Carbon Dioxide Transport

- Carbon dioxide is transported in the blood in three forms
  - Dissolved in plasma – 7 to 10%
  - Chemically bound to hemoglobin – 20-23% is carried in RBCs as carbaminohemoglobin
  - Bicarbonate ion in plasma – 70% is transported as bicarbonate (HCO₃⁻)
Transport and Exchange of Carbon Dioxide

- Carbon dioxide diffuses into RBCs and combines with water to form carbonic acid ($\text{H}_2\text{CO}_3$), which quickly dissociates into hydrogen ions and bicarbonate ions

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{CO}_2 & + & \text{H}_2\text{O} & \leftrightarrow & \text{H}_2\text{CO}_3 & \leftrightarrow & \text{H}^+ & + & \text{HCO}_3^- \\
\text{Carbon} & & \text{Water} & & \text{Carbonic} & & \text{Hydrogen} & & \text{Bicarbonate} \\
\text{dioxide} & & & & \text{acid} & & \text{ion} & & \text{ion} \\
\hline
\end{array}
\]

- In RBCs, the enzyme carbonic anhydrase reversibly catalyzes the conversion of carbon dioxide and water to carbonic acid

Figure 22.22a

(a) Oxygen release and carbon dioxide pickup at the tissues
Transport and Exchange of Carbon Dioxide

At the tissues:

- Bicarbonate quickly diffuses from RBCs into the plasma
- The chloride shift – to counterbalance the outrush of negative bicarbonate ions from the RBCs, chloride ions (Cl\(^-\)) move from the plasma into the erythrocytes

Transport and Exchange of Carbon Dioxide

At the lungs, these processes are reversed

- Bicarbonate ions move into the RBCs and bind with hydrogen ions to form carbonic acid
- Carbonic acid is then split by carbonic anhydrase to release carbon dioxide and water
- Carbon dioxide then diffuses from the blood into the alveoli
Haldane Effect

- The amount of carbon dioxide transported is markedly affected by the $P_{O_2}$
- Haldane effect – the lower the $P_{O_2}$ and hemoglobin saturation with oxygen, the more carbon dioxide can be carried in the blood
Haldane Effect

- At the tissues, as more carbon dioxide enters the blood:
  - More oxygen dissociates from hemoglobin due to the hydrogen influence (Bohr effect)
  - More carbon dioxide combines with hemoglobin, and more bicarbonate ions are formed
- This situation is reversed in pulmonary circulation
Influence of Carbon Dioxide on Blood pH

- The carbonic acid–bicarbonate buffer system resists blood pH changes
- If hydrogen ion concentrations in blood begin to rise, excess $H^+$ is removed by combining with $HCO_3^-$
- If hydrogen ion concentrations begin to drop, carbonic acid dissociates, releasing $H^+$
- Changes in respiratory rate can also:
  - Alter blood pH
  - Provide a fast-acting system to adjust pH when it is disturbed by metabolic factors (those not related to respiratory activities)

Control of Respiration:

Medullary Respiratory Centers

- Inspiration is mostly done by movement of the diaphragm
- Diaphragm is controlled by the phrenic nerve
- Basic respiratory cycle is controlled by the PaceMaker Neurons (PN) in the medulla oblongata
- The PN communicates with the dorsal respiratory group (DRG), or inspiratory center:
  - Is located near the root of nerve IX
  - Excites the inspiratory muscles (via phrenic nerve and intercostal nerves) and sets eupnea (12-15 breaths/minute)
The dorsal respiratory group (DRG), also sends signals to the ventral respiratory group (VRG):

- Appears to be involved in expiration
- Sends signals to the solitary nuclei in medulla
- They in turn send inhibitory signals to the DRG. This thus turns off the stimulation of the phrenic nerve and starts the exhalation process.
Pons Respiratory Centers

- Pons centers or Pontine Respiratory Group (PRG):
  - Influence and modify activity of the medullary centers
  - Smooth out inspiration and expiration transitions and vice versa
  - Contains two centers
    - Pneumotaxic center
    - Apneustic center

Pneumotaxic center (PC)
- Provides inhibition to the DRG, resulting in shorter periods of inspiration

Apneustic Center
- Provides stimulation of the DRG and could result in deeper inspiration or even breath-holding at end of inspiration

Main function of PC is to provide smooth transition between inspiration and expiration. It tends to inhibit the apneustic center as well.
Regulation of Respiration

- Mammals contain two groups of chemoreceptors that influence respiration
  - Central chemoreceptors in medulla
  - Peripheral chemoreceptors (aortic and carotid bodies)

Depth and Rate of Breathing: $P_{CO_2}$

- Changing $P_{CO_2}$ levels are monitored by chemoreceptors of the brain stem
- Carbon dioxide in the blood diffuses into the cerebrospinal fluid where it reacts with water to form hydrogen ions and bicarbonate ions
- Since the CFS does not have proteins, it cannot buffer the hydrogen ions and CSF pH drops rapidly
- The rising $H^+$ levels, due to an increase in $P_{CO_2}$ levels, prods the central chemoreceptors into activity and results in increased depth and rate of breathing
**Depth and Rate of Breathing: \( P_{CO_2} \)**

- Hyperventilation – increased depth and rate of breathing that:
  - Quickly flushes carbon dioxide from the blood
  - Occurs in response to **hypercapnia**
- Hypoventilation – slow and shallow breathing due to abnormally low \( P_{CO_2} \) levels
  - **Apnea** (breathing cessation) may occur until \( P_{CO_2} \) levels rise

**Depth and Rate of Breathing: \( P_{O_2} \)**

- Arterial oxygen levels are monitored by the aortic and carotid bodies
- Substantial drops in arterial \( P_{O_2} \) (to 60 mm Hg) are needed before oxygen levels become a major stimulus for increased ventilation
- If carbon dioxide is not removed (e.g., as in emphysema and chronic bronchitis), chemoreceptors become unresponsive to \( P_{CO_2} \) chemical stimuli
- In such cases, \( P_{O_2} \) levels become the principal respiratory stimulus (hypoxic drive)
Depth and Rate of Breathing: Reflexes

- Pulmonary irritant reflexes – irritants promote reflexive constriction of air passages

- Inflation reflex (Hering-Breuer) – stretch receptors in the lungs are stimulated by lung inflation

- Upon inflation, inhibitory signals are sent to the medullary inspiration center to end inhalation and allow expiration
Depth and Rate of Breathing: Higher Brain Centers

- Hypothalamic controls act through the limbic system to modify rate and depth of respiration
  - Example: breath holding that occurs in anger
- A rise in body temperature acts to increase respiratory rate
- Cortical controls are direct signals from the cerebral motor cortex that bypass medullary controls
  - Examples: voluntary breath holding, taking a deep breath

Depth and Rate of Breathing: Arterial pH

- Changes in arterial pH can modify respiratory rate even if carbon dioxide and oxygen levels are normal
- Increased ventilation in response to falling pH is mediated by peripheral chemoreceptors
- Acidosis may reflect:
  - Carbon dioxide retention
  - Accumulation of lactic acid
  - Excess fatty acids in patients with diabetes mellitus
- Respiratory system controls will attempt to raise the pH by increasing respiratory rate and depth
COPD is characterized by chronic bronchitis and obstructive emphysema

- Patients show signs of:
  - Dyspnea, where labored breathing occurs and gets progressively worse
  - Coughing and frequent pulmonary infections

- COPD victims develop respiratory failure accompanied by hypoxemia, carbon dioxide retention, and respiratory acidosis

- COPD is a major cause of death and illness, and it is the fourth leading cause of death in the United States and throughout the world.

- There is no cure for COPD.
Chronic Obstructive Pulmonary Disease (COPD)

- COPD is a lung disease in which the lungs are damaged, making it hard to breathe.

- In COPD, the airways—the tubes that carry air in and out of your lungs—are partly obstructed, making it difficult to get air in and out.
  - The airways and air sacs lose their elasticity (like an old rubber band).
  - The walls between many of the air sacs are destroyed.
  - The walls of the airways become thick and inflamed (swollen).
  - Cells in the airways make more mucus (sputum) than usual, which tends to clog the airways.

Pathogenesis of COPD

- Tobacco smoke
- Air pollution
- α-1 antitrypsin deficiency
- Chronic bronchitis
  - Bronchial edema, chronic productive cough, bronchospasm
- Emphysema
  - Destruction of alveolar walls, loss of lung elasticity, air trapping
- Continuous bronchial irritation and inflammation
- Breakdown of elastin in connective tissue of lungs
- Airway obstruction or air trapping
- Dyspnea
- Frequent infections
- Abnormal ventilation-perfusion ratio
- Hypoxemia
- Hypoventilation

Figure 22.28
Asthma

- Characterized by dyspnea, wheezing, and chest tightness
- Active inflammation of the airways precedes bronchospasms
- Airway inflammation is an immune response caused by release of IL-4 and IL-5, which stimulate IgE and recruit inflammatory cells
- Airways thickened with inflammatory exudates magnify the effect of bronchospasms
- Asthma can't be cured. Even when you feel fine, you still have the disease and it can flare up at any time.
- But with today's knowledge and treatments, most people who have asthma are able to manage the disease.
Asthma

- The exact cause of asthma isn't known. Researchers think a combination of factors (family genes and certain environmental exposures) interact to cause asthma to develop, most often early in life. These factors include:
  - An inherited tendency to develop allergies, called atopy (AT-o-pe)
  - Parents who have asthma
  - Certain respiratory infections during childhood
  - Contact with some airborne allergens or exposure to some viral infections in infancy or in early childhood when the immune system is developing

- If asthma or atopy runs in your family, exposure to airborne allergens (for example, house dust mites, cockroaches, and possibly cat or dog dander) and irritants (for example, tobacco smoke) may make your airways more reactive to substances in the air you breathe.

Asthma

The "Hygiene Hypothesis"

- One theory researchers have for what causes asthma is the "hygiene hypothesis." They believe that our Western lifestyle—with its emphasis on hygiene and sanitation—has resulted in changes in our living conditions and an overall decline in infections in early childhood.

- Many young children no longer experience the same types of environmental exposures and infections as children did in the past. This affects the way that the immune systems in today's young children develop during very early childhood, and it may increase their risk for atopy and asthma. This is especially true for children who have close family members with one or both of these conditions.
Pleurisy (Pleuritis)

- Pleurisy (PLUR-is-see) is inflammation (swelling) of the pleura.
- Pleurisy occurs when the two layers of the pleura become red and inflamed. Then they rub against each other every time your lungs expand to breathe in air. This can cause sharp pain with breathing.
- Infections like pneumonia are the most common cause of swelling, or inflammation, of the pleura and pleurisy.

**Pleural Effusion**

- Excess fluid builds up in the pleural space. The buildup of fluid can push the pleura against your lung until the lung, or a part of it, collapses.
- You can develop a pleural effusion if you don't have pleurisy. For example, pneumonia, heart failure, cancer, or a pulmonary embolism can lead to a pleural effusion.

**Pneumothorax**

- Air or gas also can build up in the pleural space. It can result from acute lung injury or a lung disease like emphysema. Lung procedures, like surgery, drainage of fluid with a needle, examination of the lung from the inside with a light and a camera, or mechanical ventilation, also can cause it.
- A pneumothorax also can put pressure on the lung and cause it to collapse.

Pleurisy

**Hemothorax**

- Blood also can collect in the pleural space. This is called hemothorax (he-mo-THOR-aks). The most common cause is injury to your chest from blunt force or chest or heart surgery. Hemothorax also can occur in people with lung or pleural cancer.
- This can cause your lung to collapse as well
**Tuberculosis**

- Infectious disease caused by the bacterium *Mycobacterium tuberculosis*
- Transmission can only occur from people with active — not latent — TB
- When people suffering from active pulmonary TB cough, sneeze, speak, or spit, they expel infectious aerosol droplets 0.5 to 5 µm in diameter. A single sneeze can release up to 40,000 droplets. Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very low and the inhalation of just a single bacterium can cause a new infection.
- Symptoms include fever, night sweats, weight loss, a racking cough, and splitting headache
- TB infection begins when the mycobacteria reach the pulmonary alveoli, where they invade and replicate within the endosomes of alveolar macrophages.
- Treatment entails a 12-month course of antibiotics (The two antibiotics most commonly used are rifampicin and isoniazid)

---

**Lung Cancer**

- Accounts for 1/3 of all cancer deaths in the U.S.
- 90% of all patients with lung cancer were smokers
- The three most common types are:
  - Squamous cell carcinoma (20-40% of cases) arises in bronchial epithelium
  - Adenocarcinoma (25-35% of cases) originates in peripheral lung area
  - Small cell carcinoma (20-25% of cases) contains lymphocyte-like cells that originate in the primary bronchi and subsequently metastasize