

## LEARNING OBJECTIVES OUTLINE

### I. FEATURES & FUNCTIONS

#### A. Composition

1. Cells
2. ECM (limited)

#### B. Classification of epithelia

1. Surface epithelia
2. Glandular epithelia
3. Special epithelia

#### C. Important characteristics

1. Covers or lines all body surfaces
2. Polarity (epithelial cells have specific apical, lateral & basal domains)
3. Characterized by specific intermediate filaments called cytokeratins
4. Attached to underlying CT via ECM basement membrane
5. Generally avascular
6. Gives rise to majority of glands
7. High regenerative capacity; plasticity
8. Great diversity of function

### II. SURFACE EPITHELIA

#### A. Simple epithelia

1. Definition: single layer of cells
2. Types & examples
  - a. Simple squamous
    - i. Kidney: Bowman's capsule, loop of Henle
    - ii. Lung: alveoli
    - iii. Endothelium: vasa, heart
    - iv. Mesothelium: serosae
  - b. Simple cuboidal
    - i. Kidney: PCT, DCT, small collecting ducts
    - ii. Exocrine glands: small ducts
  - c. Simple columnar
    - i. Alimentary tract: e.g., stomach, intestines, gallbladder
    - ii. Exocrine glands: small ducts

#### B. Stratified epithelia

1. Definition: multiple layers of cells
2. Types & examples
  - a. Stratified squamous (SSE)

- i. Wet surfaces (mucosae)
    - "Nonkeratinizing" (=mucous) (= "hypokeratinizing") (SSNKE)
    - Parakeratosis (physiologic)
    - Orthokeratosis (physiologic)
  - ii. Dry surfaces (skin)
    - "Keratinizing" (=cutaneous); orthokeratosis (SSKE)
    - Parakeratosis (pathologic)
  - iii. Keratins: cytoskeletal proteins present in all SSE
- b. Stratified cuboidal
    - i. Exocrine glands: larger ducts
    - ii. Often mixed with stratified columnar
  - c. Stratified columnar
    - i. Exocrine glands: larger ducts
    - ii. Portion of male urethra

#### C. Pseudostratified epithelia

1. Definition: all cells touch basal lamina, but all cells don't reach free surface
2. Types & examples
  - a. Respiratory: pseudostratified ciliated columnar with goblet cells
  - b. Urinary: urothelium (=transitional epithelium)
  - c. Male genital tract
    - i. Ductus epididymidis
    - ii. Ductus deferens
    - iii. Seminal vesicles
    - iv. Prostate

### III. GLANDULAR EPITHELIA

#### A. Classification

1. Types of glands
  - a. Exocrine
  - b. Endocrine (hemocrine)
  - c. Paracrine
  - d. Autocrine
2. Exocrine gland criteria
  - a. Ducts
  - b. Secretory components
  - c. Types of secretion
  - d. Mechanisms of secretion

**B. Ducts: structure in exocrine glands**

1. Simple glands (=unbranched ducts)
2. Compound glands (=branched ducts)

**C. Secretory components**

1. Number of secretory cells
  - a. Unicellular (e.g., goblet cells)
  - b. Multicellular glands (majority)
2. Structure of secretory units
  - a. Tubular
  - b. Acinar/alveolar

**D. Types of secretion (secretory product)**

1. Mucous
2. Serous
3. Seromucous
  - a. Mixed secretions
  - b. Serous demilunes (fact or artifact)
  - c. Intercellular canaliculi

**E. Mechanisms of secretion (methods of release)**

1. Merocrine
  - a. Exocytosis
  - b. Examples
    - i. Salivary glands
    - ii. Pancreas
2. Apocrine
  - a. Decapitation secretion
  - b. Examples
    - i. Apocrine sweat glands
    - ii. Mammary glands
3. Holocrine
  - a. Secretion of whole disintegrated cells
  - b. Sebaceous glands

**F. Myoepithelial cells**

1. Contractile, branched epithelial cells
2. Located between glandular epithelial cells and basement membrane
3. Contain actin filaments; smooth muscle-like
4. Facilitate glandular secretion

**IV. SPECIAL EPITHELIA**

**A. Myoepithelium**

**B. Neuroepithelium**

1. Non-neuronal
  - a. Receptor cells of taste buds
  - b. Hair cells of inner ear
2. Neuronal
  - a. Sensory cells of olfactory epithelium
  - b. Rods and cones of retina

**C. Seminiferous epithelium**

1. Germinal epithelium of testis
  - a. Spermatogenic (germ) cells
  - b. Supporting (Sertoli) cells
2. Sertoli cells: simple epithelium
3. Spermatogenic cells: stratified

**V. EPITHELIAL SPECIALIZATIONS**

**A. Definition: morphologic & functional specializations at, on and/or within membrane surfaces of epithelial cells**

**B. Nomenclature of epithelial surfaces**

1. Apical
2. Lateral
3. Basal

**C. Specializations of apical surfaces**

(=free cell surfaces facing lumen)

1. Microvilli [L. *villus* =shaggy hair]
  - a. Structure
    - i. Evagination of cell membrane
    - ii. Core of actin filaments
  - b. Important locations
    - i. Striated (cuticular) border (gut)
    - ii. Brush border (kidney)
    - iii. Stereocilia (epididymis)
2. Cilia and flagella
  - a. Structure
    - i. Evagination of cell membrane
    - ii. Core of microtubules: 9x2+2 (=axoneme)
    - iii. Basal bodies: 9x3
  - b. Important locations: respiratory, reproductive systems
3. Glycocalyx
  - a. Glycoproteins
  - b. Glycolipids
  - c. Proteoglycans

**D. Specializations of lateral surfaces**

(=surfaces facing adjacent cells)

1. Junctional (jxnal) complexes
  - a. Array of multiple cell-to-cell jxns
  - b. Terminal bars of LM
2. Zonula occludens (=tight junction)
  - a. Integral membrane proteins
    - i. Claudins
    - ii. Occludin
    - iii. Homotypic junctions
  - b. Peripheral membrane proteins
    - i. ZO-1, -2, -3
    - ii. Others (cingulin, spectrin)
  - c. Cytoskeleton binding (F-actin)
  - d. Major functions
    - i. Regulate paracellular transport
    - ii. Restrict membrane flow
  - e. Occurrence: Usually part of junctional complex
3. Zonula adherens (=adhering band)
  - a. Integral membrane proteins
    - i. E-cadherins
    - ii. Homotypic junctions
  - b. Peripheral membrane proteins
    - i. Catenins ( $\alpha$   $\beta$ )
    - ii. Plakoglobin ( $\gamma$ -catenin)

- iii.  $\alpha$ -Actinin
      - iv. Vinculin
    - c. Cytoskeleton binding: F-actin
    - d. Major function: adhesion
    - e. Occurrence: part of jxn complex
  - 4. Macula adherens (=desmosome; adhering spot)
    - a. Integral membrane proteins
      - i. Desmocollins (cadherins)
      - ii. Desmogleins (cadherins)
      - iii. Homotypic junctions
    - b. Peripheral membrane proteins
      - i. Desmoplakin
      - ii. Plakoglobin ( $\gamma$ -catenin)
      - iii. Plakophilin
    - c. Cytoskeleton binding: cytokeratins
    - d. Major functions: adhesion; support
    - e. Occurrence: alone or part of jxn complex
  - 5. Macula communicans (=nexus, gap junction, communicating junction)
    - a. Integral membrane proteins
      - i. Connexins (monomers)
      - ii. Connexons (hexamer channels)
      - iii. Homotypic or heterotypic jxns
    - b. Major function: communication
    - c. Occurrence: widespread in epithelia and other tissues
- E. Specializations of basal surfaces**  
(=surfaces along basement membrane)
- 1. Basement membrane
    - a. Basal lamina (epithelial)
      - i. Lamina lucida (rara): laminin, perlecan
      - ii. Lamina densa: type IV collagen
      - iii. Analogous to external lamina of adipose, muscle, perineurial, and Schwann cells
    - b. Reticular lamina (CT; not constant)
      - i. Type III collagen
      - ii. Ground substance
    - c. Anchoring fibrils: type VII collagen
  - 2. Hemidesmosome
    - a. Integral membrane proteins
      - i. Integrins
      - ii. Binds to laminin of ECM
      - iii. Heterotypic junction
    - b. Peripheral protein (plectin)
    - c. Cytoskeleton binding (cytokeratins)
    - d. Major function: adhesion to ECM
  - 3. Basal (basolateral) foldings of plasma membrane
    - a. Infoldings
      - i. Transporting epithelia (PCT & DCT: kidneys; striated salivary ducts)
      - ii. Increased surface area (membrane redundancy) for transport

- b. Outfoldings
      - i. Dermal-epidermal junction
      - ii. Increased area for attachment
- F. Cytoskeleton and cytoarchitecture**
  - 1. Terminal web
  - 2. Filaments
    - a. Microfilaments (actin): 6-8 nm diameter
    - b. Intermediate filaments (tonofibrils; tonofilaments): 9-11 nm
    - c. Thick filaments (myosin): 15 nm
  - 3. Microtubules (tubulin): 23-25 nm

## VI. Light Micrographs TO KNOW

- A. Types of surface epithelia**
  - 1. Simple
  - 2. Stratified
  - 3. Pseudostratified
- B. Types of glandular epithelia**
  - 1. Unicellular glands
  - 2. Mucous, serous, seromucous glands
  - 3. Merocrine, apocrine & holocrine glands
  - 4. Myoepithelial cells
- C. Types of epithelial specializations**
  - 1. Apical
    - a. Striated/brush borders; stereocilia
    - b. Glycocalyx
  - 2. Lateral
    - a. Terminal bars
    - b. Desmosomes & tonofibrils
  - 3. Basal
    - a. Basement membrane
    - b. Basal infoldings
    - c. Basal outfoldings

## VII. Electron Micrographs TO KNOW

- A. Goblet cells; types of secretion**
- B. Apical specializations**
  - 1. Microvilli
  - 2. Cilia
  - 3. Glycocalyx
- C. Lateral specializations**
  - 1. Zonula occludens
  - 2. Zonula adherens
  - 3. Macula adherens
  - 4. Macula communicans
- D. Basal specializations**
  - 1. Basal lamina
  - 2. Reticular lamina (when present)
  - 3. Hemidesmosomes
  - 4. Infoldings for transport
  - 5. Outfoldings for attachment

## OVERVIEW

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**Definition & properties.** An **epithelium** is a **society of cells** in functional association that covers and lines all free body surfaces. Epithelial cells are held together in intimate contact with each other as well as to the underlying connective tissue. These contacts are mediated by small amounts of extracellular components and a number of plasma membrane specializations on the contact surfaces. In most instances, these specializations represent integral membrane proteins that are linked to cytoplasmic proteins via specific peripheral proteins. Thus, an epithelium is a tissue that consists mainly of cells with a relatively small amount of **extracellular matrix** (ECM).

**1. Classification.** Since epithelia cover the external surface of the body, line all internal cavities and tubular organs, and constitute the **parenchyma** (=specific functional cells of organ or gland) of many glands, they are typically classified into three categories (surface, glandular, special) even though this classification is quite arbitrary since there is considerable overlap between each of them.

**a. Surface epithelia** are simply defined as those epithelia that cover and line all body surfaces. They are also the varieties that are given specific names based largely on their layers and cell shape (see below).

**b. Glandular epithelia** represent all the varieties of epithelia that are specialized for **secretion** [L. *secretus* =to separate], which is the process by which cells release specific substances onto their apical surfaces. These cells may be located within the surface epithelium or at some distance, but are still connected to the surface via ducts. In some instances, they may lose these connections (e.g., thyroid epithelium).

**c. Special epithelia** may also be classified as surface or glandular, but have specialized functions. Examples of these include neuroepithelium (e.g., gustatory, olfactory), reproductive epithelium (e.g., seminiferous epithelium), and myoepithelium (epithelial cells specialized for contraction). The latter is described below in this chapter, whereas the others are discussed in later chapters in the context of their organs and systems.

**2. Polarity.** All epithelia are polarized and exhibit specific **domains** that are related to one of their surfaces: **apical** (located at the free surface),

**lateral** (surfaces facing adjacent members of epithelium), and **basal** (surface adjacent to underlying connective tissue). In some instances, the lateral and basal domains are considered as a unit, i.e., **basolateral** domain.

**3. Intermediate filaments\* (IFs)** are essential components of the cytoskeleton and nucleoskeleton of all cells. IFs are products of the largest family of cytoskeleton protein genes. In humans, at least 65 members of this multigene family are presently known to encode these 10-12 nm filaments (Hermann, H et al. *Int Rev Cytol* 223:83-175, 2003).

Epithelia have been characterized by containing specific types of IF proteins known as **cytokeratins**, which form the largest group of IFs with about 50 genes (Hesse, M et al. *J Cell Sci* 114:2569-2575, 2001).

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\*Based on gene structure and sequence homologies at least 5 classes of IFs have been described: **I** =acidic cytokeratins; **II** =basic cytokeratins; **III** =vimentin, desmin, etc; **IV** =neurofilaments; **V**=nuclear lamins (for reviews, see Hermann, H & Foisner, R. *Cell Mol Life Sci* 60:1607-1612, 2003; Strelkov, SV et al. *BioEssays* 25:243-251, 2003; Helfand, BT et al. *J Cell Sci* 117:133-141, 2004). Some authors also include a sixth class. In addition, these filaments can also be placed into at least 3 groups based upon their assembly mechanisms and cytoplasmic or nuclear localization: **assembly groups 1 & 2** =cytoplasmic IFs; **assembly group 3** =nuclear IFs (e.g., Hermann, H & Aebi, U. *Annu Rev Biochem* 73:749-789, 2004).

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**a. Organization.** In epithelia, cytokeratin IFs have been referred to as **tonofilaments** (~10nm filaments visualized with TEM) and bundles of tonofilaments are called **tonofibrils** (aggregates visualized at LM). It is now known that cytokeratin IFs are linear aggregates of heterodimers of acidic (class I) and basic (class II) keratins in a 1:1 ratio (e.g., Kirfel, J et al. *Cell Mol Life Sci* 60:56-71, 2003). Therefore, a wide variety of epithelial cytokeratins are possible from this 1:1 partnership of an acidic keratin with a basic keratin. Indeed, specific keratins are now known to be associated with specific epithelial types as well as to stages of development (e.g., Fuchs, E & Cleveland, DW. *Science* 279:514-519, 1998).

**b. Cytokeratin and IF functions.** Although a primary function of tonofilaments, and IFs in general, is structural and supportive (IFs are often referred to as intracellular “ligaments”), a large body of growing evidence also demonstrates their important roles in cell signaling (see Paramio, JM &

**4. Basement membrane.** Epithelial cells rest upon a condensation of ECM called the **basement membrane**. As seen in the light microscope, this structural specialization is resolved with the electron microscope as consisting of a narrow **basal lamina** (that includes type IV collagen) just beneath the epithelium, and often (but not always) a subjacent **reticular lamina** (that includes type III collagen) of varying width, which is continuous with the underlying connective tissue. In those areas where a reticular lamina is absent (e.g., kidney glomerulus), the basal lamina is the basement membrane.

**5. Regulatory roles of epithelia.** Epithelia provide important *interfaces* between the internal and external environments of the body. Since all materials entering or exiting the body must traverse an epithelium, this tissue serves important regulatory functions--not just for nutrients and wastes, but also for microorganisms and other potential pathogens. Thus, epithelia also have a critically important role as part of the innate immune system.

**6. Renewal and stem cells.** Epithelia have a high regenerative capacity and many turn over in a matter of days. This capacity is not only important for normal maintenance and wound healing of these barrier layers, but it also plays a critical role in innate immunity. The continuous sloughing of cells to which microorganisms may have become attached is an important mechanism in preventing the potential uptake of pathogens into other epithelial cells or underlying tissues. Stem cells may reside within the epithelium proper, within specific areas connected with the epithelium (e.g., glands or ducts), or they may arise from outside of the epithelium (e.g., bone marrow).

**7. Blood supply.** Epithelial tissue is generally **avascular**, and thus is dependent on the blood vessels in the underlying connective tissue for oxygen and nutrients. In thicker (i.e., multilaminar) epithelia (e.g., epidermis of skin), intercellular channels between adjacent epithelial cells are important for distribution of oxygen and nutrients.

**Shapes of epithelial cells** vary depending upon whether they are viewed vertically (from basement membrane to free surface) or in surface view. In vertical view, three shapes are typical: squamous, cuboidal, and columnar. In surface view, epithelial cells are almost always polygonal.

**1. Squamous cells** [L. *squama* =scale] are characterized as being much wider than tall. These very thin, scale-like or flattened “pavement” cells present a minimal barrier to passage of materials through the epithelium. The cytoplasm can be so thin as to be difficult or impossible to see with the light microscope (e.g., gas exchange epithelium of lung alveoli). Nuclei are flattened and elongated in the direction of the long axis of the cell.

**2. Cuboidal cells** are characterized by having their height approximately equal to their width. Thus, they appear more or less square in vertically-sectioned profiles. Nuclei are generally spherical in cuboidal cells. However, the term “cuboidal”, which implies a cube in 3 dimensions, is actually a misnomer due to their polygonal surface profiles.

**3. Columnar cells** are characterized by being taller than they are wide in vertical section. Nuclei are usually (but not always) more oval in shape and elongated in the long axis of the cell.

**4. Surface views.** Seen from above, all epithelial cells are usually polygonal (more or less hexagonal) in shape. The strategy of hexagonal packing and arrays in cells and tissues is common.

**Important points to remember.** Epithelial tissue consists of a wide variety of cell types with a minimal amount of extracellular material/matrix (ECM), which together line and cover virtually all free surfaces of the body. Epithelia are derived from all three germ layers and form sheets composed of groups of cells, in one or more layers, joined by specialized adhesions. The **apical** surfaces of epithelia face the free surface of the body or lumen of an organ or gland; **lateral** surfaces interact with adjacent epithelial cells; and the **basal** surfaces are attached to an underlying basal lamina/basement membrane. Epithelial tissues are avascular so that nutrients and blood gases must diffuse from blood vessels located in the underlying connective tissues to the more superficially located epithelial cells.

## **SURFACE EPITHELIA**

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Epithelia that cover and line all surfaces within the body are principally named and identified on the basis of two major characteristics: 1) the **number of cell layers** in the epithelium [i.e., **simple** (one layer) or **stratified** (two or more layers)], and 2) the **shape of the cells in the surface layer** (i.e., **squamous, cuboidal, columnar**). These conventions apply when the epithelium is viewed in

vertical section, i.e., a plane of section that extends perpendicularly from the free surface to the basement membrane. As described previously, in surface view all epithelia have a polygonal shape that often appears hexagonal. The exception to the above naming convention is seen in **pseudostratified epithelium** (vide infra)

**Simple Epithelia** are defined as a single layer (monolayer) of cells, all or which are attached to the basement membrane. Stem cells may reside in the epithelium or arise from outside the epithelium. Three varieties are identified on the basis of cell shape.

**1. Simple squamous epithelium** is a monolayer of flattened, scale-like cells [L. *squama* = a scale].

**a. Functions.** Simple squamous cells are well suited to facilitate exchange (e.g., diffusion, osmosis) across the epithelium.

**b. Examples** of this type occur in Bowman's capsule of the renal corpuscle, and in alveoli of lungs (type I cells). Two special types of squamous monolayers are endothelium and mesothelium.

**c. Endothelium** is the society of simple squamous endothelial cells (ECs) that forms the lining of the entire cardiovascular system (heart, arteries, capillaries, veins) and lymphatic vessels. It has been estimated that this lining consists of about  $1 \times 10^{13}$  cells with a mass of nearly 1 kg in adults (Sumpio BE et al. *Int J Biochem Cell Biol* 34:1508-1512, 2002). Although typically a squamous monolayer, this epithelium can take on a different shape in certain locations; e.g., in the high endothelial venules (HEVs) of lymphoid organs, it resembles a simple cuboidal variety.

**i. Functions.** In addition to their primary function as a semipermeable membrane for facilitating and controlling the exchange of large and small molecules, ECs have now been recognized to have a multitude of synthetic and metabolic roles. Some of these important functions include growth and development of new blood vessels (angiogenesis); participation in control of vasomotor tone and blood flow; regulation of immune and inflammatory responses by targeting and trafficking of white blood cells to specific sites in body; and maintenance of blood fluidity and hemostasis by regulating thrombosis, thrombolysis, and platelet adherence (e.g., Sumpio BE et al. *Int J Biochem Cell Biol* 34:1508-1512, 2002; Aird WC *Crit Care Med* 32[Suppl]:S271-

S279, 2004).

**ii. Differences from other epithelia.** Although cytokeratin expression has been demonstrated in ECs by PCR (Traweek, ST et al. *Am J Pathol* 142:1111-1118, 1993), apparently the major intermediate filament in endothelium is **vimentin** (e.g., DePianto, D & Coulombe, PA. *Exp Cell Res* 301:68-76, 2004). It should be noted that these class III IFs are characteristic of fibroblasts and leukocytes. Perhaps this similarity is due to a common mesenchymal origin.

**iii. Differences among endothelia.** Although endothelia from different locations share many similarities, it is now becoming evident that both structural and functional aspects of these cells are differentially regulated in space [i.e., in different types of blood vessels (e.g., large vessels vs microcirculation) and in specific organs where they are found] and time (see reviews by Aird WC *Crit Care Med* 31[Suppl]:S221-S230, 2003; Conway EM & Carmeliet P. *Genome Biol* 5:207, 2004). It is believed that these differences have important implications for the pathophysiology of ECs and their associated organs.

**iv. Renewal, repair and stem cells.** During development as well as in adults, it appears that new ECs may arise from a number of sources: from existing ECs, from ECs that delaminate and circulate as potential stem cells, from CT stem cells, and from bone-marrow derived stem cells (see reviews by Nishikawa S-I. *Curr Opin Cell Biol* 13:673-678, 2001; Drake, CJ *Birth Defects Res (Part C)* 69:73-82, 2003; Urbich C & Dimmeler S. *Circ Res* 95:343-353, 2004; Urbich C & Dimmeler S. *Trends Cardiovasc Med* 14:318-322, 2004).

**v. Weibel-Palade Bodies.** ECs were found to contain unique rod-shaped structures in their cytoplasm (Weibel ER & Palade GE. *J Cell Biol* 23:101-112, 1964), which are called Weibel-Palade bodies (WPBs). Subsequently, WPBs were determined to be specialized secretory granules that contain several proteins, but mainly **von Willebrand factor** (vWF) (Wagner DD et al. *J Cell Biol* 95:355-360, 1982). vWF is a circulating plasma glycoprotein with important functions in hemostasis (=arrest of bleeding). In this regard, vWF has the following essential roles. First, vWF serves as a binding protein that chaperones the essential clotting factor VIII (the protein missing in hemophilia A) in the circulation; in the absence of vWF, factor VIII is rapidly cleared from the circulation and is unable to perform its function. Second, vWF mediates the adhesion of platelets to sites of vascular damage by binding to specific glycoproteins on platelet membranes on one side and to components of subendothelial connective tissue on the other; in the absence of vWF, the formation of platelet plugs at sites of vascular injury is defective (see **HistoCAPS**: von Willebrand Disease below). In addition, WPBs contain the

leukocyte adhesion molecule P-selectin within their limiting membranes, which is important for recruiting leukocytes at sites of inflammation (Bonfanti R et al. *Blood* 73:1109-1112, 1989; McEver RP et al. *J Clin Invest* 84:92-99, 1989). Thus, exocytosis of WPBs at endothelial surfaces broadcasts and targets the vWF and P-selectin signals for their critical roles in hemostasis and inflammation, respectively (e.g., Hannah MJ et al. *Sem Cell Devel Biol* 13:313-324, 2002).

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**HistoCAPS®**: Capsules of Clinical And Pathologic Significance

**Von Willebrand Disease (vWD)** (see review by Sadler JE *Annu Rev Med* 56:173-191, 2005) is typically described as a congenital bleeding disorder due to deficiencies in vWF. VWD, which is characterized clinically by spontaneous bleeding (primarily at mucous membranes) and prolonged bleeding times despite normal platelet counts, represents several types of inherited disorders that range from partial to complete deficiencies in vWF (Sadler JE. *Thromb Haemost* 71:520-525, 1994). In addition, a rare acquired syndrome with similarities to congenital vWD appears to be particularly associated with lympho- or myeloproliferative and cardiovascular diseases (Federici AB et al. *Thromb Haemost* 84:345-349, 2000). With vWF deficiencies, both of the important functions of this protein as described above (namely clotting factor VIII protection and mediation of platelet binding to sites of blood vessel injury) are negated and as a result hemostasis is compromised.

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**d. Mesothelium** is the simple squamous epithelium that lines all coelomic cavities and thus forms the visceral and parietal coverings of the serous membranes (serosae) of the pleura, pericardium, and peritoneum (see reviews by Mutsaers SE *Respirology* 7:171-191, 2002; Mutsaers SE. *Int J Biochem Cell Biol* 36:9-16, 2004; Herrick SE & Mutsaers SE. *Int J Biochem Cell Biol* 36:621-642, 2004). In males, an extension derived from the peritoneum, called the *tunica vaginalis*, forms a sac around the descended testes. In females, the abdominal ostium of the uterine tube, which is located proximal to the ovarian surface, communicates with the peritoneal cavity. Thus, in females the peritoneal cavity is not completely closed. For this reason, a number of anomalies are possible [e.g., ectopic peritoneal implantation; peritoneal endometriosis (see **HistoCAPS** that follows)].

Beneath the monolayer of mesothelial cells

(MCs) is a thin basement membrane and underlying CT stroma. Although typically squamous, cuboidal MCs can also be found in certain locations (e.g., visceral layer of liver and spleen). In response to injury, MCs are also cuboidal and have been described as “reactive MCs” (Ueda J et al. *Pathol Int* 51:431-439, 2001).

**i. Functions.** In addition to facilitating the transport of fluids, molecules and cells across serosae, MCs have a number of other important functions. These include secretion of surfactant, proteoglycans, and glycosaminoglycans to provide non-adhesive surfaces for protection against friction and microorganisms; and roles in antigen presentation, inflammation and tissue repair (e.g., Hills BA et al. *Periton Dial Int* 18:157-165, 1998; Mutsaers SE *Respirology* 7:171-191, 2002; Mutsaers SE *Int J Biochem Cell Biol* 36:9-16, 2004; Raftery, AT et al. *Clin Anat* 2:69-85, 1989; Yao V et al. *Br J Surg* 90:1187-1194, 2003).

**ii. Differences from other epithelia.** MCs, like other epithelial cells, express cytokeratin intermediate filaments. However, unlike typical epithelial cells and apparently due to their mesodermal origins, MCs also express the mesenchymal IFs of desmin and vimentin (Ferrandez-Izquierdo A et al. *Diagn Cytopathol* 10:256-262, 1994). Mesothelial renewal and repair also appears to be different from other epithelia (see following section).

**iii. Renewal, repair and stem cells.** Although mesothelium is viewed as a more slowly renewing tissue (compared to other epithelia) with 0.16-0.5% of cells in mitosis at any one time, injury to the serosal surface causes 30-80% of mesothelial cells at the wound edge and on the apposing surface to begin DNA synthesis within 48 hrs (Mutsaers SE. *Int J Biochem Cell Biol* 36:9-16, 2004). In this regard, serosal repair appears interesting. Whereas typical epithelial repair occurs from the wound edges, it has been shown that mesothelial repair not only occurs from the edges but also takes place diffusely across the wound surface in the following way: 1) MCs away from the wound as well as on opposing surfaces proliferate, 2) they detach from their basement membranes, 3) they migrate through the serosal fluid, and 4) they then settle on the wound surface where they proliferate and repopulate the damaged area (Foley-Comer AJ et al. *J Cell Sci* 115:1383-1389, 2002). Thus, stem cells seem to derive from activated MCs. Whether this is the only mechanism of mesothelium renewal and repair remains to be determined.

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**HistoCAPS®**: Capsules of **Clinical And Pathologic**  
**Significance**

**Adhesions** [L. *adhaesio* =clinging together; *adhaerere* =to stick to] in relation to the coelomic cavities are defined as areas of fibrous or fibrinous bands that connect opposing serosal surfaces. Thus, these areas of attachment are more accurately called **serosal adhesions**. Since the visceral layer on an organ becomes attached to the parietal layer on the adjacent body wall, a significant impairment of organ function may result (e.g., perforation of the vermiform appendix following acute inflammation can lead to peritonitis, which may cause adhesions in the area of the ovaries and uterine tubes resulting in female infertility). Although adhesions are more common with peritoneal and pleural serosae, pericardial involvement may result from pericarditis or may cause chronic constrictive pericarditis.

Serosal adhesions develop due to direct damage to the mesothelium and resultant compromise of the frictionless serosal interfaces. This damage is mainly caused by recurrent effusions [L. *effusio* =a pouring out], i.e., increases in serous cavity fluid, and surgery. It has been estimated that 70-80% of intestinal obstructions and up to 20% of infertility cases in women are the result of serosal adhesions (Mutsaers SE. *Int J Biochem Cell Biol* 36:9-16, 2004). Effusion and accumulation of serous fluid in the peritoneal cavity is called **ascites**.

In studies on the development of **peritoneal endometriosis** (i.e., presence of functional endometrial tissue in locations outside the uterus, viz. the peritoneum in this case), the authors conclude that the intact mesothelium has properties of Teflon, while areas of denuded mesothelium and exposed extracellular matrix responds like Velcro (Dunselman GAJ et al. *Hum Reprod* 16:605-607, 2001). Thus, it appears that any condition that damages the mesothelial monolayer and exposes the underlying ECM can lead to serosal adhesions; and the terms Teflon and Velcro are excellent descriptors of the normal and damaged mesothelium, respectively.

**Peritoneal dialysis (PD)**, especially continuous ambulatory PD (CAPD), has become a less stressful alternative to hemodialysis for treatment of patients with chronic renal failure in end-stage renal disease. This procedure takes advantage of the inherent "ultrafiltration membrane" that is provided by the extensive mesothelial surface of the peritoneum and its underlying CT vasculature. Dialysis fluids are perfused into the peritoneal space via catheter and periodically drained and reinfused in order to remove wastes in a tidal fashion. Two important factors that can cause failure of PD are 1) chronic inflammation/infection of the peritoneum, and 2) loss of the ultrafiltration function (Slingeneyer A et al. *Nephron* 33:133-138, 1983; Krediet RT. *Kidney Int* 55:341-356, 1999). Both of these factors are ultimately related to the normal structure and function of the mesothelium (e.g., Yanez-Mo M et al. *N Engl J Med* 348:403-413, 2003).

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**2. Simple cuboidal epithelium** is a monolayer of cells that are approximately as tall as they are wide in vertical section.

**a. Functions.** Simple cuboidal cells also facilitate exchange, but are more involved in active mechanisms that require extensive organelles and membrane systems, which necessitate greater cell volume.

**b. Examples** can be found in the proximal and distal kidney tubules, and in the transporting ducts of glands.

**3. Simple columnar epithelium** is a monolayer of cells that are taller than they are wide in vertical section.

**a. Functions.** Simple columnar cells also are important for active mechanisms of exchange where a large volume of related organelles are required. The taller nature of columnar cells may also provide a greater degree of protection while still maintaining the benefits of a simple epithelium.

**b. Examples** of simple columnar epithelium can be found in the alimentary canal (e.g., intestinal absorptive cells).

**Stratified Epithelia** are defined as two or more layers of cells in which only the basal layer is attached to the basement membrane. In general, stratified epithelia are more protective in function than those of the simple variety. The basal layer contains the stem cells necessary for regeneration of this renewable tissue.

**1. Stratified squamous epithelium (SSE)** is characterized by multiple layers of cells called **keratinocytes\***, and exhibits a surface layer(s) of flattened, squamous cells.

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\*Traditionally, the term **keratinocyte** has been reserved for the cells in the epidermis of skin and those in the oral mucosa that are responsible for orthokeratinization (vide infra). However, since all SSE contain cytokeratins to various degrees, this limited usage is no longer tenable.  
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**a. Cytokeratins.** Although epithelium as a tissue is characterized by containing a class of intermediate filaments that belong to the family of cytokeratins, SSE are particularly well endowed in this respect. As mentioned above, these IFs in keratinocyte cytoplasm can be seen at the EM level as **tonofilaments** or at the LM level as aggregates of filaments called **tonofibrils**. On their intercellular surfaces, keratinocytes display

abundant **desmosomes**, which function as strong linkages between cells via the keratin cytoskeletons (see below).

**b. Important functions.** Thus, SSE is well suited for protective functions, and is found on surfaces subjected to frictional forces and other potential environmental insults. Other important functions include protective barriers to pathogens, and resistance to dehydration and swelling.

**c. Three variations of SSE** are classically described. It is important to remember that *all* variants contain cytokeratins despite their nomenclature; the differences between them relate to the *degrees* of keratinization (cornification) and locations within the body. However, since cytokeratin filaments are acidophilic (see Table 1-1), and the intensity of staining is proportional to the amounts of cytoplasmic filaments, staining can be another helpful tool in histologic identification of the 3 variants.

**i. Stratified squamous "keratinizing" epithelium (SSKE).** Also called **orthokeratinizing** or the **cutaneous type**, this variety has the greatest amount of cytokeratins and is largely found in the epidermis of the skin. However, in certain areas of the masticatory mucosa in the oral cavity, SSKE may also occur. In the intensely acidophilic surface layers, the degree of keratinization is so high that nuclei and other organelles are absent. Keratohyalin granules are generally prominent and abundant in cells subjacent to the superficial cornified layers.

**ii. Stratified squamous "parakeratinizing" epithelium (SSPKE).** Intermediate in the amount of cytokeratins, this epithelium is mostly found in the oral cavity on masticatory surfaces (e.g., gingiva, hard palate). Nuclei are still seen in the surface layers, but acidophilia is more prominent in these cells when compared to those in the basal layers. Keratohyalin granules may or may not be present; when present their numbers are far less than those in the SSKE variety.

**iii. Stratified squamous "nonkeratinizing" epithelium (SSNKE).** Also called the **mucous type**, this variety could best be described as "hypokeratinizing" because this variant has the lower amount of cytokeratins. Examples can be found in the oral cavity, esophagus, and vagina. Nuclei are present in the surface layers and among the three variants acidophilia is the least prominent, which reflects the lower cytokeratin content in SSNKE.

**2. Stratified cuboidal epithelium** consists

of two or more layers and exhibits cuboidal-like surface cells. Examples of this variety are found lining the ducts of glands (e.g., salivary).

**3. Stratified columnar epithelium** consists of two or more layers and exhibits columnar surface cells. Examples of this variety can be found in portions of the male urethra, and also in the larger ducts of glands.

***Pseudostratified epithelia***, which are exceptions to the typical naming convention of epithelia, are defined according to the following characteristics: *all* cells are attached to the basal lamina, but *not all* cells reach the free surface. Several varieties are identified, often by the particular morphology of certain cells that reach the free surface. This variety is often found in areas subjected to stretching. It has the advantages of a simple epithelium in that many of the cells are in contact with both the internal (basal surface) and external (apical surface) environments, but is also well suited to protect its basal stem cells from potential insults from the external surface (e.g., inhaled pollutants; hypertonic urine).

#### 1. Structure

**a. Similarity to simple epithelia.** Since all pseudostratified epithelial cells are attached to their basal laminae, these epithelia are similar in this regard to simple varieties; indeed, one could view these types as a variant of simple epithelium with a basal stem cell compartment. However, they do differ in that the pseudostratified cells exhibit varying heights, which accounts for the fact that only the tallest cells reach the apical surface of the epithelium.

**b. Similarity to stratified epithelia.** In histologic sections, these epithelia may appear to be stratified (i.e., two or more layers of cells; see above) due to nuclei arranged at different levels. However, since the basal surfaces of *all* cells rest on the basement membrane, the cells are not stratified. N.B.: only their nuclei appear "stratified".

**2. Occurrence.** Pseudostratified epithelia are found in several locations, but two important examples occur in the respiratory and urinary systems.

**a. Respiratory epithelium** (*pseudostratified ciliated columnar with goblet cells*) is largely found in the conducting airways of the respiratory tract. It is readily distinguished

histologically by the combination of its columnar ciliated cells, goblet cells, and nuclei at several different levels. However, at the EM level seven or eight different cell types have been described in this epithelium (e.g., Jeffery PK *Ciba Found Symp* 54:5-23, 1978).

**b. Urothelium** (*transitional epithelium*) is found only in the urinary tract from the kidney calyces to the urethra. In a relaxed state, it is characterized by its unique “dome cells”, which reach the free surface and are often binucleate. This epithelium is often described as stratified in some textbooks, but has been shown to be pseudostratified (Petry G, Amon H Z *Zellforsch Mikrosk Anat* 69:587-612, 1966; Phillips SJ, Griffin T *Anat Rec* 211:153A, 1985).

**c. Other locations** of pseudostratified epithelia include some glandular ducts, and some organs of the male reproductive tract including the ductus epididymidis and ductus deferens. The epithelium of the latter two organs are distinguished by apical stereocilia (long microvilli).

## GLANDULAR EPITHELIA

Glandular epithelia consist of single cells or groups of cells specialized for secretion. They can be classified as **exocrine** (secretions distributed by duct systems) or **endocrine** (secretions distributed by blood vessels). Exocrine glands are generally classified on the basis of the following factors.

### Number of Cells

**1. Unicellular glands** are defined as single cells interspersed among other epithelial cells of different functions (e.g., mucus-secreting goblet cells).

**2. Multicellular glands** occur as many adjacent secretory cells within the epithelium (e.g., surface mucous cells of stomach) or as complex glands with ducts (see next section).

**Pattern of Duct System** (simple; compound) **and Secretory Portion** (tubular; acinar/ alveolar; tubuloacinar)

**1. Simple glands** have a simple, unbranched duct with tubular or acinar [L. *acinus* =grape] shaped secretory pieces.

**2. Compound glands** have a branched duct system with tubular, acinar, or tubuloacinar shaped secretory units.

**Types of the Secretion** (mucous, serous, mixed)

**1. Mucous glands** are characterized by their viscous secretions and typical histologic appearance.

**a. Secretions** contain a variety of **mucins** consisting of carbohydrate-rich glycoproteins. When mucins combine with water, they form the viscous solution known as **mucus** that has important protective and lubricating functions at epithelial surfaces. Mucous coverings on apical epithelial surfaces are important components of innate immunity.

**b. Structure of mucous secretory units** are mostly **tubular** and composed of tall pyramidal to columnar secretory cells. Although the cytoplasm of these cells contains many mucin granules (mucigens), their staining with standard dyes (e.g., H&E) is poor and renders the cytoplasm quite pale in sections. However, with PAS or other mucin stains, their closely-packed cytoplasmic mucigens are brightly colored. Nuclei with a squamous-like appearance and other organelles are characteristically flattened at the base of cells due to abundant mucigens. Much of this flattening appears to be artifactual due to swelling of mucins during processing; however, the distinctive appearance of mucin units is in marked contrast to that of serous glands.

**2. Serous glands** are characterized by their watery, protein-containing secretions and morphology that is consistent with protein-secreting cells.

**a. Secretions** are made up of a watery fluid [L. *serum* =whey], which contains proteins and other components, including zymogens, bactericidal compounds, and ions.

**b. Structure of serous secretory units** are **acinar** [L. *acinus* =grape, berry] and composed of shorter pyramidal cells arranged around a small lumen. Characteristically, the nucleus is basal in location, but round in shape and surrounded by obvious cytoplasmic basophilia due to the RER. The apical cytoplasm typically contains numerous secretory granules.

**3. Mixed glands** contain both mucous and serous secretory units, either separate or as mixed units. It is now clear that even single cells may be of the mixed variety.

**a. Serous demilunes** are crescent-

shaped groups of serous cells that appear to cap the distal ends of mucous secretory units in mixed units (also called *crescents of Giannuzzi* or *c. of Heidenhain*). Although these structures have long been described as discrete entities, they may largely be due to a fixation artifact, which results from the swelling of mucins in mixed secretory units (e.g., Ichikawa, M & Ichikawa, A. *Cell Tiss Res* 250:350-314, 1987; Yamashina, S et al. *Arch Histol Cytol* 62:347-354, 1999; Yamashina, S et al. *Eur J Morphol* 38:213-218, 2000). **Artifacts or not, these structures do provide important histologic landmarks for distinguishing the different types of glands.**

**b. Intercellular canaliculi**, located between mucous cells in mixed glands, have been described as delicate secretory channels that connect serous cells of demilunes with the central lumen. Their structure may also be largely due to the fixation artifact that produces the displacement of serous cells in mixed units to form the demilunes.

### Mechanisms of the Secretion

**1. Merocrine secretion** [Gr. *mēros* =part, share + *krinō* =to separate] is the method of exocytosis; the membrane of the secretory granule fuses with the plasma membrane to release the contents of the granule. Most exocrine glands secrete by this mechanism, including salivary glands and pancreas.

**2. Apocrine secretion** [Gr. *apo-* =off, away from] is the mechanism whereby both the secretory product and a portion of the apical secretory cell cytoplasm are pinched off and released. This process has been described as **decapitation secretion** (Schiefferdecker *P Zentralbl Biol* 37:534, 1917; Schaumburg-Lever G & Lever WF *J Invest Dermatol* 64:38-41, 1975). Examples of this mechanism apparently occur in all apocrine glands (see review by Aumuller G et al *Anat Anz* 181:437-446, 1999) and have been clearly demonstrated in apocrine sweat glands (Schaumburg-Lever G & Lever WF *J Invest Dermatol* 64:38-41, 1975), mammary glands (Bargmann W & Knoop A *Z Zellforsch Mikrosk Anat* 49:344, 1959), ceruminous glands of the external ear canal (Testa-Riva F, Puxeddu P *Anat Rec* 196:363-372, 1980), and glands of Moll in the eyelid (Stoekelhuber et al *J Invest Dermatol* 121:28-36, 2003). Apocrine secretion has also been described in nonciliated bronchiolar epithelial (Clara) cells of lung (e.g., Clara, M *Z Mikrosk Anat Forsch* 41:321-347, 1937; Stinson, SF & Loosli, CG. *J Anat* 127:291-298, 1978; Etherton, JE et al. *J Anat* 129:305-322, 1979).

**3. Holocrine secretion** [Gr. *holos* =whole, entire, complete] is the method involving the release of entire cells and their contained secretory product.

This process is apparently the result of **apoptosis** [Gr. *apo-* =off + *ptosis* =a falling], which is programmed secretory cell death (see Wrobel et al. *J Invest Dermatol* 120:175-181, 2003).

**a. Sebaceous glands**, which secrete a lipid-rich sebum into hair follicles or onto free surfaces (e.g., Fordyce spots of oral mucosa; tarsal glands of eyelids) are the classic examples of secretion by this mechanism.

**b. Other examples.** The holocrine mechanism has been used to describe any process where whole cells are released; e.g., dermatologists sometimes refer to the exfoliation of the stratum corneum of skin as holocrine, since whole keratinocytes are shed.

**Myoepithelial cells**, also called *basket cells*, are myoid (smooth muscle-like) contractile cells that assist in the secretion of certain glands (e.g., sweat, salivary, lacrimal, mammary). Although myoepithelial cells resemble smooth muscle cells and contain a similar contractile apparatus, they are considered as true epithelial cells for the following reasons (e.g., Deugnier M—A et al. *Breast Cancer Res* 4:224-230, 2002): 1) their major IFs are cytokeratins (5 and 14); 2) they form cadherin-mediated junctions (desmosomes and hemidesmosomes); and 3) they are located between the luminal epithelium and the basement membrane, which like other epithelial cells are separated from underlying connective tissue by this specialized ECM (vide infra).

### EPITHELIAL SURFACE SPECIALIZATIONS

**Definition.** Surface specializations of epithelial cells, which are morphologic adaptations for specific functions, are located at, on and/or within particular plasma membrane domains. Although these specializations are highly developed within epithelia, several are found in other tissues as well and will be encountered again.

#### Nomenclature of epithelial surfaces as plasma membrane domains

**1. Apical** [L. *apex* =summit, peak] **surface specializations** occur at epithelial surfaces facing the lumen, which are also known as *free* surfaces since there are no attachments to other cells or tissues at these locations. These surfaces represent the interface between epithelial cells and their external environment. Apical specializations include **microvilli**, **cilia**, and the **glycocalyx**.

**2. Lateral** [L. *latus* =side] **surface specializations** occur at the surfaces between adjacent epithelial cells. These surfaces are the interfaces between each member of an epithelial society. Lateral specializations include **occluding junctions, adhering junctions, and communicating junctions.**

**3. Basal surface specializations** occur at the base/bottom of epithelia. These surfaces are the interfaces between an epithelium and its underlying connective tissue or vasculature. Basal specializations include **basement membranes, hemidesmosomes,** and redundant surface membrane increases (**infoldings and outfoldings**).

### Apical (Free) Surface Specializations

**1. Microvilli** [L. *villus* =tuft of hair] are plasma membrane evaginations of the apical surface that greatly increase the area available for absorption (or secretion). They contain a core of actin microfilaments and are covered by a coat of surface-bound carbohydrates, called the **glycocalyx** (see below), which gives a PAS-positive appearance under the light microscope.

**a. Striated border** of the intestines consists of densely packed ( $\sim 60/\mu\text{m}^2$ ) microvilli that assist and enhance nutrient absorption.

**b. Brush border** of the kidney proximal tubules also consists of thousands of densely packed microvilli, which facilitate the reabsorption that takes place in this location.

**c. Stereocilia** are elongated microvilli found at the apices of cells lining the ductus epididymidis and ductus deferens of the male genital tract. Stereocilia also occur on cochlear and vestibular hair cells of the internal ear.

**d. Other locations.** Microvilli are found on many other cells including mesothelium. In general, their purpose is to increase membrane surface area for absorption or secretion. Typically, they are shorter and less numerous in cells that are not highly specialized for absorption or transport.

**2. Cilia** are also plasma membrane and cytoplasmic projections from the apical surface. They are specializations for motility and contain a core of microtubules arranged in a specific configuration called the **axoneme**. Cilia are longer and thicker than microvilli, and their core of

microtubules are extensions of centriole-like basal bodies that are located in the terminal web.

**a. Axoneme** is the characteristic array of microtubules that makes up the longitudinal core structure found in all cilia and flagella. As revealed by TEM, it contains a central pair of microtubules encircled by nine doublets ( $9 \times 2 + 2$ ). Attached to one end of each doublet and facing the adjacent doublet are two dynein arms that represent molecular motors that run along the adjacent microtubular tracks. These motors are powered by ATP and are responsible for ciliary/flagellar motion.

**b. Basal bodies,** which can arise from centrioles and have a similar structure, are responsible for giving rise to cilia and for anchoring axonemes into a cell's terminal web. Their characteristic structure is a pinwheel arrangement of nine triplets of microtubules ( $9 \times 3$ ).

**c. Motility.** Cilia move back and forth to propel fluid and particles unidirectionally. Movement is brought about by differential sliding of adjacent doublets past each other, which is facilitated by the energy-dependent movement motor proteins along adjacent microtubules.

**3. Flagella,** which have the same microstructure as cilia, occur singly and are much longer in length. They provide motility for spermatozoa.

**4. Glycocalyx** [Gr. *glykys* =sweet + *kalyx* =husk, shell] typically refers to a carbohydrate-rich, PAS-positive covering on the apical surface of certain epithelial cells, which can be seen with the LM due to the high density of carbohydrate residues. However, all cell membranes consist of externally-directed glycoproteins and glycolipids, which can be observed with the TEM and comprise the glycocalyx.

### Lateral Surface Specializations

**1. Junctional complexes in epithelia.** Intercellular specializations called *terminal bars* and *desmosomes* have been recognized at the light microscopic level for a century or more. When the terminal bars of many hollow organs and glands were examined with the electron microscope, a characteristic tripartite junctional complex was observed, which consisted of the following components in a luminal to abluminal direction: 1) tight junction (called **zonula occludens**), an intermediate zonary adhering junction (called **zonula adherens**), and a punctate desmosome

(called **macula adherens**) (Farquhar MG & Palade GE. *J Cell Biol* 17:375-412, 1963).

**2. Zonula occludens** (occluding junction, tight junction) occurs on the lateral cell surfaces just beneath the apical poles.

**a. Structure.** Formed by inosculation/interactions of special transmembrane proteins (**claudins, occludin**) in the plasma membranes of adjacent cells, these junctions form a network that extends completely around the cell perimeter and represent the closest contacts between cells (see Table 3-1).

**b. Functions.**

**i. Restrict Paracellular Flow.** Occluding junctions serve as permeability seals to isolate the underlying intercellular clefts (paracellular compartment) from the outside environment, therefore restricting intercellular movement of materials.

**ii. Restrict Membrane Flow.** In addition, they separate the apical and basolateral domains in cell membranes, which insures that specific proteins will remain in specific domains.

**3. Zonula adherens** lies subjacent to the zonula occludens. It is also a band-like junction that extends around the perimeter of cells; it serves in the attachment of adjacent epithelial cells (see Table 3-1).

**4. Macula [L. =spot] adherens (desmosome).** Desmosomes [Gr. *desmos* =bond, ligament + *soma* =body] are adhesive intercellular junctions, which are found in tissues subjected to mechanical strain. They are widespread in epithelia, particularly in stratified squamous varieties, and also occur in cardiac muscle. They not only link the membranes of adjacent cells, but also the intermediate (keratin) filament cytoskeletons across cells (Garrod, DR et al. *Curr Opin Cell Biol* 14:537-545, 2002). Essentially, these junctions are “spot welds” between adjacent cells, which are formed by the juxtaposition and attachment of two symmetrical disk-shaped structures provided by each cell.

**a. Structure: light microscopic.** At the LM level, desmosomes are difficult to resolve, but can be readily observed in SSE due to their high density between cells. Here, they appear as small punctate bodies, which were once thought to connect areas of cytoplasmic continuity between adjacent cells and thus believed to mediate what was called “cytoplasmic bridges”.

**b. Structure: electron microscopic.**

Although EM studies showed that desmosomes are complex junctions morphologically (McNutt, NS & Weinstein, RS. *Prog Biophys Mol Biol* 26:45-101, 1973; Staehelin, LA. *Int Rev Cytol* 39:191-283, 1974), it was clear that cytoplasmic continuity at these structures does not exist. Rather, their ultrastructure revealed that desmosomes are bipartite junctions, which consist of symmetrical, mirror-image-like components provided by each adjacent cell.

**i. Intracellular components.**

Inside each cell, just beneath their lateral plasma membranes, electron dense structures called **attachment plaques** were found to connect the cell membrane on one side with intermediate filaments of the keratin cytoskeleton on the cytoplasmic side.

**ii. Extracellular components.**

Between each cell in the middle of the intercellular space, an intermediate **dense midline** was observed, which appeared to be a region of attachment between adjacent cells.

**c. Structure: submicroscopic.** At the molecular level, desmosomes are constructed of specialized adhesive proteins (see Table 3-1). The major components are integral membrane glycoproteins that belong to the cadherin superfamily of adhesion molecules (e.g., Angst, BD et al. *J Cell Sci* 114:629-641, 2001). To date, several isoforms of two major desmosomal cadherins have been described and a schema for their nomenclature proposed (Buxton, RS et al. *J Cell Biol* 121:481-483, 1993): **desmocollins** (Dsc1a,b; Dsc2a,b; Dsc3a,b) and **desmogleins** (Dsg1, Dsg2, Dsg3). Region-specific expression for various isoforms of these proteins has also been shown to occur in SSE: e.g., Dsg1 is normally located in upper layers of oral mucosa but throughout entire epidermis (especially in upper layers), while Dsg3 is located in basal layers of epidermis but throughout oral mucosa (Arneemann, J et al. *J Cell Sci* 104:741-750, 1993; Amagai, M et al. *J Invest Dermatol* 106:351-355, 1996; Amagai, M et al. *J Am Acad Dermatol* 40:167-170, 1999; Mahoney, MG et al. *J Clin Invest* 103:461-468, 1999). This localization has proved to be important for understanding certain diseases (see below).

**i. Extracellular components.** The integral transmembrane desmocollins and desmogleins have extracellular, intramembrane, and intracellular (cytoplasmic) domains. Their extracellular domains include the following. 1) **Cell adhesion recognition sites** at the distal ends, which mediate the intercellular binding of these cadherins between adjacent cells. These binding domains appear to be the molecular basis of the dense midline seen at the EM level. 2) **Calcium-**

**binding repeats**, which occur at various sites along the extracellular domains. These sites are important for the cadherin-cadherin binding because removal of calcium results in disassociation of the desmosomal junction.

**ii. Intracellular components.** On the cytoplasmic sides of adjacent cell membranes, the intracellular domains are associated with specialized cytoplasmic proteins (**desmoplakins, plakoglobin, and plakophilins**), which together are components of the disk-shaped, dense attachment plaques seen with EM. Keratin tonofilaments of the cytoskeleton are securely anchored into these plaques via desmoplakin (Ruhrberg, C & Watt, FM. *Curr Opin Genet Dev* 7:392-397, 1997).

**b. Function.** Most abundant in lining membranes subject to wear and tear, but present in all epithelia, desmosomes are important cellular spot welds that hold cells together by a calcium-dependent adhesion mechanism. They represent an important means of resistance to lateral shearing forces between cells by coupling external attachment of adjacent cells to internal linkage of their keratin cytoskeletons across the epithelium.

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**HistoCAPS®:** Capsules of Clinical And Pathologic Significance

**Pemphigus** [Gr. *pemphix* = a blister] is a potentially fatal autoimmune disorder that affects cell adhesion at desmosomes. Recent advances in basic and clinical research have shown that this condition is actually a group of bullous [L. *bullus* = bubble] or blistering disorders of skin and mucous membranes, which are characterized by disruption of intercellular adhesion and caused by antibodies against various desmosomal proteins (e.g., Hashimoto, T *Arch Dermatol Res* 295:S2-S11, 2003). Although about a dozen variants have been described worldwide, pathology textbooks (e.g., Kumar, V et al. *Robbins and Cotran Pathologic Basis of Disease*, Elsevier Saunders, Philadelphia, 2005) describe four classic types of pemphigus: 1) *pemphigus vulgaris*, 2) *p. vegetans*, 3) *p. foliaceus*, and 4) *p. erythematosus*. However, based on the similarity of autoantigens, it now appears that *p. vegetans* is a subtype of *p. vulgaris*, and *p. erythematosus* is a subtype of *p. foliaceus* (see Hashimoto, 2003). From this work, the following important features of blister formation in two classic variants can be summarized. If blisters form in the deep layers, they are classified as “suprabasal”; if blisters occur higher up in the more superficial layers, they are classified as “subcorneal” (=superficial). In this regard, it is important to recall the distribution of Dsg isoforms in SSE (see above).

**Pemphigus vulgaris** can be divided into two types based upon which antigens are reactive. In the *mucosal dominant type*, the pathomechanism of blister formation is due to autoantibodies against Dsg3. Thus, blisters occur suprabasally in the oral mucosa since Dsg1 provides some compensation for the epidermis of skin. In the mucocutaneous type, pathology is due to autoantibodies against both Dsg1 and Dsg3. Thus, no compensation occurs and suprabasal blisters form in both oral mucosa and epidermis. *P. vegetans* pathology appears to have a similar mechanism to the mucocutaneous type.

**Pemphigus foliaceus** is characterized by antibodies against Dsg1 only. Thus, blisters occur subcorneally due to the higher concentration of Dsg1 more superficially. *P. erythematosus* pathology appears to have a similar mechanism.

**Impetigo** [L. = a scabby eruption] is a common childhood disease of the skin, which is mainly caused at the present time by the bacteria *Staphylococcus aureus*. It is characterized by superficial bullous pustules in the epidermis that form as a result of exfoliative toxins (ETs) produced and released by the bacteria. Recent studies (Amagai, M et al. *Nat Med* 6:1275-1277, 2000; Amagai, M et al. *J Invest Dermatol* 118:845-850, 2002; Hanakawa Y et al. *J Clin Invest* 110:53-60, 2002) have shown that ETs act by attacking Dsg1 proteins of desmosomes. Genes for three toxins have been cloned and amino acid sequences of the toxins show homology to chymotrypsin-like proteases. Thus, impetigo, like pemphigus foliaceus, is a superficial blistering disease of skin affecting the integrity of desmosomes.

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**5. Macula communicans** (communicating junction, gap junction, nexus) is a junctional area of between adjacent cells that facilitates intercellular communication by allowing the passage of small molecules and ions across the narrow intercellular gap through a multitude of junctional pores (see Table 3-1). Although these structures have been given a variety of names and described in many tissues and species by many investigators, it was George Palade and coworkers (Simionescu M et al. *J Cell Biol* 67:863-885, 1975) who proposed the term communicating junction (macula communicans, maculae communicantes) based upon its principal function.

**a. Structure.** The junction consists of a hexagonal lattice of **connexin** protein subunits called **connexons**, which form intramembrane hydrophilic channels connecting the cytoplasm of adjacent cells.

**b. Function.** The low resistance

communicating channels through the gap junction permit intercellular signaling and electrical coupling by allowing the regulated passage of ions and small molecules between cells. These junctions are perhaps an important cellular strategy for approaching the efficiency of a syncytium.

**c. Distribution.** Gap junctions are not only found between epithelial cells, but also in all primary tissues. They occur between cells of other tissues that require direct communication, e.g., osteocytes in bone matrix. In addition, impulses for cardiac and smooth muscle contraction pass from one cell to the next through gap junctions.

### Basal Surface Specializations

**1. Basement membrane** is a sheet-like layer that underlies virtually all epithelia, and isolates them from the subjacent CT. (Exceptions are found in lymphatic capillaries and certain blood capillaries where the basement membrane may be poorly developed or discontinuous.) At LM level, visualization usually requires special stains such as PAS reaction, silver, and CT trichromes, except in some locations such as the trachea where it is exceptionally thick. TEM revealed that it consists of a basal lamina and a variably-present reticular lamina.

**a. Basal lamina** is a product of the epithelium and consists of an electron-lucent zone called the **lamina lucida** (rara), located next to the basal plasmalemma, and an electron-dense layer called the **lamina densa**, located next to the CT.

**i. Composition** is complex and may vary in different locations, but consists primarily of **type IV collagen**, glycoproteins [mainly **laminin**; also nidogen (=entactin)], and the large heparan sulfate proteoglycan called **perlecan**.

**ii. External lamina** is the basal lamina that surrounds muscle cells, peripheral glial cells (e.g., Schwann cells), and adipocytes. It serves both anchoring and separating functions in relation to the surrounding CT compartment.

**b. Reticular lamina** is a product of the CT and is composed of delicate reticular (**type III collagen**) and type I collagen fibers.

**c. Anchoring fibrils**, which are composed of **type VII collagen**, form an important linkage between the basal and reticular laminae.

**2. Hemidesmosomes** have the appearance of half-desmosomes and are found at sites where

epithelial cells are attached to underlying extracellular matrix. However, in hemidesmosomes, **integrins** are the integral membrane proteins and not cadherins as with desmosomes (see Table 3-1).

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**Bullous** [L. *bulla* =bubble] **pemphigoid** is a blistering autoimmune disease, which is caused by antibodies that react with proteins at the basal lamina area of stratified squamous epithelium in skin and oral mucosa. These proteins, referred to as bullous pemphigus antigens 1 and 2, are associated with hemidesmosomes. The attack at this location results in the formation of subepithelial blisters that cause the epithelium to separate away from the underlying basement membrane and CT. Since the entire epithelium covers these blisters, they do not rupture as easily as those occurring in pemphigus (see above).

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**3. Basolateral infoldings of plasma membrane.** As microvilli provide increases in surface area on the apical surface, these infoldings increase the surface area of the basolateral surfaces. They are found in transporting epithelia and are associated with numerous mitochondria, which provide energy for the ionic pumps. Important examples include the proximal and distal kidney tubules, and the striated ducts of salivary glands.

**4. Basal outfoldings of plasma membrane.** Another specialization of the plasma membrane is seen as elaborate basal protrusions in certain epithelia. These outfoldings occur along the basement membrane and serve the purpose of increasing surface area for attachment of the epithelial cells to the underlying CT. An important example of this specialization is found at the dermal-epidermal junction in the skin. |Ω|

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**Table 3-1. Cellular Junctions: Description and Components.**

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	<b>Junction Type</b>	<b>Principal Function</b>	<b>Extracellular Binding</b>	<b>Intracellular Binding</b>	
			<b>IMP*</b>	<b>PMP*</b>	<b>CP*</b>
<b>Cell-Cell Jxns (homotypic interactions**)</b>	<i>Zonula occludens</i> (tight jxn)	Seal intercellular space; restrict movement within cell membrane; regulate paracellular transport	Claudin-Claudin; Occludin-Occludin	ZO-1, -2, -3, cingulin, spectrin	Actin filaments
	<i>Zonula adherens</i>	Cell-cell adhesion	Cadherin-Cadherin (E-cadherin)	Catenins, plakoglobin, α-actinin, vinculin	Actin filaments
	<i>Macula adherens</i> (desmosome)	Cell-cell adhesion	Cadherin-Cadherin (desmocollins; demogleins)	Desmoplakin, plakoglobin, plakophilins	Keratin (intermediate) filaments
	<i>Macula communicans</i> (communicating jxn; gap jxn; nexus)	Cell-cell communication	Connexin-Connexin Connexon-Connexon (channels may be homo- or heterotypic)		
<b>Cell-ECM Jxns (heterotypic interaction***)</b>	<i>Hemidesmosome</i>	Cell-ECM adhesion	Integrin-Laminin	Plectin	Keratin (intermediate) filaments

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\***IMP** =Integral Membrane Proteins; **PMP** =Peripheral Membrane Proteins; **CP** = Cytoplasmic (intracellular; cytoskeletal) Proteins. Cell junction proteins consist of IMPs that are transmembrane proteins with extracellular, transmembrane, and intracellular domains: extracellular domains interact with their counterparts on adjacent cells; transmembrane domains are generally hydrophobic and may have multiple spans; intracellular domains are generally attached to cytoskeleton (CPs) via PMPs.

\*\*Homotypic interactions =association between like receptors

\*\*\*Heterotypic interactions =association between unlike receptors

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