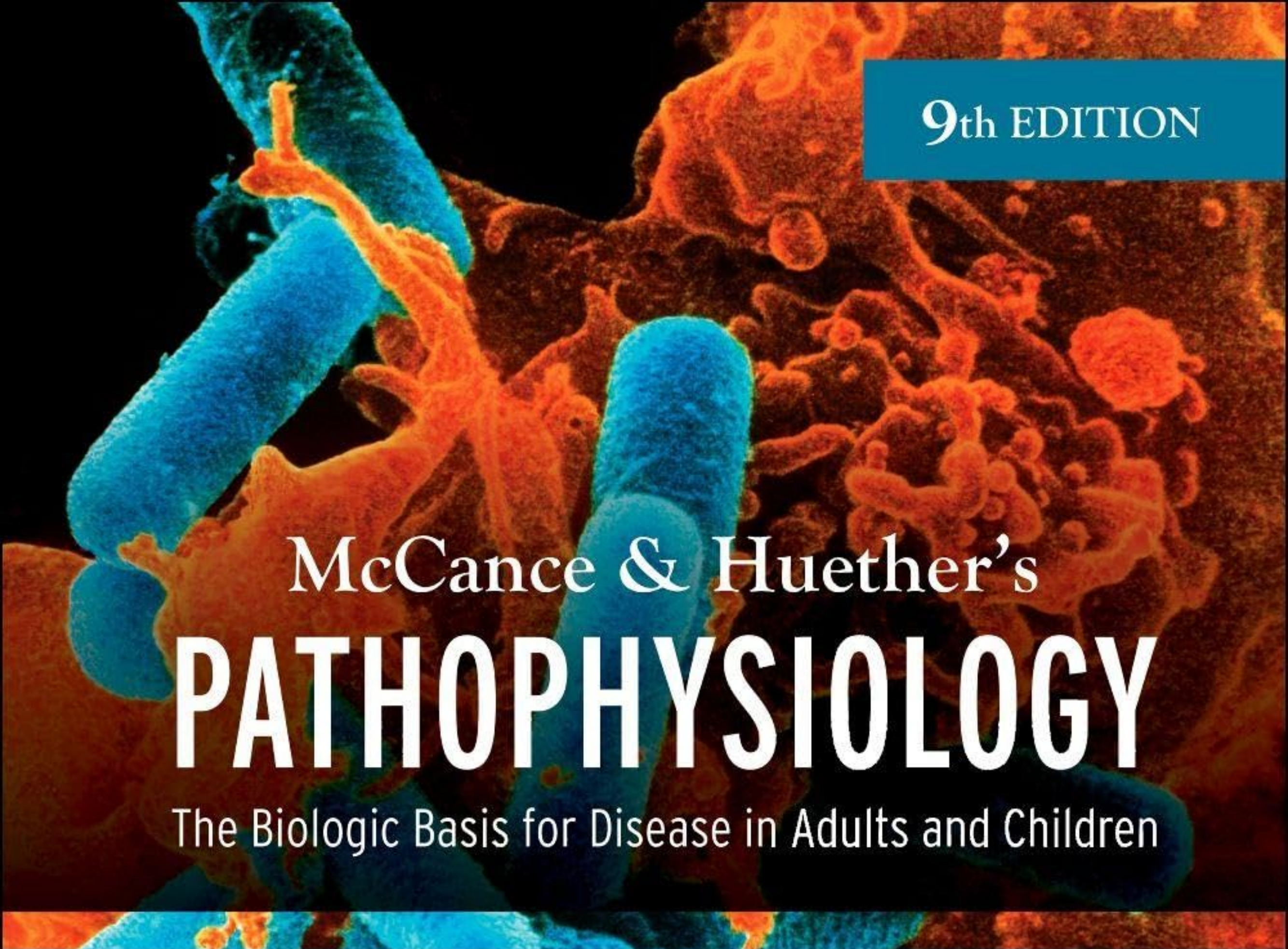




9th EDITION

McCance & Huether's
PATHOPHYSIOLOGY

The Biologic Basis for Disease in Adults and Children

JULIA L. ROGERS

SECTION EDITOR
VALENTINA L. BRASHERS



Evolve®

Student Resources on Evolve
Details Inside

CONTENTS

PART ONE: Central Concepts of Pathophysiology: Cells and Tissues

UNIT I The Cell

- 1 Cellular Biology, 1
- 2 Altered Cellular and Tissue Biology: Environmental Agents, 43
- 3 The Cellular Environment: Fluids and Electrolytes, Acids and Bases, 106

UNIT II Genes and Gene-Environment Interaction

- 4 Genes and Genetic Diseases, 140
- 5 Genes, Environment-Lifestyle, and Common Diseases, 167
- 6 Epigenetics and Disease, 187

UNIT III Mechanisms of Self-Defense

- 7 Innate Immunity: Inflammation and Wound Healing, 202
- 8 Adaptive Immunity, 231
- 9 Alterations in Immunity, 255
- 10 Infection, 281
- 11 Stress and Disease, 310

UNIT IV Cellular Proliferation: Cancer

- 12 Cancer Biology, 331
- 13 Cancer Epidemiology, 388
- 14 Cancer in Children and Adolescents, 430

PART TWO: Structure, Function, and Pathophysiologic Alterations: Organs and Systems

UNIT V The Neurologic System

- 15 Structure and Function of the Neurologic System, 441
- 16 Pain, Temperature Regulation, Sleep, and Sensory Function, 474
- 17 Alterations in Cognitive Systems, Cerebral Hemodynamics, and Motor Function, 509
- 18 Alterations of the Brain, Spinal Cord, and Peripheral Nerves, 570
- 19 Neurobiology of Schizophrenia, Mood Disorders, Anxiety Disorders, Posttraumatic Stress Disorder, and Obsessive-Compulsive Disorder, 618
- 20 Alterations of Neurologic Function in Children, 640

UNIT VI The Endocrine System

- 21 Mechanisms of Hormonal Regulation, 662
- 22 Alterations of Hormonal Regulation, 688
- 23 Obesity, Starvation, and Anorexia of Aging, 723

UNIT VII The Reproductive Systems

- 24 Structure and Function of the Reproductive Systems, 738
- 25 Alterations of the Female Reproductive System, 767
- 26 Alterations of the Male Reproductive System, 823
- 27 Sexually Transmitted Infections, 865

UNIT VIII The Hematologic System

- 28 Structure and Function of the Hematologic System, 892
- 29 Alterations of Hematologic Function, 925
- 30 Alterations of Hematologic Function in Children, 987

UNIT IX The Cardiovascular and Lymphatic Systems

- 31 Structure and Function of the Cardiovascular and Lymphatic Systems, 1020
- 32 Alterations of Cardiovascular Function, 1059
- 33 Alterations of Cardiovascular Function in Children, 1109

UNIT X The Pulmonary System

- 34 Structure and Function of the Pulmonary System, 1131
- 35 Alterations of Pulmonary Function, 1153
- 36 Alterations of Pulmonary Function in Children, 1191

UNIT XI The Renal and Urologic Systems

- 37 Structure and Function of the Renal and Urologic Systems, 1211
- 38 Alterations of Renal and Urinary Tract Function, 1232
- 39 Alterations of Renal and Urinary Tract Function in Children, 1270

UNIT XII The Digestive System

- 40 Structure and Function of the Digestive System, 1285
- 41 Alterations of Digestive Function, 1318
- 42 Alterations of Digestive Function in Children, 1375

UNIT XIII The Musculoskeletal System

- 43 Structure and Function of the Musculoskeletal System, 1399
- 44 Alterations of Musculoskeletal Function, 1427
- 45 Alterations of Musculoskeletal Function in Children, 1476

UNIT XIV The Integumentary System

- 46 Structure, Function, and Disorders of the Integument, 1504
- 47 Alterations of the Integument in Children, 1541

UNIT XV Multiple Interacting Systems

- 48 Shock, Multiple Organ Dysfunction Syndrome, and Burns in Adults, 1557
- 49 Shock, Multiple Organ Dysfunction Syndrome, and Burns in Children, 1591

Glossary, 1622

Index, 1645

EMERGING SCIENCE BOXES

- Metabolic Reprogramming and Cancer Cells, 21
Exosome-Based Therapies, 29
Long-Term Exposure to Air Pollution and Increased Risk of Severe COVID-19 Outcomes, 63
Lead Poisoning, 63
COVID-19 and Postmortem Changes, 96
Veverimer for Treatment of Chronic Metabolic Acidosis, 134
Predictions of Individual Response to Pharmacotherapies Based on Genotype-Phenotype Correlations, 145
Polygenic Risk Scores and Disease Prediction, 172
Parsing Apart Contributions of Genotype and Childhood Adversity to Methylation States in Adulthood, 192
Vaccination History, COVID-19, and Epigenetics, 199
The Microbiome and Disease, 206
The Role of Toll-like Receptors (TLRs) and Nuclear Factor-KappaB (NF- κ B) in Disease, 210
Understanding the Causes of Chronic Inflammatory Disease, 220
Mechanisms of Impaired Wound Healing in Diabetes, 225
IL-17 in Health and Disease, 242
Monoclonal Antibodies, 248
Immunologic Memory, 250
The Microbiome and Food Allergy, 263
T Regulatory Cells and Autoimmunity, 265
Future Treatments for HIV Infection, 298
Post-Acute COVID-19, 300
The Gut Microbiota in Stress, Inflammation, and Disease, 321
Repetitive Negative Thinking Is a Risk Factor for Alzheimer Disease, 322
Stress and Inflammation Are Causal Factors Linking Heart Disease With Depression, 322
Liquid Biopsy Enters the Clinic, 364
Exercise and Anticancer Effects of Myokines, 409
Increasing Use of Computed Tomography Scans and Risks, 413
A Paradigm Shift? Responses to Ionizing Radiation Mediated by Inflammatory Mechanisms, 416
Cancer Predisposition Genes and Pediatric Cancer, 436
Risks from CT Imaging Scans and Pediatric Cancer, 437
Magnetic Fields and Development of Pediatric Cancer, 438
Schwann Cells, 444
Brain Networks, 449
Pain Management With Pharmacogenics, 480
Shift Work Disorder, 491
Loss of Taste and Smell in SARS-CoV-2-Positive Persons, 502
The Oral and Gut Microbiome and Alzheimer Disease, 532
Aducanumab for the Treatment of Alzheimer Disease, 533
Tourette Syndrome, 547
Melatonin and the Central Nervous System, 599
SARS-CoV-2 Infection and Neurologic Manifestations, 600
Genetic Basis of Anxiety and Depression, 625
Chronic Posttraumatic Stress Disorder Treatment, 634
In Utero Myelomeningocele Surgery, 645
Gene Therapy for Pediatric Neurologic Conditions, 647
The New Evolving Classification System for Pediatric Brain Tumors, 657
Thyromimetics and Liver Disease, 674
Vitamin D Deficiency, 674
Klotho Protein and Aging, 684
Combination Therapy for the Treatment of Hypothyroidism, 699
Pancreatic β Cell Regeneration as a Plausible Diabetic Therapy, 706
Inflammation and Its Importance to the Pathophysiology of Insulin Resistance in Prediabetes and Diabetes Mellitus Type 2, 707
Smart Pens for Improved Safety and Efficacy of Insulin Therapy, 709
SGLT-2 Use for the Treatment of Obesity, 730
Weight Loss, 730
Gender Reassignment and Gender Affirming Hormone Therapy, 742
Vitamin D and Breast Cancer, 814
Benign Prostatic Hyperplasia, 844
Prostate Cancer, 847
New Therapeutics for Human Immunodeficiency Virus Prevention and Treatment, 876
Treatment Effectiveness for Hepatitis C, 887
Tumor Associated Neutrophils, 896
Red Blood Cells and Hemostasis, 916
Traumatic Coagulopathy, 928
Immunotherapy, 962
Gene Therapy for Sickle Cell, 998
Molecular Characterization of Childhood Leukemia and Treatment Considerations, 1011
Myocardial Regeneration, 1023
Coronary Lymphatics in Health and Disease, 1028
Hypertension as a Metabolic Disease, 1065
Lipid-Lowering and Antihypertensive Medication Effects on Atherosclerosis-Associated Inflammation, 1072
Takotsubo Syndrome, 1079
Cardioprotection Therapies for Myocardial Infarction and Reperfusion Injury, 1082
Diabetes and Heart Failure, 1096
Stem Cell Therapies for Congenital Heart Disease, 1122
COVID-19 Post-Infective Myocarditis in Children, 1124
The Pulmonary Microbiome, 1136
Silent Hypoxemia in COVID-19, 1140
Future Treatments for Idiopathic Pulmonary Fibrosis, 1164
The Pathogenesis of the Acute Respiratory Distress Syndrome in COVID-19 Infection, 1166
Biological Treatments for Uncontrolled Asthma, 1172
E-Cigarettes and Respiratory Disease, 1173
Molecular and Immune Therapies for Lung Cancer, 1185
COVID-19 Infection in Children, 1201
Obesity and Childhood Asthma, 1203
CFTR Modulators, 1207
Renalase, 1219
Renin-Angiotensin-Aldosterone System Inhibitors in Patients With COVID-19, 1249
Biomarkers for Acute Kidney Injury Risk Stratification, 1257
Promising Biomarkers to Predict Chronic Kidney Disease in Children With Congenital Anomalies of Kidney and Urinary Tract, 1272
The Appendix in Health and Disease, 1302
Digestive Manifestations Related to COVID-19, 1312
Oral Treatments for Ulcerative Colitis, 1338
Portal Hypertension, 1343
Colorectal Cancer, 1362
COVID-19 and the Gastrointestinal System in Children, 1390
The Role of miRNAs as Biomarkers of Obesity, 1394
Factors Affecting Bone Healing, 1408
Progress in Rebuilding Cartilage, 1413
Understanding Tendon and Ligament Repair, 1422
Cartilage Regeneration, 1455
Invasive Therapies to Treat Musculoskeletal Conditions, 1471
Idiopathic Scoliosis, 1485
Serum Interleukin-18 and Systemic Juvenile Idiopathic Arthritis, 1487
Skin Engineering, 1514
COVID-19 and Cutaneous Manifestations, 1514
Coronavirus Rash, 1549
Pro-Inflammatory and Anti-Inflammatory Responses in Sepsis, 1562
Pathophysiology of the Burn Wound, 1580
Therapies for Shock and Sepsis, 1607
Advances in Burn Wound Care, 1615

Evolve®

YOU'VE JUST PURCHASED MORE THAN A TEXTBOOK!

Enhance your learning with Evolve Student Resources.

These online study tools and exercises can help deepen your understanding of textbook content so you can be more prepared for class, perform better on exams, and succeed in your course.



Activate the complete learning experience that comes with each NEW textbook purchase by registering with your scratch-off access code at

<http://evolve.elsevier.com/Rogers/pathophysiology/>

If your school uses its own Learning Management System, your resources may be delivered on that platform. Consult with your instructor.

If you rented or purchased a used book and the scratch-off code at right has already been revealed, the code may have been used and cannot be re-used for registration. To purchase a new code to access these valuable study resources, simply follow the link above.

Place
Sticker
Here

REGISTER TODAY!



You can now purchase Elsevier products on Evolve!
Go to evolve.elsevier.com/shop to search and browse for products.

A tailored education experience — *Sherpath book-organized collections*



Sherpath book-organized
collections offer:



Objective-based, digital lessons, mapped chapter-by-chapter to the textbook, that make it easy to find applicable digital assignment content.



Adaptive quizzing with personalized questions that correlate directly to textbook content.



Teaching materials that align to the text and are organized by chapter for quick and easy access to invaluable class activities and resources.



Elsevier ebooks that provide convenient access to textbook content, even offline.



Sherpath is the digital teaching and learning technology designed specifically for healthcare education.

VISIT
myevolve.us/sherpath
today to learn more!



Set a course for success with individualized quizzing

Elsevier Adaptive Quizzing (EAQ) offers a bank of high-quality practice questions that allows students to advance at their own pace — based on their performance — through multiple mastery levels for each chapter, topic, or concept. EAQ integrates seamlessly into the curriculum to help students of all skill levels focus their study time and effectively prepare for class, course exams, and summative exams.



- **Elsevier's trusted, market-leading content** serves as the foundation for all questions, which are written, reviewed, and leveled by experienced educators, item writers, and authors.
- **Detailed rationales for each question and essential test-taking tips and strategies** help students learn how to successfully dissect and tackle different question types and improve test-taking skills for both course exams and summative exams.
- **A robust performance dashboard** highlights usage and performance summaries and areas of strength and weakness tied to topics.



Find out how EAQ can help improve learning and program outcomes!

VISIT
myevolve.us/EAQ

9th EDITION

McCance & Huether's PATHOPHYSIOLOGY

The Biologic Basis for Disease in Adults And Children

Julia L. Rogers, DNP, APRN, CNS, FNP-BC, FAANP

Assistant Professor, College of Nursing

Purdue University Northwest

Hammond, Indiana;

Certified Nurse Practitioner

Northwest Medical Group Pulmonary and Critical Care Medicine

Valparaiso, Indiana

SECTION EDITOR

Valentina L. Brashers, MD, FACP, FNAP

Professor Emerita, School of Nursing

Attending Physician in Internal Medicine

University of Virginia Health System

Charlottesville, Virginia



Elsevier
3251 Riverport Lane
St. Louis, Missouri 63043

MCCANCE & HUETHER'S PATHOPHYSIOLOGY: THE BIOLOGIC BASIS FOR
DISEASE IN ADULTS AND CHILDREN, NINTH EDITION

ISBN: 978-0-323-78987-5

Copyright © 2023 by Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notice

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds or experiments described herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made. To the fullest extent of the law, no responsibility is assumed by Elsevier, authors, editors or contributors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Previous editions copyrighted 2019, 2014, 2010, 2006, 2002, 1998, 1994, and 1990.

Executive Content Strategist: Sonya Seigafuse
Senior Content Development Specialist: Laura Goodrich
Publishing Services Manager: Julie Eddy
Senior Project Manager: Rachel E. McMullen
Design Direction: Maggie Reid

Printed in Canada

Last digit is the print number: 9 8 7 6 5 4 3 2 1



This book is dedicated to all those who think they can't: guess what—
YOU CAN!

To my family, Dwayne, Zachery, and Shane. Your willingness to support this endeavor means more than I can express. I appreciate all the time and space you provided me to work on and complete this project. Your love surrounds me in every aspect of my life and inspires me to be a better human.

Dwayne, thanks for always letting me know that everything will be alright. I guess you were right. You have always been my rock, and I couldn't have made it the last 22 years without you believing in me.

Shane, thanks for never giving up and being the strongest woman I have ever known. Your beautiful smile brightens even the worst of days. You are loved more than you know. P.S. Please call your parents more often.

Last, but not least, my dearest Zachery, the calm in my storm, you have always amazed me with your uncanny ability to see the best in everyone. Never lose your gentle spirit and do not let anyone steal your joy. Believe in yourself and finish writing your own story. You are an inspiration.

P.S. Thanks for introducing me to dunking Oreos; life has not been the same since, Oh, and I almost forgot: you have lost the game.

J.L.R.

CONTRIBUTORS

Jodi A. Allen, DNP, RN, FNP-C

Assistant Professor and FNP Program Coordinator
College of Nursing
Purdue University Northwest
Hammond, Indiana

Rose Ann U. Baker, PhD, PMHCNS-BC

Assistant Lecturer, School of Nursing
College of Health Professions
University of Akron
Akron, Ohio

Casey Bor, MS, CPNP-AC, BSN, RN

Pediatric Cardiothoracic Surgery Nurse Practitioner
Pediatric Cardiothoracic Surgery and Pediatric Critical Care
University of Maryland Medical Center
Baltimore, Maryland

Valentina L. Brashers, MD, FACP, FNAP

Professor Emerita, School of Nursing
Attending Physician in Internal Medicine
University of Virginia Health System
Charlottesville, Virginia

Dennis J. Cheek, PhD, RN, FAHA

Professor
Harris College of Nursing and Health Sciences
Texas Christian University
Fort Worth, Texas

Devra Davis, PhD, MPH, FACE

Visiting Professor
Ondokuz Mayıs Medical University
Samsun, Turkey;
President, Environmental Health Trust
Teton Village, Wyoming

Corinne M. Djuric, MSN, FNP-C

Assistant Clinical Professor
College of Nursing
Purdue University Northwest
Hammond, Indiana

Linda Felver, PhD, RN

Associate Professor
School of Nursing
Oregon Health & Science University
Portland, Oregon

Diane P. Genereux, PhD

Scientist
Vertebrate Genome Biology
Broad Institute of MIT and Harvard
Cambridge, Massachusetts

Victoria Gray, MS

Biologist
Science Department
Michigan City High School
Michigan City, Indiana

Anne Harvey, DNP

Nurse Practitioner
Hematology
Primary Children's Hospital;
APP Director—Pediatric Hem/Onc/BMT
Intermountain Healthcare
Salt Lake City, Utah

Mary Fran Hazinski, RN, MSN, FAAN, FAHA, FERC

Professor
Vanderbilt University School of Nursing
Assistant
Departments of Surgery and Pediatrics
Vanderbilt University School of Medicine;
Clinical Nurse Specialist
Monroe Carell, Jr. Children's Hospital at Vanderbilt
Nashville, Tennessee

Kathleen E. Hubner, DNP, APRN, ACNS-BC, ANVP, CNRN

Clinical Assistant Professor
Science of Nursing Care
Indiana University School of Nursing
Indianapolis, Indiana

Sue E. Huether, MS, PhD

Professor Emeritus
College of Nursing
University of Utah
Salt Lake City, Utah

Lynn B. Jorde, PhD

Mark and Kathie Miller Presidential Professor and Chair
Department of Human Genetics
University of Utah School of Medicine
Salt Lake City, Utah

Lauri A. Linder, PhD, APRN, CPON

Associate Professor
College of Nursing
University of Utah;
Clinical Nurse Specialist
Center for Cancer and Blood Disorders
Primary Children's Hospital
Salt Lake City, Utah

Kathryn L. McCance, RN, MS, PhD

Professor Emeritus
Nursing
University of Utah
Salt Lake City
Utah

Sean McConnell, PhD

President
Genomics
McConnell Consulting
Valparaiso, Indiana

Mary A. Mondoizzi, MSN, BSN, WCC
Burn Center Education/Outreach Coordinator
The Paul and Carol David Foundation Burn Institute
Akron Children's Hospital
Akron, Ohio

Noreen Heer Nicol, PhD, RN, FNP, NEA-BC
Associate Professor
College of Nursing
University of Colorado
Aurora, Colorado

Judith O'Haver, PhD, RN, CPNP-PC, FAANP, FAAN
Pediatric Nurse Practitioner
Pediatric Dermatology
Phoenix Children's Hospital,
Assistant Professor of Pediatrics
Mayo Clinic College of Medicine,
Clinical Assistant Professor
Department of Child Health
University of Arizona College of Medicine
Phoenix, Arizona;
Nurse Scientist
Rady Children's Hospital
San Diego, California

Jan Powers, PhD, RN, CCNS, CCRN, NE-BC, FCCM
Director Nursing Research and Professional Practice
Nursing, Patient Care System
Parkview Health
Fort Wayne, Indiana

Geri Cage Reeves, PhD, APRN, FNP-BC
Associate Professor
School of Nursing
Vanderbilt University
Nashville, Tennessee

George W. Rodway, PhD
Adjunct Professor of Family Medicine—Sports Medicine
School of Medicine
University of Nevada—Reno
Reno, Nevada

Julia L. Rogers, DNP, APRN, CNS, FNP-BC, FAANP
Assistant Professor, College of Nursing
Purdue University Northwest
Hammond, Indiana;
Certified Nurse Practitioner
Northwest Medical Group Pulmonary and Critical
Care Medicine
Valparaiso, Indiana

Kaveri Roy, DNP, RN
Assistant Professor
School of Nursing
MGH Institute of Health Professions
Boston, Massachusetts

John Ruge, MD, FAANS
Chairman
Neurosurgery
Advocate Lutheran General;
Chief
Pediatric Neurosurgery
Advocate Children's Hospital
Park Ridge, Illinois

Suzanne M. Ruiz, MBA, MSN, NP-C
Adjunct Faculty, Nursing
Purdue University Northwest
Hammond, Indiana

Melanie L. Scala, MS, CRNP-AC
Senior Nurse Practitioner II
Pediatric Cardiac Surgery Nurse Practitioner
University of Maryland Medical Center
Baltimore, Maryland

Mary C. Selzer, DNP, APRN, ACNP-BC
Assistant Professor Professional Practice
Nursing
Texas Christian University;
Manager
Trauma & Acute Care Surgery Advanced Practice Surgery
John Peter Smith Hospital
Fort Worth, Texas

Benjamin Allan Smallheer, PhD, RN, ACNP-BC, FNP-BC, CCRN, CNE
Associate Professor
School of Nursing
Duke University,
Acute Care Nurse Practitioner
Critical Care Medicine
Duke Regional Hospital
Durham, North Carolina;
Acute Care Nurse Practitioner
Critical Care Medicine
Duke Raleigh Hospital
Raleigh, North Carolina

William E. Somerall, Jr., MD, MAEd
Associate Professor of Nursing
Acute, Chronic, and Continuing Care
University of Alabama at Birmingham
Birmingham, Alabama

Scarlet R. Spain, DNP, RN, CNS, FNP-BC
Assistant Professor
CONHP
Valparaiso University
Valparaiso, Indiana;
Occupational Health Nurse Practitioner
Community Healthcare Systems
Hobart, Indiana;
Occupational Health Consultant
Medix
Chicago, Illinois

Lorey K. Takahashi, PhD
Professor of Psychology
Department of Psychology
University of Hawaii at Manoa
Honolulu, Hawaii

Karen C. Turner, BS
Freelance Editor
TurnKey Content, LLC
Melbourne, Florida

Mary Beth Winton, PhD, RN, ACANP-BC
Associate Professor
School of Nursing
Tarleton State University
Stephenville, Texas

The intent of the ninth edition of *Pathophysiology* is to continue the extraordinary work of Kathy McCance and Sue Huether, which started 30 years ago, by illustrating the principles of pathophysiology with clarity and accuracy.

Pathophysiology incorporates basic, translational, and clinical research to advance the understanding of disease and dysfunction. The study of pathophysiology involves many biomedical sciences and a wide range of research activities. Multiple aspects of cellular physiology are progressing rapidly, generating vast amounts of data to understand. This was made ever more present during the writing of this edition, when the world began to see the effects of cellular changes and adaptations from the coronavirus (COVID-19; severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) pandemic. The information gained provided a greater understanding of the behavior of individual cells, their neighboring microenvironment, and the molecules that not only make up those cells but also communicate with their surroundings. Importantly, the forward movement of biomedical sciences occurs within the context of social, economic, and political processes that determine how disease is defined, experienced, and treated.

Interdisciplinary research has led to significant advancements in genetics, epigenetics, cell signaling and communication, control of cell behavior, metabolism, and cell fate. Knowledge about normal cell structures, function, and signaling pathways is at the forefront of translational science and foundational to the understanding of pathophysiology. Advancements in technology that allow close observation of cells are providing new understanding of cellular processes, including how cells function and prioritize their activities, monitor their environment, move, differentiate, and regenerate. Advances in the molecular mechanisms of disease, particularly cell signaling, genetic directives, and immune and metabolic modulators, are providing an understanding of individual differences in disease risk, biologic markers, diagnostic strategies, and individualized treatment.

Although these advancements have created an ever-increasing state of excitement, they have also created the problem of how students, professors, and clinicians can cope with the expanding new information. Translating and compressing these data into simplified discussions for students and clinicians is challenging. The approach for this edition of the book was to streamline the content and present the information in an organized, logical sequence of content based on current literature and research reports with understandable explanations and accompanied by illustrations and summary tables. The primary focus is on pathophysiology, and there is less emphasis on the evaluation and treatment that is found in clinical management textbooks.

This edition has been extensively revised with the following specific goals:

- Organize the content in a logical and uniformed format to facilitate learning and teaching.

- Place emphasis on the readability of the material for improved comprehension.
- Focus on updating outdated terminology and use inclusive language.
- Present emerging new data on disease including controversial topics.
- Provide the most current and relevant information on the etiology, epidemiology, pathophysiology, clinical manifestations, and treatment for disease processes.
- Integrate health promotion and disease prevention by updating risk factors, explaining relationships between nutrition and disease, and referencing screening recommendations.

ORGANIZATION AND CONTENT: WHAT'S NEW IN THE NINTH EDITION

The book is organized into two parts. Part One presents the cellular and tissue responses common to disease. Normal organ system structure and function and the pathophysiology of disease, organized by body systems, are presented in Part Two. All content has been reviewed and updated with extensive new references and revised figures. The previous [Chapter 18](#) in the eighth edition titled *Disorders of the Central and Peripheral Nervous Systems and the Neuromuscular Junction* has been renamed in the ninth edition as *Alterations of the Brain, Spinal Cord, and Peripheral Nerves*. Alterations of the hematologic system, which were previously discussed over two chapters, have been combined into one chapter.

PART ONE: CENTRAL CONCEPTS OF PATHOPHYSIOLOGY: CELLS AND TISSUES

Part One begins with an in-depth study of the cell and progresses to cover the underlying processes of disease. Concepts covered include cell signaling and cell communication processes; genes and common genetic diseases; epigenetics and disease; fluid, electrolyte, and acid-base balance; inflammation, cytokines and their biologic functions, and normal and altered immunity; infection, stress, coping, and immunity; and tumor biology, epidemiology of cancer, and cancer in children. Revisions and updated additions to Part One include the following:

- Updated content on cellular organelles, the plasma membrane, cell signaling, and communication ([Chapter 1](#))
- Reorganized with extensive updates throughout the chapter with close attention to air pollution and climate change ([Chapter 2](#))
- Updated content on fluids, electrolytes and acids and bases ([Chapter 3](#))
- Updated content on genes and diseases related to genetics, the environment and lifestyle patterns ([Chapter 4 and 5](#))
- Updated content on epigenetics and disease ([Chapter 6](#))

- Updated to content on normal innate and adaptive immunity ([Chapters 7 and 8](#))
- Extensively updated to content on alterations of immunity and inflammation including up-to-date information on coronavirus (COVID-19) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ([Chapter 9](#))
- Extensively revised with up-to-date information on COVID-19 and SARS-CoV-2 ([Chapter 10](#))
- Updated content on stress and disease ([Chapter 11](#))
- Updated content on tumor biology and invasion and metastases ([Chapter 12](#))
- Updated content on the epidemiology of cancer ([Chapter 13](#))

PART TWO: PATHOPHYSIOLOGIC ALTERATIONS: ORGANS AND SYSTEMS

Part Two is a systematic survey of diseases within body systems. Each unit focuses on a specific body system and begins with an anatomy and physiology chapter to provide a basis of comparison for understanding the alterations created by disease. A brief summary of geriatric considerations is included at the end of the section on anatomy and physiology. The discussion of each disease in the alterations chapters is developed in a logical manner that begins with an introductory paragraph on etiology and epidemiology, followed by pathophysiology, clinical manifestations, and evaluation and treatment. Separate chapters are dedicated to pediatric pathophysiology, with a particularly sensitive approach to sex at birth and age. Significant revisions and updated additions to Part Two include the following:

- Updated content on pediatric cancers ([Chapter 14](#))
- Updated content on the anatomy and physiology of the neurologic system ([Chapter 15](#))
- Updated content on pain syndromes and sleep disorders ([Chapter 16](#))
- Rewritten and extensively revised content on Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, multiple sclerosis, and myasthenia gravis with updates to content on consciousness, memory, dementia, and delirium syndromes ([Chapter 17](#))
- Chapter renamed as Alterations of the Brain, Spinal Cord, and Peripheral Nerves. Rewritten and extensively revised content on the manifestations for specific central and peripheral nervous system disorders including brain and spinal cord injury, stroke, seizure, and headache syndromes ([Chapter 18](#))
- Updated content and terminology on schizophrenia, mood disorders, and anxiety ([Chapter 19](#))
- Updated content on cerebral palsy, seizure disorders, and pediatric brain tumors ([Chapter 20](#))
- Updated content on the mechanisms of hormonal regulation ([Chapter 21](#))
- Extensive updates on diabetes mellitus, insulin resistance, and thyroid and adrenal gland disorders ([Chapter 22](#))
- Updated content on obesity and disorders of nutrition ([Chapter 23](#))
- Updated content on anatomy and physiology of the reproductive system ([Chapter 24](#))
- Updated content on female reproductive disorders including cancers, benign breast diseases, and breast cancer ([Chapter 25](#))
- Updated content on male reproductive disorders and cancer with extensive updating and reorganization ([Chapter 26](#))
- Extensive updating of sexually transmitted infections ([Chapter 27](#))
- Updated content on the anatomy and physiology of the hematologic system ([Chapter 28](#))
- Extensively rewritten chapter on the alterations of hematologic function, combining two previous chapters into one with updated content on anemia ([Chapter 29](#))
- Updated content on alterations of hematologic function in children ([Chapter 30](#))
- Updated chapter on the anatomy and physiology of the cardiovascular and lymphatic systems ([Chapter 31](#))
- Updated content on atherosclerosis, endothelial injury and dysfunction, coronary artery disease, myocardial infarction, and heart failure ([Chapter 32](#))
- Updated content on the alterations of cardiovascular function in children ([Chapter 33](#))
- Updated content on the anatomy and physiology of the pulmonary system ([Chapter 34](#))
- New content on COVID-19 and SARS-CoV-2, and updated content on pulmonary embolism asthma, chronic lung disease, respiratory tract infection, pulmonary hypertension, and lung cancers ([Chapters 35](#))
- New content on COVID-19 and SARS-CoV-2 with updated content on childhood asthma, respiratory distress syndrome, cystic fibrosis, lung infections, and sudden infant death syndrome ([Chapter 36](#))
- Updated content on the anatomy and physiology of the renal and urologic system ([Chapter 37](#))
- Updated content on kidney stones, urinary tract infection, glomerulopathies, acute and chronic renal failure, and bladder and kidney tumors ([Chapter 38](#))
- Updated content on urinary tract infection and renal failure in children ([Chapter 39](#))
- Updated content on the anatomy and physiology of the digestive system ([Chapter 40](#))
- Updated content on gastroesophageal reflux disease, peptic ulcer disease, irritable bowel syndrome, inflammatory bowel disease, colon cancer, and hepatitis ([Chapter 41](#))
- Updated content on gluten-sensitive enteropathy, necrotizing enterocolitis, infections of the intestine, and liver disease in children ([Chapter 42](#))
- Updated content on the anatomy and physiology of the musculoskeletal system ([Chapter 43](#))
- Updated content on alterations of the musculoskeletal system ([Chapter 44](#))
- Updated content on alterations of the musculoskeletal system in children ([Chapter 45](#))
- Updated content on integumentary system disorders including pressure ulcers, dermatitis, psoriasis, scleroderma, and melanoma ([Chapter 46](#))

- Updated content on childhood atopic dermatitis, skin infections, and immune drug reactions ([Chapter 47](#))
- Extensively updated content on septic shock, multiple organ dysfunction syndrome, included recent guideline updates, and burns for adults ([Chapters 48](#))
- Extensively updated content on septic shock, multiple organ dysfunction syndrome, included recent guideline updates, and burns for children ([Chapters 49](#))

FEATURES TO PROMOTE LEARNING

Ease of learning has been enhanced by designing a number of features that guide and support understanding, including:

- *Chapter Outlines* for each chapter
- *Consistent Headings* to underscore the consistent treatment of each disease—Pathophysiology, Clinical Manifestations, and Evaluation and Treatment
- More than 70 *Emerging Science* boxes that review the most current research and clinical developments of disease.
- End-of-chapter *Summary Review* sections that summarize the content in each chapter and serve as built-in content review guides
- Boldface *Key Terms* found within all the chapters
- A comprehensive *Glossary* with approximately 1000 terms to help students with the often-difficult terminology related to pathophysiology

ART PROGRAM

The art program is extensive and has received as much attention and revision as the narrative. Nearly 100 new or revised full-color illustrations were created and strategically placed throughout the textbook. Also included are many new high-quality, full-color photographs of clinical manifestations, pathologic specimens, and clinical imaging techniques. The combination of illustrations, algorithms, and photographs and the use of color for tables and boxes allow clarification for complex concepts and the emergence of easily recognized essential information.

ANCILLARIES

For Students

On **Evolve**, at <http://evolve.elsevier.com/Rogers/pathophysiology/>, students can access Evolve-only figures, tables, and boxes, 570 review questions, 100 animations to help them master the text

content, 26 case studies with questions and answers, and downloadable chapter summaries documents for each chapter.

The **Study Guide** includes a variety of question styles, aiming to help the diverse way students learn. Question types include the following:

- Respond to Clinical Scenarios
- Categorize Clinical Examples
- Match the Definitions
- Order the Steps
- Choose the Correct Words
- Complete These Sentences
- Explain the Pictures
- Teach People About Pathophysiology
- Plus many more...

Answers are found in the back of the Study Guide for easy reference for students.

For Instructors

The **Evolve Instructor Resources** for this textbook provide the following teaching aids:

- Image Collection with all of the approximately 1200 figures from the text
- PowerPoint lecture slides for each chapter (approximately 3300 slides total), including integrated Audience Response Questions in each chapter (218 total), and integrated case studies at the end of each unit (15 total)
- Teach for Nurses Instructor's Manual, broken down by chapter, detailing the resources available to instructors for their lesson planning, and including unique case studies and class activities they can share with students
- Test Bank in ExamView with 1560 questions (in multiple-choice and multiple-response formats) with answers, rationales, and textbook page references

Evolve is an Internet-based learning environment that works in coordination with the text. This resource enables you to publish your class syllabus, outline, and lecture notes; set up “virtual office hours” and e-mail communication; share important dates and information through the online class calendar; and encourage student participation through chat rooms and discussion boards. Free with qualified adoption. Contact your sales representative or visit <http://evolve.elsevier.com> for more information about integrating **Evolve** into your curriculum.

ACKNOWLEDGMENTS

It is with gratitude that I dedicate this book to the creative pioneers who started it all, Kathy McCance and Sue Huether. Over the last 30 years, you have worked tirelessly to update the textbook to remain relevant using the most current research advancements, and I applaud your dedication. Thanks for having the confidence to pass the torch to me.

To Tamara, thank you for taking a chance on me. You are a sparkle in this world that can light up an entire room. I am forever grateful for your kindness.

To Tina Brashers, a mentor throughout this journey that had several sharp turns. Thank you for your devotion to the book and passion to create. You are brilliant, and I could not have done it without you. I appreciate you more than you will ever know and will forever be slightly envious.

To Melanie, the eagle eyes of the project. Thank you for all the time and commitment you put into this textbook. Words cannot express the gratitude I have for all your hard work.

To the Development and Production teams—Laura, Laurie, Rachel, artists, and editors, thanks for your mastery and caring about this project as much as I do.

To all the contributors—thanks for hanging in there over the last few years. It was a time of change and constraints with COVID, but all of you produced phenomenal work. Thank you!

To my amazing father, who provided me with strength and courage throughout the entire project.

To the WOW women, thanks for helping me pick up the broken pieces and make time for what is most important in life.

To Patti Ludwig-Beymer thank you for taking the time to guide me. You have been a true mentor and reminded me to breathe, believe, and be the very best version of me.

To Dr. Douglas Mazurek, you have been an inspiration to me. You believed in me since the beginning of my nursing career and opened the door to see the possibilities as a nurse practitioner. Thanks for igniting my passion and love for pathophysiology.

To Emily, thanks for making sure everything was in order. You are a gem in the world.

Seek joy. Live your life as your message. Be the change in the world that you wish to see. Most of all.....be kind.

Julia L. Rogers

PART ONE: Central Concepts of Pathophysiology: Cells and Tissues

UNIT I The Cell

1 Cellular Biology, 1

Victoria Gray and Kathryn L. McCance

Prokaryotes and Eukaryotes, 1

Cellular Functions, 2

Structure and Function of Cellular Components, 2

Nucleus, 2

Cytoplasmic Organelles, 2

Plasma Membranes, 3

Cellular Receptors, 9

Cell-to-Cell Adhesions, 12

Extracellular Matrix and Basement Membrane, 12

Specialized Cell Junctions, 14

Cellular Communication and Signal Transduction, 15

Cellular Metabolism, 17

Role of Adenosine Triphosphate, 18

Food and Production of Cellular Energy, 20

Oxidative Phosphorylation, 20

Membrane Transport: Cellular Intake and Output, 21

Electrolytes as Solutes, 23

Transport by Vesicle Formation, 26

Movement of Electrical Impulses: Membrane

Potentials, 27

Cellular Reproduction: The Cell Cycle, 31

Phases of Mitosis and Cytokinesis, 32

The Cell Cycle Control System, 33

Control of Cell Division and Cell Growth: Mitogens,

Growth Factors, and Survival Factors, 34

DNA Damage Response: Blocks Cell Division, 34

Tissues, 34

Tissue Formation and Differentiation, 34

2 Altered Cellular and Tissue Biology: Environmental Agents, 43

Victoria Gray, Kathryn L. McCance, and Julia L. Rogers

Cellular Adaptation, 44

Atrophy, 44

Hypertrophy, 45

Hyperplasia, 45

Dysplasia: Not a True Adaptive Change, 46

Metaplasia, 47

Cellular Injury, 47

General Mechanisms of Cell Injury, 48

Ischemic and Hypoxic Injury, 48

Ischemia–Reperfusion Injury, 50

Free Radicals and Reactive Oxygen Species—

Oxidative Stress, 50

Chemical or Toxic Injury, 53

Common Environmental Toxins, 56

Unintentional and Intentional Injuries, 69

Infectious Injury, 73

Immunologic and Inflammatory Injury, 73

Impacts of Climate Change on Human Health, 73

Ionizing Radiation, 74

Changes in Atmospheric Pressure, 78

Manifestations of Cellular Injury, 80

Cellular Manifestations: Accumulations, 80

Water, 81

Lipids and Carbohydrates, 82

Glycogen, 83

Proteins, 83

Pigments, 83

Calcium, 84

Urate, 84

Systemic Manifestations of Cellular Injury, 85

Cellular Death, 85

Necrosis, 85

Apoptosis, 88

Autophagy, 90

Aging and Altered Cellular and Tissue Biology, 91

Normal Life Span and Life Expectancy, 92

Frailty, 92

Somatic Death, 95

3 The Cellular Environment: Fluids and Electrolytes, Acids and Bases, 106

Linda Felver

Distribution of Body Fluids, 106

Aging and Distribution of Body Fluids, 107

Water Movement Between ICF and ECF, 107

Water Movement Between Plasma and Interstitial

Fluid, 108

Alterations in Water Movement, 109

Edema, 109

Sodium, Chloride, and Water Balance, 111

Alterations in Sodium, Water, and Chloride

Balance, 113

Isotonic Alterations, 114

Hypertonic Alterations, 114

Hypotonic Alterations, 116

Alterations in Potassium, Calcium, Phosphate, and

Magnesium Balance, 118

Potassium, 118

Calcium and Phosphate, 123

Magnesium, 126

Acid-Base Balance, 127

Hydrogen Ion and pH, 127

Buffer Systems, 127

Acid-Base Imbalances, 129

UNIT II Genes and Gene-Environment Interaction

4 Genes and Genetic Diseases, 140

Lynn B. Jorde

- DNA, RNA, and Proteins: Heredity at the Molecular Level, 140
 - Definitions, 140
 - From Genes to Proteins, 145
- Chromosomes, 147
 - Chromosome Aberrations and Associated Diseases, 150
- Elements of Formal Genetics, 155
 - Phenotype and Genotype, 155
 - Dominance and Recessiveness, 155
- Transmission of Genetic Diseases, 155
 - Autosomal Dominant Inheritance, 156
 - Autosomal Recessive Inheritance, 158
 - X-Linked Inheritance, 160
- Linkage Analysis and Gene Mapping, 162
 - Classic Pedigree Analysis, 162
 - Complete Human Gene Map: Prospects and Benefits, 163

5 Genes, Environment-Lifestyle, and Common Diseases, 167

Lynn B. Jorde

- Factors Influencing Incidence of Disease in Populations, 167
 - Concepts of Incidence and Prevalence, 167
 - Analysis of Risk Factors, 168
- Principles of Multifactorial Inheritance, 168
 - Basic Model, 168
 - Threshold Model, 169
 - Recurrence Risks and Transmission Patterns, 170
- Nature and Nurture: Disentangling the Effects of Genes and Environment, 172
 - Twin Studies, 172
 - Adoption Studies, 173
- Genetics of Common Diseases, 174
 - Congenital Malformations, 174
 - Multifactorial Disorders in the Adult Population, 174

6 Epigenetics and Disease, 187

Diane P. Genereux

- Overview of Epigenetic Mechanisms, 187
- Epigenetic Mechanisms, 188
- Three Types of Epigenetic Processes, 190
 - Epigenetics and Human Development, 190
 - Genomic Imprinting, 190
 - Epigenetics in Development and Mental Health, 192
- Exploring the Multigenerational Persistence of Epigenetic States, 195
 - Epigenetics and Nutrition, 195
 - Epigenetics and Maternal Care, 195
- Epigenetic Change Over the Life span, 196
 - Twin Studies Provide Insights on Epigenetic Modification, 196
- Tools for Exploring Epigenetic States, 196

- Detecting DNA Methylation in Populations of Molecules: Methyl-Sensitive Restriction Enzymes, 196
- Detecting DNA Methylation in Single Molecules: Bisulfite Conversion, 196
- Detecting DNA Hydroxymethylation: Fluorescence Resonance Energy Transfer, 196
- Identifying Histone-Modification States: Chromatin Immunoprecipitation, 196
- Detecting DNA Accessibility States: DNase Hypersensitivity Testing, 197
- Detecting DNA Accessibility States in Single Molecules: Assay for Transposase-Accessible Chromatin, 197
- Detecting Overall Chromatin State on Individual Chromatin Fibers: Fiber-seq, 197
- Publicly Available Resources Enable Exploration of Epigenetic States at Genome Scale, 197
- Epigenetics and Cancer, 198
 - DNA Methylation and Cancer, 198
 - Global Epigenomic Alterations and Cancer, 198
 - Epigenetic Screening for Cancer, 198
 - Misregulation of miRNAs in Cancer, 198
 - Emerging Strategies for the Treatment of Epigenetic Disease, 199
 - DNA Demethylating Agents, 199
 - Histone Deacetylase Inhibitors, 199
 - miRNA Coding, 199
- Epigenetics and COVID-19, 199
- Epigenetic Modification of mRNA, 199
- Future Directions, 199

UNIT III Mechanisms of Self-Defense

7 Innate Immunity: Inflammation and Wound Healing, 202

Valentina L. Brashers

- Innate Immunity, 202
- First Line of Defense: Physical and Biochemical Barriers and the Human Microbiome, 203
 - Physical and Mechanical Barriers, 203
 - Biochemical Barriers, 203
 - The Normal Microbiome, 203
- Second Line of Defense: Inflammation, 205
 - Plasma Protein Systems and Inflammation, 207
 - Initial Cellular Responders in Inflammation, 209
 - The Vascular Response in Inflammation, 215
 - The Cellular Response in Inflammation, 215
 - Acute and Chronic Inflammation, 218
- Wound Healing, 221
 - Phase I: Hemostasis (Coagulation), 222
 - Phase II: Inflammation, 223
 - Phase III: Proliferation and New Tissue Formation, 223
 - Phase IV: Remodeling and Maturation, 224
 - Dysfunctional Wound Healing, 224
 - Wound Disruption, 225

8 Adaptive Immunity, 231*Valentina L. Brashers***Overview of Adaptive Immunity, 231****Antigens, 232****Lymphocyte Development, 233***Development of B Lymphocytes, 233**Development of T Lymphocytes, 236**Clonal Diversity, Clonal Deletion, Clonal Selection, and Clonal Expansion, 237***Induction of the Immune Response, 238***Antigen-Presenting Cells, 238**Antigen Processing, 238**Antigen Presentation, 239**T-Helper Cells, 240***Humoral Immunity, 241***B-Cell Activation, 241**Molecular Structure and Classes of Antibodies, 242**Function of Antibodies, 244**Primary and Secondary Humoral Immune Responses, 246***Cell-Mediated Immunity, 247***T-Cytotoxic Cells, 247**Natural Killer Cells, 248**Macrophages, 249***Immunologic Memory, 250****9 Alterations in Immunity, 255***Valentina L. Brashers***Hypersensitivity Reactions, 255***Immunologic Mechanisms of Hypersensitivity Reactions, 255**Antigenic Targets of Hypersensitivity Reactions, 262***Deficiencies in Immunity, 271***Initial Clinical Presentation, 271**Primary (Congenital) Immune Deficiencies, 271**Evaluation of Those With Primary Immune Deficiency, 275**Therapies for Primary Immune Deficiencies, 275**Secondary (Acquired) Immune Deficiencies, 275***10 Infection, 281***Valentina L. Brashers***Microorganisms and Humans: A Dynamic***Relationship, 281**The Process of Infection, 282**Stages of Infection, 283***Infectious Disease, 283***Bacterial Infection, 284**Viral Infection, 287**Fungal Infection, 301**Parasitic Infection, 303***Antibiotic/Antimicrobial Resistance, 304****Vaccines and Protection Against Infection, 305***Active Immunization, 305**Passive Immunotherapy, 305***11 Stress and Disease, 310***Lorey K. Takahashi***Background and General Concepts of Stress, 310***Early Years of Stress Biology, 310**Modern Overview of Stress: Allostasis and Allostatic Overload, 312***The Stress Systems, 312***Adaptive Roles of Stress Systems, 312**Regulation of the Hypothalamic-Pituitary-Adrenal Axis, 313**The Autonomic Nervous System, 316**Role of the Immune System, 317***The Impact of Chronic Stress Across the Life Span, 322***Negative Effects of Chronic Stress at an Early Age, 322**Negative Effects of Chronic Stress in Adolescents and Adults, 323***Coping and Intervention Strategies, 324***Staying on the Good Side of the Stress Spectrum, 324**Effects of Exercise, 324**Mindfulness Therapy, 326***UNIT IV Cellular Proliferation: Cancer****12 Cancer Biology, 331***Kathryn L. McCance***Cancer Terminology and Characteristics, 331***Tumor Classification and Nomenclature, 331***The Biology of Cancer Cells, 334***Genomic Hallmarks, 338**Cellular Adaptations, 345**Resistance to Destruction, 347***Activating Invasion and Metastasis, 354***Biologic Processes of Metastasis, 354**Intravasation, 361**Extravasation, 364**Colonization, 364***Clinical Manifestations of Cancer, 367***Paraneoplastic Syndromes, 367**Molecular Mechanisms of Cachexia, 368***Diagnosis and Staging of Cancer, 371***Histologic Staging, 371**Tumor Markers, 371**Classification of Tumors: Immunohistochemical and Genetic Analysis, 372***Treatment of Cancer, 373***Classic Approaches, 373***Targeted Disruption of Cancer, 376****13 Cancer Epidemiology, 388***Devra Davis, Kathryn L. McCance, and Valentina L. Brashers***Incidence, Mortality Trends, and Race, 388****Genetics, Epigenetics, Tumor Microenvironment, and Cellular Signaling in Cancer, 395***Genetics and Epigenetics, 395**Tumor Microenvironment, 395**Cellular Signaling, 395***In Utero and Early Life Conditions, 397****Environmental-Lifestyle Factors, 399***Tobacco Use, 399*

Diet and Nutrition, Obesity, Alcohol Consumption, and Physical Activity: Impacts on Cancer, 401
Air Pollution, 409
Ionizing Radiation, 412
Nonionizing Radiation and Electromagnetic Radiation, 416
Ultraviolet Radiation, 418
Infection, Sexual and Reproductive Behavior, 419
Other Viruses and Microorganisms, 420
Environmental and Occupational Hazards as Carcinogens, 420

14 Cancer in Children and Adolescents, 430

Lauri A. Linder

Incidence and Types of Childhood Cancer, 430
Etiology, 433
Genetic and Genomic Factors, 433
Environmental Factors, 435
Prognosis, 437

PART TWO: Structure, Function, and Pathophysiologic Alterations: Organs and Systems

UNIT V The Neurologic System

15 Structure and Function of the Neurologic System, 441

Karen C. Turner

Overview and Organization of the Nervous System, 441
Cells of the Nervous System, 442
Neurons, 442
Neuroglia, 444
Nerve Injury and Regeneration, 445
Nerve Impulse, 446
Synapses, 446
Neurotransmitters, 447
Central Nervous System, 448
Brain, 448
Spinal Cord, 453
Motor Pathways, 454
Sensory Pathways, 457
Protective Structures, 457
Blood Supply, 459
Blood Supply to the Brain, 459
Blood-Brain Barrier, 460
Blood Supply to the Spinal Cord, 460
Peripheral Nervous System, 461
Autonomic Nervous System, 465
Anatomy of the Sympathetic Nervous System, 465
Anatomy of the Parasympathetic Nervous System, 465
Neurotransmitters and Neuroreceptors, 465
Functions of the Autonomic Nervous System, 467
Tests of Nervous System Structure and Function, 470
Skull and Spine Roentgenograms, 470
Computed Tomography, 470

Magnetic Resonance Imaging, 470
Magnetic Resonance Angiography, 470
Positron Emission Tomography Scan, 470
Single Photon Emission Computed Tomography, 471
Cerebral Angiography, 471
Echoencephalography (Ultrasound), 472
Electroencephalography, 472
Magnetoencephalography, 472
Evoked Potentials, 472
Cerebrospinal Fluid Analysis, 472

16 Pain, Temperature Regulation, Sleep, and Sensory Function, 474

Jodi A. Allen

Pain, 474
Neuroanatomy of Pain, 474
Pain Modulation, 478
Clinical Descriptions of Pain, 480
Temperature Regulation, 484
Control of Body Temperature, 484
Temperature Regulation in Infants and Older Adult Persons, 484
Pathogenesis of Fever, 485
Benefits of Fever, 487
Disorders of Temperature Regulation, 487
Sleep, 489
Sleep Disorders, 489
The Special Senses, 491
Vision, 491
Hearing, 498
Olfaction and Taste, 500
Somatosensory Function, 502
Touch, 502
Proprioception, 502

17 Alterations in Cognitive Systems, Cerebral Hemodynamics, and Motor Function, 509

Kaveri Roy and Sue E. Huether

Alterations in Cognitive Systems, 509
Alterations in Arousal, 509
Alterations in Awareness, 516
Data Processing Deficits, 521
Alterations in Cerebral Hemodynamics, 534
Increased Intracranial Pressure, 534
Cerebral Edema, 536
Hydrocephalus, 537
Alterations in Neuromotor Function, 538
Upper and Lower Motor Neuron Syndromes, 538
Extrapyramidal Motor Syndromes, 541
Alterations in Complex Motor Performance, 543
Alterations in Muscle Tone, 544
Alterations in Muscle Movement, 546
Chronic Diseases and Disorders Involving Motor Function, 547
Chronic Progressive Motor Diseases of the Central Nervous System, 547
Demyelinating Disorders, 557
Neuromuscular Junction Disorders, 560

18 Alterations of the Brain, Spinal Cord, and Peripheral Nerves, 570

Jan Powers and Kathleen E. Hubner

Central Nervous System Disorders, 570

Traumatic Brain and Spinal Cord Injury, 570

Degenerative Disorders of the Spine, 584

Seizure Disorders and Epilepsy, 588

Cerebrovascular Disorders, 591

Primary Headache Syndromes, 597

Infection and Inflammation of the Central

Nervous System, 599

Meningitis, 600

Encephalitis, 602

West Nile Virus, 603

Brain or Spinal Cord Abscess, 604

Neurologic Complications of Human Immunodeficiency Virus, 604

Peripheral Nervous System Disorders, 605

Peripheral Neuropathies, 605

Tumors of the Central Nervous System, 606

Brain Tumors, 606

Spinal Cord Tumors, 610

19 Neurobiology of Schizophrenia, Mood Disorders, Anxiety Disorders, Posttraumatic Stress Disorder, and Obsessive-Compulsive Disorder, 618

Lorey K. Takahashi

Schizophrenia, 618

Mood Disorders: Depression and Bipolar Disorder, 623

Anxiety Disorders, 630

Panic Disorder, 631

Social Anxiety Disorder, 632

Generalized Anxiety Disorder, 632

Posttraumatic Stress Disorder, 633

Obsessive-Compulsive Disorder, 634

20 Alterations of Neurologic Function in Children, 640

John Ruge

Development of the Nervous System in Children, 640

Structural Malformations, 641

Defects of Neural Tube Closure, 641

Craniosynostosis, 645

Malformations of Brain Development, 646

Alterations in Function: Encephalopathies, 649

Static (Nonprogressive) Encephalopathies, 649

Inherited Metabolic Disorders of the Central Nervous System, 649

Intoxications of the Central Nervous System, 651

Infections of the Central Nervous System, 652

Cerebrovascular Disease in Children, 653

Perinatal Stroke, 653

Childhood Stroke, 653

Epilepsy and Seizure Disorders in Children, 654

Childhood Tumors, 654

Brain Tumors, 654

Embryonal Tumors, 655

UNIT VI The Endocrine System

21 Mechanisms of Hormonal Regulation, 662

Karen C. Turner and Valentina L. Brashers

Mechanisms of Hormonal Regulation, 662

Regulation of Hormone Release, 662

Hormone Transport, 663

Hormone Receptors, 664

Hormone Effects, 666

Structure and Function of the Endocrine

Glands, 667

Hypothalamic-Pituitary System, 667

Thyroid and Parathyroid Glands, 672

Endocrine Pancreas, 675

Adrenal Glands, 678

Tests of Endocrine Function, 682

Aging and the Endocrine System, 682

Thyroid Gland, 683

Endocrine Pancreas, 683

Growth Hormone and Insulin-Like Growth Factors, 683

Parathyroid Glands, 683

Adrenal Glands, 683

Antidiuretic Hormone and Aldosterone, 684

22 Alterations of Hormonal Regulation, 688

Jodi A. Allen

Mechanisms of Hormonal Alterations, 688

Alterations of the Hypothalamic-Pituitary System, 688

Diseases of the Posterior Pituitary, 688

Syndrome of Inappropriate Antidiuretic Hormone Secretion, 689

Diseases of the Anterior Pituitary, 691

Alterations of Thyroid Function, 694

Thyrotoxicosis/Hyperthyroidism, 694

Hypothyroidism, 697

Alterations of Parathyroid Function, 700

Hyperparathyroidism, 700

Hypoparathyroidism, 701

Dysfunction of the Endocrine Pancreas: Diabetes Mellitus, 702

Types of Diabetes Mellitus, 702

Acute Complications of Diabetes Mellitus, 709

Chronic Complications of Diabetes Mellitus, 711

Alterations of Adrenal Function, 715

Disorders of the Adrenal Cortex, 715

Tumors of the Adrenal Medulla, 718

23 Obesity, Starvation, and Anorexia of Aging, 723

Jodi A. Allen and Julia L. Rogers

Adipose Tissue, 723

Adipose Tissue as an Endocrine Organ, 724

Regulation of Food Intake and Energy Balance, 724

Obesity, 724

Starvation, 730

Anorexia of Aging, 731

UNIT VII The Reproductive Systems

24 Structure and Function of the Reproductive Systems, 738

Karen C. Turner

Development of the Reproductive Systems, 738

Sexual Differentiation and Hormone Production in Utero, 738

Puberty and Reproductive Maturation, 740

The Female Reproductive System, 742

External Genitalia, 742

Internal Genitalia, 743

Female Sex Hormones, 746

Menstrual (Ovarian) Cycle, 748

Structure and Function of the Breast, 751

Female Breast, 751

Male Breast, 753

The Male Reproductive System, 753

External Genitalia, 753

Internal Genitalia, 756

Spermatogenesis, 757

Male Sex and Reproductive Hormones, 757

Tests of Reproductive Function, 759

Aging and Reproductive Function, 759

Aging and the Female Reproductive System, 759

Aging and the Male Reproductive System, 763

25 Alterations of the Female Reproductive System, 767

Corinne M. Djuric, Suzanne M. Ruiz, and Kathryn L. McCance

Abnormalities of the Female Reproductive Tract, 767

Alterations of Sexual Maturation, 768

Delayed or Absent Puberty, 769

Precocious Puberty, 769

Disorders of the Female Reproductive System, 770

Hormonal and Menstrual Alterations, 770

Infection and Inflammation, 777

Pelvic Organ Prolapse, 782

Benign Growths and Proliferative Conditions, 784

Cancer, 790

Sexual Dysfunction, 800

Impaired Fertility, 801

Disorders of the Female Breast, 802

Galactorrhea, 802

Benign Breast Disease and Conditions, 803

Breast Cancer, 804

26 Alterations of the Male Reproductive System, 823

George W. Rodway and Kathryn L. McCance

Alterations of Sexual Maturation, 823

Puberty: Premature, Delayed, and Contraseual Development, 823

Disorders of the Male Reproductive System, 825

Disorders of the Urethra, 825

Disorders of the Penis, 826

Disorders of the Scrotum, Testis, and Epididymis, 834

Disorders of the Prostate Gland, 843

Sexual Dysfunction: Erectile Dysfunction, 853

Disorders of the Male Breast, 855

Gynecomastia, 855

Male Breast Cancer, 855

27 Sexually Transmitted Infections, 865

William E. Somerall, Jr.

Sexually Transmitted Urogenital Infections, 867

Bacterial Infections, 867

Viral Infections, 879

Parasitic Infections, 884

Sexually Transmitted Infections of other body Systems, 886

Hepatitis, 887

Acquired Immunodeficiency Syndrome, 888

UNIT VIII The Hematologic System

28 Structure and Function of the Hematologic System, 892

Karen C. Turner

Components of the Hematologic System, 892

Composition of Blood, 892

Lymphoid Organs, 899

Development of Blood Cells, 902

Bone Marrow, 902

Cellular Differentiation, 903

Hematopoiesis, 906

Mechanisms of Hemostasis, 911

Function of Blood Vessel Endothelium, 911

Function of Platelets, 912

Function of Clotting Factors, 914

Control of Hemostatic Mechanisms, 916

Retraction and Lysis of Blood Clots, 917

Clinical Evaluation of the Hematologic System, 917

Tests of Bone Marrow Function, 917

Blood Tests, 918

Pediatrics and the Hematologic System, 918

Aging and the Hematologic System, 922

29 Alterations of Hematologic Function, 925

Sean McConnell and Valentina L. Brashers

Anemia, 925

Classification and General Characteristics, 925

Anemias of Blood Loss, 928

Anemias of Diminished Erythropoiesis, 929

Anemias of Increased Destruction, 937

Myeloproliferative Red Cell Disorders, 939

Polycythemia Vera, 940

Iron Overload, 941

Alterations of Leukocyte Function, 942

Quantitative Alterations of Leukocytes, 943

Alterations of Lymphoid Function, 957

Lymphadenopathy, 957

Malignant Lymphomas, 957

Plasma Cell Malignancy, 963

Alterations of Splenic Function, 966

Hemorrhagic Disorders and Alterations of Platelets and Coagulation, 967

Disorders of Platelets, 968

Alterations of Platelet Function, 973

Disorders of Coagulation, 973

30 Alterations of Hematologic Function in Children, 987*Lauri A. Linder and Anne Harvey*

- Fetal and Neonatal Hematopoiesis, 987**
- Postnatal Changes in the Blood, 988**
 - Erythrocytes, 988*
 - Leukocytes and Platelets, 990*
- Disorders of Erythrocytes, 990**
 - Acquired Disorders, 990*
 - Inherited Disorders, 994*
- Disorders of Coagulation and Platelets, 1005**
 - Inherited Hemorrhagic Disease, 1005*
 - Antibody-Mediated Hemorrhagic Disease, 1008*
- Neoplastic Disorders, 1010**
 - Leukemia, 1010*
 - Lymphomas, 1013*

UNIT IX The Cardiovascular and Lymphatic Systems

31 Structure and Function of the Cardiovascular and Lymphatic Systems, 1020*Karen C. Turner and Valentina L. Brashers*

- Circulatory System, 1020**
- Heart, 1020**
 - Structures that Direct Circulation Through the Heart, 1021*
 - Structures that Support Cardiac Metabolism: Coronary Circulation, 1026*
 - Structures that Control Heart Action, 1028*
 - Factors Affecting Cardiac Output, 1036*
- Systemic Circulation, 1039**
 - Structure of Blood Vessels, 1039*
 - Factors Affecting Blood Flow, 1043*
 - Regulation of Blood Pressure, 1045*
 - Regulation of the Coronary Circulation, 1049*
- Lymphatic System, 1050**
- Tests of Cardiovascular Function, 1051**
 - Cardiac and Coronary Artery Evaluation, 1051*
 - Systemic Vascular Evaluation, 1054*
- Aging and the Cardiovascular System, 1054**

32 Alterations of Cardiovascular Function, 1059*Valentina L. Brashers*

- Diseases of the Veins, 1059**
 - Varicose Veins and Chronic Venous Insufficiency, 1059*
 - Thrombus Formation in Veins, 1060*
 - Superior Vena Cava Syndrome, 1061*
- Diseases of the Arteries, 1061**
 - Hypertension, 1061*
 - Orthostatic (Postural) Hypotension, 1067*
 - Aneurysm, 1067*
 - Thrombus Formation in Arteries, 1069*
 - Embolism, 1069*
 - Peripheral Vascular Diseases, 1069*
 - Atherosclerosis, 1070*
 - Peripheral Artery Disease, 1073*
 - Coronary Artery Disease, Myocardial Ischemia, and Acute Coronary Syndromes, 1074*

Disorders of the Heart Wall, 1084

- Disorders of the Pericardium, 1084*
- Disorders of the Myocardium: Cardiomyopathies, 1086*
- Disorders of the Endocardium, 1088*
- Manifestations of Heart Disease, 1096**
 - Heart Failure, 1096*
 - Dysrhythmias, 1101*

33 Alterations of Cardiovascular Function in Children, 1109*Melanie L. Scala and Casey Bor*

- Congenital Heart Disease, 1109**
 - Classification of Congenital Heart Disease, 1109*
 - Defects With Increased Pulmonary Blood Flow, 1110*
 - Obstructive Defects, 1114*
 - Defects With Decreased Pulmonary Blood Flow, 1117*
 - Mixing Defects, 1119*
- Acquired Cardiovascular Disorders, 1122**
 - Heart Failure, 1123*
 - Kawasaki Disease, 1124*
 - Pediatric Hypertension, 1125*

UNIT X The Pulmonary System

34 Structure and Function of the Pulmonary System, 1131*Karen C. Turner and Valentina L. Brashers*

- Structures of the Pulmonary System, 1131**
 - Conducting Airways, 1131*
 - Gas-Exchange Airways, 1133*
 - Pulmonary and Bronchial Circulation, 1135*
 - Chest Wall and Pleura, 1137*
- Function of the Pulmonary System, 1137**
 - Ventilation, 1137*
 - Gas Transport, 1143*
- Tests of Pulmonary Function, 1148**

35 Alterations of Pulmonary Function, 1153*Mary Beth Winton and Valentina L. Brashers*

- Clinical Manifestations of Pulmonary Alterations, 1153**
 - Signs and Symptoms of Pulmonary Disease, 1153*
 - Conditions Caused by Pulmonary Disease or Injury, 1156*
- Disorders of the Chest Wall and Pleura, 1158**
 - Chest Wall Restriction, 1158*
 - Pleural Abnormalities, 1159*
- Pulmonary Disorders, 1161**
 - Restrictive Lung Diseases, 1161*
 - Obstructive Lung Diseases, 1167*
 - Respiratory Tract Infections, 1176*
 - Abscess Formation and Cavitation, 1179*
 - Pulmonary Vascular Disease, 1179*
 - Malignancies of the Respiratory Tract, 1182*

36 Alterations of Pulmonary Function in Children, 1191*Valentina L. Brashers*

- Disorders of the Upper Airways, 1191**
 - Infections of the Upper Airways, 1191*
 - Aspiration of Foreign Bodies, 1194*
 - Obstructive Sleep Apnea, 1194*

- Disorders of the Lower Airways, 1195
 - Disorders of Prematurity, 1195*
 - Respiratory Tract Infections, 1199*
 - Asthma, 1203*
 - Pediatric Acute Respiratory Distress Syndrome, 1204*
 - Cystic Fibrosis, 1205*
- Sudden Infant Death Syndrome, 1207

UNIT XI The Renal and Urologic Systems

37 Structure and Function of the Renal and Urologic Systems, 1211

Karen C. Turner

- Structures of the Renal System, 1211
 - Structures of the Kidney, 1211*
 - Urinary Structures, 1216*
- Renal Blood Flow and Glomerular Filtration, 1217
 - Autoregulation of Intrarenal Blood Flow, 1217*
 - Neural Regulation of Renal Blood Flow, 1218*
 - Hormones and Other Factors Regulating Renal Blood Flow, 1218*
- Kidney Function, 1219
 - Nephron Function, 1219*
 - Hormones and Nephron Function, 1225*
 - Renal Hormones, 1225*
- Tests of Renal Function, 1226
 - Renal Clearance, 1226*
 - Urinalysis, 1227*

38 Alterations of Renal and Urinary Tract Function, 1232

Julia L. Rogers

- Urinary Tract Obstruction, 1232
 - Upper Urinary Tract Obstruction, 1232*
 - Lower Urinary Tract Obstruction, 1237*
 - Tumors, 1241*
- Urinary Tract Infection, 1242
 - Causes of Urinary Tract Infection, 1242*
 - Types of Urinary Tract Infection, 1242*
- Glomerular Disorders, 1245
 - Glomerulonephritis, 1245*
 - Nephrotic and Nephritic Syndromes, 1250*
- Acute Kidney Injury, 1252
 - Classification of Kidney Dysfunction, 1252*
 - Acute Kidney Injury, 1252*
- Chronic Kidney Disease, 1258
 - Creatinine, Cystatin C, and Urea Clearance, 1260*
 - Fluid and Electrolyte Balance, 1260*
 - Calcium, Phosphate, Magnesium, and Bone, 1263*
 - Protein, Carbohydrate, and Fat Metabolism, 1263*
 - Hematologic System, 1264*
 - Cardiovascular System, 1264*
 - Pulmonary System, 1264*
 - Immune System, 1264*
 - Neurologic System, 1264*
 - Gastrointestinal System, 1264*
 - Endocrine and Reproductive Systems, 1264*
 - Integumentary System, 1265*

39 Alterations of Renal and Urinary Tract Function in Children, 1270

Julia L. Rogers

- Structure and Function of the Urinary System in Children, 1270
 - Development of the Urinary System, 1270*
- Alterations in Renal and Bladder Function in Children, 1271
 - Congenital Abnormalities, 1271*
 - Hypoplastic/Dysplastic Kidneys, 1271*
 - Polycystic Kidney Disease, 1273*
 - Renal Agenesis, 1273*
 - Ureteropelvic Junction Obstruction, 1273*
 - Hypospadias, 1273*
 - Epispadias and Exstrophy of the Bladder, 1274*
 - Bladder Outlet Obstruction, 1275*
- Glomerular Disorders, 1275
 - Glomerulonephritis, 1275*
 - Immunoglobulin A Nephropathy, 1276*
 - Nephrotic Syndrome, 1276*
 - Hemolytic Uremic Syndrome, 1278*
- Nephroblastoma, 1279
- Bladder Disorders, 1280
 - Urinary Tract Infections, 1280*
 - Vesicoureteral Reflux, 1280*
- Urinary Incontinence, 1281

UNIT XII The Digestive System

40 Structure and Function of the Digestive System, 1285

Karen C. Turner

- The Gastrointestinal Tract, 1285
 - Mouth and Esophagus, 1286*
 - The Abdominal Cavity, 1288*
 - Stomach, 1290*
 - Small Intestine, 1294*
 - Large Intestine, 1301*
 - The Gastrointestinal Tract and Immunity, 1303*
 - Intestinal Microbiome, 1303*
 - Splanchnic Blood Flow, 1304*
- Accessory Organs of Digestion, 1304
 - Liver, 1304*
 - Gallbladder, 1308*
 - Exocrine Pancreas, 1309*
- Tests of Digestive Function, 1310
 - Gastrointestinal Tract, 1310*
 - Liver, 1310*
 - Gallbladder, 1313*
 - Exocrine Pancreas, 1313*

41 Alterations of Digestive Function, 1318

Scarlet R. Spain

- Disorders of the Gastrointestinal Tract, 1318
 - Clinical Manifestations of Gastrointestinal Dysfunction, 1318*
 - Disorders of Motility, 1322*
 - Gastritis, 1328*
 - Peptic Ulcer Disease, 1331*

- Malabsorption Syndromes, 1335*
- Inflammatory Bowel Disease, 1336*
- Irritable Bowel Syndrome, 1340*
- Diverticular Disease of the Colon, 1340*
- Mesenteric Vascular Insufficiency, 1342*
- Disorders of the Accessory Organs of Digestion, 1342**
 - Common Complications of Liver Disorders, 1342*
 - Disorders of the Liver, 1347*
 - Disorders of the Gallbladder, 1353*
 - Disorders of the Pancreas, 1355*
- Cancer of the Digestive System, 1357**
 - Cancer of the Gastrointestinal Tract, 1357*
 - Cancer of the Accessory Organs of Digestion, 1363*

42 Alterations of Digestive Function in Children, 1375

Corinne M. Djuric

- Disorders of the Gastrointestinal Tract, 1375**
 - Congenital Impairment of Motility, 1375*
 - Meconium Syndromes, 1380*
 - Acquired Impairment of Motility, 1381*
 - Impairment of Digestion, Absorption, and Nutrition, 1383*
 - Diarrhea, 1390*
- Disorders of the Liver, 1391**
 - Disorders of Biliary Metabolism and Transport, 1391*
 - Inflammatory Disorders, 1392*
 - Portal Hypertension, 1394*
 - Metabolic Disorders, 1394*

UNIT XIII The Musculoskeletal System

43 Structure and Function of the Musculoskeletal System, 1399

Geri Cage Reeves and Benjamin Allan Smallheer

- Structure and Function of Bones, 1399**
 - Elements of Bone Tissue, 1399*
 - Types of Bone Tissue, 1406*
 - Characteristics of Bone, 1407*
 - Maintenance of Bone Integrity, 1407*
- Structure and Function of Joints, 1408**
 - Fibrous Joints, 1408*
 - Cartilaginous Joints, 1408*
 - Synovial Joints, 1411*
- Structure and Function of Skeletal Muscles, 1413**
 - Whole Muscle, 1413*
 - Components of Muscle Function, 1418*
 - Tendons and Ligaments, 1422*
- Tests of Musculoskeletal Function, 1423**
 - Tests of Bone Function, 1423*
 - Tests of Joint Function, 1423*
 - Tests of Muscular Function, 1423*

44 Alterations of Musculoskeletal Function, 1427

Benjamin Allan Smallheer and Geri Cage Reeves

- Musculoskeletal Injuries, 1427**
 - Skeletal Trauma, 1427*
 - Support Structure Trauma, 1432*
- Disorders of Bones, 1437**

- Metabolic Bone Diseases, 1437*
- Infectious Bone Disease: Osteomyelitis, 1446*
- Bone Tumors, 1448*
- Disorders of Joints, 1452**
 - Osteoarthritis, 1452*
 - Inflammatory Joint Disease, 1456*
- Disorders of Skeletal Muscle, 1462**
 - Secondary Muscular Dysfunction, 1462*
 - Fibromyalgia, 1463*
 - Chronic Fatigue Syndrome, 1465*
 - Disuse Atrophy, 1465*
 - Muscle Membrane Abnormalities, 1466*
 - Metabolic Muscle Diseases, 1466*
 - Inflammatory Muscle Diseases: Myositis, 1468*
 - Myopathy, 1469*
- Muscle Tumors, 1470**
 - Rhabdomyoma, 1470*
 - Rhabdomyosarcoma, 1470*
 - Other Tumors, 1471*

45 Alterations of Musculoskeletal Function in Children, 1476

Corinne M. Djuric

- Musculoskeletal Development in Children, 1476**
 - Bone Formation, 1476*
 - Bone Growth, 1477*
 - Skeletal Development, 1477*
 - Muscle Growth, 1478*
- Musculoskeletal Alterations in Children, 1478**
 - Congenital Defects, 1478*
 - Abnormal Density or Modeling of the Skeleton, 1482*
 - Bone and Joint Infection, 1485*
 - Septic Arthritis, 1486*
- Rheumatologic Disorders, 1487**
 - Juvenile Arthritis, 1487*
- Avascular Disease of the Bone, 1487**
 - Osteochondroses, 1487*
 - Legg-Calvé-Perthes Disease, 1488*
 - Osgood-Schlatter Disease, 1489*
 - Sever Disease, 1489*
 - Neuromuscular Disorders, 1490*
 - Cerebral Palsy, 1490*
 - Duchenne Muscular Dystrophy, 1491*
 - Spinal Muscular Atrophy, 1494*
 - Facioscapulohumeral Muscular Dystrophy, 1494*
 - Myotonic Muscular Dystrophy, 1494*
- Musculoskeletal Tumors in Children, 1495**
 - Bone Tumors, 1495*
 - Muscle Tumors, 1497*
- Nonaccidental Trauma, 1498**
 - Fractures in Nonaccidental Trauma, 1498*

UNIT XIV The Integumentary System

46 Structure, Function, and Disorders of the Integument, 1504

Corinne M. Djuric and Karen C. Turner

- Structure and Function of the Skin, 1504**
 - Layers of the Skin, 1504*
 - Dermal Appendages, 1506*

Blood Supply and Innervation, 1507
Tests of Skin Function, 1507
Clinical Manifestations of Skin Dysfunction, 1507

Disorders of the Skin, 1514

Inflammatory Disorders, 1514
Papulosquamous Disorders, 1516
Vesiculobullous Diseases, 1520
Infections, 1521
Vascular Disorders, 1526
Benign Tumors, 1527
Skin Cancer, 1529
Cold Injury, 1533

Disorders of the Hair, 1534

Alopecia, 1534
Hirsutism, 1535

Disorders of the Nail, 1535

Paronychia, 1535
Onychomycosis, 1535

47 Alterations of the Integument in Children, 1541

Noreen Heer Nicol and Judith O'Haver

Acne Vulgaris, 1541

Dermatitis, 1542

Atopic Dermatitis, 1542
Contact Dermatitis, 1543

Infections of the Skin, 1543

Bacterial Infections, 1544
Fungal Infections, 1545
Viral Infections, 1546

Insect Bites and Parasites, 1550

Scabies, 1550
Fleas and Bedbugs, 1550
Pediculosis (Lice Infestation), 1551

Vascular Anomalies, 1551

Infantile Hemangiomas, 1551

Other Skin Disorders, 1553

Psoriasis, 1553
Newborn Rashes, 1553

UNIT XV Multiple Interacting Systems

48 Shock, Multiple Organ Dysfunction Syndrome, and Burns in Adults, 1557

Mary C. Selzer, Dennis J. Cheek, and Julia L. Rogers

Shock, 1557

Cellular Alterations and Impairment of Cellular Metabolism, 1557

Types of Shock, Clinical Manifestations, and Treatment, 1560

Multiple Organ Dysfunction Syndrome, 1569

Thermal Injury and Burns, 1575

Epidemiology and Etiology, 1575
Burn Wound Depth, 1575

49 Shock, Multiple Organ Dysfunction Syndrome, and Burns in Children, 1591

Mary A. Mondozi, Dennis J. Cheek, and Mary Fran Hazinski

Shock and Multiple Organ Dysfunction Syndrome, 1591

Types of Shock, 1592

Assessment of Shock, 1592

Reperfusion and Inflammatory Injury, 1606

Burns, 1607

Severity of Injury, 1608

Pathophysiology, Clinical Manifestations, and Treatment, 1609

Glossary, 1622

Index, 1645

Cellular Biology

Victoria Gray and Kathryn L. McCance

 <http://evolve.elsevier.com/Rogers/pathophysiology/>

CHAPTER OUTLINE

Prokaryotes and Eukaryotes,	1
Cellular Functions,	2
Structure and Function of Cellular Components,	2
Nucleus,	2
Cytoplasmic Organelles,	2
Plasma Membranes,	3
Cellular Receptors,	9
Cell-to-Cell Adhesions,	12
Extracellular Matrix and Basement Membrane,	12
Specialized Cell Junctions,	14
Cellular Communication and Signal Transduction,	15
Cellular Metabolism,	17
Role of Adenosine Triphosphate,	18
Food and Production of Cellular Energy,	20

Oxidative Phosphorylation,	20
Membrane Transport: Cellular Intake and Output,	21
Electrolytes as Solutes,	23
Transport by Vesicle Formation,	26
Movement of Electrical Impulses: Membrane Potentials,	27
Cellular Reproduction: The Cell Cycle,	31
Phases of Mitosis and Cytokinesis,	32
The Cell Cycle Control System,	33
Control of Cell Division and Cell Growth: Mitogens, Growth Factors, and Survival Factors,	34
DNA Damage Response: Blocks Cell Division,	34
Tissues,	34
Tissue Formation and Differentiation,	34

All body functions are dependent on the integrity of cells. These trillions of complex cells are the basic building blocks of the human body. Therefore an understanding of cellular biology is fundamental to understanding health, wellness, and disease processes. Cells behave as a multicellular “social” organism in that they message between, among, and within one another through cellular communication (cellular “crosstalk”). Cells have the ability to originate, transmit, receive, interpret, and use information to maintain cellular function and specialization. Cells must demonstrate a “chemical fondness” for other cells to maintain the integrity of the entire organism. When they no longer tolerate this fondness, the conversation breaks down, and cells either adapt (e.g., altering function) or become vulnerable to isolation, injury, or disease.

PROKARYOTES AND EUKARYOTES

Living cells generally are divided into eukaryotes and prokaryotes. The cells of animals and plants are eukaryotes, as are

the single-celled organisms, fungi, protozoa, and most algae. **Prokaryotes** include bacteria and archaea. Prokaryotes traditionally were studied as core subjects of molecular biology, which generated an abundance of data related to prokaryotic **genomes** (a set of genes carried on molecules of deoxyribonucleic acid [DNA]). Currently, emphasis is on the eukaryotic cell, which contains genomes that are more complex.¹

Eukaryotes (*eu* = true; *karyon* = nucleus; also spelled “eucaryotes”) are larger and have more extensive intracellular anatomy and organization than prokaryotes. Eukaryotic cells have a characteristic set of membrane-bound intracellular compartments, called *organelles*, that includes a well-defined nucleus. The prokaryotes contain no organelles, and their nuclear material is not encased by a nuclear membrane.

Besides having structural differences, prokaryotic and eukaryotic cells differ in chemical composition and biochemical activity. The *nuclei* of prokaryotic cells carry genetic information in a single circular chromosome, and they lack a class of proteins called *histones*, which in eukaryotic cells

bind with DNA and are involved in the supercoiling of DNA. Eukaryotic cells have several chromosomes, the number of which is dependent on species. Protein production, or synthesis, in the two classes of cells also differs because of major structural differences in ribonucleic acid (RNA) protein complexes. Other distinctions include differences in mechanisms of transport across the outer cellular membrane and in enzyme content.

CELLULAR FUNCTIONS

Cells become specialized through the process of **differentiation**, or maturation, so that some cells eventually perform one function and other cells perform other functions. Cells with a highly developed function, such as movement, often lack some other property, such as hormone production, which is more highly developed in other cells.

The eight chief cellular functions are as follows:

- **Movement.** Muscle cells can generate forces that produce motion. Muscles that attach to bones produce limb movements, whereas muscles that enclose hollow tubes or cavities move or empty contents when they contract (e.g., the colon).
- **Conductivity.** Conduction as a response to a stimulus is manifested by a wave of excitation, an electrical potential that passes along the surface of the cell to reach its other parts. Conductivity is the chief function of nerve cells. (e.g., the brain or heart).
- **Metabolic absorption.** All cells can take in and use nutrients and other substances from their surroundings. (e.g., cells of the intestines or kidneys).
- **Secretion.** Certain cells, such as mucous gland cells, can synthesize new substances from substances they absorb and then secrete the new substances to serve elsewhere as needed.
- **Excretion.** All cells can rid themselves of waste products resulting from the metabolic breakdown of nutrients. Membrane-bound sacs (lysosomes) within cells contain enzymes that break down, or digest, large molecules, turning them into waste products that are released from the cell (e.g., urine).
- **Respiration.** Cells absorb oxygen, which is used to transform nutrients into energy in the form of adenosine triphosphate (ATP). Carbohydrates, fats, and proteins can be used as fuels. Cellular respiration, or oxidation, occurs in organelles called *mitochondria* (e.g., glucose).
- **Reproduction.** Tissue growth occurs as cells enlarge and reproduce themselves. Even without growth, tissue maintenance requires that new cells be produced to replace cells that are lost normally through cellular death. Not all cells are capable of continuous division (see [Chapter 2](#)) (e.g., mitosis and meiosis).
- **Communication.** Communication is vital for cells to survive as a society of cells. Appropriate communication allows the maintenance of a dynamic steady state. [Table 1.1](#)

STRUCTURE AND FUNCTION OF CELLULAR COMPONENTS

[Fig. 1.1A](#) shows a “typical” eukaryotic cell, which consists of three components: an outer membrane called the **plasma membrane**; a fluid “filling” called **cytoplasm** (see [Fig. 1.1B](#)); and the “organs” of the cell—the membrane-bound intracellular **organelles**, among them the nucleus.

Nucleus

The **nucleus**, which is surrounded by the cytoplasm and generally is located in the center of the cell, is the largest membrane-bound organelle. Two pliable membranes compose the **nuclear envelope** ([Fig. 1.2A](#)). The nuclear envelope is pockmarked with pits, called **nuclear pores**, which allow chemical messages to exit and enter the nucleus (see [Fig. 1.2A, B, and D](#)). The outer membrane is continuous with membranes of the endoplasmic reticulum (see [Fig. 1.1](#)). The nucleus contains the **nucleolus** (a small dense structure composed of DNA, RNA, and ribosomal proteins), most of the cellular DNA, and the DNA-binding proteins (i.e., the histones) that regulate its activity. The DNA chain in eukaryotic cells is so long that it is easily broken. Therefore the histones that bind to DNA cause DNA to fold into chromosomes (see [Fig. 1.2C](#)). The wrapping of DNA into tight packages of chromosomes is essential for cell division in eukaryotes. The primary functions of the nucleus are cell division and control of genetic information. These functions include the replication and repair of DNA and the transcription of the information stored in DNA into RNA.

Cytoplasmic Organelles

Cytoplasm is an aqueous solution (**cytosol**) that fills the **cytoplasmic matrix**—the space between the nuclear envelope and the plasma membrane. The cytosol represents approximately half the volume of a eukaryotic cell. It contains thousands of enzymes involved in intermediate metabolism and is *crowded* with ribosomes making proteins (see [Fig. 1.1B](#)). Newly synthesized proteins remain in the cytosol if they lack a signal for transport to a cell organelle.²

The organelles suspended in the cytoplasm are enclosed in biologic membranes, so they can simultaneously carry out functions requiring different biochemical environments. Many of these functions are directed by coded messages carried from the nucleus by RNA. Functions of organelles can be divided into four major categories: (1) genetic control; (2) manufacturing, distributing, and breaking down molecules; (3) energy processing; and (4) structural support, movement, and communication between cells. The cytosol is a storage unit for fat, carbohydrates, and secretory vesicles. [Table 1.1](#) lists the principal cytoplasmic organelles.

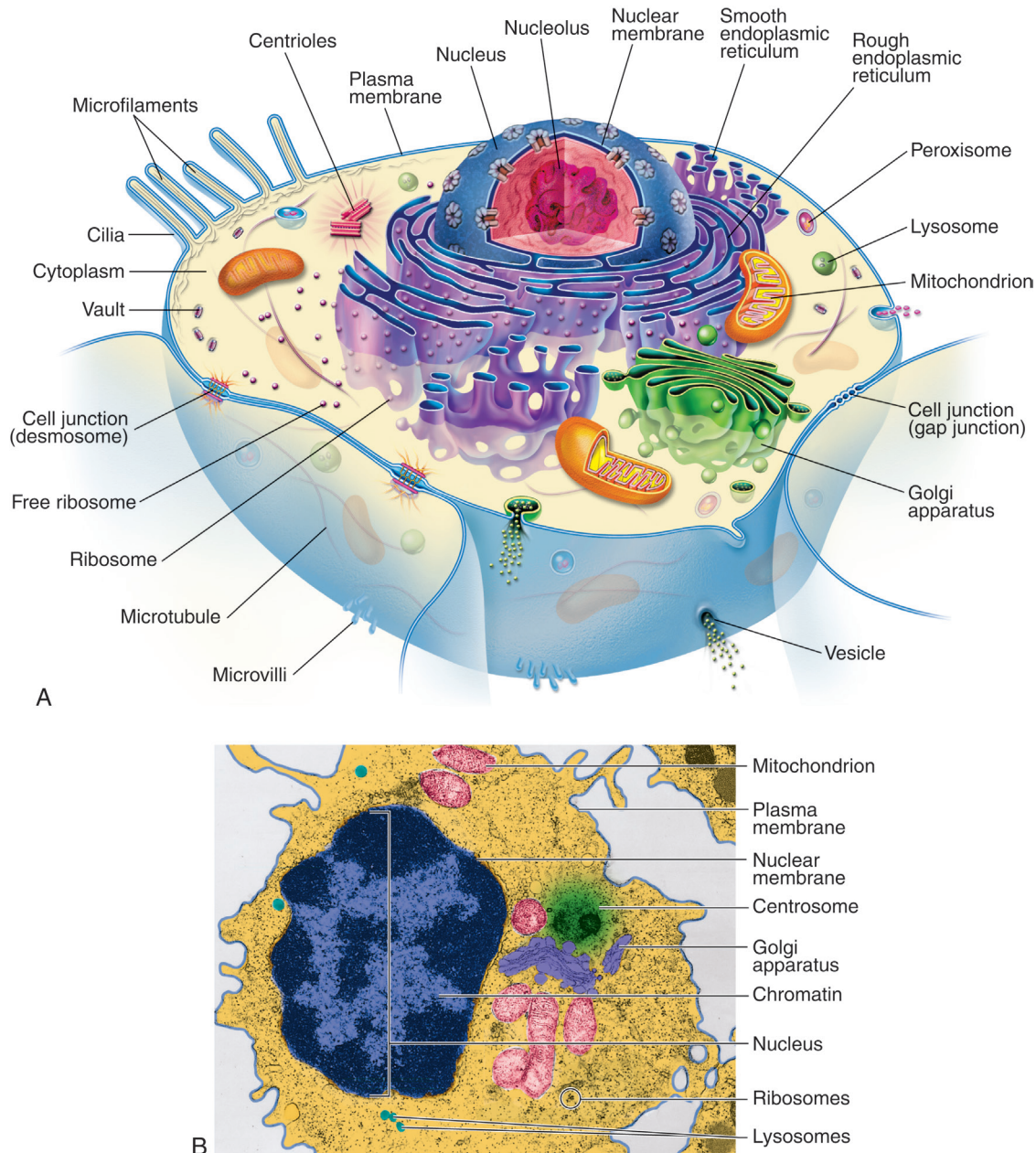


Fig. 1.1 Typical Components of a Eukaryotic Cell and Structure of the Cytoplasm. (A) Artist's interpretation of cell structure. (B). Color-enhanced electron micrograph of a cell. Both show the many mitochondria known as the "power plants" of the cell. Note, too, the innumerable dots bordering the endoplasmic reticulum. These are ribosomes, the cell's "protein factories." (B, From Patton KT, Thibodeau GA. *Anatomy & physiology*, 9th edition. St. Louis: Mosby; 2016.

Plasma Membranes

Membranes define the cell's boundaries. Membranes surround the cell or enclose an intracellular organelle and are exceedingly important to normal physiologic function because they control the composition of the space, or compartment, they enclose. Membranes can allow or exclude various molecules, and because of selective transport systems, they can move molecules in or out of the space (Fig. 1.3). By controlling the movement of substances from one compartment to another, membranes exert a powerful influence on metabolic pathways. Directional transport is facilitated by polarized domains, distinct apical and

basolateral domains. The plasma membrane also has an important role in cell-to-cell recognition, cellular mobility, and the maintenance of cellular shape (Table 1.2).

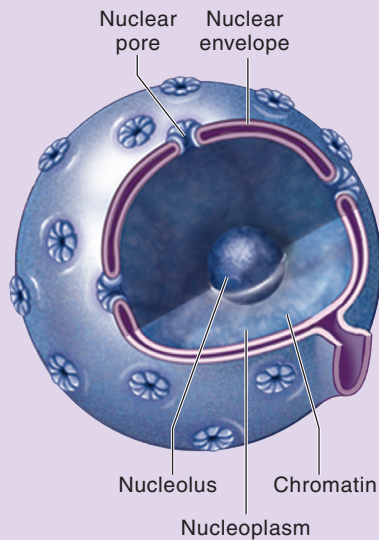
Membrane Composition

The main components of cell membranes are lipids and proteins. The cell membrane is a **lipid bilayer**, composed of two opposing leaflets and proteins that span the bilayer or interact with the lipids on either side of the two leaflets (Fig. 1.4). Historically, the plasma membrane was described as a fluid lipid bilayer (*fluid mosaic model*) composed of a uniform lipid distribution with

TABLE 1.1 Principal Cytoplasmic Organelles

Genetic Control**Organelle**

Nucleus

(From Patton KT: *Anatomy & Physiology, 10 ed.*, Mosby, 2019, Elsevier.)

Nucleolus

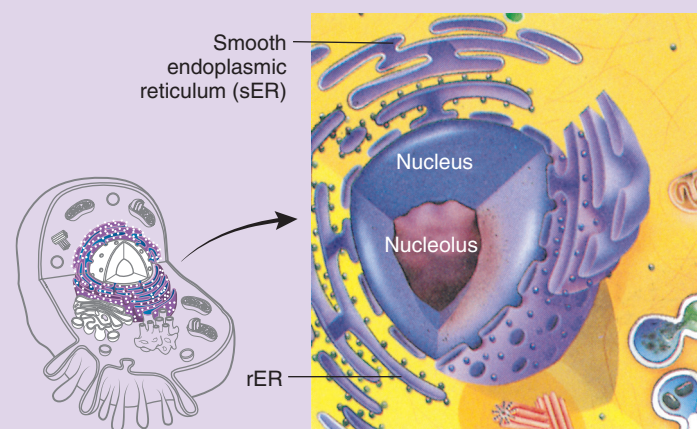
Characteristics and Description*(See text for further description of function and structure)***Manufacturing, Distributing and Breaking Down Molecules****Organelle**

Ribosomes

Characteristics and Description

Ribonucleic acid (RNA)-protein complexes (nucleoproteins) synthesized in nucleolus and secreted into cytoplasm. Provide sites for cellular protein synthesis. Uses the information from deoxyribonucleic acid (DNA), written in messenger RNA (mRNA), to build proteins.

Endoplasmic reticulum (rough and smooth)

(From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children*, St. Louis, 2019, Elsevier.)

Network of tubular channels (cisternae) that extend throughout the outer nuclear membrane.

Rough Endoplasmic Reticulum (RER)—

bumpy exterior due to ribosomes and ribonucleoprotein particles attached to it; is responsible for much of a cell's protein synthesis and folding.

Smooth Endoplasmic Reticulum (SER)—does

not contain ribosomes or ribonucleoprotein particles. Rather, membranous surfaces of the SER contain enzymes involved in the synthesis of steroid hormones and are responsible for a variety of reactions required to remove toxic substances from the cell. The SER communicates with the Golgi complex and interacts with other organelles, particularly lysosomes and peroxisomes.

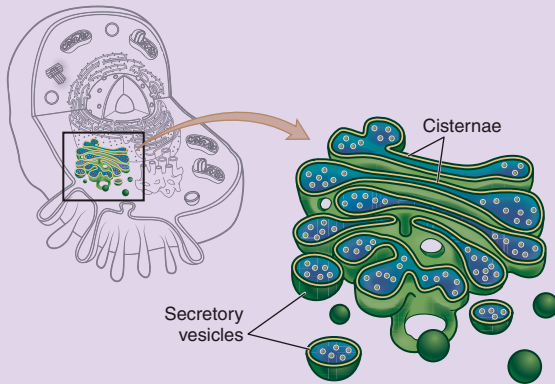
Continued

TABLE 1.1 Principal Cytoplasmic Organelles—cont'd

Manufacturing, Distributing and Breaking Down Molecules

Organelle

Golgi complex

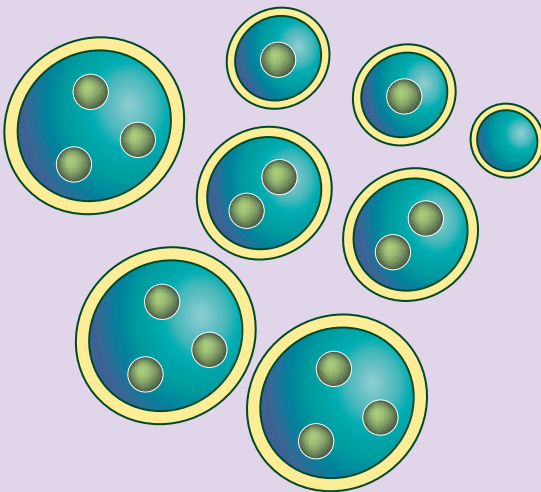


Characteristics and Description

Network of flattened, smooth membranes and vesicles located near the nucleus and the RER. Proteins from the endoplasmic reticulum are processed and packaged into small membrane-bound sacs or vesicles called **secretory vesicles**, which collect at the end of the membranous folds of the Golgi bodies—called **cisternae** (like a stack of pita breads). The secretory vesicles then break off from the Golgi complex and migrate to a variety of intracellular and extracellular destinations, including the plasma membrane. The vesicles fuse with the plasma membrane, and their contents are released from the cell. The best-known vesicles are those that have coats made largely of the protein **clathrin** and are called *clathrin-coated vesicles*. The Golgi complex is a refining plant and directs cellular traffic (e.g., protein, polynucleotide, polysaccharide molecules) in the cell.

(From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children*, St. Louis, 2019, Elsevier.)

Lysosomes



Sac-like, membrane-bound structures containing enzymes for digesting most cellular substances to their basic forms, such as amino acids, fatty acids, and carbohydrates (sugars). The lysosomal membrane acts as a protective shield between the powerful digestive enzymes within the lysosome and the cytoplasm, preventing their leakage into the cytoplasmic matrix. Lysosomes maintain cellular health because of efficient removal of toxic cellular components, removal of useless organelles, termination of signal transduction, and maintenance of metabolic homeostasis. Aging can lead to progressive loss of lysosomal efficiency and decline of the regenerative capacity of organs and tissues. Cellular injury leads to release of lysosomal enzymes that cause cellular self-digestion.

(From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children*, St. Louis, 2019, Elsevier.)

Peroxisomes

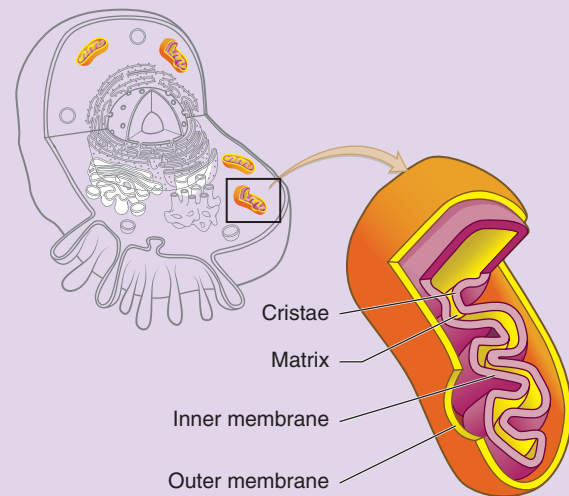
Similar to lysosomes in appearance but contain several oxidative enzymes (e.g., catalase, urate oxidase) that can detoxify compounds and fatty acids. Peroxisomes are so named because they usually contain enzymes that use oxygen to remove hydrogen atoms from specific substrates in an oxidative reaction that produces hydrogen peroxide (H_2O_2). Hydrogen peroxide is a powerful oxidant, potentially destructive if it accumulates or escapes from peroxisomes. Peroxisomes also have an important role in the synthesis of specialized phospholipids necessary for nerve cell myelination. Such reactions are important in detoxifying various wastes within the cell or foreign components that enter the cell, such as ethanol. Impairment of peroxisomes can lead to disease (see Fig. 1.1A).

TABLE 1.1 Principal Cytoplasmic Organelles—cont'd

Energy Processing

Organelle

Mitochondria



(From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children*, St. Louis, 2019, Elsevier.)

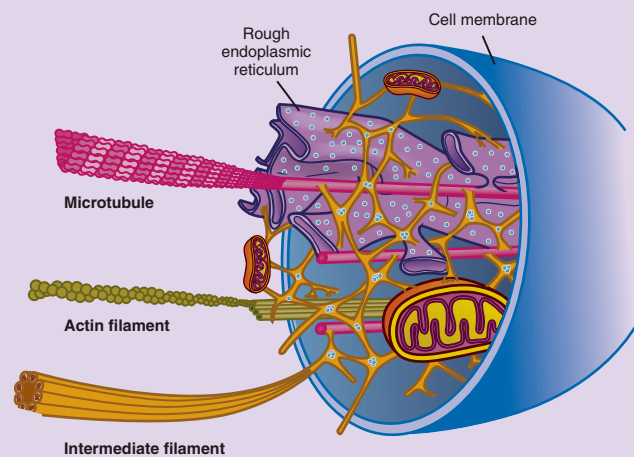
Characteristics and Description

Organelles, found in large numbers in most cells, are responsible for cellular respiration and energy production. These cytoplasmic organelles appear as spheres, rods, or filamentous bodies that are bound by a double membrane. The **outer membrane** is smooth and surrounds the mitochondrion itself; the inner membrane is convoluted in the mitochondrial matrix to form partitions called **cristae**. The **inner membrane** contains the enzymes of the **respiratory chain**—the name given to the electron transport chain. These enzymes are essential to the process of oxidative phosphorylation that generates most of the cell's adenosine triphosphate. Metabolic pathways involved in the metabolism of carbohydrates, lipids, and amino acids and special pathways involving urea and heme synthesis are located in the mitochondrial matrix. Mitochondria contain their own DNA that codes for enzymes needed for oxidative phosphorylation.

Structural Support, Movement, and Communication Between Cells

Structures

Cytoskeleton



(From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children*, St. Louis, 2019, Elsevier.)

Characteristics and Description

All eukaryotic cells contain elaborate and specialized internal structures in the cytosol that provide the “bones and muscles” of the cell—the **cytoskeleton**. The cytoskeleton maintains the cell's shape and internal organization, and it permits movement of substances within the cell and movement of external projections (cilia or microvilli; flagella in sperm) outside the plasma membrane. The internal skeleton is composed of a network of protein filaments; the three main types of filaments include actin filaments, microtubules, and intermediate filaments. These filaments collectively promote cell strength, shape, and movement. Intermediate filaments bridge the cytoplasm from one cell junction to another, strengthening and supporting the sheet of epithelium.

inserted moving proteins. Although the notion is controversial, it now appears that the lipid bilayer is a much more complex structure where lipids and proteins are not uniformly distributed, but may separate into discrete units called *microdomains*, differing in their protein and lipid compositions. Different membranes have varying percentages of lipids and proteins. Intracellular membranes may have a higher percentage of proteins than do plasma membranes, presumably because most enzymatic activity occurs within organelles. The membrane organization is

achieved through noncovalent bonds that allow different physical states called phases (solid gel, fluid liquid–crystalline, and liquid ordered). These phases can change under physiologic factors, such as temperature and pressure fluctuations. Carbohydrates are mainly associated with plasma membranes, in which they are chemically combined with lipids, forming **glycolipids**, and with proteins, forming **glycoproteins** (Fig. 1.5).

The outer surface of the plasma membrane in many types of cells, especially endothelial cells and adipocytes, is not smooth

TABLE 1.2 Plasma Membrane Functions

Cellular Mechanism	Membrane Functions
Structure	Usually thicker than membranes of intracellular organelles Containment of cellular organelles Maintenance of relationship with cytoskeleton, endoplasmic reticulum, and other organelles Maintenance of fluid and electrolyte balance (ion channels) Outer surfaces of plasma membranes in many cells are not smooth but are dimpled with cave-like indentations called <i>caveolae</i> ; they are also studded with cilia or even smaller cylindrical projections called <i>microvilli</i> ; both are capable of movement
Protection	Barrier to toxic molecules and macromolecules (proteins, nucleic acids, polysaccharides) Barrier to foreign organisms and cells
Activation of cell	Hormones (regulation of cellular activity) Mitogens (cellular division; see Chapter 2) Antigens (antibody synthesis; see Chapter 7) Growth factors (proliferation and differentiation; see Chapter 11)
Storage	Storage site for many receptors Transport (e.g., sodium [Na ⁺] pump) Diffusion and exchange diffusion Endocytosis (pinocytosis, phagocytosis) Exocytosis (secretion) Active transport
Cell-to-cell interaction	Communication, anchors (integrins), and attachment at junctional complexes Symbiotic nutritive relationships Release of enzymes and antibodies to extracellular environment Relationships with extracellular matrix

Modified from King DW, Fenoglio CM, Lefkowitz JH. *General pathology: Principles and dynamics*. Philadelphia: Lea & Febiger; 1983.

but dimpled with flask-shaped invaginations known as *caveolae* (“tiny caves”). Caveolae, considered to serve as a storage site for many receptors, provide a route for transport into the cell and may act as the initiator for relaying signals from several extracellular chemical messengers into the cell’s interior.

Lipids. Each lipid molecule is polar, or **amphipathic**, which means that one part is **hydrophobic** (uncharged, or “repelled by water”) and another part is **hydrophilic** (charged, or “attracted to water”) (see Fig. 1.4B). The membrane spontaneously organizes itself into two layers because of these two incompatible solubilities. The hydrophobic region (hydrophobic tail) of each lipid molecule is protected from water, whereas the hydrophilic region (hydrophilic head) is immersed in it. The bilayer serves as a barrier to the diffusion of water and hydrophilic substances, while allowing lipid-soluble molecules, such as oxygen (O₂) and carbon dioxide (CO₂), to diffuse through the membrane readily.

Cell membranes may contain many different lipid classes, but in animals, the main ones are phospholipids, cholesterol, and glycolipids. **Phospholipids**, the most abundant lipids, have a phosphate-containing hydrophilic head connected to a hydrophobic tail. Phospholipids and glycolipids form self-sealing lipid bilayers. Lipids along with protein assemblies act as “molecular glue” for the structural integrity of the membrane. Phospholipids are key for repairing the membrane—they tend to spontaneously rearrange themselves to avoid a tear by folding on themselves and forming a sealed compartment.²

Proteins. Proteins perform most of the plasma membrane’s tasks and are the major workhorses of the cell. A **protein** is made

from a chain of amino acids, known as **polypeptides**. There are 20 types of amino acids in proteins and each type of protein has a unique sequence of amino acids. After translation (the synthesis of protein from RNA, see Chapter 4) of a protein, **posttranslational modifications (PTMs)** are the methods used to diversify the limited numbers of proteins generated. These modifications alter the activity and functions of proteins. PTMs have become very important in understanding disease processes. An emerging field of study in science is **proteomics**, the study of the **proteome**. This molecular approach is used to study an entire set of proteins expressed by a genome from synthesis, translocation, and modification (e.g., folding). Biologists are analyzing and uncovering information related to the roles of proteomes in a staggering number of diseases.

Membrane proteins associate with the lipid bilayer in different ways (Fig. 1.6), including:

1. **Transmembrane proteins** that extend across the bilayer and are exposed to an aqueous environment on both sides of the membrane (see Fig. 1.6A)
2. Proteins located almost entirely in the cytosol and associated with the cytosolic half of the lipid bilayer by an α helix exposed on the surface of the protein (see Fig. 1.6B)
3. Proteins that exist outside the bilayer, on one side or the other, and attached to the membrane by one or more covalently attached lipid groups (see Fig. 1.6C)
4. Proteins bound indirectly to one or the other bilayer membrane face and held in place by their interactions with other proteins (see Fig. 1.6D).³

Proteins directly attached to the membrane bilayer can be removed by dissolving the bilayer with detergents called

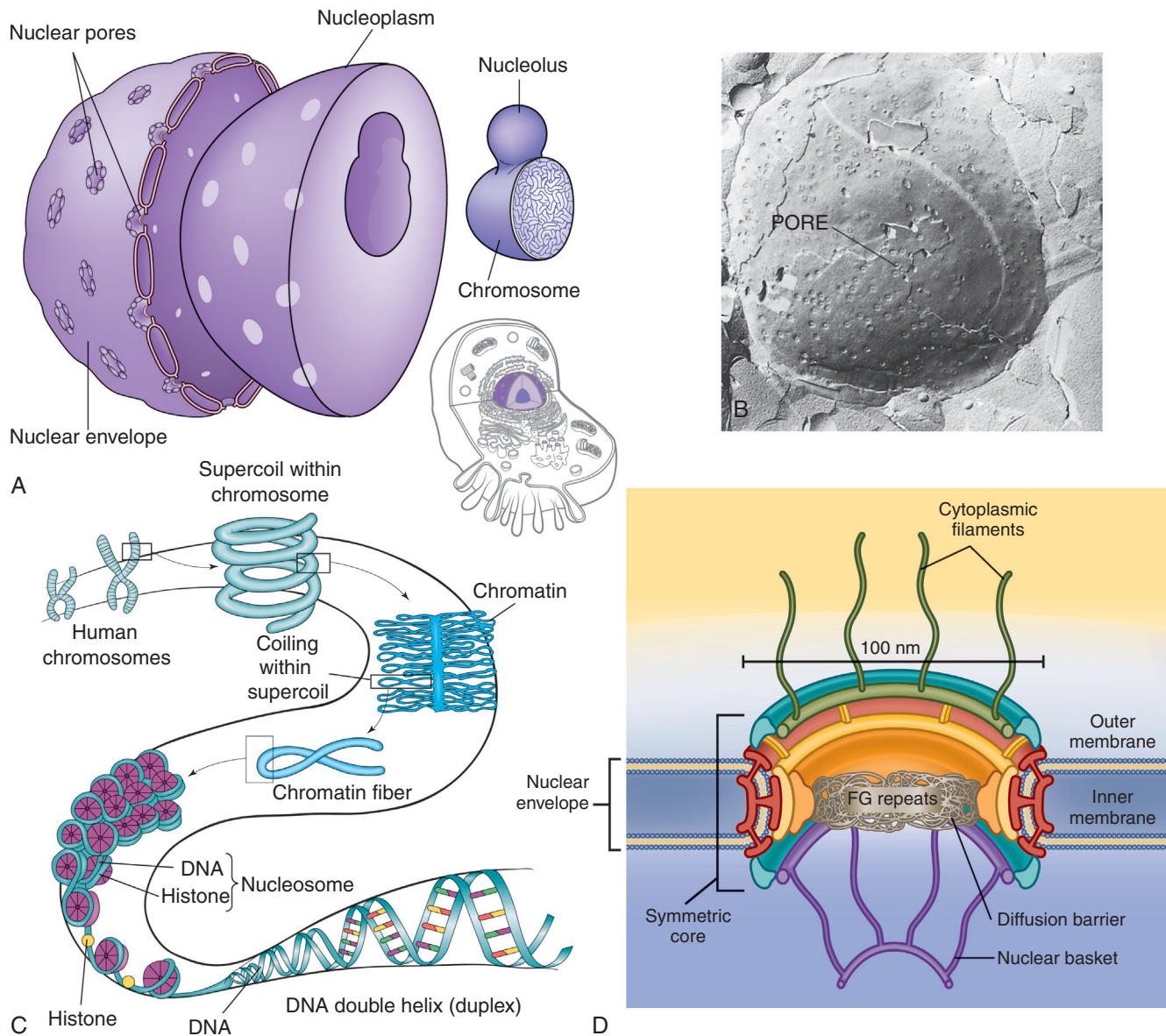


Fig. 1.2 The Nucleus. The nucleus is composed of a double membrane, called a nuclear envelope, which encloses the fluid-filled interior, called *nucleoplasm*. The chromosomes are suspended in the nucleoplasm (illustrated here much larger than actual size to show the tightly packed deoxyribonucleic acid [DNA] strands). Swelling at one or more points of the chromosome, shown in **(A)** occurs at a nucleolus where genes are being copied into ribonucleic acid. The nuclear envelope is studded with pores. **(B)** The pores are visible as dimples in this freeze-etch of a nuclear envelope. **(C)** Histone-folding DNA in chromosomes. **(D)** Nuclear pore complex. (A, C, From McCance KL, Huether S *Pathophysiology: The biologic basis for disease in adults and children*. St. Louis: Elsevier; 2019 B, From Raven PH, Johnson GB. *Biology*. St. Louis: Mosby; 1992. D, Adapted from The-scientist infographic: the nuclear pore complex. Available at <https://www.The-scientist.com/infographics/infographic-the-nuclear-pore-complex-32456>)

integral membrane proteins. The remaining proteins that can be removed by gentler procedures, that interfere with protein-protein interactions, but do not dissolve the bilayer, are known as **peripheral membrane proteins**.

Proteins exist in densely folded molecular configurations rather than straight chains; thus most hydrophilic units are at the surface of the molecule, and most hydrophobic units are inside. Membrane proteins, like other proteins, are synthesized

by the ribosome and translocate, called *trafficking*, to different membrane locations of a cell. Trafficking puts unique demands on membrane proteins for folding, translocation, and stability.

Although membrane structure is determined by the lipid bilayer, membrane functions are determined largely by proteins (see Fig. 1.3). Proteins act as:

1. Recognition and binding units (receptors) for substances moving into and out of the cell

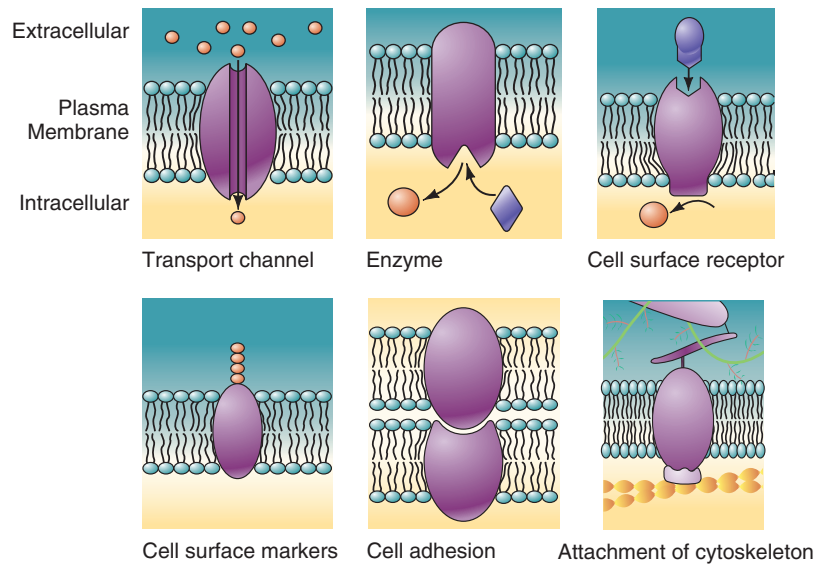


Fig. 1.3 Functions of Plasma Membrane Proteins. The plasma membrane proteins illustrated here show a variety of functions performed by the different types of plasma membranes. (From Raven PH, Johnson GB. *Understanding biology*, 3rd edition. Dubuque, IA: Brown; 1995.

2. Pores or transport channels for various electrically charged particles, called **ions** or **electrolytes**, and specific carriers for amino acids and monosaccharides
3. Specific enzymes that drive active pumps to promote concentration of certain ions, particularly potassium (K^+), within the cell while keeping concentrations of other ions (e.g., sodium [Na^+]), less than concentrations found in the extracellular environment
4. Cell surface markers, such as **glycoproteins** (proteins attached to carbohydrates), which identify a cell to its neighbor
5. **Cell adhesion molecules (CAMs)**, or proteins that allow cells to hook together and form attachments of the cytoskeleton for maintaining cellular shape
6. Catalysts of chemical reactions (e.g., conversion of lactose to glucose)

Membrane proteins are key components of energy transduction, converting chemical energy into electrical energy, or electrical energy into either mechanical energy or synthesis of ATP. Investigators are studying ATP enzymes and the changes in shape of biologic membranes, particularly mitochondrial membranes, and their relationship to aging and disease.⁴

In animal cells, the plasma membrane is stabilized by a meshwork of proteins attached to the underside of the membrane called the **cell cortex**. Human red blood cells have a cell cortex that maintains their flattened biconcave shape.³

The cellular protein pool is in constant change or flux. **Proteostasis** is the process that regulates protein synthesis, folding, and degradation within and around a cell. This adaptable system depends on how quickly proteins are made, how long they survive, or when they are broken down. The proteostasis network comprises ribosomes (makers); chaperones (helpers); and two protein breakdown systems or **proteolytic** systems—lysosomes and the ubiquitin-proteasome system (UPS). These systems regulate protein homeostasis under a large variety of

conditions, including variations in nutrient supply, the existence of oxidative stress or cellular differentiation, changes in temperature, and the presence of heavy metal ions and other sources of stress. Proteostasis is vital to health, and failure to maintain protein homeostasis is associated with aging and numerous degenerative diseases (Fig. 1.7).

Carbohydrates. The short chains of sugars or carbohydrates (**oligosaccharides**) contained within the plasma membrane are mostly bound to membrane proteins (glycoproteins) and lipids (glycolipids). Long polysaccharide chains attached to membrane proteins are called **proteoglycans**. All of the carbohydrate on the glycoproteins, proteoglycans, and glycolipids is located on the outside of the plasma membrane and the carbohydrate coating is called the **glycocalyx**. The glycocalyx helps to protect the cell from mechanical damage.⁵ In addition, the layer of carbohydrate gives the cell a slimy surface that assists the mobility of other cells, such as leukocytes, to squeeze through the narrow spaces.³ Other functions of carbohydrates include specific cell-to-cell recognition and adhesion. Intercellular recognition is an important function of membrane oligosaccharides; for example, the transmembrane proteins called **lectins**, which bind to a particular oligosaccharide, recognize neutrophils at the site of bacterial infection. This recognition allows the neutrophil to adhere to the blood vessel wall and migrate from blood into the infected tissue to help eliminate the invading bacteria.³

Cellular Receptors

Cellular receptors are protein molecules on the plasma membrane, in the cytoplasm, or in the nucleus that can recognize and bind with specific smaller molecules called **ligands** (from the Latin *ligare*, “to bind”) (Fig. 1.8). The region of a protein that associates with a ligand is called its **binding site**. For example, hormones are ligands. Numerous receptors are found in

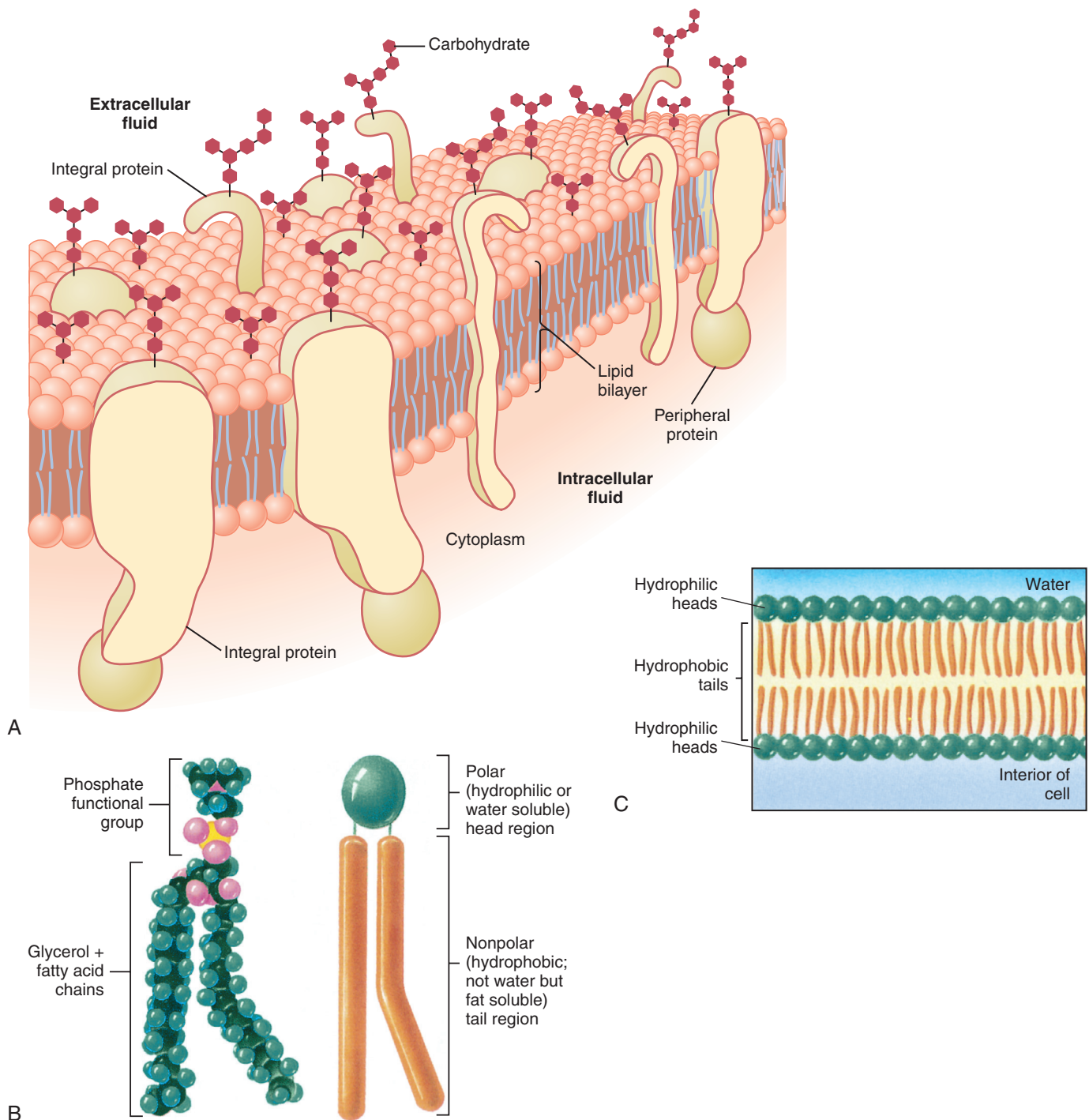


Fig. 1.4 Lipid Bilayer Membranes. **(A)** The structure of a cell membrane showing the lipid bilayer, embedded proteins, and attached extracellular carbohydrates. **(B)** Each phospholipid molecule consists of a phosphate functional group and two fatty acid chains attached to a glycerol molecule. **(C)** The fatty acid chains and glycerol form nonpolar, hydrophobic “tails,” and the phosphate functional group forms the polar, hydrophilic “head” of the phospholipid molecule. When placed in water, the hydrophobic tails of the molecule face inward, away from the water, and the hydrophilic head faces outward, toward the water. (A, From Guyton AC, Hall JE. *Textbook of medical physiology*, 11th edition. Amsterdam: Elsevier Saunders; 2006. B and C, From Raven PH, Johnson GB. *Understanding biology*, 3rd edition. Dubuque, IA: Brown; 1995.

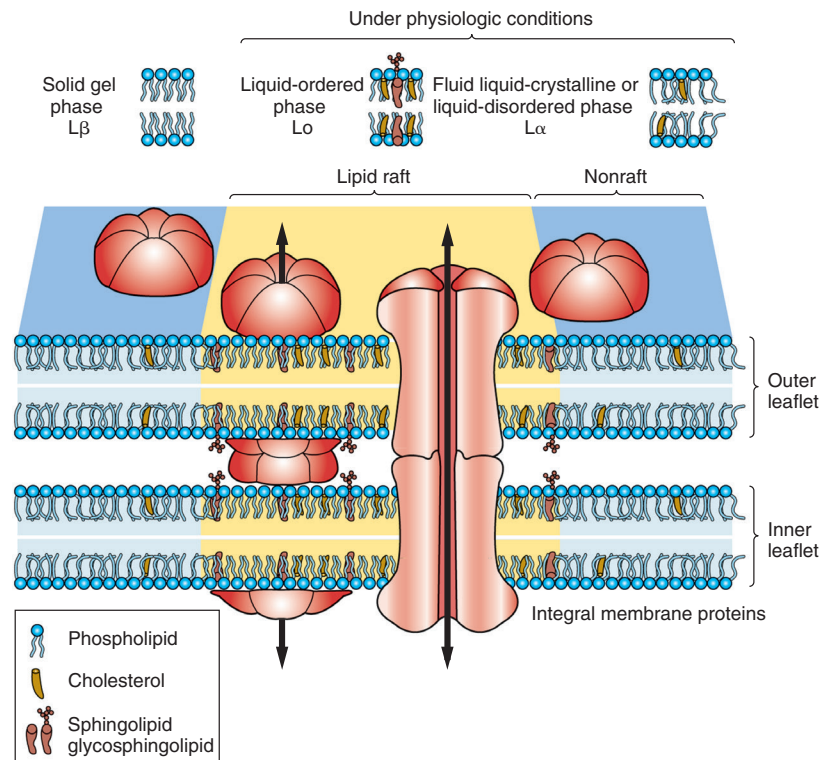


Fig. 1.5 Lipid Bilayer Membranes. Concepts of biologic membranes have markedly changed in the last two decades, from the classic fluid mosaic model to the current model that lipids and proteins are not evenly distributed but can isolate into microdomains, differing in their protein and lipid composition. The three major phases of lipid bilayer organization include a solid gel phase (e.g., with low temperatures), a liquid-ordered phase (high temperatures), and a fluid liquid-crystalline (or liquid-disordered) phase.

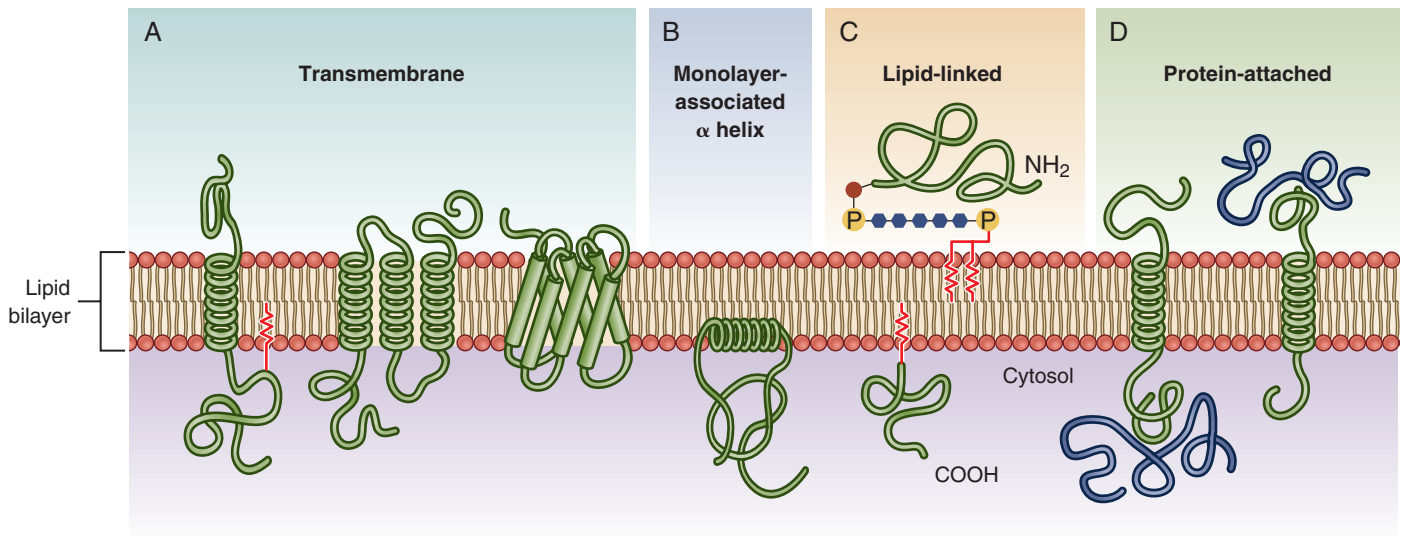


Fig. 1.6 Proteins Attach to the Plasma Membrane in Different Ways. (A) Transmembrane proteins extend through the membrane as a single α helix, as multiple α helices, or as a rolled-up barrel-like sheet called a β barrel. (B) Some membrane proteins are anchored to the cytosolic side of the lipid bilayer by an amphipathic α helix. (C) Some proteins are linked on either side of the membrane by a covalently attached lipid molecule. (D) Proteins are attached by weak noncovalent interactions with other membrane proteins. (D, Adapted from Alberts B, Bray D, Hopkin K, et al. *Essential cell biology*, 4th edition. New York: Garland; 2014.

most cells. Ligand binding to receptors activates or inhibits the receptor's associated signaling or biochemical pathway (see the Cellular Communication and Signal Transduction section). Recognition and binding depend on the chemical configuration of the receptor and its smaller ligand, which must fit together somewhat like the pieces of a jigsaw puzzle. Binding selectively to a protein receptor with high affinity to a ligand depends on formation of weak, noncovalent interactions—hydrogen bonds, electrostatic attractions, and van der Waals attractions—and favorable hydrophobic forces.³

Plasma membrane receptors protrude from or are exposed at the external surface of the membrane and are important for cellular uptake of ligands (see Fig. 1.8). The ligands that bind with membrane receptors include hormones, neurotransmitters, antigens, complement components, lipoproteins, infectious agents, drugs, and metabolites. Specific interactions of cellular receptors with their respective ligands have provided a basis for understanding disease.

Although the chemical nature of ligands and their receptors differs, receptors are classified based on their location and function. Cellular type determines overall cellular function, but plasma membrane receptors determine which ligands a cell will bind with and how the cell will respond to the binding. Specific processes also control intracellular mechanisms.

Receptors for different drugs are found on the plasma membrane, in the cytoplasm, and in the nucleus. Membrane receptors have been found for certain anesthetics, opiates, endorphins, enkephalins, antibiotics, cancer chemotherapeutic agents, digitalis, and other drugs. Membrane receptors for endorphins, which are opiate-like peptides isolated from the pituitary gland, are found in large quantities in pain pathways of the nervous

system (see Chapters 15 and 16). With binding to the receptor, the endorphins (or drugs, e.g., morphine) change the cell's permeability to ions, increase the concentration of molecules that regulate intracellular protein synthesis, and initiate molecular events that modulate pain perception.

Receptors for infectious microorganisms, or antigen receptors, bind bacteria, viruses, and parasites to the cell membrane. Antigen receptors on white blood cells (lymphocytes, monocytes, macrophages, granulocytes) recognize and bind with antigenic microorganisms and activate the immune and inflammatory responses (see Chapter 7).

CELL-TO-CELL ADHESIONS

Cells are small and squishy, *not* like bricks. They are enclosed only by a flimsy membrane, yet the cell depends on the integrity of this membrane for its survival. How can cells be connected strongly, with their membranes intact, to form a muscle that can lift this textbook? Plasma membranes not only serve as the outer boundaries of all cells but also allow groups of cells to be held together robustly, in **cell-to-cell adhesions**, to form tissues and organs (Box 1.1). Once arranged, cells are linked by three different means: (1) the extracellular matrix (ECM), (2) CAMs in the cell's plasma membrane, and (3) specialized cell junctions.

Extracellular Matrix and Basement Membrane

Cells can be united by attachment to one another or through the ECM (including the basement membrane), which the cells secrete around themselves. The **extracellular matrix (ECM)** is an intricate meshwork of fibrous proteins embedded in a watery, gel-like substance composed of complex carbohydrates (Fig. 1.9).

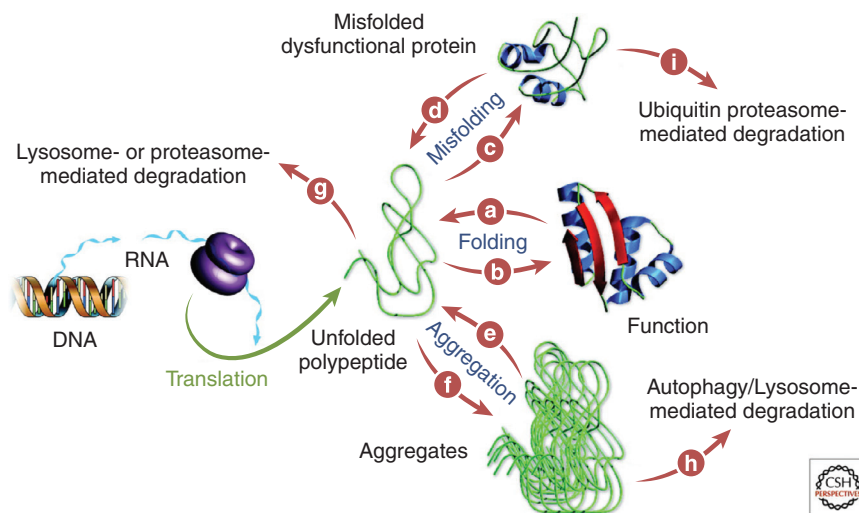


Fig. 1.7 Protein Homeostasis System and Outcomes. A main role of the protein homeostasis network (*proteostasis*) is to minimize protein misfolding and protein aggregation. The network includes ribosome-mediated protein synthesis, chaperone (folding helpers in the ER) and enzyme mediated folding, breakdown systems of lysosome and proteasome-mediated protein degradation, and vesicular trafficking. The network integrates biologic pathways that balance folding, trafficking, and protein degradation depicted by arrows *a*, *b*, *c*, *d*, *e*, *f*, *g*, *h*, and *i*. ER, Endoplasmic reticulum. (Adapted from Balch WE, Morimoto RI, Dillin A, et al. Adapting proteostasis for disease intervention. *Science* 2008;319:916–919.)

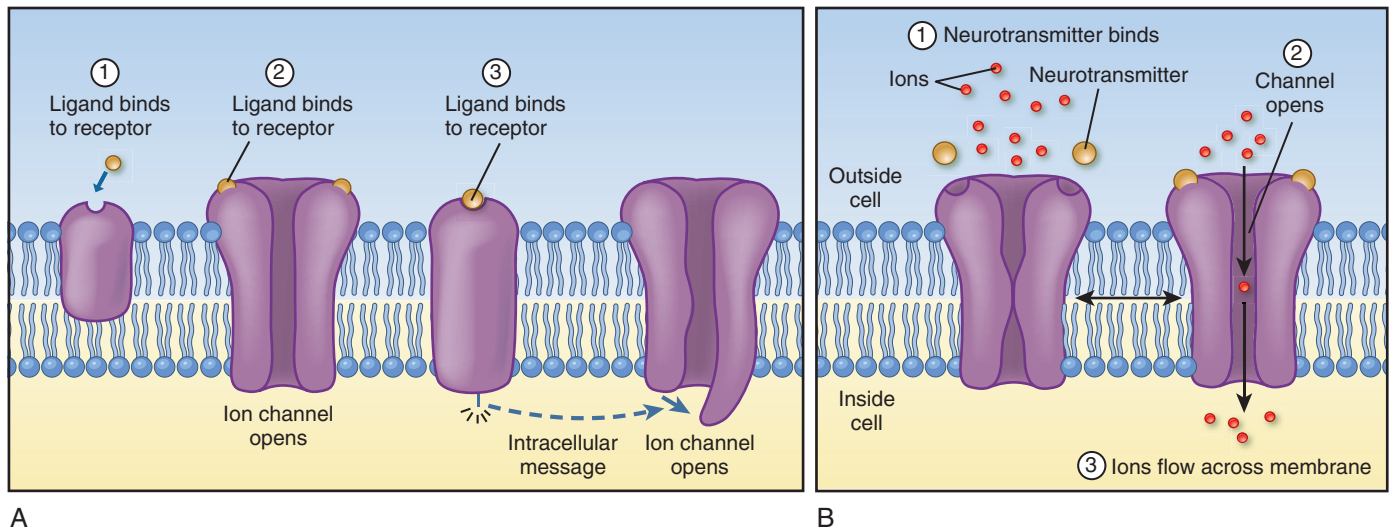
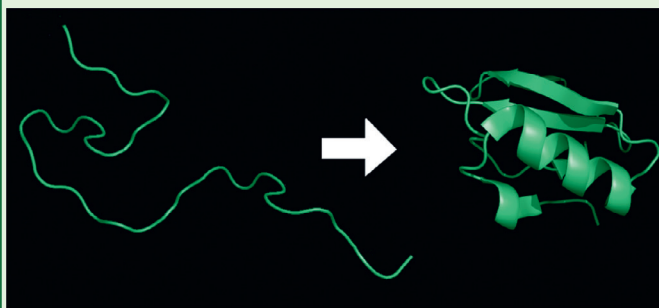


Fig. 1.8 Cellular Receptors. (A) 1, Plasma membrane receptor for a ligand (here, a hormone molecule) on the surface of an integral protein. A neurotransmitter can exert its effect on a post-synaptic cell by means of two fundamentally different types of receptor proteins. **2,** Channel-linked receptors. **3,** Non-channel-linked receptors. Channel-linked receptors are also known as *ligand-gated channels*. **(B)** Example of ligand-gated ion channels. The channel structure is changed when, for example, a neurotransmitter binds and ions can now enter.

BOX 1.1 Cell Adhesion Molecules

Cell adhesion molecules (CAMs) are cell surface proteins that bind the cell to an adjacent cell and to components of the extracellular matrix (ECM). CAMs include four protein families: (1) the integrins, (2) the cadherins, (3) the selectins, and (4) the **immunoglobulin superfamily CAMs** (IgSF CAMs). **Integrins** are receptors within the ECM and regulate cell-ECM interactions with collagen. **Cadherins** are calcium (Ca^{2+})-dependent glycoproteins throughout tissue (e.g., epithelial [E-cadherin]). **Selectins** are proteins that bind some carbohydrates (e.g., mucins). The IgSF CAMs bind integrins and other IgSF CAMs.



The **basement membrane (BM)** (also known as **basal lamina**) is a specialized type of ECM. This sheet of matrix is very thin, tough, and flexible; lies beneath epithelial cells; occurs between two cell sheets (kidney glomerulus); and surrounds individual muscle cells, fat cells, and Schwann cells (which wrap around peripheral nerve cell axons) (Fig. 1.10). The ECM is similar to glue; however, it provides a pathway for diffusion of nutrients, wastes, and other water-soluble substances between the blood and tissue cells. Interwoven within the matrix are three groups of large molecules or **macromolecules**: (1) fibrous structural proteins, including

collagen and elastin; (2) adhesive glycoproteins, such as fibronectin; and (3) proteoglycans and hyaluronic acid.

- Collagen** forms cable-like fibers or sheets that provide tensile strength or resistance to longitudinal stress. Collagen breakdown, such as occurs in osteoarthritis, destroys the fibrils that give cartilage its tensile strength.
- Elastin** is a rubber-like protein fiber most abundant in tissues that must be capable of stretching and recoiling, such as found in the lungs.
- Fibronectin**, a large glycoprotein, promotes cell adhesion and cell anchorage. Reduced amounts have been found in certain types of cancerous cells; this allows cancer cells to travel, or metastasize, to other parts of the body. All of these macromolecules occur in intercellular junctions and cell surfaces and may assemble into two different components: interstitial matrix and BM (see Fig. 1.9).

The ECM is secreted by **fibroblasts** (“fiber formers”) (Fig. 1.11), local cells that are present in the matrix. The matrix and the cells within it are known collectively as *connective tissue* because they interconnect cells to form tissues and organs. Human connective tissues are enormously varied. They can be hard and dense (e.g., bone), flexible (e.g., tendons or the dermis of the skin), resilient and shock absorbing (e.g., cartilage), or soft and transparent, similar to the jelly-like substance that fills the eye. In all these examples, the majority of the tissue is composed of ECM, and the cells that produce the matrix are scattered within it like raisins in a pudding (see Fig. 1.11).

The matrix is not just passive scaffolding for cellular attachment but also helps to regulate the function of the cells with which it interacts. The matrix helps to regulate important functions, such as cell growth and differentiation.

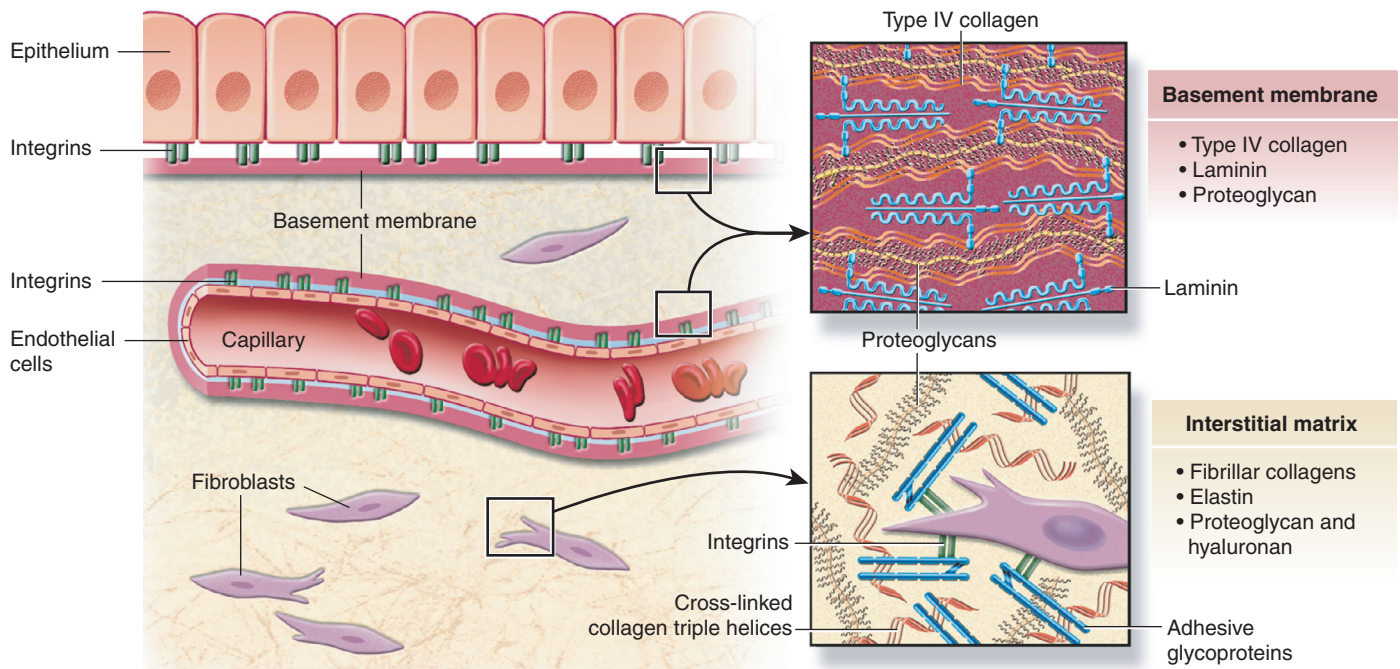


Fig. 1.9 Extracellular Matrix. Tissues are not just cells but also extracellular space. The extracellular space is an intricate network of macromolecules called the *extracellular matrix (ECM)*. The macromolecules that constitute the ECM are secreted locally (by mostly fibroblasts) and assembled into a meshwork in close association with the surface of the cell that produced them. Two main classes of macromolecules include proteoglycans, which are bound to polysaccharide chains called *glycosaminoglycans*; and fibrous proteins (e.g., collagen, elastin, fibronectin, and laminin), which have structural and adhesive properties. Together the proteoglycan molecules form a gel-like ground substance in which the fibrous proteins are embedded. The gel permits rapid diffusion of nutrients, metabolites, and hormones between blood and the tissue cells. Matrix proteins modulate cell-matrix interactions, including normal tissue remodeling (which can become abnormal, for example, with chronic inflammation). Disruptions of this balance result in serious diseases such as arthritis, tumor growth, and other pathologic conditions. (Adapted from Kumar A, Abbas K, Jon C. *Robbins and Cotran pathologic basis of disease*, 9th edition. Philadelphia: Saunders; 2015.

Cell Adhesion Molecules

Cell adhesion molecules (CAMs) are cell surface proteins that bind the cell to adjacent cells and to components of the ECM. CAMs are divided into four protein families: integrins, cadherins, selectins, and the immunoglobulin superfamily (IgSF).⁶ **Integrins** are a major class of molecules that typically bind to the ECM, whereas selectins, cadherins, and IgSF are associated with cell-to-cell adhesion. Integrins regulate cell interactions with collagen, fibronectin, vitronectin, and fibrinogen in the ECM. **Cadherins**, an abbreviation of “calcium-dependent adherent proteins,” are associated with cell-cell adhesive bonds in solid tissues. They are calcium-dependent glycoproteins that have specific functions and distributions within tissues. For example, epithelial cells express E-cadherin, which cause tight adhesions between cells that interface between the body and the environment to create a protective barrier. Neural and endothelial cells express N-cadherin which helps to maintain the structural integrity of nerve cells and blood vessels.⁷ **Selectins** are a family of proteins that bind certain carbohydrates. Selectins are divided into subgroups based on which cell types they are found in: P—platelets, E—endothelial, and L—leukocytes. Their primary function is to allow blood cells to bind to the endothelial

surfaces of blood vessels during the inflammatory response (see Chapter 7). The **immunoglobulin superfamily CAMs (IgSF CAMs)** is one of the largest and most diverse protein families. These CAMs include vascular (VCAM), intercellular (ICAM), neural (NCAM), and nectins. Their functions include adhesion between immune and endothelial cells, neural development, and cellular migration and growth.

Specialized Cell Junctions

Cells in direct physical contact with neighboring cells are often interconnected at specialized plasma membrane regions called **cell junctions**. Cell junctions are classified by their function:

1. **Tight Junction:** To hold cells together and form a tight seal and to maintain apicobasal polarity of individual epithelial cells (Fig. 1.12)
2. **Adherens junctions, desmosomes, hemidesmosomes:** To provide strong mechanical attachments
3. **Gap junctions:** To provide a special type of chemical communication (e.g., inorganic ions and small water-soluble molecules to move from the cytosol of one cell to the cytosol of another cell), such as those causing an electrical wave

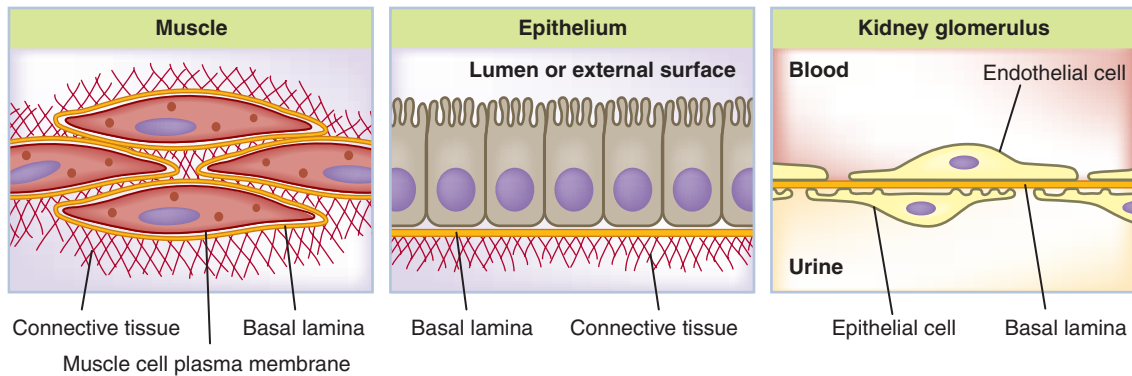


Fig. 1.10 Three Ways Basement Membranes (Basal Laminae) Are Organized. Basal laminae (yellow) surround certain cells like skeletal cells, underlie epithelia, and occur between two cell sheets (kidney glomerulus). (Adapted from Alberts B, Bray D, Hopkin K, et al. *Essential cell biology*, 4th edition. New York: Garland; 2014.

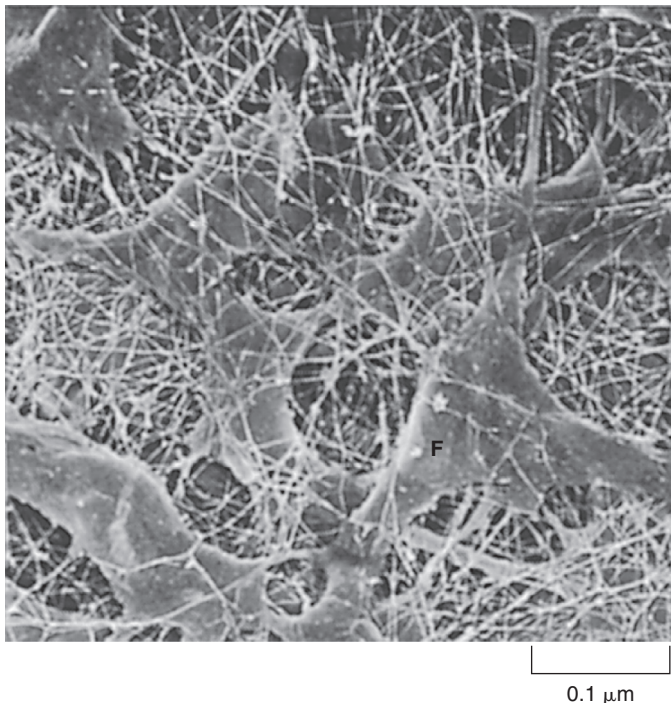


Fig. 1.11 Fibroblasts in Connective Tissue. This micrograph shows tissue from the cornea of a rat. The extracellular matrix surrounds the fibroblasts (F). (Adapted from Nishia T, et al. The extracellular matrix of animal connective tissues. *Invest Ophthalmology Visual Science*, 1998; 29:1887-1880.)

In summary, cell junctions make the epithelium leak-proof and mediate mechanical attachment of one cell to another, allowing communicating tunnels and maintaining cell polarity.⁸

Cell junctions can be classified as symmetric and asymmetric. Symmetric junctions include tight junctions (zonula occludens), the belt desmosome (zonula adherens), desmosomes (macula adherens), and gap junctions (also called *intercellular channel* or *communicating junctions*). An asymmetric junction is the hemidesmosome (see Fig. 1.12A). Together they form the **junctional complex**. **Tight junctions** are barriers to diffusion, prevent the movement of substances through transport proteins in the plasma membrane, and prevent the

leakage of small molecules between the plasma membranes of adjacent cells.⁹ **Desmosomes** unite cells either by forming continuous bands or belts of epithelial sheets or by developing button-like points of contact. Desmosomes also act as a system of braces to maintain structural stability (see Fig. 1.12B). **Gap junctions** are composed of integral membrane proteins called connexins. **Connexins** are hemichannels that extend outward from each of the adjacent plasma membranes (see Fig. 1.12C). Gap junctions facilitate intercellular communication by allowing small ions and signaling molecules to pass directly from the inside of one cell to the inside of another. This process of cell communication is a critical feature for the development, function, and homeostasis of tissues and organs.¹⁰ Multiple factors regulate gap junction intercellular communication, including voltage across the junction, intracellular pH, intracellular calcium (Ca^{2+}) concentration, and protein phosphorylation. **Cell polarity**, the direction of cellular transport, maintains normal cell and tissue structure for numerous functions (e.g., movement of nutrients in and out of the cell) and becomes altered with diseases (see Fig. 1.12D).

The junctional complex is a highly permeable part of the plasma membrane where permeability is controlled by a process called **gating**. Increased levels of cytoplasmic calcium cause decreased permeability at the junctional complex. Gating enables uninjured cells to protect themselves from injured neighbors.

CELLULAR COMMUNICATION AND SIGNAL TRANSDUCTION

Cells need to communicate with each other to maintain a stable internal environment, or **homeostasis**; to regulate their growth and division; to oversee their development and organization into tissues; and to coordinate their functions. Cells communicate by using hundreds of signal molecules (e.g., insulin-like growth factor 1). Cells communicate in three main ways:

1. They display plasma membrane-bound signaling molecules (receptors) that affect the cell itself and other cells in direct physical contact (Fig. 1.13A).

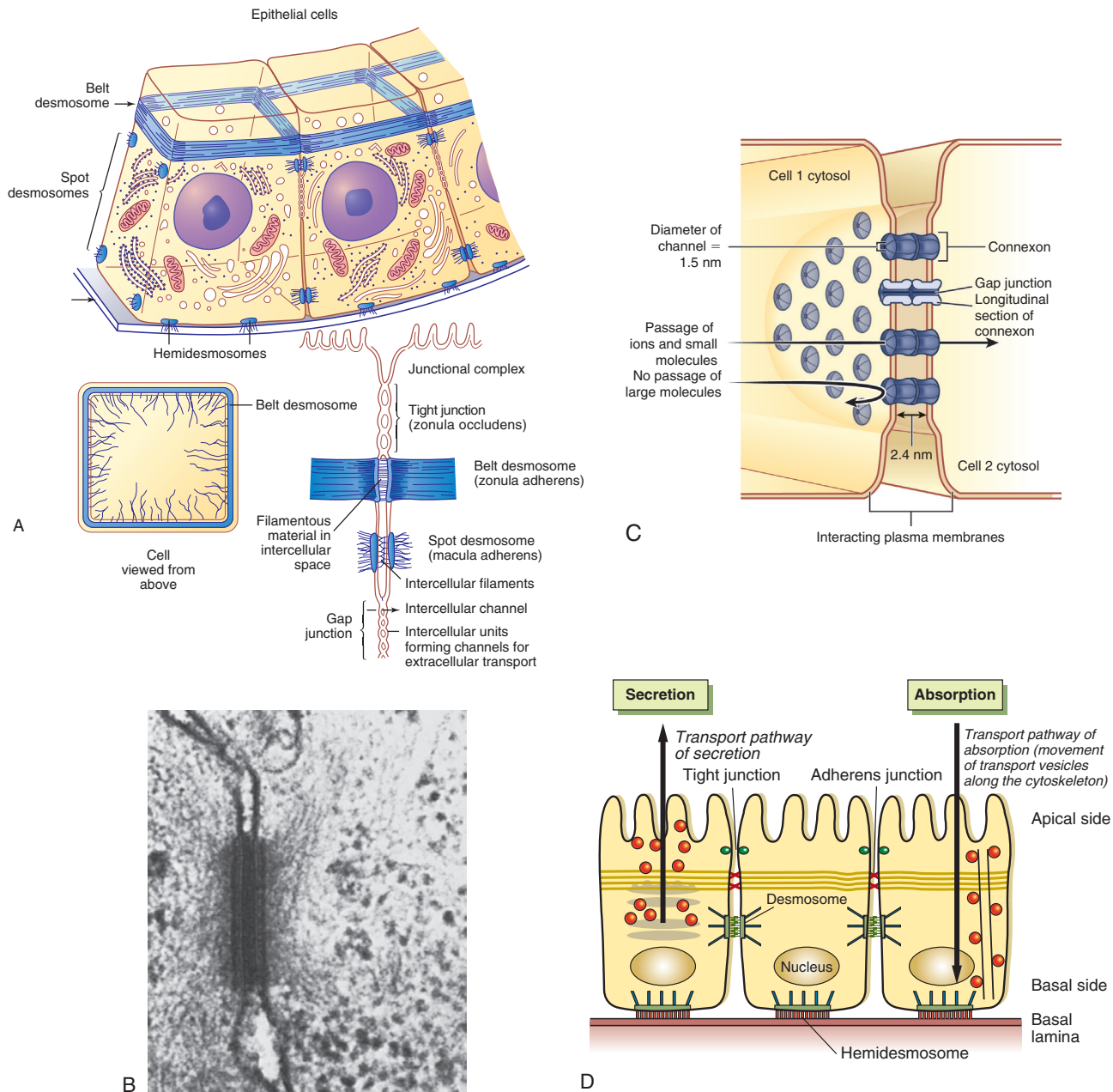


FIG. 1.12 Junctional Complex. (A), Schematic drawing of a belt desmosome between epithelial cells. This junction, also called *zonula adherens*, encircles each interacting cell. The spot desmosomes and hemidesmosomes, like the belt desmosomes, are adhering junctions. The tight junction is an impermeable junction that holds cells together but seals them in such a way that molecules cannot leak between them. The gap junction, as a communicating junction, mediates the passage of small molecules from one interacting cell to the other. (B) Electron micrograph of desmosomes. (C) Connexons. The connexin gap junction proteins have four transmembrane domains, and they play a vital role in maintaining cell and tissue function and homeostasis. Cells connected by gap junctions are considered ionically (electrically) and metabolically coupled. Gap junctions coordinate the activities of adjacent cells; for example, they are important for synchronizing contractions of heart muscle cells through ionic coupling and for permitting action potentials to spread rapidly from cell to cell in neural tissues. The reason gap junctions occur in tissues that are not electrically active is unknown. Although most gap junctions are associated with junctional complexes, they sometimes exist as independent structures. (D) Cell Polarity of Epithelial Cells. Schematic of cell polarity (cell direction) of epithelial cells. Shown are the directions of the basal side and the apical side. Organelles and cytoskeleton are also arranged directionally to enable, for example, intestinal cell secretion and absorption. (A and B, From Raven PH, Johnson GB. *Biology*. St. Louis: Mosby; 1992.; C, Adapted from Gartner LP, Hiatt JL. *Color textbook of histology*, 3rd edition. St. Louis: Saunders Elsevier; 2006; Sherwood L. *Learning*, 8th edition. Belmont, CA: Brooks/Cole CENGAGE; 2013; D, Adapted from *Life science web textbook*, The University of Tokyo.)

2. They affect receptor proteins *inside* the target cell and the signal molecule has to enter the cell to bind to them (see Fig. 1.13B).
3. They form protein channels (gap junctions) that directly coordinate the activities of adjacent cells (see Fig. 1.13C). Alterations in cellular communication affect disease onset and progression. In fact, if a cell cannot perform gap junctional intercellular communication, normal growth control and cell differentiation is compromised, thereby favoring cancerous tumor development (see Chapter 12).

Secreted chemical signals involve communication locally and at a distance. Primary modes of intercellular signaling are contact dependent, paracrine, hormonal, neurohormonal, and neurotransmitter. Autocrine stimulation occurs when the secreting cell targets itself (Fig. 1.14).

Contact-dependent signaling requires cells to be in close membrane-to-membrane contact. In **paracrine signaling**, cells secrete local chemical mediators that are quickly taken up, destroyed, or immobilized. Paracrine signaling usually involves different cell types; however, cells also can produce signals to which they alone respond, and this is called **autocrine signaling** (see Fig. 1.14). Cancer cells use this form of signaling to stimulate their survival and proliferation. The mediators act only on nearby cells. **Hormonal signaling** involves specialized endocrine cells that secrete chemicals called *hormones*; hormones are released by one set of cells and travel through the bloodstream to produce a response in other sets of cells. In **neurohormonal signaling** hormones are released into blood by neurosecretory neurons. Like endocrine cells, neurosecretory neurons release blood-borne chemical messengers, whereas ordinary neurons secrete short-range neurotransmitters into a small discrete space (i.e., synapse). Neurons communicate directly with the cells they innervate by releasing chemicals or **neurotransmitters** at specialized junctions called **chemical synapses**; the neurotransmitter diffuses across the synaptic cleft and acts on the postsynaptic target cell (see Fig. 1.14). Many of these same signaling molecules are receptors used in hormonal, neurohormonal, and paracrine signaling. Important differences lie in the speed and selectivity with which the signals are delivered to their targets.²

Plasma membrane receptors belong to one of three classes that are defined by the signaling (transduction) mechanism used. Table 1.3 summarizes these classes of receptors. Cells

respond to external stimuli by activating a variety of **signal transduction pathways**, which are communication pathways, or signaling cascades (Fig. 1.15). Signals are passed between cells when a particular type of molecule is produced by one cell—the **signaling cell**—and received by another—the **target cell**—by means of a **receptor protein** that recognizes and responds specifically to the signal molecule (see Fig. 1.15A and B). In turn, the signaling molecules activate a pathway of intracellular protein kinases that results in various responses, such as growing and reproducing, dying, surviving, or differentiating (see Fig. 1.15). If deprived of appropriate signals, most cells undergo a form of cell suicide known as *programmed cell death*, or *apoptosis* (see Chapter 2).

Binding of the extracellular signaling messenger (i.e., ligand), or **first messenger**, to the membrane receptors causes (1) opening or closing of specific channels in the membrane to regulate the movement of ions into or out of the cell; and (2) transfer of the signal to an intracellular messenger or **second messenger**, which triggers a cascade of biochemical events within the cell (Fig. 1.16).

CELLULAR METABOLISM

All of the chemical tasks of maintaining essential cellular functions are referred to as **cellular metabolism**. The energy-using process of metabolism is called **anabolism** (*ana* = upward), and the energy-releasing process is known as **catabolism** (*kata* = downward). Metabolism provides the cell with the energy it needs to produce cellular structures.

Dietary proteins, fats, and starches (i.e., carbohydrates) are hydrolyzed in the intestinal tract into amino acids, fatty acids, and glucose, respectively. These constituents are then absorbed, circulated, and incorporated into the cell, where they may be used for various vital cellular processes, including the production of ATP. The process by which ATP is produced is one example of a series of reactions called a **metabolic pathway**. A metabolic pathway involves several steps whose end products are not always detectable. A key feature of cellular metabolism is the directing of biochemical reactions by protein catalysts or enzymes. Each enzyme has a high affinity for a **substrate**, a specific substance converted to a product of the reaction.

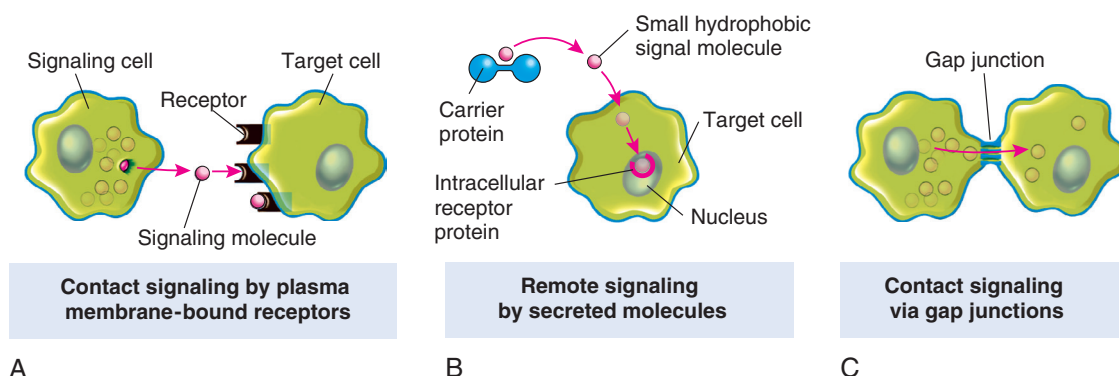


Fig. 1.13 Cellular Communication. Three primary ways (A–C) cells communicate with one another. (B, Adapted from Alberts B, Johnson A, Lewis J, et al. *Molecular biology of the cell*, 5th edition. New York: Garland; 2008.

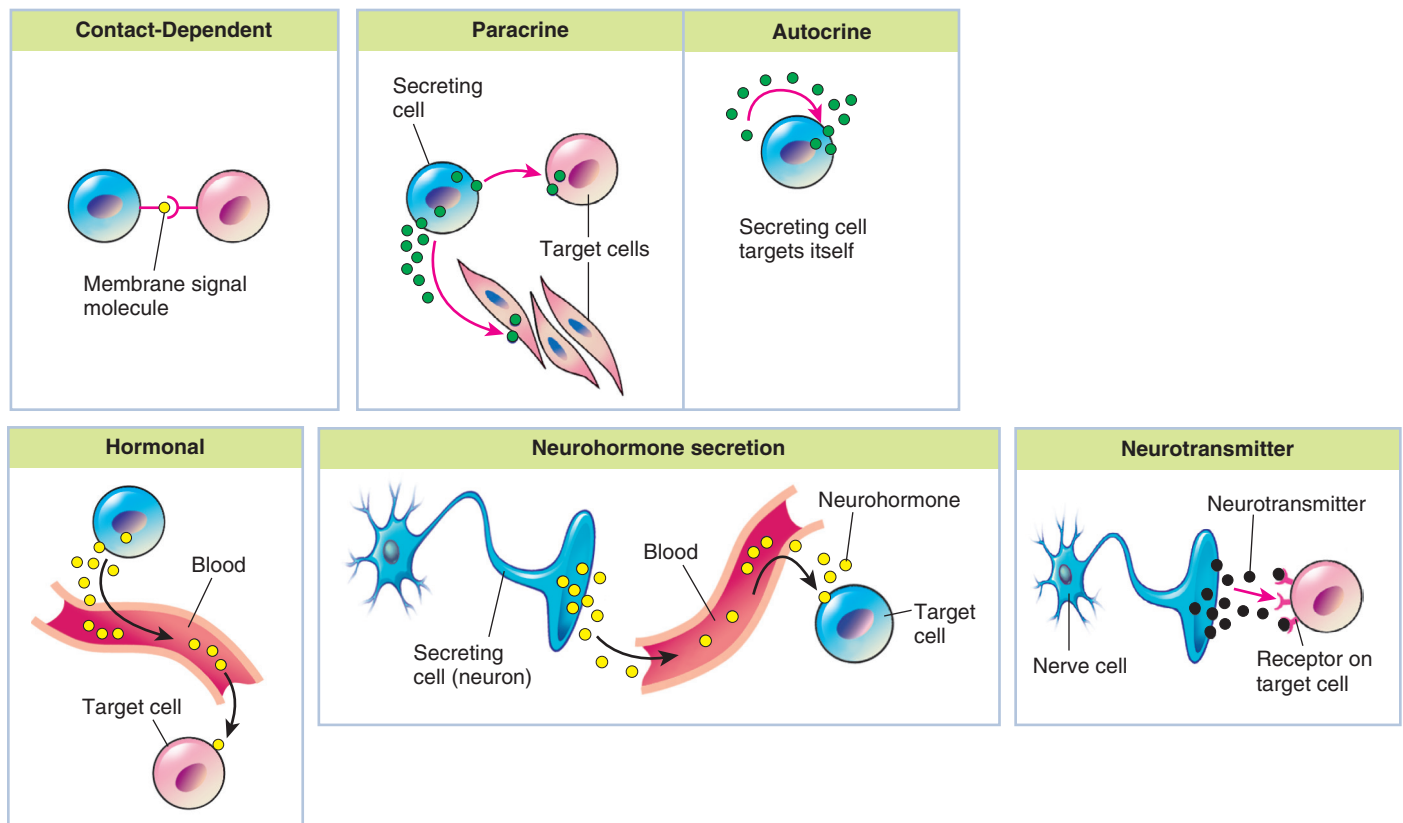


Fig. 1.14 Primary Modes of Chemical Signaling. Five forms of signaling mediated by secreted molecules. Hormones, paracrine, neurotransmitters, and neurohormones are all intercellular messengers that accomplish communication between cells. Autocrines bind to receptors on the same cell. Not all neurotransmitters act in the strictly synaptic mode shown; some act in a contact-dependent mode as local chemical mediators that influence multiple target cells in the area.

TABLE 1.3 Classes of Plasma Membrane Receptors

Type of Receptor	Description
Channel linked	Also called <i>ligand-gated channels</i> ; involve rapid synaptic signaling between electrically excitable cells. Channels open and close briefly in response to neurotransmitters, changing ion permeability of plasma membrane of postsynaptic cell.
Catalytic	Once activated by ligands, function directly as enzymes. Composed of transmembrane proteins that function intracellularly as tyrosine-specific protein kinases.
G-protein linked	Indirectly activate or inactivate plasma membrane enzyme or ion channel; interaction mediated by guanosine triphosphate (GTP)-binding regulatory protein (G protein). When activated, a chain of reactions occurs that alters concentration of intracellular messengers, such as cyclic adenosine monophosphate (cAMP) and calcium, or signaling molecules. Behaviors of other target proteins are also altered. May also interact with inositol phospholipids, which are significant in cell signaling, and molecules involved in the inositol-phospholipid transduction pathway. A G-protein-linked receptor activates the enzyme phosphoinositide-specific phospholipase, which, in turn, generates two intracellular messengers: (1) inositol triphosphate (IP_3) releases calcium (Ca^{2+}), and (2) diacylglycerol remains in the plasma membrane and activates protein kinase C. Protein kinase C further activates various cell proteins. Several different plasma membrane receptors are known to use the inositol-phospholipid transduction pathway.

Data from Alberts B, Bray D, Hopkin K, et al. *Molecular biology of the cell*, 5th edition. New York: Garland; 2008.

Role of Adenosine Triphosphate

What is best known about ATP is its role as a universal “fuel” *inside* living cells. This fuel, or energy, drives biologic reactions necessary for cells to function. For a cell to function, it must be able to extract and use the chemical energy in organic molecules. When 1 mole (mol) of glucose metabolically breaks

down in the presence of oxygen into CO_2 and water, 686 kilocalories (kcal) of chemical energy are released. The chemical energy lost by one molecule is transferred to the chemical structure of another molecule by an energy-carrying or energy-transferring molecule, such as ATP. The energy stored in ATP can be used in various energy-requiring reactions and in the

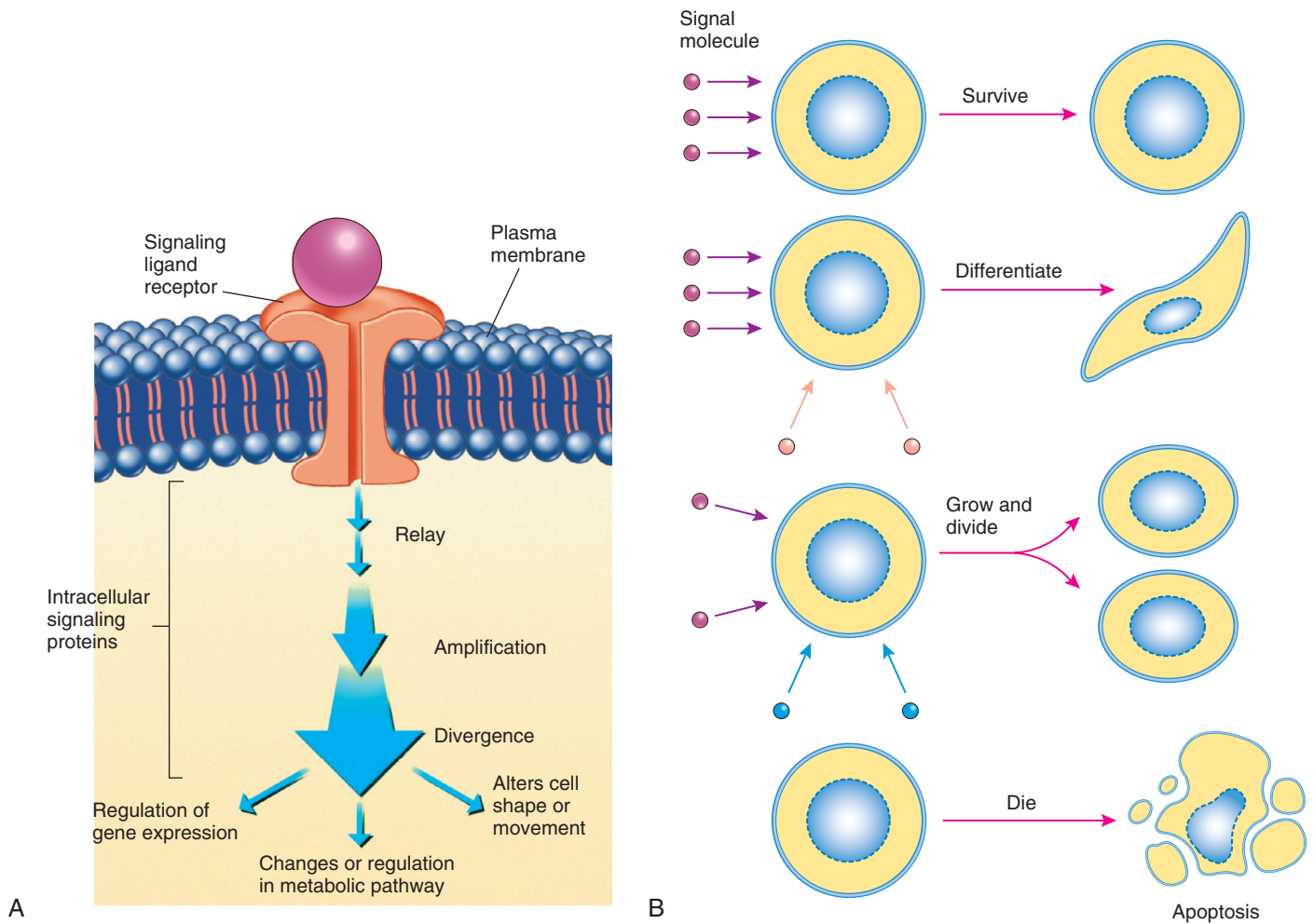


Fig. 1.15 Schematic of a Signal Transduction Pathway. Like a telephone receiver that converts an electrical signal into a sound signal, a cell converts an extracellular signal. **(A)** An extracellular signal molecule (ligand) binds to a receptor protein located on the plasma membrane, where it is transduced into an intracellular signal. This process initiates a signaling cascade that relays the signal into the cell interior, amplifying and distributing it during transit. Amplification is often achieved by stimulating enzymes. Steps in the cascade can be modulated by other events in the cell. **(B)** Different cell behaviors rely on multiple extracellular signals.

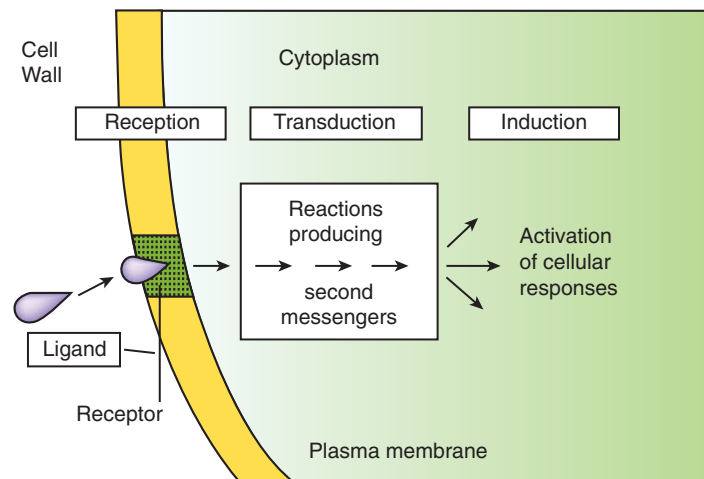


Fig. 1.16 First and Second Messengers. The first messenger or ligand attaches to the membrane receptor relaying the message across the membrane and intracellular messengers or second messengers trigger the cascade of intracellular events. The two major second-messenger pathways are cyclic adenosine monophosphate and calcium. A large number of human disorders involve problematic signaling.

process is generally converted to adenosine diphosphate (ADP) and inorganic phosphate (Pi). The energy available as a result of this reaction is approximately 7 kcal/mol of ATP. The cell uses ATP for muscle contraction and active transport of molecules across cellular membranes. ATP not only stores energy but also *transfers* it from one molecule to another. Energy stored by carbohydrate, lipid, and protein is catabolized and transferred to ATP.

ATP can also be found outside of cells. *Extracellular ATP* is released from cells in a variety of conditions and is considered important in inflammation and immunity. High levels of extracellular ATP may contribute to chronic inflammatory responses and to metastasis of cancer cells.¹¹

Food and Production of Cellular Energy

Catabolism of the proteins, lipids, and polysaccharides found in food must be broken down into smaller molecules before cells can use them as a fuel source for energy or as building blocks for other molecules. The process can be divided into the following three phases (Fig. 1.17):

Phase 1: Digestion. Large molecules are broken down into smaller subunits: proteins into amino acids, polysaccharides into simple sugars (i.e., monosaccharides), and fats into fatty acids and glycerol. These processes occur outside the cell within the intestines or within the specialized lysosome organelle within the cell and are activated by secreted enzymes.

Phase 2: Glycolysis and oxidation. The most important part of phase 2 is glycolysis, the splitting of one glucose molecule into two molecules of pyruvate. During pyruvate formation, ATP and reduced nicotinamide adenine dinucleotide (NADH) are produced through oxidation, or the removal and transfer of a pair of electrons. The total process is called *oxidative cellular metabolism* and involves 10 biochemical reactions (see Fig. 1.17).

Phase 3: Citric acid cycle (Krebs cycle, tricarboxylic acid cycle). Most of the ATP is generated during this final phase, which begins with the citric acid cycle and ends with oxidative phosphorylation. Approximately two-thirds of the total oxidation of carbon compounds in most cells is accomplished during this phase. The major end products are CO₂ and two dinucleotides—NADH and the reduced form of flavin adenine dinucleotide (FADH₂)—both of which transfer their electrons into the electron transport chain.

Oxidative Phosphorylation

Oxidative phosphorylation occurs in the mitochondria and is the mechanism by which the energy produced from carbohydrates, fats, and proteins is transferred to ATP. During the breakdown (catabolism) of foods, many reactions involve the removal of electrons from various intermediates. These reactions generally require a coenzyme (a nonprotein carrier molecule), such as nicotinamide adenine dinucleotide (NAD), to transfer the electrons and thus are called **transfer reactions**.

Molecules of NAD and flavin adenine dinucleotide (FAD) transfer electrons they have gained from the oxidation of substrates to molecular O₂. The electrons from reduced NAD and FAD, NADH and FADH₂, respectively, are transferred to the **electron transport chain** on the inner surfaces of the

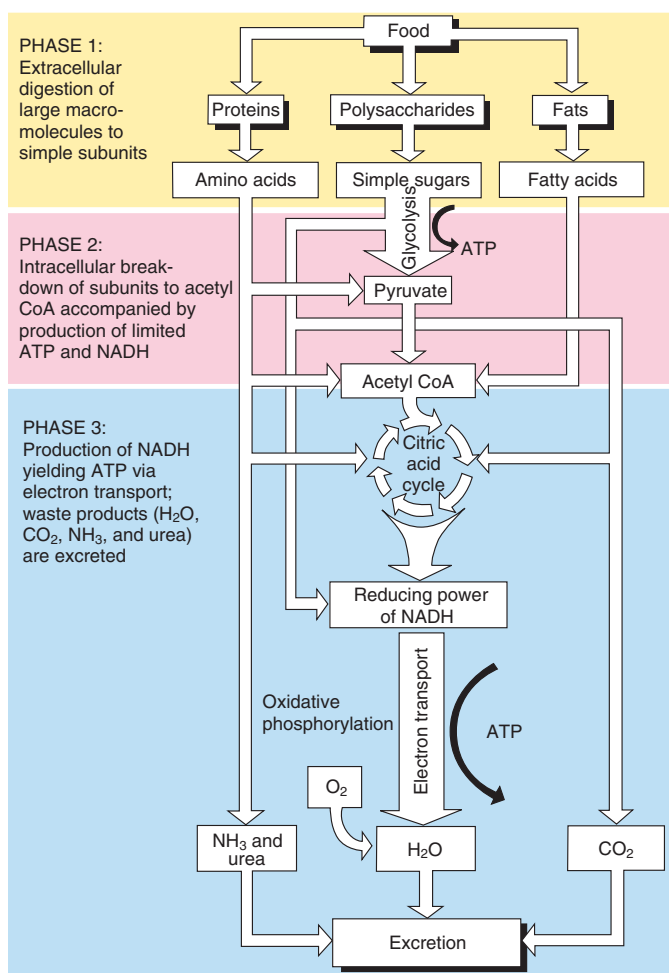


Fig. 1.17 Three Phases of Catabolism, Which Lead From Food to Waste Products. These reactions produce adenosine triphosphate (ATP), which is used to power other processes in the cell. NADH, Nicotinamide adenine dinucleotide.

mitochondria with the release of hydrogen ions. Some carrier molecules are brightly colored, iron-containing proteins known as **cytochromes**, which accept a pair of electrons. These electrons eventually combine with molecular oxygen.

If O₂ is not available to the electron transport chain, ATP will not be formed by the mitochondria. Instead, an anaerobic (without O₂) metabolic pathway synthesizes ATP. This process, called **substrate-level phosphorylation** or **anaerobic glycolysis**, is linked to the breakdown (glycolysis) of carbohydrate (Fig. 1.18). Because glycolysis occurs in the cytoplasm of the cell, it provides energy for cells that lack mitochondria. The reactions in anaerobic glycolysis involve the conversion of glucose to pyruvic acid (pyruvate) with the simultaneous production of ATP. With the glycolysis of one molecule of glucose, two ATP molecules and two molecules of pyruvate are liberated. If O₂ is present, the two molecules of pyruvate move into the mitochondria, where they enter the citric acid cycle (Fig. 1.19).

If O₂ is absent, pyruvate is converted to lactic acid, which is released into the extracellular fluid (ECF). The conversion of pyruvic acid to lactic acid is reversible; therefore, once O₂ is restored, lactic acid is quickly converted back to either pyruvic

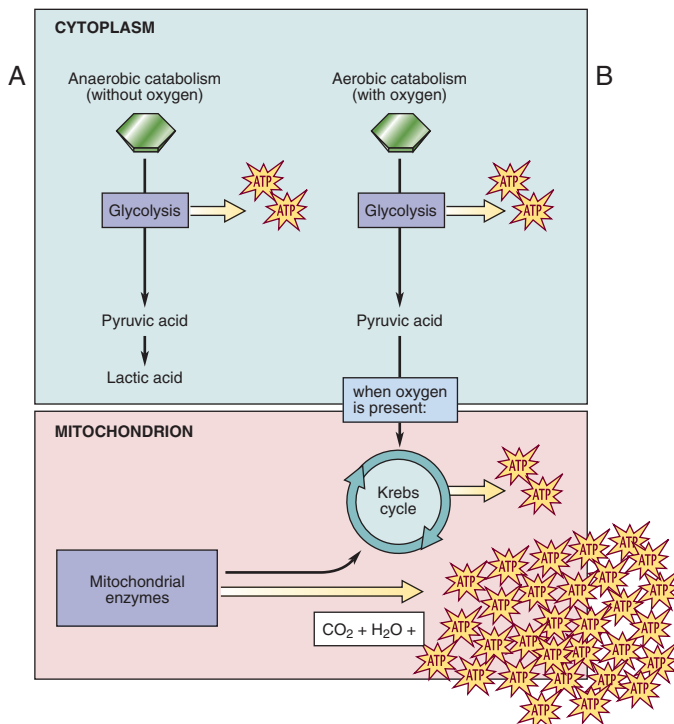


Fig. 1.18 Glycolysis. Sugars are important for fuel or energy, and they are oxidized in small steps to carbon dioxide and water. Glycolysis is the process for oxidizing sugars or glucose. Breakdown of glucose. **(A)** Anaerobic catabolism, to lactic acid and little adenosine triphosphate (ATP). **(B)** Aerobic catabolism, to carbon dioxide, water, and lots of ATP. (From Herlihy B. *The human body in health and illness*, 5th edition. St. Louis: Saunders; 2015.

acid or glucose. The anaerobic generation of ATP from glucose through glycolysis is not as efficient as the aerobic generation process. Adding an oxygen-requiring stage to the catabolic process (phase 3; N see Fig. 1.18) provides cells with a much more powerful method for extracting energy from food molecules. A field of cancer research examines how tumor cells are able to alter their metabolic pathways (metabolic reprogramming)

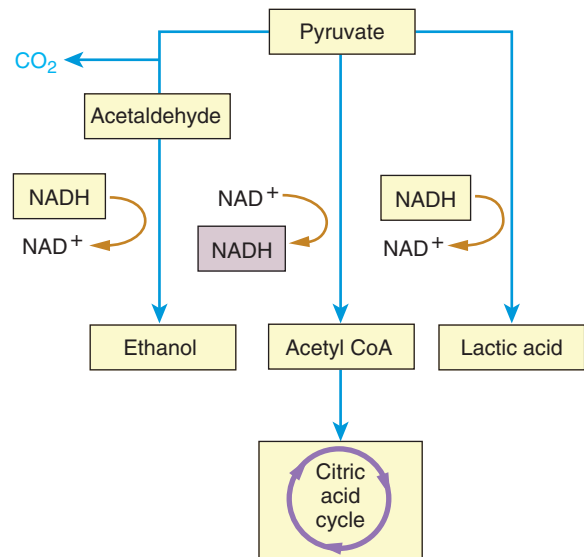


Fig. 1.19 What Happens to Pyruvate, the Product of Glycolysis? In the presence of oxygen, pyruvate is oxidized to acetyl coenzyme A (*Acetyl CoA*) and enters the citric acid cycle. In the absence of oxygen, pyruvate instead is reduced, accepting the electrons extracted during glycolysis and carried by reduced nicotinamide adenine dinucleotide (*NADH*). When pyruvate is reduced directly, as it is in muscles, the product is lactic acid. When carbon dioxide (*CO₂*) is first removed from pyruvate and the remainder is reduced, as it is in yeasts, the resulting product is ethanol.

to promote cancer progression (see the [Emerging Science Box: Metabolic Reprogramming and Cancer Cells box](#)).¹²

MEMBRANE TRANSPORT: CELLULAR INTAKE AND OUTPUT

Cell survival and growth depend on the constant exchange of molecules with their environment. Cells continually import nutrients, fluids, and chemical messengers from the extracellular environment and expel metabolites, or the products of metabolism, and end products of lysosomal digestion. Cells also

EMERGING SCIENCE BOX

Metabolic Reprogramming and Cancer Cells

Proliferating cancer cells require a great deal of cellular energy to support their rapid growth and spread through the body. Cancer cells create more energy by altering their metabolic pathways for all types of fuel sources, including carbohydrates, proteins, and lipids. These alterations are known as metabolic reprogramming. An example of metabolic reprogramming is the ability of tumor cells to greatly increase their uptake of glucose and to use it in multiple alternative pathways for generating energy and the molecules required for rapid growth. Not only do cancer cells use glucose to generate ATP in mitochondria, they also can convert glucose-derived pyruvate into lactate even in the presence of oxygen (Warburg effect) and can use nonmitochondrial pathways that do not require high levels of oxygen in order to generate energy and important metabolites. These nonmitochondrial pathways are stimulated by mutated genes (oncogenes such as c-MYC) and by growth factors that promote cancer cell proliferation. Glutamate, serine, and amino acid metabolic

pathways may also be altered in cancer cells. An increasing understanding of metabolic reprogramming is leading to innovative experimental approaches toward slowing cancer growth.

Data from DeBerardinis RJ, et al. We need to talk about the Warburg effect. *Nature Metabolism*, 2020; 2:127–129; Dong Y, et al. Regulation of cancer cell metabolism: oncogenic MYC in the driver's seat. *Signal Transduction and Targeted Therapy*, 2020;5:124; Lin X, Xiao Z, Chen T, et al. Glucose metabolism on tumor plasticity, diagnosis, and treatment. *Frontiers in Oncology*, 2020; 10:317; Orang AV, et al. Micromanaging aerobic respiration and glycolysis in cancer cells. *Molecular Metabolism*, 2019; 23:98–125; Samec M, et al. Flavonoids against the Warburg phenotype—concepts of predictive, preventive and personalised medicine to cut the Gordian knot of cancer cell metabolism. *EPMA Journal*, 2020; 11:377–398

must regulate ions in their cytosol and organelles. Simple diffusion across the lipid bilayer of the plasma membrane occurs for such important molecules as O_2 and CO_2 . However, the majority of molecular transfer depends on specialized **membrane transport proteins** that span the lipid bilayer and provide private conduits for select molecules.³

Membrane transport proteins occur in many forms and are present in all cell membranes. Transport by membrane transport proteins is sometimes called **mediated transport**. Most of these transport proteins allow selective passage (e.g., Na^+ but not K^+ , or K^+ but not Na^+). Each type of cell membrane has its own transport proteins that determine which solute can pass into and out of the cell or organelle.³ The two main classes of membrane transport proteins are *transporters* and *channels*. These transport proteins differ in the type of **solute**—small particles of dissolved substances—they transport. A **transporter** is specific, allowing only those ions that fit the unique binding sites on the protein (Fig. 1.20A). A transporter undergoes conformational changes to enable membrane transport. A **channel**, when open, forms a pore across the lipid bilayer that allows ions and selective polar organic molecules to diffuse across the membrane (see Fig. 1.20B). Transport by a channel depends on the size and electrical charge of the molecule. Some channels are controlled by a gate mechanism that determines which solute can move into it. Ion channels are responsible for the electrical excitability of nerve and muscle cells and play a critical role in the membrane potential.

The mechanisms of membrane transport depend on the characteristics of the substance to be transported. In **passive transport**, water and small electrically uncharged molecules move easily through pores in the plasma membrane's lipid bilayer (Fig. 1.21). This process occurs naturally through any semipermeable barrier. Molecules will easily flow “downhill” from a region of high concentration to a region of low concentration; this movement is called *passive* because it does not require expenditure of energy or a driving force. It is driven by osmosis, hydrostatic pressure, and diffusion, all of which depend on the laws of physics and do not require life (see the Passive Transport: Diffusion, Filtration, and Osmosis section).

Other molecules are too large to pass through pores or are ligands bound to receptors on the cell's plasma membrane. Some of these molecules are moved into and out of the cell by **active transport**, which requires life, biologic activity, and the cell's expenditure of metabolic energy (Fig. 1.22). Unlike passive transport, active transport occurs across only living membranes that have to drive the flow “uphill” by coupling it to an energy source. Movement of a solute against its concentration gradient occurs by special types of transporters called *pumps* (see Fig. 1.22). These transporter pumps must harness an energy source to power the transport process. Energy can come from ATP hydrolysis,

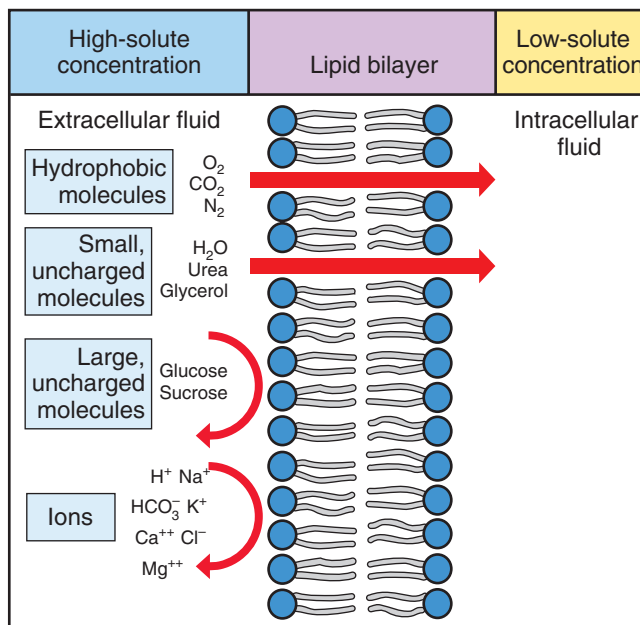


Fig. 1.21 Passive Diffusion of Solute Molecules Across the Plasma Membrane. Oxygen, nitrogen, water, urea, glycerol, and carbon dioxide can diffuse readily down the concentration gradient. Macromolecules are too large to diffuse through the pores in the plasma membrane. Ions may be repelled if the pores contain substances with identical charges. If the pores are lined with cations, for example, other cations will have difficulty diffusing because the positive charges will repel one another; diffusion can still occur, but it occurs more slowly.

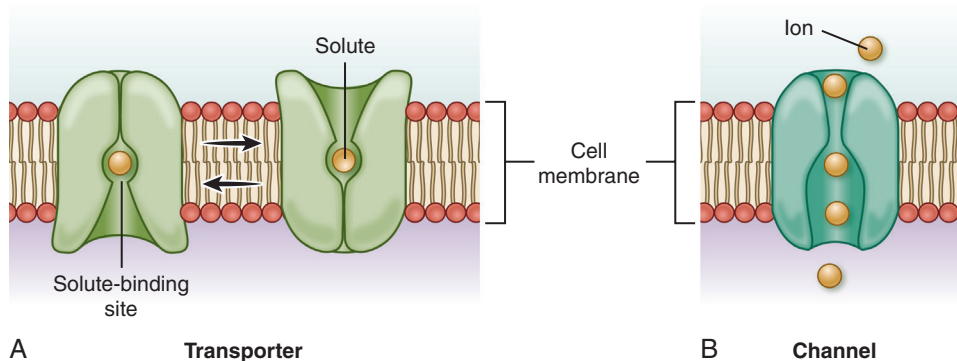


Fig. 1.20 Inorganic Ions and Small, Polar Organic Molecules Can Cross a Cell Membrane Through Either a Transporter or a Channel. (Adapted from Alberts B, Bray D, Hopkin K, et al. *Essential cell biology*, 4th edition. New York: Garland; 2014.

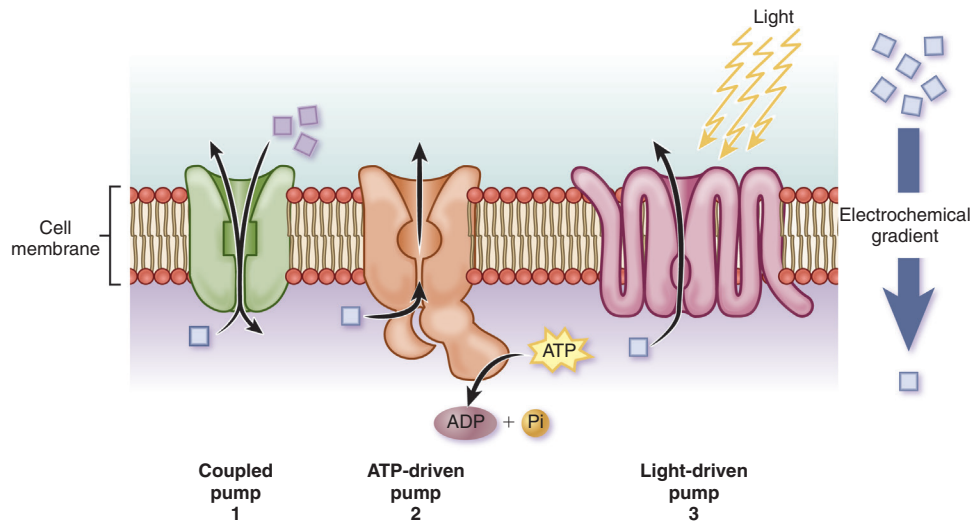


Fig. 1.22 Pumps Carry Out Active Transport in Three Ways. **1**, *Coupled pumps* link the uphill transport of one solute to the downhill transport of another solute. **2**, *Adenosine triphosphate (ATP)-driven pumps* drive uphill transport from hydrolysis of ATP. **3**, *Light-driven pumps* are mostly found in bacteria and use energy from sunlight to drive uphill transport. (Adapted from Alberts B, Bray D, Hopkin K, et al. *Essential cell biology*, 4th edition. New York: Garland; 2014.

a transmembrane ion gradient, or sunlight (see Fig. 1.22). The best-known energy source is the $\text{Na}^+\text{-K}^+$ -dependent adenosine triphosphatase (ATPase) pump. It continuously regulates the cell's volume by controlling leaks through pores or protein channels and maintaining the ionic concentration gradients needed for cellular excitation and membrane conductivity (see the Active Transport of Na^+ and K^+ section). The maintenance of intracellular K^+ concentrations is required also for enzyme activity, including enzymes involved in protein synthesis. Large molecules (macromolecules), along with fluids, are transported by endocytosis (taking in) and exocytosis (expelling) (see the Transport by Vesicle Formation section). Receptor-macromolecule complexes enter the cell by means of receptor-mediated endocytosis.

Mediated transport systems can move solute molecules singly or two at a time. Two molecules can be moved simultaneously in one direction (a process called **symport**; e.g., sodium-glucose in the digestive tract) or in opposite directions (called **antiport**; e.g., the sodium-potassium pump in all cells), or a single molecule can be moved in one direction (called **uniport**; e.g., glucose) (Fig. 1.23).

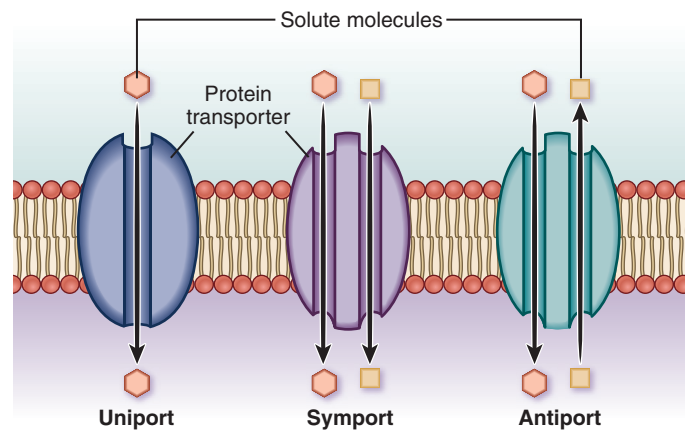


Fig. 1.23 Mediated Transport. Illustration shows simultaneous movement of a single solute molecule in one direction (*uniport*), of two different solute molecules in one direction (*symport*), and of two different solute molecules in opposite directions (*antiport*).

Electrolytes as Solutes

Body fluids are composed of **electrolytes**, which are electrically charged and dissociate into constituent **ions** when placed in solution. Nonelectrolytes, such as glucose, urea, and creatinine, do not dissociate. Electrolytes account for approximately 95% of the solute molecules in body water. Electrolytes exhibit **polarity** by orienting themselves toward the positive or negative pole. Ions with a positive charge are known as **cations** and migrate toward the negative pole, or cathode, if an electrical current is passed through the electrolyte solution. **Anions** carry a negative charge and migrate toward the positive pole, or anode, in the presence of electrical current. Anions and cations are located in both the intracellular fluid (ICF) and the ECF compartments, although their concentration depends on their location. (Fluid

and electrolyte balance between body compartments is discussed in Chapter 3). For example, Na^+ is the predominant extracellular cation, and K^+ is the principal intracellular cation. The difference in ICF and ECF concentrations of these ions is important to the transmission of electrical impulses across the plasma membranes of nerve and muscle cells.

Electrolytes are measured in milliequivalents per liter (mEq/L) or milligrams per deciliter (mg/dL). The term *milliequivalent* indicates the chemical-combining activity of an ion, which depends on the electrical charge, or **valence**, of its ions. In abbreviations, valence is indicated by the number of plus or minus signs. Monovalent ions, or ions with one charge, include sodium (Na^+), chloride (Cl^-), and potassium (K^+). Divalent ions, which have two charges, include calcium (Ca^{2+}) and

magnesium (Mg^{++}). One milliequivalent (mEq) of any cation can combine chemically with 1 mEq of any anion: one monovalent anion will combine with one monovalent cation. Divalent ions combine more strongly than monovalent ions. To maintain electrochemical balance, one divalent ion will combine with two monovalent ions (e.g., $\text{Ca}^{2+} + 2 \text{Cl}^- = \text{CaCl}_2$).

Passive Transport: Diffusion, Filtration, and Osmosis

Diffusion. Diffusion is the movement of a solute molecule from an area of greater solute concentration to an area of lesser solute concentration. This difference in concentration is known as a **concentration gradient** (see Fig. 1.21). Although particles in a solution move randomly in any direction, if the concentration of particles in one part of the solution is greater than that in another part, the particles distribute themselves evenly throughout the solution. According to the same principle, if the concentration of particles is greater on one side of a *permeable membrane* than on the other side, the particles diffuse spontaneously from the area of greater concentration to the area of less concentration until equilibrium is reached. Molecules still move back and forth to maintain this equilibrium; however, there is no net change in concentration of the molecules on either side of the permeable membrane. The higher the concentration on one side, the greater is the diffusion rate.

The diffusion rate is influenced by differences of electrical potential across the membrane (see the Movement of Electrical Impulses: Membrane Potentials section). Because the pores in the lipid bilayer are often lined with Ca^{2+} , other cations (e.g., Na^+ and K^+) diffuse slowly because they are repelled by positive charges in the pores.

The rate of diffusion of a substance depends also on its size (diffusion coefficient) and its lipid solubility (Fig. 1.24). Usually, the smaller the molecule and the more soluble it is in oil, the more hydrophobic or nonpolar it is, and the more rapidly it will diffuse

across the bilayer. Oxygen, CO_2 , and the steroid hormones (e.g., androgens and estrogens) are all nonpolar molecules. Water-soluble substances, such as glucose and inorganic ions, diffuse very slowly, whereas uncharged lipophilic (“lipid-loving”) molecules, such as fatty acids and steroids, diffuse rapidly. Ions and other polar molecules generally diffuse across cellular membranes more slowly compared with lipid-soluble substances.

Water readily diffuses through biologic membranes because water molecules are small and uncharged. The dipolar structure of water allows it to rapidly cross the regions of the bilayer containing the polar phosphate head groups. The polar phosphate head groups constitute the two outer regions of the lipid bilayer.

Filtration: hydrostatic pressure. Filtration is the movement of water and solutes through a membrane because of a greater pushing pressure (force) on one side of the membrane than on the other side. **Hydrostatic pressure** is the mechanical force of water pushing against cellular membranes (Fig. 1.25A). In the vascular system, hydrostatic pressure is the *blood pressure* generated in vessels when the heart contracts. Blood reaching the capillary bed has a hydrostatic pressure of 25 to 30 millimeters of mercury (mm Hg), which is sufficient force to push water across the thin capillary membranes into the interstitial space. Hydrostatic pressure is partially balanced by osmotic pressure, whereby water moving *out* of the capillaries is partially balanced by osmotic forces that tend to *pull* water *into* the capillaries (Fig. 1.25B). Water that is not osmotically attracted back into the capillaries moves into the lymph system (see the discussion of Starling forces in Chapter 3).

Osmosis. Osmosis is the movement of water “down” a concentration gradient—that is, across a semipermeable membrane from a region of higher water concentration to one of lower concentration. For osmosis to occur, (1) the membrane must be more permeable to water than to solutes, and (2) the concentration of solutes on one side of the membrane must be greater than that on the other side so that water moves more

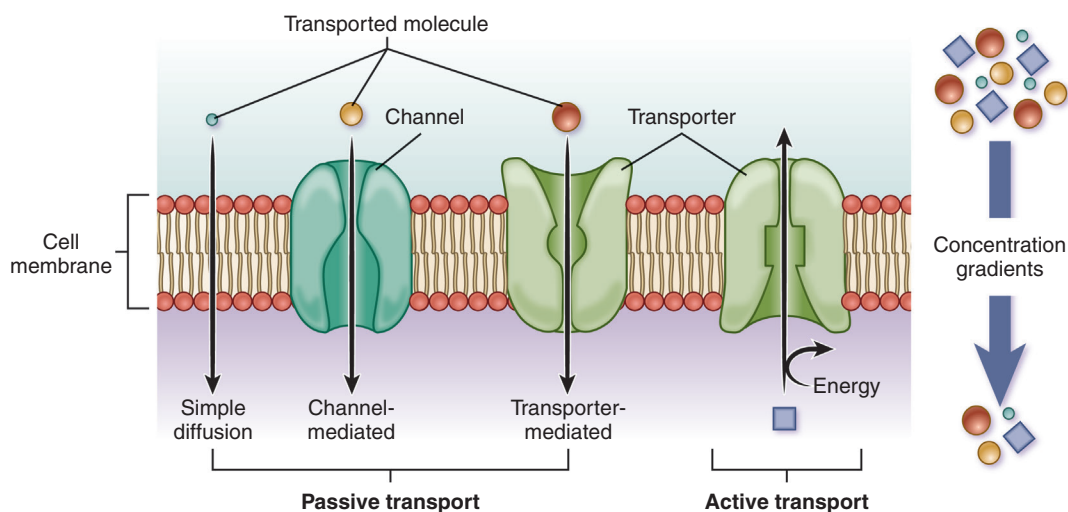


Fig. 1.24 Passive Diffusion of Solute Molecules Across the Plasma Membrane. Oxygen, nitrogen, water, urea, glycerol, and carbon dioxide can diffuse readily down the concentration gradient. Macromolecules are too large to diffuse through pores in the plasma membrane. Ions may be repelled if the pores contain substances with identical charges. If the pores are lined with cations, for example, other cations will have difficulty diffusing because the positive charges will repel one another. Diffusion can still occur, but it occurs more slowly.

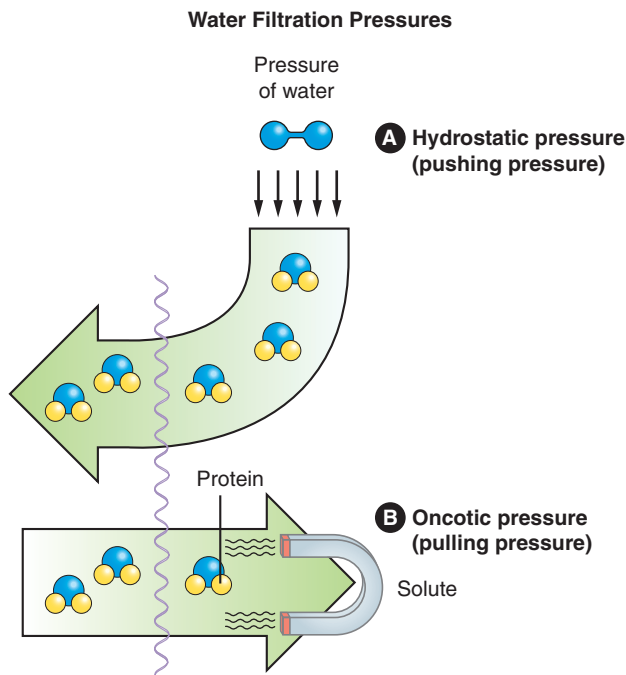


Fig. 1.25 Hydrostatic Pressure and Oncotic Pressure in Plasma. **(A)** Hydrostatic pressure in plasma is a pushing pressure in relation to water. **(B)** Oncotic pressure exerted by proteins in the plasma usually tends to *pull* water into the circulatory system. Individuals with low protein levels (e.g., starvation) are unable to maintain a normal oncotic pressure; therefore water is not reabsorbed into the circulation and, instead, causes body edema.

easily. Osmosis is directly related to both hydrostatic pressure and solute concentration but *not* to particle size or weight. For example, particles of the plasma protein albumin are small but are more concentrated in body fluids compared with the larger and heavier particles of globulin. Therefore albumin exerts a greater osmotic force compared with globulin.

Osmolality controls the distribution and movement of water between body compartments. The terms *osmolality* and *osmolarity* often are used interchangeably in reference to osmotic activity, but they define different measurements. *Osmolality* measures the number of milliosmoles per kilogram (mOsm/kg) of water, or the concentration of molecules per *weight* of water. *Osmolarity* measures the number of milliosmoles per liter (mOsm/L) of solution, or the concentration of molecules per *volume* of solution.

In solutions that contain only dissociable substances, such as Na^+ and Cl^- , the difference between the two measurements is negligible. When considering all the different solutes in plasma (e.g., proteins, glucose, lipids), the difference between osmolality and osmolarity becomes more significant. Less of plasma's weight is water, and the overall concentration of particles is therefore greater. The osmolality will be greater than the osmolarity because of the smaller proportion of water. Osmolality is thus preferred in human clinical assessment.

The normal osmolality of body fluids ranges from 280 to 294 mOsm/kg. The osmolalities of ICF and ECF tend to equalize, providing a measure of body fluid concentration and thus the body's hydration status. Hydration is affected also by hydrostatic pressure because the movement of water by osmosis can

be opposed by an equal amount of hydrostatic pressure. The amount of hydrostatic pressure required to oppose the osmotic movement of water is called the *osmotic pressure* of the solution. Factors that determine osmotic pressure are the type and thickness of the plasma membrane, the size of the molecules, the concentration of molecules or the concentration gradient, and the solubility of molecules within the membrane.

Effective osmolality is sustained osmotic activity and depends on the concentration of solutes remaining on one side of a permeable membrane. If the solutes penetrate the membrane and equilibrate with the solution on the other side of the membrane, the osmotic effect will be diminished or lost. For example, urea is a small solute that readily diffuses across cellular membranes. Solutions containing urea quickly lose their effective osmolality because they rapidly equilibrate. Solutes too large to pass through the membrane sustain an effective osmolality, meaning that they enhance osmotic activity. Plasma proteins are examples of molecules that provide effective osmolality because they normally do not cross cellular membranes.

Plasma proteins influence osmolality because they have a negative charge (Fig. 1.25B). The principle involved is known as *Gibbs-Donnan equilibrium*; it occurs when the fluid in one compartment contains small, diffusible ions, such as Na^+ and Cl^- , together with large, nondiffusible, charged particles, such as plasma proteins. Because the body tends to maintain an electrical equilibrium, the nondiffusible protein molecules cause asymmetry in the distribution of small ions. Anions such as Cl^- are thus driven out of the cell or plasma, and cations, such as Na^+ , are attracted to the cell. The protein-containing compartment maintains a state of electroneutrality, but the osmolality is higher. The overall osmotic effect of colloids, such as plasma proteins, is called the *oncotic pressure*, or *colloid osmotic pressure*.

Tonicity describes the effective osmolality of a solution. (The terms *osmolality* and *tonicity* may be used interchangeably.) Solutions have relative degrees of tonicity. An *isotonic solution* (or isosmotic solution) has the same osmolality or concentration of particles (285 mOsm) as ICF or ECF (Fig. 1.26A). Examples of isotonic solutions include 5% dextrose in water and normal (0.9%) saline solution. A *hypotonic solution* has a lower concentration and is thus more dilute than body fluids (Fig. 1.26B). Water is a hypotonic solution. Consequently, water is osmotically pulled into the cells, causing cells to swell or burst. A *hypertonic solution* has a concentration of more than 285 to 294 mOsm/kg (Fig. 1.26C). An example of a hypertonic solution is 3% saline solution. Cells shrink in a hypertonic solution because water is being pulled out of the cells. The concept of tonicity is important when correcting water and solute imbalances by administering different types of replacement solutions (see Chapter 3).

Active Transport of Na^+ and K^+

The active transport system for Na^+ and K^+ is found in virtually all mammalian cells. The Na^+ - K^+ -antiport system (i.e., Na^+ moving out of the cell and K^+ moving into the cell) uses the direct energy of ATP to transport these cations. The transporter protein is ATPase, which requires Na^+ , K^+ , and magnesium (Mg^{++}) ions. The concentration of ATPase in plasma membranes is directly related to Na^+ - K^+ -transport activity. Approximately