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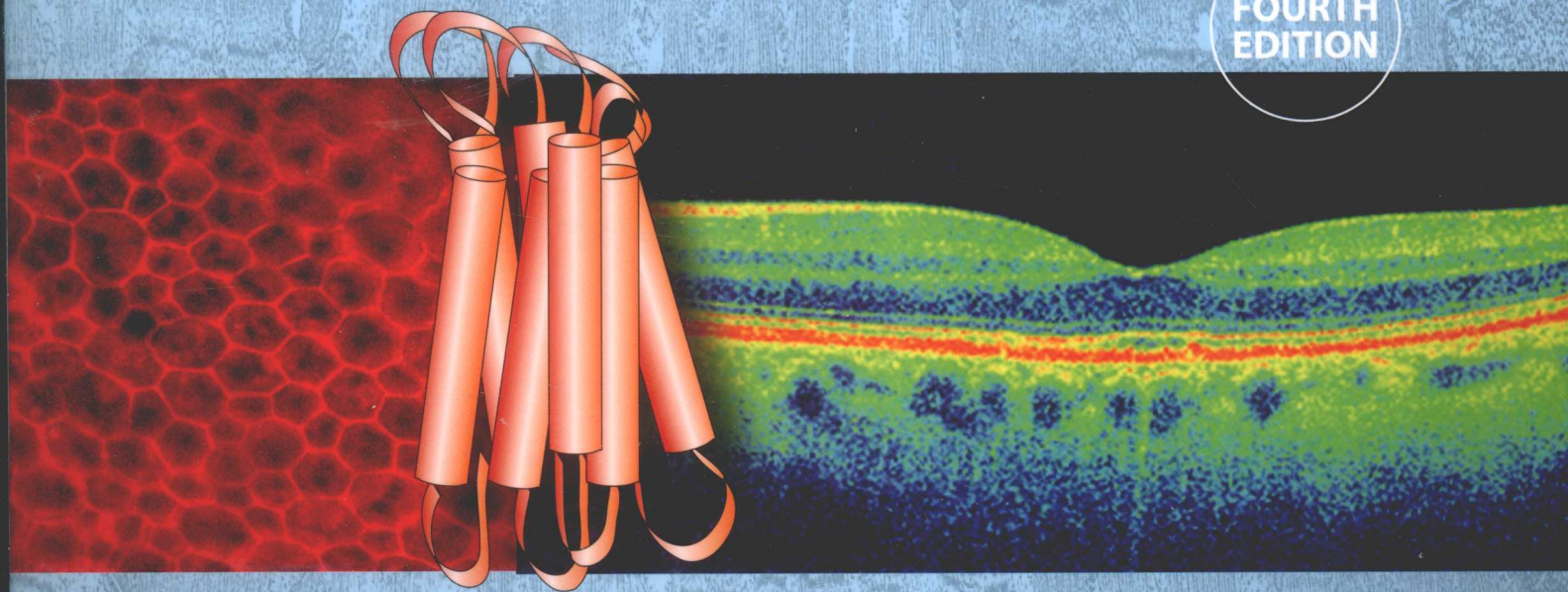
Abraham L. Kierszenbaum
Laura L. Tres

HISTOLOGY AND CELL BIOLOGY

An Introduction to Pathology

FOURTH EDITION



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Abraham L. Kierszenbaum, M.D., Ph.D.
Emeritus Medical (Clinical) Professor
The Sophie Davis School of Biomedical Education
The City University of New York
New York, New York

Laura L. Tres, M.D., Ph.D.
Emeritus Medical (Clinical) Professor
The Sophie Davis School of Biomedical Education
The City University of New York
New York, New York

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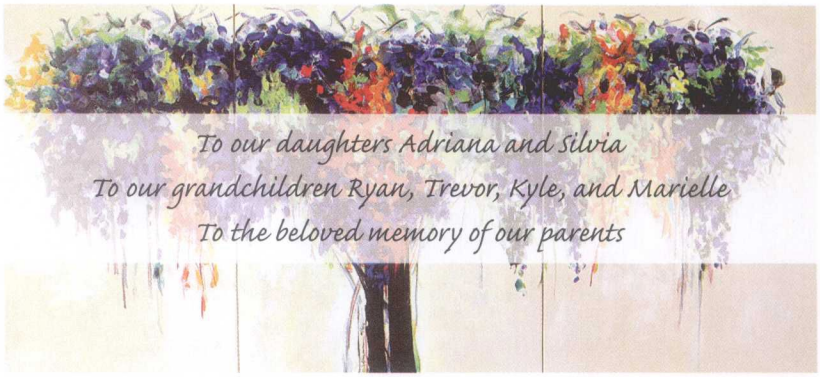


PREFACE

The fourth edition of *Histology and Cell Biology: An Introduction to Pathology* contains revisions and additions that strengthen the visual approach to learning histology within the context of cell biology and pathology introduced in the previous editions. New in the fourth edition are a greater emphasis on pathology topics and the online audiovisual version of the histology-oriented Concept Mappings. The combined histology–cell biology–pathology approach intends to prepare medical students for the forthcoming learning of pathophysiology and clinical medicine. The practice of medicine changes relentlessly as new knowledge becomes known. Future physicians can find in this book the basis for continuing education to better help their patients by constantly integrating basic and clinical sciences.

New in the fourth edition are a greater emphasis on pathology topics and the online audiovisual version of the histology-oriented *Concept Mappings*.

The visual approach presented in this book emerged from many years of practicing pathology and teaching cell biology, histology, and pathology to medical students. Through the years, it became clear the need to communicate and reinforce relevant concepts of histology and pathology to be mastered under increasing time constraints resulting from changes in the basic science curriculum in most medical schools. The focal point of the teaching approach is to provide medical students with an integrated method wherein the learning of normal structure and pathologic conditions can reinforce each other. The cell biology and pathology components, although not complete, provide the necessary foundation for further learning and integration with medical sciences. Pathology students and residents may find this book useful for refreshing basic concepts of histology and cell biology. Histology and pathology are visually oriented sciences, and the visual cues included in this book can facilitate interpretation opportunities in clinical practice.

The focal point of the teaching approach is to provide medical students with an integrated method wherein the learning of normal structure and pathologic conditions can reinforce each other.

Similar to the previous editions, the fourth edition consists of six parts. Part I brings together histology, cell biology, and general pathology within the context of the basic tissues. Chapter 3, Cell Signaling, is an uncommon section in a histology book. It serves to unify the concept that the study of tissues and organs cannot be separated from molecular biology and general pathology. Parts II through VI present several organ systems grouped by their most relevant function for the purpose of integration. Instructors and students may find the grouping of organs useful for teaching and learning. Teachers may find the material beneficial for delivering a lecture using the same or a different presentation sequence. In Part VI, Organ Systems: The Reproductive System, the chapter headings depart from the traditional designation to emphasize prominent functions. All the information is presented in a clear, concise, and student-friendly manner using color graphics and photographs that are meant to be studied. In some cases the graphics reiterate the concise text; in others they add new information complementing or extending the text. Several boxes dispersed in most of the chapters introduce students to clinical and pathologic conditions based on recent and evolving molecular and biochemical knowledge.

Most chapters include one or more *Concept Mappings*. Each Concept Mapping provides a basic framework of interconnected concepts arranged in a hierarchical form leading to integration and critical thinking. Concept Mapping and Essential Concepts highlight key issues to remember, correlate, and extend in forthcoming courses during medical education. Students may find the new online audiovisual version of Concept Mappings convenient for reviewing and integrating the material when the time of in-course and board examinations arrives.

Each *Concept Mapping* provides a basic framework of interconnected concepts arranged in a hierarchical form leading to integration and critical thinking.

There are many people to be acknowledged and thanked. We are grateful for the numerous suggestions, comments, and encouragements from faculty and students. All of them provided valuable feedback to make the message clearer and more consistent. We also thank publishers who made available to students the Chinese, French, Greek, Japanese, Portuguese, Spanish, and Turkish editions. Our special appreciation goes to the production team of Elsevier in the Philadelphia and St. Louis offices for their magnificent effort in making sure that the fourth edition met high publishing standards.

Abraham L. Kierszenbaum and Laura L. Tres

PART I | BASIC TISSUES AND INTEGRATED CELL BIOLOGY AND GENERAL PATHOLOGY

1. Epithelium

Epithelia separate the internal environment from the external environment by forming sheets of polarized cells held together by specialized junctional complexes and cell adhesion molecules. Epithelial cells participate in embryo morphogenesis and organ development in response to intrinsic and extrinsic signaling by tailoring cell proliferation, differentiation and cell death. We address the structural characteristics of epithelial cells within a biochemical and molecular framework as an introduction to the transition from a normal to a pathologic status.

General classification of epithelia

The epithelium is a tightly cohesive sheet of cells that covers or lines body surfaces (for example, skin, intestine, secretory ducts) and forms the functional units of secretory glands (for example, salivary glands, liver). The main characteristics of epithelia are summarized in Box 1-A.

The traditional classification and nomenclature of different types of epithelia are based on two parameters:

1. The **shapes of individual cells.**
2. **The arrangement of the cells in one or more layers** (Figure 1-1).

Individual epithelial cells can be flattened (**squamous cells**), have equal dimensions (**cuboidal cells**), and be taller than wider (**columnar cells**).

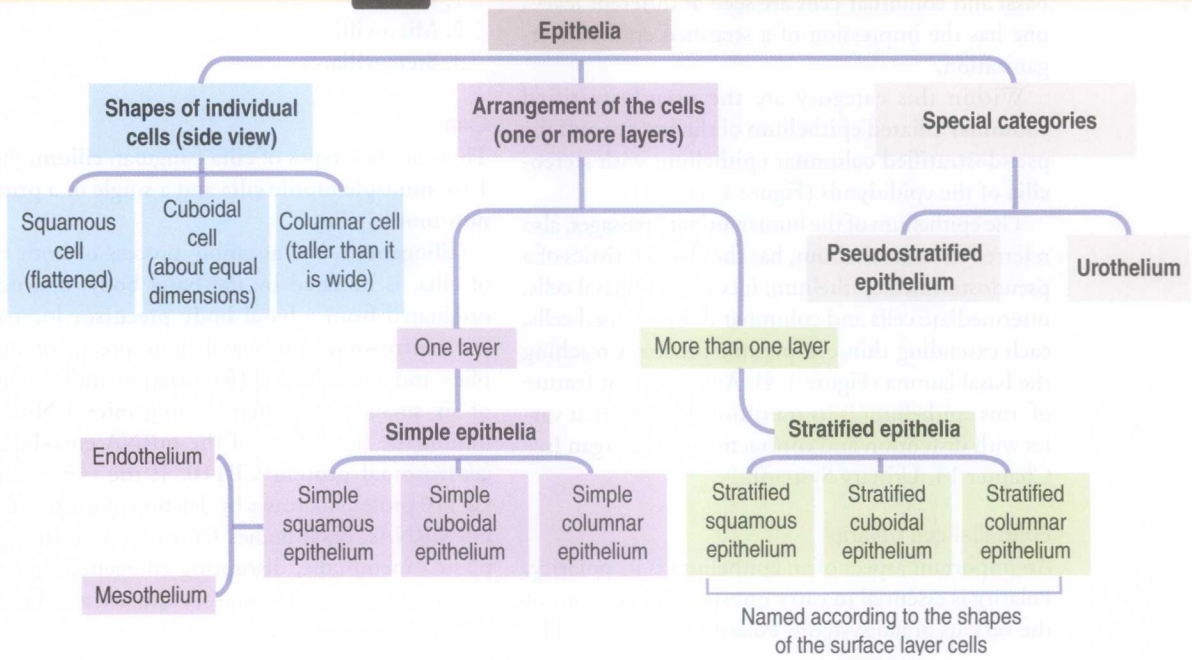
According to the number of cell layers, an epithelium consisting of a **single cell layer** is classified as **simple epithelium.**

Simple epithelia, in turn, are subdivided into **simple squamous epithelium, simple cuboidal epithelium,** and **simple columnar epithelium,** according to the shape of their cell components. The specific name **endothelium** is used for the simple squamous epithelium lining the blood and lymphatic vessels. **Mesothelium** is the simple squamous epithelium lining all body cavities (peritoneum, pericardium, and pleura). Figure 1-2 provides examples of simple epithelia.

Stratified epithelia are composed of **more than one cell layer.** Stratified epithelia are subclassified according to the shapes of the cells at the superficial or outer layer into **stratified squamous epithelium, stratified cuboidal epithelium,** and **stratified columnar epithelium.**

Stratified squamous is the epithelium most frequently found and can be subdivided into **moderately keratinized** (also known as nonkeratinizing) or **highly keratinized** types (Figure 1-3). The cells of the outer layer of a nonkeratinizing squamous epithelium **retain**

Figure 1-1. Concept mapping: Types of epithelia



Box 1-A | Main characteristics of epithelia

- Epithelia derive from the ectoderm, mesoderm, and endoderm.
- Epithelia line and cover all body surfaces except the articular cartilage, the enamel of the tooth, and the anterior surface of the iris.
- The basic functions of epithelia are **protection** (skin), **absorption** (small and large intestine), **transport of material** at the surface (mediated by cilia), **secretion** (glands), **excretion** (tubules of the kidneys), **gas exchange** (lung alveolus), and **gliding between surfaces** (mesothelium).
- Most epithelial cells renew continuously by mitosis.
- Epithelia lack a direct blood and lymphatic supply. Nutrients are delivered by diffusion.
- Epithelial cells have almost no free intercellular substances (in contrast to connective tissue).
- The cohesive nature of an epithelium is maintained by **cell adhesion molecules** and **junctional complexes**.
- Epithelia are anchored to a **basal lamina**. The basal lamina and connective tissue components cooperate to form the **basement membrane**.
- Epithelia have structural and functional **polarity**.

nuclei (for example, esophagus and vagina). **Nuclei are absent in the outer layer of the highly keratinized stratified squamous epithelium** (for example, the epidermis of the skin). Stratified epithelia have **basal cells** aligned along the basal lamina. Basal cells are mitotically active and continuously replace the differentiating cells of the upper layers.

Although rare, there are also **stratified cuboidal epithelia** (for example, in the ovarian follicles) and **stratified cuboidal epithelia** (for example, lining the intralobular ducts of salivary glands).

Two special categories are the **pseudostratified epithelium** and the **urothelium**. The pseudostratified epithelium consists of basal and columnar cells resting on the basal lamina. Only the columnar cells reach the luminal surface. Because the nuclei of the basal and columnar cells are seen at different levels, one has the impression of a stratified epithelial organization.

Within this category are the **pseudostratified columnar ciliated epithelium** of the trachea and the **pseudostratified columnar epithelium with stereocilia** of the epididymis (Figure 1-4).

The epithelium of the human urinary passages, also referred to as **urothelium**, has the characteristics of a pseudostratified epithelium: it consists of basal cells, intermediate cells and columnar dome-shaped cells, each extending thin cytoplasmic processes reaching the basal lamina (Figure 1-4). An important feature of this epithelium is its transitional height that varies with distention and contraction of the organ (see Chapter 14, Urinary System).

Epithelial cell polarity

An important aspect of an epithelium is its **polarity**. Polarity is essential to carry out specific functions of the various organ systems. Polarity is determined by the distribution of proteins and lipids and the rearrangement of the cytoskeleton.

Most epithelial cells lining surfaces and cavities and have three **geometric** domains (Figure 1-5):

1. The **apical (uppermost) domain** is exposed to the lumen or external environment and displays **apical differentiations**.
2. The **lateral domain** faces neighboring epithelial cells linked to each other by **cell adhesion molecules** and **junctional complexes**.
3. The **basal domain** is associated with a **basal lamina** that separates the epithelium from underlying connective tissue, representing the internal environment. The basal lamina, of epithelial cell origin, is reinforced by components of the connective tissue. The basal lamina–connective tissue complex is designated the **basement membrane**.

From the **functional** perspective, sealing junctions segregate the plasma membrane of an epithelial cell into an **apical domain** and a **basolateral domain**. This segregation is supported by the asymmetric distribution of transporting molecules ensuring polarized secretory and absorptive functions of an epithelium.

For example, the apical domain has structures important for the **protection** of the epithelial surface (such as **cilia** in the respiratory tract) or for the **absorption** of substances (such as **microvilli** in the intestinal epithelium). In contrast, the basolateral domain facilitates directional or vectorial transport functions prevented from trespassing the sealing junctions.

Apical differentiations

The **apical domain** of some epithelial cells can display three types of differentiation:

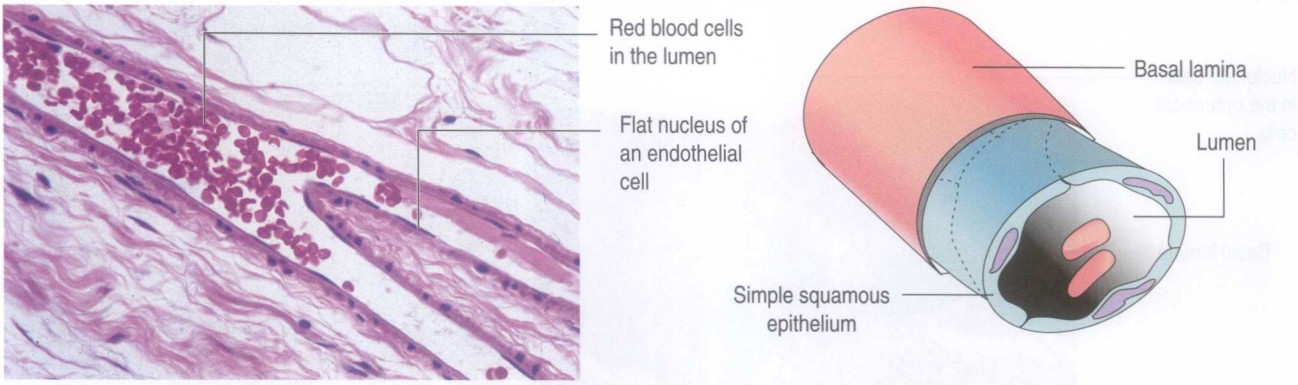
1. **Cilia.**
2. **Microvilli.**
3. **Stereocilia.**

Cilia

There are two types of **cilia** (singular, **cilium**; Figure 1-6): **multiple motile cilia** and a **single** or a **primary non-motile cilium**.

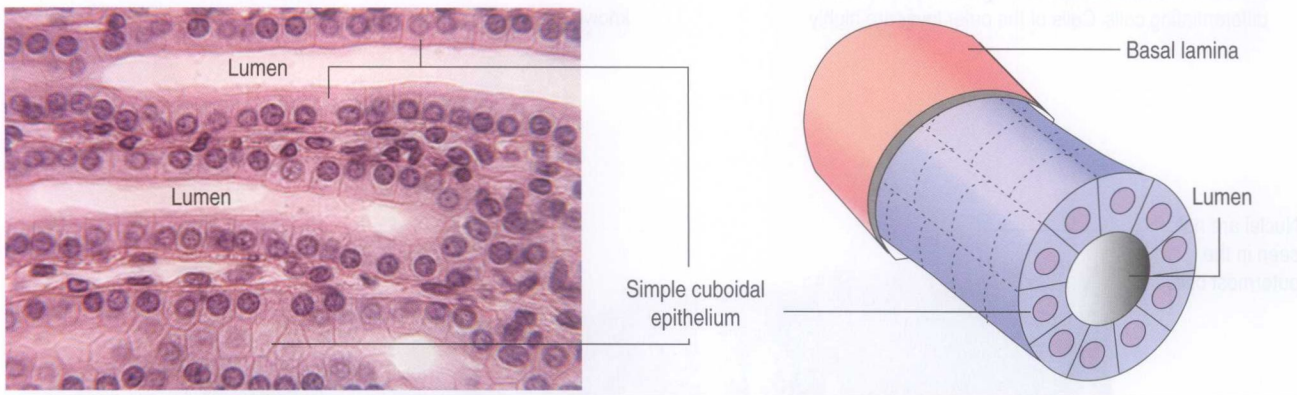
Ciliogenesis, the assembly process of both types of cilia, is initiated by the **basal body**, a structure originated from a **basal body precursor** located in the **centrosome**. The basal body precursor multiplies and undergoes differentiation under control of six small, non-protein coding microRNAs that inhibit the translation of the mRNA encoding the **centrosomal protein CP110**. If the expression of CP110 protein increases by deletion of the regulatory microRNAs, basal bodies fail to dock to the apical plasma membrane, disrupting ciliogenesis and giving rise to **human respiratory disease** and **primary ciliary dyskinesia**.

Figure 1-2. Simple epithelium



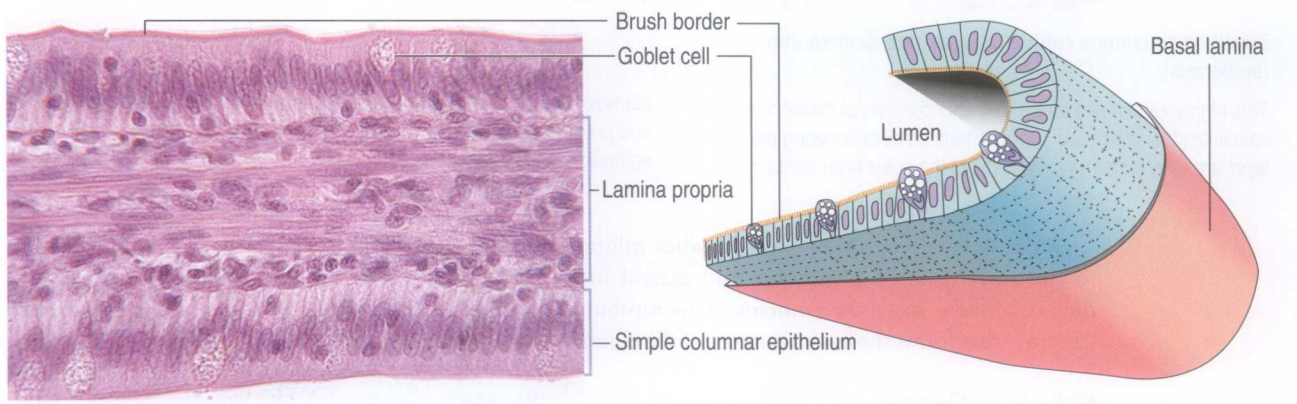
Simple squamous epithelium (endothelium)

The inner lining of all blood vessels consists of a single layer of squamous endothelial cells. The thinness of the simple squamous epithelial cells reflects their primary function in rapid exchange of substances between blood and tissue. A similar epithelium (called **mesothelium**) covers the peritoneum, pleura, and pericardium.



Simple cuboidal epithelium (collecting tubule, kidneys)

The inner lining of kidney tubules and thyroid follicles consists of a single layer of cuboidal cells. Cuboidal cells are highly polarized and participate in absorption, secretion (thyroid gland), and active ion transport (kidneys). Similar to the endothelium, a basal lamina attaches the cell to the subjacent connective tissue.

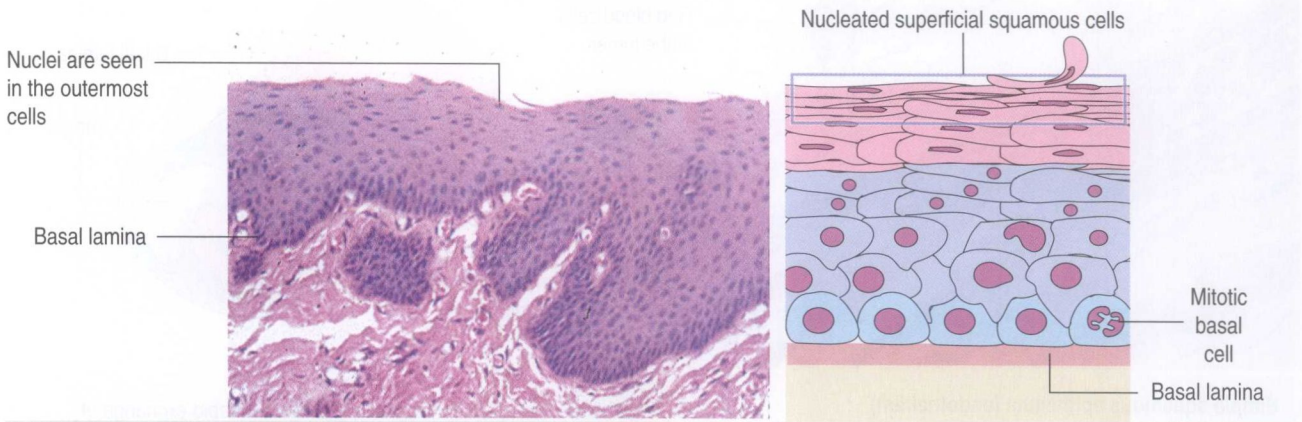


Simple columnar epithelium (small intestine)

The small intestine is lined by columnar epithelial cells with the nucleus in the medial portion of the cell. The apical domain contains finger-like projections called **microvilli** forming a **brush border**. Microvilli participate in the absorption of proteins, sugar, and lipids, which are released at the basolateral domain into the blood circulation for transport to the liver.

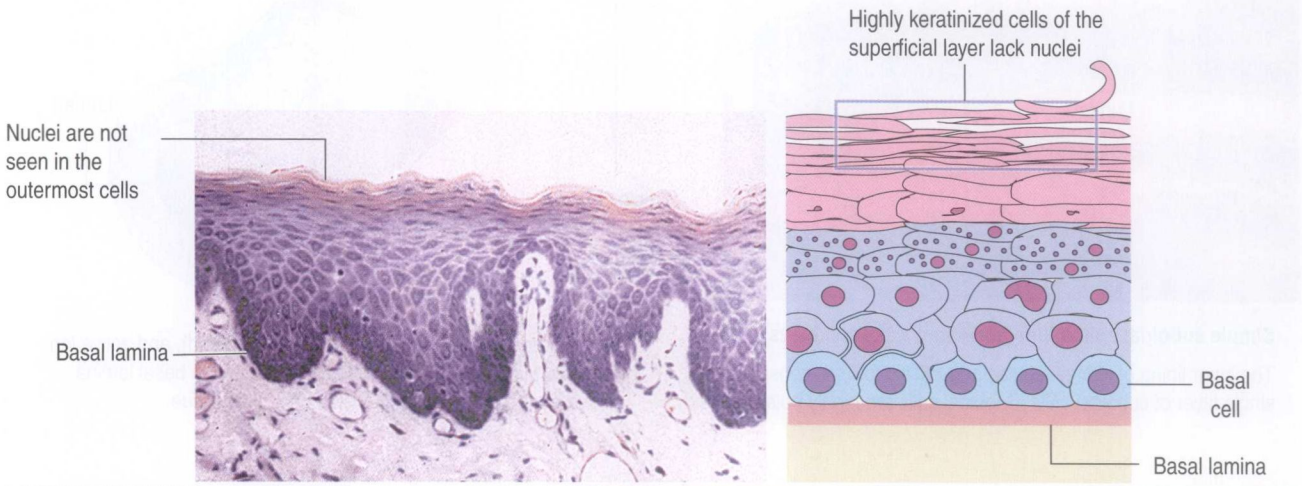
Goblet cells are present among the columnar epithelial cells. They can be distinguished by a dilated, goblet-like apical cytoplasm containing a light-stained mucus material. Mucus is released into the lumen and coats the epithelial cell surface. The **lamina propria** consists of loose connective tissue located beneath the epithelium.

Figure 1-3. Stratified epithelium



Stratified squamous epithelium with moderate keratin (esophagus)

This epithelium consists of **basal cells** specialized for **mitotic division**. Stratified cells covering the basal layer are differentiating cells. Cells of the outer layer are highly differentiated: they increase their **keratin content** to protect the tissue from the mechanical action of ingested food. **The outermost cells retain their nuclei**. This epithelium is also known as **nonkeratinizing**.



Stratified squamous epithelium with abundant keratin (epidermis)

This highly keratinized epithelium also consists of **basal cells** specialized for **mitotic division**. Stratified cells covering the basal layer are differentiating cells. Cells of the outer layer contain abundant **keratin** to prevent water loss and penetration of chemical and physical insults. **The outermost cells lack nuclei**. This epithelium is also known as **keratinizing**.

Under normal conditions, basal bodies migrate to the apical plasma membrane and extend into the extracellular space the **axoneme**, a microtubular structure that forms the basic structure of the cilium.

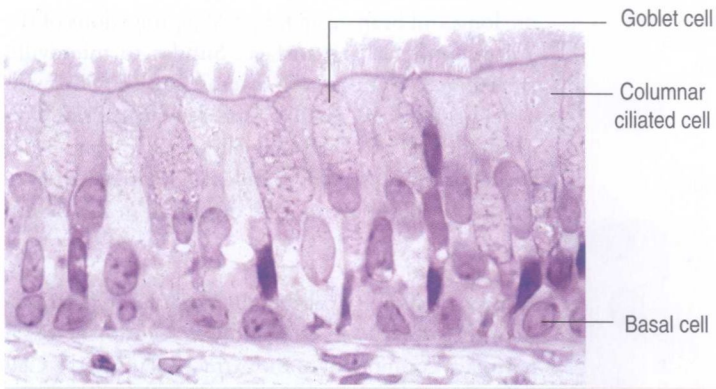
Multiple motile cilia

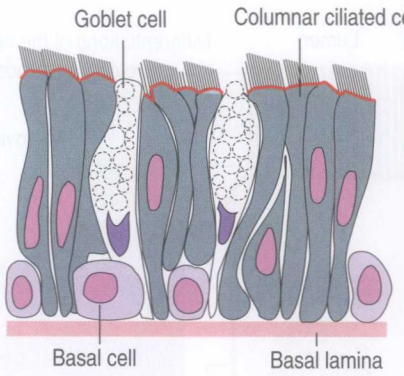
Multiple motile cilia function to **coordinate fluid or cargo flow on the surface of an epithelium.** They are cell projections originating from **basal bodies** anchored by **rootlets** to the apical portion of the cytoplasm (Figure 1-6).

A basal body contains nine **triplet** microtubules in a **helicoid array** without a central microtubular component. By contrast, a cilium consists of an **axoneme formed by a central pair of microtubules surrounded by nine concentrically arranged microtubular pairs. This assembly is known as** the **9 + 2 microtubular doublet arrangement**. The axoneme is also a component of the sperm tail, or **flagellum**.

The trachea and the oviduct are lined by **ciliated epithelial cells**. In these epithelia, ciliary activity is important for the local defense of the respiratory system and for the transport of the fertilized egg to the uterine cavity.

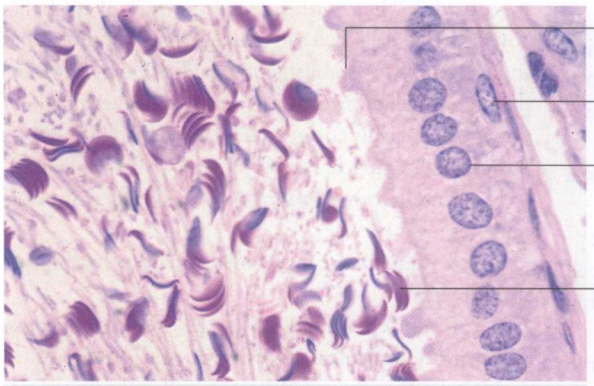
Figure 1-4. Pseudostratified epithelia

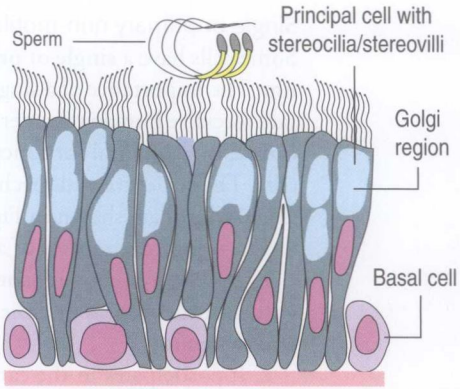




Pseudostratified columnar ciliated epithelium (trachea)

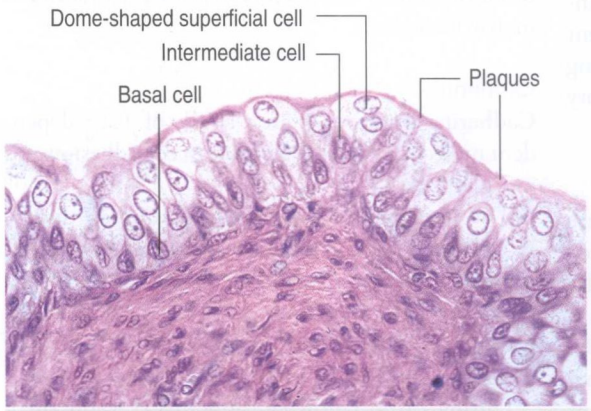
This epithelium consists of three major cell types: (1) **Columnar cells** with **cilia** on their apical domain. (2) **Basal cells** anchored to the basal lamina. (3) **Goblet cells**, mucus-secreting epithelial cells. Columnar ciliated and goblet cells attach to the basal lamina and reach the lumen. Basal cells do not reach the lumen.

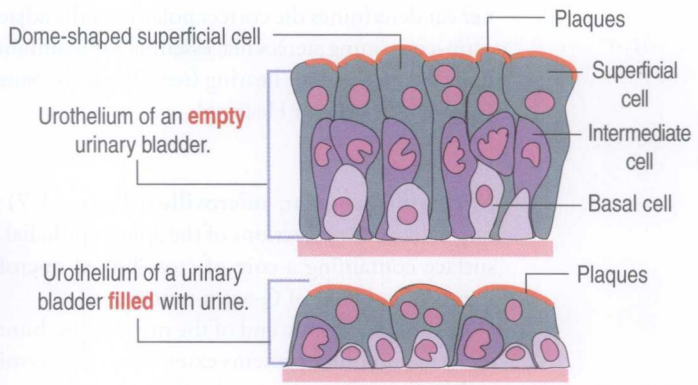




Pseudostratified columnar epithelium with stereocilia/stereovilli (epididymis)

The epididymal epithelium contains two major cell types. (1) **Columnar cells** with stereocilia and highly developed Golgi apparatus (called principal cells). (2) **Basal cells** attached to the basal lamina. Basal and principal cells are associated with the basal lamina. Only principal cells reach the lumen. Sperm can be visualized in the lumen. Stereocilia is an early misnomer as they lack microtubules. An appropriate name is **stereovilli**.





Urothelium (urinary bladder)

The epithelium lining the urinary passages (also called **urothelium**), consists of three cell types. (1) **dome-shaped superficial cells** (often binucleated); (3) **pyriform-shaped intermediate cells**; and (2) **polyhedral-shaped basal cells**, all of them extending cytoplasmic processes anchored to the basal lamina. In humans, the urothelium is a pseudostratified epithelium. A characteristic of the urothelium is its **transitional configuration** in response to distension and contraction tensional forces caused by urine. **Plaques** of aggregated proteins (**uroplakins**) are found on the apical plasma membrane of the dome-shaped superficial cells.