HISTOLOGY OF THE RESPIRATORY SYSTEM

I. Introduction
A. The respiratory system provides for gas exchange between the environment and the blood.
B. The human respiratory system may be subdivided into two parts.
   1. The **conducting portion** is a continuum of air passageways that conduct air from the environment into respiratory spaces (and back out).
   2. The **respiratory (gas exchange) portion** consists of many interconnected air-filled spaces with very thin linings which allow rapid gas exchange.
C. The human respiratory system includes numerous organs.
   1. Nose/nasal cavity
   2. Pharynx (nasopharynx, oropharynx)
   3. Larynx
   4. Trachea
   5. Bronchi
   6. Lungs (bronchial tree and alveoli)
   7. Skeletal muscles (diaphragm, intercostal muscles)
D. Most organs in the conducting parts of the respiratory system follow the general organizational pattern for tubular organs (as seen in the digestive system) with the following exceptions
   1. No muscularis mucosae are present; therefore a mucosa and submucosa cannot be easily distinguished.
   2. As a result of the lack of muscularis mucosae, connective tissues of the lamina propria and submucosa are continuous. The combined layer is frequently called the lamina propria even though it usually consists of relatively loose FECT directly under the epithelium and denser FECT in deeper regions.
   3. The muscularis externa contains cartilage in the epiglottis, larynx, trachea, and bronchi. The cartilage holds the respiratory passageways open during inhalation and exhalation.

II. Microanatomy of the Respiratory System
I. Nose (nasal cavity)
   i. Mucosa
      Epithelium - varies according to location
      a. The anterior (outer) region of the nasal cavity is lined with **stratified squamous epithelium** which makes a gradual transition from keratinized to nonkeratinized.
      b. The posterior (inner) region of the nasal cavity is lined by two types of epithelia.
Olfactory epithelium (pseudostratified columnar epithelium containing modified bipolar neurons which function as chemoreceptive olfactory cells) occurs in small patches in several regions in the posterior part of the nasal cavity. The structure of this epithelium was described in the sensory receptor unit.

Pseudostratified ciliated columnar epithelium with Goblet cells (frequently called "respiratory epithelium") covers most of the luminal surface of the posterior region of the nasal cavity. This epithelium contains multiple cell types.

a. **Ciliated columnar cells** are tall cells with densely packed apical cilia. These cells are responsible for moving mucus along the surface of the epithelium.

b. **Goblet cells** are mucus-secreting exocrine cells which are scattered individually throughout the epithelium. They secrete a large part of the mucus which covers the epithelial surface.

c. **Basal cells** are rounded cells embedded in the basal surface of the epithelium. These cells are the reserve population which replaces lost ciliated cells and goblet cells and possibly other cell types in the epithelium.

d. **Brush cells** are columnar cells with apical microvilli instead of cilia. Brush cells synapse with dendritic endings of sensory nerve fibers and serve as apparent sensory receptors. They are usually described as "general sensation" receptors, which I assume translates as mechanoreception.

e. **Dense core granule cells** (small granule cells or argyrophilic cells) contain small secretory vesicles concentrated in their basal cytoplasm and are therefore solitary endocrine cells. Dense core granule cells appear related to APUD cells in the stomach and intestine and may release vaso-active substances.

ii. The **Lamina propria** of the nasal cavity is primarily loose FECT with numerous blood vessels. Compound serous tubuloacininar glands occur in scattered locations, particularly near olfactory areas. Hair follicles extend into the lamina propria in the anterior and superficial part of the posterior region of the nasal cavity.

iii. The "**Muscularis externa**" region in the nasal cavity is occupied by cartilage of the nose and the skeletal elements of the skull.

2. Nasal passageways have multiple functions in addition to the obvious function of carrying air from the environment to the deeper parts of the conducting passageways.

a. Removal of particulate matter by trapping among hairs or sticking to the mucus covering the surface in the posterior region.
b. Moistening/humidifying of air by evaporation of water from mucous or serous glandular secretions.
c. Warming of air by heat conduction from blood flowing through vessels in the lamina propria.

3. The pharynx can be viewed as consisting of an upper nasopharynx and a lower oropharynx. The oropharynx lining was described with the digestive system. The nasopharynx is described here.

I. Mucosa

a. The epithelium lining the lumen of the nasopharynx varies according to location.

- **Pseudostratified ciliated columnar epithelium with Goblet cells** covers most areas. The cellular composition is similar to the same epithelium in the nasal cavity.

- **Stratified squamous epithelium** covers regions of "wear and tear" (i.e., areas that contact food or contact each other during swallowing).

b. The lamina propria in the nasopharynx consists primarily of loose to moderately dense FECT with many elastic fibers. Serous, mucous, and mixed glands (usually compound) are scattered throughout the pharynx. As described under the immune system, lymphoid nodules underlie the epithelium in the tonsils.

The nasopharynx lacks a muscularis externa of its own and is surrounded by skeletal muscle of the head and neck regions of the body wall.

4. Larynx

1. Mucosa

a. The epithelium of the larynx varies according to location.

- **Pseudostratified ciliated columnar epithelium with Goblet cells** very similar to the same epithelial type in the nasal cavity lines most areas in the larynx.

- **Stratified squamous epithelium** lines regions of "wear and tear" (vocal cords, epiglottis, upper part of larynx) in the larynx.

b. The lamina propria in the larynx varies with location.

1. Dense FECT underlies a thin region of loose FECT in the vocal cords.

2. Loose to moderately dense FECT, frequently containing serous, mucous, and mixed glands (most are compound), occupies the lamina propria in most of the larynx.

- The **"muscularis" externa** region in the wall of the larynx contains two types of tissue assemblages.

  a. The inner part of the muscularis externa region in much of the larynx consists of cartilages (mainly hyaline cartilage, some elastic cartilage) and dense FECT.
The outer part of the muscularis externa region of the larynx contains skeletal muscle in most locations.

5. **Trachea and Extrapulmonary (Primary) Bronchi**

   **I. Mucosa**

   a. The epithelium lining the trachea and bronchi is very similar to the pseudostratified ciliated columnar "respiratory" epithelium described for the nasal cavity. The epithelium may be stratified in areas, particularly in smaller experimental animals. In humans, the epithelium in the trachea and bronchi typically contains ciliated columnar cells, Goblet cells, basal cells, brush cells, and dense core granule cells similar to those seen in the nasal and pharyngeal cavities and the larynx. In addition, Clara cells begin to appear in the lower trachea and become more numerous in the bronchi. Clara cells have a smooth apical surface which protrudes as a dome toward the lumen and contain apical secretory vesicles and well developed sER and rER. Clara cell secretions include a phospholipid-rich lipoprotein surfactant which reduces surface tension in air passageways. Recent studies on the effects of the cystic fibrosis gene on the epithelium of the air passageways indicate that one or more cell types in the epithelium are capable of killing bacteria. Since this is likely to be difficult for a cell covered by apical cilia or sensory microvilli or whose apical cytoplasm is filled with secretory granules containing mucus, the most likely candidate for the bacteria-killing cells would be a population which resemble Clara cells but which are macrophages.

   b. The lamina propria of the trachea and bronchi consists of a thin layer of loose FECT which is rich in elastic fibers and which frequently contains diffuse or nodular lymphoid tissue.

   **II. A submucosa** is visible in most parts of the human trachea and bronchi as a zone of denser (than the lamina propria) loose to moderately dense FECT which frequently contains tubuloacinar glands.

   - The muscularis externa in the trachea and bronchi contains three types of tissues.

     a. **Tracheal rings** (C-shaped; open dorsally) of hyaline cartilage enclosed by a perichondrium of dense regular collagenous CT are evenly spaced along the length of the trachea and the extrapulmonary bronchi. In the intrapulmonary bronchi the hyaline cartilages become irregular plates.

     b. Smooth muscle tissue forms the *trachealis muscles* which connect the ends of each tracheal ring in the trachea and the extrapulmonary bronchi. Smooth muscle occurs as a more or less complete circular layer between the cartilage plates and the lamina propria in the intrapulmonary bronchi.
c. Moderately dense FECT occurs between adjacent tracheal rings in the trachea and extrapulmonary bronchi and between adjacent cartilage plates in the intrapulmonary bronchi.

- An adventitia of loose FECT is visible around the trachea and extrapulmonary bronchi and merges with the loose FECT stroma of the lungs around the intrapulmonary bronchi.

6. **Lungs**
   
i. **Gross anatomy of the lungs**
   
   a. Each lung is a lobed structure which contains all of the subdivisions arising from one bronchus.
   
   (1) Each lung is subdivided into lobes. Each lobe is served by an intrapulmonary bronchus which is a branch of an extrapulmonary bronchus.
   
   (2) Each lobe is subdivided into smaller lobules. Each lobule is supplied by bronchioles (branches of intrapulmonary or secondary bronchi). The smallest of these branches are referred to as terminal bronchioles.
   
   (3) Each terminal bronchiole branches into one to three respiratory bronchioles.
   
   (4) Each respiratory bronchiole branches into two to eleven alveolar ducts.
   
   (5) Alveolar sacs are clusters of alveoli at the end of alveolar ducts.
   
   (6) Essentially all gas exchange between air and blood occurs across the walls of alveoli. Most alveoli are associated with alveolar sacs or are part of the wall of an alveolar duct. A minority of alveoli are part of the wall of respiratory bronchioles.

   b. Each lung is covered by a serosa (visceral pleura) consisting of an outer mesothelium and underlying loose FECT.

   c. The lungs contain a sparse loose FECT stroma. Loose FECT septa separate lobules and lobes, but very little intralobular connective tissue occurs which is not associated with the wall of one of the air passageways or of one of the alveoli. Some apparently interstitial or stromal loose FECT occurs where large air passageways pass close to large blood vessels, but most available space in the lungs is filled by clumps of alveoli.

7. Each lung has two blood supplies which partially interconnect.

   (1) Branches of the pulmonary artery supply capillary networks associated with alveoli, and this blood leaves the lungs in the pulmonary veins.

   (2) Branches of the bronchial arteries which originate from the aorta supply the capillary networks in the bronchi and larger bronchioles. This blood leaves the lungs in the bronchial veins.
(3) The terminal branches of the bronchial arterial tree connect to the microvessels of the pulmonary arterial tree.

2. Microanatomy of the lungs
   a. Intrapulmonary Bronchi
      (1) Mucosa
         (a) The epithelium is a pseudostratified ciliated columnar epithelium with Goblet cells (only a few present in smallest bronchi), brush cells, Clara cells, and small granule cells.
         (b) The lamina propria is loose FECT which may contain solitary lymphoid nodules.
         (2) The submucosa is loose to moderately dense FECT.
         (3) The muscularis externa contains hyaline cartilage plates (which may not be present in all sections of smaller bronchi) surrounded by dense FECT interspersed with spirally oriented smooth muscle.
         (4) A sparse tunica adventitia of loose FECT is usually visible around most intrapulmonary bronchi.

   b. Bronchioles (less than 1 mm diameter, includes larger bronchioles, terminal bronchioles, and respiratory bronchioles)
      (1) Mucosa
         (a) The epithelium varies according to the size of the air passageway. Pseudostratified ciliated columnar epithelium with a few scattered Goblet cells occurs in larger bronchioles. Ciliated simple columnar epithelium occurs in terminal bronchioles. Ciliated and non-ciliated simple low columnar or cuboidal epithelium with patches of simple squamous epithelium (actually alveoli) occurs in respiratory bronchioles. Non-ciliated Clara cells become more numerous in terminal bronchioles and increase in number until they are the most frequent columnar or cuboidal cell type in respiratory bronchioles and alveolar ducts.
         (b) A lamina propria of loose FECT which may contain solitary lymphoid nodules occurs in most bronchioles.
         (2) A muscularis externa of smooth muscle spirals around bronchioles and terminal bronchioles but is usually scattered or absent around respiratory bronchioles.
         (3) A tunica adventitia of very sparse loose FECT occurs in most bronchioles.

   c. Alveoli, Alveolar Ducts, and Alveolar Sacs (clusters of alveoli)
      (1) Mucosa
         (a) The epithelium varies with location. Patched of simple cuboidal epithelium occur in the walls of alveolar ducts and alveolar sacs. Alveoli are lined by simple squamous epithelium containing three major cell types.
[1] **Type I pneumocytes** (small alveolar cells) are squamous cells across which most gas exchange occurs.

[2] **Type II pneumocytes** (giant alveolar cells) are rounded cells which secrete surfactant.

[3] **Pulmonary or alveolar macrophages** are irregular-shaped monocyte-derived cells which remove foreign materials from alveoli and small air passageways.

(b) The **lamina propria** is very thin loose FECT containing scattered fibroblasts and very fine collagenous fibers. Numerous capillaries are wrapped around each alveolus.

(2) The **submucosa and *muscularis* externa layers** are absent in most areas around alveoli, but a few scattered smooth muscle fibers occur around some alveolar ducts.

d. **Histological criteria for classifying intrapulmonary structures**

(1) **Bronchi**
   - large lumen
   - pseudostratified columnar epithelium
   - hyaline cartilage plates in the wall

(2) **Bronchioles**
   - smaller lumen
   - pseudostratified columnar to simple cuboidal epithelium with no areas of simple squamous epithelium
   - one or more layers of smooth muscle in the wall (which frequently contract during fixation causing folds in the luminal lining)
   - no cartilage in the wall

(3) **Respiratory bronchioles**
   - some simple squamous lining epithelium (actually alveoli)
   - more than 50% of the luminal surface is lined by simple cuboidal or columnar epithelium

(4) **Alveolar ducts and sacs**
   - some simple cuboidal lining epithelium
   - more than 50% of the luminal surface is lined by simple squamous epithelium (actually alveoli)

(5) **Alveoli**
   - lined by simple squamous epithelium (with occasional rounded cells)
   - lumen is small and spherical