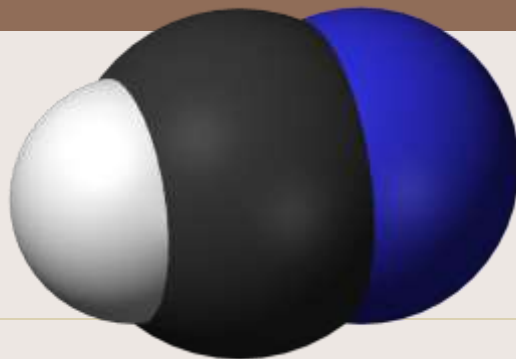


# CYANIDE

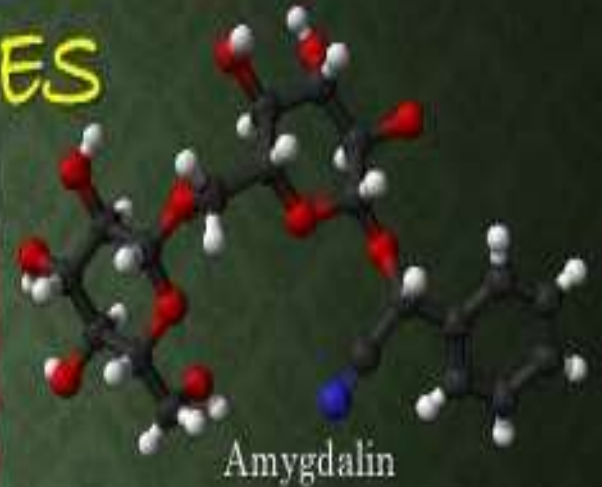


*Лектор: доц. д-р В. Данчева, дм*



- **Cyanide (CN)** is one of the **oldest** and **most rapidly fatal toxins** known to human.
- Its use as an agent of **homicide** and of **suicide** is well documented from the days of the **ancient Egyptians** to modern times.
- **Fortunately**, it also is one of the few poisons for which **specific** and **effective antidotes** are available.
- Cyanide occurs both **naturally** and as the result of **human activities**. **Many plants**, including **fruits** and **vegetables**, can release cyanide when ingested. Well-known sources include the pits of cherry, apricots, almond etc.

# CYANOGENIC GLYCOSIDES



Amygdalin (Almond seed)

HCN in Hydrangea, Linum  
(Linseed)

Prunus (Wild cherry)

Sorghum vulgare (Jowar)

Sorghum sudanese (Sudan grass)

Gossypol (cotton seed)



# CYANIDE PLANTS

**Almonds**



**250 mg CN/100g plant tissue**

**Cassava**



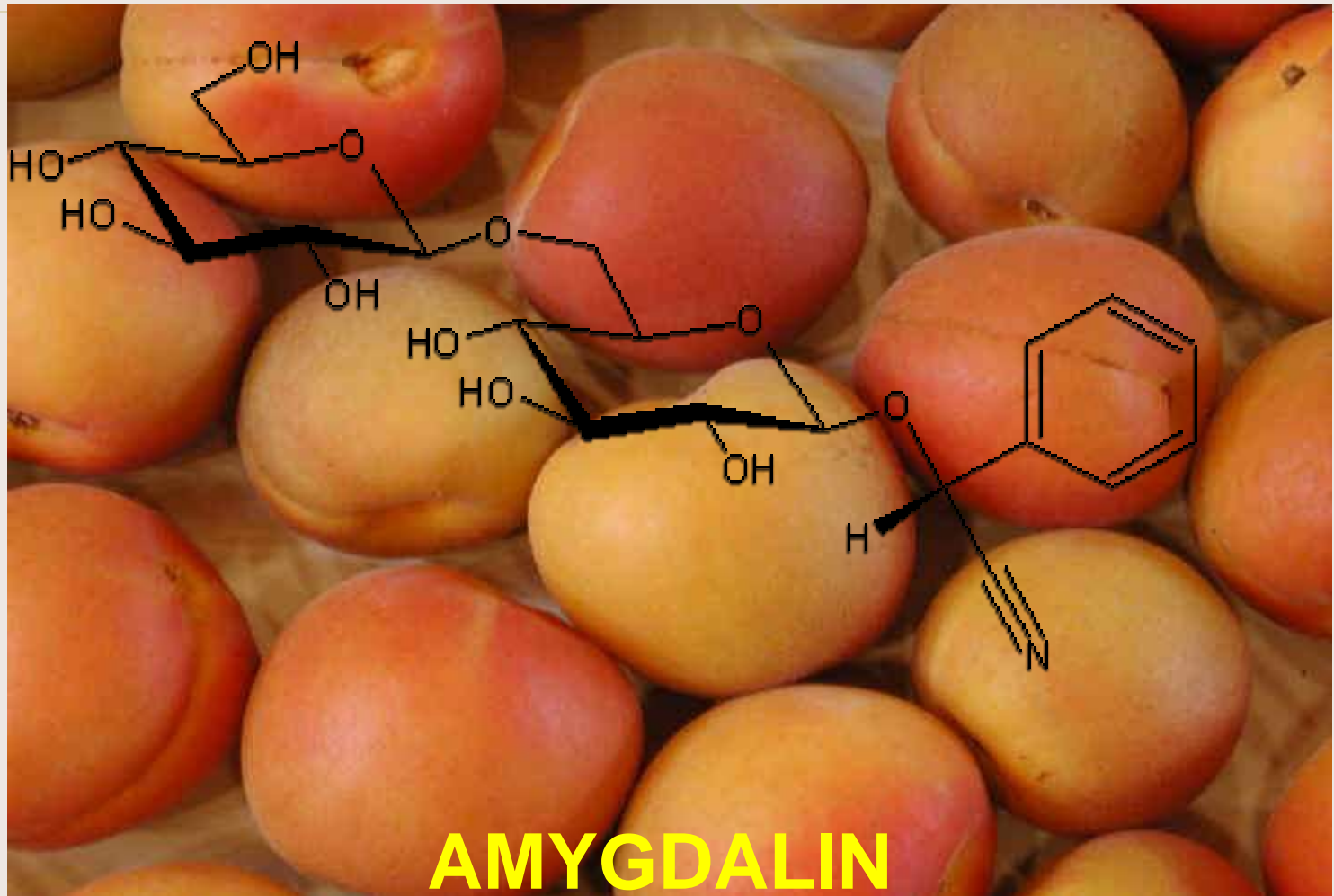
**104 mg CN/ 100 g plant  
tissue**

**Wild Cherries**



**140-370 mg CN/ 100 g  
plant material**

# CYANIDE PLANTS



# Sources and uses

- The many **industrial sources** include **fumigants, insecticides, pesticides**, and the production of **plastic and rubber, electroplating, metallurgy** and the processing of **photographic film**.
- The presence of HCN in various industrial gases results from an incomplete combustion of nitrogen-containing organic compounds, and its presence often is not suspected until an accident occurs.



# CYANIDE INDUSTRY



ELECTROPLATING  
HARDENING METALS  
GOLD EXTRACTION  
LABORATORIES

# CYANIDE FIRE

- Victims of smoke inhalation have been shown to have toxic levels of both carbon monoxide and hydrogen cyanide.



**CYANIDE/CARBON  
MONOXIDE**  
**Toxic twins**



# **CYANIDE**

## **RODENTICIDE/FUMIGANT**

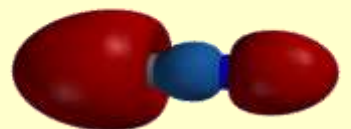
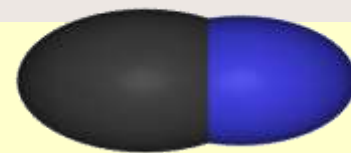


**FERATOX/CYANIDE PASTE**

**Cyanide** can be released from a **large number** of different **compounds** (all having the **CN** group).



- **Hydrogen cyanide** (HCN)
- **Sodium cyanide** (NaCN)
- **Potassium cyanide** (KCN)
- **Calcium cyanamid** (CaCN<sub>2</sub>) etc
- **Hydrogen cyanide** - the base compound of the group - is a **colorless** gas or liquid with a faint, bitter **almond odor**.



# Types of Cyanide

## Solid



**POTASSIUM CYANIDE**  
**SODIUM CYANIDE**

## Gas



**HYDROGEN CYANIDE**  
**CYANOGEN CHLORIDE**

## Liquid

**HYDROGEN CYANIDE**



# TOXICITY

## INGESTION

### LETHAL DOSES

**60- 90 mg**

**Hydrogen Cyanide (HCN)**

**200 mg**

**Potassium Cyanide (KCN)**

# TOXICITY

## INHALATION

<b>Concentration (mg.m<sup>3</sup>)</b>	<b>Effect</b>
300	immediately lethal
200	lethal after 10 minutes
150	lethal after 30 minutes
120-150	lethal after 30-60 minutes
50-60	20 minutes to 1 hour without effect
20-40	light symptoms after several hours

# Mechanism of action

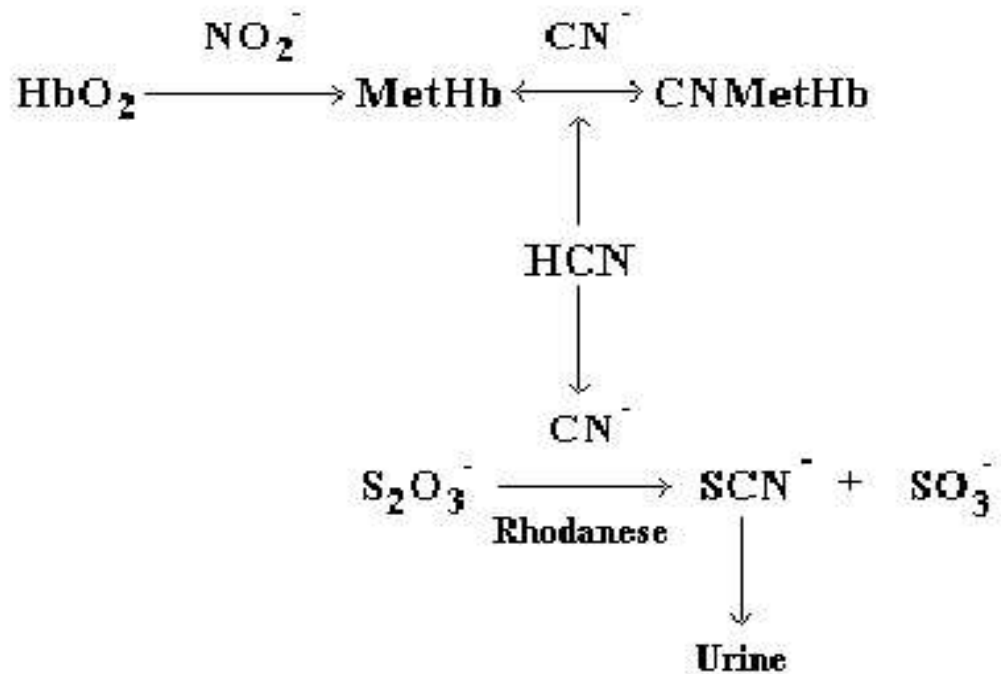
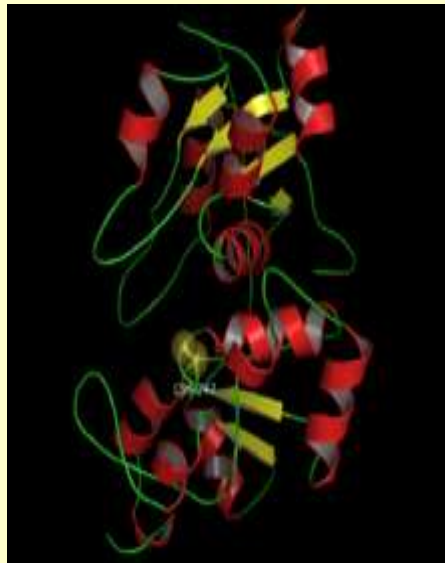
- Cyanide is **rapidly absorbed** through the **lungs, skin and gastrointestinal tract** because of its unionized state and low molecular weight. **Symptoms occur within seconds of inhalation** and within **minutes of ingestion** of cyanide salts.

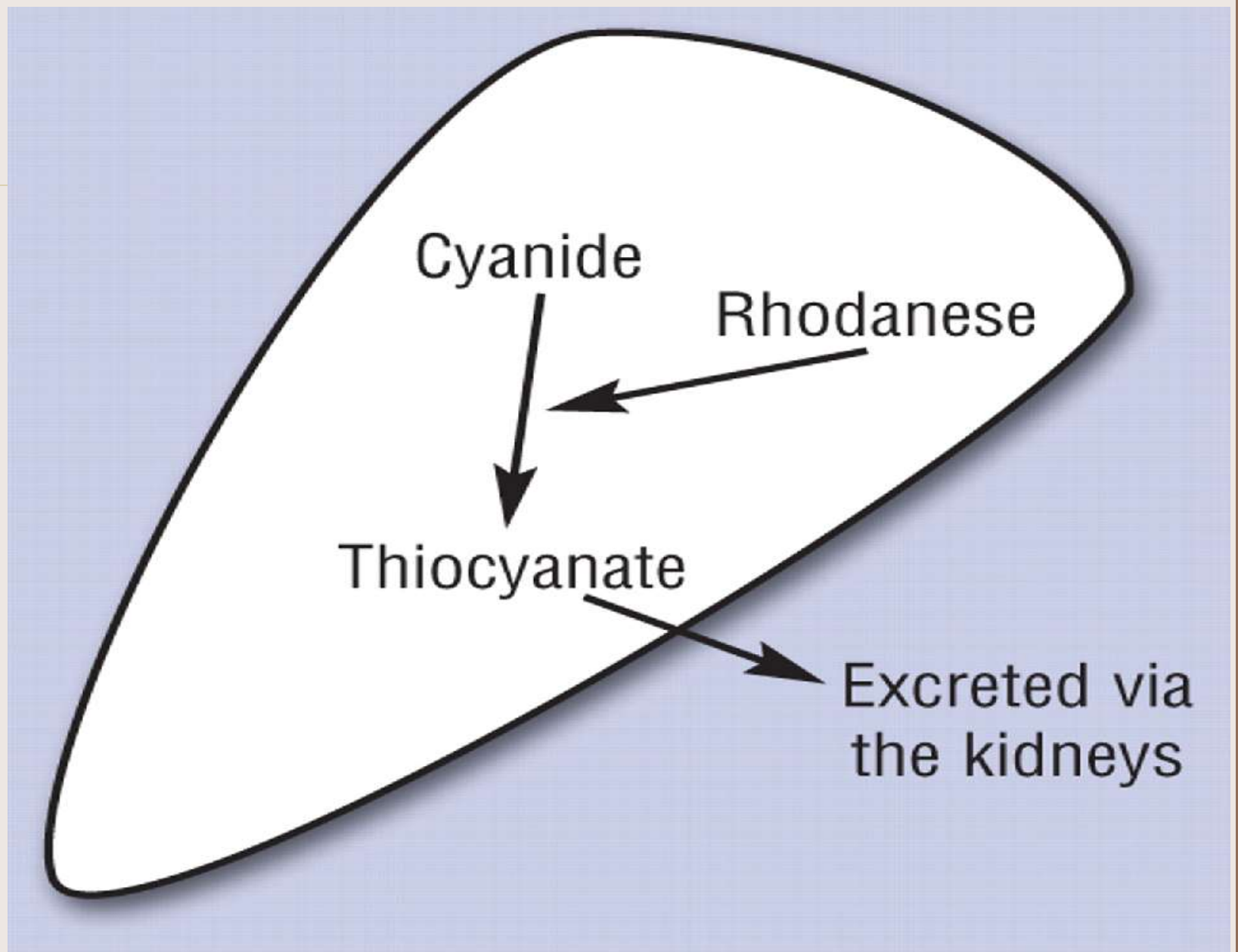
Cyanide can be **metabolized by five mechanisms.**

Only **two** of these five **ways** are **clinically important:**



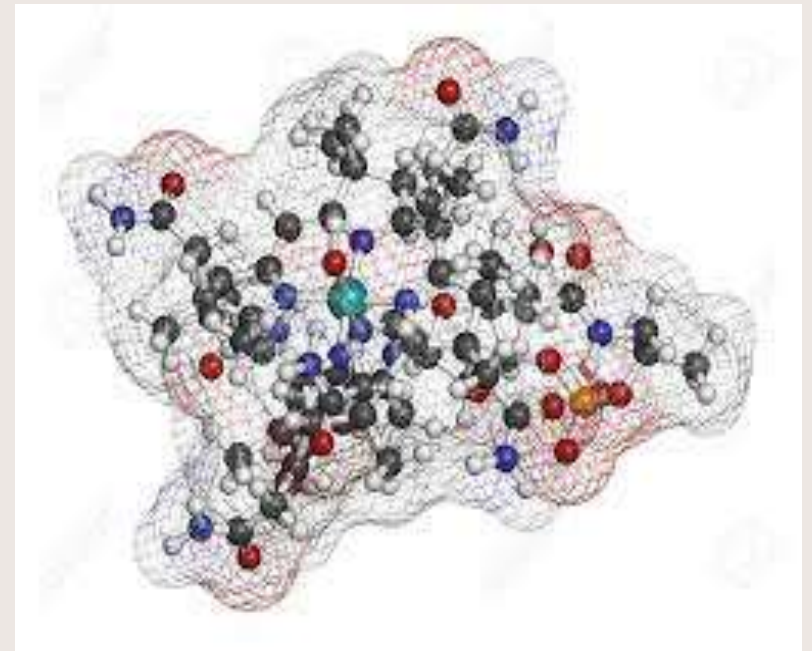
1. The major process of detoxification of the cyanide (80%) occurs mostly in the liver. **The mitochondrial enzyme rhodanase** catalyses the transfer of **sulfur** from **thiosulfate to cyanide**, forming the less toxic **thiocyanate**, which is excreted in the urine.







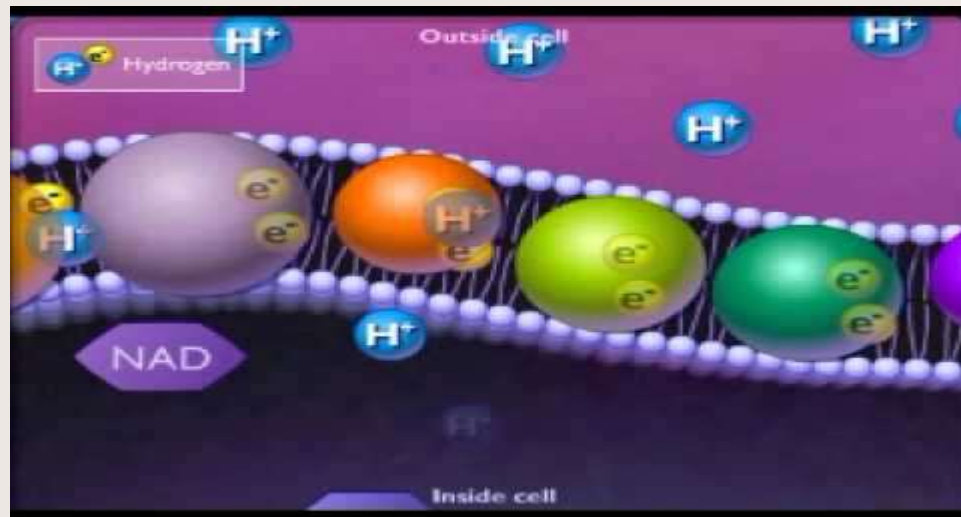
2. Cyanide forms **cyanocobalamin** through a reaction with **hydroxocobalamin** (Vit.B<sub>12</sub>).



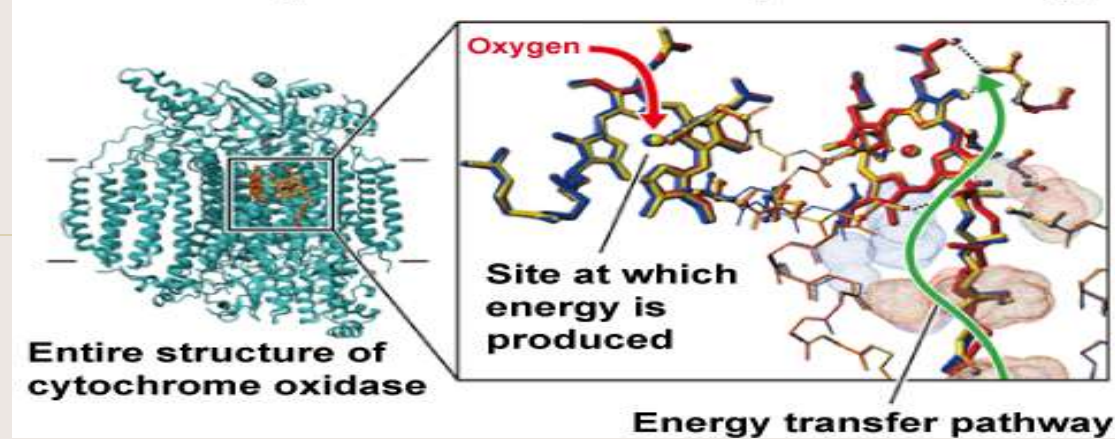


- 3. Cyanide is oxidized and incorporated into **choline** and **methionine**.
- 4. Cyanide reacts with **cystine**, which product is excreted.
- 5. **Small amount** of the cyanide is **excreted** unchanged in the **lung** and **urine**;

- The toxicity of cyanide arises from its ability to inhibit the enzymes of the cellular respiration. Cyanide can form stable complex with the **ferric ion in cytochrome oxidase**. So, this poison inhibits the final step of oxidative phosphorylation, preventing the production of adenosine triphosphate (**ATP**) and results in anaerobic metabolism. Cellular anoxia results from the inability to use oxygen and a severe **lactic acidosis** ensues.

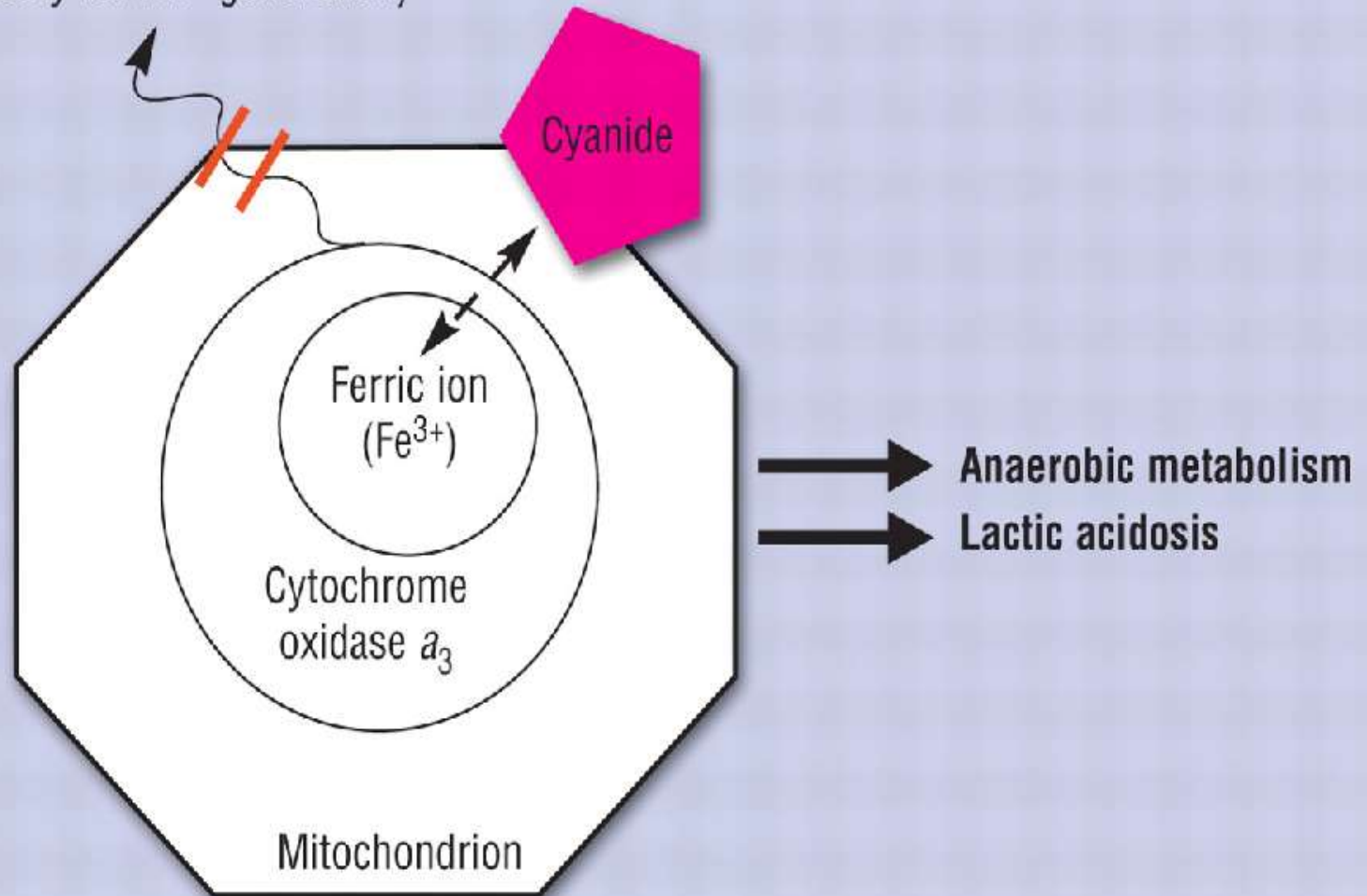
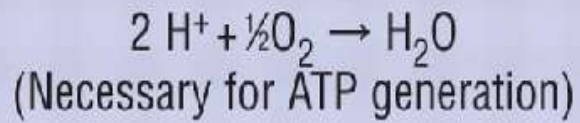


### Structure of cytochrome oxidase that produces energy

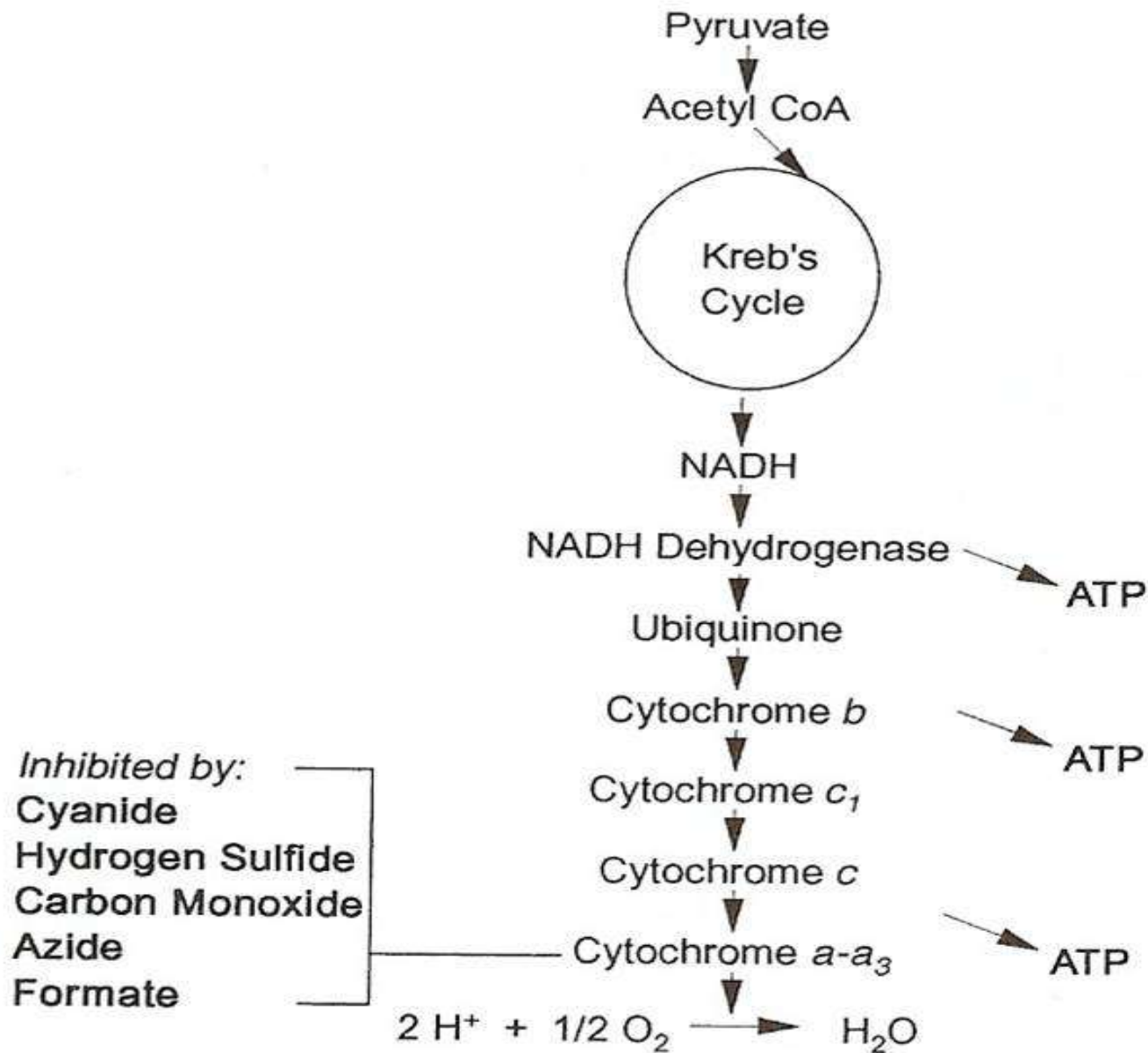


- CN has high affinity for metals
  - Complexes with metallic cations at catalytic sites of several enzymes
- Binds **ferric (3+)** iron of mitochondrial cytochrome oxidase (**cytochrome a-a3**)
- **cytochrome a-a3** – mediates transfer of electrons to molecular oxygen (final step in oxidative phosphorylation)



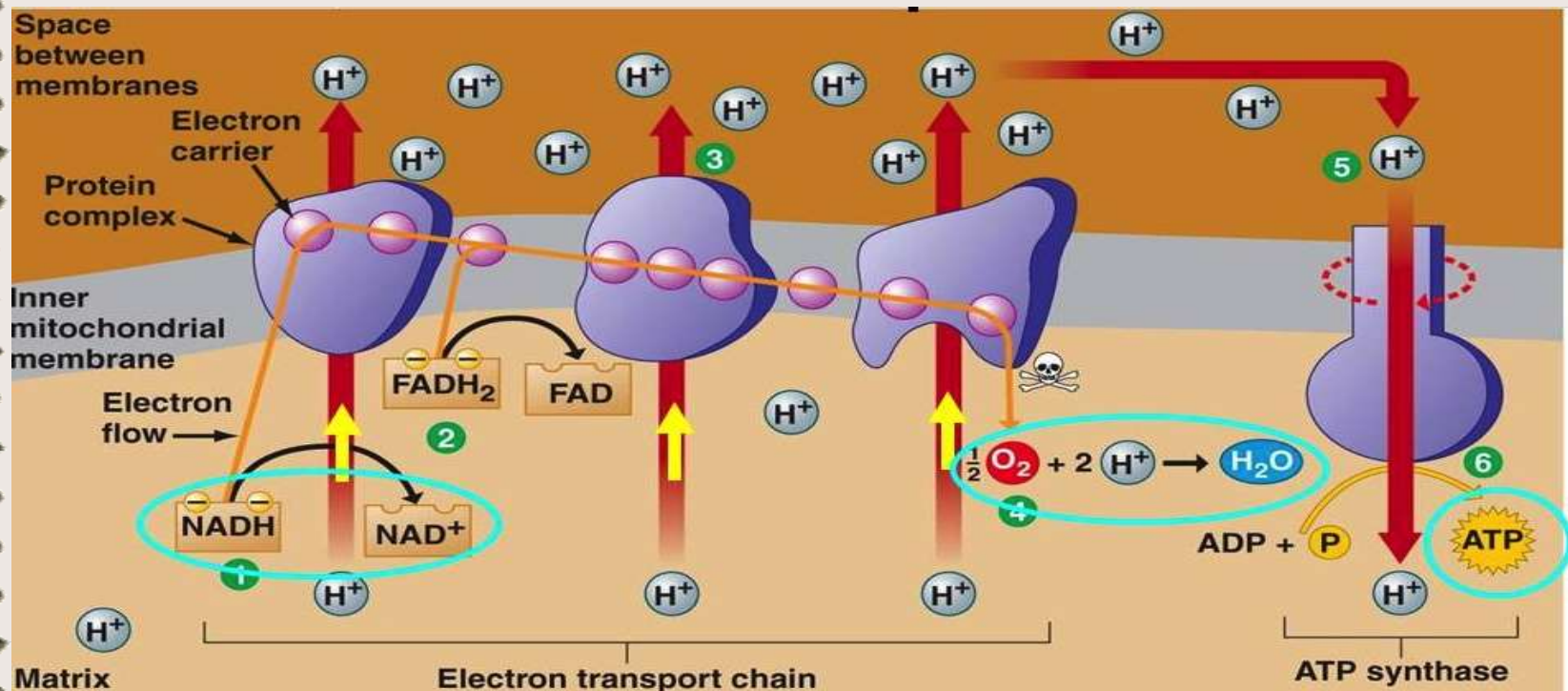


Abbreviation: ATP, adenosine triphosphate.



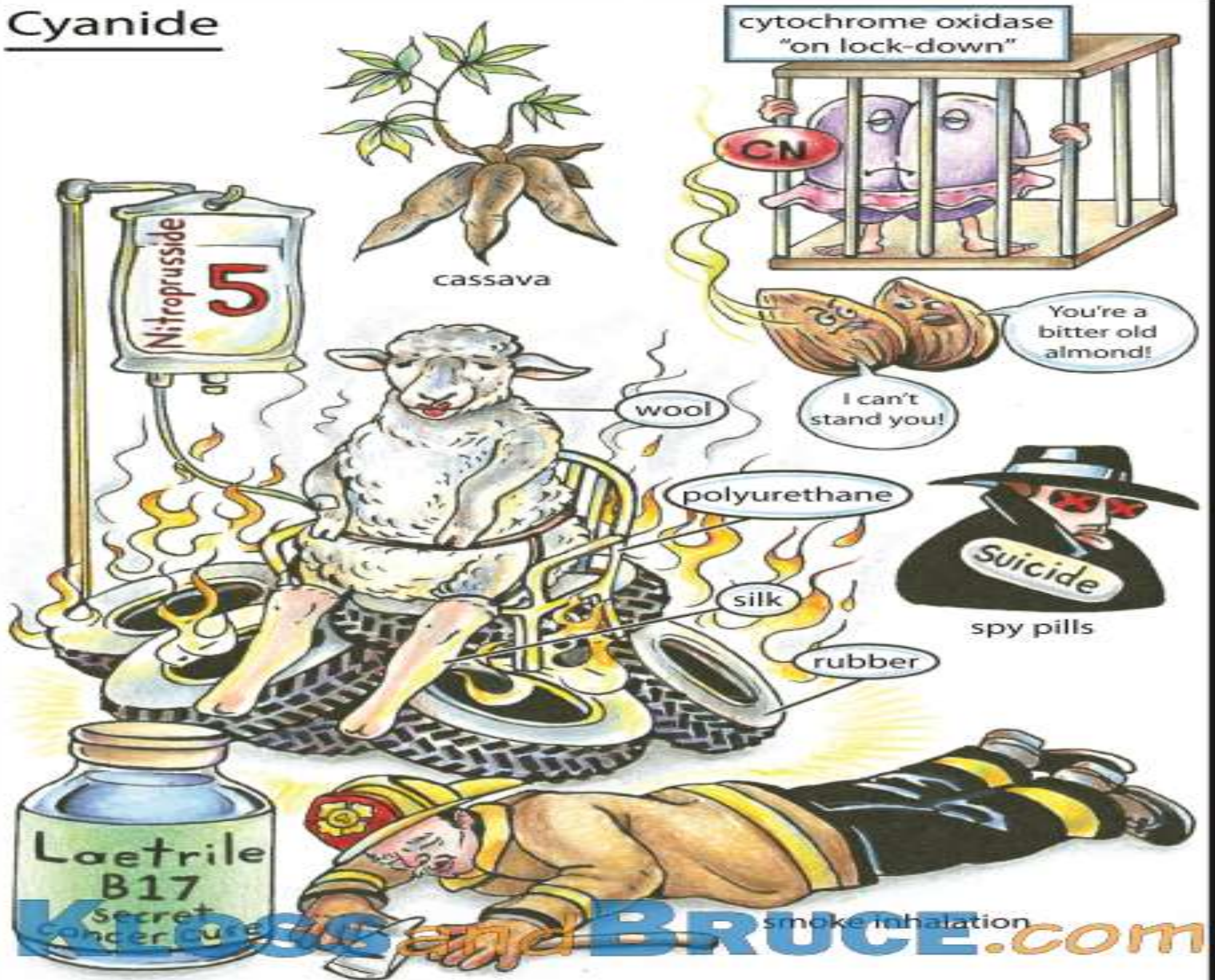
# Blockade of oxidative phosphorylation

- Tissue anoxia
- Anaerobic metabolism
- Lactic acidosis • Arterialization of venous blood





# Cyanide





# Acute effects

- Acute exposure to lower concentration (5 to 50 mg/m<sup>3</sup>) of hydrogen cyanide cause a variety of effects in humans - **weakness, headache, nausea, increased rate of respiration and eye and skin irritation.**

# Acute effects

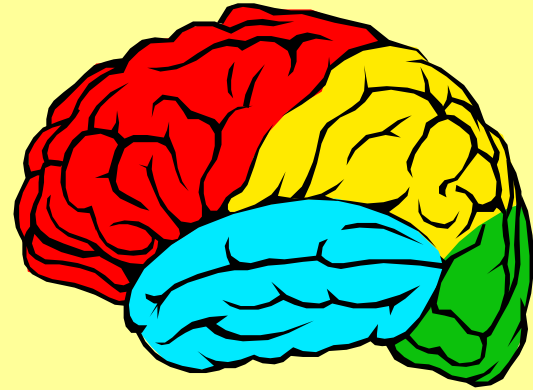
- Acute cyanide poisoning has primarily central nervous system effects. After inhalation - dry mouth, irritated eyes, itchy nose and throat and **metallic taste** is rapidly followed by air hunger and hyperpnea. Headache, **flushed skin**, **stertorous breathing**, agitation, muscle rigidity, ataxia, aphasia and confusion progress to loss of consciousness, and coma. Finally, bradycardia and hypotension lead to a **terminal cardiovascular collapse**.

# Acute effects

- **Pulmonary edema** and **lactic acidosis** have been observed after cyanide ingestion.
- **Ingested cyanide** follows a similar course, with **vomiting** caused by the strong **irritant effect** on the gastric mucosa.

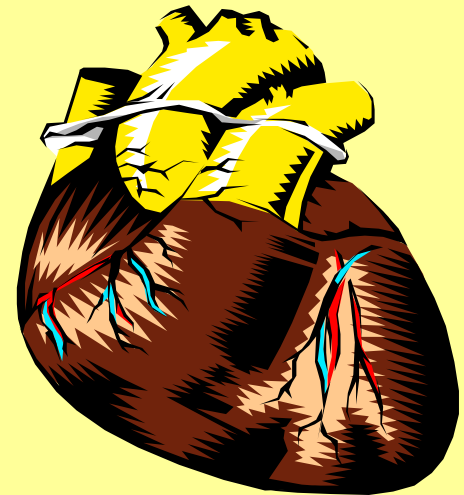
- **CNS**

- Headache
- Dizziness
- Seizures
- Coma



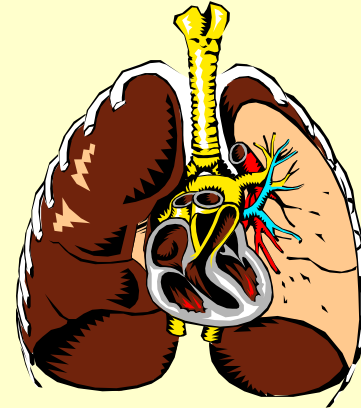
- **Cardiovascular**

- Hypertension, tachycardia
- Hypotension, later in course
- Bradycardia
- Asystole
- Cardiovascular collapse





- **Pulmonary**
  - Dyspnea
  - Tachypnea
  - Pulmonary edema
  - Apnea



- **Gastrointestinal**
  - Nausea, vomiting
  - Caustic effects



# Chronic exposure

- **Chronic exposure** involves the **CNS** (headache, tremor and loss of visual acuity) and **endocrine systems** (enlarged thyroid gland) and **irritation** to the eyes and skin.
- dermatitis in workers who are chronically exposed to cyanide solutions because the solution is strongly irritating and causes severe itching;
- cyanide rash - papules and vesicles;
- blotchy eruption on the face;
- **cyanide - induced Parkinson's disease**;
- visual disturbances;
- **depletion of vit. B12**;
- **endocrine toxicity** - enlarged thyroid gland and altered thyroid function;

# Diagnosis

---

- An odor of bitter almonds, but up to 40% of the population is unable to detect cyanide by odor.
- **A cherry red colour of venous blood**, arising from poor oxygen utilization.
- Metabolic acidosis.
- Absence of cyanosis.

# Differential Diagnosis (DD)

- **Ingestion** with altered LOC (level of consciousness) and acidosis
  - ☐ Salicylates
  - ☐ Iron
  - ☐ Beta-adrenergic antagonists (beta-blockers)
  - ☐ Cocaine
  - ☐ Isoniazid (prophylaxis and treatment of tuberculosis)
  - ☐ toxic alcohols



# Differential Diagnosis (DD)

---

- **Inhalational Exposures**

- hydrogen sulfide
- carbon monoxide
- simple asphyxiants

# TREATMENT

- When cyanide has been inhaled the patient must be removed from the toxic atmosphere, contaminated clothing removed and exposed skin washed. When cyanide has been ingested, gastric aspiration and lavage should be carried out.
- The **treatment** begins with **artificial respiration** with **100 percent oxygen** in patient with **respiratory difficulty** or **apnea**.
- The role of the **antidotes** in the therapy of cyanide intoxications is exceptional important, but they are potentially dangerous in the absence of cyanide ions. So, the diagnosis must be absolutely sure.

# Treatment

## Antidotes

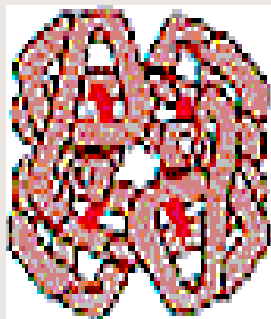
### 1. Methemoglobin-producers

Formation of **methemoglobin** competes for CN bound to **cytochrome oxydase**. Methemoglobin **removes the CN** from the enzyme and **restores its function** because the **iron (FeO3+)** is **oxidized** in methemoglobin. This leads to the **formation** of **cyanmethemoglobin**, which has a **low toxicity**.

- The **methemoglobinemia** **higher than 25%** induced by methhemoglobin-producers can **intensify tissue hypoxia**.

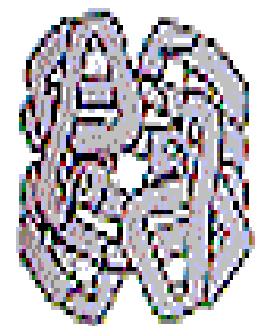
# What is methemoglobinemia?

Oxidation of iron within heme from **Fe<sup>2+</sup>** to **Fe<sup>3+</sup>**



Hb 4(O<sub>2</sub>)

Oxidation in the presence of O<sub>2</sub>



methHb



Reduction by NADH Diaphorase in the presence of NADH

❖ Methemoglobinemia is due to an imbalance of MHb production and MHb reduction



# Toxins causing MHb

- Chloroquine (malaria, amebiasis)
- dapson (treating leprosy)
- local anaesthetics
- methylene blue
- Metoclopramide (emesis)
- nitrates
- nitrites
- NTG (nitroglycerin)
- Nitroprusside (congestive heart failure, hypertension)
- Phenacetin (analgesic, pain, fever)
- Pyridium (pain releiver)
- Rifampin (tuberculosis)
- sulfonamides
- vitamin K<sub>3</sub>
- Chlorhexidine (antiseptic agent)

# Treatment

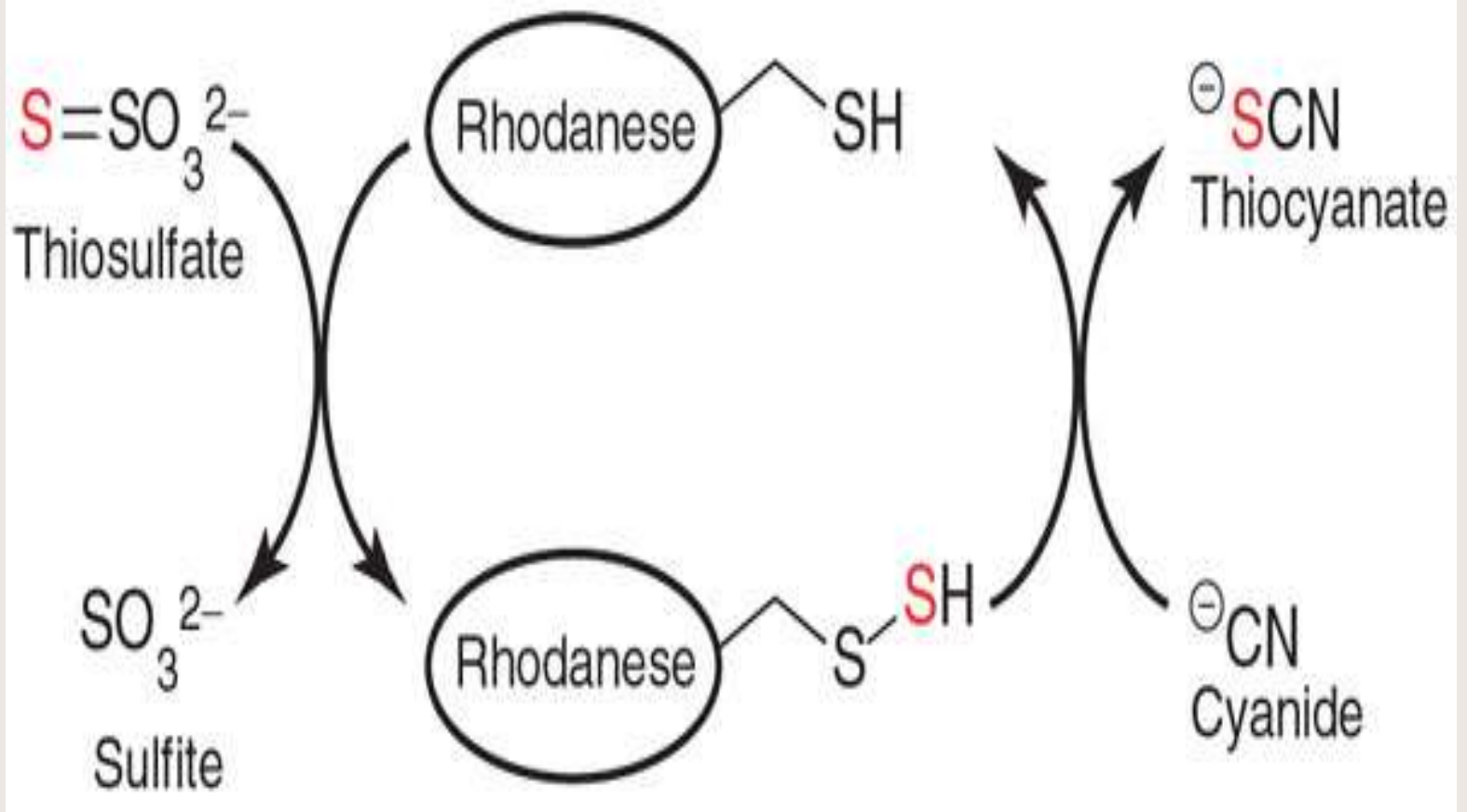
## Antidotes

### 1. Methemoglobin-producers

- **Amyl nitrite** 0.2-0.4 ml via Ambu bag (first-aid measure).
- **Sodium nitrate**, **300 mg** (10 ml of 3% solution), **i.v.** should be administered to adults to attain a desired methemoglobin level of **approximately 25%**. A dose of **10 mg/kg for children** is recommended.
- **DMAP** (**4-Dimethylaminophenol**) 5 ml of 5% solution (250 mg or 3-4 mg/kg) i.v. for 1 minute

2. Cyanide is detoxified by conversion to **thiocyanate**

- **Sodium thiosulfate** (50 ml of 25% solution) should be **immediately given i.v.**





## Nitrites

- ☐ Therapeutic induction of methemoglobinemia
- ☐  $\text{NO}_2 + \text{Hb} = \text{MHb}$
- ☐ Methemoglobin binds strongly to  $\text{CN}^-$  and removes it from tissues
- ☐  $\text{CN}^- + \text{MHB} = \text{cyanomethemoglobin}$
- ☐ cyanomethemoglobin is relatively non-toxic

## Sodium Thiosulfate

donates sulfur molecule to rhodanese  
(enzyme which catalyzes formation of  
thiocyanate)



❖ Synergistic effect

## Oxygen

❖ Synergy of 100%  $\text{O}_2$  with  
nitrites/thiosulfate



### 3. Hydroxycobalamin (vitamin B12)

10ml of 40% **hydroxocobalamin** solution (**vit.B12**)  
(4 g) i.v. for 20 minutes.

- Reduces cyanide to cyanocobalamin



- When combined with sodium thiosulfate end product is thiocyanate
  - **$\text{Na}_2\text{S}_2\text{O}_3 + \text{B12} = \text{HSCN} + \text{B12}_a$**
  - Recycling of hydroxycobalamin
  - Renally cleared
  - Synergistic effect of thiosulfate and B12a

# TREATMENT

## Antidotes

4. **CoNa<sub>2</sub>EDTA** (dicobalt edetate) 20 ml of 1.5% solution (300 mg) i.v. for 1 minute. This chelating agent should be reserved for cases of severe poisoning because of its side effects, which include nausea vomiting, retrosternal pain, cardiac arrhythmia and facial edema. It may lead to loss of calcium and magnesium ions.
5. **Glucosa** - 25 g i.v. may be given a few minutes

# Antidote: Cyanide Poisoning

