Syllabus

Metal ion excess toxicity-Fe excess toxicity- African siderosis, hemosiderosis, hemochromatosis (bronze diabetes) and detoxification. Cu excess toxicity: Wilson's disease and treatment.

Heavy metal ion toxicity: Hg, Pb, Cd, As toxic effects – mechanism of toxic effects. Heavy metal toxicity treatment- chelation therapy: chelating agents for Hg, Pb, Cd, As toxicity.

Metal complexes as drugs: cis-plain as anticancer agent: mechanism of action and side effects; gold complexes as antiarthritic drugs- chrysotherapy. Metal complexes in diagnosis - Gd complexes in magnetic resonance imaging (MRI).

METAL ION EXCESS TOXICITY

Iron excess toxicity

- ✓ It is due to accidental intake of $FeSO_4$ tablets causing erosion of the gastrointestinal tract.
- ✓ Hemochomatosis is a genetic disorder, deposition of iron occurs in vital organs like liver, spleen, pancreas, skin etc. It leads to bronze pigmentation on the skin is called bronze diabetes.
- ✓ Siderosis (deposition of FeO dust in the lungs) is associated with excess of iron.
- ✓ African siderosis is an iron overload disorder first observed among people of Southern Africa and Central Africa. Dietary iron overload is the consumption of large amount of home-brewed beer with high amount of iron content in it.

  Detoxification : Siderophore desferrioxamine is a chelating antidote used for Fe removal

Copper toxicity

Copper is a principal component of several metalloproteins and some naturally occurring pigments. A healthy adult possesses copper between 200 to 300 mg and the highest amount is concentrated in the locus of brain. Wilson's disease and Menkes' kinky hair syndrome are associated with a genetic disorder in the metabolism of copper.

Wilson's disease

- ✓ In Wilson's disease, the copper-content is more than hundred times greater than the normal content. The clinical symptoms of Wilson's disease include hepatic

cirrhosis(liver disease),neurological damage,brown or green rings in the cornea of the eyes,lack of coordination etc.The excess copper is deposited first in the liver and then in the central nervous system.

- ✓ In Wilson's disease,the patients are found to have the low levels of apoceruloplasmin which is responsible for copper transport. Thus this disease is associated with the genetic failure to synthesise apoceruloplasmin.
- ✓ In this disease,there is a large amount of copper in blood stream and it causes the damage of erythrocyte membrane(hemolyticanemia). Copper is finally deposited in liver and brain developing the hepatic and neurologic symptoms.

Treatment:

To reduce the copper overload, the chelating dugs like Na_2Ca(EDTA), D-penicillamine , 2, 3-dimercaptopropan-1-ol are clinically recommended.

Zn-salts are now recommended for the treatment of Wilson disease. Probably,the Zn-salts involve the induction of thionein protein in the intestinal cells. The thionein protein tightly binds the copper. Thus it inhibits the intestinal uptake of copper .The major advantage of Zn-therapy is its low toxicity.

12.4.3 Arsenic Poisoning

[A] Arsenic in ground water : Ground water contamination by arsenic now appears as a threat to different areas in West Bengal and Bangladesh. The affected zones of W. Bengal are in the vicinity of Ganga river. In fact, about 30 million people living on the upper delta plain of Ganga basin (both in West Bengal and Bangladesh) are threatened to severe As-poisoning as the As-content in ground water in this area is much above the WHO maximum permissible limit 0.05 mg per litre. In West Bengal, the affected districts are North and South 24 Parganas, Bardhaman, Nadia, Malda and Murshidabad. In these different districts, As-content in water sample ranges from 0.05 – 3.5 mg per litre. As-pollution is also reported in many other countries like Taiwan, Chile, Argentina, North Mexico, Minnesota (USA), etc.

It has been proposed that excessive withdrawal of ground water for irrigation in agricultural field is the cause of As-contamination in ground water. In the underground, the iron pyrite (FeS_2) layer is the potential source of arsenic. The probable mineral is ***arsenopyrite* (FeAsS)** which was probably produced in a volcanic belt. These are deposited in the alluvium of Bengal Basin. The ***aquifers*** are responsible to supply arsenic in soluble forms to the ground water. Due to the excessive withdrawal of ground water, **the zone of aeration,** has increased and consequently the *arsenopyrite material* comes in contact with aerial O_2. It leads to aerial oxidation of the pyrite material. The aerial oxidation leads to the formation of the ***secondary mineral scorolite* ($FeAsO_4$, $2H_2O$)** from the primary mineral arsenopyrite (FeAsS). The probable routes of aerial oxidations are shown below.

$$4FeAsS + 13O_2 + 6H_2O \longrightarrow 4Fe^{2+} + 4AsO_4^{3-} + 4SO_4^{2-} + 12H^+ \quad (12.4.3.1)$$

$$2FeS_2 + 7O_2 + 2H_2O \longrightarrow 2Fe^{2+} + 4HSO_4^- \quad (12.4.3.2)$$

$$4Fe^{2+} + O_2 + 4H^+ \longrightarrow 4Fe^{3+} + 2H_2O \quad (12.4.3.3)$$

$$FeS_2 + 14Fe^{3+} + 8H_2O \longrightarrow 15Fe^{2+} + 2SO_4^{2-} + 16H^+ \quad (12.4.3.4)$$

$$Fe^{3+} + AsO_4^{3-} + 2H_2O \longrightarrow FeAsO_4 \cdot 2H_2O \quad (12.4.3.5)$$

(scorcolite)

The similar reactions are involved in the process of **acid mine drainage (AMD).** The aerial oxidation of pyrite material lowers the pH of the ground water and it facilitates the hydrolysis of ferric arsenate ($FeAsO_4$) and ferric arsenite ($FeAsO_3$) which are the ***common alteration products*** of arsenopyrite (the basic mineral for arsenic).

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$$FeAsO_4 + 3H_2O \rightleftharpoons H_3AsO_4 + Fe(OH)_3 \quad (12.4.3.6)$$

$$FeAsO_3 + 3H_2O \rightleftharpoons H_3AsO_3 + Fe(OH)_3 \quad (12.4.3.7)$$

Thus the released arsenic acids (*i.e.* H_3AsO_4 and H_3AsO_3) contaminate the ground water. Analysis of bore-hole sediments in As-affected area indicates the presence of $FeSO_4$, FeS_2 and As-contaminated FeS_2. Thus it is quite reasonable to conclude that due to heavy withdrawal of ground water, the *underground aquifer is aerated and oxygenated* and it causes the degradation of As-rich source, arsenopyrite meterial.

Arsenic containing insecticides, fungicides and herbicides are also causing problems.

[B] Removal of arsenic from ground water : Arsenic contaminated ground water collected is allowed to stand in an open tank in contact with air. It may be noted that most ground water contains Fe(II) which is readily oxidized on standing in air to Fe(III) which is then thrown out as $Fe(OH)_3$ precipitate along with arsenic (*i.e.* arsenic is coprecipitated). **Laterite treatment** (in Sweden) has been found quite effective in removing arsenic from ground water. Arsenic is absorbed on the reactive surface area of the grained laterites.

As-contamination in drinking water can be removed by the oxidation of As(III) to As(V) (using bleaching powder or $KMnO_4$) followed by *coprecipitation of* AsO_4^{3-} by using Fe(III) or Al(III) salts.

[C] Biochemical aspects of arsenic poisoning : Among the different species, the compounds containing As(III) are the most toxic. As(III) being soft prefers the —SH groups of different enzymes to inhibit the enzymatic process. It also binds with the **keratin disulfides** present in hair, nail and skin. Chronic arsenic poisoning leads to clinical symptoms like loss of appetite, gastrointestinal problems, diarrhoea with alternating constipation, dermatitis and sometimes skin cancer. As(III) is more toxic than As(V). The toxicity of arsenic depends on the nature of the species under consideration. The inorganic arsenic species is converted into different organoarsenic compounds through biomethylation in aerobic and anaerobic conditions. The speciation of arsenic is shown in Scheme 13.8.3.1. The toxicity order is : As(III) > As(V) > monomethylarsonic acid [$MeAs(O)(OH)_2$] > dimethylarsonic acid [$Me_2As(O)(OH)$]. Organoarsenic compounds (*e.g. arsenobetaine*) present in sea food is almost nontoxic.

The clinical symptoms of As-poisoning at different stages are :

(i) initial stage : gastroenteritis, dermatitis, keratosis;

(ii) second stage : depigmentation and hyperkeratosis, peripheral neuropathies, melanosis;

(iii) last stage : gangrene and ulceration in the limbs and skin cancer;

• During the second world war, Germany was suspected to use the Lewisite gas, an organoarsenic compound. The toxicity originates due to its interaction with the —SH groups of different enzymes (Scheme 12.4.3.1) such as succinooxidase, pyruvate dehydrogenase (*cf.* Sec. 9.4.3.8; ***in this route synthesis of acetyl CoA is arrested***), etc. Arsenic can inhibit many other enzymes like DNA-ligase, methyl transferase, glutathione reductase, phosphoenolpyruvate mutase etc.

• Arsenic can show its *carcinogenic activity*, though it cannot directly damage the DNA. Probably, As(III) binds with some —SH group containing enzymes which are involved in DNA repair

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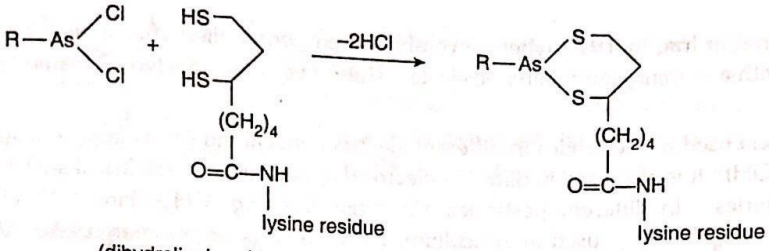

(dihydrolipoic acid-protein, a compentnt of *pyruvate dehydrogenase*)
(*cf.* **Scheme 9.4.3.8**)

Scheme 12.4.3.1 : *Untoward interaction between Lewisite and —SH groups of dihydrolipomide (a component of pyruvate dehydrogenase).*

mechanism. For example, As(III) can bind with the DNA repairing enzyme, poly(ADP-ribose)polymerase having two vicinal thiol groups. As(III) can bind with the cysteine —SH groups of *methyl transferase* to induce the **heavy-atom effect** (HAE).

• Chemistry of arsenic (As) is very much comparable with that of phosphorus (P). In fact, several arsenic analogues are enzymatically recognised by the enzymes like RNA-polymerase, adenylate cyclase which act normally on P-compounds. Several As-compounds can inhibit many enzymes competitively. 3-Arsonopyruvate [HO—As(O)(OH)—CH_2COCO_2H] can competitively inhibit phosphoenolpyruvate mutase (*PEP mutase*) which is required for the biosynthesis of C—P bonds in living bodies.

• AsO_4^{3-} being chemically similar can substitute PO_4^{3-} in different biochemical reactions through the **principle of competitive inhibition**. As for example, in the enzymatic synthesis of 1,3-diphosphoglycerate(1,3-DPG) from glyceraldehyde-3-phosphate through *oxidative phosphorylation*, arsenate may participate to produce 1-arseno-3-phosphoglycerate which is spontaneously hydrolysed without generating ATP. But, 1,3-DPG can generate ATP at the subsequent step. Thus, arsenate can prevent the generation of ATP. This aspect has been discussed in glucose metabolism (*cf.* Eqn. 9.4.1.3 and Sec. 9.4.1).

• As-compounds can also denature different proteins by attacking the –SH groups which are required to maintain the secondary and tertiary structure of the proteins.

Thus the toxicity due to As-compounds arises from three possible routes. **(a) *blocking of —SH groups of different enzymes;* (b) *competitive inhibition of different enzymes like PEP mutase and uncoupling of phosphorylation as in glucose metabolism,* (c) *denaturation of different proteins.***

[D] Detoxification : The recommended chelating antidotes for detoxification of arsenic are : 2,3-dimercaptopropanol (BAL), D-penicillamine.

[E] Beneficial role of arsenic : Here it is important to mention that though no beneficial role of arsenic in human beings is known, it is essential for some animals. As-deficiency in rats induces poor growth, rough fur and low fertility. Some marine organisms are found to contain arsenolipids. In mammals it may participate in arginine and zinc metabolism.

12.4.4 Mercury Toxicity

[A] Sources : The **Minamata disaster** (1953) occurred among the people eating see-fish from Minamata bay. The reason for this disease has been already discussed (Sec. 12.3.3). Another

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disaster occurred in Iraq in 1972 where several hundred people died after eating wh eat which had been dusted with a mercury containing pesticide. These two tragic incidents created an awareness of Hg-toxicity.

Hg is widely used as electrodes in different electrochemical industries (*e.g.* industrial production of Cl_2 and NaOH). It is also used in different electrical apparatus, *e.g.* electrical switches, Hg-vapour lamp, Hg-batteries. In different pesticides and fungicides (*e.g.* CH_3—Hg—CN, C_2H_5—Hg—Cl, CH_3—CO_2Hg—C_6H_5, etc.) used in agriculture, Hg is used as organomercurials. Very often, the seeds are treated with these fungicides. This leads to an wide distribution of mercury in environment. These are the major sources of Hg in environment. The inorganic Hg-compounds are very often absorbed on sediments and these may be biomethylated subsequently.

Elemental Hg is fairly inert and it is nontoxic. But its conversion into CH_3Hg^+ by anaerobic microorganisms produces a serious health hazard. HgS is quite insoluble and trapped in soils; and it is also nontoxic. Hg_2^{2+} (mercurous) species are of low toxicity. In stomach, it forms insoluble Hg_2Cl_2 which is ultimately excreted. Hg^{2+} is toxic but it cannot pass across the biological membrane. In 19th century, $Hg(NO_3)_2$ was used in cleaning felt hats and consequently, **the hatters became the victims of Hg-poisoning**. Organomercurials (specially CH_3Hg^+) are highly toxic due to their lipid solubility. Diorganomercurials (*i.e.* R_2Hg) are of low toxicity but they may be converted into toxic forms RHg^+.

[B] Toxicity :

- Both Hg^{2+} and RHg^+ preferably bind with the —SH groups of proteins and enzymes. Thus they can interact with hemoglobin and serum albumin having —SH groups. **$CH_3Hg(II)$ is found to bind with the *glutathione in red blood cells.*** They can also inhibit the activity of *δ-aminolevulinic acid dehydrase*, and *cholin esterase activity*.

- In R—Hg^+, the Hg—C bond is retained unchanged for a long period in cells and tissues. CH_3Hg^+ is lipid soluble and it can pass across the biological membrane and it is accumulated in the brain tissues. It can even move through the *placental barrier* and enter *fetal tissues* from mother. This explains the ***congenital defect*** (*i.e.* teratogenic effect) in newly born babies.

- The attachment of the toxic species of Hg with the membrane prevents the *active transport* of glucose and the membrane becomes leaky towards K^+. Thus it can induce neurological problems including mental retardation and **cerebral palsy (*i.e.* cerebral paralysis)**. It can damage the central nervous system (CNS). CH_3Hg^+ can also attack chromosomes and prevent cell division.

Toxic effects of mercury poisoning may manifest in several forms :

(i) *Enzyme inhibition* : by blocking the active —SH groups. (ii) **Cellular dysfunction** : binding with the cellular proteins through soft-soft interaction. **(iii) *Neurological disorders*** : methyl mercury [CH_3Hg^+] poisoning irreversibly damages the cells of the nervous system in brain. **(iv) *Teratogenic effect*** : methyl mercury cation can pass through the placental barrier to invade the fetus. **(v) *Erethism*:** mild dose of Hg-poisoning produces neurological disorders manifested through the behavioural problems and personality change.

[C] Detoxification : For detoxification of Hg(II) or $CH_3Hg(II)$, D-penicillamine (DPA) and its N-acetyl derivative (NAPA), unithiol (*i.e.* 2,3-dimercapto-1-propanesulfonic acid), etc. are recommended. In detoxification of $CH_3Hg(II)$, *NAPA is a better antidote than DPA because of the presence of the lipophilic acetyl group in NAPA.*

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