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

CYANIDE

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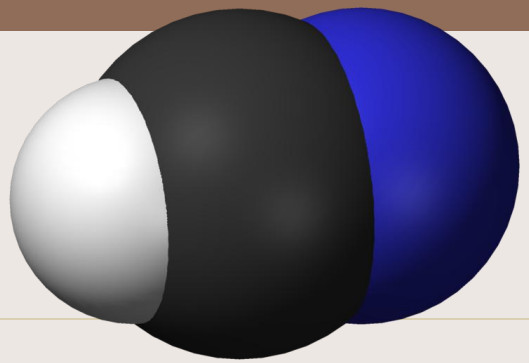
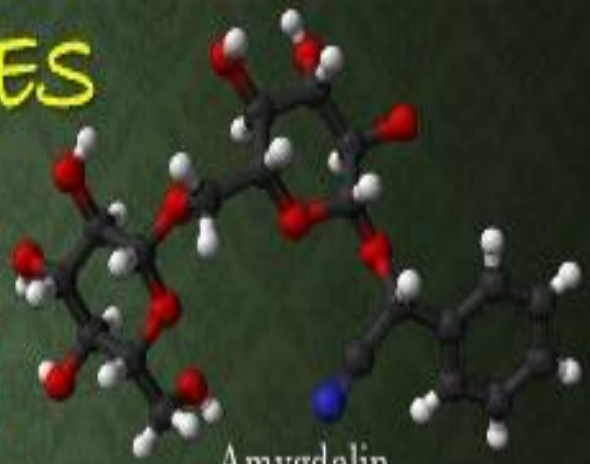


H—C≡N

- **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

Amygdalin (Almond seed)

HCN in Hydrangea, Linum (Linseed)

Prunus (Wild cherry)

Sorghum vulgare (Jowar)

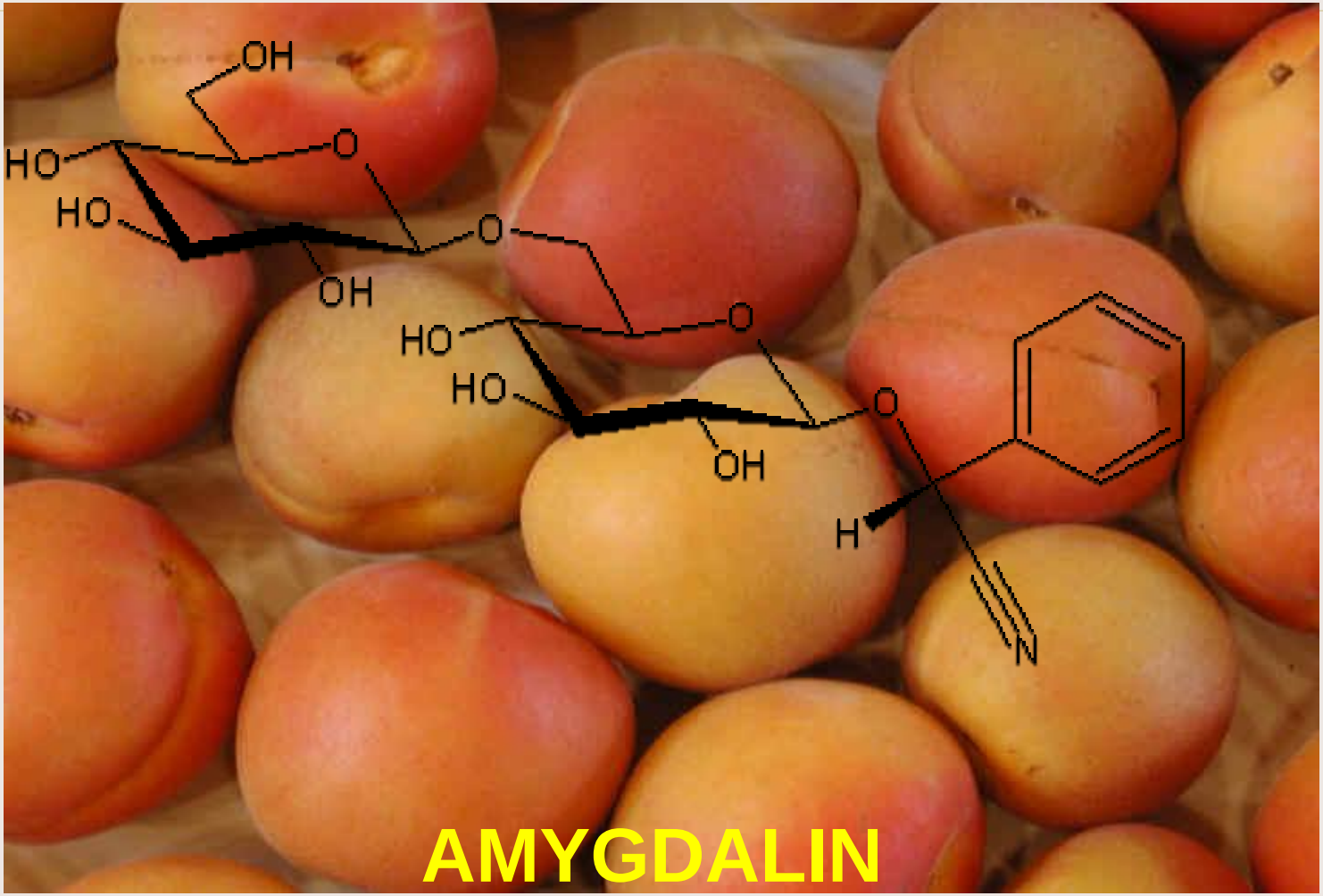
Sorghum sudanese (Sudan grass)

Gossypol (cotton seed)

CYANIDE PLANTS

CYANIDE

PLANTS



AMYGDALIN

Sources and uses

- The many **industrial sources**: **fumigants**, **insecticides**, **pesticides**, production of **plastics and rubber**, **electroplating**, **metallurgy**, 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.

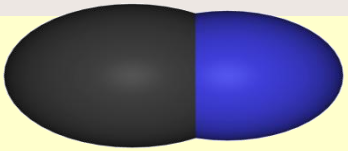
CYANIDE/CARBON MONOXIDE

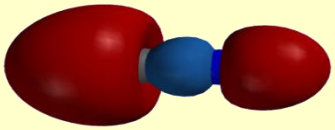
Toxic twins

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 ($CaCN_2$) 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

Concentration ($mg.m^3$)	Effect
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

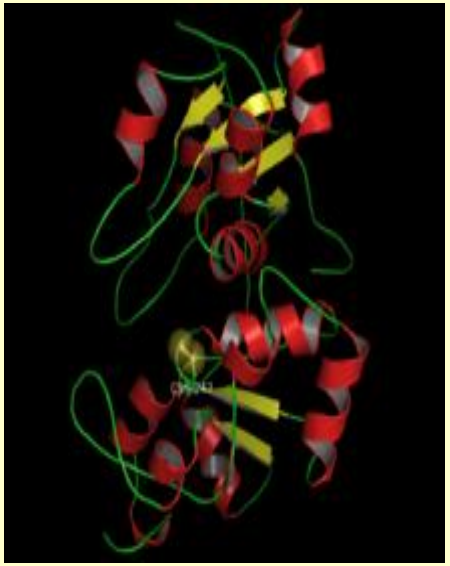
Mechanism of action

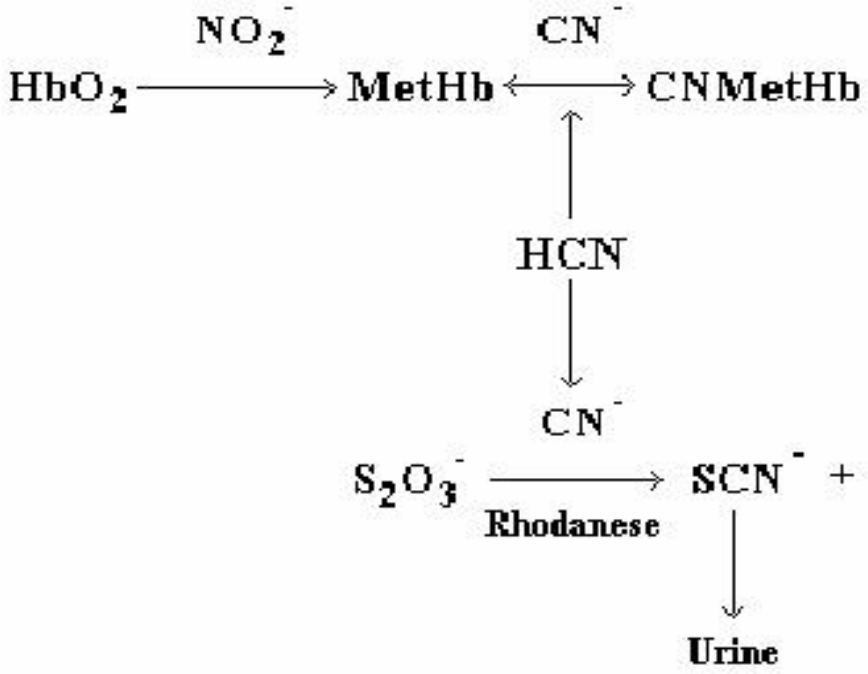
- Cyanide is **rapidly absorbed** through the **lungs**,**skin** and **gastrointestinal tract** because of its unionized state and low molecular weight. **Symptoms** occur **within seconds of inhalation** and within **minutes of ingestion** of cyanide salts.

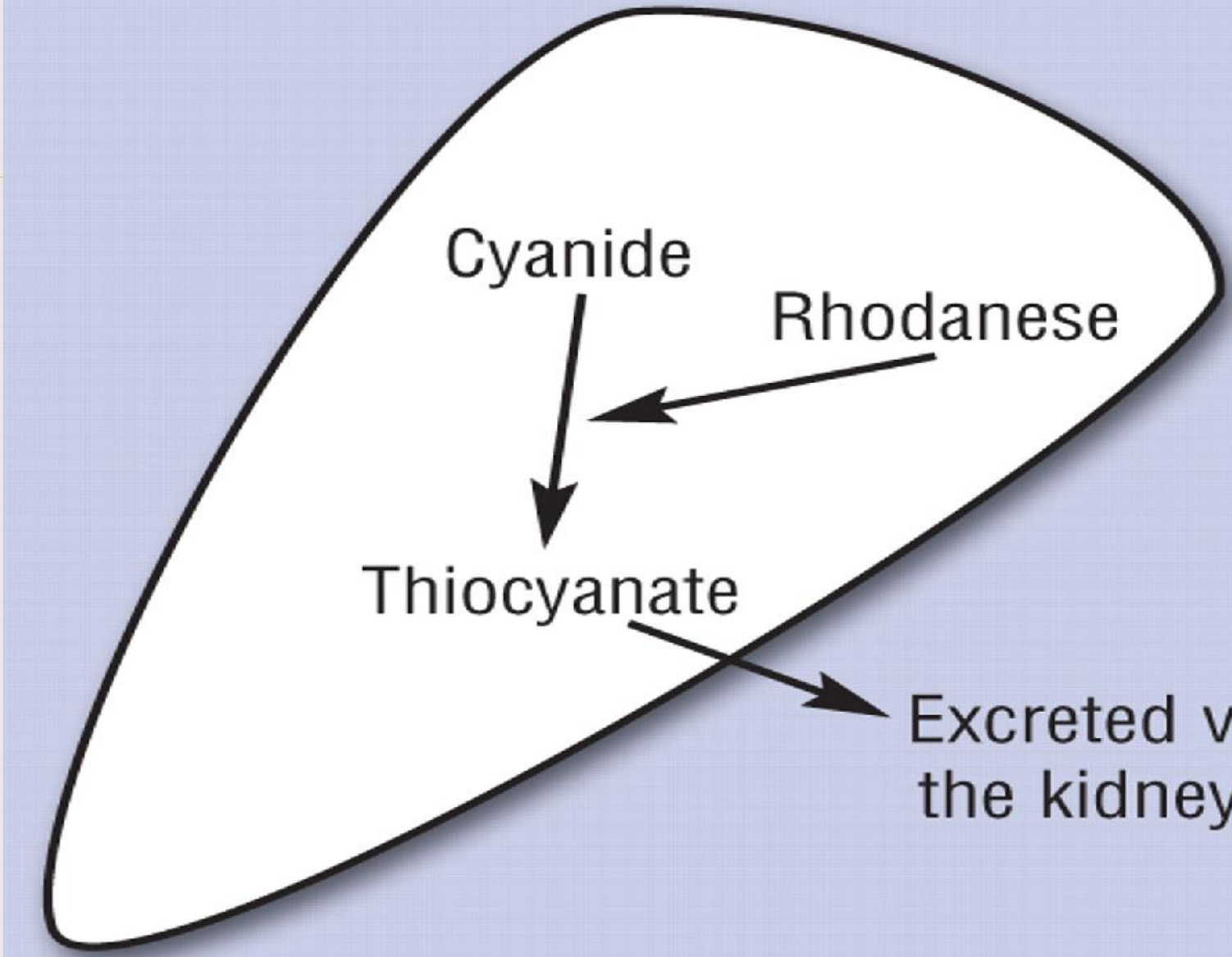
Cyanide can be **metabolized** by **five mechanisms.**

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

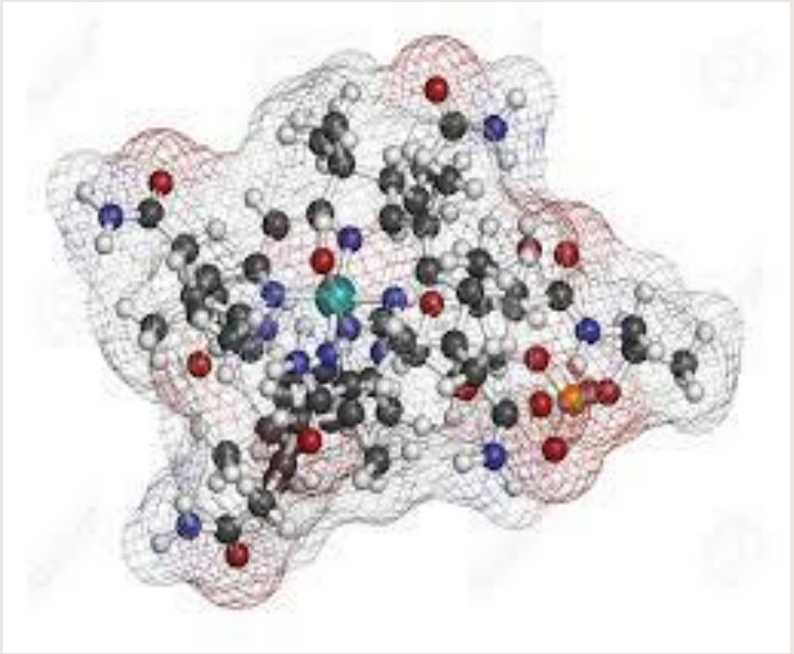
1. The major process of detoxification of the cyanide (80%) occurs mostly in the liver. **The mitochondrial enzyme rhodanase** catalyses the transfer of **sulfur** from **thiosulfate to cyanide**, forming the less toxic **thiocyanate**, which is excreted in the urine**.**





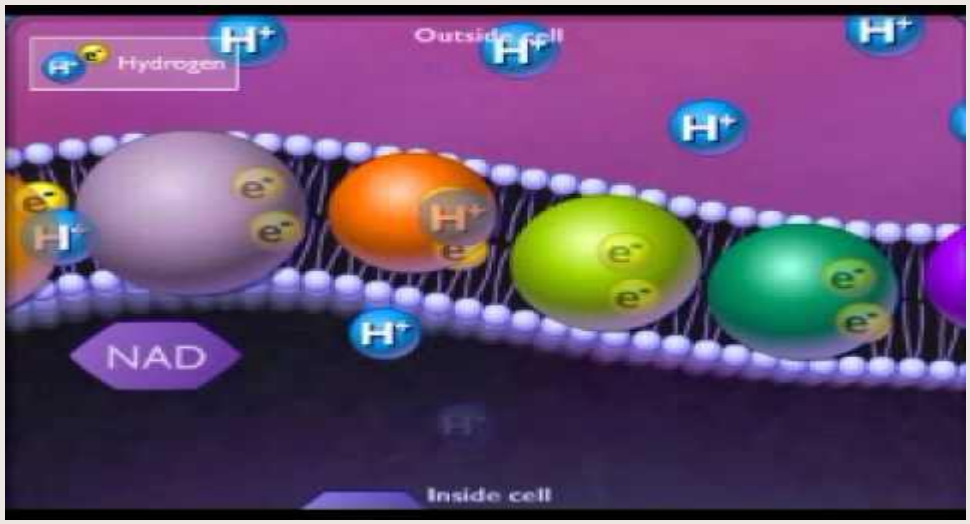

Cyanide
Rhodanese
Thiocyanate
Excreted via
the kidneys

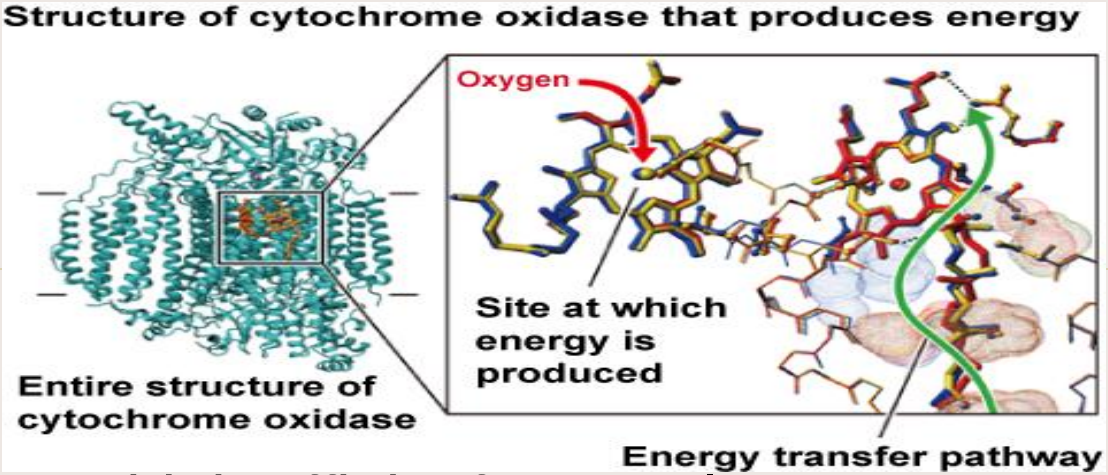
2. Cyanide **forms** **cyanocobalamin** through a reaction with **hydroxocobalamin** (**Vit.B_{12}**).



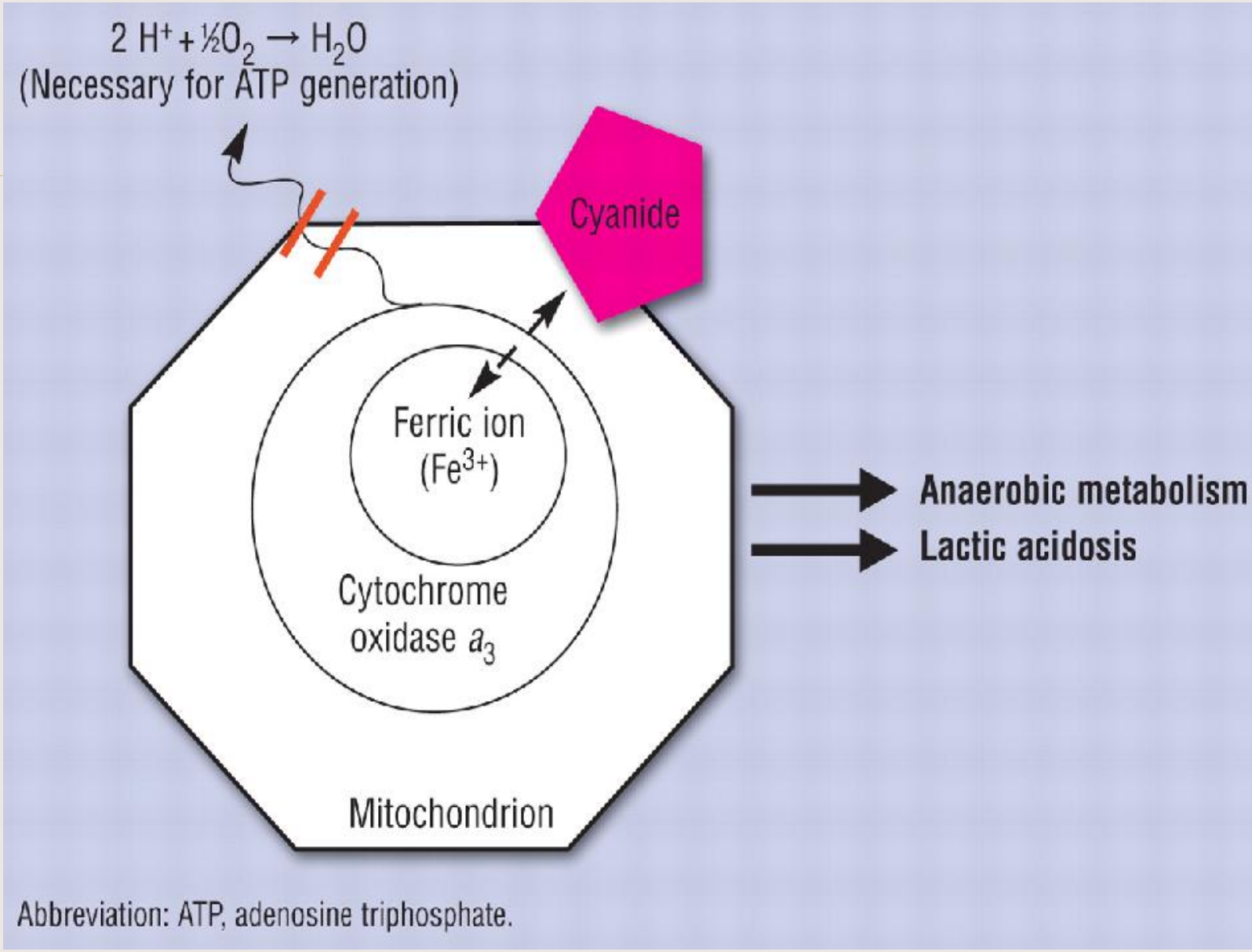
- 3.Cyanide **is oxidized** and **incorporated** into **choline and methionine**.
- 4.Cyanide reacts with **cystine**, which product is excreted.
- 5.**Small amount** of the cyanide is **excreted** unchanged in the **lung and urine**;

- **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.

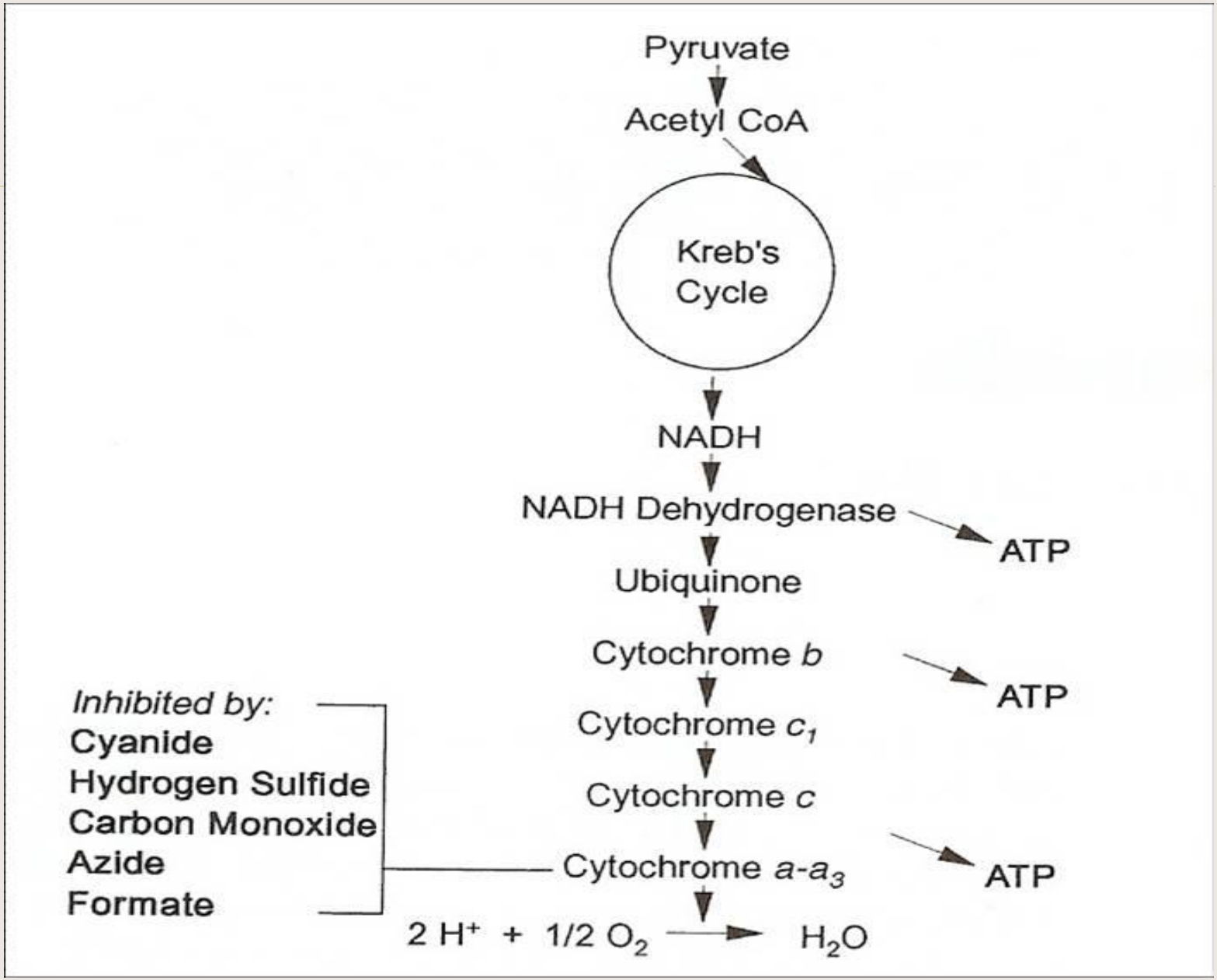




- CN has a high affinity for metals
  - Complexes with metallic cations at catalytic sites of several enzymes
- Binds **ferric (3+)** iron of mitochondrial cytochrome oxidase (**cytochrome a-a3**)
- **cytochrome a-a3** – mediates transfer of electrons to molecular oxygen (final step in oxidative phosphorylation)

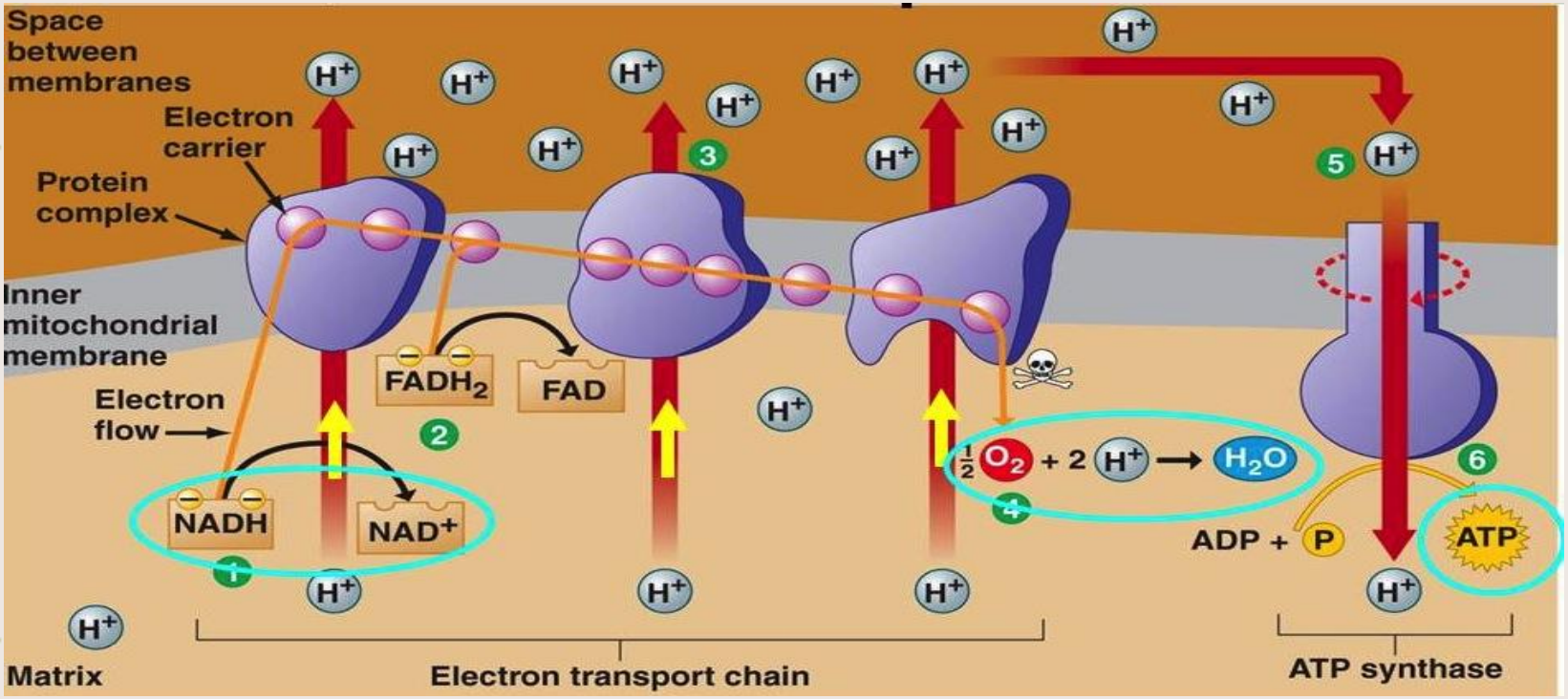


Abbreviation: ATP, adenosine triphosphate.


Pyruvate
Acetyl CoA
Kreb's Cycle
NADH
NADH Dehydrogenase
ATP
Ubiquinone
Cytochrome b
ATP
Cytochrome c_1
Cytochrome c
Cytochrome a-a_3
ATP
$2 H^+ + 1/2 O_2 \rightarrow H_2O$
Inhibited by:
Cyanide
Hydrogen Sulfide
Carbon Monoxide
Azide
Formate

Blockade of oxidative phosphorylation

- **Tissue anoxia** **A-V (arteriovenous**
- **Anaerobic metabolism** **oxygen difference)**
- **Lactic acidosis** **•Arterialization of venous blood**



Acute effects

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

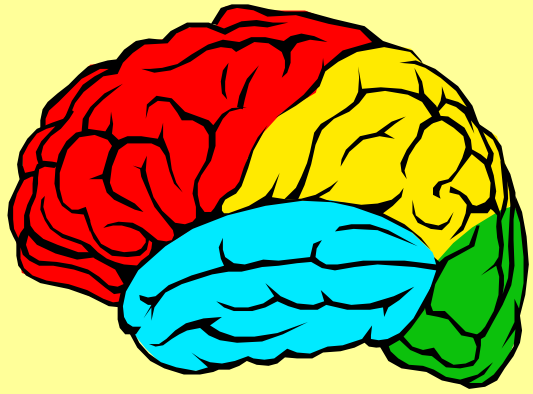
Acute effects

- **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**.

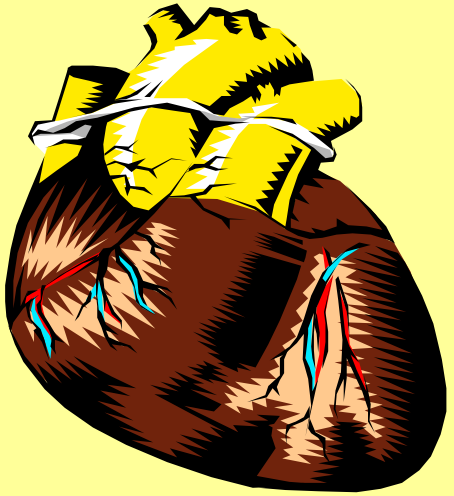
Acute effects

- **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.

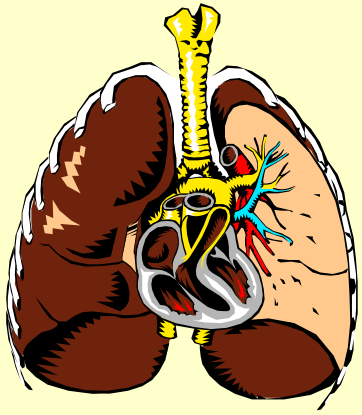
- **CNS**
  - **Headache**
  - **Dizziness**
  - **Seizures**
  - **Coma**



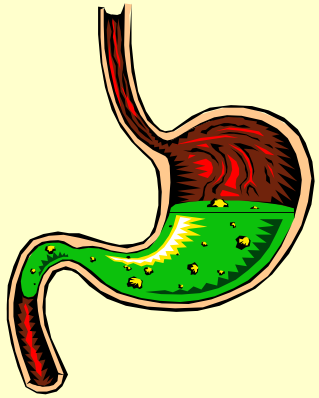
- **Cardiovascular**
  - **Hypertension, tachycardia**
  - **Hypotension, later in course**
  - **Bradycardia**
  - **Asystole**
  - **Cardiovascular collapse**



- **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 (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.

T r e a t m e n t
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**.

Drugs causing MHb

- Chloroquine (malaria, amebiasis)
- dapsone (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_3
- Chlorhexidine (antiseptic agent)

T r e a t m e n t

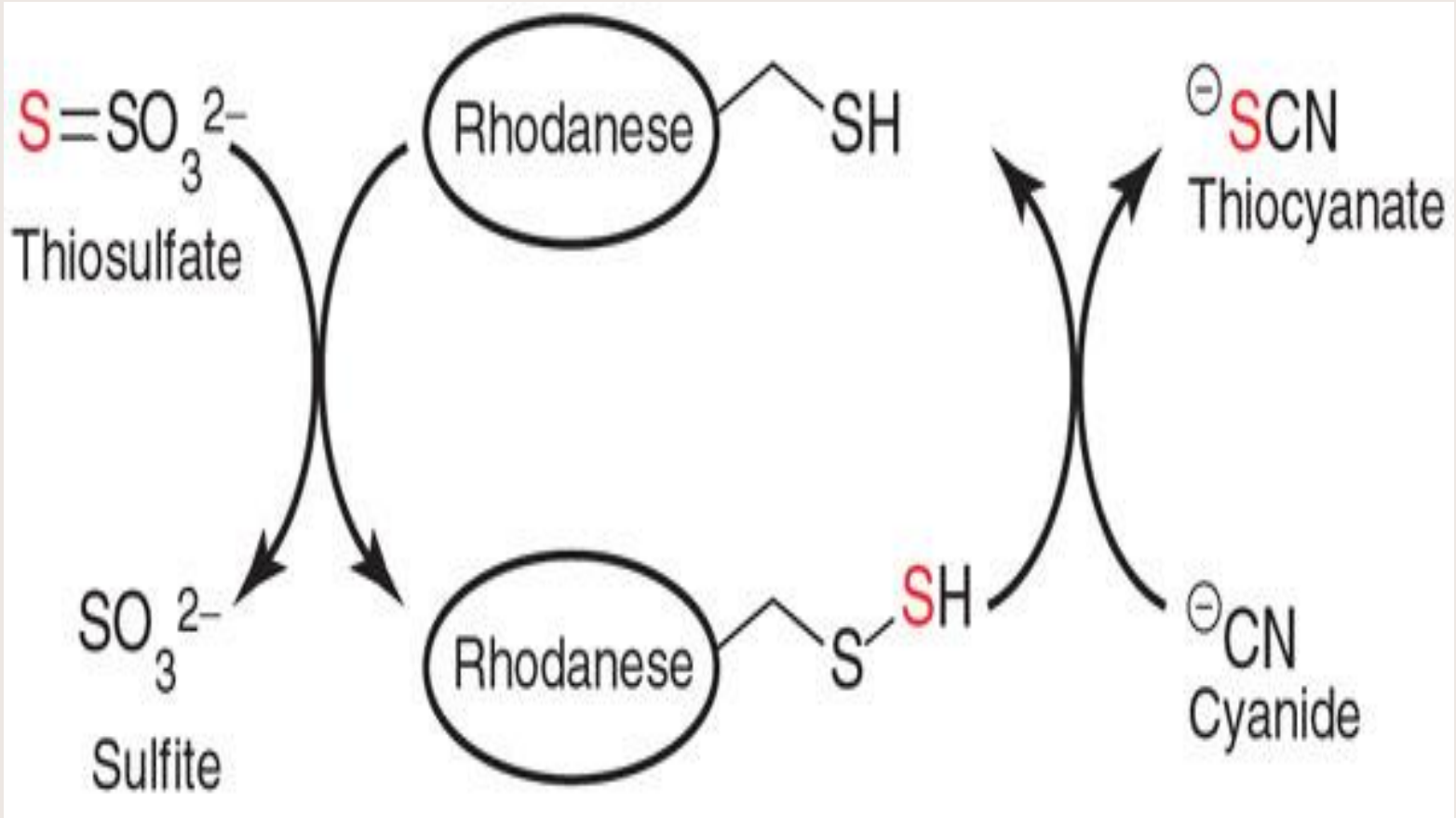
Antidotes

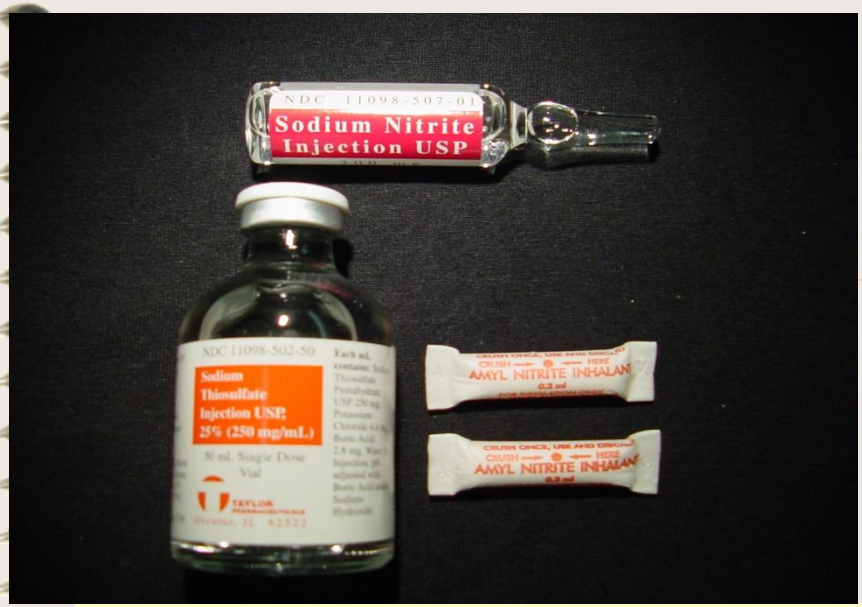
1. Methemoglobin-producers

- **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**.


S=SO3 2–
Thiosulfate
Rhodanese
SH
⊖SCN
Thiocyanate
SO3 2–
Sulfite
Rhodanese
S
SH
⊖CN
Cyanide



Nitrites

- Therapeutic induction of methemoglobinemia
- NO_2 + Hb = MHb
- Methemoglobin binds strongly to CN- and removes it from tissues
- CN- + MHB = cyanomethemoglobin
- cyanomethemoglobin is relatively non-toxic

Sodium Thiosulfate

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

- **$Na_2S_2O_3 + HCN + O = HSCN$**
- Synergistic effect

Oxygen

- Synergy of 100% 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

$$B12_a + CN^- = B12$$

- When combined with sodium thiosulfate end product is thiocyanate

  - **Na2S2O3 + B12 = HSCN + B12a**
  - Recycling of hydroxycobalamin
  - Renally cleared
  - Synergistic effect of thiosulfate and B12a

TREATMENT
Antidotes

4. **$CoNa_2EDTA$** (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