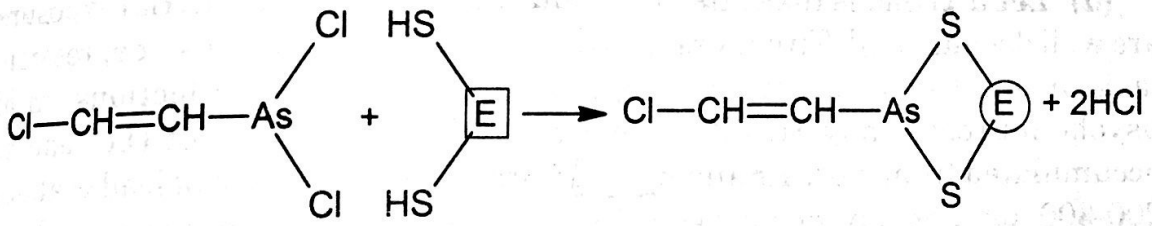
potent, protoplasmic poison. Elemental arsenic is not absorbed. Its salts are readily absorbed through the gastrointestinal tract. Chronic poisoning by arsenic compounds leads to loss of appetite and weight, diarrhoea alternating with constipation, gastrointestinal problems, peripheral neuritis, conjunctivitis, dermatitis and sometimes skin cancer, which collectively constitute what is called *arsenic poisoning*. It is carcinogenic in mouth, esophagus, larynx and bladder.

Arsenate inhibits ATP synthesis by uncoupling *substrate level phosphorylation* by replacing the phosphate group (*cf.* p.95). It also blocks the thiol (–SH) functions of the enzymes and binds to tissue proteins. It binds to keratin disulphide in hair, nail and skin. In general, the toxic action of arsenic in living cells is belived to be due to its binding to some essential thiol derivatives present in the protoplasm. Binding of arsenic with suitably disposed –SH groups of the enzymes leads to enzyme denaturation.

Lewisite (1), an arsenic containing poisonous gas, that was used during World War II, is believed to react with active enzyme proteins (E) (2) by blocking the thiol groups of the cysteine residues. In this way it denatures the enzyme (3).



(1) (2) (3)

In short, the three major biochemical actions of arsenic are coagulation of proteins, complexation with coenzymes and uncoupling of phosphorylation from metabolic oxidation. $LD_{50}\,(rat)$: 0.07 *g/kg* .

(c) ***Cadmium*** : Cadmium is not an essential element for human. It is a toxic metal. Intake of cadmium occurs mainly through the food chain by about 40 *mg* per day. Exposure to metallic dust, or, fume from industrial operations causes hypertension and cardiovascular problems, which finally lead to acute damage to workers lung. It is the cause of proteinuria, glycosuria, carcinomas, edematons along with proliferative and fibrogenic effects on lungs. Zinc appears to give some protection against the toxic effects of cadmium. The reported hypertensive effect of cadmium in man is associated with a high cadmium to zinc ratio in the kidney. Cadmium depresses growth and reduces the digestion of protein and fat. Once absorbed, cadmium is incorporated into *thionein*, a protein, which, by means of its thiol groups, binds upto 11% by its weight of cadmium. Enzyme bound cadmium accumulates in kidney, liver and reproductive organs.

...of this chapter. ...compounds as

10.1. Metal Ion Toxicity

Because of their non-biodegradable nature, the intake of various metallic compounds causes local irritation, tissue damage, or, systematic poisoning, if the intake is sufficiently large. Metal ion toxicity may also disturb the electrolytic balance, damage specific organs, *viz.*, brain, kidney, liver, *etc.*, and even the central nervous system, or, interfere with the vital enzymic processes. There are considerable variations in the safe concentration levels of toxic metal ions. Toxicity caused by some metals are briefly reviewed in this section.

(*a*) *Copper* : Although copper in trace amounts is essential for life due to its role in the metalloenzymes and metalloproteins, *viz.*, cytochrome *c* oxidase, superoxide dismutase, blue copper proteins, ascorbic acid oxidase, ceruloplasmin, hemocyanin, *etc.*, but copper salts even in moderately low concentrations may cause vomiting and considerable gastrointestinal irritation. The action of copper is due to its affinity for -SH groups of the enzyme proteins. Therefore, whenever such groups are bound to copper, the enzymic activities are often lost.

In patients, suffering from *Wilson's disease* (*p.*282), the copper level control mechanisms are damaged. Absorption of copper is increased and excretion cannot keep pace with the intake. So, copper accumulates in various organs, such as liver, kidney and brain. Such absorption of copper severely damages central nervous system, leading to tremor, rigidity, mental subnormality, *etc.* Accumulation of copper may also lead to cirrhosis of liver, which ultimately causes painful death. LD_{50} (*mouse*) : 0.05 *g/kg.*

(*b*) *Arsenic* : Arsenic is not an essential element for human, although it is found in tissues in very small quantities. It causes serious air and water pollution problems in the environment. Arsenic is an accumulative,

The kidney is the main target of attack of cadmium. Renal damage takes place when a critical level of 200 μg of cadmium per gram is exceeded. The excess cadmium-thoinein is the toxic factor. The affected kidney is unable to retain plasma proteins and other substances including calcium and phosphate. These substances are excreted in excess, leading to renal stone formation and bone damage in severe cases.

A specific disease, known as *itai-itai*, broke out in Japan, was attributed to *cadmium poisoning*. The epidemic was related to exposure to cadmium, released from mining operation. Itai-itai shows painful symptoms of multiple fractures arising from osteomalacia. It is largely confined to post-menopausal women with initial signs of lumbar pains and myalgia in the legs. Skelatal deformation takes place at later stages, with marked decrease in body weight, proteinuria and glaucoma. The metal causes an increase in serum alkaline phosphatase and a decrease in inorganic phosphate. In the terminal stage, multiple fractures occur after very mild excretion, such as coughing. Histological findings at autopsy are similar to those associated with osteomalacia. The disease takes a prolonged course, about more than 12 years. $LD_{50}(mouse) = 0.027\,g/kg$.

(d) *Lead* Lead is toxic. Its hazardous effects due to industrial exposure are well documented. Tiredness, run down feeling, nervousness, depression, lack of mind concentration, frequent cold and other infections, mild psychoneuroses may result from *lead poisoning*. Most of the lead is accumulated from diet, air and water. Rate of accumulation of lead is about 200-300 μg per day per person. Laboratory diagnosis of excessive lead absorption is usually obtained by blood lead analysis. Biochemical signs of lead toxicity are seen from the disturbance to porphyrin metabolism. Clinical signs of lead toxicity are most often seen at blood lead levels above $4\mu mol.lit^{-1}$.

Lead is accumulated in bones and soft tissues, particularly in brain, leading to depressed functioning. It forms complexes with thiol groups of enzyme proteins, inhibits biosynthesis of heme, particularly in the conversion of δ-amino levulinic acid to porphobilinogen. It also inhibits the formation of heme from iron (II) and protoporphyrin IX. It depresses the formation of δ-amino levulinic acid and decreases the conversion of porphobilinogen to protoporphyrin IX. It causes structural damage to mitochondria of kidney cells. It is responsible for the loss of amino acids, glucose and phosphate in urine. Lead is also responsible for increased dental caries, as it is poorly excreted. It damages liver, kidney and gastrointestinal tract and causes anorexia, muscle pains, weakness, joint pain, tremor, anaemia. It also causes abnormalities in fertility and pregnancy. Organic lead compounds are primarily neurotoxic. $LD_{50}(rat)$:0.15g/kg.

(e) ***Mercury*** : Mercury is toxic in all its forms, *e.g.*, Hg^0, Hg^+, Hg^{2+}. It is discharged into the environment either in the form of metallic mercury, or inorganic mercury compounds and alkyl, aryl and other organo-mercury compounds from industrial processings involving mercury. Use of organomercurials as fungicides appears to be another source of mercury in the environment. Once in the environment, mercury compounds may undergo variety of transformations. Inorganic mercury is transformed into methylmercury and dimethylmercury by the action of microorganisms and vitamin B_{12} coenzyme (*p.* 295). Organomercury compounds can enter into food chains through their uptake by aquatic plants and fishes. Methylmercury compounds are much more toxic than all the other forms of mercury. Absorption of mercury in the organism depends upon the chemical form of mercury. The extent of absorption of dietary mercury from inorganic compounds, such as mercuric chloride and mercuric acetate, *etc.*, may range from 2% to 50%. The extent of absorption of mercury may range from 50% to 80% for phenylmercury and upto 90% for methylmercury. Metabolism of organomercury compounds also depends upon their chemical forms. There are marked differences in the metabolism and excretion mechanism of alkyl and aryl mercury compounds. Owing to their non-polar nature, the alkylmercury compounds easily penetrate biological membranes and rapidly distribute throughout the body. Being a *class b* metal, mercury binds to the thiol groups of proteins in the manner as described in case of arsenic. Mercury (II) binds to the A....T rich regions of DNA and denatures it (p. 79). Concentration of the order of 20 $\mu g/g$ of mercury in the brain tissues is required to produce clinical effects. The passage of organomercury compounds across the placenta and their accumulation in the foetus may cause serious problems in pregnancy.

The first report of *mercury poisoning* from industrial waste discharges came from Minamata Bay in Japan (1952). 120 odd persons were affected by the so called *Minamata disease*. This was caused by methylmercury, a waste product from an acetaldehyde manufacturing process, which involved an inorganic mercury compound as the catalyst. Though methylmercury was released in water at an undetectably low level, it was taken up by fishes and shellfishes in which mercury accumulated in increasing amounts. As a result, Minamata disease broke out among the heavy fish eaters, mostly among the fishermen families. A number of babies with cerebral defects were born to mothers contaminated by methylmercury enriched fish proteins.

Mercurous ion in tissues is oxidized to highly toxic mercuric ions. Mercury diffuses through skin and is retained by liver, kidney, brain, heart, lung and muscle tissues. It binds to protein –SH groups and inhibits δ-aminolevulinic acid dehydratase and cholin esterase activities. Mercury

is a protoplasmic poison, it damages central nervous system. LD_{50} (*mouse*) = 0.027 *g / kg* .

(f) *Beryllium* : Pollution due to beryllium occurs from industrial smokes. The metal is toxic and it may cause two kinds of diseases, *viz.*, acute pneumonitis and *berylliosis*. The latter is a chronic progressive disease, located primarily in the alveolar walls. Beryllium acts as a carcinogen in lungs and bones. It damages skin and mucous membrane. It is not excreted from mammalian tissues. It inhibits enzymes, *viz.*, alkaline phosphatase, DNA polymerase, *etc.* Beryllium combines with unphosphorylated enzymes and competes with magnesium for the enzyme active sites. Beryllium-enzyme complexes are unreactive and do not bind to ATP. LD_{50} (*mouse*) = 0.5 *mg / kg* .

(g) *Manganese* : Manganese is an essential nutrient for animals and plants. But airborne manganese is responsible for increased incidence of *manganic pneumonia* in populations living in industrial areas. Toxicity due to manganese is responsible for *Parkinson's syndrome*. Chronic manganese poisoning through ingestion causes progressive deterioration in the central nervous system, resulting in cramps, tremors, hallucinations and lethargy. It also causes renal degeneration, LD_{50} (*mouse*) = 0.21 *g / kg* .

(h) *Selenuim* : Selenuim in trace amounts serves as a micronutrient. At higher levels (over 2000 $\mu g.lit^{-1}$) selenium has adverse effects on mammals. It forms complexes with plasma proteins and gets distributed into the tissues. It can substitute sulfur in cysteine and methionine. It is also responsible for dental caries in children, irritation in eyes, nose, throat and respiratory tract. It causes throat and liver cancer, pneumonia, degeneration of liver and kidney and gastrointestinal disturbances. LD_{50} (*rat*) = 0.003 *g / kg* .

(i) *Vanadium* : Vanadium appears to be an essential element for normal growth of animals and plants. But exposure to vanadium pentaoxide dusts, results conjunctivitis, nasopharyngitis and persistent cough. Vanadium inhibits synthesis of amino acids, cholesterol, phospholipids and other lipids. It inhibits the activities of many enzymes, *viz.*, tyrosinase, nitrate reductase, *etc.* It has adverse effects on tissue oxidation. It inhibits sulfydryl activity of many other enzymes. It reduces blood lecithin content and precipitates serum proteins. It also inhibits excretion of corticosteroids, acetylcholine metabolism and liver acetylation process. Vanadate ion may compete with phosphate (p. 19) and may affect phosphorylation. LD_{50} (*rabbit*) = 0.2 *g / kg* .

(j) *Nickel* : It is an essential trace element. It's deficiency in chicks and rats shows impaired liver function. It stabilizes ribosome conformation. Nickel dust, or, nickel containing asbestos powder inhaled on occupational