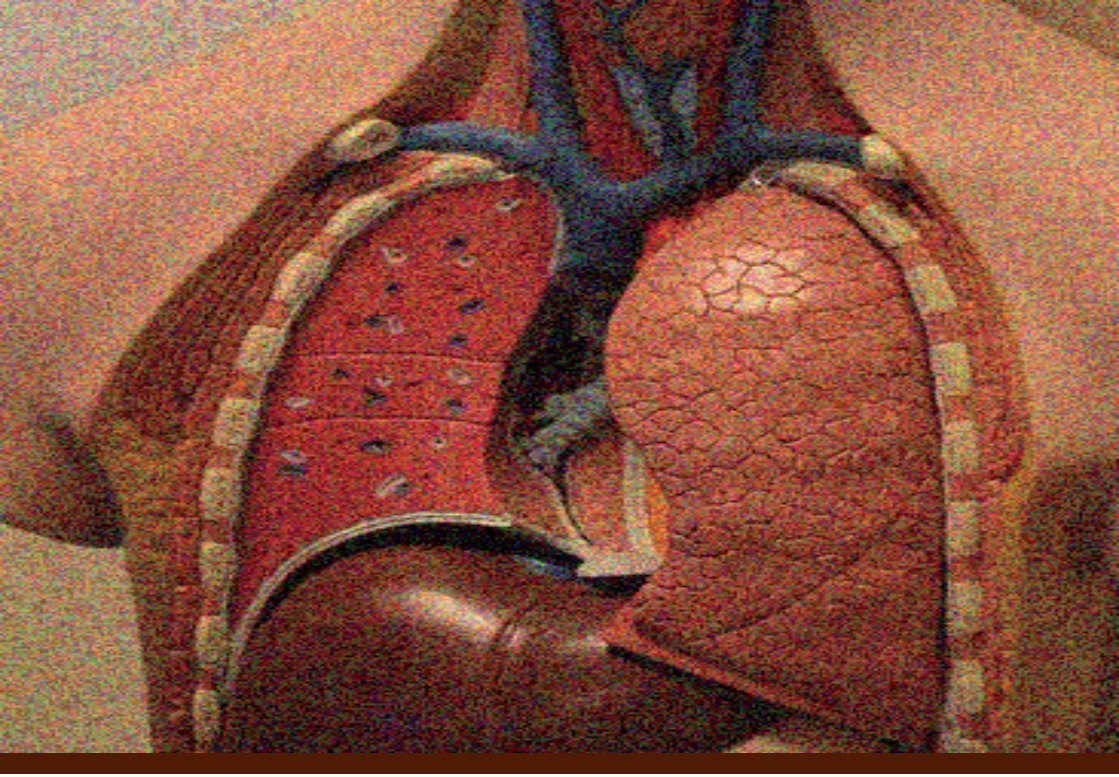

RESPIRATORY SYSTEM

ŞAMİL ÖZTÜRK, İLHAN ÖZDEMİR

İKSAD
Publishing House

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PREFACE

The importance of the lungs as the effector organ of respiration cannot be underestimated. Respiration and life depend on the absorption of oxygen from the atmosphere and the removal of carbon dioxide through pulmonary ventilation. Healthy life depends on the quality of the vital system. Especially the recent epidemic diseases (Sars, Covid-19 etc.) affecting this system have caused the picture of lower respiratory tract involvement and epidemic diseases to reach alarming dimensions. In addition, impairment of the respiratory system through loss of respiratory muscle function, increased airway resistance, decreased lung compliance, alveolar destruction or physical obstruction leads to a general loss of functional ability. While certain disease states, such as emphysema, are progressive and can ultimately be fatal, a mild case of bronchial asthma can only limit a person's exercise capacity. However, with every untreated case of respiratory disease, quality of life always declines. In this study, the tissues that make up the respiratory system were dealt with in detail and it was tried to be explained with the support of the current literature review. It is aimed to support basic education and research in the field of health. We would like to thank our dear colleague Latife Ceyda İRKİN, who contributed to the writing of this book.

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1. INTRODUCTION

The respiratory system begins with the nostrils through which air is taken in, continues with canal structures called respiratory tracts and ends with structures where gas exchange takes place (Aughey and Frye, 2001). In addition, the respiratory system consists of a pair of lungs and a series of airways that deliver air to the lungs. In the lung, airways branch into tubes that gradually get smaller until the smallest air space, the alveoli, is reached. The three main functions performed by the respiratory system are: air conduction, air filtration and gas exchange (breathing). Respiration takes place within the alveoli. In addition, air passing through the larynx is used to generate sound, and air passing over the olfactory mucosa in the nasal cavities (nasal cavities) carries stimuli for the sense of smell. In addition, the respiratory system is less involved in endocrine functions (hormone production and secretion), as well as in the regulation of immune responses to inhaled antigens. The canals of the respiratory system have the opportunity to remain open continuously as the wall structures are strengthened by cartilages, connective tissue threads and muscles (Figure 1).

The conducting portion is made up of: nasal cavities, nasopharynx, larynx, trachea, bronchii and bronchioles

The trachea branches to give rise to two primary (main) bronchii**.** These then branch successively to give rise in turn to secondary and tertiary bronchii (Figure 2)**.**

These then branch to give rise to several orders of progressively smaller airways called bronchioles**,** the smallest of which are called terminal bronchioles. These are the last components of the conducting portion of the respiratory system.

Terminal bronchioles give rise to respiratory bronchioles, which ultimately lead to the alveoli (Ross and Pavvlina, 2014, Figure 3).

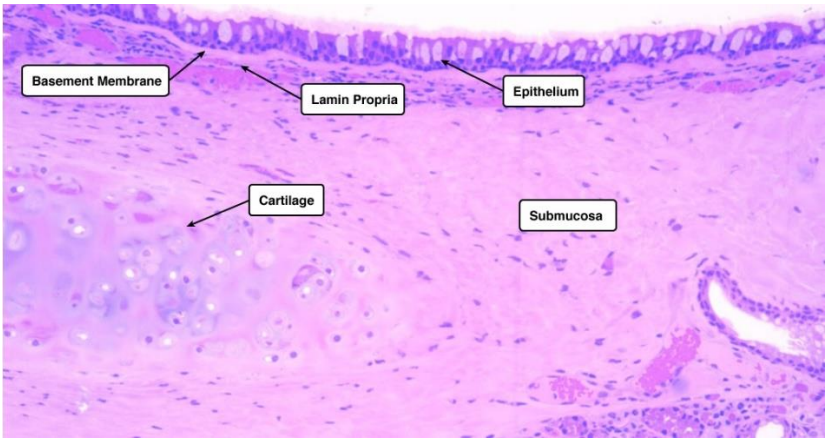


Figure 1. The conducting airways are lined by pseudostratified of respiratory systems. http://medcell.med.yale.edu/histology/respiratory _system_lab/conducting_airway.php, Access; 22.11.2020).

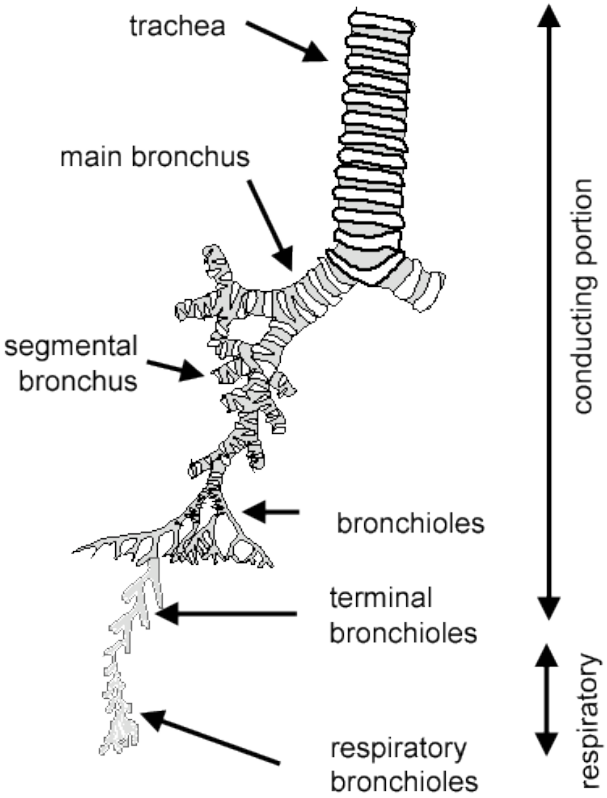


Figure 2. Conduction portion and respiratory region *of the respiratory system (*https://www.histology.leeds.ac.uk /respiratory/conducting.php #:~:text=The%20epithelium%20is %20tall%20columnar,vessels%20that%20warm%20the%20air*, Access; 22.11.2020).*

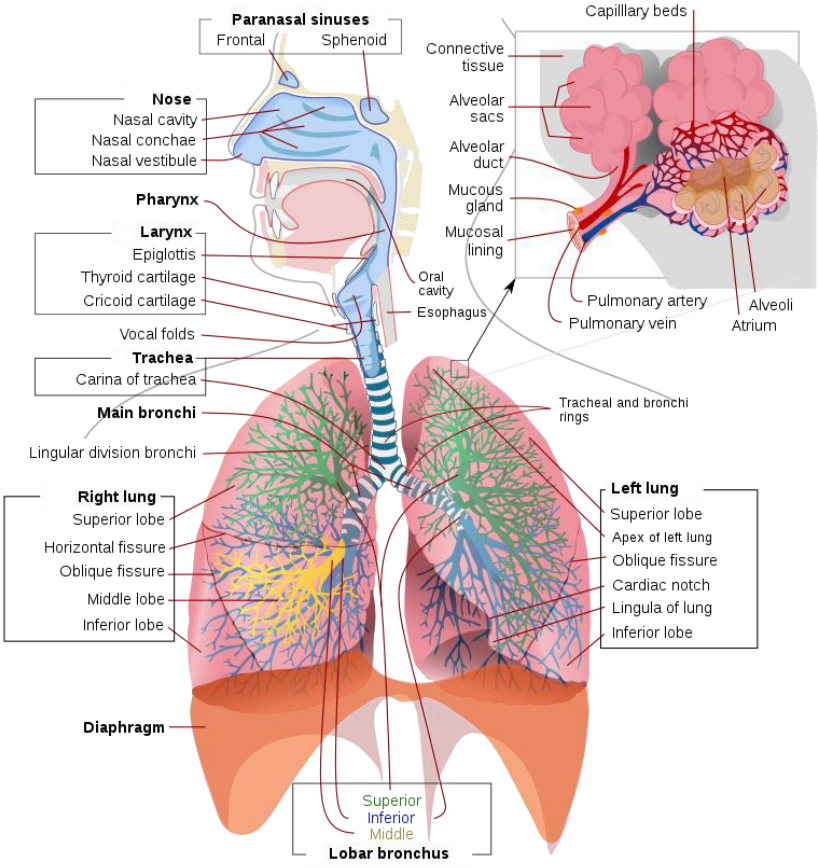


Figure 3. Schematic view of respiratory system (https://en.wikipedia.org/wiki/Respiratory_system#/media/File:Respiratory_system_complete_en.svg, Access; 22.11.2020).

Sections outside of the lungs:

- Nasal cavities are two large air-filled cavities at the top of the respiratory system (they also contribute to the oral cavity under the nasal cavities during a strong breathing).
- The nasopharynx is located behind the nasal cavities above the level of the soft palate and is connected to the oropharynx, which is located posterior to the oral cavity in the inferior.
- The larynx is a hollow tubular organ that is responsible for sound generation and contains a cartilaginous skeleton.
- Trachea is a flexible air tube that runs from the larynx to the thorax. It serves as a passageway for air and divides into two main bronchi within the mediastinum.
- Two main (primary) bronchi enter the right or left lung.

The main bronchi show extensive branching within the lungs, eventually forming distributive bronchioles. The bronchioles represent the last part of the conducting section. Internal bronchi and bronchioles together form the bronchial tree. Gas exchange

takes place in the respiratory part of the respiratory system (respiratory part). It includes the following sequential structures:

- Respiratory bronchioles are involved in air conduction and gas exchange.
- Alveolar channels are long airways formed by the joining of the openings to the alveoli.
- Alveolar sacs are spaces surrounded by clusters of alveoli.
- Alveoli are the main gas exchange areas.

Blood vessels enter the lungs along with the bronchi. As the arteries follow the bronchial tree to enter the lungs, they branch off into smaller vessels. Capillaries come into close contact with the alveoli, which are terminal respiratory units. This close relationship between the alveolar air spaces and pulmonary capillaries is the structural basis of gas exchange within the lung parenchyma (Carvalho and Gonçalves, 2011; Cormack, 2001).

1.1. Development of the Respiratory System

The part of the respiratory system mucosa outside the nostrils is covered with a glandular respiratory mucosa. There is also a specialized mucosa section in the nasal cavity to smell. The

lungs develop as a ventral evagination of the foregut in the embryo. The development of the human lungs arise from the laryngotracheal groove and develop to maturity over several weeks in the foetus and for several years following birth (Sadler, 2010). The larynx, trachea, bronchi and lungs that make up the respiratory tract, begin to form during the fourth week of embryogenesis from the lung bud which appears ventrally to the caudal portion of the foregut (Moore and Persaud, 2006; Hill and Mark 2016). The respiratory tract has a branching structure, and is also known as the respiratory tree (Miura, 2008). In the embryo this structure is developed in the process of branching morphogenesis, and is generated by the repeated splitting of the tip of the branch. In the development of the lungs (as in some other organs) the epithelium forms branching tubes.The lung has a left-right symmetry and each bud known as a bronchial bud grows out as a tubular epithelium that becomes a bronchus. Each bronchus branches into bronchioles. The branching is a result of the tip of each tube bifurcating. The branching process forms the bronchi, bronchioles, and ultimately the alveoli (Wolpert and Lewis, 2015). The four genes mostly associated with branching morphogenesis in the lung are the intercellular signalling protein – sonic hedgehog (SHH), fibroblast growth

factors FGF10 and FGFR2b, and bone morphogenetic protein BMP4. FGF10 is seen to have the most prominent role. FGF10 is a paracrine signalling molecule needed for epithelial branching, and SHH inhibits FGF10 (Wolpert and Lewis, 2015). The development of the alveoli is influenced by a different mechanism whereby continued bifurcation is stopped and the distal tips become dilated to form the alveoli (Figure 4). Therefore, the epithelium of the respiratory system is of endodermal origin. This initial respiratory diverticulum (lung bud) develops into the thoracic mesenchyme. Bronchial cartilages, smooth muscle, and other connective tissue elements originate from the thoracic mesenchyme. The airways of the respiratory system consist of the conductive respiratory section and the respiratory section. The conducting part of the respiratory system consists of the airways that advance to the respiratory part where gas exchange occurs in the lungs (Figure 5). The conductive parts are located both inside and outside the lungs. The organs that make up the system are the nasal cavity, nasopharynx, larynx, air tube and lungs (Ross and Pavvlina, 2014).

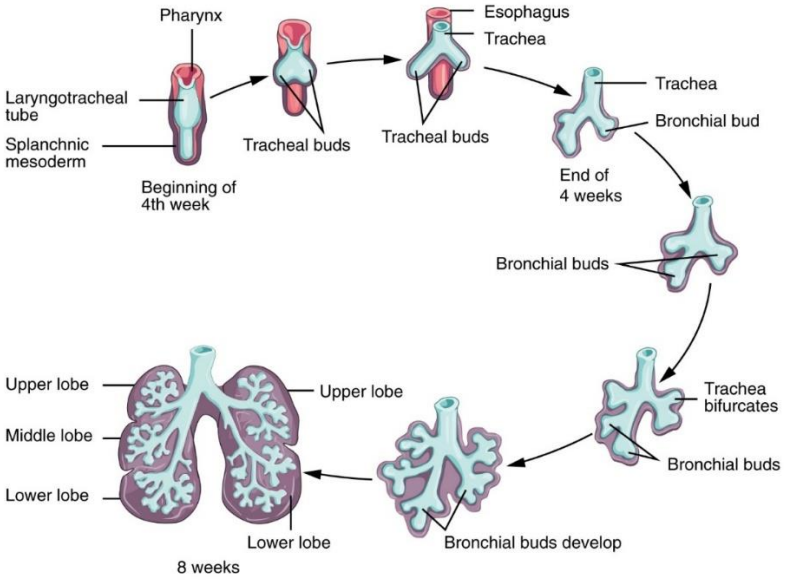


Figure 4. Development of the respiratory system (https://open.oregonstate.education/aandp/chapter/22-7-embryonic-development-of-the-respiratory-system, Access; 22.11.2020).

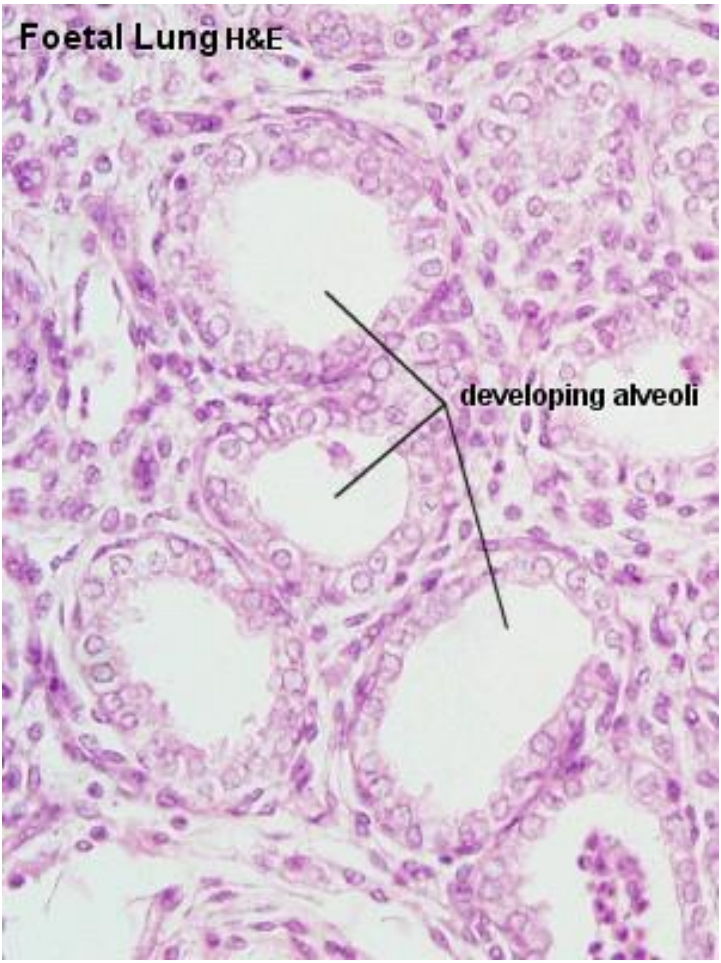


Figure 5. Foetal lung, human-H&E

(https://www.lab.anhb.uwa.edu.au/mb140/CorePages/Respiratory/respir.htm, Access; 14.12.2020)

1.2. Cavum Nasi (Nasal Cavity)

This section, which forms the entrance to the system, starts with the nostrils. It is then widened and divided by the septum nazi longitudinally into two halves. Inside these sections, towards the posterior parts are cavernous bone structures (Patwa and Shah, 2015). Again in these sections, there are three bony protrusions in the form of a shelf called konha. These are the upper, middle and lower konha regions. Since the skin covering the body is folded in from the nostrils, the skin structure continues even in a narrow area. This part is covered with cutaneous mucosa (Bacha and Wood, 1990). In addition, nasal cavities (nasal cavities) are a pair of chambers separated by bone and cartilage septums (Figure 6). They are long cavities with a wide base resting on the hard and soft palate and a narrow apex extending towards the anterior cranial fossa. The skeleton of the nasal cavities consists of bone and cartilage. Most of these bones and cartilages are centrally located in the skull, except for the small anterior area flanked by the external nose. Each cavity or chamber is connected to the anterior nares (nostrils, nostrils) with the external environment, the posterior to the nasopharynx through the choanas, and laterally by the paranasal sinuses and

the nasolacrimal canal that drains the tear from the eye into the nasal cavity. Specialized mucosa structures in the advanced parts of the nasal cavity are divided into 3 main areas (Kia'i and Bajaj, 2020).

The nasal vestibule is the enlarged part of the nasal cavity. It is located right inside the nostrils and is lined with leather.

- The respiratory zone (respiratory zone) is the largest part of the nasal cavities (2/3 inferior) and is lined with respiratory mucosa.

- The olfactory area is located at the apex (upper 1/3) of each nasal cavity and is lined with specialized olfactory mucosa.

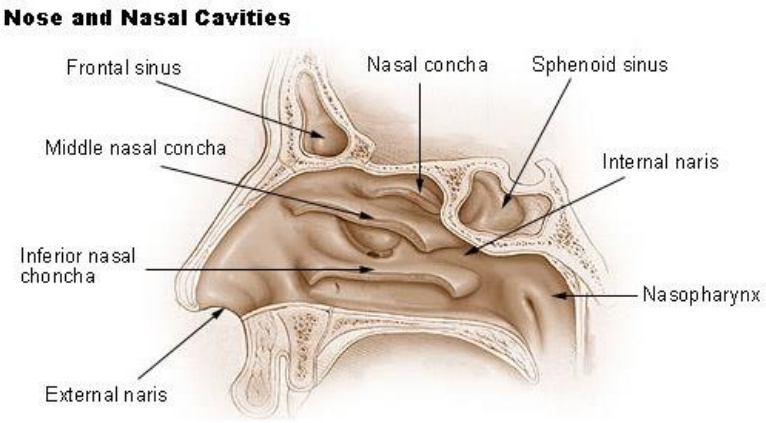


Figure 6. Nose and nasal cavity (https://training.seer.cancer.gov/anatomy/respiratory/passages/nose.html,Access; 22.11.2020).

1.3. Vestibule of The Nasal Cavity

This narrow area forming the entrance to the nasal cavity is covered with cutaneous mucosa and has a multi-layer flat epithelium with microscopic papillae. Lamina propria contains sebaceous and sweat glands. It is connected to the outer tissue by the submucosa consisting of tight connective tissue. Again, there are hairs as a feature of this region. Lamina propria and submucosa are rich in blood vessels and nerves. The cutaneous mucosa covering the vestibular region transforms backwards

into respiratory mucosa. In addition, the nasal vestibule forms part of the external nose and is connected to the external environment in the anterior leads. It is lined with multilayered flat epithelium, which is the continuation of the facial skin, and contains a large number of vibrissa (nose hair) that catch large particles before they are transported by air flow to other parts of the cavity. In addition, the secretions of the sebaceous glands it contains also help to capture the particles. At the point where the vestibule ends in the posterior, the stratified squamous epithelium becomes thinner and turns into a pseudo stratified epithelium specific to the respiratory region. There is no sebaceous gland in this area (Britannica, 2020; Ross and Pavvlina, 2014) (Figure 7, Figure 8).

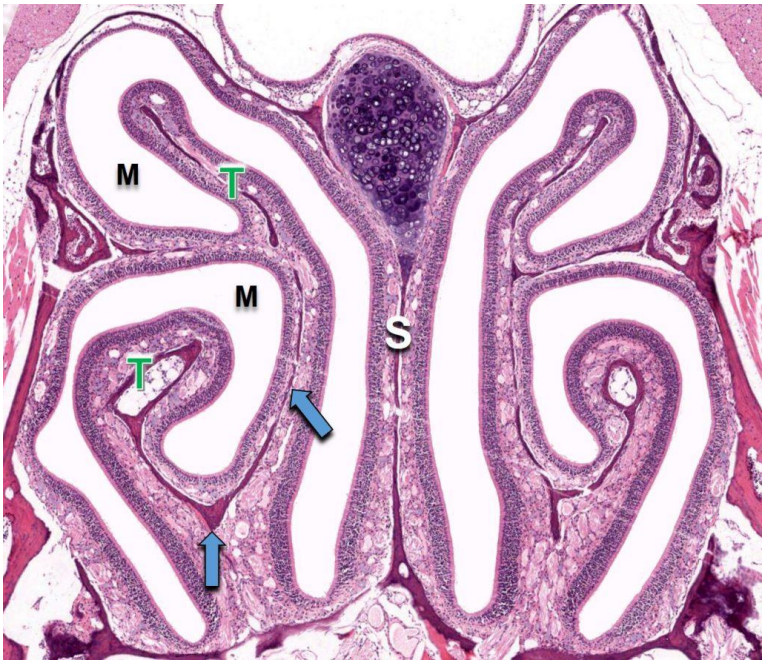


Figure 7. Nasal cavity, mouse. The nasal cavity is a bilaterally symmetric structure with left and right sides separated by a bony to cartilaginous nasal septum (S). The nasal cavities are composed of air filled openings, called meati (singular = meatus; M) filled with scroll-like structures termed nasal turbinates (T). Nasal turbinates are composed of thin cores of trabecular bone (arrows) lined by stroma and epithelium, H&E. (https://ohiostate.pressbooks.pub/vethisto/chapter/10-respiratory-tract-air-conduction/, Access; 22.11.2020).

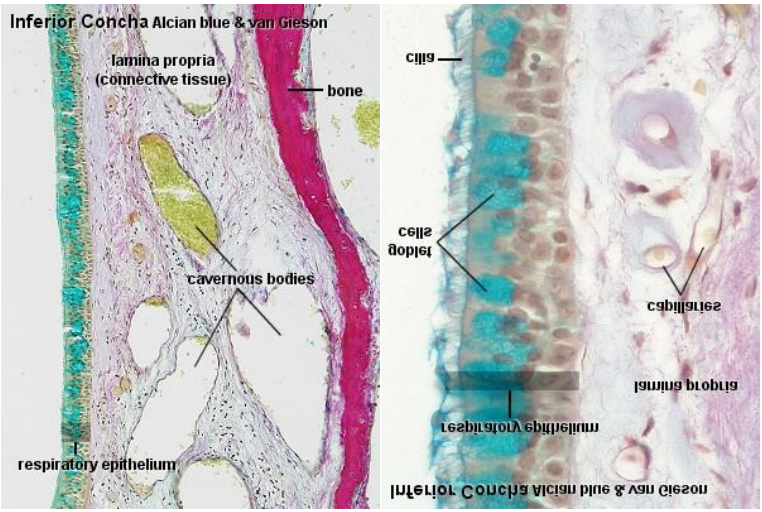


Figure 8. Concha inferior, Human-Alcian blue & Van Gieson (http://lecannabiculteur.free.fr/SITES/UNIV%20W.AUSTRALIA/mb140/CorePages/Respiratory/Respir.htm, Access: 19.12.2020)

1.4. Respiratory Area of The Nasal Cavity

The respiratory area constitutes the majority of the nasal cavity volume. It is lined by the respiratory mucosa (respiratory mucosa) with pseudo-stratified silylated prismatic epithelium on its surface. The lamina propria below the epithelium is tightly attached to the periosteum or perichondrium of the adjacent bone or cartilage. The nasal septum, which forms the medial wall of

the respiratory area, is flat, but its lateral walls are folded due to three shelf-like protrusions with bony extensions called concha or turbinates (Sobiesk and Munakomi, 2020). The turbinates divide each nasal cavity into separate air chambers and thus play a two-way role. The turbinates increase the surface area and enable more effective conditioning of the inhaled air by causing turbulence in the air flow.

The pseudo-stratified silylium prismatic epithelium of the respiratory mucosa consists of five cell types. Cells with silylium are elongated, prismatic cells and have ciliums that extend into the mucus that covers the surface of the epithelium. Goblet cells synthesize and secrete mucus (Dao and Le, 2020). Brush-like cells (brush cells) are the general name for cells in the respiratory tract that contain short, blunt microvilli (Pavelka and Roth, 2010). Small granular cells (Kulchitsky cells) are similar to basal cells but contain secretory granules, they are enteroendocrine cells of the APUD system (Evsyukova, 2006). Basal cells are cells from which other cell types originate.

The epithelium of the respiratory region of the nasal cavity is essentially the same as the epithelium lining most of the following parts in the conducting system of the respiratory

system. Since the study and examination of the respiratory epithelium of the trachea is preferred over the nasal cavity epithelium, the above cell types are given more extensive coverage in the section on trachea. The mucous membrane of the respiratory region of the nasal cavity warms, moisturizes and filters the inhaled air. The lamina propria of the respiratory mucosa has a rich vascular network and this network contains a complex set of capillary folds. The arrangement of the veins allows the inspired air to be heated by the blood flowing from the part of the fold closest to the surface. Capillaries close to the surface are arranged in rows. Blood flow is perpendicular to the air flow, similar to that found in a mechanical heat exchange system. The same veins become overfilled and leaky during allergic or viral infections such as the common cold. In this case, the lamina propria swells due to fluid accumulation. Consequently, excessive swelling of the mucous membrane causes restriction of air passage and difficulty in breathing. The lamina propria also contains mucous glands, most of which have serous crescents. The secretions of the glands contribute to the secretion of Goblet cells in the respiratory epithelium (Georg et al., 2012) (Figure 9).

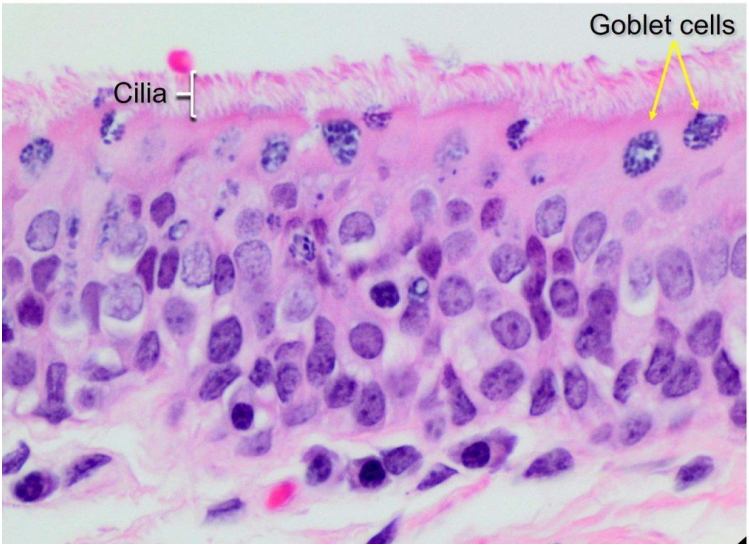


Figure 9. Nasal cavity, dog. The olfactory epithelium is ciliated pseudostratified epithelium composed of three major cell types: olfactory receptor cells, sustentacular cells, and basal cells. Olfactory receptor cells and sustentacular cells are difficult to distinguish readily on H&E, https://ohiostate.pressbooks .pub/vethisto/chapter/10-respiratory-tract-air-conduction/, Access; 22.11.2020).

1.5. Olfactory Area of The Nasal Cavity

The olfactory region is located in the dome of each nasal cavity and in the adjacent lateral and medial nasal walls with variable

prevalence (Figure 10). It is lined with specialized olfactory mucosa. The total surface area of the olfactory mucosa in humans is approximately 10 cm2, with its light yellow-brown color in living tissue due to the pigment in this mucosa olfactory epithelium and associated olfactory glands, in animals with an acute sense of smell, the total olfactory mucosa is differentiated, its area is relatively large e.g. some dog species. It has a larger mucosal area than 150 cm^2.

The lamina propria of the olfactory mucosa is directly adjacent to the periosteum of the underlying bone. This connective tissue contains numerous blood vessels and lymph vessels, unmyelinated olfactory nerves, myelinated nerves, and olfactory glands. The olfactory epithelium, like the epithelium of the respiratory region, is pseudo-multilayered, but contains quite different cell types (Figure 11). Also, it lacks Goblet cells.

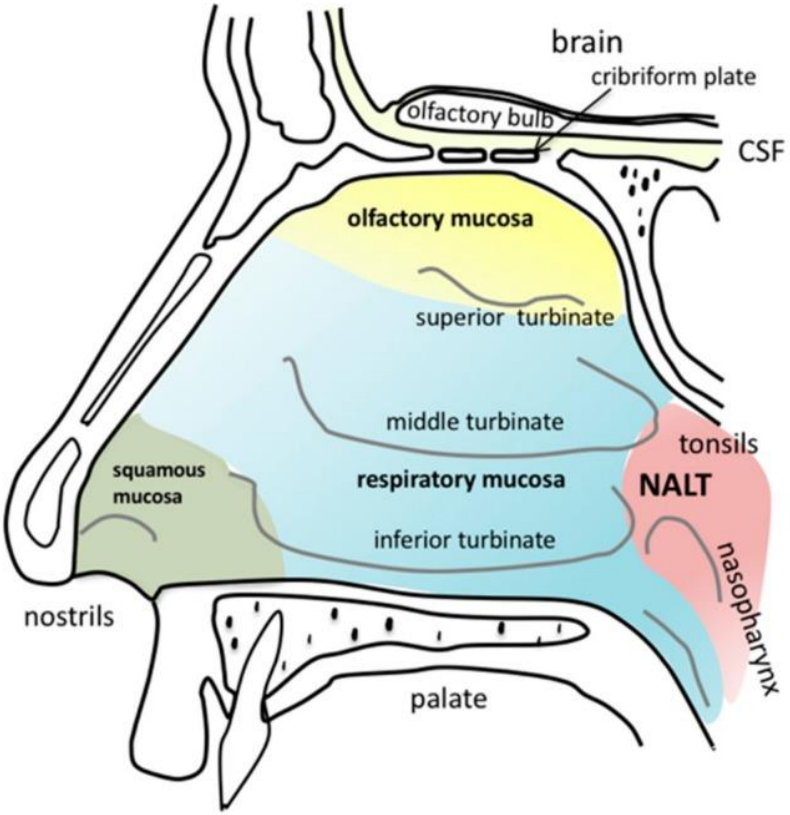


Figure 10. Anatomy of the human nasal cavity. The olfactory mucosa (yellow) is located next to the cribriform plate at the skull base down to the superior turbinate (Gänger and Schindowski, 2018).

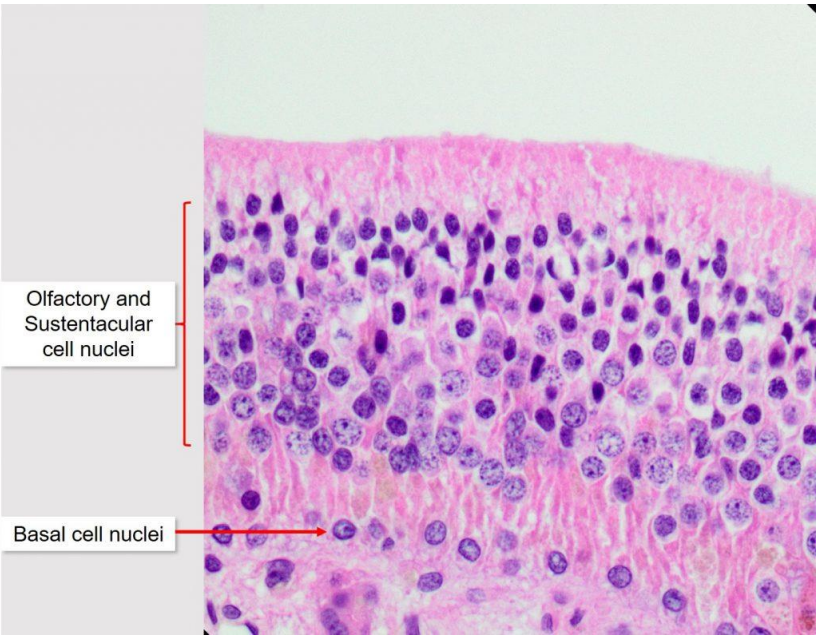


Figure 11. Olfactory receptor cells and sustentacular cells are difficult to distinguish readily on H&E. (https://ohiostate.pressbooks.pub/vethisto/chapter/10-respiratory-tract-air-conduction/, Access; 22.11.2020).

1.5.1. Olfactory mucosa

The mucosa covering the olfactory region is composed of the neuronal cells detecting odorants in the inhaled air. The neurons

are surrounded by either supportive cells in the epithelial layer and cells ensheathing the olfactory axons in the lamina propria on their way to the olfactory bulb. Basal stem cells ensure the recovery of olfactory mucosa after injury or tissue maintenance related cell death. Bowman's glands produce and secrete mucus. The various cell types and structures are sketched in Figure 12 and will be described in detail below.

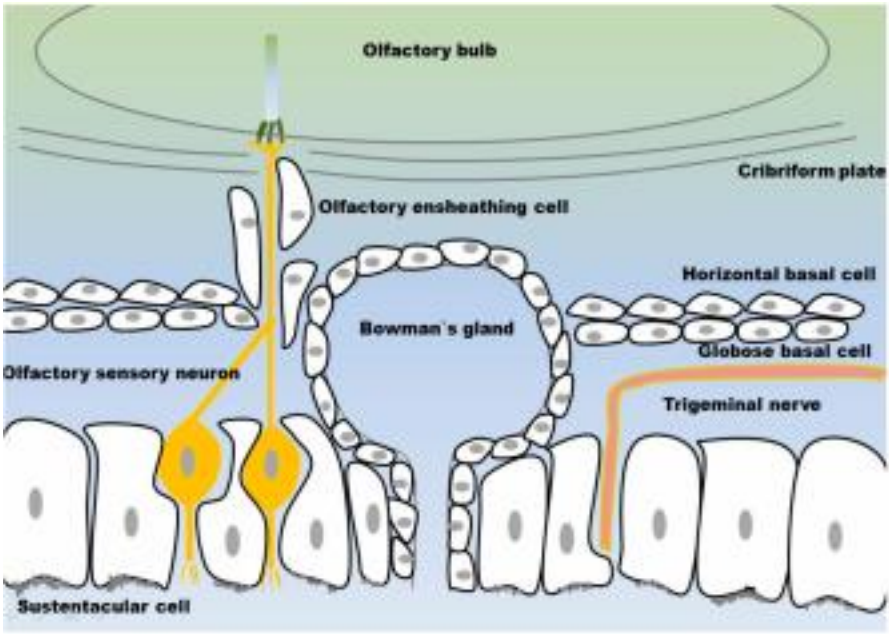
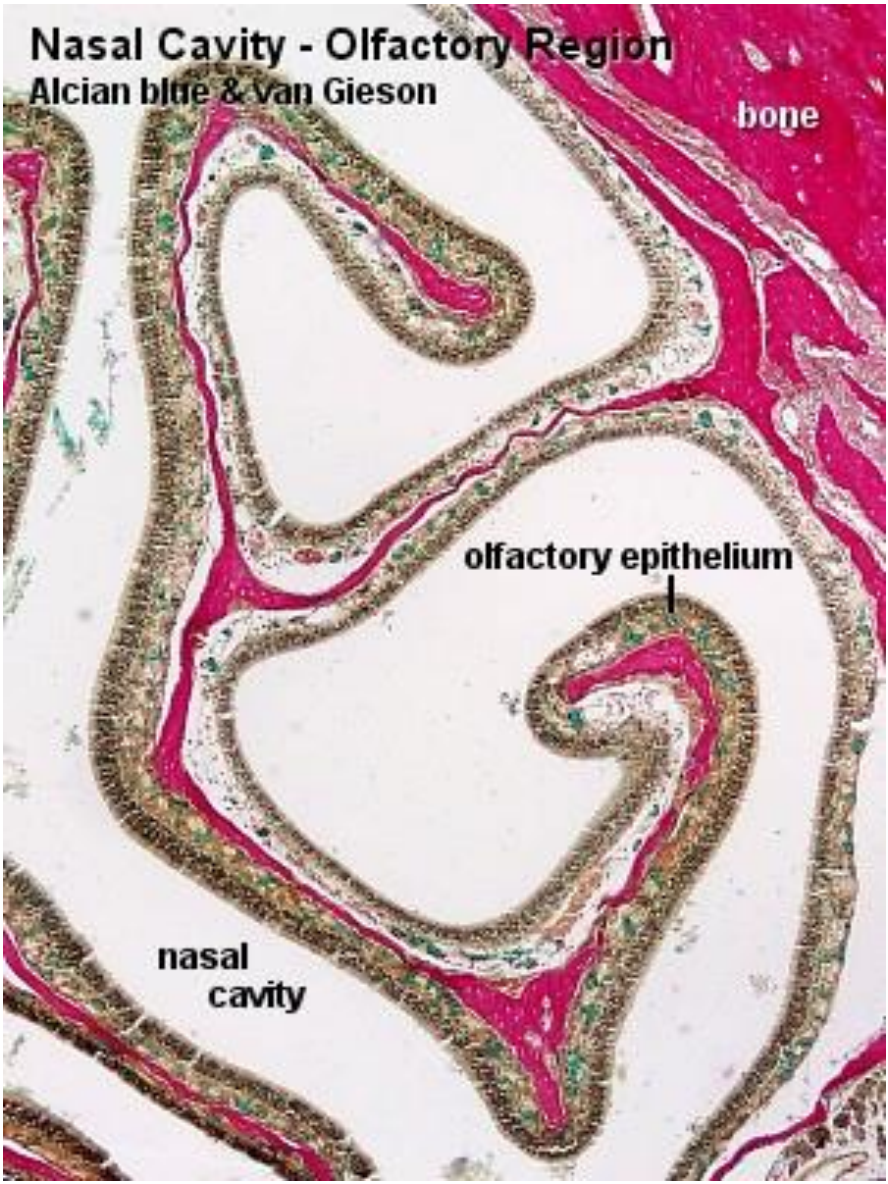


Figure 12. Structure of the olfactory mucosa (Gänger and Schindowski, 2018).


Nasal Cavity - Olfactory Region
Alcian blue & van Gieson
bone
olfactory epithelium
nasal
cavity

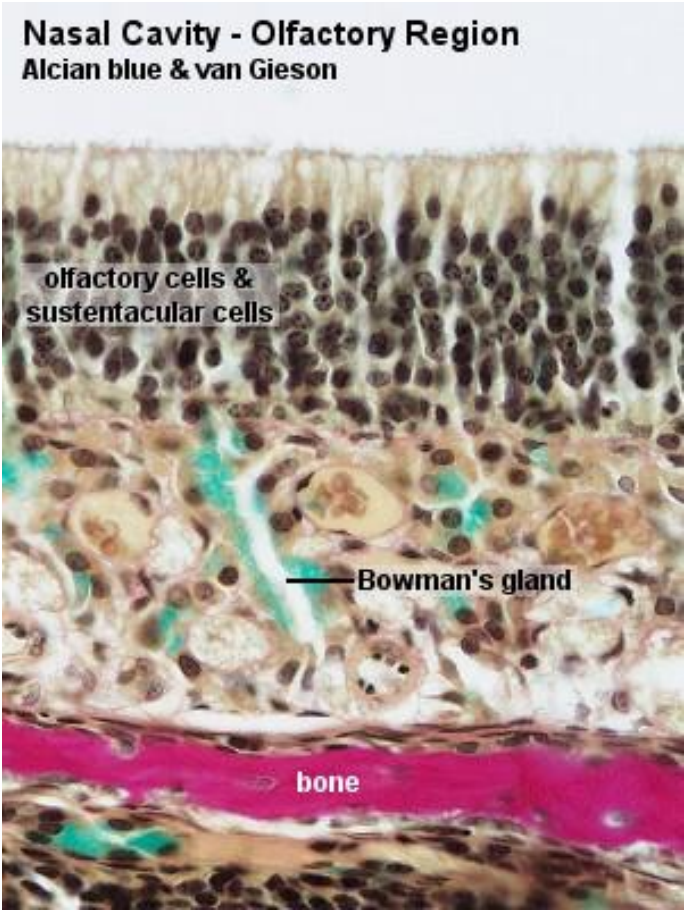


Figure 13. Nasal cavity, Olfactory region, rat-Alcian blue & van Gieson

(http://lecannabiculteur.free.fr/SITES/UNIV%20W.AUSTRALIA/mb140/CorePages/Respiratory/Respir.htm, Access: 19.12.2020)

1.5.2. Olfactory sensory neurons

The olfactory nerve is the so-called first cranial nerve. The olfactory system is unique as the olfactory nerve shows some atypical features. Olfactory sensory neurons (OSN) are non-myelinated neurons enwrapped by specialized ensheathing cells. Axons projecting from the olfactory nerve do not from a single bundle, as other nerves do. OSN form glomeruli, the so-called fila olfactoria, which project in bundles to the olfactory bulb (Crespo et al., 2018). For maintenance, the olfactory mucosa contains two different types of basal stem cells (Schwob, 2002; MacKay-Sim, 2010) differentiating to OSN. The dying OSN leave gaps in the epithelial layer until a new OSN regrows into the same space. During their replacement there is a delay in tight junction formation. Non-motile primary cilia cover the OSN are on their apical side and harbour the olfactory receptors. Binding of exogenous odour molecules is transduced into electrochemical stimulation, which travels along the olfactory axons to the brain (French et al., 2010; Challis et al., 2016). The mammalian olfactory system is able to detect thousands of odorants. The OSN express olfactory receptors, which recognize specific odours. Humans express up to 400 different olfactory

receptors, while there are even up to 1200 different receptors in rodents (Trimmer et al., 2014).

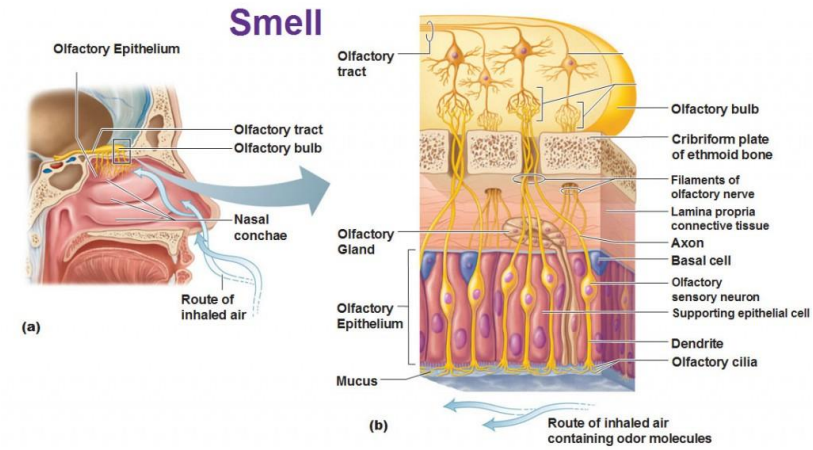


Figure 14. The olfactory epithelium. https://antranik.org/chemical-sense-smell-olfaction/ (Access; 13.12.2020)

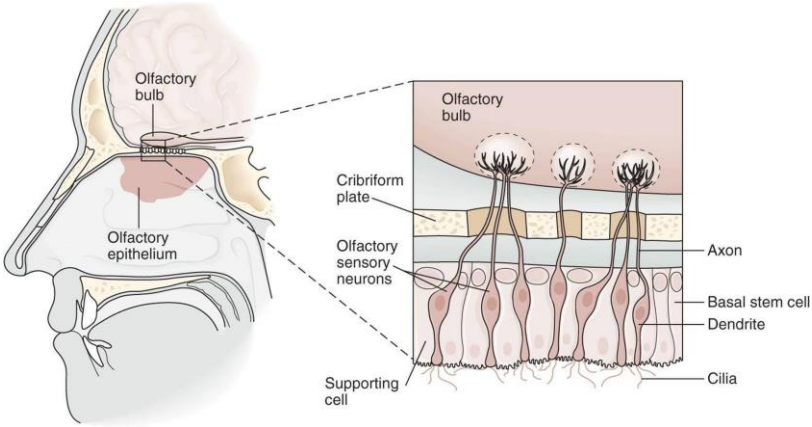


Figure 15. Structure of the olfactory epithelium. There are three cell types: olfactory sensory neurons, supporting (sustentacular) cells, and basal stem cells at the base of the epithelium. Each olfactory sensory neuron has a dendrite that projects to the epithelial surface. Numerous cilia protrude into the mucus layer lining the nasal lumen. Odorants bind to specific odorant receptors on the cilia and initiate a cascade of events leading to generation of action potentials in the sensory axon. Each olfactory sensory neuron has a single axon that projects to the olfactory bulb, a small ovoid structure that rests on the cribriform plate of the ethmoid bone (Figure 14, Figure 15) (Kandel et al., 2000).

Olfactory receptor cells are bipolar neurons and have apical extensions containing syllium. The apical region of each olfactory receptor cell has a single dendritic extension called the olfactory vesicle, a lump-like structure that extends over the epithelial surface. Long, thin ciliums (10-23 pieces) with typical basal bodies emerge from the olfactory vesicle and extend radially in the plane parallel to the epithelial surface. Ciliums can usually be up to 200 microns long and overlap with the ciliums of the neighboring olfactory receptor cell. Ciliums are considered immobile, but some research suggests they have limited mobility. An unmyelinated axonal extension emerges from the basal region of the cell and leaves the epithelial compartment. Axons from olfactory receptor cells do not become a single nerve. Instead, they are grouped into bundles and pass through the thin cribriform plate of the ethmoid bone. They cross the dura and arachnoid layers and eventually enter the olfactory bulb of the brain, surrounded by the pia mater. The ensemble of olfactory receptor cell axons forms the olfactory nerve (I. cranial nerve). Olfactory axons are very delicate and can be damaged by traumatic head injuries. They can be cut off permanently, resulting in anosmia (loss of sense of smell). Autoradiographic studies show that olfactory receptor cells have

a lifespan of approximately one month. If damaged, they are quickly renewed. In postnatal life, olfactory receptor cells (and some neurons of the enteric part of the autonomic nervous system) are known as the only neurons in the nervous system that can be easily regenerated. All of the olfactory transduction pathways take place in the ciliums of the olfactory receptor cells. All of the molecules involved in olfactory transduction are located in the long syllium emanating from the olfactory bulb. Chemical signals (odorants, fragrances) are detected and selectively bind to concentrated odorant-binding proteins (OBP) in olfactory mucus. OBPs are small (10-30 kilodaltons), water-soluble proteins and are synthesized and secreted by support cells. First, the incoming odor molecules dissolve in the olfactory mucus, and then the OBPs act as molecular carriers, carrying odorants and transmitting them to the olfactory receptors (OR) in the plasma membrane of the syllium. Support cells provide mechanical and metabolic support to olfactory receptor cells (Kandel et al., 2012).

1.5.3. Olfactory ensheating cells

Olfactory ensheathing cells (OEC) surround and isolate the olfactory axons from their origin in the epithelial membrane up

to the lamina propria, where these axons form glomeruli with axons from matching OSN. In the outer layer of the olfactory bulb, olfactory ensheathing cells enwrap axonal bundles from OSN, where they defasciculate and finally terminate into olfactory bulb glomeruli (Mackay-Sim and St John, 2011). The diverse expression patterns of OEC at different localizations imply the presence of different types of OEC: OEC resident in the lamina propria (LP-OEC), OEC present along the outer olfactory nerve fibre layer (NFL-OEC) and OEC located in the inner olfactory nerve layer on the olfactory bulb (OB-OEC). OEC located in the mucosa mainly interact with each other by adhesion. They guide several axons to form bundles, whereas the OEC of the olfactory bulb do have a broader spectrum of interaction. The OB-OEC may interact by adhesion or by repulsion or simply do not interact at all. OB-OEC also do not cause fasciculation of axon bundles (Au and Roskams, 2003; Barnett and Chang, 2004). OEC do not only maintain the electrophysiology of mature OSN, they also contribute to a great extent to regeneration. They provide the environment needed for neurite outgrowth and assist in the setup of new functional synapses. In contrast to that they take also part in the controlled death of OSN (Mackay-Sim and St John, 2011). Additionally, OEC

are currently discussed for their potential use in regeneration of spinal cord lesions. Although OEC do not normally myelinate OSN, they are able to remyelinate damaged axons to restore physiological function. Chuah et al. showed that if the olfactory mucosa is damaged, OEC are contributing to host defence by nitric oxide production, leading to an increase of inducible nitric oxide synthase (iNOS). Furthermore, chemokines like interleukin-6 (IL-6), monocyte chemoattractant protein 1 (MCP-1), chemokine C-X-C motif ligand 1 (CXCL1) and tumour necrosis factor-alpha (TNF-alpha) were elevated to initiate an immune response. This could not prevent pathogen invasion in total, but decreased its extent and prevented spreading to the deeper levels of the olfactory bulb. Also, OEC and supporting cells produced pituitary adenylate cyclase-activating peptide (PACAP), a protein protecting against TNF-alpha induced cell death by activating anti-apoptotic pathways (Harris et al., 2009). Based on this and other findings it is hypothesized that microglia of the olfactory bulb have a low activation threshold, lower than that of other brain regions (Herbert et al., 2012) (Figure 16).

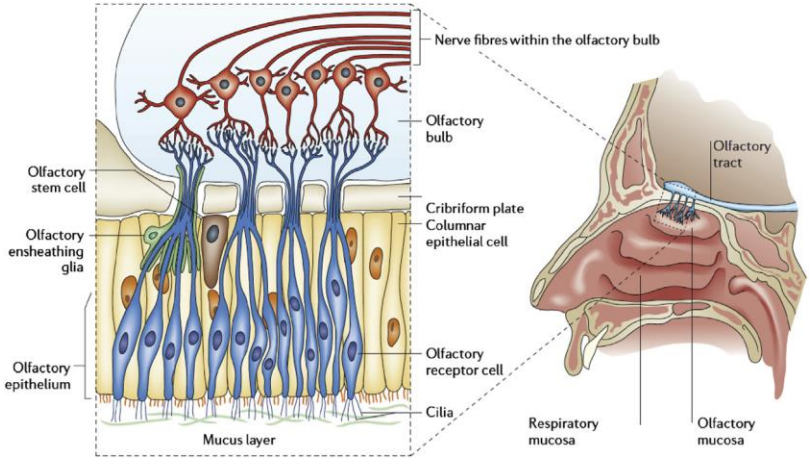


Figure 16. Schematic of the olfactory system showing the location of the olfactory bulb within the human head (right) and a detailed illustration of olfactory receptor neurons extending from the olfactory mucosa to the olfactory bulb (left) (Thuret et al., 2006).

1.5.4. Sustentacular cells

Support cells are the most abundant cells in the olfactory epithelium (Figure 17). The nuclei of these elongated, prismatic or sustentacular cells are located in a more apical position compared to other cells in the epithelium. This helps these cells to be recognized under the light microscope. They have

numerous microvilli on their apical surface and are rich in mitochondria. In the cytoplasm, many sections of the endoplasmic reticulum (aER) without granules and a smaller amount of granular endoplasmic reticulum (GER) are observed. They also have lipofuscin granules. There are adherence type connections between these cells and olfactory receptor cells, but there are no corrugated and tight connections. Support cells function similar to neuroglial cells, providing both metabolic (secretion of OBP molecules) and physical support to olfactory receptor cells (Liang 2018).

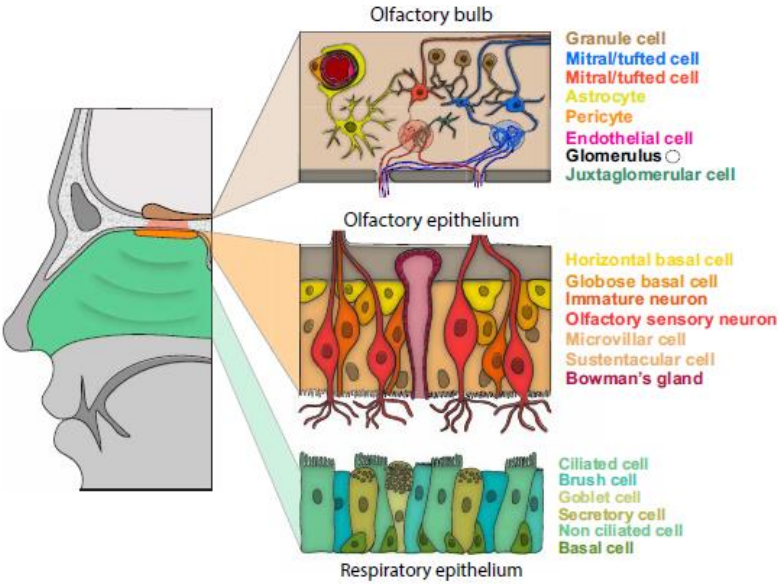


Figure 17. Schematic of the nasal oespiratory ephitelium, Olfactory ephitelium, olfactory bulb (Brann et al., 2020).

Enwrapping occurs with OSN maturation: while most of the immature OSN dendrites are unwrapped, the majority of mature OSN dendrites are enwrapped with SUS. Juxtanodin, an actin cytoskeleton-related protein, is present in SUS that plays also an important role in forming the myelin sheaths of oligodendroglia in the CNS. It is thought that juxtanodin regulates the interaction of SUS cells with OSN in the same way as it is described for

oligodendroglia. Cell membranes of SUS enwrapping adjacent OSN contain gap junctions (Le Bourhis et al., 2014; Zhang et al., 2005). SUS do not only enwrap mature OSN dendrites, they also provide an environment for regeneration. Immature OSN migrate alongside SUS during maturation. Endothelin signaling provides a way of SUS and OEC damage control. Endothelin also acts as survival factor, it uncouples gap junctions between SUS enwrapping adjacent OSN to limit cell death.

1.5.5. Brush- like cells

Brush-like cells are prismatic cells and are specialized for the transmission of the general sensation. The olfactory epithelium also contains fewer brush-like cells. As mentioned, these cells are also found in the epithelium of other parts of the respiratory tract conducting airways. With electron microscopy (EM), brushy cells exhibit large, blunt microvilli on their apical surface, a feature that gives the cell its name. The basal surface of the brush-like cell makes synaptic connections with nerve fibers that penetrate the basal lamina. Nerve fibers are the terminal branches of the trigeminal nerve (V. cranial nerve) that are involved in the reception of general senses. Brushy cells appear to be involved in the transduction of general sensory

stimulation of the mucosa. In addition, the presence of microvilli border, vesicles close to the apical cell membrane and the presence of a prominent Golgi apparatus suggest that brush-like cells may be responsible for absorption as well as secretory function (Ualiyeva et al., 2019; Bankova et al., 2018) (Figure 18).

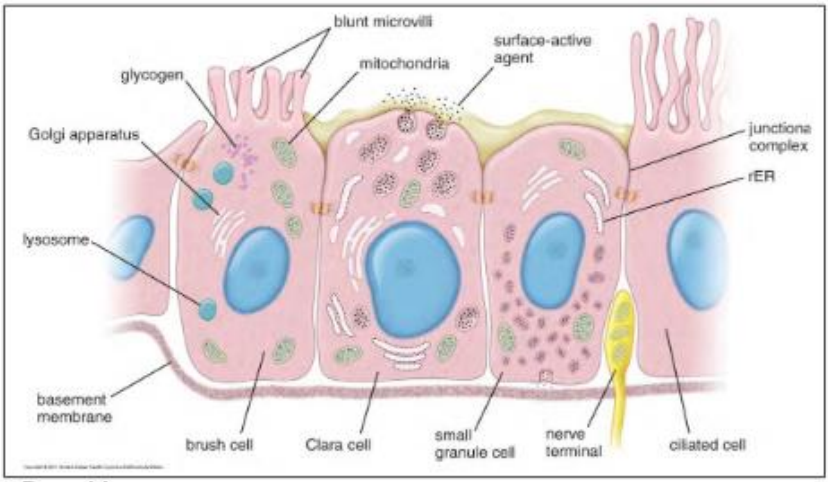


Figure 18. Brush- like cells. (https://www.memorangapp.com/flashcards/79169/Histology+of+Respiratory+System/ Access; 13.12.2020).

1.5.6. Globose basal cells

Globose basal cells (GOB) are active cycling stem cells frequently differentiating into neuronal as well as non-neuronal cells for the regeneration of the olfactory mucosa (Figure 15). GOB maintain renewal of the mucosa in normal tissue homeostasis and also in response to injury. Proliferation of GOB cells is stimulated by dying neurons releasing leukemia inhibitory factor (LIF), or nitric oxide release during inflammation or cell death. Fibroblast growth factor-2 (FGF-2) also stimulates GOB cell proliferation. Proliferation of stem cells is regulated through local cell density via a negative feedback (Joiner et al., 2015; Iwai et al., 2008).

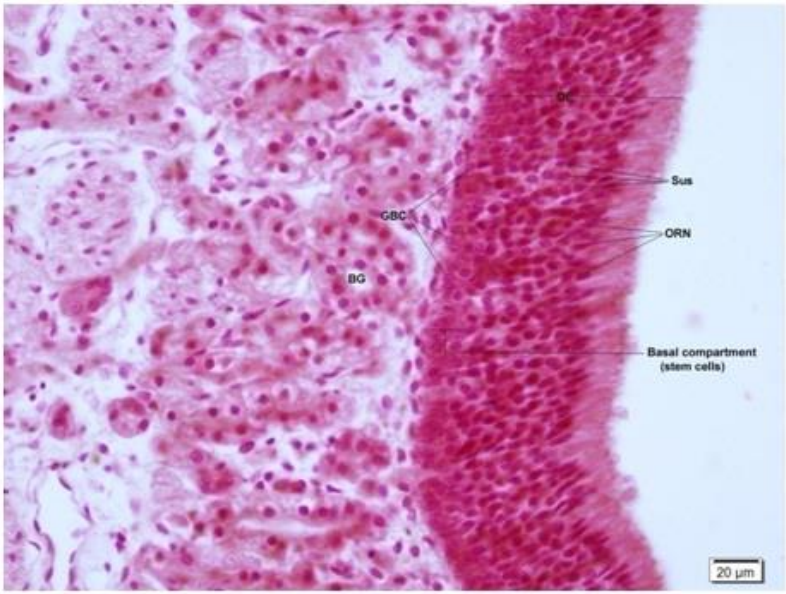


Figure 19. H&E staining of human olfactory mucosa. OE-olfactory epithelium, GBC-globose basal cell, Sus-sustetacular cell, ORN-olfactory receptor neuron, BG-bowman's gland. Basal compartment is seen to contain only globose shaped cells(GBC) and no horizontal basal cells as seen in rat olfactory epithelium (Thakur et al., 2013).

1.5.7. Horizontal basal cells

Horizontal basal cells (HBC) are mainly quiescent basal stem cells (Figure 20). They only take part in olfactory mucosa maintenance in case of extensive tissue injury. It is supposed that GOB differentiation is sufficient for mucosa preservation and HBC are only needed in case of lager injuries. HBC and GOB are both able to replace neuronal as well as non-neuronal cells. Behringer et al. suggest a more prominent role for HBC in maintenance: HBC show waves of activity soon after birth as well as after tissue injury. The authors also assume that HBC give rise to new GOB and if needed take also part in cell replacement by differentiating into OSN, Bowman's glands or SUS. In contrast to GOB, HBC have primary cilia, which may play a role in communication with SUS. Proliferation of HBC is stimulated by epidermal growth factor (EGF) and transforming growth factor alpha (TGF-alpha) (Joiner et al., 2015; Iwai et al., 2008).

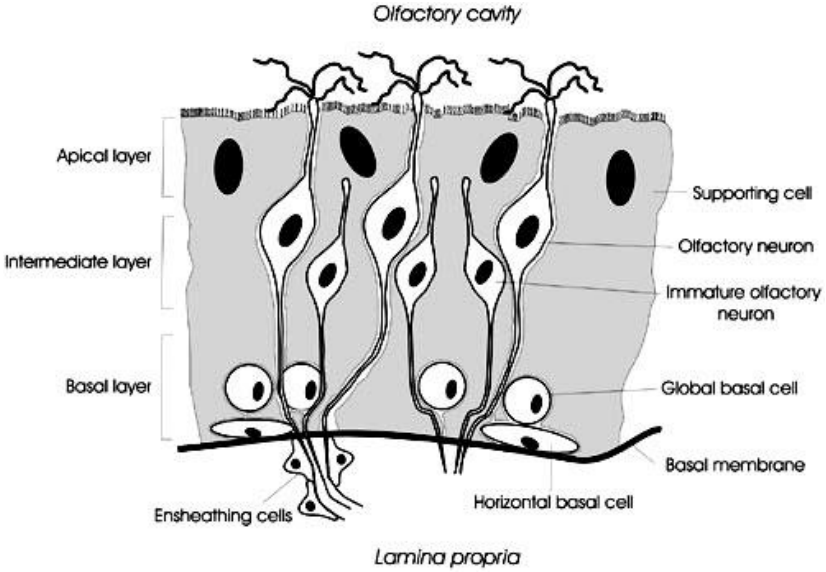


Figure 20. Olfactory epithelium displaying its different cell types in their characteristic spatial distribution in the tissue (Sulz and Bacigalupo, 2006).

Basal cells are progenitors of other mature cell types. Basal cells are small, round cells and are located close to the basal lamina. Their nuclei are often recessed and located below the level of olfactory receptor cell nuclei. There are few organelles in their cytoplasm. This feature is compatible with their reserve or stem cell roles. The observation that the protrusions in some basal cells form a sheath around the first part of the olfactory receptor

cell axons is a feature compatible with the differentiation of basal cells into support cells. Thus, they maintain their relationships with olfactory receptor cells even in their undifferentiated state (Figure 20).

1.5.8. Bowman's glands

Bowman's glands are located in the lamina propria of the olfactory mucosa. They have a simple tubular structure with no branches. Vesicles are located at the apical pole, close to the lumen. The nucleus is located at the basal pole where a few microvilli are present (Figure 17). Two different kinds of secretory vesicles were observed in Bowman's glands. One type appears to contain mucus glycoprotein as MUC5AC and the other vesicles are packed with proteinaceous and serous content (Solbu and Holen 2012). Aquaporins (AQP) AQP1, AQP3, AQP4 and AQP5 pump water needed for the olfactory mucus. The ducts of Bowman's glands transmigrate the OE. In other areas of the nasal cavity, secretory glands do not penetrate the epithelium to the surface, they secrete via duct systems to the nasal Pharmaceutics 2018, 10, 116 7 of 28 vestibule (Solbu and Holen 2012; Lu et al., 2008; Ablimit et al., 2006). Bowman's glands are surrounded by multiple bundles of OSN axons. Furthermore

OEC, fibroblasts and large bundles of collagen fibres are observed in the entourage of Bowman's glands. The exact composition of the olfactory mucus secreted from Bowman's glands is still unknown. Histological approaches showed, that these glands are positive for periodic acid-Shiff (PAS) staining which indicates neutral glycoproteins. In another study sulphated glycoproteins were found. Acidic glycoproteins were identified with Alcian blue staining. Septal nasal glands and submucosal glands in the lower respiratory tract express a chloride channel at the apical site of secretory cells (cystic fibrosis transmembrane conductance regulator protein, CFTR), which regulates secretion. This regulatory protein is not present on Bowman's glands and, thus, the secretion mechanisms are yet unknown (Kondo et al., 2009). Short canals made up of cubic cells exit the glands, pass the basal lamina, reach the olfactory epithelium, reach the surface of the epithelium and drain their contents. The serous secretion of the olfactory glands serves as a trap and solvent for odorous substances. The continuous flow of secretion from the glands clears the mucosa from the residues of perceived odorous substances, so that new odors can be detected continuously. Nerves are particularly notable because

of the large diameters of the individual unmyelinated fibers they contain (Figure 21).

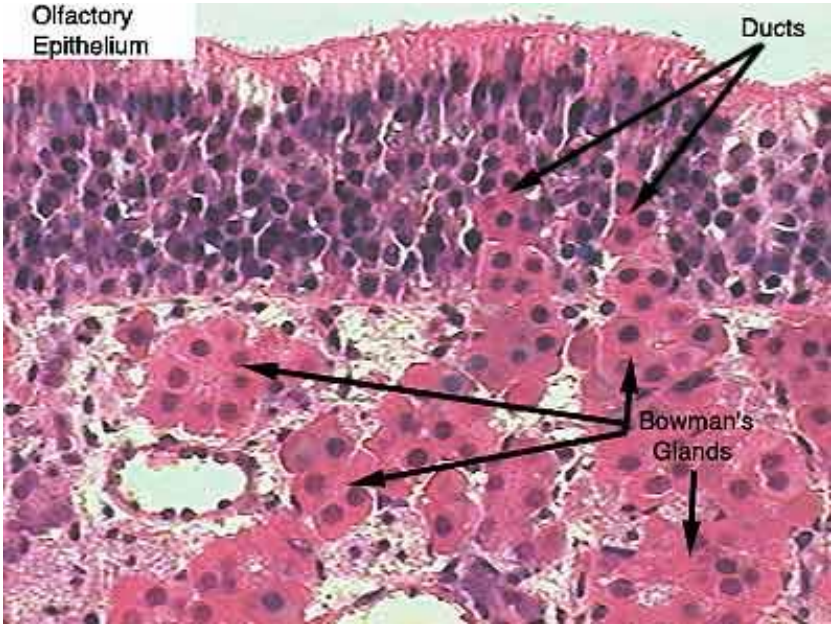


Figure 21. The fluid coating the olfactory epithelium is secreted by Bowman's glands, which are not found elsewhere in the nasal epithelium, so the presence of these glands is a criterion for identification (http://faculty.une.edu/com/abell/histo/histolab3c.htm, Access; 13.12. 2020).

1.6. Paranasal sinuses

Paranasal sinuses are air-filled cavities within the bones of the walls of the nasal cavity. The extensions of the nasal cavity recessive region, the paranasal sinuses, are lined with respiratory epithelium. Sinuses are named according to the bones they are in (ethmoid, frontal, sphenoid and maxillary bones). The sinuses are connected to the nasal cavity through narrow openings opened on the respiratory mucosa. The mucosal surface of the sinuses is a thin, pseudo-stratified silylated prismatic epithelium with many Goblet cells. The mucus produced in the sinuses is swept into the nasal cavity with the help of coordinated ciliary movements. Sinuses are often subjected to acute infection after viral infection of the upper respiratory tract. Severe infections may require physical drainage (Dalgorf and Harvey, 2013) (Figure 22).

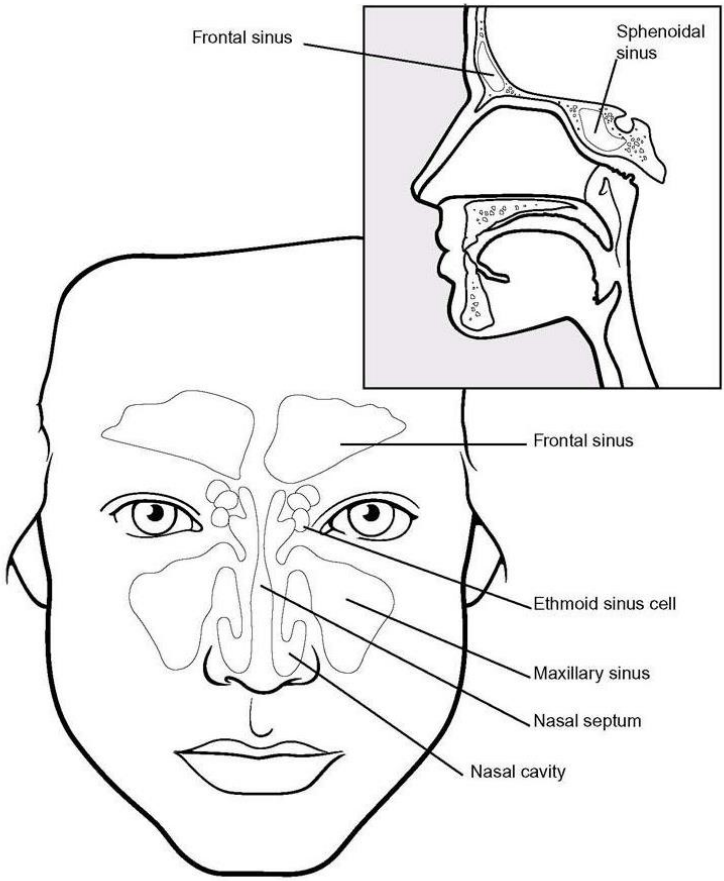


Figure 22. Paranasal sinuses (http://cnx.org/content/col11496/1.6/, Access; 13.12.2020).

1.7. Pharynx

It is an area where the oral cavity of the digestive system and the nasal cavity of the respiratory system intersect. For this reason, the pharynx has an oropharynx belonging to the digestive system and a nasopharynx part of the respiratory system. It also connects the pharynx, nasal and oral cavities to the larynx and esophagus. It is a gateway for food and air and acts as a resonance chamber for speech. The pharynx is located in the posterior of the nasal and oral cavities and is divided into two regions, the nasopharynx and the oropharynx, respectively. Tuba auditiva (Eustachian) connect the nasopharynx to each middle ear. Diffuse lymphoid tissue and lymph nodes are located in the wall of the nasopharynx. The group of lymph nodes located at the junction between the superior and posterior walls of the pharynx is called the pharyngeal tonsil (Schuknecht and Smoker, 2008) (Figure 23).

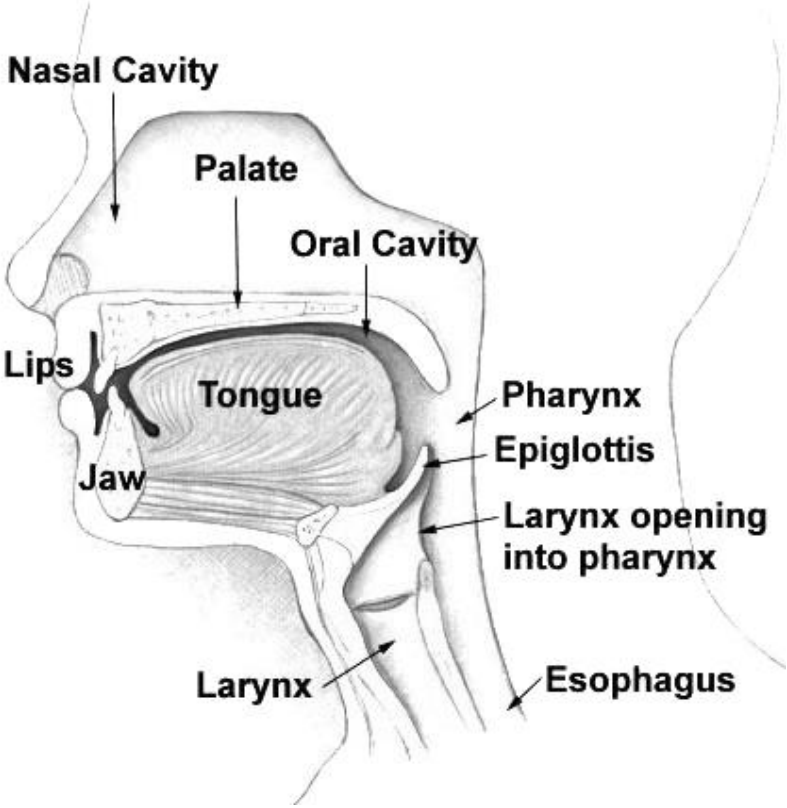


Figure 23. Upper respiratory system (pharynx) (Blaus, 2014).

The wall structure of the oropharynx and nasopharynx parts is the same except for the lamina epithelialis. The oropharynx is covered by the cutaneous mucosa, which is the continuation of the oral cavity. Accordingly, the lamina epithelial consists of stratified squamous epithelium. Since the nasopharynx is

covered by the respiratory mucosa, which is the continuation of the nasal cavity, the lamina epithelialis has a pseudo-multilayered prismatic epithelium. The apical parts of the cells that extend down to the lumen have quinosyllium. There are goblet cells among them. Other layers of the tunica mucosa, other than the lamina epithelialis, are common to both regions. Lamina propria is non-glandular, instead of lamina muscularis, there is an inner pharynx fascia and submucosa layer rich in elastic threads and connective tissue. Tunica muscularis and tunica adventisia, the main layers outside the tunica mucosa, are common to both regions. Tunica muscularis consists of skeletal muscle cells and a connective tissue rich of elastic fibers surrounds the outer pharynx fascia. Tunica adventitia has a loose connective tissue structure and surrounds the pharynx externally (Maynard and Downes 2019).

1.8. Larynx

The larynx is the passageway between the oropharynx and trachea. This complex tubular region of the respiratory system consists of irregularly shaped hyaline and elastic cartilage (vocal extensions of arytenoid cartilages and epiglottis) plates. It is the part of the respiratory system that comes after the nasopharynx

and is at the beginning of the air tube (Zhang et al., 2019). In the larynx, there are cartilages outside the tunica mucosa surrounding the cavity. Cartilages are connected to each other by ligaments. Apart from this, the skeletal muscle type includes laryngeal muscles. With this structure, the larynx is loosely connected to the surrounding tissue. With the contraction of the larynx muscles, foreign material passes into the trachea are prevented. These muscles also provide the cough reflex. In addition to serving as a transmission channel for air, it also serves as the organ that produces sounds. Vocal folds control the airflow towards the larynx and vibrate to produce sound. Vocal folds, also called vocal cords, are two mucous folds that extend to the laryngeal lumen. They are oriented in the anteroposterior direction and define the lateral limits of the laryngeal opening known as the rima glottis. Inside each vocal fold is a supporting ligament and a skeletal muscle-like vocalis muscle. Ligaments and intrinsic laryngeal muscles join adjacent cartilage plates and are responsible for creating tension in the vocal cords for opening and closing the glottis. Extrinsic laryngeal muscles attach to the cartilages of the larynx, but they arise from extra-laryngeal structures. These muscles move the larynx during swallowing. The air exhaled from the lungs passes through the

narrow space of the rima glottis, causing the vocal folds to vibrate. The vibrations are changed by regulating the tension on the vocal folds and adjusting the glottal aperture. Changing the vibrations creates sounds in different pitches. During the phonation process, the sounds generated in the larynx are rnodified in the upper parts of the respiratory system (nasopharynx, nasal cavities and paranasal sinuses) and oral cavity (oropharynx, soft and hard palate, tongue, teeth, lips, etc.) and thus individual speech sounds (different vowels and consonants) occurs. Ventricular folds located on the vocal folds are called "pseudo-vocal cords" (Ross and Pavvlina 2014).

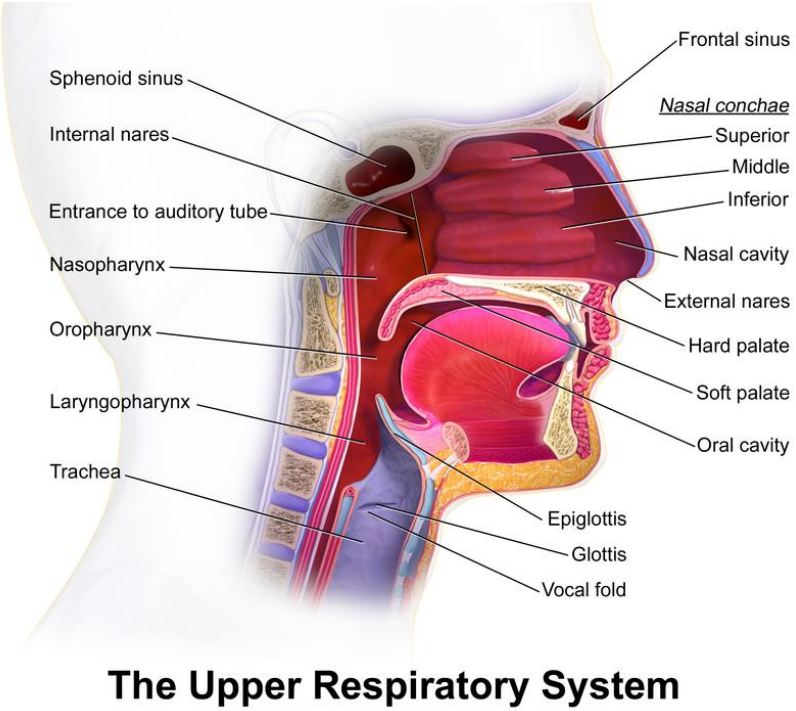


Figure 24. Upper respiratory system (larynx) (Blaus, 2014).

In the larynx, there is a long recess called the ventricle above the vocal folds. Just above the ventricle is another pair of mucosal folds called the ventricular fold or pseudo-vocal cord. These folds do not alter the phonation, as they do not have the intrinsic muscles of the true vocal cords. However, the ventricular folds and ventricle together are important in establishing voice

resonance. Inflammation and swelling of the larynx due to viruses (such as the common cold virus) and other microbial agents is called acute laryngitis. Symptoms of acute laryngitis may include hoarseness or, in more severe cases, complete loss of voice, cough, difficulty swallowing and breathing difficulties. Chronic laryngitis usually develops after prolonged exposure to irritating agents such as cigarette smoke, dust or air pollution. Larynx lining multilayer flat and pseudo multilayered prismatic epithelium with silyli. The luminal surface of the vocal cords, like most of the epiglottis, is lined with stratified squamous epithelium. The epithelium protects the mucosa against abrasion caused by rapid air flow. The remainder of the larynx is lined with pseudo-stratified silylated prismatic epithelium characteristic of the airways. The connective tissue of the larynx contains mixed mucosarous glands, and the secretions of the glands are carried to the laryngeal surface via the ducts (Bergman et al., 1996; Dworkin and Paul 2007).

1.9. Trachea

It is a tubular organ that starts from the larynx and continues to the lungs. The most distinctive feature of this organ is that it is supported by incomplete cartilage rings. In this way, the air tube

is kept open continuously and it is not affected by the pressure of the food passing through the esophagus. Also, the Trachea is a short, flexible air tube, about 2,5 cm in diameter and 10 cm in length. It serves as a gateway for air and also, its wall helps in conditioning the breathing air (Figure 25). The trachea extends from the larynx approximately to the middle of the thorax, where it divides into two main (primary) bronchi. The lumen of the trachea remains open due to the arrangement of a series of cartilage rings (Aspinall et al., 2009).

The wall of the trachea consists of four distinct layers:

- The mucosa consists of pseudo-multilayered silylated prismatic epithelium and a lamina propria rich in elastic fibers. The submucosa consists of a slightly denser connective tissue than the lamina propria

- The cartilaginous layer (cartilaginous layer) consists of C-shaped hyaline cartilages.

- Adventitia consists of connective tissue that connects the trachea to neighboring structures

A characteristic feature of the trachea is the presence of a series of C-shaped hyaline cartilages that are overlapped to form a supporting structure. These cartilages, which can also be defined as skeletal roofs, prevent the lumen of the trachea from collapsing, especially during expiration. At the posterior border of the trachea adjacent to the esophagus, fibroelastic tissue and smooth muscle (trachealis muscle) form a bridge between the free ends of the C-shaped cartilages (Figure 26) (Ibe et al., 2011).

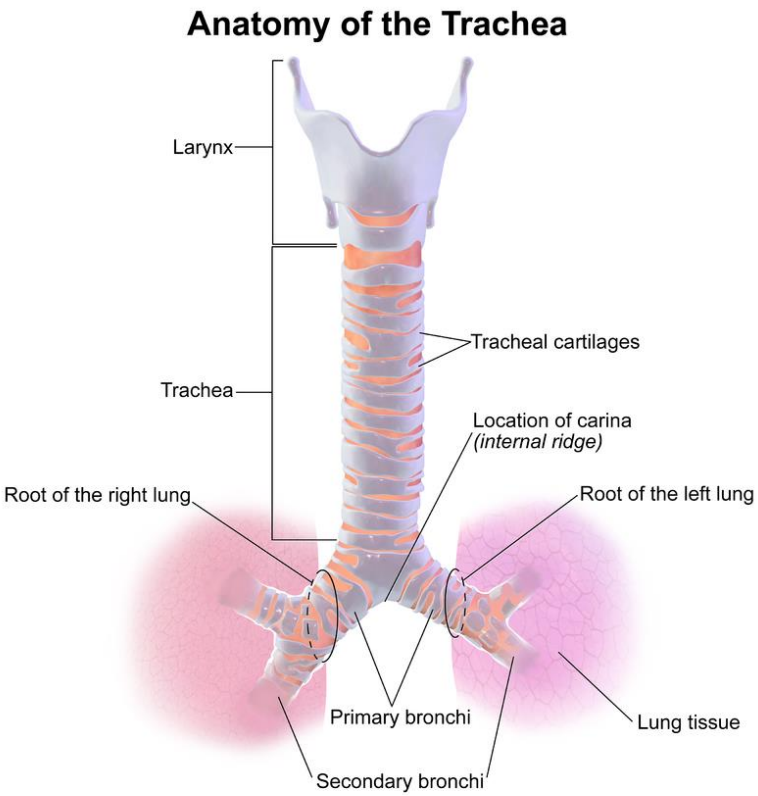


Figure 25. Anatomy of the trachea (Blaus, 2014).

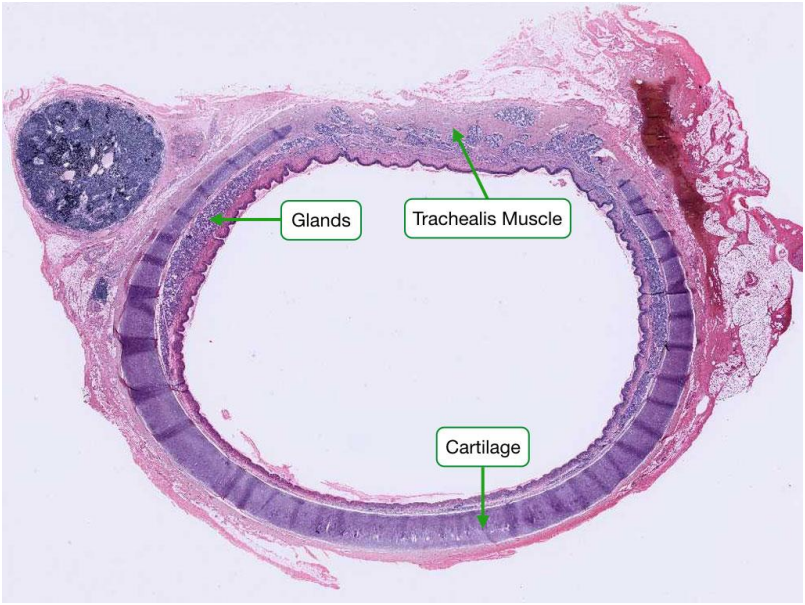


Figure 26. Cross-section of trachea (http://histology.med.yale.edu/respiratory_system/respiratory_system_reading.php, Access; 14.12.2020)

1.9.1. Tracheal epithelium

The tracheal epithelium resembles the respiratory epithelium in other parts of the conducting airways. Silylium prismatic cells, mucous (Goblet) cells and basal cells are the main cell types in the tracheal epithelium. There are also brush-like cells, but they are few, like cells with small granules. Cells with cilium are the

most numerous of the tracheal cell types, they extend the entire thickness of the epithelium. On histological sections, the ciliums appear as short, hair-like extensions extending from the apical surface. Each cell has about 250 syllium. Just below the cilium is a dark line formed by the collection of ciliary basal bodies. The ciliums provide the coordinated sweeping movement of the mucous cover from the furthest parts of the airways to the pharynx. In fact, silylium cells function as 'mucocyte escalator', which serves as an important protection mechanism in clearing inhaled small particles from the lungs (Ibe et al., 2011; Susan, 2016).

- Mucous cells resemble intestinal Goblet cells in appearance and are therefore often referred to by the same name. They are scattered among the cells with silyli, and these cells extend the entire thickness of the epithelium. They are easily seen under a light microscope after they deposit mucinogenic granules in their cytoplasm. Although mucinogen is typically lost in hematoxylin and eosin (H&E) preparations, the cell can be identified by the remaining empty space in the syncytosis and the absence of siliums on the apical surface. Unlike cells with

silyli, the number of mucous cells increases as a result of chronic irritation of the airways (Della Maggiore, 2020).

- Brush-like cells have the same general features as those in the respiratory epithelium of the nasal cavity. They are prismatic cells and have blunt microvilli. The basal surface of the cells makes synaptic connections with afferent nerve endings (epitheliondendritic synapse). Thus, brush-like cells are considered as receptor cells (Pavelka and Roth, 2010).

- Small granular cells are representatives in the respiratory system of the general class of enteroendocrine cells of intestinal (gout) and intestinal derivatives. The presence of these cells is explained by the development of the airways and lungs from an evagination of the primitive foregut. Small granular cells are usually found individually in the trachea and are scattered among other cell types. They are difficult to distinguish from basal cells under light microscopy without the use of special techniques such as silvering interacting with the grandis. The nucleus is located next to the basement membrane. It has more cytoplasm than basal cells that are smaller than itself. Thin, conical cytoplasmic protrusions are observed extending towards the lumen with transmission electron microscopy (TEM). With

TEM, the cytoplasm displays granules with dense centers, confined to multiple membranes. In one type of small granular cells the secretory substance is catecholamine. The second cell type produces polypeptide hormones such as serotonin, calcitonin, and gastrin-releasing peptide (bombesin). Some small granular cells appear to innervate. The function of these cells is not fully understood. Some small granular cell groups that are in contact with nerve fibers form neuroepithelial bodies, and these bodies are thought to play a role in reflexes that regulate the diameter of the airway or vessel.

- Basal cells serve as reserve cell populations that ensure continuity in the replacement of individual cells in the epithelium. The nuclei of the basal cells form a line close to the basal lamina and are therefore prominent. Other cell nuclei within the epithelium appear relatively sparse, although they are usually located at the same level. Thus, most of the nuclei next to the basement membrane belong to basal cells *(*Antunes, and Cohen, 2007; Habib and Mahammed, 2011) (Figure 27, Figure 28).

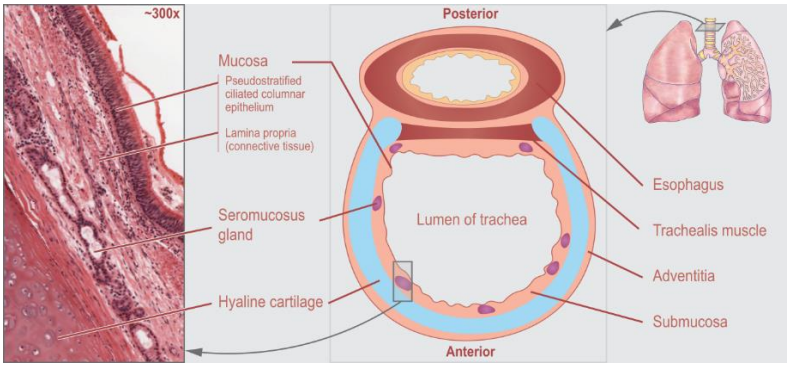


Figure 27. Cross section of a trachea (https://en.wikipedia.org/wiki/Trachea#/media/File:Cross_section_of_a_trachea_and_esophagus.svg, Access; 13.12.2020).

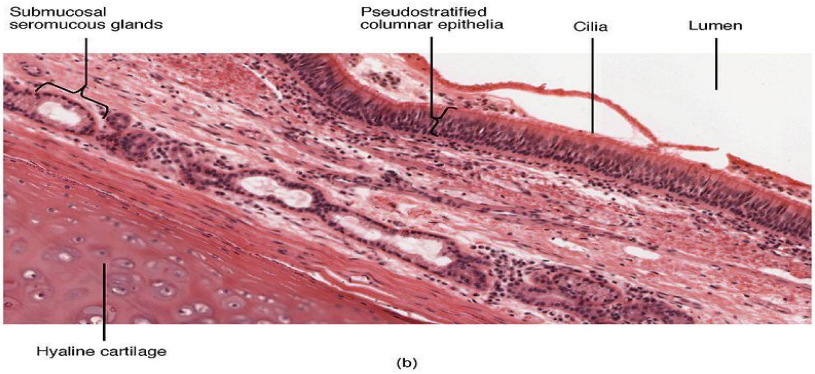


Figure 28. Cross-section of the trachea, with pseudostratified ciliated columnar epithelium and goblet cells labelled (https://cnx.org/contents/FPtK1zmh@8.25:fEI3C8Ot@10/Preface, Access; 13.12.2020)

1.9.2. Basal membrane and *Lamina propria*

The characteristic feature of tracheal epithelium is a thick basement membrane. The prominent layer under the tracheal epithelium is defined as the basement membrane (9). It generally appears as a glassy or homogeneously light-colored layer of approximately 25-40 microns thick. Electron microscopy reveals that it is composed of densely packed collagen fibers that lie just below the epithelial basal lamina. Structurally, it can be thought of as an unusually thick and dense reticular lamina that is part of the lamina propria. This layer is quite thick in smokers and especially those with chronic cough in response to mucosal irritation. The lamina propria has the typical appearance of loose connective tissue, except for the part defined as the basement membrane. It is very cellular and contains a large number of lymphocytes that infiltrate most epithelium. Plasma cells, mast cells, eosinophils and fibroblasts are other cell types easily observed in this layer. In the lamina propria and submucosa layers of the tracheal wall, lymphoid tissue in both diffuse and nodular form is constantly present. Lymphoid tissue is also found in other parts of the respiratory system that are responsible for air conduction. This lymphoid tissue is the developmental

and functional equivalent of bronchial-associated lymphoid tissue (BALT). The border between mucosa and submucosa is defined by an elastic membrane. There are many elastic fibers among the collagen fibers. Elastic material is more where the lamina propria ends and elastic material is observed as a distinct band in samples dyed for these fibers. This band or elastic membrane marks the border between the lamina propria and the submucosa. However, the border cannot be clearly observed in H&E preparations. The submucosa differs from the submucosa of most other organs, which are typically tight connective tissue. It consists of relatively loose connective tissue in the submucosa in the trachea. Where does his lamina propria-like appearance start from. makes it difficult to detect. Diffuse lymphoid tissue and lymph nodes extend from the lamina propria to the submucosa. In the submucosa there are wider distribution vessels and lymphatics of the tracheal wall. There are also submucosal glands with a serous pleura in the submucosa and acini secreting mucus. Their channels consist of single-layered cubic epithelium and run along the lamina propria to discharge their products, mostly glycoproteins, onto the epithelial surface. The glands are especially abundant in the non-cartilaginous area in the posterior part of the trachea. Some penetrate the muscle

layer in this area and therefore also lie within the adventitia. The submucosa layer ends where the connective tissue fibers mix with the perichondrium of the cartilage layer (Carvalho and Gonçalves, 2011) (Figure 29).

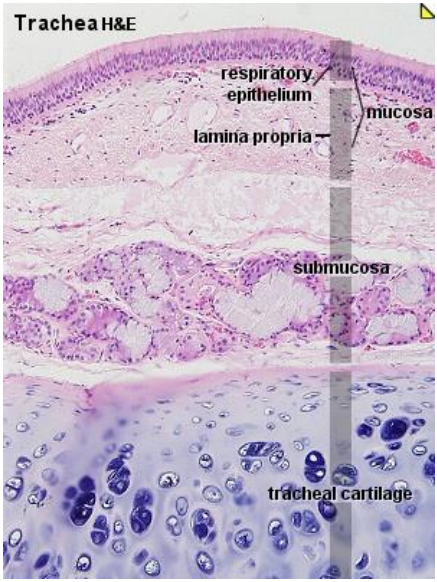


Figure 29. Trachea, human - H&E. In the trachea you should be able to identify the following structures: respiratory epithelium, basement membrane, submucosal glands (both serous and mucous parts), perichondrium, tracheal cartilage and trachealis muscle (smooth muscle) (https://www.lab.anhb.uwa.edu.au/mb140/CorePages/Respiratory/respir.htm, Access; 14.12.2020).

Tracheal cartilages and trachealis muscle separate the submucosa from the adventitia. Tracheal cartilages, which are about 16-20 in human, formed the next layer of the tracheal wall and, as stated, cartilages are C-shaped. Sometimes they anastomose with adjacent cartilages. Their arrangement gives flexibility to the tracheal tube and keeps the lumen open. With aging, hyaline cartilage can be partially replaced by bone tissue, and this causes a great loss of flexibility. The outer layer, the adventitia, is located at the periphery of the cartilage rings and trachealis muscle. It connects the trachea to adjacent tissues in the neck and mediastinum and contains the largest blood vessels and nerves of the wall, as well as the large lymphatics that drain the tracheal wall (Fedde, 1998; Schwarzkopf et al., 2010).

1.10. Bronches

The trachea divides into two branches and forms the main (primary) bronchi. Anatomically, primary bronchi are defined as right and left main bronchi, which are more appropriate terms due to physical differences between the two bronchi. The right bronchus is wider and significantly shorter than the left one. At the point where they enter the lung hilum, each main bronchus is divided into lobar bronchi (secondary bronchi). The left lung

is divided into two lobes and the right lung into three lobes. Thus, the right bronchus divides into three lobar bronchial branches, the left bronchus into two lobar bronchial branches, each branch supporting one lobe. The left lung is then divided into 8 bronchopulmonary segments and the right lung into 10 segments. Thus, the lobar bronchi in the right lung give 10 segmental bronchi (tertiary bronchi), while the lobar bronchi of the left lung give 8 segmental bronchi. They can be recognized by the bronchi, cartilage plaques and circular smooth muscle layer. The second change observed in the wall of the intrapulmonary bronchus is the addition of smooth muscle forming a complete circular layer. As the amount of cartilage decreases, smooth muscle gradually becomes a prominent layer. Initially smooth muscle is arranged in bundles that intertwine and form a continuous layer. In smaller bronchi, it can be seen that smooth muscle is not continuous (Netter, 2014). Smooth muscle. The bronchial wall can be considered to have five strands, as it forms a separate layer called the muscularis (Figure 30).

- It consists of pseudo-stratified epithelium with the same cellular composition as in the mucosa trachea. As the bronchial

diameter decreases, the size of the cells decreases. In H&E samples, the “basement membrane” is prominent in primary bronchi, whereas in secondary bronchi its thickness immediately decreases and is not seen as a separate structure. Lamina propria is similar to that of the trachea, but its amount is small in proportion to the diameter of the bronchus (Figure 31).

Muscularis is a continuous layer of smooth muscle in large bronchi. In smaller bronchi, it is thin and loosely arranged and may appear intermittent due to its spiral-shaped course in these areas. The proper diameter of the airway regulates the contraction of the muscle.

-The submucosa remains a relatively loose connective tissue. There are adipose tissue as well as glands in large bronchi.

- The cartilaginous layer consists of discontinuous cartilage plates and as the diameter of the bronchus decreases, the plaques become smaller.

- Adventitia is a moderately tight connective tissue and shows continuity with neighboring structures such as the pulmonary artery and lung parenchyma (Elaine and Katja, 2012).

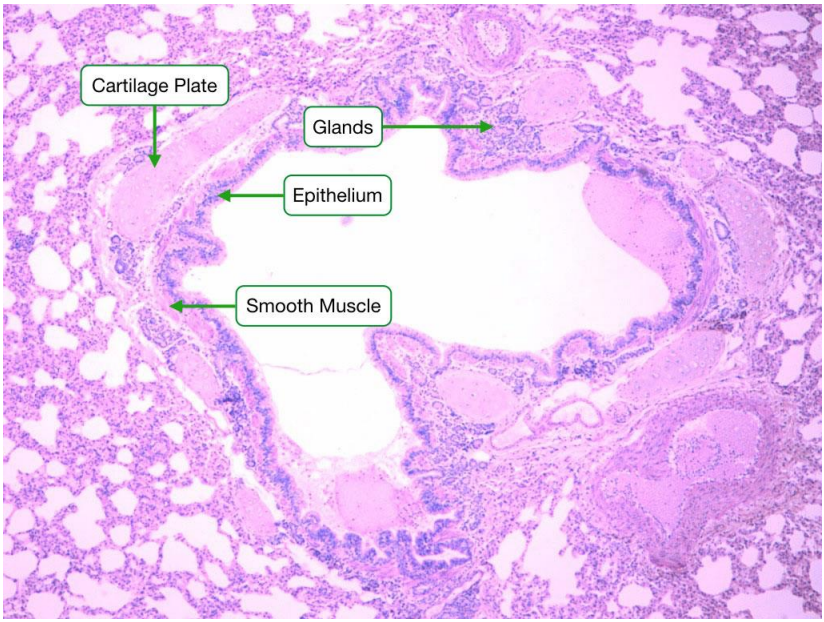


Figure 30. *Cross-section of bronchus (http://histology.med.yale.edu/respiratory_system/respiratory_system_reading.php, Access; 14.12.2020).*

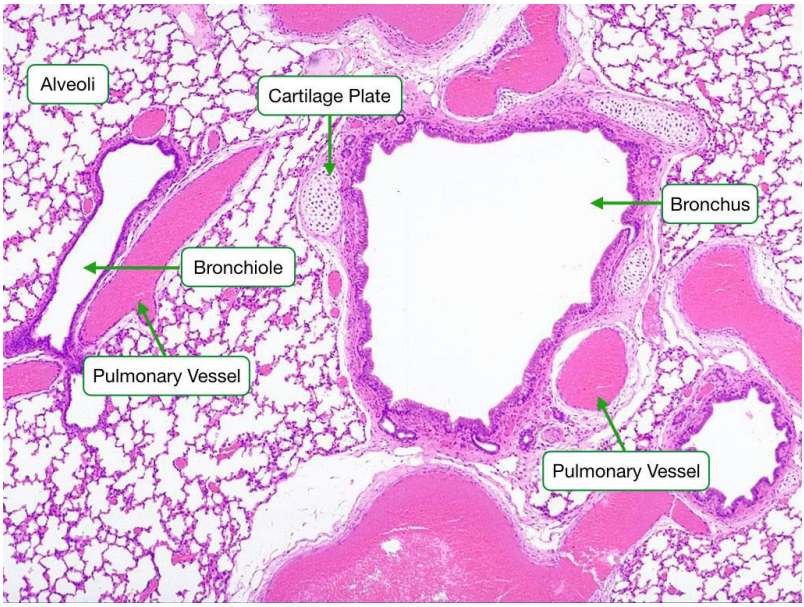


Figure 31. Low power section of lung

(http://histology.med.yale.edu/respiratory_system/respiratory_system_reading.php, Access; 14. 12.2020)

1.11. Bronchios

The bronchopulmonary segments further divide into pulmonary lobules and each lobule supports one bronchiole. Thin septums in the connective tissue structure that partially separate neighboring lobules can be represented by pale polygonal areas on the surface of the lung. Pulmonary acini are smaller units that

form lobules. Each acine consists of a terminal bronchiole, respiratory bronchioles, and alveoli that supply air. The smallest functional unit of the pulmonary structure is the respiratory bronchiolar unit. This structure consists of a single respiratory bronchiole and its supported alveoli (Fu-Chieh et al., 2009).

1.11.1. Structure of the bronchiole

Bronchioles are air conducting ducts with a diameter of 1 mm or less. The larger bronchioles are branches of the segmental bronchi. These ducts repeatedly branch off to give smaller terminal bronchioles. Terminal bronchioles also branch and eventually form respiratory bronchioles (10). There are no cartilaginous plaques and glands in the bronchioles Initially, the epithelium in large-diameter bronchioles is pseudo-multi-layered silylium prismatic, but gradually transforms into a single-silylium prismatic epithelium as the channel narrows. Goblet cells are still found in the largest bronchioles, but not in the terminal bronchioles that follow them (11). Smokers and those exposed to other irritating agents in the air are excluded. There are no subepithelial glands in the bronchioles. There are no cartilaginous plaques in the bronchioles, which are characteristic of the bronchi. Instead, small cartilage elements

can be found, especially at the branching points. All bronchioles have a relatively thick layer of smooth muscle in their walls. Small bronchioles have a single layer of cubic epithelium. Terminal bronchioles, the smallest conducting bronchioles, are lined with a single-layered cubic epithelium in which Clara cells are distributed among the silylium cells (Çevik Demirkan et al., 2006). While the number of Clara cells increases along the length of the bronchiole, the silylium cells decrease. There are also rare scrub-like cells and small granular cells. There is a thin connective tissue layer under the epithelium, and a circular smooth muscle layer is located under the connective tissue in the conductive parts (Junqueira and Carneiro, 2005) (Figure 32).

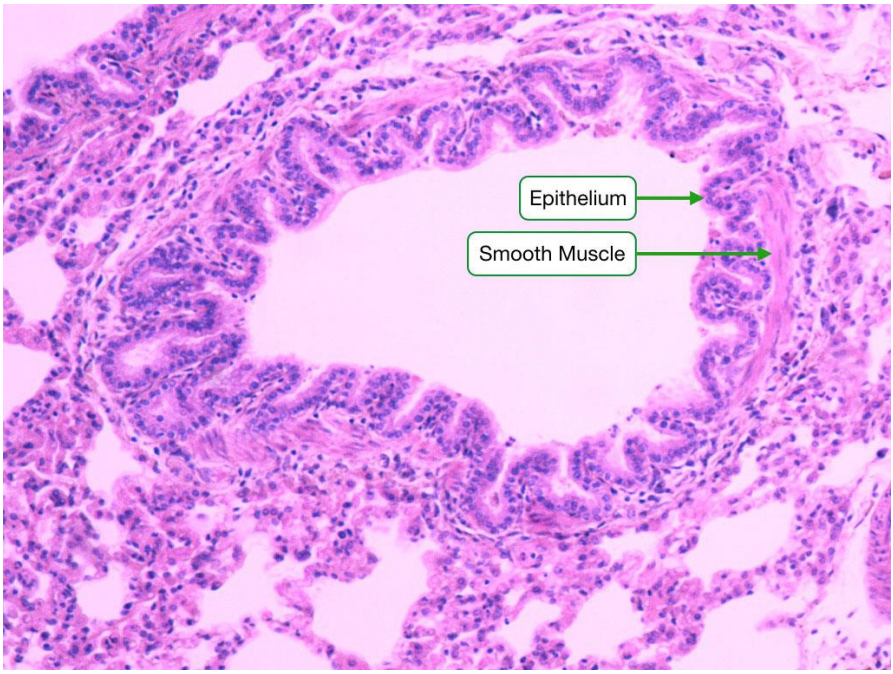


Figure 32. *Cross-section of bronchiole*

(http://histology.med.yale.edu/respiratory_system/respiratory_system_reading.php, Access; 14.12.2020).

1.12. Alveoles

The alveoli are regions of gas exchange. The surface area available for gas exchange is increased by lung alveoli. The alveoli are the extreme air spaces of the respiratory system and are the main areas of gas exchange between air and blood. Each alveoli is surrounded by a capillary network that carries blood to

the area close to the air within the alveoli. There are approximately 150-250 million alveoli in each adult lung. The total inner surface area of these alveoli is approximately 75 m and is roughly the size of a tennis court. Each alveol is a thin-walled, approximately 0,2 mm diameter polyhedral chamber and joins with an alveolar sac (Ross an Pavvlina, 2014). The alveolar ducts (ductus alveolaris) are long, almost without walls. There are only alveoli as peripheral border. There are smooth muscle rings in lump-like interalveolar septums.

- Alveolar sacs (saccus alveolaris) are spaces surrounded by clusters of alveoli. The alveoli open into the alveolar sacs.

The alveolar sacs are usually found at the ends of the alveolar ducts, but they can also be found anywhere along the length of the alveolar canal. A fairly thin connective tissue containing blood capillaries envelops and separates the alveoli. The tissue between the adjacent alveolar air spaces is called the alveolar septum or septal Wall (Knudsen and Ochs, 2018; Hall 2011) (Figure 33, Figure 34, Figure 35).

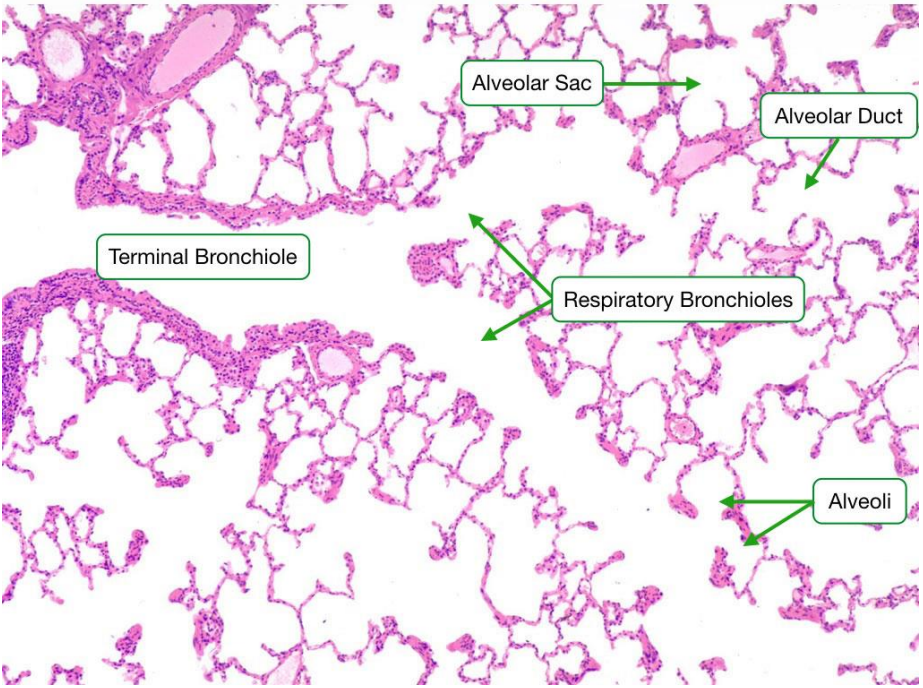


Figure 33. Section of respiratory airways

(http://histology.med.yale.edu/respiratory_system/respiratory_system_reading.php, Access; 14.12.2020).

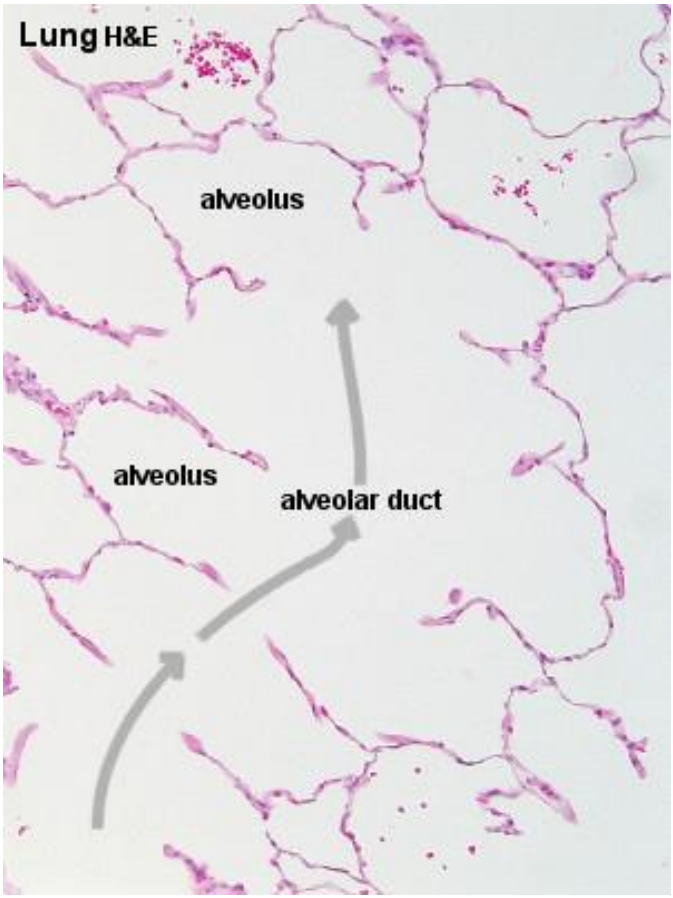


Figure 34. Lung, human-H&E, elastin. *You should be able to find at least bronchioles, alveolar ducts and alveoli in the section*

(https://www.lab.anhb.uwa.edu.au/mb140/CorePages/Respiratory/respir.htm, Access;14.12.2020).

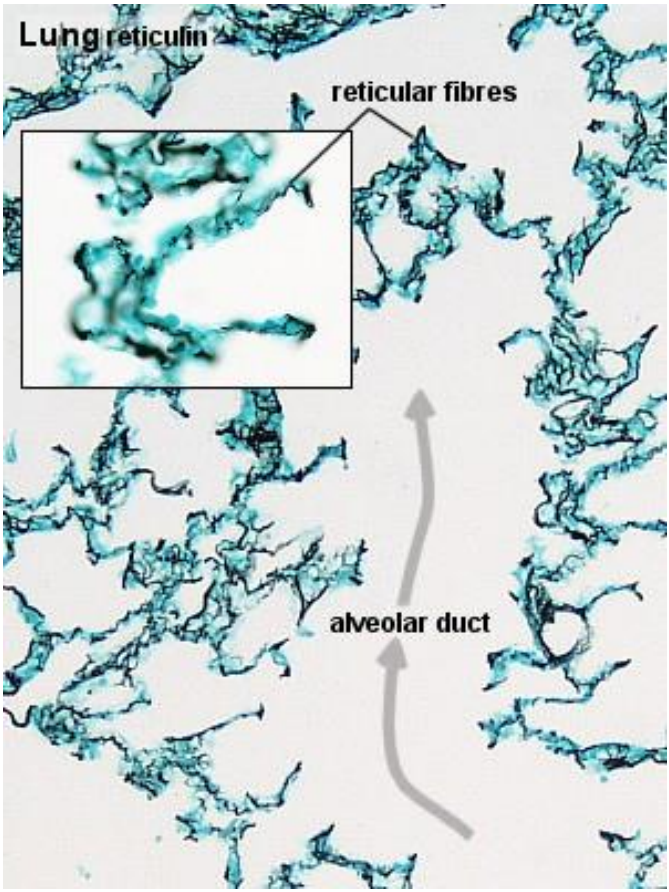


Figure 35. Lung, cat-reticulin Reticular and elastic fibres form the bulk of the connective tissue present in the walls of the alveoli (https://www.lab.anhb.uwa.edu.au/mb140/CorePages/Respiratory/respir.htm, Access; 14.12.2020).

1.12.1. Pneumocytes

The alveolar epithelium consists of type I and II alveolar cells and a small number of brush-like cells. The alveolar surface creates a sensitive biological interface that is constantly exposed to surface destabilizing forces and inhaled particles, pathogens and toxins. The alveolar epithelium consists of several specialized cells and the products of these cells. Some of these products play a defensive and protective role:

-Type I alveolar cells are also known as type I pneumocytes. They make up 40% of all alveolar lining cells. They are very thin flat cells and cover most of the alveolar surface. These cells are connected to each other and other cells of the alveolar epithelium by occlusive junctions.

-Type I alveolar cells are secretory cells, also called septal cells, in type II pneumocytes. These cubic cells are scattered among type I cells but tend to accumulate in the septal junctions.

- Brush-like cells are also found in the alveolar wall and they are few in number. They may serve as receptors that monitor the air quality in the lungs.

The surfactant reduces alveolar surface tension and actively participates in the removal of impurities. The surfactant layer produced by type II alveolar cells reduces surface tension at the air-epithelial interface. The most critical agent for the stability of the airspace is a specific phospholipid called dipalmitoylfos fatidylcholine (DPPC) and is responsible for almost all of the surfactant's surface tension reducing properties. Surfactant synthesis in the fetus begins *after the 35th week of gestation and is regulated by various hormones such as cortisol, insulin, prolactin and thyroxine (*Weinberger et al., 2019; Fehrenbach, 2001; Ross and Pawlina, 2014*) (Figure 36, Figure 37).*

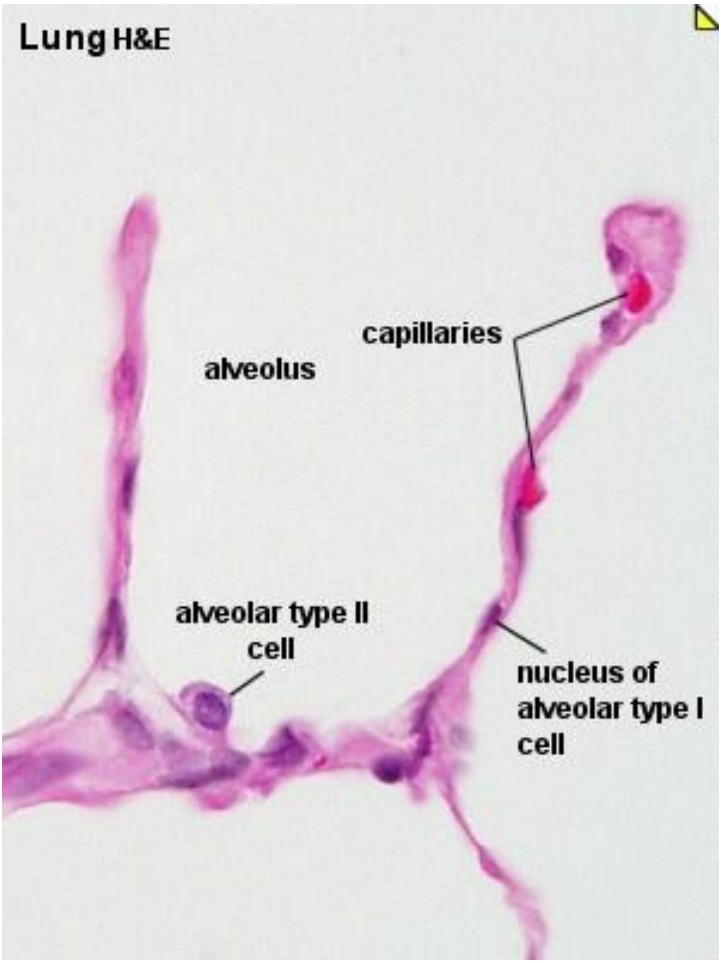


Figure 36. Lung, human-H&E, elastin, You should be able to identify both type I and II alveolar cells and capillaries in the alveolar walls

(https://www.lab.anhb.uwa.edu.au/mb140/CorePages/Respiratory/respir.htm, Access; 14.12.2020).

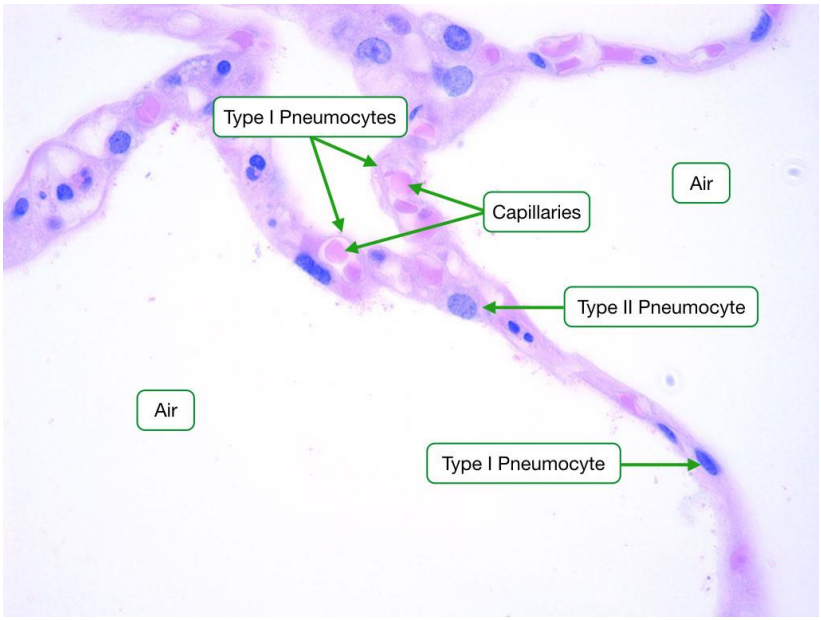


Figure 37. Pneumocytes-H&E stain

(http://histology.med.yale.edu/respiratory_system/respiratory_system_reading.php, Access; 14.12.2020).

Surfactant proteins help regulate the surfactant layer and regulate alveolar immune responses (Saladin, 2007). In addition to phospholipids, hydrophobic proteins are also essential for the structure and function of the surfactant. The alveolar septum is

the region where the air-blood barrier is located. The air-blood barrier refers to the cells and cell products through which gases must pass through the diffusion between the alveolar and capillary compartments. The thinnest air-blood barrier consists of a thin surfactant layer, type I epithelial cell and its basal lamina, and capillary endothelial cell and its basal lamina. Usually these two basal laminae are fused. Connective tissue cells and fibers that can be found between two basal lamina thicken the air-blood barrier. These two configurations make up the thin part and the thick part of the barrier. Most gas exchange is thought to occur in the thin section of the barrier. The thick part is thought to be the area where tissue fluid can accumulate and even pass into the alveoli. The lymph vessels in the connective tissue of the terminal bronchioles drain the fluid accumulated in the thick part of the septum (Ross and Pawlina, 2014; Weinberger et al., 2019).

1.12.2. Alveolar macrophages

Alveolar macrophages reside within the airspaces of alveoli and serve to remove particulate matter such as dust and pollen. Alveolar macrophages also called dust cells. Alveolar macrophages derive from monocytes and also exist in the

connective tissue of the lung. An increase in macrophages in the airways is often an indicator of a pathologic condition (Misharin et al., 2017) (Figure 38).

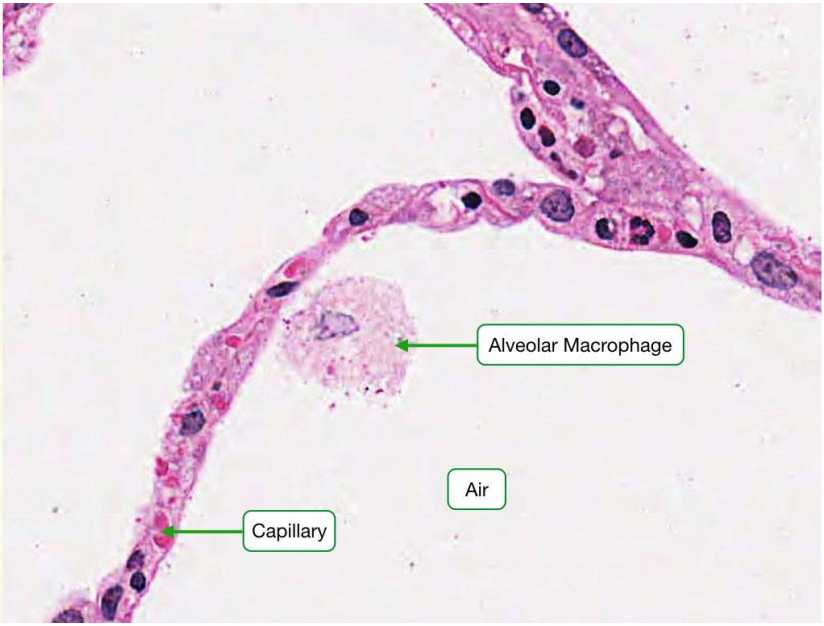


Figure 38. Alveolar macrophage (dust cell) in airway

(http://histology.med.yale.edu/respiratory_system/respiratory_system_reading.php, Access; 14.12.2020).

1.12.3. Pneumocytes EM

Begin by distinguishing the capillaries from the airway. Identify type I pneumocytes lining the lumen of the alveolus and endothelial cells lining the capillary. Type II pneumocytes are considerably larger and more cuboidal than its type I counterparts. Easily visible are its nucleus and some microvilli. The lamellar bodies are distinct features of this cell; these contain the phospholipid precursors to pulmonary surfactant, which will be released into the airway to disrupt the forces of surface tension that would otherwise cause the alveolus to collapse (Yang et al., 2016; Naeem et al., 2020) (Figure 39).

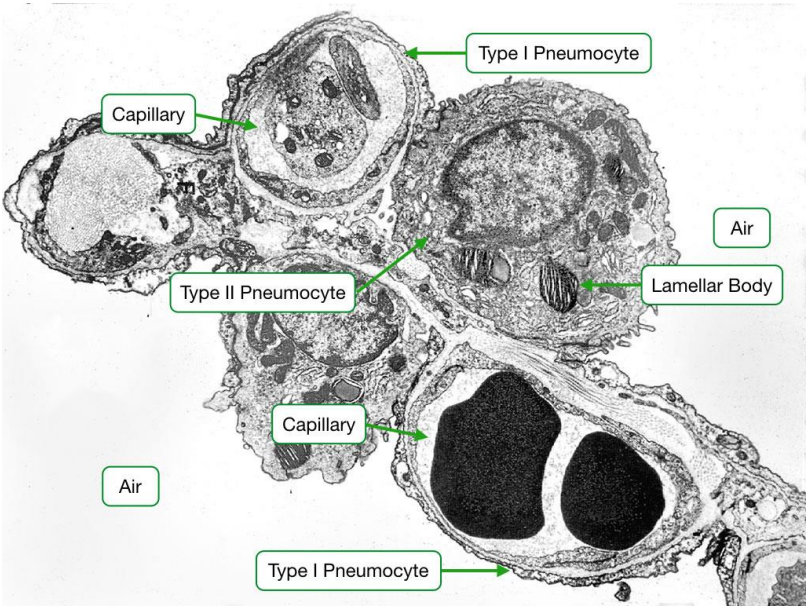


Figure 39. Pneumocytes-Electron micrograph

(http://histology.med.yale.edu/respiratory_system/respiratory_system_reading.php, Access; 14.12.2020).

1.12.4. Air-blood barrier

This electron micrograph shows the three lays of the air-blood barrier across which gas exchange occurs. The type I pneumocyte is part of the simple squamous epithelium of the alveolus and the endothelial cell represents the capillary

epithelium. The two cells share a fused basement membrane, which allows for the minimization of the barrier across which exchange of gases occur. Oxygen in the air diffuses through the cytoplasm of type I pneumocytes, across the basement membrane and then through the cytoplasm of the endothelial cell to reach the blood. Carbon dioxide in the blood diffuses in the opposite direction (Kindlen 2003).

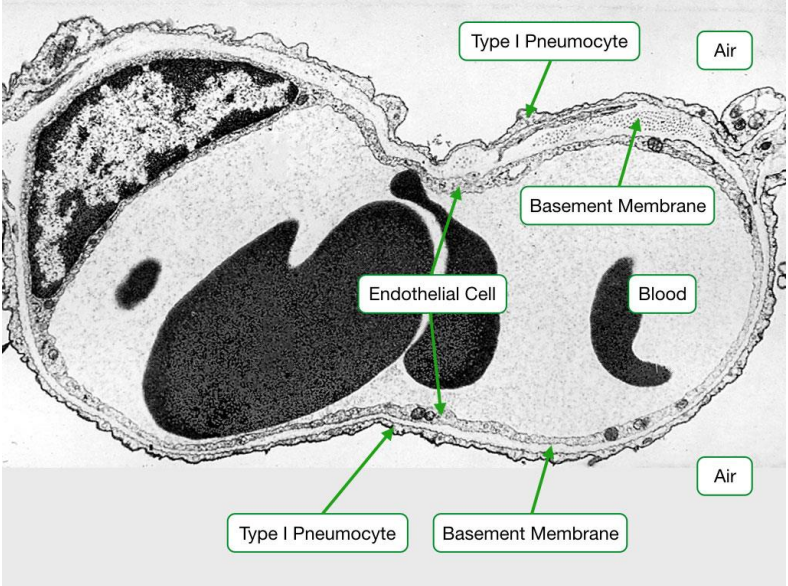


Figure 40. Structures that compose the air-blood barrier (http://histology.med.yale.edu/respiratory_system/respiratory_system_reading.php, Access; 14.12.2020)

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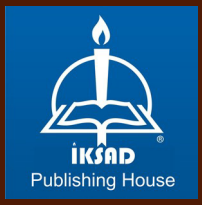

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