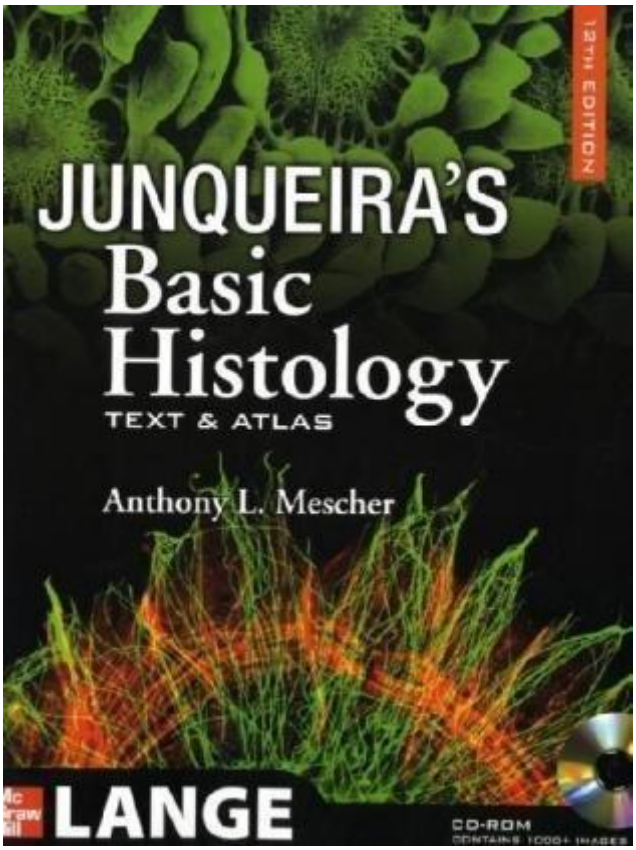
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CONTENTS

EPITHELIAL TISSUE: INTRODUCTION

Despite its complexity, the human body is composed of only **four basic types of tissue:** epithelial, connective, muscular, and nervous. These tissues, which are formed by cells and molecules of the **extracellular matrix,** exist not as isolated units but rather in association with one another and in variable proportions, forming different organs and systems of the body. The main characteristics of these basic types of tissue are shown in Table 4–1. Also of great functional importance are the free cells found in body fluids such as blood and lymph.

Table 4–1. Main characteristics of the four basic types of tissues.

Tissue	Cells	Extracellular Matrix	Main Functions
Nervous	Intertwining elongated processes	None	Transmission of nervous impulses
Epithelial	Aggregated polyhedral cells	Small amount	Lining of surface or body cavities, glandular secretion
Muscle	Elongated contractile cells	Moderate amount	Movement
Connective	Several types of fixed and wandering cells	Abundant amount	Support and protection

Connective tissue is characterized by the abundance of extracellular material produced by its cells; muscle tissue is composed of elongated cells specialized for contraction and movement; and nerve tissue is composed of cells with elongated processes extending from the cell body that have the specialized functions of receiving, generating, and transmitting nerve impulses. Organs can be divided into **parenchyma,** which is composed of the cells responsible for the main functions typical of the organ, and **stroma,** which is the supporting tissue. Except in the brain and spinal cord, the stroma is made of connective tissue.

Epithelial tissues are composed of closely aggregated polyhedral cells with very little extracellular substance. These cells have strong adhesion and form cellular sheets that cover the surface of the body and line its cavities.

The principal functions of epithelial (Gr. *epi,* upon, + *thele,* nipple) tissues are:

- Covering, lining, and protecting surfaces (eg, skin)
- Absorption (eg, the intestines)
- Secretion (eg, the epithelial cells of glands)
- Contractility (eg, myoepithelial cells).

Specific cells of certain epithelia are also highly specialized sensory cells, such as those of taste buds or the olfactory epithelium. Because epithelial cells line all external and internal surfaces of the body, everything that enters or leaves the body must cross an epithelial sheet.

CHARACTERISTIC FEATURES OF EPITHELIAL CELLS

The forms and dimensions of epithelial cells range from high **columnar** to **cuboidal** to low **squamous** cells. Their common polyhedral form results from their close juxtaposition in cellular layers or masses and is similar to what would be observed if a large number of inflated balloons were compressed into a limited space. Epithelial cell nuclei have a distinctive shape, varying from spherical to elongated or elliptic. The nuclear form often corresponds roughly to the cell shape; thus, cuboidal cells have spherical nuclei, and squamous cells have flattened nuclei. The long axis of the nucleus is always parallel to the main axis of the cell.

Because the lipid-rich membranes between cells are frequently indistinguishable with the light microscope, the stained cell nucleus is a clue to the shape and number of cells. Nuclear form is also useful to determine whether the cells are arranged in layers, a primary morphologic criterion for classifying epithelia.

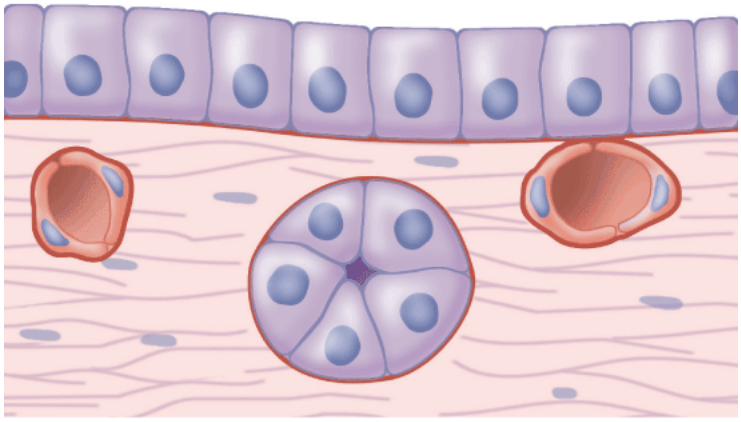
Most epithelia rest on connective tissue. In the case of epithelia lining the cavity of internal organs (especially in the digestive, respiratory, and urinary systems) this layer of connective tissue is often called the **lamina propria**. The lamina propria not only serves to support the epithelium but also provides nutrition and binds it to underlying structures. The area of contact between epithelium and lamina propria is increased by irregularities in the connective tissue surface in the form of small evaginations called **papillae** (L. diminutive of *papula*, nipple; singular **papilla**). Papillae occur most frequently in epithelial tissues subject to friction, such as the covering of the skin or tongue.

Epithelial cells generally show **polarity**, with organelles and membrane proteins distributed unevenly in different parts of the cell. The region of the cell that faces the connective tissue is called the **basal pole**, whereas the opposite pole, usually facing a space, is the **apical pole** and the intervening sides apposed in neighboring cells are the **lateral surfaces**. The membranes on the lateral surfaces of adjoining cells often have numerous infoldings to increase the area of that surface, increasing its functional capacity. The different regions of polarized cells may have different functions.

Basal Laminae & Basement Membranes

All epithelial cells in contact with subjacent connective tissue have at their basal surfaces a felt-like sheet of extracellular material called the **basal lamina** (Figure 4–1). This structure is visible only with the electron microscope, where it appears as an electron-dense layer, 20–100 nm thick, consisting of a network of fine fibrils, the **dense layer** or **lamina densa** (Figure 4–2). In addition, basal laminae may have electron-lucent layers on one or both sides of the dense layer, called **clear layers** or **laminae lucida.** Between epithelia with no intervening connective tissue, such as in lung alveoli and renal glomeruli, the basal lamina is often thicker due to the fusion of the basal laminae from each epithelial layer.

Figure 4–1.



Basal laminae.

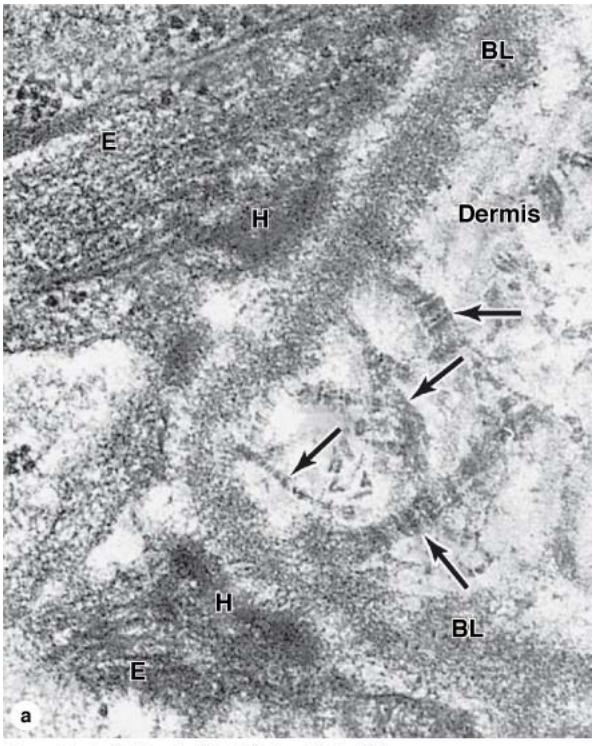
An extracellular **basal lamina** always lies at the interface of epithelial cells and connective tissue. The basal laminae to two neighboring epithelia can fuse or appear to fuse in places where there is no intervening connective tissue. Nutrients for epithelial cells must diffuse across the basal lamina. Nerve fibers normally penetrate this structure, but small blood capillaries (being epithelial themselves) never enter an epithelium across a basal lamina. When components of a basal lamina are resolved with the light microscope, the structure is often called a **basement membrane**.

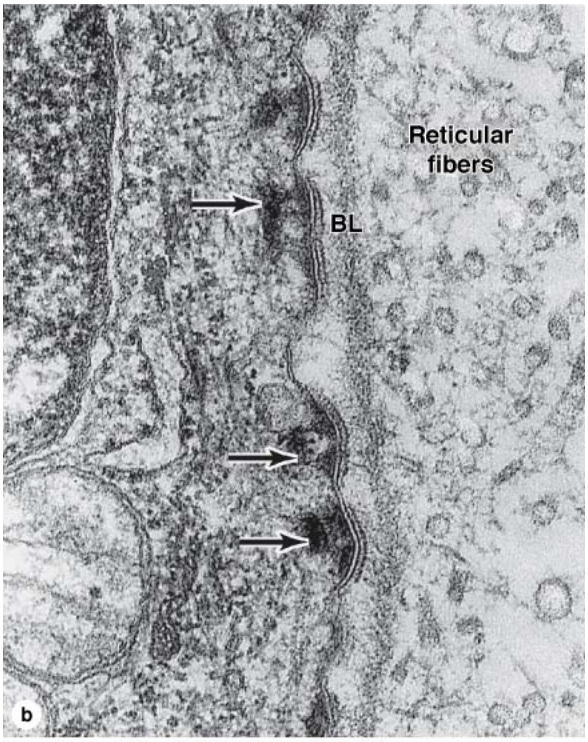
The macromolecular components of basal laminae form precise three-dimensional arrays and are described individually in the next chapter. The best known of these include:

- **Laminin**: These are large glycoprotein molecules that self-assemble to form a lace-like sheet immediately below the cells' basal poles where they are held in place by the transmembrane integrins.
- **Type IV collagen**: Monomers of type IV collagen contain three polypeptide chains and self-assemble further to form a felt-like sheet associated with the laminin layer.
- **Entactin (nidogen)**, a glycoprotein, and **perlecan**, a proteoglycan with heparan sulfate side chains: these glycosylated proteins and others serve to link together the laminin and type IV collagen sheets.

All these components are secreted at the basal poles of the epithelial cells. Their precise proportions in basal laminae vary between and within tissues. Basal laminae are attached to **reticular fibers** made of **type III collagen** in the underlying connective tissues by **anchoring fibrils** of **type VII collagen**. These proteins are produced by cells of the connective tissue and form a layer below the basal lamina called the **reticular lamina** that is also visible by TEM (Figure 4–2).

Figure 4–2.





Ultrastructural components of the basal lamina.

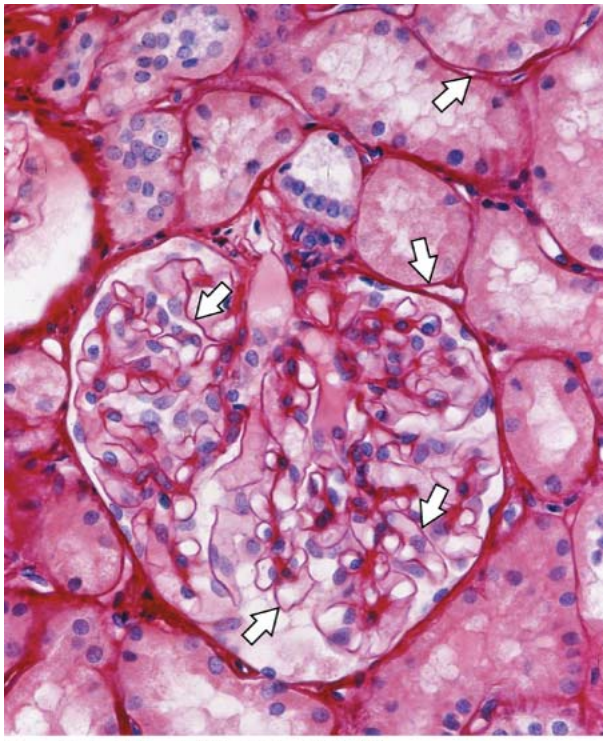
Details of the basal lamina are revealed by two TEM of sectioned human skin. **(a):** The basal lamina (BL) is shown to have a dense layer with a clear layer on each side. The underlying dermis contains **anchoring fibrils** (arrows) of collagen which help anchor the epithelium to the underlying connective tissue. Hemidesmosomes (H) occur at the epithelial–connective tissue junction. X54,000. **(b):** The basal lamina, hemidesmosomes (arrows), and underlying **reticular fibers** of the reticular lamina typically comprise a basement membrane sometimes visible with the light microscope. X80,000.

Basal laminae are found not only in epithelial tissues but also where other cell types come into contact with connective tissue. Muscle cells, adipocytes, and Schwann cells secrete laminin, type IV collagen, and other components that provide a barrier limiting or regulating exchanges of macromolecules between these cells and connective tissue.

Basal laminae have many functions. In addition to simple structural and filtering functions, they are also able to influence cell polarity; regulate cell proliferation and differentiation by binding and concentrating growth factors; influence cell metabolism and survival; organize the proteins in the adjacent plasma membrane (affecting signal transduction); and serve as pathways for cell migration. The basal lamina seems to contain the information necessary for many cell-to-cell interactions, such as the reinnervation of denervated muscle cells. The presence of the basal lamina around a muscle cell is necessary for the establishment of new neuromuscular junctions.

The term **basement membrane** is used to specify a periodic acid–Schiff (PAS)-positive layer, visible with the light microscope beneath epithelia (Figure 4–3). The basement membrane is formed by the combination of a basal lamina and a reticular lamina and is therefore thicker. The terms basement membrane and basal lamina are often used indiscriminately, causing confusion. In this book, "basal lamina" is used to denote the lamina densa and its adjacent layers and structures seen with the TEM. "Basement membrane" is used to denote the structures seen with the light microscope.

Figure 4–3.



Basement membranes.

This section of kidney shows the typical basement membranes (arrows) of several tubules and of structures within the single glomerulus included here. In renal glomeruli the basement membrane, besides having a supporting function, has an important role as a filter. X100. Picrosirius-hematoxylin (PSH).

Intercellular Adhesion & Other Junctions

Several membrane-associated structures contribute to adhesion and communication between cells. They are present in most tissues but are particularly numerous and prominent in epithelia and will be described here. Epithelial cells are extremely cohesive and relatively strong mechanical forces are necessary to separate them. Intercellular adhesion is especially marked in epithelial tissues that are subjected to traction and pressure (eg, in the skin).

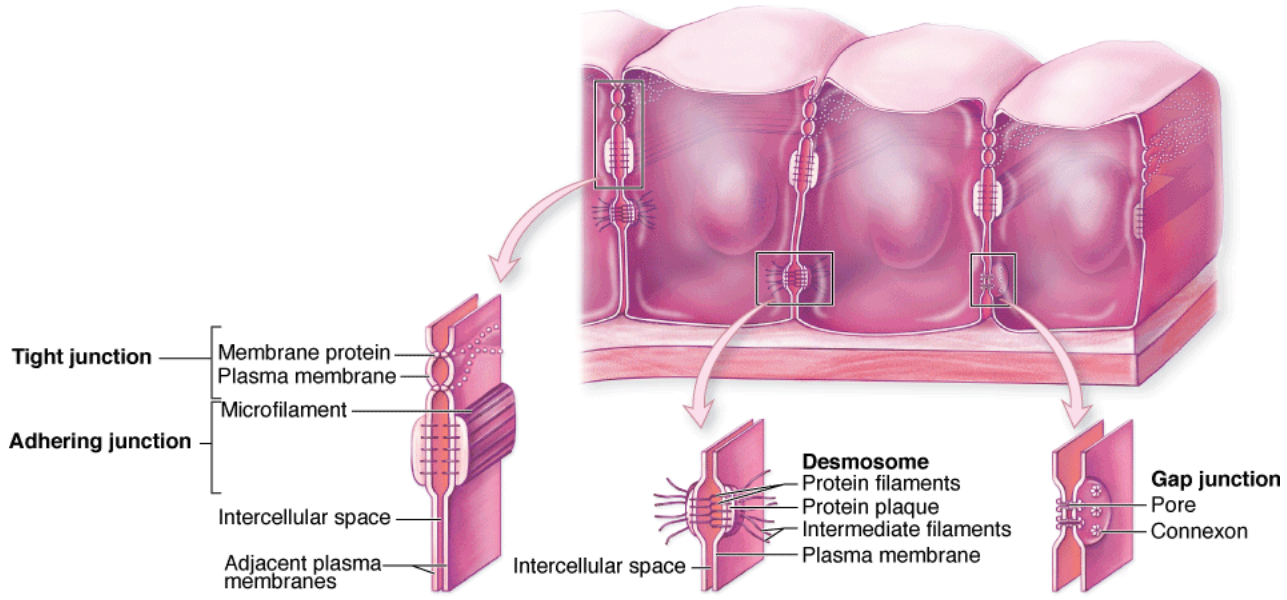
The lateral membranes of epithelial cells exhibit several specialized **intercellular junctions.** Various junctions serve to function as:

- Seals to prevent the flow of materials between the cells (**occluding junctions**)
- Sites of adhesion (**adhesive** or **anchoring junctions**)
- Channels for communication between adjacent cells (**gap junctions**).

In several epithelia such junctions are present in a definite order from the apical to the basal ends of the cells.

Tight junctions, or **zonulae occludens** (singular, **zonula occludens**), are the most apical of the junctions. The Latin terminology gives important information about the geometry of the junction. "Zonula" indicates that the junctions form bands completely encircling each cell, and "occludens" refers to the membrane fusions that close off the space between the cells. In properly stained thin sections viewed in the TEM, the adjacent membranes appear tightly apposed or fused (Figures 4–4 and 4–5). The seal between the membranes is due primarily to direct interactions between the transmembrane protein **claudin** on each cell. After cryofracture (Figure 4–6), the replicas show these fusion sites as a band of branching strands around each cell. The number of these sealing strands or fusion sites is inversely correlated with the leakiness of the epithelium. Epithelia with one or very few fusion sites (eg, proximal renal tubule) are more permeable to water and solutes than are epithelia with numerous fusion sites (eg, the lining of the urinary bladder). Thus, the principal function of the tight junction is to form a seal that prevents the flow of materials between epithelial cells (the paracellular pathway) in either direction. In this way, zonulae occludens in sheets of epithelial cells help form two functional compartments: an apical compartment that is composed of an organ cavity (such as the lumen of a secretory unit or the gut) and a basal compartment that begins at the junctions and encompasses the underlying tissue.

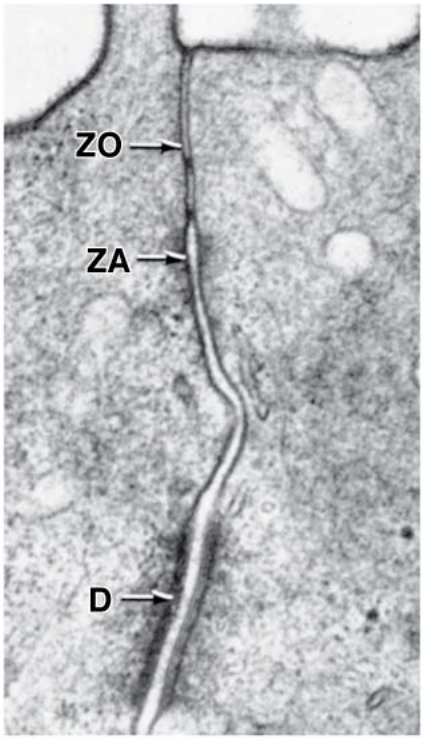
Figure 4–4.



Junctional complexes of epithelial cells.

Three cuboidal epithelial cells, emptied of their contents, show the four major types of junctional complexes between cells. The **tight junction** (zonula occludens) and **adherent junction** (zonula adherens) are typically close together and each forms a continuous ribbon around the cell's apical end. Multiple ridges of the tight, occluding junctions prevent passive flow of material between the cells, but are not very strong; the adhering junctions immediately below them serve to stabilize and strengthen these circular bands around the cells and help hold the layer of cells together. Both desmosomes and gap junctions make spotlike plaques between two cells. Bound to intermediate filaments inside the cells, **desmosomes** form very strong attachment points which supplement the role of the zonulae adherens and play a major role to maintain the integrity of an epithelium. **Gap junctions**, each a patch of many **connexons** in the adjacent cell membranes, have little strength but serve as intercellular channels for flow of molecules. All of these junctional types are also found in certain other cell types besides epithelia.

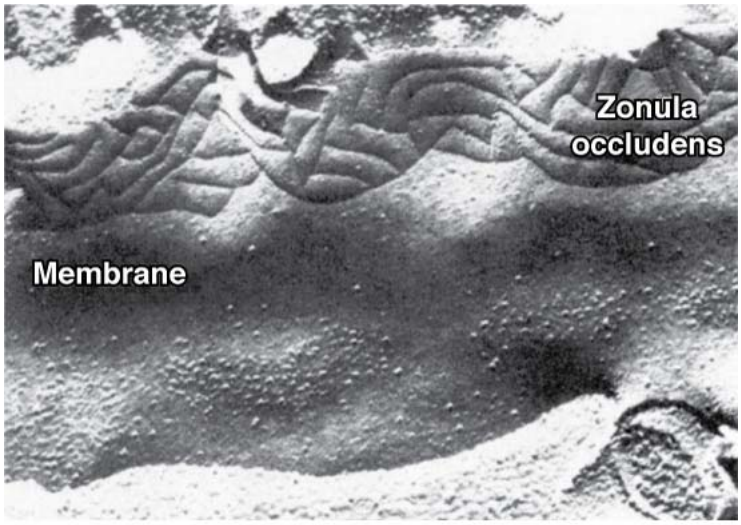
Figure 4–5.



Junctional complex as seen in the TEM.

A section showing the apical regions of two epithelial cells reveals a junctional complex with its zonula occludens (ZO), zonula adherens (ZA), and a desmosome (D). The major components of zonula occludens are each cell's transmembrane proteins called claudins which make tight contact across the intercellular space, creating a seal. The cytoplasmic electron-dense material at the zonula adherens includes cadherins, catenin, actin-binding proteins and actin filaments, but that of the desmosomes consists of a plaque of "anchoring proteins," such as plakophilin, plakoglobin, and desmoplakin, which are bound by intermediate filaments primarily those composed of keratins. X80,000.

Figure 4–6.



View of zonula occludens after cryofracture.

In this electron micrograph of an epithelial cell after cryofracture, the fracture crosses through the cytoplasm in the lower portion, then shows a region of relatively smooth cell membrane, above which are the ridges and grooves of the zonula occludens. The membranes of adjoining cells basically fuse in the zonula occludens caused by tight interaction between claudins. X100,000.

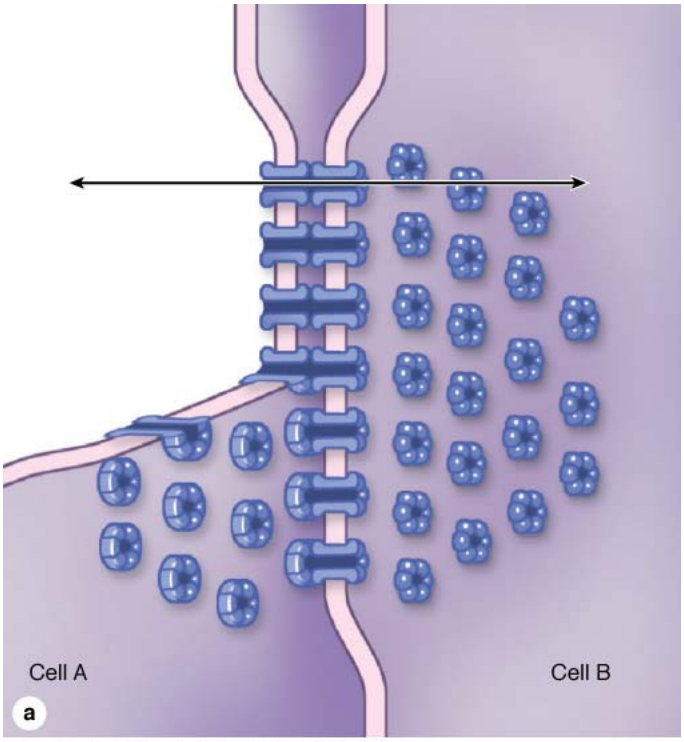
Besides forming a seal between compartments on either side of an epithelium, the zonulae occludens of epithelial cells help prevent the integral membrane proteins of the apical surface from being transferred to the basolateral surface and vice versa. This allows the two sides of the epithelium to maintain different receptors and function differently.

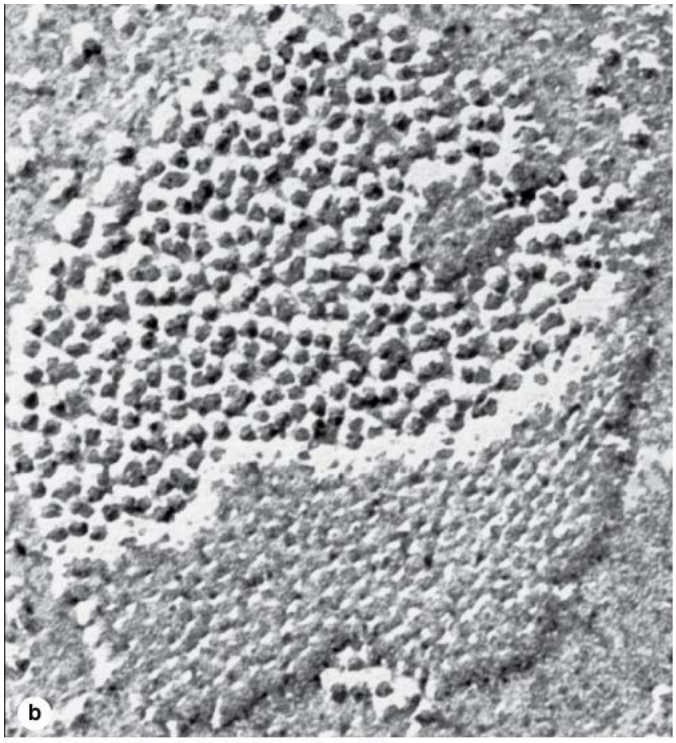
The next type of junction is the **adherent junction** or **zonula adherens** (Figures 4–4 and 4–5). This junction also encircles the cell, usually immediately below the zonula occludens, and provides for the firm adhesion of one cell to its neighbors. Adhesion is mediated by transmembrane glycoproteins of each cell, the **cadherins**, which lose their adhesive properties in the absence of Ca^{2+}. Inside the cell, cadherins bind the protein catenin which is linked by means of actin-binding proteins to actin filaments, all of which produce electron-dense plaques of material on the cytoplasmic surfaces of adherent junctions. The numerous actin filaments form part of the **terminal web,** a cytoskeletal feature at the apical pole in many epithelial cells with a role in cytoplasmic motility and other functions.

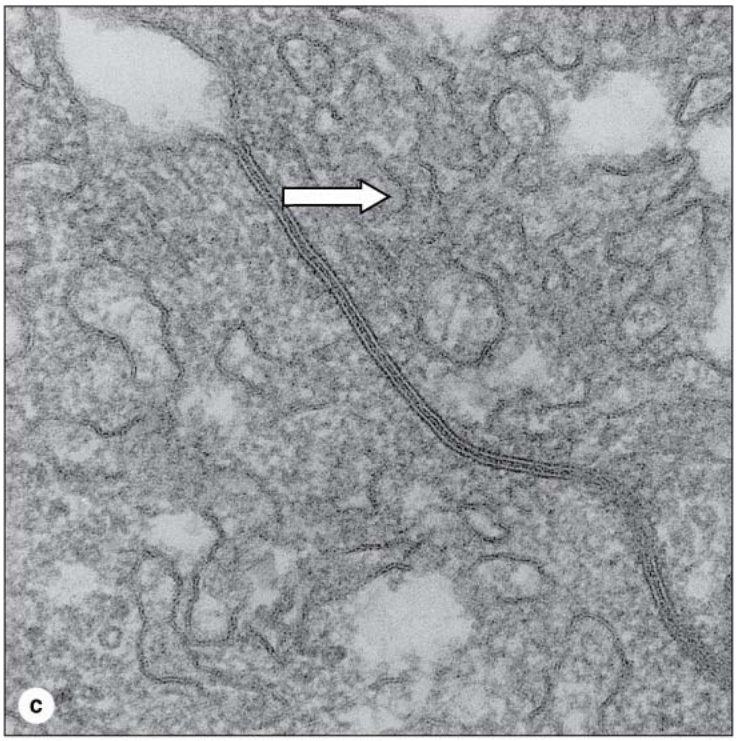
Another junction specialized for adhesion is the **desmosome** or **macula adherens** (L. *macula,* spot). As the names imply, this junctional type resembles a single "spot-weld" and does not form a belt around the cell. The desmosome is a disk-shaped structure at the surface of one cell that is matched with an identical structure at the surface of an adjacent cell (Figures 4–4 and 4–5). Between cell membranes at a desmosome are variable amounts of electron-dense material, principally larger members of the cadherin family. On the cytoplasmic side of each cell membrane these cadherin-type proteins inset into a dense **attachment plaque** of anchoring proteins (**plakophilin, plakoglobin,** and **desmoplakin**) which bind intermediate filaments rather than actin filaments. Cable-like filaments of **cytokeratin** are most common in desmosomes of epithelia. Because intermediate filaments of the cytoskeleton are very strong, desmosomes provide firm adhesion among the cells. In nonepithelial cells, the intermediate filaments attached to desmosomes are composed of other proteins, such as desmin or vimentin.

Gap or **communicating junctions** can occur almost anywhere along the lateral membranes of epithelial cells, but are also found between cells in nearly all mammalian tissues. With conventional TEM, gap junctions appear as regions where adjacent cell membranes are closely apposed (Figure 4–7a). After cryofracture, these junctions are seen as aggregated transmembrane protein complexes that form circular patches in the plasma membrane (Figure 4–7b).

Figure 4–7.







Gap junctions.

(a): The diagram of a gap junction (oblique view) depicts the structural elements that allow the exchange of nutrients and signal molecules between cells without loss of material into the intercellular space. The communicating channels are formed by pairs of abutting particles (**connexons**), which are in turn composed of six dumbbell-shaped protein subunits (connexins) that span the lipid bilayer of each cell membrane. The channel passing through the cylindrical bridges (arrow) is about 1.5 nm in diameter, limiting the size of the molecules that can pass through it. **(b):** A cryofracture preparation shows a gap junction between epithelial cells. The junction appears as a plaquelike agglomeration of intramembrane protein particles, the connexons. X45,000. **(c):** A section through a gap junction between two cells shows that the two cell membranes are very closely apposed, separated only by a 2-nm-wide electron-dense space. Individual connexons are not resolved in cell sections. X193,000. (Figure 4–7c, with permission, from Mary C. Williams, Pulmonary Center, Boston University School of Medicine.)

The proteins of gap junctions, called **connexins**, form hexameric complexes called **connexons**, each of which has a central hydrophilic pore about 1.5 nm in diameter. When two cells attach, connexins in the adjacent cell membranes move laterally and align to form connexons between the two cells (Figure 4–4), with each gap junction having dozens or hundreds of aligned pairs of connexons. Gap junctions permit the rapid exchange between cells of molecules with small (<1.5 nm) diameters. Some molecules mediating signal transduction, such as cyclic AMP, cyclic GMP, and ions, move readily through gap junctions, allowing cells in many tissues to act in a coordinated manner rather than as independent units. A good example is heart muscle, where abundant gap junctions are greatly responsible for the heart's coordinated beat.

In the contact area between epithelial cells and the subjacent basal lamina, **hemidesmosomes** (Gr. *hemi,* half, + *desmos* + *soma*) can often be observed ultrastructurally. These adhesive structures resemble a half-desmosome and bind the cell to the basal lamina (Figure 4–2). However, while in desmosomes the attachment plaques contain cadherins, in hemidesmosomes the plaques contain abundant **integrins,** transmembrane proteins that are receptor sites for the extracellular macromolecules laminin and collagen type IV.

Blood vessels do not normally penetrate an epithelium and nutrients for the epithelial cells must pass out of the capillaries in the underlying lamina propria. These nutrients then diffuse across the basal lamina and are taken up through the basolateral surfaces of the epithelial cell, usually by an energy-dependent process. Receptors for chemical messengers (eg, hormones, neurotransmitters) that influence the activity of epithelial cells are localized in the basolateral membranes. In absorptive epithelial cells, the apical cell membrane contains, as integral membrane proteins, enzymes such as disaccharidases and peptidases, which complete the digestion of molecules to be absorbed.

SPECIALIZATIONS OF THE APICALCELL SURFACE

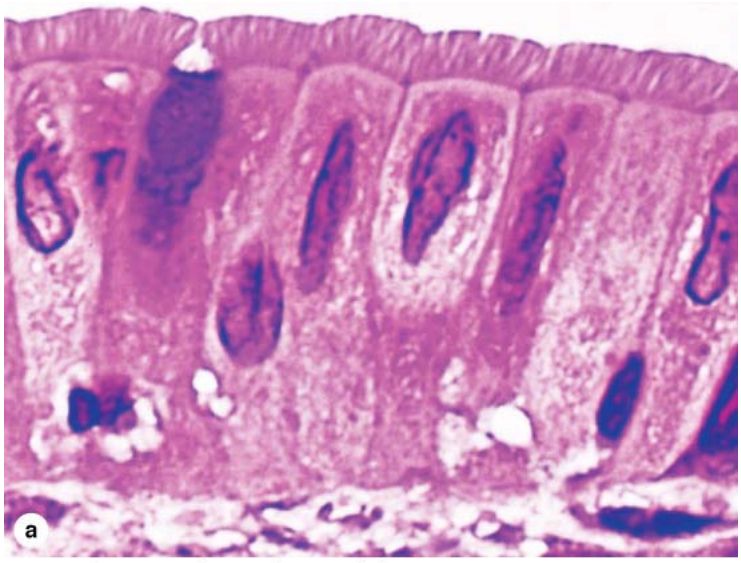
The free or apical surface of many types of epithelial cells has specialized structures to increase the cell surface area or to move substances or particles bound to the epithelium.

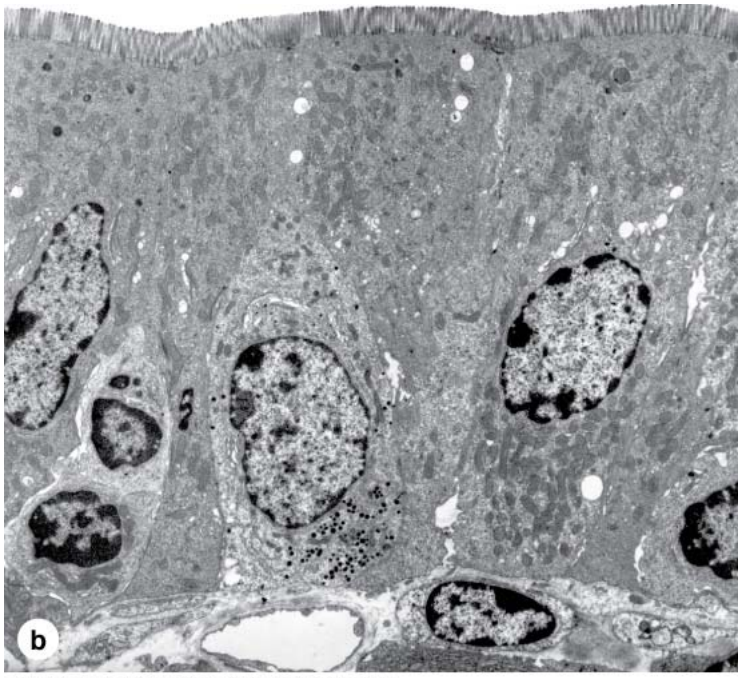
Microvilli

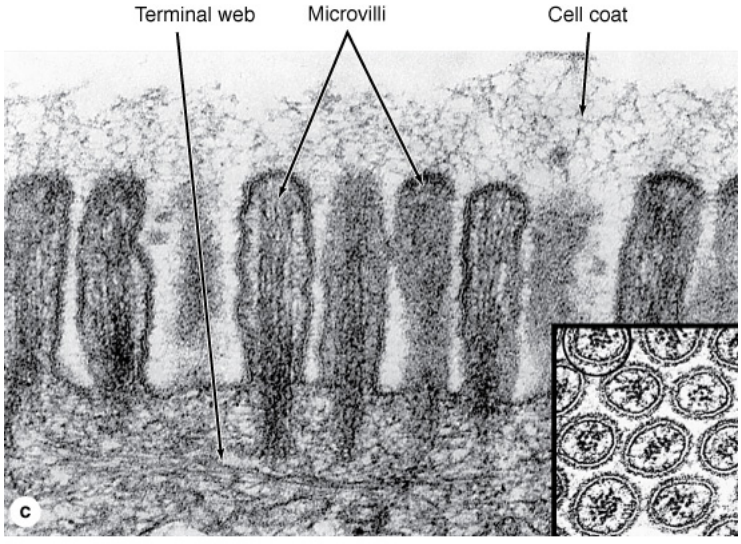
When viewed in the electron microscope, many cells are seen to have cytoplasmic projections. These projections may be short or long fingerlike extensions or folds that pursue a sinuous course, and they range in number from a few to many. Most are temporary, reflecting cytoplasmic movements and the activity of actin filaments.

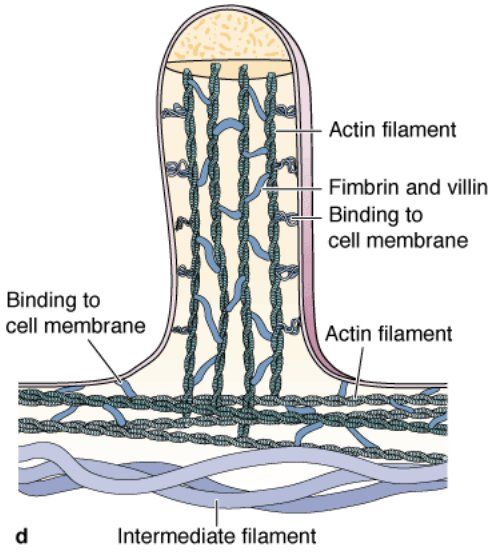
In absorptive cells, such as the lining epithelium of the small intestine, the apical surface presents orderly arrays of many hundreds of more permanent **microvilli** (L. *villus,* tuft) (Figure 4–8). The average microvillus is only about 1 μm high and 0.08 μm wide, but with hundreds or thousands present on the end of each absorptive cell, the total surface area can be increased as much as 20- or 30-fold. In these absorptive cells the glycocalyx is thicker than that of most cells and includes enzymes for the final stages of certain macromolecules' breakdown. The complex of microvilli and glycocalyx is easily seen in the light microscope and is called the **brush** or **striated border.**

Figure 4–8.









Microvilli.

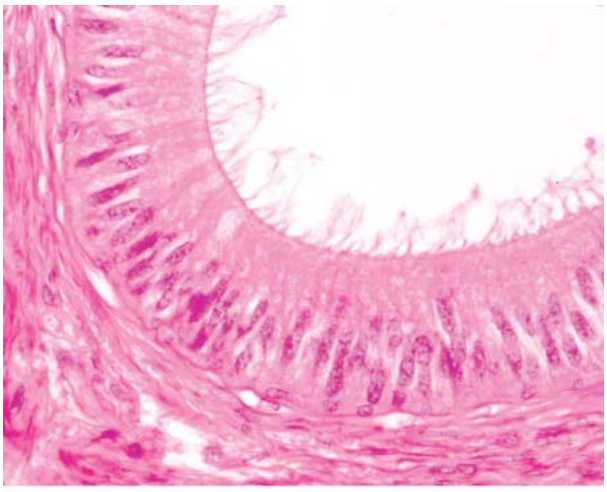
Absorptive cells lining the small intestine demonstrate microvilli particularly well. **(a):** With the light microscope microvilli at the apical side of the epithelium are usually faintly visible and make up the so-called **striated border** of the cells. **(b):** Individual microvilli are better seen by the TEM with a slightly higher magnification. Scattered endocrine cells (E) in this epithelium do not extend to the apical surface and lack microvilli. **(c):** At higher magnification the bundles of vertical microfilaments constituting the core of each microvillus are clearly seen. Below the microvilli is the terminal web, a horizontal network of actin microfilaments and associated proteins including myosins. On the plasmalemma of the microvilli is a thick extracellular cell coat (glycocalyx) containing glycoproteins and enzymes that allow the final stages of digestion to be linked to the uptake of digestion products across the cell membrane. The inset of cross-sectioned microvilli shows the internal disposition of the bundled actin filaments, the surrounding cell membrane, and the glycocalyx. X45,000. **(d):** The diagram indicates important proteins in a microvillus: the **actin filaments** cross-linked to one another by proteins such as **fimbrin** and **villin** and bound to the plasma membrane by proteins such as myosin I. The actin filaments are oriented in the same direction, with their plus ends associated with amorphous material at the tip of the microvillus.

Within each microvillus are bundles of actin filaments (Figure 4–8c,d) cross-linked to each other and to the surrounding plasma membrane by other proteins. These filaments insert into the actin filaments of the terminal web. The array of microfilaments stabilizes the microvillus and allows it to contract slightly and intermittently which helps maintain optimal conditions for absorption across its plasmalemma.

Stereocilia

Stereocilia are long apical processes of cells in other absorptive epithelia such as that lining the epididymis (Figure 4–9) and ductus deferens. These structures are much longer and less motile than microvilli, are branched, and should not be confused with true cilia. Like microvilli, stereocilia also increase the cells' surface area, facilitating the movement of molecules into and out of the cell.

Figure 4–9.



Stereocilia.

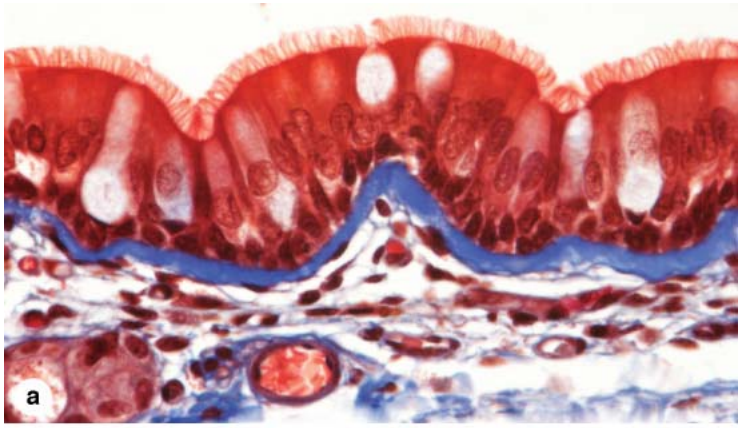
At the apical ends of the tall epithelial cells lining organs such as the epididymis (shown here) are numerous very long stereocilia, which increase the surface area available for cellular absorption. Each stereocilium is typically much longer than a microvillus and may show a branching structure. Stereocilia have cytoplasmic actin filament bundles and external cell coats similar to those of microvilli. X400. H&E.

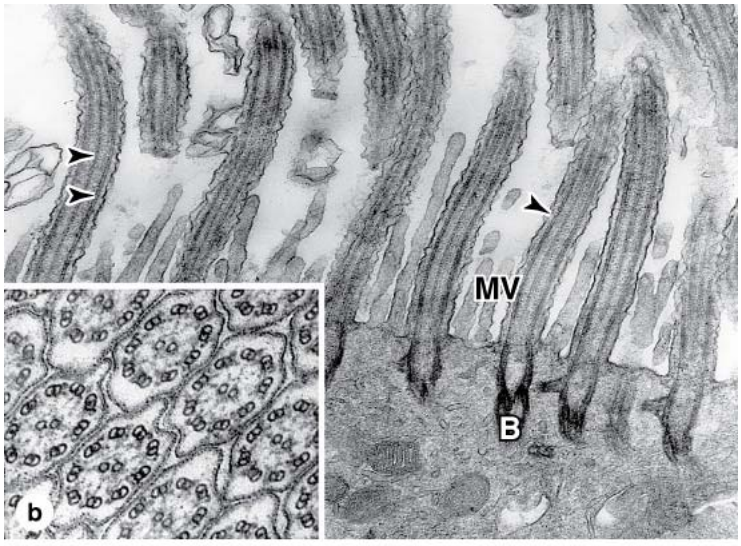
Cilia

Cilia are elongated, highly motile structures on the surface of some epithelial cells, 5–10 μm long and 0.2 μm in diameter, which is much longer and two times wider than a typical microvillus. As discussed in Chapter 2, each cilium is bounded by the cell membrane and contains an axoneme with a central pair of microtubules surrounded by nine peripheral microtubular pairs (Figure 4–10). Cilia are inserted into **basal bodies,** which are electron-dense structures at the apical pole just below the cell membrane (Figure 4–10). Basal bodies have a structure similar to that of centrioles. In living organisms, cilia exhibit rapid back-and-forth movements coordinated to propel a current of fluid and suspended matter in one direction over the ciliated epithelium. The motion occurs due to activity of **ciliary dynein** present on the peripheral microtubular doublets of the axoneme, with adenosine triphosphate (ATP) as the energy source. A ciliated cell of the trachea lining is estimated to have about 250 cilia. Flagella, present in the human body only in spermatozoa (Chapter 21), are similar in structure to cilia but are much longer and are normally

limited to one flagellum per cell.

Figure 4–10.





Cilia.

TEMs of the apical portions of cells lining the respiratory tract show very well-developed cilia. **(a):** By light microscopy cilia usually appear as long, somewhat tangled projections. X400. Mallory trichrome. **(b):** TEM of cilia sectioned longitudinally reveals the axoneme of each, with arrowheads on the left side showing the central and peripheral microtubules. The arrowhead at right indicates the plasma membrane surrounding a cilium. At the base of each cilium is a basal body (B) from which it grows. Much shorter microvilli (MV) can be seen between the cilia. X59,000. **Inset:** Cilia seen in cross section clearly show the 9 + 2 array of the axoneme microtubules in each cilium. X80,000.

TYPES OF EPITHELIA

Epithelia can be divided into two main groups according to their structure and function: **covering (or lining) epithelia** and **glandular epithelia.** This is an arbitrary division, for there are lining epithelia in which all the cells secrete (eg, the lining of the stomach) or in which glandular cells are distributed among the lining cells (eg, mucous cells in the small intestine or trachea).

Covering or Lining Epithelia

Covering epithelia are tissues in which the cells are organized in layers that cover the external surface or line the cavities of the body. They are classified according to the number of cell layers and the morphologic features of the cells in the surface layer (Table 4–2). **Simple epithelia** contain only one layer of cells and **stratified epithelia** contain more than one layer.

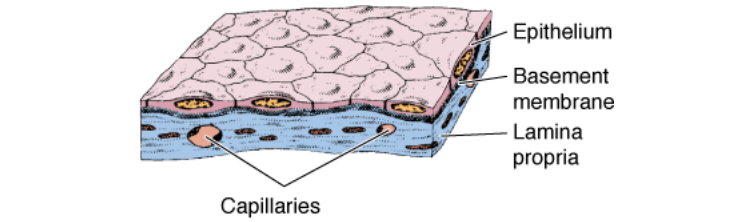
Table 4–2. Common types of covering epithelia in the human body.

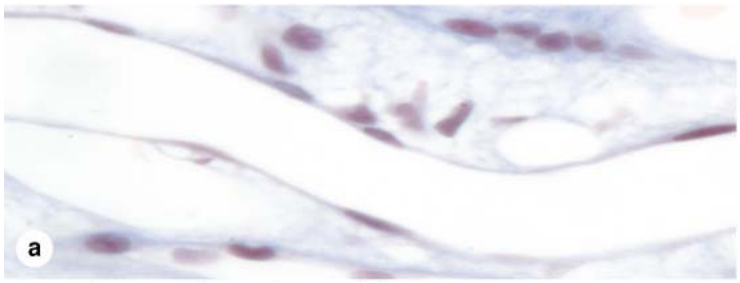
Number of Cell Layers	Cell Form	Examples of Distribution	Main Function
Simple (one layer)	Squamous	Lining of vessels (endothelium). Serous lining of cavities; pericardium, pleura, peritoneum (mesothelium).	Facilitates the movement of the viscera (mesothelium), active transport by pinocytosis (mesothelium and endothelium), secretion of biologically active molecules (mesothelium).
	Cuboidal	Covering the ovary, thyroid.	Covering, secretion.
	Columnar	Lining of intestine, gallbladder.	Protection, lubrication, absorption, secretion.
Pseudostratified (layers of cells with nuclei at different levels; not all cells reach surface but all adhere to basal lamina)		Lining of trachea, bronchi, nasal cavity.	Protection, secretion; cilia-mediated transport of particles trapped in mucus out of the air passages.
Stratified (two or more layers)	Squamous keratinized (dry)	Epidermis.	Protection; prevents water loss.

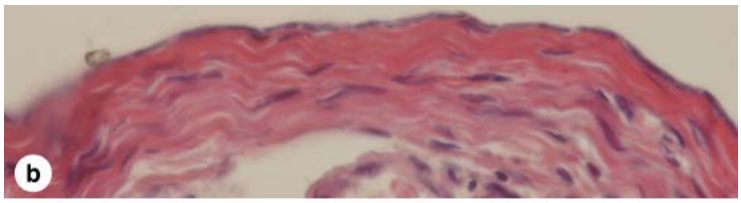
Number of Cell Layers	Cell Form	Examples of Distribution	Main Function
	Squamous nonkeratinized (moist)	Mouth, esophagus, larynx, vagina, anal canal.	Protection, secretion; prevents water loss.
	Cuboidal	Sweat glands, developing ovarian follicles.	Protection, secretion.
	Transitional	Bladder, ureters, renal calyces.	Protection, distensibility.
	Columnar	Conjunctiva.	Protection.

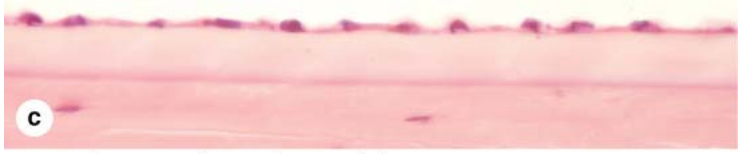
Based on cell shape, simple epithelia are classified as **squamous** (thin cells)**, cuboidal** (cells roughly as thick as they are wide) or **columnar** (cells taller than they are wide) Examples of simple epithelia are shown in Figures 4–11, 4–12, and 4–13.

Figure 4–11





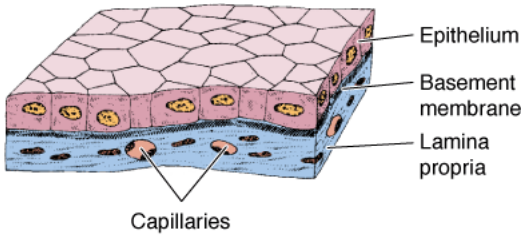


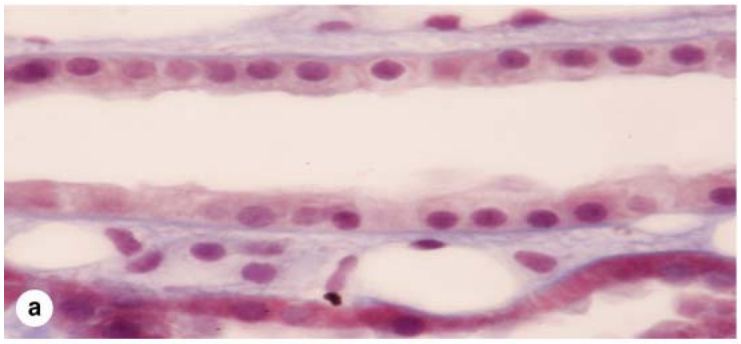


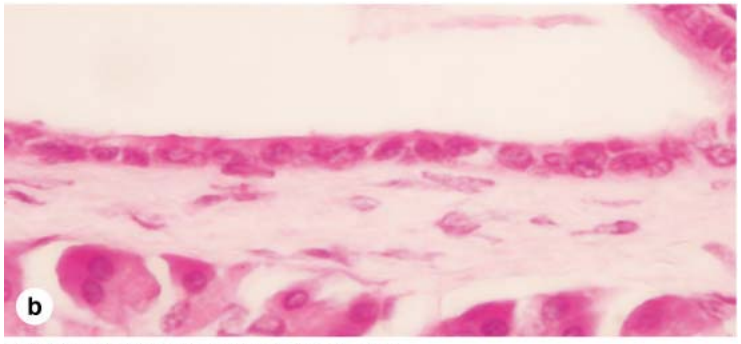
Simple squamous epithelia.

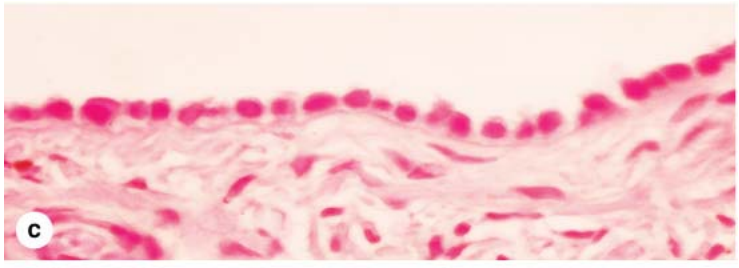
In simple squamous epithelium, cells of the single layer are flat and usually very thin, with only the thicker cell nucleus appearing as a bulge to denote the cell. Simple epithelia are typically specialized as lining of vessels and cavities and regulate substances which can enter underlying tissue from the vessel or cavity. The thin cells often exhibit transcytosis. Examples shown here are those lining the renal loops of Henle **(a),** the mesothelium lining a mesentery **(b),** and the endothelium lining the inner surface of the cornea **(c).** Endothelium and mesothelium are nearly always simple squamous. All X400. H&E.

Figure 4–12.





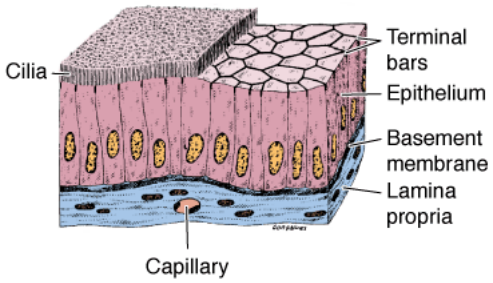


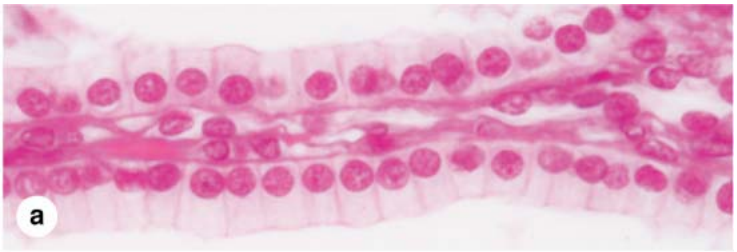


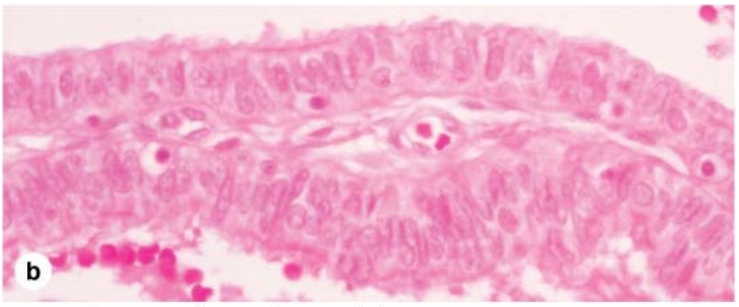
Simple cuboidal epithelium.

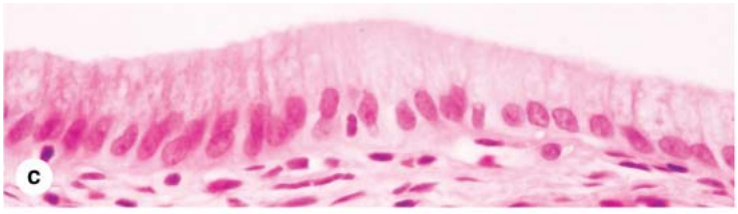
Cells of simple cuboidal epithelia vary in their height but are roughly as tall as they are wide. Their greater thickness often includes cytoplasm rich in mitochondria providing energy for a high level of active transport of substances across the epithelium. Examples of simple cuboidal epithelia shown here are from a renal collecting tubule **(a),** a pancreatic duct **(b),** and the mesothelium covering an ovary **(c).** All X400. H&E.

Figure 4–13.









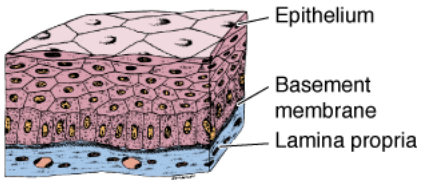
Simple columnar epithelium.

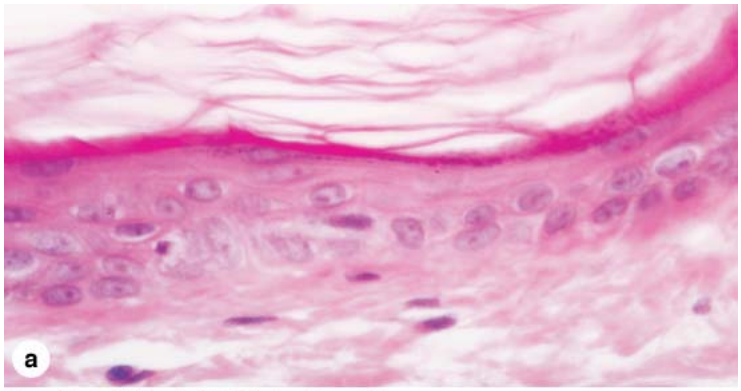
Cells of simple columnar epithelia are taller than they are wide. Such cells are usually highly specialized for absorption, with microvilli, and often have interspersed secretory cells or ciliated cells. Such epithelial cells always have tight and adherent junctional complexes at their apical ends, but are often loosely associated in more basolateral areas. This allows for rapid transfer of absorbed material to the space between the cells rather than transport the full length of the cells. The additional cytoplasm in columnar cells allows additional mitochondria and other organelles needed for absorption and processing. The examples shown here are from a renal collecting duct **(a),** the oviduct lining, with both secretory and ciliated cells **(b),** and the lining of the gall bladder **(c).** All X400. H&E.

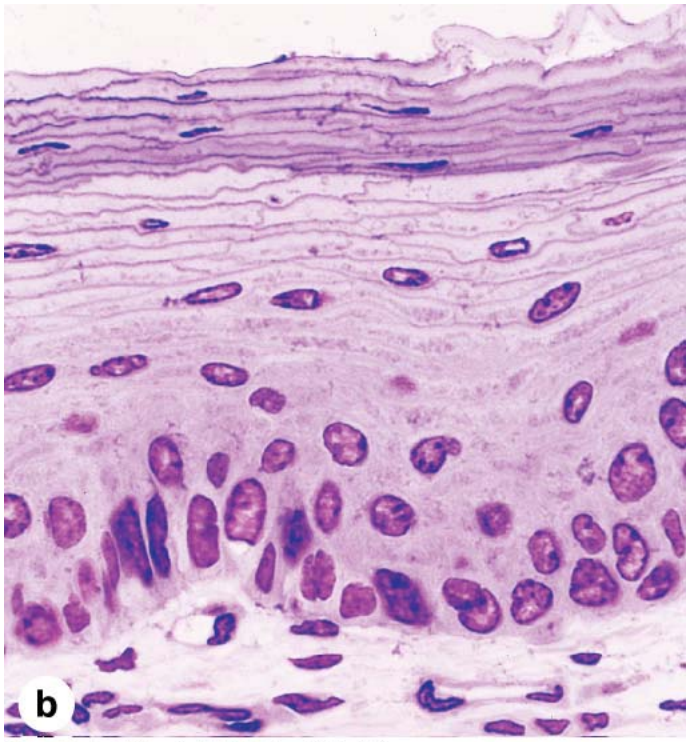
Stratified epithelia are classified according to the cell shape of the *superficial* layer(s): **squamous, cuboidal, columnar,** and **transitional.**

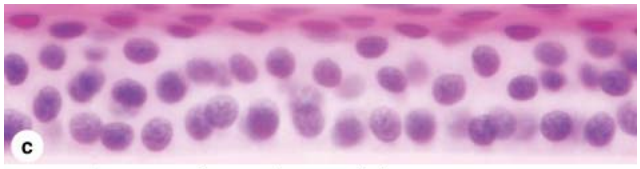
The very thin surface cells of stratified squamous epithelia can be "keratinized" (rich in keratin intermediate filaments) or "nonkeratinized" (with relatively sparse amounts of keratin). **Stratified squamous keratinized epithelium** is found mainly in the epidermis of skin. Its cells form many layers, and the cells closer to the underlying connective tissue are usually cuboidal or low columnar. The cells become irregular in shape and flatten as they accumulate keratin in the process of **keratinization** and are moved progressively closer to the surface, where they become thin, metabolically inactive packets (**squames**) of keratin lacking nuclei. This surface layer of cells helps protect against water loss across this epithelium. (See Chapter 18 for more detailed information on skin.) **Stratified squamous nonkeratinized epithelium** (Figure 4–14) lines wet cavities (eg, mouth, esophagus, and vagina). In such areas where water loss is not a problem, the flattened cells of the epithelial surface layer are living cells containing much less keratin and retaining their nuclei.

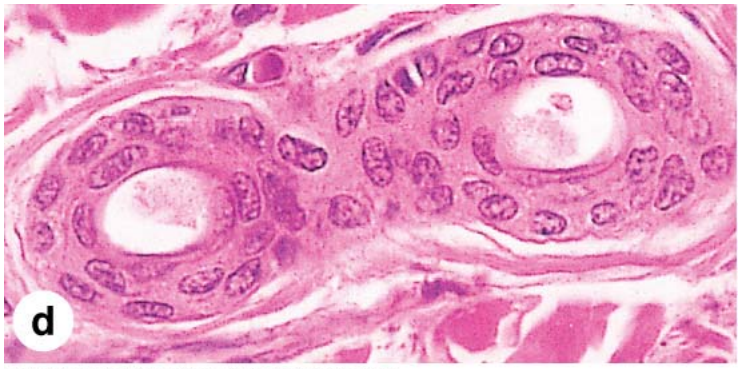
Figure 4–14.











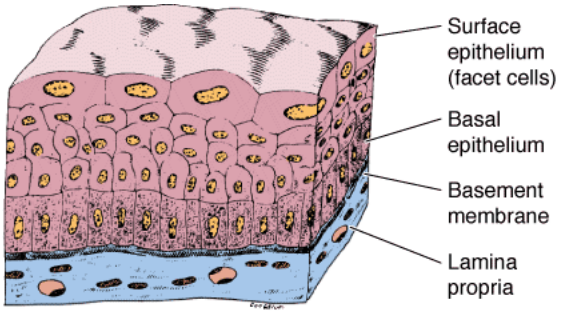
Stratified epithelia.

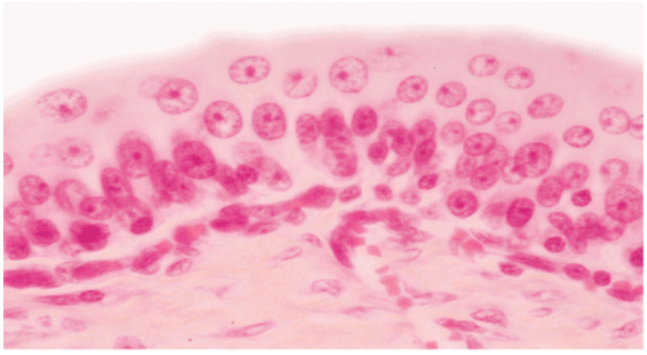
Stratified squamous epithelia have protective functions: protection against easy invasion of underlying tissue by microorganisms and protection against water loss. In the skin, protection against water loss and desiccation is particularly important and the epithelium is **keratinized**. As epidermal cells of the skin **(a)** differentiate they become filled with keratin and other substances and eventually lose their nuclei and other organelles. The superficial flattened squames form a layer which impedes water loss and eventually slough off and are replaced from below. Keratinization will be discussed fully in Chapter 18. Epithelia lining many internal surfaces such as the esophagus **(b),** or covering the cornea **(c)** are considered **nonkeratinized** because the differentiating cells accumulate much less keratin and retain their nuclei. Such epithelia still provide protection against microorganisms, but do not fill with keratin because water loss is less of an issue. Stratified cuboidal or columnar epithelia are fairly rare, but are found in excretory ducts of some glands (**d**) where the double layer of cells apparently provides a more robust lining than a simple epithelium would. All X400; (b) PT, (a, c, and d) H&E.

Stratified cuboidal and **stratified columnar epithelia** are rare. Stratified columnar epithelium can be found in the conjunctiva lining the eyelids, where it is both protective and mucus secreting. Stratified cuboidal epithelium is restricted to large excretory ducts of sweat and salivary glands, where it apparently provides a lining more robust than that of a simple epithelium.

Transitional epithelium or **urothelium**, which lines only the urinary bladder, the ureter, and the upper part of the urethra, is characterized by a superficial layer of domelike cells that are neither squamous nor columnar (Figure 4–15). These cells, sometimes called umbrella cells, are essentially protective against the hypertonic and potentially cytotoxic effects of urine. Importantly, the form of the surface cells changes according to the degree of distention of the bladder wall. This type of epithelium is discussed in detail in Chapter 19.

Figure 4–15.





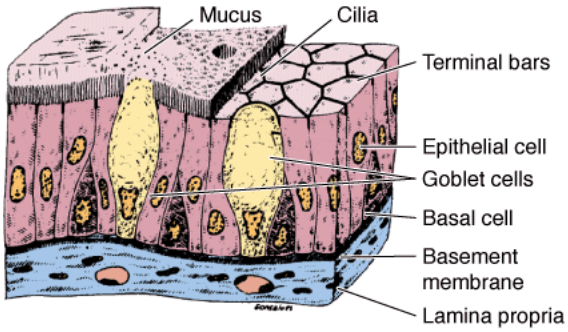
Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

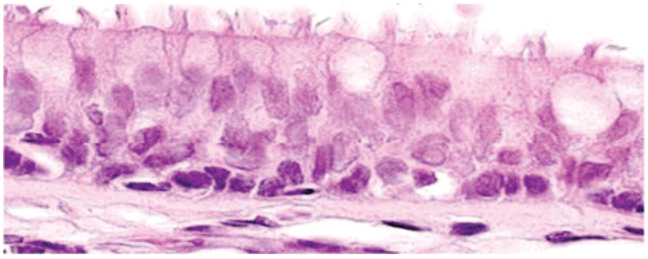
Transitional epithelium or urothelium.

Stratified transitional epithelium lining the urinary bladder has rounded or dome-shaped superficial cells with two unusual features. The surface cells have specialized membranes and are able to withstand the hypertonic effects of urine and protect underlying cells from this toxic solution. Cells of transitional epithelium are also able to adjust their relationships with one another as the bladder fills and the wall is stretched, so that the transitional epithelium of a full, distended bladder seems to have fewer cell layers than that of an empty bladder. These unique features of urothelium will be discussed more fully in Chapter 19. X400. H&E.

In addition to these various stratified epithelia, there is another type classified as **pseudostratified columnar epithelium**, so called because all cells are attached to the basal lamina even though their nuclei lie at different levels in the epithelium and the height of some cells does not extend to the surface. The best-known example of pseudostratified columnar epithelium is that lining the passages of the upper respiratory tract (Figure 4–16). The columnar cells of this epithelium are also heavily ciliated.

Figure 4–16.





Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

Pseudostratified epithelium.

Cells of pseudo-stratified epithelia appear to be in layers, but the basal ends of the cells are all in contact with the basement membrane, which is often very thick in these epithelia. The best example of this epithelial type is the pseudostratified ciliated columnar epithelium of the upper respiratory tract, which contains cell types with their nuclei at different levels that give the false appearance of cellular stratification. This epithelium is discussed in detail in Chapter 17. X400. H&E.

Glandular Epithelia

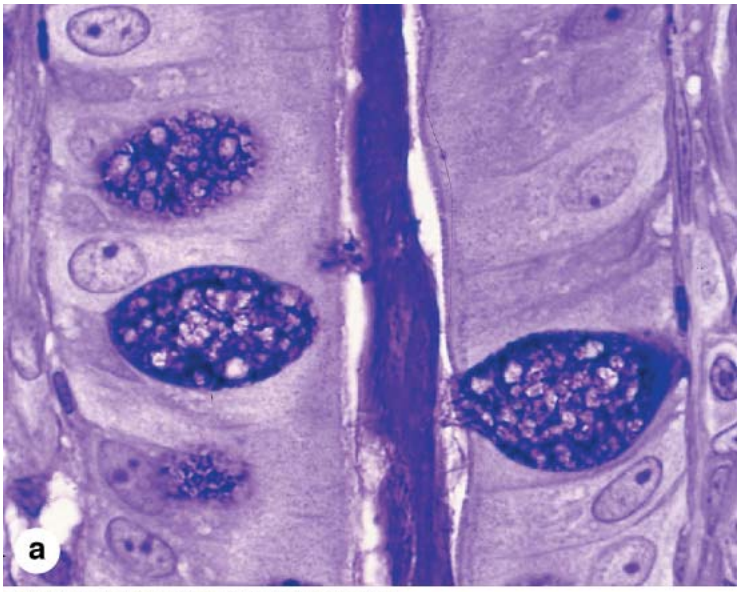
Glandular epithelia are formed by cells specialized to secrete. The molecules to be secreted are generally stored in the cells in small membrane-bound vesicles called **secretory granules.**

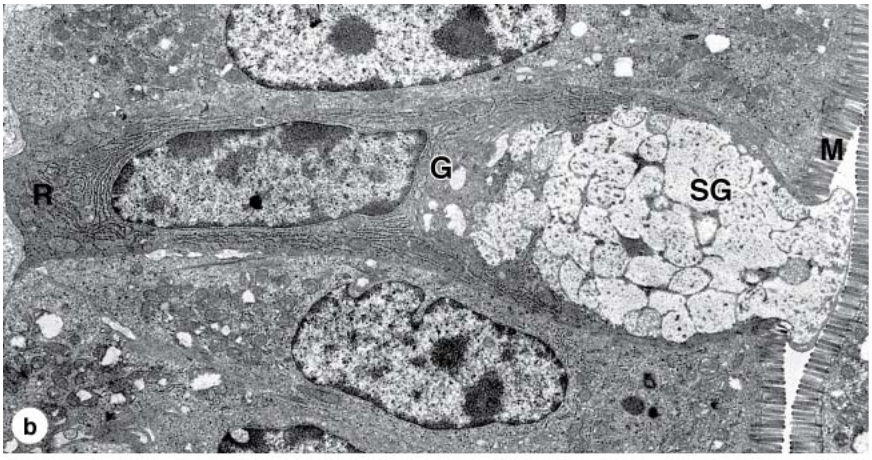
Glandular epithelial cells may synthesize, store, and secrete proteins (eg, in the pancreas), lipids (eg, adrenal, sebaceous glands), or complexes of carbohydrates and proteins (eg, salivary glands). Mammary glands secrete all three substances. The cells of some glands have low synthetic activity (eg, sweat glands) and secrete

mostly water and electrolytes transferred into the gland from the blood.

The epithelia that form glands can be classified according to various criteria. Unicellular glands consist of large isolated secretory cells and multicellular glands have clusters of cells. The classic unicellular gland is the **goblet cell** in the lining of the small intestine (Figure 4–17) or respiratory tract. The term "gland," however, is usually used to designate large aggregates of secretory epithelial cells, such as in the salivary glands and the pancreas.

Figure 4–17.



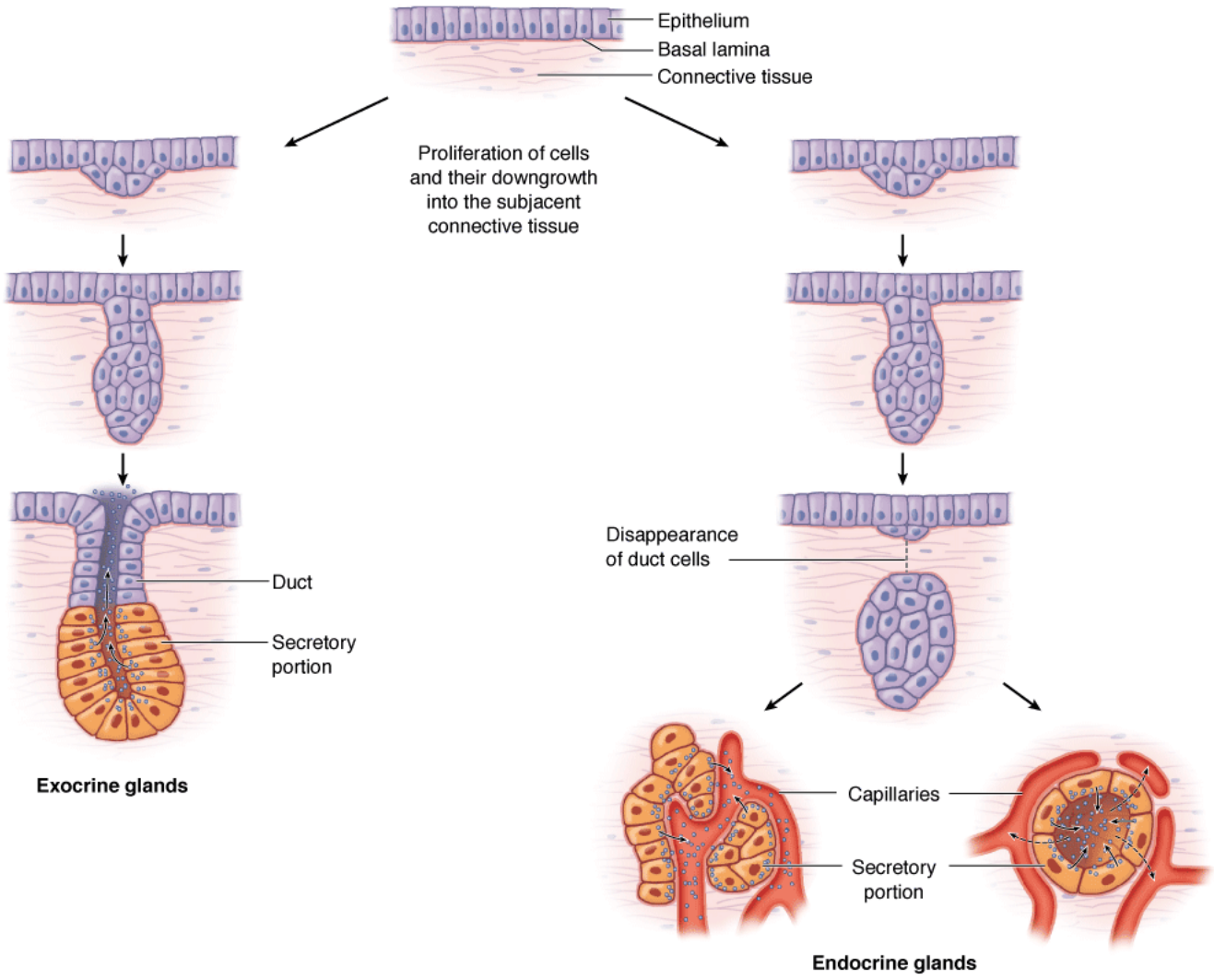


Goblet cells: unicellular glands.

A section of epithelial lining of the large intestine shows scattered goblet cells secreting mucus to the extracellular space **(a):** With the stain for glycoproteins used here, both the mucus precursor stored in cytoplasmic graules of the goblet cells as well as the secreted mucus are stained dark blue. X400. PAS-PT. **(b):** Ultrastructurally a goblet cell shows a basal nucleus surrounded by RER (R), a large Golgi complex (G) just above the nucleus, and an apical end filed with large secretory granules (SG) containing mucins. This highly viscous material is secreted by exocytosis and is then hydrated to form mucus in the lumen lined by microvilli (M). X17,000.

Glands develop during fetal life from covering epithelia by means of cell proliferation and invasion of the subjacent connective tissue, followed by further differentiation (Figure 4–18). **Exocrine glands** retain their connection with the surface epithelium, the connection taking the form of tubular ducts lined with epithelial cells through which the secretions pass to the surface. **Endocrine glands** have lost their connection to the surface from which they originated during development. These glands are therefore ductless and their secretions are picked up and transported to their sites of action by the bloodstream rather than by a duct system. Multicellular glands, whether exocrine or endocrine, also have connective tissue in a surrounding capsule and in septa that divide the gland into lobules. These lobules then subdivide, and in this way the connective tissue separates and binds the glandular components together (Figure 4–19).

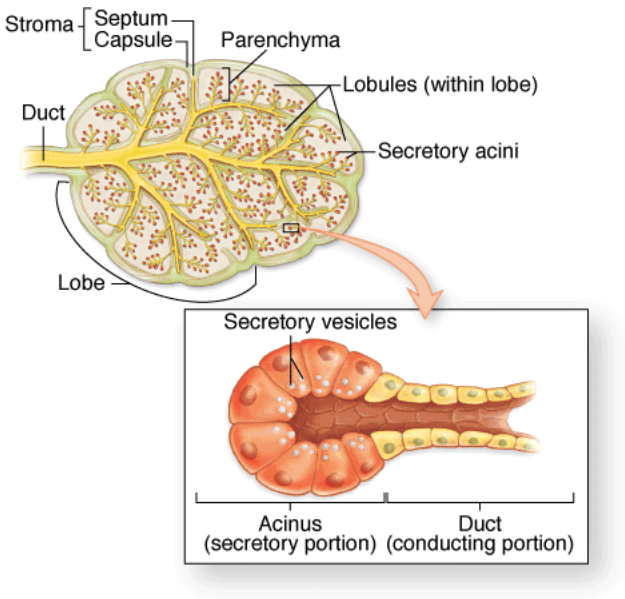
Figure 4–18.



Formation of glands from covering epithelia.

During fetal development epithelial cells proliferate and penetrate the underlying connective tissue. They may—or may not—maintain a connection with the surface epithelium. When the connection is maintained, exocrine glands are formed; with the connection lost, endocrine glands are formed. Exocrine glands secrete to the body surface or gut via duct systems formed from the epithelial connection. The cells of endocrine glands, which secrete hormones (see Chapter 20) can be arranged in cords or in follicles with lumens for storing the secretory product. From either the cords (left) or follicles (right) of endocrine cells, the secretory product is released outside the cells and picked up by the blood vessels for distribution throughout the body.

Figure 4–19.



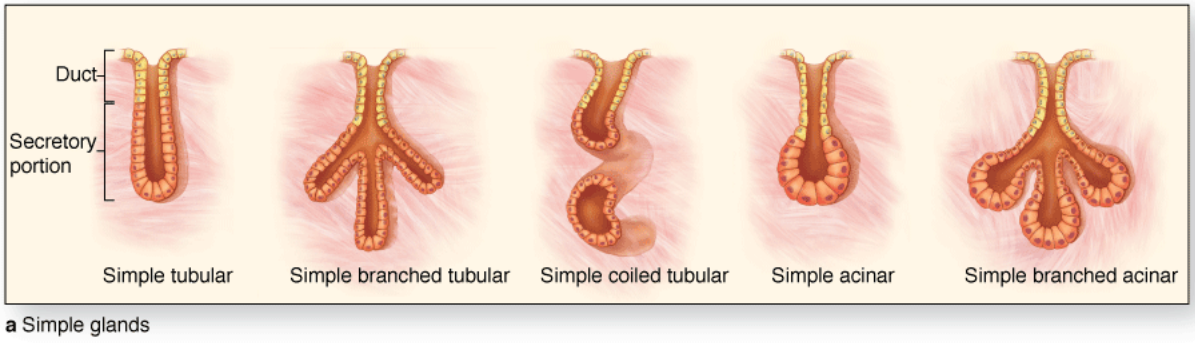
General structure of *e*xocrine glands.

Exocrine glands by definition have ducts that lead to an organ or body surface. Inside the gland the duct runs through connecting septa and branches repeatedly, until its smallest branches end in the secretory portions of the gland.

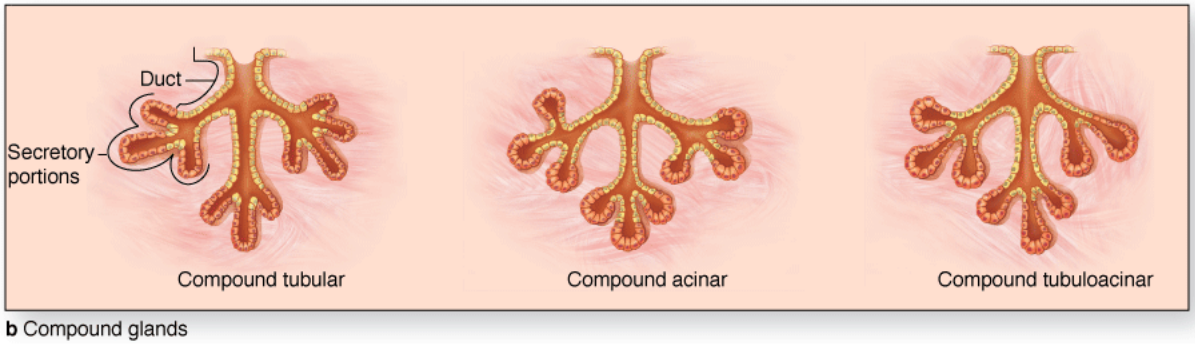
Exocrine glands have a **secretory portion,** which contains the cells specialized for secretion, and **ducts,** which transport the secretion out of the gland. The morphology of these components allows the glands to be classified according to the scheme shown in Figure 4–20 and summarized as follows:

- Ducts can be **simple** (unbranched) or **compound** (with two or more branches).
- Secretory portions can be **tubular** (either short or long and **coiled**) or **acinar** (round or globular).
- Either type of secretory portion may be **branched**.
- Compound glands can have tubular, acinar, or tubuloacinar secretory portions.

Figure 4–20.



a Simple glands



b Compound glands

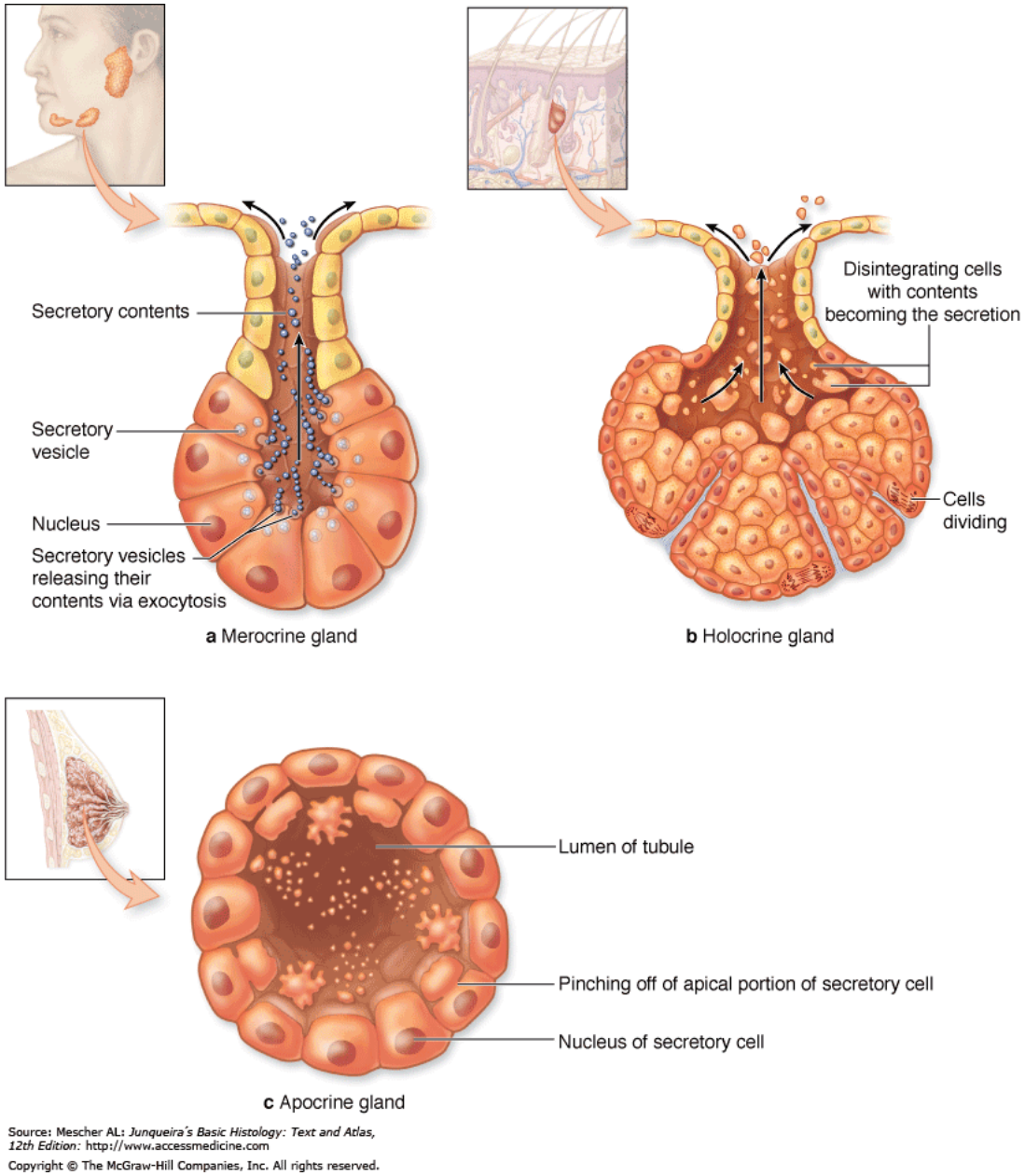
Structural classes of exocrine glands.

(a): Simple glands have unbranched ducts, although the ducts may be short or long and coiled. The secretory portions attached to these ducts may themselves be branched. The secretory portions are either **tubular**, if more or less cylindrical in shape, or **acinar**, if bulbous or saclike. **(b):** If the ducts branch to serve multiple secretory units, the gland is **compound**. On compound glands, the secretory units may be all tubular, all acinar, or a combination of the two shapes.

Exocrine glands are also classified functionally according to the way the secretory products leave the cell (Figure 4–21):

- **Merocrine secretion** (sometimes called eccrine) involves typical exocytosis of proteins or glycoproteins. This is the most common mode of secretion.
- **Holocrinesecretion** involves the cell filling with secretory product and then the whole cell being disrupted and shed. This is best seen in the sebaceous glands of skin (Figure 4–22).
- In an intermediate type, **apocrinesecretion**, the secretory product is typically a large lipid droplet and is discharged together with some of the apical cytoplasm and plasmalemma (Figure 4–23).

Figure 4–21.

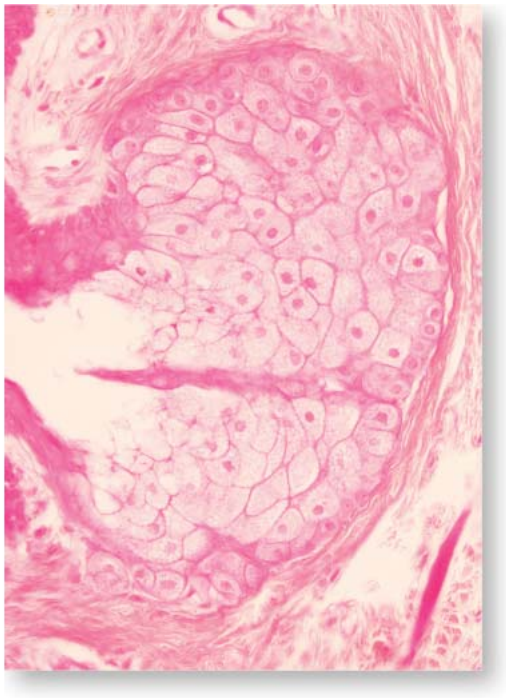


Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

Functional classification of exocrine glands.

Different cellular secretion processes are used in exocrine glands, depending on what substance is being secreted. **(a):** Merocrine glands secrete products, usually containing proteins, by means of exocytosis at the apical end of the secretory cells. Most exocrine glands are merocrine. **(b):** Holocrine gland secretion is produced by the disintegration of the secretory cells themselves as they complete differentiation which involves becoming filled with product. Sebaceous glands of hair follicles are the best examples of holocrine glands. **(c):** Apocrine gland secretion involves loss of a large membrane-enclosed portion of apical cytoplasm, usually containing one or more lipid droplets. This apical portion of the cell may subsequently break down to release its contents during passage into the duct. Apocrine secretion, along with merocrine secretion, is seen in mammary glands.

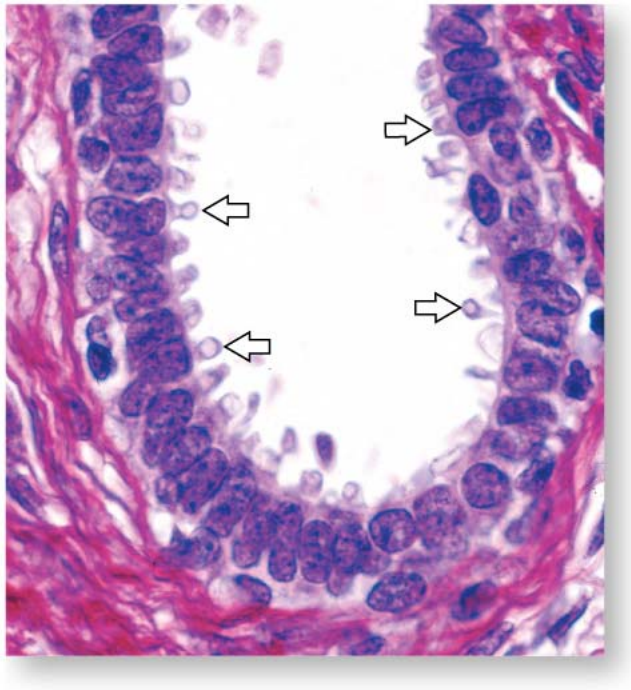
Figure 4–22.



Holocrine secretion in a sebaceous gland.

In holocrine secretion, best seen in the sebaceous gland adjacent to hair follicles, entire cells fill with a product and are released during secretion. Undifferentiated cells deep and peripheral in the gland fill with lipid-rich granules and become metabolically inactive as they mature and move upward and toward the gland's center. When terminally differentiated, the cells separate and quickly disintegrate to form the secretion which serves to protect and lubricate adjacent skin and hair. Sebaceous glands lack myoepithelial cells; cell proliferation inside a dense, inelastic connective tissue capsule continuously forces product into the duct. X200. H&E.

Figure 4–23.

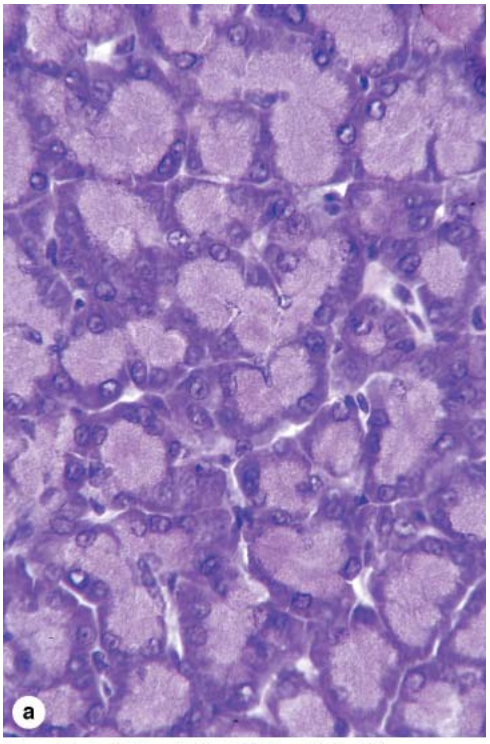


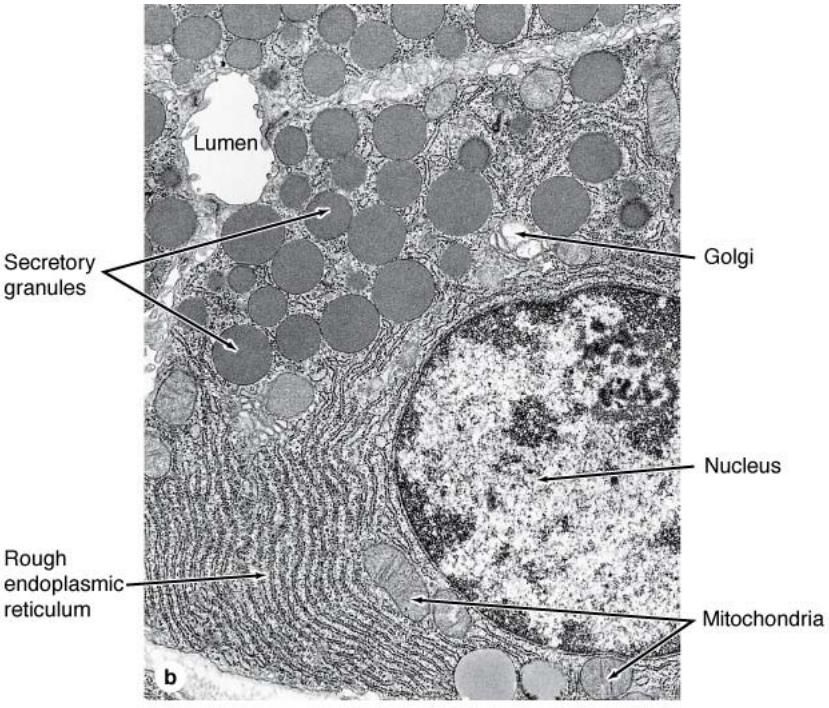
Apocrine secretion in the mammary gland.

The secreting portions of a mammary gland demonstrate apocrine secretion and are characterized by the discharge of the secretion product with a pinched off portion of the apical cytoplasm (arrows). The released portion of cell contains lipid droplet(s). Merocrine secretion also occurs from the same and other cells of the secretory units. X400. PSH.

Exocrine glands with merocrine secretion can be further categorized as either **serous** or **mucous** according to the nature of the proteins or glycoproteins secreted and the resulting staining properties of the secretory cells. The acinar cells of the pancreas and parotid salivary glands are examples of the serous type which secrete **digestive enzymes**. The basal ends of serous cells have well-developed RER and Golgi complexes and the cells are filled apically with secretory granules in different stages of maturation (Figure 4–24). Serous cells therefore stain intensely with any basophilic or acidophilic stain.

Figure 4–24.



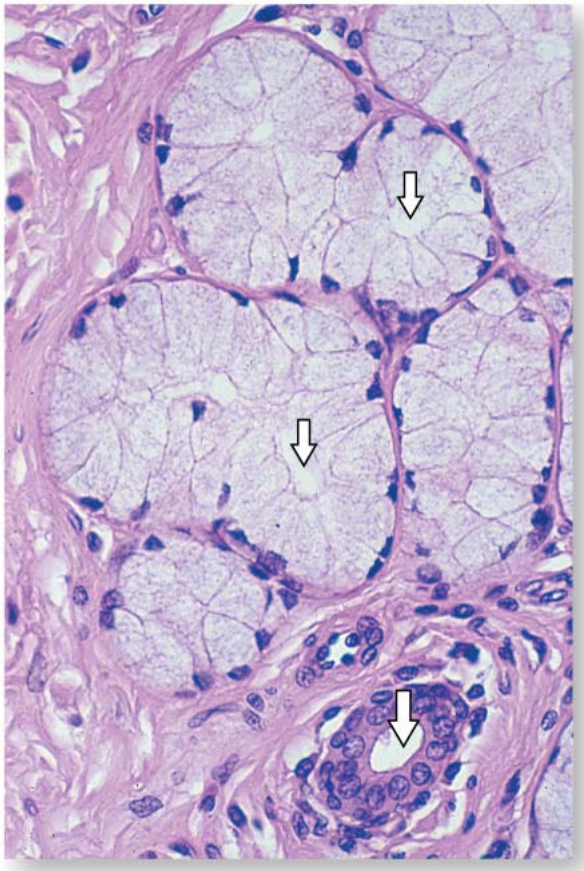


Serous cells.

Serous acinar cells of the exocrine pancreas are arranged in small acini of 5-10 cells with a very small central lumen. Each acinar cell is roughly pyramid-shaped, with its apex at the lumen. **(a):** As seen by light microscopy, the apical ends are eosinophilic due to the abundant immature and mature secretory granules present there. The cells' basal ends contain the large rounded nuclei and an abundance of rough ER, making the cells highly basophilic basally. X200. PT. **(b):** A portion of one acinar cell is shown ultrastructurally, indicating the abundant RER, Golgi complexes, and secretory granules and the very small size of the acinus lumen. X13,000. Secretion here is merocrine and typically the mature zymogen granules, filled with digestive enzymes, remain in the apical cell region until the cell is stimulated to secrete. Other cells secrete constitutively, with small granules undergoing exocytosis as soon as they emerge fully formed from the Golgi apparatus.

Mucous cells, such as goblet cells, while also rich in RER and Golgi complexes are filled apically with secretory granules containing strongly hydrophilic glycoproteins called **mucins.** When mucins are released from the cell, they become hydrated and form **mucus**, a viscous, elastic, protective lubricant material. Mucin-containing granules stain well with the periodic acid-Schiff (PAS) method for glycoproteins (Figure 4–17a), but are not intensely acidophilic like zymogen granules of serous cells (Figure 4–25). Mucous cells of large glands are organized as secretory tubules and in mixed seromucous salivary glands crescent-shaped clumps of serous cells frequently share the ends of the tubules as serous demilunes (Figure 4–26).

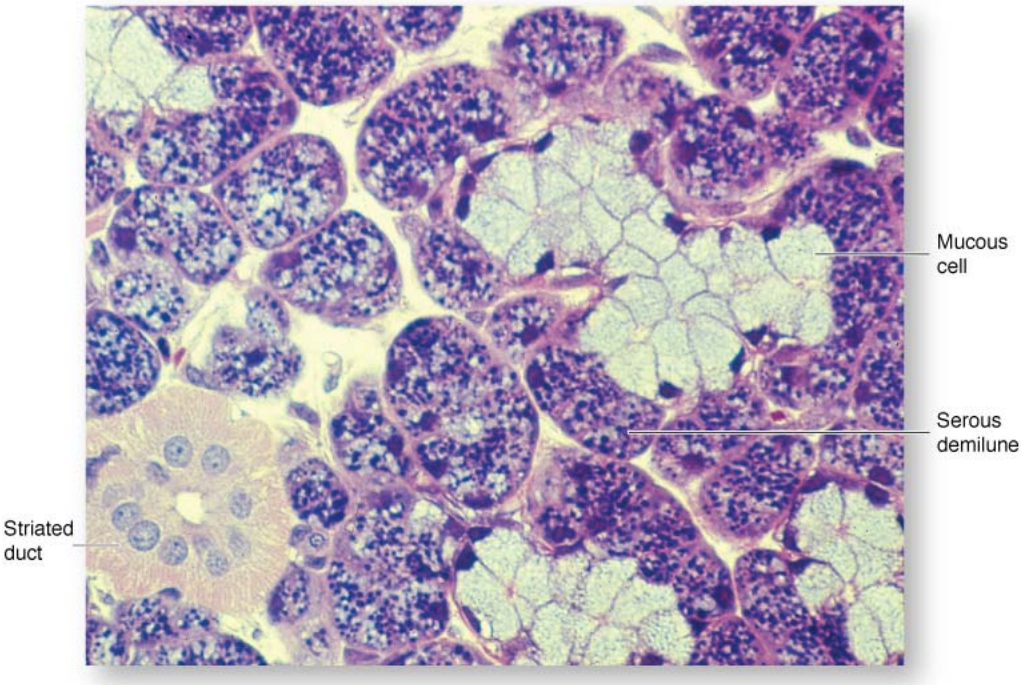
Figure 4–25.



Mucous cells.

Mucous cells are typically larger than serous cells, with more flattened basal nuclei. The apical region and most of the other cytoplasm of each mucous cell is filled with secretory granules containing mucin like that of goblet cells. The basal region contains the RER, nucleus, and a well-developed Golgi apparatus. The RER and Golgi are very rich in enzymes called glycosyltransferases, which attach sugars to polypeptide chains to make glycoproteins. Mucus contains many glycoproteins with important water-binding properties. The lumens (small arrows) of mucous tubules are larger than those of serous acini. The large arrow indicates a secretory duct. X200. PT. Other types of mucous cells are found in the stomach, the various salivary glands, the respiratory tract, and the genital tract. These cells show great variability in both their morphologic features and in the chemical nature of their secretions.

Figure 4–26.

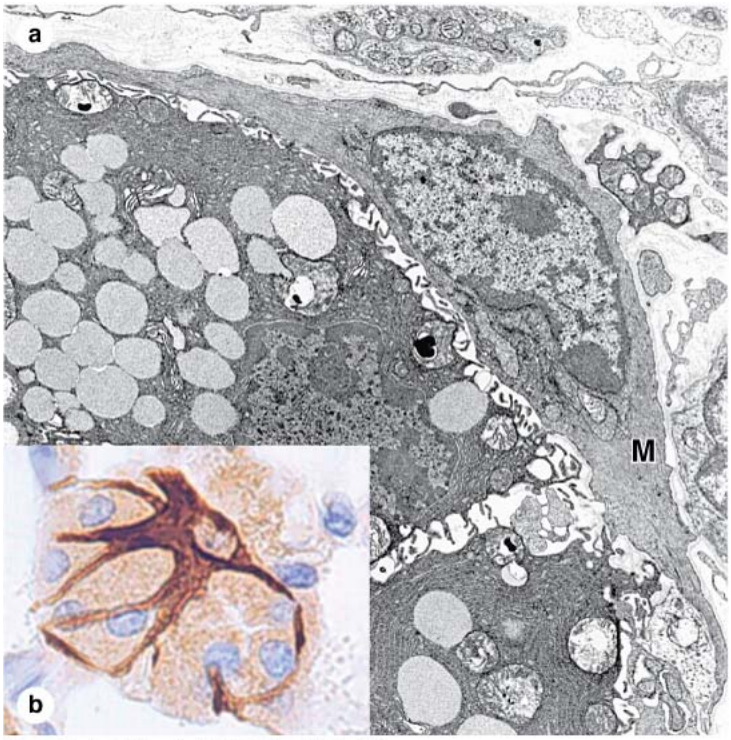


Seromucous, compound tubuloacinar gland.

The submandibular salivary glands have both mucous and serous secretory units, typically shaped as acini and tubules respectively. Clumps of serous cells at the ends of some mucous tubules appear as crescent-shaped structures called **serous demilunes.** At the left is seen a **striated duct** whose cells' basal membranes are folded into long folds with many mitochondria, an arrangement specialized for ion transport across the epithelium. X400. PT.

Several exocrine glands (eg, sweat, lachrymal, salivary, and mammary glands) contain stellate or spindle-shaped **myoepithelial cells** located between the basal lamina and the basal pole of secretory or duct cells (Figure 4–27). Long processes of these cells embrace an acinus as an octopus might embrace a rounded boulder. Along ducts they are more longitudinally arranged. Myoepithelial cells are connected to each other and to the epithelial cells by both gap junctions and desmosomes. These cells are specialized for contraction, containing myosin and a large number of actin filaments. Their major function is to contract around the secretory or conducting portion of the gland and thus help propel secretory products into the duct.

Figure 4–27.



Myoepithelial cells.

(a): Portion of a salivary gland acinus shows two secretory cells with secretory granules. A myoepithelial cell (M) embraces the acinus with contractile processes. X20,000. **(b):** A myoepithelial cell immunostained against smooth muscle actin shows its association with an entire acinus. Contraction of the myoepithelial cell compresses the acinus and aids in the expulsion of secretory products into the duct. X200. H&E counterstain.

Endocrine glands are the producers of **hormones**, which are generally polypeptide or lipid-derived factors that are released into the interstitial fluid. Hormones diffuse into the blood for circulation and bind specific receptors on target cells elsewhere in the body, often within other endocrine glands. The receptors may also be on cells very close to the hormone-secreting cells or on the secreting cell itself; in these cases the cellular signaling is termed **paracrine** or **autocrine,** respectively. Hormones can be secreted from single cells that are sparsely distributed or from cells with other major functions, such as certain cardiac muscle cells. In the large endocrine glands the parenchymal cells form strands or cords interspersed between dilated capillaries (eg, the adrenal cortex; see Figure 4–18) or can line a follicle filled with stored secretory product (eg, the thyroid gland; Figure 4–18). Some endocrine glands have cells releasing more than one hormone.

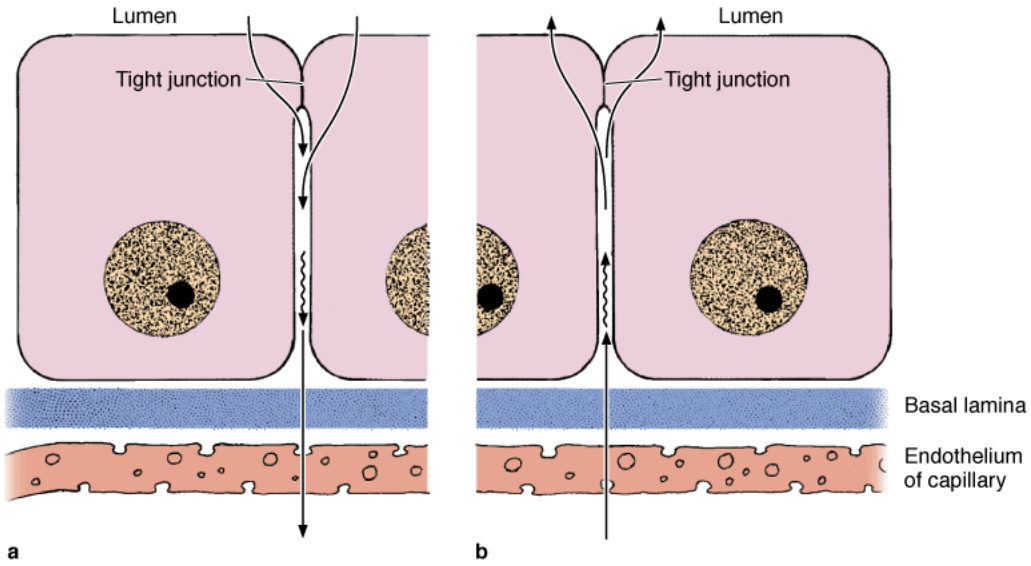
Some organs such as the pancreas have both endocrine and exocrine functions, and in the liver one cell type may function both ways, secreting bile components into a duct system, as well as releasing other products into the bloodstream.

TRANSPORT ACROSS EPITHELIA

As discussed in Chapter 2, all cells have the ability to actively transport certain ions against a concentration and electrical-potential gradient. An important example is the active extrusion of Na^+ by means of Mg^{2+}-activated Na^+/K^+-ATPase (**sodium pump**), by which cells maintain the required low intracellular sodium concentration (5-15 mmol/L vs. ~140 mmol/L in extracellular fluid).

Some epithelial cells actively transfer ions and fluid across the epithelium, from its apex to its base or vice-versa; this is known as **transcellular transport** (Figure 4–28). For transport in either direction, the tight junctions play an important role in the transport process, sealing the apical portions of the epithelium and preventing back-diffusion of materials already transported across the epithelium. A well-studied site of epithelial transport is the proximal renal tubule cell, where the apical surface is freely permeable to Na^+ in the lumen. To maintain electrical and osmotic balance, equimolar amounts of chloride and water follow the Na^+ ion into the cell. The basal surfaces of these cells are elaborately folded and many long invaginations of the basolateral membrane are seen in electron micrographs (Figure 4–29). In addition, there is interdigitation of membrane folds between adjacent cells, all of which increase the surface area for transport. Sodium pumps are localized in both the basal and the lateral plasma membranes and located between the folds are vertically oriented mitochondria that supply the ATP for the active extrusion of Na^+ from the cell basally. Chloride and water again follow passively. In this way, sodium is returned to the circulation and is not lost in massive amounts in the urine.

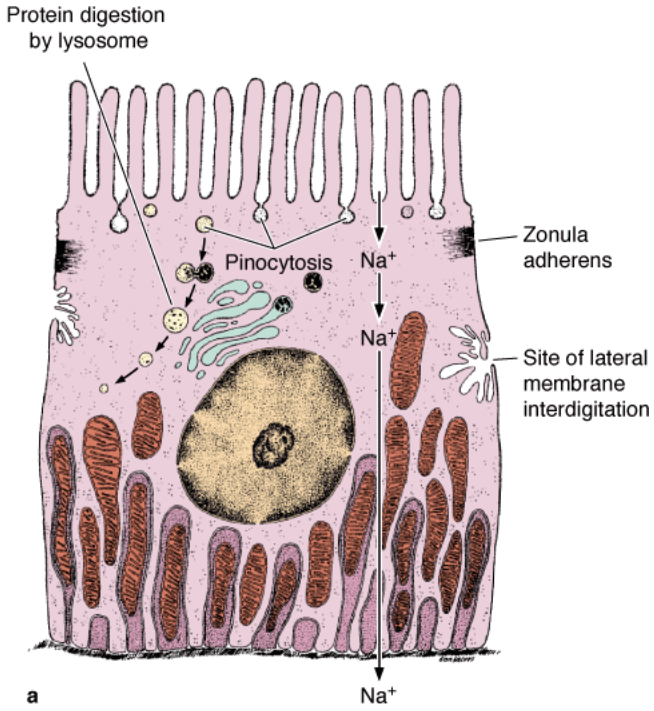
Figure 4–28.

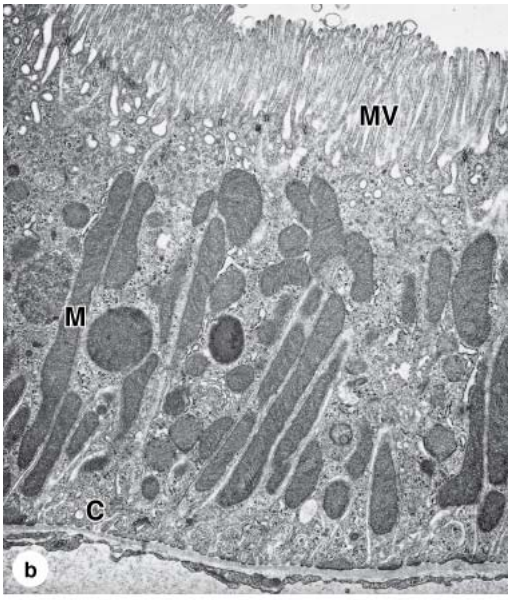


Ion and water absorption and secretion.

Ion and water transport across epithelia can occur in different directions, depending on which tissue is involved. **(a):** The direction of transport is from the lumen to the blood vessel, as in the gallbladder and intestine. This process is called **absorption**, and serves to concentrate bile and obtain water and ions in these organs**. (b):** Transport in the opposite direction, as in the choroid plexus, ciliary body, and sweat glands, is called **secretion** and serves to expel water from the interstitial fluid into specialized aqueous fluids in these tissues**.** Whether the epithelia are absorbing or secreting water, the presence of apical occluding junctions is necessary to maintain tight compartmentalization and consequent control over ion distribution.

Figure 4–29.





Absorptive cells.

An ultrastructural diagram and TEM of epithelial cells highly specialized for absorption: cells of proximal convoluted tubule of the kidney. Long invaginations of the basal cell membrane outline regions filled with vertically oriented mitochondria, a typical disposition present in ion-transporting cells. Interdigitations from neighboring cells interlock with those of this cell. Immediately below the microvilli are junctional complexes between individual cells. The basolateral membranes can be discerned in continuity with the junctional complexes. Apically are vesicles that have undergone pinocytosis, soon to fuse with lysosomes, as shown in the upper left portion of the diagram. Sodium ions diffuse passively through the apical membranes of renal epithelial cells and are then actively transported out of the cells by Na^+/K^+ -ATPase located in the basolateral membranes of the cells. Energy for this sodium pump is supplied by the nearby mitochondria. Immediately below the basal lamina is a capillary for removal of the water absorbed across this part of the epithelium. X9600.

Extracellular molecules and fluid are also internalized in the cytoplasm of most cells by pinocytotic vesicles that form abundantly at the plasmalemma. This activity is clearly observed in the simple squamous epithelia that line the blood and lymphatic capillaries (endothelia) or the body cavities (mesothelia). These cells have few organelles other than the abundant pinocytotic vesicles, which cross the thin cells in both directions and secrete their contents on the opposite side by exocytosis. This process, termed **transcytosis**, is not restricted to simple squamous epithelia. Uptake of material at the apical epithelial pole followed by exocytosis at the basolateral surface occurs actively in many simple cuboidal and columnar epithelia and is important in various physiological processes.

RENEWAL OF EPITHELIAL CELLS

Epithelial tissues are relatively labile structures whose cells are renewed continuously by mitotic activity. The renewal rate is variable; it can be fast in tissues such as the intestinal epithelium, which is replaced every week, or slow, as in the large glands. In stratified epithelial tissues, mitosis only occurs within the basal layer in contact with the basal lamina. In some functionally complex epithelia, stem cells have been identified only in restricted niches some distance from the transit amplifying cells and differentiating cells. For example, the epithelium lining the small intestine is derived completely from stem cells found in the simple glands between the intestinal villi. In the epidermis, stem cells are located at a characteristic position along the wall of hair follicles.

MEDICAL APPLICATION

Both benign and malignant tumors can arise from most types of epithelial cells. A **carcinoma** (Gr. *karkinos,* cancer, + *oma,* tumor) is a malignant tumor of epithelial cell origin. Malignant tumors derived from glandular epithelial tissue are usually called **adenocarcinomas** (Gr. *adenos,* gland, + *karkinos*); these are by far the most common tumors in adults. In children up to age 10 years, most tumors develop (in decreasing order) from hematopoietic organs, nerve tissues, connective tissues, and epithelial tissues. This proportion gradually changes, and after age 45 years, more than 90% of all tumors are of epithelial origin.

Carcinomas composed of differentiated cells reflect cell-specific morphologic features and behaviors (eg, the production of keratins, mucins, and hormones). Undifferentiated carcinomas are often difficult to diagnose by morphologic analysis alone. Since these carcinomas usually contain keratins, the detection of keratins by immunocytochemistry often helps to determine the diagnosis and treatment of these tumors.

Epithelia are normally capable of rapid repair and replacement of apoptotic or damaged cells. In some large glands, most notably the liver, mitotic activity is normally rare but is actively renewed following major damage to the organ. When a portion of liver tissue is removed surgically or lost by the acute effects of toxic substances, cells of undamaged regions quickly begin active proliferation and normal functional mass of liver tissue is soon regenerated.

MEDICAL APPLICATION

Some epithelial cells are prone to abnormal growth called neoplasia that may lead to cancers. Neoplastic growth is reversible and does not always result in cancer.

Under certain abnormal conditions, one type of epithelial tissue may undergo transformation into another type in another reversible process called **metaplasia**, which is illustrated by the following examples.

In heavy cigarette smokers, the ciliated pseudo-stratified epithelium lining the bronchi can be transformed into stratified squamous epithelium.

In individuals with chronic vitamin A deficiency, epithelial tissues of the type found in the bronchi and urinary bladder are gradually replaced by stratified squamous epithelium.

Metaplasia is not restricted to epithelial tissue; it may also occur in connective tissue.