

SECOND EDITION

PRINCIPLES OF
PHYSIOLOGY

ROBERT M. BERNE



MATTHEW N. LEVY

SECOND EDITION

PRINCIPLES OF PHYSIOLOGY

Edited by

ROBERT M. BERNE, M.D., D.Sc. (Hon.)

Professor of Physiology, Emeritus
Department of Physiology,
University of Virginia School of Medicine,
Charlottesville, Virginia

MATTHEW N. LEVY, M.D.

Chief of Investigative Medicine,
Mount Sinai Medical Center
Professor of Physiology and Biophysics and of
Biomedical Engineering, Emeritus
Case Western Reserve University,
Cleveland, Ohio

With 620 illustrations

Mc **MUSBY**

St. Louis Baltimore Boston Carlsbad Chicago Naples New York Philadelphia Portland
London Madrid Mexico City Singapore Sydney Tokyo Toronto Wiesbaden



Publisher: Anne S. Patterson
Editor: Emma D. Underdown
Developmental Editor: Christy Wells
Editorial Assistant: Alicia E. Moten
Project Manager: Mark Spann
Production Editor: Stephen C. Hetager
Designer: David Zielinski
Manufacturing Supervisor: Betty Richmond
Cover Design: Bill Schraeder

SECOND EDITION

Copyright © 1996 by Mosby-Year Book, Inc.

Previous edition copyrighted 1990

Greek edition: Crete University Press

Indonesian edition: Binarupa Aksara

Italian edition: Casa Editrice Ambrosiana

Portuguese edition: Editôra Guanabara Koogan

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the publisher.

Permission to photocopy or reproduce solely for internal or personal use is permitted for libraries or other users registered with the Copyright Clearance Center, provided that the base fee of \$4.00 per chapter plus \$.10 per page is paid directly to the Copyright Clearance Center, 27 Congress Street, Salem, MA 01970. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collected works, or for resale.

Printed in the United States of America
Composition by The Clarinda Company
Printing/binding by Von Hoffmann Press

Mosby-Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, Missouri 63146

ISBN 0-8151-0523-1

96 97 98 99 00 / 9 8 7 6 5 4 3 2 1

PRINCIPLES OF
PHYSIOLOGY

EDITED BY
ROBERT H. BEANE, M.D., D.Sc. (HON.)

PROFESSOR OF PHYSIOLOGY, HARVARD
UNIVERSITY, CAMBRIDGE,
MASSACHUSETTS, U.S.A.
AND VICE-CHANCELLOR, UNIVERSITY OF
NEWCASTLE, NEWCASTLE, AUSTRALIA

WITH THE ASSISTANCE OF
MATTHEW W. C. C. C. C.

CHIEF OF THE PHYSIOLOGY

DEPARTMENT, HARVARD UNIVERSITY

AND VICE-CHANCELLOR, UNIVERSITY OF

NEWCASTLE, NEWCASTLE, AUSTRALIA

AND VICE-CHANCELLOR, UNIVERSITY OF

NEWCASTLE, NEWCASTLE, AUSTRALIA

AND VICE-CHANCELLOR, UNIVERSITY OF

NEWCASTLE, NEWCASTLE, AUSTRALIA

AND VICE-CHANCELLOR, UNIVERSITY OF

NEWCASTLE, NEWCASTLE, AUSTRALIA

AND VICE-CHANCELLOR, UNIVERSITY OF

NEWCASTLE, NEWCASTLE, AUSTRALIA

AND VICE-CHANCELLOR, UNIVERSITY OF

NEWCASTLE, NEWCASTLE, AUSTRALIA

AND VICE-CHANCELLOR, UNIVERSITY OF

NEWCASTLE, NEWCASTLE, AUSTRALIA

AND VICE-CHANCELLOR, UNIVERSITY OF

NEWCASTLE, NEWCASTLE, AUSTRALIA

AND VICE-CHANCELLOR, UNIVERSITY OF

NEWCASTLE, NEWCASTLE, AUSTRALIA

AND VICE-CHANCELLOR, UNIVERSITY OF

NEWCASTLE, NEWCASTLE, AUSTRALIA

AND VICE-CHANCELLOR, UNIVERSITY OF

NEWCASTLE, NEWCASTLE, AUSTRALIA

AND VICE-CHANCELLOR, UNIVERSITY OF

NEWCASTLE, NEWCASTLE, AUSTRALIA

CONTRIBUTORS

SAUL M. GENUTH, M.D.

Professor, Department of Medicine,
School of Medicine,
Case Western Reserve University,
Cleveland, Ohio

BRUCE M. KOEPPEN, M.D., Ph.D.

Associate Professor,
Department of Medicine and Physiology,
University of Connecticut Health Center,
Farmington, Connecticut

HOWARD C. KUTCHAI, Ph.D.

Professor,
Department of Physiology,
University of Virginia School of Medicine,
Charlottesville, Virginia

RICHARD A. MURPHY, Ph.D.

Professor,
Department of Physiology,
University of Virginia School of Medicine,
Charlottesville, Virginia

BRUCE A. STANTON, Ph.D.

Dean, Academic Affairs and Education,
Associate Professor,
Department of Physiology,
Dartmouth College Medical School,
Hanover, New Hampshire

NORMAN C. STAUB, M.D.

Professor of Physiology, Emeritus,
University of California School of Medicine,
San Francisco, California

WILLIAM D. WILLIS, JR., M.D., Ph.D.

Professor and Chairman,
Department of Anatomy and Neurosciences,
The University of Texas Medical Branch at Galveston,
Galveston, Texas

PREFACE

Principles of Physiology has been carefully designed to present the important features of mammalian physiology clearly and concisely. General principles and underlying mechanisms are emphasized, and nonvital details are minimized. Considerable attention is directed to cell physiology, which serves as the basis for body functions. The first section of the text is devoted to this topic, and a new chapter on the mechanisms of cell signaling has been added to this section. Furthermore, the relevant cell physiology has been included in each of the succeeding sections. We have tried to show that the processes that take place in living cells in general are usually also applicable to the specific cell types in the various organ systems.

The major emphasis in *Principles of Physiology* is on regulation. The mechanisms that regulate the functions of the individual organ systems are thoroughly described. These mechanisms are then applied to the complex interactions among the systems as they maintain the internal environment constant, a process that is so important for the optimal function of the constituent cells.

In this edition, Dr. Norman Staub has rewritten the section on respiratory physiology. At the end of the section on cardiovascular physiology, a chapter has been added on the responses to physical exercise and to hemorrhage. The purpose of this chapter is mainly to illustrate the ways in which the various components of the circulatory system are coordinated to allow the body to adapt to certain substantial stresses.

To contribute to our goal of clarity, multicolored illustrations are used to portray concepts as simply as possible. When sequential mechanisms are involved, multipaneled diagrams have been designed to illustrate each step clearly. Block diagrams are used to depict the interrelationships among the various factors that may affect

a specific function. Finally, figures are included to illustrate some of the concepts that appear in the text and to inform the reader about important investigative techniques.

Because the intent of this text is to offer, clearly and concisely, all information needed to master a complete course in physiology, the use of mathematics has been minimized, and succinct, lucid descriptions have been substituted wherever feasible. Controversial issues have been omitted to allow ample room for the explanation of important, generally accepted physiological mechanisms. We have refrained from citing the sources of the statements or assertions that appear in the text. Throughout the book, we have used italics to emphasize important concepts, and we have used boldface to denote new terms and definitions. We have also emphasized many of the important concepts by citing clinical conditions in which such concepts are involved. These clinical illustrations are highlighted in screened areas throughout the text.

Summaries are provided at the end of each chapter to emphasize the key points in the chapter, and brief bibliographies are included to direct the student to more detailed information. The references listed in these bibliographies are mainly review articles or recent, relevant scientific papers. At the end of the book, we have included a number of multiple-choice review questions and answers. These questions can serve as a guide for the readers to evaluate their comprehension of the material covered in the text.

Robert M. Berne
Matthew N. Levy

CONTENTS

PART I

Cell Physiology

Howard C. Kutchai

1 Cellular Membranes and Transmembrane Transport of Solutes and Water, 3

Cellular Membranes, 3
Membrane Composition, 4
Membranes as Permeability Barriers, 6
Transport Across, But Not Through, Membranes, 6
Transport of Molecules Through Membranes, 7
Osmosis, 10
Protein-Mediated Membrane Transport, 14
Summary, 18

2 Ionic Equilibria and Resting Membrane Potentials, 19

Ionic Equilibria, 19
Resting Membrane Potentials, 23
Summary, 26

3 Generation and Conduction of Action Potentials, 29

Action Potentials in Different Tissues, 29
Membrane Potentials, 29
Ionic Mechanisms of Action Potentials, 30
Properties of Action Potentials, 36
Conduction of Action Potentials, 37
Summary, 41

4 Synaptic Transmission, 43

Neuromuscular Junctions, 43
Synapses Between Neurons, 47
Neurotransmitters and Neuromodulators, 52
Summary, 56

5 Membrane Receptors, Second Messengers, and Signal Transduction Pathways, 59

Overview, 59
Protein Kinases and Second Messengers in Signal Transduction Pathways, 59
G-Protein-Mediated Signal Transduction Pathways, 61
Membrane Phospholipids and Signal Transduction Pathways, 62
Membrane Receptors for Regulatory Molecules, 63

GTP-Binding Proteins (G-Proteins), 63
Second Messenger-Dependent Protein Kinases, 66
Protein Tyrosine Kinases, 68
Protein Phosphatases and Their Modulation, 69
Atrial Natriuretic Peptide Receptor and Guanylyl Cyclases, 72
Summary, 72

PART II

Nervous System

William D. Willis, Jr.

6 Cellular Organization of the Nervous System, 77

General Functions of the Nervous System, 77
Organization of the Nervous System, 78
Composition of the Nervous Tissue, 78
Microscopic Anatomy of the Neuron, 79
Transmission of Information, 80
Reactions to Injury, 85
Environment of the Neuron, 87
Summary, 89

7 The General Sensory System, 91

Principles of Sensory Physiology, 91
Somatovisceral Sensory System, 96
Summary, 108

8 Special Senses, 111

Visual System, 111
Auditory System, 118
Vestibular System, 124
Chemical Senses, 128
Summary, 130

9 The Motor System, 133

Spinal Cord Motor Organization, 133
Organization of Descending Motor Pathways, 146
Brainstem Control of Posture and Movement, 149
Cortical Control of Voluntary Movement, 153
Cerebellar Regulation of Posture and Movement, 156
Regulation of Posture and Movement by the Basal Ganglia, 158
Summary, 158

10 The Autonomic Nervous System and its Control, 161

Organization of the Autonomic Nervous System, 161
Autonomic Functions, 165
Functions of the Hypothalamus, 166
The Limbic System, 167
Summary, 168

11 Higher Functions of the Nervous System, 169

The Electroencephalogram, 169
Evoked Potentials, 169
States of Consciousness, 169
Learning and Memory, 172
Cerebral Dominance, 173
Summary, 174

PART III

Muscle

Richard A. Murphy

12 The Molecular Basis of Contraction, 177

The Contractile Unit, 177
The Crossbridge Cycle, 177
The Biological Response: Characterizing Contraction, 178
Summary, 183

13 Muscles Acting on the Skeleton, 185

Musculoskeletal Relationships, 185
Regulation of Contraction and Relaxation, 188
Function Diversity in Skeletal Muscle, 190
Growth and Adaptation, 193
Summary, 194

14 Muscle in the Walls of Hollow Organs, 197

Muscle Function in Hollow Organs, 197
Control Systems: Inputs to the Sarcolemma and Ca^{++} Mobilization, 201
 Ca^{++} and Crossbridge Regulation in Smooth Muscle, 204
Cardiac Muscle, 208
Summary, 210

PART IV

Cardiovascular System

Robert M. Berne

Matthew N. Levy

15 Blood and Hemostasis, 213

Blood, 213
Hemostasis, 216
Summary, 218

16 Overview of the Circulation, 219

Summary, 222

17 Electrical Activity of the Heart, 223

Transmembrane Potentials of Cardiac Cells, 223
Ionic Basis of the Membrane Potential, 225
Conduction in Cardiac Fibers, 228
Cardiac Excitability, 229
Natural Excitation of the Heart, 231
Reentry, 238
Electrocardiography, 238
Summary, 239

18 The Cardiac Pump, 243

Anatomical Basis of Cardiac Function, 243
Heart Sounds, 251
Cardiac Cycle, 252
Measurement of Cardiac Output, 255
Summary, 257

19 Regulation of the Heartbeat, 259

Control of Heart Rate, 259
Regulation of Myocardial Performance, 265
Summary, 274

20 Hemodynamics, 277

Velocity of the Bloodstream, 277
Relationship Between Pressure and Flow, 278
Resistance to Flow, 280
Laminar Flow and Turbulent Flow, 283
Rheological Properties of Blood, 284
Summary, 286

21 The Arterial System, 289

Hydraulic Filter, 289
Arterial Compliance, 289
Determinants of the Arterial Blood Pressure, 291
Blood Pressure Measurement in Humans, 298
Summary, 299

22 The Microcirculation and Lymphatics, 301

Functional Anatomy, 301
Transcapillary Exchange, 304
Lymphatics, 310
Summary, 311

23 The Peripheral Circulation and Its Control, 313

Vascular Smooth Muscle, 313
Intrinsic or Local Control of Peripheral Blood Flow, 313
Extrinsic Control of Peripheral Blood Flow, 315
Balance Between Intrinsic and Extrinsic Factors in the Regulation of Peripheral Blood Flow, 320
Summary, 321

24 Control of Cardiac Output: Coupling of the Heart and Blood Vessels, 323

Controlling Factors, 323
Vascular Function Curve, 324
Coupling Between the Heart and the Vasculature, 329
Role of Heart Rate, 332
Ancillary Factors, 333
Summary, 336

25 Special Circulations, 339

Cutaneous Circulation, 339
 Skeletal Muscle Circulation, 341
 Coronary Circulation, 342
 Cerebral Circulation, 346
 Splanchnic Circulation, 346
 Fetal Circulation, 348
 Summary, 350

26 Interplay of Central and Peripheral Factors in the Control of the Circulation, 353

Exercise, 353
 Hemorrhage, 358
 Summary, 365

PART V**Respiratory System**

Norman C. Staub

27 An Overview of the Respiratory System, 369

Necessity of Respiration, 369
 Blood Gas Transport and Tissue Gas Exchange, 370
 Control System, 371
 Structure-Function Relationships, 372
 The Physiological Lung Unit, 377
 Summary, 378

28 Mechanical Aspects of Breathing, 381

Ventilation, 381
 The Chest Wall is the Breathing Pump, 382
 The Breathing Cycle, 385
 How the Lung is Supported in the Thorax, 393
 Summary, 393

29 Pulmonary and Bronchial Circulations and the Distribution of Ventilation and Perfusion, 395

Overview, 395
 Pressure and Resistance, 395
 Pulmonary Blood Flow, 397
 Regulation of the Pulmonary Circulation, 401
 Bronchial Circulation, 402
 Matching Ventilation to Perfusion, 403
 Distribution of Ventilation, 404
 Distribution of Perfusion, 406
 The Effect of V/Q Mismatching, 406
 Summary, 408

30 Transport of Oxygen and Carbon Dioxide Between Lungs and Cells of the Body, 411

Arterial and Venous Streams, 411
 Oxygen Transport, 411
 Respiratory Gas Diffusion in the Body, 416
 Carbon Dioxide Transport, 418
 Summary, 421

31 Control of Breathing, 423

Central Organization of Breathing, 423
 Spinal Integration, 427
 Chemoreceptor Control of Breathing, 427
 Mechanical Control of Breathing, 429
 Respiratory Failure, 431
 Abnormal Breathing Patterns, 431
 Sleep, 431
 Acclimatization to Altitude, 432
 Summary, 433

PART VI**Gastrointestinal System**

Howard C. Kutchai

32 Motility of the Gastrointestinal Tract, 437

Structure of the Gastrointestinal Tract, 437
 Innervation of the Gastrointestinal Tract, 438
 Gastrointestinal Smooth Muscle, 440
 Integration and Control of Gastrointestinal Motility, 442
 Chewing (Mastication), 444
 Swallowing, 444
 Esophageal Function, 445
 Gastric Motility, 447
 Vomiting, 450
 Motility of the Small Intestine, 452
 Motility of the Colon, 455
 Summary, 457

33 Gastrointestinal Secretions, 459

Secretion of Saliva, 459
 Gastric Secretion, 462
 Pancreatic Secretion, 470
 Functions of the Liver and Gallbladder, 473
 Intestinal Secretions, 478
 Summary, 478

34 Digestion and Absorption, 481

Digestion and Absorption of Carbohydrates, 481
 Digestion and Absorption of Proteins, 483
 Intestinal Absorption of Water and Electrolytes, 485
 Absorption of Calcium, 490
 Absorption of Iron, 491
 Absorption of Other Ions, 492
 Absorption of Water-Soluble Vitamins, 493
 Digestion and Absorption of Lipids, 494
 Summary, 498

PART VII**Renal System**

Bruce M. Koeppen

Bruce A. Stanton

35 Elements of Renal Function, 503

Overview of the Kidneys, 503
 Functional Anatomy of the Kidneys, 503
 Anatomy and Physiology of the Lower Urinary Tract, 509
 Assessment of Renal Function, 511
 Glomerular Filtration, 515
 Renal Blood Flow, 517
 Summary, 520

36 Solute and Water Transport Along the Nephron: Tubular Function, 523

General Principles of Transepithelial Solute and Water Transport, 523
 Proximal Tubule, 524
 Henle's Loop, 529
 Distal Tubule and Collecting Duct, 530
 Regulation of NaCl and Water Reabsorption, 533
 Summary, 536

37 Control of Body Fluid Volume and Osmolality, 537

The Body Fluid Compartments, 537
 Control of Body Fluid Osmolality: Urine Concentration and Dilution, 539
 Control of Extracellular Fluid Volume, 547
 Summary, 553

38 Renal Regulation of Potassium, Calcium, Magnesium, and Phosphate Balance, 555

Potassium (K^+), 555
 Multivalent Ions, 562
 Summary, 569

39 Role of the Kidney in Acid-Base Balance, 571

The CO_2/HCO_3^- Buffer System, 571
 Production of Nonvolatile Acid, 572
 Renal Acid Excretion, 572
 Bicarbonate Reabsorption Along the Nephron, 573
 Regulation of Bicarbonate Reabsorption, 575
 Formation of New Bicarbonate, 575
 Response to Acid-Base Disorders, 578
 Simple Acid-Base Disorders, 579
 Analysis of Acid-Base Disorders, 580
 Summary, 581

PART VIII**Endocrine System**

Saul M. Genuth

40 General Principles of Endocrine Physiology, 585

Patterns of Hormone Synthesis, Storage, and Secretion, 586
 Regulation of Hormone Secretion, 588
 Hormone Turnover, 590
 Hormone Action, 591
 Summary, 596

41 Whole Body Metabolism, 599

Energy Metabolism, 599
 Energy Generation, 600
 Energy Storage and Transfers, 602
 Carbohydrate Metabolism, 604
 Protein Metabolism, 605
 Fat Metabolism, 606
 Metabolic Adaptations, 609
 Regulation of Energy Stores, 611
 Summary, 611

42 Hormones of the Pancreatic Islets, 613

Insulin, 613
 Glucagon, 620
 Insulin/Glucagon Ratio, 622
 Islet Somatostatin, 623
 Summary, 623

43 Endocrine Regulation of the Metabolism of Calcium and Related Minerals, 625

Calcium, Phosphate, and Magnesium Turnover, 625
 Bone Turnover, 627
 Vitamin D, 629
 Parathyroid Gland Function, 632
 Calcitonin, 636
 Integrated Regulation of Calcium and Phosphate, 637
 Summary, 638

44 The Hypothalamus and Pituitary Gland, 641

Anatomy and Embryological Development, 641
 Hypothalamic Function, 643
 Posterior Pituitary Function, 646
 Anterior Pituitary Function, 649
 Summary, 657

45 The Thyroid Gland, 659

Functional Anatomy, 659
 Synthesis and Secretion of Thyroid Hormones, 659
 Regulation of Thyroid Gland Activity, 663
 Metabolism of Thyroid Hormones, 665
 Actions of Thyroid Hormone, 667
 Summary, 670

46 The Adrenal Cortex, 673

Synthesis of Corticosteroid Hormones, 673
Corticosteroid Hormone Metabolism, 675
Regulation of Cortisol Secretion, 676
Actions of Cortisol (Glucocorticoids), 678
Regulation of Aldosterone Secretion, 683
Actions of Aldosterone (Mineralocorticoids), 685
Summary, 686

47 The Adrenal Medulla, 689

Synthesis, Storage, and Secretion of Medullary Hormones, 689
Metabolism of Catecholamine Hormones, 690
Regulation of Adrenal Medullary Secretion, 690
Actions of Catecholamine Hormones, 691
Integration of the Response to Stress, 695
Summary, 695

48 Overview of Reproductive Function, 697

Synthesis of Sex Steroid Hormones, 697
Regulation of Gonadal Steroid Hormone Secretion, 699
Age-Related Changes in Reproduction, 700
Sexual Differentiation, 702
Summary, 706

49 Male Reproduction, 709

Anatomy, 709
The Biology of Spermatogenesis, 709

Delivery of Spermatozoa, 711
Male Puberty, 711
Regulation of Spermatogenesis, 711
Secretion and Metabolism of Androgens, 715
Actions of Androgens, 715
Summary, 717

50 Female Reproduction, 719

Biology of Oogenesis, 719
Development of the Ovarian Follicle, 719
Corpus Luteum Formation, 721
Atresia of Follicles, 721
Hormonal Patterns During the Menstrual Cycle, 721
Hormonal Regulation of Oogenesis, 722
Hormonal Regulation of Reproductive Tract Function, 726
Mechanisms of Action of Ovarian Steroids, 728
Metabolism of Ovarian Steroids, 728
Female Puberty, 728
Menopause, 728
Pregnancy, 729
Maternal-Fetal Metabolism, 733
Parturition, 734
Lactation, 735
Summary, 735

Multiple-Choice Review Questions, 739

Cellular Membranes and Transmembrane Transport of Solutes and Water

CELLULAR MEMBRANES

Each cell is surrounded by a plasma membrane that separates it from the extracellular milieu. The **plasma membrane** serves as a permeability barrier that allows the cell to maintain a cytoplasmic composition far different from the composition of the extracellular fluid. The plasma membrane contains enzymes, receptors, and antigens that play central roles in the interaction of the cell with other cells and with hormones and other regulatory agents in the extracellular fluid.

The membranes that enclose the various organelles divide the cell into discrete compartments and allow the localization of particular biochemical processes in specific organelles. Many vital cellular processes take place in or on the membranes of the organelles. Striking examples are the processes of electron transport and oxidative phosphorylation, which occur on, within, and across the mitochondrial inner membrane.

Most biological membranes have certain features in common. However, in keeping with the diversity of membrane functions, the composition and structure of the membranes differ from one cell to another and among the membranes of a single cell.

Membrane Structure

Proteins and phospholipids are the most abundant constituents of cellular membranes. A **phospholipid** molecule has a polar head group and two very nonpolar, hydrophobic fatty acyl chains (Figure 1-1, A). In an aqueous environment phospholipids tend to form structures that allow the fatty acyl chains to be kept away from contact with water. One such structure is the **lipid bilayer** (Figure 1-1, B). Many phospholipids, when dispersed in water, spontaneously form lipid bilayers. Most

of the phospholipid molecules in biological membranes have a lipid bilayer structure.

The phospholipid bilayer is responsible for certain passive permeability properties of biological membranes. Substances that are highly soluble in water typically permeate cellular membranes very slowly, while nonpolar compounds that are more soluble in nonpolar or organic solvents cross cell membranes more rapidly. High concentrations of barium salts are administered by mouth or by enema in order to make the interior of the gastrointestinal tract opaque to x-rays and improve the contrast of diagnostic x-ray films of the gastrointestinal tract. Barium ions in this concentration would be highly toxic, but because barium is highly water-soluble, it is barely absorbed at all from the gastrointestinal tract. Hence, the concentrations of barium in the blood rise very little after administration of barium salts.

Figure 1-2 depicts the **fluid mosaic model** of membrane structure. This model is consistent with many of the properties of biological membranes. Note the bilayer structure of most of the membrane phospholipids. The membrane proteins are of two major classes: (1) **integral** or **intrinsic membrane proteins** that are embedded in the phospholipid bilayer and (2) **peripheral** or **extrinsic membrane proteins** that are associated with the surface of the membrane. The peripheral membrane proteins interact with the membrane predominantly by charge interactions with integral membrane proteins. Thus peripheral proteins may often be removed from the membrane by altering the ionic composition of the medium. Integral membrane proteins have important hydrophobic interactions with the interior of the membrane.

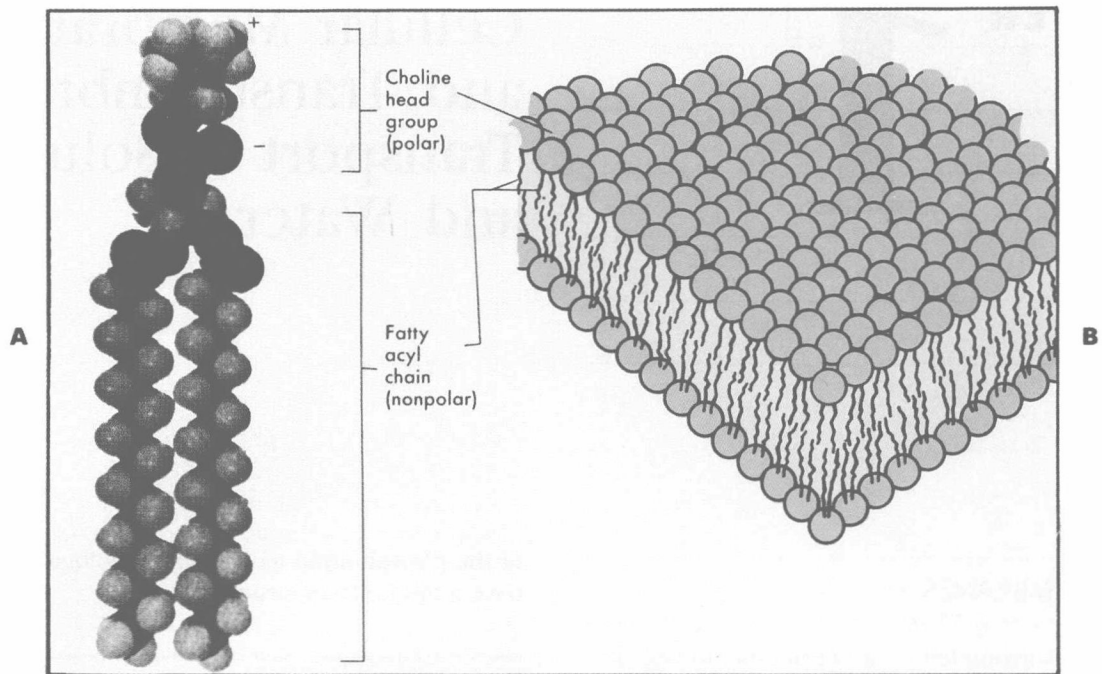


FIGURE 1-1 A, Structure of a membrane phospholipid molecule, in this case a phosphatidylcholine. B, Structure of a phospholipid bilayer. The open circles represent the polar head groups of the phospholipid molecules. The wavy lines represent the fatty acyl chains of the phospholipids.

These hydrophobic interactions can be disrupted only by detergents that make the integral proteins soluble by interacting hydrophobically with nonpolar amino acid side chains.

Cellular membranes are fluid structures in which many of the constituent molecules are free to diffuse in the plane of the membrane. Most lipids and proteins can move freely in the bilayer plane, but they “flip-flop” from one phospholipid monolayer to the other at much slower rates. A large hydrophilic moiety is unlikely to flip-flop if it must be dragged through the nonpolar interior of the lipid bilayer.

In some cases membrane components are not free to diffuse in the plane of the membrane. Examples of this motional constraint are the sequestration of acetylcholine receptors (integral membrane proteins) at the motor endplate of skeletal muscle and the presence of different membrane proteins in the apical and basolateral plasma membranes of epithelial cells. The cytoskeleton appears to tether certain membrane proteins. The **anion exchanger**, a major protein of the human erythrocyte membrane, is bound to the spectrin network that undergirds the membrane via a protein called **ankyrin**.

If the motor nerve that innervates a skeletal muscle is accidentally severed, the acetylcholine receptors are no longer sequestered at the motor endplate, but instead they spread out over the entire plasma membrane of the muscle cells. Then the entire surface of the cell becomes excitable by acetylcholine, a phenomenon known as **denervation supersensitivity**.

MEMBRANE COMPOSITION

Lipid Composition

Major Phospholipids In animal cell membranes the most abundant phospholipids are often the choline-containing phospholipids: the lecithins (phosphatidylcholines) and the sphingomyelins. Next in abundance are frequently the amino phospholipids: phosphatidylserine and phosphatidylethanolamine. *The phospholipid bilayer is primarily responsible for the passive permeability properties of the membrane.* Other important phos-

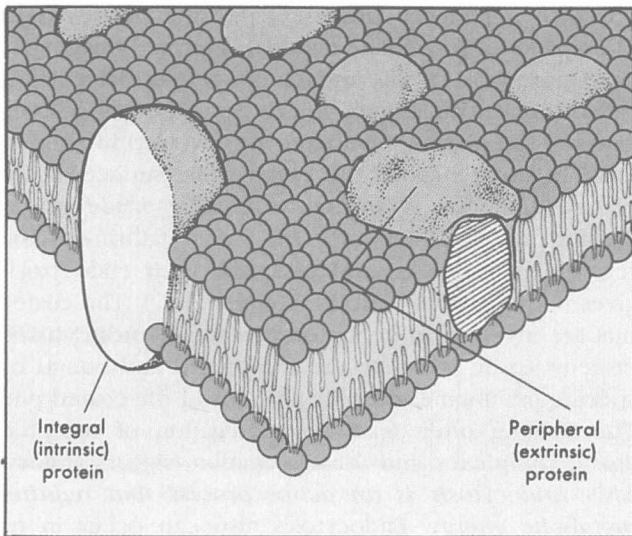


FIGURE 1-2 Schematic representation of the fluid mosaic model of membrane structure. The integral proteins are embedded in the lipid bilayer matrix of the membrane, and the peripheral proteins are associated with the external surfaces of integral membrane proteins.

pholipids present in smaller amounts are phosphatidylglycerol, phosphatidylinositol, and cardiolipin.

Certain phospholipids present in tiny proportions in the plasma membrane play a vital role in cellular signal transduction processes. **Phosphatidylinositol bisphosphate**, when cleaved by a receptor-activated phospholipase C, releases **inositol trisphosphate (IP_3)** and **diacyl glycerol**. IP_3 is released into the cytosol, where it acts on receptors in the endoplasmic reticulum to cause release of stored Ca^{++} , which affects a wide variety of cellular processes. Diacylglycerol remains in the plasma membrane, where it participates, along with Ca^{++} , in activating **protein kinase C**, an important signal transduction protein.

Cholesterol Cholesterol is a major constituent of plasma membranes, and its steroid nucleus lies parallel to the fatty acyl chains of membrane phospholipids. Cholesterol functions as a “fluidity buffer” in the plasma membrane in that its presence tends to keep the fluidity of the acyl chain region of the phospholipid bilayer in an intermediate range in the presence of agents, such as alcohols and general anesthetics, that tend to fluidize biological membranes.

Glycolipids Glycolipids are not abundant, but they have important functions. Glycolipids are found mostly in plasma membranes, where their carbohydrate moieties protrude from the external surface of the membrane. The carbohydrate parts of glycolipids frequently function as receptors or antigens.

The receptor for cholera toxin (Chapter 34) is the carbohydrate moiety of a particular glycolipid, ganglioside (GM_1). The A and B blood group antigens (Chapter 15) are the carbohydrate moieties of other gangliosides on the human erythrocyte membrane.

Asymmetry of Lipid Distribution In many membranes the lipid components are not distributed uniformly across the bilayer. The glycolipids of the plasma membrane are located almost exclusively in the outer monolayer. Phospholipids are also distributed asymmetrically between the inner and outer monolayers of membranes. In the red blood cell membrane, for example, the outer monolayer contains most of the choline-containing phospholipids, whereas the inner monolayer contains most of the amino phospholipids.

Membrane Proteins The protein composition of membranes may be simple or complex. The functionally specialized membranes of the sarcoplasmic reticulum of skeletal muscle and the disks of the rod outer segment of the retina contain only a few different proteins. By contrast, plasma membranes, which perform many functions, may have more than 100 different protein constituents. Membrane proteins include enzymes, transport proteins, and receptors for hormones and neurotransmitters.

Glycoproteins Some membrane proteins are glycoproteins with covalently bound carbohydrate side chains. As with glycolipids, the carbohydrate chains of glycoproteins are located almost exclusively on the external surfaces of plasma membranes. The carbohydrate moieties of membrane glycoproteins and glycolipids have important functions. The negative surface charge of cells is caused by the negatively charged sialic acid of glycolipids and glycoproteins.

Fibronectin is a large fibrous glycoprotein that helps cells attach, via cell surface glycoproteins called **integrins**, to proteins of the extracellular matrix. This linkage mediates communication between the extracellular matrix and the cell’s cytoskeleton during embryonic development.

The major membrane proteins of enveloped viruses are glycoproteins. Their carbohydrate moieties stud the outer surface of the virus with “spikes” that are required for the virus to bind to a host cell.

Asymmetry of Membrane Proteins The Na^+K^+ -ATPase of the plasma membrane and the Ca^{++} pump

protein (Ca^{++} -ATPase) of the sarcoplasmic reticulum membrane are examples of the asymmetric disposition of membrane proteins. In both cases ATP is split on the cytoplasmic face of the membrane, and some of the energy liberated is used to pump ions in specific directions across the membrane. In the case of the Na^+ - K^+ -ATPase, K^+ is pumped into the cell and Na^+ is pumped out, whereas the Ca^{++} -ATPase actively pumps Ca^{++} into the sarcoplasmic reticulum.

MEMBRANES AS PERMEABILITY BARRIERS

Biological membranes serve as **permeability barriers**. Most of the molecules present in living systems are highly soluble in water and poorly soluble in nonpolar solvents. Such molecules are poorly soluble in the nonpolar environment in the interior of the lipid bilayer of biological membranes. As a consequence, biological membranes pose a formidable barrier to most water-soluble molecules. *The plasma membrane is a permeability barrier between the cytoplasm and the extracellular fluid.* This barrier allows the maintenance of large concentration differences for many substances between the cytoplasm and the extracellular fluid.

The localization of various cellular processes in certain organelles depends on the barrier properties of cellular membranes. For example, the inner mitochondrial membrane is impermeable to the enzymes and substrates of the tricarboxylic acid cycle, and thus it allows the localization of the tricarboxylic cycle in the mitochondrial matrix. The spatial organization of chemical and physical processes in the cell depends on the barrier functions of cellular membranes, much as the walls of a house separate rooms with different functions.

The passage of important molecules across membranes at controlled rates is central to the life of the cell. Examples are the uptake of nutrient molecules, the discharge of waste products, and the release of secreted molecules. As discussed in the next section, molecules may move from one side of a membrane to another without actually moving through the membrane itself. In other cases molecules cross a particular membrane by passing through or between the molecules that make up the membrane.

TRANSPORT ACROSS, BUT NOT THROUGH, MEMBRANES

Endocytosis

Endocytosis is the process that allows material to enter the cell without passing through the membrane (Fig-

ure 1-3); it includes **phagocytosis** and **pinocytosis**. The uptake of particulate material is termed phagocytosis (Figure 1-3, *A*). The uptake of soluble molecules is called pinocytosis (Figure 1-3, *B*). Sometimes special regions of the plasma membrane are involved in endocytosis. In these regions the cytoplasmic surface of the plasma membrane is covered with bristles made primarily of a protein called **clathrin**. These clathrin-covered regions are called **coated pits**, and their endocytosis gives rise to coated vesicles (Figure 1-3, *C*). The coated pits are involved in **receptor-mediated endocytosis**. Proteins to be taken up are recognized and bound by specific membrane receptor proteins in the coated pits. The binding often leads to aggregation of receptor-ligand complexes, and the aggregation triggers endocytosis. *Endocytosis is an active process that requires metabolic energy.* Endocytosis also can occur in regions of the plasma membrane that do not contain coated pits.

Most cells cannot synthesize cholesterol, which is needed for synthesis of new membranes (see also Chapter 41). Cholesterol is carried in the blood, predominantly in low-density lipoproteins (LDL). Many cells have LDL receptors in their plasma membranes. When LDL binds to these receptors, the receptor-LDL complexes migrate to coated pits, where they aggregate and are taken into the cell by receptor-mediated endocytosis. Individuals who lack LDL receptors have high levels of cholesterol-laden LDL in their blood. Consequently such individuals tend to develop arterial disease (**atherosclerosis**) at an early age, which makes them more likely to experience heart attacks prematurely.

Exocytosis

Molecules can be ejected from cells by **exocytosis**, a process that resembles endocytosis in reverse. The release of neurotransmitters, which is considered in more detail in Chapter 4, takes place by exocytosis. Exocytosis is responsible for the release of secretory proteins by many cells; the release of pancreatic enzymes from the acinar cells of the pancreas is a well-studied example. The pancreatic enzymes play vital roles in digestion of protein, carbohydrates, and lipids (see Chapter 33). In such cases the proteins to be secreted are stored in secretory vesicles in the cytoplasm. *A stimulus to secrete causes the secretory vesicles to fuse with the plasma membrane and to release the vesicle contents by exocytosis.*

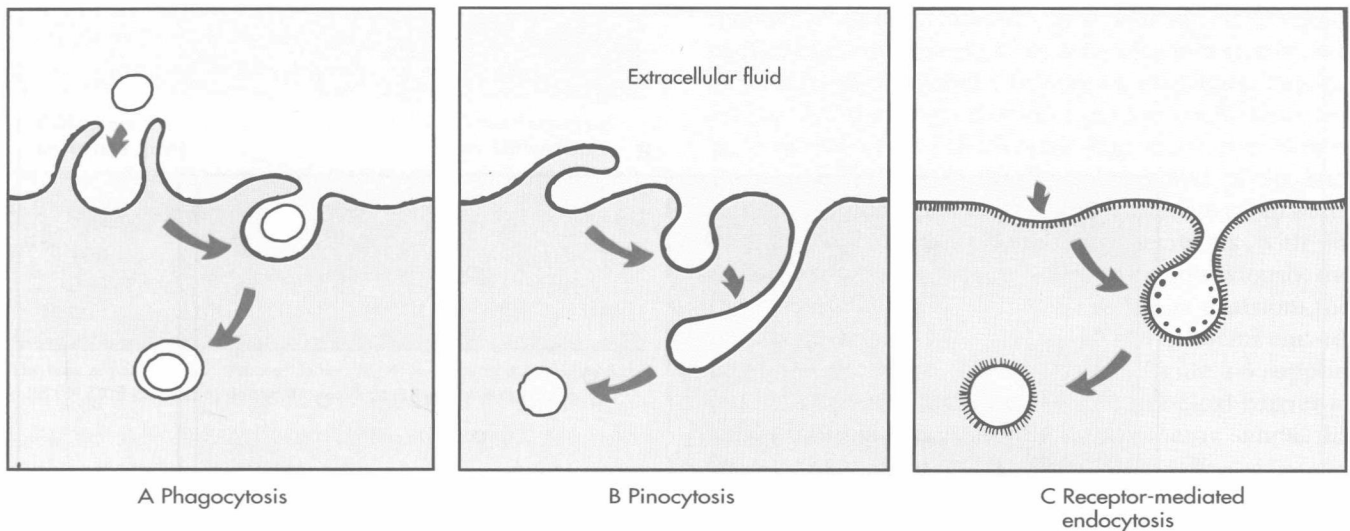


FIGURE 1-3 Schematic depiction of endocytotic processes. **A**, Phagocytosis of a solid particle. **B**, Pinocytosis of extracellular fluid. **C**, Receptor-mediated endocytosis by coated pits.

Fusion of Membrane Vesicles

The contents of one type of organelle can be transferred to another organelle by fusion of the membranes of the organelles. In some cells, secretory products are transferred from the endoplasmic reticulum to the Golgi apparatus by fusion of endoplasmic reticulum vesicles with membranous sacs of the Golgi apparatus. Fusion of phagocytic vesicles with lysosomes allows the phagocytosed material to be digested by proteolytic enzymes in the lysosomes. The turnover of many normal cellular constituents involves their destruction in lysosomes, followed by their resynthesis.

Influenza viruses have membrane proteins that undergo a dramatic conformational change to insert a "fusion peptide" into the host cell. The fusion peptide promotes the fusion of the viral membrane with the plasma membrane of the host cell, allowing entry of the viral genome into the host cell.

TRANSPORT OF MOLECULES THROUGH MEMBRANES

The traffic of molecules through biological membranes is vital for most cellular processes. Some molecules move through biological membranes simply by diffusing among the molecules that make up the membrane, whereas the passage of other molecules involves

the mediation of specific transport proteins in the membrane.

Oxygen, for example, is a small molecule that is fairly soluble in nonpolar solvents. It crosses biological membranes by diffusing among membrane lipid molecules. Glucose, on the other hand, is a much larger molecule that is not very soluble in the membrane lipids. Glucose enters cells via specific glucose transport proteins in the plasma membrane.

Diffusion

Diffusion is the process whereby atoms or molecules intermingle because of their random thermal motion, also called **Brownian motion**. Imagine a container divided into two compartments by a removable partition (Figure 1-4). A much larger number of molecules of a compound is placed on side A than on side B, and then the partition is removed. Every molecule is in random thermal motion. It is equally probable that a molecule that begins on side A will move to side B in a given time and that a molecule beginning on side B will end up on side A. Because many more molecules are present on side A, the total number of molecules moving from side A to side B will be greater than the number moving from side B to side A. In this way the number of molecules on side A will decrease, whereas the number of molecules on side B will increase. This process of net diffusion of molecules will continue until the concentration of molecules on side A equals that on side B. Thereafter the rate of diffusion of molecules from A to B will equal that from B to A, and