Al Mustaqbal University College
Department of Pharmacy
4th stage
Toxicology

Lect. 7

TOXIC RESPONSE OF THE BLOOD (PART2)

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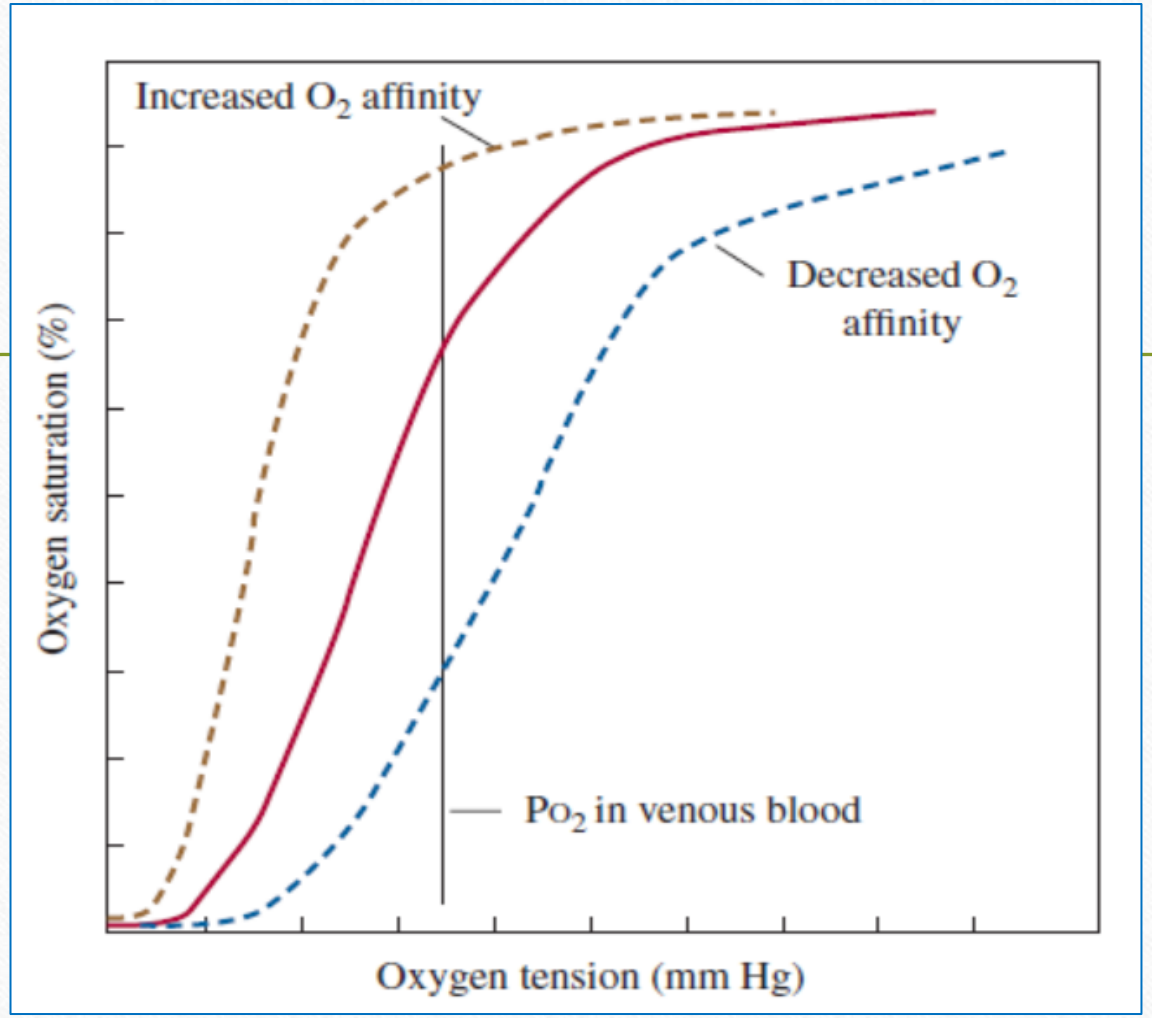
Respiratory Function of Hemoglobin

- **The respiratory function of hemoglobin is to transport of oxygen from the lungs to the tissues.**
- **Electrostatic charges hold the globin chains of deoxyhemoglobin in a "tense" (T) conformation characterized by a relatively low affinity for oxygen.**
- **Binding of oxygen alters this conformation to a "relaxed" (R) conformation that is associated with a 500-fold increase in oxygen affinity.**



Oxygen dissociation curve

Respiratory Function of Hemoglobin

The ability of hemoglobin to safely and efficiently transport oxygen is dependent on:

- **Intrinsic (homotropic) factors**
- **Extrinsic (heterotropic) factors**

Homotropic Effects Leading to Methemoglobinemia

- **The slow but consistent oxidation of heme iron from the ferrous (Fe^{+2}) to the ferric (Fe^{+3}) state to form methemoglobin renders methemoglobin unable to bind and transport oxygen.**
- **In addition, there will be increase the affinity of oxyhemoglobin for oxygen, resulting in a leftward shift of the oxygen dissociation curve.**
- **These two effects will significantly impair delivery of oxygen to tissues when the concentration of methemoglobin rises beyond critical levels (<1% of Hb).**

Homotropic Effects Leading to Methemoglobinemia

- **In humans, there are two mechanisms by which erythrocytes counteract the formation of methemoglobin.**
- **The most predominant is via nicotine adenine dinucleotide (NADH)-methemoglobin reductase, which converts 95% to 99% of methemoglobin to hemoglobin.**

Homotropic Effects Leading to Methemoglobinemia

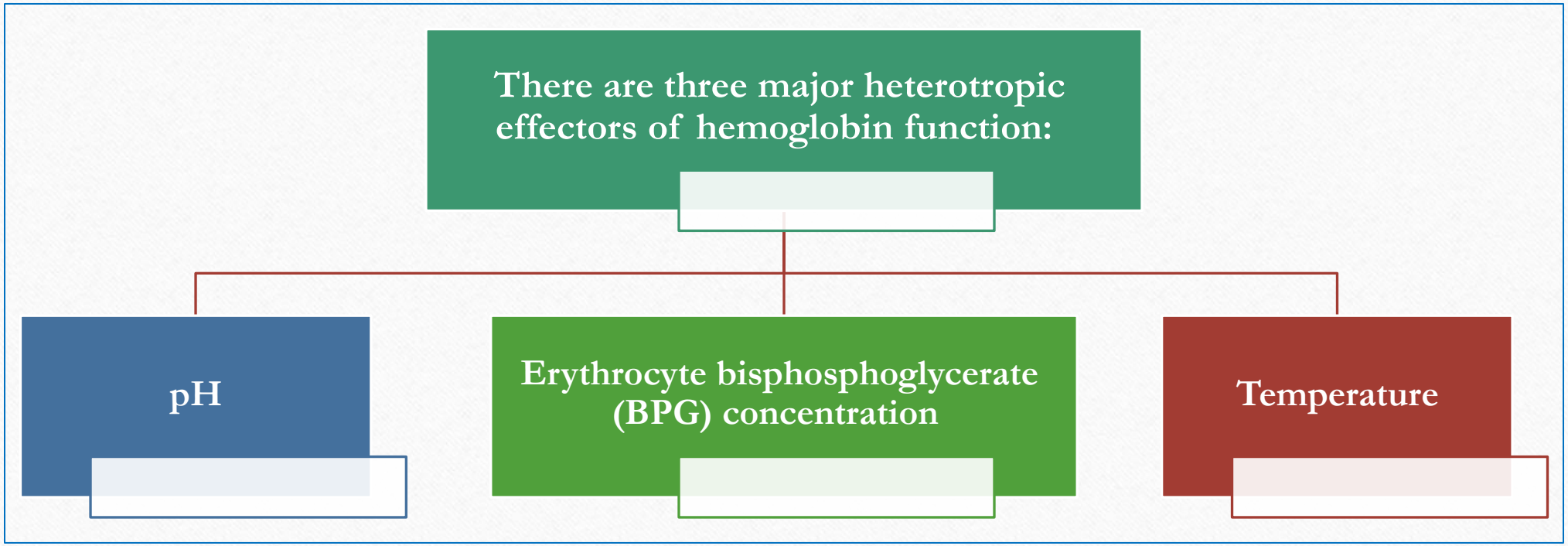
- **The second mechanism is via nicotine adenine dinucleotide phosphate (NADPH)- methemoglobin reductase, which requires a cofactor or electron receptor such flavin to reduce methemoglobin.**
- **This pathway converts about less than 5% of the reduction of methemoglobin.**
- **The most common cause of methemoglobinemia is exposure to an oxidizing xenobiotic that overwhelms the NADH-methemoglobin reductase system.**

Homotropic Effects Leading to Methemoglobinemia

- **A large number of chemicals and therapeutic agents may cause methemoglobinemia such as:**

1. **Therapeutics agents like amyl nitrate, isobutyl nitrite, nitroglycerine, primaquine**
2. **Environmental agents like butyl nitrite, potassium chlorate, gasoline additives**

Heterotropic Effects



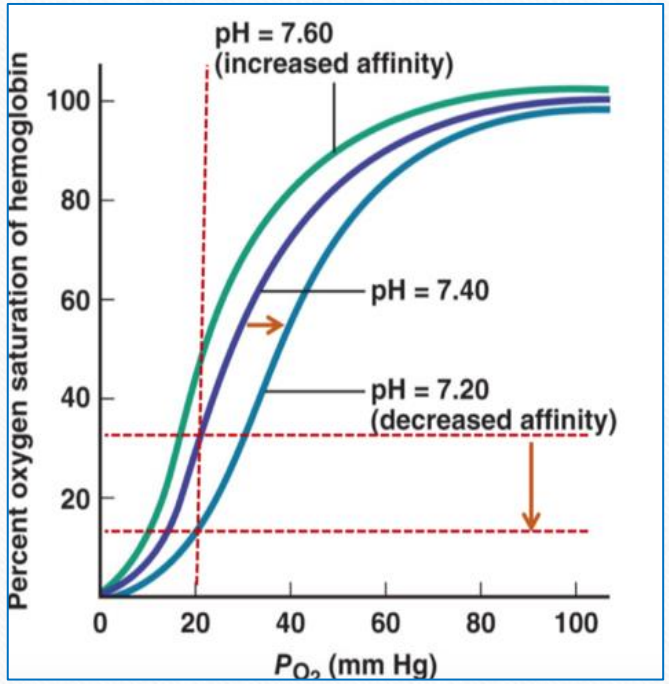
Heterotropic Effects/ pH

A decrease in pH (e.g., lactic acid, carbon dioxide)

It causes a right shift in the oxygen dissociation curve,

Lowers the affinity of hemoglobin for oxygen, that is,

Facilitating the delivery of oxygen to tissues.



Oxygen dissociation curve

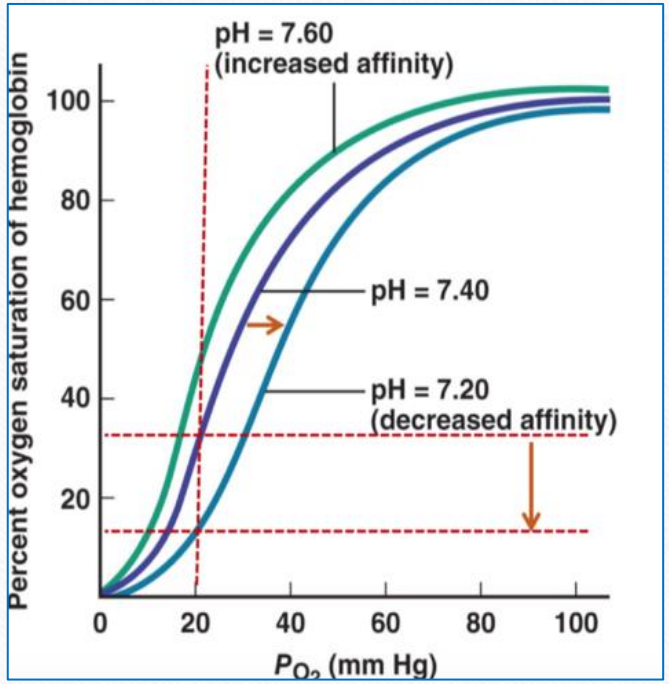
Heterotropic Effects/ pH

As bicarbonate and carbon dioxide equilibrate in the lung,

The hydrogen ion concentration decreases causing increasing pH

Increasing the affinity of hemoglobin for oxygen

Facilitating oxygen uptake.



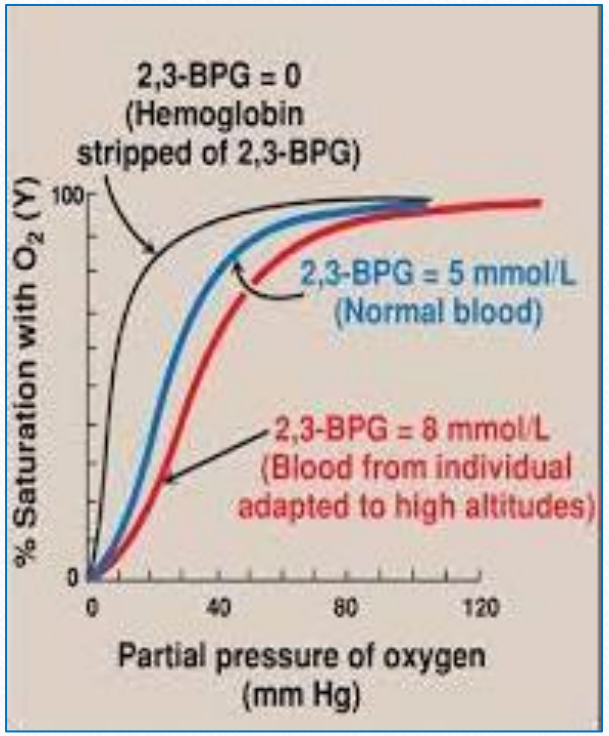
Oxygen dissociation curve

Heterotropic Effects

Binding of BPG to deoxyhemoglobin stabilizes the "T" conformation, reducing oxygen affinity (a shift to the right).

BPG conc. increases whenever there is tissue hypoxemia but may decrease in case of acidosis or hypophosphatemia.

Clofibrate and bezafibrate, as BPG analogue, capable of lowering the Hb oxygen affinity.



Heterotropic Effects

The oxygen affinity of hemoglobin decreases as the body temperature increases, facilitating delivery of oxygen to tissues during periods of extreme exercise and febrile illnesses.

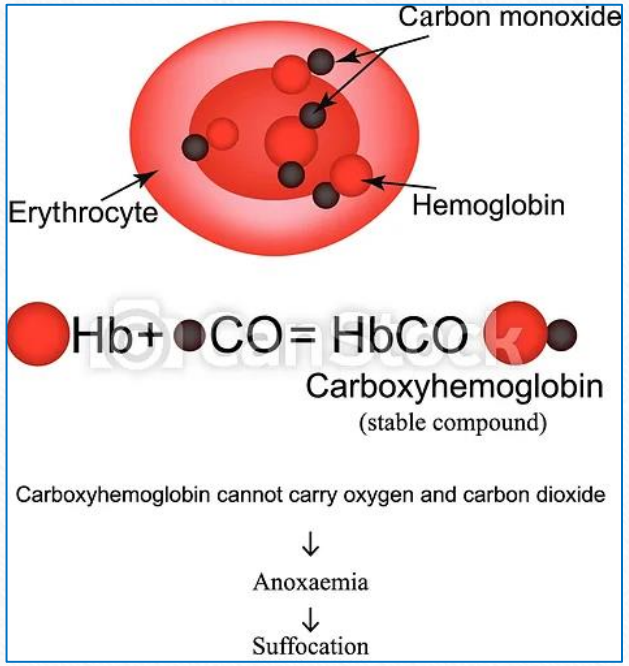
Correspondingly, oxygen affinity increases during hypothermia, which may lead to decreased oxygen delivery under these conditions.

Carboxyhemoglobinemia

CO has a relatively low rate of association with deoxyhemoglobin but has high affinity once bound (200 times that of oxygen).

Thus persistent exposure to a low level of CO (e.g., 0.1%) may lead to 50% saturation of hemoglobin.

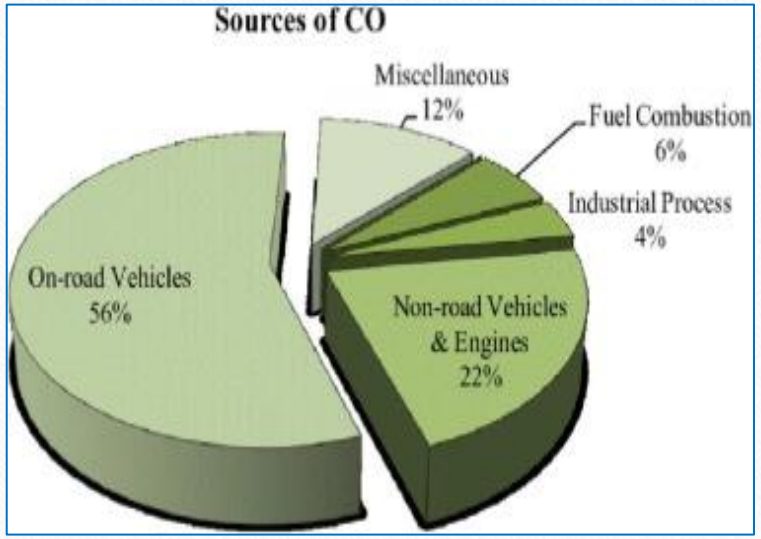
Binding of carbon monoxide also results in stabilization of the hemoglobin molecule in the high-affinity "R" conformation.



Carboxyhemoglobinemia

Low amounts of CO are produced at low levels by the body through the metabolism of heme and equilibrate across the pulmonary capillary/alveolar bed.

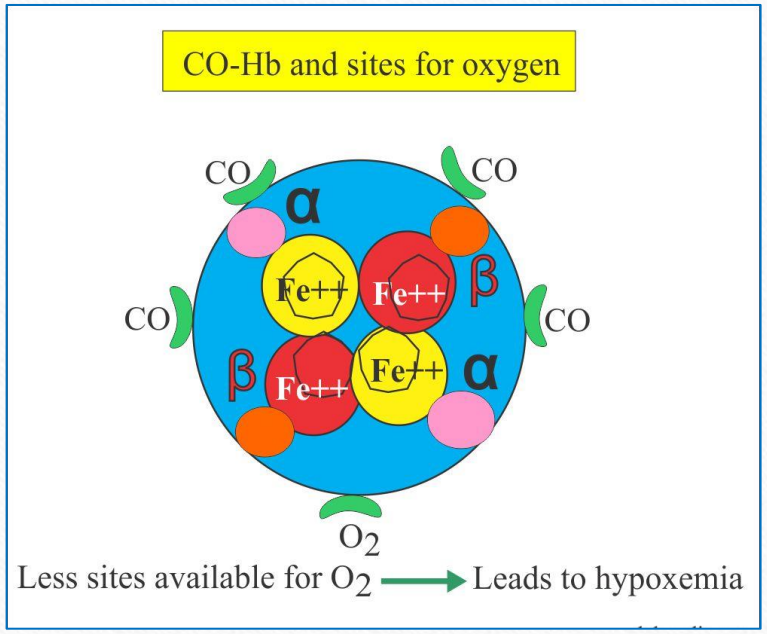
The major sources of significant exogenous exposure to CO are smoking and burning of fossil fuels (including automobiles), particularly in enclosed spaces.



Carboxyhemoglobinemia

Smoking tobacco or marijuana elevates levels of carboxyhemoglobin in the blood turning it bright cherry red.

Smoking during pregnancy may also result in significant levels of carboxyhemoglobin being formed in fetal blood and diminished oxygenation of fetal tissues.



Alterations in Erythrocyte Survival

The normal survival of erythrocytes in the circulation is about 120 days.

Senescence occurs over time until the aged erythrocytes are removed by the spleen, where the iron is recovered for reutilization in heme synthesis.

Any insult that increases oxidative injury, decreases metabolism, or alters the membrane may cause a decrease in erythrocyte concentration and a corresponding anemia.

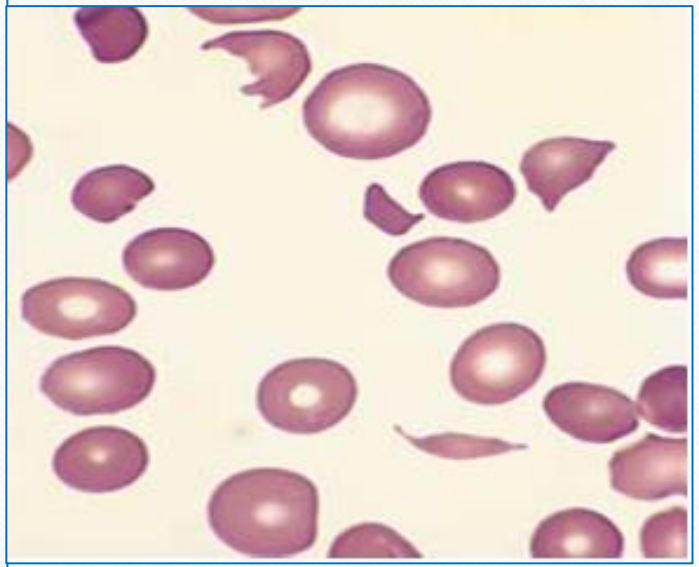
Hemolytic Anemia

1. **Nonimmune Hemolytic Anemia**
   - ✓ **Microangiopathic Anemias**
   - ✓ **Oxidative Hemolysis**
   - ✓ **Nonoxidative Chemical-Induced Hemolysis**
2. **Immune Hemolytic Anemia**

Microangiopathic Anemias

Intravascular fragmentation of erythrocytes gives rise to microangiopathic hemolytic anemia, the hallmark of this process is the presence of schistocytes (fragmented RBCs) in the peripheral blood.

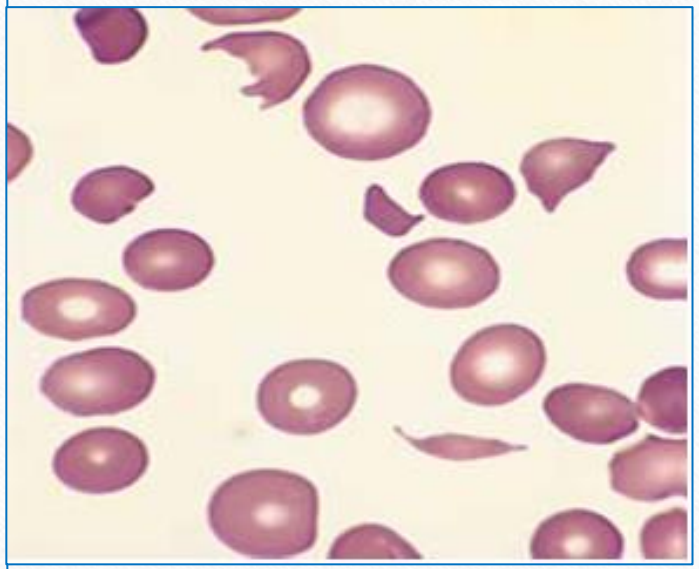
The presence of schistocytes in peripheral blood samples indicates either an increased rate of formation or abnormal clearance function of the spleen.



Microangiopathic Anemias

The formation of fibrin strands in the microcirculation is a common mechanism for RBC fragmentation.

The erythrocytes are sliced into fragments by the fibrin strands that extend across the vascular lumen and impede the flow of erythrocytes through the vasculature.



Microangiopathic Anemias

This may occur in the setting of disseminated intravascular coagulation, sepsis, the hemolytic-uremic syndrome (HUS), and thrombotic thrombocytopenic purpura (TTP).

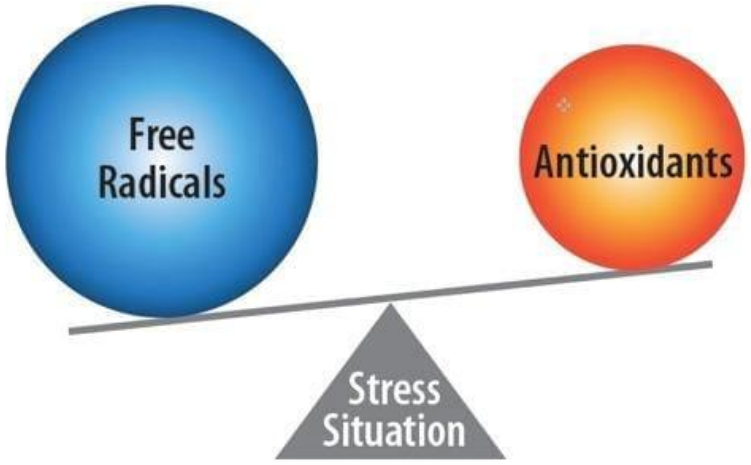
Excessive fragmentation can also be seen in the presence of abnormal vasculature, as occurs with damaged cardiac valves, arteriovenous malformations, vasculitis, and widely metastatic carcinoma

Oxidative Hemolytic Anemia

The normal respiratory function of erythrocytes generates oxidative stress on a continuous basis.

Excessive oxidative stress associated with formation of free radicals that must be detoxified to prevent oxidative injury to hemoglobin and other critical erythrocyte components.

The major mechanisms that protect against oxidative injury in erythrocytes include NADH-methemoglobin reductase, superoxide dismutase, catalase, and the glutathione pathway.

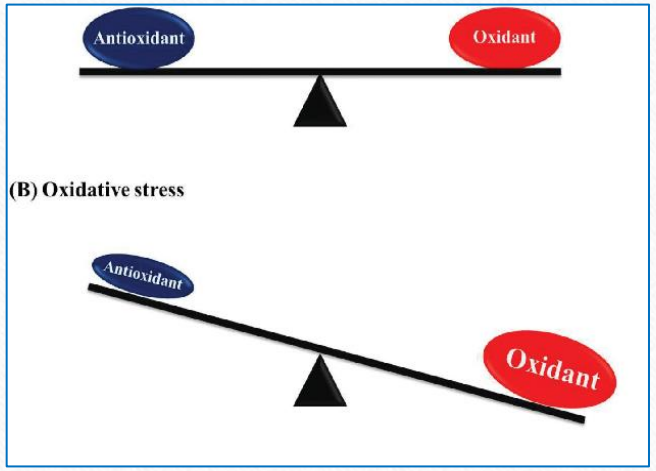


Oxidative Hemolytic Anemia

A number of xenobiotics, particularly compounds containing aromatic amines, are capable of inducing oxidative injury in erythrocytes.

These chemicals appear to potentiate the normal redox reactions and are capable of overwhelming the usual protective mechanisms.

Such effect can leads to the formation of free radicals that denature critical proteins, including hemoglobin, thiol-dependent enzymes, and components of the erythrocyte membrane.

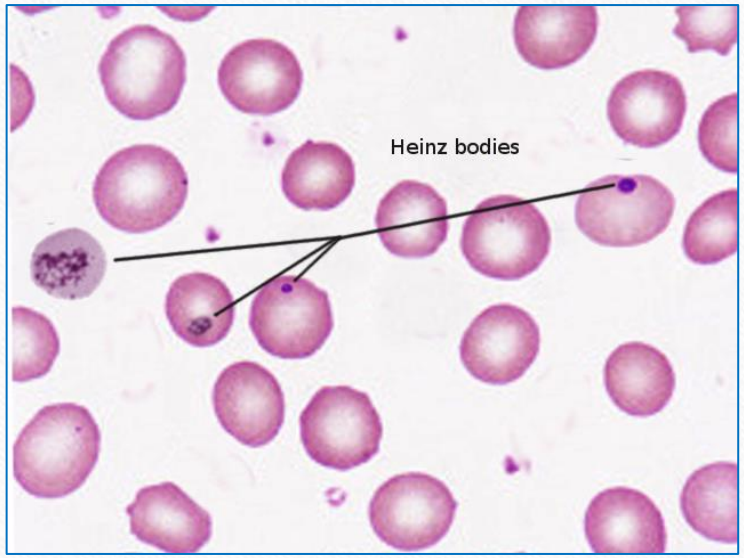


Oxidative Hemolytic Anemia

The denatured hemoglobin can form aggregates that bind to the cell membrane to form inclusions called Heinz bodies, a hallmark of oxidative injury to erythrocytes

Heinz bodies are usually visualized by use of phase contrast microscopy or supravital stains such as crystal violet or more recently by flow cytometry.

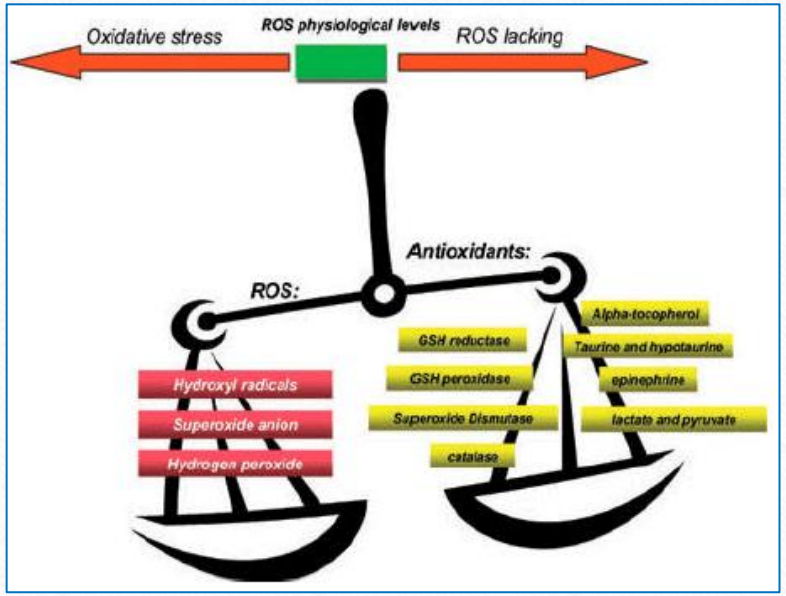
Heinz bodies are effectively removed from the erythrocyte by the spleen, so they are not often observed in peripheral blood samples from patients despite ongoing oxidative cascade.



Oxidative Hemolytic Anemia

Xenobiotics associated with oxidative injury may include but not limited to:

Nitrofurantoin, phenacetin, dapsone, phenol, aminosalicylic acid, hydroxylamine, and sulfasalazine.



Nonoxidative Chemical-Induced Hemolytic Anemia

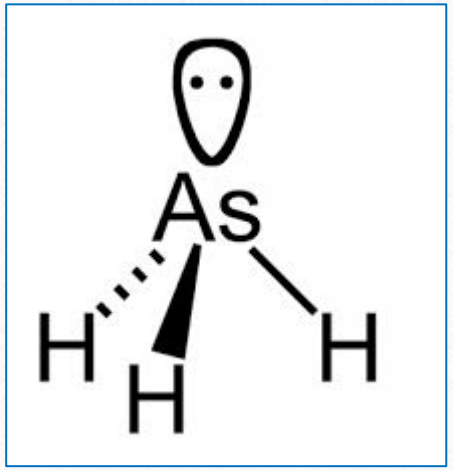
Some xenobiotics act by both oxidative and nonoxidative mechanisms, while some are associated with hemolysis without significant oxidative injury.

Significant hemolysis may also occur with biologic toxins found in insect and snake venoms, through unknown mechanisms.

Nonoxidative Chemical-Induced Hemolytic Anemia

Arsenic hydride is a gas that is formed during several industrial processes, its inhalation can result in severe hemolysis, with anemia, jaundice, and hemoglobinuria.

Arsine has oxidative effects and also possibly acts on the Na+/K+ pump mechanism, leading to swelling and hemolysis

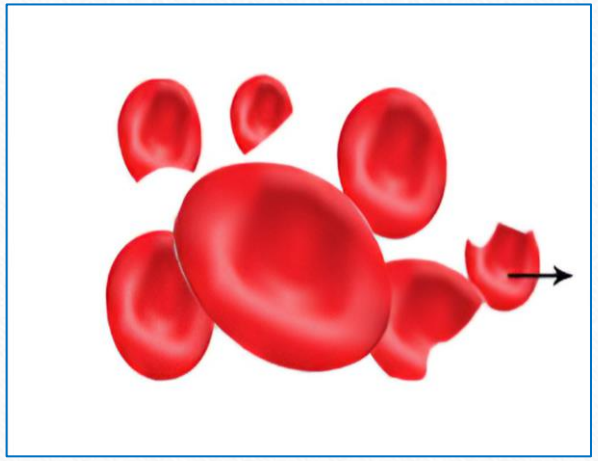


Nonoxidative Chemical-Induced Hemolytic Anemia

Lead poisoning is associated with defects in heme synthesis and a shortening of erythrocyte survival.

The cause of the hemolysis is may be relate to fact that, lead can cause membrane damage and interfere with the Na+/K+ pump.

These effects may cause premature removal of erythrocytes from the circulation.



Immune Hemolytic Anemia

Immunologic destruction of erythrocytes is mediated by the interaction of IgG or IgM antibodies with antigens expressed on the surface of the erythrocyte intrinsically .

Certain drugs may enhanced binding of immunoglobulin to the erythrocyte surface and shortened RBC survival.

Immune Hemolytic Anemia

Drug-induced intravascular hemolysis may be associated with:

- **Fever, chills, back pain**
- **Hypotension**
- **Rapid fall in hemoglobin concentration**
- **Decrease in serum haptoglobin**
- **Marked increase in serum lactate dehydrogenase, and hemoglobinuria**

Immune Hemolytic Anemia

Some drugs, of which penicillin is a prototype, appear to bind to the surface of the cell, with the "foreign" drug acting as a hapten and eliciting an immune response.

The antibodies that arise in this type of response only bind to drug-coated erythrocytes.

Immune Hemolytic Anemia

Other drugs, of which quinidine is a prototype, bind to components of the erythrocyte surface and induce a conformational change in one or more components of the membrane.

This type of interaction can give rise to a confusing array of antibody specificities.

Immune Hemolytic Anemia

Some xenobiotics, such as cephalosporins and cisplatin , are associated with nonspecific deposition of proteins on erythrocytes.

Immunoglobulin and complement proteins may be among the proteins deposited on the erythrocyte surface.

THANK YOU FOR YOUR ATTENTION