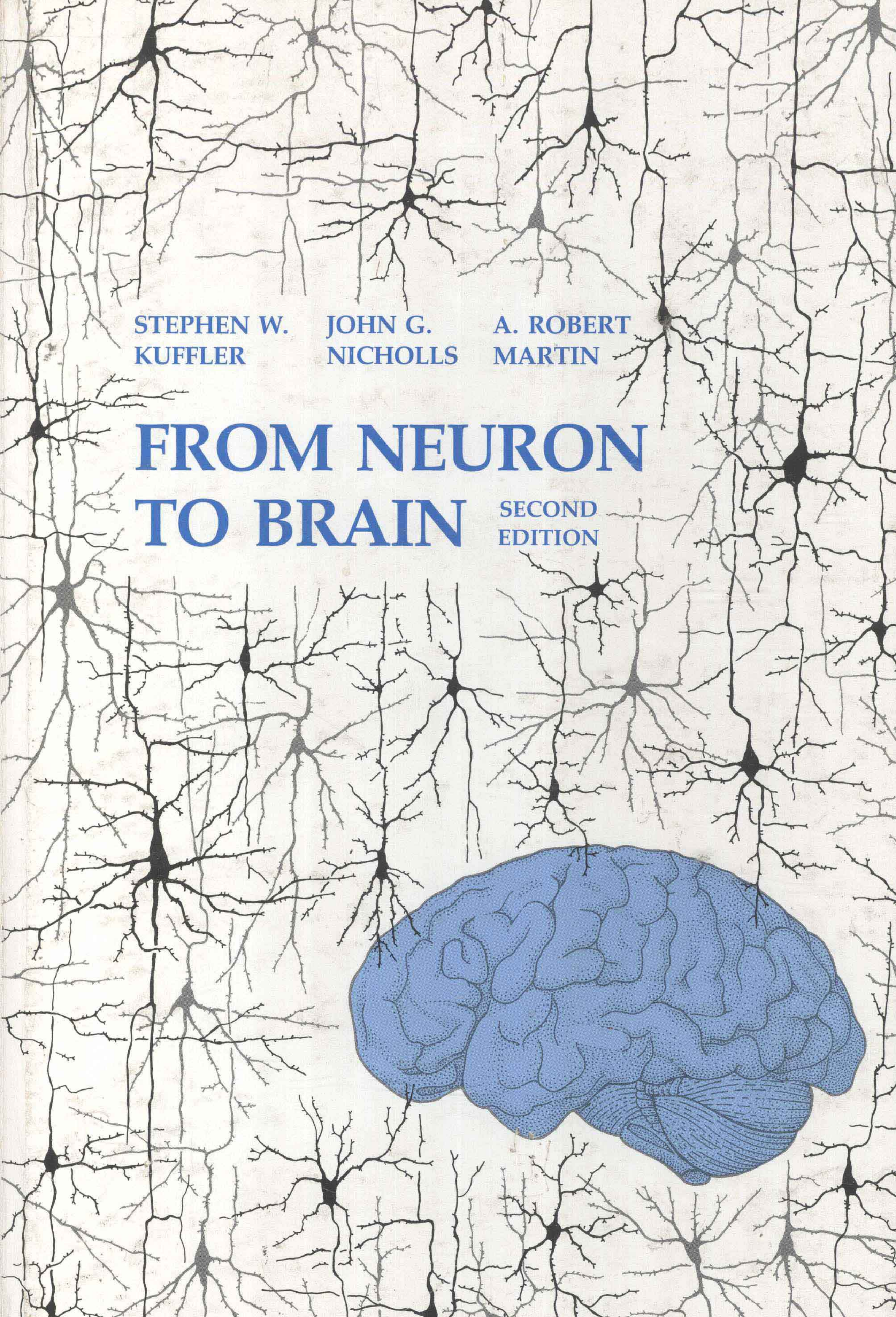

STEPHEN W. KUFFLER
JOHN G. NICHOLLS
A. ROBERT MARTIN

# FROM NEURON TO BRAIN

SECOND EDITION

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## A Cellular Approach to the Function of the Nervous System

SECOND EDITION

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FROM NEURON TO BRAIN:
A Cellular Approach to the
Function of the Nervous System

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*This book is dedicated to*
*our friend and colleague,*
*Steve Kuffler.*

# PREFACE TO THE SECOND EDITION

The aims of this new edition remain similar to those outlined in the original preface: "to describe how nerve cells go about their business of transmitting signals, how these signals are put together, and how out of this integration higher functions emerge. This book is directed to the reader who is curious about the workings of the nervous system but does not necessarily have a specialized background in biological sciences." Again, as in the first edition, we have chosen to present examples that lend themselves to a narrative description and with which we have some first-hand experience. The scope of the book has, however, been broadened. One entirely new chapter on the control of movement, somatic sensation, and pain has been added. In addition, to help readers unfamiliar with the structure of the mammalian brain, Laszlo Meszoly has drawn for us a new section on neuroanatomy; this appears in the form of a short appendix. Another new feature is the greater use of "Boxes." These provide short, self-contained descriptions of important topics that could detract from the flow of the argument if included in the text. Into this category fall derivations of equations, descriptions of techniques, and points of interest related to but outside the main thrust of the chapter.

In addition to bringing all the chapters up to date, we have drastically rewritten most of them. An appreciation of how much new material is now available and how many new concepts have developed in the last few years has been vividly impressed on us as we set out to face each chapter. This is apparent from a cursory glance at the table of contents. Consider just a few examples: the microcircuitry and the laminar structure of the visual cortex, patch clamp analysis of single channel currents, peptide transmitters and neuromodulators, demyelination and remyelination, the development and application of monoclonal antibodies, descending control of pain, the role of the basal lamina in regeneration, long-term changes in the *Aplysia* nervous system, retraction of geniculate axons in the neonatal cortex—all these represent just a few of the problems in which major experimental progress has been made since the last edition. Inevitably the book is longer than it was. What we have tried to do, however, is to retain the flavor of the original.

The pleasure and satisfaction that we might hope to feel in recreating a book that has seemed to fill a need has been diminished by the death of our friend and colleague, Steve Kuffler. We have tried to produce a book he would not have minded keeping his name on.

J. G. N.
A. R. M.



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# ACKNOWLEDGMENTS

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Original plates for this edition were kindly provided by Drs. A. Aguayo, D. Baylor, A. Grinvald, D. Hubel, A. Kaneko, S. LeVay, U. J. McMahan, K. Muller, S. Palay, C. Shatz, E. Weber, D. Weisblat, and T. Woolsey.

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To Laszlo Meszoly, who has done the artwork, Joseph Vesely, who has handled production matters, and Andy Sinauer, our editor, we owe special thanks not only for their skill, insight, and taste but for making the collaboration such a pleasure.

# PREFACE TO THE FIRST EDITION

Our aim is to describe how nerve cells go about their business of transmitting signals, how these signals are put together, and how out of this integration higher functions emerge. This book is directed to the reader who is curious about the workings of the nervous system but does not necessarily have a specialized background in biological sciences. We illustrate the main points by selected examples, preferably from work in which we have first-hand experience. This approach introduces an obvious personal bias and certain omissions.

We do not attempt a comprehensive treatment of the nervous system, complete with references and background material. Rather, we prefer a personal and therefore restricted point of view, presenting some of the advances of the past few decades by following the thread of development as it has unraveled in the hands of a relatively small number of workers. For example, in Part One (Neural Organization for Perception) we emphasize the approach used by Hubel and Wiesel, which we were fortunate to witness step by step in laboratories next to our own. Similarly, Part Two (Mechanisms for Neuronal Signaling) leans heavily on the work of Hodgkin, Huxley, Katz, Miledi, and their colleagues, and omits comprehensive treatment of many other aspects. A survey of the table of contents reveals that many essential and fascinating fields have been left out: subjects like the cerebellum, the auditory system, eye movements, motor systems, and the corpus callosum, to name a few. Our only excuse is that it seems preferable to provide a coherent picture by selecting a few related topics to illustrate the usefulness of a cellular approach.

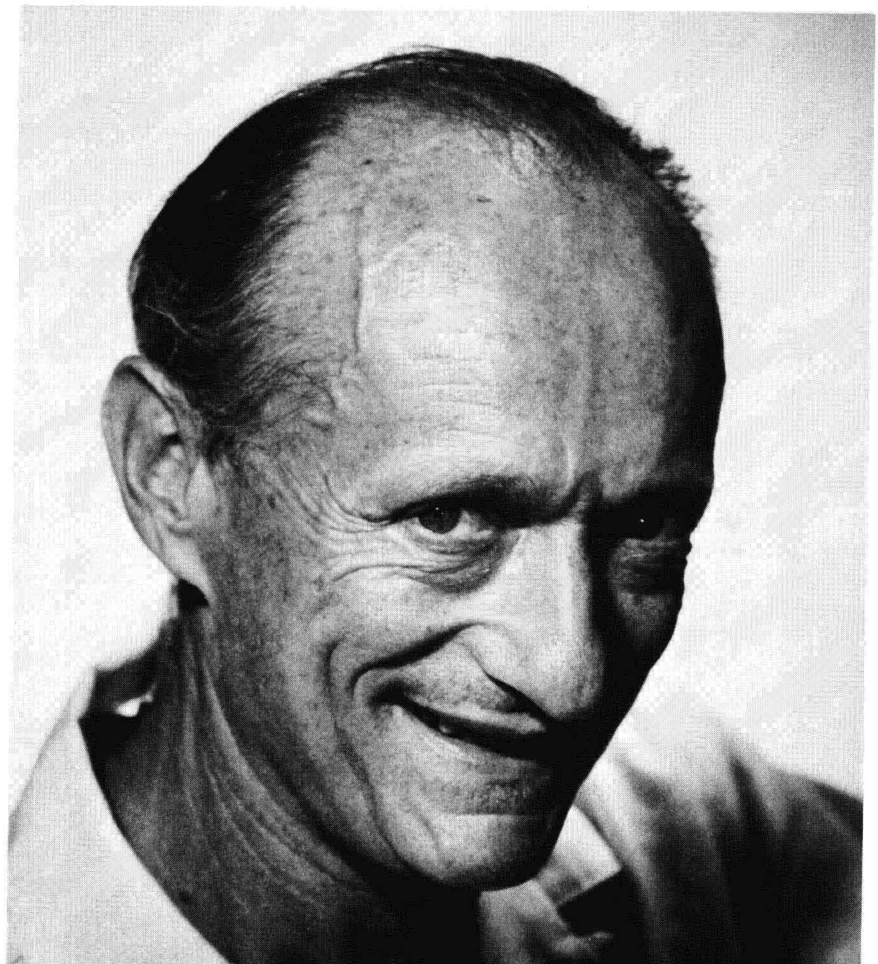
We describe the more complex functions first, because the visual systems of the cat and the monkey lend themselves well to an initial presentation of the neuronal events that are clearly correlated with such higher functions as perception. This approach puts in perspective the subsequent discussion in Parts Two and Three of the cellular machinery that is used to bring about the brain's more complex activity. Throughout, we describe experiments on single cells or analyses of simple assemblies of neurons in a wide range of species. In several instances the analysis has now reached the molecular level, an advance that enables one to discuss some of the functional properties of nerve and muscle membranes in terms of specific molecules.

Fortunately, in the brains of all animals that have been studied there is apparent a uniformity of principles for neurological signaling. Therefore, with luck, examples from a lobster or a leech will have relevance for our own nervous systems. As physiologists we must pursue that luck, because we are convinced that behind each problem that appears extraordinarily complex and insoluble there lies a simplifying principle that will lead to an unraveling of the events. For example, the human brain consists of over 10,000 million cells and many more connections that in their detail appear to defy comprehension. Such complexity is at times mistaken for randomness; yet this is not so, and we can show that the brain is constructed according to a highly ordered design, made up of relatively simple components. To perform all its functions it uses only a few signals and a stereotyped repeating pattern of activity. Therefore, a relatively small sampling of nerve cells can sometimes reveal much of the plan of the organization of connections, as in the visual system.

In Part Three and especially in Part Six, we discuss "open-ended business," areas that are developing and whose direction is therefore uncertain. As one might expect, the topics cannot at present be fitted into a neat scheme. We hope, however, that they convey some of the flavor that makes research a series of adventures.

*From Neuron to Brain* expresses our approach as well as our aims. We work mostly on the machinery that enables neurons to function. Students who become interested in the nervous system almost always tell us that their curiosity stems from a desire to understand perception, consciousness, behavior, or other higher functions of the brain. Knowing of our preoccupation with the workings of isolated nerve cells or simple cell systems, they are frequently surprised that we ourselves started with similar motivations, and they are even more surprised that we have retained those interests. In fact, we believe we are working toward that goal (and in that respect probably do not differ from most of our colleagues and predecessors). Our book aims to substantiate this claim and, we hope, to show that we are pointed in the right direction.

S. W. K.
J. G. N.
Woods Hole
August 1975



# THE AUTHORS

**STEPHEN KUFFLER (1913–1980)**

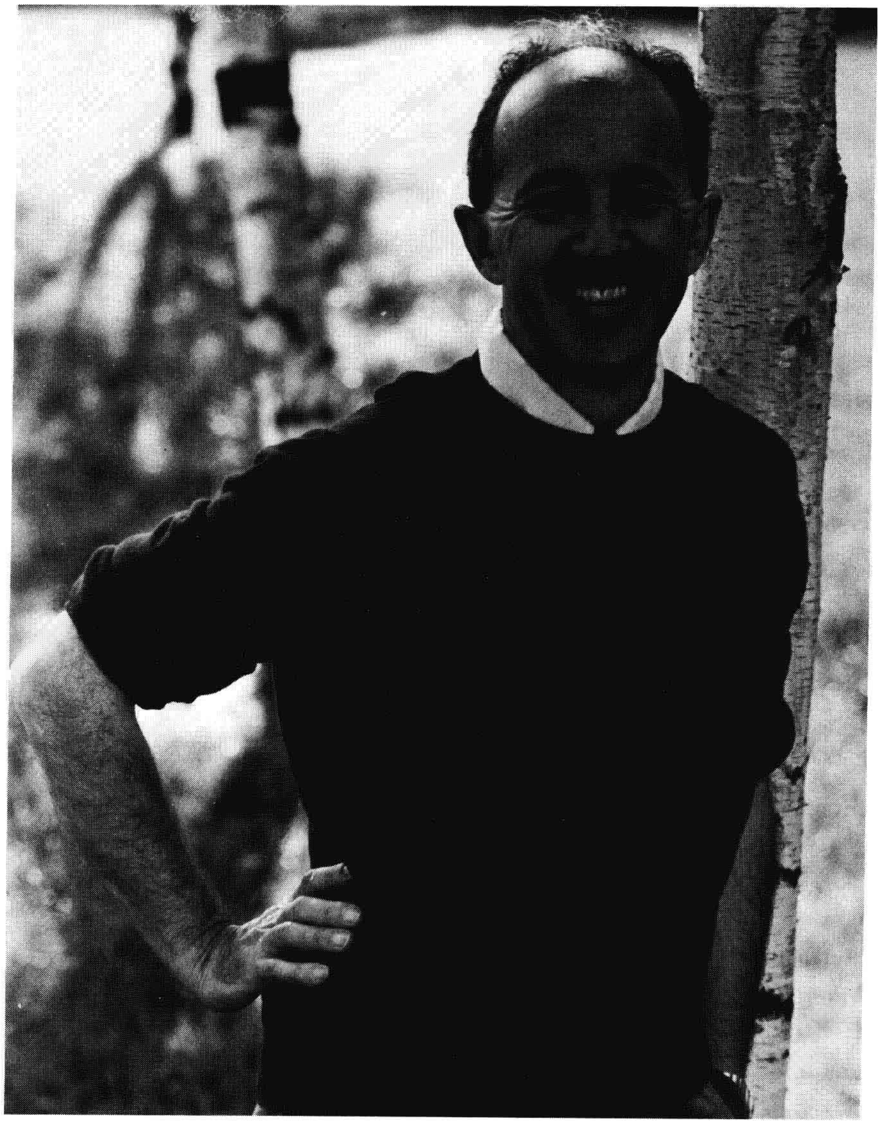
Time after time, in a career that spanned 40 years, Stephen Kuffler made experiments on fresh topics, hitherto confused or ignored, in which he revealed fundamental mechanisms and laid paths for future research to follow. In each instance a striking feature of his work is the way in which the right problem was tackled at the right time, using the right preparation. Examples that spring to mind are his studies on denervation supersensitivity, stretch receptors and muscle spindles, efferent control, presynaptic and postsynaptic inhibition, GABA and peptides as transmitters, integration in the retina, the properties of glial cells, and the detailed analysis of synaptic transmission. In books on neurobiology, Kuffler's papers form a sizeable fraction of the reading list and one is struck by the clear-cut answers that were provided to well-defined problems that continue to be important.

What was it that gave each new paper by Stephen Kuffler that special quality which made it such a pleasure to read? Partly it was the unremittingly high standards of evidence, partly the elegance of the approach and the beautiful figures, and partly the underlying excitement of wondering—what would he tackle next? In addition, most of the experiments combined high technical virtuosity with directness of approach and clarity of thought matched by the style of the writing. Moreover, one knew that, right up to the end, he himself had done *every* experiment he described.

A striking feature of Stephen Kuffler's work is the multidisciplinary approach. To this end, he, more than anyone else, gave meaning to the idea of "Neurobiology"—a discipline in which the nervous system is studied in terms of cell biology, using biochemical, physiological, immunological, and anatomical approaches. At Harvard he created for the first time a department of Neurobiology in which he brought together people from widely different disciplines who actively collaborated, and thereby allowed new ways of thinking to evolve. He helped also to create interdisciplinary courses for young scientists at Woods Hole.

The list of his personal attributes is difficult to describe adequately. Those who knew him remember that unique combination of tolerance and firmness, kindness without sentimentality, good sense with enduring humor, with jokes and puns that often had an end but no beginning but still made one laugh. Long walks, long talks, relaxed meals, and quiet silences with friends were among his pleasures and contributed to the indelible memories he gave his friends.

He was the John Franklin Enders University Professor at Harvard and was closely associated with the Marine Biological Laboratory at Woods Hole. Among his many honors and distinctions was his election as a foreign member of the Royal Society.



**JOHN G. NICHOLLS** is Professor of Pharmacology at the Biocenter, Basel University, and until recently was Professor of Neurobiology at Stanford University School of Medicine. He was born in 1929 in London, where he graduated in medicine from Charing Cross Hospital, London University, and received a doctorate in physiology from the Department of Biophysics at University College. He has taught at University College, London, at Oxford, and at Yale, Harvard, and Stanford Medical Schools. During the summers he has given courses at the Marine Biological Laboratory in Woods Hole and at the Cold Spring Harbor Laboratory. His research has contributed to sensory and nerve–muscle physiology and to the physiology of neuroglial cells, an area in which he and Stephen Kuffler collaborated. For some years he has used the relatively simple nervous system of the leech to study synaptic transmission and the regeneration of synaptic connections.

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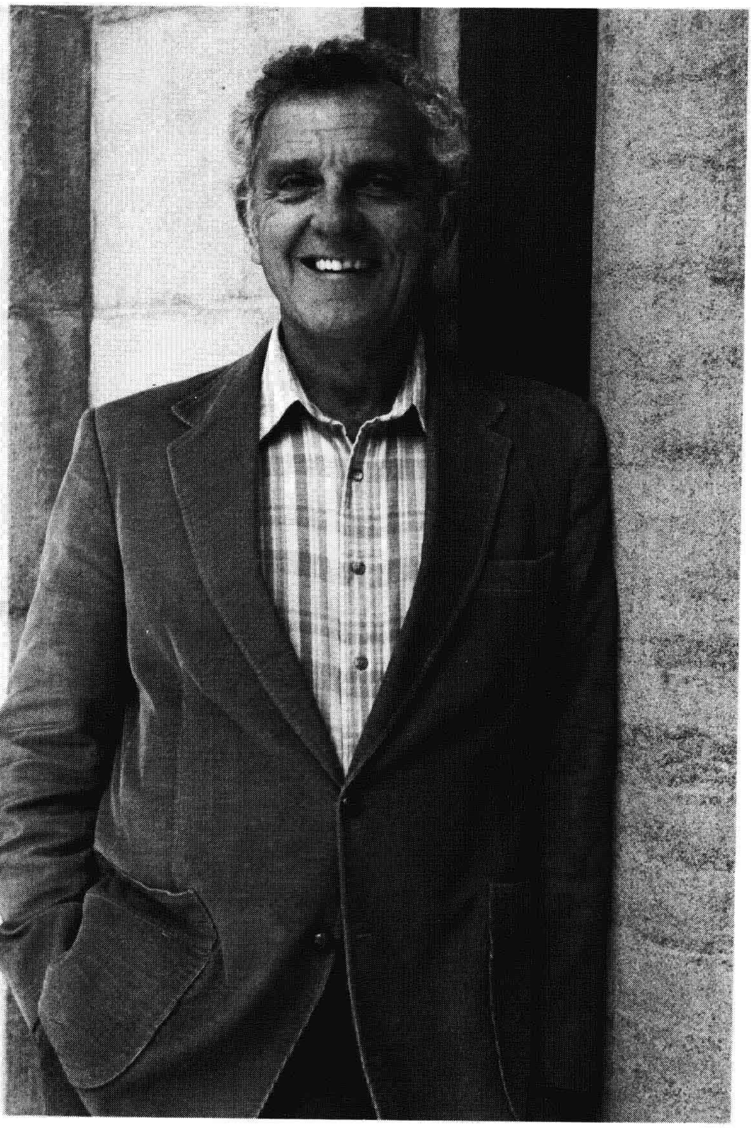

**A. ROBERT MARTIN** is Professor and Chairman of the Department of Physiology at the University of Colorado School of Medicine. He was born in Saskatchewan in 1928 and majored in mathematics and physics at the University of Manitoba. He received a doctorate in biophysics from University College London in 1955, where he and John Nicholls studied together, with Sir Bernard Katz as their advisor. He has taught at McGill University, the University of Utah, Yale University and the University of Colorado Medical Schools, and has been a visiting professor at Monash and Edinburgh Universities. His major research interests are synaptic transmission in the central and peripheral nervous systems, processes of release of neurotransmitter from presynaptic nerve terminals, and membrane channels activated by neurotransmitters. Recently, he has turned his attention to synaptic mechanisms in the central nervous system of the lamprey.

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