29: Micronutrients: Minerals

Overview

Minerals are inorganic substances (elements) required in small amounts by the body. They function in a number of processes including formation of bones and teeth, fluid balance, nerve conduction, muscle contraction, signaling, and catalysis. (Note: Several minerals are essential enzyme cofactors.) Like the organic vitamins (see Chapter 28), minerals are micronutrients required in mg or µg amounts. Those required by adults in the largest amounts (>100 mg/day) are referred to as the macrominerals. Minerals required in amounts between 1 and 100 mg/day are the microminerals (trace minerals). Ultratrace minerals are required in amounts <1 mg/day (Fig. 29.1). (Note: The classification of specific minerals into these categories can vary among sources.) Mineral concentrations in the body are influenced by their rates of absorption and excretion.

FIGURE 29.1

Classification of minerals and recommended amounts to be consumed/day by adults.

(Note: *An adequate intake [AI] is set if insufficient scientific evidence is available to calculate a Recommended Dietary Allowance [RDA].)

MINERAL CLASSIFICATIONS	RDA (OR AI*) FOR ADULTS
MACROMINERALS	
Calcium (Ca)	1,000–2000 mg
Chloride (Cl)	1,800–2,300 mg*
Magnesium (Mg)	310–420 mg
Phosphorus (P)	700 mg
Potassium (K)	4,700 mg*
Sodium (Na)	1,500 mg*
MICROMINERALS (TRACE)	
Chromium (Cr)	30–35 mg
Copper (Cu)	900 µg
Fluorine (as fluoride [F^-])	3–4 mg
Iron (Fe)	8–18 mg
Manganese (Mn)	1.8–2.3 mg*
Zinc (Zn)	8–11 mg
MICROMINERALS (ULTRATRACE)	
Iodine (I)	150 µg
Molybdenum (Mo)	45 µg
Selenium (Se)	55 µg

Macrominerals

The macrominerals include calcium (Ca^{2+}), phosphorus ([P] as inorganic phosphate [P_i, or PO_4^{3-}]), magnesium (Mg^{2+}), sodium (Na^+), chloride (Cl^-), and potassium (K^+). (Note: The free ionic forms are electrolytes.)

Calcium and phosphorus

These macrominerals are considered together because they are components of hydroxylapatite ($Ca_5[PO_4]_3OH$), which makes up bones and teeth.

Calcium

Ca^{2+} is the most abundant mineral in the body, with approximately 98% being found in bones. The remainder is involved in a number of processes such as signaling, muscle contraction, and blood clotting. Ca^{2+} binds to a variety of proteins including calmodulin (see Chapter 11), **phospholipase A_2** (see p. 236), and **protein kinase C** (see p. 227) and alters their activity. (Note: Calbindin is a vitamin D–induced intracellular Ca^{2+}-binding protein involved in Ca^{2+} absorption in the intestine [see p. 439].) Dairy products, many green vegetables (e.g., broccoli, but not spinach), and fortified orange juice are good dietary sources. Although dietary deficiency syndromes are unknown, average Ca^{2+} intake in the United States is insufficient for optimal bone health. Toxicity is seen only with supplements (tolerable upper limit [UL] = 2,500 mg/day for adults). Hypercalcemia (elevated serum Ca^{2+}) can result from overproduction of parathyroid hormone (PTH). This may cause constipation and kidney stones. Hypocalcemia (low serum Ca^{2+}) can result from a deficiency of PTH or vitamin D. It can lead to bone demineralization (resorption). (Note: The hormonal regulation of serum Ca^{2+} levels was presented in the vitamin D section of Chapter 28 and is reviewed in 3. below.)

Bone mass increases from infancy through the early reproductive years and then shows an age-related loss in both men and women that increases the risk for fracture. This loss is greatest in postmenopausal Caucasian women. Some studies have shown that supplementation with Ca^{2+} and vitamin D decreases this risk.

Phosphorus

Free phosphate (P_i) is the most abundant intracellular anion. However, 85% of the body's phosphorus is in the form of inorganic hydroxylapatite, with most of the remainder in intracellular organic compounds such as phospholipids, nucleic acids, ATP, and creatine phosphate. Phosphate is supplied as ATP for **kinases** and as P_i for **phosphorylases** (e.g., **glycogen phosphorylase**, see Chapter 11). (Note: Its addition by **kinases** or removal by **phosphatases** is an important means of covalent regulation of enzymes [see Chapter 24].) Phosphorus is widely distributed in food (milk is a good source), and dietary deficiency is rare. Hypophosphatemia can be caused by refeeding carbohydrates to malnourished patients (refeeding syndrome, see p. 414), overuse of aluminum-containing antacids (aluminum chelates P_i), and increased urinary loss in response to increased production of PTH (see below). Muscle weakness is a common symptom. Hyperphosphatemia is caused primarily by decreased PTH levels. The excess P_i can combine with Ca^{2+} and form crystals that deposit in soft tissue (metastatic calcification). (Note: The Ca^{2+}/P_i ratio is important for bone formation [the ratio is approximately 2/1 in bone], and some experts are concerned that replacement of Ca^{2+}-rich milk by Ca^{2+}-poor, P_i-rich soft drinks can affect bone health.)

Hormonal regulation

Serum levels of Ca^{2+} and P_i are primarily controlled by calcitriol (1,25-dihydroxycholecalciferol, the active form of vitamin D) and PTH, both of which respond to a decrease in serum Ca^{2+}. Calcitriol, produced by the kidneys, increases serum Ca^{2+} and P_i by increasing bone resorption and intestinal absorption and renal reabsorption of Ca^{2+} and P_i (Fig. 29.2). PTH (from the parathyroid glands) increases serum Ca^{2+} by increasing bone resorption, increasing renal reabsorption of Ca^{2+}, and activating the renal **1-hydroxylase** that produces calcitriol from calcidiol (25-OH-D3) (Fig. 29.3). In contrast to calcitriol, PTH decreases P_i reabsorption in the kidneys, lowering serum P_i. (Note: High serum P_i increases PTH and decreases calcitriol.) A third hormone, calcitonin (from the C cells of the thyroid gland), responds to elevated serum Ca^{2+} levels by promoting bone mineralization and increasing renal excretion of Ca^{2+} (and P_i).

FIGURE 29.2

Effect of calcitriol on serum calcium (Ca^{2+}).

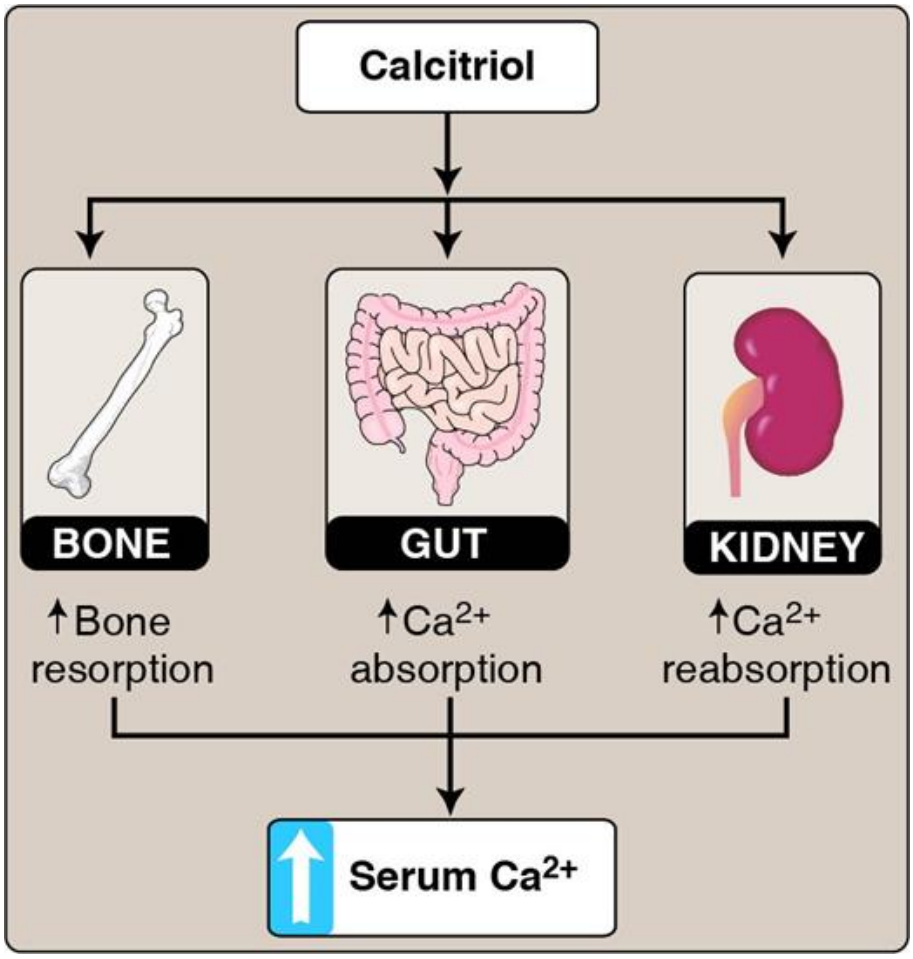
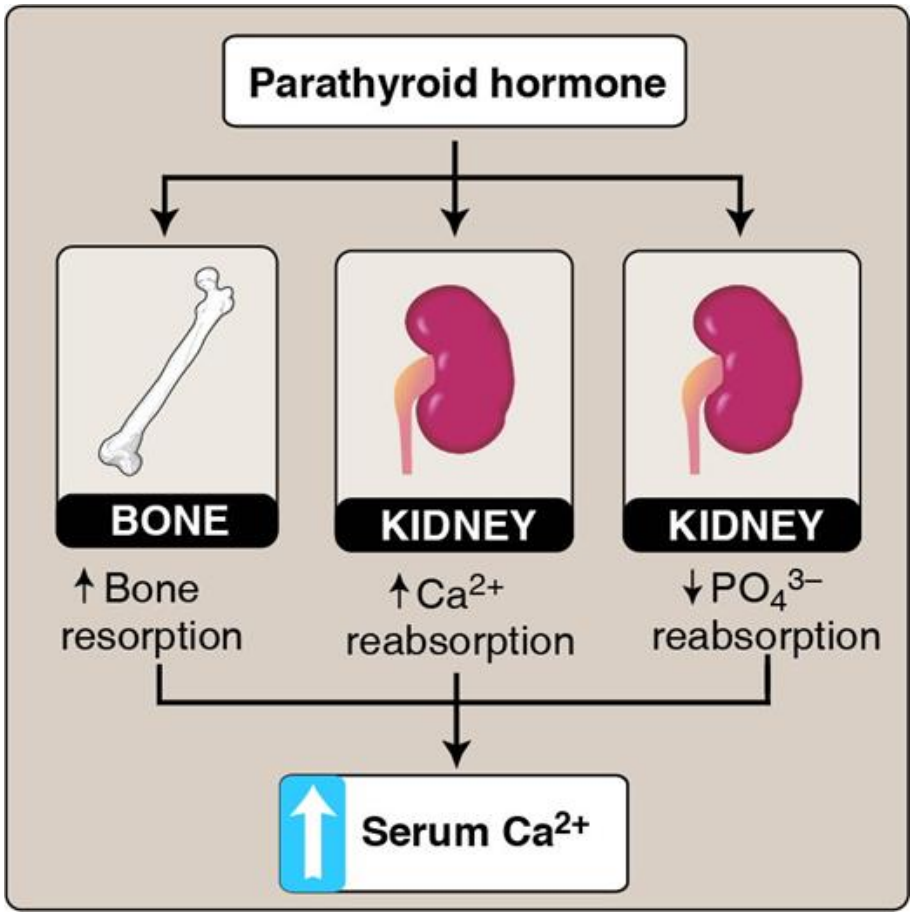


FIGURE 29.3

Effect of parathyroid hormone on serum calcium (Ca^{2+}).

PO_4^{3-} = phosphate.



Magnesium

About 60% of the body's Mg^{2+} is in bone, but it accounts for just 1% of the bone mass. The mineral is required by a variety of enzymatic reactions, including phosphorylation by **kinases** (Mg^{2+} binds the ATP cosubstrate) and phosphodiester bond formation by **DNA** and **RNA polymerase**s. Mg^{2+} is widely distributed in foods, but the average intake in the United States is below the recommended level. Hypomagnesemia can result from decreased absorption or increased excretion of Mg^{2+}. Symptoms include hyperexcitability of skeletal muscles and nerves and cardiac arrhythmias. With hypermagnesemia, hypotension is seen. (Note: Magnesium sulfate is used in the treatment of preeclampsia, a hypertensive disorder of pregnancy.)

Sodium, chloride, and potassium

These macrominerals are considered together because they play important roles in several physiologic processes. For example, they maintain water balance, osmotic equilibrium, acid–base balance (pH), and the electrical gradients across cell membranes (membrane potential) that are essential for the functioning of neurons and myocytes. (Note: These processes are discussed in *Lippincott ® Illustrated Reviews: Physiology*.)

Sodium and chloride

Na^+ and Cl^- are primarily extracellular electrolytes. They are readily absorbed from foods containing salt (NaCl), much of which comes from processed foods. (Note: Na^+ is required for the intestinal absorption [and renal reabsorption] of glucose and galactose [see Chapter 7] and free amino acids [see p. 275] by Na^+-linked transporters. Cl^- is used to form hydrochloric acid required for digestion [see p. 274].) In the United States, the average daily consumption of NaCl is 1.5 to 3 times the adequate intake (AI) of 3.8 mg/day (UL = 5.8 g/day). Dietary deficiency is rare.

Hypertension

Na^+ intake is related to blood pressure (BP).

Ingestion of Na^+ stimulates thirst centers in the brain and secretion of antidiuretic hormone from the pituitary, leading to water retention. This results in an increase in plasma volume and, consequently, an increase in BP. Chronic hypertension can damage the heart, kidneys, and blood vessels. Modest reductions in Na^+ intake have been shown to result in modest reductions in BP.

Hyper- and hyponatremia

Hypernatremia, typically caused by excess water loss, and hyponatremia, typically caused by decreased ability to excrete water, can result in severe brain damage. (Note: Chronic hyponatremia increases Ca^{2+} excretion and can result in osteoporosis [low bone mass].)

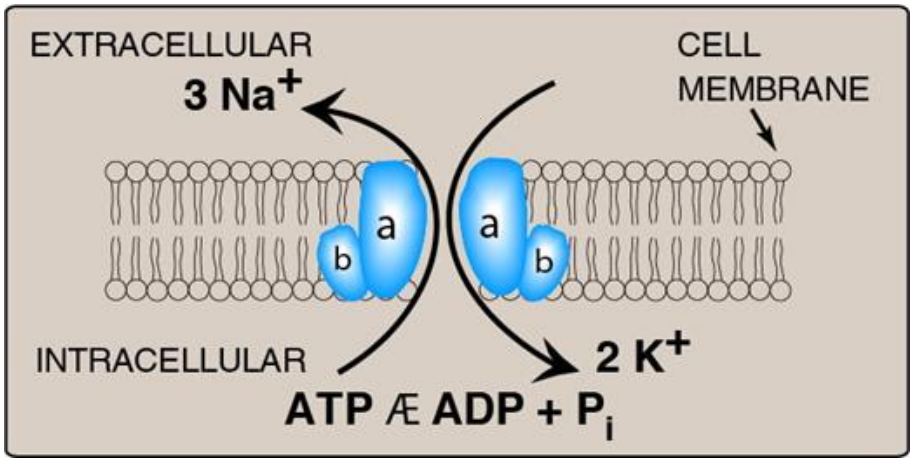
Potassium

In contrast to Na^+, K^+ is primarily an intracellular electrolyte. (Note: The concentration differential of Na^+ and K^+ across the cell membrane is maintained by the **Na^+/K^+ ATPase** [Fig. 29.4].) In contrast to Na^+ and Cl^-, K^+ (like Mg^{2+}) is underingested in Western diets because its primary sources, fruits and vegetables, are underingested. (Note: Increasing dietary K^+ decreases BP by increasing Na^+ excretion.) There is a narrow range for normal serum K^+ levels, and even modest changes (up or down, resulting in hyper- or hypokalemia) can result in cardiac arrhythmias and skeletal muscle weakness. (Note: Hypokalemia can result from the inappropriate use of laxatives to lose weight.) No UL for K^+ has been established.

FIGURE 29.4

Na^+/K^+ ATPase.

Na^+ = sodium; K^+ = potassium; ADP = adenosine diphosphate; P_i = phosphate.



Trace Minerals (Microminerals)

The trace minerals include copper (Cu), iron (Fe), manganese (Mn), and zinc (Zn). They are required by adults in amounts between 1 and 100 mg/day.

Copper

Cu is a key component of several enzymes that play critical functions in the body (Fig. 29.5). These include **ferroxidases** such as the **ceruloplasmin** and **hephaestin** involved in the oxidation of ferrous iron (Fe^{2+}) to the ferric form (Fe^{3+}) that is required for its intracellular storage or transport through blood (see B.1. below). Meat, shellfish, nuts, and whole grains are good dietary sources of Cu. Dietary deficiency is uncommon. If a deficiency does develop, anemia may be seen because of the effect on Fe metabolism. Toxicity from dietary sources is rare (UL = 10 mg/day). Menkes syndrome and Wilson disease are genetic causes of Cu deficiency and Cu overload, respectively.

Menkes syndrome

In Menkes syndrome (“kinky hair” disease), a rare X-linked (1:140,000 males) disorder, efflux of dietary Cu out of intestinal enterocytes into the circulation by a Cu-transporting *ATPase* (*ATP7A*) is impaired. This results in systemic Cu deficiency. Consequently, urinary and serum-free (unbound) Cu are low, as is the concentration of **ceruloplasmin**, which carries over 90% of the Cu in the circulation (Fig. 29.6). Progressive neurologic degeneration and connective tissue disorders are seen, as are changes to hair. Parenteral administration of Cu has been used as a treatment with varying success. (Note: The mildest form of Menkes syndrome is called occipital horn syndrome.)

FIGURE 29.5

Examples of enzymes that require copper (Cu).

ETC = electron transport chain.

Cu-REQUIRING ENZYME	FUNCTION
Cytochrome c oxidase	Transfers electrons from cytochrome c to oxygen in the ETC
Dopamine b-hydroxylase	Hydroxylates dopamine to norepinephrine
Ferroxidases	Oxidize iron
Lysyl oxidase	Forms cross-links in collagen and elastin
Tyrosinase	Synthesizes melanin
Superoxide dismutase (nonmitochondrial form; also requires zinc)	Converts superoxide to hydrogen peroxide

FIGURE 29.6

Comparison of Menkes syndrome and Wilson disease.

Cu = copper; AR = autosomal recessive.

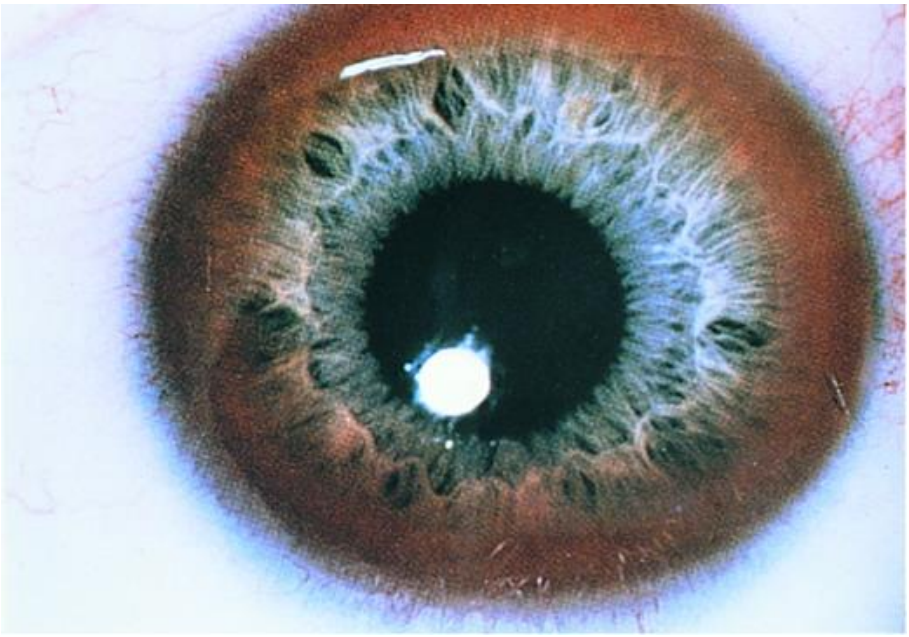
VARIABLE	MENKES	WILSON
Whole-body Cu	Low	High
Free serum Cu	Low	High
Urinary Cu	Low	High
Inheritance	X-linked	AR
Cu-transporting ATPase affected	ATP7A	ATP7B

Wilson disease

In Wilson disease, an autosomal-recessive (AR) disorder affecting 1:35,000 live births, efflux of Cu from the liver by **ATP7B** is impaired. Cu accumulates in the liver; leaks into the blood; and is deposited in the brain, eyes, kidneys, and skin. In contrast to Menkes syndrome, urinary and serum-free Cu are high (see Fig. 29.6). Hepatic dysfunction and neurologic and psychiatric symptoms are seen. Kayser–Fleischer rings (corneal deposits of Cu) may be present (Fig. 29.7). Life-long use of Cu-chelating agents, such as penicillamine, is the treatment.

FIGURE 29.7

Kaiser–Fleischer rings.



The bioavailability (percent of the amount ingested that is able to be absorbed) of a mineral can be influenced by other minerals. For example, excess Zn decreases the absorption of Cu, and Cu is needed for the absorption of Fe.

Iron

The adult body typically contains 3 to 4 g of Fe. It is a component of many proteins, both catalytic (e.g., **hydroxylases** such as **prolyl hydroxylase** and noncatalytic. Iron can be linked to sulfur (S) as seen in the Fe–S proteins of the electron transport chain, or it can be part of the heme prosthetic group in proteins such as hemoglobin (approximately 70% of all Fe), myoglobin, and the cytochromes. (Note: Free ionic Fe is toxic because it can cause production of the hydroxyl radical, a reactive oxygen species [ROS].) Dietary Fe is available as Fe^{2+} in heme (animal sources) and Fe^{3+} in nonheme sources (plants). Heme iron is less abundant, but it is better absorbed. Meat, poultry, some shellfish, iron-fortified foods such as breakfast cereals and grains, lentils, and green leafy vegetables are good dietary sources of Fe. About 10% of ingested Fe is absorbed. This amount, approximately 1 to 2 mg/day, is sufficient to replace Fe lost from the body primarily by the sloughing of cells.

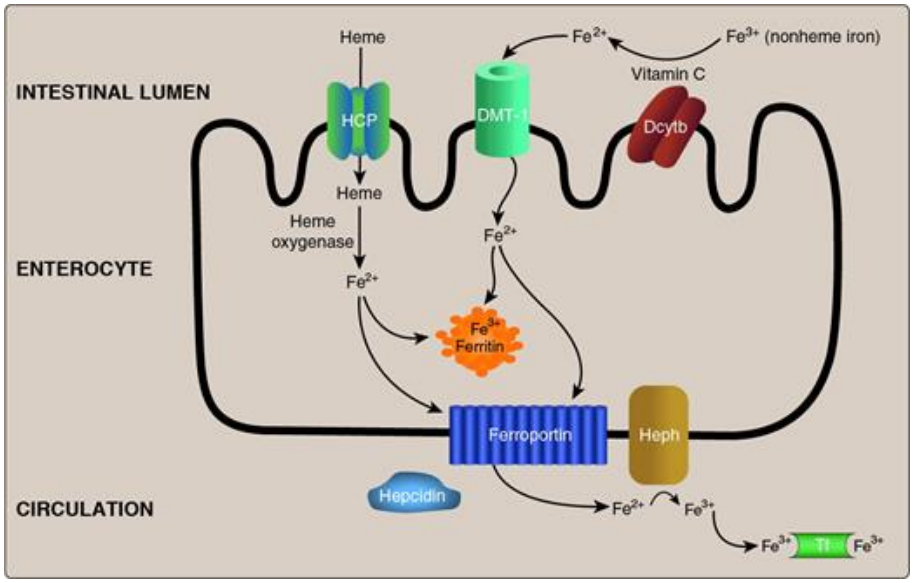
Absorption, storage, and transport

Intestinal uptake of heme is by a heme carrier protein (Fig. 29.8). Within the enterocytes, **heme oxygenase** releases Fe^{2+} from heme (see p. 314). Nonheme Fe is taken up via the apical membrane protein divalent metal ion transporter-1 (DMT-1). (Note: Vitamin C enhances absorption of nonheme Fe because it is the coenzyme for **duodenal cytochrome b [Dcytb]**, a **ferrireductase** that reduces Fe^{3+} to Fe^{2+}.) Absorbed Fe^{2+} from heme and nonheme sources has two possible fates: It can be (1) oxidized to Fe^{3+} and stored by the intracellular protein ferritin (up to 4,500 Fe^{3+}/ferritin) or (2) transported out of the enterocyte by the basolateral membrane protein ferroportin, oxidized by the Cu-containing membrane protein **hephaestin**, and taken up by the plasma transport protein transferrin (2 Fe^{3+}/transferrin), as shown in Figure 29.8. (Note: Cells other than enterocytes use the Cu-containing plasma protein **ceruloplasmin** in place of **hephaestin**.) In normal individuals, transferrin (Tf) is about one-third saturated with Fe^{3+}. Ferroportin, the only known exporter of Fe from cells to the blood in humans, is regulated by the hepatic peptide hepcidin that induces internalization and lysosomal degradation of ferroportin. Therefore, hepcidin is the central molecule in Fe homeostasis. (Note: Transcription of hepcidin is suppressed when Fe is deficient.)

FIGURE 29.8

Absorption, storage, and transport of dietary iron (Fe).

HCP = heme carrier protein; DMT = divalent metal ion transporter; *Dcytb* = *duodenal cytochrome b* (a *ferrireductase*); *Heph* = *hephaestin*; Tf = transferrin.



Recycling

Macrophages phagocytose old and/or damaged red blood cells (RBCs), freeing heme Fe that is sent out of the cells via ferroportin, oxidized by **ceruloplasmin**, and transported by Tf as described above. This recycled Fe meets approximately 90% of our daily need, which is predominantly for erythropoiesis.

Uptake

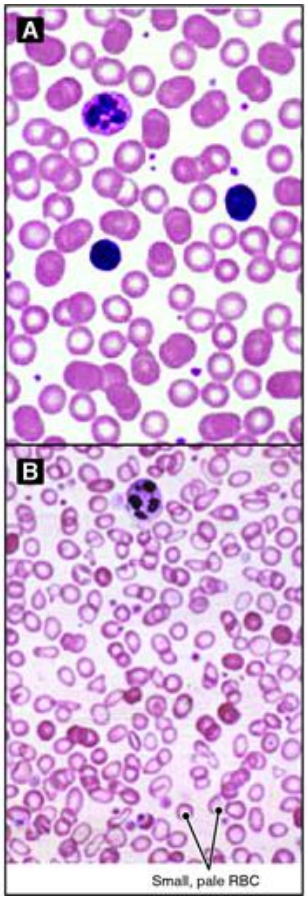
Tf-bound Fe^{3+} from enterocytes and macrophages binds to receptors (TfR) on erythroblasts and other Fe-requiring cells and is taken up by receptor-mediated endocytosis. The Fe^{3+} is released from Tf for use (or stored on ferritin), and the TfR (and Tf) is recycled in a process similar to the receptor-mediated endocytosis seen with low-density lipoprotein particles (see p. 257). (Note: Regulation of the translation of the messenger RNA for ferritin and the TfR by iron regulatory proteins and iron-responsive elements is discussed in Chapter 33.)

Deficiency

Fe deficiency can result in a microcytic, hypochromic anemia (Fig. 29.9), the most common anemia in the United States, as a result of decreased hemoglobin synthesis and, consequently, decreased RBC size. Treatment is the administration of Fe in various ways depending on the severity of anemia.

FIGURE 29.9

A: Normal red blood cells (RBCs). **B:** Small (microcytic), pale (hypochromic) RBC in microcytic anemia.



Excess

Fe overload can occur with accidental ingestion. (Note: Acute Fe poisoning is the most common cause of poisoning deaths of children age <6 years [UL = 40 mg/day for children, 45 mg/day for adults].) Treatment is use of an Fe chelator. Overload can also occur with genetic defects. An example is hereditary hemochromatosis (HH), an AR disorder of Fe overload found primarily in those of Northern European ancestry. It is most commonly caused by mutations to the HFE (high Fe) gene. Hyperpigmentation with hyperglycemia ("bronze diabetes") and damage to the liver (a major storage site for Fe), pancreas, and heart may be seen. In HH, serum Fe and Tf saturation are elevated. Treatment is phlebotomy or use of Fe chelators. (Note: Fe overload is seen with mutations to proteins of Fe metabolism that result in inappropriately low levels of hepcidin. It can result in hemosiderosis [the deposition of hemosiderin, an intracellular, insoluble storage form of Fe].)

Manganese

Mn is important for the function of several enzymes (Fig. 29.10). Whole grains, legumes (e.g., beans and peas), nuts, and tea (especially green tea) are good sources of the mineral. Consequently, Mn deficiency in humans is rare. Toxicity from foods and/or supplements is also rare (UL = 11 mg/day for adults).

FIGURE 29.10

Examples of enzymes that require manganese (Mn).

OAA = oxaloacetate.

Mn-REQUIRING ENZYME	FUNCTION
Arginase-I	Hydrolyzes arginine to urea plus ornithine in the urea cycle
Glycosyltrans-ferases	Transfer sugars in proteoglycan synthesis
Pyruvate carboxylase	Carboxylates pyruvate to OAA in gluconeogenesis
Superoxide dismutase (mitochondrial form)	Converts superoxide to hydrogen peroxide

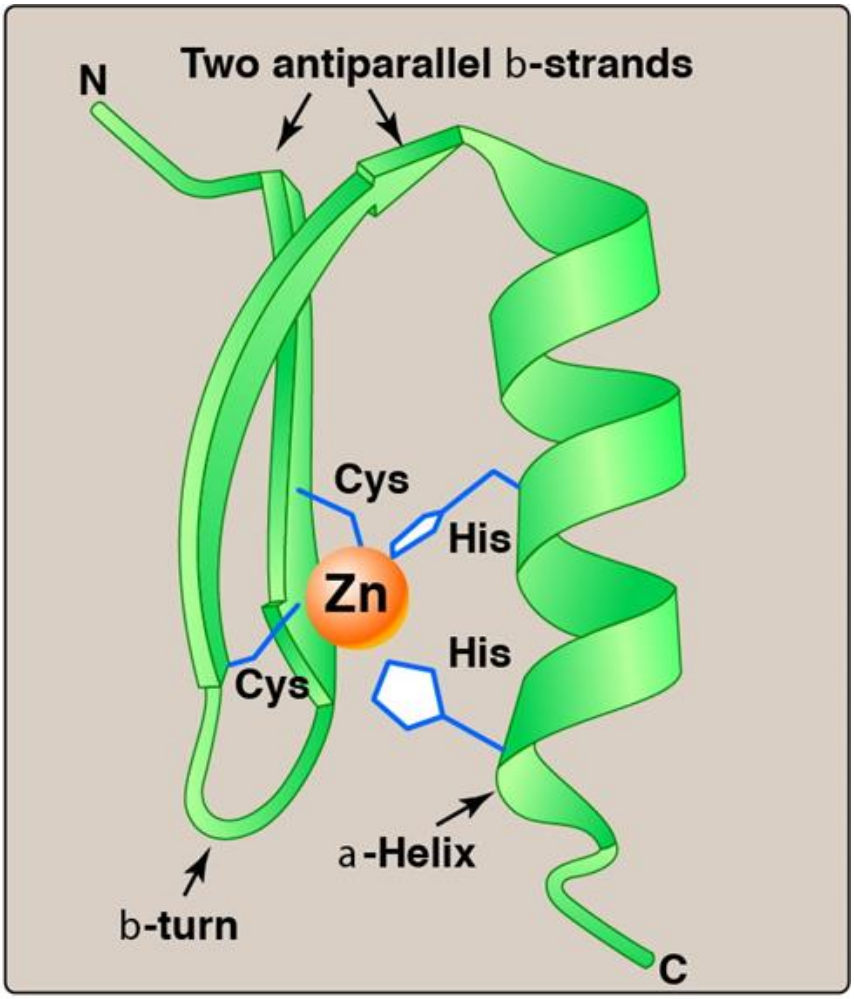
Zinc

Zn plays important structural and catalytic functions in the body. Zinc fingers are supersecondary structures in proteins (e.g., transcription factors) that bind to DNA and regulate gene expression (Fig. 29.11). Hundreds of enzymes require Zn for activity. Examples include **alcohol dehydrogenase**, which oxidizes ethanol to acetaldehyde (see p. 352); **carbonic anhydrase**, which is important in the bicarbonate buffer system (see Chapter 3); **ALA dehydratase** (porphobilinogen synthase) of heme synthesis, which is inhibited by lead (lead replaces the zinc; see p. 310); and the nonmitochondrial isoform of **superoxide dismutase** (SOD), which also requires Cu (see Fig. 29.5). Dietary sources of Zn include meat, fish, eggs, and dairy products. Phytates (phosphate storage molecules in plants such as grains, seeds, legumes, some nuts) irreversibly bind Zn in the intestine, decreasing its absorption, and can result in a deficiency. (Note: Phytates may also bind Ca^{2+} and nonheme Fe.) Several drugs (e.g., penicillamine) chelate metals, and their use may cause Zn deficiency. (Note: Severe Zn deficiency is seen in acrodermatitis enteropathica, an autosomal recessive disorder which arise due to a defect in the intestinal transporter for Zn. Symptoms include rashes around the orifices and in the limbs, slowed growth and development, diarrhea, and immune deficiencies. Vision problems may also occur because Zn is needed in the metabolism of vitamin A.)

FIGURE 29.11

Zinc (Zn) finger is a common motif in proteins that bind DNA.

Cys = cysteine; His = histidine.



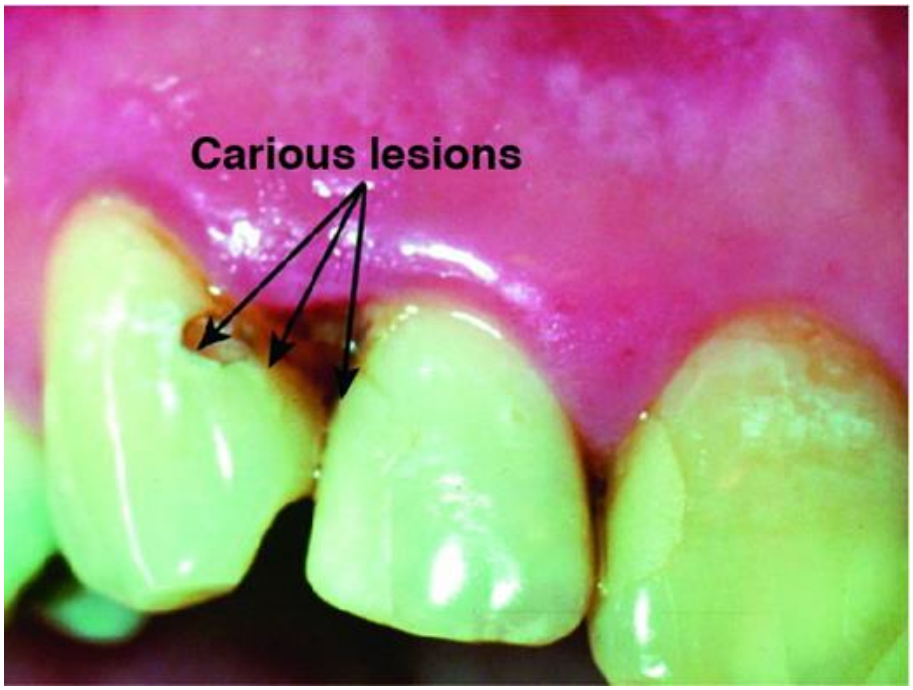
Eukaryotic cells infected with bacteria can restrict availability of the essential micronutrients Fe, Mn, and Zn to the pathogens. This decreases the intracellular survival of the pathogen and is known as “nutritional immunity.”

Other microminerals

Chromium (Cr) and fluorine (F) also play roles in the body. Cr potentiates the action of insulin by an unknown mechanism. It is found in fruits, vegetables, dairy products, and meat. F (as fluoride [F^-]) is added to water in many parts of the world to reduce the incidence of dental caries (Fig. 29.12). F^- replaces the hydroxyl group of hydroxylapatite, forming fluoroapatite that is more resistant to the enamel-dissolving acid produced by mouth bacteria.

FIGURE 29.12

Dental caries (cavities).



Ultratrace Minerals

The ultratrace minerals include iodine (I), selenium (Se), and molybdenum (Mo). They are required by adults in amounts <1 mg/day.

Iodine

Iodine is utilized in the synthesis of the thyroid hormones triiodothyronine (T_3) and thyroxine (T_4) that are required for development, growth, and metabolism. Circulating iodide (I^-) is taken up ("trapped") and concentrated in the epithelial follicular cells of the thyroid gland. It then is sent into the colloid of the follicular lumen where it is oxidized to iodine (I_2) by **thyroperoxidase (TPO)**, as shown in Figure 29.13. *TPO* then uses I_2 to iodinate selected tyrosine residues in thyroglobulin (Tg), forming monoiodinated tyrosine (MIT) and diiodinated tyrosine (DIT), as shown in Figure 29.14. (Note: Tg is synthesized and secreted into colloid by follicular cells.) The coupling of two DIT on Tg gives T_4, whereas coupling one MIT and one DIT gives T_3. The iodinated Tg is endocytosed and stored in follicular cells until needed, at which time it is proteolytically digested to release T_3 and T_4, which are secreted into the circulation (see Fig. 29.13). Under normal conditions, approximately 90% of secreted thyroid hormone is T_4 that is carried by transthyretin. In target tissues (e.g., the liver and developing brain), T_4 is converted to T_3 (the more active form) by Se-containing **deiodinases**. T_3 binds to a nuclear receptor that binds DNA at thyroid response elements and functions as a transcription factor. (Note: Thyroid hormone production is controlled by thyrotropin [thyroid-stimulating hormone (TSH)] from the anterior pituitary. TSH secretion is itself controlled by thyrotropin-releasing hormone [TRH] from the hypothalamus.)

Hypothyroidism

Underingestion of iodine (I) can result in goiter, an enlargement of the thyroid in response to excessive stimulation by TSH, as shown in Figure 29.15. More severe deficiency results in hypothyroidism that is characterized by fatigue, weight gain, decreased thermogenesis, and decreased metabolic rate (see p. 404). If hormone deficiency occurs during fetal and infant development (congenital hypothyroidism), irreversible intellectual disability (formerly called "cretinism"), hearing loss, spasticity, and short stature can result. In the United States, dairy products, seafood, and meat are the primary sources of I. The use of iodized salt has greatly reduced dietary I deficiency. (Note: Autoimmune destruction of *TPO* is a cause of Hashimoto thyroiditis [a primary hypothyroidism].)

FIGURE 29.13

Thyroid hormone synthesis.

Tg = thyroglobulin; I^- = iodide; I_2 = iodine; *TPO* = *thyroperoxidase*; MIT = monoiodinated tyrosine; DIT = diiodinated tyrosine; T_3 = triiodothyronine; T_4 = thyroxine.

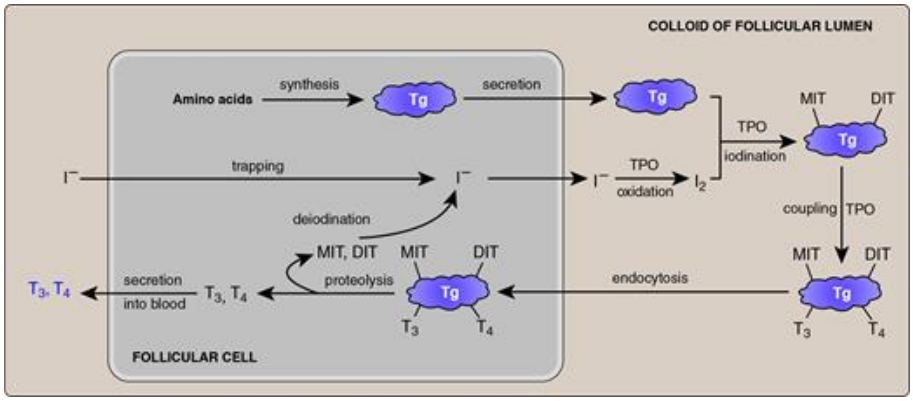


FIGURE 29.14

Iodination of thyroglobulin (Tg) with production of MIT and DIT.

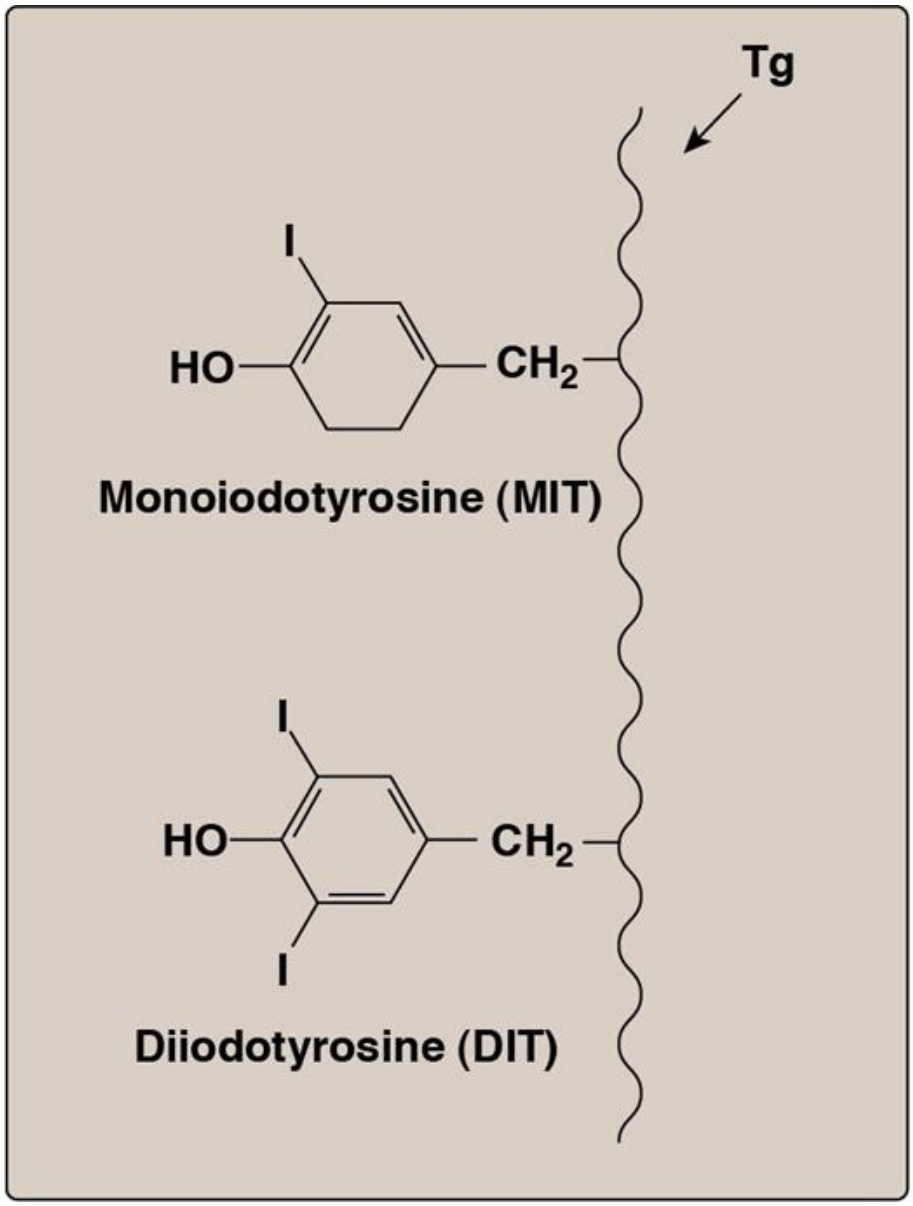
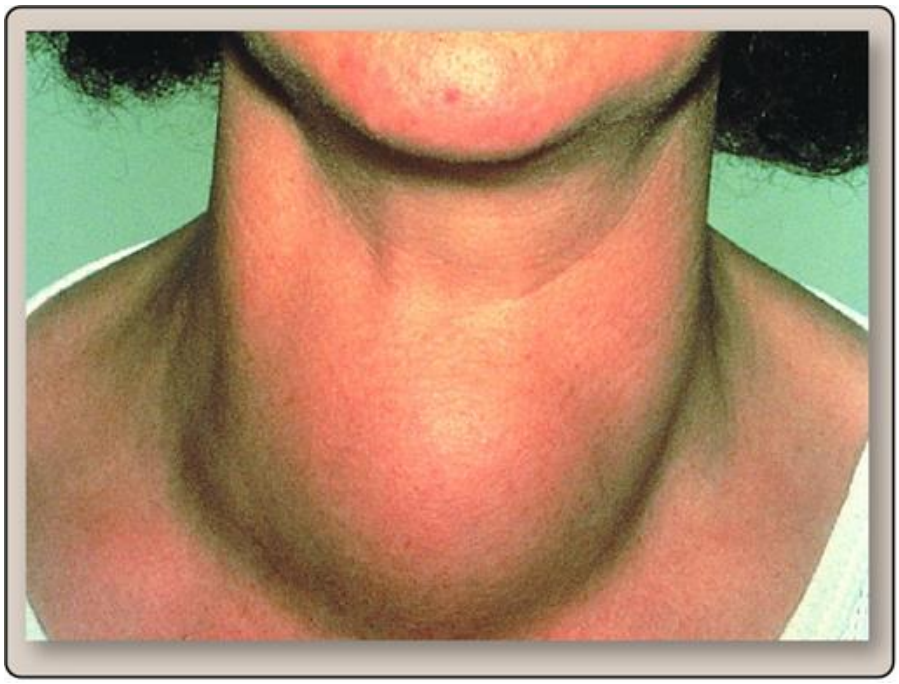


FIGURE 29.15

Goiter.

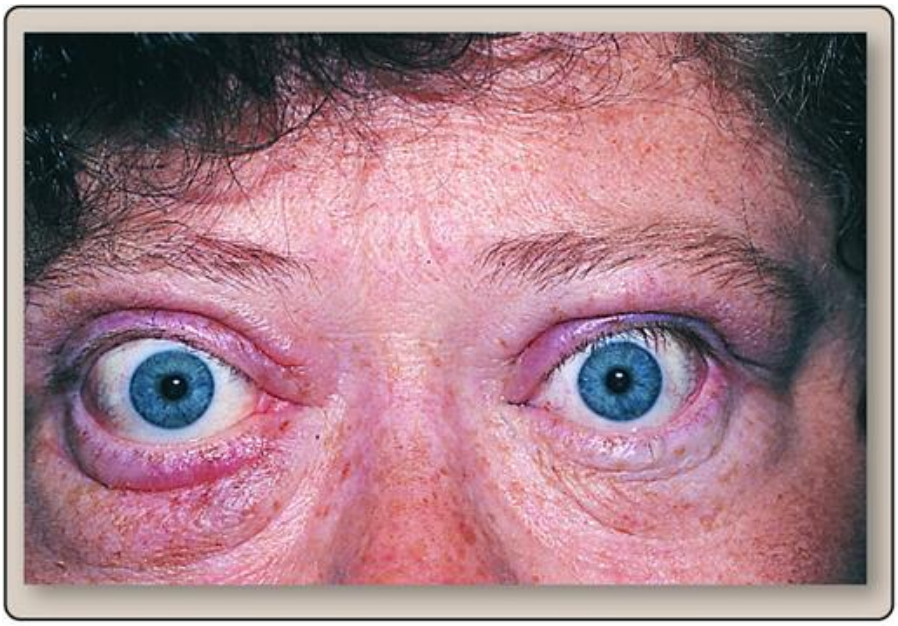


Hyperthyroidism

This condition is the result of overproduction of thyroid hormone. Although it can be caused by overingestion of I-containing supplements (UL = 1.1 g/day for adults), the most common cause of hyperthyroidism is Graves disease, in which an antibody that mimics the effect of TSH is produced, resulting in dysregulated production of thyroid hormone. This can cause nervousness, weight loss, increased perspiration and heart rate, protruding eyes (exophthalmos, Fig. 29.16), and goiter.

FIGURE 29.16

Exophthalmos.



Selenium

Selenium (Se) is present in approximately 25 human proteins (selenoproteins) as a constituent of the amino acid selenocysteine, which is derived from serine (see p. 297). Selenoproteins include **glutathione peroxidase** that oxidizes glutathione in the reduction of hydrogen peroxide, a ROS, to water (see Chapter 13); **thioredoxin reductase** that reduces thioredoxin, a coenzyme of **ribonucleotide reductase** (see p. 330); and **deiodinases** that remove iodine from thyroid hormones. Meat, dairy products, and grains are important dietary sources. Keshan disease, first identified in China, is a cardiomyopathy caused by eating foods produced from Se-deficient soil. Toxicity (selenosis) caused by overingestion of supplements causes brittle nails and hair. Cutaneous and neurologic effects may also be seen (UL = 400 µg in adults).

Molybdenum

Molybdenum (Mo) functions as a cofactor for a small number of mammalian **oxidases** (Fig. 29.17). Legumes are important dietary sources. No dietary deficiency syndromes are known. Mo has low toxicity in humans (UL = 2 mg/day in adults).

FIGURE 29.17

Enzymes (*oxidases*) that require molybdenum (Mo).

Mo-REQUIRING ENZYME	FUNCTION
Aldehyde oxidase	Metabolizes drugs
Sulfite oxidase	Converts sulfite to sulfate in metabolism of the sulfur-containing amino acids methionine and cysteine
Xanthine oxidase	Oxidizes hypoxanthine to xanthine and xanthine to uric acid in purine degradation

Cobalt (Co), an ultratrace mineral, is a component of vitamin B_{12} (cobalamin, see p. 425), which is required as methylcobalamin in the remethylation of homocysteine to methionine (see p. 293) or adenosylcobalamin in the isomerization of methylmalonyl coenzyme A (CoA) to succinyl CoA (see p. 215). No Recommended Dietary Allowance or Daily Reference Intake (see p. 403) has been established for Co.

Chapter Summary

The minerals are summarized in Figure 29.18.

FIGURE 29.18

Summary of minerals.

PTH = parathyroid hormone; Cl^- = chloride; S = sulfur; T_3 = triiodothyronine; T_4 = thyroxine.

CLASSIFICATION	FUNCTION(S)	NOTES
Macrominerals: >100 mg/day for adults		
Calcium (Ca)	Component of hydroxylapatite ($Ca_5[PO_4]_3OH$) of bone and teeth, muscle contraction, signaling, blood clotting	Dietary deficiencies unknown; toxicity from supplements; hypocalcemia with PTH or vitamin D deficiency causes kidney stones; hypercalcemia with increased PTH causes bone resorption
Chloride (Cl)	Fluid balance (along with Na, K), digestion	Dietary deficiency rare; overingested as NaCl
Magnesium (Mg)	Component (minor) of bone; regulates enzyme activity (binds substrate or enzyme)	Average U.S. intake is below recommended level; hyperexcitability and arrhythmias seen with hypomagnesemia; hypotension with hypermagnesemia
Phosphorus (P)	Component of hydroxylapatite of bone and teeth, energy storage, membrane structure, regulation	Dietary deficiency rare; hypophosphatemia with muscle weakness in refeeding syndrome, increased PTH, and use of aluminum-containing antacids; hyperphosphatemia with metastatic calcification in PTH deficiency
Potassium (K)	Membrane potential, blood pressure	Average U.S. intake is below recommended level; modest changes up or down in serum level result in arrhythmias and muscle weakness
Sodium (Na)	Membrane potential; blood volume and pressure; uptake of glucose, galactose, and amino acids	Dietary deficiency rare; overingested as NaCl; hyponatremia seen with excess water loss; hypernatremia with water retention
Microminerals (Trace): 1–100 mg/day		
Chromium (Cr)	Potentiates insulin action	Mechanism unknown
Copper (Cu)	Enzyme cofactor	Dietary deficiency rare; Menkes (genetic systemic Cu deficiency) and Wilson (genetic systemic Cu overload)
Fluorine (as fluoride [F^-])	Increases resistance to enamel-dissolving acid of mouth bacteria	Deficiency results in dental caries
Iron (Fe)	Enzyme cofactor, oxygen binding, Fe-S proteins	Dietary deficiency results in microcytic anemia; hereditary hemochromatosis, a genetic disease of Fe overload, with "bronze diabetes" (hyperglycemia, hyperpigmentation)
Manganese (Mn)	Enzyme cofactor	Dietary deficiency rare
Zinc (Zn)	Enzyme cofactor, protein structure (Zn finger)	Phytates and some drugs decrease absorption; severe deficiency (acrodermatitis enteropathica) with transporter defect
Microminerals (Ultratrace): <1 mg/day		
Iodine (I)	Thyroid hormone (T_3, T_4) synthesis	Underingestion causes goiter, hypothyroidism with fatigue, weight gain, and decreased metabolic rate; neurologic damage in congenital deficiency; hyperthyroidism (overproduction of T_3, T_4) in Graves disease
Molybdenum (Mo)	Enzyme cofactor	Dietary deficiency unknown
Selenium (Se)	Found (as selenocysteine) in selenoproteins	Dietary deficiency rare (Keshan disease with Se-deficient soil), toxicity from supplements

Study Questions

For Questions 29.1–29.7, match the mineral to the most appropriate description.

A. Calcium

B. Chloride

C. Copper

D. Iodine

E. Iron

F. Magnesium

G. Manganese

H. Molybdenum

I. Phosphorus

J. Potassium

K. Selenium

L. Sodium

M. Zinc

29.1. Elevated levels of which mineral may result in hypertension in certain populations?

29.2. Which mineral is the major extracellular anion?

29.3. A decrease of which mineral is seen in refeeding syndrome and with overuse of aluminum-containing antacids?

29.4. Which mineral is a constituent of some amino acids found in proteins involved in antioxidant defense, thyroid hormone metabolism, and redox reactions?

29.5. Which mineral is required for the formation of a supersecondary protein structure that allows binding to DNA? (Its deficiency can result in a dermatitis.)

29.6. Deficiency of which mineral can cause bone pain, tetany (intermittent muscle spasms), paresthesia (a "pins and needles" sensation), and an increased tendency to bleed?

29.7. Deficiency of which mineral can result in goiter and a decreased metabolic rate?

Correct answers = L, B, I, K, M, A, D. Hypernatremia (elevation of serum sodium) can lead to water retention that can cause hypertension in salt-sensitive populations (e.g., African Americans). Chloride is the major extracellular anion. (Note: Sodium is the major extracellular cation, potassium is the major intracellular cation, and phosphate is the major intracellular anion. The concentration differential across the membrane is maintained by active transport.) Carbohydrate metabolism involves the generation of phosphorylated intermediates. Refeeding severely malnourished individuals traps phosphate and results in hypophosphatemia. Muscle weakness is a common symptom. Selenocysteine, an amino acid formed from serine and selenium, is found in proteins (selenoproteins) such as glutathione peroxidase, deiodinases, and thioredoxin reductase. Zinc fingers are a type of structural motif found in proteins (e.g., transcription factors) that bind to DNA. Severe deficiency of zinc as a result of mutations to its intestinal transporter can result in acrodermatitis enteropathica, which is characterized by dermatitis, diarrhea, and alopecia. Calcium is required for bone mineralization, muscle contraction, nerve conduction, and blood clotting. Its deficiency will affect all of these processes. Thyroid hormones are iodinated tyrosines released by proteolytic digestion of thyroglobulin. Underingestion of iodine causes enlargement of the thyroid in an attempt to increase hormone synthesis. (Note: Goiter can also result if too much hormone is made, as in Graves disease, or if too little is made, as in Hashimoto disease. Both are autoimmune diseases.) Thyroid hormone increases the resting metabolic rate.

29.8. DiGeorge syndrome is a congenital condition that results in structural anomalies and failure of the thymus and parathyroid glands to develop. Clinical manifestations include recurrent infections as a consequence of a deficiency in T cells. Which one of the following is an expected clinical consequence of the deficiency in parathyroid hormone?

A. Increased bone resorption

B. Increased calcium reabsorption in the kidney

C. Increased serum calcitriol

D. Increased serum phosphate

Correct answer = D. Parathyroid hormone (PTH) increases bone resorption (demineralization) resulting in the release of calcium and phosphate. It also increases the renal reabsorption of calcium, because PTH activates the renal hydroxylase that converts calcidiol to calcitriol. PTH also increases the renal excretion of phosphate. With the hypoparathyroidism of DiGeorge syndrome, all of these activities of PTH are impaired. Consequently, hypocalcemia and hyperphosphatemia are seen.

For questions 29.9 and 29.10, match the signs and symptoms to the pathology.

A. Graves disease

B. Hereditary hemochromatosis

C. Hypercalcemia

D. Hyperphosphatemia

E. Keshan disease

F. Menkes syndrome

G. Selenosis

H. Wilson disease

29.9. A 28-year-old male is seen for complaints of recent, severe, upper-right-quadrant pain. He also reports some difficulty with fine motor tasks. No jaundice is observed on physical examination. Laboratory tests were remarkable for elevated liver function tests (serum aspartate and alanine aminotransferases) and elevated urinary calcium and phosphate. Ophthalmology consult revealed Kayser–Fleischer rings in the cornea. The patient was started on penicillamine and zinc.

Correct answer = H. The patient has Wilson disease, an autosomal-recessive disorder that decreases copper efflux from the liver because of mutations to the hepatic copper transport protein ATP7B. Some copper leaks into the blood and is deposited in the brain, eyes, kidney, and skin. This results in liver and kidney damage, neurologic effects, and corneal changes caused by the excess copper. Administration of the metal chelator penicillamine is the treatment. (Note: Because zinc is also chelated, supplementation with zinc is common.) Graves disease results in hyperthyroidism. Hereditary hemochromatosis is a disorder of iron overload. Keshan disease is the result of selenium deficiency, whereas selenosis is caused by selenium excess. Menkes syndrome is the result of a systemic deficiency in copper as a result of mutations to ATP7A, an intestinal copper transport protein.

29.10. A 52-year-old female is seen because of unplanned changes in the pigmentation of her skin that give her a tanned appearance. Physical examination shows hyperpigmentation, hepatomegaly, and mild scleral icterus. Laboratory tests are remarkable for elevated serum transaminases (liver function tests) and fasting blood glucose. Results of other tests are pending.

Correct answer = B. The patient has hereditary hemochromatosis, a disease of iron overload that results from inappropriately low levels of hepcidin caused primarily by mutations to the HFE (high iron) gene. Hepcidin regulates ferroportin, the only known iron export protein in humans, by increasing its degradation. The increase in iron with hepcidin deficiency causes hyperpigmentation and hyperglycemia (“bronze diabetes”). Phlebotomy or use of iron chelators is the treatment. (Note: Pending lab tests would show an increase in serum iron and transferrin saturation.)