Lesson XI: The Respiratory System

As we learned in previous lessons, the tissues of the body are dependent upon oxygen for the generation of ATP. Oxygen is gathered from the atmosphere with each inhalation, carried in the hemoglobin molecules of red blood cells and is delivered to the tissues of the body. The by-product of O₂ utilization is carbon dioxide (CO₂), and in addition to delivering oxygen, hemoglobin and the processes of exhalation prevent toxic amounts of CO₂ from building up in the body. Thus, both the cardiovascular and respiratory systems play a shared role in the delivery of O₂ and the removal of CO₂. The failure of any one of these systems results in the rapid death of cells, either from oxygen starvation or from the accumulation of waste products such as CO₂.

The process of the exchange of O₂ for CO₂ in the lungs is called respiration. There are three major components to respiration:

1. **Pulmonary ventilation**: also called breathing, it is the inspiration (inflow) and expiration (outflow) of air between the atmosphere and lungs
2. **Pulmonary respiration**: is the exchange of gases between the blood and the lungs
3. **Tissue respiration**: refers to the exchange of gases between the blood and the cells of the body.

I. Respiratory organs

The respiratory system is comprised of the nose, pharynx (throat), larynx (voice box), trachea (wind pipe), bronchi and lungs. The upper respiratory system refers to the nose, pharynx and associated structures. The lower respiratory system refers to the larynx, trachea, bronchi and lungs. Functionally, the respiratory system is divided into two parts:

1. **Conduction portion**: consisting of interconnecting tubes and cavities: nose, pharynx, larynx, trachea, bronchi and terminal bronchioles;
2. **Respiratory portion**: referring to those portions of the respiratory system where the exchange of gases occur: respiratory bronchioles, alveolar ducts and alveoli.

**Nose**

Anatomically, the **nose** has two portions: an external portion that protrudes from the face, and an internal portion inside the skull. The external portion of the nose consists of a supporting network of bone and hyaline cartilage covered in muscle and skin, and lined by a mucous membrane. Whereas the bridge of the nose is formed by the nasal bones, the remainder of the external nose is composed of pliable cartilage, providing the nose with a large degree of flexibility. On the undersurface of the nose are two openings called the **external nares**, or **nostrils**.

The internal portion of the nose is a large cavity that lies inferior to the cranium and superior to the mouth. Its anterior portion of the internal nose fuses with the nostrils, which in turn merge with the **internal nares** or **choanae**. The posterior portion of the internal nose fuses with the upper portions of the pharynx. Ducts from the paranasal sinuses and the nasalacrimal ducts also empty into the internal nose. The floor of the choanae is comprised of the hard palate, separating the nasal and oral cavities.

The inside of both the external and internal nose is the **nasal cavity**. It is divided into left and right sides by a vertical partition called the **nasal septum**. The anterior portion of the nasal cavity is called the **vestibule** and is surrounded by cartilage; the upper nasal cavity is surrounded by bone.

The nose has three primary functions, including warming, filtering, and moisturizing incoming air, and to receive olfactory stimuli called odour. The nose also acts as a resonating chamber to modify sounds.

When air enters the nostrils, it passes through the vestibule, which is lined by skin containing coarse hairs that filter out large dust particles. The air then passes through the upper nasal cavity, which is divided into three lateral projections called the superior, middle and inferior **conchae**. The conchae, which almost extend to the septum, subdivide each side of nasal cavity into passageways called the...
superior, middle and inferior **meatuses**. In turn, the mucous membranes line the cavity and the shelves formed by the conchae. The olfactory receptors lie in the olfactory epithelium in the membrane that lines the superior nasal conchae and adjacent septum. Below the olfactory epithelium the mucous membrane contains capillaries and pseudostratified ciliated columnar epithelial cells, with many goblet cells. The mucous secreted by these goblet cells moistens the incoming air and traps foreign particles. The ciliated cells then move the mucous to pharynx to be expectorated, or swallowed.

**Pharynx**

The **pharynx** is a funnel-shaped tube that begins at the terminal end of the internal nares and extends to the larynx. It lies posterior to the nasal cavity, oral cavity and larynx, and just anterior to the cervical vertebrae. The wall of the pharynx is composed of skeletal muscles lined with mucous membranes, and functions as a passageway for air and food, and serves as a resonating chamber for speech.

The uppermost portion of the pharynx is the **nasopharynx**, lying posterior to the internal portion of the nose and extending downward, its anterior wall fusing with the soft palate. Four openings can be found in its wall: the two internal nares and the two openings of the **Eustachian tubes**, or auditory canals. The nasopharynx is lined with cilia that move mucus down towards the inferior part of the pharynx. The nasopharynx also exchanges a small amount of air with the Eustachian tubes to equalize the pressure on both sides of the tympanic membrane of the middle ear. The Eustachian tube is normally closed at its medial end, but opens during swallowing and yawning. Infections of the upper respiratory tract often migrate to the Eustachian tubes, especially so in children in which case the Eustachian tubes are arranged in a horizontal fashion. Mucus-forming foods such as dairy and flour products allow for the production of a thicker, more tenacious mucus, and these factors in addition to the anatomical placement of the Eustachian tubes, make children more susceptible to ear infections.

The **oropharynx** lies posterior to the oral cavity and extends from the soft palate, which makes up its posterior wall, inferiorly to the hyoid bone. The lowest portion of
the pharynx is the **laryngopharynx**, extending downwards from the hyoid bone, becoming continuous with the esophagus of the digestive tract.

**Larynx**
The larynx, or voice box, connects the terminal portion of the pharynx with the trachea. It is located anterior to the fourth through sixth cervical vertebrae. It is composed of nine pieces of cartilage, three of which are single, and six of which are paired. Of the paired cartilages, the arytenoid cartilage forms the vocal cords. The thyroid cartilage forms the anterior portion of the larynx giving it a triangular shape. In men the thyroid cartilage enlarges during puberty, and is also called the **Adam’s apple**.

The epiglottis is a large leaf-shaped piece of elastic cartilage, the “stem” of which is attached to the thyroid cartilage, and the “leaf” portion remaining unattached, moving up and down, acting as a trap door. During swallowing the larynx is slightly elevated, causing the free edge of the epiglottis to form a lid over the glottis, a pair of folds of mucus membrane that sit on top of the vocal cords. In this way, the larynx becomes closed off and food is routed down into the esophagus and is prevented from entering the trachea.

**Trachea**
The trachea, or windpipe is tubular passageway for air, located anterior to the esophagus, extending from the larynx to the fifth thoracic vertebra. The wall of the trachea consists of a mucosa, submucosa, hyaline cartilage, and adventitia (outer layer of areolar connective tissue). The epithelium of the trachea is pseudostratified ciliated columnar epithelium, and functions identically to that found in the nose and pharynx. The trachea is composed of 16 to 20 C-shaped rings of hyaline cartilage, arranged horizontally and stacked upon one another. Transverse smooth muscle fibers and elastic tissue attach the open ends of cartilage rings. The solid C-shaped construction of the cartilage provides for a high degree of rigidity, ensuring that the trachea does not collapse inward and obstruct breathing. If an obstruction occurs to the trachea, a **tracheostomy** is an emergency procedure in which a small incision is made just below the larynx and a plastic or metal tube inserted into the incision, allowing for the passage of air into and out of the lungs.
The point at which the trachea subdivides into the right and left bronchi is an internal ridge called carina. The mucous membranes of carina are one of the most sensitive areas of respiratory system, and is associated with the cough reflex.

**Bronchi**
The trachea divides into the right and left primary bronchi, the right bronchus is typically more vertical, shorter and wider than left. The primary bronchi then divide into smaller bronchi called the secondary bronchi, which in turn divide into the tertiary bronchi, the bronchioles, and lastly, the terminal bronchioles. As the branching becomes more extensive, two changes occur to the arrangement of tissues. Firstly, the epithelium changes from pseudostratified ciliated columnar epithelium to nonciliated simple cuboidal epithelium in terminal bronchioles. Secondly, the incomplete C-shaped rings of the bronchi are gradually replaced by plates of cartilage, and the finally disappear in the bronchioles. As the cartilage decreases, the amount of smooth muscle increases, spiraling around the lumen of the respiratory passages.

The activities of the autonomic nervous control the dilation and contraction of the smooth muscle that surrounds the lumen of the respiratory tract. The parasympathetic division of the ANS and mediators of the allergic reaction, such as histamine, promote the constriction of the bronchioles. The sympathetic division on the other hand, promotes the dilation of the bronchioles. During an asthma attack the smooth muscle of bronchioles contract, narrowing the lumen. These spasms, if particularly strong or prolonged can prevent oxygen from being circulated in the blood, leading to hypoxia and irreversible damage to the heart and brain. Herbs that act as muscarinic-antagonists such as *Datura stramonium*, and sympathomimetics such as *Ephedra sinica*, have long been used to treat to treat acute asthma attacks, dilating the bronchioles and bronchi, used along with herbs such as *Prunus virginiana* and *Verbascum thapsus* that help to thin the mucus and reduce mucosal irritability.

**Lungs**
The lungs are a pair of cone-shaped organs located in the thoracic cavity, separated from each other by heart and other structures of the mediastinum. Two layers of serous
membrane called the plural membrane enclose and protect each lung. The outer layer that attaches to the wall of the thoracic cavity is the parietal pleura, and the inner layer that is attached to the lungs is called the visceral pleura. The space between these two membranes is called the pleural cavity, and is filled with serous fluid, reducing friction between the two membranes during breathing.

The lungs extend from the diaphragm to just slightly above the clavicles, lying against the ribs anteriorly and posteriorly. The right lung is thicker and broader than the left because the diaphragm is higher on the right side to accommodate the liver that lies below it, and because the left lung shares space with the heart in the thorax.

Each lung is divided into lobes by one or more fissures. Both lungs have an oblique fissure that extends downward and forward. In addition, the right lung has a horizontal fissure. The oblique fissure separates both lungs into a superior and inferior lobe, and the horizontal fissure in the right lung creates the middle lobe. Each lobe receives its own secondary bronchus: in the right lung, the superior, middle and inferior secondary bronchi; and in the left lung, the superior and inferior secondary bronchi. With each lobe of the lungs, the secondary bronchi give rise to tertiary bronchi, ten of which are found in each lung. Each area of the lung supplied by a tertiary bronchus is called a bronchopulmonary segment, and in turn, each bronchopulmonary segment is comprised of many small compartments called lobules.

The terminal bronchioles in each lobule segment subdivide into microscopic respiratory bronchioles, which in turn divide into alveolar ducts. Surrounding the alveolar ducts are numerous alveoli (plural) and alveolar ducts. An alveolus (singular) is a cup-shaped outpouching lined by epithelium and a thin lining of basement membrane. Alveolar sacs are two or more alveoli that share a common opening. The walls of the alveoli consist of two kinds of epithelial cells: type I alveolar cells, forming a continuous lining interrupted by occasional type II alveolar cells that secrete alveolar fluid. This fluid helps to keep the alveolar cells moist and acts as a surfactant, lowering the surface tension of the alveolar fluid and thereby reducing the potential of the alveoli collapsing due to the attractive force.
among polar water molecules. In addition to alveolar cells, **alveolar macrophages** are also located in the alveolar wall, functioning to remove any dust or foreign debris that enters the lung.

Blood supply to the lungs is provided by two sets of arteries, the **pulmonary arteries** and **bronchial arteries**. Deoxygenated blood from the right ventricle of the heart enters into the lungs via the **pulmonary trunk**, which is divided into a left and right **pulmonary artery**, servicing the left and right lungs, respectively. Once the blood has become reoxygenated it returns back to the left atrium of the heart through four **pulmonary veins**. The supply of oxygen rich blood to the lungs however is primarily derived from the **bronchial arteries** that arise from the aorta, some of which connect to branches of the pulmonary arteries to perfuse the lungs with blood.

**II. Physiology of Respiration**

**Pulmonary ventilation**, or breathing, is process by which gases are exchanged between the atmosphere and the alveoli, occurring due to the existence of a **pressure gradient**. Thus, when the pressure in the lungs is less than the pressure in the atmosphere, air is pulled into the lungs. Likewise, when the pressure in the lungs exceeds that of the atmosphere, air is released by the lungs. Take a deep breath in and hold the breath momentarily, and notice the increase in pressure in your lungs. Now let the air out – notice how it takes no muscular effort to release the air – this is because the pressure of the air was greater in your lungs, and by exhaling you are normalizing the pressure gradient between the atmosphere and your lungs. Now forcefully exhale all the air out of your lungs, and during inhalation, allow the air to come into your lungs without any effort. Once again, the pressure difference between your lungs and the atmosphere causes the air to move into your lungs due to the negative pressure created by exhalation. Thus ventilation occurs in part due to the difference in the pressure gradient between your lungs and the atmosphere, a process that is assisted by the intercostals muscles and diaphragm.
**Inspiration**

**Inhalation**, or breathing in, is called inspiration. Before inspiration, the alveolar pressure is about 760 mm Hg (1 atmosphere), at sea level. For inspiration to occur, the lungs must expand, and it is this increase in lung volume that decreases the pressure in the lungs below atmospheric pressure. Inspiration involves the contraction of diaphragm and intercostal muscles. The **diaphragm** is domed-shaped muscle that forms the floor of thoracic cavity. When it is contracted it becomes flattened, and thus increases the vertical dimension of the thoracic cavity. The diaphragm is responsible for about 75% of the air that enters the lung, the **intercostals** responsible for the remainder.

When the volume of the lungs increases, the alveolar pressure drops from 760 to 758 mm Hg, establishing a pressure gradient. Air then rushes into the lungs and inspiration takes place. Thus, inspiration is mostly an active process, assisted by the change in the pressure gradient.

The term for normal, quiet breathing is **eupnea**, involving shallow, deep or a combined shallow and deep breathing. **Shallow breathing**, or **costal breathing**, involves the outward movement of the chest as the result of the contraction of the intercostal muscles. **Deep breathing**, or **diaphragmatic breathing** involves the outward movement of the abdomen due to the downward contracting movement of the diaphragm. Deep breathing is generally thought to involve the activities of the parasympathetic division of the ANS, and the practice of deep breathing exercises can modulate the activities of the ANS and promote a more relaxed, stress-free state.

**Expiration**

**Exhalation**, or breathing out, is called expiration. In this case, the pressure gradient is reversed and occurs when the alveolar pressure is greater than the atmosphere, about 762 mm Hg. Unlike inspiration, expiration is entirely a passive process, dependent upon the recoil of elastic fibers in the diaphragm and intercostal muscles that were stretched during inhalation, and the inward pull of surface tension due to the film of alveolar fluid.
Pulmonary volumes and capacities
During normal breathing about 500 ml of air is inhaled, and the same amount moves out with each exhalation, called collectively, the tidal volume. With each inspiration, only 350 ml reaches alveoli, the remaining 150 ml contained within the spaces of respiratory tract. A very deep breath, averaging about 3100 ml above the 500 ml of tidal volume is called the inspiratory reserve volume. Exhaling forcibly allows for the expiration of about 1200 ml in addition to the tidal volume, called the expiratory reserve volume. About 1200 ml of air remains in lungs at all times to keep alveoli slightly inflated, called the residual volume.

Pulmonary capacities are combinations of specific lung volumes. Inspiratory capacity, or the total inspiratory volume of the lungs, is the sum of the tidal volume plus the inspiratory reserve volume (3600 ml). Functional residual capacity is the sum of the residual volume plus the expiratory volume (2400 ml). The vital capacity is the sum of the inspiratory reserve volume, tidal volume and expiratory reserve volume (4800 ml). The total lung capacity is the sum of all volumes (6000 ml).

Physiology of External Respiration
The exchange of oxygen and CO\textsubscript{2} between the alveoli and the pulmonary blood capillaries is called external respiration. This results in the conversion of deoxygenated blood coming from the heart via the pulmonary arteries to oxygenated blood, which then returns back to the heart via the pulmonary veins.

In order to understand the physiology of respiration and the exchange of oxygen and carbon dioxide, we need to know how much of each kind of gas is present in the air at any given point. This is calculated by a measurement called the partial pressure ($p$), a measurement of the pressure of a specific gas in a mixture of gases. The atmospheric pressure at sea level for example is 760 mm Hg, the sum of the partial pressure of oxygen, carbon dioxide, nitrogen and water, i.e. $p\text{O}_2 + p\text{CO}_2 + p\text{N}_2 + p\text{H}_2\text{O}$.

The partial pressure exerted by each component in the atmosphere is obtained by multiplying the sum pressure (760 mm Hg) by the percentage of the gas in the mixture. Oxygen, for example, makes up about 21% of the gas in the
atmosphere (at sea level) and thus the \( pO_2 \) is 159.6 mm Hg (760 mm Hg \( \times 0.21 \)).

The amounts of \( CO_2 \) and \( O_2 \) vary in inspired (atmospheric), alveolar air, and expired air. Inspired air contains about 21% oxygen and about 0.04% carbon dioxide. Alveolar air contains less oxygen (14%) and much more carbon dioxide (5.5%). Expired air contains slightly more \( O_2 \) than alveolar air (16%), and slightly less \( CO_2 \) (4.5%). Also, inspired air and alveolar air have a higher water vapour content (\( H_2O \)) because the lungs humidify the air during inhalation.

The \( pO_2 \) of alveolar air is 105 mm Hg, and the \( pO_2 \) of the deoxygenated blood in pulmonary capillaries is only 40 mm Hg. Thus, because of the arising of this pressure gradient there is net diffusion of \( O_2 \) from alveoli to the blood in the capillaries until 105 mm Hg of \( O_2 \) in the blood is reached and equilibrium is establish. Conversely, the \( pCO_2 \) of deoxygenated blood is 45 mm Hg and the alveolar \( pCO_2 \) is 40 mm Hg. Thus, there is net diffusion of \( CO_2 \) until equilibrium is reached, at about 40 mm Hg.

**Physiology of Internal Respiration**

As blood passes through the capillaries it picks up the maximal amount of oxygen it can and returns it to the heart for distribution throughout the body, no matter how quickly the blood is flowing. The exchange of oxygen and carbon dioxide between the various tissue cells and blood capillaries is called internal respiration.

The oxygenated blood that enters the tissue capillaries has average \( pO_2 \) of 105 mm Hg, whereas tissue cells have \( pO_2 \) of around 40 mm Hg. Thus, there is a diffusion of \( O_2 \) through the interstitial fluid to cells until the \( pO_2 \) of the blood decreases to 40 mm Hg. At rest only 25% of available \( O_2 \) actually enters cells, and thus deoxygenated blood can retain a considerable amount of \( O_2 \). During exercise however, the \( O_2 \) needs increase, and more \( O_2 \) diffuses from the blood into the tissues.

The average \( pCO_2 \) of tissue cells is 45 mm Hg, and the capillary blood has an average \( pCO_2 \) of 40 mm Hg. This difference facilitates the diffusion of \( CO_2 \) from the cells of the body into the blood until the \( pCO_2 \) is equal to that of tissues (45 mm Hg).
Transport of Oxygen

Since oxygen does not readily dissolve in water, very little oxygen is transported in the plasma of the blood (about 1.5%). The remainder of the oxygen is transported in chemical combination with the hemoglobin inside of the red blood cells. For every 100 ml of oxygenated blood there is about 20 ml of oxygen, 0.3 ml free in the cytosol and the remaining 19.7 ml bound to hemoglobin.

As mentioned in Lesson IX: The Cardiovascular System, hemoglobin is comprised of a protein portion called globin and an iron-containing pigment called heme. Each hemoglobin molecule has four heme groups that can combine with one molecule of oxygen (O₂). Oxygen and hemoglobin combine in a reversible reaction to form oxyhemoglobin:

\[
\text{Hb} + \text{O}_2 \rightleftharpoons \text{Hb-O}_2
\]

The most important factor in how much O₂ combines with hemoglobin is the \( pO_2 \). When hemoglobin is completely converted to HbO₂, it is said to be fully saturated. When the hemoglobin is a mixture of HbO₂ and Hb, it is said to be partially saturated. The percent saturation of hemoglobin is the percentage of HbO₂ in total hemoglobin. The greater the \( pO_2 \) the greater the percent of HbO₂. In pulmonary capillaries, where the \( pO_2 \) is high, a lot of O₂ binds with hemoglobin, but in tissue capillaries, where the \( pO_2 \) is lower, hemoglobin does not hold as much oxygen and oxygen is released into the tissue cells. When the \( pO_2 \) is between 60 and 100 mm Hg, hemoglobin is 90% or more saturated with hemoglobin, and thus the blood picks up a nearly maximal amount of O₂ from the lungs. This explains why even in low oxygen environments, such as high altitudes, mountain climbers can still perform. Between 10 and 40 mm Hg however, large amounts of oxygen are released from hemoglobin in response to only small changes in the \( pO_2 \). In active tissues, such as muscle, the \( pO_2 \) may dip well below 40 mm Hg. Such pressures ensure that a large amount of oxygen is released to the tissues.

Several other factors however, besides the \( pO_2 \), contribute to hemoglobin-oxygen binding. In an acid environment
hemoglobin’s affinity for oxygen is lower and oxygen splits more readily from hemoglobin. Thus, a lowered pH drives oxygen off hemoglobin, increasing oxygen availability. CO₂ can also bind to hemoglobin, and as the pCO₂ rises, O₂ is more readily released from hemoglobin. Acidity and pCO₂ are related, since low blood pH results from a high pCO₂. As CO₂ is taken up by the red blood cells, it is temporarily converted into carbonic acid (H₂CO₃) by an enzyme called **carbonic anhydrase**:

\[
\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^- 
\]

Carbonic acid formed in red blood cells then dissociates into hydrogen ions and bicarbonate ions. As the hydrogen ion concentration increases, the pH decreases. Thus, an increased pCO₂ produces a more acid environment, helping to split O₂ from hemoglobin. A low pH can also result from lactic acid build up due to anaerobic metabolism within muscles.

Temperature is another factor that can affect hemoglobin-oxygen binding, with the heat energy released by the metabolic activity of cells inducing the release of oxygen from hemoglobin. Thus contracting skeletal muscles produce both heat and lactic acid, increasing oxygen supply. Lastly, a substance called **2,3-biphosphoglycerate (BPG)** found in red blood cells acts to decrease the affinity of hemoglobin for oxygen and thus helps to release oxygen. BPG is formed in RBCs from the breakdown of glucose to produce ATP. BPG binds with the terminal amino groups of the two beta globin chains of hemoglobin, causing O₂ to be bound less tightly to hemoglobin. Certain hormones, such as thyroxine, human growth hormone, the catecholamines and testosterone increase the formation of BPG. Typically, BPG is also found in higher amounts in people living at higher elevations.

**Transport of Carbon dioxide**
Under normal resting conditions, each 100 ml of deoxygenated blood contains about 5 ml of CO₂, carried in three main forms:

1. **Dissolved CO₂**: representing only about 9% of the total, some of CO₂ is dissolved in the blood plasma, and upon reaching the lungs, diffuses into the alveoli.
2. **Carbaminohemoglobin**: About 13% of the CO\(_2\) combines with the amino groups of amino acids found in RBCs to form carbamino compounds. Since the dominant form of protein found in the RBC is hemoglobin, most of the amino-bound CO\(_2\) combines with the globin portion of hemoglobin to form carbaminohemoglobin (HbCO\(_2\)):

\[
\text{Hb} + \text{CO}_2 \rightleftharpoons \text{HbCO}_2
\]

The formation of HbCO\(_2\) is influenced by the \(p\text{CO}_2\). When the \(p\text{CO}_2\) in the tissue capillaries is high, it promotes the formation of carbaminohemoglobin. When the \(p\text{CO}_2\) is low however, the CO\(_2\) readily splits from the hemoglobin to diffuse into the alveoli.

3. **Bicarbonate ions**: The greatest percentage of CO\(_2\) (70%) is transported in the plasma as bicarbonate ions, the same reaction noted earlier:

\[
\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-
\]

As CO\(_2\) diffuses into the tissue capillaries and enters the red blood cells it reacts with water, and in the presence of carbonic anhydrase, forms carbonic acid (H\(_2\)CO\(_3\)). Carbonic acid then disassociates into hydrogen and sodium bicarbonate ions. Some of the \(H^+\) then combines with hemoglobin or other buffers. As sodium bicarbonate ions accumulate in the red blood cell, some them diffuse into the plasma, down the concentration gradient. In exchange, chloride ions (Cl\(^-\)) diffuse into the red blood cell, maintaining the ionic balance between the red blood cells and the plasma.

**Regulation of breathing**

The activities of the respiratory system are controlled by a group of neurons in the brain stem called the respiratory center, which from a functional perspective, are separated into three groups: the medullary rhythmicity area, the pneumotaxic area, and the apneustic area.

The **medullary rhythmicity area** controls the basic rhythm of respiration through the activity of inspiratory and
expiratory centers. Nerve impulses are generated in the **inspiratory area** for about two seconds, and are propagated to the external intercostal muscles via the intercostals nerves and to the diaphragm via the phrenic nerves causing the muscles to contract. At the end of these two seconds the inspiratory area becomes inactive for about 3 seconds, allowing the external intercostal muscles and diaphragm to relax, only to be stimulated again by the inspiratory center. The neurons that form the **expiratory area** typically remain inactive during quiet breathing, but during forceful breathing during the excitatory area functions to cause the internal intercostals muscles and the abdominal muscles to contract. The **pneumotaxic area** helps to coordinate the transition between inhalation and exhalation, transmitting inhibitory nerve impulses to the inspiratory area to prevent the lungs becoming to full of air, thereby shortening the length of inspiration. Somewhat opposite to the pneumotaxic area, the **apneustic area** sends stimulatory impulses to the inspiratory center thereby prolonging inspiration.

The regulation of the basic rhythm established by the inspiratory center can be modified by a range of influences. The build up of up of CO₂ and H⁺ strongly stimulates the inspiratory center. **Central chemoreceptors** located in the medulla oblongata monitor H⁺ and pCO₂ concentrations in the cerebrospinal fluid. **Peripheral chemoreceptors** are clustered as **aortic bodies** embedded in the wall of the arch of the aorta, and as **carotid bodies** located in the wall of the left and right carotid arteries. These chemoreceptors are sensitive to changes in pO₂, H⁺, and pCO₂ in the blood. A decrease in the pO₂ and/or an increase in the pCO₂ (resulting in an increase in the H⁺ concentration), stimulates the inspiratory center.