CH524: bioinorganic chemistry

What do you think is bioinorganic chemistry?

Progressive modification of Nomenclature

1960s - Inorganic biochemistry

1980s - Bioinorganic Chemistry

2000 - Biological Inorganic Chemistry

What would we roughly cover in this course?

INTRODUCTORY ASPECTS

Introductory awareness of the role of metal ions in biology and medicine

Very general features of coordination chemistry, bio-molecules, spectral and biochemical techniques

BIOINORGANIC CHEMISTRY APPROACH

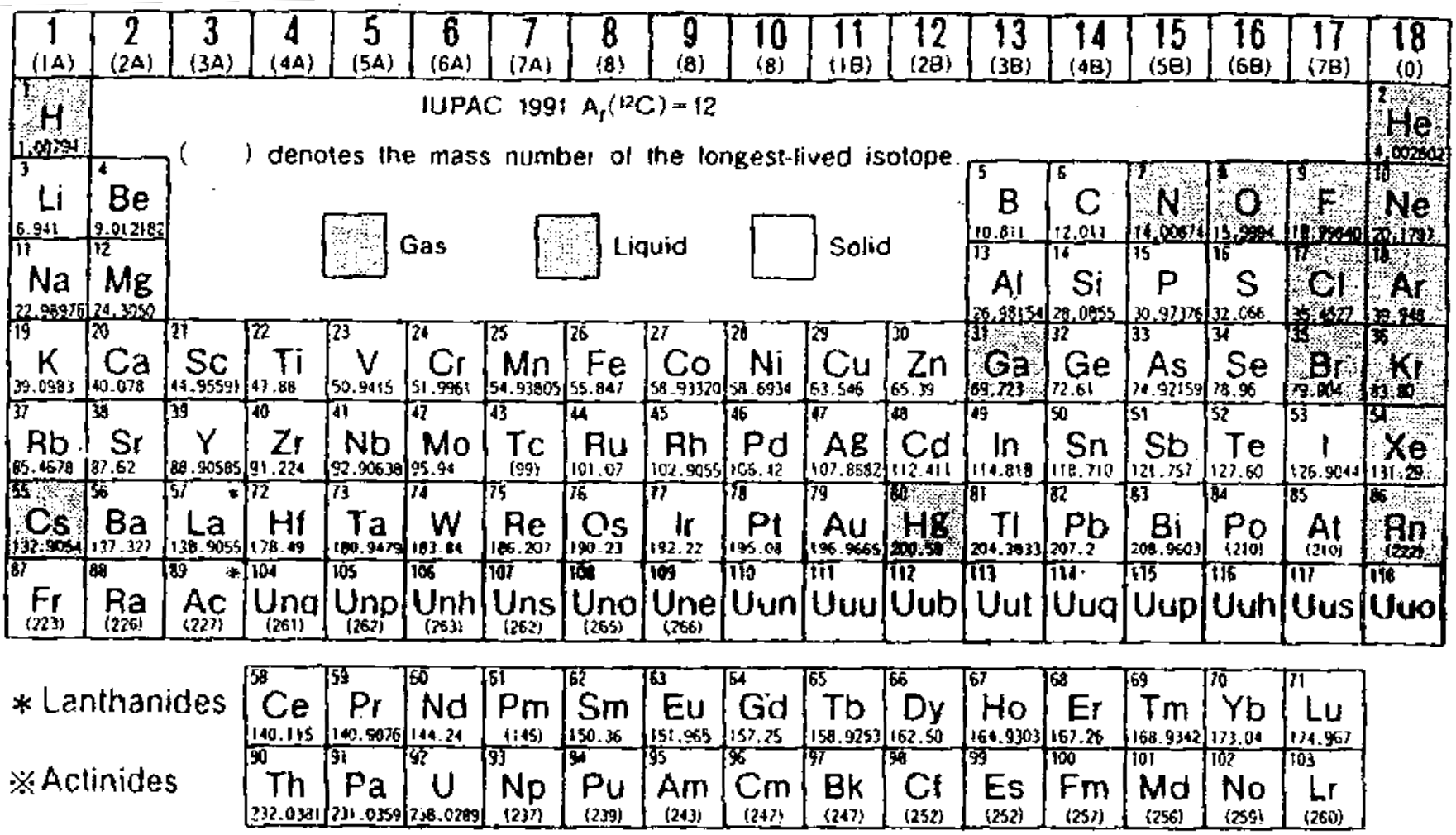
Metalloproteins, metalloenzymes & metal activated enzymes

Some anion based aspects

Metalloproteins, metalloenzymes and metal activated enzymes

- Transport of alkali and alkaline earth ions and functioning of ATPases
- Toxic role of chromium
- Vanadium in haloperoxidases and nitrogenases
- Role of manganese in the oxygen evolution cluster of photosystem – II
- Iron proteins & Enzymes: Transport & storage;
- Porphyrin and non-porphyrin based: Electron Transport; Monooxygenases, Dioxygenases; Phosphatases; Reductases; Superoxide dismutase
- Cobalt: Cobalamine based enzymes
- Nickel: Urease; Hydrogenases; Carbonmonooxide Dehydrogenases
- Copper: Electron Transport; Oxidases; Monooxygenases; Dioxygenases; Various types of copper centers; Super oxide dismutase
- Zinc: Hydrolases; Peptidases; Lyases; Ligages; Oxido-reductases; Transferases
- Molybdenum: Nitrogenase; all types of Oxido-reductases
- Selenoenzymes (if time permits)

Periodic table



Aspects concerned in bioinorganic chemistry

- Which are the elements ESSENTIAL for living cells in biology?
- What AMOUNTS are these present?
- How are these CHOSEN?
- Are there any MUTUAL INTERACTIONS AMONG these elements of biology? (either cooperatively or antagonistically?)
- HOW and WHERE are these present in biological systems?
- WHAT do these elements DO in biological systems?
- HOW do these elements DO THOSE FUNCTIONS/JOBS?

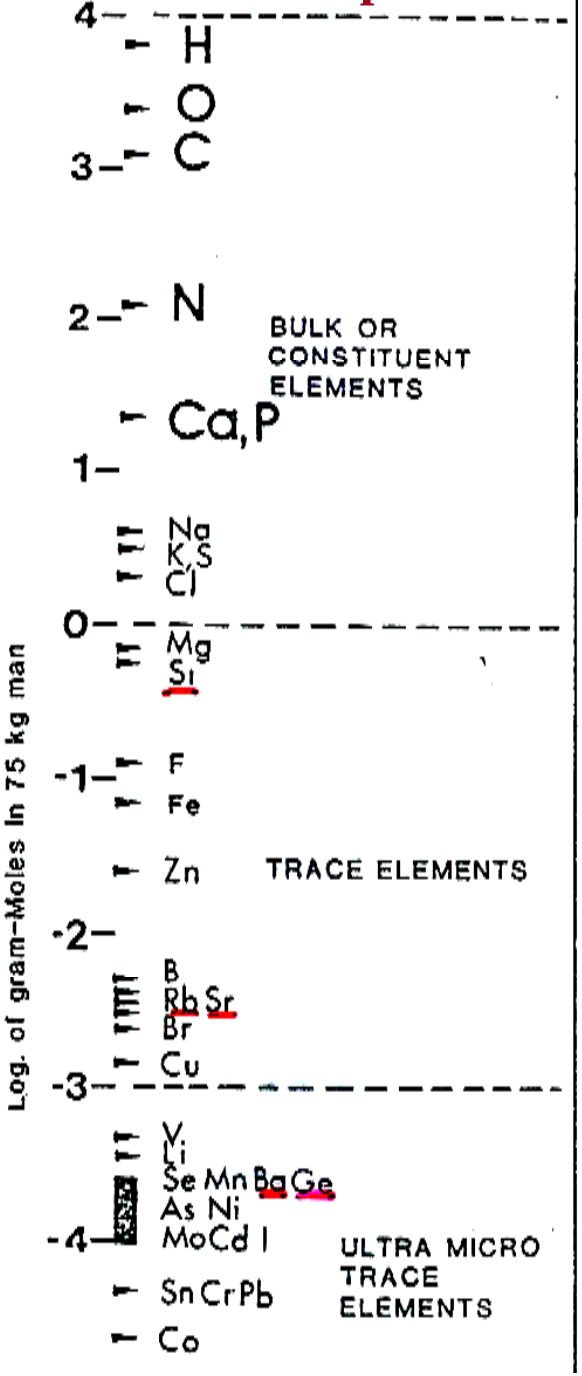
Recent Concerns

- HOW important is that particular element in that particular function?
- WHAT HAPPENS when you replace that element of biology by a different one?
- WHAT HAPPENS when you replace that particular binding site or amino acid residue by another?

Chronological order of the discovery of the essential elements of biology

Iron	17th century
Iodine	1850
Copper	1928
Manganese, Zinc, Cobalt	1931-35
Molybdenum, Selenium, Chromium	1953-59
Tin, Vanadium, Fluorine, Silicon	1970-72
Nickel, Arsenic	1974-75
Lithium, Bromine, Cadmium, Lead	Essentially was not well proven
Tungsten	1985

Elemental Composition of Humar



Element	g/man
Main group metals	
Sodium	70
Potassium	250
Magnesium	42
Calcium	1 700
Transition series metals	
Vanadium	<0·1
Chromium	<0·1
Manganese	<1
Iron	~6
Cobalt	1–2
Nickel	<0·1
Copper	<1
Zinc	1–2
Molybdenum	<1
Main group elements	
Hydrogen	6 500
Carbon	12 500
Nitrogen	1 815
Oxygen	43 550
Phosphorus	680
Sulphur	100
Chlorine	115
Iodine	<1
Silicon	≤1
Bromine, fluorine, selenium and tin	<1 g in toto
Others	
Arsenic, cadmium, lead and polluting metals	~1 g in toto

Intake and/or utility of metal ions in life

(those other than through food particularly through drug preparations)

Element	Compound as	Used for
Al	Hydroxide	antacid
	Silicate	antidiarrhoeal
Sb	Gluconate	antileishmaniasis
Bi	Tripotassiumdicitrate	antacid & antiulcer
B	Boric acid	antifungal
Co	Vitamin B12	pernicious anaemia
Fe	Glycine sulphate	Iron deficiency – anaemia
Au	Thiomalate	antiarthritis
Mg	sulphate, hydroxide	laxative, antacid
Pt	dichlorodiammine	antineoplastic disorders
Se	sulphate	antidandruff
Ag	sulphadiazene	antibacterial
Sn	Fluoride	anticaries
Zn	sulphate	nutrition & wound healing

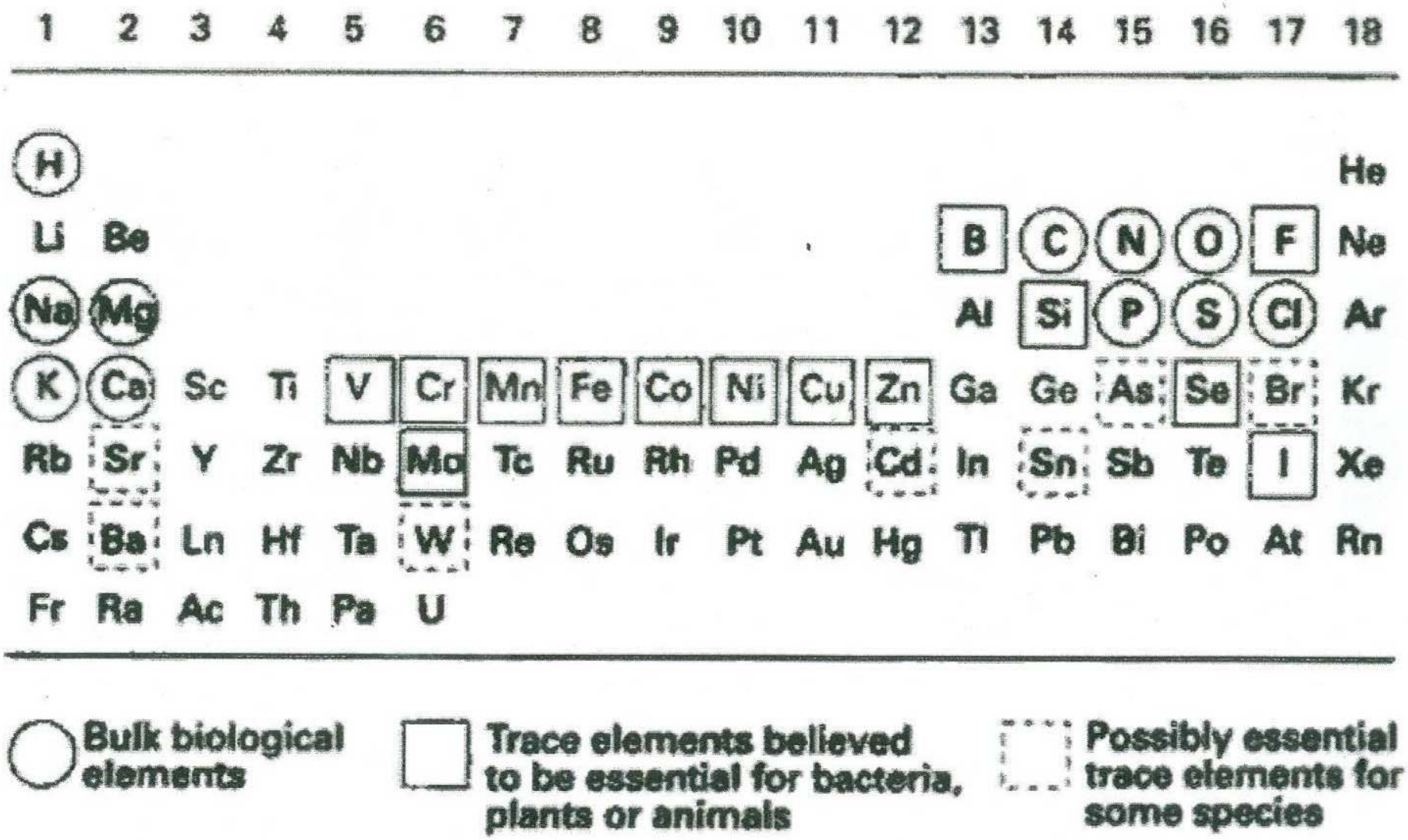
Criteria for ESSENTIALITY of Elements in biology

- Should be present in the tissues of different animals at comparable concentrations
- A specific biochemical function (structural or catalytic or regulatory type) should be associated with that particular element
- Physiological deficiency appears when the element is removed from a purified diet
- The deficiency can be relieved by the addition of that specific element

Additional Criterion that needs to be met before the element is accepted as essential is

- The essentiality of that particular element should be demonstrated by at least two research groups

Periodic Table Relevant to Biology



Elemental concentrations present in body, blood, sea water, earth crust

Table of quantitative parameters of various elemen

Sr. No.	Element	Total body (70 kg adult) (g)	(ppm)	Blood plasma (ppm)	Sea water (ppm)	Earth's crust (ppm)
BIOLOGICAL						
(A) Bulk Structural Elements:						
1.	H	7000	100000	–	110000	1400
2.	C	16000	230000	–	28	200
3.	N	1800	26000	–	0.5	20
4.	O	43000	610000	–	900000	500000
5.	P	780	11000	–	0.07	1000
6.	S	140	2000	–	885	260
(B) Macrominerals :						
7.	Na	100	1400	3220	10500	28300
8.	K	140	2000	74	380	25900
9.	Mg	19	270	24	1350	20900
10.	Ca	1000	14000	120	400	36300
11.	Cl	95	1200	3550	19000	130
(C) Trace Elements T						
12.	Fe	4	60	1.1	0.01	50000
13.	Zn	2–3	30–40	1.3	0.007	70
14.	Cu	0.05–0.12	0.7–1.7	1.0	0.003	75
(D) Ultratrace Elements :						
15.	V	0.015	0.2	–	0.002	135
16.	Cr	0.002	0.03	–	0.00005	100
17.	Mn	0.012–0.02	0.17–0.3	–	0.002	950
18.	Co	0.002	0:02	0.12	0.0001	25
19.	Ni	0.01	0.15	–	0.002	75
20.	Mo	0.01	0.15	–	0.01	1.5
21.	Cd	0.05	0.7	–	0.0001	0.2
22.	Sn	0.014	0.2	–	0.0008	2
23.	Pb	0.12	1.7	–	0.00003	13
24.	Li	0.003	0.04	–	0.07	20
25.	F	2.6	37	–	1.3	625
26.	I	0.014	0.2	–	0.06	0.5
27.	Se	0.014	0.2	–	0.0004	0.05
28.	Si	–	–	–	3.0	277000
29.	As	0.007	0.1	–	0.003	1.8
30.	B	0.05	0.7	–	4.6	10
NON-BIOLOGICAL						
1.	Al	–	–	–	0.01	81300
2.	Ti	–	–	–	0.001	4400
3.	Sr	–	–	–	8.0	375
4.	Zr	–	–	–	–	165
5.	Ba	–	–	–	0.03	425

a .. Care is taken to reproduce the quantitative parameter that are most consistent in the literature.

Criteria for the selection of elements

Elemental abundance is not only the determining factor

- Solubility of the element
- Charge type/Oxidation state
- Ionic Radius
- Ligating atoms
- Preferential coordination geometry
- Spin-pairing stablization
- Kinetic reactivity and other controls
- Thermodynamic aspects
- Chemical reactivity

Some essential elements: Syndromes of deficiency & excess

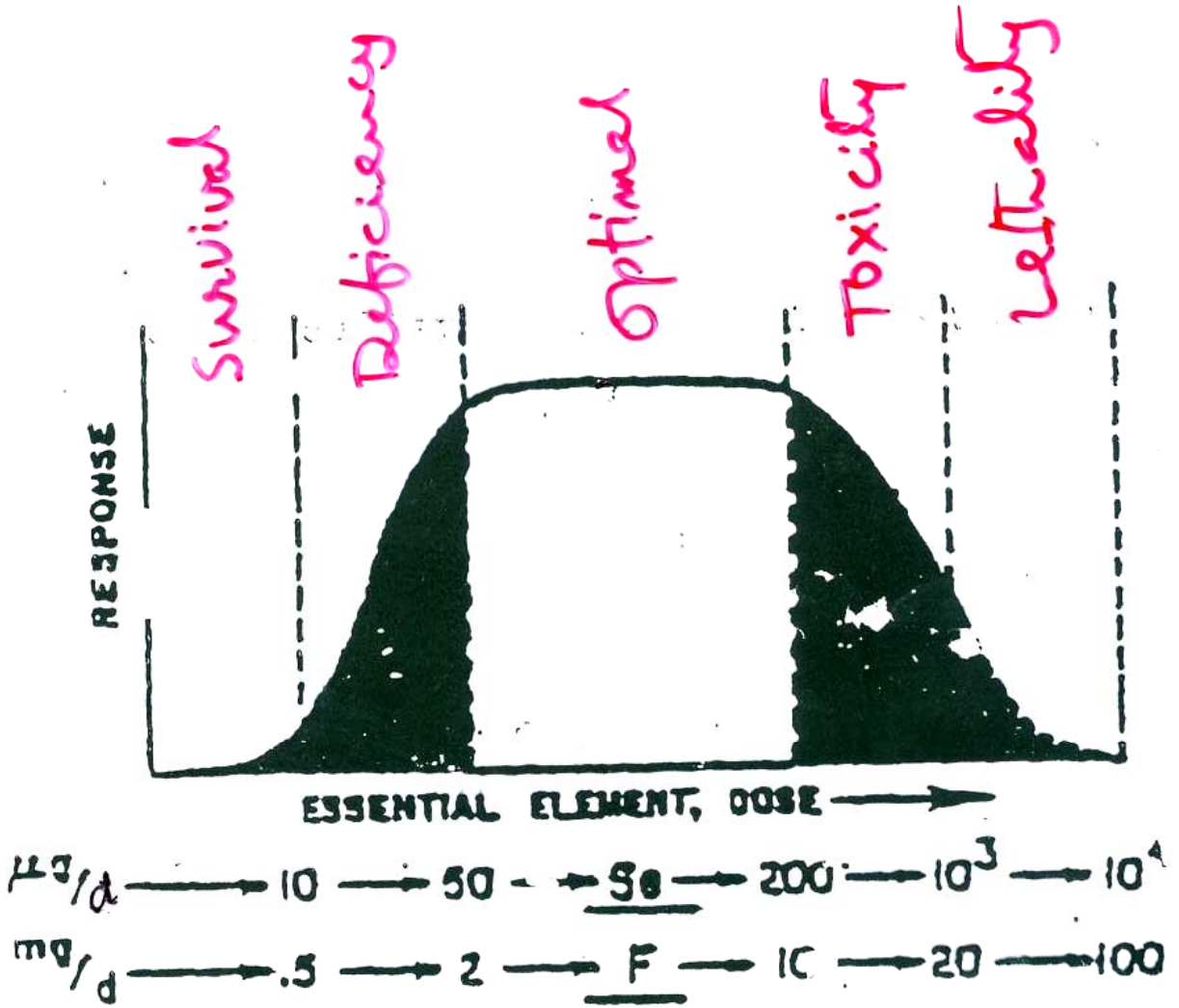
Metal	Intake/day mg
Sodium	4400
Potassium	3300
Magnesium	310
Calcium	1100
Vanadium	~~100~~
Manganese	2.5 to 5.0
Iron	10 to 20
Cobalt	0.3
Nickel	
Copper	2 to 5
Zinc	15
Molybdenum	0.15 to 0.5
Tungsten	

Essential or beneficial element	Disease arising from deficiency	Disease associated with an excess of the element
Calcium	Bone deformities, tetany	Cataracts, gall stones, atherosclerosis
Cobalt	Anaemia	Coronary failure, polycythaemia
Copper	Anaemia, kinky hair syndrome	S.A.K. Wilson's disease
Chromium	Incorrect glucose metabolism	Carcinogenic
Iron	Anaemias	Haemochomatosis, siderosis
Lithium	Manic depression	
Magnesium	Convulsions	Anaesthesia
Manganese	Skeletal deformities gonadal dysfunctions	Ataxia
Potassium		Addison's disease
Selenium	Necrosis of liver, white muscle disease	Blind staggers in cattle
Sodium	Addison's disease, stoker's cramps	
Zinc	Dwarfism, hypogonadism	Metal fume fever
Polluting element		
Cadmium	–	Nephritis
Lead, Mercury	–	Anaemia, encephalitis, neuritis

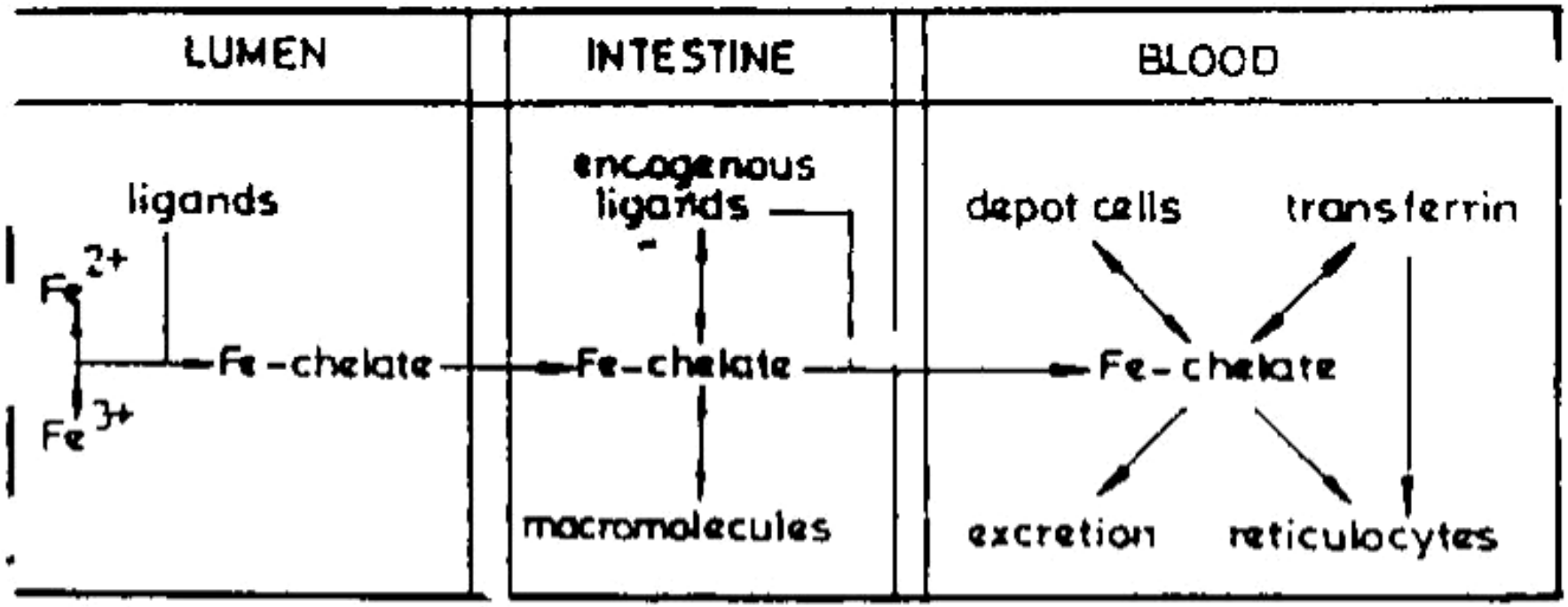
Intake per day

Metal	Intake/day (mg)
Sodium	4400
Potassium	3300
Magnesium	310
Calcium	1100
Vanadium	~~100~~
Manganese	2-5 5.0
Iron	10 6 20
Cobalt	0.3
Nickel	
Copper	2 to 5
Zinc	15
Molybdenum	0.15 0.5
Tungsten	

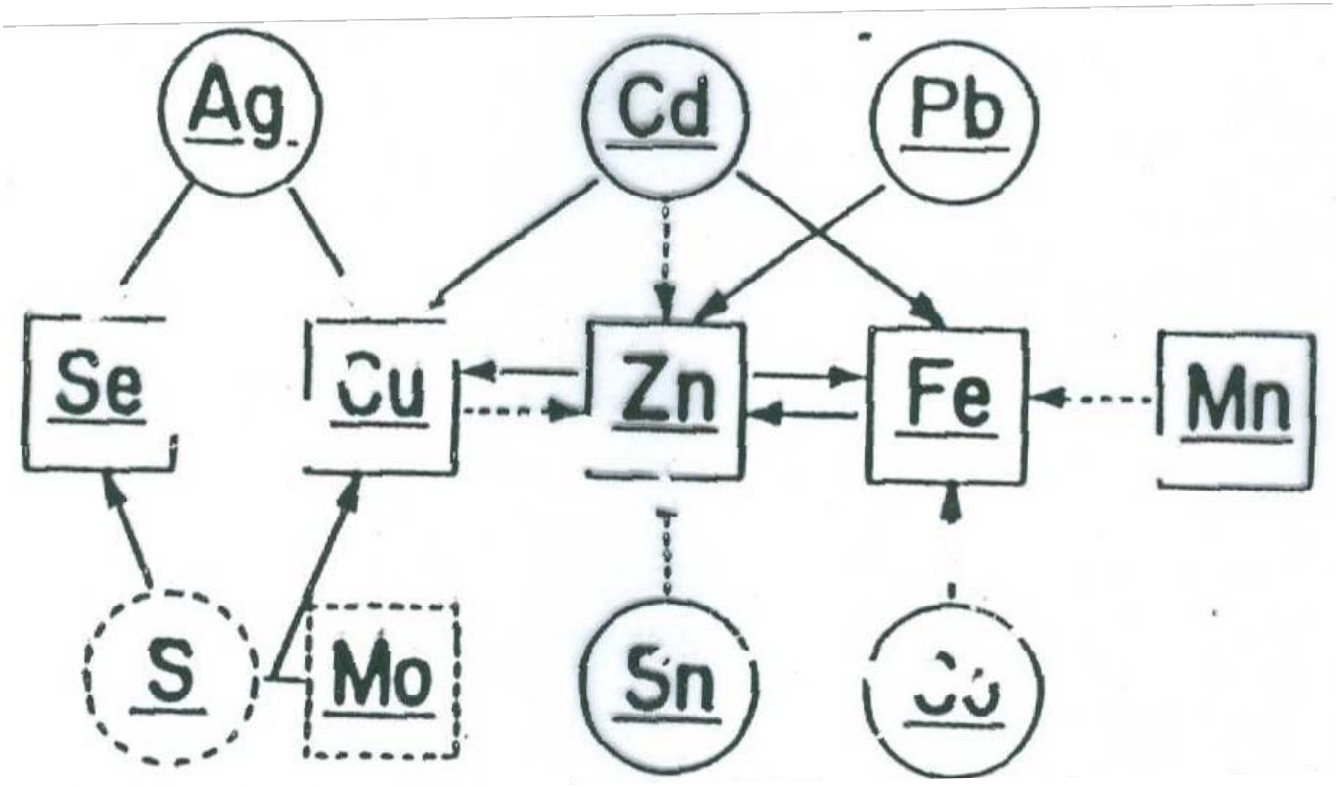
Dose – Response Relation (Bertrend's plot)



Iron absorption by intestines and release into blood



Antagonism among different metal ions during uptake



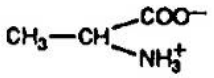
Synergism among different metal ions during uptake

Increasing intake of copper in creases the hemoglobin as the same is coupled with the increase uptake of iron through its mobilization

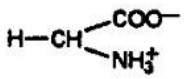
Naturally occurring amino acids

Nonpolar

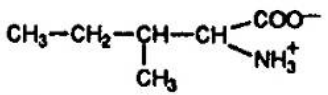
Alanine (Ala, A, 89)



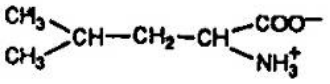
Glycine (Gly, G, 75)



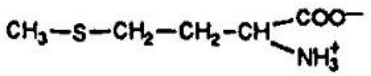
Isoleucine (Ile, I, 131)



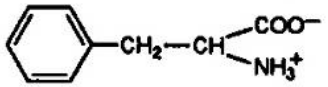
Leucine (Leu, L, 131)



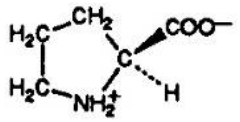
Methionine (Met, M, 149)



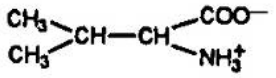
Phenylalanine (Phe, F, 165)



Proline (Pro, P,115)

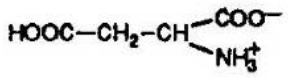


Valine (Val, V, 117)

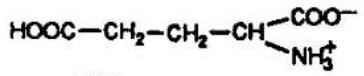


Acidic

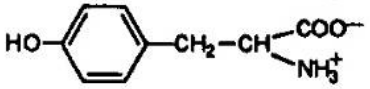
Aspartic acid (Asp, D,132)



Glutamic acid (Glu, E,147)

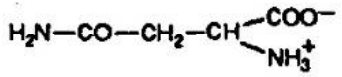


Tyrosine (Tyr, Y,181)

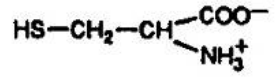


Neutral - polar

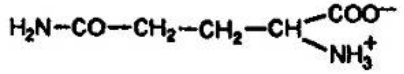
Asparagine (Asn, N, 132)



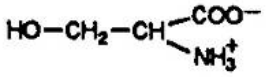
Cysteine (Cys, C, 121)



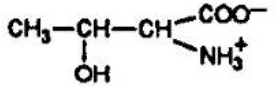
Glutamine (Gln, Q, 146)



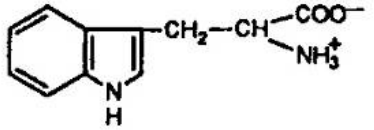
Serine (Ser, S,105)



Threonine (Thr, T, 119)

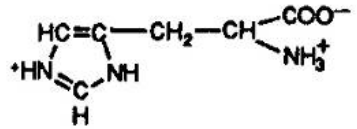


Tryptophan (Trp, W, 204)

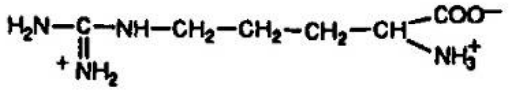


Basic

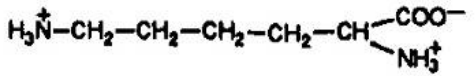
Histidine (His, H,155)



Arginine (Arg, R,174)



Lysine (Lys, K,146)



Protein groups which participate in metal ion binding

Ionizable group	Location/Residue	Intrinsic pKa
α-COOH	Carboxyl terminal	3.5 – 4
β,γ-COOH	Aspartic (Asp) & Glutamic (Glu)	4 – 5
Imidazole	Histidine (His)	6 – 8
α-NH_3^+	Amino terminal	7.5 – 8
Sulfhydryl (-SH)	Cysteine (Cys)	10
ε-NH3+	Lysine	10
Phenolic	Tyrosine (Tyr)	9.5 – 10.5
Guanidine	Arginine (Arg)	12
Hydroxyl (-OH)	Serine (Ser), Threonine (Thr)	12 - 14

Some metal ion binding motifs in biology (in proteins)

Donor groups of protein side chains —CONHCHCONH—
X

Oxygen donors

Aspartic acid —CH_2CO_2H

β-Hydroxyaspartic acid —$CH(OH)CO_2H$

Glutamic acid —$CH_2CH_2CO_2H$

γ-Carboxyglutamic acid —$CH_2CH(CO_2H)_2$

Tyrosine —CH_2–C$_6$H$_4$–OH

Serine —CH_2OH

Nitrogen donors

Histidine —CH_2–imidazole

Lysine —$CH_2CH_2CH_2CH_2NH_2$

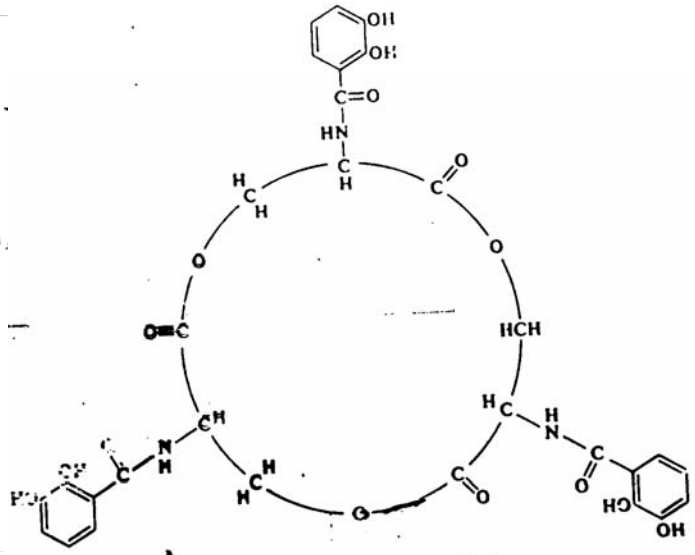
Arginine —$CH_2CH_2CH_2NH$–C(=NH_2^+)–NH_2

Amino terminus
Deprotonated peptide

Sulfur donors

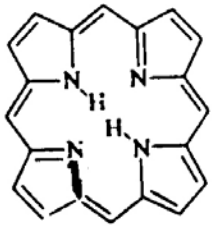
Cysteine —CH_2SH

Methionine —$CH_2CH_2SCH_3$

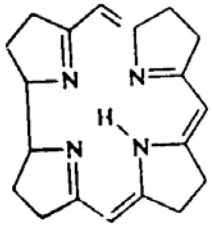


Enterochelin, an iron carrier

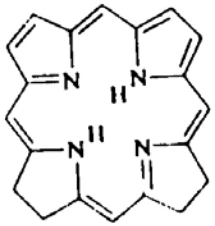
Tetrapyrrole macrocycles:



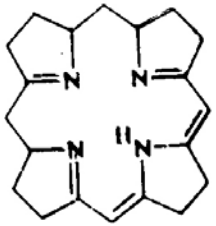
Porphyrin



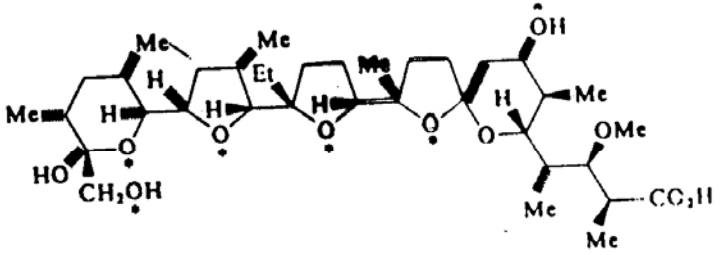
Corrin



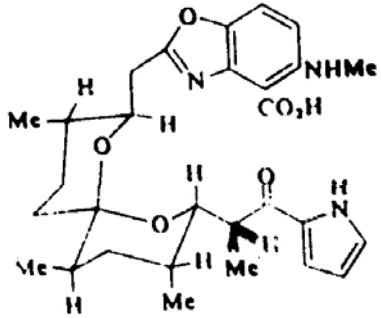
Chlorin



Factor 430

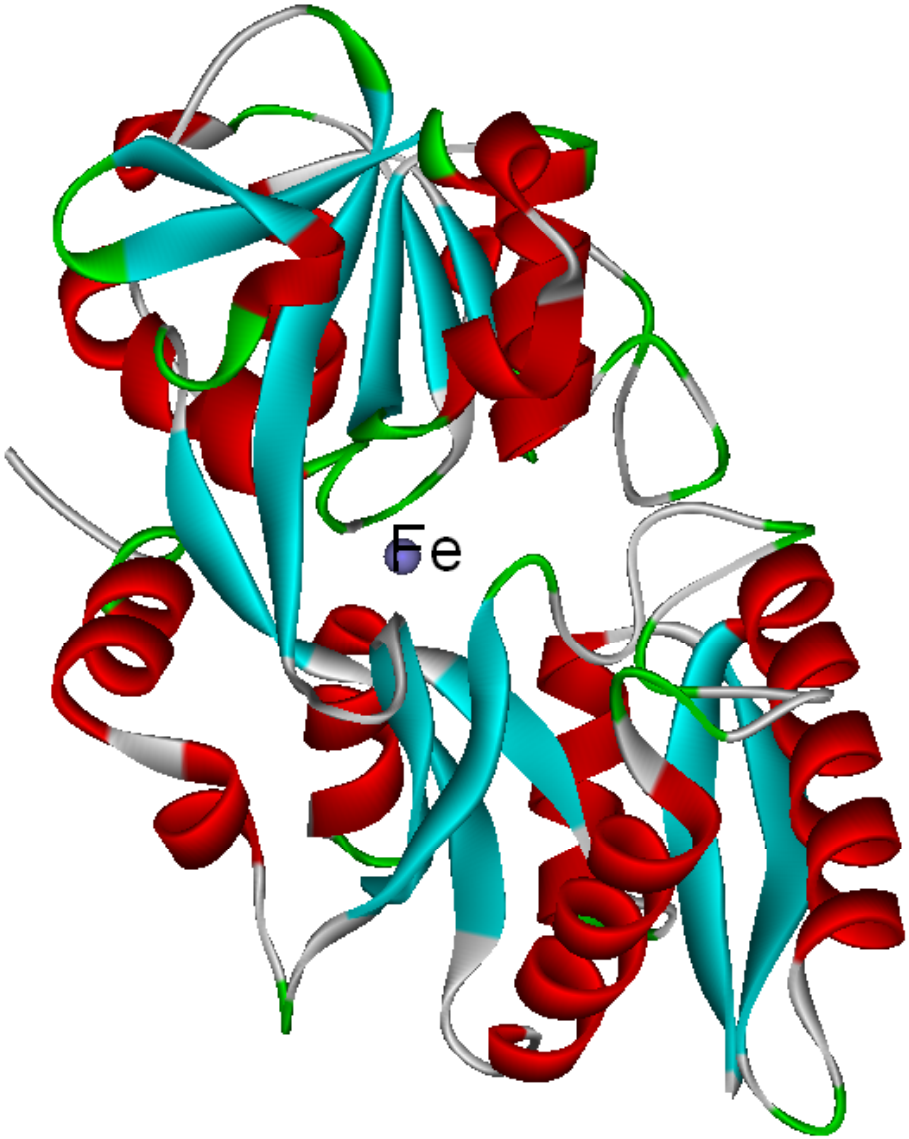


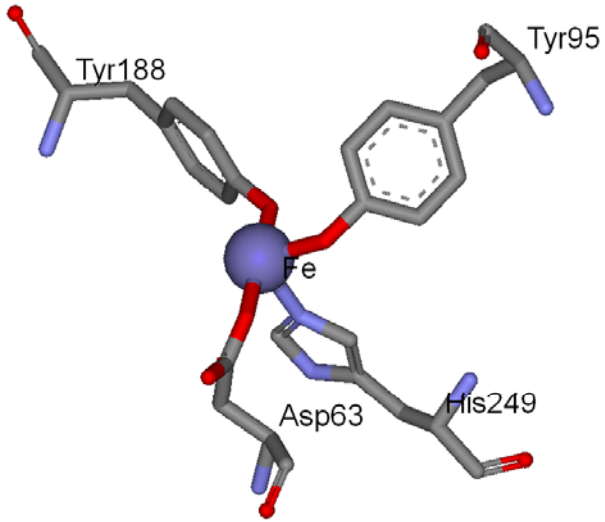
Monensin, a sodium-binding monocarboxylic acid ionophore



A23187, a calcium-binding ionophor

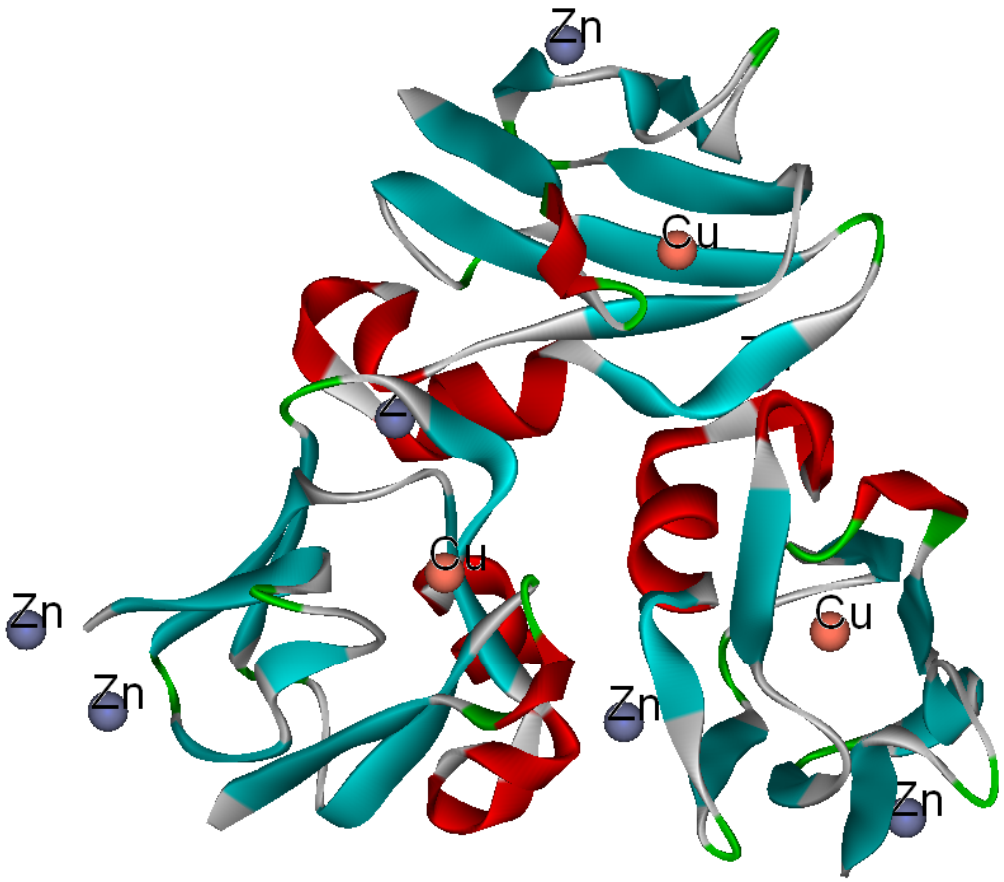
Structure of human serum transferrin – Coordination about Fe

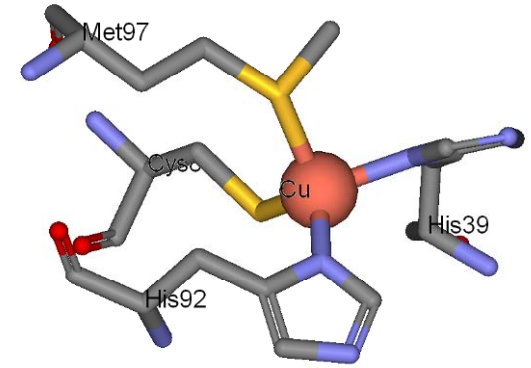


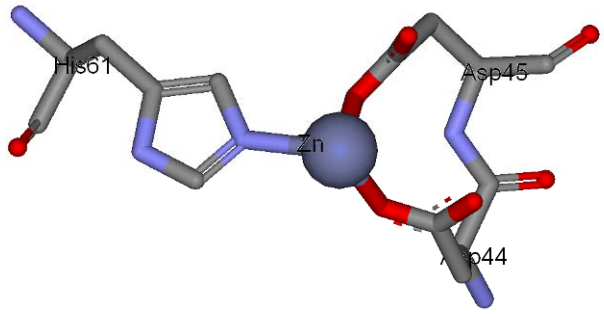


HUMAN SERUM TRANSFERRIN
pdb code:1a8e

Structure of plastocyanin – Coordination about Cu & Zn

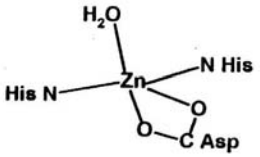




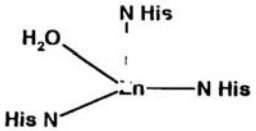


PLASTOCYANIN-pdb code:2w88

Primary coordination spheres in different Zn-enzymes

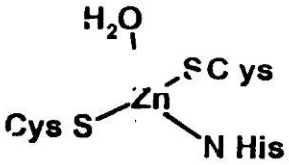


Carboxy Peptidase A

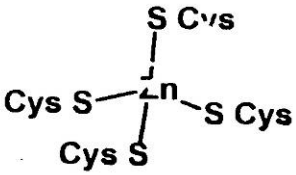


O Tyr

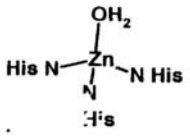
Astacin/Thermolysin



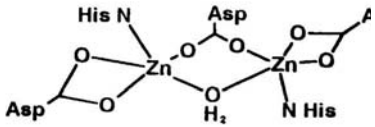
Alcohol Dehydrogenase
(Catalytic Site)



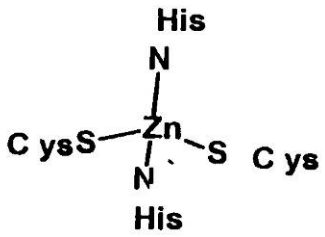
Alcohol Dehydrogenase
(Structural Site)



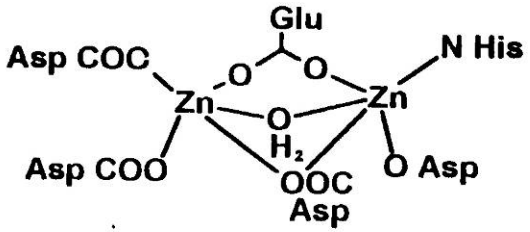
Carbonic Anhydrase



Amir opeptidase

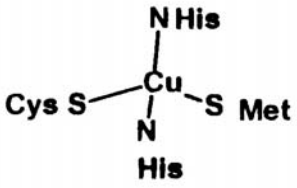


Zinc Fingers

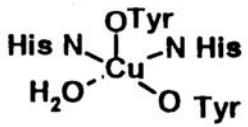


Leucine Aminopeptidase

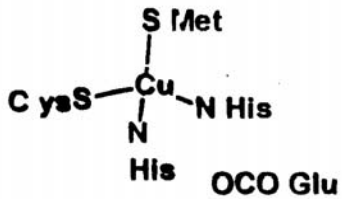
Primary coordination spheres in different Cu-enzymes



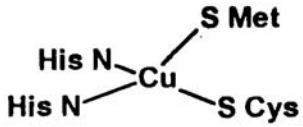
Plastocyanin



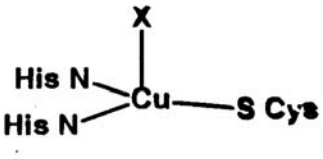
Galactose Oxidase



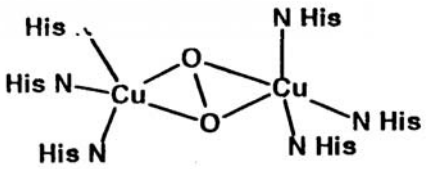
Azurin



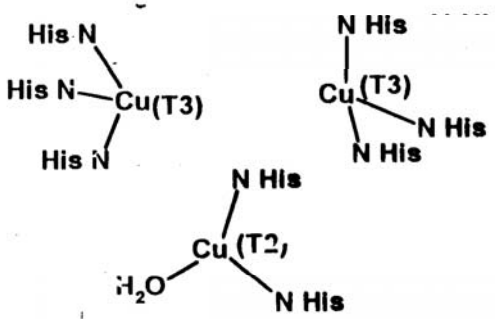
Perturbed Blue Copper Sites

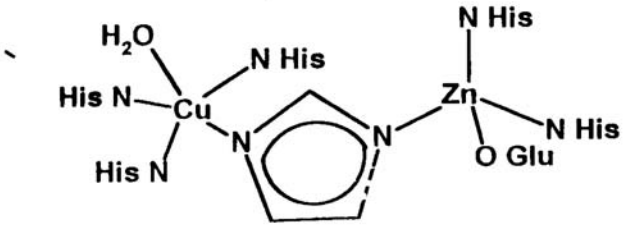


Axially Substituted Blue Copper Sites

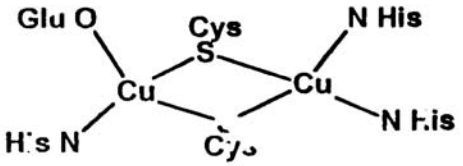


Oxyhemocyanin



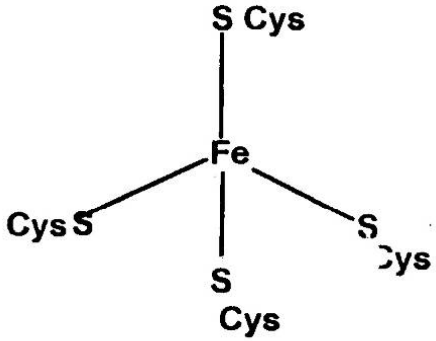


Copper/Zinc Super Oxide Dismutase

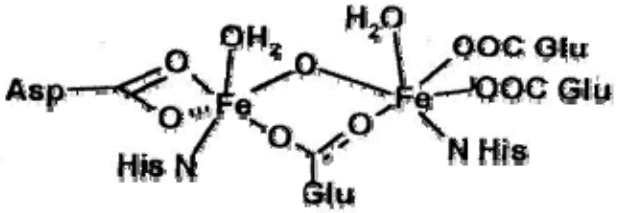


Cytochrome C oxidase

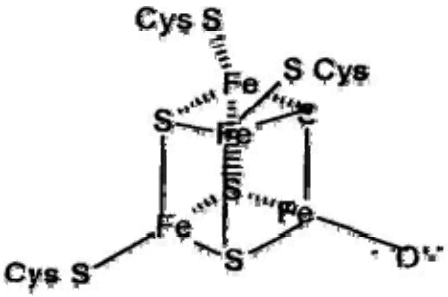
Primary coordination spheres in different Fe-enzymes



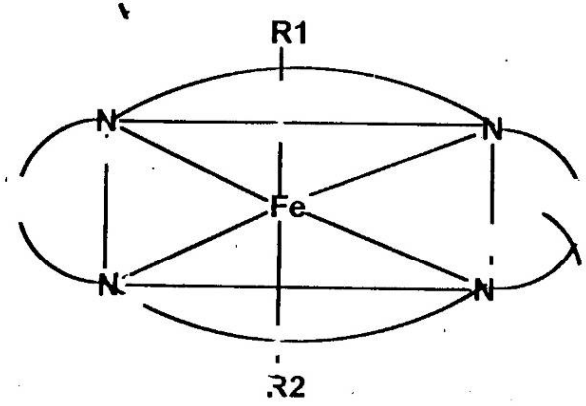
Rubredoxin



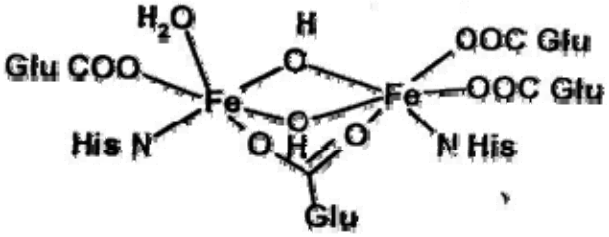
Ribo nucleotide Reductase (oxidized)



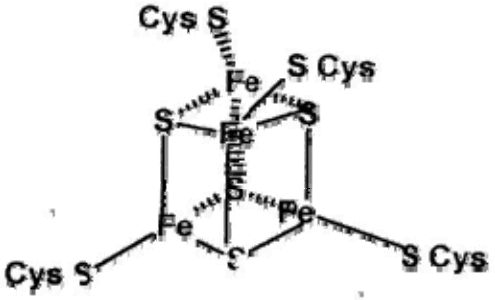
Aconitase



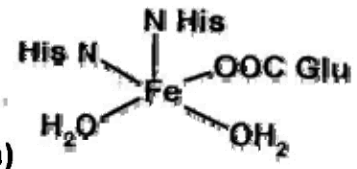
(R1=His,R2= His, Cytochrome C;
(R1=Nil, R2=His, Myoglobin, Hemoglobin)
(R1=Nil, R2=Cys,Cytochrome P450)



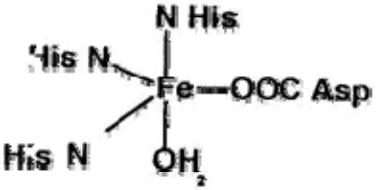
Methane Monoxygenase (oxidized)



[4-Fe,4-S]



Extradiol Dioxygenase



Super Oxide Dismutase

Likely binding groups for biologically active metal ions

ion	Binding group(s)	Geometry
K^+	Singly charged or neutral oxygen ligands	
Mg^{2+}	Carboxylate; Phosphate; Nitrogen ligands	
Ca^{2+}	Carboxylate particularly ‘gla’ proteins proteins; Less affinity than Mg^{2+} for N-ligands; Phosphate	
Mn^{2+}	Similar to Mg^{2+}	
Mn^{3+}	Imidazole; Tyrosine; sulfur donor (in acid phosphate)	
Fe^{2+}	Porphyrin; S^{2-}; thiols (-SH); NH_2; carboxylates; O^{2-}	
Fe^{3+}	Porphyrin; carboxylate; tyrosine and other phenolic groups; NH_2; S^{2-}; hydroxamic acids; O^{2-}	
Co^{2+}	Corrin	
Ni^{2+}	Porphyrin; -SH	
Cu^{1+}	-SH	
Cu^{2+}	Amines; carboxylates; imidazole	
Zn^{2+}	Imidazole; cysteine (-SH); glutamic acid (COO-)	
Cd^{2+}	Cysteine (-SH)	

General functions performed by essential elements in biology

Metal	Intake/day	Function
Sodium	4400	Charge Carrier, Osmotic Balance
Potassium	3300	Charge Carrier, Osmotic Balance
Magnesium	310	Structure,Hydrolase & Isomerase
Calcium	1100	Structure, Trigger, Charge carrier
Vanadium	~~100~~	Nitrogen Fixation, Oxygenation, Halogenation, ATPase inhibition
Manganese	2.5 to 5.0	Photosynthesis, Oxidase, Structure, Superoxide Dismutase, Dehydrogenase
Iron	10 to 20	Oxygenation and deoxygenation, Dioxygen transport and storage, Electron transfer, Nitrogen fixation, Superoxide dismutase
Cobalt	0.3	Oxidase, group transfer
Nickel		Hydrogenase, Hydrolase, Dehydrogenase
Copper	2 to 5	Oxidase, Dioxygen Transport, Electron Transfer, Oxygenation, Superoxide Dismutase
Zinc	15	Structure, Hydrolase, Oxidoreductases, Transferase, Lipases, Ligases
Molybdenum	0.15 to 0.5	Nitrogen fixation, Oxidoreductases, Oxotransfer
Tungsten		Dehydrogenase

Biological essential ions:

Functions, recommended intake & binding groups

Element	Function(s)	Recommended intake per day (mg)	Binding groups
Sodium	Osmotic balance, charge neutralization, gradients and control mechanisms	4400	Charged or neutral oxygen ligands
Potassium	as above + structure stabilization, enzy activation, etc.	3300	-- do --
Magnesium	Enzyme activation, structure stabilizati etc.	310	Carboxylate; phosphate; nitrogen containing ligands
Calcium	as above + trigger effects	1100	as above, but less affinity for 'N' ligands
Chlorine	As counter charge for cations	5100	
Vanadium	Control of sodium pump; inhibition of AT P-transferances.	-	-
Chromium	Potentiation of insulin, action on carbohydrates and lipids	0.05 to 0.5	
Manganese	Carbohydrate metabolism, superoxide dism pyruvate carboxylase, etc.	2.5 to 5.0	Similar to magnesium. $\underline{Mn}^{3+}$; imidazole, tyrosine, S-donors
Iron	Oxygen, electron transport	10 (males) 18 (Females)	$\underline{Fe}^{2+}$:Porphyrin; S^{2-}; thiols; NH_2; CO_2; O_2 $\underline{Fe}^{3+}$; as above + phenolic groups + hydroxymic acids

Biological essential ions:

Functions, recommended intake & binding groups

Cobalt	Part of vitamin B_{12}	0.3	Corrin
Nickel	Constituent g urease; reduced hemopoiesi: nickel hydrogenase		Porphyrin, SH etc.
Copper	Oxidative enzymes; interaction with iron; linking of elastin	2 to 5	SH; amines; carboxylates; imidazole
Cadmium	Stimulates elon ation factors in ribosome		SH
Zinc	as Lewisacid; structure stabilizrtion;inv in energy metabolism; intranscription and tion	15	imidazole; SH; glutamic acid
Molybdenum	Oxidases; aldehyde, sulfite, xanthine me:	0.15 to 0.5	Oxo, SH and 'N' containing ligands
Lithium	Control of sodium pump		
Tin	(interaction with riboflaven)		
Lead	(many enzyme effects)		SH
Florine	Structure of teeth and bones; replaces OH' inhibits enolase, pyrophosphatase	1.5 to 4	
Iodine	Constituent of thyroid hormones	0.15	
Selenium	Constituent of glutathione peroxidase and enzymes; protection against oxidation of erythrocytes; interaction with heavy meta.	0.05 to 0.2	
Silicon	Calcification; structures rese linconnective tissue and osteogenic cells	3	
Arsenic	increased arginine -> urea + ornithines; me bolism of methyl compounds		
Boron	control of membrane function; nucleic acic synthesis; lignin biosynthesis		

Books where you may find SOME relevant material

S. No	*Name of the book*	*Author(s)*	*Year of Publi-cation*	*Publisher*
1	Bioinorganic Chemistry: a short course	Rosette M. Roat-Malone	2007	John Wiley & sons, Inc.
2	Bioinorganic Chemistry- an inorganic perspective of life	Dimitris P. Kessissoglou	1995	Kluwer Academic Publishers
3	Principles of Bioinorganic Chemistry	Stephen J. Lippard, Jeremy Mark Berg	1994	University Science Books
4.	Inorganic Biochemistry: An Introduction	James A Cowan	1993	VCH
5	Bioinorganic Chemistry	Eckhard Bill	1991	Springer-Verlag
6	Bioinorganic Chemistry	Ivano Bertini	1994	University Science Books
7	Bioinorganic Chemistry: The Biological Chemistry of Transition Metals	Michael Watkinson	2009	John Wiley & Sons, Limited
8	Physical methods in bioinorganic chemistry: spectroscopy and magnetism	Lawrence Que	2000	University Science Books
9	Handbook on metalloproteins	Ivano Bertini, Astrid Sigel, Helmut Sigel	2001	CRC Press
10	Bioinorganic chemistry: transition metals in biology and their coordination chemistry	Alfred Trautwein, Deutsche Forschungsgemeinschaft	1997	Deutsche Forschungsgemeinschaft