NINTH EDITION

Anderson's PATHOLOGY

VOLUME ONE

Edited by

JOHN M. KISSANE

IE INTERNATIONAL EDITION

VOLUME ONE

Anderson's PATHOLOGY

Edited by

JOHN M. KISSANE, M.D.

Professor of Pathology and of Pathology in Pediatrics,
Washington University School of Medicine;
Pathologist, Barnes and Affiliated Hospitals,
St. Louis Children's Hospital, St. Louis, Missouri

NINTH EDITION

with **2269** *illustrations and* **8** *color plates*

The C. V. Mosby Company

ST. LOUIS • BALTIMORE • PHILADELPHIA • TORONTO 1990

Editor: George Stamathis
Developmental Editor: Elaine Steinborn
Assistant Editor: Jo Salway
Project Manager: Kathleen L. Teal
Production Editor: Carl Masthay
Book and Cover Design: Gail Morey Hudson
Production: Ginny Douglas, Teresa Breckwoldt

Two volumes

NINTH EDITION

Printed in the United States of America

The C.V. Mosby Company
11830 Westline Industrial Drive, St. Louis, Missouri 63146

Library of Congress Cataloging in Publication Data

Pathology (Saint Louis, Mo.)
Anderson's pathology.—9th ed. / edited by John M. Kissane.
p. cm.
Includes bibliographies and index.
ISBN 0-8016-2772-9 (set)
1. Pathology. I. Kissane, John M., 1928- . II. Anderson, W.A.D. (William Arnold Douglas), 1910-1986. III. Title. IV. Title: Pathology.
[DNLM: 1. Pathology. QZ 4 P2984]
RB111.P3 1990
616.07—dc19
DNLM/DLC
for Library of Congress 89-3072
CIP

C/VH/VH 9 8 7 6 5 4 3 2 1

Contributors

ARTHUR C. ALLEN, M.D.

Professor of Pathology, State University of New York,
Downstate Medical Center; Consultant Pathologist,
The Brooklyn Hospital–Caledonian Hospital,
Brooklyn, New York

ROBERT E. ANDERSON, M.D.

Frederick H. Harvey Professor and Chairman,
Department of Pathology, The University of New Mexico,
Albuquerque, New Mexico

FREDERIC B. ASKIN, M.D.

Professor of Pathology
University of North Carolina School of Medicine;
Director of Surgical Pathology,
North Carolina Memorial Hospital,
Chapel Hill, North Carolina

SAROJA BHARATI, MD.

Professor of Pathology, Department of Pathology,
Rush Medical School, Rush–Presbyterian–
St. Luke's Medical Center, Chicago;
Director, Congenital Heart and Conduction System Center,
Heart Institute for Children of Christ Hospital,
Palos Heights, Illinois

CHAPMAN H. BINFORD, M.D.

Formerly Chief, Special Mycobacterial Diseases Branch,
Geographic Pathology Division,
Armed Forces Institute of Pathology,
Washington, D.C.

FRANCIS W. CHANDLER, D.V.M., Ph.D.

Professor of Pathology, Department of Pathology,
Medical College of Georgia,
Augusta, Georgia

JOSÉ COSTA, M.D.

Professor of Pathology, Director, Institute of Pathology,
University of Lausanne,
Lausanne, Switzerland

JOHN REDFERND CRAIG, M.D., Ph.D.

Associate Clinical Professor, Department of Pathology,
University of Southern California School of Medicine,
Los Angeles;
Chief Pathologist, Department of Pathology,
St. Luke Medical Center, Pasadena;
St. Jude Hospital and Rehabilitation Center,
Fullerton, California

CHARLES J. DAVIS, Jr., M.D.

Associate Chairman, Department of Genitourinary
Pathology, Armed Forces Institute of Pathology,
Professor of Pathology,
Uniformed Services University of Health Sciences,
Washington, D.C.

KATHERINE De SCHRYVER-KECSKEMÉTI, M.D.

Professor of Pathology, Director, Anatomic and
Surgical Pathology, Case Western Reserve University,
Cleveland, Ohio

MICHAEL D. FALLON, M.D.

Associate Professor of Pathology and Cell Biology,
Department of Pathology,
Thomas Jefferson Medical College;
Attending Pathologist, Division of Surgical Pathology;
Director of the Division of Orthopaedic Pathology,
Department of Pathology,
Thomas Jefferson University Hospital,
Philadelphia, Pennsylvania

ROBERT E. FECHNER, M.D.

Royster Professor of Pathology and Director,
Division of Surgical Pathology,
University of Virginia Health Sciences Center,
Charlottesville, Virginia

GERALD FINE, M.D.

Formerly Chief, Division of Anatomic Pathology,
Henry Ford Hospital, Detroit;
Consulting Pathologist, Holy Cross Hospital, Detroit;
St. Joseph's Hospital,
Mt. Clemens, Michigan

KAARLE O. FRANSSILA, M.D. Ph.D.

Chief of Pathology Laboratory, Department of Radiotherapy and Oncology, Helsinki University Central Hospital, Helsinki, Finland

VICTOR E. GOULD, M.D.

Professor and Associate Chairman of Pathology, Rush Medical College, Chicago, Illinois

ROGERS C. GRIFFITH, M.D.

Assistant Professor of Pathology, Brown University, Providence, Rhode Island

JOHN G. GRUHN, M.D.

Associate Professor of Pathology, Rush Medical College, Chicago, Illinois

DONALD B. HACKEL, M.D.

Professor of Pathology, Department of Pathology, Duke University Medical Center, Durham, North Carolina

REID R. HEFFNER, Jr., M.D.

Professor of Pathology, Department of Pathology, State University of New York, Buffalo, New York

GORDON R. HENNIGAR, M.D.

Professor of Pathology, Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, South Carolina

CHARLES S. HIRSCH, M.D.

Chief Medical Examiner, Suffolk County, New York; Professor of Forensic Pathology, SUNY Medical School at Stony Brook, Stony Brook, New York

PHILIP M. IANNACCONE, M.D., D.Phil. (Oxon)

Associate Professor of Pathology, Northwestern University, Chicago; Associate Staff Attending, Pathology, Northwestern Memorial Hospital, Chicago, Illinois

CHRISTINE G. JANNEY, M.D.

Assistant Professor of Pathology, St. Louis University School of Medicine, St. Louis, Missouri

HAN-SEOB KIM, M.D.

Associate Professor of Pathology, Baylor College of Medicine; Attending Pathologist, The Methodist Hospital, Harris County Hospital District, Houston, Texas

JOHN M. KISSANE, M.D.

Professor of Pathology and Pathology in Pediatrics, Washington University School of Medicine; Pathologist, Barnes and Affiliated Hospitals, St. Louis Children's Hospital at Washington University Medical Center, St. Louis, Missouri

FREDERICK T. KRAUS, M.D.

Professor of Pathology (Visiting Staff), Washington University School of Medicine; Director of Laboratory Medicine, St. John's Mercy Medical Center, St. Louis, Missouri

CHARLES KUHN III, M.D.

Professor of Pathology, Brown University, Providence, Rhode Island; Pathologist in Chief, Memorial Hospital of Rhode Island, Pawtucket, Rhode Island

MICHAEL KYRIAKOS, M.D.

Professor of Pathology, Washington University School of Medicine; Surgical Pathologist, Barnes Hospital; Consultant to St. Louis Children's Hospital at Washington University Medical Center and to Shriner's Hospital for Crippled Children, St. Louis, Missouri

PAUL E. LACY, M.D.

Mallinckrodt Professor and Chairman, Department of Pathology, Washington University School of Medicine, St. Louis, Missouri

RUSSELL M. LEBOVITZ, M.D., Ph.D.

Assistant Professor of Pathology, Baylor College of Medicine, Houston, Texas

MAURICE LEV, M.D.

Professor of Pathology, Department of Pathology, Rush Medical School, Rush–Presbyterian–St. Luke's Medical Center, Chicago; Associate Director, Congenital Heart and Conduction System Center, Heart Institute for Children of Christ Hospital, Palos Heights, Illinois

MICHAEL W. LIEBERMAN, M.D. Ph.D.

Professor and The W.L. Moody, Jr., Chairman, Department of Pathology, Baylor College of Medicine, Houston, Texas

CHAN K. MA, M.D.

Staff Pathologist, Department of Pathology, Henry Ford Hospital, Detroit, Michigan

JOSEPH A. MADRI, M.D., Ph.D.

Department of Pathology,
Yale University School of Medicine,
New Haven, Connecticut

MANUEL A. MARCIAL, M.D.

Associate Professor and Chairman,
Department of Pathology and Laboratory Medicine,
Universidad Central del Caribe, Escuela de Medicina,
Bayamón, Puerto Rico

RAÚL A. MARCIAL-ROJAS, M.D., J.D.

Professor and Dean, Universidad Central del Caribe,
Escuela de Medicina,
Bayamón, Puerto Rico

ROBERT W. McDIVITT, M.D.

Director, Division of Anatomic Pathology,
Department of Anatomic Pathology,
Washington University School of Medicine;
Chief of Anatomic Pathology,
Department of Anatomic Pathology, Barnes Hospital;
Consultant St. Louis Children's Hospital at Washington
University Medical Center, St. Louis, Missouri

WAYNE M. MEYERS, M.D., Ph.D.

Chief, Division of Microbiology,
Armed Forces Institute of Pathology,
Washington, D.C.

F. KASH MOSTOFI, M.D.

Chairman, Department of Genitourinary Pathology,
Armed Forces Institute of Pathology, Washington, D.C.;
Professor of Pathology,
Uniformed Services University of Health Sciences,
Bethesda, Maryland;
Associate Professor of Pathology,
Johns Hopkins University School of Medicine,
Clinical Professor of Pathology,
University of Maryland Medical School,
Baltimore, Maryland;
Clinical Professor of Pathology,
Georgetown University School of Medicine,
Washington, D.C.

JAMES S. NELSON, M.D.

Clinical Professor of Pathology, Department of Pathology,
University of Michigan, Ann Arbor, Michigan;
Division Head, Neuropathology, Department of Pathology,
Henry Ford Hospital, Detroit, Michigan

JAMES E. OERTEL, M.D.

Chairman, Department of Endocrine Pathology,
Armed Forces Institute of Pathology,
Washington, D.C.

JEFFREY M. OGORZALEK, M.D.

Major, US Air Force, Medical Corps;
Pathologist, Department of Endocrine Pathology,
Armed Forces Institute of Pathology,
Washington, D.C.

ALAN S. RABSON, M.D.

Director, Division of Cancer Biology and Diagnosis,
National Cancer Institute,
Bethesda, Maryland

KEITH A. REIMER, M.D., Ph.D.

Professor of Pathology, Department of Pathology,
Duke University Medical Center,
Durham, North Carolina

JUAN ROSAI, M.D.

Professor and Director of Anatomic Pathology,
Department of Pathology,
Yale University School of Medicine,
New Haven, Connecticut

DANTE G. SCARPELLI, M.D., Ph.D.

Ernest J. and Hattie H. Magerstadt Professor and Chairman,
Department of Pathology,
Northwestern University Medical School;
Chief of Service, Northwestern Memorial Hospital,
Chicago, Illinois

HARRY A. SCHWAMM, M.D.

Chairman, Department of Pathology,
The Graduate Hospital;
Clinical Professor of Orthopaedic Surgery (Pathology),
Department of Orthopaedic Surgery;
Clinical Professor of Pathology, Department of Pathology,
University of Pennsylvania School of Medicine,
Philadelphia, Pennsylvania

STEWART SELL, M.D.

Professor, Department of Pathology and Laboratory Medicine,
University of Texas Health Science Center at Houston,
Houston, Texas

GEORGE F. SCHREINER, M.D. Ph.D.

Assistant Professor of Medicine and Pathology,
Department of Medicine, Pathology,
Washington University School of Medicine;
Assistant Physician, Department of Medicine,
Barnes Hospital,
St. Louis, Missouri

HERSCHEL SIDRANSKY, M.D.

Professor and Chairman, Department of Pathology,
The George Washington University Medical Center,
Washington, D.C.

RUTH SILBERBERG, M.D.

Visiting Scientist,
Hadassah Hebrew University School of Medicine,
Jerusalem, Israel

MORTON E. SMITH, M.D.

Professor of Ophthalmology and Pathology,
Washington University School of Medicine,
St. Louis, Missouri

JACK L. TITUS, M.D., Ph.D.

Director, Jesse E. Edwards Registry of Cardiovascular Disease, United Hospital;
Clinical Professor of Pathology, University of Minnesota, St. Paul, Minnesota;
Formerly Professor and The W.L. Moody, Jr., Chairman, Department of Pathology, Baylor College of Medicine;
Chief, Pathology Service, The Methodist Hospital;
Pathologist-in-Chief, Harris County Hospital District, Houston, Texas

CHARLES A. WALDRON, D.D.S., M.S.D.

Professor Emeritus and Consultant, Oral Pathology,
Emory University School of Postgraduate Dentistry,
Atlanta, Georgia

DAVID H. WALKER, M.D.

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

NANCY E. WARNER, M.D.

Hastings Professor of Pathology,
University of Southern California School of Medicine,
Los Angeles, California

JOHN C. WATTS, M.D.

Attending Pathologist, Department of Anatomic Pathology,
William Beaumont Hospital, Royal Oak, Michigan;
Clinical Associate Professor of Pathology,
Wayne State University School of Medicine,
Detroit, Michigan

ROSS E. ZUMWALT, M.D.

Associate Professor, Department of Pathology,
University of New Mexico School of Medicine;
Assistant Chief Medical Investigator–State of New Mexico,
Office of the Medical Investigator,
Albuquerque, New Mexico

Preface to the Ninth Edition

My first responsibility, and it is a sad one, as editor of this ninth edition of *Anderson's Pathology*, is to mourn the loss of Dr. W.A.D. Anderson, creator and through nearly four decades guiding spirit of this book, which bears his name. He was an Emeritus Professor of Pathology and former Chairman of the Department of Pathology at the University of Miami School of Medicine in Miami, Florida. When he died on January 20, 1986, many of us lost a friend, and Pathology lost a scholarly spokesman. We will all miss him.

This edition continues the tradition of prior editions' concern. In the introductory chapters, mechanisms of human disease are addressed; these are followed by chapters that consider diseases of the several organ systems. Consideration of diseases of the various organ systems is deliberately made thorough so that the book can remain a useful and reliable source of information not only for medical students and trainees in pathology, but also for those training and practicing in other disciplines.

The eighth edition witnessed the emergence of acquired immunodeficiency syndrome (AIDS) as a major public health problem in industrialized societies as well as, by virtue of its protean clinical and morphologic manifestations, an important diagnostic consideration in specific patients. In preparing for this ninth edition, I considered allocating a separate chapter to AIDS. Eventually I decided to leave the consideration of AIDS within the several chapters addressing various organ systems, both for its basic aspects and for the descriptions of specific clinicopathologic features. Somewhat similar considerations related to the treatment of transplantation pathology, and the same decision was reached. These decisions remain very much open and may be amended in future revisions.

This edition of *Pathology* includes more than the usual number of chapters by new contributors. I welcome each of them and at the same time express my gratitude to their predecessors who have participated so importantly in the success this book has enjoyed throughout its long life.

John M. Kissane

Preface to First Edition

Pathology should form the basis of every physician's thinking about his patients. The study of the nature of disease, which constitutes pathology in the broad sense, has many facets. Any science or technique which contributes to our knowledge of the nature and constitution of disease belongs in the broad realm of pathology. Different aspects of a disease may be stressed by the geneticist, the cytologist, the biochemist, the clinical diagnostician, etc., and it is the difficult function of the pathologist to attempt to bring about a synthesis, and to present disease in as whole or as true an aspect as can be done with present knowledge. Pathologists often have been accused, and sometimes justly, of stressing the morphologic changes in disease to the neglect of functional effects. Nevertheless, pathologic anatomy and histology remain as an essential foundation of knowledge about disease, without which basis the concepts of many diseases are easily distorted.

In this volume is brought together the specialized knowledge of a number of pathologists in particular aspects or fields of pathology. A time-tested order of presentation is maintained, both because it has been found logical and effective in teaching medical students and because it facilitates study and reference by graduates. Although presented in an order and form to serve as a textbook, it is intended also to have sufficient comprehensiveness and completeness to be useful to the practicing or graduate physician. It is hoped that this book will be both a foundation and a useful tool for those who deal with the problems of disease.

For obvious reasons, the nature and effects of radiation have been given unusual relative prominence. The changing order of things, with increase of rapid, worldwide travel and communication, necessitates increased attention to certain viral, protozoal, parasitic, and other conditions often dismissed as "tropical," to bring them nearer their true relative importance. Also, given more than usual attention are diseases of the skin, of the organs of special senses, of the nervous system, and of the skeletal system. These are fields which often have not been given sufficient consideration in accordance with their true relative importance among diseases.

The Editor is highly appreciative of the spirit of the various contributors to this book. They are busy people, who, at the sacrifice of other duties and of leisure, freely cooperated in its production, uncomplainingly tolerated delays and difficulties, and were understanding in their willingness to work together for the good of the book as a whole. Particular thanks are due the directors of the Army Institute of Pathology and the American Registry of Pathology, for making available many illustrations. Dr. G.L. Duff, Strathcona Professor of Pathology, McGill University, Dr. H.A. Edmondson, Department of Pathology of the University of Southern California School of Medicine, Dr. J.S. Hirschboeck, Dean, and Dr. Harry Beckman, Professor of Pharmacology, Marquette University School of Medicine, all generously gave advice and assistance with certain parts.

To the members of the Department of Pathology and Bacteriology at Marquette University, the Editor wishes to express gratitude, both for tolerance and for assistance. Especially valuable has been the help of Dr. R.S. Haukohl, Dr. J.F. Kuzma, Dr. S.B. Pessin, and Dr. H. Everett. A large burden was assumed by the Editor's secretaries, Miss Charlotte Skacel and Miss Ann Cassady. Miss Patricia Blakeslee also assisted at various stages and with the index. To all of these the Editor's thanks, and also to the many others who at some time assisted by helpful and kindly acts, or by words of encouragement or interest.

W.A.D. Anderson

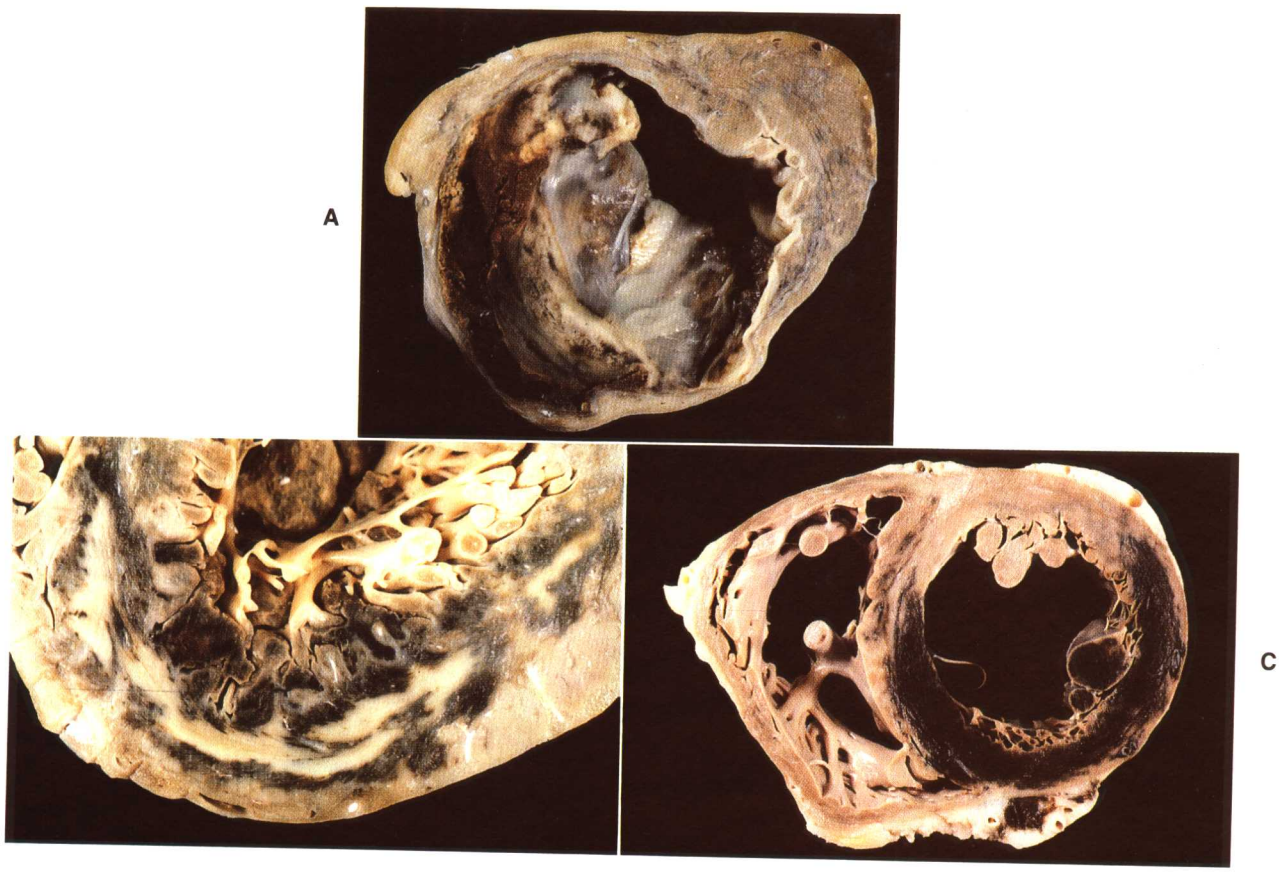

Plate 1

A, Cross section of left ventricle showing an old infarct with pronounced thinning of the wall. The infarct is the white scar, which is transmural; the wall bulges; and the resulting aneurysm is largely filled with a mural thrombus. A fragment of this thrombus had broken off and caused a cerebral infarct.

B, Cross section of the anterior wall of the left ventricle of a 51-year-old man who had chest pain 13 days before his death. Notice the yellowish tan necrotic center and the hyperemic border. This infarct microscopically showed necrosis in the central portion and organization in the periphery (that is, in the hyperemic zone).

C, This acute hemorrhagic myocardial infarct was from a 60-year-old man who had suffered from chest pain 3 days before death. A cardiac catheterization showed a complete occlusion of the left anterior descending coronary artery. Streptokinase was infused into the left coronary artery, which then opened partially. The hemorrhage is caused by the reflow into the infarcted region.

Contents

VOLUME ONE

VOLUME TWO

Color Plates

1 Cell Injury and Errors of Metabolism

DANTE G. SCARPELLI
PHILIP M. IANNACCONE

Fundamental knowledge of the morphologic and functional reactions of cells and tissues to various injurious agents and genetic defects is critical for the understanding of disease processes. In recent years, the march of biologic science has allowed the study of cellular processes at the molecular level. Thus, as we near the twenty-first century, pathology (the study of disease) has undergone a metamorphosis from a visual science, in which descriptive morphology was the centerpiece, to one where diseases are defined and interpreted in molecular terms. The foregoing, correlated with morphologic and functional alterations of cells and tissues, form the content of this chapter.

Cells are complex units driven by vital processes whose function depends on the fine integration of numerous extracellular and intracellular events. Injury occurs when adverse chemical, physical, or biologic elements in the environment alter these processes such that cells lose their capacity to generate energy, mediate transport of small molecules of biologic importance such as electrolytes, glucose, and amino acids, and finally synthesize vital macromolecules and assemble cell membranes. A few of the more common elements in the environment that are known to cause cell injury in humans are classified and listed below:

Chemical
- Industrial chemicals
- Therapeutic drugs
- Ethanol
- Tobacco smoke
- Aflatoxins and other toxic natural products

Physical
- Ultraviolet and ionizing radiation
- Mechanical trauma
- Heat and cold

Biologic
- Bacteria
- Fungi
- Viruses
- Metazoan parasites

Diseases attributable to errors of gene function are included because they are both a form of cell injury and, as they are expressed, ultimately a cause of cell injury.

MAJOR FUNCTIONS OF NORMAL CELLS

Since deterioration of cell function is the hallmark of cell injury, it seems appropriate to consider major functions of cells as an introduction to general cellular pathology. Although this is necessarily brief, it is intended to review some of the cellular and molecular mechanisms involved in cell structure and function. Inasmuch as the fine structure of cells is now the routine content of beginning courses in biology, it is not dealt with in any detail; instead, function is considered from the point of view of more recent developments in cell and molecular biology.

Energy production

The generation of energy in the form of adenosine triphosphate (ATP) is derived largely from the oxidative metabolism of glucose, fatty acids, and amino acids. The various enzymes and cofactors involved in these reactions are localized in mitochondria and their adjacent cytosol. Glucose converted to pyruvate by glycolysis in the cytosol, and fatty acids oxidized in mitochondria are broken down to the two-carbon acetyl group, which interacts with coenzyme A (CoA) to form acetyl CoA. CoA facilitates the entry of acetyl groups into the citric acid cycle localized in the matrix and inner membrane of mitochondria for further metabolism, the generation of high-energy electrons, and their capture by NAD^+ and FAD to form NADH and $FADH_2$. The conversion of this energy to the storable form (ATP) is accomplished by electron transport along the respiratory chain and ATP synthetase embedded in the inner mitochondrial membrane culminating in the phosphorylation of ADP to ATP and the formation of water according to the reaction $2H^+ + \frac{1}{2}O_2 \rightarrow H_2O$, the end product of respiratory oxidative metabolism. The foregoing is made possible by the specific orientation of respiratory and electron transport enzymes in the inner membrane, as well as its impermeability to the H^+ and OH^- ions produced during oxidative metabolism. It turns out that the active sites of the enzymes that dis-

charge H^+ during dehydrogenation of substrates are placed in the membrane such that these ions are released on one side of the membrane while OH^- ions are discharged on the other side as a result of the orientation of cytochrome oxidase, the terminal enzyme in the respiratory chain. The vectorial separation of H^+ and OH^- creates an electrochemical gradient across the inner mitochondrial membrane. As a result of the gradient, protons (H^+) flow from the intermembrane space across the inner mitochondrial membrane and drive the generation of ATP from ADP and inorganic phosphate (P_i) as they interact with ATP synthetase. This enzyme extracts H^+ and OH^- asymmetrically from ADP and HPO_4^{-2} in directions opposite to those during dehydrogenation and electron transport noted previously.[107] As is probably evident to the reader, the reaction responsible for the conversion and conservation of energy by the formation of ATP is the reverse of that for its release by dephosphorylation. It is not surprising then that ATP synthetase can also function in reverse to hydrolyze ATP and actively pump H^+ ions. The reactions involved in ATP formation and hydrolysis respectively are shown below.

ATP formation from glucose oxidation

Glycolysis (cytosol)

$$\text{Glucose} + 2P_i + 2ADP + 2NAD^+ \longrightarrow 2\ \text{Pyruvate} + 2NADH + 2H^+ + 2ATP + 2H_2O$$

Oxidation of NADH

$$2NADH + 2H^+ + O_2 + 4P_i + 4ADP \longrightarrow 2NAD^+ + 4ATP + 6H_2O$$

Citric acid cycle (mitochondria)

$$2\ \text{Pyruvate} + 5O_2 + 30ADP + 30P_i \longrightarrow 6CO_2 + \underline{30ATP} + 34H_2O$$

TOTAL ATP FORMED 36ATP

Free energy of hydrolysis of ATP

$$ATP + H_2O \longrightarrow ADP + P_i + H^+$$

$$\Delta G = -7.3\ \text{kcal/mol}$$

Under cellular conditions ΔG is higher at about -12 kcal/mol.

The foregoing aspects of energy production are presented to emphasize its high efficiency, the importance of the vectorial movement of ions, and its dependence on the organization and orientation of the multiple membrane-bound enzymes involved in the extraction of protons and electron transport. These points assume greater significance when we consider the loss of oxidative metabolism and energy generation that accompany the extensive structural alterations encountered in injured cells.

Synthesis of proteins and macromolecules

A typical mammalian cell synthesizes more than 10,000 different proteins, many of which are enzymes, as well as numerous species of structural proteins, lipoproteins, glycoproteins, and complex polysaccharide-protein molecules called "proteoglycans." These macromolecules are the means by which the "cryptic" functions encoded in DNA are expressed and activated. They serve to impart the many functions to cells that allow them not only to maintain and renew themselves, but also to recognize and signal other cells and organize into multicellular aggregates called "tissues," which provide a greater functional complexity and diversity than they can achieve as single cells. Protein synthesis is localized in the cytosolic, endoplasmic reticular, and to a lesser extent mitochondrial compartment. Protein synthesis is a complex process that begins with RNA polymerase copying a specific sequence of DNA into messenger RNA (mRNA), a process known as "transcription." The polymerase binds to the promoter that signals the site on the DNA molecule from which RNA synthesis must begin to encode for the synthesis of a specific protein; mRNA synthesis ceases when the polymerase encounters a second site on the DNA, which signals that the appropriate mRNA has been produced and the molecule is released.[17,69]

A family of more than 20 different RNA molecules called "transfer RNAs" (tRNA), including at least one tRNA for each amino acid, are responsible for specifically binding amino acids, a reaction catalyzed by enzymes named aminoacyl-tRNA synthetases, again one for each amino acid. The amino acyl-tRNAs thus formed serve to bring each specific amino acid to its appropriate place in the protein molecule being synthesized by recognizing its appropriate codon in the mRNA molecule and pairing with complementary nucleotides at their anticodon tips.[133] Amino acids are added to the carboxyl terminal end of the growing chain of peptides. These events occur on ribosomes, large multienzyme complexes consisting of protein and RNA.[110] Ribosomes are composed of a small and large subunit and have two grooves, one that fits onto an mRNA molecule and the other accommodating the growing polypeptide chain. In addition, there are two binding sites for tRNAs, one for the molecule that is contributing its amino acid to the protein being synthesized, the other for binding the tRNA carrying the next amino acid to be inserted.

Initiation of protein synthesis involves binding of the small ribosomal subunit to mRNA that has previously bound an initiator rRNA molecule that recognizes its AUG starter codon.[80] Once the initiation reaction is complete, the various factors involved are discharged from the small subunit and the large ribosomal subunit is bound and all is ready for protein synthesis to begin. It is noteworthy that initiation factors not only initiate the process of synthesis, but can also regulate its overall rate presumably by their phosphorylation by protein kinases in one system and perhaps by other cellular mechanisms that modulate the function of proteins.[113] The conversion of information in a molecule of mRNA

by its interaction with ribosomes and to RNAs culminating in the synthesis of a specific cellular protein is known as "translation."

Ribosomes exist as free 30 nm particles or as multiple ribosomes bound to a single mRNA molecule giving rise to polymorphous complex structures called polyribosomes in the cytosol, or as highly ordered parallel tubular arrays composed of membrane-bound ribosomes termed "rough-surfaced endoplasmic reticulum" (RER).[2] Proteins synthesized by the first of the two varieties of ribosomal profiles are released directly into the cytosol where they function as soluble proteins. Those that are targeted for a specific intracellular site are guided there by a specific carrier molecules as apparently is the case for some molecular components of mitochondria. In the case of RER organized into tubular structures (cisternae) with ribosomes attached to their outer surface, the proteins once synthesized are extruded across the RER membrane into the cisternal lumen. Although the problem of directed intracellular transport is at least partially solved, there still remains the need to assist proteins to reach their ultimate correct destination. This is accomplished by a system of coated vesicles that enclose proteins, especially those destined for insertion into or on a cell membrane. Transportation to specific locations is guided by so-called specific "docking" proteins that recognize complementary acceptor proteins at the various sites. The RER serves as the site for the synthesis of proteins and macromolecules for most of the cell's organelles, which undergo the addition of O-linked oligosaccharides, a reaction known as "glycosylation."[93] This occurs as soon as the growing polypeptide chain enters the cisternal lumen and is completed before it is released. Soluble proteins not destined for transport to membranous cell structures are not glycosylated.

The Golgi apparatus, with its parallel arrays of stacked cisternae and vacuoles, plays a major role in the biology of cell proteins and macromolecules. This is so because all such molecules destined for either membranous sites or export pass through this complex cell organelle and are chemically modified by it. These modifications include alterations of the O-linked oligosaccharide residues just mentioned, as well as a variety of other reactions such as glycosylation, sulfation, the addition of fatty acids, and proteolysis because these are required to allow proteins to achieve their full functional capacity.[49] In the case of proteins that are exported, the Golgi apparatus packages the product into secretory vacuoles that ultimately fuse with the plasma membrane during their secretion.

Transport, endocytosis and exocytosis

The plasma membrane serves both as an effective barrier that maintains the essential differences between the cell interior and its external environment and as a highly competent monitor regulating the entry and exit of specific molecules. In certain types of specialized cells it mediates the ingestion of large particles. The various properties of the plasma membrane are the result of transport enzymes specific for the uptake and output of ions, sugars, and amino acids and other small molecules, numerous different and specific receptors that recognize various molecules, and the ability to undergo gross conformational changes as a result of membrane fluidity and flow. The plasma membrane consists of a lipid bilayer[57] rich in cholesterol, four phospholipids with head groups of different sizes and charges, and glycolipids. The fluidity of the membrane is a function of its composition, that is, the amount of cholesterol and the types and amounts of constitutive fatty acids.[18,123] Since the majority of phospholipids are neutral at a physiologic pH, they readily accommodate intramembrane and transmembrane proteins embedded in the membrane bilayer. Membrane proteins have hydrophilic and hydrophobic domains; the former are localized at the external and internal surfaces of the membrane that are exposed to water, whereas the latter lie within the lipid-rich interior of the bilayer.[90] The latter interactions serve to firmly hold membrane proteins in the bilayer, and so they can be considered as integral constituents, whereas proteins that are inserted more superficially are not so anchored and are referred to as superficial proteins.[140]

The transport of ions involves membrane proteins, the best studied of which is the Na^+-K^+ pump, energized by ATP, where Na^+ is pumped out while K^+ ions are transported into the cell.[40] The vectorial movements of both ions in opposite directions are believed to occur in tandem; first Na^+ is bound on the cytoplasmic face of the carrier protein complex followed by hydrolysis of ATP and phosphorylation of the protein, which causes a conformational change and release of Na^+ to the cell exterior. This is then followed by binding of K^+ at the external surface of the protein and its subsequent dephosphylation and release of K^+ into the cytoplasm. For each molecule of ATP hydrolyzed $3Na^+$ and $2K^+$ ions are translocated. The Na^+-K^+ pump serves to control cell volume by regulating levels of these ions inside cells.[141] Other Na^+-carrier protein systems not driven by ATP are involved in the transport of other vital small molecules such as glucose and other sugars and amino acids in which these are taken into the cell driven by the chemical gradient of Na^+ uptake.[40] A third means by which ion transport occurs in excitable cells such as nerve and muscle involves so-called channels formed by parallel transmembrane proteins that "open" and "close" either by changes in membrane potential or by binding of a specific substance to a membrane receptor.[147] The latter is exemplified by the binding of acetylcholine at the activated neuromuscular junction causing the loss of K^+ and the

uptake of Na^+, ultimately resulting in muscular contraction.

The uptake of macromolecules such as large proteins, polysaccharides and nucleic acids, small bits of plasma membrane, and in specialized cells large particles across the cell membrane is accomplished by the formation and fusion of membrane-bounded vesicles a process called "endocytosis."[139] In the case of the uptake of macromolecules, the plasma membrane invaginates and pinches off small vesicles enclosing a bit of the extracellular fluid, a process termed "pinocytosis" ('cell drinking'). Cells are continuously ingesting materials at different rates depending on the cell type. Although most pinocytic vesicles move inward into the cytoplasm and fuse with primary lysosomes (organelles that contain hydrolytic enzymes), some bypass lysosomes and transport their contents through the cytoplasm to the cell periphery, fuse with the plasma membrane, and discharge their contents to the outside, a process called "exocytosis."[115] An excellent example of this is afforded by endothelial cells, which directly transport material from the blood into the extracellular fluid. A special class of endocytotic vesicles that bear mention are the "coated" variety, so called because they are composed of specific fibrous proteins that form a basketlike network.[55] These vesicles are capable of internalizing large numbers of specific macromolecules with only a minimum of extracellular fluid. This is accomplished by the presence of specific receptors in the vesicle membrane that bind and thus concentrate certain macromolecules. Cases in point are the insulin and low-density lipoprotein (LDL) molecules and their respective receptors. In these two examples there are special features of both that merit mention. Binding of insulin to its receptor mediates the entry of glucose into the cell; subsequent proteolysis of the insulin-receptor complex limits the action of the hormone and simultaneously regulates the number of receptor molecules on the cell surface.[117] Binding of LDL to its receptor and their endocytosis and delivery to lysosomes supplies the cell with cholesterol, after hydrolysis of the cholesterol ester moiety of LDL and, in contrast to the fate of insulin receptor, recycles the LDL receptor to the plasma membrane into which it is reinserted.

The cellular uptake of large particles including bacteria, is a subset of endocytosis, referred to as phagocytosis,[139] and a property largely of specialized cells such as polymorphonuclear (PMN) leukocytes and macrophages. These are major components of the host cellular defense mechanisms against infection by microorganisms, as well as for the removal of senescent and dead cells and internalized foreign materials such as mineral dusts and pigments. In this instance endocytosis involves the formation of a very large invagination of the plasma membrane and subsequently a correspondingly large vacuole or phagosome. This then fuses with primary lysosomes, which release their complement of hydrolytic enzymes and digest its contents. Phagocytosis is not a random process but one that is mediated by specific receptors on PMNs and macrophages.[149] Some of these receptors recognize antibody molecules, and in individuals with specific immunity, avidly bind, internalize, and destroy microorganisms that have previously bound the specific antibody. The foregoing represents the major humoral protective mechanism against infection. Although intracellular digestion is a very efficient process, the cell not infrequently ingests materials that cannot be totally degraded; these remain in secondary lysosomes for the lifetime of the cell and are called "residual bodies."

Exocytosis is the reverse of endocytosis and involves the formation of intracellular vacuoles containing specific macromolecules. These migrate to the cell periphery, fuse with the plasma membrane, and release their contents into the extracellular fluid or, in the case of exocrine gland cells, into ductules. This is the means by which cells secrete macromolecules. Some are released continuously, whereas others are packaged into secretory vesicles, stored, and released after an extracellular signal.[96] A specific signal triggers the secretion of a particular substance, or in the case of certain cells a group of macromolecules packaged into single vesicles. Macromolecules synthesized in the RER move to the Golgi apparatus via transport vesicles that bud off the cisternae and transfer their content to so-called condensing vesicles. Here they are progressively concentrated and end up as mature dense secretory granules on the luminal face of the Golgi appartus.

Digestion and detoxication

Controlled intracellular digestion is a vital property of all mammalian cells and is mediated by lysosomes, organelles that contain a spectrum of acid hydrolases capable of degrading proteins, carbohydrates, lipids, and nucleic acids.[33] Because of their important role, lysosomes are an integral part of the pathways involved in the uptake of materials, are formed by budding from the Golgi membranes facing the apical surface of the cells, and are strategically localized to degrade ingestive substances. Special features of this organelle that allow lysosomes to function optimally as the principal sites of intracellular digestion are localization of an ATPase-driven membrane transport protein that accumulates H^+ within them to create an acid milieu and a selective membrane that, together with that of the phagosome, allows free passage of the products of digestion while sequestering hydrolases from the cytosol. The logistics of incorporating the 40 or so appropriate hydrolytic enzymes into lysosomes during their formation is presumably accomplished by receptors (docking proteins) lo-