Kirk-Othmer Encyclopedia of Chemical Technology.

MINERAL NUTRIENTS

Minerals that are essential to life are the source of metals and other inorganic elements involved in the most fundamental processes. For example, oxygen, required by the cells of animals, is utilized with the aid of metal complexes. In humans both iron-containing hemoglobin and zinc-containing carbonic anhydrase play pivotal roles in binding oxygen and delivering it to the cells. Moreover, enzymes developed to protect cells from high levels of oxygen also contain metals. One such class of protective enzymes is known as the superoxide dismutases (SODs). These contain metals such as manganese, copper, zinc, and iron (1). Mutations in the copper- and zinc-containing superoxide dismutase gene have been linked to amyotrophic lateral sclerosis (2).

The human skeleton is composed of calcium and phosphorus and traces of other ions, eg, magnesium, sulfur, and sodium, embedded in an organic matrix. The regulation of body fluid volume and acid–base balance requires the cations sodium, potassium, magnesium, and calcium. The principal anion is chloride. Calcium also plays a role in neuromuscular excitability and blood coagulation. Metabolic energy, cellular homeostasis, and most enzyme activities are dependent on phosphorus. The electron-transport chain requires copper and iron. Several vitamins (qv) contain sulfur; one contains cobalt. Hormones (qv) contain iodine, sulfur, and zinc. Each cell contains a complex set of enzymes, many requiring metal ions, either as part of the basic structure, eg, copper, iron, molybdenum, selenium, and zinc, or as activators, eg, chromium, magnesium, and manganese.

As for other biological substances, states of dynamic equilibrium exist for the various mineral nutrients as well as mechanisms whereby a system can adjust to varying amounts of these minerals in the diet. In forms usually found in foods, and under circumstances of normal human metabolism, most nutrient minerals are not toxic when ingested orally. Amounts considerably greater than the recommended dietary allowances (RDAs) can generally be eaten without concern for safety (Table 1) (3).

Some elements found in body tissues have no apparent physiological role, but have not been shown to be toxic. Examples are rubidium, strontium, titanium, niobium, germanium, and lanthanum. Other elements are toxic when found in greater than trace amounts, and sometimes in trace amounts. These latter elements include arsenic, mercury, lead, cadmium, silver, zirconium, beryllium, and thallium. Numerous other elements are used in medicine in nonnutrient roles. These include lithium, bismuth, antimony, bromine, platinum, and gold (Fig. 1). The interactions of mineral nutrients with carbohydrates, fats, and proteins, minerals with vitamins (qv), and mineral nutrients with toxic elements are areas of active investigation (7–9).

The amount of each element required in daily dietary intake varies with the individual bioavailability of the mineral nutrient. Bioavailability depends both on body need as determined by absorption and excretion patterns of the element and by general solubility, and on the absence of substances that may cause formation of insoluble products, eg, calcium phosphate $Ca_3(PO_4)_2$. In some cases, additional requirements exist either for transport of substances or for uptake or binding. For example, calcium-binding proteins are involved in calcium transport; an intrinsic factor is needed for vitamin B_{12}, ie, cobalt, uptake (see Vitamins, vitamin B_{12}).

The essential mineral nutrients are classified either as principal elements or as trace and ultratrace elements. The distinction between these groups is the relative amounts in the dietary requirement (see Table 1).

Table 1. Essential Mineral Nutrients[a]

Element[b]	Body content, mg/kg body wt	Daily requirement,[c] mg
	Principal elements	
calcium	14,000–20,000	800–1,200[d,e]
phosphorus	11,000–12,000	800–1,200[d,e]
sulfur	1,600–2,500	[f]
potassium	2,000–3,500	2,000[g]
sodium	1,500–1,600	500[g]
chlorine	1,200–1,500	750[g]
magnesium	270–500	280[d,e,h];350[d,i]
	Trace and ultratrace elements	
iron	60–66	10[d,i];15[d,h]
fluorine	37	1.5–4.0[d,j]
zinc	33–50	12[d,e,h];15[d,i]
silicon	15–16	5–20
copper	1.0–2.5	1.5–3.0[j]
boron	0.69	0.5–1.0
selenium	0.2–0.3	0.055[d,e,h];0.07[d,i]
iodine	0.2–0.4	0.15[d,e]
manganese	0.2–4.0	2.0–5.0[d,j]
molybdenum	0.1–0.5	0.075–0.25[d,j]
chromium	0.06–0.2	0.05–0.2[d,j]
cobalt	0.02	0.003[k]
tin	0.2	
vanadium	0.14	< 0.01
nickel	0.07–0.14	< 0.10

[a] Refs. 4–6.
[b] Generally not ingested in elemental form.
[c] RDA values from Ref. 3 unless otherwise noted.
[d] Values are for adults.
[e] Increased amounts are required during pregnancy and lactation.
[f] Adequate intake with adequate intake of protein.
[g] Estimated minimum requirement from Ref. 3.
[h] Value for females.
[i] Value for males.
[j] Estimated safe and adequate daily intake from Ref. 3.
[k] As vitamin B_{12}.

Normal blood plasma or serum levels of the mineral nutrients and the usual form in circulating blood are given in Table 2. Modes of absorption and excretion are summarized in Table 3. Standard treatises on mineral nutrients (r4–r6, r10–r21) and standard sources of nutrient composition (22, 23) are available in the literature.

1. The Principal Elements

1.1. Calcium

Calcium, the most abundant mineral element in mammals, comprises 1.5–2.0 wt % of the adult human body, over 99 wt % of which is present in bones and teeth (24). About 48% of serum calcium is ionic, ca 46% is bound to blood proteins, the rest is present as diffusible complexes, eg, of citrate (24). The calcium ion level must be

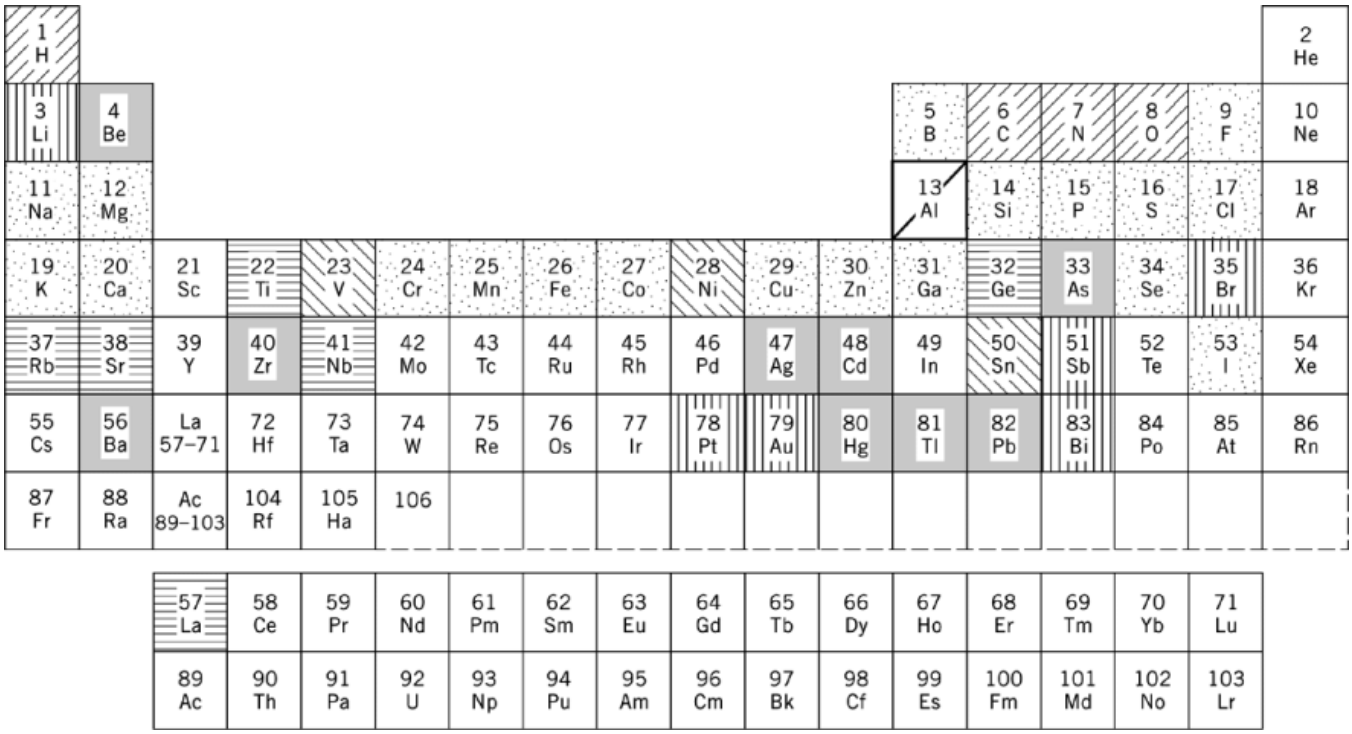


Fig. 1. Periodic Table showing elements of importance in biological systems: principal element of bioorganic compounds; essential mineral nutrients for humans and other animals; essential mineral nutrient for animals, probably for humans; present in body, not known to be a nutrient or toxic element; element used in medicine; element generally poisonous; and present in body, possibly toxic.

maintained within definite limits (see Table 2). Common food sources rich in calcium are listed in Table 4 (see also Calcium compounds).

1.1.1. Metabolic Functions

Bones act as a reservoir of certain ions, in particular Ca^{2+} and $PO^{3-}{}_4$, which readily exchange between bones and blood. Bone structure comprises a strong organic matrix combined with an inorganic phase which is principally hydroxyapatite [1306-06-5], $3Ca_3(PO_4)_2{\cdot}Ca(OH)_2$. Bones contain two forms of hydroxyapatite. The less soluble crystalline form contributes to the rigidity of the structure. The crystals are quite stable, but because of the small size present a very large surface area available for rapid exchange of ions and molecules with other tissues. There is also a more soluble intercrystalline fraction. Bone salts also contain small amounts of magnesium, sodium, carbonate, citrate, chloride, and fluoride (25). Osteoporosis is reported to result when bone resorption is relatively faster than bone formation (24).

The calcium ion, necessary for blood-clot formation, stimulates release of bloodclotting factors from platelets (see Blood, coagulants and anticoagulants) (25). Neuromuscular excitability also depends on the relative concentrations of Na^+ K^+ Ca^{2+} Mg^{2+}, and H^+(26). Upon a decrease in Ca^{2+} concentration, termed hypocalcemia, excitability increases. If this condition is not corrected, the symptoms of tetany, ie, muscular spasm, tremor, and even convulsions, can appear. Too great an increase in Ca^{2+} concentration, hypercalcemia, may impair muscle function to such an extent that respiratory or cardiac failure may occur.

Table 2. Blood Values and Carriers for Mineral Nutrients[a]

Mineral nutrient	Concentration,[b] mg/100 mL	Form in circulating blood
	Principal elements	
calcium	9.0–10.6	free Ca^{2+}; chelated to organic acids; bound to prealbumin
phosphorus	3.0–4.5	70% in organic phospholipids; as orthophosphate: $H_2PO_4^-$ and $H_2PO_4^{2-}$
sulfur	2.9–3.5[c]	free SO_4^{2-}; bound in protein
potassium	14–20	free K^+
sodium	310–340	free Na^+
chlorine	360–375	free Cl^-
magnesium	1.3	free Mg^{2+}; chelated to organic acids; bound to albumin
	Trace and ultratrace elements	
iron	0.065–0.175	bound to transferrin
fluorine	0.280[d]	in albumin
zinc	0.072–0.120[c] 0.408–1.170[d]	in albumin; in α_1-, α_2-macroglobulins
silicon	0.00016–0.00131	monosilicic acid
copper	0.100–0.200	bound to ceruloplasmin; albumin; amino acids
boron		probably borate ion
selenium	0.00013–0.0034[d]	bound in protein
iodine	0.004–0.008	mainly as thyroid compounds T_3 and T_4
manganese	0.0024–0.0069[d]	in transferrin
molybdenum	0.00135–0.00159[d]	bound in protein; in α_2-macroglobulin
chromium	0.0005–0.0031	bound to transferrin
cobalt	0.00035–0.0063[d]	bound to albumin
vanadium	0.0005–0.0023[e]	bound to transferrin
nickel	0.002–0.004[e]	some free Ni^{2+}; bound to albumin

[a] Refs. (4–18).
[b] In serum unless otherwise noted.
[c] In serum or plasma.
[d] In whole blood.
[e] In plasma.

Contraction of muscle follows an increase of Ca^{2+} in the muscle cell as a result of nerve stimulation. This initiates processes which cause the proteins myosin and actin to be drawn together making the cell shorter and thicker. The return of the Ca^{2+} to its storage site, the sarcoplasmic reticulum, by an active pump mechanism allows the contracted muscle to relax (27). Calcium ion, also a factor in the release of acetylcholine on stimulation of nerve cells, influences the permeability of cell membranes; activates enzymes, such as adenosine triphosphatase (ATPase), lipase, and some proteolytic enzymes; and facilitates intestinal absorption of vitamin B_{12} [68-19-9] (28).

1.1.2. Blood Calcium Ion Level

In normal adults, the blood Ca^{2+} level is established by an equilibrium between blood Ca^{2+} and the more soluble intercrystalline calcium salts of the bone. Additionally, a subtle and intricate feedback mechanism responsive to the Ca^{2+} concentration of the blood that involves the less soluble crystalline hydroxyapatite comes into play. The thyroid and parathyroid glands, the liver, kidney, and intestine also participate in Ca^{2+} control. The salient features of this mechanism are summarized in Figure 2 (29–31).

Factors controlling calcium homeostasis are calcitonin, parathyroid hormone(PTH), and a vitamin D metabolite. Calcitonin, a polypeptide of 32 amino acid residues, mol wt $\sim$3600, is synthesized by the thyroid gland. Release is stimulated by small increases in blood Ca^{2+} concentration. The sites of action of calcitonin are the bones and kidneys. Calcitonin increases bone calcification, thereby inhibiting resorption. In the kidney,

Table 3. Primary Sites of Absorption and Excretion of Mineral Nutrients

Nutrient	Absorption[a]	Excretion[b]
	Principal elements	
calcium	duodenum and jejunum (a,f)	kidney; intestine as digestive juices
phosphorus	small intestine (a)	kidney
sulfur	small intestine (a,f transport of S-containing amino acids)	kidney; intestine as bile acids
potassium	small intestine (p)	kidney; skin
sodium	large intestine, ileum (a); jejunum (f); stomach, skin (p); some two-step absorption in parts of small intestine (p or a)	kidney; intestine; some from skin as perspiration
chlorine	absorbed with Na^+, K^+, and Ca^{2+}	kidney; intestine; and skin
magnesium	ileum (a)	kidney; skin; very small amount from intestine
	Trace and ultratrace elements	
iron	duodenum and jejunum (a,f)	no significant excretion mechanism; skin as perspiration; exfoliation of cells, eg, intestinal, etc
fluorine	stomach (p); possibly intestine	kidney
zinc	duodenum (f)	intestine as bile and pancreatic juices; skin as perspiration; almost none from kidney
silicon	intestine	kidney
copper	stomach and upper intestine with low pH (p,f)	intestine as bile and pancreatic enzymes; kidney
boron	across gastrointestinal epithelia (p)[c]	kidney
selenium	duodenum (p)	kidney; intestine as bile and pancreatic juices; lungs (in expired air) if excess is ingested
iodine	small intestine, entire gastrointestinal tract as I (p)	kidney
manganese	small intestine in two-step mechanism (p or a)	intestine as bile and pancreatic juices
molybdenum	small intestine (f)[c]	kidney; skin as perspiration
chromium	small intestine (p)[c]	kidney
cobalt	as B_{12} in ileum (f); as inorganic Co (a,f)	kidney; skin as perspiration
tin	possibly small intestine (u)	kidney
vanadium	small intestine (u)	kidney
nickel	small intestine (u)	kidney

[a] Role is (a), active; (p), passive; (f), facilitated; or (u), mechanism not reported.
[b] Usually some fraction of the mineral nutrient ingested is not absorbed and passes into the feces. Modes of excretions listed pertain only to the fraction of mineral nutrient absorbed.
[c] Mechanism is possible.

it inhibits Ca^{2+} reabsorption and increases Ca^{2+} excretion in urine. Calcitonin operates via a cyclic adenosine monophosphate (cAMP) mechanism.

Parathyroid hormone, a polypeptide of 83 amino acid residues, mol wt 9500, is produced by the parathyroid glands. Release of PTH is activated by a decrease of blood Ca^{2+} to below normal levels. PTH increases blood Ca^{2+} concentration by increasing resorption of bone, renal reabsorption of calcium, and absorption of calcium from the intestine. A cAMP mechanism is also involved in the action of PTH. Parathyroid hormone induces formation of 1-hydroxylase in the kidney, required in formation of the active metabolite of vitamin D (see Vitamins, vitamin D).

Metabolites of vitamin D, eg, cholecalciferol (CC), are essential in maintaining the appropriate blood level of Ca^{2+}. The active metabolite, 1,25-dihydroxycholecalciferol (1,25-DHCC), is synthesized in two steps. In the liver, CC is hydroxylated to 25-hydroxycholecalciferol (25-HCC) which, in combination with a globulin carrier, is transported to the kidney where it is converted to 1,25-DHCC. This step, which requires 1-hydroxylase formation, induced by PTH, may be the controlling step in regulating Ca^{2+} concentration. The sites of action

Table 4. Common Food Sources Rich in Calcium[a]

Food[b]	Calcium in serving, mg
canned sockeye salmon with bones	543
yogurt, nonfat	452
sardines, Atlantic[c]	433
flour, self-rising	423
cheese[d]	
Parmesan	390
Romano	301
Swiss	272
Cheddar	204
Muenster	203
milk	
goat	325
whole cow	291
rhubarb, cooked	348
figs, dried[e]	269
turnip greens, cooked	198
broccoli, cooked	136

[a] Refs. 22 and 23.
[b] Serving corresponds to 236 mL (1 cup) unless otherwise noted.
[c] Serving corresponds to 113 g (4 oz).
[d] Serving corresponds to 28 g (1 oz).
[e] Serving corresponds to 187 g (10 whole figs).

of 1,25-DHCC are the bones and the intestine. Formation of 1,25-DHCC is limited by an inactivation process, ie, conversion of 25-HCC to 24,25-DHCC, catalyzed by 24-hydroxylase.

Calcium is absorbed from the intestine by facilitated diffusion and active transport. In the former Ca^{2+} moves from the mucosal to the serosal compartments along a concentration gradient. The active transport system requires a cation pump. In both processes, a calcium-binding protein (CaBP) is thought to be required for the transport. Synthesis of CaBP is activated by 1,25-DHCC. In the active transport, release of Ca^{2+} from the mucosal cell into the serosal fluid requires Na^{2+}.

1.1.3. Paget's Disease of Bone

Paget's disease, *osteitis deformans,* occurs mainly in people over 40. About twice as many men as women are affected. The disease, caused by faulty utilization of Ca^{2+} may be mild and asymptomatic requiring little or no treatment. Clinical signs are high alkaline phosphatase and high urine hydroxyproline as well as abnormal bone structure which usually goes unrecognized until discovered accidentally by routine x-ray examination (32).

About 10% of the cases are highly symptomatic, ie, considerable disability and even crippling may occur. In these cases, the disease affects many bones including the long bones of the legs, the pelvis, and the skull. The bones soften and buckle, the skull may become enlarged, and height may decrease if the spine is involved resulting in a bent-over stooped posture. In addition there may be severe bone pain and other neurologic complications such as deafness.

One method of treatment is to inject calcitonin, which decreases blood Ca^{2+} concentration and increases bone calcification (33). Another is to increase the release of calcitonin into the blood by increasing the blood level of Ca^{2+}(34). This latter treatment is accomplished by increasing Ca^{2+} absorption from the intestine requiring dietary calcium supplements and avoidance of high phosphate diets. The latter decrease Ca^{2+} absorption by precipitation of the insoluble calcium phosphate.

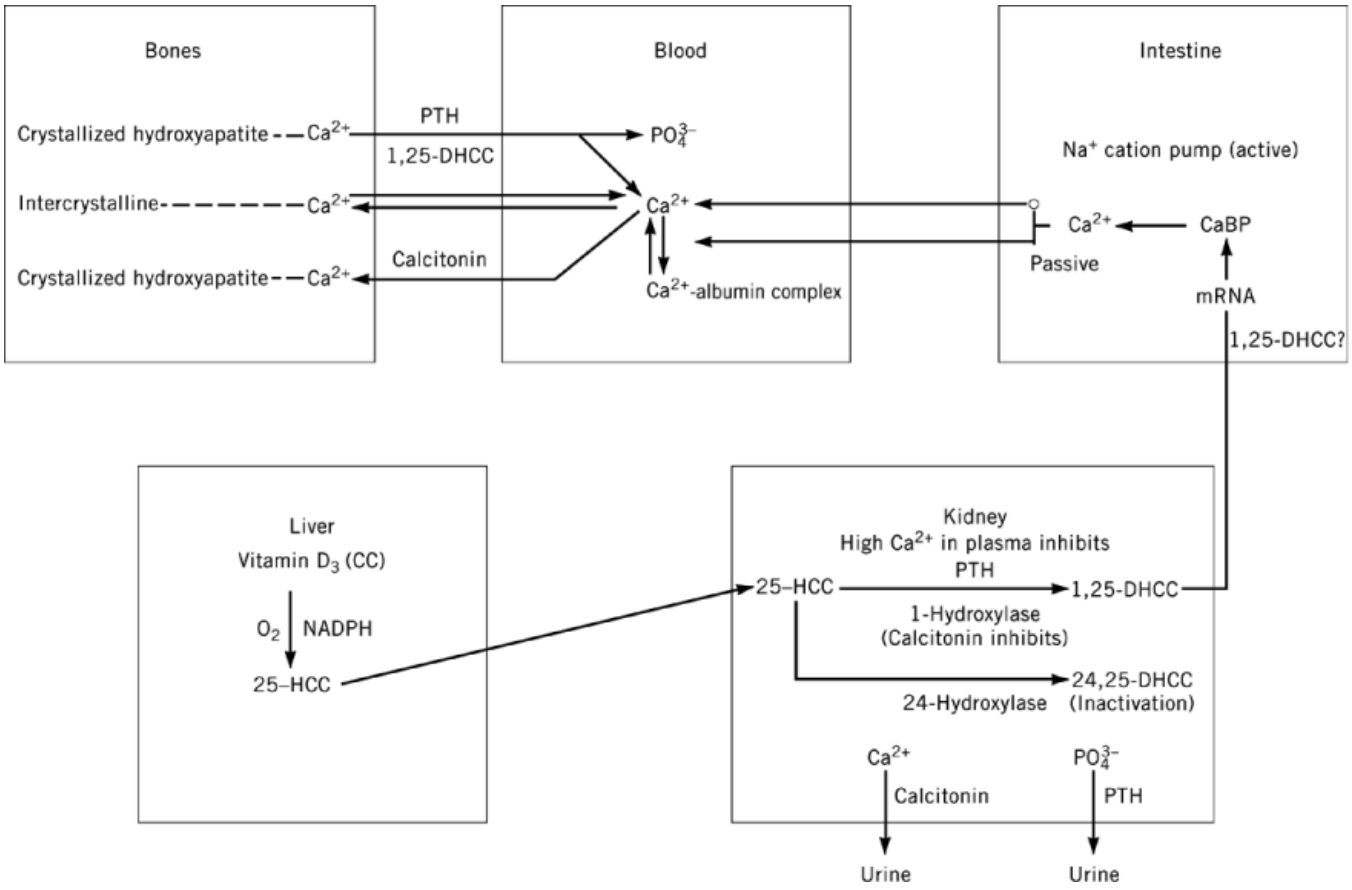


Fig. 2. Homeostatic control of blood Ca^{2+} level where PTH is parathyroid hormone [9002-64-6]; CC, cholecalciferol, ie, vitamin D_3; HCC, hydroxycholecalciferol; DHCC, dihydroxycholecalciferol; CaBP, calcium-binding protein; NADPH, protonated nicotinamide-adenine dinucleotide phosphate; and mRNA, messenger ribonucleic acid.

1.1.4. Other Calcium Disorders

In addition to hypocalcemia, tremors, osteoporosis, and muscle spasms (tetary), calcium deficiency can lead to rickets, osteomalacia, and possibly heart disease. These, as well as Paget's disease, can also result from faulty utilization of calcium. Calcium excess can lead to excess secretion of calcitonin, possible calcification of soft tissues, and kidney stones when combined with magnesium deficiency.

1.2. Phosphorus

Eighty-five percent of the phosphorus, the second most abundant element in the human body, is located in bones and teeth (24, 35). Whereas there is constant exchange of calcium and phosphorus between bones and blood, there is very little turnover in teeth (25). The Ca: P ratio in bones is constant at about 2:1. Every tissue and cell contains phosphorus, generally as a salt or ester of mono-, di-, or tribasic phosphoric acid, as phospholipids, or as phosphorylated sugars (24). Phosphorus is involved in a large number and wide variety of metabolic functions. Examples are carbohydrate metabolism (36, 37), adenosine triphosphate (ATP) from

Table 5. Common Food Sources Rich in Phosphorus[a]

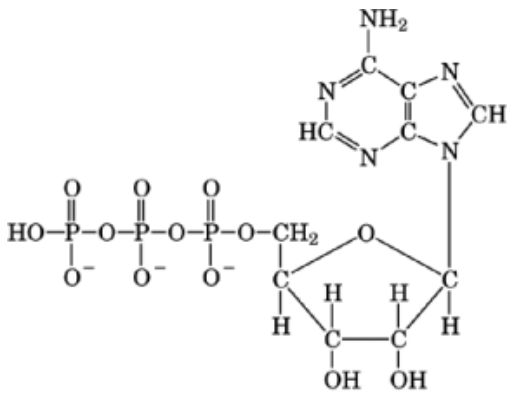
Food[b]	Phosphorus in serving, mg
pumpkin kernels, roasted	2658
sunflower seeds, roasted	1548
almonds, dry roasted	756
peanuts, shelled	744
wheat bran	608
black walnuts	580
sardines, Atlantic[c]	555
split peas, cooked	536
brains[c]	438
soybeans, cooked	422
chicken, liver[c]	352
whitefish[c]	323

[a] Refs. 22 and 23.
[b] Serving corresponds to 236 mL (1 cup) unless otherwise noted.
[c] Serving corresponds to 113 g (4 oz).

fatty acid metabolism (38), and oxidative phosphorylation (36, 39). Common food sources rich in phosphorus are listed in Table 5 (see also Phosphorus compounds).

1.2.1. Energy-Rich Compounds

Reactions of energy-rich compounds are required to drive the many endergonic metabolic processes, such as active transport, muscle contraction, and biosynthesis of fats and macromolecules, eg, nucleic acids (qv) and proteins (qv). Energy-rich compounds contain high energy bonds where the negative free energy resulting from breaking these bonds is large. Most of the high energy compounds are phosphates, eg, adenosine triphosphate (ATP) **(1)**, which can undergo hydrolysis of the P–O bond.



(1)

Two and twelve moles of ATP are produced, respectively, per mole of glucose consumed in the glycolytic pathway and each turn of the Krebs (citrate) cycle. In fat metabolism, many high energy bonds are produced per mole of fatty ester oxidized. For example, 129 high energy phosphate bonds are produced per mole of palmitate. Oxidative phosphorylation has a remarkable 75% efficiency. Three moles of ATP are utilized per

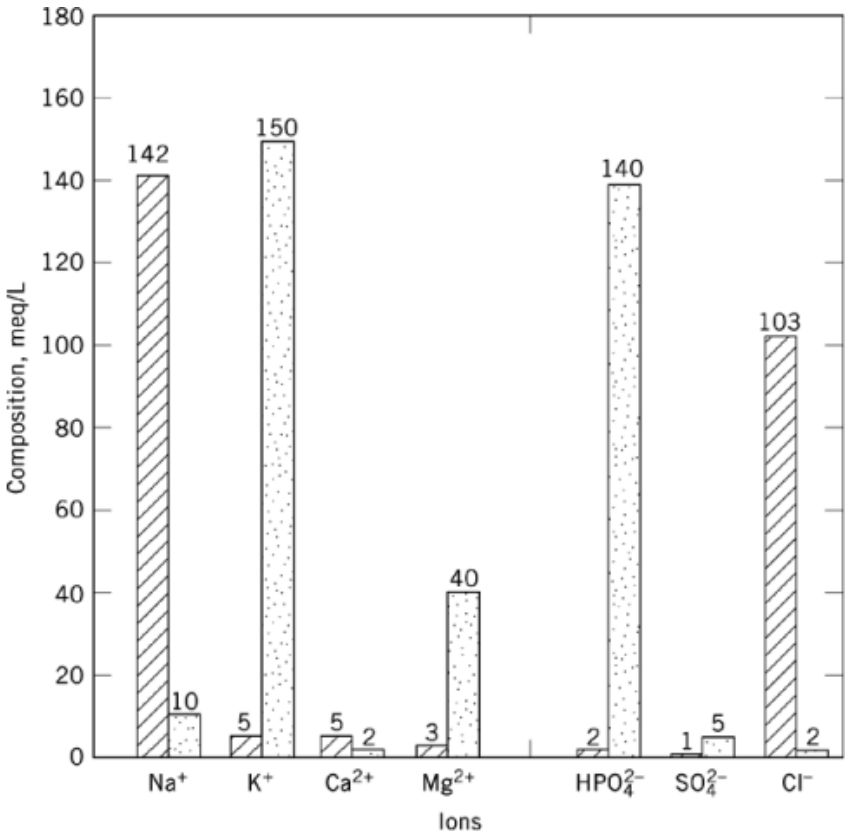


Fig. 3. Cation and anion composition of extracellular ▨ and intracellular ⊡ fluids.

transfer of two electrons, compared to the theoretical four. The process occurs via a series of reactions involving flavoproteins, quinones such as coenzyme Q, and cytochromes.

1.2.2. Metabolic Functions

The formation of phosphate esters is the essential initial process in carbohydrate metabolism (see Carbohydrates). The glycolytic, ie, anaerobic or Embden-Meyerhof pathway comprises a series of nine such esters. The phosphogluconate pathway, starting with glucose, comprises a succession of 12 phosphate esters.

Cyclic adenosine monophosphate (cAMP), produced from ATP, is involved in a large number of cellular reactions including glycogenolysis, lipolysis, active transport of amino acids, and synthesis of protein (40). Inorganic phosphate ions are involved in controlling the pH of blood (41). The principal anion of intercellular fluid is $HP^{2-}{}_4$ (Fig. 3) (41).

1.2.3. Phospholipids

Phospholipids, components of every cell membrane, are active determinants of membrane permeability. They are sources of energy, components of certain enzyme systems, and involved in lipid transport in plasma. Because of their polar nature, phospholipids can act as emulsifying agents (42). The structure of most phospholipids resembles that of triglycerides except that one fatty acid radical has been replaced by a radical derived from phosphoric acid and a nitrogen base, eg, choline or serine.

Table 6. Common Food Sources Rich in Sulfur[a,b]

Food[c]	Sulfur in serving, mg
peanuts, roasted	555
brazil nuts	406
sardines[d]	350
soybean flour	348
pork chops, lean[d]	339
turkey[d]	328
beef, lean[d]	305
chicken[d]	288
lamb[d]	271
whole grain flour	228
wheat germ[e]	136
navy beans	136
brewer's yeast[f]	76
molasses, blackstrap[f]	70
eggs, whole[g]	67
cheese, Cheddar[h]	64

[a] Refs. 22 and 23.
[b] Calculated as sulfur-containing amino acids, methionine plus cystine.
[c] Serving corresponds to 236 mL (1 cup) unless otherwise noted.
[d] Serving corresponds to 113 g (4 oz).
[e] Serving corresponds to 140 mL (1/2 cup).
[f] Serving corresponds to 20 g (2 tbsp).
[g] Serving corresponds to one medium 48-g egg.
[h] Serving corresponds to 28 g (1 oz).

1.2.4. Nucleic Acids

Phosphorus is an essential component of nucleic acids, polymers consisting of chains of nucleosides, a sugar plus a nitrogenous base, and joined by phosphate groups (43, 44). In ribonucleic acid (RNA), the sugar is D-ribose; in deoxyribonucleic acids (DNA), the sugar is 2-deoxy-D-ribose.

1.2.5. Phosphorus Disorders

Phosphorus nutrient deficiency can lead to rickets, osteomalacia, and osteoporosis, whereas an excess can produce hypocalcemia. Faulty utilization of phosphorus results in rickets, osteomalacia, osteoporosis, and Paget's disease, and renal or vitamin D-resistant rickets.

1.3. Sulfur

Sulfur is present in every cell in the body, primarily in proteins containing the amino acids methionine, cystine, and cysteine. Inorganic sulfates and sulfides occur in small amounts relative to total body sulfur, but the compounds that contain them are important to metabolism (45, 46). Sulfur intake is thought to be adequate if protein intake is adequate and sulfur deficiency has not been reported. Common food sources rich in sulfur are listed in Table 6.

Sulfur is part of several vitamins and co-factors, eg, thiamin, pantothenic acid [79-83-4], biotin [58-85-5], and lipoic acid. Mucopolysaccharides, eg, heparin [9005-49-6] and chondroitin sulfate [9007-28-7], contain a monoester of sulfuric acid having an $HSO^{-}{}_{3}$ group. Sulfur-containing lipids isolated from brain and other tissues usually are sulfate esters of glycolipids. The sulfur-containing amino acid taurine [107-35-7] is conjugated to bile acids (45). Labile sulfur is attached to nonheme iron in stoichiometric amounts in the respiratory chain where it is associated with the flavoproteins and cytochrome b (47).

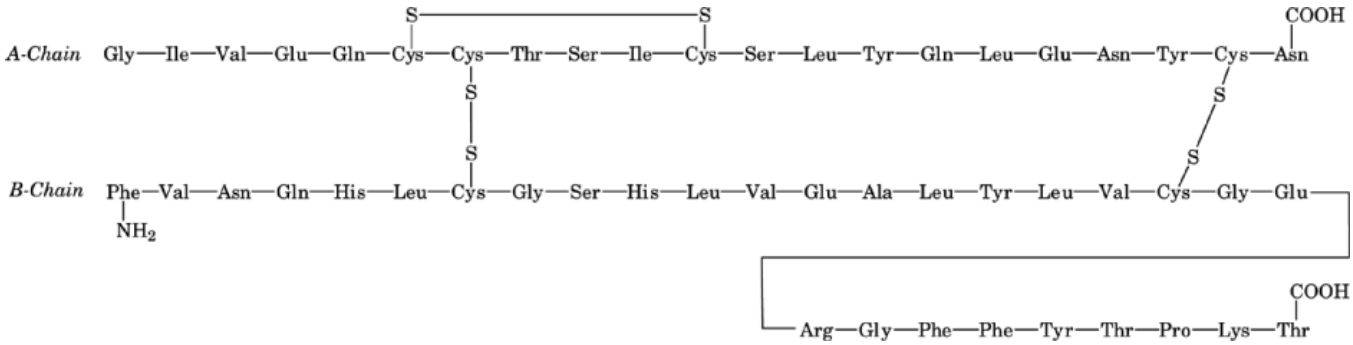


Fig. 4. Sulfur bridges in human insulin.

1.3.1. Disulfides

As shown in Figure 4, the *A*- and *B*-chains of insulin are connected by two disulfide bridges and there is an intrachain cyclic disulfide link on the *A*-chain (see Insulin and other antidiabetic drugs). Vasopressin [9034-50-8] and oxytocin [50-56-6] also contain disulfide links (48). Oxidation of thiols to disulfides and reduction of the latter back to thiols are quite common and important in biological systems, eg, cysteine to cystine or reduced lipoic acid to oxidized lipoic acid. Many enzymes depend on free SH groups for activation–deactivation reactions. The oxidation–reduction of glutathione (Glu-Cys-Gly) depends on the sulfhydryl group from cysteine.

1.3.2. Sulfur in Fat Metabolism

Although sulfur is in the same group of the Periodic Table, Group 16(VIA), as oxygen, sulfur functions much more like phosphorus, Group 15(VA), in biological systems. In fat metabolism, sulfur plays a key role analogous to that of phosphorus in carbohydrate metabolism. Fatty acid synthesis and degradation begin and end with the same compound, acetyl-S coenzyme A (acetyl–SCoA) (49).

1.3.3. Detoxification

Detoxification systems in the human body often involve reactions that utilize sulfur-containing compounds. For example, reactions in which sulfate esters of potentially toxic compounds are formed, rendering these less toxic or nontoxic, are common as are acetylation reactions involving acetyl–SCoA (45). Another important compound is *S*-adenosylmethionine [29908-03-0] (SAM), the active form of methionine. SAM acts as a methylating agent, eg, in detoxification reactions such as the methylation of pyridine derivatives, and in the formation of choline (qv), creatine [60-27-5], carnitine [461-06-3], and epinephrine [329-65-7] (50).

1.3.4. Sulfur Disorders

Sulfur nutrient deficiency results in retarded growth, and faulty utilization in homocystinuria.

1.4. Sodium and Potassium

Whereas sodium ion is the most abundant cation in the extracellular fluid, potassium ion is the most abundant in the intracellular fluid. Small amounts of K^+ are required in the extracellular fluid to maintain normal muscle activity. Some sodium ion is also present in intracellular fluid (see Fig. 5). Common food sources rich in potassium may be found in Table 7. Those rich in sodium are listed in Table 8.

Table 7. Common Food Sources Rich in Potassium[a]

Food[b]	Potassium in serving, mg
pumpkin kernels	1829
figs, dried[c]	1331
pistachio, dry roasted	1241
apricots, dried and cooked	1222
raisins, not packed[d]	1088
almonds, whole, dried	1039
peanuts, shelled	982
soybeans, cooked	972
Swiss chard, cooked	961
potato, baked[e]	903
buckwheat, whole grain	805
split peas, cooked	710
prunes, dried	710
kidney beans, canned	658
avocado[f]	622
Florida	742
California	548
banana[g]	594
orange juice[h]	496

[a] Refs. 22 and 23.
[b] Serving corresponds to 236 mL (1 cup) unless otherwise noted.
[c] Serving corresponds to 187 g (10 whole figs).
[d] Serving corresponds to 145 g (1 cup).
[e] Serving corresponds to one large potato (202 g).
[f] Serving corresponds to $1/2$ an average (Florida, 152 g; California, 86.5 g) avocado.
[g] Serving corresponds to an average banana (150 g).
[h] Serving corresponds to 227 g (8 oz).

Table 8. Common Food Sources Rich in Sodium and Chloride[a]

	Composition, mg	
Food[b]	Na^+	Cl^{-c}
table salt[d]	2132	3324
Canadian bacon, cooked	1745	2690
pickle[e]	833	1284
ham, cured	1364	2103
corned beef	1139	1756
beans with frankfurters[f]	1105	1703
cheese, processed American[g]	406	626
tuna, canned	400	617
vegetables, canned (beans, carrots, and peas)[f]	350	540
hamburger	86	133

[a] Refs. 22 and 23.
[b] Serving corresponds to 113 g (4 oz) unless otherwise noted.
[c] Calculated from sodium.
[d] Serving corresponds to 5.5 g (1 tsp).
[e] Serving corresponds to one large pickle (65 g).
[f] Serving corresponds to 236 mL (1 cup).
[g] Serving corresponds to 28 g (1 oz).

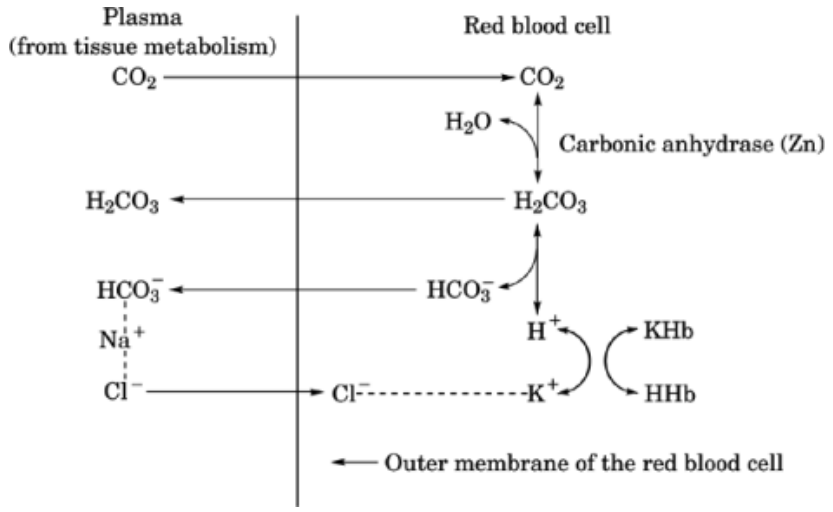


Fig. 5. Chloride shift where KHb is potassium hemoglobin and HHb is acid hemoglobin (16).

1.4.1. Metabolic Functions

Sodium ion acts in concert with other electrolytes, in particular K^+, to regulate the osmotic pressure and to maintain the appropriate water and pH balance of the body. Homeostatic control of these functions is accomplished by the lungs and kidneys interacting by way of the blood (51, 52). Sodium is essential for glucose absorption and transport of other substances across cell membranes. It is also involved, as is K^+, in transmitting nerve impulses and in muscle relaxation. Potassium ion acts as a catalyst in the intracellular fluid, in energy metabolism, and is required for carbohydrate and protein metabolism.

1.4.2. Active Transport

Maintenance of the appropriate concentrations of K^+ and Na^+ in the intra- and extracellular fluids involves active transport, ie, a process requiring energy (53). Sodium ion in the extracellular fluid (0.136–0.145 *M* Na^+) diffuses passively and continuously into the intracellular fluid ($<$0.01 *M* Na^+) and must be removed. This sodium ion is pumped from the intracellular to the extracellular fluid, while K^+ is pumped from the extracellular (ca 0.004 *M* K^+) to the intracellular fluid (ca 0.14 *M* K^+) (53–55). The energy for these processes is provided by hydrolysis of adenosine triphosphate (ATP) and requires the enzyme Na^+–K^+ATPase, a membrane-bound enzyme which is widely distributed in the body. In some cells, eg, brain and kidney, 60–70 wt % of the ATP is used to maintain the required Na^+–K^+ distribution.

Sodium and potassium ions are actively absorbed from the intestine. As a consequence of the electrical potential caused by transport of these ions, an equivalent quantity of Cl^- is absorbed. The resulting osmotic effect causes absorption of water (56).

1.4.3. Excretion and Reabsorption of Na^+ and K^+

Selective excretion and reabsorption of Na^+ and K^+ are accomplished by means of the kidney tubular cell membranes (51, 55). Water Na^+ and Cl^- passively diffuse into the proximal tubular cells. Potassium ion is pumped into the cells and Na^+ is pumped out by the Na^+–K^+ pump. In the extracellular fluid Na^+ and K^+ account for 90–92 wt % and 3 wt %, respectively, of the cations; in the intracellular fluid, the distribution is ca 70–80 wt % K^+ and 6 wt % Na^+ In the adult, ca 160 L of fluid is filtered daily. Urinary volume is 0.5–2.5 L/d so that ca 99 wt % of the filtered water is reabsorbed.

The volume of extracellular fluid is directly related to the Na^+ concentration which is closely controlled by the kidneys. Homeostatic control of Na^+ concentration depends on the hormone aldosterone. The kidney secretes a proteolytic enzyme, rennin, which is essential in the first of a series of reactions leading to aldosterone. In response to a decrease in plasma volume and Na^+ concentration, the secretion of rennin stimulates the production of aldosterone resulting in increased sodium retention and increased volume of extracellular fluid (51, 55).

1.4.4. Sodium and Hypertension

Salt-free or low salt diets often are prescribed for hypertensive patients (57). However, sodium chloride increases the blood pressure in some individuals but not in others. Conversely, restriction of dietary NaCl lowers the blood pressure of some hypertensives, but not of others. Genetic factors and other nutrients, eg Ca^{2+} and K^+, may be involved. The optimal intakes of Na^+ and K^+ remain to be established (58, 59).

1.4.5. Other Potassium and Sodium Disorders

Potassium and/or sodium deficiency can lead to muscle weakness and sodium deficiency to nausea. Hyperkalemia resulting in cardiac arrest is possible from 18 g/d of potassium combined with inadequate kidney function. Faulty utilization of K^+ and/or Na^+ can lead to Addison's or Cushing's disease.

1.5. Chlorine

Foods rich in chloride are listed in Table 8.

1.5.1. Metabolic Functions

The chlorides are essential in the homeostatic processes maintaining fluid volume, osmotic pressure, and acid–base equilibria (11). Most chloride is present in body fluids; a little is in bone salts. Chloride is the principal anion accompanying Na^+ in the extracellular fluid. Less than 15 wt % of the Cl^- is associated with K^+ in the intracellular fluid. Chloride passively and freely diffuses between intra- and extracellular fluids through the cell membrane. If chloride diffuses freely, but most Cl^- remains in the extracellular fluid, it follows that there is some restriction on the diffusion of phosphate. As of this writing (ca 1994), the nature of this restriction has not been conclusively established. There may be a transport device (60), or cell membranes may not be very permeable to phosphate ions minimizing the loss of HPO^{2-}_4 from intracellular fluid (61).

Some of the blood Cl^- is used for formation in the gastric glands of hydrochloric acid, HCl, required for digestion. Hydrochloric acid is secreted into the stomach where it acts with gastric enzymes in the digestive processes. The chloride is then reabsorbed with other nutrients into the blood stream. Chloride is actively transported in gastric and intestinal mucosa. In the kidney, chloride is passively reabsorbed in the thin ascending loop of Henle and actively reabsorbed in the thick segment of the ascending loop, ie, the distal tubule.

In the chloride shift Cl^- plays an important role in the transport of carbon dioxide (qv). In the plasma CO_2 is present as HCO^-_3, produced in the erythrocytes from CO_2. The diffusion of HCO^-_3 requires the counterdiffusion of another anion to maintain electrical neutrality. This function is performed by Cl^- which readily diffuses into and out of the erythrocytes (see Fig. 5). The carbonic anhydrase-mediated Cl^-–HCO^-_3 exchange is also important for cellular *de novo* fatty acid synthesis and myelination in the brain (62).

Numerous neurotransmitter receptors, eg, glutamate, γ-aminobutyric acid (GABA), benzodiazepine (called the valium receptor), have been identified as chloride channel proteins. The genetic defect in cystic fibrosis involves defective-functioning chloride channel proteins with excessive Cl^- loss. Deficient Cl^- during development adversely affects language skills in humans (63), as well as impaired growth in infants and metabolic alkalosis.

Table 9. Common Food Sources Rich in Magnesium[a]

Food[b]	Magnesium in serving, mg
pumpkin kernels	1212
sunflower seeds	510
buckwheat, whole grain	404
almonds, whole, dried	400
wheat germ, toasted	362
wheat bran	366
spinach, cooked	157
Swiss chard, cooked	150
oysters, eastern	135
corn meal, whole grain	125
navy beans, cooked from dry	107
chocolate, baking[c]	82
molasses, blackstrap[d]	52

[a] Refs. 22 and 23.
[b] Servings correspond to 236 mL (1 cup) unless otherwise noted.
[c] Servings correspond to 28 g (1 oz).
[d] Servings correspond to 15 mL (1 tbsp).

Fruit and vegetable juices high in potassium have been recommended to correct hypokalemic alkalosis in patients on diuretic therapy. Apparently the efficacy of this treatment is questionable. A possible reason for ineffectiveness is the low Cl^- content of most of these juices. Because Cl^- is high only in juices in which Na^+ is high, these have to be excluded (64).

1.6. Magnesium

In the adult human, 50–70% of the magnesium is in the bones associated with calcium and phosphorus. The rest is widely distributed in the soft tissues and body fluids. Most of the nonbone Mg^{2+}, like K^+, is located in the intracellular fluid where it is the most abundant divalent cation. Magnesium ion is efficiently retained by the kidney when the plasma concentration of Mg^{2-} falls; in this respect it resembles Na^+. The functions of Na^+ K^+ Mg^{2+}, and Ca^{2+} are interrelated so that a deficiency of Mg^{2+} affects the metabolism of the other three ions (26). Foods rich in magnesium are listed in Table 9.

1.6.1. Metabolic Functions

Magnesium is essential in numerous metabolic processes. It is the activator of many enzymes, eg, adenyl cyclase, alkaline phosphatases, and the phosphokinases, pyrophosphatases, and thiokinases (9, 65, 6, 67). Because the phosphokinases are required for the hydrolysis and transfer of phosphate groups, magnesium is essential in glycolysis and in oxidative phosphorylation. The thiokinases are required for the initiation of fatty acid degradation. Magnesium is also required in systems in which thiamine pyrophosphate is a coenzyme.

As an activator of the phosphokinases, magnesium is essential in energy-requiring biological processes, such as activation of amino acids, acetate, and succinate; synthesis of proteins, fats, coenzymes, and nucleic acids; generation and transmission of nerve impulses; and muscle contraction (67).

1.6.2. Regulation of Serum Mg^{2+} Concentration

Regulation of serum Mg^{2+} appears to result from a balance among intestinal absorption, renal reabsorption, and excretion (64, 68). The controlling factor is probably the renal threshold (65). In the normal adult, intestinal absorption is, to a large extent, proportional to the Mg^{2+} supplied in the diet. The system responds to a wide range of dietary intake by increasing or decreasing urinary excretion; the plasma Mg^{2+} concentration varies

only within the normal range. Although exchange of bone salt Mg^{2+} with blood Mg^{2+} is slow as compared to exchange of Ca^{2+}, the bone salts serve as a reservoir of Mg^{2+} to buffer depletions developing over long (weeks or months) periods (69). Parathyroid hormone may be involved in mobilizing bone Mg^{2+} and increasing tubular reabsorption of Mg^{2+}, but not to as great an extent as with Ca^{2+}. PTH may also increase absorption of Mg^{2+} from the intestine.

1.6.3. Magnesium Deficiency

A severe magnesium deficiency in humans is seldom encountered except as a secondary effect resulting from numerous disease states, eg, chronic alcoholism with malnutrition, acute or chronic renal disease, long-term Mg^{2+}-free parenteral feeding, protein–calorie malnutrition, and hyperthyroidism. In these situations, it is difficult to attribute specific clinical manifestations to magnesium deficiency (64). The specific role of magnesium in cardiovascular disease, eg, arrythmia, spasms, or ischemia, remains a subject of conflicting research findings (64).

Magnesium ion is essential for normal Ca^{2+} and K^+ metabolism. In acute experimental magnesium deficiency in humans, hypocalcemia occurs despite adequate calcium intake and absorption and despite normal renal and parathyroid functions. Negative K^+ balance is also observed. All biochemical and clinical abnormalities disappear upon restoration of adequate amounts of magnesium to the diet (64).

Magnesium supplements, such as MgO, have been used successfully in the treatment of patients with a history of calcium oxalate stone formation (70–73). Marginal magnesium deficiencies may occur in areas where food crops are grown on magnesium-deficient soil. One such area is a narrow strip of the Atlantic coast of the United States extending from Pennsylvania to Florida, sometimes called the stone belt because of the high incidence of calcium oxalate kidney stones (70). Stone formation may be the consequence of low magnesium intake. Evidently a high Mg^{2+} concentration in the kidney increases the solubility of calcium oxalate.

1.6.4. Other Magnesium Disorders

Neuromuscular irritability, convulsions, muscle tremors, mental changes such as confusion, disorientation, and hallucinations, heart disease, and kidney stones have all been attributed to magnesium deficiency. Excess Mg^{2+} can lead to intoxication exemplified by drowsiness, stupor, and eventually coma.

2. Trace Elements and Ultratrace Elements

2.1. Iron

The total body content of iron, ie, 3–5 g, is recycled more efficiently than other metals. There is no mechanism for excretion of iron and what little iron is lost daily, ie, ca 1 mg in the male and 1.5 mg in the menstruating female, is lost mainly through exfoliated mucosal, skin, or hair cells, and menstrual blood (74–76). Common food sources rich in iron and other trace elements are listed in Table 10.

Table 10. Common Food Sources Rich in Trace Elements[a]

Food[b]	In serving, mg
Iron[c]	
fortified cereal	33.0
Grapenuts cereal	32.6
bran flakes fortified	24.8
liver[d]	
lamb	20.2
veal	16.1
chicken	9.6
wheat germ, toasted	10.3

Table 10. *Continued*

Food[b]	In serving, mg
prune juice	10.2
oysters, fried[d]	9.2
molasses, blackstrap[e]	6.4
wheat bran, raw	6.3
apricots, dried	6.1
Fluorine	
dried seaweed[f]	9.1
tea	7.7
fluoridated water	0.2
mackerel[d]	2.1
sardines[d]	1.2
salmon[d]	0.7
Zinc	
raw oysters[d]	167.9
wheat germ, toasted	14.8
beef[d]	5.0
crab, steamed[d]	4.9
pork[d]	4.3
almonds	4.0
walnuts and pecans	3.0
lobster[d]	2.1
chicken[d]	2.0
tuna, canned	1.8
Silicon[g]	
high fiber grains (eg, oats)	
Barbados brown sugar	
organ meats	
Copper	
oysters, raw[d]	15.5
beef or veal liver[d]	13.6
lamb liver[d]	11.3
cocoa powder, nonfat	4.8
brazil nuts	3.4
sunflower seeds	2.6
lobster[d]	2.0
wheat germ	1.0
brewers' yeast[f]	0.9
Boron	
apple sauce	0.690
grape juice	0.5111
apple juice	0.4665
peaches, canned	0.4643
cherries, dark	0.3592
broccoli flowerette, frozen	0.3408
pears, canned	0.3026
orange juice	0.1021
cinnamon, ground[h]	0.0518
parsley flakes[i]	0.0269
grape jelly[e]	0.0265
catsup[e]	0.0130
Selenium	
herring, kippered[d]	0.1600
brazil nuts	0.1483
lobster[d]	0.1775

Table 10. *Continued*

Food[b]	In serving, mg
lamb liver[d]	0.1140
grains grown on seleniferous soils[d]	0.0907
torula yeast[j]	0.0246
butter[e]	0.0219
brewer's yeast[j]	0.0182
coconut, fresh grated	0.0158
Chromium	
liver[d]	0.0565
beef[d]	0.0362
brown sugar	0.0261
eggs, whole[k]	0.0250
wheat bran	0.0240
brewer's yeast[j]	0.0236
molasses, blackstrap[e]	0.0230
oysters, raw[d]	0.0226
wheat germ[l]	0.0141
Manganese	
chestnuts	5.9
filberts	5.7
Brazil nuts, raw	3.9
barley, dry	3.4
brown rice	3.2
almonds, raw	2.7
sunflower seeds	2.6
sesame seeds	2.4
peanuts, roasted	2.2
carrot[m]	2.2
Cobalt[d,n]	
liver	
beef	127.0
veal	98.7
lamb	91.7
turkey	53.8
chicken	22.0
brains	17.2
liverwurst	15.2
beef, lean	2.8
lamb	2.2
chicken breast	0.4

[a] Refs. 22 and 23.
[b] Serving corresponds to 236 mL (1 cup) unless otherwise noted.
[c] Not all iron from different sources is equally absorbed; see text.
[d] Serving corresponds to 113 g (4 oz).
[e] Serving corresponds to 15–20 g (1 tbsp).
[f] Serving corresponds to 28 g (1 oz).
[g] Accurate quantitative data unavailable; best reported sources listed.
[h] Serving corresponds to 5 g (1 tsp).
[i] Serving corresponds to 59 mL (1/4 cup).
[j] Serving corresponds to 20 g (2 tbsp).
[k] Serving corresponds to one medium egg (48 g).
[l] Serving corresponds to 118 mL (1/2 cup).
[m] Serving corresponds to one large carrot.
[n] Cobalt as μg of vitamin B_{12}.

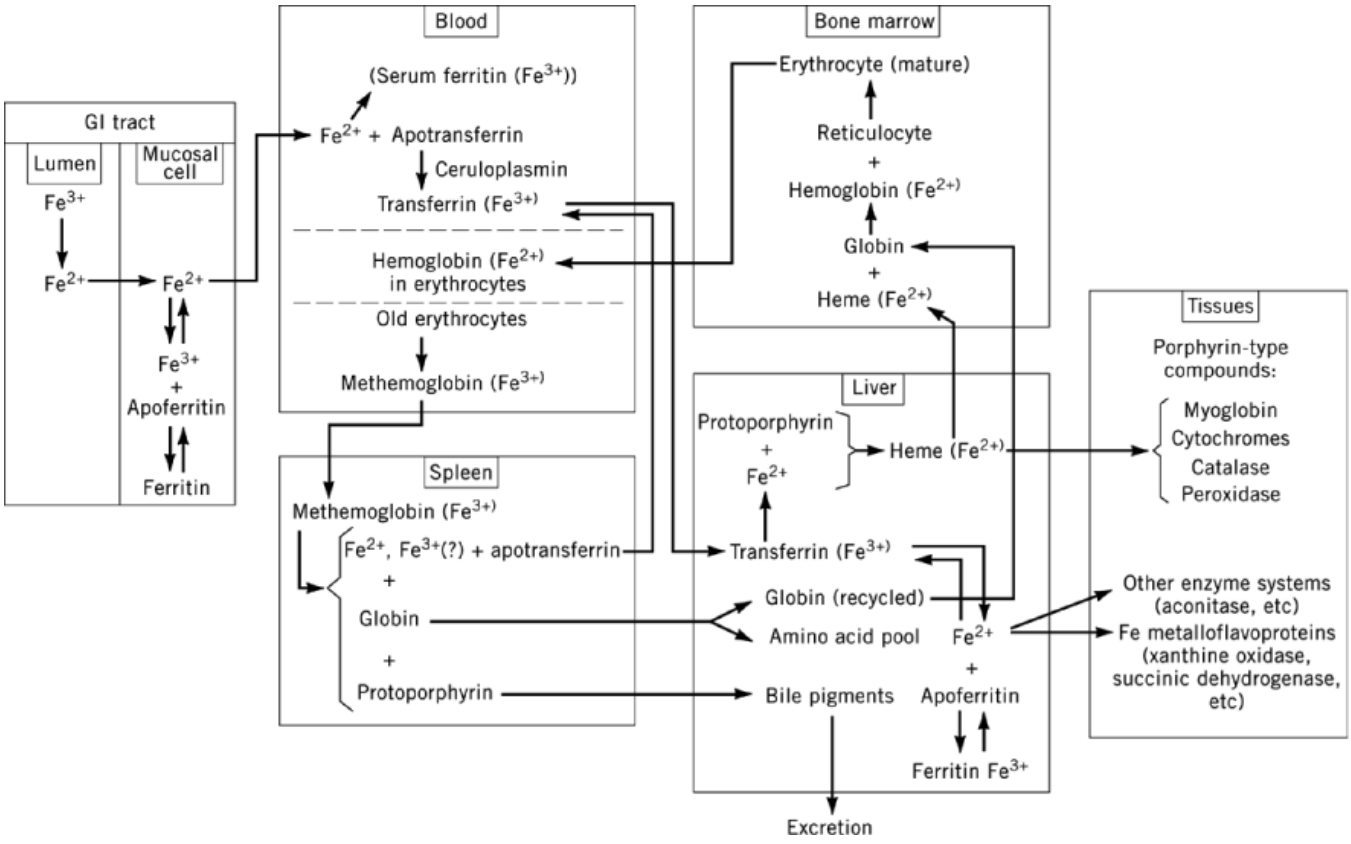


Fig. 6. Iron metabolism.

2.1.1. Metabolic Functions

A large percentage of the iron in the human body is in hemoglobin: 85 wt % in the adult female, 60 wt % in the adult male (75). The remainder is present in other iron-containing compounds involved in basic metabolic functions, or in iron transport or storage compounds. Myoglobin, the cytochromes, catalase, sulfite oxidase, and peroxidase are all heme iron enzymes. NADH-dehydrogenase, succinate dehydrogenase, α-glycerophosphate dehydrogenase, monoamine oxidase, xanthine oxidase, and alcohol dehydrogenase are nonheme metalloflavoproteins that contain iron. Aconitase and microsomal lipid peroxidase do not contain iron but do require it as a co-factor. The transport and storage proteins for iron are transferrin, ferritin, and hemosiderin (Fig. 6) (74–76). The iron in transferrin in the blood is a combination of freshly absorbed iron and recycled iron.

The hemoglobin molecule (mol wt 65,000) is a tetramer containing four iron atoms (77). The iron reversibly binds oxygen, allowing the hemoglobin molecule to function as an oxygen carrier to the tissues (78). Myoglobin, a monomer containing one iron atom, functions accepting oxygen from the blood and storing it for use during muscle contraction. The iron in both hemoglobin and myoglobin is in the ferrous state Fe^{2+}. The iron in methemoglobin and metmyoglobin is oxidized to the ferric state Fe^{3+}. These latter species do not bind oxygen (77).

The ability of iron to exist in two stable oxidation states, ie, the ferrous Fe^{2+}, and ferric Fe^{3+}, states in aqueous solutions, is important to the role of iron as a biocatalyst (79) (see Iron compounds). Although the cytochromes of the electron-transport chain contain porphyrins like hemoglobin and myoglobin, the iron ions

therein are involved in oxidation–reduction reactions (78). Catalase is a tetramer containing four atoms of iron; peroxidase is a monomer having one atom of iron. The iron in these enzymes also undergoes oxidation and reduction (80).

2.1.2. Homeostatic Control of Iron Levels

Absorption of iron from food to maintain homeostasis, tightly controlled, increases in instances of increased demands, such as during pregnancy and lactation, and iron-deficiency states which are the result of blood loss or iron-deficiency anemia resulting from inadequate iron intake (74–76). Iron absorption is greatly reduced in the normal individual when iron stores are adequate or excessive. Absorption is enhanced by acid conditions and reducing agents. Heme iron from animal sources is absorbed more readily than nonheme iron from cereals and vegetables (74–76).

A system of internal iron exchange exists which is dominated by the iron required for hemoglobin synthesis. For formation of red blood cells, iron stores can furnish 10–40 mg/d of iron, as compared to 1–3 mg from dietary sources (74). Only ca 10 wt % of ingested iron actually is absorbed. Transferrin is essential for movement of iron and without it, as in genetic absence of transferrin, iron overload occurs in tissues. This hereditary atransferrinemia is coupled with iron-deficiency anemia. The iron overload in hereditary or acquired hemochromatosis results in fully saturated transferrin and is treated by phlebotomy (10).

2.1.3. Iron Deficiency and Toxicity

Iron deficiency is a significant worldwide nutritional problem and cause of anemia which can also lead to a decreased resistance to infection. Insufficient dietary iron intake; iron losses, eg, bleeding and parasite infestation; and malabsorption of iron are the principal causes. The groups at greatest risk for developing iron-deficiency anemia are menstruating females, pregnant or nursing females, and young children. Children can experience impaired psychomotor development and intellectual performance.

Iron toxicity resulting from excess absorbable iron ingestion is rare except in Africa where fermented beverages made in large iron pots have levels of iron approaching 80 mg/L in a brew where the pH is very low. This results in Bantu siderosis which can result in hemochromatosis, ie, damage to various organs from excessive storage of iron. This condition can cause numerous disease states, eg, hepatic fibrosis and diabetes in 80% of the cases of idiopathic hemochromatosis patients (74–76). Iron overload is frequently a complication of repeated blood transfusions in anemias, eg, thalassemia (74, 76). The lethal dose of ferrous sulfate for a two-year old is 2 g; for an adult the lethal dose is from 200–300 g.

2.2. Fluorine

Fluoride is present in the bones and teeth in very small quantities. Human ingestion is from 0.7–3.4 mg/d from food and water. Evidence for the essentiality of fluorine was obtained by maintaining rats on a fluoride-free diet, resulting in decreased growth rate, decreased fertility, and anemia. These impairments were remedied by supplementing the diets with fluoride (81). Similar effects have been reported in goats (82).

2.2.1. Fluoridation and Dental Caries

Fluoridation of public water supplies, a common practice throughout much of the United States, may be an effective means of significantly reducing the incidence of dental caries (83–85) (see Dental materials; Fluorine compounds, inorganic). Concern regarding the narrow range of safety between effective and toxic fluoride concentrations has been expressed and poisoning from excessive fluoride, fluorosis, added to public water has been reported (86). Assertions that fluoridation of water supplies increases the incidence of cancer have not been substantiated (87).

2.2.2. Other Effects of Fluoride

Excess fluoride ingestion damages developing teeth, causing mottling, chalky-white coloration, and pitting (83, 84). Adding fluoride to animal feed leads to fragile and brittle teeth and bones (88). Fluoride is an inhibitor of enzymes, especially enolase in the glycolytic pathway (88). Fluoride may have some effect on osteoporosis (83). Fluoride supplementation results in poorly mineralized bone unless very high pharmacologic levels, ie, 50,000 IU of vitamin D and 900 mg of calcium are included in the regimen (89).

2.3. Zinc

The 2–3 g of zinc in the human body are widely distributed in every tissue and tissue fluid (90–92). About 90 wt % is in muscle and bone; unusually high concentrations are in the choroid of the eye and in the prostate gland (93). Almost all of the zinc in the blood is associated with carbonic anhydrase in the erythrocytes (94). Zinc is concentrated in nucleic acids (90), and found in the nuclear, mitochondrial, and supernatant fractions of all cells.

2.3.1. Metabolic Functions

Zinc is essential for the function of many enzymes, either in the active site, ie, as a nondialyzable component, of numerous metalloenzymes or as a dialyzable activator in various other enzyme systems (91, 92). Well-characterized zinc metalloenzymes are the carboxypeptidases A and B, thermolysin, neutral protease, leucine amino peptidase, carbonic anhydrase, alkaline phosphatase, aldolase (yeast), alcohol dehydrogenase, superoxide dismutases, and aspartate transcarbamylase. Other enzymes reported to contain zinc include the RNA and DNA polymerases and a number of dehydrogenases, eg, lactic, malic, and glutamic (91–93). Generally, enzymes that contain zinc in one species often contain zinc in other species. This is true across species for carbonic anhydrase, but it is not true for aldolase which is a zinc enzyme in yeast but not in mammalian muscle (93). In addition to its role in the various enzyme activities, zinc is a membrane stabilizer and a participant in electron-transfer processes (93).

Zinc–hormone interactions include hormonal influence on absorption, distribution, transport, and excretion of zinc and zinc influence on synthesis, secretion, receptor binding, and function of numerous hormones (qv). Zinc enhances pituitary activity by increasing circulating levels of growth hormone, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, and adrenocorticotropin (93). The role of zinc in insulin action is recognized but not well understood (93). Zinc is required for maintenance of normal plasma concentrations of vitamin A and for normal mobilization of vitamin A from the liver (93, 95).

2.3.2. Zinc Deficiency

Zinc was confirmed as essential for humans in 1956 (92, 94) and deficiency symptoms were reported in 1961 (96). The size of the human fetus is correlated with zinc concentration in the amniotic fluid and habitual low zinc intake in the pregnant female is thought to be related to several congenital anomalies in humans (92, 95). Low zinc intakes result in hypogonadism, dwarfism, mental retardation, low serum and red blood cell zinc in humans and animals, and retarded growth and teratogenic effects on the nervous system in rats.

In children suffering from marginal zinc deficiency, impaired taste acuity, poor appetite, and suboptimal growth can be reversed upon zinc supplementation (93, 95). Accelerated wound healing occurs in humans upon zinc supplementation (95), suggesting that marginal zinc deficiency in humans may be more widespread than has been thought. Zinc supplementation has also been effective in alleviating symptoms of active rheumatoid arthritis in clinical trials (97). Acrodermatitis enteropathica, a hereditary disease that involves aberrant zinc metabolism, responds to oral zinc supplementation (93, 95) (see Table 10). Excessive zinc intake may interfere with copper metabolism.

2.4. Silicon

Silicon comes mainly from ingestion of silicates, primarily from vegetables. It is found in the serum as silicic acid [1343-98-2], $Si(OH)_4$, and normal blood serum levels are ca 1 mg/100 mL regardless of intake because of efficient kidney excretion of excess (98). Silicon is necessary for calcification, growth, and as cross-linking material in mucopolysaccharide formation (98). Essentiality of silicon in rats and chicks has been established (98–101). Silicon, recognized as essential for humans in 1991, is especially helpful in situations where the diet is low in calcium or high in aluminum, or thyroid function is inadequate (98). The human requirement may be 5–20 mg/d (98). Silicon deficiency may lead to altered metabolism of connective tissue and bone and/or aluminum accumulation in the brain.

2.5. Copper

All human tissues contain copper. The highest amounts are found in the liver, brain, heart, and kidney (102). In blood, plasma and erythrocytes contain almost equal amounts of copper, ie, ca 110 and 115 mg/100 mL, respectively.

2.5.1. Metabolic Functions

In plasma, ca 90 wt % of copper is in the metalloprotein ceruloplasmin, also known as a_2-globulin, mol wt 151,000, which contains 8 atoms of copper per molecule (103). Ceruloplasmin has been identified as a ferroxidase(I) which catalyses the oxidation of aromatic amines and of Fe^{2+} to Fe^{3+}(79, 104). The ferric ion is then incorporated into transferrin which is necessary for the transport of iron to tissues involved in the synthesis of iron-containing compounds, eg, hemoglobin. Lowered levels of ceruloplasmin interfere with hemoglobin synthesis.

Erythrocuprein, which contains about 60 wt % of the erythrocyte copper, hepatocuprein, and cerebrocuprein act as superoxide dismutases. Each contains two atoms of copper per molecule, having mol wt ca 34,000. The superoxide ion $O^+{}_-$, and peroxide $O^{2-}{}_2$, are the two main toxic by-products of oxygen reduction in the body (1, 105). Superoxide dismutase catalyzes the dismutation, ie, the simultaneous oxidation, reduction, and decarboxylation, of superoxide, a free-radical anion, thus protecting the cell from oxidative damage.

The oxidation of the ϵ-amino groups of lysine is required for the cross-linking of polypeptide chains of collagen and elastin. The catalyst for this reaction is the copper metalloenzyme lysyl oxidase (103). Copper deficiency is characterized by poorly formed collagen which leads to bone fragility and spontaneous bone fractures in animals, and also results in cardiac hypertrophy (103). Abnormal electrocardiographs have been noted when low copper diets were fed to humans (103). Anemia, neutropenia, and bone disease have been reported in children having protein calorie malnutrition (PCM) and accompanying hypocupremia (102). Some other copper metalloproteins are cytochrome c oxidase, dopamine B hydroxylase, urate oxidase, tyrosinase, and ascorbic acid oxidase. Most copper enzymes are involved in redox reactions (102).

2.5.2. Genetic Disease

At least two genetic diseases involving copper are known. Wilson's disease, an autosomal recessive disease, is usually detected in adulthood. There is a toxic increase in copper storage upon neurological and liver damage, but a decrease in the amount of circulating copper because of decreased ceruloplasmin (103, 104, 106). Menkes' kinky-hair syndrome is an x-linked defect of copper transport out of the intestinal cell that results in lowered activity of several copper-dependent enzymes, lowered copper levels in the serum, progressive mental deterioration, defective keratinization of hair, and degenerative changes in the aorta (103, 104, 107, 108).

2.5.3. Dietary Copper

Analytical data indicate that many diets contain less than the RDA for copper (109). Excessive copper has been reported to be fatal for oral dose levels of copper sulfate of 200 mg/kg body weight for a child and 50 mg/kg for adults.

2.6. Boron

The essentiality of boron, first accepted for higher plants in 1923, then for animals, was recognized in 1981 for human metabolism (110, 111). Boron is reported to help maintain function or stability of cell membranes and is thought to be involved with hormone reception and transmembrane signaling (101). Boron forms complexes with organic compounds having hydroxyl groups, especially those having more than two such groups, such as sugars and polysaccharides, adenosine-5-phosphate, pyridoxine, riboflavin, dehydroascorbic acid, and pyridine nucleotides (112). Enhanced need for boron may develop with nutritional or metabolic stress involving other nutrients, eg, magnesium deprivation or physiological changes in calcium metabolism (101). Boron depletion impairs cognitive function (112). Organs known to contain the highest levels of boron are bone, spleen, and thyroid (112). An excess of boron can, however, cause seizures in infants, riboflavinuria, and gastrointestinal upset.

2.7. Selenium

Selenium, thought to be widely distributed throughout body tissues, is present mostly as selenocysteine in selenoproteins or as selenomethionine (113, 114). Animal experiments suggest that greater concentrations are in the kidney, liver, and pancreas and lesser amounts are in the lungs, heart, spleen, skin, brain, and carcass (115).

2.7.1. Metabolic Functions

The most clearly documented role for selenium is as a necessary component of glutathione peroxidase (Fig. 7) (113, 114). Glutathione peroxidase reduces hydrogen peroxide, which is formed by free-radical oxidant–stresser reactions, to H_2O and reduces organic peroxides, eg, those formed by the peroxidation of unsaturated fatty acids, to alcohols and H_2O(79, 113, 116). Phospholipid hydroperoxide glutathione peroxidase inhibits lipid peroxidation (114). Selenium is also involved in the functions of additional enzymes, eg, type 1 iodothyronine deiodinase (114), leukocyte acid phosphatase, and glucuronidases (117). A role for selenium in electron transfer has been suggested (115, 118) as has involvement in nonheme iron proteins (114, 115). Selenium and vitamin E appear to be necessary for proper functioning of lysosomal membranes (119). A role for selenium in metabolism of thyroid hormone has been confirmed (114).

2.7.2. Toxicity, Deficiency, and Medicinal Aspects

Interest in biological effects of selenium developed upon recognition that alkali disease and blind staggers of grazing livestock in the western United States were the result of selenium poisoning. There are unusually high concentrations of selenium in certain plants, because of selenium-accumulating properties, or in ordinary plants growing on highly seleniferous soils. No treatment for this type of poisoning is known (114), thus excess selenium in the animal diet must be avoided. Prolonged ingestion of up to 600 mg/d of selenium did not produce toxic effects in humans (120). Toxic effects in humans have been reported, however, from chronic ingestion of food in China supplying 5 mg/d of Se, and from supplements in the United States of 27–2387 mg/d of Se(113, 114). Effects include hair loss, changes in the nails, gastrointestinal upset, and peripheral neuropathy.

Pure selenium deficiency, without concurrent vitamin E deficiency, is not generally seen except in animals on experimental diets (113). In China, selenium deficiency in humans has been associated with Keshan disease,

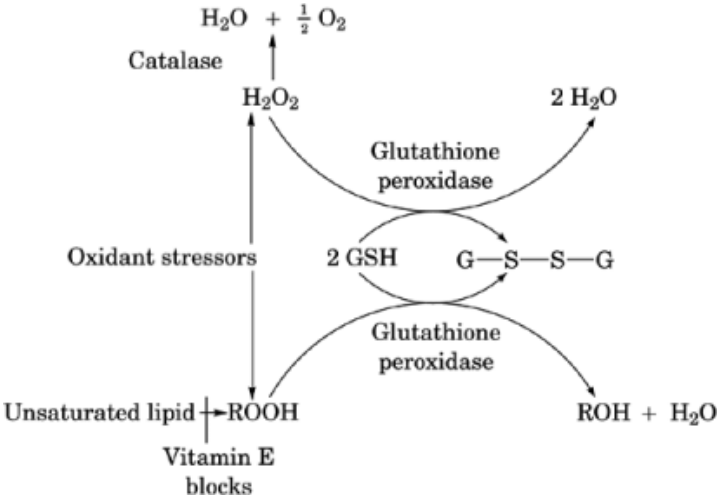


Fig. 7. The glutathione peroxidase (a selenium enzyme) system where GSH=*N*–(*N*–L–γ–glutamyl–L–cysteinyl)glycine and G–S–S–G, the disulfide.

a cardiomyopathy seen in children and in women of child-bearing ages, and Kashin-Beck disease, an endemic osteoarthritis in adolescents (113).

Selenium may have anticarcinogenic effects possibly because of the antioxidant properties of selenium compounds (114, 115). Animals involved in early carcinogenicity studies lived significantly longer when fed supplementary selenium. The role of selenium in the prevention of cancer and other chronic diseases, eg, heart conditions, and as an antiaging and antimutagenic agent are under investigation (113).

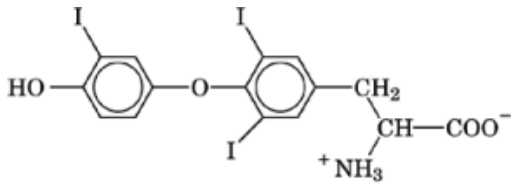
2.8. Iodine

Of the 10–20 mg of iodine in the adult body, 70–80 wt % is in the thyroid gland (see Thyroid and antithyroid preparations). The essentiality of iodine, present in all tissues, depends solely on utilization by the thyroid gland to produce thyroxine [51-48-9] and related compounds. Well-known consequences of faulty thyroid function are hypothyroidism, hyperthyroidism, and goiter. Dietary iodine is obtained from eating seafoods and kelp and from using iodized salt.

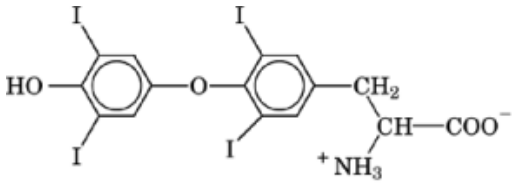
2.8.1. Metabolic Functions

The functions of the thyroid hormones and thus of iodine are control of energy transductions (121). These hormones increase oxygen consumption and basal metabolic rate by accelerating reactions in nearly all cells of the body. A part of this effect is attributed to increase in activity of many enzymes. Additionally, protein synthesis is affected by the thyroid hormones (121, 122).

2.8.1.1. Thyroid Hormones. Iodine, absorbed as I^-, is oxidized in the thyroid and bound to a thyroglobulin. The resultant glycoprotein, mol wt 670,000, contains 120 tyrosine residues of which ca two-thirds are available for binding iodine in several ways. Proteolysis introduces the active hormones 3,5,3′-triiodothyronine (T_3) and 3,5,3′,5′-tetraiodothyronine (T_4), (thyroxine) in the ratio T_4:T_3 of 4:1 (121, 122).



T_3



T_4

Only small amounts of free T_4 are present in plasma. Most T_4 is bound to the specific carrier, ie, thyroxine-binding protein. T_3, which is very loosely bound to protein, passes rapidly from blood to cells, and accounts for 30–40% of total thyroid hormone activity (121). Most of the T_3 may be produced by conversion of T_4 at the site of action of the hormone by the selenoenzyme deiodinase (114). That is, T_4 may be a prehormone requiring conversion to T_3 to exert its metabolic effect (123).

Thyroid-stimulating hormone (TSH), also called thyrotropin, influences thyroid activity by a feedback mechanism (121–123). TSH, secreted by the pituitary gland, stimulates the thyroid to increase production of thyroid hormones when the blood hormone level is low. This results in an increase in size of thyroid cells. If this continues, the increase in size of the thyroid becomes noticeable as simple goiter. In many parts of the world, simple goiter is endemic and usually results from dietary iodine deficiency (121) or goiterogens in foods which bind iodine. Iodine deficiency disorders (IDD) include cretinism, myxedema, hypothyroidism, and goiter (121, 122). In technologically advanced countries, the problem of iodine deficiency has been minimized by the use of iodized salt (121, 122). Faulty utilization of iodine can lead to Grave's disease. A sodium iodide excess can also produce goiter and an excess of 500 mg/kg body weight can be fatal.

2.9. Manganese

The adult human body contains ca 10–20 mg of manganese (124, 125), widely distributed throughout the body. The largest Mg^{2+} concentration is in the mitochondria of the soft tissues, especially in the liver, pancreas, and kidneys (124, 126). Manganese concentration in bone varies widely with dietary intake (126) (see Table 10).

2.9.1. Metabolic Functions

Manganese is essential for normal body structure, reproduction, normal functioning of the central nervous system, and activation of numerous enzymes (126). Synthesis of the mucopolysaccharide chondroitin sulfate involves a series of reactions where manganese is required in at least five steps (127). These reactions are responsible for formation of polysaccharides and linkage between the polysaccharide and proteins that form the mucopolysaccharide of cartilage (124). In addition to the glycosyl transferases of mucopolysaccharide synthesis that require manganese, a number of metalloenzymes contain Mn^{2+}(124, 126, 127). Superoxide dismutase and pyruvic carboxylase contain two and four atoms of manganese per molecule, respectively. Most enzymes that require magnesium, eg, kinases, can use manganese *in vitro,* and Mg**2+** can also substitute for

Mn^{2+} in some enzyme activations (124, 126). An excess of manganese can lead to neural damage and possible impaired insulin production.

2.9.2. Manganese Deficiency

In animals, manganese deficiency results in wide-ranging disorders, eg, impaired growth, abnormal skeletal structure, disturbances of reproduction, and defective lipid and carbohydrate metabolism (124). The common denominator appears to be the impairment of activity of enzymes that have a specific requirement for manganese. Although overt manganese deficiency has not been induced in humans, some forms of epilepsy in humans and animals and a decrease in glucose tolerance in animals have been linked to low levels of manganese in the tissues (128, 129).

2.10. Molybdenum

Molybdenum is a component of the metalloenzymes xanthine oxidase, aldehyde oxidase, and sulfite oxidase in mammals (130). Two other molybdenum metalloenzymes present in nitrifying bacteria have been characterized: nitrogenase and nitrate reductase (131). The molybdenum in the oxidases, is involved in redox reactions. The heme iron in sulfite oxidase also is involved in electron transfer (132).

Foods rich in molybdenum include legumes, dark green vegetables, liver, whole-grain cereals, and milk.

Xanthine oxidase, mol wt ca 275,000, present in milk, liver, and intestinal mucosa (131), is required in the catabolism of nucleotides. The free bases guanine and hypoxanthine from the nucleotides are converted to uric acid and xanthine in the intermediate. Xanthine oxidase catalyzes oxidation of hypoxanthine to xanthine and xanthine to uric acid. In these processes and in the oxidations catalyzed by aldehyde oxidase, molecular oxygen is reduced to H_2O_2(133). Xanthine oxidase is also involved in iron metabolism. Release of iron from ferritin requires reduction of Fe^{3+} to Fe^{2+} and reduced xanthine oxidase participates in this conversion (133).

2.10.1. Copper–Molybdenum Antagonism

A copper–molybdenum antagonism involving sulfate occurs in animals, ie, large amounts of molybdenum and sulfate can depress copper absorption (133). Cattle grazing on pasturage of high Mo content succumb to teart or peat scours, characterized by diarrhea and general wasting. Control involves increasing copper intake. The Cu– Mo antagonism has been observed in humans (133, 134). Significant increases in urinary copper excretion have been observed with increasing Mo intake (135).

2.10.2. Deficiency or Toxicity in Humans

Molybdenum deficiency in humans results in deranged metabolism of sulfur and purines and symptoms of mental disturbances (130). Toxic levels produce elevated uric acid in blood, gout, anemia, and growth depression. Faulty utilization results in sulfite oxidase deficiency, a lethal inborn error.

2.11. Chromium

The history of the investigations establishing the essentiality of chromium has been reviewed (136). An effect of brewer's yeast in preventing or curing impaired glucose tolerance in rats was revealed, and the active factor was identified as a Cr(III) organic complex, glucose tolerance factor (GTF) (137, 138).

2.11.1. Metabolic Functions

Chromium(III) potentiates the action of insulin and may be considered a cofactor for insulin (137, 138). In *in vitro* tests of epididymal fat tissue of chromium-deficient rats, Cr(III) increases the uptake of glucose only in the presence of insulin (137). The interaction of Cr(III) and insulin also is demonstrated by experimental

results indicating an effect of Cr(III) in translocation of sugars into cells at the first step of sugar metabolism. Chromium is thought to form a complex with insulin and insulin receptors (136).

There appears to be a chromium pool in individuals who are not chromium deficient (136). When there is an increase in level of circulating insulin in response to a glucose load, an increase in circulating chromium occurs over a period of 0.5–2 h. This is followed by a decline and excretion of chromium in urine increases. Chromium deficiency is indicated when no increase or a small increase in blood chromium level or urine chromium occurs.

2.11.2. Test Results with Humans

Studies of elderly people and mildly diabetic patients showed significant improvement in the glucose tolerance test (GTT) when chromium supplementation of 150–200 μg/d was given (136, 139–141). In other tests, these positive results were not obtained (142). It is possible that not all subjects are capable of utilizing inorganic chromium to the same extent. Some may require a preformed GTF. Chromium chloride supplementation has been effective in normalizing impaired glucose tolerance in malnourished children and in patients receiving total parenteral nutrition for a long time (143, 144). The most available form of chromium is GTF obtained from brewer's yeast. In human studies in which GTF was administered, one of the most significant results was normalization of the exaggerated insulin responses to glucose loads (145).

Attempts to isolate GTF from brewer's yeast have resulted in production of very active concentrates, but the substance is too labile to be obtained in the solid state (136). However, it has been shown that GTF is a Cr(III) complex containing two coordinated nicotinate radicals and other amino acid anions (146). Active preparations containing similar complexes have been synthesized (147). Chromium deficiency may also lead to atherosclerosis and peripheral neuropathy.

2.11.3. Chromium(III) Chemistry

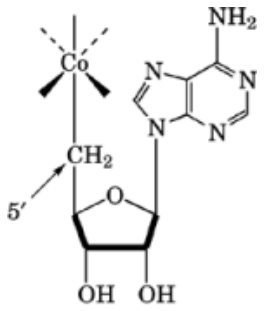
The most characteristic reactions of Cr(III) in aqueous solution at >4 pH, eg, in the intestine and blood, and hydrolysis and olation (147). As a consequence, inorganic polymeric molecules form that probably are not able to diffuse through membranes. This may be prevented by ligands capable of competing for coordination sites on Cr(III) (see Coordination compounds) (147). Thus any large fraction of ingested Cr(III) should be absorbed. Chromium(III) in the form of GTF may be more efficiently absorbed.

2.12. Cobalt

Cobalt is nutritionally available only as vitamin B_{12} (148). Although Co^{2+} can function as a replacement *in vitro* for other divalent cations, in particular Zn^{2+}, no *in vivo* function for inorganic cobalt is known for humans (149). In ruminant animals, B_{12} is synthesized by bacteria in the rumen.

2.12.1. B_{12} Vitamins

In foods, vitamin B_{12} (partial structure, **2**) occurs only in animal products (148). A particularly rich source is liver from which it was originally isolated following the successful use of liver in treatment of pernicious anemia, a form of megalo-blastic anemia not responsive to iron supplementation. Vitamin B_{12} is produced commercially by bacterial fermentation in the form of cyanocobalamin for use as a dietary supplement and for injection in the treatment of pernicious anemia. In vitamin B_{12}, the cobalt atom is at the center of the corrin ring coordinated to nitrogen atoms of four five-membered heterocyclic rings. In cyanocobalamin, the source of the cyanide is apparently contamination from the reagents used. Naturally occurring forms of B_{12} contain little or no cyanide (150). In coenzyme B_{12} the 5′-C of the deoxyadenosyl group is bonded to the cobalt atom. The chemical and biological activities of coenzyme B_{12} are dependent on this carbon–metal bond (151).



(2)

2.12.1.1. Metabolic Functions. In pernicious anemia, the bone marrow fails to produce mature erythrocytes as a result of defective cell division, a consequence of impaired DNA synthesis which requires vitamin B_{12}. If the disease goes untreated, extensive neurological damage, eg, irreversible degeneration of the spinal cord by demyelinization, may occur because of faulty fatty acid metabolism (148, 151). Coenzyme B_{12} is required in mammalian enzyme systems involving methylmalonyl CoA and methyl transferase (transmethylase). Methylmalonyl CoA is an intermediate in the metabolism of propionate which is converted to succinyl CoA. Transmethylase is required for methylation of homocysteine to methionine (150, 152).

2.12.1.2. Intrinsic Factor. Vitamin B_{12} deficiency commonly is caused by inadequate absorption resulting from a lack or insufficient intrinsic factor (IF) (153). Intrinsic factor is a glycoprotein, mol wt ca 50,000, which binds vitamin B_{12} in a 1:1 molar ratio. The B_{12}–IF complex, formed in the stomach, is absorbed in the ileum. Absorption in this part of the intestine occurs because of the specific characteristics of the cells of the microvilli (brush border) of the ileum (153). The IF remains in the intestine attached to the epithelial cells. Transport of B_{12} into the blood stream requires Ca^{2+}. In the blood, B_{12} is bound to transcobalamin II (transport protein). Whatever bound B_{12} is not utilized immediately is stored in the liver. With increasing quantities of dietary B_{12}, the fraction that is absorbed decreases. Generally, vitamin B_{12} is excreted in the urine, but with large intake, some is excreted in the bile. A nutritional excess of cobalt can lead to polycythemia.

2.13. Tin

The widespread use of canned foods results in a daily intake of tin that is ca 1–17 mg for an adult male (154). At this level it has not been shown to be toxic. Some grains also contain tin. Too much tin can adversely affect zinc balance and iron metabolism. Essentiality has not been confirmed for humans. It has been shown for the rat. An enhanced growth rate results from tin supplementation of low tin diets (85). Animals on deficient diets exhibit poor growth and decreased feed efficiency (155).

2.14. Vanadium

Vanadium is essential in rats and chicks (85, 156). Estimated human intake is less than 4 mg/d. In animals, deficiency results in impaired growth, reproduction, and lipid metabolism (157), and altered thyroid peroxidase activities (112). The levels of coenzyme A and coenzyme Q_{10} in rats are reduced and monoamine oxidase activity is increased when rats are given excess vanadium (157). Vanadium may play a role in the regulation of (NaK)–ATPase, phosphoryl transferases, adenylate cyclase, and protein kinases (112).

2.15. Nickel

There is considerable evidence for the essentiality of nickel in animals. Various pathological manifestations of nickel deficiencies have been observed in chicks, cows, goats, pigs, rats, and sheep (112, 158, 159). Average intake is reported to be about 60–260 μg/d, and a dietary requirement for humans of less than 100 μg/d has been suggested (101, 112). *In vitro* studies have shown nickel to be an activator of several enzymes. Nickel stabilizes RNA and DNA against thermal denaturation and may have a role in membrane structure or metabolism (158). Nickel may be required for metabolism of odd-chain fatty acids (112). A nickel metalloprotein has been isolated from human serum (158).

2.16. Arsenic

Arsenic is under consideration for inclusion as an essential element. No clear role has been established, but aresenic, long thought to be a poison, may be involved in methylation of macromolecules and as an effector of methionine metabolism (158, 160). Most research has focused on the toxicity or pharmaceutical properties of arsenic (158).

3. Health and Safety Factors

Under unusual circumstances, toxicity may arise from ingestion of excess amounts of minerals. This is uncommon except in the cases of fluorine, molybdenum, selenium, copper, iron, vanadium, and arsenic. Toxicosis may also result from exposure to industrial compounds containing various chemical forms of some of the minerals. Aspects of toxicity of essential elements have been published (161).

Efficient homeostatic controls of mammalians generally prevent serious toxicity from ingestion of the mineral nutrients. Toxicity may occur under conditions far removed from those of nutritional significance or for individuals suffering from some pathological conditions. Because of very low concentrations in foods, the trace elements are not toxic under normal nutritional conditions. Exceptions are selenium and iron (162).

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