I. The main functions of the respiratory system include:
   a. Exchange of **O_2** and **CO_2**.
   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** is the movement of air into/out of the **lungs**
   b. **External respiration** is the movement of O_2 from the lungs to the **blood** and CO_2 from the blood to the lungs.
   c. **Gas transport** refers to the mechanisms by which O_2 and CO_2 are moved thru the blood.
   d. **Internal respiration** is the movement of O_2 from the blood to the **cell** interior and CO_2 from the cell interior to the blood.

III. **Cellular respiration**
   a. Breakdown of **glucose**, **fatty acids** and **amino acids** that occurs in **mitochondria** and results in production of **ATP**.
   b. Requires O_2 and produces CO_2.
   c. Note that this type of cellular respiration, which requires O_2, is known as "**aerobic metabolism**," whereas breakdown of glucose that produces ATP but does not require O_2 is "**anaerobic metabolism**."

IV. The structures of the respiratory system can be 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 can also be 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 are involved in transporting, filtering, humidifying, and warming air.
   b. **Respiratory zone** refers to structures where exchange of O_2 and CO_2 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. Structure of the respiratory zone
   a. Walls of the alveoli are made of simple squamous epithelial cells known as **type I alveolar cells**.
   b. Cobwebbing the external surface of the alveoli are **pulmonary capillaries**. These capillaries are lined by endothelium.

c. O_2 and CO_2 are exchanged as they pass through both sets of simple squamous epithelia (alveolar and capillary) as well as the basement membrane between the 2.
    i. This structure is collectively known as the **respiratory membrane**.
        1. Its extreme thinness facilitates the diffusion of O_2 and CO_2.

d. 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.

e. Alveoli are connected to one another via **alveolar pores**. These allow pressure to be equalized among alveoli

f. **Alveolar macrophages** (**dust cells**) monitor the surface of the alveoli.

g. In addition to capillaries, alveoli are also covered by a network of **elastic fibers** – which assist with normal expiration.

VII. The **pleurae**

a. Thin, double-layered serosa that covers each lung.

b. **Parietal pleura** covers the thoracic wall, the superior surface of the diaphragm, and the mediastinum. It continues around the heart and between the lungs.

c. At the hilum, the parietal pleura is continuous w/ the **visceral pleura**, which covers the external surface of the lungs themselves.

d. The pleurae produce pleural fluid which fills the slit-like **pleural cavity** btwn them.
    i. Pleural fluid reduces friction and helps the parietal and visceral pleurae adhere to one another.

VIII. Basic mechanism of breathing

a. Includes 2 phases – **inspiration** and **expiration**.

b. Air movement occurs when a pressure gradient exists between the air within the lung alveoli and the air in the surrounding atmosphere.

c. There are 3 pressures vital for lung function:
    i. **Atmospheric pressure** – pressure exerted by the air surrounding the body. Normal value is 760 mmHg.
    ii. **Intrapulmonary pressure** – pressure exerted by the 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.

IX. Lung Elasticity

a. The lungs are naturally elastic and would have a tendency to collapse if there was not an opposing force keeping them open.

b. The basis of the opposing force is provided by the presence of a pressure gradient (**transpulmonary pressure**) between the alveoli and the pleural cavity.
    i. Intrapleural pressure is always lower than alveolar pressure. Thus, the air within the alveoli is always “attempting” to leave the alveoli and enter the pleural cavity. This prevents alveolar collapse.

   ii. 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.

X. Relationship between pressure and volume
   a. Given by **Boyle's Law**, which states that at constant temperature, the pressure of a gas varies inversely with its volume.
   b. Thus changes in lung pressure (i.e., the creation of gradients btwn the lungs and the atmosphere) can be achieved by changing lung volume.
   c. Changing lung volume is achieved by changing the volume of the thoracic cavity via skeletal muscle contraction.

XI. 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.
      i. Contraction of the diaphragm lengthens the thoracic cavity top to bottom.
      ii. Contraction of the external intercostals lifts the ribs and sternum increasing the side-to-side and front-to-back dimensions of the thoracic cavity.
   d. Volume of the thoracic cavity increases.
   e. Lung volume increases.
   f. Alveolar pressure decreases. Alveolar pressure is now < atmospheric pressure.
   g. Air flows from atmosphere into alveoli until alveolar P = atmospheric P.

XII. **Forced inspiration**
   a. Other muscles are involved so as to further increase thoracic volume (and further decrease alveolar pressure).
   b. Such muscles include the **scalenes** and **sternocleidomastoids** of the neck, the **pectoralis minors** of the chest, and the **erector spinae** of the back.

XIII. **Quiet expiration**
   a. Passive process, (i.e., not powered by skeletal muscle contraction).
   b. Occurs as follows:
      i. Phrenic and intercostal nerves cease firing.
      ii. Diaphragm and external intercostals relax.
      iii. The thoracic volume decreases.
      iv. Lung volume decreases.
      v. Alveolar pressure increases until it is > atmospheric pressure.
      vi. Air flows from the alveoli into the atmosphere until alveolar P = atmospheric P.

XIV. **Forced expiration**
   a. Muscles contract in order to further reduce the size of thoracic cavity (and further increase alveolar pressure).
   b. Such muscles include the **rectus abdominis**, **transverse abdominis**, **obliques**, and **internal intercostals**.

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

XVI. **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.

XVII. **Compliance**
  a. Refers to the ability of the lungs to expand.
  b. The ease with which the lungs can expand facilitates efficient ventilation.
  c. Replacement of the elastic lung tissue with inelastic scar tissue as well as reduced surfactant production will decrease lung compliance.
  d. The thoracic cage also needs to be compliant as it expands during the inspiratory process.
  e. Too much compliance is undesirable since it hinders the ability to exhale.

XVIII. **Dead space**
  a. Anatomical dead space
    i. Refers to the volume of the conducting zone. Air within the conducting zone cannot be exchanged.
  b. Alveolar dead space
    i. Refers to any alveoli not involved in exchange (due to collapse or obstruction
  c. Total dead space
    i. Refers to the combination of anatomical and alveolar dead spaces.

XIX. **Non-respiratory air movements**
  a. Include coughing, sneezing, laughing, yawning, and hiccupping.

XX. Air components
  a. Air is made up of 79% nitrogen, 20% oxygen, smaller amounts of carbon dioxide and water vapor, and minute amounts of other gases.

XXI. **Dalton's law of partial pressures**
  a. The pressure exerted by atmospheric air is a sum of the pressures exerted by each individual gas in the air.
  b. Each gas in a mixture of gases exerts a certain amount of pressure, which is known as the **partial pressure** for that gas.

c. Individual gases tend to move from one place to another based on their partial pressure gradient.

XXII. **Henry's Law**

a. The solubility of a gas in a liquid is proportional to the pressure of that gas above the liquid.
b. CO_2 is much more **soluble** than O_2 in water; thus it enters the plasma much more readily than does O_2.

XXIII. Partial pressures and gas exchange

a. During gas exchange in the lungs:
   i. The partial pressure of O_2 in the alveoli is 104mmHg.
   ii. The partial pressure of O_2 in blood entering pulmonary capillaries is 40mmHg.
   iii. The PO_2 gradient favors flow of O_2 from alveolar air into the pulmonary capillary blood.
   iv. Meanwhile, the partial pressure of CO_2 in the alveoli is 40mmHg.
   v. The partial pressure of CO_2 in blood entering the pulmonary capillaries is 45mmHg.
   vi. The PCO_2 gradient favors flow of CO_2 from pulmonary capillary blood into the alveolar air.
b. During gas exchange in the systemic tissues:
   i. Arterial blood PO_2 is 104mmHg while tissue PO_2 is less than 40mmHg.
   ii. The PO_2 gradient favors flow of O_2 from the systemic capillary blood into the interstitial fluid and tissue cells.
   iii. Meanwhile, arterial blood PCO_2 is 40mmHg while tissue PCO_2 is greater than 45mmHg.
   iv. The PCO_2 gradient favors flow of CO_2 from interstitial fluid and tissue cells into systemic capillary blood.
c. Notice that the partial pressure gradients for CO_2 are much smaller than the partial pressure gradients for O_2.

XXIV. Oxygen transport

a. O_2 is carried by blood in 2 ways.
   i. 1.5% of the O_2 is simply dissolved in plasma.
   ii. The other 98.5% is bound to **hemoglobin** within red blood cells.
b. Each Hb molecule can combine with up to 4 oxygen molecules.
c. Hemoglobin with bound O_2 is **oxyhemoglobin**.
d. Hemoglobin w/o bound O_2 is **reduced hemoglobin**.
e. The loading and unloading of O_2 by hemoglobin is given by a single reversible equation: $\mathbf{HHb + O_2 \leftrightarrow HbO_2 + H^+}$.
   i. In the lungs (highPO_2), the reaction runs from left to right.
   ii. In the tissues (low PO_2), the reaction runs from right to left.
f. When Hb has 4 O_2 molecules bound to it, it's **saturated**.
g. When Hb has less than 4 O_2 molecules bound to it, it's **unsaturated**.
h. In the lungs (PO_2 is 104mmHg), Hb is fully saturated.
i. In the tissues (PO_2 is 40mmHg), Hb is 75% saturated, meaning that, on average, each Hb molecule has 3 molecules of O_2 bound to it.

i. Thus, substantial amounts of O_2 are still available in the venous blood. This provides a reserve for use during increased activity.

j. During aerobic respiration, working muscle cells produce CO_2, heat, and acid. These factors decrease the affinity that Hb has for O_2, making Hb more likely to release O_2 to these working cells.

k. Note that carbon monoxide binds to hemoglobin in the same binding site as oxygen, but far more tightly.

XXV. CO_2 transport

a. CO_2 is transported w/i blood in 3 ways.
   i. About 10% is dissolved in plasma.
   ii. Another 20% is bound to hemoglobin.
      1. The equation for this combination is: **Hb + CO_2 ↔ $HbCO_2$**.
      2. $HbCO_2$ is known as **carbaminohemoglobin**.
      3. CO_2 binds to Hb in a different place than O_2.
   iii. 70% is transported as part of the **bicarbonate ion** in plasma.

b. When CO_2 diffuses out of the tissue fluid, it enters the systemic capillary plasma and then the RBC.

c. Within the RBC, CO_2 combines with water to form **carbonic acid**, which dissociates into a **bicarbonate ion** and a **hydrogen ion**.
   i. The equation is: $\mathbf{CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+}$.
   ii. This reaction is catalyzed by the enzyme **carbonic anhydrase**.

d. 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 charge balance and is known as the **chloride shift**.

e. At the pulmonary capillaries, the above events reverse themselves.

XXVI. Respiratory Control

a. The primary control center for respiration is a cluster of neurons in the medulla oblongata known as the **ventral respiratory group** (**VRG**).
   i. It contains both **inspiratory neurons** and **expiratory neurons**.
   ii. When the inspiratory neurons fire, signals travel down the phrenic and intercostal nerves and excite the diaphragm and external intercostals – resulting in inspiration.
   iii. When the expiratory neurons fire, the output to the diaphragm and external intercostals ceases and expiration occurs.
   iv. The on/off cycle of both these types of neurons creates the basic respiratory rhythm – known as **eupnea**.

b. There is also a **dorsal respiratory group (DRG)**, which helps to integrate information from peripheral chemoreceptors and stretch receptors. It then inputs this info to the VRG.

c. In the pons, we find the **pontine respiratory group**, which helps modify, breathing rhythm during sleep, talking, and exercise.

XXVII. Primary factors influence 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 P_{CO_2}** and **pH**

iii. **Plasma PO_2.**

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 PCO_2, $[H^+]$, and PO_2 of the plasma.

e. When plasma CO_2 levels rise:
   - i. CSF CO_2 levels rise (since CO_2 can easily diffuse thru the blood-brain barrier and enter the CSF from the plasma).
   - ii. Within the CSF, CO_2 combines with H_2O to form HCO_3^- and H^+.
   - iii. Thus, as plasma CO_2 levels rise, CSF pH will decrease.
   - iv. A drop in CSF pH can be quite damaging. Luckily, the medullary chemoreceptors sense the low pH and initiate an ↑ in respiratory rate and depth to rid the body of excess CO_2.
   - v. The lowering in pH of the CSF as caused by the rise of CSF PCO_2 as caused by the rise of plasma PCO_2 is the most powerful respiratory stimulus.

f. When plasma PCO_2 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 CO_2 combines with H_2O to form bicarbonate and a hydrogen ion. This is why ↑ plasma CO_2 results in ↑ plasma H^+ and ↓ plasma pH.

g. Arterial PO_2 must drop substantially (i.e., to below 60mmHg) before the chemoreceptors sensitive to PO_2 play a role in activating the respiratory centers.
   - i. In people who chronically retain CO_2, (perhaps due to **emphysema** or chronic bronchitis) the peripheral PCO_2 receptors become unresponsive. In such individuals, arterial PO_2 levels play a significant role in respiration regulation.

XXVIII. Factors outside the brainstem also influence respiratory rate and depth.

a. The presence of irritants in the respiratory tract can lead to coughing and sneezing as well as cause other changes in rate and depth.

b. The **Hering-Breuer reflex** describes another factor. As forced inhalation proceeds, the lungs stretch. Excess stimulation of lung stretch receptors inhibits the medullary inspiratory neurons and activates medullary expiratory neurons.

c. 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 ↓.

d. Changes in BP affect respiration rate and depth. When BP falls, the respiratory rate increases. When BP rises, the respiratory rate declines.

e. The **cerebral cortex** also influences respiratory rate, e.g., our ability to hold our breath (for a limited time at least).

f. Respiratory rhythm is of course altered by laughing, yawning, crying, speech, hiccupping, etc.

XXIX. 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 CO_2 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 CO_2 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**

i. Any alkalosis not caused by respiratory malfunctions.

ii. Causes of metabolic alkalosis include:

1. Vomiting – due to the loss of gastric HCl.
2. Ingestion of excessive antacids (e.g., sodium bicarbonate).
3. Constipation – decreased loss of HCO_3^- in feces.

iii. In response to metabolic alkalosis, respiratory rate and depth decrease. This will increase plasma CO_2 levels and decrease plasma pH.

c. **Metabolic acidosis**

i. Any acidosis not caused by respiratory malfunctions.

ii. Causes of metabolic acidosis include:

1. Severe diarrhea – excess HCO_3^- 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. Untreated **diabetes mellitus** – fats are broken down and ketone bodies are produced.

iii. In response to metabolic acidosis, respiratory rate and depth will increase. This will decrease plasma CO_2 levels and increase plasma pH.