KRAUSE'S ESSENTIAL HUMAN HISTOLOGY FOR MEDICAL STUDENTS

Third Edition

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Preface

The format of *Essential Human Histology* departs considerably from that of the usual presentations on human tissue/organ biology. This presentation was not designed as a formal textbook but as a **tool solely for students** and **is designed for rapid student learning** as well as **rapid review** in preparation **for USMLE examinations**. The narrative used was developed primarily around the second edition of "Essentials of Human Histology" and incorporates a series of lectures presented at the University of Missouri, School of Medicine. *Essential Human Histology* focuses the beginning student's attention on the most important aspects of this discipline which are presented as a series of learning units. In general, the text follows the traditional and logical sequence of cells to tissues to organs, but within this sequence, the discussion on mitosis is presented immediately after the cell and discussion on meiosis just prior to a consideration of the reproductive systems.

Use of the Text

To understand human structural biology, it is essential to learn a specialized vocabulary and to assimilate a large body of facts. Learning, as distinct from memorization, depends to a great degree on repetition and reinforcement and is made easier if the material to be learned can be presented in discrete, manageable segments. The format of *Essential Human Histology* is designed specifically to meet these requirements and, if used properly, will enable the student to master this knowledge quickly and efficiently.

The subject matter is broken down into small learning units, each of which is introduced by a **vocabulary** appropriate to that unit. The vocabulary introduces the main features of the subject to be discussed and provides the basic vocabulary for that unit. As each segment is read, note the vocabulary words (identified by **bold print**) in the text and how they contribute to the discussion. After completing the narrative segment, return to the vocabulary words, using them as **prompts** to recall the details of the material just read. The vocabulary serves as a summary of the topic and *provides a means for rapid review*. If a vocabulary word fails to prompt a response, it and the associated text can be found quickly from the **bold type** in the appropriate segment.

A segment entitled either **Histogenesis** or **Organogenesis** provides an introduction into the development of each tissue and/or organ and provides another means of reinforcement that contributes to an overall understanding of the tissue or organ being considered.

Summaries briefly outline the structural/functional relationships and serve to draw the information together and to provide an additional review of the topic.

During preparation of *Essential Human Histology*, three major considerations were kept in mind: **(1)** most curricula place considerable time constraints on the student; **(2)** function and structure are inextricably related; and **(3)** the learning process essentially is a matter of repetition and reinforcement. The narrative strives to present the vast amount of information available on this topic, in a concise and logical manner, without sacrificing the detail that is necessary for a basic understanding of human tissue and organ biology.

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1 The Cell

Multicellular organisms are made up of two distinct structural components: cells and those products of cells that form the intercellular (extracellular) substances. Cells are the fundamental units of living material and show a variety of functional specializations that are essential for the survival of the individual. Each cell is a distinct entity; each contains all the machinery necessary for independent existence and is separated from its surroundings by an individual cell membrane. It is estimated that the human body consists of between 80 and 100 trillion cells.

Protoplasm

VOCABULARY: protein, carbohydrate, lipid, nucleic acid, inorganic material, water

Protoplasm, the living substance of a cell, consists of protein, carbohydrate, lipid, nucleic acids, and inorganic materials dispersed in water to form a complex, semifluid gel. The consistency of protoplasm differs in different cells and may change from a viscous to a more fluid state.

Protein, alone or combined with lipid or carbohydrate, forms the major structural component of the cell and the intercellular substances. Enzymes and many hormones are proteins. The major **carbohydrates** are glucose, which is the chief source of energy in human cells, and glycogen, the storage form of glucose. Complexes of carbohydrates and proteins form the main constituents of intercellular substances that bind cells together. Other carbohydrate-protein complexes form some hormones and antibodies. **Lipids** serve as an energy source; they also have important structural functions and are major components of the membrane systems of cells.

Nucleic acids are divided into two classes. *Deoxyribonucleic acid (DNA)* represents the genetic material and is found primarily but not exclusively in the nucleus. *Ribonucleic acid (RNA)* is present in the cytoplasm and nucleus and carries information from the nucleus to the cytoplasm. It also serves as a template for synthesis of proteins by the cell.

Inorganic materials are as much an integral component of protoplasm as proteins, carbohydrates, and lipids; without them physiologic processes are impossible. Among the inorganic constituents of protoplasm are calcium, potassium, sodium, and magnesium present as carbonates, chlorides, phosphates, and sulfates; small quantities of iron, copper, and iodine; and trace elements such as cobalt, manganese, zinc, and other metals. The inorganic materials have many functions, including maintenance of intracellular and extracellular osmotic pressures, transmission of nerve impulses, contraction of muscle, adhesiveness of cells, activation of enzymes, transport of oxygen, and maintenance of the rigidity of tissues such as bone.

Water makes up about 75% of protoplasm. Part of the water is free and available as a solvent for various metabolic processes, and part is bound to protein.

Properties of Protoplasm

VOCABULARY: irritability, conductivity, contractility, absorption, metabolism, secretion, excretion, growth, reproduction

Protoplasm is characterized by several physiologic properties that distinguish it from inanimate material. All living cells show these properties, but in some cells a particular property may be emphasized.

Irritability is a fundamental property of all living cells and refers to the ability to respond to a stimulus.

Conductivity refers to the ability of a cell to transmit a stimulus from the point of origin to another point on the cell surface or to other cells. Conductivity also is a property of all cells but, like irritability, is most highly developed in nerve tissue.

Contractility is the ability of a cell to change shape in response to a stimulus and generally is indicated by a shortening of the cell in some direction. This property is most prominent in muscle.

Absorption involves transfer of materials across the cell membrane into the interior of the cell, where it might be used in some manner. All cells show the ability to absorb material, some very selectively.

Metabolism refers to the ability of a cell to break down absorbed material to produce energy.

Secretion is the process by which cells elaborate and release materials for use elsewhere. **Excretion**, on the other hand, is the elimination from cells of metabolic waste products.

Growth of an organism can occur by increasing the amount of cytoplasm in existing cells or by increasing the number of cells. There are limits to the size a cell can attain without sacrificing the efficiency with which nutrients and oxygen reach the interior of the cell. Beyond a maximum size, increase in the amount of protoplasm occurs through **reproduction** (division) of cells.

Organization of Protoplasm

VOCABULARY: nucleus, nuclear envelope, cytoplasm, plasmalemma (cell membrane), organelle, inclusion, cytoskeleton, cytoplasmic matrix (cytosol), karyolymph

Although cells differ in size, shape, and function, the protoplasm of each cell consists of two major components: nucleus and cytoplasm. The **nucleus** contains the hereditary or genetic material and is completely surrounded by cytoplasm, from which it is separated by a **nuclear envelope**. The **cytoplasm** is limited by a **plasmalemma (cell membrane)**, which separates the cell from the external environment. Within the cytoplasm are several structures representing organelles and inclusions. **Organelles** are highly organized, living structural units of the cytoplasm that perform specific functions in the cell. **Inclusions** generally represent inert cell products or metabolites that often are only temporary components. Most, but not all, of the organelles are membranous structures whose size and concentration vary with the type and activity of the cell. The different organelles tend to be localized in discrete areas of the cytoplasm so that they and their associated metabolic processes remain separate from other components of the cell. Cell shape is maintained by a three-dimensional **cytoskeleton** that provides structural support for the cell and serves in cell motility and intracellular transport. The cytoskeleton consists of various microfilaments and microtubules.

The organelles and inclusions are suspended in an amorphous medium called the **cytoplasmic matrix (cytosol)**. Nuclear material also is suspended in a structureless ground substance called the **karyolymph**. Other than their differences in location, karyolymph and cytosol appear to be equivalent.

Cytoplasmic Organelles

Organelles are specialized units of the cell that perform specific functions and constitute part of the living substance of the cell. Organelles include structures such as the plasmalemma, granular and smooth forms of endoplasmic reticulum, ribosomes, Golgi complexes, mitochondria, lysosomes, peroxisomes, and centrioles. Many organelles are limited by membranes that are similar in structure to the boundary (plasmalemma) of the cell itself. These membranes, including the cell membrane, are metabolically active sheets that are essential to the life of the cell. In electron micrographs, the membranes exhibit a trilaminar structure consisting of inner and outer dense lines separated by a light zone. Because the trilaminar structure is representative of all biologic membranes of a cell, it has been called a *unit membrane*. The thickness of the unit membrane varies from organelle to organelle and generally is greatest where it forms the plasmalemma. While the membranes of different organelles appear to have only minor morphologic variations, they vary considerably in chemical composition, enzymatic properties, and functions. The membranous organelles act to *compartmentalize* the cell interior into discrete functional units so the biochemical events associated with one organelle do not interfere with those occurring in adjacent organelles.

Plasmalemma (Cell Membrane)

VOCABULARY: unit membrane, phospholipid bilayer, integral membrane protein, transmembrane protein, peripheral membrane protein, glycocalyx, ion channel-linked receptor proteins, G-protein-linked receptors, enzyme-linked receptors, aquaporins, endocytosis, phagocytosis, pinocytosis, micropinocytosis, fluid-phase micropinocytosis, transcytosis, adsorptive (clathrin-mediated) micropinocytosis, coated pit, coated vesicle, clathrin, endosome, exocytosis, regulated exocytosis, constitutive exocytosis

Each cell is enclosed by a plasmalemma that is 8 to 10 nm thick and has the typical trilaminar structure of the **unit membrane**. It appears as two dense lines, each 3 nm wide, separated by a 2 to 4 nm clear zone.

The plasmalemma is composed of proteins, lipids, glycolipids, and carbohydrates. Lipid forms about 50% of the mass of the plasmalemma and consists of three major classes of lipid: phospholipids, glycolipids, and cholesterol.
Of these phospholipids are the most abundant. Four major types of phospholipid have been identified in the plasmalemma. These are sphingomyelin, phosphatidylserine, phosphatidylcholine, and phosphatidylethanolamine. Each phospholipid molecule has a polar head region that is charged and an uncharged, nonpolar tail region that consists of two chains of fatty acids. The polar heads are hydrophilic and so lie on both the inner and outer surfaces of the plasmalemma. The nonpolar tail regions are hydrophobic and line up in the center of the plasmalemma. The result is two parallel layers of phospholipid molecules lying tail to tail and forming a **phospholipid bilayer** in which the hydrocarbon (fatty acid) chains are directed inward and the polar groups are directed outward (**Fig. 1-1**). Phosphatidylcholine and sphingomyelin are usually found in the outer layer of the plasmalemma whereas phosphatidylethanolamine and phosphatidylserine are located in the inner layer adjacent to the cytosol. The plasmalemma behaves as a *fluid* due to the lateral movement of adjacent phospholipid molecules. Therefore, breaks and tears seal spontaneously due to the polar nature of the phospholipids. *Cholesterol* molecules within the plasmalemma tend to limit the lateral fluid movement of the phospholipids and contribute to the mechanical stability of the plasmalemma. Because of the polar lipid composition of the plasmalemma, it is highly permeable to substances such as oxygen and nitrogen, and small, uncharged molecules. It is impermeable to charged ions such as potassium, sodium, chloride, calcium, larger uncharged molecules, and all charged large molecules. Entry of these substances into the cell depends on integral proteins of the plasmalemma.
Glycolipids - lipids with attached sugar residues - are a minor component (about 10%) of the lipids comprising the plasmalemma. Sugar residues of this class of lipid usually extend from the external surface of the plasmalemma and contribute to the negative charge of the cell surface. Glycolipids are important in cell-to-cell and cell-to-interstitial matrix interactions. They also may play a role in immune reactions. Human glycolipids are derived primarily from ceramide and are called *glycosphingolipids*. Important glycolipids of the plasmalemma are gangliosides and galactocerebrosides, major components of nerve cell membranes and myelin, respectively.

Although membrane lipids form the *foundation* of the bilayered structure of the plasmalemma, *membrane proteins* are primarily *responsible for its specialized functions*. By weight, proteins constitute about 50% of the plasmalemma. The membrane proteins are able to move laterally in the lipid bilayer over the surface of the cell if they are not bound to filamentous proteins in the underlying cytoplasm. Membrane proteins function to transport molecules into or out of cells (membrane pump proteins, ion-channel proteins, carrier proteins), act as receptors for chemical signals between cells (hormone receptors) and generate messenger molecules that diffuse into the cytoplasm, attach elements of the cytoskeleton to the plasmalemma, attach cells to the extracellular matrix (cell adhesion molecules), or may even possess specific enzymatic activity when stimulated.

There are two basic types of membrane proteins: integral and peripheral proteins. Various subtypes of integral and peripheral membrane proteins exist.

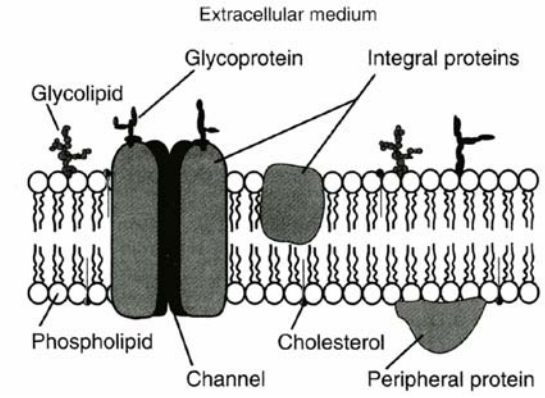

Fig. 1-1. Fluid mosaic model of the plasmalemma. Lipids are arranged in a bilayer. Integral proteins are embedded in the bilayer and often span it, forming a channel. Peripheral proteins do not span the bilayer.

Integral membrane proteins are firmly embedded in the lipid bilayer and cannot be removed. Some integral proteins are **transmembrane proteins** that span the entire width of the plasmalemma and protrude from both surfaces. This type of integral protein has three parts: a region to the cell exterior, a region passing through the lipid bilayer, and a region to the interior of the cell.

The amino acids of this type of integral protein form a α-helix, and the protein is referred to as a *tripartite single-pass integral membrane protein*. Not all transmembrane proteins are of this type. Transmembrane proteins that make multiple passes through the plasmalemma also occur, and most transporters and ion channels identified thus far are multipass transmembrane proteins. Specific transmembrane proteins occur in areas of the plasmalemma specialized for attachment to other cells or the extracellular matrix. Here they pass through the lipid bilayer and link cells together or anchor the cell to the extracellular matrix. Not all integral proteins are transmembrane proteins.

Peripheral membrane proteins are defined as those proteins which can be removed from the plasmalemma without disrupting the lipid bilayer. Peripheral membrane proteins are generally attached to the surface of the plasmalemma - usually the inner surface - and contribute to its stability. Peripheral membrane proteins can attach to the surface of the plasmalemma by ionic interactions with an integral protein, another peripheral membrane protein, or by interaction with the polar head groups of the phospholipids. Examples of peripheral membrane proteins are *spectrin* and *ankyrin*, which are found on the cytoplasmic surface of the erythrocyte plasmalemma. Both function to anchor elements of the cytoskeleton to the cytoplasmic surface of the plasmalemma. Similar peripheral membrane proteins are present in most other cells. Peripheral membrane proteins also function to keep the molecules of the plasmalemma from separating and the cell membrane from tearing apart.

The membrane proteins include proteoglycans. The protein core of this molecule spans the lipid bilayer, and the portion of the long molecule bearing the carbohydrate side chains projects from the exterior surface of the plasmalemma. The sugar residues of the carbohydrate portion of these molecules, as well as glycoproteins and glycolipids, form the fuzzy coat observed by electron microscopy that is referred to as the **glycocalyx**. Such a coat is present on all cells, and the ionized carboxyl and sulfate groups of the polysaccharide units give the external surface of the cell a strong *negative charge*. The glycocalyx also plays an important role in determining the immunologic properties of the cell and its relationships and interactions with other cells. Carbohydrates offer far greater structural diversity for recognition than do proteins. The infinite variety of molecular configurations of the subunits of the large polysaccharides that extend from the plasmalemma forms the basis for *cell recognition*. Some integral membrane proteins consist of a polypeptide chain linked to a carbohydrate (sialic acid) and function as adhesion molecules; these are called *cell-adhesion molecules* or CAMs. Several CAMs have been identified: one for neurons, one for hepatocytes, one for muscle, one for the adhesion of glial cells to neurons, and several others.

Thus, the plasmalemma is a selectively permeable membrane in which ions and small water-soluble molecules (amino acids, glucose) must be pumped through protein-lined channels that traverse the plasmalemma to gain access to the cell interior.

The most common **ion channel-linked receptor proteins** are *voltage-gated ion channels* that require a transmembrane potential to open, *mechanically-gated ion channels* that sense movement in the plasmalemma that stimulate them to open, and *neurotransmitter-gated ion channels*. Neurotransmitter-gated ion channels are receptors that bind neurotransmitters and mediate ion movement. These include the glycine receptor, the N-methyl-D-aspartate receptor, nicotinic acetylcholine receptor, the 5-hydroxytrptamine serotonin receptor, and the γ-aminobutyric acid receptor. The channel proteins undergo an allosteric change that opens the channel when stimulated. Thus, the movement of solutes across the plasmalemma depends on the activity of specific transmembrane transport proteins. Movement of a single solute (molecule) by transmembrane transport proteins is referred to as a *uniport mechanism*. The movement of two or more solutes across the plasmalemma in the same direction involves a *symport* or *cotransport mechanism*. Coupled transport involving the movement of two or more solutes, but in opposite directions across a cell membrane, is referred to as a *countertransport or antiport mechanism*.

G-protein-linked receptors are proteins that span the plasmalemma and are linked to G proteins (trimeric GTP-binding proteins). Important G-protein-linked receptors are the dopamine receptor, the glucagon receptor, the α- and β-adrenergic receptors, and the muscarinic acetylcholine receptor. These receptors activate a chain of cellular events either through a *calcium ion pathway* or through a *cyclic adenosine monophosphate* (*c-AMP*) pathway.

The latter pathway increases or decreases c-AMP levels by stimulation or inhibition of adenylate cyclase. The calcium ion pathway activates phospholipase C, the enzyme which splits phosphatidylinositol biphosphate into inositol triphosphate and diacetylglycerol.
Inositol triphosphate promotes the release of calcium ions from the endoplasmic reticulum resulting in the activation of calcium ion/calmodulin-dependent protein kinase (Cam-kinase). Diacylglycerol activates protein kinase C.

Enzyme-linked receptors are transmembrane proteins linked to an enzyme. When the appropriate signal binds to the receptor, a chain of cellular events is put in motion which may eventually affect gene transcription within the nucleus. Some important enzyme-linked receptors include the fibroblast growth factor (FGF) receptor, the insulin receptor, and the epidermal growth factor (EGF) receptor.

Aquaporins are channel-forming integral membrane proteins that function as selective pathways to facilitate water transport across the plasmalemma of several cell types in different organs. Ten different types of aquaporins have been identified in mammalian tissues to date.

The plasmalemma also plays an active role in bringing macromolecular materials into the cell (**endocytosis**), as well as discharging materials from the cell (exocytosis).

Phagocytosis is a form of endocytosis in which particulate matter is taken into a cell. During the attachment phase, particles bind to receptors on the plasmalemma, while during the ingestion phase, the cytoplasm forms pseudopods that flow around the particles, engulf them, and take them into the interior of the cell in membrane-bound vacuoles. In a similar way, fluid may be incorporated into the cell in small cytoplasmic vesicles by a process called **pinocytosis**. Phagocytosis and pinocytosis can be seen by light microscopy.

Some materials may enter the cell in even smaller vesicles formed by minute invaginations of the plasmalemma. This process, called **micropinocytosis**, is visible only with the electron microscope. Nonselective fluid-phase and selective adsorptive types of micropinocytosis have been recognized. In most cells, **fluid-phase micropinocytosis** occurs with the formation of small vesicles or caveolae from the plasmalemma. The caveolae, which contain fluid and substances dispersed in the fluid, traverse the cytoplasm to the opposite side of the cell, fuse with the plasmalemma and discharge their contents. In certain cells, such as endothelial cells, this process is termed **transcytosis** and is an important mechanism for moving material across a cellular barrier to the extracellular spaces (**Fig. 1-2**).
Specific proteins known as *caveolins* coat the external surface of the caveolae and makes the transport across the endothelial cell cytoplasm to the plasmalemma of the opposite side of the cell possible without interference. Caveolae also can form from the plasmalemma of a variety of cell types and some are involved in the selective transport of specific molecules. Three different caveolin proteins have been identified and are currently under study. Other proteins known as *coatomer proteins* coat a variety of other cytoplasmic transport vesicles and provide a mechanism for the movement of materials from one organelle to another including transport to the plasmalemma.

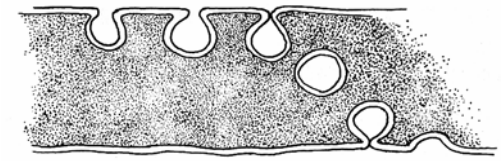

Fig. 1-2. Diagrammatic representation of fluid-phase micropinocytosis.

Adsorptive (clathrin-mediated) micropinocytosis is the selective uptake of specific macromolecules at certain receptor-binding sites in the plasmalemma. This form of micropinocytosis is important in the internalization of nutrients, growth factors, antigens, recycling receptors, and pathogens. Short, bristle-like projections may be present on the cytoplasmic surface at these sites and form **coated pits** from which **coated vesicles** arise. The cytoplasmic surfaces of the vesicles are coated with **clathrin**, a protein that appears as radiating spikes that give a fuzzy appearance to the vesicles. Clathrin may prevent fusion of coated vesicles with membranous organelles (**Fig.1-3**).

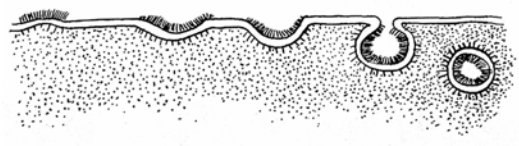

Fig. 1-3. Adsorptive (receptor-mediated) micropinocytosis via coated vesicles.

Following the formation of the coated vesicle, the clathrin coat is lost and the vesicles fuse with preexisting vacuoles to form structures called **endosomes**.

As the molecules being transported are released from these early endosomes into the cytosol, portions of the endosome membrane containing unoccupied receptors bud off as small vesicles, return to the plasmalemma, and fuse with it. Thus, some receptors are recycled. Late endosomes may fuse with lysosomes and their contents are broken down.

Materials such as secretory granules are released from the cell by **exocytosis**, a process in which *SNARE proteins* in the limiting membranes of the granules recognize and then fuse with the plasmalemma before discharging their contents. In this way, a breach in the limiting plasmalemma is avoided. The excess membrane incorporated into the plasmalemma during exocytosis is removed by endocytosis of small vesicles. Two types of exocytosis are known to occur: regulated and constitutive.

Regulated exocytosis is stimulus-dependent and occurs in cells specialized for the release of a large volume of secretory material as in pancreatic acinar cells. **Constitutive exocytosis** occurs in cells in which the secretory product is not concentrated in a number of large granules but is released continuously in small vesicles.

Ribosomes

VOCABULARY: ribonucleoprotein, free ribosome, polyribosome (polysome), messenger RNA (mRNA), protein synthesis, codon, transfer RNA (tRNA)

Ribosomes are small, uniformly sized particles of **ribonucleoprotein** 12 to 15 nm in diameter and composed of large and small subunits. They may be attached to the membranes of the endoplasmic reticulum or be present as **free ribosomes** suspended in the cytosol, unassociated with membranes. Free ribosomes often occur in clusters called **polyribosomes (polysomes)**; in which individual ribosomes are united by a thread of ribonucleic acid (RNA) called **messenger RNA** (**mRNA)**. Free ribosomes are sites of **protein synthesis**, the protein formed being used by the cell itself rather than secreted. Free ribosomes synthesize cytosolic proteins, peripheral membrane proteins, and proteins destined for use by mitochondria, peroxisomes, and the nucleus. Individual free ribosomes are not active; only when they are attached to mRNA to form polyribosomes do they become active in protein synthesis. Similarly, ribosomes on the endoplasmic reticulum must be associated with mRNA before they engage in the synthesis of protein.

Messenger RNA is formed in the nucleus on a template of uncoiled deoxyribonucleic acid (DNA). It contains a message that is encoded as successive sets of three nucleotides called **codons** that specify the sequence in which amino acids are to be incorporated into newly forming protein. During synthesis, mRNA enters the cytoplasm from the nucleus and attaches to ribosomes that move along the mRNA, translating the code and assembling amino acids in the proper order. On reaching the end of the mRNA, ribosomes detach and simultaneously release the newly synthesized protein molecule. Amino acids are brought to the ribosomes for incorporation into the protein by **transfer RNA (tRNA)**, another form of ribonucleoprotein. There is a specific tRNA for each of the amino acids. Ribosomal and transfer RNA are formed by transcription of specific segments of the DNA molecule. Thus, unlike mRNA, formation of ribosomal RNA is directed by a specific region of a chromosome.

Endoplasmic Reticulum

VOCABULARY: tubule, cisternae, granular endoplasmic reticulum (GER), ribosome, smooth endoplasmic reticulum (SER)

The cytoplasm of almost all cells contains a continuous, irregular network of membrane-bound channels called the *endoplasmic reticulum*. Typically, this organelle appears as anastomosing **tubules**, but the membranes also form parallel, flattened saccules called **cisternae**. Small transport vesicles not attached to tubules or cisternae may be present also and are considered to be part of the endoplasmic reticulum. Smooth and granular forms of endoplasmic reticulum can be distinguished.

Granular endoplasmic reticulum (GER) usually consists of an array of flattened cisternae bounded by a membrane. The outer surface is studded with numerous **ribosomes** (**Fig. 1-4**).

The granular endoplasmic reticulum is the site of protein synthesis for secretory proteins, lysosomal enzymes, and plasmalemmal proteins (receptors). The proteins are synthesized by ribosomes on the external surface of the GER, and then enter the lumen of the endoplasmic reticulum, where they are isolated from the surrounding cytoplasm.

Proteins destined for secretion, organelles, and some membranes have an NH_2-terminal signal sequence (a leader sequence) that is recognized by a signal-recognition particle in the cytosol as it is being translated from mRNA. The signal-recognition particle (SRP) binds to both the signal peptide and the ribosome, an event that stops the translation process. The SRP together with the ribosome and the newly translated NH_2 terminus of the forming polypeptide become bound to an integral membrane-docking protein called a *signal-recognition receptor* (*ribosome receptor protein*) in the membrane of the endoplasmic reticulum. After docking translation resumes, and the signal peptide together with the forming polypeptide enters a transmembrane channel (pore) to gain access to the cisternal lumen of the granular endoplasmic reticulum. Once inside the lumen of the endoplasmic reticulum the signal sequence of the polypeptide is clipped off by a signal peptidase located along the inner membrane surface of the granular endoplasmic reticulum. Following translation of the message and synthesis of the secretory polypeptide, the ribosome is released from the endoplasmic reticulum and the transmembrane channel is obliterated by lateral movement of phospholipid molecules in the membrane of the endoplasmic reticulum. Once inside the cisternal lumen these polypeptides and forming proteins remain isolated from the remainder of the cytosol. Here the nascent, unfolded proteins undergo folding into a new three-dimensional configuration. Most proteins synthesized by the granular endoplasmic reticulum also become glycosylated after entry into the cisternal lumen the process of which is completed in the Golgi complex.

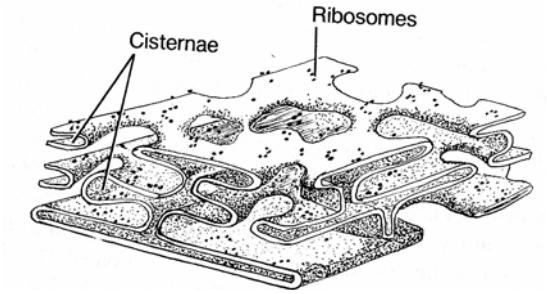

Fig. 1-4. Diagrammatic representation of granular endoplasmic reticulum.

Smooth endoplasmic reticulum (SER) lacks ribosomes and consists primarily of a system of interconnecting tubules without cisternae (**Fig. 1-5**). In most cells, one form of endoplasmic reticulum usually predominates. Protein-secreting cells such as pancreatic acinar cells or plasma cells are characterized by an abundance of GER, whereas the smooth type predominates in cells that secrete steroid hormones. In still other cells, such as liver cells, both types of endoplasmic reticulum are present in nearly equal amounts and may be continuous. Granular endoplasmic reticulum is known to be involved in the synthesis of protein, but the precise role of SER varies in different cells. It functions in the synthesis of steroid hormones in certain endocrine cells, in the synthesis of membrane phospholipids, cholesterol, ceramide and glycogen, in the detoxification of drugs using cytochrome P450 , and in the elongation of fatty acids. The smooth endoplasmic reticulum also has a role in the release and recapture of calcium ions during contraction and relaxation of striated muscle.

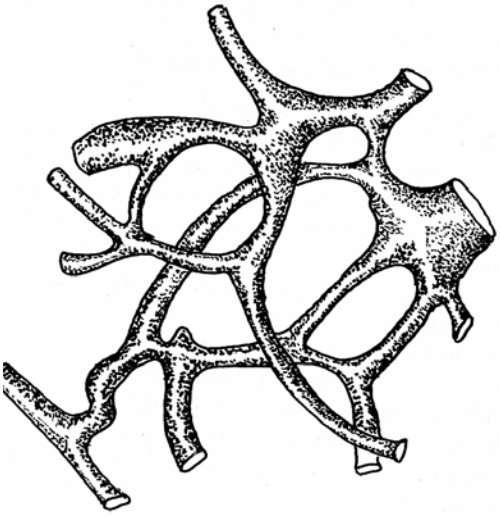

Fig. 1-5. Diagrammatic representation of smooth endoplasmic reticulum.

Golgi Complex

VOCABULARY: negative image, saccule, forming (cis)-face, maturing (trans)-face, transport vesicle, condensing vacuole, secretory granule, trans-Golgi network

The Golgi complex (apparatus) does not stain in ordinary histologic preparations, nor is it visible in living cells; it does sometime appear as a **negative image** - a nonstaining area of the cytoplasm usually close to the nucleus. The size and appearance of the Golgi complex vary with the type and activity of the cell and may be small and compact or large and netlike. Some cells contain multiple Golgi complexes.

In electron micrographs, the Golgi complex is seen to consist of several flattened **saccules** (cisternae), each limited by a smooth membrane. The saccules are disc-shaped, slightly curved, and often appear to be compressed near the center and dilated at the edges. The saccules are arranged in stacks and are separated by spaces 20 to 30 nm wide. Because of the curvature of the saccules, the Golgi complex has convex and concave faces. The convex face usually is directed toward the nucleus and is called the **forming** or **cis-face**; the concave **maturing** or **trans-face** is oriented toward the cell membrane. The forming face is associated with numerous small transport vesicles, and at this face the outer saccule is perforated by many small openings. The saccules at the maturing face tend to be more dilated than those at the convex face.

Secretory products are concentrated in the Golgi complex, whose size varies with the activity of the cell. In protein-secreting cells, peptides first accumulate within the lumen of the GER and then are transported to the Golgi complex in small **transport vesicles**, which are formed by budding off from ribosome-free areas of the GER adjacent to the Golgi complex. The coatomer-coated transport vesicles carry small quantities of protein to the Golgi complex, where they coalesce with and contribute membrane to the developing outer saccule at the forming face. Proteins accumulate within the cisternae of the Golgi membranes and are modified as they pass through the Golgi complex. At the maturing face, the saccules expand and bud off to form limiting membranes that enclose the protein in structures called **condensing vacuoles**. Addition of new membrane to the forming face balances loss of membrane from the maturing face. Secretory materials within the vacuoles become more concentrated, and the condensing vacuoles eventually mature into **secretory granules**.

It is now known that this simplified version of Golgi function is much more complex. The GER and SER synthesize a large number of proteins and lipids, respectively. Some for export as secretory products and others destined to become incorporated into the structural components of the cell itself. The Golgi complex functions in *the post-translational modification*, *packaging*, and *sorting* of the proteins and lipids synthesized by the endoplasmic reticulum. It is also involved in membrane recycling. Essential enzymes involved in glycosylation and other functions are found on the luminal side of the endoplasmic reticulum and Golgi membrane cisternae. As a result, the Golgi complex can be subdivided into functional compartments depending on the enzymes present within its cisternae. The *cis*-compartment of the forming face receives transport vesicles that have budded off from the transitional elements of the endoplasmic reticulum. This compartment is highly fenestrated and appears as a network of anastomosing tubules and vesicles. Following modification of the proteins and lipids received from the endoplasmic reticulum, vesicles bud off from cisternae of this compartment and fuse with cisternae of a medial compartment. After the transported lipids and proteins are acted on by enzymes in this compartment, vesicles form once again and transport these molecules to the cisternae of the *trans*-compartment at the maturing face of the Golgi complex. Some terminal cisternae of this region are highly fenestrated and form a network of anastomosing tubules and vesicles. This specialized region of the Golgi complex is called the **trans-Golgi network**. It is in the trans-Golgi network that proteins, glycoproteins, and lipids are sorted into different transport vesicles. The specific chemical groups added to the proteins in the endoplasmic reticulum and later modified in the various compartments of the Golgi complex designate where specific proteins will go within the cell. Thus, sorting takes place at the maturing face within the trans-Golgi network, where certain proteins are designated to be packaged into larger secretory granules, some are enclosed in small, smooth-surfaced vesicles, and others are placed in clathrin-coated vesicles.

The larger, membrane-limited secretory granules are usually destined for regulated exocytosis (stimulated secretion). Those products in small, smooth-surfaced vesicles are involved primarily in constitutive exocytosis as well as transport of membrane to other organelles. Many cell membrane proteins (receptor proteins) packaged into nonclathrin-coated vesicles are inserted into the plasmalemma via this mechanism. The small coated vesicles that transport enzymes (acid hydrolases) fuse specifically with endosomes to form developing (primary) lysosomes.

During release of secretory granules, the membranes of the secretory granules fuse only with the plasmalemma and become incorporated into the cell membrane. The membranes bounding secretory granules have specific proteins known as *vSNAREs* that recognize and bind specifically with distinct plasmalemmal proteins known as *tSNAREs* and not with the membranes of other organelles. Both of these proteins are necessary for the phospholipid bilayer of both membranes to join together thereby incorporating the granule membrane into the plasmalemma and releasing the contents contained within the granule to the exterior of the cell. Thus, the membranous packaging provided by the Golgi complex provides the vacuoles/vesicles at the maturing face with special properties. The limiting membranes of the secretory granules have the capacity to recognize and fuse only with the apical plasmalemma to discharge their contents during regulated exocytosis. Other Golgi vesicles recognize the basolateral plasmalemma and fuse only with this region during constitutive exocytosis. Yet other vesicles fuse with other specific organelles or with endosomes and are not discharged from the cell as is the case during the formation of primary lysosomes.

There is a continuous movement of membrane through the cell, from endoplasmic reticulum to transport vesicles, to Golgi complex, to secretory granules, and then to the plasmalemma. Internalization of plasmalemma for use within the cell occurs during phagocytosis, pinocytosis, and micropinocytosis. Proteins associated with the membrane bounding these vesicles, regardless of type, are thought to aid in guiding the membranous vesicles to their destination and then recognize complementary proteins within the membranes of the target organelles.

Lysosomes

VOCABULARY: acid hydrolase, autolysis, primary lysosome, secondary lysosome, phagocytosis, heterophagy, phagosome, heterophagic vacuole, residual body, autophagy, cytolysosome, multivesicular body

Lysosomes are small, membrane-bound, dense bodies measuring 0.2 to 0.55 μm in diameter. More than 50 enzymes have been identified in lysosomes. Since they are active at an acid pH, lysosomal enzymes often are referred to as **acid hydrolases**. The limiting membrane of lysosomes protects the remainder of the cell from the effects of the contained enzymes which, if released into the cytosol, would digest or lyse the cell. Such an occurrence is called **autolysis** and is presumed to occur normally during such diverse events as regression of the mesonephros during kidney development and regression of mammary tissue after cessation of lactation. Increased lysosomal activity also occurs during the regression of some tumors.

The appearance of lysosomes varies according to the state of activity in which they are observed and their association with cell structures or material brought into the cell. Because lysosomes exhibit such variable morphologic features, a histochemical test identifying at least two acid hydrolases must be done for positive identification.

Primary lysosomes are those which have been newly released at the Golgi complex and have not engaged in digestive activities. The enzymes of the primary lysosomes are synthesized in the GER and transported to the Golgi complex. Within the Golgi cisternae, mannose components of enzymes destined for lysosomes are phosphorylated, and as they move through the Golgi complex, they are bound to a transmembrane glycoprotein (mannose-6-phosphate receptor) on the luminal side of membranes forming the trans-Golgi network. These receptor-enzyme complexes are then segregated to regions of the trans-Golgi network that form small vesicles coated with the protein clathrin. Coated vesicles containing receptor-bound acid hydrolases bud from the trans-Golgi network and soon after formation lose their clathrin coat. The small transport vesicles, filled with inactive acid hydrolases, then fuse with a late endosome derived from the plasmalemma which contains H^+-ATPase.

This enzyme produces an acidic environment (pH 5.0) that activates the acid hydrolases of the forming primary lysosome. Primary lysosomes usually remain within the cell and are not secreted. However, some cells (neutrophils, osteoclasts) do release primary lysosomes into the extracellular environment.

Secondary lysosomes are vacuolar structures that represent sites of past or current lysosomal activity and include heterophagic vacuoles, residual bodies, and cytolysosomes. The relationships of these structures are best understood from a description of the processes involved in **phagocytosis** (**Fig. 1-6**).

Some cells, such as macrophages and some granular leukocytes of the blood, have a special capacity to engulf extracellular materials and destroy them. The process by which substances are taken into the cell from the external environment and broken down by lysosomal activity is called **heterophagy**. The process involves invagination of the cell membrane and containment of the material in a membrane-bound vacuole. Thus, the extracellular material taken into the cell is sequestered in a vacuole called a **phagosome** and remains isolated from the cytoplasm. As the phagosome moves through the cytoplasm of the cell, it encounters a primary lysosome. The membranes of the two structures fuse and the enzymes of the lysosome are discharged into the phagosome. The combined primary lysosome and phagosome is now called a **heterophagic vacuole**, a type of secondary lysosome. The material within the heterophagic vacuole is digested by the lysosomal enzymes, and any useful materials are transferred into the cytosol for use by the cell. Nondegradable materials such as some dye particles, asbestos fibers, silica, or carbon may remain within the vacuole, now called a **residual body**. A residual body is another form of secondary lysosome that is thought by some to be eliminated from the cell by exocytosis. However, in many cells the residual bodies accumulate and persist for long periods of time.

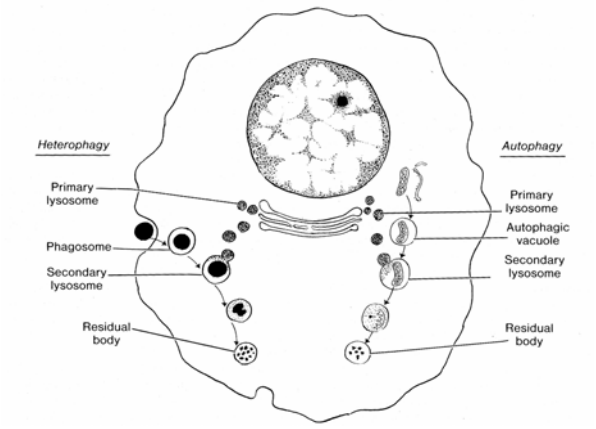

Fig. 1-6. Schematic representation of heterophagy and autophagy.

Autophagy refers to the lysosomal breakdown of cytoplasmic organelles in normal, viable cells. The lysosomal system is involved in the destruction of excess or damaged organelles and in the remodeling of the cytoplasm. During the process, a portion of the cytoplasm containing excess or damaged organelles becomes surrounded by a membrane to form an *autophagic vacuole*. The membrane is thought to be derived from SER. The vacuole fuses with a primary lysosome to form another type of secondary lysosome called a **cytolysosome**. The fate of the materials within the autophagic vacuoles (which may be the cell's own mitochondria, ribosomes, endoplasmic reticulum, and so forth) is the same as that of heterophagic vacuoles and again results in the formation of residual bodies. In many cells, indigestible substances within autophagic vacuoles form a brownish material called *lipofuscin pigment*, the amount of which increases with age.

In addition to these activities, lysosomes form an *intracellular digestive system* with the capacity of taking in and breaking down most molecules *produced in excess* by cells. The absence of a specific lysosomal enzyme results in the accumulation of its normal substrate within the lysosome. Large accumulations of substrate within lysosomes seriously affect lysosome function and are the basis of numerous lysosomal storage disorders such as Tay-Sachs and Gaucher's diseases (**Table 1-1**).

Table 1-1. Lysosomal storage diseases.

Disease	Missing enzyme	Accumulating substance
Sphingolipidoses		
Gaucher's disease	β-Glucosidase	Glucocerebroside
Fabry's disease	α-Galactosidase	Ceramide trihexoside
Krabbe's disease	β-Galactosidase	Galactocerebroside
Farber's disease	Acid ceramidase	Ceramide, gangliosides
Niemann-Pick disease	Sphingomyelinase	Sphingomyelin
Tay-Sachs disease	N-Acetyl-β-glucosaminidase A	Ganglioside GM2
Glycoproteinoses		
Fucosidosis	α-Fucosidase	Fucoglycoproteins
Sialidosis	Sialidase	Sialyl oligosaccharides
Mannosidosis	α-Mannosidase	Mannose-containing oligosaccharides
Mucolipidoses		
I cell disease	Severe deficiency of several hydrolases	Variety of undegraded substances
Mucolipidosis	Ganglioside sialidase	Gangliosides
Mucopolysaccharidoses		
Sanfilippo disease	Heparan-N-sulfatase	Heparan sulfate
Morquio's syndrome	N-acetyl-galactosamine-6-sulfatase, galactose-6-sulfatase	Keratan sulfate
Maroteaux-Lamy syndrome	Arylsulfatase	Dermatan sulfate
Sly syndrome	β-Glucuronidase	Heparin sulfate Dermatan sulfate
Other lysosomal storage diseases		
Pompe's disease	α-1,4-Glucosidase	Glycogen
Wolman's disease	Acid lipase	Cholesterol ester, triglycerides
Cystinosis	Defective transport system in lysosomal membrane	Cysteine disulfide

Another form of lysosome is the **multivesicular body**, a membrane-bound vacuolar structure, 0.5 to 0.8 μm in diameter that contains several small, clear vesicles. Its origin, function, and exact relationship to other lysosomes is obscure.

Peroxisomes

VOCABULARY: nucleoid, hydrogen peroxide, catalase

Peroxisomes, or microbodies, comprise another class of the membrane-bound organelles. Usually larger than lysosomes, their internal structure varies and can be crystalline or dense. The crystalline structures are called **nucleoids**. Peroxisomes lack acid hydrolases but do contain as many as 40 other enzymes.

Peroxisomes contain amino acid oxidase and hydroxy acid oxidase that generate a considerable amount of **hydrogen peroxide** (H_2O_2) which in excess is lethal to cells. Peroxisomes also contain an abundance of the enzyme **catalase** which can make up as much as 40% of the total peroxisomal enzyme. The excess hydrogen peroxide produced by this organelle is converted to oxygen and water by catalase and other peroxidases. Peroxisomes are essential in the oxidation of several substrates, particularly *very long chain fatty acids* by fatty acid β-oxidation enzymes. Peroxisomal oxidases also function to *neutralize free radicles*, normal byproducts of cellular metabolism, which if allowed to accumulate are detrimental to the health of the cell.

Formation of peroxisomes does not appear to involve the Golgi complex.

Peroxisomes are thought to form by the growth and fission of existing peroxisomes and their contents (proteins, phospholipids, membrane lipids) imported from the cytosol. Peroxisomes are abundant in metabolically active cells such as hepatocytes (liver cells) and proximal tubular cells of the kidney.

Mitochondria

VOCABULARY: outer mitochondrial membrane, porins, inner mitochondrial membrane, cristae, elementary particles, membrane space, intracristal space, intercristal space, mitochondrial matrix, tricarboxylic acid cycle (TAC), DNA, ribonucleoprotein, matrix granule, production of ATP

Mitochondria are membranous organelles that play a vital role in the production of energy required by cells. They are visible in living cells examined by phase contrast microscopy and can change shape as they slowly move about in the cytosol. Mitochondria can be stained in appropriately fixed tissues, where they appear as rods or thin filaments. They usually are not visible in routine tissue sections because of the lipid solvents used during tissue preparation.

Ultrastructurally, mitochondria show a variety of shapes and sizes, but all are enclosed by two membranes, each of which has the typical trilaminar substructure. However, the inner and outer mitochondrial membranes differ markedly in their chemical composition and physiologic properties.

The **outer mitochondrial membrane** is a continuous, smooth structure that completely envelops the organelle. It contains specialized transmembrane transport proteins called **porins** that allow permeability to certain metabolic substrates.

An **inner mitochondrial membrane** runs parallel to the outer membrane but is thrown into numerous folds, the **cristae**, that extend into the interior of the mitochondrion. Cristae greatly increase the surface area of the inner mitochondrial membrane and may be either shelf-like or tubular in shape; the tubular form is seen most often in cells involved in steroid synthesis. The inner mitochondrial membrane is studded with club-shaped structures called **elementary particles**. Each consists of a globular head and a narrow stalk. The inner mitochondrial membrane is the site of many enzymatic reactions. The inner mitochondrial membrane contains enzymes of the electron transport chain (NADH dehydrogenase, succinate dehydrogenase, ubiquinone-cytochrome c oxidoreductase, cytochrome oxidase), ATP synthase (confined to elementary particles), and ATP-ADP translocator. The ATP-ADP translocator moves ADP into the matrix and ATP out of the mitochondrial matrix.

The narrow space between inner and outer membranes, the **membrane space**, is continuous with the small **intracristal space** within each crista. The membrane space is rich in hydrogen ions.

The inner mitochondrial membrane surrounds the larger **intercristal space** that contains a slightly more electron-dense material called the **mitochondrial matrix** (**Fig. 1-7**). Enzymes of the **tricarboxylic acid cycle (TAC)**, fatty acid β-oxidation enzymes, amino acid oxidation enzymes, carbamoylphosphate synthetase I, ornithine transcarbamoylase, and pyruvate dehydrogenase reside within the mitochondrial matrix. Substrates metabolized in the matrix produce acetyl CoA which is oxidized by the tricarboxylic acid cycle to carbon dioxide. The energy from this oxidation is captured by nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2). As these nucleotides are oxidized they produce hydrogen ions and electrons. The electrons are transferred along the electron transport chain and the hydrogen ions move into the membrane space. Hydrogen ions then flow from the membrane space through transmembrane hydrogen ion pores and into the matrix. It is within the matrix that ATP synthase catalyzes the reaction converting adenosine diphosphatase (ADP) to adenosine triphosphatase (ATP).

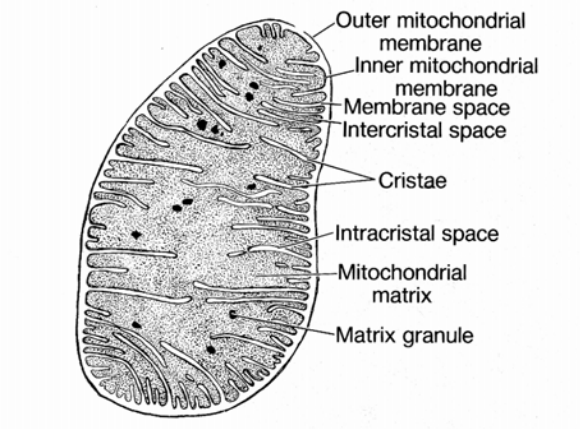

Fig. 1-7. Structure of a mitochondrion.

Mitochondria are unique among organelles because they contain their own complement of **DNA** and are capable of self-replication. Mitochondrial DNA differs from nuclear DNA in its lower molecular weight and is unusual in that it consists of branched filaments of variable thickness arranged in a circular manner. Mitochondrial DNA represents less than 1% of the total DNA in a cell. The human mitochondrial genome contains 16,569 nucleotides. These nucleotides can encode 13 of the protein subunits involved in electron transport and oxidative phosphorylation. Therefore, mitochondria must import the majority of their proteins from the cytosol. The mitochondrial matrix also contains small particles of **ribonucleoprotein** that are 12 nm in diameter and are similar in structure and function to cytoplasmic ribosomes. Messenger RNA and transfer RNA also have been identified in mitochondria.

Scattered throughout the mitochondrial matrix are the more conspicuous **matrix granules**, which measure 30 to 50 nm in diameter. These granules contain calcium and magnesium ions and are thought to regulate the internal ionic composition of the mitochondrion.

Thus, mitochondria function in oxidative phosphorylation (which results in the **production of ATP** driven by electron transfer to oxygen), fatty acid oxidation, amino acid oxidation, and in the production of acetyl coenzyme A (CoA). Adenosine triphosphate (ATP) is a primary source of energy for cell activities.

Annulate Lamellae

The annulate lamellae are membranous organelles consisting of parallel cisternae arranged in stacks. At regular intervals along their lengths, the cisternae show numerous small pores that appear to be closed by thin, electron-dense diaphragms. Because they contain pores, they exhibit a morphologic similarity to the nuclear envelope. The cisternae are spaced uniformly throughout the stack, and the pores in successive cisternae may be aligned. Annulate lamellae often have a perinuclear location and might be continuous with elements of GER. They have been seen in germ cells, various somatic cells, and in tumor cells but are relatively uncommon. The functional significance of the annulate lamellae is unknown.

Centrioles

VOCABULARY: centrosome, diplosome, microtubule, triplet, procentriole, centriolar satellite, basal body, ciliogenesis, procentriole organizer

Under the light microscope, centrioles appear as minute rods or granules usually located near the nucleus in a specialized region of the cytoplasm called the **centrosome**. In some cells centrioles are located between the nucleus and the free surface of the cell at some distance from the nucleus. Two centrioles usually are present in the nondividing cell and together form the **diplosome**. As seen in electron micrographs, the two centrioles that make up the diplosome lie perpendicular to each other. The wall of each centriole consists of nine subunits, each of which is made up of three fused **microtubules**; the subunits are referred to as triplets. The nine sets of **triplets** are so arranged in the centriolar wall that they resemble a pinwheel when seen in cross section. The microtubules within each triplet are called the A, B, and C microtubules, the innermost being the A microtubule, the central tubule being the B, and the most peripheral tubule being the C microtubule. The clear center of the centriole contains a thin filament that passes in a helix immediately adjacent to the inner surface of the centriolar wall. Multinucleated cells contain several centrioles.

Centrioles are self-replicating organelles that duplicate just before cell division. A new centriole, called a **procentriole**, forms at right angles to each of the parent centrioles. Initially, the wall of the procentriole consists of a ring of amorphous material with no microtubules. As the procentriole elongates by addition of material at its distal end, microtubules appear in the wall, and the new structure assumes the configuration of the parent centriole. Immediately after duplication, each parent centriole together with a newly formed daughter centriole migrates to the opposite poles of the cell, where they function in the development of the mitotic spindle. Small, dense bodies, the **centriolar satellites**, are associated with the centrioles and initiate the development and polymerization of microtubules during formation of the mitotic spindle.

In some cells, centrioles migrate close to the surface, where they form **basal bodies** from which arise cilia or flagella; these also are microtubule-containing structures. During the process of **ciliogenesis**, dense spherical bodies (**procentriole organizers**) appear in the cytoplasm, and numerous procentrioles form around each. Multiple newly formed centrioles migrate to sites immediately beneath the plasmalemma and become oriented perpendicular to it. The two innermost microtubules (A and B) of each centriolar triplet begin a rapid polymerization of tubulin and serve as templates for formation of the microtubules of the axoneme. Elongation of the cilium is usually complete within 1 hour.

Cytoskeleton

The cytoskeleton gives structural support to the cytoplasm and consists of microfilaments, intermediate filaments, microtubules, and a microtrabecular lattice. Interaction between the cytoskeleton and the plasmalemma is essential for cell movement, intracellular transport, endocytosis, focal mobility of the plasmalemma, maintenance of cell shape, stabilization of cell junctions, and spatial orientation of enzymes and other molecules in the cytosol.

Microfilaments

VOCABULARY: actin, myosin II, actin-binding proteins, myosin V

Cytoplasmic filaments are responsible for contractility, a property shown in some degree by almost all cells. Filaments are best developed in muscle cells, where the proteins **actin** and **myosin II** form two different types of filaments whose interactions are responsible for the contractile properties of muscle cells.

Microfilaments have a diameter of 7 nm and usually are located immediately beneath the plasmalemma. Actin shows the same dimensions as the microfilaments and has been identified chemically in microfilaments. Actin is an important component of the cytoskeleton and occurs in two molecular forms: *G-actin*, which consists of globular monomers of actin, and *F-actin*, the polymerized form that consists of two identical strands helically coiled around one another. Actin filaments may be organized into parallel bundles or randomly distributed to form an extensive, interwoven network. **Actin-binding proteins** such as filamin link actin filaments together under certain conditions to form a stiff supportive framework for the plasmalemma. Actin also may be linked to transmembrane proteins in specialized regions of the plasmalemma at junctional complexes, contributing further to the cytoskeleton of individual cells. A number of actin-binding proteins exist and interact with either G-actin monomers or F-actin filaments and influence the distribution and function of actin in the cytoplasm (**Table 1-2**). Under different conditions actin filaments participate in cell locomotion, ruffling of the cell membrane, invagination of the plasmalemma during endocytosis, and formation of the contraction ring of dividing cells. In this case, a thin layer of actin filaments located along the cytoplasmic surface of the cell membrane may interact with myosin. Myosin is an actin-activated ATPase protein that exists in several monomeric forms.

Myosins are a diverse protein family consisting of 18 different subtypes, of which myosin II of muscle is the best characterized. **Myosin V** also is present in most cells and interacts with actin filaments to generate movement of intracellular vesicles and organelles.

Table 1-2. Actin-binding proteins.	
Protein	**Action**
Profilin	Binds to G-actin monomers preventing polymerization and thus providing a pool of monomer for future use
Capping protein	Binds to ends of actin filaments limiting a further increase in length
Fimbrin	Binds parallel actin filaments into bundles
Filamin	Cross-links actin filaments into a three-dimensional network
Gelosin	Fragments actin filaments into shorter segments
Vinculin	Mediates binding of actin to plasmalemma
α-Actinin	Mediates binding of actin to plasmalemma
Spectrins I & II	Links actin protofilaments to plasmalemma and cytoplasmic vesicles
Tropomyosin	Stabilizes actin filaments
Myosin V	Interacts with actin filaments in locomotion of cells and movement of vesicles and organelles
Myosin II	Actin filaments slide between myosin filaments during contraction of muscle and other contractile cells

Intermediate Filaments

VOCABULARY: keratin, vimentin, desmin, neurofilament, glial filaments

The thicker intermediate filaments measure 9 to 12 nm in diameter and form a more diverse population of filaments; they may be present as individual strands or loose bundles. Intermediate filaments often are attached to the internal surface of the plasmalemma at cell junctions and contribute to the cytoskeleton of the cell, providing support. Microfilaments and intermediate filaments may occur in the same cell.

Although indistinguishable structurally, five types of intermediate filaments have been identified by immunocytochemical means. Most cells contain only a single type, but occasionally a cell type may contain two. **Keratin** filaments are present in epithelial cells and form bundles that end in cell attachments. Such an arrangement aids in linking individual cells into structural units. They are most abundant in the stratified squamous epithelia, especially in the skin. **Vimentin** filaments occur in fibroblasts and other cells derived from mesenchyme; **desmin** filaments are found in skeletal, cardiac, and smooth muscle cells and provide for the mechanical integration of the contractile proteins actin and myosin; **neurofilaments** are found only in nerve cell bodies and their processes and often occur in bundles. **Glial filaments** are confined to the supporting (glial) cells of the central nervous system and consist of *glial fibrillary acidic protein*. Glial filaments and neurofilaments provide internal support for their respective cell types. Knowledge of this restricted distribution is often useful for the assessment of malignant tumors to determine their site of origin.

Microtubules

VOCABULARY: tubulin, microtubule-associated proteins (MAPs)

Microtubules are straight or slightly curved, nonbranching tubules measuring 21 to 25 nm in diameter and several micrometers in length. Their walls, about 6 nm thick, consist of 13 parallel protein filaments, each 4 to 5 nm in diameter, arranged in a helix. The central zone is electron-lucent, so the structure appears to be hollow. Microtubules are composed primarily of the protein **tubulin**, which occurs in *alpha* and *beta* forms.

The number of microtubules in the cytoplasm varies from one cell type to another and at different times within the same cell. Microtubules can rapidly form or disappear depending on cell activity. Microtubules are in dynamic equilibrium with a large reserve of soluble tubulin in the cytoplasm. Once formed, microtubules elongate by adding subunits at one end and usually depolymerize at the distal end, recycling subunits to the cytoplasm. Small quantities of high-molecular-weight proteins called **microtubule-associated proteins (MAPs)** also have been isolated and are thought to correspond to the slender, lateral filamentous projections of the microtubules. Four different types of MAPs have been identified: kinesin, dynein, dynamin, and axonemal dynein. *Kinesin* links transport vesicles to microtubules and through cyclic interaction moves the vesicle toward the forming end of the microtubule. *Dynein* also links transport vesicles to microtubules, but those destined to move toward the end of the microtubule where depolymerization occurs, providing for two-way traffic within a cell. *Dynamin* links neighboring microtubules into bundles, and *axonemal dynein* is responsible for the sliding action of microtubules within cilia and flagella, resulting in their beating action.

Microtubules usually are scarce in resting cells but are present in large numbers in dividing cells, where they make up the mitotic spindle. After the cell has divided, most of the microtubules disappear. In interphase cells, microtubules form prominent components of centrioles, cilia, and flagella and, in some cells, contribute to the cytoskeleton. Within platelets, microtubules form stiffening elements that help maintain their shape. In nerve cells, microtubules are important for transport of material from one region of the cytoplasm to another. A transient increase in the number of microtubules is seen in nondividing cells during changes in shape associated with cell movement and during differentiation.

It also has been suggested that a three-dimensional molecular framework (a *microtrabecular lattice*) exists in the cytoplasmic matrix, that links the cell organelles and cytoskeleton into a coordinated functional unit during cell movement and other activities.

Cytoplasmic Inclusions

Inclusions are nonliving elements found in the cytoplasm and include such diverse materials as pigment granules, glycogen, lipid droplets, and crystals. They are not essential to the life or functioning of the cell and represent metabolic products, storage materials, or foreign substances taken into the cell from the environment.

Pigment Granules

VOCABULARY: melanin, melanosome, hemosiderin, lipofuscin

Naturally occurring pigments in human cells include melanin, hemosiderin, and lipofuscin, each of which has its own inherent color. **Melanin** is contained within **melanosomes**, which are membrane-bound granules formed and found in melanocytes and sometimes secondarily deposited in certain other cells. They are especially prominently at the skin's dermal-epidermal junction, contributing to the color of the skin. The pigment epithelium of the retina and iris and certain cells of the brain also contain melanin.

Hemosiderin is a golden brown pigment derived from breakdown of hemoglobin present in red blood cells. Phagocytic cells of the liver, bone marrow, and spleen normally contain this type of pigment.

Lipofuscin is found in many cells throughout the body, particularly in older persons. Sometimes called the "wear and tear" pigment, lipofuscin is light brown in color, increases with age, and represents an end product of lysosomal activity. Lipofuscin pigment provides an indication of free radical damage and consists of phospholipids complexed with proteins. Neurons, hepatocytes, and skeletal muscle cells normally contain this type of pigment.

Glycogen

VOCABULARY: glucose polymer, beta particle, alpha particle

Glycogen is a large **glucose polymer** and is the storage form of glucose. The glucose units are linked by α1, 4 glycosidic bonds.

Glycogen synthesis is catalyzed by the enzyme *glycogen synthase* and glycogen break down to glucose is catalyzed by the enzyme *glycogen phosphorylase*. Glycogen cannot be seen in usual tissue preparations unless selectively stained. Hepatocytes (liver cells) and skeletal muscle cells contain the largest glycogen stores of cells in the body. The total amount of glycogen stored in skeletal muscle is greater than that of the liver although the liver has the highest content of glycogen per gram of tissue. Ultrastructurally, glycogen appears either as **beta particles** or glycosomes, which are irregular, small, dense particles 15 to 45 nm in diameter, or as **alpha particles**, which measure 90 to 95 nm in diameter and represent several smaller beta particles of glycogen clumped to form rosettes.

Lipid

VOCABULARY: fat cell, lipid droplet

Fat cells are the chief storage sites for lipid, but many other cell types store **lipid droplets** of various sizes. Lipid synthesized by a cell accumulates in cytoplasmic droplets that lack a limiting membrane. Intracellular lipid serves as a source of energy and as a supply of short-chain carbon molecules for synthesis by the cell. During preparation of routine tissue sections, lipid usually is extracted, and sites of lipid storage appear as clear vacuoles. In electron micrographs, preserved lipid droplets appear as homogeneous spheres of different densities.

Crystals

Crystalline inclusions are normal constituents in several cell types and may be free in the cytoplasm or contained within secretory granules, mitochondria, endoplasmic reticulum, the Golgi complex, or even the nucleus. Many of the observed intracellular crystals are believed to represent a storage form of protein.

Nucleus

The nucleus is an essential organelle *present in all complete "true" cells*. The only cytoplasmic structures in which nuclei are absent are mature erythrocytes and blood platelets; these should not be regarded as true cells. Generally, each cell has a single nucleus, but some, such as the parietal cells of the stomach, cardiac muscle cells, and liver cells, may possess two nuclei. Giant cells, such as the osteoclasts of bone, megakaryocytes of marrow, and skeletal muscle cells, may have several nuclei.

The shape of the nucleus varies and may be spherical, ovoid, or elongated corresponding to the cell shape, or it might be lobulated as in the granular leukocytes of the blood.

The nucleus contains all the information necessary to initiate and control the differentiation, maturation, and metabolic activities of each cell. The nondividing nucleus is enclosed in a nuclear envelope and contains the chromatin material and one or two nucleoli. These are suspended in a nuclear ground substance called the *karyolymph* or *nuclear matrix*.

Chromatin and Chromosomes

VOCABULARY: karyosome, heterochromatin, histone, euchromatin, diploid, haploid, homologous chromosome, sex chromosome, autosome, karyotype, metacentric, acrocentric, submetacentric

Genetic information is stored in the molecules of DNA that make up the chromosomes. Each chromosome contains a single long molecule of DNA that consists of two linear polymers of nucleotide subunits each made up of a phosphate group, a pentose sugar (deoxyribose), and four organic bases (adenosine, cytosine, guanine, thymidine). The bases project toward and bind to complementary bases of the adjacent polymer. Together the two polynucleotide chains intertwine and form the antiparallel double helix of the DNA molecule. Genetic information of the DNA molecules is encoded in the sequence of the bases. A *gene* refers to that unit of heredity that involves a sequence of bases necessary for the synthesis of a protein or a nucleic acid. It is estimated that the *human genome* consists of between 20,000 and 25,000 genes. In non-dividing nuclei, chromosomes are largely uncoiled and dispersed, but some regions of the chromosomes remain condensed, stain deeply, and are visible by the light microscope as chromatin. Nuclear DNA is associated with a variety of proteins that form chromatin. These proteins can be divided into two general categories: histones and nonhistone proteins.

The latter include structural proteins, regulatory proteins, and the enzymes needed for nuclear function (DNA and RNA polymerases). Histones are the most abundant proteins in the nucleus and form the inner core of a DNA-protein complex called a *nucleosome*. The nucleosome is the basic unit of the chromatin fiber. The nucleosome has a string of beads appearance and represents the basic structural unit of chromatin. Each fiber consists of a double helix of DNA wrapped about a core of histones. Individual masses of chromatin are called **karyosomes**, and although not entirely constant, the chromatin masses do tend to be characteristic in size, pattern, and quantity for any given cell type. Collectively, the karyosomes form the **heterochromatin** of the nucleus and represent coiled portions of the chromosomes (**Fig. 1-8**). Heterochromatin is believed to be complexed to **histones** and to be non-active. Histones are simple proteins that contain a high proportion of basic amino acids. The dispersed region of the chromatin stains lightly and forms **euchromatin**, which is active in controlling the metabolic processes of the cell. The distinction between heterochromatin and euchromatin disappears during cell division when all the chromatin condenses and becomes metabolically inert.

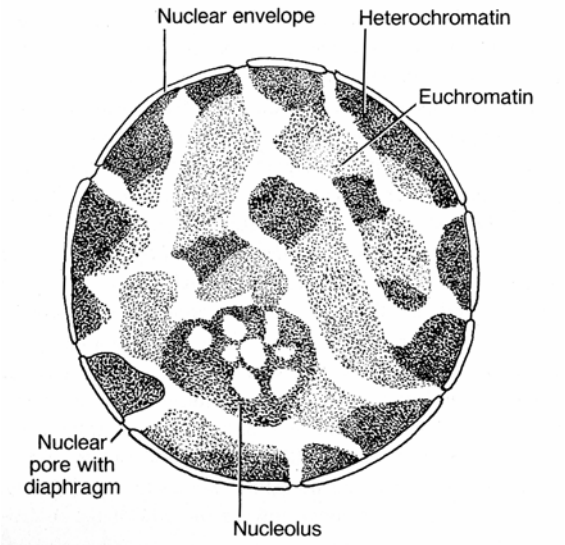

Fig. 1-8. Diagrammatic representation of nuclear structures.

Chromosomes are permanent entities of the cell and are present at every stage of the cell cycle, but their appearance depends on the physiologic state of the cell. At interphase the chromosomes form delicate, tortuous threads, and it is only during cell division that they assume the appearance of discrete, solid, rodlike structures. Analysis and study of chromosomes can be carried out most conveniently in dividing cells that have been arrested in metaphase. Alkaloids such as the *Vinca* drugs and *colchicine* interfere with spindle formation and permit intracellular accumulation of metaphase chromosomes for study.

The number of chromosomes typically is constant for each species but varies considerably between species. In humans, the *chromosome number* is *46*. The figure given is for the **diploid** number in somatic cells. Germ cells (ova and sperm) contain half this number and are said to be **haploid**. The chromosomes present in somatic cells represent the inheritance of two sets of chromosomes, one from each male and female parent. In the male and female sets, chromosomes that are similar are called **homologous chromosomes**. In many diploid higher animals, a pair of **sex chromosomes** is specialized for and participates in the determination of sex; all other chromosomes are called **autosomes**. In humans there are 44 autosomes and a pair of sex chromosomes that are homologous (XX) in the female and heterologous (XY) in the male.

Homologous chromosomes can be recognized at metaphase and are arranged in groups representing the **karyotype** of a species. Individual chromosomes often can be identified by the length of their arms and the location of the centromere. If the centromere is in the middle of the chromosome and the arms (telomeres) are of equal length, the chromosome is said to be **metacentric**. If the centromere is close to one end, the chromosome is **acrocentric**, and if the centromere is between the midpoint and the end, the chromosome is **submetacentric**.

Nuclear Envelope

VOCABULARY: unit membrane, perinuclear space, nuclear pore, nuclear pore complex, lamins, nuclear lamina

The nuclear envelope consists of two concentric **unit membranes**, each 7.5 nm thick, separated by a **perinuclear space** 40 to 70 nm wide. The inner membrane is smooth, whereas the outer membrane often contains numerous ribosomes on its cytoplasmic surface and is continuous with the surrounding endoplasmic reticulum.

At irregular intervals around the nucleus, the inner and outer membranes of the envelope become continuous with one another to form small octagonal openings called **nuclear pores**. The pores measure about 10 nm in diameter and are closed by a **nuclear pore complex** that consists of two rings, one of which faces the cytoplasm. Eight radial spokes extend inward from the rings toward a central granule. The number and distribution of nuclear pores depend on the type of cell and its activity.

The nuclear envelope aids in organization of the chromatin and controls the two-way traffic of ions and molecules moving between the nucleus and cytoplasm. Molecules less than 10 nm in diameter pass through the nuclear pore complex by passive diffusion, whereas large molecules (entering newly synthesized proteins, exiting ribonucleoproteins) require an energy-dependent transport mechanism. It is thought that a signal sequence of amino acids directs them to the nuclear envelope, and after binding of a signal sequence to a receptor in the nuclear pore complex, the nuclear pore opens much like an iris diaphragm of a camera to permit passage of the larger molecules.

A thin meshwork of filaments called **lamins** is made up of three polypeptides and lies along the inner surface of the nuclear membrane to form the **nuclear lamina**. The lamins are structurally similar to intermediate filaments and are classified as types A, B, and C according to their location and chemical properties. Type B lamins lie nearer the outer surface of the nuclear lamina and binds to specific integral (receptor) proteins of the inner nuclear membrane. Types A and C lamins lie along the inner surface of the nuclear lamina and link the membrane-bound lamin B to chromatin. The three lamins are thought to function in the formation and maintenance of the nuclear envelope of interphase cells. They also may aid in maintaining the shape of the nucleus.

Nucleolus

VOCABULARY: ribosomal RNA (r-RNA), nucleolus-organizing region, pars granulosa (nucleolonema), pars fibrosa, nucleolus-associated chromatin

A nucleolus appears as a dense, well-defined body, 1 to 3 μm in diameter, contained within a nucleus. Nucleoli are sites where **ribosomal RNA (rRNA)** is synthesized. Since these sites (**nucleolus-organizing regions**) are located on five different chromosomes, any one cell may contain several nucleoli. Usually only one or two large nucleoli are found, since the nucleolus-organizing regions tend to associate and the RNA produced at these regions aggregates into larger masses.

As seen in electron micrographs, nucleoli lie free in the nucleus, not limited by a membrane. They show two regions, each associated with a particular form of ribonucleoprotein. The dominant region, the **pars granulosa (nucleolonema)**, consists of a network of dense granules of RNA 13 to 15 nm in diameter. The second region, the **pars fibrosa**, tends to be centrally placed and consists of dense masses of filaments 5 nm in diameter.

Deoxyribonucleoprotein also is associated with the nucleolus and is present in filaments of chromatin that surround or extend into the nucleolus. This chromatin forms the **nucleolus-associated chromatin**; its DNA constitutes the template for synthesis of rRNA. In humans, rRNA genes represent clusters of DNA segments located near the tips of chromosomes 13, 14, 15, 21, and 22. *RNA polymerase I* catalyzes the formation of ribosomal RNA. Elsewhere within the nucleus *RNA polymerase II* catalyzes the formation of messenger RNA (mRNA) and *RNA polymerase III* catalyzes the formation of transfer RNA (tRNA). Ribosomal gene transcription occurs in the fibrillar region of the nucleolus. Following transcription, the rRNAs are processed and then assembled in the pars granulosa. With the addition of the small ribosomal subunit, ribosomes are then transported to the cytoplasm through nuclear pores.

Nucleoli are found only in interphase nuclei and are especially prominent in cells that are actively synthesizing proteins. They are dispersed during cell division but reform at the nucleolus-organizing regions during reconstruction of the daughter nuclei after cell division.

Summary

Cells are the fundamental units of structure of all tissues and organs and perform all the activities necessary for the survival, growth, and reproduction of an individual. They carry out energy transformations and biosynthetic activities and are able to replicate themselves.