HISTOLOGY
OF THE
RESPIRATORY SYSTEM

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Divisions of the respiratory system

**Anatomical division** includes all parts of the respiratory system that are derived from the laryngotraceheal diverticulum.

Fig. 1: Anatomical division of the respiratory system.
Conducting Zone

- Conditions the air conducted from the external environment making it more suitable to enter the body.
- Includes:
  - Nasal cavity
  - Pharynx
  - Larynx
  - Trachea
  - Bronchi
  - Bronchioles → Terminal bronchioles
- Mainly lined by Respiratory Epithelium.
- Kept patent by cartilage, fibers, and smooth muscles.

Respiratory Zone

- Site where gas exchange occurs.
- Includes:
  - Respiratory bronchioles
  - Alveolar ducts
  - Alveolar sacs
  - Alveoli
- Mainly lined by simple squamous epithelium.
- Supported by fibers.

Functional division
The Respiratory Epithelium

- Pseudostratified columnar ciliated epithelium.
- Lines most of the conducting zone of the respiratory system.
- Formed of 5 types of cells:

1. **Ciliated columnar cells**: The most common type with hundreds of cilia on its apical surface. They also possess microvilli.

Fig.2: Cilia (C), and some microvilli (MV), on the apical surface of the columnar cells of the respiratory epithelium.
2. **Goblet cells:**

- Mucus secreting cells found between the epithelial cells.
- Their number varies according to location.
- Apical part is distended with mucinogen granules.
- Golgi apparatus forms a wide cup just below the granules.
- The stem shaped basal part contains the nucleus, numerous rough endoplasmic reticula, and mitochondria.
- Microvilli form a thin rim that surrounds the apical part.

Fig. 3: Goblet cell.
3. **Brush cells:** Few columnar cells with few microvilli on the apical surface and nerve endings near the basal surface. They may act as chemoreceptors.

4. **Granule (neuroendocrine) cells:** These few, small, and granulated cells are similar to enteroendocrine cells. A thin, tapering cytoplasmic process extends from the cell to the lumen. These cells are thought to detect the level of gases in the lumen of the airway passages and release chemicals that change the diameter of these passages accordingly.

5. **Basal cells:** Mitotically active stem cells that form the other cells of this epithelium. They rest on the basal lamina, but do not reach the surface.
Fig. 4: Respiratory epithelium. In (a), we can clearly see the cilia (C) on the apical surface and the thick basement membrane (BM) below the epithelium. Goblet cells (G) are also seen. The top-view SEM image (b) shows the numerous cilia and goblet cells.
Other features of the respiratory epithelium:
1. Rests on a thick basement membrane.
2. The lamina propria under it contains:
   - Seromucous glands
   - Plasma cells
   - Numerous blood vessels
   - Lymphatic tissue

Functions of the respiratory epithelium:
1. Blood vessels in the lamina propria warms the incoming air.
2. Secretions of goblet cells and the lamina propria glands moisten the air and trap foreign particles.
3. Cilia move trapped particles towards the pharynx where they can be expelled to the outside (mucociliary escalator).
4. Immune role due to the presence of lymphatic tissue and plasma cells which secretes IgA.
Lined by *skin* with sweat and sebaceous glands, and thick hairs called *vibrissae*. These hairs act as a barrier to filter out particles from the inspired air.

Lined by *respiratory epithelium*. The lamina propria here has capillary loops and seromucous glands to warm and moist the inspired air. Also numerous plasma cells are present.
Located in the lamina propria of the conchae are large venous sinuses known as *swell bodies*. Every 20–30 minutes, the swell bodies on one side become temporarily engorged with blood, resulting in distension of the conchal mucosa and a concomitant decrease in the flow of air. During this time, most of the air is directed through the other nasal fossa, allowing the engorged respiratory mucosa to recover from dehydration.

This can be clearly felt when we have infection of the nasal mucosa (as in common cold) when the mucosa is swollen from the infection. The patient will feel that air passes easily through one half of the nose, while the other half is blocked. After some time, the position is reversed.
Olfactory Epithelium:

- Pseudostratified columnar epithelium.
- Responsible for the sense of smell.
- Formed of 3 types of cells:

1. **Olfactory neurons:** Bipolar neurons. The apical process of these cells is a dendrite which has a knoblike swelling from which arise several cilia (the *olfactory hairs*). The cilia act as chemoreceptors to detect odoriferous molecules. The axon exits from the basal surface of the cell. In the lamina propria, these axons form small nerves that pass through the foramina of the cribriform plate of the ethmoid bone.
2. **Supporting cells**: These are columnar cells with microvilli arising from the apical surface. They are connected to the olfactory neurons by intercellular junctions.

3. **Basal cells**: Small stem cells that can replace the other two types of cells. (Olfactory neurons are replaced every 2-3 months). This is why loss of smell due to damage to the epithelium is usually temporary.

- In the lamina propria of the olfactory epithelium, there are large *serous* glands called the *olfactory (Bowman’s) glands*. The fluid secretions of these glands pass to the surface of the epithelium to clean the area for new odoriferous substances.
Fig. 6: Olfactory epithelium.
Paranasal sinuses

- These cavities are lined by a thin respiratory epithelium.
- Fewer goblet cells.
- Lamina propria has smaller glands.
- Mucus produced here is moved towards the nasal cavity by action of the cilia.

In **sinusitis**, the blockage of the connection between the paranasal sinuses and the nasal cavity will lead to accumulation of the mucus in the sinuses. This will affect the resonance of the voice.
The Pharynx

- The pharynx is a funnel shaped tube that lies behind the nasal cavity (nasopharynx), the oral cavity (oropharynx), and the larynx (laryngopharynx).

- The wall of the pharynx is formed of the following layers:
  1. Mucosa
  2. Submucosa
  3. Muscularis
  4. Advenitia

Fig. 7: Anatomical regions of the pharynx.
1. **Mucosa:**
   - *Nasopharynx:* This part is lined by respiratory epithelium. The lamina propria contains lymphatic nodules called the *pharyngeal tonsil.*
   - *Oropharynx and laryngopharynx:* In addition to air, these parts are passages for food and drink. Therefore, they are lined by stratified squamous (non-keratinized) epithelium to provide greater protection. The lamina propria of the oropharynx contain lymphatic nodules.

2. **Submucosa:** Connective tissue layer.

3. **Muscularis:** Formed of the skeletal pharyngeal muscles.

4. **Adventitia:** Connective tissue layer.
Fig. 8: The lining epithelium of the different regions of the pharynx.
The Larynx

Δ A short tube that is responsible for the (1) conduction of air from the oropharynx to the trachea, (2) prevention of the passage of food or drink into the lower respiratory tract, and (3) production of sounds (phonation).

Δ Its wall is formed of cartilages that are lined by mucosa, moved by muscles, and held together by ligaments and membranes.

<table>
<thead>
<tr>
<th>Cartilages of the larynx</th>
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<tbody>
<tr>
<td><strong>Hyaline Cartilage</strong></td>
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<tr>
<td>Thyroid</td>
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<tr>
<td>Cricoid</td>
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<td>Parts of the arytenoids</td>
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Fig. 9: Anatomy of the larynx.
Mucosa of the larynx

Δ The lingual surface of the epiglottis is covered by a stratified squamous non-keratinized epithelium. The laryngeal surface, on the other hand, is covered by respiratory epithelium with seromucous glands in the lamina propria.

Δ Within the larynx the mucosa creates two pairs of folds:

1. Superior **vestibular folds** (ventricular folds, false vocal cords):
   - Lined by respiratory epithelium (with some stratified squamous non-keratinized epithelium).
   - Lamina propria contains seromucous glands and lymphatic nodules.
   - Lamina propria is highly vascular; therefore, these folds appear pink in color through a laryngoscope.
2. Inferior **vocal folds** (true vocal cords):
   - Lined by stratified squamous non-keratinized epithelium. This is important to protect this fold from damage by the rapidly moving air.
   - Lamina propria contains the **vocal ligament** formed of dense elastic connective tissue. This ligament is the upper border of the cricothyroid membrane.
   - Vocalis muscle is also present in the lamina propria.
   - There are no glands in these folds. The vocal folds are kept moist by secretions from glands present in the saccules.
   - There are no blood vessels in this fold; therefore, these folds appear white in color.

**Fig. 10:** Diagram showing the appearance of the two laryngeal folds through a laryngoscope.
Fig.11: Coronal section of the larynx seen from behind.
Between these two folds, there’s a narrow space called the ventricle. It’s here that epithelium changes from respiratory to stratified squamous.

Below the vocal folds, the epithelium becomes respiratory again.

Fig. 12: Coronal section through the larynx. Notice the different histological features of the two laryngeal folds.
The Trachea

The wall of the trachea is formed of the following layers:

1. **Mucosa:** with a typical respiratory epithelium and a lamina propria containing seromucous glands. A layer of elastic fibers separate the lamina propria from the submucosa.

2. **Submucosa:** with lymphatic nodules and mucous glands.

3. **Cartilage layer:** wall of the trachea is reinforced by about 20 C-shaped hyaline cartilages. The gap of the C is directed posteriorly and is bridged by some elastic fibers and a smooth muscle called the *trachealis* muscle.

4. **Adventitia:** connective tissue layer that binds the trachea to surrounding structures.
Fig. 13: The four layers of the wall of the trachea. Remember that in the posterior aspect of the trachea, the third layer of the wall is the trachealis muscle.
The Bronchial Tree

- The trachea will divide into the main bronchi. These will give rise to secondary (lobar) bronchi. The lobar bronchi will form tertiary (segmental) bronchi. Continuous branching of the bronchi will form smaller and smaller bronchi.

- As the bronchi become smaller and smaller, several changes in their histology will occur.

Fig.14: The bronchial tree
1. **Mucosa**: the epithelium lining the bronchi is respiratory epithelium and it appears folded. The lamina propria contains seromucous glands and some lymphatic nodules. Elastic fibers are also present in the lamina propria.

2. **Smooth muscles**: these are arranged helically along the bronchus and they crisscross each other.

3. **Submucosa**: contains several mucous glands.

4. **Cartilage**: in the larger bronchi, the hyaline cartilages form a ring around the bronchus. As the bronchi become smaller, the cartilages become in the form of plates that gradually decrease in size.

5. **Adventitia**: binds the bronchi to surrounding structures.
Fig. 15: Cross section through a bronchus. E = epithelium, SM = smooth muscle, G = glands, C = cartilage, V = vein.
Bronchioles

- The smallest of the bronchi will give rise to bronchioles.

- A bronchiole is that part of the bronchial tree that’s characterized by the following features:
  - Diameter very small (<1mm)
  - Absence of cartilage in the wall
  - Absence of glands
  - Smooth muscles form an almost complete circle around the wall. Compared to thickness of wall, it’s relatively thick.

Fig. 16: Cross section through a bronchiole. E = epithelium, CT = connective tissue adventitia. Notice how the smooth muscles surrounds the bronchiole and it’s relatively thick (outer arrows).
The part of the lung aerated by a bronchiole is called a pulmonary lobule which’s a pyramidal shaped unit of the lung surrounded by a connective tissue layer.

The larger bronchioles are still lined by respiratory epithelium, but with fewer goblet cells. As the bronchioles become smaller, the epithelium becomes simple columnar ciliated epithelium. In the smallest bronchioles, the terminal bronchioles, the epithelium becomes simple cuboidal ciliated epithelium with no goblet cells.

Brush cells and the small granule cells may still be present.

Lamina propria contains elastic fibers.

**Bronchioles** = **Mucosa** + **Smooth muscle layer** + **Adventitia**
Club (Clara) cells

- Club cells start to appear in the simple cuboidal epithelium of the terminal bronchioles.

- These cells:
  - Are non-ciliated
  - Have a dome-shaped apical surface with club-shaped processes
  - Cytoplasm contains:
    - Well developed RER and Golgi apparatus
    - Numerous cisternae of smooth endoplasmic reticulum
    - Numerous secretory vesicles

- Functions of club cells:
  1. Secretion of surfactant and antimicrobial agents
  2. Detoxification of harmful substances
  3. May act as a stem cell
Fig. 17: The diagram above shows the features of club cells. To the left, the vesicles of these cells (C) are clearly seen.
Respiratory Bronchioles

- First part of the respiratory zone.
- They branch from the terminal bronchioles.
- The wall of the respiratory bronchioles has the same histological features as that of the terminal bronchioles. The difference, however, is that, in a respiratory bronchiole, there are openings for alveoli along its wall.
- Club cells become more abundant as we go down the respiratory bronchiole.
**Alveolar ducts and Sacs**

- Distally, the respiratory bronchioles give rise to alveolar ducts. These are tube-like structures completely lined by alveoli.

- The epithelium of the ducts (and alveoli) is a simple squamous epithelium.

- The smooth muscles are restricted to the alveolar openings. The thin lamina propria is rich in elastic fibers and capillary networks.

- Alveolar ducts terminate at the alveolar sacs. These are spaces surrounded by several alveoli that open into these spaces. Sacs may, sometimes, open along the wall of the ducts.
Fig. 18: The respiratory zone. Terminal bronchioles (TB) give rise to respiratory bronchioles (RB). Tube-like alveolar duct (AD) emerges from these. Alveolar sacs (AS) are the terminal part of the AD. The image above shows several alveoli (A) opening into the AS.
Alveoli

- Alveoli are sac-like evagination of the respiratory bronchioles, alveolar ducts, and alveolar sacs. They are the site of gas exchange between the air and blood.

- There about 200 million alveoli in each lung with a total area of 75m². The alveoli (and the airways) give the lung a spongy structure.

- Alveoli are separated from each other by connective tissue called the interalveolar septum. Alveolar pores, however, pass through these septa connecting the alveoli together. This equalizes pressure in the alveoli and creates collateral passages in case of obstruction.
The *interalveolar septum* consists of:

- Fibroblasts and macrophages with sparse extracellular matrix.
- Elastic and reticular fibers. Elastic fibers allow alveoli to expand with inspiration and contract passively with expirations. Reticular fibers prevent both the collapse and over-distension of the alveoli.
- Capillary network. These capillaries are continuous. Most of the endothelial organelles are located around the nucleus. The remaining areas of the cell is very thin and suitable for gas exchange.
Cells of the Alveoli

1. **Type I alveolar cells (type I pneumocytes):** thin squamous cells that form most of the lining of the alveolus. It’s these alveolar cell across which gas exchange occurs. Most of the organelles are located around the nucleus. The remaining areas of the cell is very thin. They are connected to each other by desmosomes and tight junctions.

2. **Type II alveolar cells (type II pneumocytes or septal cells):** cuboidal cells that bulge into the cavity of the alveolus. They are connected to each other and to type I cells by desmosomes and tight junctions. The nucleus is round and cytoplasm filled with vesicles. Many of these vesicle are *lamellar bodies* which are specific for these cells. Type II cells produce surfactant factor which reduces surface tension and prevents collapse of alveolus. Also these cells may act as stem cells.

3. **Alveolar macrophages (dust cells):** these cells are present in the alveolus and in the interalveolar septum. They engulf dead red blood cells and foreign particles.
Siderophages (hemosiderin-containing macrophages)

- In conditions like congestive heart failure or pulmonary edema, there will be an increased pressure in the alveolar capillaries. This will cause the RBCs to pass through the vessel wall.

- These extravasated RBCs are engulfed and digested by the alveolar macrophages leading to the accumulation of hemosiderin in the macrophages. These cells are now called siderophages and they appear brown in color.

- This condition is not restricted to alveolar macrophages, but could occur anywhere in the body.
The Respiratory Membrane

- Gas exchange occur through a series of structures collectively called the respiratory membrane or the *blood-air barrier*. This barrier is very thin.

- These structures are:
  - Type I alveolar cells.
  - The fused basal laminae of the alveolar epithelium and capillary endothelium.
  - The endothelial cells of the capillaries.

Fig. 20: The respiratory membrane.