

**Cyanide toxicity
(also known as prussic
acid poisoning)**

Extent of Cyanide Toxicity

- > 2000 Plant species contain cyanogenic glycosides therefore have potential to produce HCN toxicity
- Actual incidences of poisoning are few because these plants are infrequently eaten by animals or humans

Plant Species and Families

- Poacea (eg. Sorghum)
- Fabaceae (e.g. Phaseolus [lima beans])
- Caprifoliaceae (e.g., Sambucus [elderberry])
- Euphorbiaceae (e.g., Manihot [Cassava])
- Rosaceae (e.g., Prunus)

Plant Species

- Food sources for humans and animals:
 - Sorghum (*Sorghum* spp.)
 - Corn (*Zea mays*)
 - Clovers (*Trifolium* spp.)
 - Cassava (*Manihot esculenta*)
- Cassava: poorly prepared diets (typically not boiling sufficiently) causes tropical ataxic neuropathy; pancreas lesions; and hypothyroidism

HCN in food

The best characterized cyanogenetic glucoside is perhaps amygdalin, which is present especially in the seeds and leaves of the cherry, almond, peach, etc.

Cherry kernels yield about 170 mg per 100 g and bitter almond pulps about 250 mg per 100 g

"Penalty of the Peach"

- Peach = *Prunus persica*
- Egyptians and Romans used peach seeds to execute people
- Peach extract known as "penalty of the peach"
- Other seeds also contain HCN-
almonds; plums; cherry (all *Prunus*)

Famous users of cyanide



- Nazi gas chambers used HCN
- U.S. gas chambers
- Various secret agents w/ poison pill (as did Hitler)





Hillbilly Gas Chamber

Lethality

- For man, the acute toxic oral dose of HCN is usually given as 0.5 - 0.35 mg/kg BW.
- The lethal dose of HCN for cattle and sheep is about 2.0 mg/kg of body weight (Kingsbury 1964).

Plant Species

- Livestock poisoning:
 - Johnson grass (*Sorghum halapense*)
 - Sudan grass (*Sorghum vulgare*)
 - Chokecherry (*Prunus virginiana*)
 - Service berry (*Amelanchier alnifolia*)
 - Arrow grass (*Triglochin* spp.)

Service berry (*Amelanchier alnifolia*)



Arrowgrass (Triglochin)



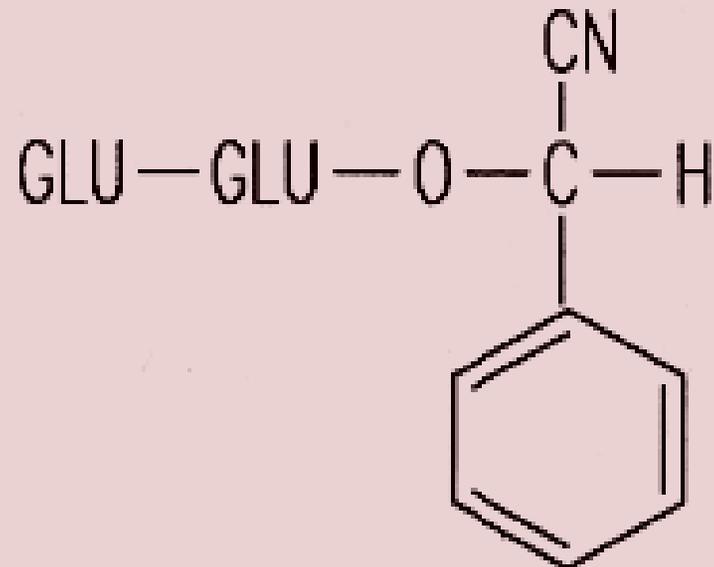
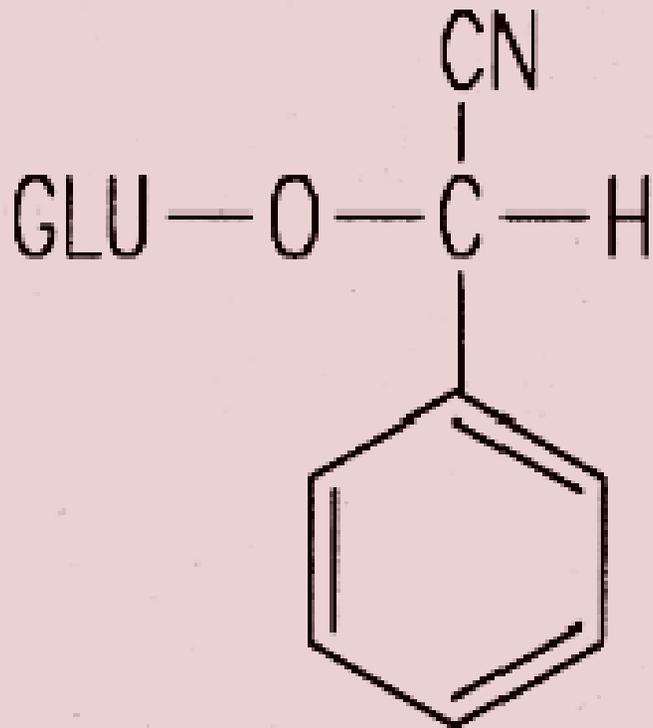
HCN in plants

- Glycosides are compounds that consist of a carbohydrate moiety (sugar) joined by an ester bond to a noncarbohydrate moiety (referred to as the aglycone). The structure and/or properties of their aglycone is used to group and identify them.

Chokecherry (*Prunus virginiana*)



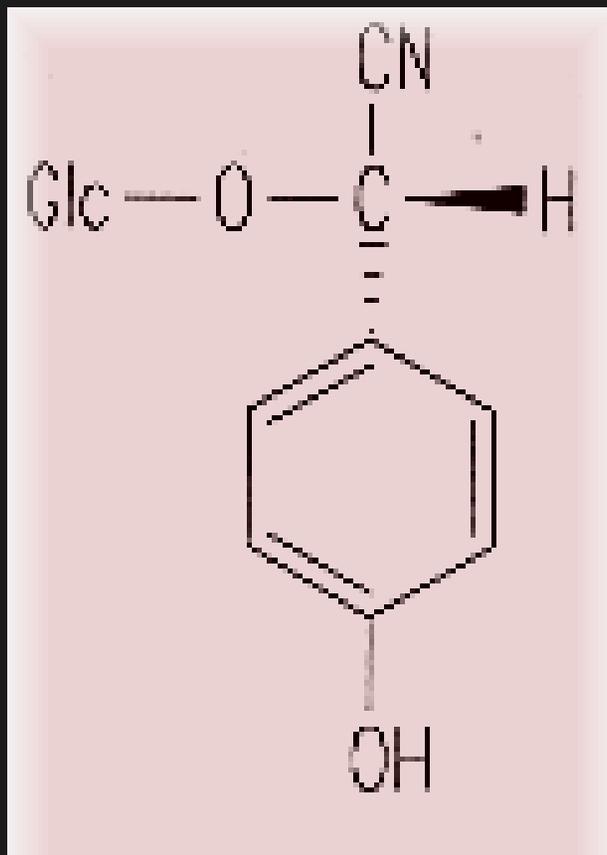
Prunasin and amygdalin (laetrile)



Johnsongrass (*Sorghum halepense*)



Dhurrin

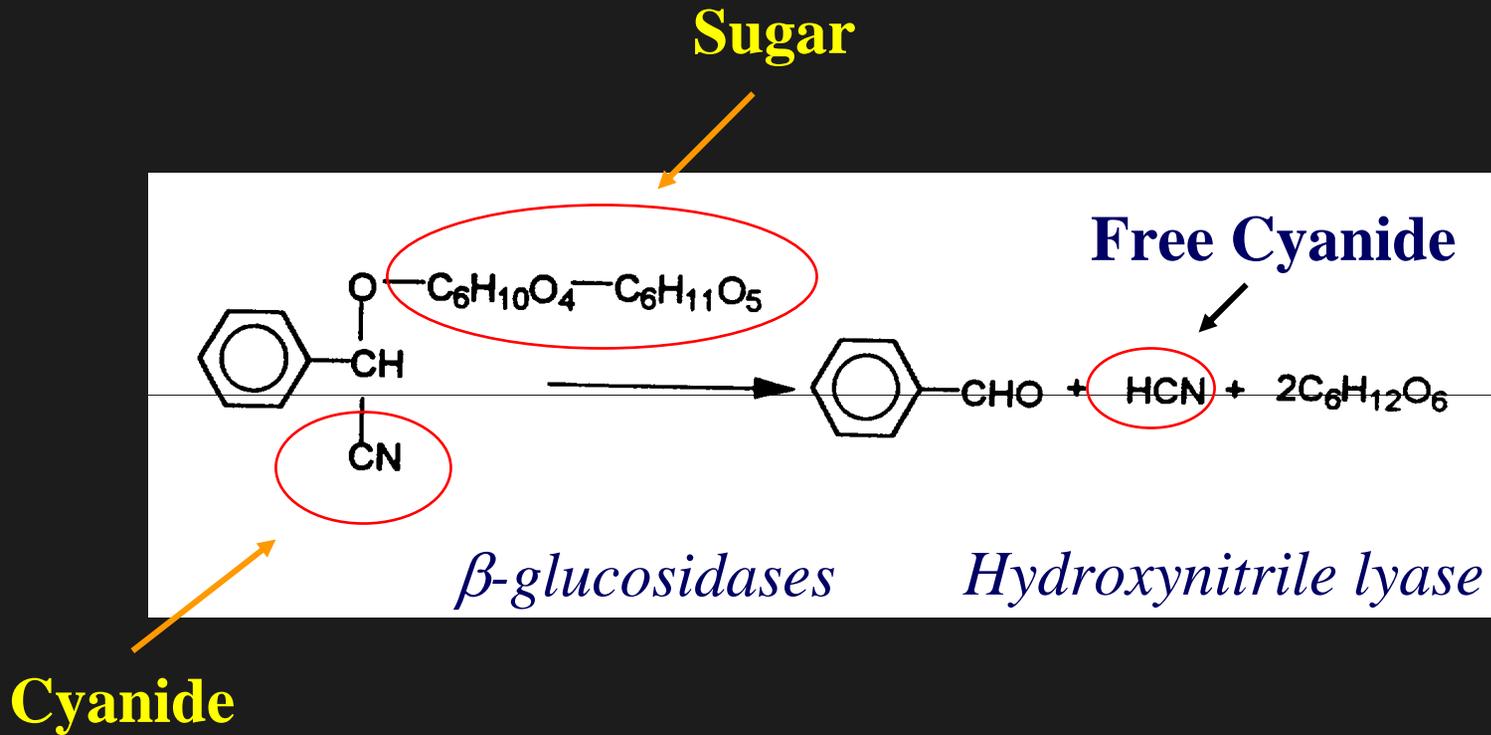


HCN in plants

- Glycosides are normally isolated in cell vacuoles
- Damage from chewing or wilting allows enzymes to form HCN
- Concentrations of cyanogenic glycosides varies with phenology and growing conditions.

HCN in plants

- Cyanogenic glycosides in plant tissues are not toxic unless hydrolyzed by plant enzymes (or rumen microorganisms) to form free HCN.
- β -glucosidases are found in plant cytoplasm
- This conversion to HCN is enhanced when:
 - Damage to plant cell (crushing, mastication)
 - Wilting or freezing stress



Cyanogenic glycoside - *Prunus* spp.

Concentrations in plants

- **A. alnifolia:**
 - Buds 2.6%
 - Flowers 2.5%
 - Fruits 0.9%

 - Also in bark
- **P. virginiana**
 - Buds 3.6%
 - Flowers 2.6%
 - Fruits 1.2%

 - Also in bark

Presence of glycosides in outer tissue (epidermis) indicates defense against herbivores (insects)

Mechanism of intoxication

Cyanide uncouples (inactivates)
cytochrome c oxidase in mitochondria

Cytochrome c oxidase =
final electron carrier
protein in the electron
transport chain

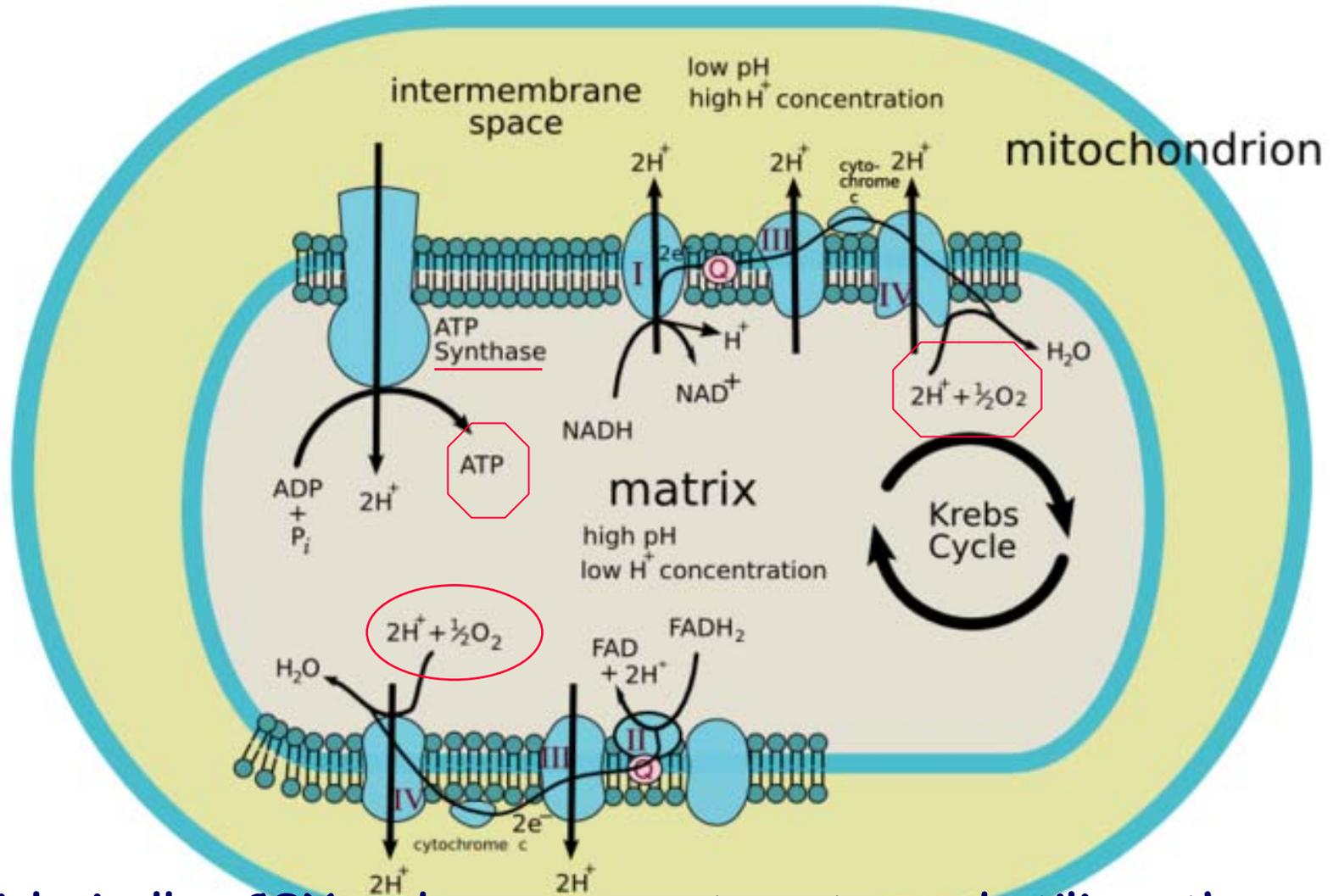
Inactivation of cytochrome c oxidase:

The electron transport chain is disrupted, meaning that the cell can no longer aerobically produce ATP for energy (95% of the energy produced by the body comes from aerobic respiration). Tissues that mainly depend on aerobic respiration, such as the central nervous system and the heart, are particularly affected.

Cytochrome c oxidase (COX) is the last enzyme in the respiratory electron transport chain of mitochondria located in the mitochondrial membrane. It receives an electron from each of four cytochrome c molecules, and transfers them to one oxygen molecule, converting molecular oxygen to two molecules of water. ATP synthase uses the energy to synthesize ATP.

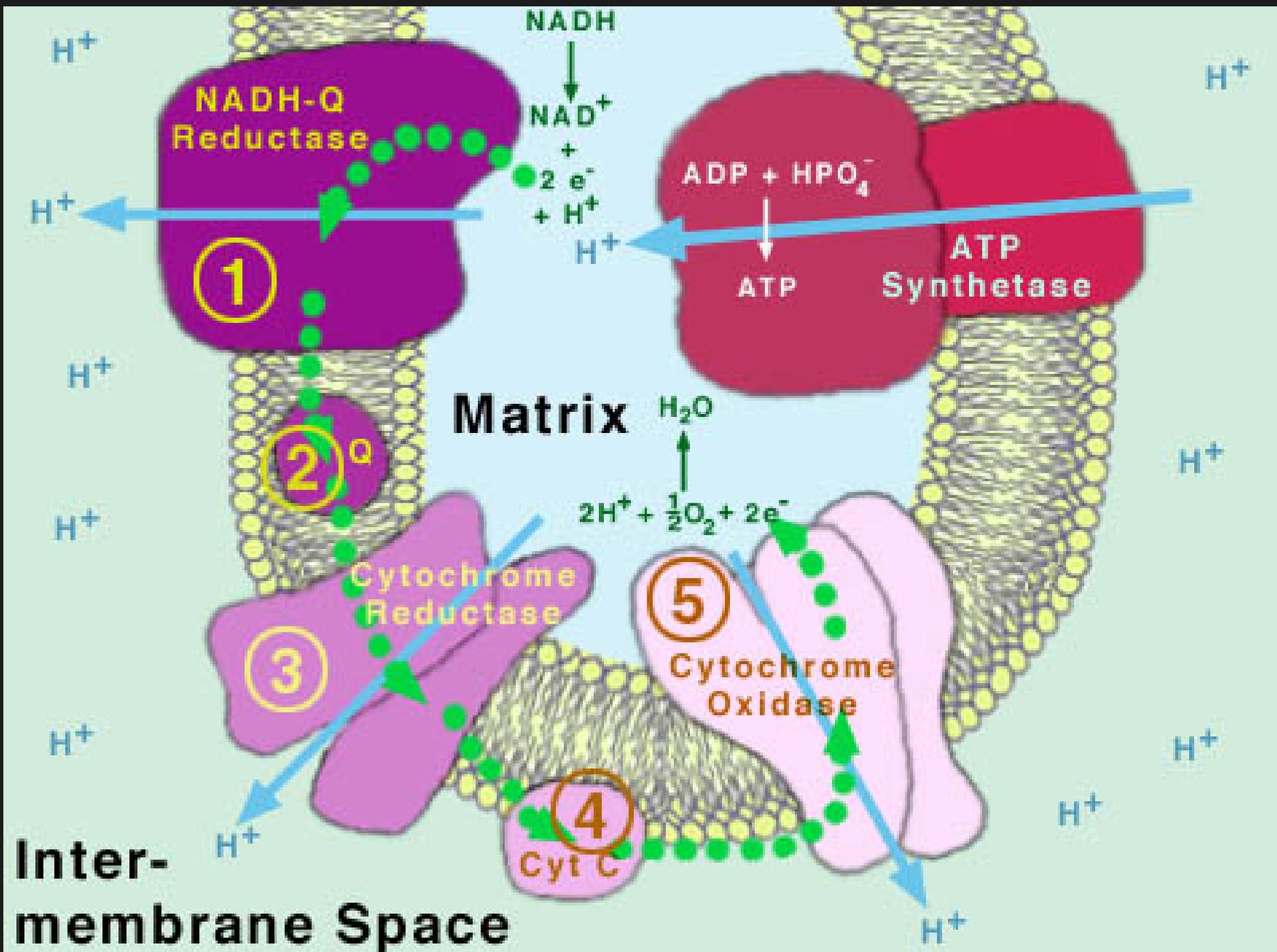
Note: One rat liver cell contains about 800 mitochondria

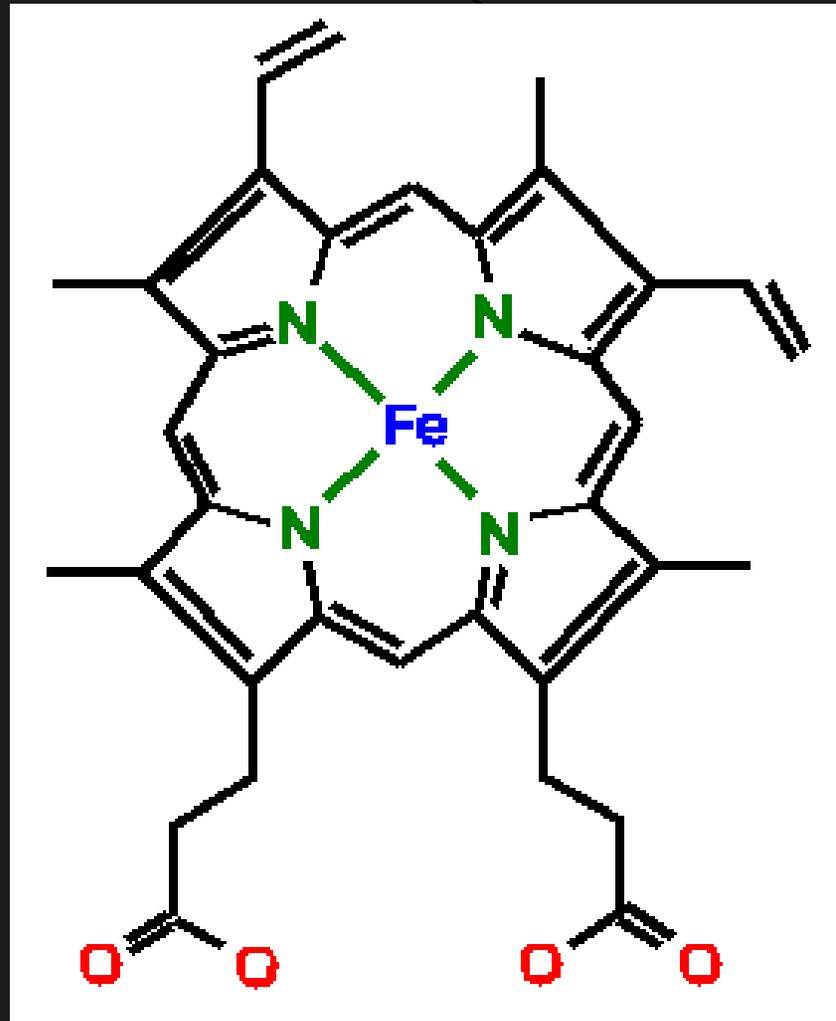
Mitochondrial Electron Transport Chain

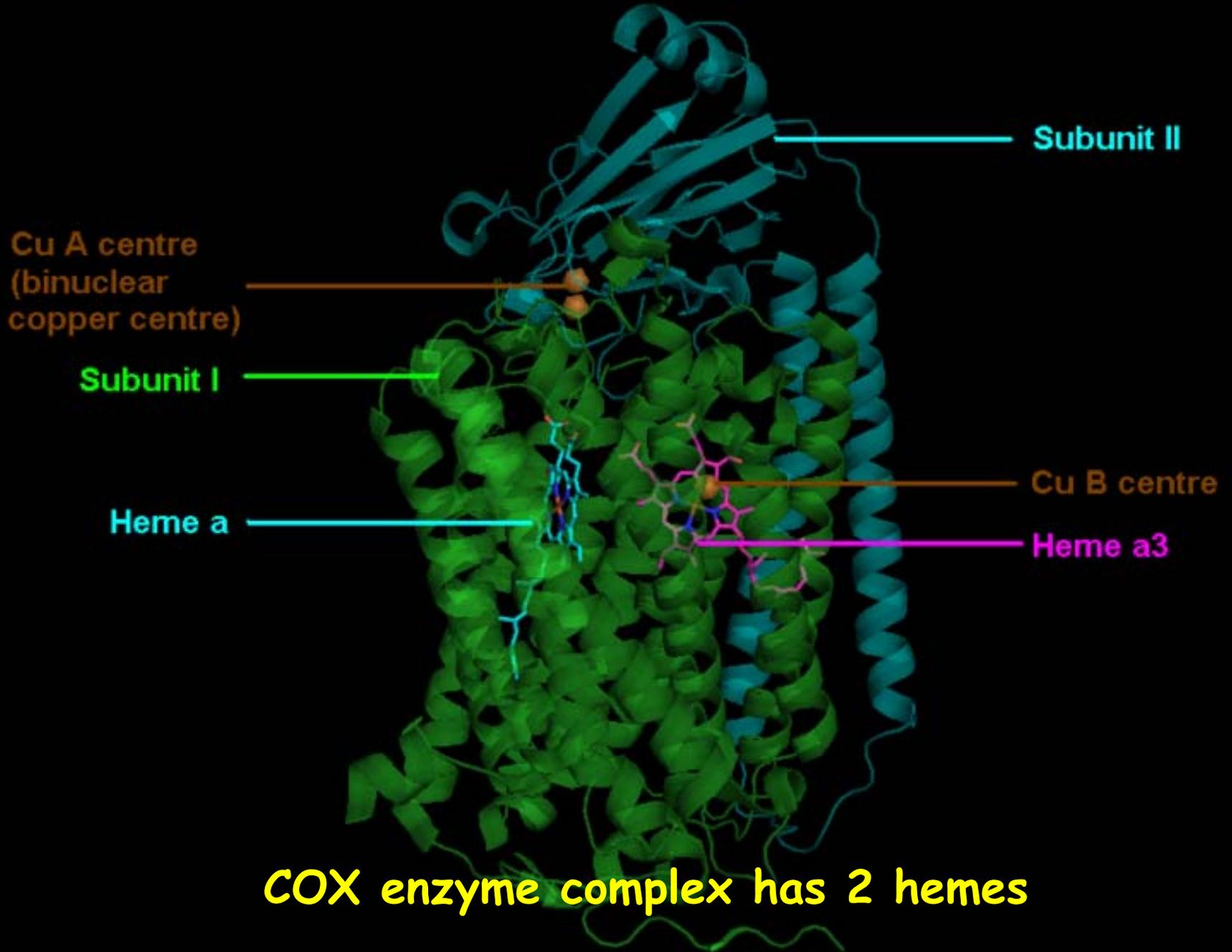


Physiologically, COX reduces oxygen to water and utilizes the excess energy to translocate protons across the mitochondrial membrane. The enzyme is responsible for over 90% of the oxygen consumption by living organisms

- Cyanide uncouples (inactivates) cytochrome oxidase therefore:
- 1) no ATP produced in mitochondria
- 2) Quick cell death results
- 3) No extraction of Oxygen from blood (rich oxygenated blood is cherry red)







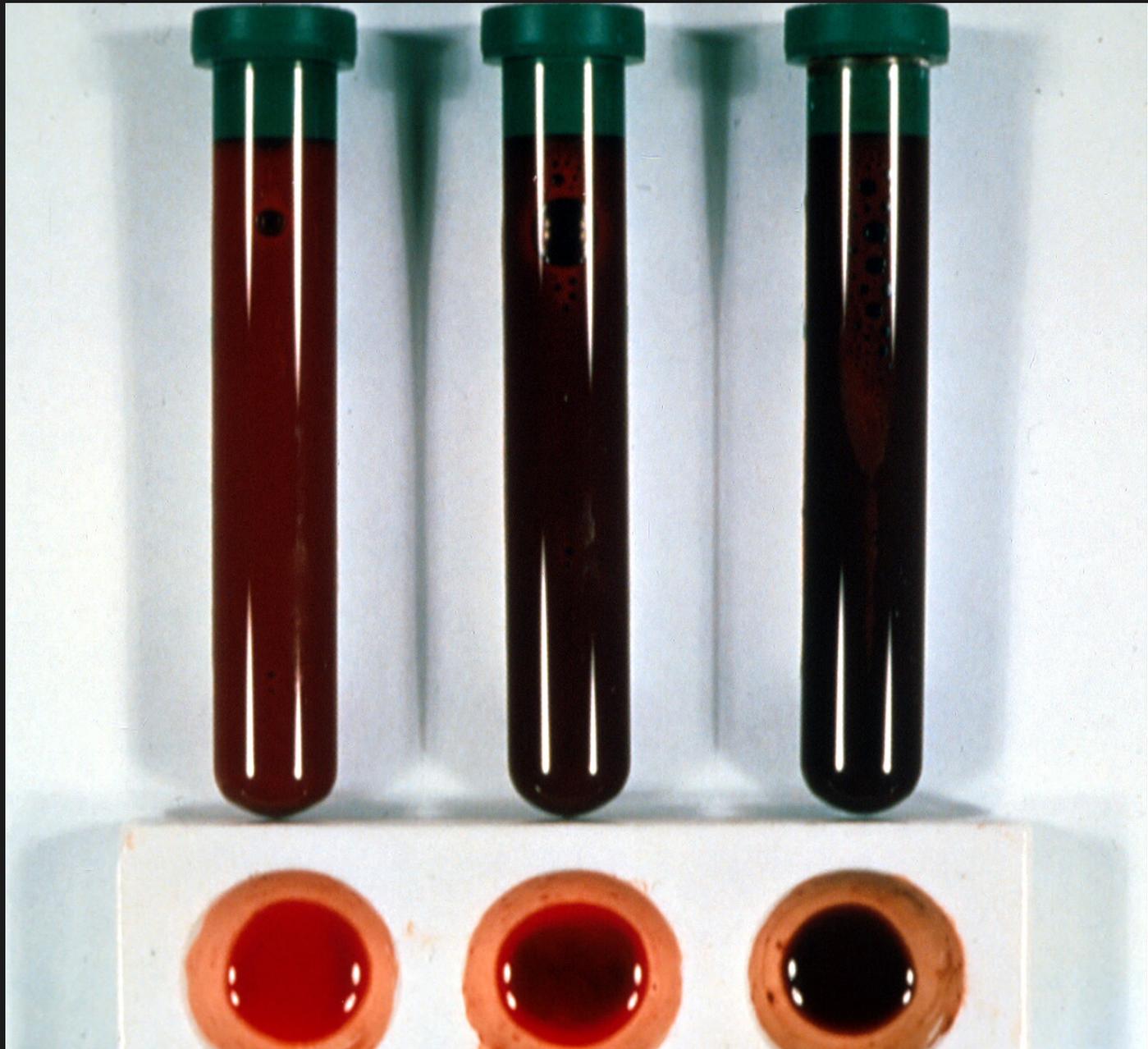
COX enzyme complex has 2 hemes

Mechanism of toxicity

- HCN can readily bind to Fe in cytochrome (stable but not irreversible)

Diagnosis?





Mechanism of toxicity

- HCN can readily bind to Fe in cytochrome (stable but not irreversible)
- HCN can also bind to Fe in methemoglobin (affinity is for MHb rather than for cytochrome) = avenue for detoxification

Diagnosis of HCN poisoning

- Sudden death with supporting evidence of cherry-red venous blood and absence of other diseases. Rumen contents or plant material can be tested for cyanide using the sodium picrate test. Commercial test kits for cyanide are available.

Toxicity to mammals

- 2 to 5 mg/kg cyanide is lethal
- Canada study: single dose - (1.43%) 14 mg HCN/g in Serviceberry; dosed at 4 g plant/kg BW was lethal (~ 5 mg/kg - Lethal to cows).
- 200 ppm HCN in fresh plants (0.02%) or 200 mg/kg in plant is considered the standard 'lowest' level for HCN above which poisoning in ~ 30 min can be expected if plant is palatable (4 kg eaten).

Ruminants vs. nonruminants

- Why are ruminants more susceptible?
 - Rumen pH around 7
 - High water content in rumen
 - Rumen microflora
- These factors combine to promote hydrolysis of glycosides to HCN
- Would humans (with acidic stomach) be poisoned from plant tissue?

Chronic vs. acute toxicity

- Cassava consumption = neuropathy in people
- Loss of myelin sheath results in loss of nerve function
- Goiters from thiocyanate
- Sudden death within 1-2 hours
- Labored breathing
- Muscle tremors
- Convulsions
- Red mucous membranes (Oxygen saturation)

Commercial cyanide antidote kits available (used for humans typically)



First step in antidote: inject nitrite!!

Sodium nitrite converts a portion of the hemoglobin's iron from ferrous iron to ferric iron, converting the hemoglobin into methemoglobin. Cyanide is more strongly drawn to methemoglobin than to the cytochrome oxidase of the cells, effectively pulling the cyanide off the cells and onto the methemoglobin. Once bound with the cyanide, the Methemoglobin becomes cyanmethemoglobin.

The next part of the cyanide antidote kit is sodium thiosulfate, which is administered IV. The sodium thiosulfate and cyanmethemoglobin become thiocyanate, releasing the hemoglobin, and the thiocyanate is excreted by the kidneys.

Treatment

- Specific antidotes available:

- Sodium nitrite $\xrightarrow{\hspace{2cm}}$ MetHB

- Sodium thiosulfate (adds sulfur) + HCN
 $\xrightarrow{\hspace{2cm}}$ thiocyanate
rhodanese \searrow Kidney

1) Sodium nitrite reacts with hemoglobin to form methemoglobin. The latter removes cyanide ions from various tissues and couples with them to become cyanmethemoglobin, which has a relatively low toxicity. 2) The function of Sodium thiosulfate is to convert cyanide to thiocyanate, by an hepatic enzyme known as rhodanese.

Treatment

- IV administration of 1 ml of 20% solution of sodium nitrite plus 3 ml of 20% solution of sodium thiosulfate
- Give this mixture IV per 100 lbs. Body weight
- Repeat in a few minutes if animal doesn't respond

Management points

- Young tissues usually highest in HCN
- Drying plants usually reduces toxicity
- Ensiling plants will also reduce toxicity as HCN is liberated during curing
- Frost and drought can increase HCN concentration in plant tissue
- Herbicides may also increase HCN

Prevention

- Don't graze plants with HCN in early growth stages, after cutting, or after frost or after wilting
- Test forages for HCN before grazing if uncertain (HCN volatile)
- Cure hay before feeding