Sixteen mineral elements are considered essential nutrients for humans: calcium, phosphorus, potassium, sulfur, sodium, chlorine, magnesium, iron, zinc, selenium, manganese, copper, iodine, molybdenum, cobalt, and chromium. The first seven of these are classified as macronutrient minerals because they contribute more than 0.005% of body weight. They are discussed in Chapter 10 in detail. The remaining nine mineral elements are classified as micronutrients, or trace elements, because they are present in the body only in "trace" amounts (less than 0.005% of body weight). The minerals discussed in this chapter include iron, zinc, copper, selenium, chromium, manganese, molybdenum, and aluminum. Each mineral’s function, metabolism, characteristics of deficiency and toxicity, and requirements are reviewed, with an emphasis on the effect of critical illness. In addition, methods for assessment of status and guidelines for supplementation are presented.

Recommendations for supplementation of trace minerals fall under the guidelines of the recommended dietary allowances (RDAs) or the estimated safe and adequate daily dietary intakes (ESADDIs) both set by the Food and Nutrition Board. RDAs are "the levels of intake of essential nutrients considered to be adequate to meet the known nutritional needs of practically all healthy individuals." When the data are sufficient to establish a range of nutritional requirements, but inadequate to set an RDA, the ESSADI may be recommended. In both cases, these standards have been set for healthy persons. They are not requirements set for an individual, but for a population. In addition, they are established to prevent deficiency, not to affect potential therapy or disease prevention. Given the foundations of both the RDA and ESSADI, the clinician is often left with little guidance for prescribing vitamins and minerals to critically ill individuals, especially those receiving enteral and parenteral nutrition (PN) support. The savvy practitioner has a keen understanding of the functions, metabolism, deficiency and toxicity levels, and the safety and efficacy of the nutrients he or she "prescribes" and uses this information to guide the decisions for patients under his or her care.

Iron

Function
The most important function of iron is as a carrier of oxygen. Iron can be characterized as either functional or nonfunctional. Functional iron is present in hemoglobin, myoglobin, and in various iron-containing enzymes. Nonfunctional iron is found stored in the liver, spleen, and bone marrow. Apotransferrin, a globulin produced by the liver, complexes with ferric iron to form transferrin, which is the main transport protein for iron. In the cell, iron is stored on ferritin. Free iron, especially in the ferrous state, is toxic because it can significantly increase free oxygen radical production.

Metabolism
Iron stores have a strong regulatory influence on the amount of iron absorbed. Absorption of iron rises slowly as stores decline and demonstrates a steep rise when stores reach depletion. Absorption also increases in iron deficiency anemia as iron requirements for erythropoiesis are unmet. Body iron content is regulated mainly through changes in the amount of iron absorbed by the intestinal mucosa. The absorption of iron is regulated by the mucosal cells in the upper small intestine and occurs mainly in the duodenum and proximal jejunum. Heme and nonheme iron are absorbed via different mechanisms. Heme iron is highly bioavailable and readily absorbed (40% of that ingested). Nonheme iron absorption is quite variable (10% to 50% of that ingested) and can be enhanced by several factors, including acid environment (from vitamin C, citric acid, lactic acid, hydrochloric acid, and acid amino acids) and the presence of animal tissue proteins. Inhibitors of nonheme iron absorption include phytates, oxalic acid, polyphenols, calcium, reduced gastric acidity, and magnesium-based antacids. Most investigators suggest that the absorption of iron is reduced after injury or during inflammation. Apotransferrin, a globulin produced by the liver, complexes with ferric iron to form transferrin, which is the main transport protein for iron. Transferrin binds to transferrin receptors on the surface of cells, and with the reduction of iron to its ferrous form, iron then readily crosses the cell membrane. In the cell, iron is stored on ferritin, or it can be used for the synthesis of iron-containing enzymes.

After injury or infection, iron transport is dramatically altered. Within hours, serum iron is depressed and the storage form of iron is elevated. Transferrin concentrations and total iron-binding capacity (TIBC) demonstrate a more gradual decline. This shift in iron that occurs during the acute-phase response that follows injury or infection has been postulated to benefit the host by moving the exchangeable iron to a sequestered storage form, thereby reducing its availability to microorganisms; however, this theory has also been questioned. In the absence of blood loss, iron is excreted in small amounts. Basal obligatory losses of iron are primarily from
**Minerals and Trace Elements**

Michele A. DeBiasse-Fortin, MS, RD, LDN, CNSD

**CHAPTER 12**

**Minerals and Trace Elements**

**SEKINEN**

Mineral and trace elements are considered essential nutrients for humans: calcium, phosphorus, potassium, sulfur, sodium, chloride, magnesium, iron, zinc, selenium, manganese, copper, iodine, molybdenum, cobalt, and chromium. The first seven of these are classified as macronutrients because they contribute more than 0.005% of body weight. They are discussed in Chapter 10 in detail. The remaining nine mineral and trace elements are classified as micronutrients, or trace elements, because they are present in the body only in “trace” amounts (less than 0.005% of body weight). The minerals discussed in this chapter include iron, zinc, copper, selenium, chromium, manganese, molybdenum, and aluminum. Each mineral’s function, metabolism, characteristics of deficiency and toxicity, and requirements are reviewed, with an emphasis on the effect of critical illness. In addition, methods for assessment of status and guidelines for supplementation are presented.

**Recommended Dietary Allowances (RDAs)** are the “levels of intake of essential nutrients considered to be adequate to meet the known nutritional needs of practically all healthy individuals.” When the data are sufficient to establish a range of nutrient requirements, the RDAs are based on the Recommended Dietary Allowances (RDAs) of the Food and Nutrition Board. RDAs are considered the levels of intake of essential nutrients considered to be adequate to meet the known nutritional needs of practically all healthy individuals. When the data are sufficient to establish a range of nutrient requirements, the RDAs are considered the levels of intake of essential nutrients considered to be adequate to meet the known nutritional needs of practically all healthy individuals.

**Iron**

Iron stores have a strong regulatory influence on the amount of iron absorbed. Absorption of iron is inversely related to iron stores and demonstrates a steep rise when iron stores decline. Absorption also increases in iron deficiency anemia as iron requirements for erythropoiesis are unmet. Body iron content is regulated mainly through changes in the amount of iron absorbed from the intestinal mucosa. The absorption of iron is regulated by the mucosal cells in the upper small intestine and occurs mainly in the duodenum and proximal jejunum. Heme and nonheme iron are absorbed via different mechanisms. Heme iron is highly bioavailable and readily absorbed (40% of that ingested). Nonheme iron absorption is quite variable (10% to 50% of that ingested) and can be enhanced by several factors, including acid environment (from vitamin C, citric acid, lactic acid, hydrochloric acid, and acid anions) and the presence of animal tissue proteins. Inhibitors of nonheme iron absorption include phytates, oxalic acid, phytates, tannins, polyphenols, and plant-based antinutrients. The optimal method to increase iron absorption is to iron supplements. Ferritin binds to transferrin receptors in the enterocytes and, with the reduction of iron to its ferrous form, it then readily crosses the cell membrane. In the cell, iron is stored on ferritin, or it can be used for the synthesis of iron-containing enzymes.

**Assessment of Status**

The status of iron stores can be assessed by measuring the levels of serum ferritin, TIBC, and iron. Reduced serum ferritin and iron concentrations, combined with elevated serum TIBC concentrations, indicate iron deprivation. During the acute-phase response, serum iron, transferrin, and TIBC concentrations become depressed, and ferritin levels become elevated. This results in a reduction of iron deficiency compared to results from net deficiency of iron resulting from stress on infection or from stress on infection.

**Deficiency and Toxicity**

Iron deficiency is one of the most common nutritional problems in both developing and developed areas of the world. Inadequate iron status leads to atherosclerosis, hyperlipidemia, and hypertension. Signs and symptoms include tachycardia, fatigue, pallor, reduced work capacity, and alterations in mental and motor development. Impaired temperature regulation and decreased resistance to infection have also been reported. Chronic iron overload can result in hemochromatosis, a disorder characterized by cirrhosis, diabetes, and hyperglycemia of the skin. Iron overload can also lead to increased oxidative stress as excess iron is released from its storage form. The result is the production of free radi- cals that can then lead to cell damage. Other factors of iron overload include fatigue, altered clotting, cirrhosis, and coagulopathy, and thyroid and cardiomyopathy.

**Requirements and Supplementation**

The RDAs for iron are set for men aged 30 to 60 years and females aged 20 to 30 years. Iron requirements are increased to 10 mg to allow for expansion of red cell mass, to provide iron to the fetus and placenta, and to replace blood loss during delivery. Iron is not stored as a nutrient reserve for the future. Iron is an important component of the treatment of iron deficiency. It is important to recognize that iron supplementation will not correct erythropoietic abnormalities caused by conditions other than iron deficiency and is not indicated for the treatment of anemia resulting from causes other than iron deficiency. The optimal method to replete iron stores is oral supplementation because it is safer, more convenient, and less expensive than other methods, and some evidence indicates that it is used more efficiently. Unfortunately, the use of large doses of iron orally may cause nausea and vomiting. The optimal method to iron therapy is to use large doses of iron orally. The optimal method to iron therapy is to use large doses of iron orally.

**Zinc**

Zinc is widely distributed in the body and is second to iron in total body content. It is involved in many biochemical processes including cellular respiration, immune function, wound healing, membrane stability, antioxidant function, and the membrane transport of calcium, synthesis of proteins, deoxyribo- nucleic acid (DNA) and ribonucleic acid (RNA), carbohydrate metabolism, utilization of nitrogen and sulfur, cell division, and hormone metabolism. Zinc is involved in the regulation of enzyme detoxification of free radicals, and bone metabolism. Zinc functions as a cofactor of more than 200 enzyme systems. Zinc plays an important role in appetite regulation. Zinc deficiency decreases appetite, while zinc supplementation increases appetite. It is postulated that this effect is the result of zinc-induced alterations in neurotransmitter metabolism. In a recent study by Mantzoros and others, serum zinc status was shown to affect serum leptin levels with the magnitude of change proportional to the changes in cellular zinc. Zinc status has also been shown to have an effect on lipid metabolism, in that high levels of zinc supplementation have been shown to increase concentrations of total serum cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol, and to decrease HDL cholesterol. In a recent study by Jern and colleagues, a positive correlation was observed between zinc concentrations and the risk of death in patients with malignancies. Parenteral zinc supplementation has also been shown to increase fecal excretion of zinc in a mixed diet containing zinc in a mixed diet containing zinc in a mixed diet containing zinc.
in patients experiencing a mild acute-phase reaction.\textsuperscript{20} Zinc can exist in several different valence states, but usually is divalent.\textsuperscript{4}

### Metabolism

Absorption of zinc occurs in the small intestine, especially the jejum, via simple diffusion and specific ligands that transport zinc with them into the mucosal cells.\textsuperscript{1,14} Zinc absorption from a supplement administered 3 or more hours after ingestion of a meal has been shown to range between 40\% and 90\%, while a supplement administered with a meal results in an absorption rate of 8\% to 38\%.\textsuperscript{19} Animal proteins, amino acids, and unsaturated fatty acids enhance zinc absorption, whereas phytates; folates; high levels of copper, cadmium, and iron; and consumption of a high-calcium diet decrease zinc absorption.\textsuperscript{14,21,22} With increasing amounts of zinc in a meal, the amount of zinc absorbed increases. Long-term zinc intake (i.e., zinc status) can also affect absorption of dietary zinc, in that prolonged low-zinc diets increase zinc absorption and retention.\textsuperscript{21} In addition, protein-energy malnutrition results in an alteration in small intestine mucosal absorptive capacity for zinc, promoting zinc malabsorption. This can lead to a self-perpetuating cycle of poor zinc absorption, and further compromise of zinc stores.\textsuperscript{23,24} Zinc is absorbed into the intestinal epithelial cells and transported via the plasma carrier proteins macroglobulin, albumin, transferrin, glycoprotein, and transthyretine.\textsuperscript{1,14} Once in the blood, 80\% to 90\% of zinc can be found within the erythrocytes, 10\% to 17\% in the plasma, and 3\% or less in white blood cells. From the circulation, zinc is taken up by the liver and other tissues\textsuperscript{4} where zinc ions form complexes with metalloenzymes, membrane proteins, and metallothioneine. Excretion of zinc is mainly via the bile, although a small amount is excreted in urine, sweat, desquamation of skin, and hair losses. Urinary zinc excretion is enhanced with the use of diuretics and in diabetic patients.\textsuperscript{18,25} It is also increased after injury during the acute-phase response.\textsuperscript{26,27}

### Assessment of Status

Plasma zinc concentration, the most commonly measured index of zinc status, is insensitive and therefore unreliable.\textsuperscript{4,16} Other methods for determining zinc status have been explored and include measurement of zinc concentrations in white blood cells, measurement of 5'NT activity, measurement of zinc kinetics, and determination of relationships between physiologic functions and zinc nutrition. Of these, measurement of zinc or 5'NT in white blood cells (or plasma) appears to be the most applicable to clinical situations.\textsuperscript{16}

### Deficiency and Toxicity

Because of zinc's role in cellular growth and differentiation, the effects of zinc deficiency are especially pronounced in tissues and organs with rapid turnover and during periods of rapid growth.\textsuperscript{24} Organ systems known to be affected by severe zinc deficiency include the skin, GI tract, central nervous, immune, skeletal, and reproductive.\textsuperscript{28} Symptoms of severe zinc deficiency include delayed wound healing, hair loss, diarrhea, growth failure, poor appetite, and impaired vision.\textsuperscript{24,29} Secondary zinc deficiency can occur in many conditions including human immunodeficiency virus (HIV), chronic liver disease, diabetes, cancer, and chronic inflammatory diseases such as rheumatoid arthritis. Neurologic diseases such as Alzheimer's disease and Down syndrome are associated with redistribution or sequestration of zinc.\textsuperscript{24} Zinc deficiency is common in the critically ill because of decreased intake, increased losses from the GI tract, and increased urinary losses resulting from hypoalbuminemia.\textsuperscript{4} Zinc toxicity is uncommon and usually occurs in accidental intake or occupational exposure.\textsuperscript{14,19} Symptoms include metallic taste, nausea, vomiting, stomach cramps, fever, diarrhea, and renal failure. Excess zinc can retard wound healing.\textsuperscript{26,31} and it reduces both phagocyte and lymphocyte functions, thereby reducing immune responses.\textsuperscript{1,32} Chronic zinc intake can lead to copper deficiency and anemia.\textsuperscript{1,4} Recently, an association between high intakes of serum zinc and a faster disease progression and death in HIV-1-infected men has been shown.\textsuperscript{33,34}

### Requirements and Supplementation

The current RDA for zinc is 12 mg/day in adult women and 15 mg/day in adult men.\textsuperscript{22,23} The RDA is lower for females because of their lower body weight. Current guidelines for parenteral intake recommend supplementing with the standard daily dose of 5 mg elemental zinc.\textsuperscript{20} The American Medical Association (AMA) guidelines for parenteral zinc supplementation for catabolic patients include an additional 2 to 4 mg of zinc per day.\textsuperscript{1}

### Copper

#### Function

Copper is an essential trace element, third in total body content after iron and zinc. It is widely distributed throughout human tissues and organs, with the highest concentrations present in the liver.\textsuperscript{25} Copper plays a role in many physiologically important pathways. It is required for proper erythropoiesis and leukopoiesis, skeletal mineralization, myelin formation, immune function, connective tissue synthesis, cardiac function, and glucose regulation.\textsuperscript{35,36} All metalloenzymes of copper possess oxidative reductase activity. A number of the key enzymes include cytochrome-C-oxidase, required for energy production; superoxide dismutase, a key cytotoxic antioxidant; and lysyl oxidase, which catalyzes the oxidation of lysyl residues on collagen.\textsuperscript{43} Copper is also an essential component of the oxidation enzyme ceruloplasmin, which oxidizes ferrous to ferric ion so it can be transported to ceruloplasmin to other tissues.\textsuperscript{4}

#### Metabolism

Copper is thought to be absorbed readily throughout the upper GI tract, including the stomach, duodenum, and jejum by both an active and passive transport system.\textsuperscript{35,36} The biologic availability of copper is enhanced significantly by dietary protein and decreased by high doses of zinc and vitamin C.\textsuperscript{1,36} Copper transport from the intestinal mucosa to the liver and other tissues is poorly understood.\textsuperscript{25} It is thought that once in the blood, copper is carried on transthyretin and albumin to the liver and secondarily to the kidneys.\textsuperscript{37} In the liver, most plasma copper is bound to ceruloplasmin and is secreted into the blood for transport to other tissues or is excreted.\textsuperscript{1} The primary route of copper excretion is via the biliary tract; therefore, conditions that lead to chronic biliary obstruction impair copper excretion and may promote hepatic accumulation. The amount of copper...
Deficiency and Toxicity

Acquired copper deficiency is an extremely rare occurrence because of the ubiquitous nature of copper in various foods, but it has been described in patients receiving PN since 1972.\(^8\) Low serum copper levels have also been described in patients recovering from major burn injury.\(^4,12\) Copper deficiency is characterized by anemia, neutropenia, and rarely, thrombocytopenia.\(^8\) Coronary artery disease has been observed in patients with the inherited form of copper deficiency (Menkes' syndrome), but it has not been observed in acquired copper deficiency. Toxicity from excess copper intake has not been well documented. A recent study by Ford cites several studies, including his own, that have found elevated serum copper concentrations in patients associated with cardiovascular disease, but it is unclear whether copper directly affects atherosclerosis or is a marker of the inflammation associated with cardiovascular disease.\(^5\)

Requirements and Supplementation

The ESSAFD recommended copper intake is between 1.5 and 3.0 mg/day.\(^7\) This recommendation is based on copper requirements that have been estimated between 1.2 and 2.0 mg/day. The AAMA recommends parenteral nutrition supplementation of copper is 0.5 to 1.5 mg/day.\(^6\) Flammig recommends reducing copper supplementation in PN to 0.155 mg/day when a patient develops chronic hyperbilirubinemia. Unfortunately, reduction of a single trace element in a PN solution is problematic because trace elements are usually added as a preparation that contains several trace elements. Fuhrman suggests that it may be more clinically feasible to reduce copper supplementation by providing a trace element preparation no more than three times per week when a patient develops chronic hyperbilirubinemia.\(^5\)

Selenium

Function

Selenium functions within mammalian systems primarily in the form of selenoproteins. Selenoproteins contain selenocysteine and selenocysteine and perform various physiologic roles.\(^8\) Eleven selenoproteins have been identified and include both classical (cellular) glutathione peroxidase and plasma (extracellular) glutathione peroxidase. Selenium plays a vital role in the cellular antioxidant defense system. This system protects the integrity of the cell membrane and the immune system.\(^8\) It is interesting to note that selenium can spare vitamin E and vice versa. As a result, the need for selenium declines as vitamin E intake increases.\(^1\)

Metabolism

Selenium is well absorbed throughout the small bowel.\(^1\) The organic forms of selenium are better absorbed than the inorganic forms. Absorption of selenium is probably by active transport, but the exact mechanism for absorption and transport is not well understood. Selenium is widely distributed in the body, with high concentrations in the liver, kidney, and testes. The primary route for excretion of selenium is via the kidneys,\(^4,10\) although ingested selenium is also exhaled by the lungs.\(^6\) Lower doses of selenium should be given when renal function is impaired.\(^5\)

Assessment of Status

Estimates of selenium status can be accomplished through a variety of means, including the measurement of specific selenoproteins; estimation of selenium intake; measurement of selenium concentrations in blood, tissues, or excreta; and determination of glutathione peroxidase activity in various blood components.\(^4\)

Deficiency and Toxicity

Human selenium deficiencies are rare. The primary group who has developed selenium deficiency includes those who received PN for prolonged periods without selenium supplementation.\(^1\) Low selenium levels have often been reported in the critically ill.\(^1\) Symptoms seen in this population include muscle weakness and fatigue.\(^4\) Selenium toxicity has occurred in areas where soil concentrations of selenium are great or, in one case in the United States, when a manufacturing error of a selenium supplement resulted in a product that contained 182 times the amount of selenium declared on the label. Signs of toxicity include nausea, vomiting, hair loss, peripheral neuropathy, fatigue, and changes in nails and teeth.\(^1\)

Requirements and Supplementation

The recently published dietary recommendation for selenium reference intakes\(^6\) fixed the new RDA for selenium at 55 mg/day for both men and women. This level was chosen because it was associated with the highest level of glutathione peroxidase activity.\(^8\) Given the documented increased requirements for the critically ill, it is recommended that selenium supplementation be increased for this population.\(^1\)

Chromium

Function

The metabolic functions for chromium are not well defined.\(^1\) The biologic functions of chromium include its involvement in both carbohydrate and lipid metabolism. Specifically, chromium functions in the regulation of insulin by increasing
insulin binding to cells through increased insulin receptor numbers. Chromium is thought to be the active component in glucose tolerance factor (GTF). Chromium exists in several forms, of which hexavalent and trivalent are the most prevalent. The hexavalent form is recognized as toxic, whereas trivalent chromium is not.

Metabolism
Chromium absorption and metabolism depend on its oxidation state, whether the chromium is complexed, and the intestinal contents. Very little of trivalent chromium is absorbed (less than 2% of the dose), although when complexed with picolinate or nicotinate, absorption is improved. The exact mechanism of absorption is unclear, but factors such as oxalate intake, iron and zinc deficiency, and diabetes increase absorption, whereas phytate and aging decrease absorption. Following absorption, chromium is bound to transferrin; albumin; and, possibly, globulin proteins for transport throughout the system. Chromium is excreted mainly in the urine, and excretion increases as the result of a glucose load, stress conditions, strenuous exercise, physical trauma, pregnancy, and lactation. Chromium excretion is also elevated in diabetics after insulin administration. Hexavalent chromium is better absorbed, and blood levels are three to five times greater than those following administration of trivalent chromium. After absorption, hexavalent chromium enters the erythrocytes and binds to the globulin fraction of hemoglobin where it then becomes reduced to the trivalent form. Because trivalent chromium cannot cross the erythrocyte membrane, it remains irreversibly trapped in the cell.

Assessment of Status
Currently no good method is available to determine chromium status. Plasma levels do not reflect tissue levels because tissue levels are ten times higher than plasma. In addition, balance studies show that there can be a negative chromium balance in the presence of raised plasma levels. The best way to diagnose chromium deficiency currently is to observe whether the hyperglycemia and neuropathy that develop unexpectedly in patients on PN responds to chromium infusion.

Deficiency and Toxicity
Signs of chromium deficiency include impaired glucose tolerance, increased levels of circulating insulin, elevated cholesterol, and triglyceride levels, and decreased high density lipoprotein levels. No credible data or reports have shown adverse effects of trivalent chromium in humans. It is extraordinarily safe and has a wide margin of safety. As previously mentioned, hexavalent chromium is recognized as toxic.

Requirements and Supplementation
The ESSADI for trivalent chromium is between 50 to 200 μg/day. The reference dose set by the U.S. Environmental Protection Agency (EPA) for trivalent chromium is 1.47 mg/kg. This conservative estimate is 350 times the upper limit of the ESSADI, which is a much larger safety factor than almost any other nutrient. Recommendations from the American Medical Association Panel suggest the daily administration of 10 to 15 μg of chromium per day in PN solutions. This conservative estimate is based on a 10 to 20 μg/day be added to PN. Anderson, in his review article on chromium, suggests both amounts may not be adequate for severely stressed patients, an assertion also made by Demling and DeBiasi in their review of micronutrients in critical illness. It should be noted that the basal chromium content of PN solutions varies widely and should be monitored.

Manganese
Function
Manganese is known to be involved in enzyme activation, component of several metalloenzymes including arginase, pyruvate carboxylase, and manganese superoxide dismutase. Enzymes activated by manganese frequently can also be activated by magnesium. As a component of various enzymes, manganese assists in energy release, fatty acid and cholesterol synthesis, release of lipid from the liver, and production of collagen fibers and ground substance for wound healing.

Metabolism
Relatively little is known about manganese absorption. The total percentage of dietary manganese absorbed from food is small, with most studies suggesting that humans absorb less than 5%. High dietary iron has been shown to decrease manganese absorption and status in rats, and there is a strong negative association between ferritin status and the absorption of manganese. Once absorbed, manganese is bound to α2-macroglobulin and transported to the liver where a portion of it is oxidized to Mn 3+, bound to transferrin, and transported throughout the body. Virtually 100% of manganese is excreted mainly in bile, although nonbiliary routes of manganese excretion are known to exist.

Assessment of Status
There is still no clearly defined method for assessing manganese status. Many authors suggest that the concentration of manganese in red cells is a better indicator of manganese accumulation than plasma manganese concentrations.

Deficiency and Toxicity
Descriptions of manganese deficiency in humans are not conclusive. Some of the symptoms reported include neurologic dysfunction, dermatitis, and hypocholesterololemia. Toxicity from dietary manganese has been reported, and the number of studies has demonstrated significant neurotoxicity and elevated blood manganese concentrations when manganese is provided in conjunction with parenteral nutrition patients with chronic liver and/or cholestatic disease. The earliest toxic phase is characterized by general symptoms including weakness, anorexia, apathy, and somnolence. This is followed by signs of basal ganglia dysfunction that resemble Parkinson disease. The final phase is characterized by muscular rigidity, staggering gait, and fine tremor. There is apparently a genetic susceptibility to manganese toxicity in elderly patients.

Requirements and Supplementation
The ESADDI for manganese has been established at 5 mg/day. Manganese is routinely administered to patients receiving PN at 100 to 800 μg daily. It is also contained
Manganese

Function
Manganese is known to be involved in enzyme activation as a component of several metalloenzymes including arginase, carbamylase, and manganese superoxide dismutase. Manganese activates many enzymes and can also be activated by magnesium. As a component of various enzymes and manganese in energy release, fatty acid and cholesterol metabolism, release of lipid from the liver, and production of prostaglandins, thiol and ground substance for wound healing.

Deficiency in humans is not considered a problem, but deficiency in animals has been associated with nervous system disorders. Symptoms include tremors, stereotypy, and muscle weakness. The toxicity of manganese is not fully understood, but it can cause respiratory irritation and gastrointestinal distress.

Assessment of Status
Manganese levels in blood and urine are commonly used to assess manganese status. Serum manganese levels have been found to be a better indicator of manganese tissue concentrations.

Aluminum

Function
Aluminum is the third most abundant naturally occurring element and the most common metallic element, composing approximately 8.8% of the earth's crust. Aluminum has no known physiologic function in either humans or animals, and it is regarded as a potential toxin, particularly in patients with compromised renal function. Although ubiquitous in nature, aluminum is largely insoluble, and the lungs, skin, and GI tract act as barriers to prevent it from entering the body. As a result, the estimated total body content of aluminum is less than 50 mg.

Metabolism
The metabolism of aluminum in normal subjects has been studied by only a few investigators. Aluminum appears to be very poorly absorbed from the GI tract, such that only a small amount of aluminum has been found in the urine of subjects consuming a normal diet. Aluminum absorption from the intestinal lumen is initially into the intestinal mucosal cells, and only a small proportion of this uptake continues into the blood. Several factors have been shown to enhance aluminum absorption including citrate, tartrate, and tannate. Inhibition of absorption include fluorides and calcium.

The primary route of aluminum excretion is the kidneys, with only trivial amounts excreted in bile.

Assessment of Status
Blood levels of aluminum are not always predictive of tissue pathology and depend, among other factors, on length of time exposed and dose. One source suggests that a plasma aluminum level greater than 10 μg/L puts individuals at risk for aluminum toxicity. In a special report published jointly by the American Society for Clinical Nutrition (ASCN) and the American Society for Parenteral and Enteral Nutrition (ASPEN), it was suggested that determinations of aluminum content in fluid or tissues be performed by flameless or electrothermal atomic absorption spectrophotometry or inductively coupled plasma emission spectroscopy.

Deficiency and Toxicity
As stated previously, there is no known requirement for aluminum, and no deficiency has been reported. In contrast, toxicity states that result from the accumulation of aluminum have been noted in the literature since the mid-1970s. These first cases were observed in patients with end-stage renal disease who were receiving hemodialysis therapy when aluminum was found as a contaminant of the water used in the dialysis process. These patients exhibited a low-turnover vitamin D-resistant osteomalacic bone disease, and an encephalopathy with dementia that existed in conjunction with elevated tissue levels of aluminum and accumulation of aluminum at the mineralization front of bone. Since that time, numerous studies have been published investigating the role of aluminum in bone disease and dementia states. Many of these studies have focused on the role of long-term PN in inducing these conditions.

Minerals and Trace Elements
toxicity effects because metabolic bone disease was observed with significant frequency in this population. As a result, the aluminum content of parenteral nutrition solutions was evaluated, and it was discovered that casein hydrolysate amino acid solutions contained a significantly greater amount of aluminum than crystalline amino acid solutions. In one such study, the concentration difference was 100-fold. These investigations lead to the use of deionized water for both hemodialysis and peritoneal dialysis for those patients with end-stage renal disease, and the substitution of crystalline amino acids for casein hydrolysate amino acids in parenteral nutrition solutions. Both interventions have resulted in decreased incidence of aluminum toxicity in the populations using these therapies.

In addition to the previously listed disorders, microcytic hypochromic anemia has also been found to be a manifestation of aluminum toxicity. Aluminum may also accumulate in the parathyroid gland, although its functional effects are unknown.

### Requirements and Supplementation

There is no known requirement for aluminum. The average adult dietary intake of aluminum is about 3 to 5 mg/day, of which only 15 µg (0.3% to 0.5%) is absorbed. There are no recommendations for aluminum supplementation.

### Conclusion

Table 12-1 contains a summary of each of the minerals presented in this chapter. When recommending supplementation of minerals and trace elements, it is important for the clinician to remember how closely regulated they are. While it is impor-
Aluminum toxicity effects because metabolic bone disease was observed with significant frequency in this population. As a result, the aluminum content of parental nutrition solutions was evaluated, and it was discovered that casein hydrolysate amino acid solutions contained a significantly greater amount of aluminum than crystalline amino acid solutions. In one such study, the concentration differences were 100-fold. These investigations lead to the use of deionized water for both hemodialysis and peritoneal dialysis for those patients with end-stage renal disease, and the substitution of crystalline amino acids for casein hydrolysate amino acids in parenteral nutrition solutions. Both interventions have resulted in decreased incidence of aluminum toxicity in the populations using these therapies.

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Requirements and Supplementation

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Conclusion

Table 12-1 contains a summary of each of the minerals presented in this chapter. When recommending supplementation of minerals and trace elements, it is important for the clinician to remember how closely regulated they are. While it is important to provide appropriate individual mineral supplements, the interrelationship between the various trace minerals should not be forgotten. Cautions should especially be used with the parenteral administration of minerals because the natural regulation and metabolic pathways of GI tract is bypassed. In addition, because many of these minerals are not readily excreted, there is a risk of toxicity. Supplementation regimens that fail to consider these facts can induce nutrient imbalances that could harm rather than benefit the patient.1

References
