UNIT 6

Minerals and Living Systems

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I. OVERVIEW

Minerals are found in every cell, tissue, and organ. They are important constituents of essential molecules such as thyroxine, hemoglobin, and vitamin B_{12}. They serve as critical cofactors in numerous enzymatic reactions, and form the hard mineral complexes that comprise bone. Minerals serve in the maintenance of pH, osmotic pressure, nerve conductance, muscle contraction, energy production, and in almost every aspect of life. While minerals are essential to normal health and development, they can also be toxic. The body defends itself against such toxicity through a variety of mechanisms. For the microminerals, the protective mechanisms center primarily around the regulation of uptake by the mucosal cells of the intestine. Many of the minerals are poorly absorbed and this, in itself, can be viewed as a protection against lethality. This protection is absolutely essential because in many of these same instances the means for excretion is very inefficient, if it exists at all.

Optimal intake is a balance between an intake that is too little and one that is toxic. With some minerals, the range of intake for optimal benefit is very large; for others it is quite small. This is illustrated in Figure 1 that arbitrarily plots a generic function against an intake of a mineral upon which that function depends. This plot has a typical bell-shaped curve with an optimal range in the middle. Almost any mineral function can be plotted in this way. In hemoglobin synthesis, too much iron results in a condition known as hemosiderosis; too little iron results in anemia. Other mineral-related functions likewise can be demonstrated, with the caveat that the body protects itself from excess intake through a reduction in mineral absorption, through deposition in the mineral apatite of bone and through a variety of excretions such as bile, urine, sweat, expired air, hair, and desquamated epithelial cells. Some of these excrements are not usually considered important pathways of excretion, but under toxic conditions they become avenues of loss of the excess mineral.

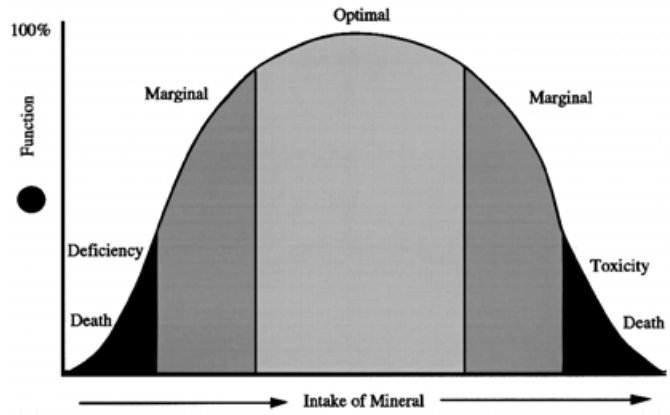

Figure 1 Dependence of biological function on intake of a mineral.

The illustration in Figure 1 is indeed quite simplistic of the need for a given mineral. Just as was discussed in the vitamin units, there are numerous interactions that affect mineral uptake and use. The ratio of calcium to phosphorus, the ratio of iron to copper and to zinc, the ratio of calcium to magnesium, and other factors both mineral and nonmineral affect the mineral status. Some of these interactions are mutually beneficial while others are antagonistic. Most of these interactions occur at the level of the gut in that most are concerned with mineral absorption. For example, zinc absorption is impaired by high iron intakes; high zinc intake impairs copper absorption. Molybdenum and sulfur antagonize copper, tungsten interferes with molybdenum, and so forth. These interactions are itemized in the individual mineral sections. These antagonisms contribute to the relative inefficiency of absorption of minerals that are poorly absorbed and just as poorly lost once absorbed.

II. BIOAVAILABILITY

One concept that nutritionists have developed relates not only to absorption efficiency but also to mineral interactions at the site for absorption and the site of use. This concept is that of bioavailability. Bioavailability is defined as the percent of the consumed mineral that enters via the intestinal absorptive cell, the enterocyte, and is used for its intended purpose. Thus, bioavailability includes not only how much of a consumed mineral enters the body, but also how much is retained and available for use. An example might be the comparison of iron from red meat to the same amount of iron in spinach. Iron from red meat has a greater bioavailability than iron from spinach because it is an integral component of the protein heme. It is this form (heme iron) that is efficiently absorbed and used. The iron in the spinach is bound to an oxalate, and, even though some of this iron can be released from the oxalate, it is in the ferric state and poorly absorbed.

III. APPARENT ABSORPTION

There is another term referring to absorption that is frequently used. That is the term “apparent absorption”. This term refers to the difference between the amount of mineral consumed and that which appears in the feces. Some minerals are recirculated via the bile while others are not. This recirculation, especially in a poorly absorbed mineral, can contribute to the mineral content of the feces, but there is no correction for the biliary contribution to the fecal mineral content. The term “apparent absorption” refers *only* to the difference between intake and fecal excretion.

Table 1 Periodic Table of the Elements

Group	I	II											III	IV	V	VI	VII	0
Period																		
1	H																	He
	1																	2
2	Li	Be											B	C	N	O	F	Ne
	3	4											5	6	7	8	9	10
3	Na	Mg					Transition elements						Al	Si	P	S	Cl	Ar
	11	12											13	14	15	16	17	18
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
5	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
6	Cs	Ba	*	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Ti	Pb	Bi	Po	At	Rn
	55	56	57–71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86
7	Fr	Ra	**															
	87	88	89–102															
*Lanthanide series				La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
				57	58	59	60	61	62	63	64	65	66	67	68	69	70	71
**Actinide series				Ac	Th	Pm	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md		
				89	90	91	92	93	94	95	96	97	98	99	100	101		

IV. THE PERIODIC TABLE AND MINERAL FUNCTION

Of the 109 known elements in the periodic table (Table 1) 30 are essential to life — 19 of these are trace elements and, of these, 12 are transition elements. Transition elements are those which have more than one charged state. For example, iron can exist as the ferrous ion (Fe^{++}) and the ferric ion (Fe^{+++}), while chromium has several oxidation states, as does copper. However, biological systems usually use only one of these states. The multivalent characteristic of iron is unique in that it allows it to serve as an oxygen carrier in hemoglobin or as an hydrogen carrier in enzymatic reactions using an iron-sulfur center within a large structure. Most transition elements are not this variable.

Because of their ionic nature, minerals can form electrovalent bonds with a variety of substances. Although ingested as salts, minerals ionize to their component parts and it is the resultant ions that are absorbed, used, stored, or excreted. For some ions there are very efficient retainment cycles. Sodium, potassium, chloride, calcium, and phosphorus fall into this category. For sodium, potassium, and chloride, conservation is energy driven via the sodium-potassium ATPase. There are several ATPases that serve in this role. The $Ca^{2+}Mg^{2+}$ATPase of the mitochondrial membrane works to optimize the ion content of this organelle. These ATPases are proteins and illustrate a further mechanism of mineral metabolism. As ions, minerals react with charged amino acid residues of intact proteins and peptides. Table 2 provides a list of minerals and the amino acids with which they react. Depending on their valence state these electrovalent bonds can form very strong, moderate, or very weak associations. The marginally charged ion (either an electron acceptor or an electron donor) will be less strongly attracted to its opposite number than will an ion with a strong charge.

Table 2 Mineral-Amino Acid Interactions

Minerals	Amino Acid
Calcium	Serine, carboxylated glutamic acid (GLA)
Magnesium	Tyrosine, sulfur-containing amino acids
Copper	Histidine
Selenium	Methionine, cysteine
Zinc	Cysteine, histidine

Table 3 Hard and Soft Acids and Bases: Some *Properties* that Can Be Used as Guidelines for Classifying Species

ACID (Electron acceptor)			BASE (Electron donor)		
Hart	**Property**	**Soft**	**Hard**	**Property**	**Soft**
Low	Polarizability	High	Low	Polarizability	High
High	Electropositivity	Low	High	Electronegativity	Low
Large	Positive charge or oxidation state	Small	Large	Negative charge	Small
Small	Size	Large	Small	Size	Large
Ionic, electrostatic	Types of bond usually associated with the acid	Covalent, π	Ionic, electrostatic	Types of bond usually associated with the base	Covalent, π
Few and not easily excited	Outer electrons on donor atoms	Several, easily excited	High energy and inaccessible	Available empty orbitals or donor atom	Low lying and accessible

Note: The entire column need not be true before a species is called hard or soft. The more factors that are true, the greater the degree of hardness or softness.

A. Lewis Acids and Bases

In biological systems, the princples of Lewis acids and bases apply. According to this concept, a Lewis base is an ion which has at least one pair of valence electrons available for sharing (an electron donor). A Lewis acid is an ion that can accept or share at least one pair of valence electrons (an electron acceptor). Thus, an acid-base reaction which produces a product is represented as A+:B $\rightarrow$ A:B. The product of this reaction can be called a coordination complex, an adduct, or an acid-base complex. Examples of this type of reaction have already been shown in Units 3 and 4. In particular, the reader should reexamine the structure of vitamin B_{12} where cobalt is held in a coordinate structure involving pterin rings.

Within the Lewis system there is a subdivision of hard and soft acids and bases. The hydrochloric acid released by the gastric parietal cells is an example of a hard acid. It meets the definition because the constituent ions, H^+ and Cl^-, readily polarize, have high electropositivity, have a large positive and negative charge, are small in size, are almost exclusively ionic in their bonding, and have few outer electrons to be donated or accepted. The constituent ions of hydrochloric acid are single-valence ions. In contrast, consider a number of compounds that are soft Lewis acids. These have properties that are the opposite of those listed above. In many instances the electron donor is one of the multivalent ions, i.e., copper or iron, and the electron acceptor is an amino acid or an organic ring structure. Some organic substances can be both an acid and a base. Consider ethyl acetate — it can be a Lewis base when it forms complexes through one of its oxygen atoms to a proton or other Lewis acid. It acts as a Lewis acid when it adds bases such as the hydroxide ion. Tables 3 to 5 provide further information about Lewis acids and bases. These reactions are important mechanisms for the hydrolysis of an ester bond (as in triacylglyceride metabolism) or in understanding the basis for ligand (mineral-protein) formation. Throughout the individual units dealing with the minerals the reader will encounter instances of ligand binding. Many minerals are carried in the blood by specific transport proteins. This is an example of a Lewis acid-base reaction.

The specificity of the transport protein has yet to be unraveled. There are preferred ligand bonding groups, as shown in Table 6, but why these are the preferred groups is not known. There are instances where a transport protein will carry more than one ion. An example is metallothionein, which will carry both zinc and copper. It will also carry some of the heavy metals, but its affinity is greater for zinc and copper. Many of the ions can be chelated by organic materials. Ethylenediaminetetraacetic acid (EDTA) is a potent chelator and is used to remove lead or other heavy metals from the body. It will also chelate calcium and magnesium, so the clinician using EDTA to treat

Table 4 Hard and Soft Acids and Bases: The HSAB Classification of Acids

Hard	Soft
H^+, Li^+, Na^+, K^+	Cu^+, Ag^+, Au^+, Tl^+, Hg^+
Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Mn^{2+},	Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}, CH_3Hg^+, $Co(CN)_5^{2-}$, Pt^{4+}, Te^{4+}
Al^{3+}, Sc^{3+}, Ga^{3+}, In^{3+}, La^{3+}	Tl^{3+}, $Tl(CH_3)_3$, BH_3, $Ga(CH_3)_3$
N^{3+}, Cl^{3+}, Gd^{3+}, Lu^{3+}	$GaCl_3$, GaI_3, $InCl_3$
Cr^{3+}, Co^{3+}, Fe^{3+}, As^{3+}, CH_3Sn^{3+}	RS^+, Rse^+, Rte^+
Si^{4+}, Ti^{4+}, Zr^{4+}, Th^{4+}, U^{4+}	I^+, Br^+, HO^+, RO^+
Pu^{4+}, Cc^{3+}, Hf^{4+}, WO^{4+}, Sn^{4+}	
UO_2^{2+}, $(CH_3)_2Sn^{2+}$, VO^{2+}, MoO^{3+}	I_2, Br_2, ICN, etc.
$BeMc_2$, BF_3, $B(OR)_3$	Trinitrobenzene, etc.
$Al(CH_3)_3$, $AlCl_3$, AlH_3	Chloranil, quinones, etc.
RPO_2^+, $ROPO_2^+$	Tetracyanoethylene, etc.
RSO_2^+, $ROSO_2^+$, SO_3	O, Cl, Br, I, N, Ro*, RO*2
I^{7+}, I^{5+}, Cl^{7+}, Cr^{6+}	M° (metal atoms)
RCO^+, CO_2, NC^+	Bulk metals
HX (hydrogen bonding molecules)	CH_2, carbenes
Borderline	
Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Sn^{2+}, Sb^{2+}, Bi^{2+}, Rh^{2+}, Ir^{2+}, $B(CH_3)_3$, SO_2, NO+, Ru^{2+}, Os^{2+}, $R3^{C+}$, $C_6H_5^+$, GaH_3	

From Pearson, R.G., *J. Chem. Educ.,* 45, 581, 1968. With permission.

Table 5 HSAB Classification of Bases

Hard	Soft
H_2O, OH^-, F^-	R_2S, RSH, RS^-
$CH_3CO_2^-$, PO_4^{3-}, SO_4^{2-}	I^-, SCN^-, $S_2O_3^{2-}$
Cl^-, CO_3^{2-}, ClO_4^-, NO_3^-	R_3P, R_3As, $(RO)_3P$
ROH, RO^-, R_2O	CN^-, RNC, CO
NH_3, RNH_2, N_2H_4	C_2H_4, C_6H_6
	H^-, R^-
Borderline	
$C_6H_5NH_2$, C_5H_5N, N_3^-, Br^-, NO_2^-, SO_3^{2-}, N_2	

Note: The symbol R stands for an alkyl group such as CH_3 or C_2H_5.

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lead overload will have to be aware of this feature as well. Penicillamine is another chelator of importance. It is used to remove excess copper in patients with the genetically inherited disease called Wilson's disease. 2,3-D-Dimercaptopropanol-1 is a chelator of lead, mercury, arsenic, copper, cadmium, tin, and other toxic metals. It solubilizes these metals and chelates them, allowing for their excretion in the urine. The mechanism of action is that of a Lewis base. Other chelates in metabolism are well known: heme, shown in Figure 2, chelates iron, and thus we have heme acting as a Lewis base and iron as a Lewis acid.

The formation of mineral-organic compound bonds is also seen when one examines the roles of minerals in gene expression. Almost every mineral is involved in one or more ways. Mineral response elements (MREs) can be found in the promoter regions of almost all genes encoding products of interest to nutritionists and biochemists. These MREs can be located very near the start site of the structural gene and thus serve as cis-acting transcription factors. Alternatively, they can be located fairly far away from the start site and, indeed, some may be located at sites some distance

Table 6 Preferred Ligand Binding Groups for Metal Ions

Metal	Ligand Groups
K^+	Singly charged oxygen donors or neutral oxygen ligands
Mg^{2+}	Carboxylase, phosphate, nitrogen donors
Ca^{2+}	$=Mg^{2+}$, but less affinity for nitrogen donors, phosphate, and other multidentate anions
Mn^{2+}	Similar to Mg^{2+}
Fe^{2+}	–SH, NH_2 > carboxylates
Fe^{3+}	Carboxylate, tyrosine, $–NH_2$, porphyrin (four 'hard' nitrogen donors)
Co^{3+}	Similar to Fe^{3+}
Cu^+	–SH (cysteine)
Cu^{2+}	Amines >> carboxylates
Zn^{2+}	Imidazole, cysteine
Mo^{2+}	–SH
Cd^{2+}	–SH

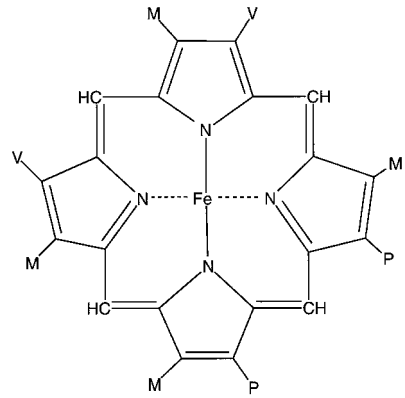

Figure 2 Heme as a chelator of iron. Abbreviations used: A, acetate (CH_2-COO_3H); M, methyl ($–CH_3$); P, proprionate ($–CH_2$-CH_2-COOH); V, vinyl ($–R$-$CH=CH_2$).

away such that there may be intervening noncoding sequences which separate the MRE from the promoter region. In this instance the MRE serves as the bending site for a mineral containing a trans-acting transcription factor. Table 7 provides some examples of minerals and the gene products that require these minerals. Zinc bonds with certain base sequences to form the zinc fingers so necessary for transcription. In fact, a large number of genes are turned on (or off) by these fingers. For example, the vitamin A receptor (RAR, RXR) protein contains several zinc fingers (see Unit 3) without which retinoic acid could not function as a transcription factor. The details of these zinc fingers are provided in the last unit (Unit 8). Minerals can bond either by themselves or in complexes with proteins to inhibit or enhance translation and, lastly, minerals by themselves or in a complex can influence post-translation protein modification. The details, where known, will be provided in the individual mineral sections.

V. MINERAL ABSORPTION AS RELATED TO RDA

Lewis base and acid interactions are at work in the intestine where mineral absorption takes place. Of all the elements needed by mammals, few enter the absorptive cell by passive diffusion. Several are carried into the body by proteins to which the minerals are loosely attached. Iron, zinc, and copper are imported via these transporters. Sodium and potassium enter (or are exchanged) by an ATPase specific for these ions. Chloride, iodide, and fluoride enter by way of an anion-cation

Table 7 Examples of Gene Products That Are Influenced by Minerals

Mineral	Gene Product
Selenium	Glutathione peroxidase 5′-Deiodinase
Copper	Metallothionein
Zinc	Carbonic anhydrase Zinc fingers Zinc transcription factor Metallothionein
Iron	Ferritin Transferrin receptor
Calcium	Calbindin
Potassium	Aldosterone synthetase
Sodium	Cholesterol SCC, a P450 enzyme Endothelin I

exchange mechanism. The uptake of calcium and phosphorus (as phosphate) occurs by a protein-mediated process. It is known that optimal absorption occurs when the calcium:phosphorus ratio is between 1:2 and 2:1 and that an adequate vitamin D supply is essential. As discussed in the section on vitamin D (Unit 3, Section II), intestinal calcium uptake is mediated by a vitamin D-dependent calcium-binding protein. It is suspected that the uptake is also dependent on a phosphorylation/dephosphorylation process; hence, the importance of the calcium:phosphorus ratio.

Although all of these mechanisms of uptake are operative for the minerals, few of the minerals are 100% absorbable. The exceptions are sodium, potassium, chloride, selenium, and magnesium. For the others, the absorption process is dependent on a number of factors: the binding capacity of the transport protein (if needed), solubility, the composition of the diet, the mixture of elements present in the gut contents, and the presence of materials such as phytate and EDTA which bind specific elements thus changing the element mixture presented to the enterocyte, and the actual amount of the element to be absorbed. All of these factors contribute to the bioavailability of the anions and cations that are essential micronutrients. In addition, there are physiological factors (age, hormonal status, and health status) that also influence absorption and subsequent use. Those elements that are variable in terms of their absorption are those that are either divalent or multivalent, that is, ions that have more than one charged state. Iron, copper, and chromium fit into this category while calcium, magnesium, selenium, manganese, zinc, and molybdenum fit into the former category. The Food and Nutrition Board of the National Academy of Sciences took absorption into account when the RDAs for minerals were devised. For example, it has been estimated that between 12 and 50% of the adult calcium intake actually enters the enterocyte and subsequently is available for use. The RDA, therefore, is set at four times this (800 mg/day) to allow for losses in the feces due to incomplete uptake. Those elements where the database on absorption and need is large have an RDA. Those where the database is modest or small (or for the human, nonexistent) do not have an RDA. In some instances where scientists have strong evidence for need as well as evidence of the usual intake by healthy people, there is a recommendation that is defined as being generally agreed to be safe and adequate. A number of the microminerals are in this category.

How are the needs of humans for minerals determined? In contrast to the vitamins, which are not recycled, mineral intake adequacy is extremely difficult to determine. The end points for determining adequate intake are not particularly clear in most instances. Again, absorption is a critical factor. In times of inadequate intake, efficiency of absorption increases as a defense against deficiency. Recycling and retention is another compensatory mechanism that defends the body from an absolute lack of the mineral.

As in studies of the protein requirement, the use of the balance method has some merit. Careful measures of intake and excretion are made and, where possible and necessary, recycling is determined. The use of isotopes as markers has made the measurement of recycling possible. Calcium

Table 8 Elemental Analysis of the Human Body

Element	Serum (mg/ml)	Kidney (ppm)	Element	Serum (mg/ml)	Kidney (ppm)
AL	0.11–0.78	0.35–1.80	K	—	—
Ba	0.025–0.08	0.01[a]	Mn	0.00054–0.061	0.4–2.4
Ca	—	—	Mo	0.006–0.027	0.63,0.4[a]
Co	0.00022–0.062	0.008–0.071	Na	—	—
Cr	0.002–0.02	0.03–0.86	Pb	0.016–0.13	0.27–1.27
Cu	0.97–1.67	1.7–4.15	P	—	—
Fe	0.87–1.87	42–110	Se	0.098–0.327	0.1–3.5
I	0.045–0.100	0.03–0.04	Zn	0.67–1.83	25–67

[a] Only two analyses were available for this element.

and iron requirements have been studied in this way. The measurement of the mineral content of the diet, excreta, and body materials, while tedious and requiring great care to prevent contamination, is straightforward. Atomic absorption spectrometry, arc emission spectrometry, neutron activation, mass spectrometry, X-ray fluorescence spectrometry, and arc emission-flame spectrometry are used with excellent results. Each element has a characteristic electronic signature and thus can be quantitated using these very sophisticated technologies. Several publications have provided the mineral content of the human body. An example of mineral analysis of serum and renal tissue is shown in Table 8.

In the next unit the macrominerals will be discussed in terms of their functions. Microminerals needed in trace amounts will also be discussed.

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