MEMBRANE PHYSIOLOGY

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Prentice-Hall, Inc.
Englewood Cliffs, New Jersey

10 9 8 7 6 5 4 3 2 1

ISBN: 0-13-574087-8

Library of Congress Catalog Card Number: 72-6153

Printed in the United States of America

PRENTICE-HALL INTERNATIONAL, INC., *London*
PRENTICE-HALL OF AUSTRALIA, PTY. LTD., *Sydney*
PRENTICE-HALL OF CANADA, LTD., *Toronto*
PRENTICE-HALL OF INDIA PRIVATE LIMITED, *New Delhi*
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ACKNOWLEDGMENTS

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PREFACE

This book is an integrated and relatively compact presentation of cytological, physiological, and molecular data on plasma membranes of animal cells. For a long time the study of the structure and function of biological membranes has been one of the more active endeavors of biological investigators. So many disciplines are involved — biophysics, biochemistry, morphology, pharmacology, physiology, physical chemistry, molecular biology — and the literature is so extensive that it is difficult for workers of diverse training and experience to fully appreciate the level of understanding and the advances within neighboring fields. A young biologist contemplating investigations on membranes and an older worker trained in another field both require a conceptual insight into the nature of membrane problems and a scientific intuition into their solution. The recent scientific conferences and symposiums dealing with general aspects of membranology, a multitude of research reviews and books, and at least one new journal devoted solely to membrane biology have served to unify the field. However, much of this material characteristically contains articles that are restricted in scope and written for scientifically sophisticated readers. None is sufficiently broad to embrace all aspects of the work on biological membranes and at the same time sufficiently integrated to provide a background necessary to relate one finding to another. None is exceptionally noted for its readability. This book may help as an introduction to that literature in several ways.

By discussing the current state of our understanding of the nature of membrane structure, permeation, and excitability of both living and artificial systems, the book covers a broad range of knowledge, but it is clearly not comprehensive. Within the areas covered, only work that I consider important or interesting is included. Investigations on cytoplasmic membranes and on plant and bacterial membranes are barely mentioned; pinocytosis and phagocytosis are only acknowledged; and the role of the cell surface in cellular contact and immunological relationships is ignored completely — to the dismay of virologists, immunologists, pathologists, tissue culturists, and cancer researchers, among others. This book is restricted but not superficial. The intent is not only to present a readable account of the major ideas of the various approaches to membrane study and their broader implications but also to include the complications, limitations, alternative explanations, and important minor points to these investigations. This book is concise and elementary but not simple. The intent is to inform the reader so that he will be able to more effectively glean the sophisticated books, reviews, and research papers on membranes and evaluate their interpretations in his own mind. Sufficient knowledge is extant to permit an uncomplicated summary of only the widely held conclusions and to tell a pretty story, but a beginner would not be well served and a seasoned veteran would not be well satisfied by such an approach. Difficulties with arguments are readily presented, but experimental and language technicalities and ponderous derivations are reduced. Experimental procedures are discussed where they are important to the proper interpretation of the data that they yield. The important quantitative analyses of membrane data are hinted at, but full and, hence, proper treatment is to be found in the publications cited.

The many references cited are intended more as a guide through the literature than as a historical account of authenticity; so a large number refer to reviews and interpretative work. The examples selected for a more detailed analysis represent my own favorites rather than an attempt to tell all or to give the most recent. Experienced investigators will undoubtedly be unhappy about the treatment given some topics as well as the exclusion of others. The success of my approach will be determined by the usefulness of this small volume to you.

Historically, this manuscript is derived in part from a series of discussions held many years ago with members of the Engineering Physics Department of the E. I. du Pont de Nemours Company, Wilmington, Delaware. The time to finish it became more readily available as a result of the freedom from academic duties beyond normal teaching and research provided by a sabbatical leave from the University of Delaware and a Special Fellowship from the National Institutes of Neurological Diseases and Stroke to work on other things at the Massachusetts Institute of Technology and the Marine Biological Laboratory at Woods Hole.

While the responsibility for this manuscript is clearly mine, I am most grateful and thankful for the encouragement, advice, assistance, and especially the criticism of A. Bortoff, Z. de Schauensee, P. B. Dunham, A. Gould, C. M. Lent, R. A. Levy, P. D. Lunger, D. W. Martin, R. A. Meiss, I. Nadelhaft, V. Shashoua, L. Smucker, W. M. Trippeer, J. T. Tupper, D. F. Wilson, R. A. Yates, and the anonymous referees found by J. R. Riina of Prentice-Hall, Inc. I am also pleased to acknowledge K. D. Roeder, C. L. Prosser, R. R. Ronkin, and F. O. Schmitt, all of whom helped to influence my scientific career.

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CONTENTS

INTRODUCTION

chapter one

Cellular activities are characterized by their occurrence at or near membranes located throughout the cell (Figs. 1–3). For example, much of cellular metabolism is associated with enzymes aligned on cristae of mitochondria; protein synthesis is associated with ribosomes attached to endoplasmic reticulum; lipid transport, with Golgi apparatus; photosynthesis, with grana within chloroplasts; light reception, with retinal rods. The interest here, however, is concerned with the surface of the cell—the cellular membrane or, more properly, the plasma membrane—the barrier or interface between the living inside and the dead outside of the cell.

A variety of physical measurements indicates that the cell surface is about 75Å thick although the published figures vary greatly. This thin structure is made of protein, some carbohydrate, and lipid, mostly sterol and phospholipid. For more than 30 years the molecular arrangement has been described as a double layer of lipid between two protein layers. Studies using X-ray diffraction, polarized light, electron microscopy, and permeability data have in general confirmed this view although newer techniques and approaches have exposed globular substructures and have confused the satisfaction with this description. Pores in membrane structures have been proposed with regularity, but, as the supporting experiments are all indirect ones and as investigators become more familiar with dynamic concepts, the need for the existence of a pore as a fixed morphological structure to understand membrane permeation is becoming less important.

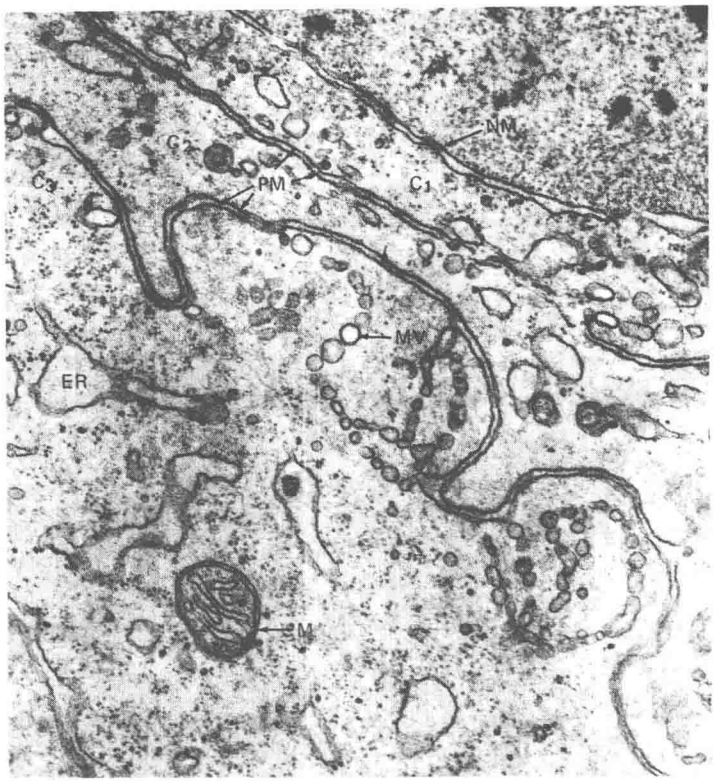

Figure 1. *Examples of membranous structures in cells:* three adjacent frog kidney cells showing at least five types of membrane. C_1, C_2, and C_3 are portions of three cells separated by plasma membranes (PM) and a small amount of extracellular space. The double nuclear membrane (NM) appears at the upper right. A mitochondrion (M) and its cristae are seen at the lower left. Smooth endoplasmic reticulum (ER) and ribosomal particles appear in the cytoplasm of C_3 especially. The rows of membranous vesicles (MV) near the plasma membrane of C_3 are considered by some workers to be plasma membrane that is either forming or degenerating ($\times$ 40,000).

Life exists in a liquid phase. Cells contain and surround themselves with liquid media; water is the solvent. Materials continuously exchange between the inside and outside of cells, dead or alive. Obviously, the cell surface is not an absolute barrier. In living cells, the plasma membrane regulates this exchange with care by processes best described by nonequilibrium thermodynamics; only a dead cell is in complete equilibrium with the solutes in its environment. Larger molecules permeate the membrane more slowly than do smaller ones. Molecules soluble in lipid cross the cell surface barrier faster than others. The transfer of polar molecules is impeded. But water

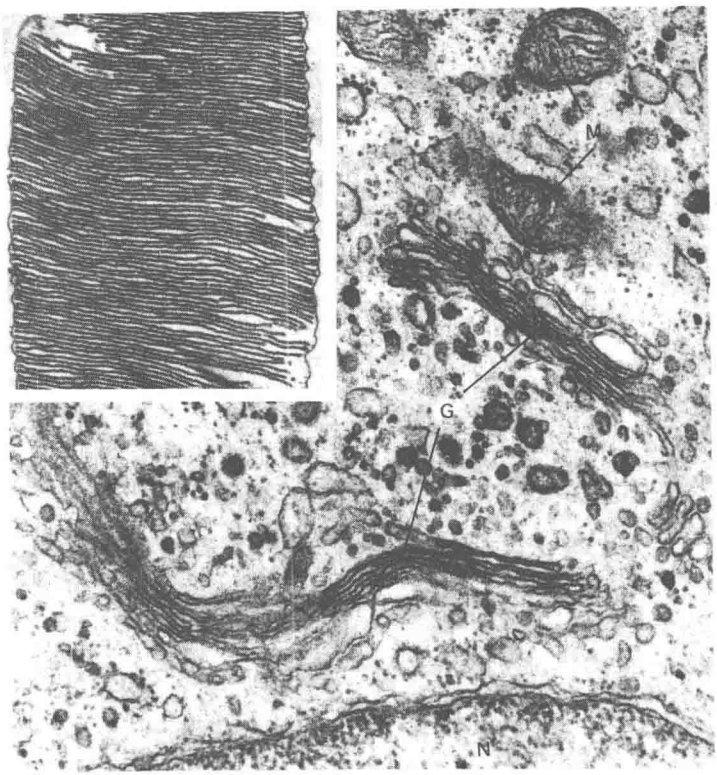

Figure 2. *Examples of membranous structures in cells:* rod membrane in turtle retina and Golgi membrane in frog kidney cells. Portions of three mitochondria (M) can be seen at the upper right and a small part of nucleus (N) and the double nuclear membrane at the bottom as well as Golgi apparatus (G). The endoplasmic reticulum in these cells is highly vesicular (× 40,000). A portion of the outer segment of a retinal rod from turtle eye (insert) illustrates the densely packed membranes characteristic of this light receptor (× 14,500).

molecules are among the fastest to permeate cells. Often the transport of molecules across the plasma membrane cannot be explained solely on the basis of concentration and charge gradients. Metabolic energy appears necessary for some transport processes and a cell will accumulate large concentrations of particular molecules while excluding others. Indeed the pronounced separation of charged molecules across the cell surface is the basis for normal functioning of excitable cells in nerve and muscle. Energy-requiring enzymes, carrier molecules, gates, and special membrane properties become involved in the explanations for the permeation by many substances even in cases where the steady state distribution appears to be adequately explained by the rules of simple diffusion.