ESSENTIAL ELEMENTS AND THEIR BIOLOGICAL ROLE

1.1 ESSENTIAL AND TRACE ELEMENTS AND BIOINORGANIC CHEMISTRY

The presence of about 40 different elements has been established in living bodies. The ***eleven most abundant elements*** in biological systems are H, O, C, N, Na, K, Ca, Mg, P, S, and Cl. Among these, ***the first four elements***, *i.e.* H, O, C and N, constitute about 99% of the total atoms of a living body. These elements are involved to produce the biomolecules like water, carbohydrate, protein and fat. The ***next eight most abundant elements*** are Mo, Mn, Fe, Co, Cu, Zn, F and I. These eight elements are present at *trace quantities*. These elements are called essential *trace elements* but the term *trace* is not well defined. For example, Fe is present in few g while Mo is present in few mg in an adult healthy body, but both are called trace elements. In fact, in this group, except for F (*ca.* 2.6 g per 70 kg body weight in human being) Fe and Zn, all other essential trace elements are present in mg scale in a living body. The ***next eight important elements*** are Li, Si, V, Cr, Se, Br, Sn and W. These elements are required at ***ultratrace concentrations*** (*i.e.* at the level of parts per ten thousand million).

The biometals are classified as *essential metals and beneficial metals*. In the absence of essential metals, the living system cannot survive and it eventually dies. On the other hand, in the absence of beneficial metals, the life process gets hampered but it cannot lead to death.

Essential metals : Na, K, Mg, Ca, Mn, Fe, Co, Cu, Zn, Mo.

Beneficial metals : Li, V, Cr, Ni, Sn, W.

The *approximate metal contents* in a healthy human body (*ca.* 70 kg body weight) are as follows :

Na (100 g), K (200 g), Mg (35 g), Ca (1500 g), V (15 mg), Cr (2 mg), Mn (15 mg), Fe (5-7 g), Co (1.5 mg), Ni (5 mg), Cu (200-300 mg), Zn (2-3 g), Mo (10 mg). ***The amount indicated does not measure the importance of the metal.*** The decreasing abundance of the transition metals in living organisms is : Fe, Zn, Cu, Mo, Cr, V and Ni. The total metal content shown here accounts for only *ca.* 2% of the total body weight. Excluding the metals Na, K, Mg and Ca, other metals collectively weigh just a few grams (*ca.* 10 g) in a healthy body of *ca.* 70 kg. But these metals are extremely essential for the survival of life process.

At biological pH, all these biometals (except for Na, K, and Ca to some extent) cannot exist as free ions. They should form insoluble hydroxides and phosphates. By using the bioligands, these biometals form soluble complexes

Table 13.1 : Essential Elements in the Human Body

Element	*Atomic Number*	*% of Total Body Weight*	*Biological Role*
Oxygen	8	65	These four elements are the primary constituents of carbohydrates, fats and proteins
Carbon	6	18	
Hydrogen	1	10	
Nitrogen	7	3.0	
Calcium	20	2.0	Most of the body calcium is present as $Ca_3(PO_4)_2$ and $3Ca_3(PO_4)_2.Ca(OH)_2$ in bone and teeth; essential for blood coagulation.

Element	*Atomic Number*	*% of Total Body Weight*	*Biological Role*
Phosphorus	15	1.1	Essential for storage and supply of energy (as adenosine triphosphate ATP) for biochemical syntheses. Also makes up the base-sugar-phosphate backbone of nucleic acids (ribonucleic acid RNA and deoxyribonucleic acid DNA)
Potassium	19	0.35	Principal intracellular cation; responsible for transmission of nerve impulses, muscle contraction
Sulphur	16	0.25	Present in some proteins and other important biological compounds.
Sodium	11	0.15	Principal extracellular cation; proper balance and distribution of water in the body.
Chlorine	17	0.15	Principal anion inside and outside the cell
Magnesium	12	0.05	Enzyme activities and muscle contraction; associated with adenosine triphosphate (ATP) and adenosine diphosphate (ADP).
Iron	26	0.004	Most important of the metal ions; present in hemoglobin, myoglobin; responsible for oxygen transport; present in electron transfer protein : ferredoxins, cytochromes
Zinc	30	0.0002	Enzyme activity
Manganese	25	0.00013	Enzyme activity
Copper	29	0.0001	Present in copper storage protein ceruloplasmin; essential constituent of vital oxidative enzymes.
Fluorine	9	0.0001	Minor constituent of some body structures, such as teeth.
Iodine	53	0.0001	Essential constituent of the thyroid hormone
Molybdenum	42	0.0001	Enzyme activity
Cobalt	27	0.0001	Present in vitamin B_{12}; deficiency causes anemia

A deficiency in one of the essential elements will affect our well being. A deficiency in iron develops anemia while a deficiency in zinc leads to retardation of growth and slow healing of wounds. Again an excess can be toxic. Keeping these in view the World Health Organisation recommended a Daily Allowances for adult humans : 1-2 g sodium, 0.8 g calcium, 10-20 mg iron, 15 mg zinc.

1.6 BIOLOGICAL FUNCTIONS (SUMMARY) OF BIOMETALS

Effects of different elements on biological growth have been discussed in Sec. 12.1 and 12.2. The effects due to the deficiency and excessive accumulation of the elements are given in Table 12.1.2. In discussing the biochemistry of some metals in Chapter 3, the role of the metals has been also discussed.

Li

Antipsychosis activity; Li_2CO_3 used as a drug in the management of mental disease.

Na

Major cation in extracellular fluid; charge carrier and electrolytic balance; osmotic balance; required in the process of nerve impulse creation and its transmission; involved in the cotransport of sugars and amino acids into the cells.

13.12 ESSENTIAL ELEMENTS AND OUR WELL BEING

Essential elements play vital roles in biological activities. Their presence in excess of or below the optimum permitted range leads to malfunctioning of our system. Prolonged malfunctioning will result in ailments. We cite below a few such cases.

Magnesium : This is very important non-transition essential element. Biological reactions need supply of heat. Heat is liberated during conversion of ATP to ADP. At biological pH (7.0 to 7.5) ATP and ADP are in anion form and remain complexed to Mg(II). This ion gets bound to phosphate groups in nucleotides (ATP, ADP) and also to phosphate groups in polynucleotides (DNA, RNA). Mg(II) also plays important roles in many metalloenzymes. Magnesium in chlorophyll is also vital in photosynthetic conversion of CO_2 and H_2O to glucose.

Calcium : We had already mentioned in Table 13.1 that this element is the major constituent of bones and teeth. *Osteomalacia* is a disease characterised by softening of bones in elderly people, particularly in women after menopause. This is equivalent to rickets in infants.

Al

Required probably in activation of the enzymes like *succinic dehydrogenase* and *δ-aminoleuulinate dehydrase* which is involved in porphyrin synthesis. Moderately toxic, toxicity. *Alzheimer's disease* (?) and other *neurologic disorders*; high Al^{3+} along with low Mg^{2+} and Ca^{2+} concentrations induce neurologic disorders.

Ca

Required in cell membranes, bones, shells as a structural component; in muscle contraction; in blood clotting; in maintaining the osmotic pressure; in Mg^{2+}-Ca^{2+}-ATP-ase; in the enzymes like *neutral protease, thermolysin, α–amylase, phospholipase* A_2.

Mg

Required in photosynthesis, ATP hydrolysis, phosphate group transfer reactions (*i.e. kinase reactions*), structure formation, stabilising DNA and RNA, construction of cell membranes, *DNA polymerase* enzyme catalysing the transcription of DNA.

K

Major cationic species in intracellular fluid in animals; charge carrier and electrolytic balance; required to maintain proper osmotic pressure, in nerve impulse transmission, in cardiac function and in glucose metabolism; toxic to mammals when administered through intravenously.

V

Required in *sea squirts hemovanadin* (oxygen transport ?) of *tunicates* and *ascidians*; in *nitrogenese* enzyme for Mo-depleted condition; cofactor in *algal bromoperoxidase*. Required in chicks and rats for growth, development of feather, and reproduction; as a plant growth factor. Higher levels of vanadium is found in maniac and depressed patients. *Insulin mimetic activity* of *some V-compounds.*

Cr

Required as a *glucose tolerance factor* (GTF) in glucose metabolism; required also in lipid and protein metabolism; carcinogenic and mutagenic activity of Cr(VI).

Mn

Required in photosynthesis (PS-II); in structure formation; in different metalloenzymes like *pyruvate kinase, pyruvate decarboxylase, arginase*; deficiency causes retarded growth and infertility in mammals and erratic bone formation in growing chicks. Required in the synthesis of cholesterol, mucopolysaccharides and glycoproteins. Deficiency causes an increased activity of serum alkaline phosphatase and low activity of β–cells of pancreas (*i.e.* low insulin). Enzyme activators in RNA and DNA polymerases; activator for most Mg(II)-containing enzymes.

Fe

Required in O_2 uptake proteins (*i.e.* hemoglobin, myoglobin and hemerythrin); in different *oxygenase enzymes*; in *catalase, peroxidase, cytochrome P-450, aconitase*; in *cyctochrome c oxidase* (also Cu); in *nitrogenase* (also Mo,); in *hydrogenase*; in different electron transport proteins like Fe-S protein, cytochromes; in storage protein ferritin; about 70 Fe-proteins are now well known.

Co

Required in vitamin B_{12} coenzymes; in the enzymes like *ribonucleotide reductase* (DNA synthesis), *glutamate mutase* (amino acid metabolism); its deficiency causes illness in sheep; excess intake in heavy bear drinkers causes *congestive heart failure* – cobalt salts added to bear to improve the foaming properties, excess beer consumption with a dietary deficiency of protein or thiamine causes the problem in heavy drinkers.

Ni

Required in the metalloenzymes *ureases* (in some plants), *hydrogenases*, CO *dehydrogenase*, *methanogenic bacteria factor F 430M*; to stabilise the coiled ribosomes. Its deficiency causes an impaired liver function and an erratic morphology in chickens and rats.

Cu

Required in several enzymes like *cytochrome c oxidase* (also Fe), *amine oxidase*, *ascorbic acid oxidase*, *tyrosinase*, etc.; in electron transport proteins like *plastocyanin*, *azurin*, *stellacyanin*; in oxygen transport protein *hemocyanin* (in lower forms of life); in storage protein *ceruloplasmin*.

Zn

Required in a large number of enzymes (about three hundred enzymes), in structure formation, and to stabilise the coiled ribosomes; to maintain the sexual maturity and reproduction process. Required in genetic materiels – *DNA, RNA polymerases*, regulatory *Zn-finger protein* (structural motif for the eukaryotic DNA-binding proteins) in forming the nucleic acid (DNA) structure. Required in hydrolytic enzymes – *alkaline phosphatase*, *carboxypeptidase*; dehydrogenases – *alcohol dehydrogenase*, *glutamic dehydrogenase*; enzyme activation – in *arginase*, *peptidases*, *enolase*. Zn, a component in insulin hormone, and in snake venom.

Mo

Required in several oxidoreductase enzymes like *nitrogenase*, *nitrate reductase*, *xanthine oxidase*, *sulphite oxidase*, *aldehyde oxidase*; antagonistic to Cu and excess Mo can cause Cu-deficiency. Presence of Mo(VI)/Mo(IV) catalytic cycle (through *oxo-group transfer*) in many redox enzymes.

Cd

Probably required at ultra-trace concentrations in rats; toxic to cause renal failure and hypertension; causes an erratic bone metabolism (*itai itai* disease) due to interference with the Ca^{2+} metabolism.

Tn

Probably required at ultra-trace concentrations in rats; antibacterial and antifungal properties of organotin compounds.

W

Required only in lower forms of life (*i.e.* bacteria). Found in the enzyme *aldehyde ferredoxin oxidoreuctase* in *Pyrococcus furosis* which grows at about 100 °C and in the activity of *formate dehydrogenase* in thermophilic anaerobes.

1.7 CHEMISTRY OF PHYSIOLOGICAL BUFFERS

Acids and bases are continually produced in different metabolic processes. Acidic or alkaline substances are also present in the diet. The acids are eliminated mainly through lungs. It is estimated that in one day a healthy adult releases acid which is equivalent to about 30 litres of 1 mol

Zinc : An adult human has some 2 to 3 g of zinc compared to 4 to 6 g iron and only ~ 250 mg of copper. The zinc comes from diet of egg, meat, milk, beans etc. Zinc is present as constituent of a huge number of enzymes—carboxypeptidase, alcohol dehydrogenase etc. Zinc deficiency is indicated by rearded growth, slow healing of wounds, loss of appetite, anemia. Labour force exposed to zinc oxide fumes often develop zinc toxicity—nausea, ulceration etc.

Iron : Iron deficiency leads to aiemia which is revealed by a lower hemoglobin content of blood. The optimum hemoglobin evel in adult male is ~ 15g/100 ml blood. Iron deficiency symptoms are retarded growth, sluggsh body functions, loss of appetite. Excess iron deposit in the body may result from cooking bod in iron utensils, repeated blood transfusions. Excess iron is not excreted but remains depsited in liver, spleen and skin.

Copper : This essential element s present as constituent of metalloproteins including metalloenzymes such as ceruloplasmi, hemocyanin, cytochrome c oxidase etc. Our copper requirement comes from green vegetales, cereals, egg, meat etc. Major amount of copper is stored as ceruloplasmin. Wilson's detase (nervous disorder) is caused by failure of binding copper as ceruloplasmin. Excess of unound copper is removed by injecting penicillamine when copper-penicillamine complex is ormed and finally excreted in urine (section 10.20).

Fluorine : It occurs as a minor contituent of bone and teeth. – OH and – F have the same size and charge. Therefore –OH group of hydroxyapatite $3Ca_3(PO_4)_2 \cdot Ca(OH)_2$ is substituted by fluorine in fluoroapatite $3a_3(PO_4)_2 \cdot CaF_2$. Presence of fluorine resists decay of tooth enamel and dental decay. Presencof small amount of fluoride in water works against dental decay. However, high level of fluorde in drinking water (>2 mg/*l*) may cause damage to tooth enamel and may jeopardise noial functioning of some enzymes. Fluorosis is development of abnormal conditions caus by fluorine and its compounds when persent in drinking water far beyond optimum tolerle limit. Contamination of drinking water by fluorine occurs in areas where the wa- passes through underground rocks having fluorapatite. Hot springs may have even hlorfluoric acid.

Iodine : Most of the iodine (~ 20 mg) in ults is bound to the protein thyroglobin present in the thyroid gland located at the base of e neck. The thyroid gland produces iodine – containing hormone. The normal daily requirent (~ 100 microgram) of iodine comes from vegetables, fruits, drinking water. Soil and ver and hence plants, vegetables etc. at high altitude have less iodine than at planes. Iodine ficiency leads to goiter—abnormal swelling of the thyroid gland. Dietary intake should supplanted with a regular consumption of iodised salt which is NaCl with a little of N and $NaIO_3$.

Biological processes are highly poised and nchronised reactions. Any imbalance, say in the intake of essential elements, may lead to tabolic disorder which in turn may inhibit growth and end up in diseases.

Undesirable accumulation of certain metals living systems may be rectified through complexing ligands.

Nature's selection of Zn in this nucleic acid binding protein is quite unique. Zn(II) is inert in terms of redox activity which cauld damage the DNA [as in the case of Fe(III) and Cu(II)]. Other softer and heavier metal ions would bind the DNA - bases (as ligands) of DNA preferably to destruct the helical structure.

Several Zn-dependent DNA and RNA polymerarses are now established and Zn(II) may play some roles to stabilise the structure of these genetic molecules. Zn-antagonists such as Cd, Pb can induce disturbance in genetic expression at the molecular level. Male fertility depdnds on Zn-content in seminal fluid. The birth weight and head circumference are also found to depend on placental content of Zn. *In fact, pregnant mothers require a higher dose of Zn.* Thus there are several evidences to support the fact that *Zn is* **a growth factor**. Some types of schizophrenia (mental disease) arise due to low levels of Zn. In such cases, administration of $ZnSO_4 . 7H_2O$ can improve the situation.

Nutritional Zn-deficiency is quite common in UK and other countries. Zn-deficiency in diets is due to the following causes :

(i) Use of phosphate fertilisers converts Zn^{2+} to insoluble $Zn_3(PO_4)_2$ which renders Zn less readily available to the growing plants.

(ii) Decreased organic contents in the agricultural soils reduces the Zn-uptake capacity of plants. Natural organic chelating agents can solubilise the different metal ions including Zn(II) into suitable forms for plant uptake. In UK, the organic content of common agricultural land has decreased to 2-4% in comparison with 10-20% for typical virgin grassland.

(iii) Due to the lack of recycling Zn to soils.

Much of the zinc in animals and plants is believed to offer only the structure forming properties towards many proteins.

Table 3.4.1.1

Some representative Zn-dependent enzymes

Enzyme	Metal	Reaction catalysed
Carboxypeptidase	Zn^{2+}	Hydrolysis of C-terminal peptide linkage
Leucine aminopeptidase	Zn^{2+}	Hydrolysis of leucine N-terminal peptide linkage
Neutral protease	Zn^{2+}, Ca^{2+}	Hydrolysis of peptides
Dipeptidase	Zn^{2+}	Hydrolysis of dipeptides
Thermolysin	Zn^{2+}, Ca^{2+}	Hydrolysis of peptides
Phospholipase C	Zn^{2+}	Hydrolysis of phospholipids
β-Lactamase II	Zn^{2+}	Hydrolysis of β-lactam ring
α-Amylase	Zn^{2+}, Ca^{2+}	Hydrolysis of glucosides
Phosphatases	Zn^{2+}, Mg^{2+}	Hydrolysis of phosphate esters
Purple acid phosphatase (PAP) (in bean)	Fe^{3+}, Zn^{2+}	Hydrolysis of phosphate ester
Carbonic anhydrase	Zn^{2+}	Hydration of CO_2 and dehydration of H_2CO_3
DNA-polymerase	Zn^{2+}, Mg^{2+}, Mn^{2+}	Polymerisation of DNA with the formation of phosphate ester
Alcohol dehydrogenase	Zn^{2+}	Hydride transfer from alcohol to NAD^+
Adenosine deaminase	Zn^{2+}	Hydrolysis of adenosine
Cytidine deaminase	Zn^{2+}	Hydrolysis of cytidine

2.4 THE ROLE OF METAL IONS IN THE BASIC BIOLOGICAL REACTIONS

The most important basic biological reactions are : *photosynthesis, respiration, nitrogen fixation, release and storage of metabolic energy.*

Photosynthesis (Sec 8.5) : In this process, solar energy is converted into chemical energy. The overall process involves the reduction of CO_2 into carbohydrates and oxidation of H_2O to O_2 in the presence of sunlight. The *plant green pigment chlorophyll* actively participates in this process. The active site of chlorophyll contains Mg^{2+} bound to the macrocyclic ring, *chlorin* (a modified porphyrin ring). In the photolysis of water, an enzyme containing a *polynuclear Mn-cluster* actively participates in the photosynthetic reaction. In the electron transport process, several metalloproteins like *ferredoxins, i.e.* Fe-S proteins (Fe^{2+}/Fe^{3+}), *cytochromes* (Fe^{2+}/Fe^{3+}), *plastocyanin* (Cu^{+}/Cu^{2+}) are also required.

Respiration (Sec 8.1) and O_2 utilisation (Sec 5.4 and 5.5) system : Respiration is an important process for the survival of living system. In this process, food stuff (produced in photosynthesis) is oxidised by O_2 to CO_2 and H_2O (starting materials for photosynthesis), and during this redox process, energy is released and it is stored in ATP. This is why, respiration is also described as ***oxidative phosphorylation***. Several electron carriers participate in the *electron transport chain* to carry the electrons from one end (*i.e.* food stuff) to the other end (*i.e.* O_2). Many metalloproteins participate in this electron transport chain. These are : *ferredoxins, i.e.*. Fe-S proteins (Fe^{2+}/Fe^{3+}), *several cytochromes* (Fe^{2+}/Fe^{3+}), *cytochrome c oxidase* (Fe^{2+}/Fe^{3+}; Cu^{+}/Cu^{2+}) which is present at the terminal position (*i.e.* O_2 end) and it shows *the oxidase activity* (*i.e.* it catalyses the reduction of O_2 to H_2O). It has been discussed in Sec. 7.6.

The O_2 required in respiration is transported and stored by *hemoglobin* and *myoglobin respectively* (in the higher forms of life). The other O_2 uptake proteins are *hemerythrin* and *hemocyanin* (in the lower forms of life). Hemoglobin, myoglobin and hemerythrin are Fe-containing proteins; and hemocyanin is a Cu-containing protein. All these O_2 uptake metalloproteins have been discussed in Chapter 5. The CO_2 produced in respiration is hydrated to bicarbonate (HCO_3^-) and it is transported to lungs. On protonation, HCO_3^- is converted into H_2CO_3 in lungs and H_2CO_3 ultimately decomposes to give away CO_2. The hydration of CO_2 and dehydration of H_2CO_3 are catalysed by a Zn-containing enzyme called *carbonic anhydrase* (Sec 6.13). In CO_2 transport process, hemoglobin also plays some important roles (Sec 5.6).

Due to the partial reduction of O_2, several toxic substances like *superoxide* (O_2^-) and *hydrogen peroxide* (O_2^{2-}) are produced. The Fe(III)-containing enzymes *catalase* and *peroxidase* (Sec. 7.9) manage to detoxify the toxic substance hydrogen peroxide; and the metalloenzyme *superoxide dismutase* (Sec. 7.8) which contains both Cu^{2+} and Zn^{2+} catalyses the disproportionation of superoxide to H_2O_2 and O_2. Several *oxygenase enzymes* (Sec 7.11) are known to catalyse the reactions of O_2 with the organic substances in which the oxygen atoms from O_2 are incorporated into the final products. The oxygenase enzymes require different metal ions like *heme iron, nonheme iron, copper* or *manganese*. Fe(III)-containing *cytochrome P-450* (an oxygenase enzyme) has been discussed in detail in Sec 7.7.

Nitrogen fixation (Sec 8.3) : Nitrogen fixation in plants is an important biological phenomenon. *Nitrogenase* enzyme containing Mo and Fe catalyses the process in the roots of some *leguminous plants.* The process leads to the reduction of atmospheric dinitrogen (N_2) to ammonia which is used in different biochemical processes to produce other nitrogenous compounds.

Regulation of metabolic energy : When energy is released in a biochemical process (*e.g.* respiration), the energy is stored in ATP through the phosphorylation of ADP. In the energy requiring processes like mechanical work, active transport, biosynthetic work, the energy is obtained from the hydrolysis of ATP to ADP. Thus, ATP *acts as a carrier of biochemical energy.* The hydrolysis of ATP is catalysed by Mg^{2+}. Sometimes, ATP is used in *phosphorylation process* (*i.e. phosphate group transfer process*). In fact, some substances are chemically activated on phosphorylation. This process is catalysed by the Mg(II)-containing enzyme *kinase*.

Metal ions in other biochemical functions : The metal ions are used in a variety of biochemical processes. These are: construction of structural material, nerve impulse creation and its propagation, blood clotting, biosynthesis of macrocyclic rings through template reactions, different hydrolytic reactions, different redox reactions, etc.