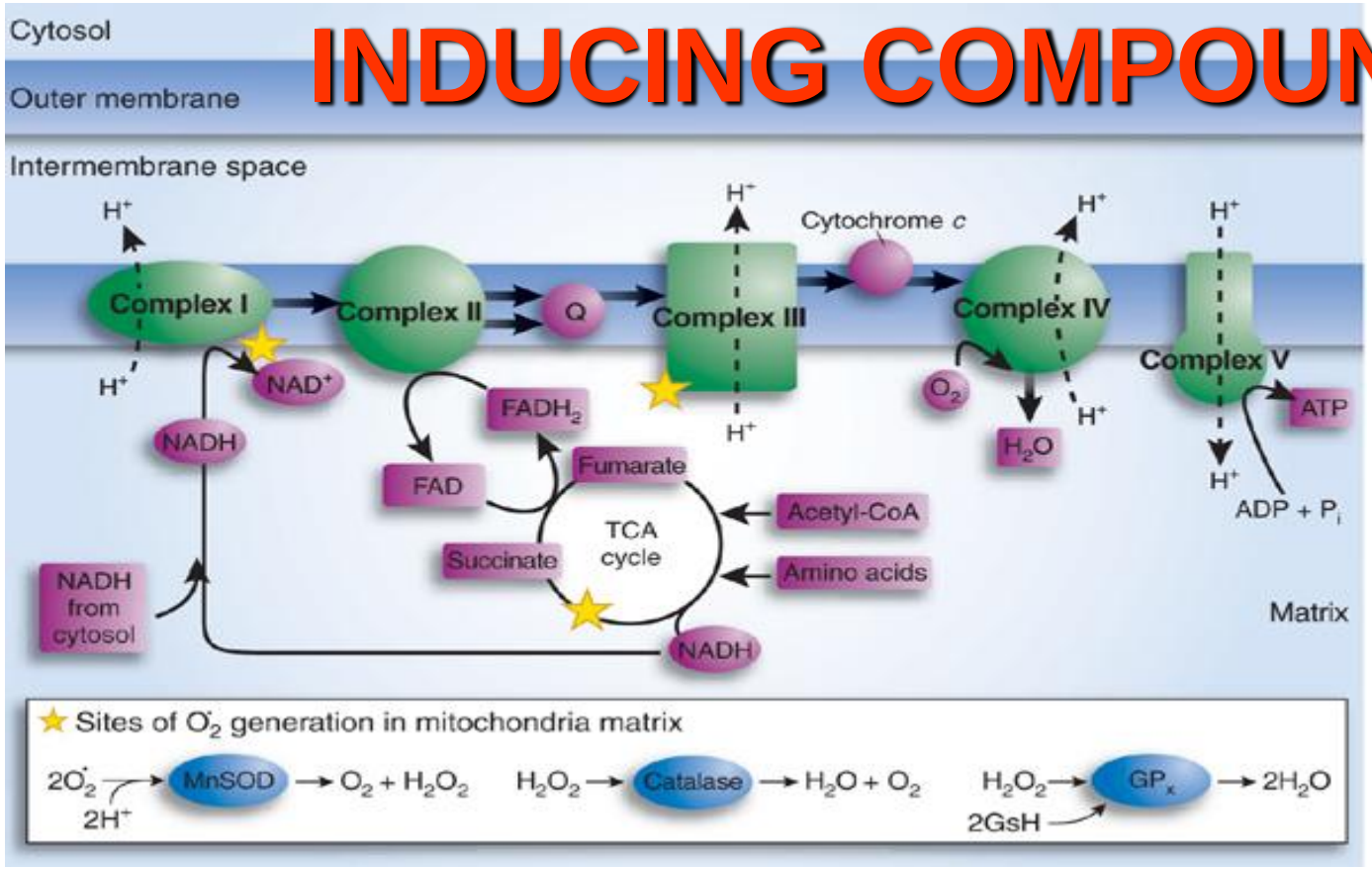
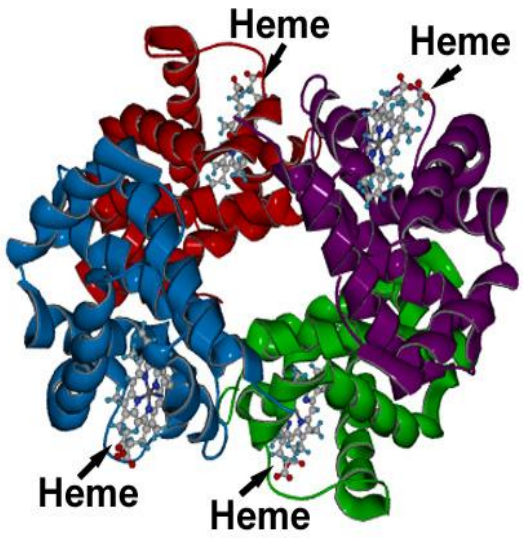
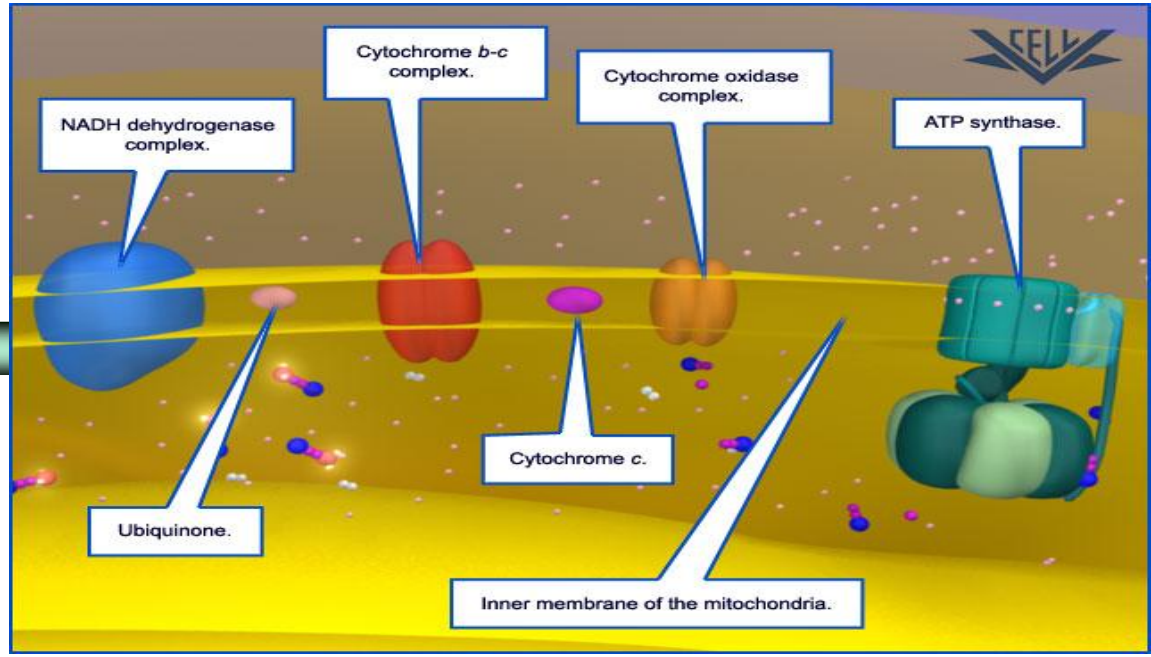
MEDICAL UNIVERSITY – PLEVEN
FACULTY OF PUBLIC HEALTH
CENTER FOR DISTANCE LEARNING

CELLULAR ASPHYXIA – INDUCING COMPOUNDS



Лектор: доц. д-р В. Данчева, дм





- This group includes: carbon monoxide, cyanide, hydrogen sulfide, etc. They induce hypoxia or anoxia by binding of the hemoglobin **(carboxyhemoglobin, CO)** or by binding of the **ferric ion atom in cytochromes (cyanides)**

Mitochondrial Toxins

- Carbon monoxide
- Cyanide
- Hydrogen sulfide

CARBON MONOXIDE

- **Natural production** of carbon monoxide is estimated to be about 10 times the amount produced by man-made sources. **Oxidation of methane** is the highest source of CO in the atmosphere and may produce 3 billion metric tons of CO annually in the Northern Hemisphere alone. Large amounts of CO are released from the ocean each year **by the float cells of kelp**.

organic materials — Anaerob conditions / Biological decay → methane → OH * → CO

Natural sources of carbon monoxide

Indirect sources: mud, bogs

anaerob conditions

methane formation from the decay of organic materials

The surface of oceans is supersaturated in carbon monoxide

Decay of chlorophyll in the soil

CARBON MONOXIDE

- **Carbon monoxide poisoning** is now the **most common of all poisonings in industry** and is responsible **for more than half of the poisoning fatalities** reported each year. It is **leading agent** of **lethal inhalation** in **the United States**, responsible for **6000 accidental** and **suicidal deaths** per year. **~40,000–50,000** emergency department visits annually result from CO poisoning.

CARBON MONOXIDE

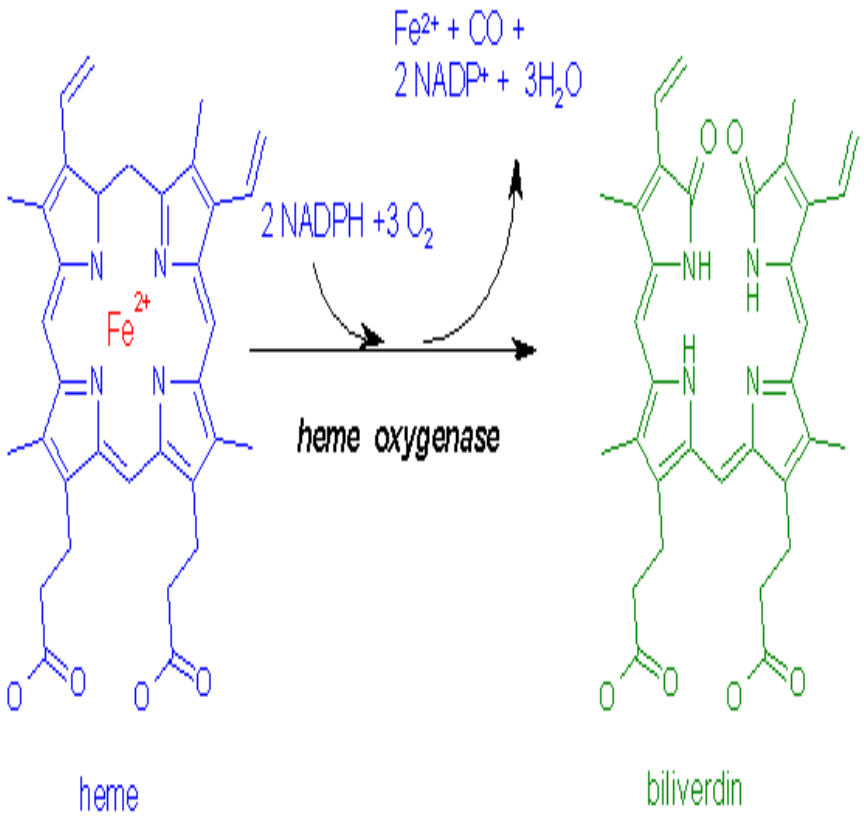
- Tremendous amounts of carbon monoxide are released into the atmosphere as a result of **human activities**. The **combustion of petroleum products** remains by far the largest source of CO and the amount generated from petroleum product has risen.

Sources of Carbon Monoxide

- Endogenous
- Exogenous
- Methylene chloride

Sources of Carbon Monoxide

- **Endogenous:**
  - Normal heme catabolism:
    - Only biochemical reaction in the body is known to produce CO.
  - Levels increase in:
    - Hemolytic anemia
    - Sepsis

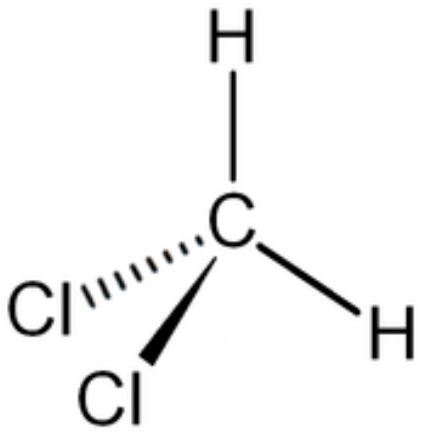


Sources of Carbon Monoxide

- **Exogenous:**
  - House fires.
  - Gas–powered electrical generators.
  - Automobile exhaust.
  - Propane-powered vehicles.
  - Heaters.
  - Camp stoves.
  - Boat exhaust.
  - Cigarette smoke.

Sources of Carbon Monoxide

- **Methylene chloride**:
  - Paint and adhesive remover.
  - Converted to CO in the liver after inhalation.



CARBON MONOXIDE

- **Motor vehicles** have accounted for about 55% to 60% of global man-made emissions of carbon monoxide. This amount however is reduced in the past decades by using of catalytic converters. Another 20% of man-made CO emissions come from **stationary sources** such as **space and water heaters** and **furnaces** and from **industrial processes**, **coal mine explosions**, and **solid waste disposal procedure**. Because most plastics contain carbon, CO is one of the primary gases generated by **heating and burning plastics**.

CARBON MONOXIDE

- Natural gas found with petroleum deposits has no CO, but carbon monoxide may be produced in processing natural gas (**e.g. cracking**).

- Additional sources of carbon monoxide include the **manufacture of synthetic methanol** and other organic compounds from CO, industrial and residential fires, charcoal burning, etc.

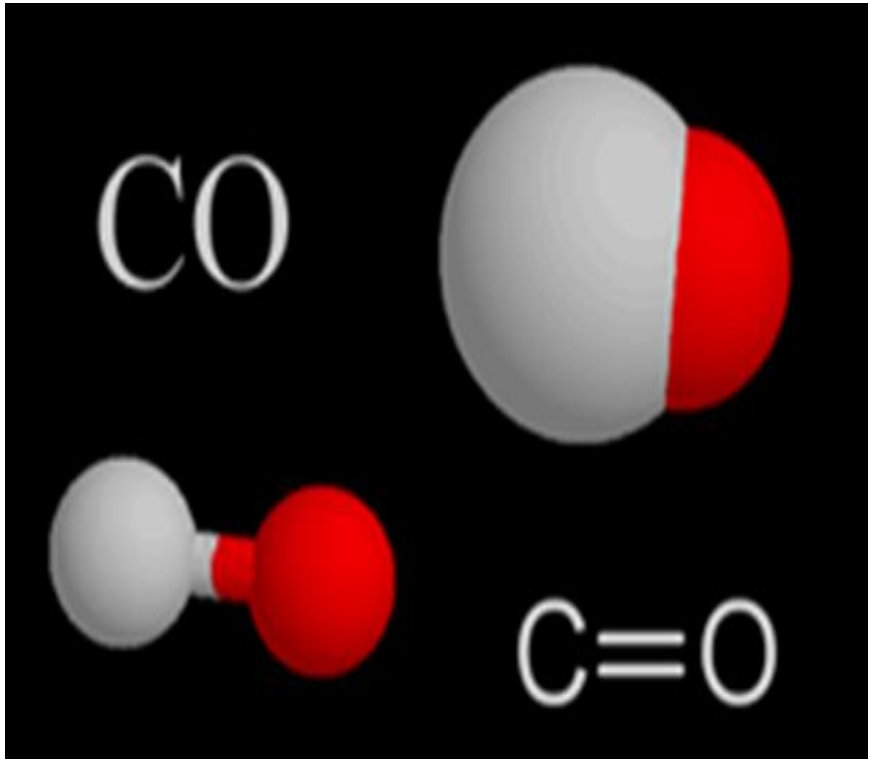
CARBON MONOXIDE

- **Epidemics** of carbon monoxide poisonings commonly occur **during winter months** and sources include misuse of non-electric heating or cooking devices.

- **Tobacco smoke** is also significant source of carbon monoxide, containing approximately 4% CO; smokers have been observed to have **COHb** levels typically in the **4 - 5% range.**

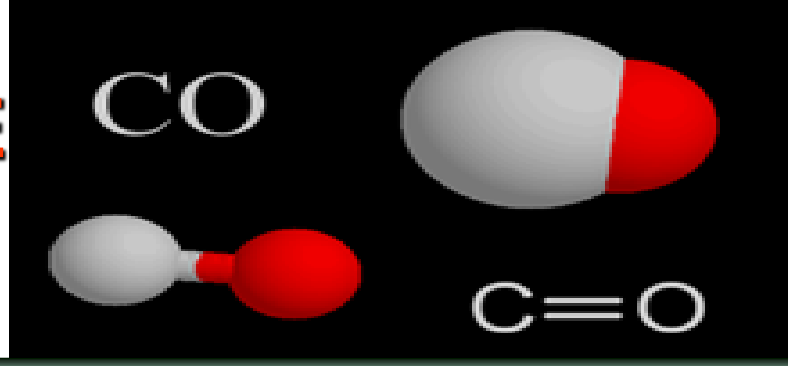
Chemistry

- Gas
- Odorless
- Colorless
- Tasteless
- Relative vapor density = 0.97
- Extremely stable
- Extremely flammable

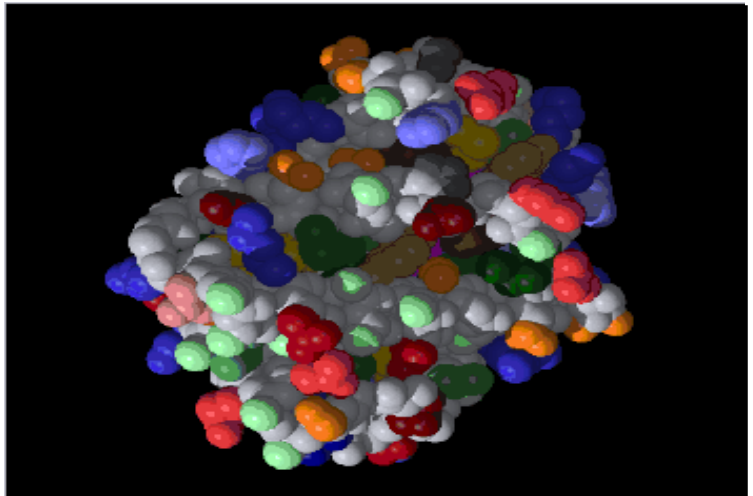


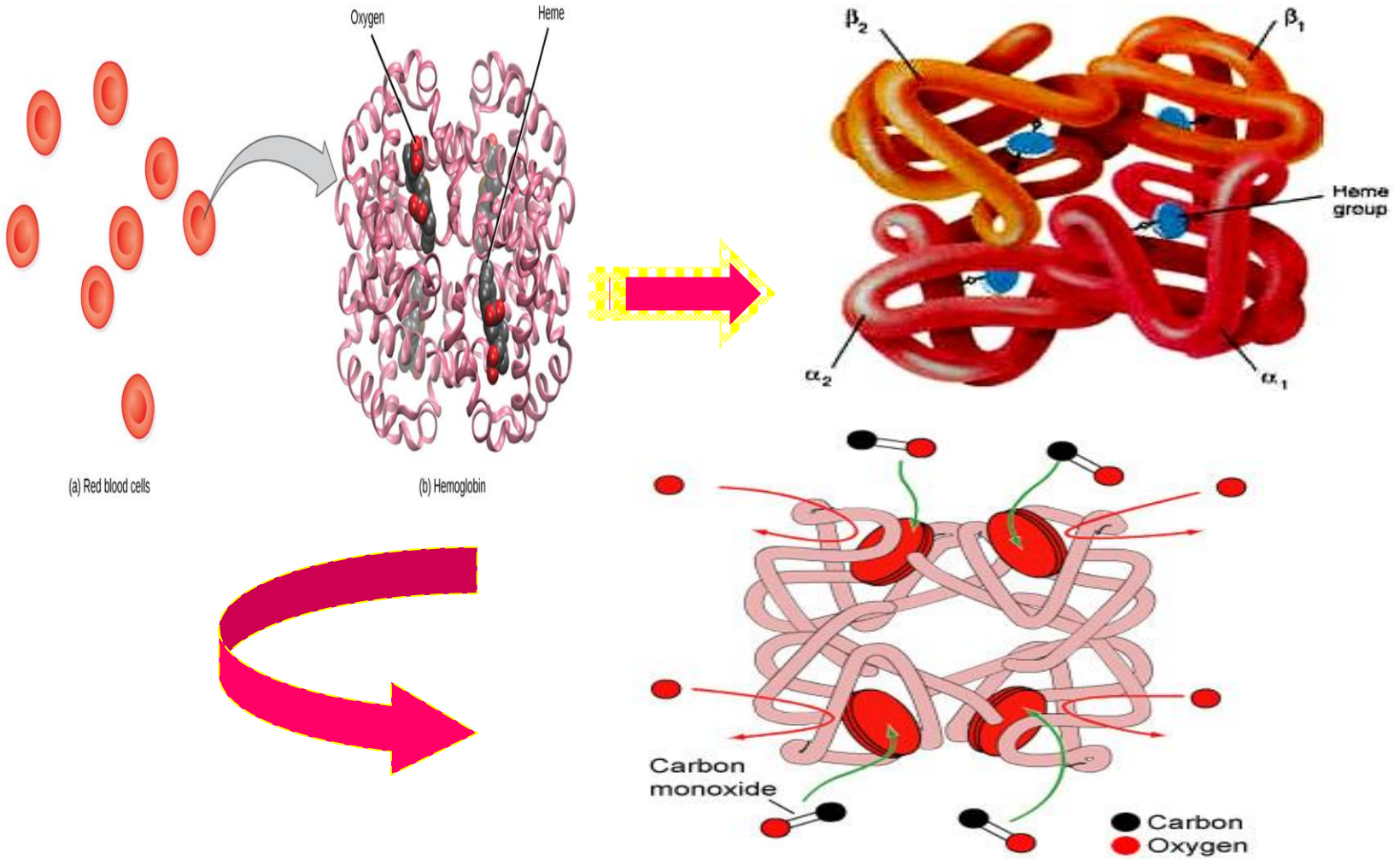
- **Half-life:**
- Room air: 240-360 minutes
- O_2 (100%): 80 minutes
- Hyperbaric O_2: 22 min

CARBON MONOXIDE
Pathogenesis



- **Carbon monoxide** is **non-irritating gas**, resulting from **incomplete burning** of **organic substances**, as gasoline, coal products, woods, tobacco building materials.
- CO is **readily absorbed** across **the respiratory tract** and **binds** to **hemoglobin, forming carboxyhaemoglobin. The affinity of hemoglobin for carbon monoxide is some 250 times greater than its affinity to oxygen.**




Oxygen
Heme
(a) Red blood cells
(b) Hemoglobin
β2
β1
Heme group
α2
α1
Carbon monoxide
Carbon
Oxygen

Pathogenesis

- The forming of the **carboxyhaemoglobin reduces** the capacity of blood to **transport oxygen (OCC – oxygen-carrying capacity)**.
- **Carboxyhaemoglobin** is **fully dissociable** and once exposure has been terminated the **pigment will revert to oxyhaemoglobin**. **Liberated** carbon monoxide is **eliminated via the lung.**

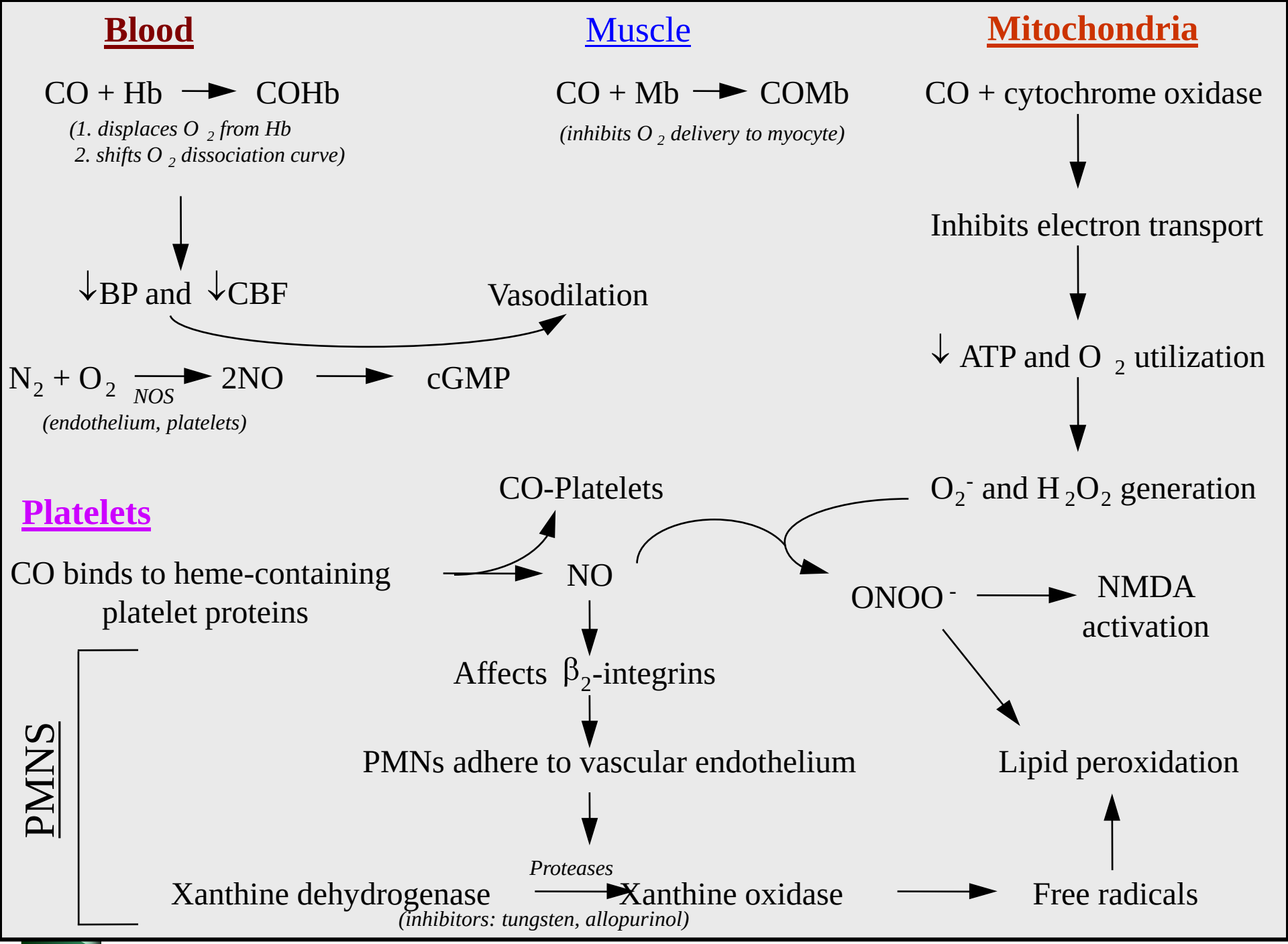
Pathogenesis

- **CO also binds to other iron-containing proteins (Fe 2+):**
  - **Myoglobin (COMyoglobin) - muscle cells**
  - **Cytochrome Oxidase**
  - **Neuroglobin**
- **Binding to myoglobin reduces O_2 available in the heart:**
  - **Ischemia**
  - Dysrhythmias
  - Cardiac dysfunction

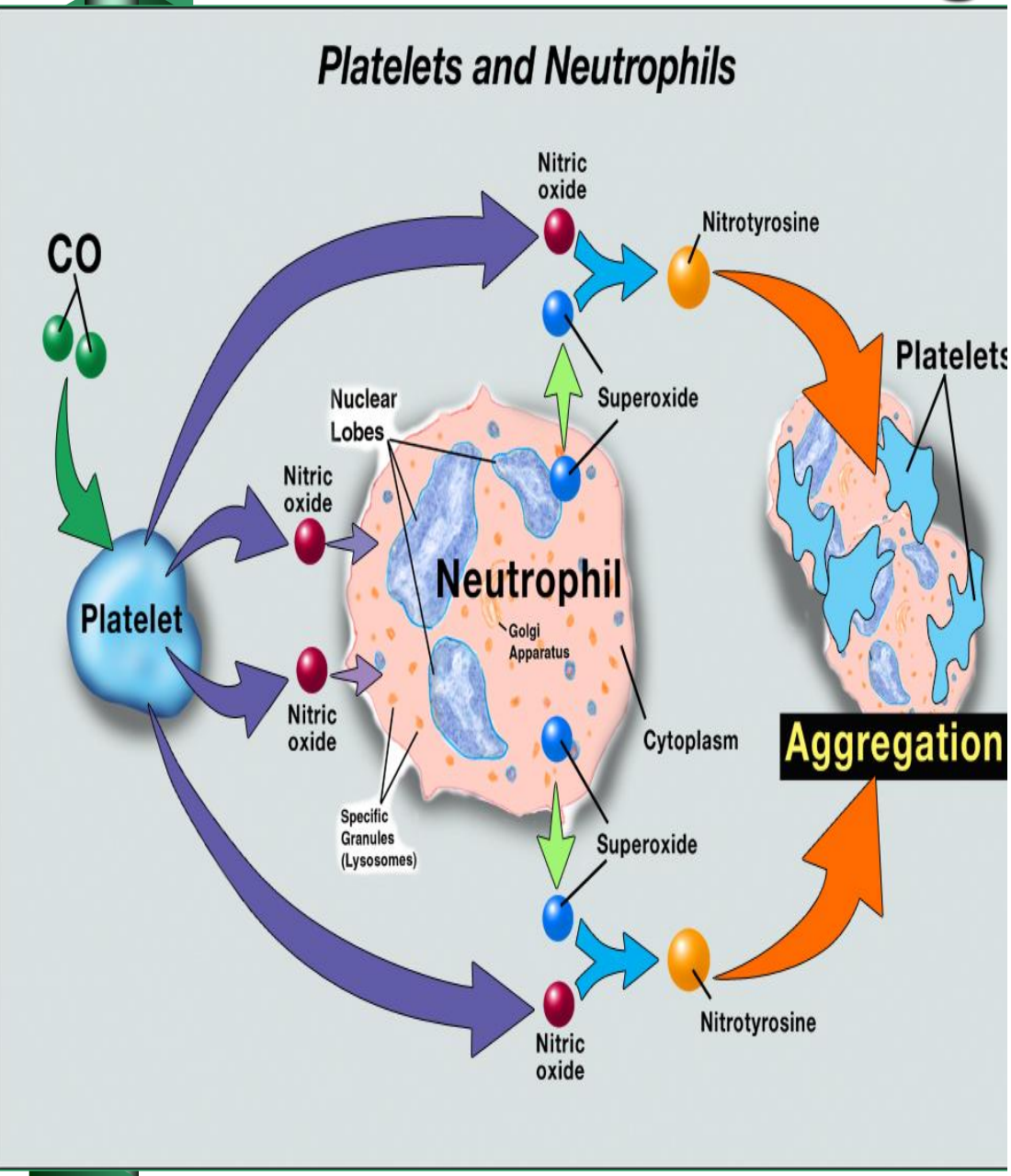
Pathogenesis

Other mechanisms:

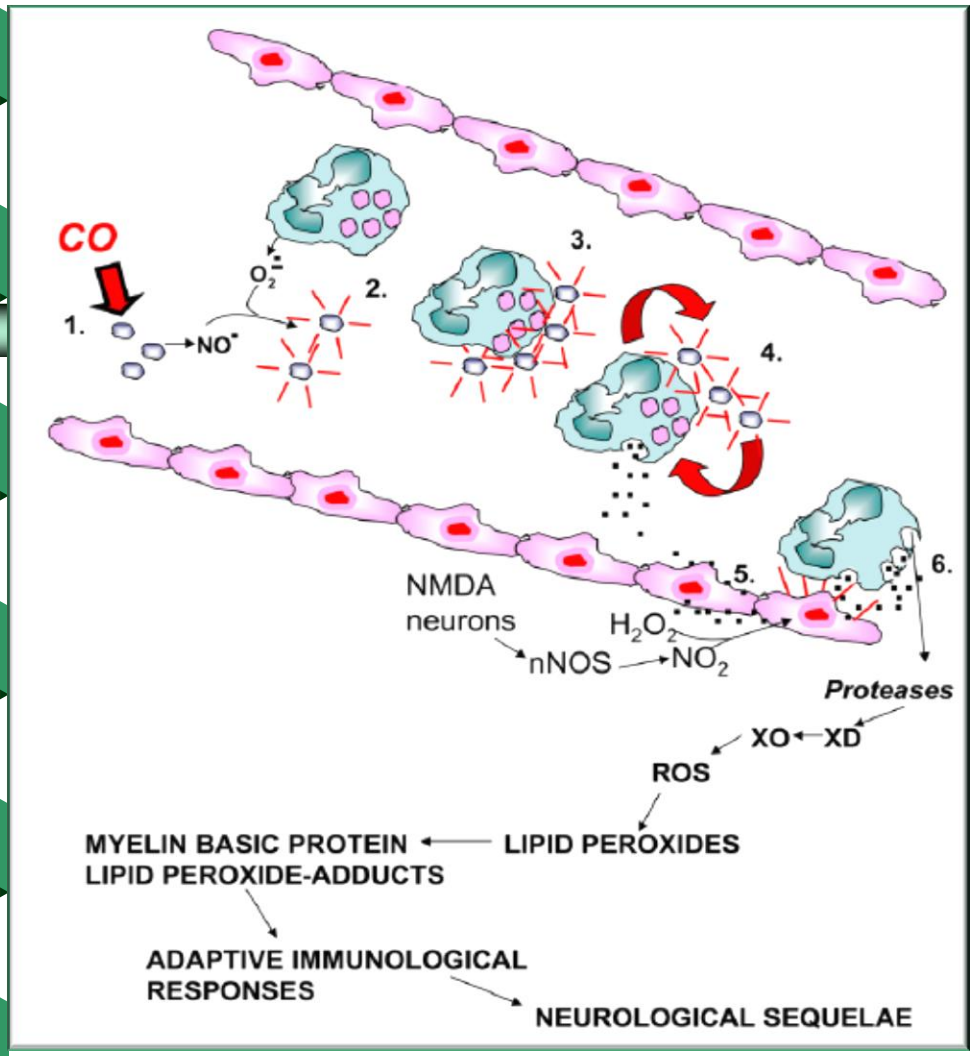
- the binding of carbon monoxide with **cytochrome oxydase**
- **cytochrome P-450**


Blood
Muscle
Mitochondria
CO + Hb → COHb
(1. displaces O 2 from Hb
2. shifts O 2 dissociation curve)
CO + Mb → COMb
(inhibits O 2 delivery to myocyte)
CO + cytochrome oxidase
Inhibits electron transport
↓ ATP and O 2 utilization
↓BP and ↓CBF
Vasodilation
N2 + O2 NOS 2NO → cGMP
(endothelium, platelets)
Platelets
CO binds to heme-containing platelet proteins
CO-Platelets
NO
O2- and H2O2 generation
ONOO- → NMDA activation
Affects β2-integrins
PMNs adhere to vascular endothelium
Lipid peroxidation
PMNS
Proteases
Xanthine dehydrogenase → Xanthine oxidase → Free radicals
(inhibitors: tungsten, allopurinol)

Pathogenesis



- CO binds to platelet hemoproteins and increases **NO** efflux.
- Platelet-derived NO reacts with neutrophil-derived **superoxide** which activates platelets and causes **platelet-neutrophil aggregates.**
- Reactive products and adhesion molecules promote firm aggregation and stimulate **degranulation of neutrophils**.
- Endothelial cells acitaved by **myeloperoxidase** facilitating firm neutrophil adhesion and further degranulation.



1. ROS initiate **lipid peroxidation** and adducts interact with **brain myelin basic protein**. The altered myelin basic protein triggers an adaptive immunologic response that causes neurologic dysfunction.

Source: Thom SR, Bhopale VM, Han S-T, Clark JM, Hardy KR. "Intravascular Neutrophil Activation Due to Carbon Monoxide Poisoning." *Am J Respir Crit Care Med.* 2006;174:1239-1248

Pathogenesis

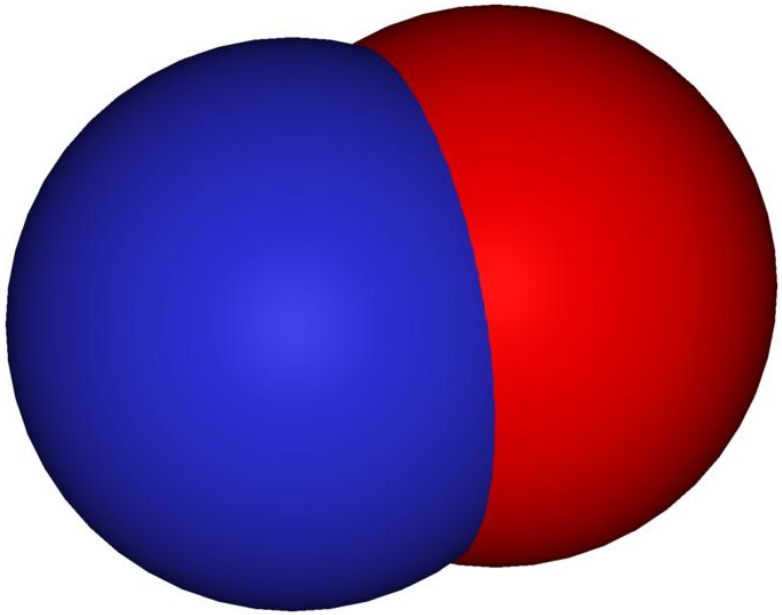
Effects:

- CO exposure can cause:
  - Increased hydroxyl radicals noted during both the hypoxic and reoxygenation stage
  - CO causes **hypoxia** due to:
    - The direct effect on hemoglobin
    - Impaired perfusion from cardiac dysfunction.
  - CO impairs mitochondrial electron transport because CO binds to CcOX (at higher COHb levels).
  - Impairs brain ATP synthesis.

Pathogenesis

Nitric oxide (NO):

- Highly-reactive gas that participates in numerous biochemical reactions.
- Oxygen free-radical
- Levels increased with CO exposure.



Pathogenesis

Nitric Oxide (NO):

- Causes cerebral **vasodilation**:
  - Syncope (short loss of conciousness)
  - Headache
- May lead to oxidative damage to the brain:
- Probable cause of delayed neurologic syndrome (**DNS**).
- Associated with reperfusion injury.

- CO and NO are known **second messengers**
- CO, NO bind to **heme** and inhibit **CcOX**.
- NO targets intracellular heme.
- NO impairs **heme synthesis** and enhances **heme destruction** by **increasing heme oxygenase activity**.

Pathogenesis

- CO exposure can cause:
  - Increased **NO** levels
  - Increased **superoxide** levels
  - These can combine to form the highly toxic **peroxynitrite**.
  - Effect of free radicals is primarily on the **vasculature.**
  - May cause **hemorrhagic necrosis**.

Source: Ischiropoulos H, et al. "Nitric oxide production and perivascular tyrosine nitration in brain after carbon monoxide poisoning in the rat." *J Clin Invest.* 1996;97:2260-2267

Pathogenesis: CO Binding

- **Myocardium**
  - CV impairment → Hypotension
- **Hemoglobin**
  - Decreased OCC (oxygen-carrying capacity) → Functional Anemia
- **Platelets and PMN**
  - Nitric oxide → Hypotension
  - Free radicals → Lipid Peroxidation
- **Mitochondria**
  - Cytochrome oxidase → Lipid Peroxidation
  - Impaired e transport → Functional Hypoxia

Pathogenesis Summary

- **Limits O_2 transport:**
  - CO more readily binds to Hb forming COHb.
- **Inhibits O_2 transfer:**
  - CO changes structure of Hb (conformational changes) causing premature release of O_2 into the tissues.
- **Tissue inflammation:**
  - Poor perfusion initiates an inflammatory response.

Pathophysiology Summary

- **Poor cardiac function:**
  - ↓ O_2 delivery can cause dysrhythmias and myocardial dysfunction.
  - Long-term cardiac damage reported after single CO exposure.
- **Increased activation of nitric oxide (NO):**
  - Peripheral vasodilation.
  - Inflammatory response.

Pathogenesis Summary

- **Vasodilation:**
  - Results from NO increase.
  - Cerebral vasodilation and systemic hypotension cause reduced cerebral blood flow.
  - NO is largely converted to methemoglobin.
- **Free radical formation:**
  - NO accelerates free radical formation.
  - Endothelial and oxidative brain damage.

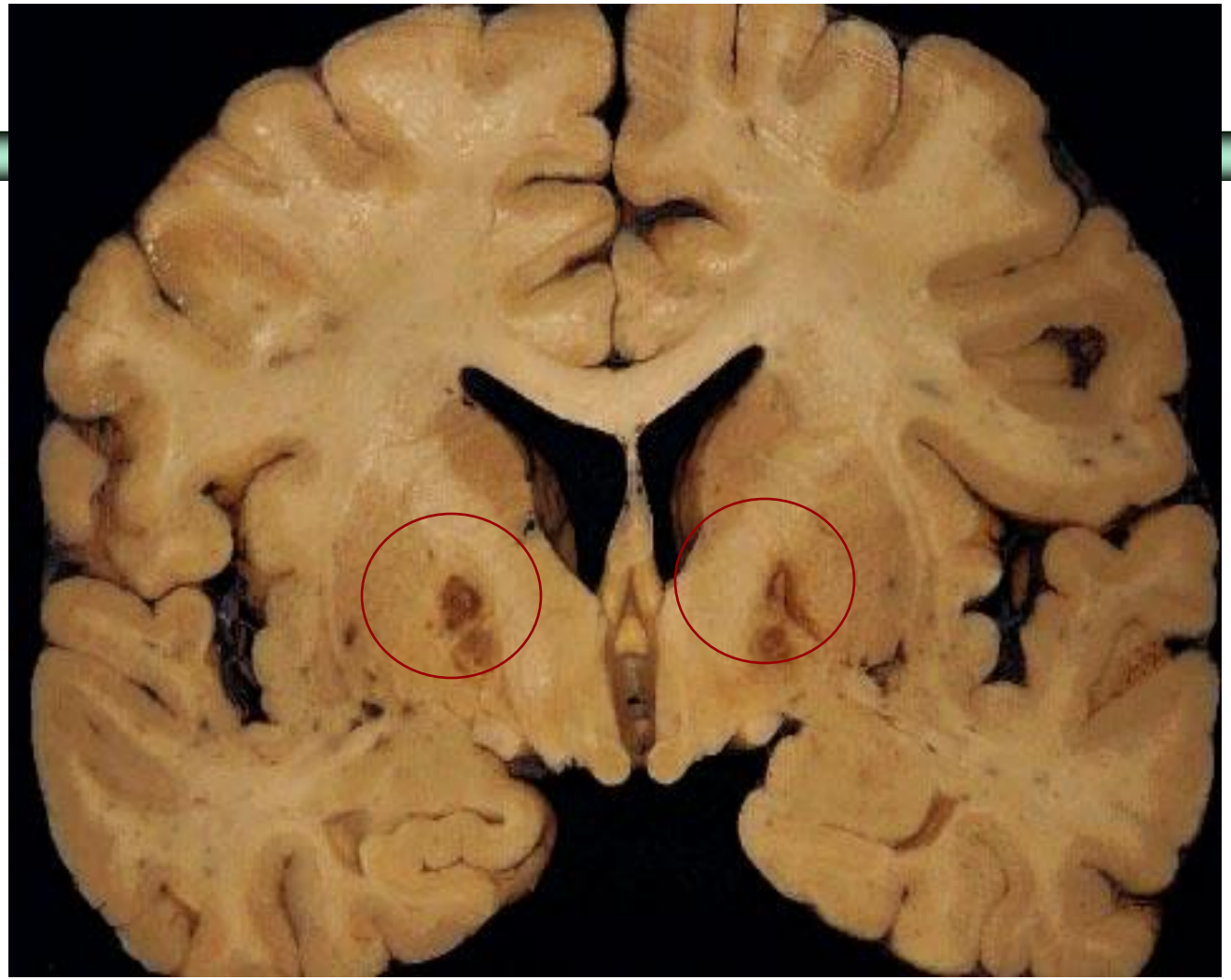
CARBON MONOXIDE

Pathology

In patient who die early following carbon monoxide poisoning **the brain** is **edematous**, and there are **diffuse petechias** and **hemorrhages**. If the victim **survives initially** but dies **within a few weeks**, findings typical of **ischemic anoxia are prominent**.

- **Manifests with cerebral edema, white matter petechial hemorrhages**
- **Congestion, hemorrhages and necrosis of globus pallidus**

CARBON MONOXIDE TOXICITY: bilateral necrosis of globus pallidus



Acute effects

Initial symptoms are **very nonspecific** and may be mistaken for **flu like symptoms**.

In order of **increasing severity**, the most commonly reported **signs and symptoms are**:

- **roaring in the ears**
- **weakness**
- **dizziness**
- **darkened vision**
- **frontal and temporal headache**
- **sleepiness**
- **adinamia**
- **collapse**
- **increased pulse and respiration**
- **unconsciousness**
- **involuntary evacuation**
- **muscle contractions**
- **coma**
- **convulsions**
- **cardiorespiratory depression**
- **death**

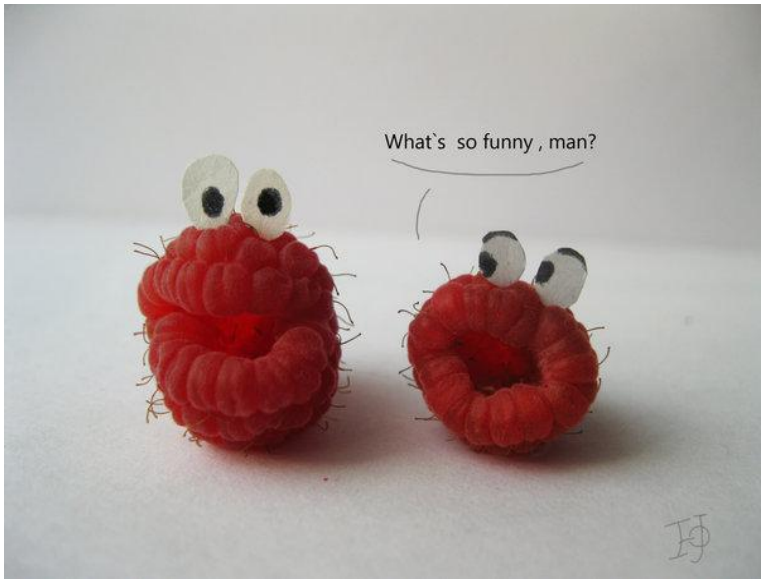
Acute effects

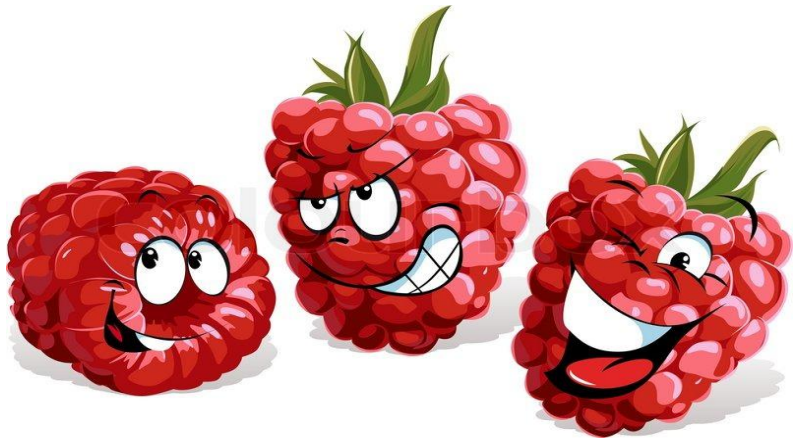
- **Pulmonary edema** is commonly found in victims who die as a result of acute exposure. **Aspiration pneumonia** also is often seen, the result of vomiting. **Ischemia** or **infarction** of brain and heart can occur.

Acute effects

- The early features of CO poisoning are headache, dizziness, nausea and vomiting. Coma is accompanied by hyperventilation hypotension, increased muscle tone, hyperreflexia, clonus and shivering. The skin may show the **cherry - pink colour** of carboxyhaemoglobin during life. **Skin blistering** may occur if the patient has been lying for some time. Renal failure is very rare. Retinal haemorrhages, **hypoxic cerebral oedema** may be present.
- Variety of neurological deficits such as **parkinsonism, hemiparesis** have been reported. The later correlate with lesions in the **globus pallidus and putamen**.

BLOOD





COHb levels (%)	Symptoms	
1-2	Normal	
5-10	Smokers	
10-20	“Flu-like” symptoms	
30-40	Fatigue; Severe headache	
40-50	Confusion; loss of consciousness	
60-70	Coma Seizures	CV collapse Death
>70	Rapidly fatal	

Summary

- Impact of CO on major body systems:

Cardiac:

- Decreased myocardial function:
  - Hypotension with tachycardia.
  - Chest pain.
  - Dysrhythmias.
  - Myocardial ischemia.
  - Most CO deaths are from ventricular fibrillation.
- Long-term effects:
  - Increased risk of premature cardiac death.

Summary
Impact of CO on major body systems:

- **Metabolic:**
  - ♦ **Respiratory alkalosis** (from hyperventilation).

  Hyperventilation leads to low [CO2] in plasma and cerebral vasoconstriction, the oxygen supply to the brain is decreased.
  - ♦ **Metabolic acidosis** with severe exposures (occurs secondary to **lactic acidosis** from ischemia).
- **Respiratory:**
  - Pulmonary edema (10-30%)
    - Direct effect on alveolar membrane.
    - Left-ventricular failure.
    - Aspiration.
    - Neurogenic pulmonary edema.
- **Multiple Organ Dysfunction Syndrome (MODS):**
  - Occurs at high-levels of exposure.

Chronic effects

Some researchers believe that chronic effects actually are the result of a slow accumulation of daily damage that results in pathological change.

Symptoms of **chronic CO effects** that are most commonly seen include:

- **headache**
- **irritability**
- **insomnia**
- **personality disturbances**
- **disturbance in ability to drive a vehicle**

Delayed Neurologic Syndrome

Signs and Symptoms:

- Memory loss
- Confusion
- Ataxia
- Seizures
- Urinary incontinence
- Fecal incontinence
- Emotional lability

Signs and Symptoms:

- Disorientation
- Hallucinations
- Parkinsonism
- Cortical blindness
- Psychosis
- Gait disturbances
- Other motor disturbances

Chronic effects

- **These manifestations** are related to the effects **of hypoxia** on the nervous system. **Basal ganglia lesions** have been found in experimental animals and in autopsies of exposed humans.
- Exposure to **low levels** of carbon monoxide can **provoke transient ischemic attacks, strokes and myocardial infarctions** in **workers** with **underlying** cardiovascular or cerebrovascular diseases.

Diagnosis

- **The diagnosis** of carbon monoxide poisoning is most reliable **confirmed** by **measuring the percentage of COHb in the blood**. Typically this is measured **in arterial blood** but it is possible **also in venous samples**. A less accurate measure is the testing of **expired air** (for carbon monoxide)

Diagnosis

- Signs and symptoms closely resemble those of other diseases.
- Often misdiagnosed as:
  - **Viral illness** (e.g., the "**flu**")
  - **Acute coronary syndrome**
  - **Migraine**
- Estimated that misdiagnosis may occur in up to 30-50% of CO-exposed patients presenting to the ED.

Source: Raub JA, Mathieu-Holt M, Hampson NB, Thom SR. Carbon Monoxide Poisoning: A Public Health Perspective. *Toxicology* 200;145:1-14

Treatment

- Treatment is based on the severity of symptoms. Individuals affected by carbon monoxide should be removed from exposure and moved to fresh air at once. If breathing has stopped, artificial respiration should be performed. If indicated, CPR should be completed.
- Treatment generally indicated with SpCO > 10-12%. (pulse CO-oximetry is a continuous and noninvasive method of measuring the levels of CO concentration (SpCO) in the blood.
- Be prepared to treat complications (i.e., seizures,dysrhythmias, cardiac ischemia).

TREATMENT

- The **specific antagonist** to carbon monoxide is the **oxygen**. **Medical treatment consist of first supplying 100% supplemental oxygen** via **face mask** the minute the diagnosis is suggested. Increasing the arterial oxygen content **both counteracts the primary effect** of the carbon monoxide and **speeds its elimination**. Immediate treatment with **hyperbaric oxygen** may be indicated.

Hyperbaric oxygen
HBO

- It is involved **2 hours or longer** at pressure **of 2 - 3 ATA**. It has been advised for patients who have:
- **been conscious at any stage since exposure;**
- **COHb concentrations exceeding 40% at any time;**
- **neurologic or psychiatric features.**
- **HBO produces a more rapid reduction in COHb levels. The half-life of COHb is 4-5 hours in a person at rest breathing room air, 80 minutes by administration of 100% oxygen at sea level and to 22-23 minutes by treatment with hyperbaric oxygen at 3 atmospheres absolute (ATA). At 3 ATA the oxygen dissolved in blood approaches 6 vol percent; this is adequate to supply basal oxygen requirements to the body with normal cardiac output in the absence of functional hemoglobin;**

TREATMENT

- HBO induces **cerebral vasoconstriction**, which may reduce intracranial pressure and cerebral edema;
- HBO results in **more rapid dissociation of CO** from respiratory cytochromes;
- HBO may antagonize the oxidative injury that occurs after CO poisoning. HBO prevents the **conversion of xanthine dehydrogenase to xanthine oxidase**, a leucocyte-mediated reaction.This effect has been postulated to occur due **to diminished B2 integrin-mediated leukocyte adherence**.

Hyperbaric chamber

TREATMENT

- In patient with **altered** level **of consciousness naloxone (narcan)** is administered.
- **Exchange transfusion of blood** has used for **the moribund victims**.
- If the patient has **acidosis**, an infusion of **sodium bicarbonate** is necessary until **the pH** of blood returned **to 7,2**.
- Giving **i.v. of fluids to increase the circulatory blood volume** and to **correct hypotension**.
- **In case of convulsions** is necessary **diazepam (Valium)**.
- **For preventing** of **ventricular dysrhythmias** should be administered **lidocaine**.
- **Mannitol** and **dexamethasone** should be given if **cerebral oedema** is present.