MECHANISM OF ANTIDOTE

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MECHANISM OF ANTIDOTE COMPLEX WITH POISON, RENDERING IT INERT

Arsenic, Lead, Mercury, Iron, Copper (heavy metals)

- The treatment of poisoning due to heavy metals offers the simplest example of the mechanism.

- The chelating agents are used to form tightly bound non toxic complexes with the metal ion, this reduces the concentration of free metal ions in the body fluids and thus promotes the dissociation of bound metal from tissue enzymes and functional macromolecules.

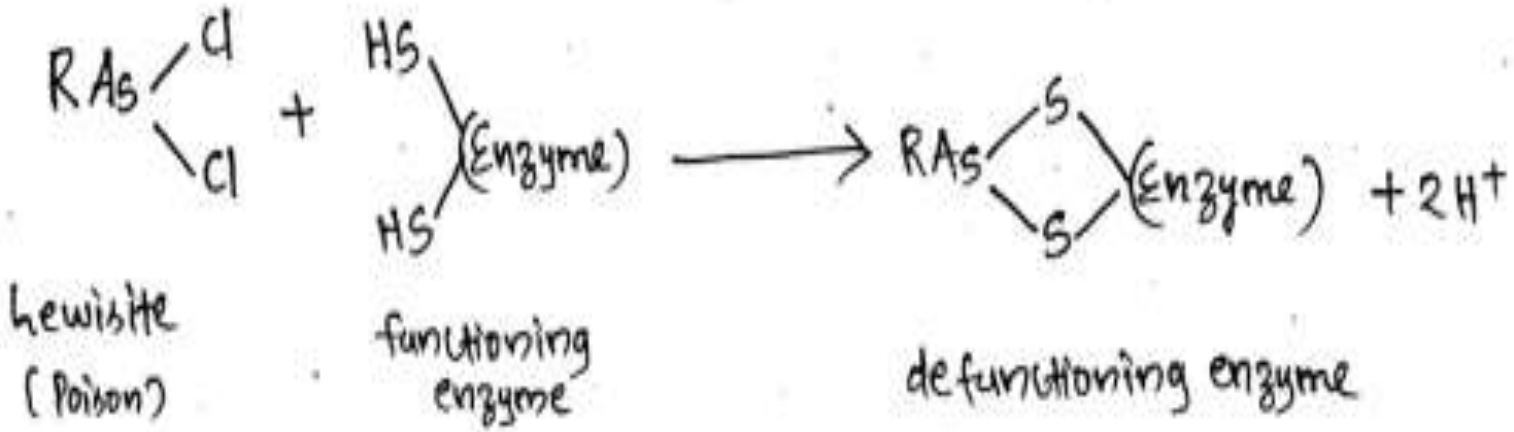
- Typical metal chelate complexes are water soluble and excreted through kidney.

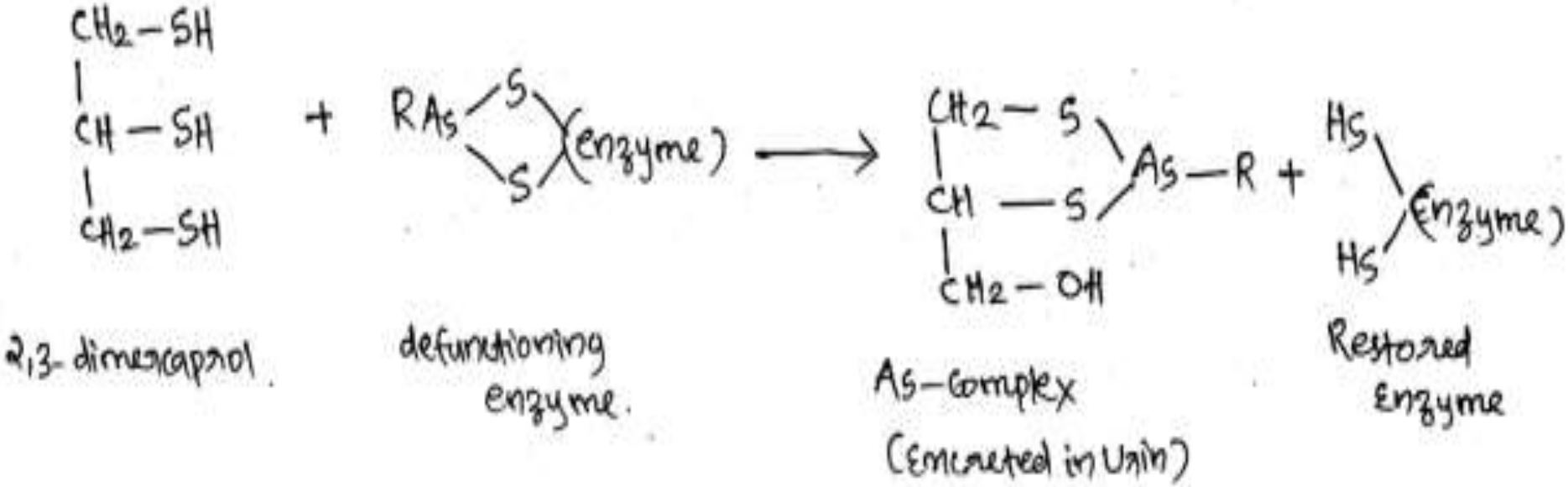
- Thus, total body load of metal is reduced.

Arsenic poisoning

- **Poisoning by Arsenic or Mercury is specifically combated by dimercaprol.**
- **This ligand was developed during World War II for protection against the Arsenical gas called lewisite, hence the original designation BAL (British Anti Lewisite) Cl-CH=CHAsCl2**
- **This compound holds the distinction of being the first antidotal agent synthesized on a rational basis.**
- **This poisonous gas functions by binding to the negative SH groups (sulfhydril) of enzymes.**
- **But BAL binds particularly strongly to the As and to remove it. BAL is also used for the treatment of poisoning due to Hg, As, Cd, Au, Ti, Tl, Bi and their compounds.**

This schematic action of BAL on Lewisite affected enzymes is shown below



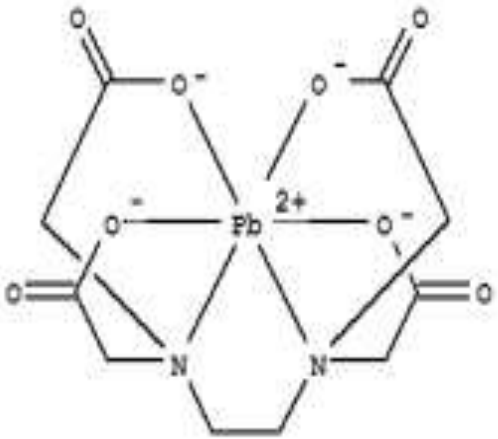


Lead poisoning/ Lead toxicity and chelation therapy

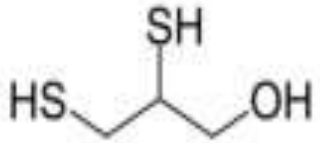
- Lead is a poison to the human system which can cause brain damage called encephalopathy.
- This disease can produce convulsion, coma, blindness, mental retardation or death.
- A person who has injected lead is fed with [Ca-EDTA] 2- ,it reacts with Pb2+ in the victim to form Pb-EDTA complex.

$$Pb^{2+} + [Ca\text{-}EDTA]^{2-} \rightarrow [Pb\text{-}EDTA]^{2-} + Ca^{2+}$$

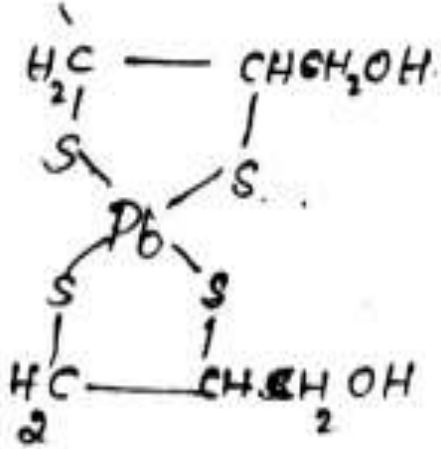
- The complex lead is excreted by the human body saving the victims from poisoning. The PbEDTA complex is highly stable than [Ca-EDTA]2- complex and therefore, Pb2+ ion in the body is readily trapped by EDTA.



Lead- EDTA complex



Dimercaprol (BAL)



Lead-dimercaprol complex

Note: BAL is also used for the treatment of lead toxicity.

- Qn: Why calcium salt of EDTA is used as antidote for the treatment of lead toxicity?

- Ans: Calcium salt is used to prevent hypocalcemia. The relatively non toxic calciumdisodium complex, rather than EDTA itself is used (EDetate) clinically to avoid complexing the essential ionized calcium in the blood plasma. Thus only metals with greater affinity than Ca will be bound by displacing Ca^{2+} from the ($CaNa_2$- EDTA) complex. The stability constant for the complex with Pb^{2+} is 107 times greater than that for the Ca^{2+} complex.
- Dimercaprol (BAL) and pencillamine also bind Pb effectively.

Copper deficiency

Role of copper

- Cu is an essential metal that is required for cellular respiration, iron oxidation, pigment formation, neurotransmitters, biosynthesis, antioxidants, defence, peptide amidation, CNS development and connective tissue formation.

- Physiologically, Cu exists in two redox states, Cuprous (Cu+) and cupric (Cu2+) with many known enzymes requiring it.

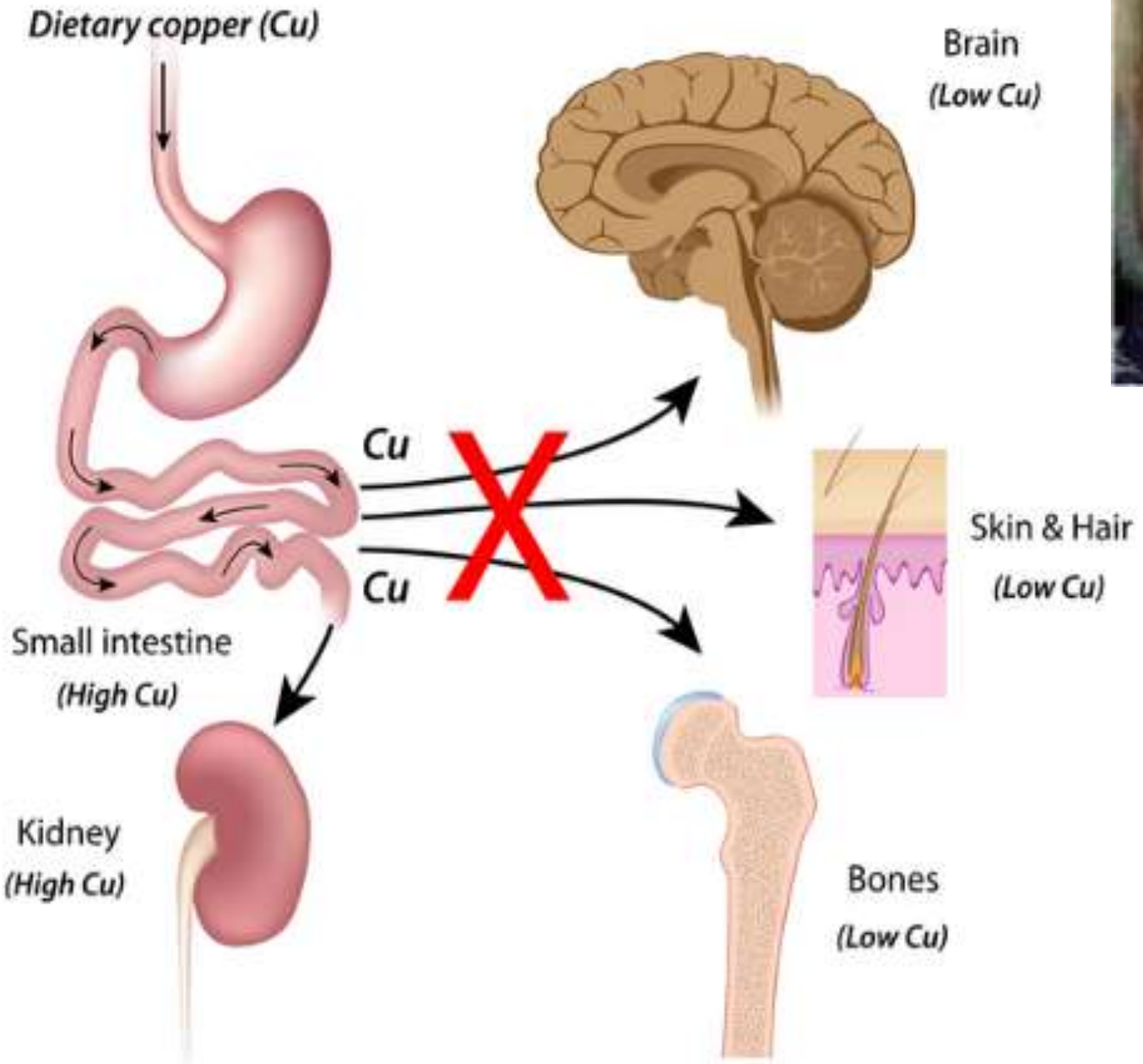
Copper deficiency: Menke's Disease (MD)

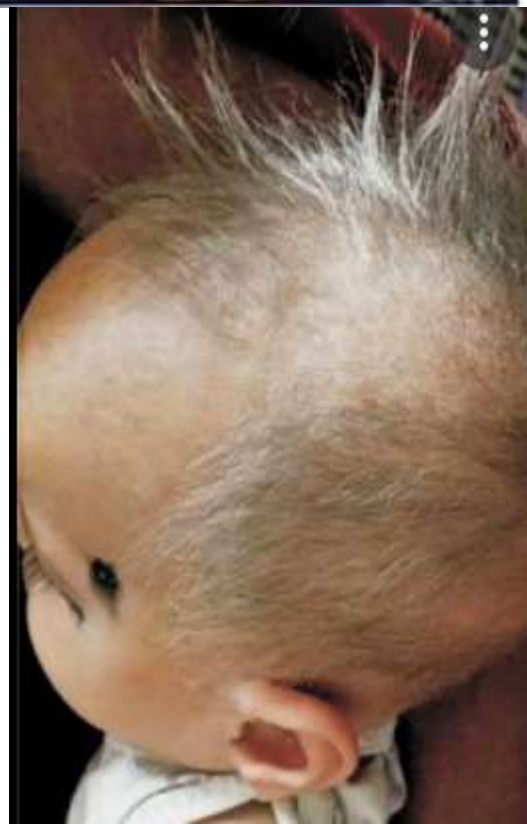
- MD is an X-linked disorder that is diagnosed by stunted growth, hypo pigmentation, brittle hair, neurodegeneration.

- These characteristic disorders are caused by mutation in the encoding of copper transporting gene (ATP- 7A) ATP- 7A activity.

- Copper deficiency causes Menke's Kinky Hair Syndrome (abnormal and spiral curly hair).

Menkes Disease





- Treatment of MD with Cu is not effective.

- Because Cu transports into the brain is dependent on the function of ATP-7A,

- however, copper-histidine therapy results in normalization of serum copper, dopamine ceruloplasmin levels in patients who undergone this treatment course.

- **Copper overload- Wilson’s Disease (WD)**
- **Wilson's disease** is a rare inherited **disorder** that causes copper to accumulate in your liver, brain and other vital organs. Most people with **Wilson's disease** are diagnosed between the ages of 5 and 35, but it can affect younger and older people, as well

- WD arises due to genetic disorder in Cu metabolism.

- A healthy adult possess Cu between 200 to 300 mg and the highest amount is concentrated in the locus of the brain.

- WD is a rare genetic disease characterized by the deficiency of Cu binding plasma protein, ceruloplasmin and deposition of Cu in the tissue (especially liver and brain).

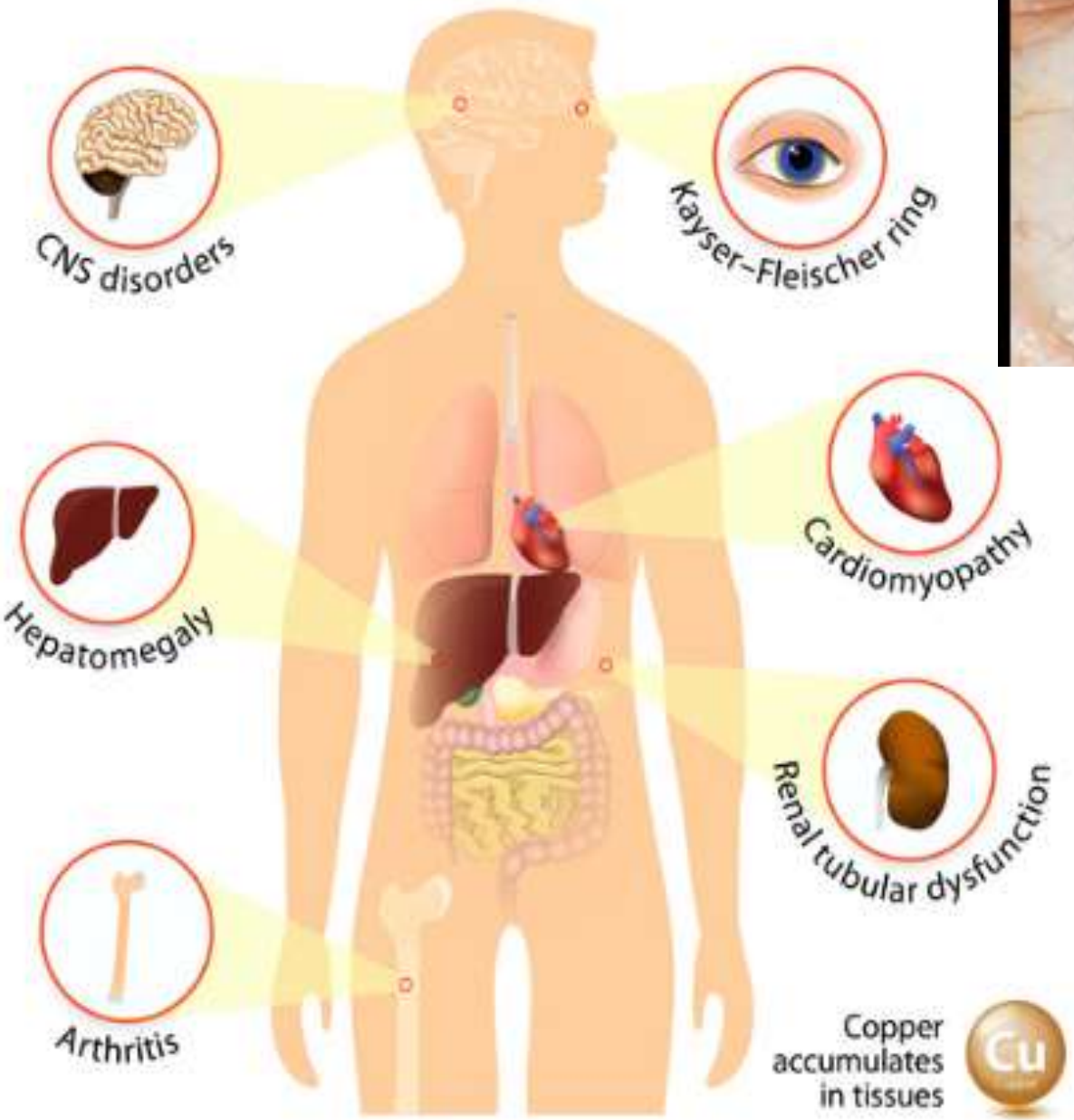
- In WD, Cu concentration up to, 100 times greater than its normal content have been found.

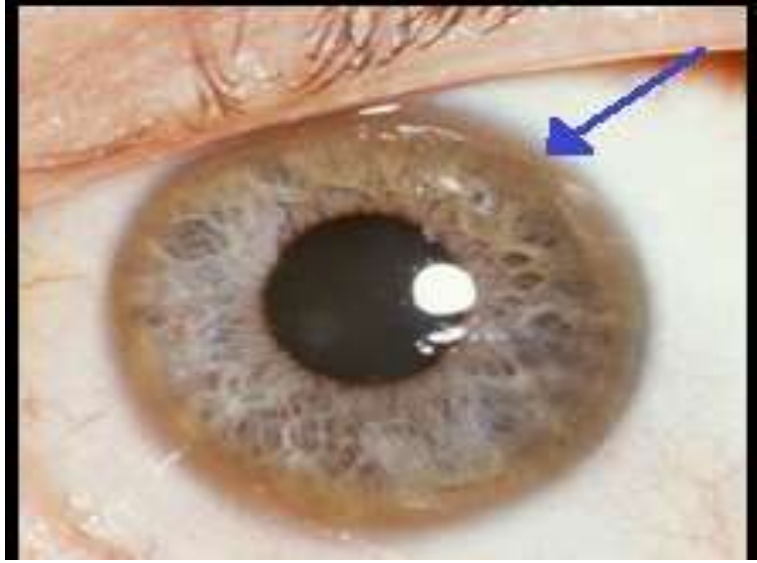
- It may be seen as brown or green rings in the cornea.

- It is now established that excess Cu is accumulated in the liver and then in the CNS.

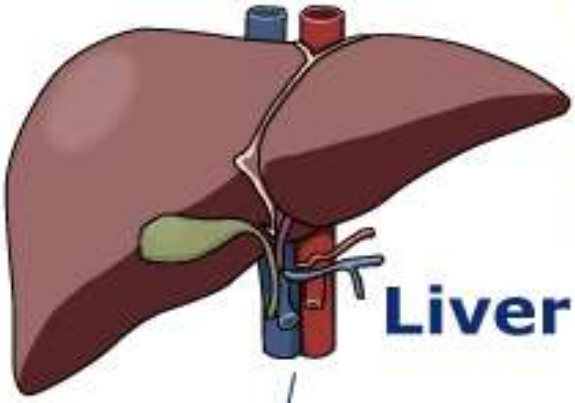
- Disorder in the liver and nervous system is manifested in this sequence.

WILSON'S DISEASE





Wilson's Disease



Liver

- Hepatomegaly
- Jaundice
- Acute hepatitis
- Fulminant hepatic failure
- Portal hypertension: bleeding varices
- Cirrhosis

Renal

- Proximal renal tubular dysfunction

Bone

- Arthritis
- Rickets

Cardiac

Haem

- Hemolysis

Central nervous system

- Deterioration in school performance
- Behavioral changes
- Inco-ordination (handwriting deteriorates)
- Resting and intention tremors
- Dystonia
- Dysarthria
- Excessive salivation
- Mask-like facies
- Dysphagia

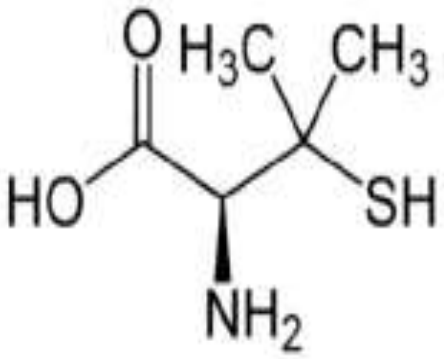
Eye

- Kayser Fleischer rings

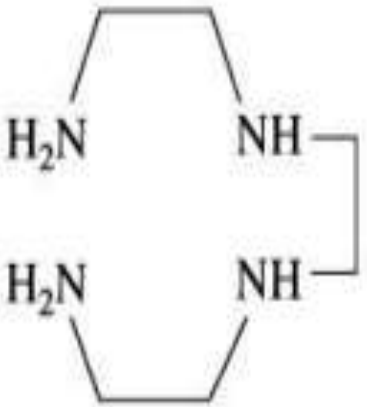
Treatment of WD: Chelation therapy

- Symptoms:
- WD is an autosomal recessive disorder that causes cirrhosis of liver, liver disease, progressive neurological disorder or psychiatric illness, affecting one in 30000 individuals.
- There is an impairment of biliary copper excretion, leading to hepatocyte, Cu accumulation and Cu mediated liver damage.
- WD was once an untreatable disorder inevitably leading to death. But now, if diagnosed at early stage the disease is treatable with Cu chelators and Zinc salt therapy.

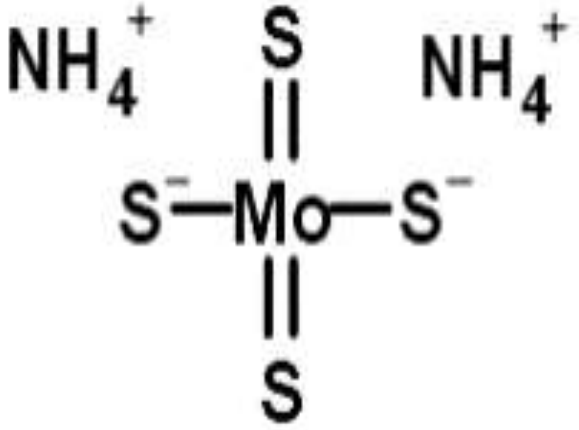
- There are three most common chelating agents available, copper chelators;
- 1. Pencillamine 2. Tientine 3. Tetrathymolybdate



Pencillamine



Trientine

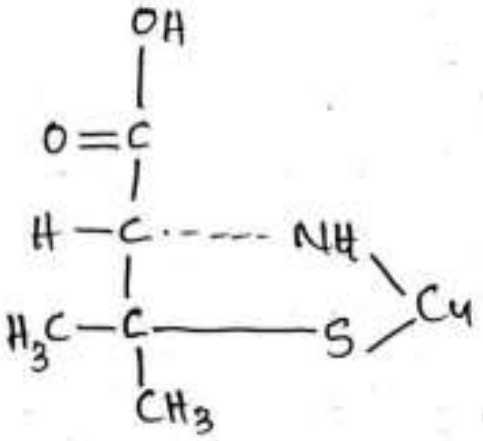


Tetrathymolybdate

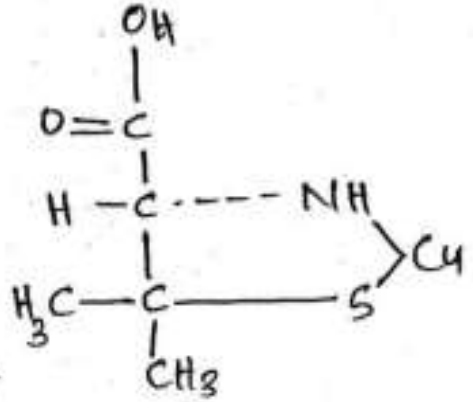
- Pencillamine binds in ambidentate fashion and can either bind in 1:1 or 1:2 ligand to metal ratio, forming Cu(I) and Cu(II) mixed valance chelate is unusually strong, binding the first Cu to the amino nitrogen and thiol sulphur and the second Cu through a deprotonated carboxyl group, both acting as bidentate donors.

- Treatment is lifelong with either oral chelating agents or zinc salts. If unresponsive, liver transplantation should be undertaken.

- Once the disease is diagnosed, large amount of Cu have to be mobilized and excreted and then the same therapy must be continued on a lifelong ba



Copper-penicillamine isomer



(β-β-dimethylcysteine)

- Pencillamine as the d- isomer is the favoured treatment at present. A dose of 1 g daily leads to the excretion of 8 to 9 mg of Cu in new patients.

- Pencillamine chelates Cu as effectively as it does its patent compound.

- The methyl substituents on the β-carbon atom, however render the agent or resistant to degradation by Cysteine disulphydras, thus prolonging its biological halflife.

- The major throwback of this chelating agent is that some patients become allergic to it.

Iron deficiency and treatment

- Iron is an essential metal necessary for cytochromes, haemoglobin, myoglobin and for the function of many known heme enzymes.

- Iron can be found in ferric and ferrous states and the thus it is involved in many redox reactions.

- Excessive amounts can be toxic leading to liver damage and death.

- Too little iron can lead to cognitude siderophore leading to anaemia.

Iron deficiency- Anemia (IDA)

- IDA is caused by low iron levels and low haemoglobin. Iron deficiency cause anaemia overwhelmingly occurs in toddlers and women of reproductive age.

- Iron deficiency may be caused by prolonged low dietary intake, increased iron requirement due to pregnancy, loss of blood through GI (Gastro Intestinal) bleeding or menstruation.

- In adults, over the age of 50, GI blood loss is an important cause of iron deficiency.

- Iron deficiency can have many negative effects on an individual's health, including changes in immune function, temperature regulation, energy metabolism and work performance.

- **Treatment**
- If iron deficiency is clinically established then to remove the iron deficiency, iron enriched or supplemented diets are recommended.

- Some oral iron drugs such as ferrous sulphate pills coated with fructose or lactose to protect from aerial oxidation.

- Ferrous fumarate, ferrous gluconate, ferrous tartrate are also clinically used.

- Sometimes ascorbic acid is added with ferrous sulphate to aid absorption in GI.

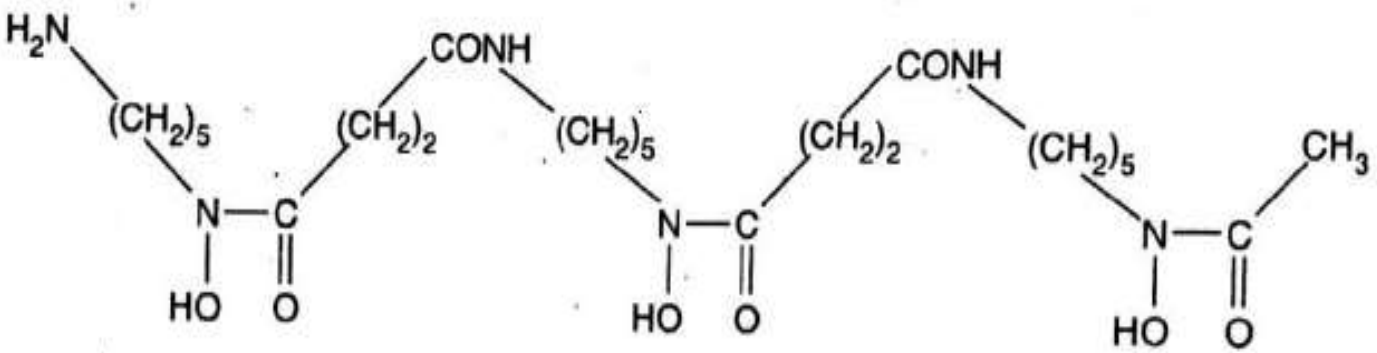
- **Iron overload**
- The main causes of iron overload in chronic hepatic diseases are alcohol induced hepatocite damage, chronic liver failure, chromic iron transfusion therapy.

- Alcohol intake can lead to chronic liver failure, which induces increased iron absorption.

- Iron poisoning occur frequently in young children who eat toxic (excess) amount ferrous sulphate tablets intended for the treatment of anaemia in an adult member of the household.

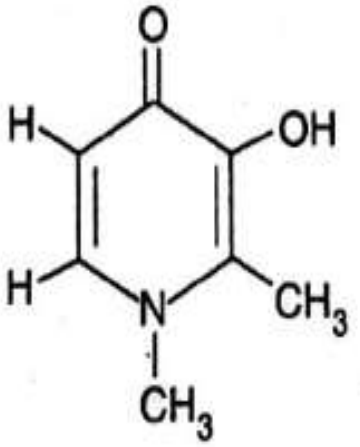
- The high stability constant of complexes between Iron and EDTA or DTPA suggest that Calsiumdisodium EDetate is enough to be the agent of choice in treating iron poisoning.

- A newly introduced agent for systematic treatment of iron poisoning is
- (a) desferrioxamine B
- (b) deferiprone



Desferrioxamine B (i.e. desferal)

(a)



(b)

Iron overload leads to “thalassemia”

- Desferrioxamine and deferiprone are isolated from bacteria and subsequently characterized synthesized also desferrioxamine chelates iron in an octahedral complex.

- Desferrioxamine removes iron from ferritin, trtansferritin not from haemoglobin or cytochrome to which metal is bound more tightly.

- Sodium is the most abundant cation in the body and is generally found in the extracellular compartment, with the exception of blood cells, which have high intracellular sodium concentration.

- ▪ Sodium deficiency- Hyponatremia is an electrolytic disorder, ie, defined as decrease in serum Na+ concentration below 135 mM.

- ▪ Hyponatremia can be associated with low, normal, high osmotic pressure. There are three types of hyponatremia.
- i. Hypotonic
- ii. Hypertonic
- iii. Isotonic

- Hyponatremia leads to Addisson's disease, due to malfunctioning of the endocrine glands, to maintain the salt balance.

- The symptoms of hyponatremia include nausea and malaise.

- Severe hyponatremia shows headache, lethargy, restlessness, disorientation.

- If sodium level fall rapidly cause, respiratory brain damage and respiratory arrest can ocuur.

Treatment

- To maintain the salt balance, a combining therapy containing minerals having sodium salts and hormones like aldosterone, cortisone etc. is recommended.

- Sometimes due to excessive persipiration (sweating) there is a marked loss of NaCl and such losses can be compensated by a simple intake of NaCl solution.

- Nowadays for this pupose, commercial preparation containing mainly NaCl, small amount of soluble potaasium and phosphate salts along with glucose are available.

- Composition of such preparation resembles to that of sweat. In diarrhea and other different physical ailments use of normal saline is (0.84% NaCl solution).

Cyanide Poisoning

- Cyanide is regarded as a notorious poison, has been used as poison for thousands of years.
- The effect of high dose of cyanide is quick and death occurs within minutes.
- Antidotes are effective if administered in time.
- A number of plants such as Sorgham and seeds including apple, apricot, peach, cherry, plum contains cyanide.

- Cyanide combines with ferric ion atom in heme protein in the tissues, destroying their capacity to undergo oxidation and the reduction in the normal electron transport process.

- The lethal dose is approximately 50mg to 200mg, it can cause death extremely rapidly, primarily by inactivating cytochrome oxidize in the tissues.

- The affinity of cyanide for cytochrome oxidize is actually greater than for methamoglobin.

- (Nitrate reacts with haemoglobin to form methamoglobin), it causes *blue baby syndrome (mathamoglobinemia disease); consumption of water containing nitrite consumption leads to methamoglobinemia.*

- The reduction of ferricytochrome to ferrocytochrome in the last stage of oxidative phosphorylation is prevented by the formation of an iron-(III) cyanide system.

- It is possible to treat cyanide poisoning by intravenous administration of sodium nitrite or by inhalation of amile nitrite (gas) and sodiumthiosulfate with high dose oxygen should be given as soon as possible.

- The rationale for nitrite therapy is that, the nitrite causes the formation of methamoglobin by combining with haemoglobin.

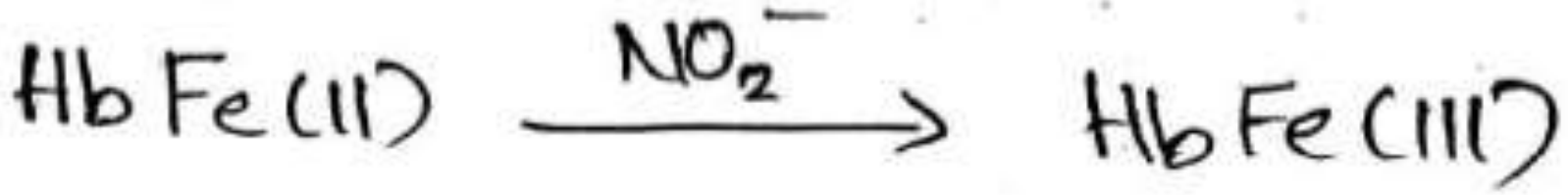
- Methamoglobin has a higher affinity for cyanide than does cytochrome-oxidase.

- And thus promotes its disssociation from this enzyme.

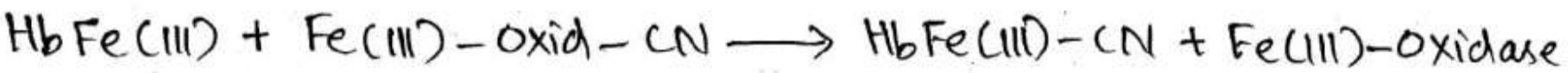
- Thiosulfate reacts with cyanide as the cyanide is slowly released from cyanomethamoglobin, forming the relatively non toxic thiocyanide, which is excreted in urine.

- The last step of the reaction is catalyzed by the enzyme Rhodanase and the sequences are given below.

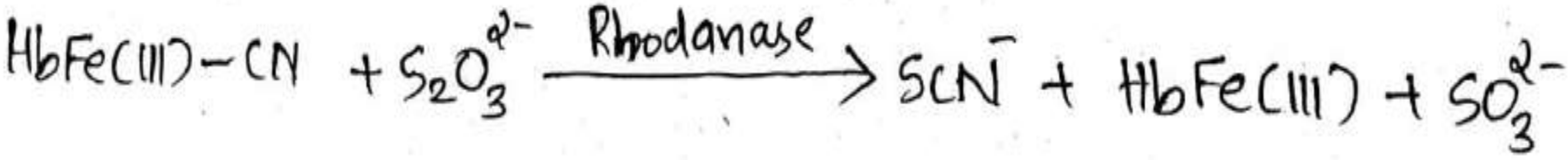
- **Step: 1**
- NO2- oxidizes haemoglobin [HbFe(II)] to methamoglobin, which is ineffective in carrying oxygen to tissues.



- **Step: 2**
- [HbFe(III)] binds cyanide, thereby releasing cyanide from the cyanide complex- ferricytochrome oxidase, Fe(III)- oxidase.



- **Step: 3**
- Further treatment with S2O32-(thiosulfate) causes elimination of CN-



- **Note:**
- ***Cyanide exerts its toxic action by inhibiting oxidative enzyme from mediating the process by which oxygen is utilized to complete the production of ATP in mitochondria.***

Carbon monoxide poisoning

- CO is toxic to animals but not to plants.
- CO is a product of incomplete combustion of fuel.
- It is found wherever the internal combustion engine is in use, is an industrial hazard, and it causes accidental poisoning in household where it is present in heating or cooking gas.

- CO may be considered as an antimetabolite of oxygen.
- It combines reversibly with haemoglobin to form carboxyhaemoglobin.
- CO binds more strongly towards iron of haemoglobin than oxygen.
- This means oxygen transport and oxidative phosphorylation are prevented by CO.

- Carboxyhaemoglobin forms stronger complex so that the net result values in the reduction in blood's capacity or carrying oxygen.

- Brain damage can occur if the exposure is formed prolonged time, ultimately causing death. A lethal concentration is (1-10mg/L).

Antidote for carbon monoxide poisoning

- The patient is removed from the contaminated environment and kept at rest, avoiding all stimulants, in order to reduce tissue oxygen demand to the lowest possible level.

- Respiration is maintained artificially, if necessary with administration of pure oxygen or a mixture of 95% O2, with 5% CO2, to promote the competitive displacement of CO.

- Raising the oxygen concentration in the inspired air from 20% to 100% reduces the biological half life of carboxyhaemoglobin in man from 250 mins to 40 mins, as would be expected.

- In sever poisoning, exchange transfusion is indicated to furnish an immediate supply of fresh oxygen.