Introduction to the Study of Disease

William Boyd

Huntington Sheldon

Eighth Edition

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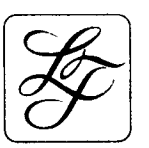

Cover (front and back)

The cover shows a multiple-gated acquisition cardiac scan (MGA) of a normal heart. The scintillation camera is synchronized to the electrocardiogram and interfaced with a computer system. A photograph is made of the computer screen with a Polaroid camera. The patient's red blood cells are prelabeled with radioactive material. This is the only invasive procedure necessary.

The first of 16 frames shown is taken coincident with the R wave of the electrocardiogram. Using this computer program one cardiac cycle of contraction is divided into 16 parts. The fifth frame shows the maximal contraction of the left ventricle (the small, round red image). Since the scintillation camera is positioned in the oblique position, the right atrium and ventricle are shown as the large red image on the left of the small, round red image. With this technique, the volume of each systolic ejection fraction and the cardiac output can be calculated. Moreover, the movement of ventricular muscle during systole and diastole can be visualized in attempts to show areas of disease. This technique eliminates the use of invasive procedures and can be used to study cardiac function before and after stress and after coronary artery operations. (Courtesy of Dr. R. Lisbona, Royal Victoria Hospital, Montreal.)

Spine

On the spine of the book is a multiple-gated nuclear scan of the left ventricle of the heart. This is taken from the left anterior oblique position and shows the cardiac cycle divided into 16 frames. It demonstrates the normal contraction of the left ventricle. The outer white line is the size of the left ventricle when it is relaxed (diastole), and the inner red line shows maximal contraction (systole). The black area in the center is proportional to the volume of the left ventricle. (Courtesy of Dr. R. Lisbona, Royal Victoria Hospital, Montreal.)

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Preface

Rapid changes in many areas of the health sciences are a stimulus to revise this text once more. The eighth edition is a complete revision that presents a contemporary view of disease, its etiology, pathophysiology, and modern techniques of diagnosis. This book is designed for students who wish an understanding of disease without a quantity of detail. I have attempted to illustrate the important principles of disease and, of necessity, have had to minimize some of the supporting evidence. More than 250 new illustrations, diagrams, and scans have been added. Every chapter has been revised and most have been rewritten and restructured, but the organization of the previous edition has been retained. I have added sections on cardiac, renal, hepatic, and respiratory failure to emphasize the correlation of physiologic changes with symptoms, signs, and morphologic alterations. Above all, I have attempted to capture some of the excitement of modern medicine and to indicate areas where our ignorance is as important as our knowledge.

Dr. Mary Senterman wrote the chapter on the female genitourinary system, and Dr. Paula Traktman the chapter on viruses. Dr. Simon Braun assembled the radiologic material from the collections of Drs. L.A. Stein, J. Toth, G.B. Skinner, D.R. Patton, R. Lisbona, R.E. Wilson, and R.E. Hanson of the Royal Victoria Hospital in Montreal and wrote the section on radiologic procedures. Material to illustrate the chapter on the central nervous system was organized by Dr. S. Horowitz from the collection of Dr. R. Ethier of the Montreal Neurological Institute. Alexander Bulzan prepared all the drawings and graphs.

Holly Lukens and Tom Colaiezzi of Lea & Febiger have prepared the manuscript for publication.

I would like to thank all of them and Elisabeth Cotton, who has edited this with me, and Irma Niemi, who painstakingly and with unfailing good humor typed and prepared the manuscript.

Montreal HUNTINGTON SHELDON, M.D.

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1 General Principles

2 The Organs and Their Diseases

General Principles

1

The Living Body

1

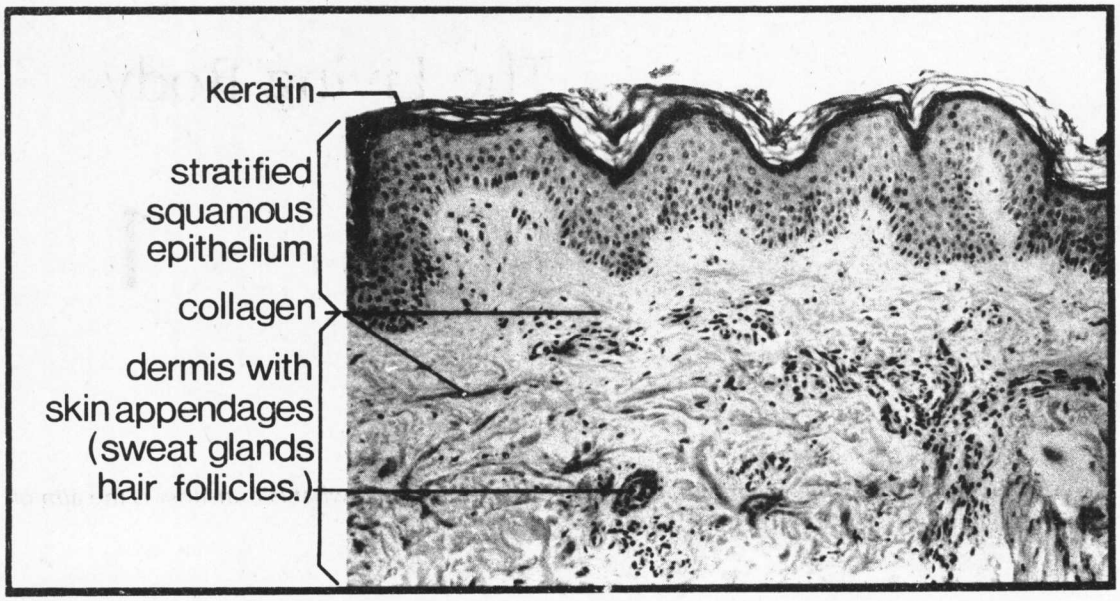
To see what is general in what is particular, and what is permanent in what is transitory is the aim of scientific thought.—A. N. WHITEHEAD

If we are to study disease, we need to be capable of distinguishing between what is disease and what is not, and this requires some knowledge of the normal workings of the human body. In fact, much of our contemporary knowledge of normal function and structure has come from comparisons between normal and abnormal. In this introduction, we outline contemporary views of how the human body is structured, from molecule to man, and how these many parts function, sometimes independently, but always in relation to the whole. This particular chapter reviews anatomy and physiology at the cellular level, and outlines the mechanisms on which the living body depends for its normal function, such as circulation and digestion, and in which various disorders of function (disease) may occur, leading ultimately to failure of the whole (death).

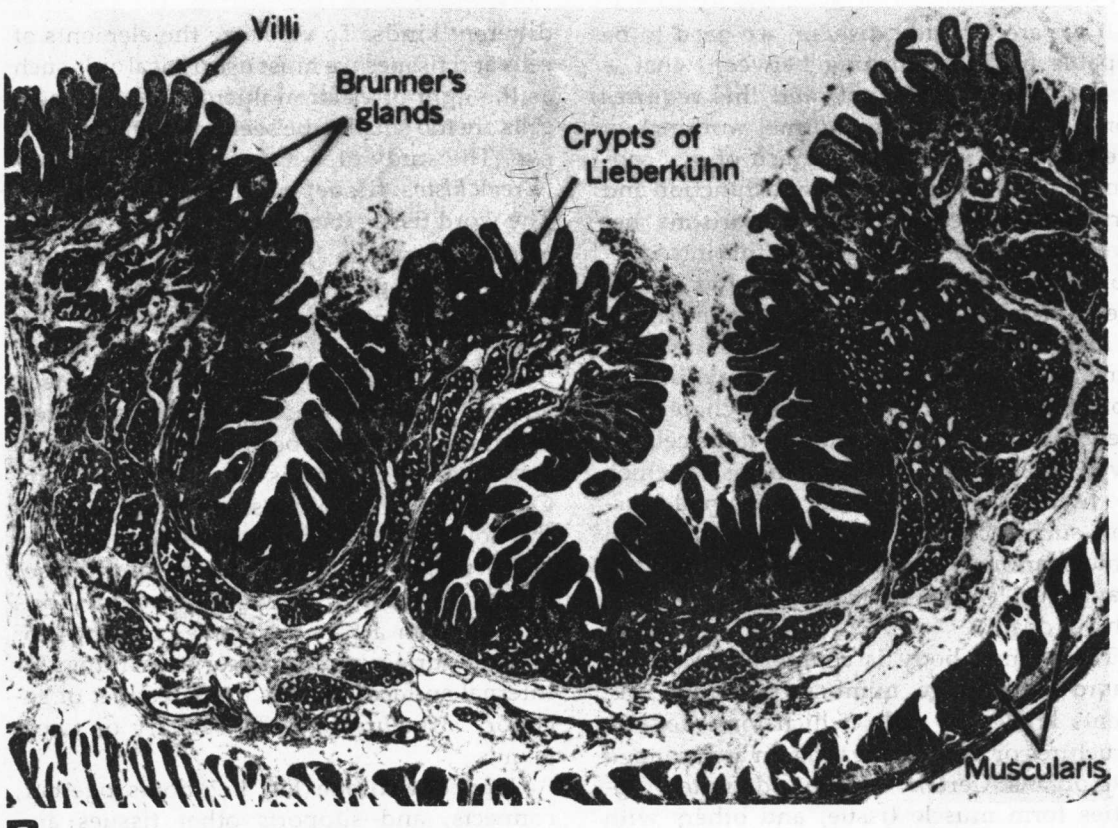
The human body is composed of an extraordinarily large number of minute elements known as **cells**, which form definite structures or **tissues**; these again are grouped into **organs**. Certain cells with definite properties form muscle tissue, and others with quite different properties form nervous tissue; these and other tissues are combined to form organs such as the heart and stomach. By definition, a tissue consists of cells of the same kind and an organ is composed of tissues of different kinds. To visualize the elements of cells and tissues we must use optical aids such as the light or electron microscope, for most cells are too small to be seen with the unaided eye. The study of tissues is called **histology** (Greek *histos*, tissue, and *logos*, the study of). The word tissue itself comes from the French term *tissu*, which means weave or texture. There are 4 general basic types of tissue: epithelial, connective, muscular, and nervous.

Epithelial tissue (Fig. 1–1) serves to protect, absorb, and/or secrete. It is anatomically effective for these cells to be arranged in sheets to cover the surface; this is called an epithelium. One modification of most epithelial layers is the down-growth of groups of cells into the underlying connective tissue to form the secretory structures known as glands. Thus epithelia can act as protective coverings for external surfaces (skin), absorptive linings for internal surfaces such as the intestine, or secretory structures such as salivary or sweat glands.

Connective tissue (Fig. 1–2) holds together, connects, and supports other tissues and cells. In addition to the connective tissue cells themselves, it is composed of a large amount of intercellular substance, which varies from one kind of connective tissue to another. Most of the intercellular substance is secreted by



A



B

Fig. 1–1. *A*, Photomicrograph of a section of skin shows the protective outer lining of stratified, squamous, keratinized epithelium, which lies over the dermis, the latter being composed principally of connective tissue. This epithelium serves as a natural defense to infectious organisms and prevents the body from drying by evaporation. *B*, Photomicrograph shows a section through the absorptive layer of the duodenum, where the epithelium is thrown up in many small folds and finger-like projections. This epithelium is specifically designed to increase the surface area. Microvilli at the surface of each cell serve the additional purpose of retaining extracellular enzymes to aid in absorption. (Courtesy of Dr. H. Mizoguchi.)

the connective tissue cells, whether they are cartilage cells, fibroblasts, or bone cells (osteoblasts). Depending on the type of connective tissue, the formed elements in the intercellular spaces will vary in appearance, so that we have collagen fibrils in the dermis, elastic fibers in tendons, and calcified collagen in bone.

Muscular tissue consists of cells whose chief characteristic is their ability to contract. Different types of muscle, such as in the heart, in the gut, and in the locomotor system, are composed of cells with varied amounts and different types of fibrils. The different types of muscle also function in various ways: automatically in the heart, voluntarily in the skeleton, and rhythmically in the gut.

Nervous tissue is highly specialized for the function of permitting quick reactions both automatically, such as a reflex, and voluntarily, as when we wish to lift a spoon to our mouths.

Thus there are general functions for each of these classes of tissue: epithelial cells cover, protect, secrete, absorb, and may be differentiated to perform special functions. Skin, gut, liver, and milk-secreting glands are all epithelial derivatives.

Connective tissue constitutes ligaments, tendons, joints, and bones, and it holds organs in place. Adipose tissue is a particular type of connective tissue.

Muscular tissue does the work in the heart, moves food along in the digestive system, and allows us to run, jump, and move about.

Nervous tissue is the responsive element that permits us to perceive the world about us, and to reflect on our being.

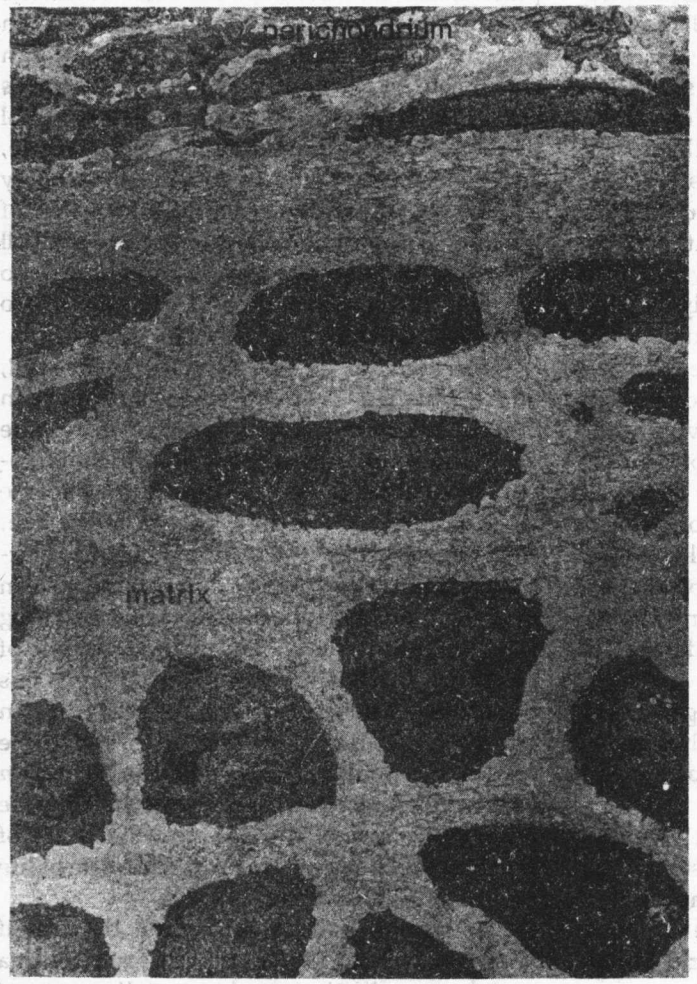
THE HEALTHY CELL

The word "cell" originally meant a small chamber, and it is still used in that sense in relation to a jail or a monastery. But it is a chamber holding a living inmate, actually the smallest unit of living matter. Some animals, such as the ameba and the malaria parasite, consist of a single cell and are therefore called unicellular organisms or protozoa. Although these elementary animals consist of only one cell, they breathe, digest, excrete, and move. One might recall that each of us started from the union of 2 cells, and recently it has been shown that a fully developed higher animal can develop from a single cell that has been artificially provoked to undertake division and replication, a process called parthenogenesis. This development can even take place in an environment different from the natural one; ova can be transplanted in mammals, and a limited development can even occur in a test tube, as the popular press is only too happy to report. During the normal development of a mammal, for a short while, all cells of the embryo appear remarkably similar to one another. Despite 70 years of study of embryonic development, we are still not sure why some cells differentiate into muscle, others into skin, and still others into nerve or connective tissue cells.

A finished muscle cell, a finished nerve cell, and a finished liver cell are as far apart in visible structure as in what they do. Some cells pour out cement that binds them together, as in cartilage and bone. Some become as clear as glass, as in the cornea of the eye. Some develop into a system transmitting electrical signals. Each of the 70,000 billion cells in every human body specializes into something helpful to the whole. The differentiation of cells for different functions leaves us breathless—those functions we recognize in our own bodies as well as the incredible senses of "dumb animals," such as the vision of the eagle, the olfactory sense of the dog, the radar-like sense of the bat, and the sense of touch of the mollusc. This is the miracle of life and its specializations.

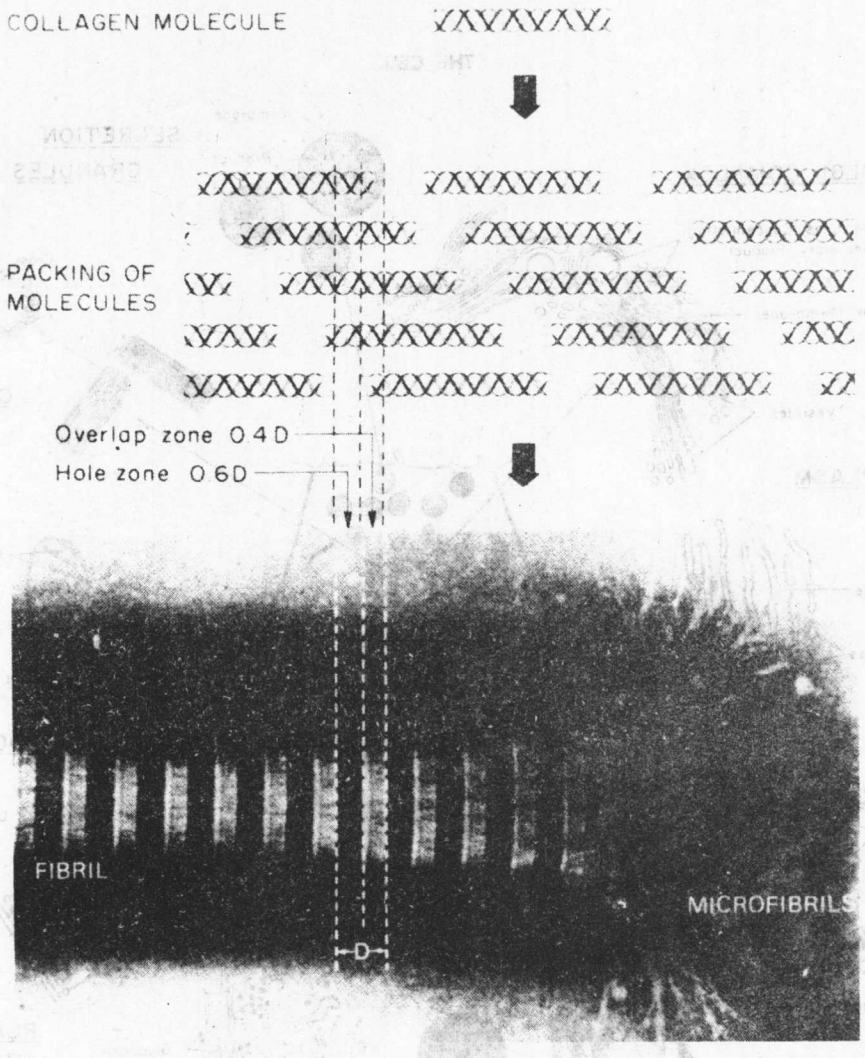
The human body was likened by Rudolf Virchow (1821 to 1902) to a "cell state" with a social organization and specialization of labor. This carries with it the hazard that one group of specialized cells becomes dependent on another group of specialists, and a strike on the part of a small group may paralyze or reduce to chaos the entire community. Thus, the normal, effective contractility of the heart depends on a small bundle of conducting fibers that synchronize the different chambers. If this is put out of business the heart may stop, and every function of the body ceases due to lack of oxygen. Death results. The ameba, consisting of only one cell, has no such hazards to fear. Specialization demands a price, in cells as well as in society.

There is a striking contrast between the



A B

Fig. 1–2. *A,* Electron micrograph shows many cells in cartilage surrounded by their matrix. The perichondrium, or outer layer of the cartilage, is at the top of the field. Cartilage is an avascular tissue. All the constituents of this tissue enter by diffusion from the periphery. *B,* High-power electron micrograph shows collagen fibrils, which are identified by their characteristic repeated cross-striations. The other structures shown are portions of thin fibroblasts, limited by the bilaminar cell-surface membrane. *C,* High-power electron micrograph of soluble collagen shows the protofibrils and their arrangement as seen with negative staining. (From Prockop, D.J., et al.: The biosynthesis of collagen and its disorders. N. Engl. J. Med., *301*:13, 1979.)


COLLAGEN MOLECULE
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Overlap zone 0.4D
Hole zone 0.6D
FIBRIL
MICROFIBRILS
D

C

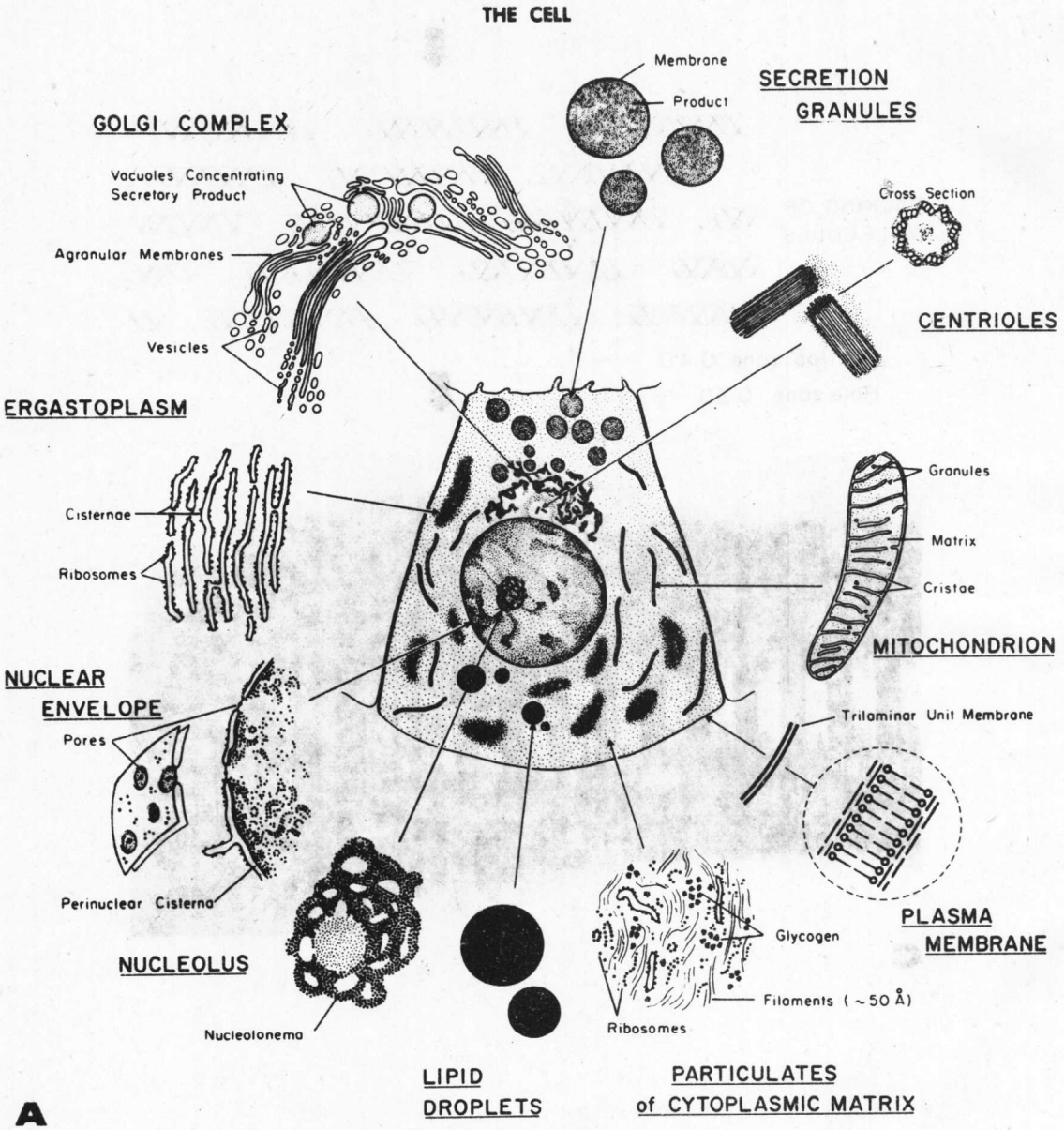
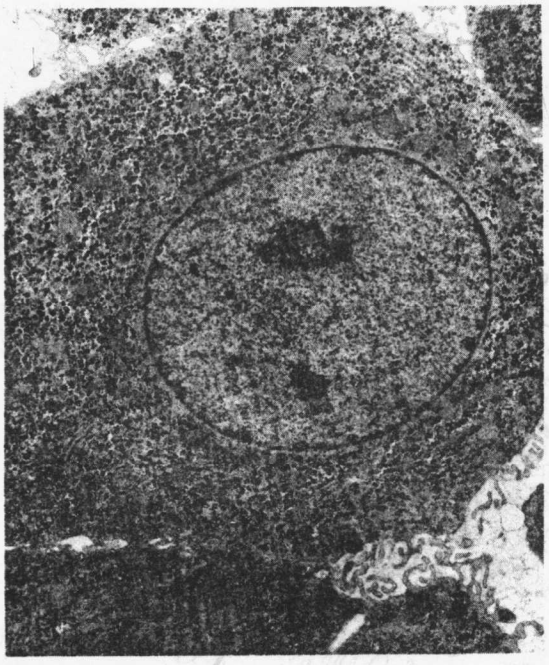


Fig. 1–3. *A*, Schematic representation of a secretory cell. Arranged around the cell are the various components that have been identified with the electron microscope. The significance of these components is discussed briefly in the text. (From Bloom, W., and Fawcett, D.W.: *A Textbook of Histology*, 9th Ed. Philadelphia, W. B. Saunders, 1968.)



B

Fig. 1–3. *B*, Electron micrograph shows a liver cell in which the various components can be identified.

durability of our body and the transitory character of its elements. Man is composed of a soft matter than can disintegrate in a few hours, and yet he lasts longer than if made of steel. Moreover, he accommodates himself marvelously to the changing conditions of his environment. The body seems to mold itself on events. Instead of wearing out like a machine, it changes. In general terms, this characteristic of *adaptation* is one of the most important features of life at any level, whether it be of a cell, tissue, or organism. We shall say more about adaptability in both health and disease.

Just as the atom is a unit of physics, so **cells are the fundamental units of every living body**, whether it be animal or vegetable, and in the last analysis it is they that eat the food, drink the water, and breathe the air, all of which are necessary for the life of the body. The marvelous arrangements of structure (anatomy) and of function (physiology) are simply a complex mechanism to bring to the cells this food, water, and air, which are beyond their normal reach, as well as to perpetuate the species to which the organism belongs.

Every cell, whether of an animal or a plant, consists of three principal constituents: **cell membrane, nucleus,** and **cytoplasm**. The nucleus contains: (1) the **chromosomes**, which are the carriers of the genes, the transmitters of hereditary characteristics, and (2) the **nucleolus**, which directs the cytoplasm and seems in turn to be the target for hormones. The cytoplasm contains a variety of structural constituents known as the **organelles**, or little organs. The cell is indeed a miniature universe (Fig. 1–3).

In recent years enormous advances have been made in our knowledge of the structure of the cell in health and, to a lesser degree, in disease. We owe these advances, in the main, to 2 new techniques: (1) The electron microscope, which gives us a magnification of 100,000 in place of one of 1,000, reveals a new wealth of structure. There are electron microscopes now being constructed at a cost of several million dollars that may make it possible for us actually to see the atom. (2) The development of new methods of cytochemistry, which demonstrate the sites of enzymes, not only in the intact cell, but also in subcellular particles such as mitochondria. These particles are obtained by disrupting the cell and then separating the organelles by means of the ultracentrifuge.

The techniques of cell fractionation have provided so much important information that it may be interesting to review some of the simple principles, methods, and results that have greatly contributed to our understanding of the cellular universe. DeDuve and his coworkers developed and refined centrifugation methods in the 1960's whereby a common soup (homogenate) could be separated into its component parts by the expedient of placing the soup in a centrifuge. If the soup, for example, were a simple pea soup, the heavy peas and their skins (pellet) would be driven to the bottom of the centrifuge tube, since they are more dense and larger than the broth that remains at the top (supernatant). In fact, it would even be possible to separate the peas from their skins if one placed some sort of screen in the tube as well, so that there might be three phases to the soup. Now the nourishment in the soup (protein) resides in the pellet of peas, and if one tested for the presence of an enzyme commonly found in peas (urease), this enzyme would be present in largest amounts not in the supernatant but in the green pellets at the

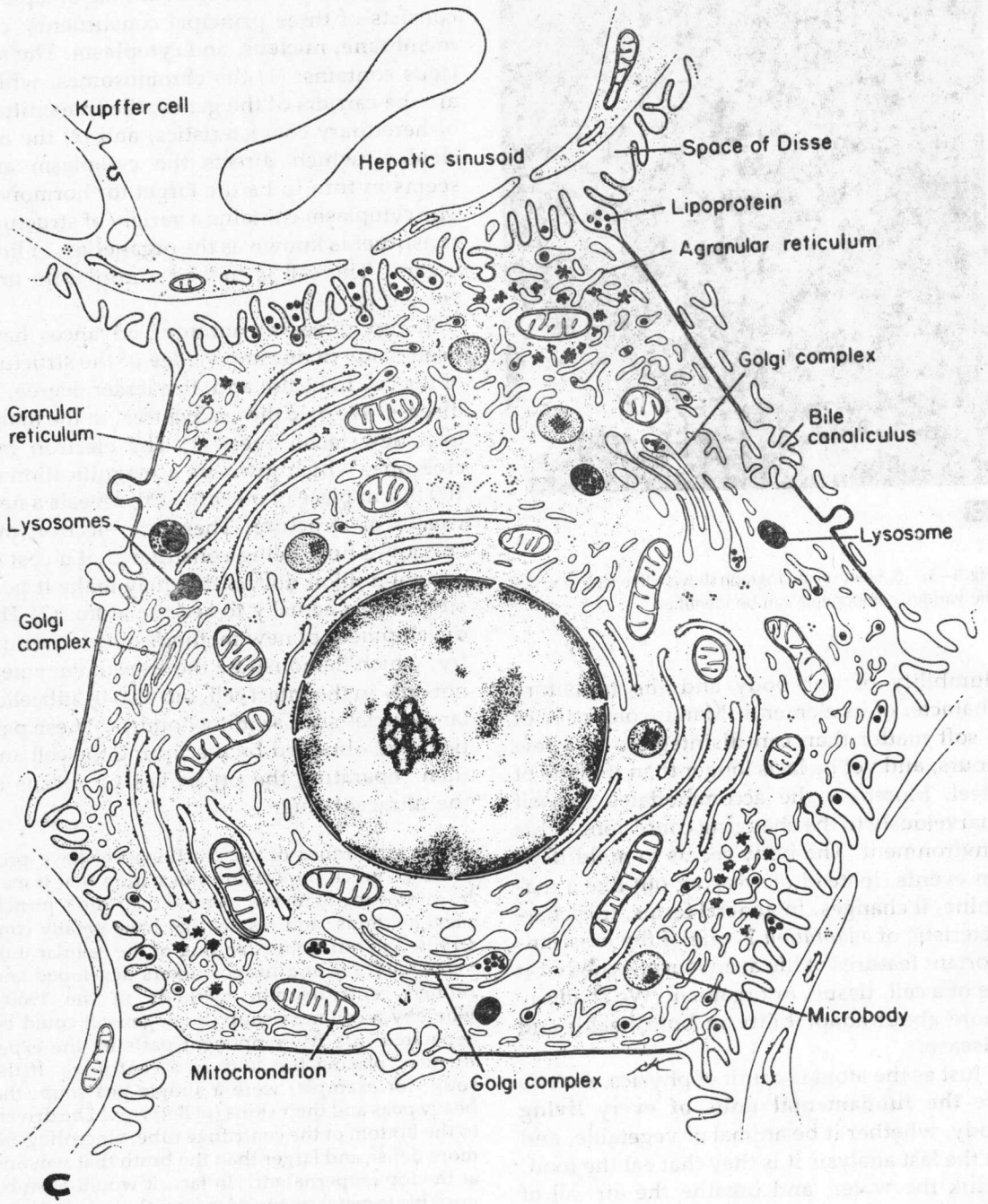


Fig. 1–3. C, Drawing interprets the electron micrograph. Labeled are various structures that have been discovered during the last 25 years. Not all of these structures can be identified in any single micrograph. For example, in Figure 1–3*B* no microbodies or lysosomes can be seen. (Drawing by Sylvia Colard Keene.)

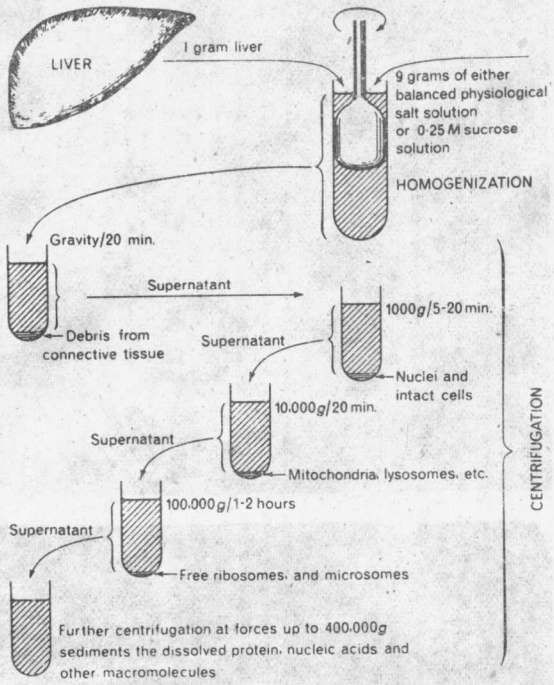


Fig. 1–4. This flow sheet shows the steps in preparing an homogenate for ultracentrifugal fractionation of liver. The preparation separates nuclei from mitochondria from the rough reticulum and the cell sap. (From Bloom, W., and Fawcett, D.W.: *A Textbook of Histology*, 9th Ed. Philadelphia, W. B. Saunders, 1968.)

bottom of the tube. The marker enzyme, which indicates where the nourishment is, would suggest that for camping trips only the precooked pellet be taken along and water added to reconstitute the soup.

DeDuve applied such differential centrifugation methods with marker enzymes to soups or homogenates made from liver and other tissues. He refined the sieving techniques by using sucrose of different densities so that he could separate particles that differed very slightly either in size or in density. Thus particles with differing shapes and surface-to-volume ratios behave differently in a gravitational field. The sedimentation coefficient of different molecules and particles (different from their density) has allowed them to be isolated and characterized enzymatically. Figure 1–4 illustrates the flow sheet of a conventional separation of tissues into the nuclear, mitochondrial, and membrane fractions. Figure 1–5 shows the appearance of each of the pellet preparations as seen with the electron microscope from a conventional, subcellular fractionation. Figure 1–6 illustrates the role of marker enzymes in discriminating among subcellular fractions.

Cell Membrane. The membrane or envelope of the cell is not evident with the light microscope, but it is well demonstrated by the electron microscope. Too little attention has been paid this membrane in the past, but it is now known to be a structure no less remarkable than the contents that it encloses. It is an all-important structure, for it regulates the internal environment of the cell, determining what goes in and what comes out. Thus it separates the high concentrations of potassium inside the cell from the high concentrations of sodium outside the cell, and it can push out processes to engulf harmful bacteria, which the cell then destroys, the process of phagocytosis. Water and all food particles must pass inward through the membrane freely, whereas metabolites must pass out. Virus particles are absorbed to the surface of the cell before penetrating to the interior. It is to the surface structure that many dyes and effective drugs become attached, and antigens are bound to the surface of the cell.

Contemporary views of the plasma membrane suggest that it is composed of lipid molecules arranged with their hydrophobic regions outward in the manner of a stockade, but interspersed among the palisades of lipids are protein molecules that may be visible from the outside of the cell only, or from the inside only, or that may extend in some areas the full thickness—60Å (Angstrom units)—and act as ports or channels. It is these protein molecules that confer the individuality of each cell; they allow cells to be recognized by one another and are the determinants of cellular specificity. This contemporary mosaic concept for the structure of the cell membrane has been developed by Singer and Nicolson as a general model (Fig. 1–7).

Nucleus. The nucleus may be regarded as the brain of the cell. When the nucleus dies, death of the cell will soon follow. There is a curious exception to this rule, for the erythrocyte (red blood cell) of man loses its nucleus when it enters the blood stream from the bone marrow, yet its life span is about 120 days. Perhaps its passive role of carrying oxygen from the lungs to the tissues makes the presence of the nucleus superfluous, although in some mammals such as the camel, and in