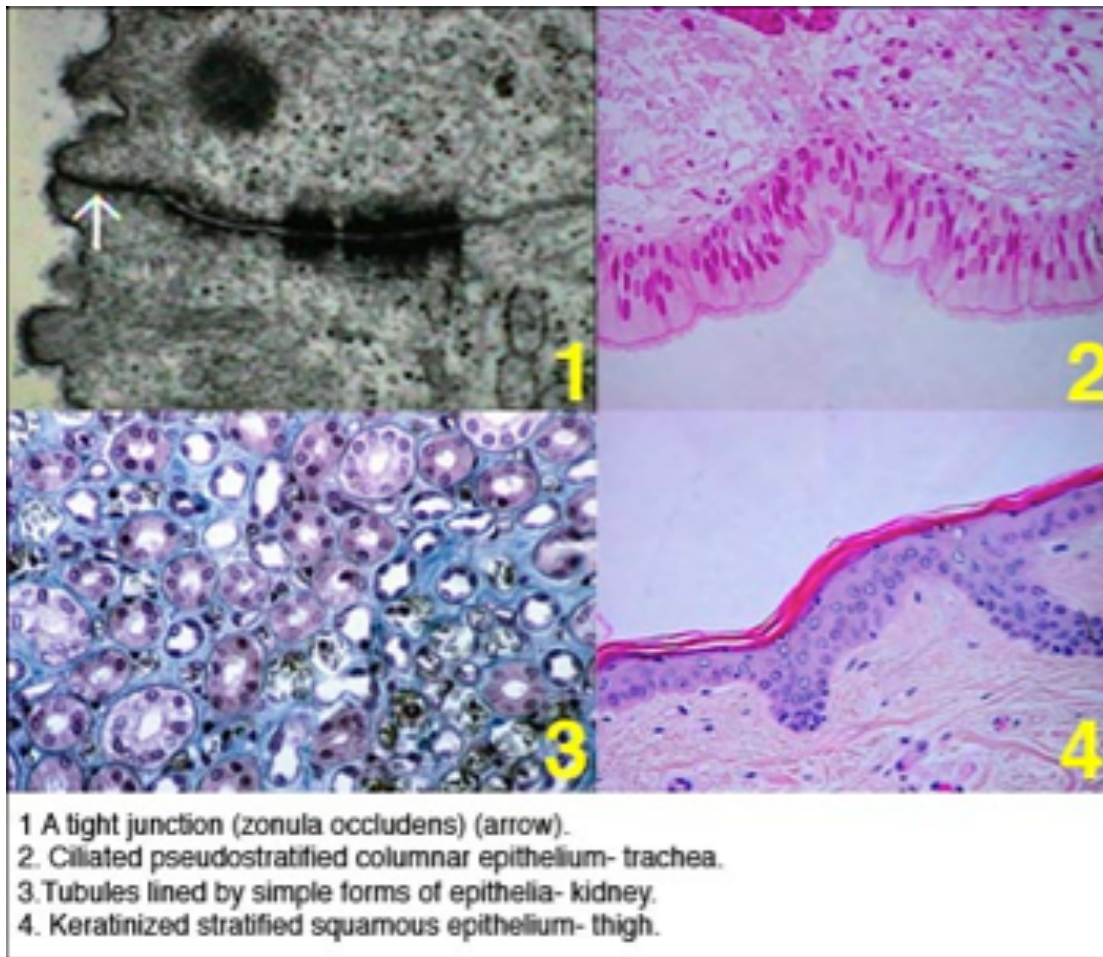


Epithelium



Epithelium is one of the four basic tissues, the others being connective, muscle, and nerve tissue. A basic tissue is a collection of cells of similar type that, together with their associated extracellular substances, are specialized to perform a common function or functions. The various epithelia consist of closely aggregated cells with only minimal amounts of intervening intercellular substances.

Sheet/Barrier Epithelium

The cells of this type of epithelium are organized into sheets or layers that form barriers which cover the external surface of the body and line the digestive, respiratory, cardiovascular, and urogenital systems as well as the major body cavities. Thus, substances that enter or leave the body must pass through an epithelial barrier. Cells within an epithelial sheet are bound firmly together and resist forces that tend to separate them. The space between the cell membranes of adjacent epithelial cells is narrow (about 20 nm) and contains a small amount of proteoglycan that is rich in cations, chiefly calcium. Glycoproteins (integral transmembrane glycoproteins) associated with the plasmalemma act as specialized adhesion molecules that aid in holding adjacent epithelial cell membranes in close apposition. Epithelial cells rest on a basal lamina that separates the epithelium from underlying connective tissue. The basal

lamina consists of an electron-lucid lamina lucida immediately adjacent to the epithelium and a denser layer, the lamina densa, next to the underlying connective tissue. The basal lamina, primarily the product of the epithelial cells, consists of the glycoprotein, laminin, limited mainly to the lamina lucida; and a proteoglycan rich in heparan sulfate, fibronectin, and type IV collagen limited mainly to the lamina densa. It is reinforced on the connective tissue side by a layer of reticular fibers embedded in proteoglycan. The basal lamina provides support and a surface for the attachment of the overlying epithelium. The basal lamina and the interface of the underlying connective tissue (reticular lamina) together make up the epithelial basement membrane that is visible with the light microscope. Additional support for the basement membrane is provided by anchoring fibers of type VII collagen which extend from the basal lamina to form loops around collagen fibers (type I) in the subjacent connective tissue prior to terminating in anchoring plaques. A glycoprotein known as filamin links the basal lamina to elastic fibers within the underlying connective tissue. With rare exceptions, epithelium is avascular and depends on diffusion of substances across the basement membrane for its nutrition. However, epithelium is innervated. Generally, epithelial cells have a high capacity for regeneration.

Classification of Epithelia

The lining or covering forms of epithelia may consist of a single layer of cells, forming a simple epithelium, or multiple layers of cells may be present to form a stratified epithelium. The epithelial cells themselves can be divided into three categories according to their geometric shapes: squamous (thin, platelike cells), cuboidal (cells in which the height and width are approximately equal), and columnar (cells in which the height is greater than the width). Cells intermediate in height between cuboidal and columnar do occur and frequently are referred to as low columnar.

Simple Epithelia

Epithelium consisting of a single layer of cells can be classified as simple squamous, simple cuboidal or simple columnar, depending on the shape of the constituent cells. A fourth type of simple epithelium, pseudostratified columnar, is composed of more than one type of cell whose nuclei are at different levels, falsely suggesting that the epithelium is made up of two or more layers. While all the cells in this type of epithelium are in contact with the basement membrane, not all extend to the surface. The surfaces of cells within an epithelial sheet show different orientations. The apical surface is free, the opposite or basal surface is directed toward the underlying basement membrane, and the lateral surfaces face adjacent epithelial cells. Differences in the orientation of the plasmalemma (apical and basolateral) are associated with differences in cell function and morphology. Organelles, including the nucleus, frequently take up preferred locations in the cell, in which case the cell is said to show polarity. An epithelial cell may be polarized apically or basally with respect to the distribution of its organelles, depending on the functional status of the cell. Likewise the apical plasmalemma contains receptors, ion channels and transporter proteins that are functionally quite different from those located in the basolateral plasmalemma. The term mesothelium is the special name given to the simple squamous epithelia that lines the pleural, pericardial, and peritoneal cavities. A specific name, endothelium, is given to the simple squamous epithelium that lines the cardiovascular and lymph vascular systems.

Stratified Epithelia

Stratified epithelia are classified according to the shape of the superficial (surface) cells, regardless of the shapes of the cells in the deeper layers. Except for those in the basal layer, cells of stratified epithelia are not in contact with the basement membrane, and only the most superficial cells have a free surface. In the thicker stratified types, the deeper cells often are irregular in shape. The types of stratified epithelia are stratified squamous, stratified cuboidal, and stratified columnar. Stratified squamous is the most abundant of the stratified epithelia with stratified cuboidal and columnar having a limited distribution. In regions where the surface is dry or subject to mechanical abrasion, as in the epidermis, the outer layers of cells are transformed and filled with a protein called keratin. Keratin is an especially tough protein. Cells comprising this layer are resistant to mechanical injury and are relatively impervious to bacterial invasion or water loss. When this transformation occurs this type of stratified epithelium is referred to as keratinized stratified squamous epithelium. The keratinized layer of cells at the surface is constantly being shed and replaced. In other regions the stratified squamous type of epithelium is found lining a moist environment and recognizable, intact cells rather than flat, keratin-filled cells are sloughed from the surface. This type of epithelium is called a wet or nonkeratinized stratified squamous epithelium. Transitional and germinal epithelia are not classified according to the cells of the surface layer. *Transitional epithelium* (uroepithelium) is restricted in distribution to the lining of the urinary passages and extends from the minor calyces of the kidneys to the urethra. It is a thick stratified epithelium consisting of large rounded cells the appearance of which varies considerably, depending on the degree of distension to which it is subjected. The superficial cells of a non-distended organ (urinary bladder for example) appear rounded or dome-shaped and often show a free convex border that bulges into the lumen. In the distended organ, the superficial cells may vary in shape from squamous to cuboidal. *Germinal epithelium* is restricted in distribution to the seminiferous tubules of the testes. It is a complex, stratified epithelium that consists of supporting cells and spermatogenic cells.

Cell Attachments

In addition to the intercellular matrix, several attachment points or junctions occur between neighboring epithelial cells that aid in holding adjacent cell membranes close together. They also serve as anchoring sites for microfilaments and intermediate filaments of the cytoskeleton, which assists in stabilizing cell shape.

Junctional Complexes

Terminal bars occur along the apical, lateral interfaces of most simple cuboidal and columnar epithelial cells that border on luminal surfaces. They are visible under the light microscope as short, dense lines. In electron micrographs, a terminal bar is seen to form an area of specialization called the junctional complex, which consists of three distinct regions. Near the free surface, the external leaflet of adjacent cell membranes fuse, and the intercellular space is obliterated. This region is the zonula occludens (tight junction), an area of specialization that forms a zone or belt around the perimeter of each cell to create an occluding seal between the apices of adjacent epithelial cells. As a result, materials that pass through the epithelial sheet must cross the cell membranes and usually cannot pass between cells through the intercellular spaces. The zonula occludens also is important in separating apical from basolateral cell

membrane domains by preventing the lateral migration of specialized transmembrane proteins (e.g., receptors, ion transport proteins) in the plasmalemma. In most cases, membrane proteins in the apical plasmalemma function quite differently from those occupying the basolateral regions. The plasmalemma of the apical domain is rich in cholesterol and glycolipids and contains ion channels, transporter proteins, hydrolytic enzymes, and hydrogen-ATPase. Regulated secretory products are released from this domain by exocytosis. In contrast, the plasmalemma of the basolateral domain is characterized by receptors for hormones, anion channels, and sodium-potassium ATPase and is where most constitutive secretion occurs. As a result of this distribution, the plasmalemma of epithelial cells functions to regulate the flow of ions and solutes between external environments and body fluids as well as between compartments within the body. Tight junctions also occur between simple squamous epithelial cells forming either an endothelium or a mesothelium. The zonula occludens can be rapidly disassembled and re-formed as occurs during leukocyte migration across an endothelial barrier. Although the zonula occludens usually prevents the diffusion of material across an epithelial barrier via the intercellular space (paracellular pathway), some epithelia are classified as tight or leaky based on the permeability of the zonula occludens. Leaky zonula occludens allow certain types of ions to pass through the epithelial barrier via the paracellular pathway.

The second part of the junctional complex, the zonula adherens, also forms an adhering belt or zone that surrounds the apex of an epithelial cell, immediately beneath the zonula occludens. Adjacent cell membranes are separated by an intercellular space 15 to 20 nm wide, and in this region plaques along the internal leaflet of the cell membranes are associated with an actin filament network. The plaques contain α -actinin and vinculin, two actin-binding proteins. Actin is linked to a transmembrane glycoprotein called E-cadherin (adherens cell adhesion molecule or A-CAM) that holds cells in this region together in the presence of calcium ions.

The third element of the junction complex is the macula adherens, also called the desmosome. These small, elliptical discs form spot-like points of attachment between cells that function to link the intermediate filament network of adjacent cells. The internal leaflet of the adjacent cell membranes appears dense and thick due to the presence of an amorphous material called an attachment plaque. Intermediate filaments (usually cytokeratin) extend into the plaque, where they appear to form hairpin loops. A thin, moderately dense lamina often is seen in the intercellular space of each desmosome. These contain transmembrane linking glycoproteins (desmoglein I and desmocollin I and II) which are calcium-binding proteins that mediate calcium-dependent cell adhesion that holds adjacent cell membranes in close apposition. Desmosomes are scattered along lateral epithelial surfaces and are not restricted to regions of tight junctions. They are especially abundant in stratified squamous epithelia, where they are associated with numerous intermediate filaments of the keratin type. Desmosome-like junctions that lack attachment plaques and associated keratin filaments also occur between epithelial cells. This type of cell junction has been called a punctum adherens. The basal cell membrane, although not immediately adjacent to another cell, also shows an attachment, the hemidesmosome, which closely resembles one-half of a desmosome. Hemidesmosomes act as points of adhesion between the basal plasmalemma and the underlying basal lamina and link the intermediate keratin filament network of the epithelial cells to the extracellular matrix via transmembrane anchoring glycoproteins. These transmembrane glycoproteins act as laminin receptors and bind to laminin, a glycoprotein within the lamina lucida of the basal lamina. Focal adherens type junctions also occur along the basal plasmalemma and link actin filaments to the extra-cellular matrix. Intracellular attachment proteins (α -actinin, vinculin, talin) link actin filaments to another of the transmembrane glycoproteins (integrin) that serves as a

fibronectin receptor. The latter binds to fibronectin, a multifunctional extracellular glycoprotein of the basal lamina that interacts with various types of collagens and proteoglycans in the extracellular matrix. Thus, through a series of transmembrane glycoproteins that constitute a large group of cellular adhesion molecules (CAMs) or integrins, epithelial cells are not only held tightly together in a contiguous layer but also are anchored firmly to the underlying extracellular matrix. Desmosomes and hemidesmosomes serve as firm anchoring sites for intermediate (keratin) filaments of the cytoskeleton. In addition, desmosomes function to interconnect the keratin filament network between adjacent cells, and hemidesmosomes link this network to the extracellular matrix. Such an arrangement of interconnected intermediate filaments gives mechanical stability to a group of cells so that they can maintain a specific three-dimensional shape and function as a cohesive unit. Likewise, actin microfilaments are linked not only to plasmalemma at zonula adherens and focal adherens junctions but also are interconnected with actin filaments of adjacent cells through these attachment points as well as to elements of the extracellular matrix. This arrangement provides epithelial cells with a degree of mobility and is particularly important in migrating epithelial cells (gastric and intestinal lining epithelial cells) that move continuously along the basal lamina. The integrity of desmosomes and hemidesmosomes appears to depend on the presence of calcium ions. Heparan sulfate-rich proteoglycans in the basal lamina give its surface a strong ionic (negative) charge that, acting with calcium ions, mediates the attachment of transmembrane linker glycoproteins to elements in the extracellular matrix.

Nexus Junction

The nexus, or gap junction, like tight junctions and desmosomes, forms a relatively firm point of attachment between adjacent cells. At a nexus, the cell membranes are separated by a gap 2 nm wide that is bridged by particles 8 nm in diameter. These particles, the connexons, mainly consist of the protein connexin. Each connexon unit consists of six identical transmembrane connexin proteins that are arranged around a small aqueous channel or pore. Connexon units extend through the plasmalemma and cross the intercellular gap to join a corresponding unit from the opposing cell membrane. The hydrophilic channel within the center of each connexon permits intercellular passage of ions, amino acids, and other small molecules. The nexus also provides an avenue whereby cyclic adenosine monophosphate (cAMP), released by one cell, can pass to adjacent cells. The closing and opening of the central pore appears to be regulated by intracellular levels of calcium. Thus, epithelial cells are electrically and metabolically coupled, and the response of a number of cells within an epithelial sheet to a specific stimulus can be coordinated. Because nexus junctions act as sites of communication between epithelial cells, they often are called communication junctions. In addition, nexus junctions appear to be capable of changing from low to high resistance and thereby inhibit cell communication. Gap junctions also occur between cardiac and smooth muscle cells, osteocytes, astrocytes, and some endocrine cells. Interestingly, gap junctions have not been observed between cancer cells. Adjacent lateral cell membranes of epithelial cells often do not run parallel to one another but show numerous interdigitations. Such interlocking of cell membranes also is thought to aid in maintaining cell-to-cell adhesion and stability in an epithelial sheet.

Specializations of Epithelial Membranes

The cells in an epithelial sheet often show special adaptations of apical or basolateral surfaces that increase the surface area of the cell or constitute motile "appendages" that move material across the surface. The surface specializations include microvilli, cilia, and basal-lateral infoldings.

Microvilli

Microvilli are minute, finger-like evaginations of the apical cell membrane that enclose cores of cytoplasm. Scattered microvilli occur on the surfaces of most cells of simple epithelia, but individually they are usually too small to be seen with the light microscope. In epithelia such as that lining the small intestine, however, microvilli are so numerous, uniform, and closely packed that they form a striated border that is visible by microscopy.

Microvilli also are numerous on cells forming the proximal convoluted tubules of the kidney, where they are somewhat longer and less uniform than those in the small intestine and appear as tufts on the cell apices. Because of this paint-brush tip appearance, they are called a brush border. Microvilli increase the surface area enormously, thereby enhancing the absorptive capacity of epithelial cells. The uniform shape of microvilli forming the striated and brush borders is maintained by a bundle of 25 to 40 actin filaments linked together by the actin-binding proteins villin, fimbrin, and fascin. Minimyosin molecules attach the actin filament bundle within the microvillus core to the inner surface of the plasmalemma. The actin filaments extend from the tips to the microvilli to the apical cytoplasm, where just beneath the cell surface they join a transverse zone rich in actin filaments called the terminal web. Epithelial cells that line the epididymis show unusually long, slender, branching microvilli that have been called stereocilia. However, stereocilia are not cilia but are true microvilli and also serve to increase the surface area of a cell.

Cilia

Like microvilli, cilia represent appendages of the apical cell membrane but are relatively large and often are motile. They may be single or occur in large numbers and are seen readily with the light microscope. The limiting plasmalemma of the cilium is continuous with that of the cell and encloses a core of cytoplasm containing 20 microtubules. Nine pairs of fused microtubules, the doublets, form a ring at the periphery of the cilium and surround a central pair of individual microtubules. This arrangement has been called the (9 + 2) configuration. Within each doublet, the microtubules are named the A and B microtubules. Microtubule A has two short, divergent arms that project toward microtubule B of the adjacent doublet. The arms consist of the protein dynein, which has adenosinetriphosphatase (ATPase) activity that splits ATP to provide energy for ciliary movement. Radial spokes project from the doublets to the central pair of microtubules. The microtubules of a cilium originate from a basal body in the apical cytoplasm of the cell. The basal body is similar in structure to the centriole and appears as a hollow cylinder, the wall of which consists of nine triplet microtubules. Since there are no central microtubules in a basal body, the arrangement of microtubules is expressed as (9 + 0). Each of the nine doublets in the cilium is continuous with the two innermost microtubules of the triplets in the basal body. The two central microtubules of the ciliary shaft terminate as they reach the basal body and do not join with it. Ciliary motion is thought to involve a sliding microtubule mechanism, dependent on the ability of the dynein protein arms to generate

energy through its ATPase-like activity. Cilia are numerous on epithelial cells that line much of the respiratory tract and parts of the female reproductive tract. Groups of cilia beat in a coordinated, rhythmic fashion to move a thin layer of fluid in one direction across the epithelial surface. In regions such as the distal tubules of the kidney, where cells bear a single cilium, or in the olfactory epithelium, where they occur in small groups on cells, the cilia are nonmotile and are believed to act as chemoreceptors. Cilia also are found in the maculae and cristae of the inner ear and act as mechanoreceptors. The most extreme modification of cilia is seen in the formation of the outer segments of the rods and cones of the retina, where the modified cilia serve as photoreceptors. The presence of cilia contributes to the classification of epithelia. Where cilia are present this term is incorporated into the nomenclature. Therefore, the simple columnar epithelium lining the oviduct is referred to as a ciliated simple columnar epithelium. When cilia are associated with pseudostratified columnar epithelium, as in the trachea, the epithelium is classified as a ciliated pseudostratified columnar epithelium. A rare type of immotile cilia syndrome (Kartagener's) occurs in which the dynein arms are absent. Patients with this congenital disorder are subject to respiratory infection because clearance from the lungs is impaired due to the absence of coordinated ciliary motion within the respiratory tree. Men with this syndrome are usually infertile because the axonemes of sperm flagella also are defective. Interestingly, women who are afflicted by Kartagener's syndrome may or may not be fertile even though the cilia associated with the epithelium lining the oviduct are defective.

Basolateral Infoldings

In addition to the apical specializations, some epithelial cells show elaborate infoldings of the basolateral plasmalemma. These are called basolateral infoldings and usually are prominent in epithelial cells active in fluid/ion transport, such as those forming the proximal and distal convoluted tubules of the kidneys and in those lining the ducts of salivary glands. Like microvilli, they greatly increase the surface area of the cell membrane. The plasmalemma of these regions is rich in ion channel proteins, in particular sodium-potassium-ATPase. Mitochondria, which often are numerous in this area of the cell, tend to lie parallel to the infoldings of the plasmalemma and provide substrate ATP. Because of this association, the infoldings are visible with the light microscope and appear as basal striations.

Glandular Epithelium

In addition to performing functions such as protection and absorption, the cells of an epithelial sheet also may secrete materials. Epithelial cells adapted specifically for secretion constitute the glands. It should be understood that most complex glands originate in an epithelial surface and grow out from this layer. Those that retain a connection with the epithelial surface of origin via ducts are called exocrine glands. Those that lose the ductal connection to the point of origin are designated endocrine glands. Glands can be classified according to their histologic organization, possession of ducts, type of material secreted, and manner in which material is secreted. Glands that consist of only a single cell are called unicellular; aggregates of secreting cells form multicellular glands. These can be divided into exocrine and endocrine types according to whether or not they secrete onto a surface or into a ductal system (exocrine) or directly into the tissue fluid of the intercellular space (endocrine). Complex exocrine glands can be subdivided further on the basis of the branching of their ducts, the configuration of the secretory end piece, and by the type and mode of secretion.

Unicellular Glands

The classic example of a unicellular, exocrine gland is the goblet cell, found scattered among epithelial cells lining the trachea, small intestine, and colon. The cell has a narrow base and an expanded apex filled with secretory granules. Goblet cells elaborate mucin, which, on hydration, produces a viscous lubricating fluid called mucus. The mucin is secreted onto an epithelial surface. Hence, a goblet cell is classified as a unicellular exocrine gland. Unicellular endocrine cells (glands) also occur. They are numerous in the epithelium lining the gastrointestinal tract and produce a number of peptide hormones and/or amines. They also are found in the epithelium lining the respiratory system. These cells secrete into the extracellular space the product of which may enter the adjacent vasculature and/or lymphatics.

Multicellular Glands

The simplest form of multicellular exocrine gland is the secretory sheet, exemplified by the gastric lining epithelium, in which the secreting cells form a continuous epithelial layer. Intraepithelial glands are small clusters of secretory cells that lie wholly within an epithelial sheet, clustered about a small lumen. Cells of both types of gland secrete their product onto the epithelial surface.

Complex Exocrine Glands

Exocrine glands secrete onto a luminal epithelial surface either directly, as in secretory sheets and intraepithelial glands, or by a ductal system. If the duct system of complex glands branches, the gland is said to be compound; if the duct system does not branch, the gland is classified as simple. The secretory cells may be organized into tubules, acini, alveoli (berry-like end pieces), or saccules (dilated, flask-like end pieces). Simple and compound glands can be named by the shape of the secretory portion. Thus, simple glands can be classed as simple tubular, simple coiled tubular, simple branched tubular, or simple branched acinar. Similarly, compound glands are subdivided into compound tubular, compound saccular, and compound tubuloacinar (tubuloalveolar). The initial subdivision into simple and compound is made according to whether or not the ducts branch. Subsequent classification depends on the shape and configuration of the secreting portion, the secretory unit.

It should be understood that the epithelial cells forming the closely packed tubular structures of complex glands remain arranged as a single layer of cells despite the complex appearance of the overall glandular structure. In this way a maximum number of secretory cells can be organized into the smallest area possible.

Endocrine Glands

Like exocrine glands, the complex endocrine glands arise from an epithelial sheet, but during their formation, endocrine glands lose their connections with the surface and thus lack ducts. Cells of endocrine glands secrete regulatory material (hormones), directly into tissue fluid of the extracellular space. The hormones released may target and stimulate the releasing cell itself (autocrine secretion) or adjacent cells (paracrine secretion) or enter the blood to target specific cells of distant organs. Scattered, solitary endocrine cells also occur in the gastrointestinal tract and along the conducting portion of the respiratory tract. The structure of the complex endocrine glands is so diverse that the glands do not readily lend themselves to

histologic classification. However, some overall structural patterns can be made out, and the cells may be arranged as clumps, cords, or hollow spherical structures called follicles.

Type and Mode of Secretion

Glands also can be classified as mucous, serous, or mixed according to the type of material secreted. Cells of mucous glands have pale, vacuolated cytoplasm and flattened, dense nuclei oriented toward the base of the cell. Serous cells show round nuclei surrounded by a basophilic cytoplasm that contains discrete secretory granules. Mixed glands contain variable proportions of serous and mucous cells. Two types of glands can be distinguished by their mode of secretion. *Merocrine* secretion refers to release of the product through fusion of secretory vesicles with the apical plasmalemma. This type of secretion is regulated/stimulated exocytosis and most exocrine secretion is by this mechanism. *Holocrine* secretion involves release of whole cells (such as sperm from the testes) or the breakdown of an entire cell to form the secretion (e.g., sebum in sebaceous glands). A third type of secretion, *apocrine*, has been described in which a portion of the apical cytoplasm is lost along with the secretory material. Electron microscopy has failed to support this mode of secretion except perhaps for the mammary glands during lactation. Even here, however, the existence of an apocrine secretion is dubious.

Myoepithelial Cells

The secretory units of some glands are associated with myoepithelial cells, which are specialized cells located between the glandular epithelial cells and the basal lamina. These cells are contractile and their cytoplasm contains the contractile proteins actin and myosin arranged in a similar manner to those of smooth muscle cells. These cells also contain the intermediate filament, desmin. Long cytoplasmic processes extend from the body of the cell to course around the secretory unit. The processes, by their contraction, aid in expressing products from the secretory units and into the ductal system. Myoepithelial cells occur in sweat, mammary, and salivary glands and in glands along the bronchi and esophagus.