SEVENTH EDITION

PATHOLOGY

EDITED BY W. A. D. Anderson
John M. Kissane

VOLUME ONE

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PREFACE to seventh edition

The preface to the sixth edition of *Pathology* mentioned a merging between pathology and other so-called basic sciences that compelled a certain arbitrariness relating to inclusion or exclusion of many subjects in which recent advances had been made. In the preparation of this seventh edition, we have taken cognizance of some of those points of merging to which highly specific, not merely arbitrary, consideration must be given, that is, consideration regarding inclusion in the undergraduate medical curriculum. In planning for and executing this seventh edition, we recognized the fact that many schools now introduce pathology in the first year of the undergraduate medical curriculum. This fact compels teachers of pathology to place their contributions even more specifically in contextual relationship with the so-called "basic sciences" while maintaining relevant contemporariness in their applications to clinical medicine.

To these ends, several chapters have been rewritten by new contributors. We welcome them to this, our joint effort, at the same time that we thank those colleagues whom they have succeeded.

We hope that this revision will continue to entitle this work to the acceptance that preceding editions have enjoyed as a source for consideration by students during their preclinical years, no less than during their clinical years. A conscious effort has been made to continue the emphasis upon clinicopathologic correlations to the end that the work would continue to merit the confidence enjoyed by previous editions as a reliable, up-to-date source of information related to pathologic anatomy, important in the practice of the many defined areas of clinical medicine, including that of pathology itself.

W. A. D. Anderson

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, world-wide 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 Char-

lotte 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

COLOR PLATES

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1 / Cellular basis of disease

JOE W. GRISHAM
WAYKIN NOPANITAYA

During the past several centuries prevailing medical opinion variously emphasized different levels of organization of the human body as the primary site at which disease was produced.[27] Generally this emphasis reflected the store of anatomic and physiologic knowledge then current and the methods available to study the diseased organism. Early physicians saw disease only at the level of the body as a whole. Morgagni and other incipient pathologists attempted to locate the origin or seat of disease in the different organs of the body. Subsequently, Bichat and his followers emphasized the importance of the fabrics, or tissues, in development and expression of disease. Virchow called attention to the importance of individual cells as the primary locus at which abnormal function and structure arise. In our own time, Peters has established the role of disturbances in specific biochemical processes,[32] and many contemporary investigators have found that the various subcellular organelles, and the biochemical reactions that go on within and around them, are primary loci for initiating disease.

The various functional and structural properties of cells and tissues provide the critical points for induction of disease. Disease is not caused by the aquisition of a new and different set of properties by the affected cell, but rather by quantitative alterations in existing functions and structures. The goal of this chapter, necessarily brief and incomplete, is to direct the reader's thoughts to the multiple overlapping levels of cell structure and function that are the ultimate loci of the many pathologic lesions discussed in the subsequent chapters. Although this presentation emphasizes the cell and its parts, disease as it afflicts a person is much more than simply an abnormality of organelle structure and function within some particular cell. The mechanism by which a fundamental subcellular lesion causes a cascade of abnormal reactions in different cells and tissues, ultimately expressed at the organismic level as disease, is the essence of modern pathology. Only at the organismic level is a disease explicit with all of its cellular and subcellular components completely integrated.

GENERAL ASPECTS OF CELL STRUCTURE

Although cells are described as having fixed, unchanging structure, this is a static distortion of the living state, wherein cellular structures are dynamic and constantly changing. The fixed, sectioned cell represents a mere shadow of reality—a thin slice of an embalmed cell, killed in action. Because cells are killed at moments when they are occupied with different functions, static structural views vary. Only by the sampling and fixing of cells according to a precise schedule and by the correlation of structure and function in the same sample, can an appreciation of the true dynamics of cell structure and function be gained.

The cell may be viewed simplistically as a membrane-enclosed compartment, subdivided into several smaller compartments and surfaces by further internal ramifications of membrane; these compartments provide distinctive domains that allow a wide variety of mutually incompatible biochemical processes to occur simultaneously. The major subcellular compartments are nucleus, mitochondria, endoplasmic reticulum, Golgi apparatus, lysosomes, and cytosol (Fig. 1-1).

Cell membranes

All cellular membranes are complex mixtures of lipids, proteins, and carbohydrates and have a generally similar morphologic appearance in fixed, sectioned specimens.[39] The morphologic pattern usually seen, termed the *unit membrane,* consists of two electron-dense lines, each 2 to 3 nanometers (nm) thick, separated

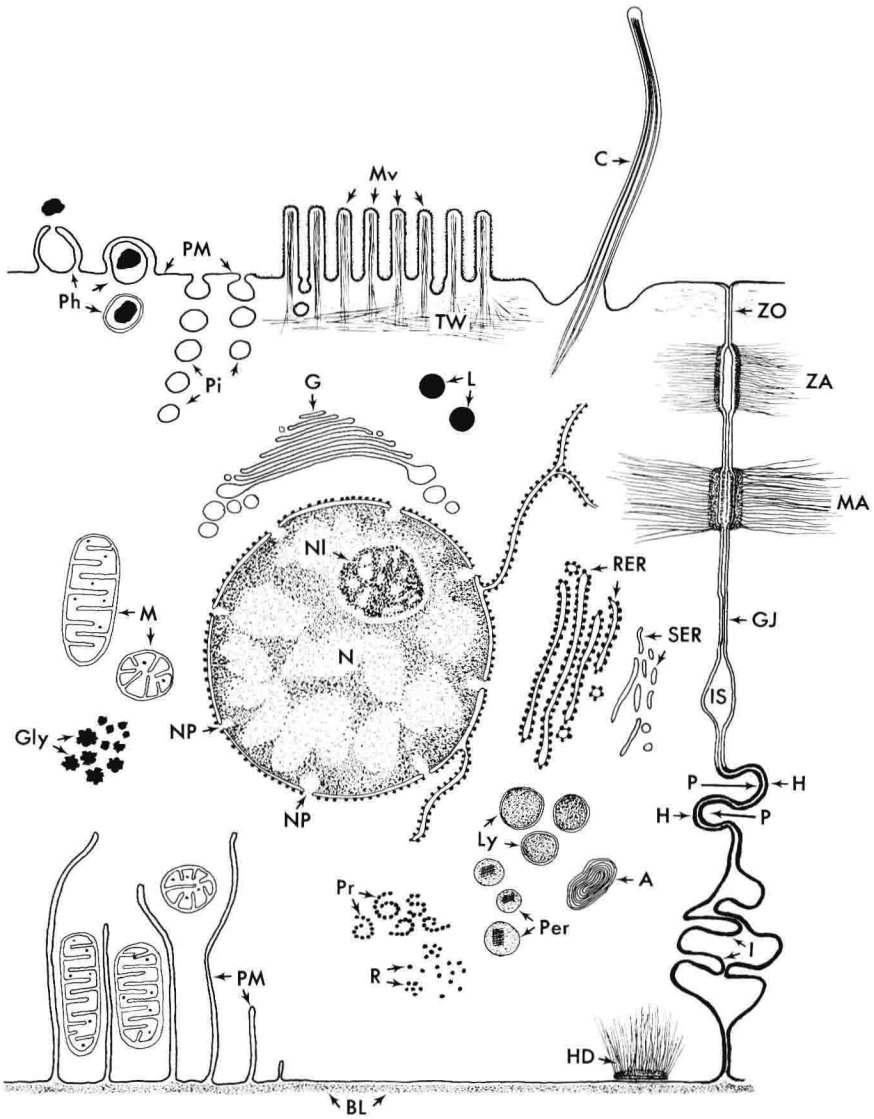

Fig. 1-1. Schematic representation of substructures of generalized mammalian cell. *Plasma membrane,* ***PM,*** *and its modifications:* **BL,** Basal lamina; **C,** cilia; **GJ,** gap junction; **H,** hole; **HD,** hemidesmosome; **I,** interdigitation; **IS,** intercellular space; **MA,** macula adherens (desmosome); **Mv,** microvilli and their "glycocalyx" coats; **P,** protrusion or peg; **Ph,** phagocytic vesicles; **Pi,** pinocytic vesicles; **ZA,** zonula adherens (intermediate junctions); **ZO,** zonula occludens (tight junction). *Cell organelles:* **A,** Autophagosome; **G,** Golgi apparatus; **Gly,** glycogen particles; **L,** lipid droplets; **Ly,** lysosome; **M,** mitochondria; **N,** nucleus; **Nl,** nucleolus; **Per,** peroxisome; **Pr,** polyribosomes; **R,** ribosome; **RER,** rough endoplasmic reticulum; **SER,** smooth endoplasmic reticulum; **TW,** terminal web and its microfilaments.

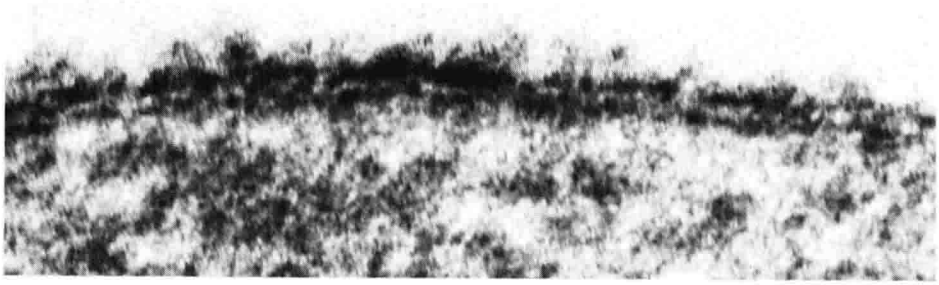

Fig. 1-2. Trilaminar appearance of unit membrane. (720,000×.)

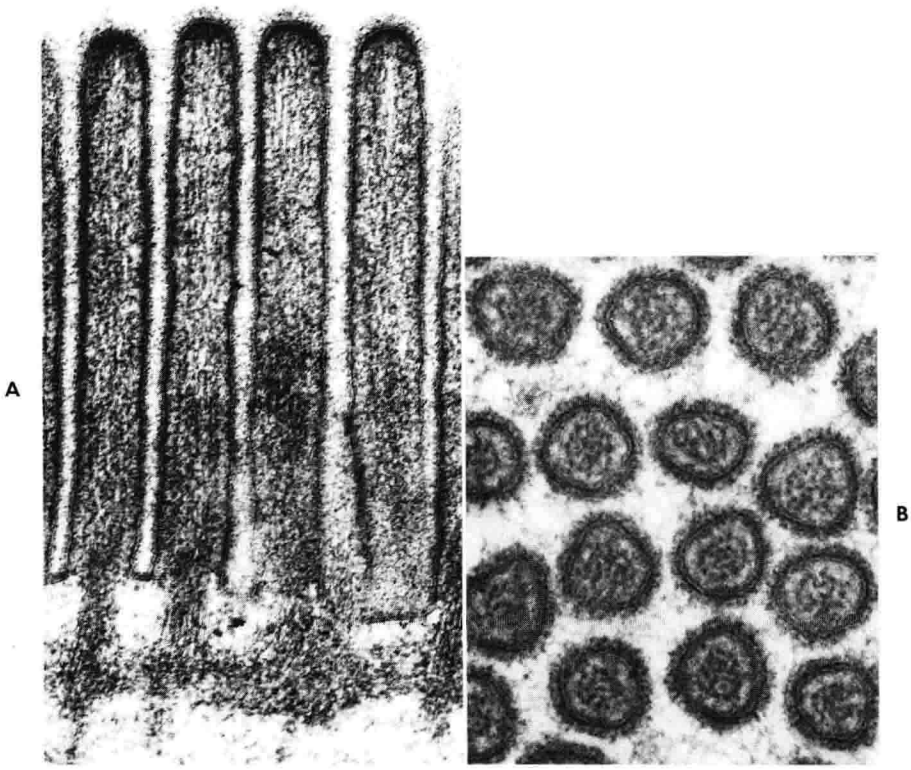

Fig. 1-3. A, Microvilli on cell surface. Outer membrane of all microvilli is covered with fine filamentous material (glycocalyx). Core of individual microvilli consists of microfilaments that interweave with those of the terminal web at their base. **B,** Cross section of microvilli showing glycocalyx on outer surface of their surface membranes and central filamentous cores. (**A,** 88,000×; **B,** 145,000×.)

by an electron-lucent line 3 to 4 nm thick (Fig. 1-2). The total thickness of this trilayer structure is 7.5 to 10 nm. Despite the general morphologic similarity of all fixed and sectioned membranes, there is a considerable diversity in both the chemical composition and the width of the layers of trilaminar membranes taken from various cells and from different membranes of the same cell. In fact, some studies of fixed, sectioned membranes suggest that true layers do not exist, but rather that certain membranes may be composed of globular units. Ultramicroscopic examination of surface replicas prepared from membranes split through their core (presumably through the electron-lucent layer) also shows tiny globular units whose distribution varies in different cells. Indeed, these globular structures can be moved

by certain manipulations of the cell before it is fixed. Globular structures in the core of the plasma membrane appear to be continuous with a variety of receptors on the outer surface of the membrane and, perhaps, with a protein "tail" that projects from the cytoplasmic side. The outer surface of the cell membrane contains a partial coating of mucopolysaccharides, such as sialic acid.[20] Properly fixed, this surface coat appears on some types of cells as a fuzzy layer, termed the *glycocalyx* (Fig. 1-3).

The molecular structure of cellular membranes is still unknown, and theorists have been challenged to provide a hypothesis for the biophysical configuration of membranes that explains morphologic observations, biochemical composition, and functional characteristics, such as permeability, antigenicity, electrical conductivity, etc. A variety of theories now exists, but the oldest still retains considerable credibility in its recently modified form. This lipid-bilayer theory postulates that lipid molecules are oriented in two layers in cell membranes, with their hydrophilic ends turned outward and their hydrophobic ends turned inward. An early version of this theory postulated that lipid-lined pores penetrated the bilayer (to explain permeability) and that the hydrophilic surfaces were covered by protein molecules in the extended form. More recent variations postulate the presence within the membrane of globular proteins that are exposed on one or both surfaces and that mediate transport and other membrane functions. Other theories hold that the cell membrane is composed of lipid in either the liquid-crystalline state or in the form of lipid micelles in which globular proteins are partly or completely embedded.

On many cells the surface area of the plasma membrane is increased by folds or projections. *Microvilli* are 1 μm long by 0.1 μm wide cylindrical protrusions of membrane surrounding a cytoplasmic core containing a bundle of microfilaments (Fig. 1-3.). The microfilaments in the cores of microvilli merge with the submembrane microfilamentous web (terminal web). Microvilli are especially numerous on absorptive and secretory surfaces of cells, where they vastly increase the cell's surface area. Membranes of cells involved in water transport may exhibit complex foldings distinct from microvilli; these also augment the cell's surface.

Cytosol

Cytosol is the cytoplasmic ground substance, the watery, gel-like mixture in which the cell's

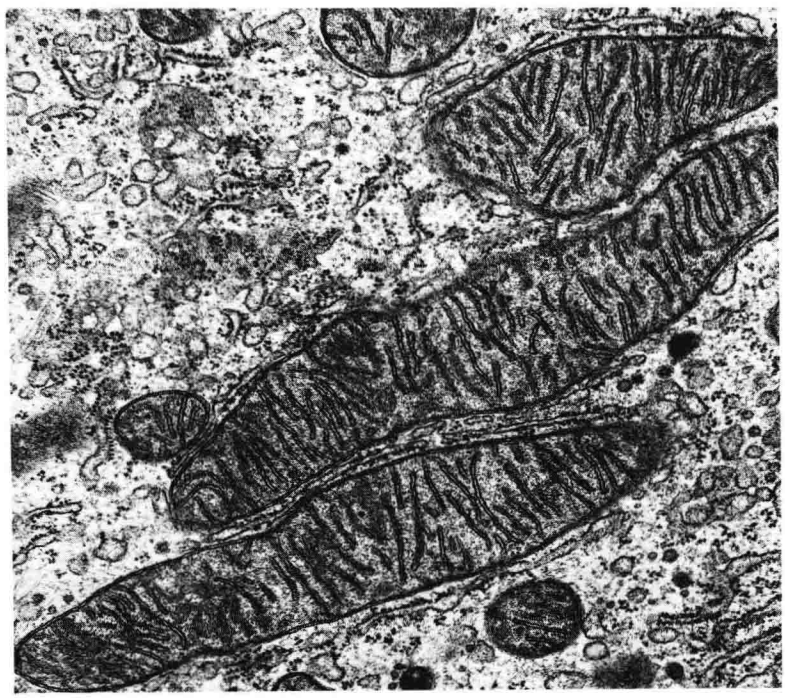

Fig. 1-4. Mitochondria sectioned both longitudinally and across. (25,000×.)

organelles and inclusions are suspended. The cytosol provides the matrix in which all the subcellular organelles are embedded. Many enzymatic reactions occur outside formed organelles, mediated by enzymes suspended or dissolved in the cytosol. Some processes occurring in the cytosol may be linked to enzymatic steps taking place in organelles. The cytosol doubtless has a highly detailed structure, which we are unable to observe with presently available techniques. Despite our lack of detailed insight into the composition and function of the cytosol, its role in cell functions should not be underestimated.

Mitochondria

Although the general morphologic features of mitochondria are similar in all mammalian cells, their precise structural details (especially the arrangement of their internal cristae) vary considerably.[36] Typical mitochondria (Fig. 1-4) are 0.5 to 1.0 μm in diameter and 3 to 5 μm in length. They are enveloped by a smooth outer membrane and contain a variably folded inner membrane.[26] The inner membrane may be composed of shelflike ridges, tubules, or concentric layers. The elaborate foldings of the inner membrane are termed *cristae*. Outer and inner membranes delimit several actual or potential spaces: the matrix space within the inner membrane, the intercristal space between the two unit membranes of cristae, and the peripheral space between outer and inner membranes. If cristae are merely folds of a continuous inner membrane, peripheral and intercristal spaces may be continuous; the situation is not established with certainty. In the so-called orthodox or typical configuration, outer and inner mitochondrial membranes are closely apposed and peripheral and intercristal spaces are minimal.

Mitochondria are composed mainly of lipid and protein. Nearly half of the protein appears to be enzymes that are components of integrated pathways, such as the Krebs tricarboxylic acid cycle. All of the lipid is in the membrane. The outer membrane closely resembles other cytomembranes, both chemically

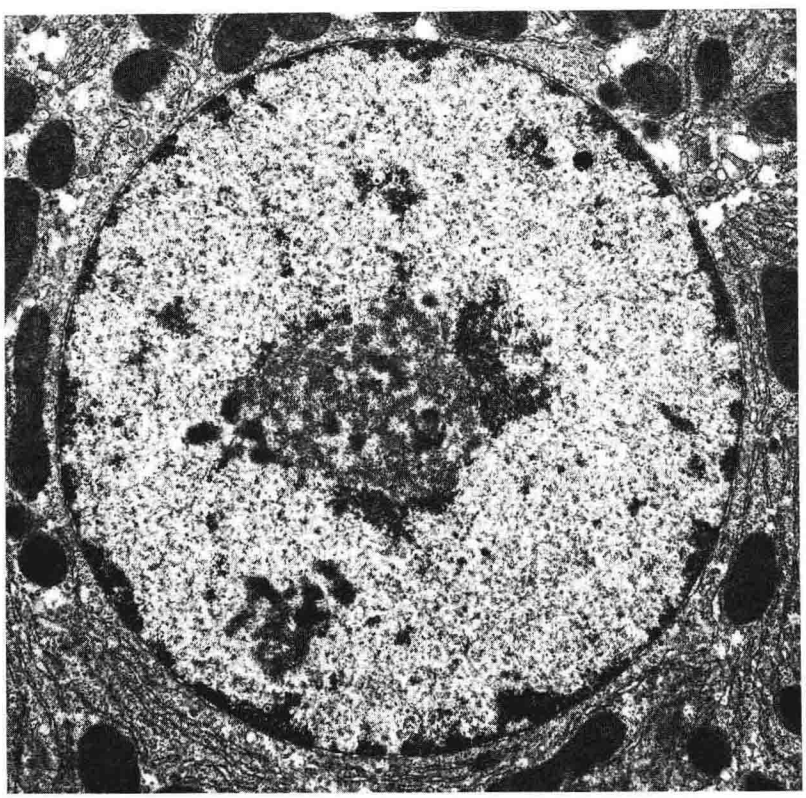

Fig. 1-5. Nucleus. Nuclear chromatin contains a few aggregates of heterochromatin around the inner nuclear membrane; most of the nucleolus is composed of euchromatin. Nucleolus is visible in center of nucleus. (11,000×.)