ANAT D502 – Basic Histology

Respiratory System
Revised 10.18.16

Reading Assignment: Chapter 19: Respiratory System; pay special attention to Folders 19.1, 19.2, 19.3 and 19.4 (Clinical Correlations)

Outline:
I. Introduction
II. Lungs
III. Divisions of the respiratory system
IV. Respiratory epithelia (air-conditioning epithelia)
V. Nasal cavity
VI. Pharynx and larynx
VII. Trachea
VIII. Overview of the bronchial tree
IX. Gas exchange epithelia
X. Bronchi to alveoli
XI. Blood supply

I. Introduction:

The respiratory system structurally consists of paired lungs and the air conduction ways that connect to them. The latter includes the nasal cavity, pharynx, larynx, trachea and extra-pulmonary bronchi.

As in all large organ systems, the respiratory system performs a number of functions:

1. Respiratory – these include (1) air conduction (2) air filtration and conditioning, and (3) gas exchange (CO2 and O2). Remember, however, gas exchange is not limited to the respiratory system but will occur across any surface adjacent to the atmosphere (e.g., integument).
2. Sensory - the conducting system contains both general somatic sensation (e.g., touch, heat, pain, etc.) as well as specialized sensations (olfaction, vomeronasal sensation, gustation).
3. Endocrine – small granule cells (corresponding to the enteroendocrine cells of the gut) within the respiratory tract provide paracrine functions related to respiration.
4. Communication – Vibrations produced by the larynx are modified into speech by the serially coupled pharyngeal and oral resonators (more below).
5. “Thoracic-stiffening” - the laryngeal aperture (glottis) closes to trap air within the expanded lungs producing a stiffened chest; this is used in conjunction with the abdominal musculature to perform the important “tion” functions: locomotion, defecation, micturition, parturition, etc.
6. Heat dissipation – as noted previously, cellular respiration is relatively inefficient with approximately two-thirds of the energy released dissipated as heat; this heat must be disposed. In humans, the circulatory, respiratory and integumentary systems act in concert to perform this important function.

Development

The lungs develop from a ventral evagination (diverticulum) of the foregut (gastrointestinal tract). The epithelium of the lungs is of endodermal origin and all other tissues are derived from the mesenchyme. Thus, the lungs are yet another example of an organ that arises through epithelial-mesenchymal interactions.

II. Lungs

The lungs are bilateral, left and right, and each is divided by connective tissue into lobes and lobules. The lobes (3 in right lung, 2 in left) are grossly visible; the lobules (bronchopulmonary segments) are unobservable grossly but are of great functional significance (see below).
In mammals such as humans, each lung is invested in the lining of its own pleural cavity. [What might the selective advantage of having separate pleural cavities be?] The lining of the pleural cavities is called the pleura and consists of a serous mesothelium and underlying lamina propria. The portions of the pleura adhering to the lung are called the visceral pleura and the portions adhering to the internal chest wall are the parietal pleura. The space between the visceral and parietal pleura is the pleural cavity. Like all true body cavities derived from the embryonic coelom, the pleural cavity is empty except for small amounts of lubricating fluid. The pleural cavity is completely sealed off and is at a negative pressure relative to the atmosphere, thus forming the physical basis for inspiration (see below).

Each lung has a hilum along its medial border that is the entry site of the pulmonary artery, primary bronchi and nerves; it also serves as the exit for the pulmonary veins and lymphatics. The parenchyma of the lung consists of alveoli that are the terminal airs spaces where the majority of gas exchange occurs. The stroma is a connective tissue matrix called the interstitium that provides passage for the air conducting system and vasculature.

III. Divisions of the respiratory system:

Physiologically, the respiration involves ventilation and gas exchange. Ventilation is the process of moving air over the gas exchange surfaces of the lung (i.e., the mechanisms involved in inspiration and expiration). Gas exchange is a passive process, governed by the mechanics of diffusion. Inspiration is accomplished by the primary (abdominal diaphragm) and secondary (e.g., intercostals) muscles of inspiration. Normal (passive) expiration is passive, accomplished by the recoil of the elastic fibers of the interstitium of the lung. Forced expiration (e.g., during hard or rapid breathing) is accomplished by a wide variety of trunk, abdominal and axial musculature. Additionally, during locomotion ground reaction forces turn the abdominal viscera into a “visceral piston” to assist in forced expiration. [This is why locomotion and ventilation are coupled; you can demonstrate this by taking a run and attempting to inhale (rather than exhale) during foot strike. Lots of luck!]

Anatomically, the respiratory system can be functionally divided into two portions: (1) conducting and (2) respiratory. The conducting portions conduct air to and from the respiratory portions; the latter are the primary site of gas exchange.

The conducting portion of the respiratory system can be divided into pulmonary (within the lung) and extra-pulmonary (external to the lung) components. These components include the nasal cavity, pharynx, larynx, trachea, bronchi and bronchioles. This portion of the respiratory systems filters (removes particulate matter) and conditions (moistens and warms) the air for optimal gas exchanges. Filtering is achieved either by trapping (vibrissae) or deflecting (turbulence) particles onto the mucous membranes (= mucosa) lining the conducting portion. Cilia covering the mucous membranes then transport this debris to the pharynx for disposal (such a polite word). Mucus is produced both by multi-cellular (mucous, seromucous and serous) and unicellular (e.g., goblet cells) glands distributed along the respiratory tract. In addition to it trapping function, mucous also serves to moisten (humidify) the air.

The respiratory portion of the respiratory system is the site of gas exchange. Its components include the respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli).

IV. Respiratory epithelium

Definitions:

mucosa – mucous membrane; a mucous tissue lining consisting of an epithelium, a lamina propria and, in the digestive tract only, a layer of smooth muscle (muscularis mucosa)

mucus – the clear, viscid secretion of mucous membranes, consisting of mucin, epithelial cells, leukocytes and various inorganic salts suspended in water.
Aside from the skin and lining of ducts and vessels, most of the linings of the body are formed by a **mucosa**. The mucus is produced by cells within the lining epithelium (e.g., goblet cells) and/or by glands intrinsic or extrinsic to the walls of the organs.

The **mucosa** of most of the conducting portion of the respiratory system is lined by a **ciliated pseudostratified columnar epithelium**, often referred to as **respiratory epithelium**. However, in areas of turbulent air flow (abrasion), the mucosa becomes lined by a stratified squamous epithelium. Respiratory epithelium in the conducting system contains 6 cell types, some of which are also found in the respiratory portion of the system.

1. **Ciliated cells** are columnar cells whose apical (lumenal) surface are covered with ~ 300 cilia. The cilia move in unison to sweep mucous and its trapped particulate matter towards the pharynx.

2. **Mucous or goblet cells** are unicellular mucous glands interspersed among the ciliated cells. They have a basal nucleus and apical mucinogen granules forming a "mucous cup".

3. Basal cells are the epithelium’s stem cells found along the basal lamina. Their apex does not reach the lumen, thus creating the pseudostratified appearance of the epithelium.

4. **Brush cells** are columnar cells covered apically with blunt **microvilli**. Their basal surface is in synaptic contact with an afferent (sensory) nerve endings. These solitary chemosensory cells initiate an aversive reflex (reduction of respiratory rate) when bitter (alkaloid) substances (such as those produced by bacteria) are present in the airway luminal fluid. Thus, this reflex may be protective.

5. **Small granule cells** correspond to the enterocendocrine cells of the gut and, like their intestinal counterparts, contain small, dense vesicles (granules) that are visible in EM. These vesicles contain neurotransmitters and hormones. Many of these cells are innervated by nerve terminals to form neuroepithelial bodies. Acting in paracrine fashion, they are thought to regulate air and vascular channel diameters.

6. **Exocrine bronchiolar cells** (club cells, formerly known as Clara cells) are more common in the respiratory portions of the respiratory tract but can be found in the distal conducting bronchioles. These non-ciliated, cuboidal cells have a characteristic apical dome and an EM profile typical of protein synthesizing cells. These cells secrete a lipoprotein **surfactant** (surface active agent) that prevents cell adhesion in the event of lumen collapse (e.g., during exhalation).

V. Nasal Cavity

Arguably the most interesting and accessible (eeeegh!) portion of the respiratory tract, the **nasal cavity** contains the fascinating **olfactory epithelium** and intriguing **nasal turbinates**.

The **nasal cavity** consists of parallel, bilateral chambers each with an anterior (naris) and posterior (choana) aperture. The choanae (plural) open into the **nasopharynx**. Each chamber is divisible into 3 regions (vestibular, respiratory, olfactory), each with its own distinct lining.

The **vestibule** or vestibular region surrounds the nares and is lined by a stratified squamous epithelium. It contains stout, highly innervated hairs called **vibrissae** that work with sebaceous gland secretions to trap large particles. [N.B. These vibrissae are **not** homologous to the vibrissae (whiskers) found on the muzzle of most mammals that form a highly specialized tactile sensory apparatus.]

The **respiratory region** comprises most of the volume of the nasal cavity. It is lined with respiratory epithelium and its lamina propria contains serous mucous glands. The capillaries within the lamina propria are abundant and oriented perpendicular to the air flow (cross-current circulation; see below). These same capillaries distend and leak fluid into the lamina propria during immune reactions resulting in the constriction of the air passage ways; a condition known in lay terms as a "stuffy nose".
Within the respiratory region are the nasal turbinates. These are mucosa-covered bony projections from the lateral wall of the cavity. They have a dual function: (1) To filter the air by creating turbulence to deflect debris within the air stream onto the mucosa (turbulent precipitation); and (2) to increase the surface area of the nasal cavity to (a) warm and humidify the incoming air (inhalation) and (b) recover water (and heat) from the returning air (exhalation). Recall from Frick’s Law that the rate of gas exchange is proportional to temperature.

[You can test the efficacy of the nasal turbinates in recovering water (and heat) by first exhaling onto the palm of your hand through the mouth (non-turbinate) and then exhaling onto the palm of your hand through the nose. Which feels cooler?]

The olfactory region lies superior to the nasal turbinates in the roof of the nasal cavity. Its mucosa is lined by the olfactory epithelium, a pseudostratified epithelium containing 3 types of cells: olfactory neurons, supporting cells, and basal cells.

(1) Olfactory cells are bipolar neurons. Their apical pole terminates in numerous, non-motile cilia that are radially arranged over the epithelial surface. The cell membrane of the cilia contains odorant-binding proteins which act as receptors. Their basal poles give rise to the axons that form cranial nerve I (CN I, olfactory nerve) that project into the brain. Olfactory neurons live approximately 1 month and must be constantly replaced.

(2) Supporting (sustenacular) cells are the most numerous cells of the olfactory epithelium. Columnar cells covered with microvilli, they serve as support (glia) cells to the olfactory neurons.

(3) The basal cells are the stem cells of the other two types.

In addition to the usual contents, the lamina propria beneath the olfactory epithelium contains olfactory (Bowman’s) glands. These are branched, tubuloalveolar serous glands. Their serous secretion is discharged over the olfactory epithelium where it traps and dissolves odoriferous substances. The constant effusion of secretions ensures refreshing of olfactory receptors to new stimuli. [Where have you seen this process before?]

VI. Pharynx and larynx

The pharynx is a muscular tube that connects the nasal and oral cavities to the larynx and esophagus. In humans, the food and air passages cross each other in the pharynx, allowing it to serve its function as a vocal resonator (see below). The pharynx is anatomically divided into 3 regions:

1. oropharynx – lies posterior to the tongue and is lined by oral mucosa (what type of epithelium?)
2. nasopharynx – lies posterior to the choanae; lined by respiratory mucosa
3. laryngopharynx – surrounds the upper larynx and is lined by oral mucosa.

The submucosa of all 3 regions is rich in mucous glands and lymphatic tissue; of the latter the most prominent are the tonsils which form encircle the entrance to the pharynx and are divided by location into lingual, pharyngeal and palatal tonsils.

Speech

The arrangement of the larynx and pharynx in humans is atypical and is associated with speech. In most mammals, the opening of the larynx projects into the nasopharynx so that the food passes around the larynx to enter the esophagus. The separation of the air and food passageways in humans is secondarily incomplete in humans. In neonates, the opening of the larynx lies in the normal position (protruding into the nasopharynx) thus allowing the infant to suckle and breath simultaneously (as an adult, don’t try this at home). Due to differential growth during the post-natal period, the larynx later “descends” into the base of the pharynx (laryngopharynx) to create a pharyngeal resonator used in speech (see below). The downside to this laryngeal “descent” is that in adult humans the food and air passage ways are no longer separate and food can (and occasionally does) enter into the respiratory passages. Not, as Martha would say, a “good thing.”
The ancestral function of the vocal folds was probably to act as a sphincter to prevent food entering the air way (most tetrapods lack separate oral and pharyngeal cavities). The vocal folds were subsequently modified for vocalizations (communication) and thoracic stiffening. In all tetrapods, vocalizations are produced by partially closing the vocal folds and forcing air out of the lungs to produce air-born vibrations (e.g., frogs, geckos, dogs). In humans, the range of vocalizations associated with speech are extended by repositioning the larynx to produce two serially coupled resonating chambers in the (1) pharynx and (2) oral cavity that modify the vocal cord vibrations. It is the changes in the shape of these 2 resonators using pharyngeal, lingual and facial muscles that produces speech. Interestingly, the larynx plays a relatively minor role in human speech as it produces only (1) the initial vibration and (2) changes in pitch. In fact human speech is possible even without a larynx. [What experiment demonstrates this? Hint: Think of Ned in South Park.]

**Definition**: resonator – a device that intensifies and elaborates an initial vibration by supplementary vibration

**Larynx**

The larynx is a musculoskeletal tube consisting of 4 major cartilages (epiglottis, thyroid, arytenoids (paired) and cricoid) and their associated skeletal muscles. The intrinsic muscles of the larynx open and close the vocal folds (sphincter) whereas the extrinsic muscles move the cartilages during swallowing and to change the vocal pitch.

The epiglottis is composed of elastic cartilage which is thought to fold over the glottis (the opening between the vocal folds) during deglutition. The cricoid, thyroid and arytenoid cartilages are composed of hyaline and tend to mineralize with age, contributing to the huskiness associated with aged voices (e.g., Drs. Brokaw and Swartz).

The lumen of the larynx can be divided into three regions (vestibule, ventricle and infraglottic cavity) by reference to two sets of folds of mucous membranes, the vestibular and vocal folds. The vestibule, as its names suggests, lies at the entrance to the larynx and is the part of the lumen between the epiglottis and vestibular folds. The ventricle or sinus is the portion of the lumen extending between the vestibular and vocal folds. Finally, the infraglottic cavity can be found below the vocal folds and leads to the trachea.

The vestibular folds (sometimes referred to as ventricular folds) are bilateral non-vibrating mucosal folds found at the base of the vestibule. The mucosa of the bilateral vibrating vocal folds is underlain by the vocal ligament and vocalis muscle. The opening between the vocal folds is called the
glottis (or more properly rima glottidis). The mucosa of the vocal folds and epiglottis (areas subject to abrasive turbulent air flow) is covered by stratified squamous epithelium; all other regions of the larynx are lined with respiratory epithelium. The lamina propria of the larynx contains numerous laryngeal glands containing seromucous cells.

VII. Trachea

The trachea is a flexible air conducting tube extending inferiorly from the larynx and terminating by bifurcation into the primary bronchi. The wall of the trachea has 3 coats (tunics): mucosa, fibromusculocartilaginous, and adventitia.

The mucosa is lined by a respiratory epithelium with an unusually thick basement membrane. The lamina propria is a cellular loose connective tissue with the usual complement of cells. Mucosal associated lymphatic tissues (M.A.L.T.s) are not uncommon. The mucosa lacks a muscularis mucosa.

The fibromusculocartilaginous coat consists of an irregular connective tissue that invests the cartilaginous rings and contains seromucous glands. The C-shaped hyaline cartilages of the trachea act to maintain the opening of the tube and their open border is spanned by the trachealis muscle, a combination of fibroelastic tissue and smooth muscle.

The adventitia of the trachea is unremarkable.

VIII. Overview of the bronchial tree

Starting at the trachea, the air passage ways undergo serial (sequential) and parallel reducing bifurcations to form an inverted bronchial tree with the alveoli forming the leaves and the primary bronchus the trunk. The resulting hierarchy is as follows:

- The trachea bifurcates into left and right primary (main) bronchi.
- Each primary bronchus divides into lobar bronchi, one for each lobe of the lungs (thus, 2 left and 3 right).
- Each lobar bronchus gives rise to segmental bronchi (8 in left lung, 10 in right lung).
- The segmental bronchi branch into bronchioles.
  - The bronchioles branch into terminal bronchioles.
  - The terminal bronchioles branch into respiratory bronchioles.
  - The respiratory bronchioles branch into alveolar ducts.
  - The alveolar ducts branch into alveolar sacs.
  - The alveolar sacs branch into alveoli.

Branches above the level of the respiratory bronchioles form part of the conducting portion of the respiratory tract; the branches at or below the respiratory bronchioles form the respiratory (gas exchange) portion.

Of functional and clinical significance is the bronchopulmonary segment which consists of a segmental bronchus and its accompanying pulmonary artery and all the lung parenchyma they supply. These are the units of surgical resection, i.e., segments which be removed without impacting the functioning of adjacent segments. Pulmonary veins cross bronchopulmonary segments and thus are termed intersegmental.

IX. Gas exchange epithelia

The epithelium of the respiratory portion (gas exchange) of the respiratory tract is lined formed by 3 types of cells: type I pneumocytes, type II pneumocytes and brush cells. The brush cells have been described previously.

Type I pneumocytes (or type I alveolar cells) are a very squamous, post-mitotic epithelium. The organelles of these cells are localized around the nucleus permitting a very thin extra-nuclear region that
promotes gas diffusion. Type I pneumocytes are joined to adjacent cells by occluding junctions and collectively account for 95% of the gas exchange surface in the lung.

**Type II pneumocytes** (or type II alveolar cells or septal cells) are cuboidal cells concentrated at the alveolar wall junctions (=: septa). While approximately equal in number to type I pneumocytes, type II pneumocytes account for only 5% of the gas exchange surface in the lung due to their non-squamous shape. In addition to their gas exchange function, these cells also provide the surfactant (surface active agent) for the gas exchange portion of the respiratory tract. Secretory vesicles within the cell contain lamellar bodies (stacks of membranous lamellae composed of lipids, phospholipids and specialized proteins (surfactant proteins A-D)), which, when secreted forms the pulmonary surfactant. This surfactant reduces surface tension in the lumen to stabilize alveolar volume during exhalation, thus preventing cell adhesion. Finally, the type II pneumocytes are the stem cells for both type I and II pneumocytes.

**X. Bronchi to alveoli**

External to the lungs, the walls of the (extrapulmonary) bronchi resemble the trachea with C-shaped cartilages. Within the lung (intrapulmonary) the cartilages of the bronchi (primary, lobar and segmental) consists of irregularly shaped, discontinuous plates. The same coats (tunics) form the wall:

1. The *mucosa* is lined by respiratory epithelium whose cell height diminishes in parallel with the diameter of the passage.
2. The *fibromusculocartilaginous* coat consists of an irregular connective tissue investing irregularly-shaped cartilaginous plates and containing seromucous glands. Within this layer smooth muscles forms spiral bundles whose contractions maintain the diameter of the passage during inhalation. As the bronchi diminish in diameter, the cartilages and glands decrease in frequency.
3. The *adventitia* is a moderately dense irregular connective tissue.

Distal to the bronchi, the cartilage and glands are lost and the three coats of the bronchiole wall are termed *mucosa*, *muscularis* and *adventitia*. The thickness of these layers decreases as the air passage ways continue to branch and diminish in diameter. Bronchioles are marked by a persistent layer of smooth muscle (*muscularis*) which is lost in the alveoli. In these small diameter (<1 mm) tubes the epithelium of the mucosa is variable, transitioning from respiratory to ciliated simple columnar to ciliated simple cuboidal as the diameter of the tube decreases. In parallel with the changes in epithelial morphology, the frequency of goblet cells decreases and the frequency of exocrine bronchial (club) cells increases. Thus, the distal-most conducting passages, the *terminal bronchioles*, are lined by a simple ciliated cuboidal epithelium consisting of exocrine bronchiolar (club) cells interspersed among ciliated cells. Goblet cells are rare.

Respiratory bronchioles are transitional zones that function in both air conduction and gas exchange. The epithelium is similar to that of the terminal bronchioles consisting initially of a ciliated simple cuboidal epithelium (containing exocrine bronchiolar (club) and ciliated cells but no goblet cells) but transitioning to non-ciliated simple low cuboidal cells adjacent to the alveolar duct. Typically opposite the wall associated with the pulmonary arteriole and extending from the lumen are alveoli which give these bronchioles their name and function. Beneath the mucosa smooth muscle bundles are still present.

The *alveolar ducts* branch from the respiratory bronchioles. These are elongated passages that lead to individual alveoli or *alveolar sacs* which are cluster of two or more alveoli. The walls of the sacs are formed by the same epithelium that forms the alveoli (see below). The walls of the alveolar duct are highly discontinuous and marked by “clumps” of collagen and smooth muscle fibers, often capped by cuboidal epithelium, adjacent to the openings of the alveoli or alveolar sacs.

The *alveolus* (plural, alveoli) is the terminal air space of the respiratory tract and the primary site of gas exchange. Each alveolus forms a polyhedral chamber with thin walls (1-2 microns) formed by type I and II pneumocytes situated atop an inconstant layer of connective tissue (interstitium) containing capillaries. In many regions the basement membranes of the epithelium and endothelium are conjoined without an intervening connective tissue layer, thus facilitating gas diffusion. Where present, the interstitium contains collagen and abundant elastic fibers (passive exhalation), fibroblasts, macrophages and mast cells. The lumenal surface of the epithelium is covered by a *surfactant* (secreted by type II
pneumocytes). Collectively, the surface area of the approximately 0.5 billion alveoli in an adult human totals 75 square meters (= tennis court).

Interalveolar septa consists of back to back alveoli walls encasing a common capillary. These septa are perforated by alveolar pores [of Köhn] which serve as shunts to adjacent alveoli in the advent of airway blockage.

Macrophages (dust cells) can be found in both the interstitium and in the alveolar air space. Part of the mononuclear phagocytic system (MPS), these cells ingest bacteria and particulate matter. Those in the alveolar air space can be expelled with mucous whereas those in the interstitium give lungs their carbonized appearance.

XI. Blood supply

The lungs receive a dual arterial supply, pulmonary and systemic. The pulmonary arteries arise from the cardiac right ventricle and carry deoxygenated blood at relatively low pressure. Branches run with the air conducting system (but do not supply it) and supplies the alveolar capillaries starting at the level of the respiratory bronchioles. This is the arterial system for gas exchange. The systemic component is represented by the bronchial arteries which arise from the aorta (oxygenated blood) and supply the cells of the interstitium and the air conducting system down to the level of the respiratory bronchioles. Both arterial systems terminate in the alveolar capillaries which are drained by the pulmonary veins that carry the blood back to the left cardiac atrium. Also within the interstitium of the lung are the bronchial veins; these vessels are inconstant and drain to the pulmonary venous system rather than the systemic circulation, interesting, no?
Diagram of the detailed structure of the respiratory tree and its blood supply and drainage, lymphatic drainage and nerve supply. Blue = vessels which contain de-oxygenated blood; red = vessels which contain oxygenated blood.