VOLUME ONE

Pathology

SIXTH EDITION

Edited by

W. A. D. Anderson

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Professor of Pathology and Chairman of the Department of Pathology, University of Miami School of Medicine, Miami, Fla.; Director of the Pathology Laboratories, Jackson Memorial Hospital, Miami, Fla.

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Preface

TO SIXTH EDITION

In this new edition of *Pathology,* much of the content has been modified to include new knowledge and concepts in medical sciences. Significant progress in the fields of ultrastructure, cytology, genetics, immunopathology, and biochemistry has led to a merging of the medical sciences—among themselves and with biology. The borderland of pathology has always been both varying and ill-defined, but never more so than now. Thus, the choice of inclusion or exclusion of many subjects must be somewhat arbitrary, although based on subjective judgment aimed at correlating pathology with the total field of medical education and clinical practice.

The entire book has undergone revision. The chapters on inflammation and healing, drug and chemical injury, ophthalmic pathology, upper respiratory tract and ear, lower urinary tract, prostate, and male genitalia, hemopoietic system (reticuloendothelium, spleen, lymph nodes, blood, and bone marrow), thymus, pituitary gland, thyroid gland, parathyroid glands, adrenal glands, and nervous system and skeletal muscle have been completely rewritten. In addition, major changes have been made in the discussions of hypersensitivity diseases and immunopathology, mycotic infections, viral diseases, neoplasms, and diseases of kidney, lung, liver, and pancreas.

The basic nature of disease, and of medical practice, does not change. However, the extent and depth of our knowledge and understanding and of our conceptual and practical approaches are changing rapidly and no doubt will continue to do so. In the life of a student of medicine and a physician, the study of disease must be a continuing program. In these times of core curricula in medical schools, the continuing study and correlation of basic subjects with clinical experience is a necessity. It is hoped that these volumes will continue to be useful in the study of medicine, not only during but also after formal courses, and will assist in the practice of pathology or of other disciplines of medicine.

I am grateful for the patient and helpful cooperation of the contributors to this book and am deeply appreciative of the interest and assistance of my secretaries, Miss Edna Mae Everitt and Mrs. Louise Rhodes.

W. A. D. ANDERSON

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. While presented in an order and form to serve as a textbook, yet 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

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Chapter 1

Cells and their behavior

John C. Finerty and E. V. Cowdry

CELLULAR STREAM OF LIFE

Cellular vital units in health and disease may be regarded as transitory individualizations of the stream of life, with the somatic cells as more or less temporary marginal, or peripheral, or terminal pools in this stream. They and their descendants are destined to shrivel up and die. Many germ cells, likewise, die without issue, but some of them unite with other germ cells of the opposite sex and provide continuities in the mainstreams of life. These mainstreams, we know, have been maintained without interruption for millions or billions of years.

There is segregation of some vital activities in areas of ultramicroscopic size, and there is integration of others by fluid streams. There are many rhythms, and there is replacement of molecules at the required rates. All cells not only are highly organized pools of water but also are themselves aquatic as long as they exist, living in watery environments adjusted by heterostatic mechanisms. They are more or less shielded by the homeostatically controlled bloodstream, which tends to create and maintain uniformity. In other words, water and water-borne materials make up the substance of all cells, of their intimate tissue fluid environments, and of the bloodstreams that bathe these environments by percolating through endothelial walls.

KINDS OF CELL LIVES

There are two great classes of cells—the intermitotic and the postmitotic, each divisible into two subclasses, making four kinds in all.

Intermitotics. Intermitotic cells exist as individuals only from the mitosis that gives them birth until the next following mitosis, when each divides and forms two other individual cells. Their intermitotic lives do not end in death but in cessation of individuality.

Some intermitotics are, throughout long years, the reservoirs within the body of new cellular life. These are the *vegetative intermitotics:* basal cells of epidermis, primordial blood cells, spermatogonia, etc. Some of their daughter cells remain in the same place and repeat in their persons the same vegetative kind of life.

Other daughter cells are edged a little away from their birthplaces in the tissue fluid and are subjected to slightly different environmental conditions so that their lives are altered. These, in turn, are the *differentiating intermitotics*—e.g., spinous cells of epidermis, myeloblasts, erythroblasts, and spermatocytes. When these divide, their daughter cells proceed from about that state of differentiation which their parents attained, and they pass on to their own descendants the still higher stage of differentiation that they, themselves, achieve.

Postmitotics. In contrast to the intermitotic cells, the second class of cells age and die. Their lives are ordinarily postmitotic, not intermitotic. They are highly specialized cells, completely fitted by one or more generations of differentiating intermitotic ancestors to serve in many capacities—e.g., secretion, conduction, or phagocytosis.

However, some of these cells can, if the demand is urgent because of loss of others like them, revert to a condition in which they do divide. Those possessing this property are called *reverting postmitotics*—e.g., hepatic cells.

Nerve cells (in children after about 2 years of age), neutrophilic leukocytes, corneal cells of the epidermis, and a host of others cannot revert to a state capable of mitosis and are, therefore, known as *fixed postmitotics.* Inevitably, these cells age and die, but at different rates. Their lives are terminal. We look to all others, but not to fixed postmitotics, as possible sources of cancer.

DIFFERENTIATION AND DEDIFFERENTIATION

Facts about race, age, and environment of people of standardized populations are required in order to assess various aspects of cancer and other diseases; so it is with cells. The behavior of cells of exactly the same kind, of approximately the same age, and in the same fluid environment must be compared under different conditions. It is not easy to sort out particular types of cells from the special and organized mixtures of cells making up our tissues. This is why red blood cells are selected for so many chemical studies. A large step in this direction was taken when methods were discovered by which epidermis could be separated from dermis in a condition suitable for chemical analysis. It remains a handicap that even within epidermis, as well as some other epithelia, there are cells of the four different kinds mentioned. Consequently, the results of chemical analysis could be influenced by shifts in their relative numbers and may not sharply indicate alterations in many of the four kinds. Hepatic parenchymatous cells are favorite subjects for chemical analysis because the other kinds of cells mixed with them are very few in number.

By differentiation is meant that the cell within its individual life (or intermitotic cells in series) becomes—by accumulation or in some other way—different in respect to microscopically visible or physiologically measurable attributes. Aging in all living organisms can best be defined, in our ignorance of what actually happens, as progressive change with the passage of time. It is not always the same as differentiation since, in the downswing of cell lives and of their lives in series, there is a decrease or loss in some attributes. A half-dead corneal cell of epidermis is, in fact, a simpler structure than it was earlier in its life when it was called a spinous cell.

A cancer cell is said to have undergone dedifferentiation.[7] In some respects, it seems more youthful than was its immediate, normal ancestral cell. Viewed microscopically, it is usually a thin slice of a cell killed in action. Exactly what its previous life was and what its life would have been had it not been killed are conjectural. Although it has lost some specialized activities in the malignant transformation, it has nevertheless acquired others. It has become invasive and more adept in protein synthesis. It has specialized in new directions. Cells become differentiated (or specialized or proficient) in specific ways: differentiated by accumulating hemoglobin, by forming cilia, etc.

In ascertaining whether dedifferentiation has taken place in a particular specimen, it must be clear whether the frame of reference is within the life of a tissue made up of many kinds of cells or within the lives of the individual cells observed. There is dedifferentiation involving the loss of cilia in nasal epithelium in the process of wound healing. Areas of epithelium look younger and therefore seem to dedifferentiate because so many cells lose their cilia. It is not always evident whether these are the same cells that would later have survived had the tissue not been killed in the process of observation. But they are so numerous and so conspicuously give character to the tissue that one is justified in accepting this as a case of dedifferentiation of tissue.

Again, dedifferentiation is commonly said to take place in the malignant transformation of previously normal cells. This is on a different basis, for there is good evidence that this is a mutation that usually takes place in only one of a very small number of individuals of the population subjected to a mutagen (which could be a chemical or physical carcinogen, a carcinogenic virus, or a nonspecific condition of stress). It is difficult to exclude the possibility that this transformation may take place not in the structurally differentiated cells of the tissue, which greatly predominate in numbers, but rather in some less conspicuous and not so highly differentiated cell. Vegetative and differentiating cells exist in all epithelial tissues at all times.

CELL STRUCTURE

Such remarkable progress has been made in the visualization and techniques of observing biologic material within the past decade that whole new disciplines have evolved in the area of microscopic form and function, where many had considered that the limits of our knowledge had been attained. Where students could be content with recognition of nucleus and cytoplasm and with gross observations of their form under varying conditions, now the molecular structures of DNA and RNA (ribonucleic acid) and the complexities of the cell membranes must be considered. Cellular organelles, which once were rarely seen except under special circumstances (mitochondria) and which were considered by many authorities as artifacts (Golgi apparatus or Golgi complex), now have their own minute

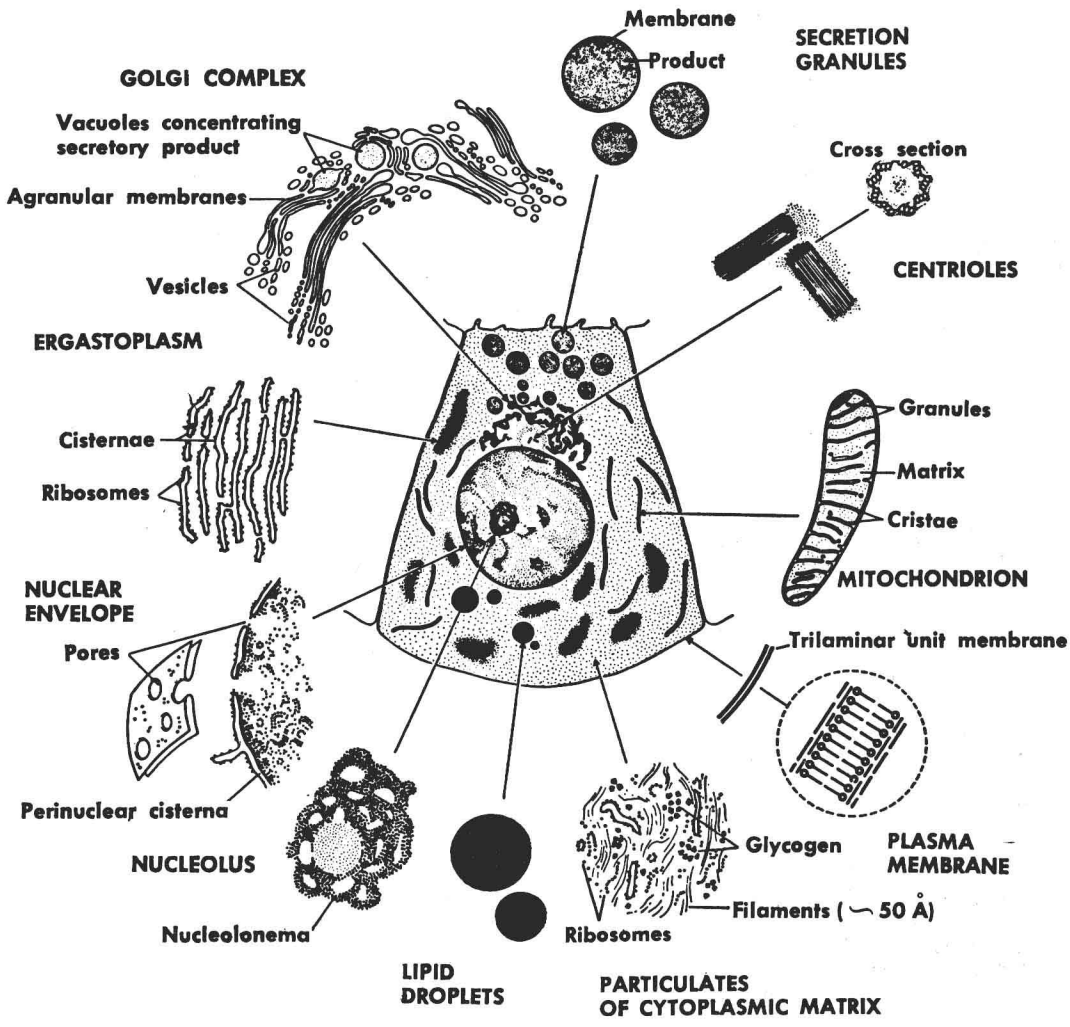

Fig. 1-1 Ultrastructure of common cell organelles and inclusions. Diagram of cell in center illustrates form of its organelles and inclusions as they appear by light microscopy. Around periphery are representations of finer structure of same components as seen by electron microscopy. As seen by light microscopy, ergastoplasm consists of aggregations of submicroscopic, membrane-limited elements with granules of ribonucleoprotein adhering to their outer surface. This component is now also called *granular endoplasmic reticulum.* Illustration of plasma membrane (encircled by broken line) does not show structure directly observed but represents one possible interpretation of arrangement of lipid and protein molecules that may be related to trilaminar appearance of cell membranes in electron micrographs. (From Bloom, W., and Fawcett, D. W.: A textbook of histology, W. B. Saunders Co.)

internal structure and are recognized as highly active centers of metabolic function.

Even though it must be understood that no generalized, typical cell exists naturally, it is helpful to diagram one for reference, as in Fig. 1-1. Most of the elements shown are present in all living animal cells in some form but are subject to great variation, depending upon the shape, functional status, and specialized type of the individual cell.

Cells have traditionally been described as consisting of a nucleus and cytoplasm. Proper functioning of a living cell, however, requires the services of many complex internal structures with which one must be familiar to understand the morphologic basis for cellular activity. Novikoff's reconstruction of a liver cell based upon electron microscopic evidence (Fig. 1-2) suggests some of the continuity between cellular components and some of the important adaptations for increased surface activity.

Contact with the environment and control of transfer of raw materials, metabolic prod-

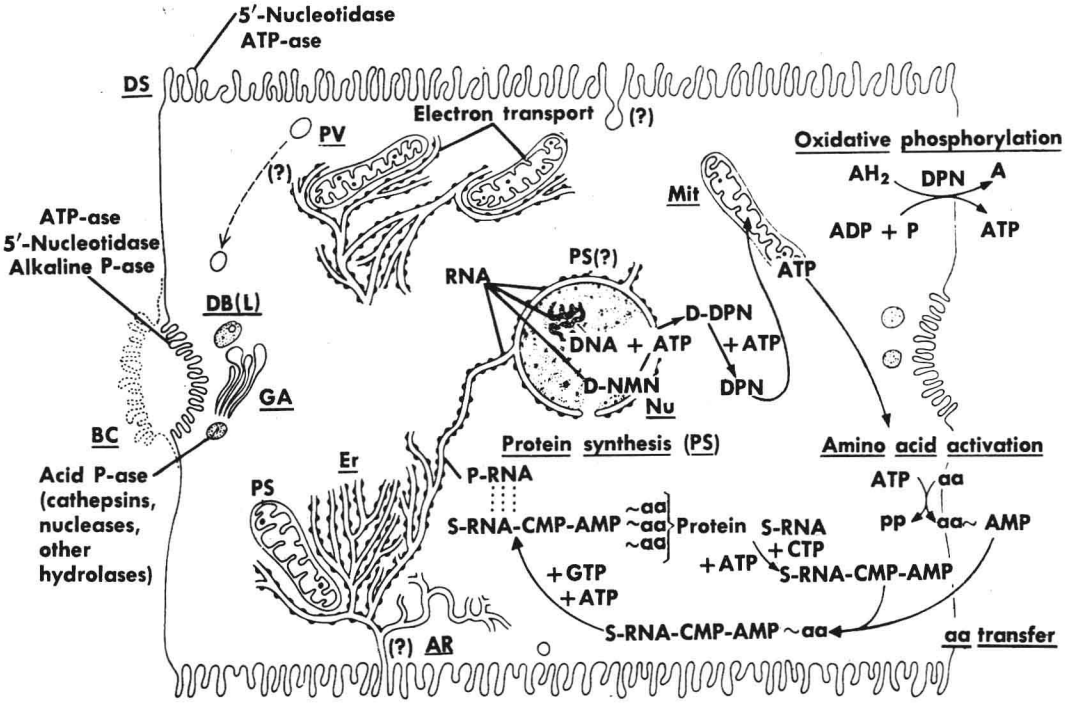

Fig. 1-2 Diagram of rat liver cell. **A,** Oxidized substrate, such as amino acid. **AH_2,** Reduced form of substrate. **ADP,** Adenosine diphosphate. **AMP,** Adenosine monophosphate. **AR,** Agranular reticulum. **ATP,** Adenosine triphosphate. **ATP-ase,** Adenosine triphosphatase. **BC,** Bile canaliculus. **CMP,** Cytosine monophosphate. **CTP,** Cytosine triphosphate. **D-DPN,** Desamide diphosphopyridine nucleotide. **DPN,** Diphosphopyridine nucleotide. **DNA,** Deoxyribonucleic acid. **D-NMN,** Desamide nicotinic acid mononucleotide. **DB,** Peribiliary dense bodies. **DS,** Perisinusoidal space of Disse. **Er,** Ergastoplasm. **GA,** Golgi apparatus (complex). **GTP,** Guanosine triphosphate. **L,** Lysosomes. **Mit,** Mitochondrion. **Nu,** Nucleus. **P,** Inorganic phosphate. **P-ase,** Phosphatase. **P-RNA,** Particle ribonucleic acid. **PP,** Inorganic pyrophosphate. **PS,** Protein synthesis. **PV,** Pinocytosis vacuoles. **RNA,** Ribonucleic acid. **S-RNA,** Soluble ribonucleic acid. (From Novikoff, A. B.: In Rudnick, D., editor: Developing cell systems and their control, The Ronald Press Co.)

ucts, and waste are regulated by the *plasma membrane*. Its approximate structure has been determined by postulating the components necessary to explain observed permeabilities. These theories have been admirably supported by electron microscopic studies. The original observation that lipid solvents generally easily penetrate cell membranes suggested that the membrane must consist of a layer of lipids. Passage of water and water-soluble small molecules led to the concept of a sievelike or porous structure, and the different permeabilities of various ions added a concept of variation in electrical charges. In 1940, Danielli postulated a membrane model that satisfied these criteria. It consisted of a double layer of lipid molecules bounded on either surface by single layers of nonlipid material.[23] The lipid molecules were oriented at right angles to the plane of the membrane with their charged, or polar, ends pointing to the two surfaces of the membrane. The total thickness of the membrane was suggested by Danielli to be about 80Å. Early in the development of electron microscopy techniques, the adjacent borders of two epithelial cells were seen to consist of "double membranes" approximately 250Å to 300Å in diameter. With permanganate fixation, these became better defined, appearing as two unit membranes of 75Å to 100Å each and consisting of two leaflets, with an intervening intercellular space of about 30Å. These paired membrane structures now appear to be the adjacent plasma membranes of two cells, each of which is comparable to Danielli's hypothesis. The electron-dense lines about 20Å thick may very well correspond to the layers of nonlipid (protein?) molecules, and the light core 35Å thick may be the lipid layer.[23]

Comparable cellular components have been found in many structures, leading to the conclusion that a double membrane or triple

Fig. 1-3 Section of pancreatic acinar cell of guinea pig. Edge of nucleus at bottom center. Mitochondria cut in section at top. In between are sections of parallel rows of elements of endoplasmic reticulum (cisternae), to the outer surface of which are attached small dense particles of ribonucleoprotein. Note apparent anastomoses between cisternae in lower third of micrograph. (×40,000; from Palade, G. E.: J. Biophys. Biochem. Cytol. **2:** 417-422, 1956.)

membrane is universally present in animal cells. Sjostrand[25] describes the plasma membrane of columnar cells in the intestinal epithelium of the mouse as triple layered and geometrically asymmetric, with a thicker opaque layer on its cytoplasmic surface and a thinner opaque layer peripherally. His measurements indicate that the plasma membrane is thicker at the brush border region than at lateral surfaces, and he differentiates various types of membranes according to their thickness: plasma membrane, 80Å; mitochondrial elements, 50Å to 60Å; and Golgi membranes, 60Å to 70Å. Continuing improvements in methods of fixation and resolution are constantly requiring reevaluation, and conclusions based upon even recent data become rapidly obsolete.

Associated with the relative amount of active transport of materials through the plasmalemma are various infoldings and complex arrangements of the plasma membrane. The processes of pinocytosis (absorption of liquids) and phagocytosis (ingestion of particles) appear to be similar in that a portion of the plasma membrane invaginates or envelops an object, and then becomes pinched off from the surface to form an intracellular vacuole.[13] The precise fate of the vacuoles and replacement of the external cell membrane are as yet poorly understood, but it has been demonstrated that the amount of membrane involved is a limiting factor in pinocytosis and phagocytosis. In very actively absorbing cells, such as the proximal convoluted tubules of the kidney, there are rather permanent pathways

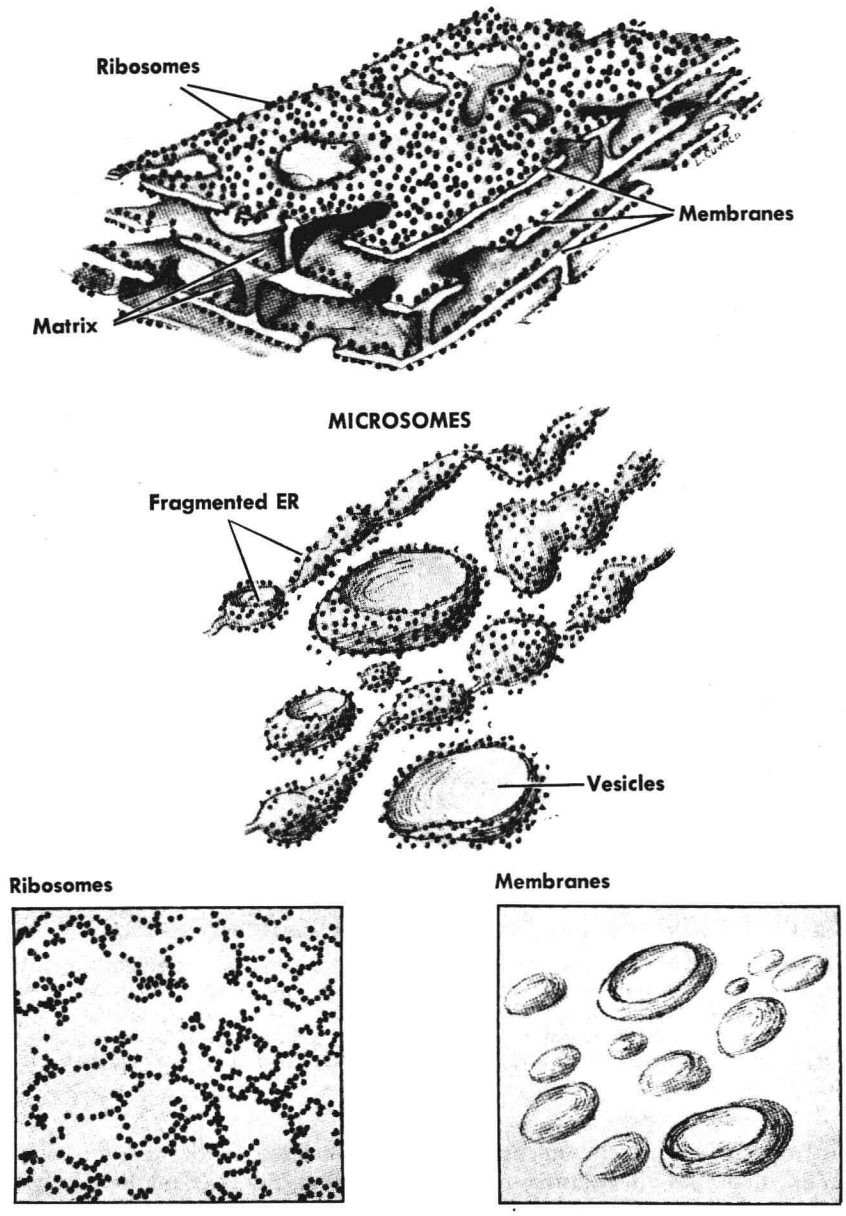

Fig. 1-4 Top, Three-dimensional disposition of granular endoplasmic reticulum with membranes and ribosomes. **Middle,** Fragmentation of endoplasmic reticulum to form microsomes. **Bottom,** Isolated ribosomes and membranes. (From DeRobertis, E. D. P., Nowinski, W. W., and Saez, F. A.: Cell biology [ed. 4 of General cytology], W. B. Saunders Co.)

along infolded plasma membranes between the bases of microvilli.

The *nuclear membrane,* which forms an envelope for the nucleus, is also a double-layered structure that is considered to be discontinuous because of the presence of interruptions or "pores" that allow communication with the cytoplasm. Its permeability to relatively large molecules agrees with this observation, but whether these are really wide-open spaces or merely areas of lower electron density that indicate structural modification is not settled.

The outer layer of the nuclear envelope extends outward at the pores and has been shown to be in continuity with a complex arrangement of double membranes within the cytoplasm known as the *endoplasmic reticulum.* This membranous structure appears to be a universal component of living cells, but with light microscopy was considered as a part of the structureless ground substance of