SYNOPSIS OF PATHOLOGY

NINTH EDITION

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Preface

Much of the text in this edition of *Synopsis of Pathology* has been revised, and several sections have been rewritten in order to improve it or to add new information. A new chapter has been included that reviews certain features of immunology and immunopathology, such as types and characteristics of immune responses, role of the thymus and cellular interactions in these responses, immunologic deficiencies, hypersensitivity reactions, autoimmunity, immunologic aspects of tumors, transplantation rejection reactions, and association of the HL-A histocompatibility antigens with various diseases. Throughout the text, many of the recent advances in the medical sciences have been incorporated along with older but equally important fundamental information.

We have adhered to our original purpose of presenting a concise but comprehensive view of pathology in a compact and condensed volume. This is not a reference work or a large, complete textbook, but neither is it an elementary manual. It has been, and we hope it will continue to be, useful to students during their formal courses in pathology and in correlation with their clinical studies, as well as to resident physicians, clinicians, and others in the medical and paramedical fields who must have an understanding of disease processes.

We are grateful to students, colleagues, and others for helpful comments and criticisms, to Mrs. Louise Rhodes for assistance in the preparation of the manuscript, and to our publishers for continued interest in this work, encouragement, and pertinent suggestions.

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Pathology is that branch of natural science which treats of the causes and nature of disease, together with the anatomical and functional changes incident thereto; the practice of human pathology is that specialty in the practice of medicine which may contribute to the diagnosis, treatment, observation and understanding of the progress of disease or medical condition in the human subject by means of information obtained by morphologic, microscopic, chemical, microbiologic, serologic or any other type of laboratory examination made on the patient or on any material obtained from the human body.

Approved definition of the College of American Pathologists

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CHAPTER 1

Cell injury and genetic disorders

The basic concepts concerning cells are as follows:

1 Cells are the fundamental morphologic and functional units of the body.
2 All tissues are composed of cells and products of cells.
3 All cells are derived from preexisting cells—i.e., *omnis cellula e cellula* (aphorism of Rudolph Virchow, 1859).

Developments in cell biology have advanced at a rapid rate in recent years, largely because of the progress that has been made in instrumental analysis (including electron microscopy and x-ray diffraction techniques) and the integration of cytology with other fields of biologic research (e.g., genetics, physiology, and biochemistry). As a result, new fields of study have come into being: *submicroscopic morphology* (ultrastructure), *molecular biology, cytogenetics, cell physiology,* and *cytochemistry.*

STRUCTURE AND FUNCTION OF CELLS

Cells vary in size and shape, but they have a number of characteristics in common (Fig. 1-1). Each cell consists of a mass of *cytoplasm* and a *nucleus.* Surrounding the cell is a very thin *plasma membrane (plasmalemma),* composed chiefly of lipids and protein, through which the exchange of materials takes place between the cell and its environment. The limiting membrane may be simple and smooth, or it may be a complex structure adapted to special functions of cells. For example, the numerous minute folds (microvilli) in the plasma membrane of epithelial cells in the intestine, renal tubules, and bile canaliculi increase the effective absorptive or secretory surface. Permeability of the cell membrane, one of its major functions, includes not only the process of diffusion or "passive transport" (in relation to water and certain solutes) but also the mechanism of "active transport" (as in the exchange of ions), which involves energy originating in the cell's own metabolism. Some substances are brought into the cell by *pinocytosis* (Gr. *pinein,* to drink). In this process, the plasma membrane encircles fluid droplets in the environment (e.g., solutions of protein, glucose, hormones). It then invaginates into the cell and becomes pinched

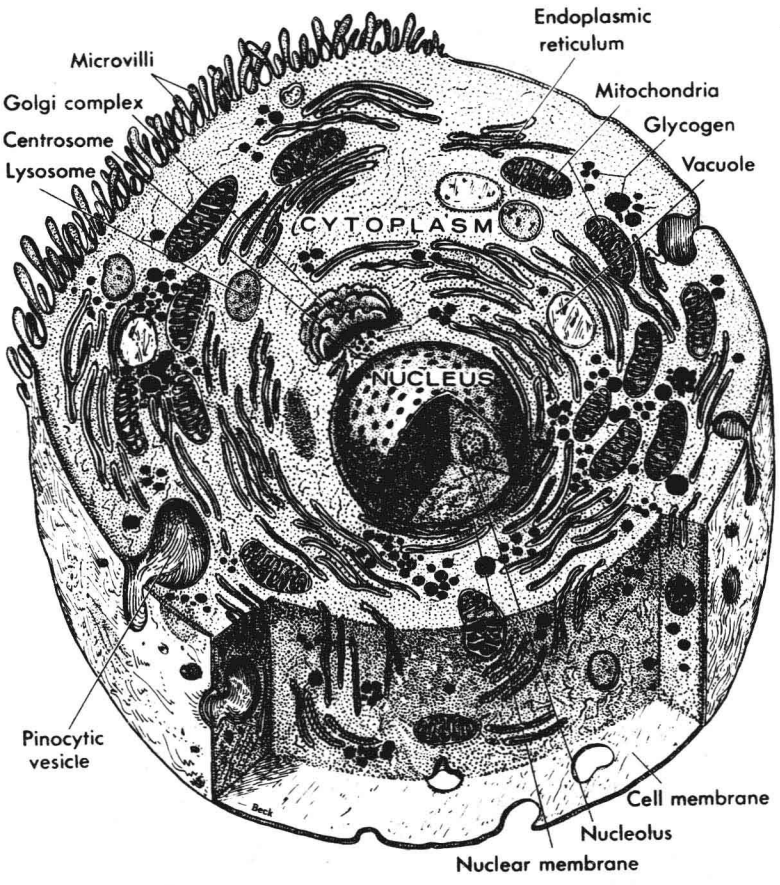

Fig. 1-1 Diagram of a typical cell based on electron microscopic appearances. (From Anthony, C. P., and Kolthoff, N. J.: Textbook of anatomy and physiology, ed. 9, St. Louis, 1975, The C. V. Mosby Co.)

off, so that the fluids can be incorporated into the cytoplasm. For the induction of pinocytosis, certain substances other than water must be present in the environment—viz., certain amino acids, proteins, and salts. Carbohydrates and nucleic acid do not induce the process. Pinocytosis is somewhat like *phagocytosis* (Gr. *phagein,* to eat), a process whereby solid particles are ingested by a cell (p. 87).

There exists on the external surface of the plasma membrane of almost all cells a thin layer of carbohydrate-rich material ("surface coat," "cell coat," or "glycocalyx") that probably is derived from the cell it coats. This surface material may have immunologic or filtration properties or may help in the maintenance of the microenvironment of the cell. It is not known to what extent it acts as an "intercellular cement," although it has been suggested that it may play some role in maintaining cohesion of cells in tissues. Certain structural modifications appear in plasma membranes, particularly in epithelial cells, which apparently serve to hold cells together. On the lateral surfaces of some cells, there are membranous folds that permit interdigitation of adjacent cells. Specialized areas or zones, referred to as *junctional complexes,* are present along lateral cellular surfaces in many types of epithelium, appearing usually in the following order in an apical-basal direction: *tight junction (zonula occludens), intermediate junction (zonula adherens),* and *desmosome (macula adherens).* At the *tight junction* the membranes of adjacent cells are closely apposed and possibly fused along their outer aspects, so that the intercellular space is obliterated. At the *intermediate junction* there is a distinct intercellular space, and the cytoplasm adjacent to the inner layer of the cell membrane contains a dense accumulation of filaments arranged parallel to this zone. At the *desmosome,* characterized as a plaquelike or buttonlike area, there is also an intercellular space, but this space contains an electron dense material. In this area the cell membrane appears thickened as fine cytoplasmic filaments *(tonofilaments)* converge on the cell membrane.

The plasma membrane connects with a membranous cytoplasmic network of tubules and vesicles, the *endoplasmic reticulum,* that courses throughout the cytoplasm to the nuclear membrane. Some of the cytoplasmic membranes are rough or granular *(ergastoplasm)* because of the attachment of dense granules to their outer surface. These granules, known as *ribosomes,* are present also in the cytoplasmic matrix outside the membrane system. They are composed of protein and ribonucleic acid (RNA) and serve as the centers for the synthesis of proteins (including enzymes, the accelerators of chemical reactions within the cell). The cytoplasmic ribosomes tend to form aggregates, referred to as *polyribosomes* or simply *polysomes.* The ribosomes are responsible for the basophilic properties of cytoplasm.

The rest of the endoplasmic reticulum is of the smooth-surfaced variety without a granular component.

The *Golgi apparatus (complex)* is generally considered to be a part of the agranular endoplasmic reticulum, although some investigators regard it as a separate membranous structure. It apparently is involved in the secretory activities of a cell, probably serving as a site where the products of secretion elaborated elsewhere in the cell are concentrated into granules or droplets prior to their liberation from the cell. The Golgi apparatus in developing spermatids participates in the formation of the *acrosome.*

Lysosomes are intracytoplasmic dense particles or vesicles, each surrounded by a single membrane, that contain hydrolytic enzymes and have a high content of acid phosphatase. There is a close relationship between the lysosomes and the Golgi complex. It is believed that the hydrolytic enzymes of the lysosomes influence phagocytosis and pinocytosis and that they assist in the digestion of parts of a living cell's own cytoplasm (cellular autophagy) or in digestion of the cell after its death (autolysis). It is possible that cells may release lysosomal enzymes to produce lytic effects upon surrounding structures, as in the removal of bone by osteoclasts. Membrane-bound *peroxisomes* or *microbodies,* which are observed in renal and hepatic cells and contain catalase, bear some similarity to lysosomes.

Autophagic vacuoles (cytolysomes or *cytosegresomes)* are membrane-lined vacuoles containing recognizable cytoplasmic components or organelles in various stages of degradation. These vacuoles are formed during the process of *cellular autophagy,* a type of intracellular digestion sometimes referred to as "focal autolysis." In this process a focus of cytoplasmic degradation, which occurs during the normal course of organelle turnover or as a result of cellular injury, is enveloped by a membrane probably derived from the endoplasmic reticulum. The resulting autophagic vacuole fuses with a lysosome, permitting digestion of the segregated cytoplasmic material by lysosomal enzymes. Cytoplasmic fragments that are incompletely digested remain as membrane-enveloped debris, known as *residual bodies.* The latter may fuse with the plasma membrane and be discharged from the cell, a process that is essentially the reverse of pinocytosis or phagocytosis, i.e., *exocytosis.*

Mitochondria are granular, rodlike, or filamentous cytoplasmic organelles. Each mitochondrion is limited by a double (outer

and inner) membrane. The inner membrane forms a series of complex infoldings (crests or cristae) that project into the mitochondrial cavity and are responsible for the characteristic striated appearance of the organelles. The inner cavity contains a granular matrix. The mitochondria are the main "power plants" of the cell that supply the energy for its metabolic functions, the generation of energy being provided by the various intramitochondrial enzyme systems. The mitochondria are one of the major sources of adenosine triphosphate (ATP) in the cell. The mitochondrial membrane seems to be selectively permeable, so that the mitochondria swell or shrink as a result of chemical or osmotic changes in the cytoplasmic medium.

The *centrosome,* within which are two small granules called the *centrioles,* usually occupies the geometric center of the cell near the nucleus and is in close relationship to the Golgi complex. During cell division, two pairs of centrioles and surrounding astral rays appear. The pairs separate and become situated at the poles of the mitotic spindle. After mitosis, each daughter cell receives two centrioles.

The *cytoplasmic matrix,* in which are embedded the various organelles previously mentioned, is a clear homogeneous substance with colloidal properties, such as those related to sol-gel transformations, viscosity changes, ameboid movements, spindle formation, and cell cleavage. In certain specialized cells, the cytoplasmic matrix is the site of differentiation of fibrillar structures (e.g., keratin fibers, myofibrils, and neurotubules). Much of the cytoplasmic matrix consists of water that contains electrolytes, soluble proteins and enzymes, lipids, carbohydrates, and soluble (transfer) RNA. Visible particles in the cytoplasm, other than the organelles, are called *inclusions* and comprise such structures as secretion granules, stored substances (lipids, glycogen), and various pigments.

The *nucleus* is the most conspicuous structure in a cell. It is present in all cells, although it disappears in the late stages of development of the human erythrocyte. Its size and shape varies in different cells. Generally, it is spherical or ovoid, but it may be indented or lobulated. Usually, a single nucleus is present, but a few cells are binucleated (e.g., some plasma cells) or multinucleated (e.g., osteoclasts). The position of the nucleus in the cell is variable, being centrally or eccentrically located. As a rule, its position is constant for a given type of cell.

The nucleus serves as the control and regulating center of

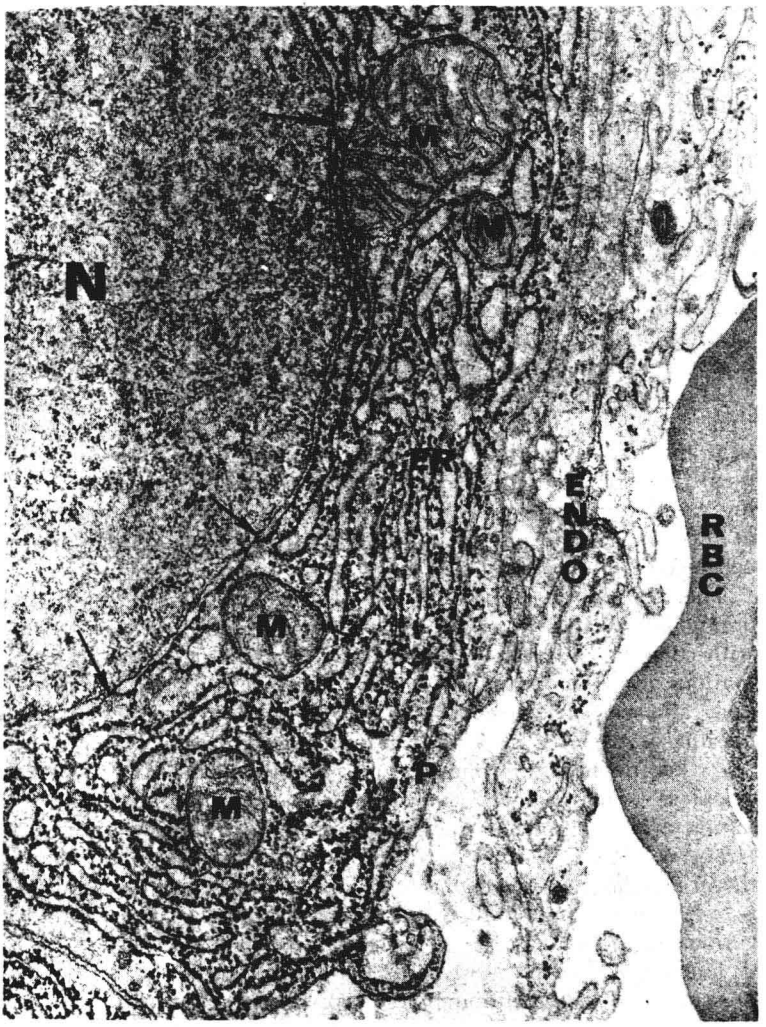

Fig. 1-2 Electron micrograph of pancreatic acinar cell showing nucleus, cytoplasmic organelles, and adjacent capillary. Nucleus, **N,** is surrounded by double-layered nuclear membrane with pores (arrows). Endoplasmic reticulum, **ER,** is of rough type (with attachment of ribosomes). Mitochondria, **M,** vary in size and show characteristic internal membranes (**cristae**). Next to edge of cell, **P,** are capillary endothelium, **ENDO,** and red blood cell, **RBC,** in capillary lumen (×52,500; courtesy Dr. D. R. Anderson.)

most of the cell's activities and plays a fundamental role in cell division and heredity. The nucleus of a living cell is not clearly visible microscopically unless phase contrast microscopy is used, by which technique only the nuclear membrane and one or two nucleoli are observed in the interphase (nondividing) stage. The details of nuclear structure are best seen in fixed cells by means of routine staining procedures, by histochemical techniques, and especially by electron microscopy (Fig. 1-2). The basic constituents are a *nuclear membrane,* filaments and granules of *chromatin* (considered to be the interphase form of chromosomes), one or more *nucleoli,* and the *nucleoplasm,* or *nuclear sap.* The latter, like the cytoplasm, is of a colloidal nature, being composed of water, electrolytes, protein (including enzymes), lipids, and carbohydrates. The most important chemical constituent in the nucleus is nucleic acid, of which there are two types: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is the more abundant, being present mainly in the chromatin. RNA is concentrated mostly in the nucleolus in the form of loosely bound, ribosome-like granules and also is found in small amounts in the chromatin. DNA, the essential component of genetic material, controls or directs protein synthesis within a cell, whereas RNA is concerned with the actual synthesis of protein.

In a high percentage of cells in females, a prominent mass of chromatin is found next to the nuclear membrane in interphase nuclei. This structure, known as the *sex chromatin* or *Barr body,* is present in persons with two or more X chromosomes. In fact, more than one Barr body may be present (the number of bodies is usually one less than the number of X chromosomes). By electron microscopy, the *nuclear membrane* is seen to consist of two porous layers with a clear space between them. There appears to be a direct connection between the outer layer of the membrane and the endoplasmic reticulum. It is possible, therefore, that certain substances formed in the nucleus pass into the cytoplasm by means of this communication.

CELLULAR INJURY

Various techniques of investigating cells, such as electron microscopy, ultracentrifugation, and cytochemistry, have increased our knowledge of the changes occurring in cells as a result of injury, which may be caused by many types of agents, including ischemia or hypoxia, hyperoxia, chemicals and drugs,

radiant energy, heat, cold, nutritional disturbances, bacteria and their products, immune complexes, etc. The injury may be *nonlethal,* resulting in reversible cellular changes (e.g., degenerations), or *lethal,* with the outcome being death of the cell (necrosis).

In some nonlethal injuries, the *cells may appear normal* morphologically by the existing methods of examination, as in certain biochemical disturbances or genetic mutations; or there may be only minimal ultrastructural changes, such as an *increase in the number of autophagic vacuoles,* which is evidence of accelerated focal cytoplasmic degradation. In other nonlethal injuries there may be more obvious changes that are characteristic of the reversible *retrograde cellular processes* or *degenerations,* the details of which are described in Chapter 2. Alterations in specific components (organelles) of the cell may readily be seen in the early stages of development of these pathologic processes. It is generally believed that damage begins in the endoplasmic reticulum and/or the mitochondria. Among the early ultrastructural and biochemical alterations that may occur are the following:

1 Loss of granules in the mitochondrial matrix, followed by swelling of the mitochondria and clearness of their matrix
2 Vesicular distention of the endoplasmic reticulum, which in some instances may result in formation of large cytoplasmic vesicles
3 Depletion of RNA granules with loss of cell basophilia
4 Decrease in cytoplasmic glycogen
5 Reduction of enzymes such as adenosine triphosphatase (ATP-ase) and succinodehydrogenase
6 Appearance of lipid droplets in vesicles of the endoplasmic reticulum and in the cytoplasmic matrix

As a result of the damage to the mitochondria and the endoplasmic reticulum and the subsequent changes in the enzymic reactions within them, certain functional derangements may occur in the cell, including alterations in the "active transport" mechanism and cell membrane permeability (with changes in water and electrolyte content) and disturbances in the metabolism of protein, fat, and carbohydrate. Thus may be explained, at least in part, such pathologic processes as *cellular (cloudy) swelling, hydropic degeneration, hyaline degeneration,* and *fatty metamorphosis.*

When cells in a living body are exposed to lethal injury, the

damage is such that it results in death of the cells. After cell death, certain intracellular and extracellular enzymes cause nuclear and cytoplasmic changes that are visible under the light microscope. These structural alterations, which represent the histologic criteria of the process known as *necrosis,* are evident mainly in the nucleus (i.e., pyknosis, karyorrhexis, and karyolysis), but cytoplasmic changes such as coagulation of proteins, cytolysis, and contraction of cells may be seen also. In a normal piece of tissue that has been killed instantly by immersion in a fixative, the cell structure may remain apparently unaltered because of the sudden cessation of all enzymatic activity. Necrosis, which is a form of acute death of cells, is commonly differentiated from the process *necrobiosis.* The latter refers to the slow gradual death of cells that occurs as part of the constant turnover of cells in certain tissues (e.g., skin) after the cells have passed through a period of "senescence."

In contrast to the degenerative cellular changes, from which the cells may recover, the structural alterations in cells following lethal injury are irreversible. Formerly, it was believed that rupture of lysosomes with release of their destructive enzymes was responsible for death of a cell. However, now it is apparent that the lysosomal membranes are intact at the time when irreversible changes have already occurred, but there may be some leakage of lysosomal enzymes because of increased permeability of their membranes. Rupture of lysosomes occurs late in the process of necrosis. Although recognition of necrotic cells under the light microscope is based chiefly upon the prominent nuclear changes, submicroscopic morphologic alterations may be demonstrated in cytoplasmic organelles (particularly mitochondria and ergastoplasm), even before modifications in the nucleus become evident. Actually, the ultrastructural changes in dead cells are essentially an accentuation and progression of the early manifestations of cell injury described previously and include the following:

1 Severe swelling of mitochondria, disappearance or disruption of cristae, formation of dense particles in matrix, occasionally calcium deposits
2 Vesiculation, distortion, and fragmentation of mitochondrial membranes
3 Breakdown of endoplasmic reticulum, loss and dissociation of polysomes
4 Alteration of plasma membrane and formation of multi-

laminated configurations ("whorls" or "myelin figures")
5 Distortion of microvilli, disruption of cell junctions
6 Clumping of nuclear chromatin, disruption and dissolution of nucleolus, irregularity of nuclear membrane
7 Formation of intranuclear and intracytoplasmic blebs and vacuoles
8 Many autophagic vacuoles, fusion with lysosomes, eventual disappearance (rupture) of many lysosomes
9 Rupture and contraction of cell

THE CELL IN GENETICS

Nuclear DNA is responsible for transmission of hereditary characteristics. The genetic information that is transmitted from generation to generation is coded in the DNA of the *genes,* the hereditary units of the chromosomes. The sequence of purine and pyrimidine bases in the DNA molecule forms the genetic code. Prior to cell division, DNA is able to replicate itself accurately so as to ensure the integrity of the genetic information during its transmission to future cells or generations. The DNA, through its genetic code, determines the biochemical processes of the cell by its control of protein synthesis. It dictates the specific sequence in which amino acids are incorporated into the polypeptides that combine to form structural proteins and enzymes. This information is transcribed to "messenger" RNA (formed in the nucleus upon a template or cast of DNA) and is carried by the RNA to the site of protein synthesis in the cytoplasm, the ribosomes.

The usually stable genetic and structural organization of chromosomes may be altered spontaneously, without apparent cause, or may be affected by injurious agents (e.g., ionizing radiation, chemicals, infections), resulting in two types of chromosomal changes: (1) a change at the molecular level in the genetic material, occurring at definite points in the chromosome and usually involving individual gene loci without detectable microscopic alterations of the chromosomes (so-called *point mutation,* or *gene mutation*), and (2) microscopically recognizable *chromosomal aberrations,* consisting of abnormalities of number or structure. The study of the microscopic appearance of chromosomes and their behavior during cell division is referred to as *cytogenetics.* The genetic makeup of an individual is called the *genotype,* and the expression of the genetic constitution