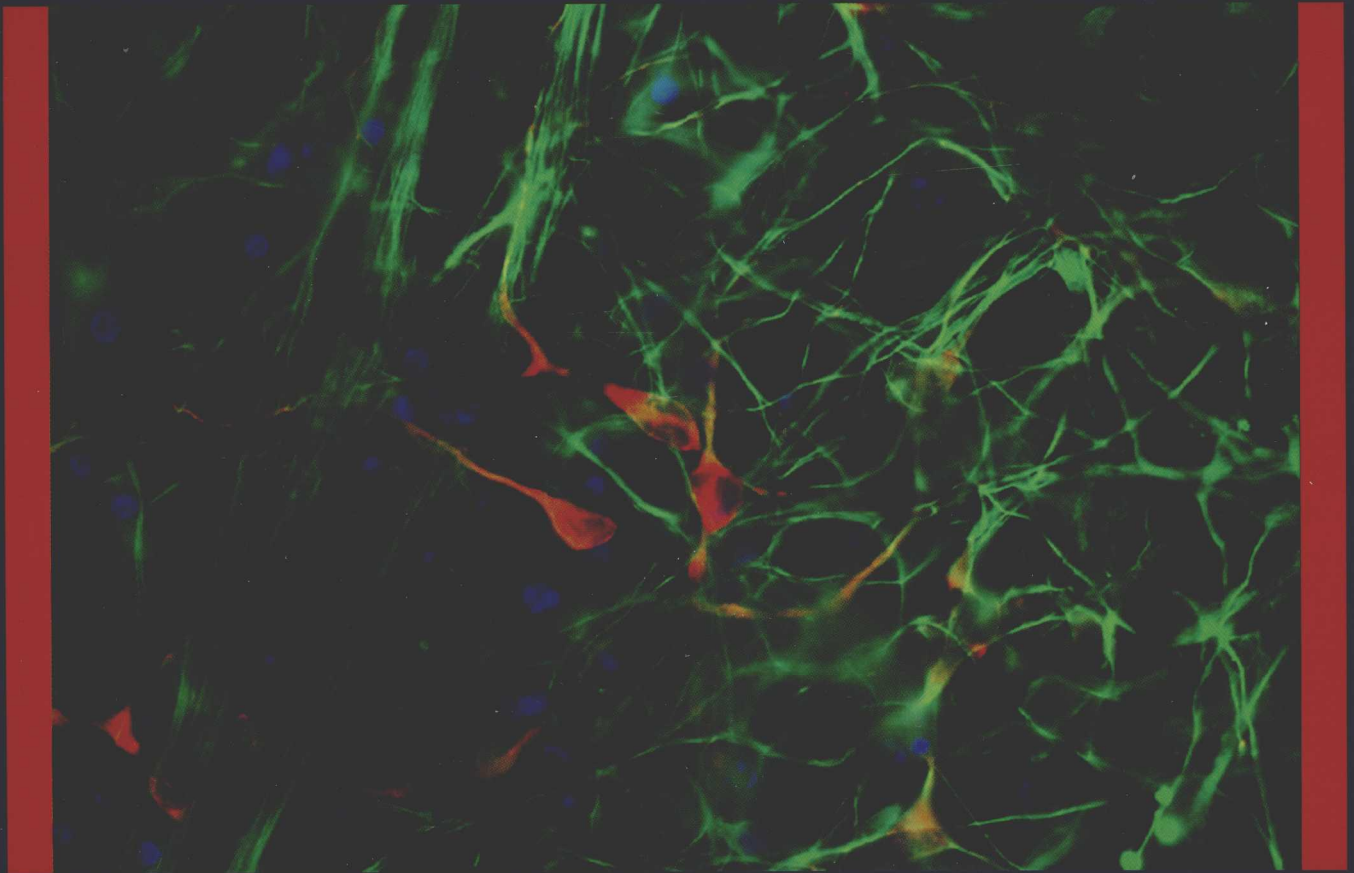


Neurobiology of **Brain Disorders**

Biological Basis of Neurological
and Psychiatric Disorders



Edited by

**Michael J. Zigmond,
Lewis P. Rowland, and Joseph T. Coyle**



NEUROBIOLOGY OF BRAIN DISORDERS

BIOLOGICAL BASIS OF NEUROLOGICAL AND PSYCHIATRIC DISORDERS

Edited by

MICHAEL J. ZIGMOND

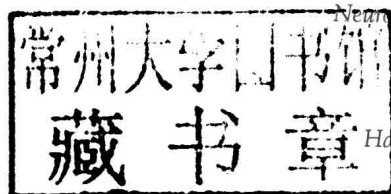
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225 Wyman Street, Waltham, MA 02451, USA
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK

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ISBN: 978-0-12-398270-4

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

For information on all Academic Press publications
visit our website at <http://store.elsevier.com/>

Typeset by TNQ Books and Journals
www.tnq.co.in

Printed in the United States of America
Transferred to Digital Printing, 2015



NEUROBIOLOGY OF BRAIN DISORDERS

Dedication

To our students and patients who, over the years, have motivated us to produce this book

and

To Nancy Wexler, whose commitment to research and education about brain disorders has been an inspiration to each of us.

Preface

Interest in understanding the basis of neurological and psychiatric disorders is thousands of years old. People of China and India, as well as the Egyptians and Greeks, all had ideas about how the brain worked and what caused the occasional functional abnormalities that they observed. Moreover, they often developed interventions to relieve symptoms, if not treat the disease. Indeed, the origins of neuroscience probably go back even farther. For example, trephination of the skull is thought to have been practiced as long as 7000 years ago and may have been designed to release evil spirits believed to be the cause of brain disorders. Since then, some of the ancient treatments have been found to be quite effective and have even served as the basis for much more recent interventions. However, the modern era of inquiry into the neurobiological basis of brain disorders did not begin until the nineteenth century. Several milestones along the path of that inquiry can be identified; here we mention just a few.

Rauwolfia serpentina is a shrub from which the people of India have been making a medicinal tea for thousands of years.^{1,2} Among the many conditions for which it was used was “moon disease”, which we now recognize as psychosis. In the early 1950s it was determined that most of the tranquilizing effects of the plant extracts resulted from a compound that was named reserpine. Over the next decade, Arvid Carlsson and colleagues, working first at the US National Institutes of Health, then at the University of Lund, and finally at the University of Göteborg, Sweden, demonstrated that the effects of this natural product were due to its depletion of the neurotransmitter dopamine from the striatum, as described in the Nobel Lecture by Arvid Carlsson.³ This led to several key observations, including the discovery by Oleh Hornykiewicz in Vienna that Parkinson disease (PD) was associated with a loss of striatal dopamine and that many of the motor symptoms of PD could be reversed by administration of the dopamine precursor, L-dopa (see Chapter 19).^{3,4}

The use of reserpine as a treatment for psychosis, together with the discovery of chlorpromazine for the treatment of schizophrenia and the realization in 1963 that it, too, acted by reducing dopaminergic transmission,⁵ led to the focus on reducing dopaminergic transmission to treat schizophrenia (see Chapter 39). Likewise, the observation that a loss of dopamine was associated

with PD, and that the behavior of reserpinized animals and patients with PD could both be improved by L-dopa, resulted in the use of drugs that activate dopamine receptors in the treatment of PD. This sequence of events, conducted over a period of less than 10 years, is a landmark in the use of behavioral and neurochemical approaches for studying the nervous system, and was largely responsible for initiating the twin fields of neuropharmacology and biological psychiatry.

There have been many other such moments in the emergence of biological approaches to neurological and psychiatric disorders. For example, Ernst Wilhelm von Brücke and colleagues, as well as their students (e.g. Sigmund Freud), working in Austria during the latter half of the nineteenth century, were among the first to apply laboratory methods to the study of the nervous system and to suggest that behavior could be understood through an understanding of biological events. The introduction of electrophysiology into neuroscience can be traced as far back as the seventeenth century to the work of Jan Swammerdam in Holland, although it is Luigi Galvani, working in Italy in the nineteenth century using nerve-muscle preparations, who is usually credited with initiating electrophysiology as an approach for understanding how the nervous system functions.⁶ Neuropathology was introduced by Paul Oscar Blocq and Georges Marinesco in the late nineteenth century in Paris. During a postmortem examination, they found a tumor in the contralateral substantia nigra of a patient who had exhibited the symptoms of PD, as reviewed by Catala and Poirier.⁷ In short, many of the principal tools for understanding the neurobiology of brain disorders – neuropathology, histochemistry, electrophysiology, biochemistry, and behavior – gradually emerged over the past 250 years as a result of investigators working in many different areas of the world. In the 1970s, two more approaches were added, molecular neurobiology and brain imaging. (For an excellent treatise on the history of neuroscience, see *Origins of Neuroscience: A History of Explorations into Brain Function*, by Stanley Finger,⁸ and excellent articles in *The Journal of the History of Neuroscience*. For a timeline and an extensive bibliography of the history of neuroscience, see also the website of Eric Chudler at the University of Washington.⁹ Additional material can be found on the website of the Society for Neuroscience.¹⁰)

Our decision to assist in the teaching of the neuroscience of brain disorders by preparing this textbook began to take shape over three decades ago. The Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts (USA) twice played a role in the origins of the project, as it has in the development of neuroscience more generally.^{11,12} The first event occurred on a rainy weekend afternoon in 1979, when Edward Kravitz invited two individuals to speak on the neurobiology course that he was co-teaching there. They were Nancy Wexler, then a program officer at the US National Institute of Neurological Diseases and Stroke, and Marjorie Guthrie, the widow of Woody Guthrie. Marjorie spoke movingly about how Woody's Huntington disease affected him and their entire family; Nancy also commented on the disease. After the presentations, Marjorie, Nancy (who was to become the president of the Huntington's Disease Foundation and whose family has also suffered from that condition), Ed, Michael Zigmond, and several others on the course went to "The Captain Kidd", a popular hang-out in Woods Hole, to continue the discussion. The group immediately began to talk about how moving the presentations by Marjorie and Nancy had been and how valuable it would be to expose others in the field to such experiences. Ed took this idea and ran with it, obtaining funding from the National Institutes of Health to underwrite the "Neurobiology of Disease" workshop now held each year just before the annual meeting of the Society for Neuroscience.

The second event was a six-day workshop for faculty on teaching about the neurobiology of disease in which the three editors of the present textbook (and many others) taught during August 2011. The objective was to provide the participants with information and instructional methods that would allow them to go back to their home institutions and mount, or substantially improve, a course on the neurobiology of disorders. Much of the impetus for moving from courses to a textbook – and a few of the book's authors (Ann McKee, Robert Brown) and consultants (Gerald Fischbach, Donald Price) – arose from that workshop. The hope was – and remains – that through this book still others will be able to develop courses on the neurobiology of disease. This textbook is not complete; there are separate chapters on the role of inflammation but not mitochondrial dysfunction, on PD but not Tourette syndrome, on depression but not anxiety, on traumatic brain injury, but not brain tumors. These and several other topics must await a second edition.

But this raises the question: Why this abiding interest in helping to stimulate training in the neurobiology of disease? It is not because we believe that basic research in this field is less important than research that more directly confronts disease. On the contrary, virtually all of our current understanding of the biological basis of brain disorders stems from discoveries made in basic science laboratories, as the examples given at the beginning of this Preface indicate (see also the excellent series of pamphlets produced by the Society for Neuroscience, "Research and Discoveries"¹³). However, knowing more about disorders of the nervous system can motivate researchers to work even harder, and who among us does not want their work to eventually make a difference in the lives of others? Moreover, we firmly believe in the aphorism of Louis Pasteur that "chance favors the prepared mind". We hope this textbook will aid in that preparation.

Michael J. Zigmond, PhD

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Acknowledgments

This textbook has been a long time in gestation. Some time around 2005, Michael Zigmond was approached by Johannes Menzel, then at the Academic Press division of Elsevier, with a proposal to organize a textbook such as this one. Donald Price was soon brought into the conversations and over the next few years played a major role in shaping the project, providing suggestions for both topics and authors. Gerald Fischbach was also a source of excellent advice. In the end, we three agreed to carry the project through to its conclusion.

Although our initial editor at Elsevier, Susan Lee, helped to get the project started, it was Mica Haley and editorial project manager April Farr who made it happen – being amazingly patient with us and the authors as one deadline after another came and went. And, in addition to being patient, Mica provided invaluable suggestions at virtually every step along the way.

Working with Michael at the University of Pittsburgh, Susan Giegel and later Beth Fischer provided essential administrative assistance. Finally, we greatly appreciate the help of all those involved in the production of this textbook, including our copy editor, Charlotte Pover and project manager Chris Wortley.

The royalties generated from this book will be used primarily to support the purchase and distribution of this textbook to trainees in developing countries.

No grant support was specifically obtained for this project. However, our institutions, the University of Pittsburgh, Harvard Medical School/McLean Hospital, and Columbia University provided us with the facilities within which to carry out the work and, in some cases, support for our salaries.

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