.

The identification of genetic disorders that lead to Parkinson’s disease has triggered the rush to research into molecular biology and cell biology of the basal ganglia and neurodegeneration. Imaging has led to greater insights about brain organization and neurotransmitter function. Physiological investigations have told us more about the genesis of the motor disorder of bradykinesia. New emphasis has been placed on the nonmotor aspects of parkinsonian symptomatology, which will help lead to a better quality of life for patients. All this new information has opened the door to new possibilities and to the development of new therapeutics.

However, the new therapies that have appeared in the last decade make the management of the patient with Parkinson’s disease more complex, sophisticated, and difficult for the clinician. Which of the various alternatives is best for the individual patient at hand? How should therapy be initiated? Is there anything that will help prevent progression of the disorder as well as ameliorate symptoms? What should be done with
agonists, with COMT inhibitors? How should complications, such as dyskinesias, be managed? How should cognitive dysfunction or depression be managed? What is the role of the different surgical options? When should they be employed and which one is best for the individual patient?

To help basic scientists and clinicians to keep up to date, information must be current, authoritative, and cohesively presented. To this end, the third edition of the *Handbook of Parkinson's Disease* is a welcome addition to the literature. It deals with all the aspects of understanding and managing this multifaceted disorder, and should be read from cover to cover and consulted for specific problems. The book will serve as an ideal reference for those working with Parkinson’s disease.

*Mark Hallett*
Chief, Human Motor Control Section
Medical Neurology Branch
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, Maryland
Parkinson’s disease is a progressive neurodegenerative condition with often devastating symptoms. In recent years, our knowledge of the disease has increased tremendously. We have achieved a greater understanding of its neurochemistry, neurophysiology, and neuropathology. Genes have been identified that are involved in the pathogenesis of some forms of familial autosomal dominant and autosomal recessive Parkinson’s disease. Advancements in neuropsychological and neuroimaging techniques have led to improvements in diagnostic accuracy. Therapeutics have come a long way, too. New medications have been approved, new compounds and therapeutic approaches are under investigation, and we have a better understanding of the use of surgical procedures in Parkinson’s disease, particularly deep brain stimulation. In spite of these advances, there continue to be many complications associated with the long-term management of both motor and nonmotor symptoms of the disease and treatment remains a challenge.

We present in this edition of the *Handbook of Parkinson’s Disease* the most up-to-date information on the scientific and therapeutic aspects of the disease. The third edition offers a more integrated approach to managing parkinsonian symptoms. There is comprehensive coverage of the latest pharmacological and surgical therapeutics as well as the newest technologies in diagnostic imaging. It is our hope that this volume, in the tradition of the first two editions, will serve as a reference source for physicians, researchers, and other healthcare professionals seeking answers to the many questions related to the understanding and treatment of Parkinson’s disease.
We thank each of the authors for their time and commitment in preparing state-of-the-art reviews of the most pertinent aspects of Parkinson’s disease. We would also like to thank Jinnie Kim, Ann Pulido, and the other Marcel Dekker, Inc., staff who assisted in the preparation of this book.

Rajesh Pahwa
Kelly E. Lyons
William C. Koller
Contributors

Joseph S. Chung, M.D  Division of Movement Disorders, University of Southern California–Keck School of Medicine, Los Angeles, California, U.S.A.

Richard B. Dewey, Jr., M.D.  Clinical Center for Movement Disorders, University of Texas Southwestern Medical School, Dallas, Texas, U.S.A.

Dennis W. Dickson, M.D.  Department of Pathology, Mayo Clinic, Jacksonville, Florida, U.S.A.

Elmyra V. Encarnacion, M.D.  Experimental Therapeutics Branch, Parkinson’s Disease and Movement Disorders Center, Neurology Department, University of South Florida and Tampa General Healthcare, Tampa, Florida, U.S.A.

Stewart A. Factor, D.O.  Parkinson’s Disease and Movement Disorders Center, Albany Medical Center, Albany, New York, U.S.A.

Matthew Farrer, Ph.D.  Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, U.S.A. and Mayo Medical School, Rochester, Minnesota, U.S.A.

Christopher G. Goetz, M.D.  Department of Neurological Sciences, Rush University, Chicago, Illinois, U.S.A.
Jay M. Gorell, M.D.  Department of Neurology, Henry Ford Health Sciences Center, Henry Ford Health System and NIEHS Center for Molecular Toxicology with Human Applications, Wayne State University, Detroit, Michigan, U.S.A.

Ruth Hagestuen, R.N., M.A.  The National Parkinson Foundation, Miami, Florida, U.S.A.

Robert A. Hauser, M.D.  Division of Movement Disorders, Departments of Neurology, Pharmacology and Experimental Pharmacology, University of South Florida and Tampa General Healthcare, Tampa Florida, U.S.A.

Michael W. Jakowec, Ph.D.  Department of Neurology and Department of Cell and Neurobiology, University of Southern California–Keck School of Medicine, Los Angeles, California, U.S.A.

Joseph Jankovic, M.D.  Department of Neurology, Baylor College of Medicine, Houston, Texas, U.S.A.

Danna Jennings, M.D  Department of Neurology, The Institute for Neurodegenerative Disorders, New Haven, Connecticut, U.S.A.

Marjorie L. Johnson, M.A./C.C.C.-S.L.P.  Struthers Parkinson’s Center, Minneapolis, Minnesota, U.S.A.

Jorge L. Juncos, M.D.  Department of Neurology and Wesley Woods Geriatric Center, Emory University School of Medicine, Atlanta, Georgia, U.S.A.

Anthony E. Lang, M.D., F.R.P.C.  Division of Neurology, Department of Medicine, The Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada

Mark F. Lew, M.D.  Department of Neurology, Univesity of Southern California–Keck School of Medicine, Los Angeles, California, U.S.A.

Kelly E. Lyons, Ph.D.  Department of Neurology, University of Kansas Medical Center, Kansas City, Kansas, U.S.A.

Kenneth Marek, M.D.  Department of Neurology, The Institute for Neurodegenerative Disorders, New Haven, Connecticut, U.S.A.
Deborah C. Mash, Ph.D. Department of Neurology and Molecular and Cellular Pharmacology, University of Miami School of Medicine, Miami, Florida, U.S.A.

Erwin B. Montgomery, Jr., M.D. American Parkinson Disease Association Advanced Center for Research, Departments of Neurology and Neuroscience, Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.

William Ondo, M.D. Department of Neurology, Baylor College of Medicine, Houston, Texas, U.S.A.

Rajesh Pahwa, M.D. Department of Neurology, University of Kansas Medical Center, Kansas City, Kansas, U.S.A.

Giselle M. Petzinger, M.D. Department of Neurology, University of Southern California–Keck School of Medicine, Los Angeles, California, U.S.A.

Ronald F. Pfeiffer, M.D. Department of Neurology, University of Tennessee Health Science Center, Memphis, Tennessee, U.S.A.

Alex Rajput, M.D. Department of Neurology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Ali H. Rajput, M.B.B.S. Department of Neurology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Michele Rajput, Ph.D. University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Jayaraman Rao, M.D. Louisiana State University Health Sciences Center, New Orleans, Louisiana, U.S.A.

Benjamin A. Rybicki, Ph.D. Biostatistics and Research Epidemiology, Henry Ford Health Sciences Center, Henry Ford Health System, Detroit, Michigan, U.S.A.

Michael Samuel, B.M.B.Ch., M.R.C.P., M.D. Division of Neurology, Department of Medicine, The Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada.
Anthony J. Santiago, M.D.  Parkinson’s Disease and Movement Disorders Center, Albany Medical Center, Albany, New York, U.S.A.

John Seibyl, M.D.  Department of Neurology, The Institute for Neurodegenerative Disorders, New Haven, Connecticut, U.S.A.

Kapil D. Sethi, M.D., F.R.C.P.  Medical College of Georgia, Augusta, Georgia, U.S.A.

Mark A. Stacy, M.D.  Muhammad Ali Parkinson Research Center, Barrow Neurological Institute, Phoenix, Arizona, U.S.A.

Alexander I. Tröster, Ph.D.  Departments of Psychiatry and Behavioral Sciences and of Neurological Surgery, University of Washington School of Medicine, Seattle, Washington, U.S.A.

Daryl Victor, M.D.  Division of Movement Disorders, Department of Neurology, Columbia University, New York, New York, U.S.A.

Cheryl Waters, M.D., F.R.C.P.(C)  Division of Movement Disorders, Department of Neurology, Columbia University, New York, New York, U.S.A.

Ray L. Watts, M.D.  Department of Neurology and Wesley Woods Geriatric Center, Emory University School of Medicine, Atlanta, Georgia, U.S.A.

Rosemary L. Wichmann, P.T.  Struthers Parkinson’s Center, Minneapolis, Minnesota, U.S.A.

Steven Paul Woods, Psy.D.  Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, Washington, U.S.A.

Zbigniew K. Wszolek, M.D.  Department of Neurology, Mayo Clinic, Jacksonville, Florida, U.S.A. and Mayo Medical School, Rochester, Minnesota, U.S.A.

Allan D. Wu, M.D.  Department of Neurology, University of Southern California–Keck School of Medicine, Los Angeles, California, U.S.A.
## Contents

*Foreword*  Mark Hallett  
*Preface*  
*Contributors*

**BACKGROUND**

1. Early Iconography of Parkinson’s Disease  
   *Christopher G. Goetz*

**CLINICAL ASPECTS**

2. Epidemiology of Parkinsonism  
   *Ali H. Rajput, Alex Rajput, and Michele Rajput*

3. Differential Diagnosis of Parkinsonism  
   *Kapil D. Sethi*

4. Pathophysiology and Clinical Assessment of Parkinsonian Symptoms and Signs  
   *Joseph Jankovic*
5. Nonmotor Symptoms of Parkinson’s Disease
   Richard B. Dewey, Jr

6. Neuropsychological Aspects of Parkinson’s Disease and Parkinsonian Syndromes
   Alexander I. Tröster and Steven Paul Woods

7. Management of Neurobehavioral Symptoms in Parkinson’s Disease
   Jorge L. Juncos and Ray L. Watts

8. Neuroimaging in Parkinson’s Disease
   Kenneth Marek, Danna Jennings, and John Seibyl

PATHOLOGY AND NEUROCHEMISTRY

9. Neuropathology of Parkinsonism
   Dennis W. Dickson

10. Neurochemistry of Nigral Degeneration
    Jayaraman Rao

11. Neurophysiology/Circuitry
    Erwin B. Montgomery, Jr.

12. Animal Models of Parkinson’s Disease and Related Disorders
    Giselle M. Petzinger and Michael W. Jakowec

13. Dopamine Receptor Diversity: Anatomy, Function, and Relevance to Parkinson’s Disease
    Deborah C. Mash

ETIOLOGY

14. Genetics
    Zbigniew K. Wszolek and Matthew Farrer

15. Environmental Risk Factors for Parkinson’s Disease
    Jay M. Gorell and Benjamin A. Rybicki
MEDICATIONS

16. Amantadine and Anticholinergics
   Joseph S. Chung, Allan D. Wu, and Mark F. Lew

17. Levodopa
   Anthony J. Santiago and Stewart A. Factor

18. Dopamine Agonists
   Mark A. Stacy

19. Monoamine Oxidase Inhibitors in Parkinson’s Disease
   Daryl Victor and Cheryl Waters

20. Catechol-O-Methyltransferase in Parkinson’s Disease
    Ronald F. Pfeiffer

21. Investigational Pharmacological Treatments for Parkinson’s Disease
    William Ondo

SURGICAL THERAPY

22. Lesion Surgeries
    Michael Samuel and Anthony E. Lang

23. Deep Brain Stimulation in Parkinson’s Disease
    Rajesh Pahwa and Kelly E. Lyons

24. Neural Transplantation in Parkinson’s Disease
    Elmyra V. Encarnacion and Robert A. Hauser
OTHER FORMS OF TREATMENT

25. Parkinson’s Disease Symptom Management: An Interdisciplinary Approach
   
   Ruth A. Hagestuen, Rosemary L. Wichmann, 
   and Marjorie L. Johnson