Demonstrating the value of interactions between neurology and the basic sciences that underpin it, this volume considers a range of topics from the points of view of both neurobiologist and clinician and reveals how advances in our understanding have been and continue to be made. The selected topics cover a wide range of levels of organization in the nervous system. For each one, distinguished researchers from around the world have made contributions, including general reviews of normal and pathological mechanisms as well as detailed accounts of the basic processes involved. The book's coverage boasts an excellent section on the physiology and pathophysiology of central and peripheral nerve fibres. This ranges from considerations of ion channels through to mechanisms of loss of function in multiple sclerosis and strategies for restitution of function in this and other disorders of myelination. Motor control is also dealt with in depth via consideration of respiratory movements – a vital system so frequently ignored in other texts. Also of particular note are the chapters on neuronal plasticity, cell death and axonal regeneration; these are active areas in neuroscience, where new knowledge will almost certainly revolutionize neurological treatments in years to come.

In dedicating this book to Tom Sears, retiring Professor at London's Institute of Neurology (Queen Square), it is hoped that, as Professor Sears has done in the past, inspiration will be given to the next generation of neurologists to pursue research at the most fundamental level possible as well as encouraging young neuroscientists to take a deeper interest in pathological processes.

THE NEUROBIOLOGY OF DISEASE

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Contributions from Neuroscience to Clinical Neurology

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CAMBRIDGE UNIVERSITY PRESS

CAMBRIDGE
UNIVERSITY PRESS

University Printing House, Cambridge CB2 8BS, United Kingdom

Cambridge University Press is part of the University of Cambridge.

It furthers the University's mission by disseminating knowledge in the pursuit of education, learning and research at the highest international levels of excellence.

www.cambridge.org
Information on this title: www.cambridge.org/9780521451321

First published 1996
First paperback edition 2011

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

Library of Congress Cataloguing in Publication data

The neurobiology of disease: contributions from neuroscience to clinical neurology/edited by
H. Bostock, P. A. Kirkwood, and A. H. Pullen.
p. cm.
Includes bibliographical references and index.
ISBN 0 521 45132 9
1. Nervous system – Diseases. 2. Neurophysiology.
I. Bostock, H. II. Kirkwood, P.A. III. Pullen, A. H.
[DNLM: 1. Nervous System – physiology. 2. Nervous System Diseases – physiopathology.
WL 102 N4945216 1996]
RC347.N473 1996
616.8–dc20 95–33564 CIP
DNLM/DLC
for Library of Congress

ISBN 978-0-521-45132-1 Hardback
ISBN 978-0-521-34238-4 Paperback

Contributions from Neuros
Clinical Neurology

Professor T.A. Sears

Dedication

This volume is dedicated to Tom Sears, who has recently retired from the chair of the Sobell Department of Neurophysiology in the Institute of Neurology in London. Nearly all his scientific career has been made in this Institute or its sister organization, the National Hospital for Neurology and Neurosurgery (Queen Square).

After graduating in physiology from University College London he moved to the National Hospital, where he collaborated with several clinical neurologists. His independent career became firmly established after a period of study with Sir John Eccles in Canberra in the early 1960s, where he performed seminal work using intracellular recordings from respiratory motoneurones. By emphasizing the Sherringtonian, integrative role of the motoneurone, these studies transformed how we think about the way in which the nervous system deals with the command signals for respiratory movements and, indeed, for movements in general. The theme of respiration as a model

motor control system has been central to his research, which has expanded to embrace respiratory mechanics, the chemical control of breathing, human stretch reflexes, cerebellar and olivary influences on motor control and a host of other related topics.

However, his interests in neuroscience have gone well beyond motor control and he developed quite separate lines of work in the physiology and pathophysiology of nerve conduction, synaptic plasticity, neural degeneration and development, with a particular interest in the motoneurone. An essential element in this catholic approach was the early addition of an anatomical section to his neurophysiological laboratory, equipped to undertake basic histological and ultrastructural studies, later incorporating *in vitro*, immunocytochemical and *in situ* hybridization technology.

His work in all fields has involved collaboration with other distinguished scientists from across the world and, most importantly, the training of young clinical neurologists in scientific methods.

His abilities were recognized by the Institute of Neurology, which created the Department of Neurophysiology for him in 1968, the department being established by London University in 1975 as the Sobell Department. He is now Emeritus Professor.

He has been an editor of many scientific journals, including chairman of the *Journal of Physiology (London)*, and his distinction was rewarded by an honorary doctorate from the University of Aix, Marseille and the Presidency of the European Neuroscience Association.

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Preface

Clinical neurology and the neurosciences can interact in various ways. Investigators often start from a given disease or clinical condition and ask 'What is the cause of this disorder?', with the hope that having identified the cause the way will be open to devise a remedy. Though apparently straightforward, this approach can be fraught with difficulty. The aetiology of neurological conditions is often so obscure that it is not evident which discipline, whether biochemistry, electrophysiology, immunology or epidemiology, is going to give the critical lead, so all must be supported. Only for inherited conditions has this approach been conspicuously successful, where recent advances in genetics and molecular biology have in several cases provided a quick path to the first stage of identifying the cause.

An alternative approach is to put science first: to ask fundamental questions about the workings of the nervous system, but to ensure that the scientific questions are always relevant to neurological ones. Not only may the science then help the neurologist, but clinical observations may help illuminate the science. This is the approach exemplified by most of the contributors to this book, and is also the approach of Tom Sears, to whom the book is dedicated. This alternative approach is well illustrated by his work on nerve conduction and demyelination, which underpins several of the chapters. In pioneering experiments with McDonald, using focal experimental demyelination with diphtheria toxin, he first showed that individual central nerve fibres could remain intact through a demyelinated region, with unimpaired conduction above and below the lesion, while transmission of impulses through the lesion was blocked or proceeded with a reduced safety factor. These experiments on the pathophysiology of demyelination were of obvious clinical significance, but also provided access to a fundamental question about axonal physiology.

Huxley & Stämpfli (1949) had shown that conduction in isolated myelinated axons was saltatory: the inward membrane currents of excitation occurred only at the nodes of Ranvier. This showed that the internodal membrane was not excited, but not whether it was actually

excitable, a question which could only be answered by demyelination. Sears therefore (with Rasminsky and later with Bostock) adapted Huxley and Stämpfli's technique to investigate demyelinated axons, taking advantage of the anatomy of rat spinal roots to record longitudinal currents from undissected but functionally isolated single axons. For some demyelinated fibres conduction was always saltatory (Rasminsky & Sears, 1972), but in smaller fibres, or at temperatures below 37 °C, continuous conduction could sometimes be recorded over one or more demyelinated internodes, at velocities about one-twentieth of normal (Bostock & Sears, 1978). These studies helped to open investigation of a range of basic questions concerning the distribution of sodium channels within the membrane and the mechanisms of regulation of this distribution (see chapters by Ritchie, Waxman). On the clinical side, these results helped to resolve the puzzling lack of correlation between degree of demyelination and conduction failure, and to explain the remarkable delays in visual and other evoked responses in multiple sclerosis. Neither the cause of demyelinating disease was revealed, nor a cure, but by clarifying the pathophysiology of conduction failure and slowing, this work led to further studies on how to overcome the conduction failure by prolonging the action potential, by reducing pump activity, or by promoting remyelination (see chapters by McDonald, Smith, Rosenbluth). The important lesson here is that the starting point for these insights in both neurobiology and clinical neurology was a basic scientific question about saltatory conduction, which was relevant to the clinical consequences of demyelination.

Tom Sears worked on many other problems, always with a clinical aspect at least at the back of his mind. This book was inspired by a symposium held in London to mark his retirement. The symposium brought together a group of distinguished scientists and neurologists, all of whom either worked directly with him at some stage of their careers, or were strongly influenced by his published work. Many were educated in their scientific approach by him, including us, the three editors of this volume, for which we are profoundly grateful.

The symposium which acted as a spur to production of this volume was made possible by the generous support of the Guarantors of *Brain*, Pfizer Central Research, The Spinal Cord Research Trust (Paralyzed Veterans of America), The Multiple Sclerosis Society of Great Britain and Northern Ireland, The Wellcome Trust, Digitimer Ltd, Lilly Industries Ltd, The Institute of Neurology, The Sobell Foundation and Merck, Sharp & Dohme Research Laboratories.

We are indebted to Julie Savvides, Kully Sunner and Peter Humphreys (Sobell Department) for their encouragement and help in organizing the symposium. We further relied a great deal on Julie Savvides during the prep-

aration of this book, for which we would also like to acknowledge the advice and assistance of the editorial staff of Cambridge University Press.

London H.B.
May 1995 P.A.K.
A.H.P.

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