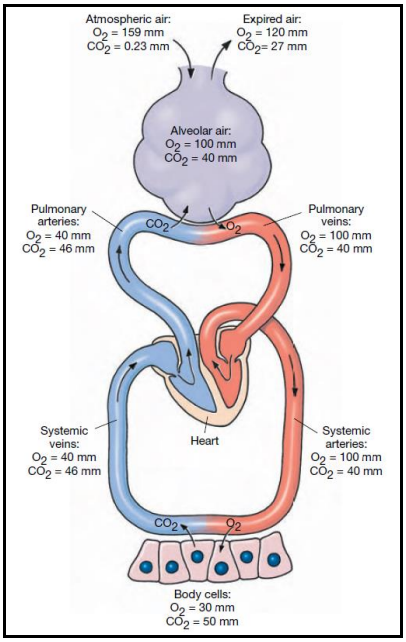
Transport of Carbon dioxide

When oxygen is used by the cells, virtually all of it becomes carbon dioxide (CO_2), and this increases the intracellular P_{CO_2}; because of this high tissue cell P_{CO_2}, CO_2 diffuses from the cells into the tissue capillaries and is then carried by the blood to the lungs. In the lungs, it diffuses from the pulmonary capillaries into the alveoli and is expired. Thus, at each point in the gas transport chain, CO_2 diffuses in the direction exactly opposite to the diffusion of oxygen. Yet there is one major difference between diffusion of CO_2 and of oxygen: *carbon dioxide can diffuse about 20 times as rapidly as oxygen.* Therefore, the pressure differences required to cause carbon dioxide diffusion are, in each instance, far less than the pressure differences required to cause oxygen diffusion.

(a)



(b)

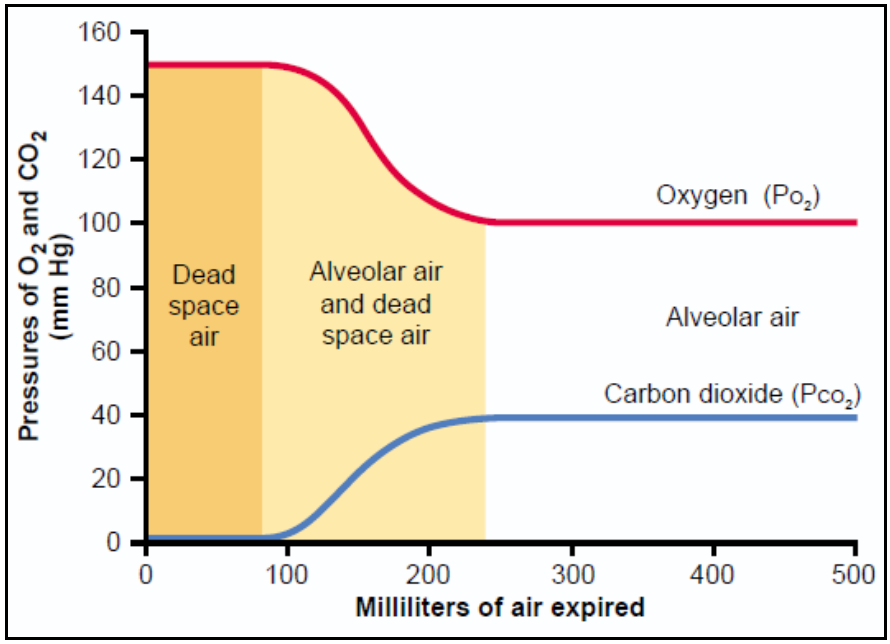


Figure: (a) Exchange of respiratory gases in lungs and tissue cells. Numbers present partial pressures in millimeters of mercury (mm Hg).(b)Oxygen and carbon dioxide partial pressures in the various portions of normal expired air.

TRANSPORT OF CO_2

The phenomena of transport of CO_2 takes place in the in following sequence of events:

A. Diffusion of CO_2 from cell to interstitial fluid:

CO_2 diffuses about 20 times as rapidly as oxygen. Therefore, the pressure difference that causes the CO_2 diffusion is far less than that is required for oxygen diffusion. Intracellular P_{CO_2} is about 46 mm of Hg whereas the interstitial P_{CO_2} is about 45 mm of Hg. This pressure difference of 1 mm of Hg is sufficient for the diffusion of CO_2 from cell to the interstitial fluid.

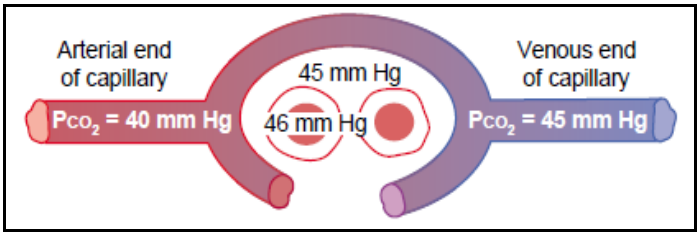


Figure: Uptake of carbon dioxide by the blood in the tissue capillaries. (P_{CO_2} in tissue cells = 46 mm Hg, and in interstitial fluid = 45 mm Hg.)

B. Diffusion of CO_2 from interstitial fluid to blood:

P_{CO_2} of arterial blood is 40 mm of Hg. The pressure difference of 5 mm of Hg causes CO_2 to diffuse from interstitial fluid to blood.

C. Carriage of CO_2 in blood:

Under normal resting condition, on an average about 4 ml of CO_2 is transported from tissue to the lungs in each 100 ml of blood. The CO_2 is carried in the blood in the following ways:

a. As physical solution:

P_{CO_2} of venous blood is 45 mm of Hg and that of arterial blood is 40 mm of Hg. The amount of CO_2 dissolved in the fluid of the blood at 95 mm of Hg is about 2.7 ml. The amount of CO_2 dissolved at 40 mm of Hg is about 2.4 ml. So, 0.3 ml of CO_2 is transported in the form of dissolved CO_2 by each 100 ml of blood and that amounts to 5% of total CO_2 transport.

b. As chemical compound:

❖ **As bicarbonates:**

- **<u>In the corpuscles</u>:**
  - When carbon dioxide diffuses into the red blood cells (erythrocytes), in the presence of the catalyst carbonic anhydrase, most CO_2 reacts with water (500 times faster) in the erythrocytes to form carbonic acid (H_2CO_3) and the following dynamic equilibrium is established.

$$H_2O + CO_2 \rightleftharpoons H_2CO_3$$

  - Carbonic acid, H_2CO_3, dissociates to form hydrogen ions and bicarbonate (HCO_3^-) ions. This is also a reversible reaction and undissociated carbonic acid, hydrogen ions and hydrogencarbonate ions exist in dynamic equilibrium with one another.

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

  - In the RBC, haemoglobin (Hb) remain in combination with K^+ ion in the form of KHb.
  - KHb reacts with H_2CO_3 in the following way: $KHb + H^+ + HCO_3^- \rightleftharpoons HHb + KHCO_3$
- **<u>In the plasma</u>:**
  - Most of the CO_2 in the plasma combines with water to form carbonic acid.
  - Carbonic acid dissociates in water into $H^+ + HCO_3^-$
  - The proteins present in the plasma combines with the H^+ and act as a buffer to maintain the acidity of the medium.
  - HCO_3^- becomes associated with plasma Na^+ to yield a reversible complex of $NaHCO_3$.

$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

$$H^+ + \text{Protein} \rightleftharpoons \text{H-Protein}$$

$$Na^+ + HCO_3^- \rightleftharpoons HHb + NaHCO_3$$

Chloride shift or Humburger phenomena:

a. CO_2 in RBC reacts with water in the presence of carbonic anhydrase to form carbonic acid (H_2CO_3). In a fraction of a second, the carbonic acid formed in the red cells (H_2CO_3) dissociates into *hydrogen* and bicarbonate ions (H^+ and HCO_3^-).

$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

b. H_2CO_3 reacts with KHb in the RBC to produce $KHCO_3$ and HHb.

$$KHb + H_2CO_3^- \rightleftharpoons HHb + KHCO_3$$

c. Most of the hydrogen ions then combine with the hemoglobin in the red blood cells, because the hemoglobin protein is a powerful acid-base buffer.

$$H^+ + \text{Protein} \rightleftharpoons \text{H-Protein}$$

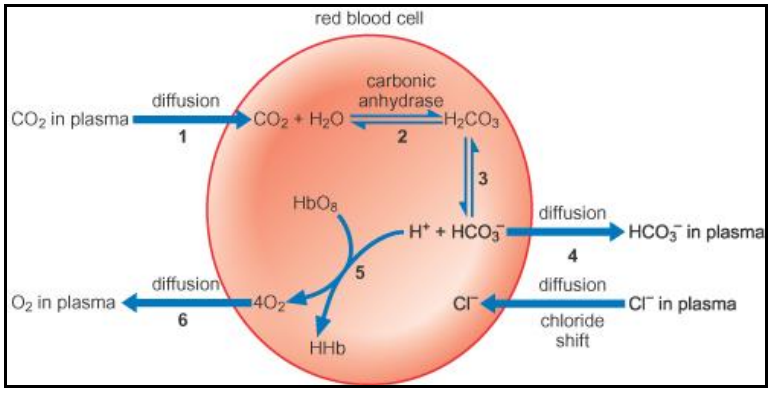
d. In the plasma, sodium chloride (NaCl) remains dissociated as sodium ion (Na^+) and chloride (Cl^-).

$$NaCl \rightleftharpoons Na^+ + Cl^-$$

e. The chloride ions diffuse into the red cells and releases HCO_3^- from $KHCO_3$

$$Cl^- + KHCO_3^- \rightleftharpoons KCl + HCO_3^-$$

f. As the free HCO_3^- ions tends to make the RBC cytoplasm alkaline; to maintain the pH of cell, the bicarbonate ions diffuse from the red cells into the plasma.



g. This is made possible by the presence of a special *bicarbonate-chloride carrier protein* in the red cell membrane that shuttles these two ions (Cl^- and HCO_3^-) in opposite directions at rapid velocities. Thus, the chloride content of venous red blood cells is greater than that of arterial red cells, a phenomenon called the *chloride shift.*

h. When the free HCO_3^- ions diffuses in the plasma, they combine with the Na^+ ions in the medium to form $NaHCO_3$ and exported in that form.

$$Na^+ + HCO_3^- \rightleftharpoons NaHCO_3$$

i. The reversible combination of CO_2 with water in the red blood cells under the influence of carbonic anhydrase accounts for about 70 % of the carbon dioxide transported from the tissues to the lungs.

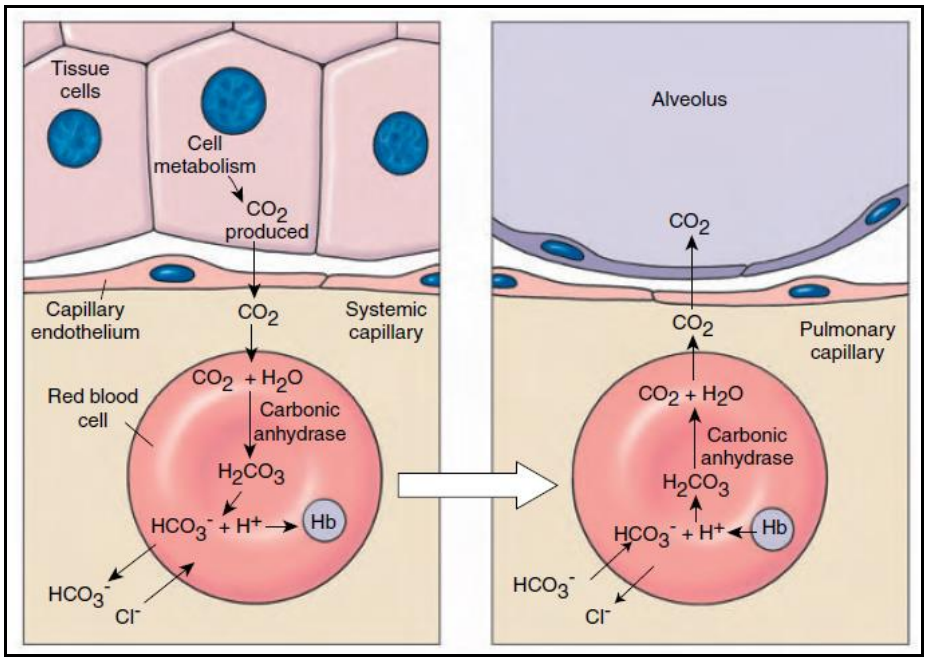


Figure: Events of Chloride shift and reverse chloride shift

2. As carbamino compounds:

- The CO_2 reacts with amino (NH_2^-) group of the globin protein of haemoglobin to form carbaminohaemoglobin (Hb CO_2).
- This CO_2 from the carbaminohaemoglobin get released into the alveoli where P_{CO2} is lower than the tissue capillaries.

$$CO_2 + Hb\text{-}NH_2 \rightleftharpoons Hb\text{-}NH\text{-}COOH$$

- A small amount of CO_2 also reacts with plasma protein and get carried with it

$$CO_2 + Protein\text{-}NH_2 \rightleftharpoons Protein\text{-}NH\text{-}COOH$$

- About 20% of the CO_2 is transported in these two forms.

<u>CO_2 Dissociation curve</u>:

The dependence of total blood CO_2 in free form or in combination with haemoglobin/ plasma protein on P_{CO2} is depicted in the form of a curve called CO_2 dissociation curve.

Haldane effect:

The Haldane effect results from the simple fact that the combination of oxygen with hemoglobin in the lungs causes the hemoglobin to become a stronger acid. This displaces CO_2 from the blood and into the alveoli in two ways:

(1) The more highly acidic hemoglobin has less tendency to combine with carbon dioxide to form carbaminohemoglobin, thus displacing much of the carbon dioxide that is present in the carbamino form from the blood.

(2) The increased acidity of the hemoglobin also causes it to release an excess of hydrogen ions, and these bind with bicarbonate ions to form carbonic acid; this then dissociates into water and CO_2, and the CO_2 is released from the blood into the alveoli and, finally, into the air.

The Haldane effect on the transport of CO_2 from the tissues to the lungs is depicted in the figure below. This figure shows small portions of two CO_2 dissociation curves:

(1) when the P_{CO2} is 40 mm Hg, which is the case in the blood capillaries of the lungs, and

(2) when the $P_{CO2}$is 45 mm Hg, which is the case in the tissue capillaries.

- Point A shows that the normal P_{CO2} of 45 mm Hg in the tissues causes 52 volumes per cent of CO_2 to combine with the blood.
- On entering the lungs, the P_{CO2} falls to 40 mm Hg and the P_{CO2} rises to 100 mm Hg.
- If the CO_2 dissociation curve did not shift because of the Haldane effect, the CO_2 content of the blood would fall only to 50 volumes per cent, which would be a loss of only 2 volumes per cent of CO_2.
- However, the increase in P_{CO2} in the lungs lowers the CO_2 dissociation curve from the top curve to the lower curve of the figure, so that the CO_2 content falls to 48 volumes per cent (point B).
- This represents an additional 2 volumes per cent loss of CO_2. Thus, the Haldane effect approximately doubles the amount of CO_2 released from the blood in the lungs and approximately doubles the pickup of CO_2 in the tissues.

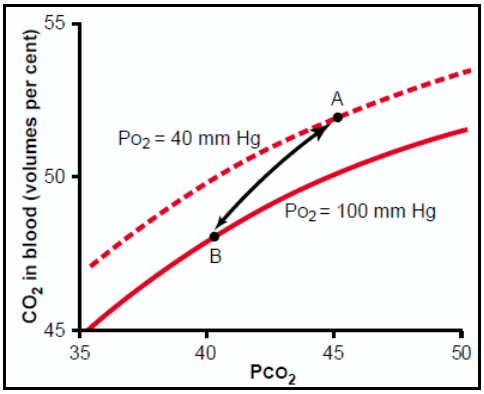


Figure: Portions of the CO_2 dissociation curve when the P_{O2} is 100 mm Hg or 40 mm Hg. The arrow represents the Haldane effect on the transport of CO_2.

B. Diffusion of CO_2 from blood to alveoli:

- P_{CO_2} of the venous blood entering the pulmonary capillary is 45 mm of Hg.
- P_{CO_2} of the alveolar air is 40 mm of Hg.
- This 5 mm of Hg pressure difference causes all the required CO_2 to diffuse from the pulmonary capillary into the alveoli.
- The other factors that facilitate the liberation of CO_2 in the lungs are formation of HbO_2, reverse Hamburger effect etc.
-

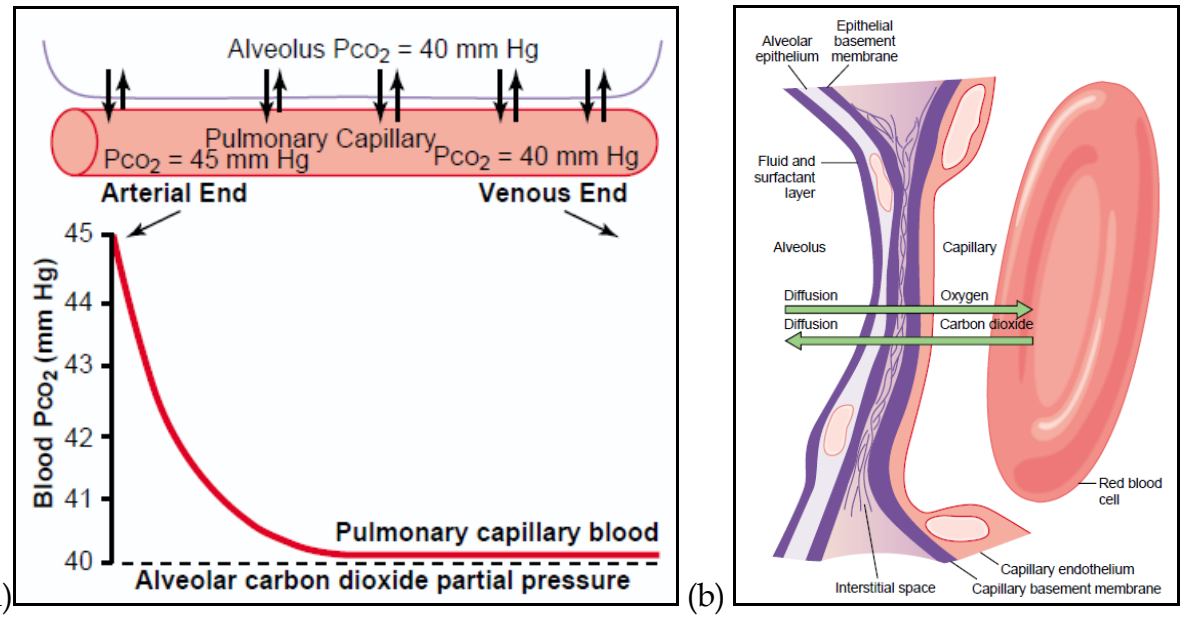


Figure: (a) Diffusion of carbon dioxide from the pulmonary blood into the alveolus (b) Ultrastructure of the alveolar respiratory membrane, shown in cross section.

Respiratory Exchange Ratio

The discerning student will have noted that normal transport of oxygen from the lungs to the tissues by each 100 milliliters of blood is about 5 milliliters, whereas normal transport of carbon dioxide from the tissues to the lungs is about 4 milliliters. Thus, under normal resting conditions, only about 82 per cent as much carbon dioxide is expired from the lungs as oxygen is taken up by the lungs. The ratio of carbon dioxide output to oxygen uptake is called the *respiratory exchange ratio* (R).

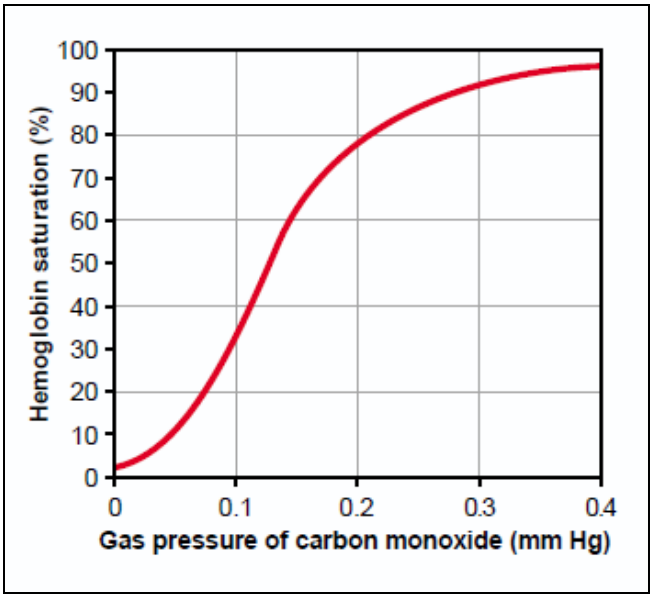
$$R = \frac{\text{Rate of carbon dioxide output}}{\text{Rate of oxygen uptake}}$$

The value for R changes under different metabolic conditions. When a person is using exclusively carbohydrates for body metabolism, R rises to 1.00. Conversely, when a person is using exclusively fats for metabolic energy, the R level falls to as low as 0.7. The reason for this difference is that when oxygen is metabolized with carbohydrates, one molecule of carbon dioxide is formed for each molecule of oxygen consumed; when oxygen reacts with fats, a large share of the oxygen combines with hydrogen atoms from the fats to form water instead of carbon dioxide. In other words, when fats are metabolized, the *respiratory quotient of the chemical reactions* in the tissues is about 0.70 instead of 1.00. For a person on a normal diet consuming average amounts of carbohydrates, fats, and proteins, the average value for R is considered to be 0.825.

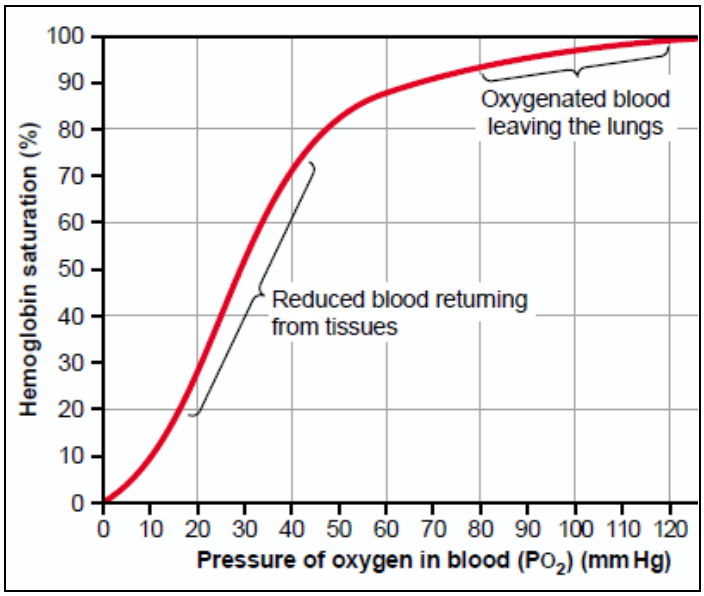
Carbon monoxide poisoning:

Carbon monoxide combines with hemoglobin (carboxyhaemoglobin) at the same point on the hemoglobin molecule as does oxygen; it can therefore displace oxygen from the hemoglobin, thereby decreasing the oxygen carrying capacity of blood. Further, it binds with about 250 times as much tenacity as oxygen, which is demonstrated by the carbon monoxide–hemoglobin dissociation curve in the Figure (a).

(a)



(b)



This curve is almost identical to the oxygenhemoglobin dissociation curve, except that the carbon monoxide partial pressures, shown on the abscissa, are at a level 1/250 of those for the oxygen-hemoglobin dissociation curve of Figure b. Therefore, a carbon monoxide partial pressure of only 0.4 mm Hg in the alveoli, 1/250 that of normal alveolar oxygen (100 mm Hg Po_2), allows the carbon monoxide to compete equally with the oxygen for combination with the hemoglobin and causes half the hemoglobin in the blood to become bound with carbon monoxide instead of with oxygen. Therefore, a carbon monoxide pressure of only 0.6 mm Hg (a volume concentration of less than one part per thousand in air) can be lethal.

- Even though the oxygen content of blood is greatly reduced in carbon monoxide poisoning, the Po_2 of the blood may be normal.
- This makes exposure to carbon monoxide especially dangerous, because the blood is bright red and there are no obvious signs of hypoxemia, such as a bluish color of the fingertips or lips (cyanosis).
- Also, Po_2 is not reduced, and the feedback mechanism that usually stimulates increased respiration rate in response to lack of oxygen (usually reflected by a low Po_2) is absent.
- As the brain is one of the first organs affected by lack of oxygen, the person may become disoriented and unconscious before becoming aware of the danger.

Treatment:

- A patient severely poisoned with carbon monoxide can be treated by administering pure oxygen, because oxygen at high alveolar pressure can displace carbon monoxide rapidly from its combination with hemoglobin.
- The patient can also benefit from simultaneous administration of 5 % carbon dioxide, because this strongly stimulates the respiratory center, which increases alveolar ventilation and reduces the alveolar carbon monoxide.
- With intensive oxygen and carbon dioxide therapy, carbon monoxide can be removed from the blood as much as 10 times as rapidly as without therapy.

Mountain sickness:

- Many individuals develop transient "mountain sickness", they first arrive at a high altitude. This syndrome develops 8 to 24 h after arrival at altitude and lasts 4 to 8 days.
- It is characterized by headache, irritability, insomnia, breathlessness, and nausea and vomiting. Its cause is unsettled, but it appears to be associated with cerebral edema.
- The low PO_2 at high altitude causes arteriolar dilation, and if cerebral autoregulation does not compensate, there is an increase in capillary pressure that favors increased transudation of fluid into brain tissue.
- Individuals who do not develop mountain sickness have a diuresis at high altitude, and urine volume is decreased in individuals who develop the condition.

High-altitude illness includes not only mountain sickness but also two more serious syndromes that complicate it: **high-altitude cerebral edema** and **high-altitude pulmonary edema.**

- In high-altitude cerebral edema, the capillary leakage in mountain sickness progresses to frank brain swelling, with ataxia, disorientation, and in some cases coma and death due to herniation of the brain.
- High-altitude pulmonary edema is a patchy edema of the lungs that is related to the marked pulmonary hypertension that develops at high altitude.
- It has been argued that it occurs because not all pulmonary arteries have enough smooth muscle to constrict in response to hypoxia, and in the capillaries supplied by those arteries, the general rise in pulmonary arterial pressure causes a capillary pressure increase that disrupts their walls (stress failure).

Treatment:

All forms of high-altitude illness are benefited by descent to lower altitude and by treatment with the diuretic acetazolamide. This drug inhibits carbonic anhydrase, producing increased HCO_3^- excretion in the urine, stimulating respiration, increasing P_{CO_2}, and reducing the formation of CSF. When cerebral edema is marked, large doses of glucocorticoids are often administered as well. Their mechanism of action is unsettled. In high-altitude pulmonary edema, prompt treatment with O_2 is essential—and, if available, use of a hyperbaric chamber. Portable hyperbaric chambers are now available in a number of mountain areas. Nifedipine, a Ca^{2+} channel blocker that lowers pulmonary artery pressure, is also useful.

Hypoxia :

Hypoxia is O_2 deficiency at the tissue level. It is a more correct term than **anoxia,** with there rarely being no O_2 at all left in the tissues. Traditionally, hypoxia has been divided into four types. Numerous other classifications have been used, but the four-type system still has considerable utility if the definitions of the terms are kept clearly in mind. The four categories are:

I. **hypoxic hypoxia,** in which the PO_2 of the arterial blood is reduced;
II. **anemic hypoxia,** in which the arterial PO_2 is normal but the amount of hemoglobin available to carry O_2 is reduced;
III. **stagnant** or **ischemic hypoxia,** in which the blood flow to a tissue is so low that adequate O_2 is not delivered to it despite a normal PO_2 and hemoglobin concentration; and
IV. **histotoxic hypoxia,** in which the amount of O_2 delivered to a tissue is adequate but, because of the action of a toxic agent, the tissue cells cannot make use of the O_2 supplied to them.