VOLUME ONE

ANDERSON'S PATHOLOGY

Edited by

JOHN M. KISSANE, M.D.

W.A.D. ANDERSON,

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Preface to eighth edition

Readers and followers of this book will have noticed that this is the first edition in which Dr. W.A.D. Anderson ("Wad" to his innumerable friends) has not actively participated. He remains vigorous and active, however, and has offered welcome encouragement and advice. We all wish him well.

Since the preparation of the seventh edition, spectacular advances have occurred in the basic sciences and in clinical medicine, on which pathology depends and to which it contributes. Advances in immunopathology and hematopathology, to mention only two general areas, and in diseases of the breast and of somatic soft tissues, to mention only two organ systems, have compelled revision of the text.

My first responsibility as editor was to examine the organization of the book to see if major structural revision was in order. I have retained the initial presentation of mechanisms both as a didactically effective transition between the basic sciences and pathology and as a review for readers whose exposure to the basic sciences has not been recent. This section of the book is followed by considerations of diseases of the various organ systems. The emphasis throughout is on the mechanisms whereby normal phenomena and processes become disturbed, giving rise to diseases and lesions.

The seventh edition introduced a chapter on geographic pathology. Even by that time, however, the Jet Age had made geographic pathology an authentic subspecialty with a language and information base of its own. It deserves separate consideration without the duplication of language and concepts that its introduction in a primary pathology text would impose. Thus, with some regret, I decided to remove the chapter on geographic pathology and rely on contributors of organ-system chapters to include geographic factors in their discussions of the epidemiology of various disorders. This effort I believe has been effectively addressed in this edition.

I chose also not to include a separate chapter on venereal diseases. Such a chapter has, over several decades, come to include sociologic and public health considerations that transcend the mechanisms and morphologic expressions of the venereal diseases. These aspects are more appropriately dealt with in works directed to public health or preventive medicine than in a work on pathology. In this edition venereally transmitted diseases are considered along with other agent-mediated diseases.

In the preparation of this edition I have been fortunate in being able to recruit several new contributors. I welcome their contributions and at the same time express my appreciation to previous contributors.

Finally, I would like to express my gratitude to the generation of supporters of *Anderson's Pathology*. I hope the eighth edition continues to merit their support.

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 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

Color Plates

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CHAPTER 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 locus at which disease was initiated.[25] 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,[31] and many contemporary investigators have found that the various subcellular organelles, and the biochemical reactions that go on within and around them, are sites 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 acquisition 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, which is 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 mechanisms by which a critical subcellular lesion leads to a cascade of abnormal reactions in different cells and tissues, ultimately expressed at the organismic level as disease, are the essence of modern pathology.

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 a cell that has been killed in action and embalmed. Because cells are killed at moments when they are occupied with different functions, static structural views vary. Only by sampling and fixing cells according to a precise schedule and by correlating 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 membranes and 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.[40] The morphologic pattern usually seen, termed the *unit membrane*, consists of two electron-dense lines, each 2 to 3 nanometers (nm) thick, separated by an electron-lucent line 3 to 4 nm thick. 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 suggest that true layers do not exist, but rather that

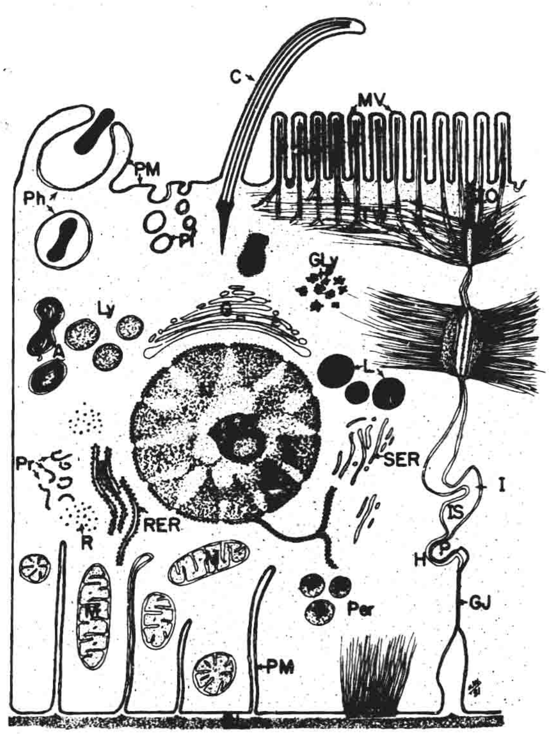

Fig. 1-1. Schematic representation of substructures of generalized mammalian cell. Plasma membrane, *PM*, and its modifications: *BL*, basal lamina; *C*, cilia; *GJ*, gap junction; *H*, hole; *HD*, hemidesmosome; *I*, interdigitation; *IS*, intercellular space; *MA*, macula adherens (desmosome); *Mv*, 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; *Nu*, nucleolus; *Per*, peroxisome; *Pr*, polyribosomes; *R*, ribosome; *RER*, rough endoplasmic reticulum; *SER*, smooth endoplasmic reticulum; *TW*, terminal web and its microfilaments.

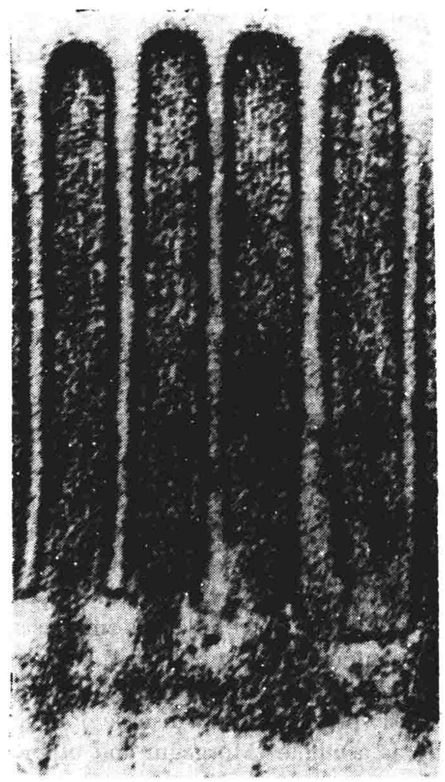

Fig. 1-2. Microvilli on cell surface. Outer membrane of all microvilli, seen in longitudinal section, is covered with fine filamentous material (glycocalyx). Core of individual microvilli consists of microfilaments that interweave with those of the terminal web at their base. (88,000×.)

certain membranes may be composed of globular units. Ultramicroscopic examination of surface replicas prepared from membranes split through their core also shows tiny, membrane-associated particles whose distribution varies in different cells. These intermembranous particles are laterally mobile within the plane of the membrane and can be caused to aggregate by environmental manipulation. Some particles 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. Membrane-associated particles have been related to receptors for phytohemagglutinin and influenza virus, to ABO blood group antigens, to sites of oxidative phosphorylation, and to sites of active transport. The outer surface of the cell membrane contains a partial coating of mucopolysaccharides, such as sialic acid.[17] Properly fixed, this surface coat appears on some types of cells as a fuzzy layer, termed the *glycocalyx* (Figs. 1-2 and 1-3). Membrane proteins and glycoproteins are responsible for antigenic characteristics of intact cells, including blood group determinants.

The precise 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, and electrical conductivity. 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 penetrate the bilayer (to explain permeability) and that the hydrophilic surfaces are 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

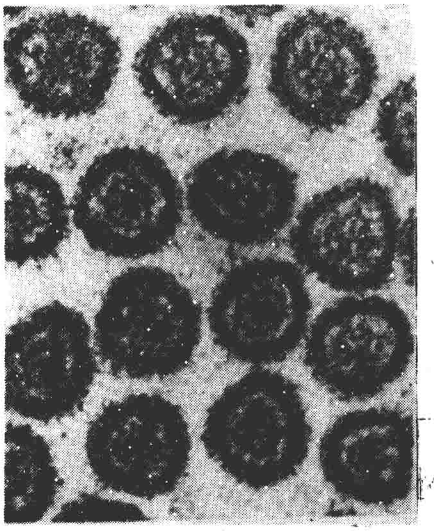

Fig. 1-3. Cross section of microvilli showing glycocalyx on outer surface of their surface membranes and central filamentous cores. (145,000×.)

of lipid either in the liquid-crystalline state or in the form of micelles in which globular proteins are partly or completely embedded. The fluid lipid-protein mosaic model is consistent with most current data. Such a model accounts for major properties of cell membranes, including fluidity, structural and functional asymmetry, and the inclusion of specialized molecular components that function as receptors.

A major structural feature of the plasma membrane, which accounts for many of its functional properties, is the presence of receptors and of markers that are not yet known to have a receptor function. Receptors, which may be composed of proteins, carbohydrates, or lipids, may be broadly defined as a class of molecules that are able to form high-affinity complexes with complementary molecules (ligands). The macromolecular combination of a ligand and a receptor causes a chemical or physical response in the cell, resulting in a functional change. Receptors exist in great variety and may participate in enzyme reactions, active transport of metabolites, and recognition and communication phenomena. Membrane receptors that have been well defined include those for peptide hormones, bacterial products, viruses, lectins, and immunoglobulins. Receptors for polypeptides are of two major types: those that lead to a change in metabolism when occupied by a ligand without requiring internalization of the ligand-receptor complex and those in which internalization of the receptor-ligand complex is required for a physiologic response. A large number of enzymes are also located within membranes, where they are important in determining that biochemical reactions occur in spatially appropriate parts of the cell.

On many cells the surface area of the plasma membrane is increased by folds or projections. *Microvilli* are cylindrical protrusions of membrane 1 μm long by 0.1 μm wide, surrounding a cytoplasmic core containing a bundle of microfilaments (Figs. 1-2 and 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 the movement of large amounts of water 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 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 has a highly organized structure, which we are unable to observe in detail with currently available techniques. The cytoskeleton (discussed later in the chapter) appears to be the major determinant of the spatial organization of the cytosol and the organelles it contains.

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.[37] Typical mitochondria (Fig. 1-4) are 0.5 to 1 μm in diameter and 3 to 5 μm in length. A cell may contain from a few score to more than 1000 mitochondria. They are enveloped by a smooth outer membrane and contain a variably folded inner membrane.[24] 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. 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. All of the lipid is in the membrane. The outer membrane closely resembles other cytomembranes, both chemically and structurally. The inner membrane is unusual in that it contains no cholesterol and a large amount of acidic phos-

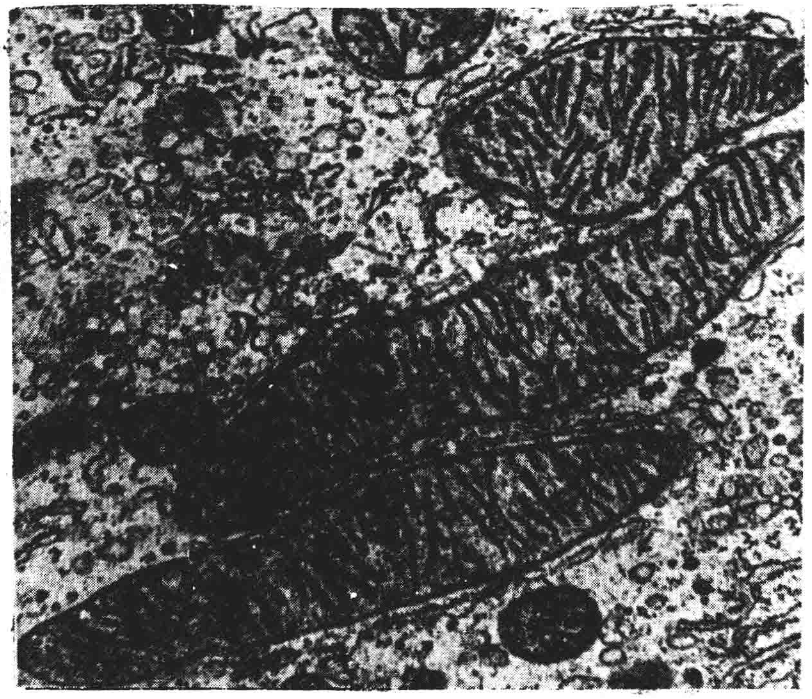

Fig. 1-4. Mitochondria sectioned both longitudinally and across. (25,000×.)

pholipid, a condition reminiscent of bacterial membranes. Both membranes are ultrastructurally trilaminar in sections, but the inner membrane shows a prominent globular substructure when negatively stained. Within the inner membranes are cylindric globular subunits about 6 by 10 nm. Apparently attached to the membrane are other globular subunits, which are shaped like "lollipops" and project into the matrix. These structures consist of a stalk, which measures about 4 nm long by about 2 to 3 nm wide, and a "headpiece" at the end of the stalk, which measures 7 to 10 nm in diameter. These globular structures and the adjacent particles in the inner membrane are the locus of the components of the electron-transfer chain. The "lollipops" are thought to contain adenosine triphosphatase, and other components of the respiratory assemblies (succinic dehydrogenase and the cytochromes of the respiratory chain) are embedded in the inner membrane. Other enzymes found in mitochondria include those belonging to the Krebs cycle and enzymes of fatty acid oxidation. The matrix often contains a variety of fibrillar or particulate inclusions, including fibrils of deoxyribonucleic acid (DNA), ribosomes, calcium-containing crystals, and glycogen.

Although this morphologic description delineates a static structural configuration, in vitro studies of isolated organelles suggest that in metabolically active mitochondria the configurations of internal membranes and spaces shift dramatically. The orthodox configuration, typically seen in fixed cells, is characteristic of the nonenergized state in vitro, when the rate of dissipation of high-energy intermediates exceeds their production. In the energized state, when production of high-energy intermediates exceeds their dissipation, the matrix space swells. Configurational changes in energized and nonenergized mitochondria predominantly involve relative shifts in the volumes of matrix and peripheral spaces, with little net change in total mitochondrial volume. The outer membrane is relatively inelastic, and when it breaks, the matrix space may balloon greatly; this event, termed *high-amplitude swelling*, heralds the complete deterioration of integrated mitochondrial function.

Mitochondria are self-replicating organelles that contain their own structurally distinct genetic apparatus. Mitochondrial DNA forms closed circles and lacks histones; mitochondrial ribosomes are smaller than are cytoplasmic ribosomes. The mitochondrial genome appears to direct the synthesis of membrane-bound proteins of this organelle, whereas soluble proteins and lipids are synthesized in the surrounding cytoplasm.

Nucleus

The nuclear contents are enclosed in an envelope composed of two layers of unit membrane (Fig. 1-5) separated by a 20 to 70 nm wide space continuous with the interstices of the endoplasmic reticulum.[21] The outer leaf of the nuclear membrane is studded with ribosomes. At many points the outer and inner unit membranes of the nuclear envelope are fused into a thin diaphragm

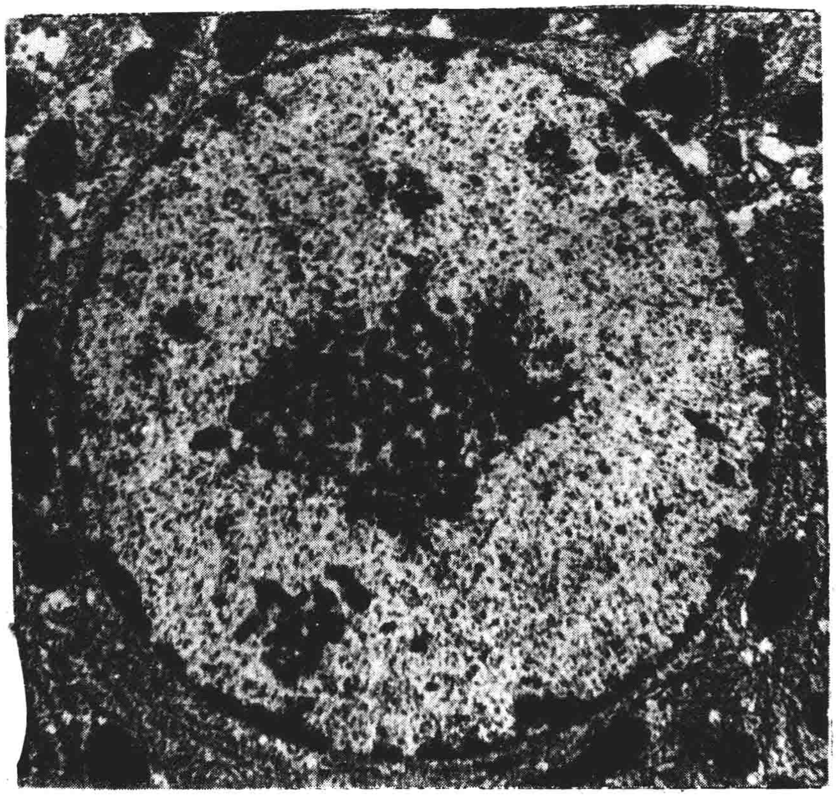

Fig. 1-5. Nucleus. Nuclear chromatin contains a few aggregates of heterochromatin around inner nuclear membrane; most of nucleolus is composed of euchromatin. Nucleolus is visible in center of nucleus. (11,000×.)

over an area about 50 to 80 nm in diameter. These foci, called *nuclear pores*, are distributed more or less uniformly over the nuclear surface (Figs. 1-6 and 1-7). When sectioned tangentially, they appear to contain a central dense granule and tiny filaments (Fig. 1-8). Surface views of freeze-cleaved specimens suggest that an octagonal thickening about 100 nm across, called the *annulus*, surrounds each pore. Pores always occur over areas of euchromatin (see the following paragraph) and are believed to represent the pathway by which ribosomes are transported from the nucleus.

Except for mitochondria, nuclei contain all of the DNA in mammalian cells. Diploid human nuclei each contain about 6 picograms (pg) of DNA, 1 to 3 pg of RNA, and 30 to 35 pg of protein. Nuclear proteins include several varieties of basic proteins (histones), which have an important role in chromatin structure, and a large group of neutral and acidic proteins.[19] At distances of about 200 base pairs, DNA in both euchromatin and heterochromatin is associated with histone proteins to form 10 nm nucleosomes.[9] Most of the associated DNA is wound over the surface of the nucleosome, with a smaller piece separating adjacent nucleosomes. Nucleosomes are arrayed along DNA strands like beads on a string. Included among the neutral and acidic proteins are the several forms of RNA and DNA polymerases and other enzymes involved in the synthesis and processing of RNA and DNA. In addition, histones and acidic nuclear proteins may have a mutually important role in the regulation of gene expression. The diploid mammalian nucleus of 6 to 8 μm contains coiled fibers of DNA complexed to protein *(chromatin)*, which if fully extended would measure more than 1 m in length. Interphase chromosomes are composed of tangled webs of extended, relatively uncoiled fibers *(euchromatin)*, interspersed with areas in which fibers are highly coiled *(heterochromatin)*. Extended strands of DNA in euchromatin are available for transcription of messenger RNA, whereas heterochromatin is believed to be transcriptionally inactive.[9] One of the X chromosomes in female cells is visible in most somatic cells as a highly condensed mass of heterochromatic DNA lying next to the nuclear membrane *(Barr body)*. The ultramicroscopic appearance of the chromatin in sectioned nuclei is disappointingly uninformative. Except that heterochromatin is more electron dense than is euchromatin, little detail can be discerned other than profiles of fibers varying in diameter from 2 to 10 nm.

Coordinated with the onset of mitosis, the chromatin strands of individual chromosomes undergo supercoiling

Fig. 1-6. Replica of nucleus showing its surface and nuclear pores. (8700×.)

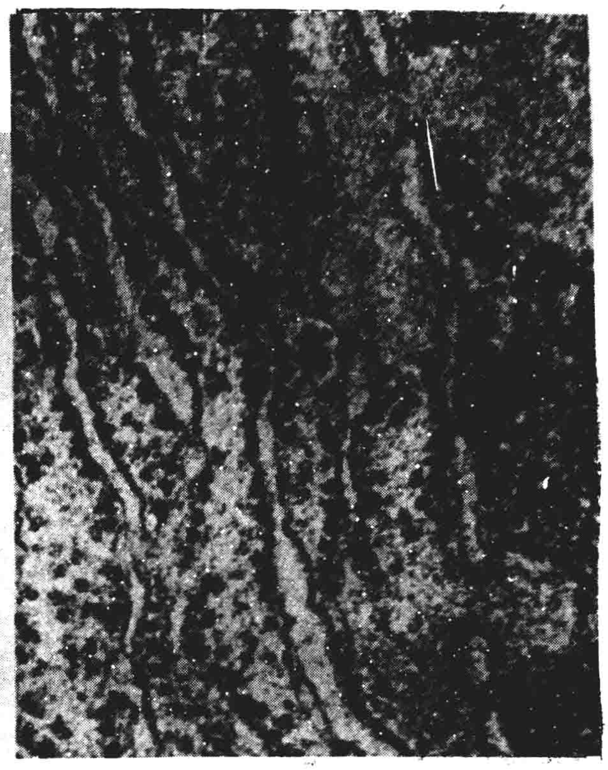

Fig. 1-7. Two nuclear pores are seen in envelope of portion of nucleus occupying lower part of this figure. Nuclear chromatin at pores is euchromatic. Rough endoplasmic reticulum and outer nuclear membrane are continuous. (144,000×.)

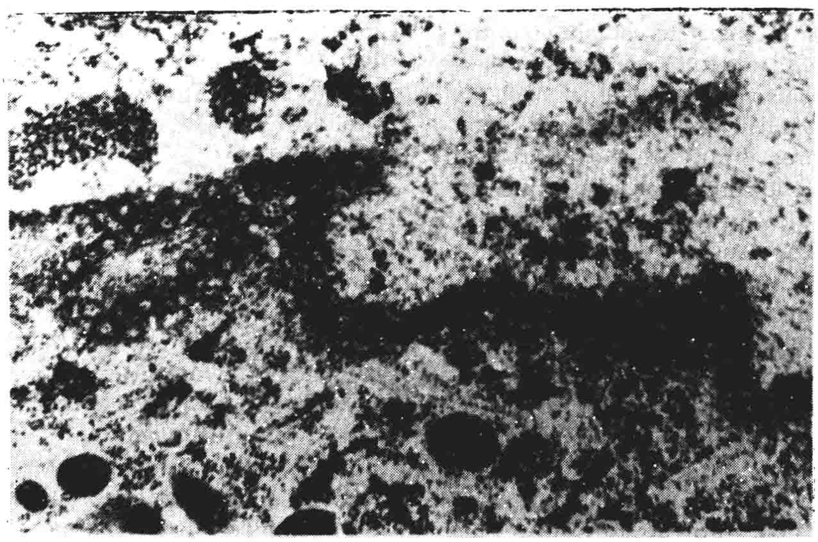

Fig. 1-8. Tangential section through nuclear envelope showing transected nuclear pores. (30,000×; courtesy W. Hanton and D.W. Misch, Chapel Hill, N.C.)