The main functions of the respiratory system include:
   a. Exchange of O₂ and CO₂.
   b. Voice production.
   c. Regulation of plasma pH.
   d. Olfaction (sensation of smell)
   e. Infection (pathogen invasion) prevention.

II. Respiration is associated with 4 processes:
   a. Pulmonary ventilation = movement of air into/out of the lungs
   b. Alveolar gas exchange = movement of O₂ from lungs to blood and CO₂ from blood to lungs.
   c. Gas transport = the mechanisms by which O₂ and CO₂ are moved thru the blood.
   d. Systemic gas exchange = movement of O₂ from blood to cells and CO₂ from cells to blood.

III. Cellular respiration = Breakdown of glucose, fatty acids and amino acids that occurs in mitochondria and results in production of ATP.
   a. Requires O₂ and produces CO₂. O₂-dependent respiration is “aerobic metabolism.”
   Breakdown of glucose that produces ATP but doesn’t require O₂ is “anaerobic metabolism.”

IV. Respiratory tract is divided into the upper respiratory tract and the lower respiratory tract.
   a. Upper respiratory tract refers to the nose, pharynx, and their associated structures.
   b. Lower respiratory tract includes the larynx, trachea, bronchi, and lungs.

V. The respiratory system is separated into a conducting zone and a respiratory zone.
   a. Conducting zone refers to structures that transport air but play no role in gas exchange.
      i. It includes: nasal cavity, nasopharynx, oropharynx, laryngopharynx, larynx, trachea, bronchi, and all bronchioles except for respiratory bronchioles.
      ii. These structures transport, filter, humidify, and warm air.
   b. Respiratory zone refers to structures where exchange of O₂ and CO₂ occurs.
      i. Sites of exchange are known as alveoli (sing. alveolus).
      ii. All respiratory zone structures contain alveoli and include: respiratory bronchioles, alveolar ducts, and alveolar sacs.

VI. Respiratory mucosa = mostly a ciliated pseudostratified columnar epithelium with goblet cells.
   a. Recall that goblet cells function in mucus secretion.
   b. Epithelium is underlain by a vascular CT layer called the lamina propria. It will often house serous and mucous glands in addition to nerves, blood vessels and lymphatic vessels.
   c. Respiratory tract mucus traps particulate matter. The mucus is constantly swept by cilia to the pharynx where it flows to the esophagus and acidic environs of the stomach.
   d. The mucosa changes as we progress inferiorly along the respiratory tract. The thickness of the epithelium and the number of cilia and goblet cells all decline.

VII. Nasal Cavity and Conchae
   a. Conchae increase the surface area of the nasal cavity and increase the turbulence of nasal airflow. This increases the filtration, humidification and heating of air by the nasal mucosa.

VIII. Paranasal Sinuses
   a. Nasal sinuses are lined by a mucus epithelium and contribute greatly to the mucus lining the nasal cavity. Sinuses also lighten the skull and contribute to the sound of one’s voice.

IX. Nasopharynx
   a. Contains the pharyngeal tonsil.
   b. Contains the auditory tubes (Eustachian tubes) which link the nasopharynx to the middle ear cavities and allow middle ear pressure to equalize with atmospheric pressure.
   c. The uvula and soft palate elevate superiorly to close off the nasopharynx when swallowing.

X. Oropharynx
   a. Lined by stratified squamous epithelium b/c it is a common passageway for food and air.

XI. Laryngopharynx = Extends alongside the epiglottis until the division of the larynx and esophagus.
   a. Lined by stratified squamous epithelium b/c it is a common passageway for food and air.

XII. Larynx
   a. Cartilaginous tube (made of 8 hyaline pieces and one piece of elastic cartilage) that extends from the laryngopharynx to the trachea and routes food/drink down the esophagus.
b. Contains vocal ligaments (ensconced within folds of mucosa known as vocal folds) that vibrate to yield voice production.
c. During swallowing the elastic epiglottis covers the laryngeal inlet forcing food into the esophagus.
d. Closure of the vocal folds helps prevent food entry and increases thoracic pressure during straining.

XIII. Trachea = Tube just anterior to the esophagus that runs from the larynx to the main bronchi.
   a. Lined by a basic respiratory mucosa with mucous and serous glands in the lamina propria.
   b. Supported by C-shaped cartilage “rings.” Posterior portion of the c-shaped ring is filled in the trachealis muscle. This muscle contracts during coughing and it allows for expansion of the esophagus during swallowing.

XIV. Bronchioles
   a. Branch from small bronchi. >1mm in diameter and have no cartilage in their walls.
   b. They have a relatively large amount of smooth muscle in their walls.
   c. Smooth muscle contraction yields bronchoconstriction and occurs during the parasympathetic response and during allergic reactions.
   d. Smooth muscle relaxation yields bronchodilation during the sympathetic response.
   e. Terminal bronchioles are the last bronchioles w/o alveoli. (The end of the conducting zone.)
   f. Respiratory bronchioles are bronchioles with alveoli budding from them.
   g. They mark the beginning of the respiratory zone and they give rise to alveolar ducts.

XV. Alveolar ducts are tubes made of side-by-side alveoli. They terminate in alveolar sacs.

XVI. Alveolar sacs and alveoli
   a. Alveolar sacs are dead-end clusters of alveoli. There are 300 million alveoli in the lungs.
   b. Alveoli are made of simple squamous epithelial cells known as type I alveolar cells.
   c. Cobwebbing the external surface of the alveoli are pulmonary capillaries.
   d. O₂ and CO₂ are exchanged through both sets of simple squamous epithelia (alveolar & capillary) as well as the basement membrane between the 2. This structure is collectively known as the respiratory membrane. Its thinness facilitates the diffusion of O₂ and CO₂.
   e. Interspersed amongst the type I alveolar cells are type II alveolar cells. These cells function primarily in the production of surfactant, a chemical that helps prevent alveolar collapse.
   f. Alveolar macrophages (dust cells) monitor the surface of the alveoli.
   g. Alveoli are also covered by a network of elastic fibers – which assist with normal expiration.

XVII. The pleurae are thin, double-layered serosa that covers each lung.
   a. Parietal pleura covers the thoracic wall, the superior surface of the diaphragm, and the mediastinum. It continues around the heart and between the lungs.
   b. At the hilum, the parietal is continuous w/ the visceral pleura, which covers the external surface of the lungs themselves.
   c. The pleurae produce pleural fluid which fills the slit-like pleural cavity btwn them. Pleural fluid reduces friction and helps the parietal and visceral pleurae adhere to one another.

XVIII. Basic mechanism of breathing includes 2 phases – inspiration and expiration.
   a. Air moves when a pressure gradient exists btwn the lung alveoli and the atmosphere.
   b. There are 3 pressures vital for lung function:
      i. Atmospheric pressure – pressure exerted by air surrounding the body. 760 mmHg.
      ii. Intrapulmonary pressure – pressure exerted by air within the alveoli. Changes during each cycle of respiration.
      iii. Intrapleural pressure – pressure within the pleural cavity. Changes during each respiratory cycle, but always less than intrapulmonary pressure.

XIX. Lung Elasticity - The lungs are naturally elastic and have a tendency to collapse if there was not an opposing force keeping them open.
   a. The basis of the opposing force is provided by the presence of a pressure gradient (transpulmonary pressure) between the alveoli and the pleural cavity.
   b. Intrapleural pressure > alveolar pressure. Thus, the air w/i the alveoli is always “attempting” to leave the alveoli and enter the pleural cavity. This prevents alveolar collapse.
c. If intrapleural pressure equilibrates with alveolar pressure, this gradient is lost and lung collapse can occur. One way the pressure gradient can be lost is if the pleural cavity is opened to the external environment – due to a stab wound perhaps.

XX. Relationship between pressure and volume
a. Boyle’s Law states that at constant T°, the pressure of a gas varies inversely with its volume.
b. Thus changes in lung pressure can be achieved by changing lung volume.
c. Lung volume is altered by changing thoracic cavity volume via skeletal muscle contraction.

XXI. Sequence of the quiet inspiratory process:
a. Respiratory centers in the ventral medulla oblongata become active.
b. Signals are sent down the phrenic nerve to the diaphragm and down intercostal nerves to the external intercostal muscles.
c. Diaphragm and external intercostals contract.
d. Contraction of the diaphragm lengthens the thoracic cavity top to bottom.
e. Contraction of the external intercostals lifts the ribs and sternum increasing the side-to-side and front-to-back dimensions of the thoracic cavity.
f. Volume of the thoracic cavity increases which causes lung volume to increase.
g. Alveolar pressure decreases. Alveolar pressure is now < atmospheric pressure.
h. Air flows from atmosphere into alveoli until alveolar P = atmospheric P.

XXII. Forced inspiration = Requires greater motor unit activation in the diaphragm and external intercostals resulting in an increase in their contraction. Contraction of other muscles further increase thoracic volume (and further decrease alveolar pressure). These muscles include the sternocleidomastoids, pectoralis minors, and erector spinae.

XXIII. Quiet expiration
a. Passive process, (i.e., not powered by skeletal muscle contraction).
b. Phrenic and intercostal nerves cease firing causing the diaphragm & ext. intercostals to relax.
c. The thoracic volume decreases which causes lung volume to decrease.
d. Alveolar pressure increases until it is > atmospheric pressure.
e. Air flows from the alveoli into the atmosphere until alveolar P = atmospheric P.

XXIV. Forced expiration = Muscles further reduce thoracic cavity volume (and further increase alveolar pressure). These muscles include the rectus abdominis, transverse abdominis, obliques, and internal intercostals.

XXV. Airway resistance
a. Normally insignificant due to the relatively large diameters of the air passages, low viscosity of air, and incredible amount of branching.
b. During severe allergic reactions histamine causes contraction of bronchiolar smooth muscle. This decreases airway volume and increase airway resistance.
c. During an asthma attack, vigorous bronchoconstriction can occur.
d. Mucus or accumulations of infectious material can increase airway resistance.
e. Epinephrine relaxes bronchiolar smooth muscle, increasing bronchiole diameter and decreasing airway resistance.

XXVI. Surface tension.
a. Water molecules line the inner surfaces of the alveoli. These water molecules have a stronger attraction for one another than for the molecules of gas within the alveolar lumen. This high surface tension can lead to alveolar collapse.
b. Collapsed alveoli require large amounts of energy to inflate during inspiration.
c. Luckily, the type II alveolar cells produce the chemical surfactant. It decreases the cohesiveness of the water molecules and thus reduces alveolar surface tension and decreases the likelihood of alveolar collapse.

XXVII. Compliance - the ability of the lungs to expand. This facilitates efficient ventilation.
a. Replacement of the elastic lung tissue with inelastic scar tissue as well as reduced surfactant production will decrease lung compliance.
b. The thoracic cage also needs to be compliant as it expands during the inspiratory process.
c. Too much compliance is undesirable since it hinders the ability to exhale.
Oxygen is transported by blood in 2 ways. Gas exchange in the systemic tissues is governed by partial pressure gradients as well.

Ventilation-perfusion coupling = means that airflow and blood flow in the lungs are matched.

Thickness of the respiratory membrane

- The respiratory membrane consists of the simple squamous epithelia of the alveoli and pulmonary capillaries, as well as their fused basement membranes. It is incredibly thin.
- Any increase in respiratory membrane thickness will decrease the efficiency of gas exchange.

Ventilation-perfusion coupling = means that airflow and blood flow in the lungs are matched.

- Exchange cannot occur if either airflow or blood flow is deficient.
- Increased alveolar CO2 levels cause pulm. arterioles to constrict and bronchioles to dilate.
- Decreased alveolar CO2 levels cause pulm. arterioles to dilate and bronchioles to constrict.

Gas exchange in the systemic tissues is governed by partial pressure gradients as well.

- Arterial blood Po2 is 104mmHg while tissue Po2 is less than 40mmHg.
- Po2 gradient favors flow of O2 from systemic capillary blood into tissues.
- Meanwhile, arterial blood Pco2 is 40mmHg while tissue Pco2 is >45mmHg.
- Pco2 gradient favors flow of CO2 from tissues into systemic capillary blood.

Oxygen is transported by blood in 2 ways.

- 1.5% of the O2 is simply dissolved in plasma.
- The other 98.5% is bound to hemoglobin within red blood cells.
- Each Hb molecule can combine with up to 4 oxygen molecules.
- Hemoglobin with bound O2 is oxyhemoglobin.
- Hemoglobin w/o bound O2 is reduced hemoglobin (deoxyhemoglobin).
- HbO2 + O2 ↔ HbO2 + H+.
- In the lungs (highPo2), the reaction runs from left to right.
- In the tissues (low Po2), the reaction runs from right to left.
- When Hb has 4 O2 molecules bound to it, it’s saturated. If less than 4, it’s unsaturated.
- In the lungs (Po2 is 104mmHg), Hb is fully saturated.
- In the tissues (Po2 is 40mmHg), Hb is 75% saturated, meaning that, on average, each Hb molecule has 3 molecules of O2 bound to it. Thus, substantial amounts of O2 are still available in the venous blood. This provides a reserve for use during increased activity.
- During aerobic respiration, working muscle cells produce CO2, heat, and acid. These factors decrease the affinity that Hb has for O2, making Hb more likely to release O2.
- Carbon monoxide binds to hemoglobin in the same binding site as O2, but far more tightly.

CO2 is transported w/i blood in 3 ways.

- About 10% is dissolved in plasma.
- Another 20% is bound to hemoglobin: Hb + CO2 ↔ HbCO2. HbCO2 is known as carbaminohemoglobin. CO2 binds to Hb in a different place than O2.
c. 70% is transported as part of the bicarbonate ion in plasma.
d. As CO₂ diffuses out of the tissue fluid, it enters systemic capillary plasma and then the RBC.
e. Within the RBC, CO₂ combines with water to form carbonic acid, which dissociates into a bicarbonate ion and a hydrogen ion.
   i. \( \text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{HCO}_3^- + \text{H}^+ \).
   ii. This reaction is catalyzed by the enzyme carbonic anhydrase.
f. Once bicarbonate is formed it diffuses out of the RBC into the plasma.
   i. As this occurs, a chloride ion diffuses from the plasma into the RBC.
   ii. This maintains RBC charge balance and is known as the chloride shift.
g. At the pulmonary capillaries, the above events reverse themselves.

XXXVII. Primary Respiratory Control occurs at a cluster of neurons in the medulla oblongata known as the ventral respiratory group. VRG contains both inspiratory neurons and expiratory neurons.
a. When the inspiratory neurons fire, signals travel down the phrenic and intercostal nerves and excite the diaphragm and external intercostals – resulting in inspiration.
b. When expiratory neurons fire, output to the diaphragm and external intercostals ceases.
c. The on/off cycle of both these neurons creates the basic respiratory rhythm – eupnea.
d. The medulla also contains a dorsal respiratory group (DRG), which integrates information from peripheral chemoreceptors and stretch receptors. It then inputs this info to the VRG.
e. In the pons, we find the pontine respiratory group, which helps modify, breathing rhythm during sleep, talking, and exercise.

XXXVIII. Primary factors influencing respiratory rate
a. The contents of the plasma and the cerebrospinal fluid.
b. The main respiratory stimuli in order of importance are:
   i. CSF pH
   ii. Plasma PCO₂ and pH
   iii. Plasma PO₂.
c. Central chemoreceptors on the medulla measure the \([H^+]\) of the CSF.
d. Peripheral chemoreceptors (located primarily in the aortic arch and carotid sinus) measure the PCO₂, \([H^+]\), and PO₂ of the plasma.
e. When plasma CO₂ levels rise:
   i. CSF CO₂ levels rise (as CO₂ diffuses thru the blood-brain barrier from plasma to CSF).
   ii. Within the CSF, CO₂ combines with H₂O to form HCO₃⁻ and H⁺. (Catalyzed by CA)
   iii. Thus, as plasma CO₂ levels rise, CSF pH will decrease.
   iv. A drop in CSF pH can be damaging. Luckily, medullary chemoreceptors sense the low pH and initiate an ↑ in respiratory rate and depth to rid the body of excess CO₂.
   v. The lowering in pH of the CSF as caused by the rise of CSF PCO₂ as caused by the rise of plasma PCO₂ is the most powerful respiratory stimulus.
f. When plasma PCO₂ reaches its threshold or when plasma pH drops to its threshold:
   i. The peripheral chemoreceptors are activated and they signal the medulla (via the vagus and glossopharyngeal nerves) to increase respiratory rate and depth.
   ii. Recall how CO₂ combines with H₂O to form bicarbonate and a hydrogen ion. This is why ↑ plasma CO₂ results in ↑ plasma H⁺ and ↓ plasma pH.
g. Arterial PO₂ must drop substantially (i.e., to below 60mmHg) before the chemoreceptors sensitive to PO₂ play a role in activating the respiratory centers.
   i. In people who chronically retain CO₂, (perhaps due to emphysema or chronic bronchitis) the peripheral PCO₂ receptors become unresponsive. In such individuals, arterial PO₂ levels play a significant role in respiration regulation.

XXXIX. Factors outside the brainstem also influence respiratory rate and depth.
a. Irritants in the respiratory tract cause coughing and sneezing and changes in rate and depth.
b. The hypothalamus exerts effects as well. An example is the changes in respiratory rate and depth associated with changes in body T°. In general, as body T° ↑, respiratory rate and depth ↑; and as body T° ↓, respiratory rate and depth ↓.
c. Changes in BP affect respiration rate and depth. When BP falls, the respiratory rate increases. When BP rises, the respiratory rate declines.

d. The cerebral cortex also influences respiratory rate, e.g., our ability to hold our breath.

e. Respiratory rhythm is of course altered by laughing, yawning, crying, speech, hiccups, etc.

XL. The respiratory system can both cause and correct disturbances in plasma pH.

a. The respiratory system can cause plasma pH disturbances in 2 ways.

i. During hyperventilation, plasma CO₂ drops.
   1. This causes a decrease in plasma H⁺ and thus, an increase in plasma pH.
   2. If plasma pH rises above normal levels, it is known as plasma alkalosis.
   3. In this case, we call it respiratory alkalosis.

ii. During hypoventilation, plasma CO₂ increases.
   1. This causes an increase in plasma H⁺ and thus, a decrease in plasma pH.
   2. If plasma pH drops below normal levels, it is known as plasma acidosis.
   3. In this case we call it respiratory acidosis.

b. Metabolic alkalosis = Any alkalosis not caused by respiratory malfunctions.

i. Causes of metabolic alkalosis include:
   1. Vomiting – due to the loss of gastric HCl.
   2. Ingestion of excessive antacids (e.g., sodium bicarbonate).

ii. In response to metabolic alkalosis, respiratory rate and depth decrease. This will increase plasma CO₂ levels and decrease plasma pH.

c. Metabolic acidosis = Any acidosis not caused by respiratory malfunctions.

i. Causes of metabolic acidosis include:
   1. Severe diarrhea – excess HCO₃⁻ loss in feces.
   2. Renal disease – failure of kidneys to secrete acids in urine.
   3. Excess alcohol ingestion. (Byproducts of alcohol metabolism are acidic.)
   4. Starvation – when the body begins to break down fat and muscle protein reserves for energy, acidic metabolites (ketone bodies) are produced.
   5. Diabetes mellitus – fats are metabolized producing ketone bodies.

ii. In response to metabolic acidosis, respiratory rate and depth will increase. This will decrease plasma CO₂ levels and increase plasma pH.