# Histology of the Airways

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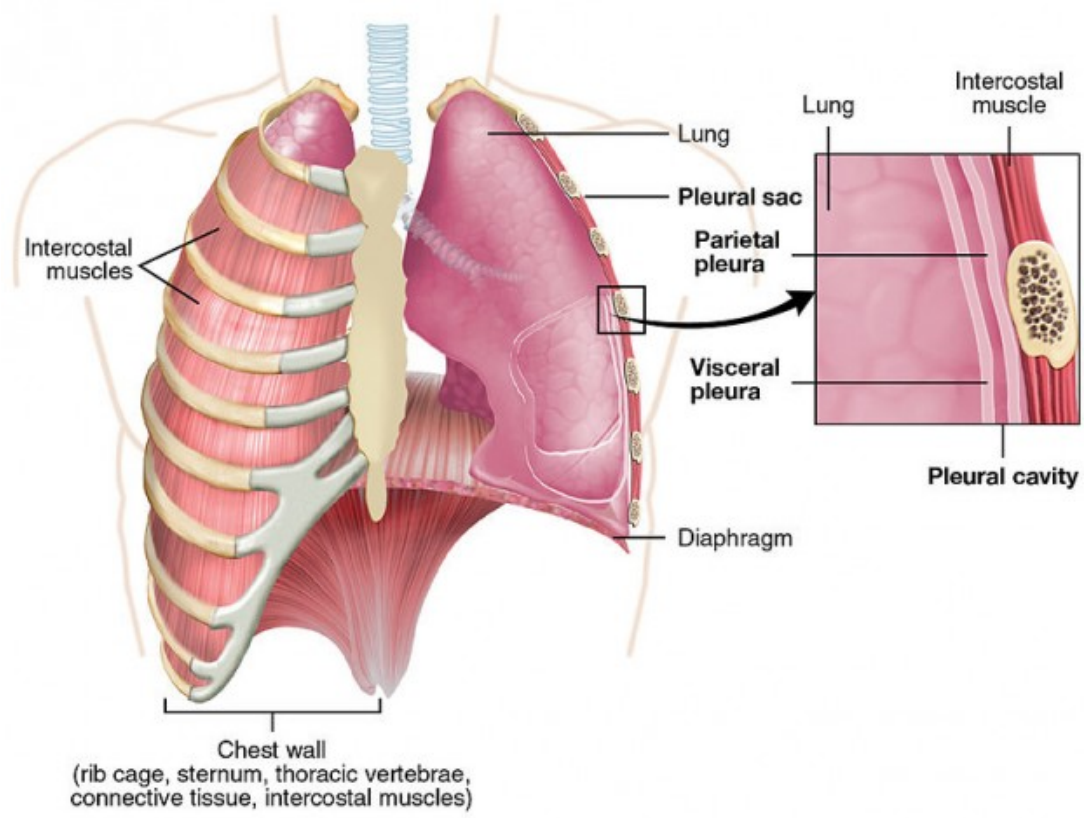
**The lung is, similar to the intestines or the skin, an organ that has direct contact with the outside world. Its function is the basis of our existence: gas exchange via diffusion. To perform this enormous task every second of our life, it needs a transport system for waste gasses and fresh air; a room in which the walls are thin enough for gas diffusion, and the transport services for gasses in chemical bonds. To achieve the various functions involved in mechanical respiration, the respiratory tract has adaptation to this function by possessing different histological features.**




## Introduction

The airway is involved in mechanical respiration of the body. Thus it is divided into:

- A conducting system.
- An interchange system.

Mechanical respiration progresses in various steps which are:

1. Inhalation of air.
2. Warming, cleaning and moistening of the air in the larger airways.

3. In the lungs oxygen is taken from the air and delivered into blood while CO2 takes the opposite direction and it is removed from blood reaching the lungs from peripheral circulation.

The air is then exhaled after gaseous exchange.

## General Principles of Airway Structures

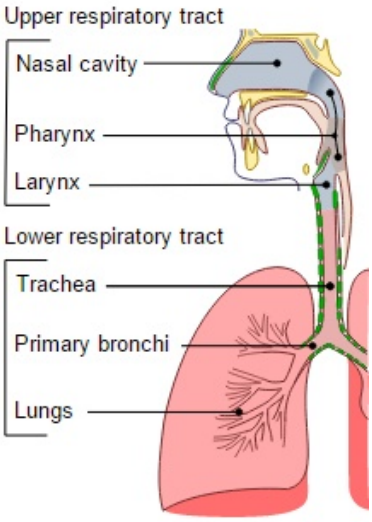



Image: "Conducting passages of the human respiratory system" by Lord Akryl. License: (Public Domain)

The airways are lined with a special kind of mucosa and are held open by reinforcements in their wall. The upper airways (nasal cavity and pharynx) are surrounded by bones; the wall of the lower airways contains a support frame made out of a special cartilage.

The mucosa (**tunica mucosa**) consists of the **epithelial lamina**, the **lamina propria** made out of connective tissue, and it holds the characteristic **respiratory epithelium**: ciliated **pseudostratified columnar epithelium** with goblet cells.

## Location and Structure of Trachea and Main Bronchi

Below the glottis, the lower airways begin. The trachea is a long tube that runs from the larynx to its bifurcation into the two main bronchi at the fourth/fifth thoracic vertebra. The right main bronchus (**bronchus principalis dexter**) supplies the **right lung** with its **three lobes**; the left main bronchus (**bronchus principalis sinister**) supplies the **left lung** with its **two lobes**. All in all, the bronchi bifurcate about 23 times into smaller branches until they reach the alveoli.

The trachea is divided into a neck and thoracic portion and is located ventrally to the **esophagus**.

The main bronchi and trachea have a support frame that consists of 16-20 C- or hoof-shaped hyaline cartilage rings. Dorsally, these rings are open but the trachea is kept closed by a connective tissue wall that has embedded transversally running muscle fibers, called **paries membranaceus**. In a longitudinal orientation, the cartilage rings are connected to each other by **annular ligaments.**

The whole support frame is referred to as the **tunica fibro-musculo-cartilaginea**.

**Note**: The structure of the trachea becomes relatively simple if you first understand the three-layered structure of the wall!

## Microscopic Structure of the Trachea

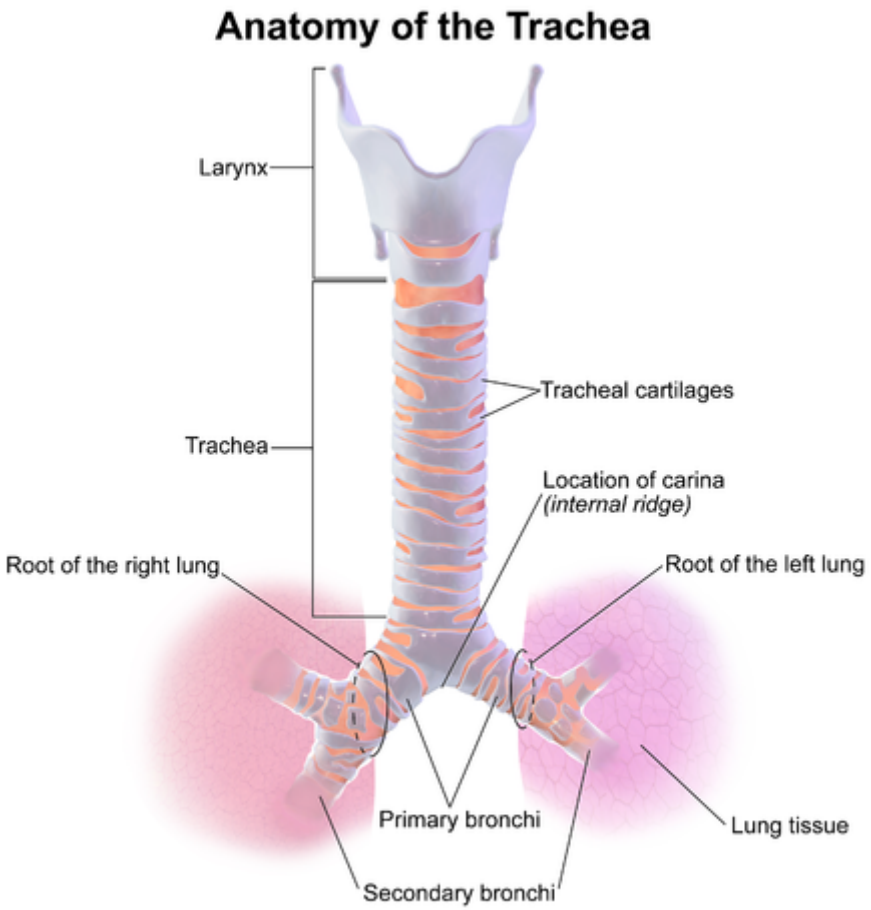



Image: “Trachea” by BruceBlaus. License: (CC BY 3.0)

The wall of the trachea consists of three layers:

## First layer of the trachea

**Tunica mucosa:** The inner layer of the mucosa carries respiratory epithelium (with the exception of the bifurcation: non-cornified squamous epithelium). In the **lamina propria**, there are sero-mucous glands (**tracheal glands**). The mucosa is rich in afferent nerve fibers (cough reflex).

## Second layer of the trachea

**Tunica fibro-musculo-cartilaginea:** The most prominent structure in this layer is the hyaline cartilage ring, which has a strong **perichondrium**. The horizontally running **tracheal muscle** in the **paries membranaceus** closes the gap that the cartilage rings leave open dorsally. Contraction of the tracheal muscle results in a change in tracheal caliber due to the horizontal orientation of the muscle fibers.

The **annular ligaments** connect the cartilage rings to each other. In this layer, there are a lot of elastic fibers that are oriented longitudinally. This makes the trachea and the main bronchi elastic tubes in the longitudinal position capable of adapting to movement from their surroundings.

## Third layer of the trachea

**Tunica adventitia:** This loose layer of connective tissue not only connects the trachea to its surrounding structures but also ensures flexibility of the trachea during processes such as swallowing or coughing.

# Excursus: Tracheomalacia

An enlarged thyroid gland (struma) can obstruct the trachea. As a consequence, **tracheomalacia** can occur, which is characterized by softening of the cartilage rings and, hence, an enormous loss in stability.There is loss of the antero-posterior diameter of the trachea. It is characterized by tracheal collapse during times of increased airflow causing cough, crying or difficulty in feeding.

**Note:** It is almost impossible to confuse the extrapulmonary airways (trachea and main bronchi) with other hollow organs in histological pictures as long as you remember its particular characteristics: macroscopy (cartilage rings), respiratory epithelium almost everywhere, and sero-mucous glands. This combination cannot be found in any other hollow organs!

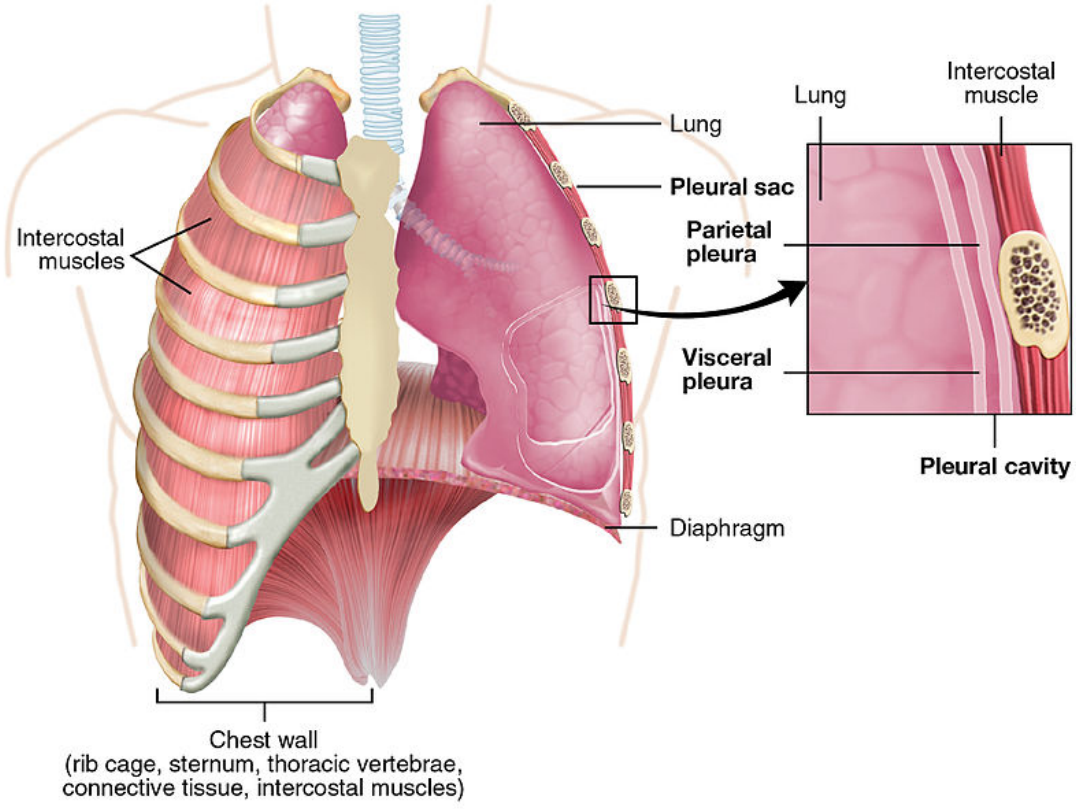



Image:" The Lung Pleura" by OpenStax College. License: (CC BY 3.0)

# Preliminary Remark

The lung is located in the pleural cavity. The lobes of the lung are covered by the **visceral pleura (pleura pulmonalis),** which is in contact with the **parietal pleura**. Physiologically, adhesion between the two serous sheets is ensured by a fluid found in the pleural cavity. This thin layer of fluid keeps them attached via capillary adhesion. This way, the surface of the lung can be moved against the thoracic walls, but cannot be separated from it. It has to go along with all its movements.

Due to a large network of elastic fibers, the lung always tends to contract. The fibers are always under constant tension and would reduce the lung to a fist-sized structure if the adhesion between the lung surface and thoracic wall disappeared (**pneumothorax**; collapsing to the minimal volume).

Basically, the lung consists of branches of the **bronchial tree** up to the air sacs (alveoli; the end section of the bronchial tree) and the branches of the pulmonary arteries and veins. The latter are intrapulmonary-located (upper airways, trachea, and main bronchi are extrapulmonary).

The branching of the bronchi follows a **dichotomous pattern**, which means that two smaller branches arise from a larger one. From the trachea to the alveoli, the human lung is estimated to branch about 21 to 23 times. Roughly 15 of these divisions form the air conducting part of the lung, the remaining parts include **respiratory bronchioles** and the **alveolar duct** which is the gas exchanging part.

The main bronchi split into lobe bronchi (**bronchi lobares**; three on the right, two on the left) after they enter the lungs, and are extrapulmonary-located.

The lobe bronchi then split **dichotomously inside the lung** into segmental bronchi (**bronchi segmentales).** From this point on, the dichotomous splitting of the bronchi often occurs in an irregular manner: One branch gives rise to two unequal ones. The stronger one of these runs in the same direction as the large one did, while the other one makes a turn and can eventually run into the opposite direction with its following branches (hence, there are terminal branches and alveoli in central areas of the lung).

Segmental bronchi split into middle and small bronchi. The small bronchi become **terminal bronchioles** after which they become **respiratory bronchioles**. The final branchings form the **alveolar duct** and the alveoli.

Here is an overview of the branching of the bronchial tree:

- Segmental bronchi
- Bronchi
- Bronchioles
- Terminal bronchioles
- Respiratory bronchioles
- Alveolar duct and sacculus

# Wall Structure of Intrapulmonary Airways

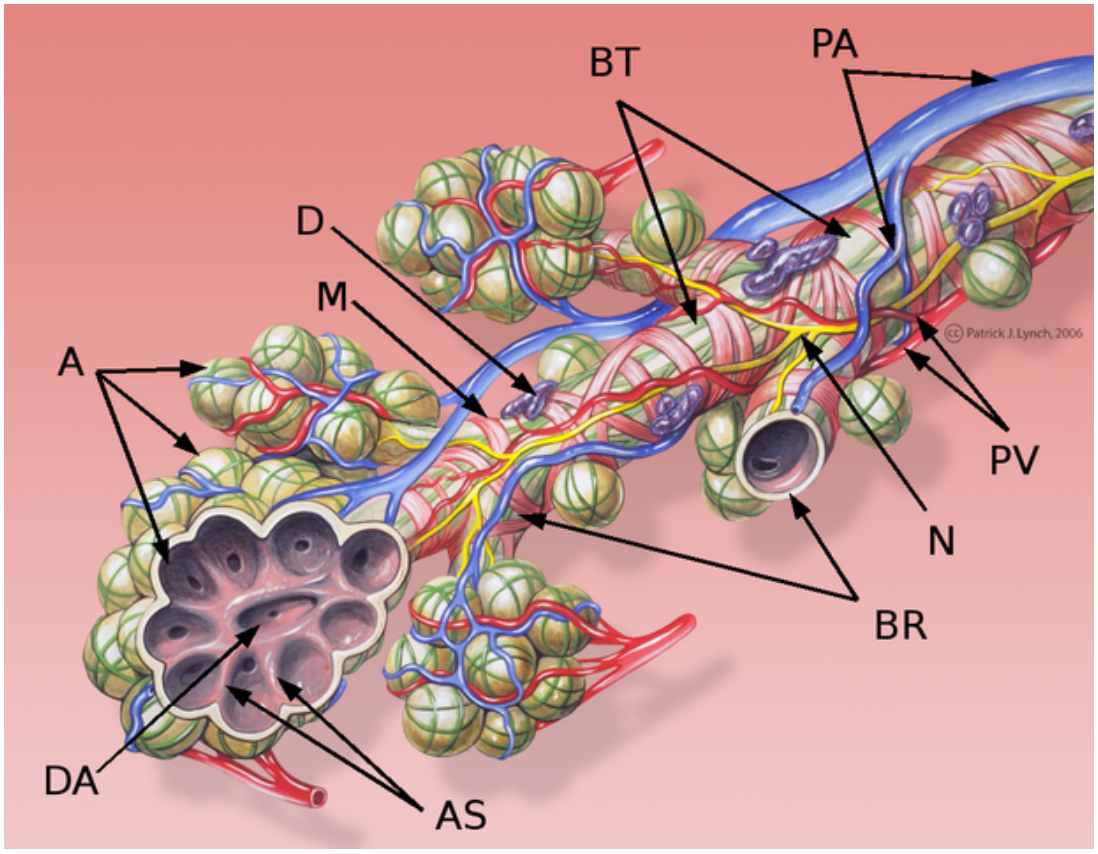



Image: “Bronchial anatomy detail of alveoli and lung circulation” by Patrick J. Lynch. License: (CC BY 2.5)

## Bronchi and segmental bronchi

The main difference that distiguishes bronchi from the trachea is that in the intrapulmonary airways, there are irregularly formed cartilage plates in the wall instead of hyaline cartilage rings. Also, there is no more **paries membranaceus**. Muscle cells are circularly arranged. The wall contains the following layers:

**Tunica mucosa:** The mucosa consists of respiratory epithelium and the **lamina propria** with embedded sero-mucous bronchial glands (**glandulae bronchiales**) and goblet cells. Elastic fibers, free cells of the immune system, and a continuous coat out of smooth muscles can be seen in the histological preparation.

**Tunica musculo-fibro-cartilaginea:** The support frame is formed from irregular hyaline cartilage plates, smooth muscles, and connective tissue. In the small bronchi, small elastic cartilage pieces can be found. The irregular cartilage pieces form the outer layer, the continuous circular muscle layer (**tunica muscularis**) is located on the inside. Sero-mucous glands are situated between the cartilage pieces. They **synthesize mucins** for the epithelium covered mucous surface. Also, they secrete antibacterial substances, IgA, and protease inhibitors for the inactivation of tissue-damaging proteases, which are liberated by immune cells.

**Tunica adventitia:** The loose **peribronchial connective tissue** forms a continuum, which accompanies the branches of the bronchial tree from the junction (**hilum)** to the bronchioles. This is where the **private vessels** of the bronchial tree, lymphatic vessels, and nerves run.

## Bronchioles

In contrast to the bronchi, the bronchioles mainly differ from the rest of the bronchial tree by not having any cartilage pieces and glands.

**Tunica mucosa:** The mucosa has a ciliated single layer mostly **cuboidal epithelium** without goblet cells. A star-shaped lumen that has a diameter of less than 1 mm is a characteristic of the cross section of bronchioles.

**Tunica adventitia:** Via elastic fibers of the surrounding alveolar walls, the peribronchial connective tissue is indirectly connected to the lung surface, the interlobular and intersegmental connective tissue septa. Thus, a radial tension is exerted on the bronchioles, which keeps them open while also preventing them from collapsing. This way, the lack of a support frame with cartilages is compensated.

## Terminal bronchioles

The final branching of the bronchioles represents the end of the conductive part of the airways. The epithelium contains non-ciliated secretory cells, the **Clara cells**. They arch into the lumen-like pistons. Apically, they contain secretory granules that have proteins, which serve as a part of the natural immune response: the surfactant proteins **SP-A** and **SP-D** as well as the Clara cell protein CC 10 (Clara cell 10 kDa protein).

These proteins decrease the **antimicrobial mechanism** of tissue-damaging inflammatory reactions. SP-A and SP-D also act as **opsonins**, which make **phagocytosis** of pathogens easier for immune cells. Clara cells are claimed to be the reserve for cell replacement in the distal airways.

**Acini** are all airways that originate from the **terminal bronchioles**.

## Respiratory bronchioles

These are the smallest bronchioles (<0.5 mm) in diameter that connect the terminal bronchioles to the alveolar ducts. The gas exchanging part of the bronchial tree begins here. The wall is fragmentary and contains embedded alveoli.

## Alveolar ducts and sacculus

**Alveolar ducts and sacculi** are the vestibules of the alveoli. A ring of smooth muscles, collagenous, and elastic fibers reinforce the entrance to the alveoli.

The simple cuboid epithelium does not have **kinocilia**, in which Clara cells can be found.

**Note:** In exams, the difference between bronchi and bronchioles in regards to their structure is a popular subject.

# Gas Exchange in the Alveoli

Alveoli are **polygonal** spaces, which are filled with air. They are separated from each other by thin walls (**interalveolar septa**). The alveolar walls – the interalveolar septa – are structures in which gas exchange occurs via diffusion.

Collagen, fibrocytes, and elastic fibers, which are responsible for the lung’s retracting forces, form the connective tissue frame of the septa. Within the septa, there are

expanded **capillary nets**. The basal lamina of the capillary endothelium and the basal lamina of the alveolar epithelium cells are fused. Thus, both structures have a common basal lamina.

On both sides of the interalveolar septa, there is a thin epithelial cover of plate-like extensions of cytoplasms of **type I** alveolar cells (**pneumocytes**), also referred to as **covering cell**s. They have an extensive soma which covers the capillaries (**blood-air barrier**) and lines the major part (95 %) of the alveoli.

In the niches between the flat type I cells – where they do not really interfere with gas exchange –, there are larger cuboid **type II** alveolar epithelial cells (pneumocytes). They contain a lot of organelles and **lamellar corpuscles**. They produce and secrete the **surfactant**. Type II cells are the replacement for type I cells.

All extensions of adjoining alveolar epithelial cells are connected to each other by tight junctions. Tight junctions are the most important barriers against the intrusion of lymph from the interstitium into the alveoli. The alveolar epithelium is not directly in contact with air but is covered using a liquid film. Its surface tension is decreased by the surfactant.

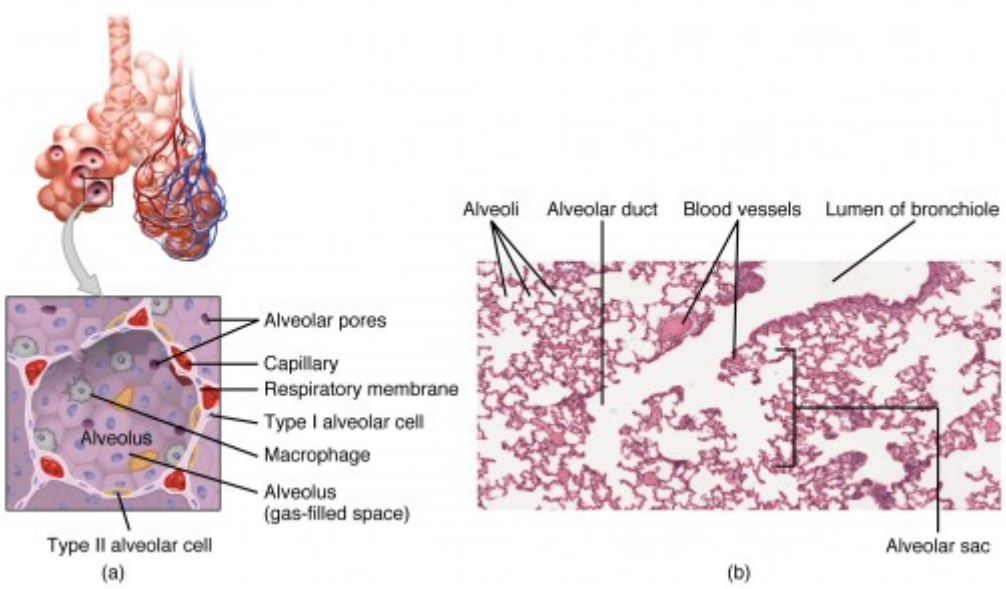



Image: “Structures of the Respiratory Zone” by philschatz. License: (CC BY 4.0)

## Blood air barrier

In the area of the blood-air barrier, there is close contact between alveoli and capillaries.Thus, it is also known as the alveolar-capillary barrier or membrane. Since gaseous exchange takes place here, the barrier is essential to avoid the formation of gas bubbles within the blood vessels.

Anatomically, it consists of a thin area which contains the following structures (from alveolus to capillary):

- Surfactant film
- Thin extension of type I alveolar epithelial cell
- Fused basal membrane of capillary endothelium and alveolar epithelium
- Endothelial cell (closed type)

In the human lung, the thickness of this tissue barrier measures only 0.6 micrometers and is thus very thin to allow for respiratory gas exchange. The distance for diffusion between air in the alveoli and erythrocytes is about 1.1 micrometers, slightly thicker since the fluid film on the alveolar epithelium and the blood plasma has to be passed besides other anatomic structures.

## Excursus: Pulmonary Edema

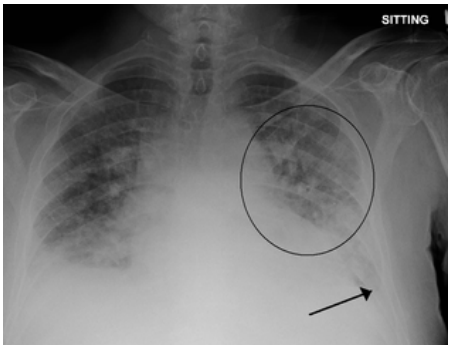



Image: "Interstitial and alveolar pulmonary edema with small pleural effusions on both sides" by James Heilman. License: (CC BY-SA 3.0)

Commonly referred to as **water in the lung**, pulmonary edema is an acute disease. Fluid accumulates in the connective tissue and the alveoli making it difficult to breathe. A pressure build-up in the capillaries can be caused by **myocardial failure** and, hence, backflow into the pulmonary circulation. The accumulation in the connective tissue (and thus in the blood-air barrier) results to an impairment in diffusion and, therefore, hinders gaseous exchange. Fluids transfer to the alveoli. Non-cardiogenic causes of pulmonary edema include severe pneumonia and other respiratory tract diseases.

Sudden/acute pulmonary edema is an emergency that presents with dyspnea, a feeling of suffocation or drowning, wheezing or gasping for breath, anxiety, chest pain and palpitations.

The condition resolves with prompt treatment using diuretics and addressing the underlying problems such as cardiac failure or severe infection.

## Surfactant – SURFace-ACTive-AgeNT

Without this substance, the surface tension at the water/air border would be so high that the alveoli would collapse in the process of exhalation and would not inflate anymore (atelectasis = not inflated alveolus). For medical practitioners it is worthwhile to study this substance in detail:

The major part (90 %) of this **anti-atelectasis factor** consists of **phospholipids** (**dipalmitoylphosphatidylcholine = lecithin)** and remaining part (10 %) consists of surfactant proteins. The phospholipids lower the surface tension of the fluid film on the alveolar surface. Surfactant is produced and secreted by **type II pneumocytes** and is stored in storing organelles (**lamellar bodies**).

Due to the **amphiphilic** characteristic (has both hydrophilic and hydrophobic characteristics)of **phospholipids**, they spread as a monomolecular layer over the water/air border after **exocytosis** out of the type II cells. A great part of the surfactant is

re-used (recirculation: reuptake and renewed liberation out of type II cells), the rest is eliminated by **alveolar macrophages**.

## Review Questions

Solutions can be found below the references.

**1. Organize the sero-mucous glands with respect to their location in the bronchial tree system.**

A. segmental bronchi
B. terminal bronchioles
C. trachea
D. respiratory bronchioles
E. main bronchi

**2. In regards to the lung's function, it is important that the lymph in the interstitium of the lung, which originates from the blood capillaries, not to pass the air space and into the alveoli. Which structure creates this barrier?**

A. keratinized squamous epithelium
B. atelectasis factor
C. tight junctions between alveolar epithelial cells
D. type II pneumocytes
E. basal membrane

**3. Component/s of the wall of respiratory bronchioles is/are:**

A. pseudostratified epithelium
B. goblet cells
C. elastic fibers
D. cartilage
E. bronchial glands

**4. During a biopsy of a segmental bronchus, you find keratinized squamous epithelium. What do you conclude from this observation?**

A. Epithelial atrophy due to chemical noxae
B. Inadequate blood supply
C. Normal finding
D. Metaplasia
E. Hypotrophy

## References

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**Correct answers:** 1A; 2C; 3C; 4D



Notes