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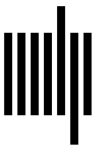

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Metal Homeostasis during Development, Maturation, and Aging

Impact on Infectious Diseases

Inga Wessels

Abstract

This chapter provides a summary of the functions of essential metallic elements in human metabolism and during infectious diseases as well as their homeostasis during development, maturation, and aging. A list of food sources as well as information on the effects of deficiency and excess is provided for each metallic element. As concentrations of metallic contaminants in the environment rise, brief characterizations of nonessential but biologically relevant metallic environmental contaminants have been added. Cases of under-, mal- and overnutrition are increasing worldwide. In combination with decreased nutritional food values, this creates a growing threat for human health, affecting societal and health systems. Potential ways of approaching this problem are suggested and discussed.

Introduction

Metals enter the environment through natural and anthropogenic means. Sources include natural weathering of Earth's crust, mining, soil erosion, industrial discharge, urban runoff, sewage effluents, pest or disease control agents applied to plants, air pollution fallout, and others. A number of metals are essential for human health, affecting different aspects of human metabolism (Appendix 8.1): cobalt (Co), copper (Cu), iron (Fe), molybdenum (Mo), manganese (Mn), selenium (Se), and zinc (Zn). Deficiency as well as excessive intake can cause severe side effects throughout life, especially during fetal development (Appendix 8.1). Therefore, metal homeostasis is tightly regulated

in the human body. The essentiality of arsenic (As), chromium (Cr), nickel (Ni), and vanadium (V) for human health has been suggested but remains to be proven. Aluminum (Al), cadmium (Cd), and mercury (Hg) do not show any beneficial effect on human health (Vieira et al. 2011) and are generally considered toxic to humans and animals; the adverse human health effects associated with exposure to these metals, even at low concentrations, are diverse and include, but are not limited to, neurotoxic and carcinogenic actions (Castro-Gonzalez and Mendez-Armenta 2008; Jomova and Valko 2011; Tokar et al. 2011; Appendix 8.1).

A well-balanced diet provides sufficient amounts of each element to meet the recommended dietary allowance (RDA) for a healthy person (Table 8.1). Risk groups including neonates, children, and pregnant women; athletes and the elderly may have different needs, which can be met by changing to a special

Table 8.1 Recommended dietary allowance (RDA) and adequate intakes (*) for essential metallic elements, adapted from the dietary reference intake (DRI) reports (www.nap.edu). RDA for chromium (**) may need adjustment, as recent literature suggests lower values (Vincent 2010). Sources: Panel on Dietary Antioxidants and Related Compounds et al. (2000); Panel on Micronutrients et al. (2001).

Element	Age (years)	Fe (mg)	Zn (µg)	S (µg)	Cu (µg)	Mn (mg)	Cr** (µg)
Infants	0–0.5*	6	2	15	200	0.003	0.2
	0.5–1	11	3	20	220	0.6	5.5
Children	1–3	7	3	20	340	1.2	11
	4–6	10	5	25	440	1.5	13
	7–10	8	7	30	550	1.7	15
Male	11–14	11	8	40	700	1.9	25
	15–18	11	11	55	890	2.2	35
	19–24	8	11	70	900	2.3	35
	25–50	8	11	70	900	2.3	35
	50+	8	11	55	900	2.3	30
Female	11–14	15	8	40	700	1.6	21
	15–18	15	9	55	890	1.6	24
	19–24	15	8	55	900	1.8	25
	25–50	18	8	55	900	1.8	25
	50+	10	8	55	900	1.8	20
Pregnant		27	12	60	1000	2.0	29
Nursing	14–18	10	13	75	1300	2.6	44
	19–50	9	12	70	1300	2.6	45

diet or through the use of supplements. A well-balanced diet may not always be easily accessible. One reason is an overall lack of food in developing countries. Moreover, the nutritional value of food is generally declining due to extensive processing and considerable use of chemical fertilizers, insecticides, and pesticides. The decreasing quality of our food creates an increased need to inform the general public on how to achieve a healthy diet so as to avoid sickness and disease. In addition to the general public, medical practitioners also need to be aware of metal deficiencies and toxicities so that they are able to understand disease symptoms and identify the appropriate diagnosis and treatment.

To provide accurate information, a detailed understanding of the homeostasis of metals in the human body during development, maturation, and aging is necessary. This chapter summarizes recent literature on metal homeostasis for essential metals as well as those thought to be necessary for human metabolism. A brief overview of nonessential metals that are most harmful to human health is also included.

Essential Metallic Elements

Cobalt

Cobalt is a metallic element with limited function in higher eukaryotes. The only known function that it has is as a component of vitamin B12, which is incorporated into three classes of enzymes: isomerases, methyl transferases, and reductive dehalogenases. These enzymes participate in reactions essential to DNA synthesis, fatty acid synthesis, and energy production, among other biological processes (Banerjee and Ragsdale 2003; Appendix 8.1).

Cobalt is accumulated primarily in the liver, kidney, pancreas, and heart, with the relative content in skeleton and skeletal muscle increasing with time after Co administration. In serum, cobalt (Co^{2+}) binds to albumin, and the concentration of free, ionized Co^{2+} is estimated at 5–12% of the total Co concentration (Simonsen et al. 2012). Cobalt is acutely toxic in larger doses, and cumulative, long-term exposure (even at a low level) can give rise to adverse health effects related to various organs and tissues (see reviews by Barceloux 1999; Lauwerys and Lison 1994). Recent concern has been raised in terms of possible systemic health effects that result from elevated blood Co concentrations in patients with Co-containing hip implants (Paustenbach et al. 2014). Adverse effects may impact the thyroid gland (inhibition of tyrosine iodinase, goiter, and myxedema), lungs (asthma, hard-metal disease), skin (allergic contact dermatitis), and the immune system (Sauni et al. 2010). Cobalt metal and salts are also genotoxic; this is primarily caused by oxidative DNA damage through reactive oxygen species, perhaps combined with inhibition of DNA repair. Of note, evidence for carcinogenicity of Co metal and Co sulfate is considered sufficient in experimental animals but is not yet considered adequate

in humans. Interestingly, some of the toxic effects of cobalt have recently been connected to disturbances of calcium metabolism. More research is needed to increase understanding of the mechanisms that lead to the strong toxicity of cobalt in humans.

Copper

Copper plays a critical role in human metabolism as a cofactor for several cupric enzymes, including cytochrome *c* oxidase, lysyl oxidase, tyrosinase, Cu/Zn superoxide dismutase (SOD), and ferroxidases (Pena et al. 1999; Prohaska and Gybina 2004; Shim and Harris 2003; Appendix 8.1). Copper is especially important for adequate uptake of iron by the body as well as for a functioning redox system (Cabrera et al. 2008; Appendix 8.1).

Copper is a potentially toxic metal because of its role in the redox cycle and in supporting Fenton chemistry, which leads to the production of free radicals (Halliwell and Gutteridge 1984). Therefore, Cu homeostasis is tightly regulated. After being absorbed in the intestine, copper is exported from enterocytes into the bloodstream (Hamza et al. 2003; Nyasae et al. 2007). Membrane transporters for copper include CTR1, DMT1, and the Cu "pumps" ATP7A and ATP7B. Liver ATP7B is particularly important in helping mammals, such as rats and humans, eliminate excess copper efficiently in bile in a relatively nonreabsorbable form. In plasma, copper is primarily transported by ceruloplasmin and albumin (Cabrera et al. 2008). Defects in ATP7A (Menkes disease) or ATP7B (Wilson disease) cause Cu accumulation in organs (liver) and result in severe embryonic malformation or are lethal to embryos (Kambe et al. 2008).

Dietary Cu deficiency during embryonic development can be teratogenic and embryotoxic. Mouse embryos with swollen hind brains and offspring with severe neurological impairment and organogenesis defects in multiple tissues (severe connective tissue abnormalities, skeletal defects, lung abnormalities, etc.) have been observed in the offspring of Cu-deficient dams (Keen et al. 1998). The extent and timing of Cu deficiency dictate the severity and tissue specificity of the effects on the embryo, fetus, and newborn. Proper transfer of copper from the mother to the developing embryo and neonate is of critical importance, if neurological abnormalities and growth retardation are to be avoided (Kambe et al. 2008).

Aging has not been associated with significant changes in the requirement for copper, suggesting that Cu metabolism is robust throughout life. Even hospitalized elderly have not show an increased demand for copper, in contrast to Zn levels, which drop significantly and need to be corrected (Belbraouet et al. 2007).

Measurement of Cu status in humans is difficult. Moreover, many factors (e.g., zinc, carbohydrates, and vitamin C intake) affect Cu bioavailability, thus making it hard to establish a requirement for copper (Table 8.1).

Iron

Iron is the most abundant transition metal in the human body: approximately 4–5 g are present in a normal human adult (weight of 70 kg). The importance of well-defined amounts of iron for the survival, growth, replication, and differentiation in humans is well established. Iron is an essential component of proteins involved in oxygen transport (Andrews 1999; Appendix 8.1). A deficiency of iron limits oxygen delivery to cells, resulting in fatigue, poor work performance, and decreased immunity (Panel on Micronutrients et al. 2001). Conversely, excess iron can result in toxicity and even death (Corbett 1995).

There are two forms of dietary iron: heme (Fe bound to heme proteins) and nonheme. Sources of nonheme iron are plant foods, such as lentils and beans (Hurrell 1997). Heme iron can be found in animal foods, such as red meats, fish, and poultry, and is absorbed better than nonheme iron. For humans, heme iron, which is derived from hemoglobin in red blood cells, is of great importance as it delivers oxygen to cells.

Iron is mainly absorbed via a transporter protein: the DMT1, which facilitates uptake of other trace metals, with both positive (Mn, Cu, Co, Zn) and negative (Cd, lead) effects. Within the enterocyte, iron is released via ferroportin into the bloodstream where it is then bound by the transport glycoprotein (or transferrin). Approximately 0.1% of the total body iron circulates in bound form to transferrin. Most absorbed iron is utilized in bone marrow for erythropoiesis. About 10–20% of absorbed iron goes into a storage pool in cells of the mononuclear phagocyte system, particularly fixed macrophages, and is recycled into erythropoiesis. This provides a balance between the storage and use of iron in the body.

Iron absorption is regulated by dietary and storage mechanisms. If stores are full, hepcidin is released from the liver, causing enterocytes to retain absorbed iron. A drop in body iron diminishes hepcidin, resulting in release of absorbed iron into circulation by the intestinal mucosa. Diet composition may also influence Fe absorption. Citrate and ascorbate can form complexes with iron that increase absorption, whereas tannates (tea), calcium, polyphenols, and phytates (legumes, whole grains) can decrease absorption (Panel on Micronutrients 2001; Hunt et al. 1994; Samman et al. 2001). Greater Fe utilization during growth in childhood, elevated Fe loss through minor hemorrhages or menstruation in women, as well as a greater need for iron during pregnancy can increase the efficiency of dietary Fe absorption to 20% (Allen 2002; Cogswell et al. 2003; see also Table 8.1).

Iron deficiency is the most frequent nutritional problem in the world, affecting 24% of the global population: approximately 4–10% in developed countries, rising dramatically to about 40% in developing countries (Baran 2004). Pregnant women, women with heavy menstrual losses, preterm and low birth weight infants, older infants and toddlers, teenage girls, and people with chronic infections, inflammatory, or malignant disorders (e.g., arthritis

and cancer) are at greatest risk of developing Fe-deficiency anemia because they have the greatest loss or need for iron (Allen 2002; Cogswell et al. 2003; see also Table 8.1). Signs of Fe-deficiency anemia include fatigue, weakness, decreased work and school performance, slow cognitive and social development during childhood, difficulty maintaining body temperature, and decreased immune function. The latter increases the susceptibility to infections, such as glossitis or an inflamed tongue (Appendix 8.1; Allen 2002; Panel on Micronutrients et al. 2001). Aging has been widely documented to be associated with dyshomeostasis of Fe metabolism and regulation in both rodents and humans. This process adversely affects muscle strength, physical performance, cognition, and longevity. Underlying mechanisms remain to be clarified. Iron-related disorders include Alzheimer disease, Parkinson disease, Friedreich's ataxia, and retinal disease. Despite the prevalence and adverse health effects associated with these disorders, the mechanisms are still not well defined and many questions remain to be answered (reviewed in Xu et al. 2012).

Considerable potential exists for Fe toxicity because very little iron is excreted from the body. Excessive iron can accumulate acutely or chronically in tissues and organs. Acute Fe poisoning is mainly seen in children. Toxicity-producing gastrointestinal symptoms, including vomiting and diarrhea, occur with ingestion of 20 mg of elemental iron per kg of body weight. If ca. 60 mg per kg body weight are ingested, systemic toxicity occurs. Early signs of Fe poisoning (within six hours after ingestion) include vomiting, diarrhea, fever, hyperglycemia, and leukocytosis. Later signs include hypotension, metabolic acidosis, lethargy, seizures, organ damage, and coma (Madiwale and Liebelt 2006).

Hereditary hemochromatosis (HHC), due to mutations in the *HFE* gene, is an example of an autosomal recessive disorder of Fe metabolism. For Caucasian populations in Northern Europe, incidence of HHC is between 1:200 and 1:500. Persons with HHC absorb dietary iron at two to three times the normal rate. Iron deposits in many organs and affects their function, presumably by direct toxic effect. The major affected organs are the liver (cirrhosis), heart (cardiomyopathy), pancreas (diabetes mellitus), skin (pigmentation), joints (polyarthropathy), and gonads (hypogonadotrophic, hypogonadism). However, in the absence of a family history or genetic testing, HHC would not be suspected. Therapeutic phlebotomy to remove excess iron is used as treatment. The most common causes of death in individuals with HHC are hepatocellular carcinoma associated with cirrhosis, hepatic failure, and cardiac failure (Crownover and Covey 2013).

Manganese

Manganese was first found as a constituent of animal tissues in 1913, although a state of Mn deficiency was not described until 1931. Its oxidation state ranges between –3 and +7. Over time Mn^{2+} (the only form absorbed by humans) is

oxidized to Mn^{3+} (the oxidative state) in plasma. The human body contains approximately 10–20 mg of manganese: 25–40% is present in bone whereas 5–8 mg is turned over on a daily basis. Manganese is essential as a cofactor for the metalloenzymes SOD, xanthine oxidase, arginase, galactosyltransferase, and pyruvate carboxylase (Buchman 2012).

Under normal circumstances, dietary manganese is the main route of exposure for most people; however, water and atmospheric contamination can also be an exposure route (Wood 2009). Homeostasis is achieved by the tightly controlled regulation of Mn absorption in the intestine and the inducible biliary excretion of manganese (Yoon et al. 2011). Dietary manganese is absorbed by a diffusion mechanism as well as a transport mechanism, both of which are rapidly saturable. Approximately 6–16% of dietary manganese is absorbed (Buchman 2012); absorption decreases in the presence of a large calcium load. After absorption into the portal circulation, manganese remains either free or bound, preferably to transferrin, 2-macroglobulin, and albumin. All three are rapidly taken up, primarily by the liver but also by the pancreas and kidney. Metabolically active tissues with high numbers of mitochondria and pigmented structures appear to have the greatest concentrations of manganese. Excretion occurs primarily through the bile and, as such, nearly all manganese is excreted in the feces (Buchman 2012).

Despite its essentiality, excessive Mn levels are toxic to the central nervous system. Manganese has been identified as an occupational health hazard for miners, battery manufacturers, and automotive repair workers. Pathological Mn concentrations lead to a neurological disorder, called manganism, which is characterized by early psychotic symptoms, frequently followed by chronic symptoms similar to Parkinson disease (Sidoryk-Wegrzynowicz et al. 2009).

Manganese is essential for proper fetal development and other important aspects of metabolism (Yoon et al. 2011). The findings of two recent studies (see Wood 2009) indicate that lower maternal blood manganese is associated with fetal intrauterine growth retardation, lower birth weight, and higher neonatal morbidity and mortality. Additional basic studies of maternal and fetal Mn physiology are needed.

In experimental animals, Mn deficiency is associated with impaired growth, skeletal defects, reduced reproductive function, abnormal glucose metabolism, and altered lipid and carbohydrate metabolism, whereas excess manganese can induce adverse neurological, reproductive, and respiratory effects (Wood 2009). In the elderly, it has been reported that Mn deposits in the basal ganglia, especially the globus pallidus, and excessive levels of this metal can induce symptoms similar to Parkinson disease (Sidoryk-Wegrzynowicz et al. 2009). In addition, the progression of cognitive decline among the elderly in this study has been associated with increased levels of copper and manganese (Ghazali et al. 2013).

Molybdenum

Molybdenum was recognized as essential for human xanthine oxidase activity in 1953 and for sulfite oxidase activity in 1971. The concentration of molybdenum in foods reflects levels in the soil and irrigation water in which they were grown. Rich sources include legumes, grains, and nuts. Lower amounts are found in animals, fruits, and vegetables (Eckhert 2012; Appendix 8.1).

Molybdenum is rapidly absorbed and excreted from the kidney, with retention regulated primarily by urinary excretion. Physiologically relevant oxidation states for molybdenum are between +4 and +6. Molybdenum accumulates as the molybdopterin cofactor in the liver, kidney, adrenal gland, and bone at concentrations that range from 0.1 to 1 mg/g wet weight (Eckhert 2012).

Molybdenum serves an essential role in the nitrogen cycle: it is a cofactor of molybdoenzymes which are involved in nitrogen fixation and nitrate reductase, an enzyme required for the conversion of nitrate to ammonia. Another important Mo function in mammalian systems is the transfer of oxygen to a two-electron substrate using one-electron-transferring compounds, such as flavin adenine dinucleotide. Three mammalian hydroxylases are molybdoenzymes (Mendel and Bittner 2006): mitochondrial sulfite oxidase, xanthine oxidase, and aldehyde oxidase.

Molybdenum toxicity has been induced in rats where it was shown to cause renal insufficiency. In rabbits, it induced weight loss and histopathologic changes in the kidney and liver (Eckhert 2012). In humans, a case of Mo toxicity may have occurred in 1961, causing gout-like symptoms and abnormalities of the gastrointestinal tract, liver, and kidneys (Eckhert 2012).

Genetic and nutritional deficiencies of molybdenum have been reported but are rare. Genetic sulfite oxidase deficiency was described, for example, by Irreverre et al. (1967). It resulted from the inability to form the Mo coenzyme despite the presence of adequate molybdenum. The deficiency caused intellectual disability, seizures, opisthotonus, and lens dislocation (Bayram et al. 2013). Molybdenum deficiency resulting in sulfite toxicity occurred in a patient who was receiving long-term total parenteral nutrition. Symptoms were tachycardia, tachypnea, headache, nausea, vomiting, and coma. Laboratory tests showed high levels of sulfite and xanthine and low levels of sulfate and uric acid in the blood and urine. Administered intravenously, daily doses of 300 μg of ammonium molybdate IV caused dramatic recovery (Eckhert 2012).

Selenium

Selenium is an essential micronutrient and exists in two forms: inorganic (selenate and selenite) and organic (selenomethionine and selenocysteine). Both have dietary sources. Selenium functions through selenoproteins and plays critical roles in reproduction, thyroid hormone metabolism, DNA synthesis, and protection from oxidative damage and infection (Hill et al. 2012; Sunda

2012; Appendix 8.1). Some tissues (e.g., testis, kidney, and bone marrow) synthesize selenoproteins for export and thus have greater requirements for selenium than other tissues.

Intestinal absorption of selenium is not regulated; in plasma, selenium is mostly bound and transported by Se-binding protein 1. In addition, the Se content of the body is regulated by hepatic production of methylated Se compounds, which are excreted predominantly into the urine (Kobayashi et al. 2002).

Skeletal muscle is the major site of Se storage, accounting for approximately 28–46% of the total Se pool (Sunda 2012). Recent changes in the Se metabolism can be analyzed via blood or urine samples; hair or nails provide good sources for long-term tests. The brain must have a reliable supply of selenium to be viable and exhibits high priority over the body's Se supply and retention under conditions of dietary Se deficiency (Steinbrenner and Sies 2013).

Selenium deficiency produces biochemical changes that might predispose people under additional stresses to develop certain illnesses or heart failure (Kucharzewski et al. 2002; Saliba et al. 2010; Appendix 8.1). It is also associated with male infertility and might play a role in Kashin-Beck disease, a type of osteoarthritis occurring in certain low Se areas of China, Tibet, and Siberia (Sunda 2012). Iodine deficiency may be exacerbated by Se deficiency, potentially increasing the risk of cretinism in infants (Sunda 2012). Risks for Se deficiency include populations living in Se-deficient regions, dialysis patients, and individuals with HIV. In preterm babies, low selenium is associated with an increased risk of complications, such as chronic neonatal lung disease and retinopathy of prematurity (Iranpour et al. 2009). Cancer, cardiovascular diseases, cognitive decline, and thyroid disease have also been connected to a disturbance in Se metabolism.

Serum Se concentrations decline with age. Marginal or deficient Se concentrations might be associated with age-related declines in brain function, possibly due to decreases in selenium's antioxidant activity (Shahar et al. 2010). Selenium status should be controlled regularly and corrected through supplementation.

Zinc

Zinc is an essential metal involved in numerous aspects of cellular metabolism. Required for the catalytic activity of approximately 300 enzymes, it plays a role in immune function, protein synthesis, wound healing, DNA synthesis, and cell division (Haase et al. 2006; Haase and Rink 2013; Appendix 8.1). Zinc also supports normal growth and development during pregnancy, childhood, and adolescence (Maret and Sandstead 2006) and is required for a proper sense of taste and smell (Prasad 2013; Appendix 8.1).

The human body contains 2–3 g Zn^{2+}, concentrated primarily in the liver, kidneys, pancreas, eyes, and bone. Daily, 0.1% of body zinc is exchanged (Maret and Sandstead 2006). Because no major storage organs for zinc exist, a

continuous nutritional supply is needed to cover Zn^{2+} requirememts . Following its uptake by the small intestine, the distribution of Zn^{2+} is carried out through plasma, where it is bound by proteins, mostly albumin (Scott and Bradwell 1983). Cellular Zn^{2+} is distributed in the nucleus (30–40%), membrane (10%), and cytoplasm (50%). The latter contains membrane-enclosed structures rich in zinc, so-called zincosomes (Haase and Rink 2013). Remaining cytoplasmic zinc is mostly bound to proteins, especially metallothioneins. Zinc homeostasis in the human body is regulated by 14 Zip (Zrt/Irt-like) proteins, which increase the amount of zinc in the cell cytoplasm, and 10 ZnTs (Zn transporters), which decrease cytoplasmic Zn concentrations. There is considerable cell-specific expression of some of the transporters, which are dynamically regulated in response to Zn status and endocrine and cytokine signaling. Expression of these transporters can also regulate signal transduction via the level of intracellular zinc (Haase and Rink 2009).

Although excessive Zn intake is very rare, recent estimates indicate that Zn deficiency affects over 17% of the world's population (Wessells and Brown 2012). The main cause of Zn deficiency is malnutrition; however, disease and aging may also play a role.

Phytates, which are present in whole grain breads, cereals, legumes, and other foods, bind zinc and inhibit its absorption (Prasad 2012). The predominantly wheat diet in the Middle East contains high quantities of phytate and fiber, which reduce Zn and Fe availability increasing the risk for Zn deficiency (Prasad 2012). Symptoms of Zn deficiency include impaired growth and development, impotence, loss of appetite, diarrhea, hypogonadism in males, eye and skin lesions, weight loss, mental lethargy, dermatitis, delayed wound healing, alopecia (hair loss), various neurological symptoms, and impaired effectiveness of the immune system, leading to a higher susceptibility to infections (Wang and Busbey 2005; Maret and Sandstead 2006; Maret 2012; Appendix 8.1). Zinc deficiency has been associated with birth defects and low birth weight, impaired learning, as well as delayed sexual development. Depending on the extent and timing of the deficiency, embryotoxicity may also occur (Kambe et al. 2008). Supplementation studies show a significant 14% reduction in preterm births in women from low-income settings, but no effect on low birth weight (Mori et al. 2012). *Acrodermatitis enteropathica* (mutation in Zip4) is a rare hereditary autosomal recessive disease of Zn deficiency. It leads to severe immunological consequences, including thymic atrophy, decreased lymphocyte counts and function, and death from infections. Mandatory clinical manifestations are skin changes, chronic diarrhea, and alopecia. Treatment with zinc is necessary to maintain life and reverses the symptoms (Haase and Rink 2009).

A decline of Zn status with age has been established, and a correlation between Zn status and immune function in the elderly seems to exist. The question remains whether Zn deficiency is caused by infections that occur more frequently in elderly people, thus leading to a subsequent loss of zinc, or whether

aging poses a risk of becoming Zn deficient, thus leading to immunosenescence and increased susceptibility to infectious diseases. Diseases associated with disturbed Zn homeostasis include diarrhea, common cold, age-related macular degeneration, and Cu deficiency (Wintergerst et al. 2007; Caruso et al. 2007; Chong et al. 2007; Whittaker 1998; Willis et al. 2005).

Metallic Elements with Suggested Essentiality

Arsenic

Exposure to the metalloid arsenic occurs daily due to its environmental pervasiveness. Arsenic presents as inorganic arsenate (iAsV), in most cases, or as inorganic arsenite (iAsIII), when anaerobic conditions are present in drinking water. Despite arsenic's reputation as a poison, it actually has fairly low toxicity compared to other metals, although chronic exposure raises concern about its carcinogenicity. In fact, arsenic may even be essential and functional in humans in very small amounts, as it has been shown to be essential in rats and other animals. However, beneficial effects in humans have not yet been defined (Mayer et al. 1993).

At least 90% of ingested iAsV and iAsIII are absorbed from the intestine and excreted primarily in the urine. Arsenic is mainly metabolized in the liver, with inorganic arsenic converted to monomethyl- and dimethylarsenicals by As methyltransferase (Lin et al. 2002). It has been reported that concentrations of iAs peak in the liver and kidney one hour after oral administration of iAsV, with dimethylarsinic acid then becoming the predominant form in the liver four hours after administration (Watanabe and Hirano 2013; Kenyon et al. 2005). Even if arsenic is not actively stored, it accumulates in bone, teeth, skin, hair, nails, and internal organs. On average, there is about 10–20 mg of arsenic in the human body; higher amounts may accumulate when kidney function is decreased. Normally, absorption of arsenic is fairly low (< 5%) as most is eliminated in urine and feces.

Arsenic is considered carcinogenic and has been related to the lung, kidney, bladder, and skin disorders. It is also toxic to developmental and reproductive systems (Chakraborti et al. 2004). Immunotoxic, biochemical, and cellular toxicities cause serious diseases such as hyperkeratosis, blackfoot disease, vascular diseases, and cancers (Sakurai et al. 2004).

In several epidemiologic studies (e.g., Bloom et al. 2010), maternal exposure to high concentrations of inorganic arsenic in naturally contaminated drinking groundwater sources has been associated with an increased risk for the spontaneous loss of pregnancies. Decreased fetal weight and malformation have also been reported. In neonates, As exposure causes encephaly, eye defects, renal agenesis, and gonadal agenesis (Domingo 1994). One study in Japan revealed that arsenic as well as mercury and cadmium accumulate in the

human body during aging and may play a role in the aging process (Yasuda et al. 2012). So far, no studies on As deficiency have been reported.

Chromium

Over fifty years ago chromium was proposed to be an essential element for mammals, with a role in maintaining proper lipid metabolism and regulating blood sugar. Over the next several decades, research recommended Cr nutritional supplements for weight loss and muscle development, without knowledge on mode of action (Anderson 1997; Vincent 2010; Appendix 8.1). A timely review by Hua et al. (2012) addresses some of the recent findings regarding the molecular mechanisms of alleviating insulin resistance by chromium, which sheds light on the potential cellular pathways that are affected.

Chromium occurs in any oxidation state from –2 to +6. Trivalent chromium (Cr^{3+}) is the biologically active form, while hexavalent chromium (Cr^{6+}) is potentially toxic to humans and carcinogenic. Absorption of Cr^{3+} from the intestinal tract is low (0.4–2.5%), and the remainder is excreted in the feces (Offenbacher et al. 1986; Eckhert 2012). Absorbed chromium is stored in the liver, spleen, soft tissue, and bone (Lim et al. 1983). Diets high in simple sugar can increase Cr excretion, while vitamin C and niacin can enhance absorption (Kozlovsky et al. 1986; Offenbacher et al. 1986). Stress, infections, exercise, pregnancy, lactation, and aging can increase Cr loss or decrease its absorbtion, and might require supplementation (Davies et al. 1997; Lukaski et al. 1996).

Although rare, Cr deficiency causes glucose-handling disorders with diabetes-like symptoms and abnormalities of the motor and sensory nerves. It is, however, easily corrected through supplementation (Jeejeebhoy et al. 1977; Anderson 1995). However, the required value of Cr supplements for diabetic patients (especially type 2) and to correct blood lipid levels and promote weight loss has not yet been established (Masharani et al. 2012).

Deficiences or overload of chromium, from conception through life, are associated with malfunctions, malformations, acute and chronic diseases, and fetal toxicity (Appendix 8.1); the nature of these depends on onset, duration, and degree of the deficiencies. Pregnant women may be at risk for Cr deficiency, but it should possible to cover the required amount by increasing Cr-rich foods in the diet, since supplements can easily result in high amounts of arsenic, which could negatively affect fetal development (Lindgren et al. 1984; Moukarzel 2009).

Nickel

The essentiality of nickel in higher organisms is questionable. In order of abundance in Earth's crust, nickel ranks as the 24th element. Thus, humans are constantly exposed to this ubiquitous element, although in varying amounts. Due to its abundance, natural Ni deficiency does not occur (Denkhaus and Salnikow

2002). The blood levels of nickel in nonsmokers range from 0.01–0.26 µg/l (Stojanovic et al. 2004). Nickel intake occurs via inhalation, ingestion, and dermal absorption and is a function of bioavailability. Nickel is excreted equally well via urine and feces. Inhaled nickel is selectively concentrated in the lung, followed by heart, diaphragm, brain, and spinal cord tissues (Tjalve et al. 1984). Exposure to high doses of nickel disturbs established cellular homeostasis via changes of intracellular Ca levels and produces oxidative stress. Nickel allergy, in the form of contact dermatitis, is the most common and well-known reaction. Other known health-related effects include skin allergies, lung fibrosis, variable degrees of kidney and cardiovascular system poisoning, and stimulation of neoplastic transformation. The mechanism of the latter effect is currently unknown and the subject of detailed investigation. Epidemiological studies have clearly implicated Ni compounds as human carcinogens based on a higher incidence of lung and nasal cancer among Ni mining, smelting, and refinery workers (Denkhaus and Salnikow 2002). Nickel exposure can result in significant embryotoxic effects in terms of increased resorption rates, decreased fetal weight, delay in skeletal ossification, and a high incidence of malformations (acephalia, ankylosis of the extremity, club foot, and skeletal anomalies) (Lu et al. 1979; Appendix 8.1).

Vanadium

Vanadium is a trace element found in living organisms with a potentially essential role. Less than 5% of ingested vanadium is absorbed. Vanadium is rapidly cleared from plasma, accumulates in kidney, liver, testes, bone, and spleen and is able to cross the placenta. Vanadium is excreted primarily through the kidney, with a small amount through bile. Tissues with the highest concentrations include lung, teeth, thyroid, and bone (Eckhert 2012).

Vanadium is a cofactor for several enzymes including haloperoxidases and nitrogenases. In oxidation state 5 it is an analog of phosphorus, and thus an inhibitor against phosphorylases such as the ATPase, protein tyrosine phosphatases, and ribonucleases. Vanadium demonstrates promising antidiabetic properties and thus has been applied as a potential therapeutic (Eckhert 2012).

No human cases of V deficiency have been reported. Vanadium deficiency in goats increased rates of abortion, convulsions, bone malformations, and early death. However, high concentrations are toxic (Nechay et al. 1986). Vanadium is a reproductive toxin that affects males more than females. The International Agency for Research on Cancer lists vanadium as a possible carcinogen based on inhalation studies of V pentoxide in animals.

Vanadate treatment resulted in micrognathia, supernumerary ribs, and alterations in sternebral ossification. Whereas embryolethality was not observed at any dosage level (Carlton et al. 1982), vanadyl sulfate pentahydrate caused maternal toxicity, embryofetotoxicity, and teratogenicity (cleft palate, micrognathia) at all dose levels tested (Paternain et al. 1990; Appendix 8.1).

Metallic Elements and Infectious Diseases

For any one or more of the trace metals discussed here, dyshomeostasis has long been associated with susceptibility and progression of inflammatory diseases (Suttle and Jones 1989; Katona and Katona-Apte 2008). Incidence of certain inflammatory diseases has been mapped to areas deficient in selenium and zinc (Di Bella et al. 2010). However, descriptions of the underlying mechanisms as well as the mode of action of supplementation strategies are just beginning to emerge.

Trace elements are structural parts and cofactors of a variety of enzymes. Lack of the metal causes alterations or loss of function as a general consequence. Proteins affected can either belong to the host, with a majority being related to immune functions (see Weiss, this volume) or to the pathogen, which is mostly responsible for their proliferation or virulence (Bachmann and Weiser, this volume; Sterritt and Lester 1980; Thurman et al. 1989; Prado et al. 2012; Haase 2013). The later finding suggests that a benefit for the host can be gained from the deficiency; this might be true for an acute translocation of trace metals away from the microbes (Bachmann and Weiser, this volume). However, prolonged deficiency has major, negative consequences for the host, especially for its immune system as described above (see also Weiss, this volume).

Another general symptom of deficiencies in cobalt, copper, molybdenum, iron, selenium, zinc, and vanadium is an increase in reactive oxygen production, due to the fact that the majority of enzymes involved in redox metabolism are metal dependent. Increased levels of reactive oxygen species can induce rapid mutation in RNA viruses, often resulting in a more virulent form. Recent published examples for Se deficiency-related viral mutation are coxsackievirus B3, influenza virus, and poliomyelitis virus (see Harthill 2011). Selenium supplementation decreased the mutation rate and improved the host response, including viral clearance. This is in concordance with the observation that H_2N_2, H_3N_2, H_5N_1, and SARS originated from regions in China where selenium is low. Experiments in mice confirm those observations: Se-deficient mice had higher rates of mutation to more virulent H_3N_2 forms than mice with balanced serum selenium. As an underlying mechanism, elevated reactive oxygen levels could be defined. Also, incidences of HIV and Ebola are high in Se-deprived regions in Sub-Saharan Africa (Di Bella et al. 2010; Harthill 2011).

For HIV, deeper insights into the incidents and severity of the disease independent of Se and Zn homeostasis have recently been established. Results of several studies showed that decreased serum selenium as well as serum zinc caused higher incidents, more severe progression, higher bacterial loads, increased susceptibility to secondary infections (such as hepatitis C), mycobacterial infections, and other especially opportunistic infections as well as higher mortality. Benefits from supplementing HIV patients with selenium or zinc are a decreased viral load, less hospitalization, and milder disease progression

(Baum et al. 2010; Harthill 2011). Because of its strong impact on immune functioning, zinc has been linked to all kinds of infectious diseases (for details, see Haase 2013). Zinc supplementation has been repeatedly shown to be beneficial in preventing diarrhea and decreases the incidents of infections in the neonates. Benefits derive from zinc's role in intestinal fluid transport, mucosal integrity, immunity, and the redox metabolism (Berni et al. 2011). Positive effects have been observed for treatment of pneumonia and other lower respiratory infections, malaria, the common cold, leprosies, tuberculosis, leishmaniasis, and sepsis, especially in risk groups such as infants, children, and the elderly. However, results from studies vary considerably and should thus be explored further in more detail (Fischer and Black 2004; Zeng and Zhang 2011; Basnet et al. 2014; Mocchegiani et al. 2013). An interesting example for the interplay of trace elements during inflammation is that zinc can starve pneumonia by blocking the bacterial Mn uptake. Unique mechanisms have been proposed for the positive role of vanadium in preventing inflammatory diseases: supplementation of mice with vanadium prior to LPS injection leads to upregulation of IL-1 antagonist, damping of brain-based proinflammatory cytokine upregulation, and blunting of central communication. Values for human use remains, however, to be established (Johnson et al. 2005b).

Although trace elements are toxic for humans if overdosed, the literature on the beneficial effects of trace metal supplements goes back ages. Ointments containing trace metals (e.g., zinc) have long been used to treat and prevent skin infections; however, benefits from oral supplementation are more recent. Effects are partly due to the support of the immune system but include direct consequences to the microorganism as well. Cobalt is mostly applied to keep surfaces sterile (e.g., in hospitals) due to its high toxicity for microbes. It is also used as an adjuvant for various infectious disease medications. One famous example is the Co chelate complex CTC-96, used to treat herpes, adenovirus, cytomegalovirus, Epstein–Barr virus, and varicella zoster virus (Schwartz et al. 2001b). The potential importance of cobalt for the host defense has been suggested, but remains to be explored in more detail.

The general antimicrobial properties of copper have been described in literature; over 300 publications were already available in 1973. More recent research has focused on defining more than thirty types of Cu-containing proteins across the animal kingdom. Similar to cobalt, most of our current knowledge stems from experiments that analyze the effect of surfaces containing high amounts of copper rather than a function within the host. A few of the recent studies have suggested an association of changes in Cu homeostasis with *Escherichia coli*, methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile*, influenza, adenovirus, and fungi (Prado et al. 2012).

As indicated earlier, not all trace elements have positive effects on the host defense against pathogens. One study in Bangladesh revealed that high intake of arsenic during pregnancy (ingested, e.g., through contaminated drinking water) increases the risk for infections of the lower respiratory tract and the

number of deaths in mothers and their infants. It has been suggested that arsenic causes immune suppression and becomes apparent through suppressed antibody formation, T cell proliferation, decreased size of the thymus, impaired macrophage activity, and elevated production of reactive oxygen species (Rahman et al. 2011). Iron overload has negative effects on the immune system as well and can result in increased susceptibility to infectious diseases.

Nonessential Metallic Pollutants

To summarize metal homeostasis throughout life, let us review some important facts on the impact of nonessential metals on human health.

Mercury is one of the most toxic metals in the environment. It is released through activities in the agriculture industry (fungicides, seed preservatives), by pharmaceuticals, as pulp and paper preservatives, catalysts in organic syntheses, in thermometers and batteries, in amalgams (dental fillings), and in chlorine and caustic soda production (Zhang and Wong 2007). Exposure to high levels of metallic, inorganic, or organic mercury can permanently damage the brain, kidneys, and the developing fetus (Chang et al. 1980; Lindgren et al. 1984; Holt and Webb 1986; Appendix 8.1). The toxicity of mercury depends on its chemical form: ionic < metallic < organic (Clarkson and Magos 2006).

Cadmium is naturally present in the environment: in air, soils, sediments, and even in unpolluted seawater. It is emitted into the air by mines, metal smelters, and industries that use Cd compounds to produce alloys, batteries, pigments, and plastics, although many countries have stringent controls on such emissions. Tobacco smoke is one of the largest single sources of Cd exposure in humans. Absorption of cadmium in the lungs through smoking is much greater than in the gastrointestinal tract, where people are exposed to cadmium through the consumption of plant- and animal-based foods. Seafood, such as mollusks and crustaceans, can also be a source of cadmium (Castro-Gonzalez and Mendez-Armenta 2008). Cadmium accumulates in the human body and can negatively affect the liver, kidney, lung, bones, placenta, brain, and central nervous system (Castro-Gonzalez and Mendez-Armenta 2008). Other damage that has been observed includes reproductive and developmentally toxic, hepatic, hematological and immunological effects; intrauterine growth retardation; and fetal death (Ahokas et al. 1980; Daston 1982; Holt and Webb 1986; Apostoli and Catalani 2011; Appendix 8.1). Interestingly, adverse effects are produced despite limited embryonic and fetal accumulation of the metal (Domingo 1994).

Oral aluminum is ingested through food and drinking water as well as therapeutic preparations administered in large quantities, such as phosphate binders, antacids, and buffered aspirins (Cannata and Domingo 1989). Although the gastrointestinal tract normally represents a barrier to Al absorption, this barrier can be breached under some circumstances. Moreover, it has been

demonstrated that concurrent ingestion of Al compounds and some organic dietary constituents (e.g., citric, lactic, and ascorbic acids) causes significant increase in the gastrointestinal absorption of aluminum (Domingo et al. 1991). Aluminum accumulation in the body manifests in impaired neurological development, Alzheimer disease, metabolic bone disease, dyslipidemia (abnormal blood lipids), and even genotoxic activity (Krewski et al. 2007; Hernandez-Sanchez et al. 2013). Of special concern is the intake of large amounts of aluminum by pregnant women. During pregnancy, "dyspepsia" (condition of disturbed ingestion) is a common complaint, and Al-containing antacids are widely used to relieve dyspeptic symptoms. Aluminum can act as a powerful neurological toxicant, provoking embryonic and fetal toxic effects in animals and humans after gestational exposure. Despite this knowledge, over-the-counter patient information leaflets for European antacids vary substantially in terms of warnings that Al toxicity will increase health risk (Reinke et al. 2003). Further studies are needed to clarify the link between Al exposure and disease in humans. Moreover, harmful and toxic doses need to be clearly defined for the public (Krewski et al. 2007).

Conclusion

The incidence of malnutrition in the world is alarming, as is the increasing problem of obesity. Furthermore, the incidence of deficiency in essential nutrients is on the rise. The World Food Programme estimates that poor nutrition is responsible for 3.1 million child deaths annually (or 45% of all child deaths).[1] The rate of maternal morbidity due to obesity has also increased.

People of all ages are at risk for deficiencies in essential nutrients, even though the metabolism of adults is often tolerant enough to cope with transient dietary deficiencies. The primary groups at risk are pregnant women, fetuses, and the increasing elderly population. Often neglected are people exposed to high psychological and physical stress, including athletes and those who work in leadership positions. (Those groups of people may, however, be generally more health conscious and thus aware of additional dietary needs.)

Balanced nutrition early in life is vitally important; undernutrition during pregnancy and the first two years of life is a major determinant of (a) stunted development and subsequent obesity and (b) incidence of infectious diseases, with possible long-term damage and manifestation of noncommunicable diseases in adulthood (Black et al. 2013). Disturbed metal balances in the elderly result from lifelong exposure to toxic metals as well as years of wear and tear on their metabolism, including enzyme and organ systems. In addition, dyshomeostasis in trace metals, especially deficiencies, strongly impacts immune function throughout life, causing increased susceptibility and more severe

[1] http://www.wfp.org/hunger/stats

progression of all kinds of infectious diseases. Nutritional interference should be approached in different ways, depending on the age group. As described, problems in metal homeostasis in the elderly do not always stem from deficiencies or excess, but rather from a disturbance in an enzymatic process. It is thus imperative to identify the reason for the disturbance rather than simply to prescribe supplements. Supplementation in pregnant women should be carefully monitored. Often, changes in the diet are much more efficient than chemical supplementation, as overexposure to supplemental nutrients can be detrimental for the developing embryo.

Recommended dietary allowances are well defined for age groups, yet how can people meet RDAs and live a healthy life? One option is to increase labeling on food and beverages, so as to indicate not only caloric and fat values but also the amounts of (trace) elements. Initial steps to provide more complete nutritional labeling have been taken, but public awareness and education is needed.

The data provided in this review are only a summary of the mass volume of information that has been generated over the last decade. Detailed reviews on the homeostasis for each element, including involved transporters and binding proteins, are available. How can this information be brought to the public? One approach is to integrate nutrition into school curricula, starting at the kindergarten and primary school levels. Such educational approaches have begun in various areas, offering children and their parents the opportunity to prepare meals together. As an example, a detailed action plan for the United States was generated by the White House Task Force on Childhood Obesity[2] and for Germany by the German Obesity Foundation (Müller et al. 2007). Initiatives such as Let's Move! are great examples of an approach that can be taken to raise a healthy generation of children (for study results, see Pirzadeh et al. 2014). Doctors and antenatal exercise groups are also well positioned to provide information to the public. Here, there is often, however, a tendency to prescribe medications, which may not always be the best solution, when alternatives (e.g., a particular diet or a visit to a dietitian) might serve a patient better.

Essential metals are generally regarded as "safe," in particular if taken up via food, which is the best source of necessary elements. However, there is always a risk of overdosage, although overdosage due to high food consumption has barely been described in the literature. In contrast, highly concentrated supplements have the potential to induce allergic or toxic reactions, and studies are lacking on the effects of supplement combinations. Taking several supplements at the same time may neutralize their impact (and have no benefit) or produce negative, synergistic side effects.

In general, there is much confusion as to what constitutes good nutrition—a situation often exacerbated (rather than remedied) by "health websites" and media reports. In addition to creating headlines, the latest "fad diet" often contradicts basic nutritional knowledge that has been trusted for decades, creating

[2] www.letsmove.gov

widespread alarm and instant dietary changes. Many such reports are biased and overgeneralized, marked by failure to evaluate fully the current literature in trusted journal publications. Thus the public is left misinformed and potentially ready to make poor dietary decisions. Yet how can people decide which information is accurate?

The pharmaceutical industry has the ability to influence the generation and updating of RDA values. Often, discrepancies exist between values given by the World Health Organization, the U.S. Food and Drug Association, and on product labels. For example, the recommended dose for chromium in healthy individuals (during pregnancy and while nursing) is high, even though research suggests that lower values are sufficient. Several years ago a conjecture was voiced, and taken up by the media, that chromium could mitigate diabetes and aid weight loss. As a result of the subsequent hype and claims for better health, the market for Cr supplements boomed, even though the claim was not substantiated. Obviously it is not in the economic interest of the pharmacological industry to rectify such ill claims.

One approach to help people eat a more balanced diet is to improve the quality of food. This requires reducing the amounts of chemical fertilizers, insecticides, pesticides, etc., as well as improving food processing methods to retain natural nutrients. In addition, people's eating habits need to be scrutinized. In many societies, there is a tendency to eat prepackaged, ready-made meals that are easily and quickly prepared. Such food, however, has typically much less nutritional value. People need to be aware of the negative health impacts that could result from consuming high amounts of processed fast food and be encouraged, instead, to consume fresh food.

Governmental involvement at all levels would be beneficial. To make fresh food more attractive to the consumer, local producers may need support to lower prices for fresh products. Schools, universities, and businesses should also be encouraged to offer more healthy food options.

The available research information is broad. However, studies have concentrated primarily on a single element; interactions between metals, their competition for transporters, and binding proteins have, for the most part, been neglected. Future research must focus on this to elucidate interactions and symbiotic effects.

Overall, societies are becoming increasingly aware of the increase in malnutrition and have begun to search for solutions. Unfortunately, these solutions have centered on prescriptions and supplements. New strategies need to be developed that are more natural and preventive. Up-to-date research should be used to inform and update nutritional recommendations. Medical professionals should be encouraged to update their knowledge regularly and to pass this on to their patients. Different media venues should be used to educate and inform people of all ages. All efforts should be geared toward expanding our understanding on disease and disease prevention, for this is always better, and usually cheaper, than treatment and medication.

Appendix 8.1 Functions, food sources, and symptoms of deficiency or overload for biologically relevant essential and nonessential metallic elements. GI: gastrointestinal; SOD: superoxide dismutase; TPN: total parental nutrition. Adapted from Dietary Supplemental Fact sheets (http://ods.od.nih.gov/factsheets/list-all/) and Ross (2012).

	Functions	Food Source	Deficiency	Overload
As	No proven physiological function in humans. Known to be essential in rats and other animals	Rice, flour, spinach, grape juice, (saltwater) fish and seafood, grains, drinking water, fertilizers	In animal models, no deficiency reported for humans: myocardial damage, reduced growth, impaired fertility, increased perinatal mortality	Encephalopathy, GI symptoms, skin pigmentation, dermatitis, peripheral vascular diseases, neuropathy, genotoxicity, cancer, anemia, hepatotoxicity
Co	Component of vitamin B12, thus involved in DNA synthesis, fatty acid synthesis, and energy production	Depends on content in soil and air, drinking water	Neurological disorders due to vitamin B12 malfunction	Nausea, vomiting, lung diseases, heart diseases, neurological problems, thyroid disorders
Cr	Cr^{6+} (industrial pollution): toxic, teratogen, carcinogen Cr^{3+}(food): suggested but unproven: regulating blood glucose levels, involved in protein and fat metabolism	Meats, poultry, fish, beer, whole grains, fruits, vegetables, spices, water	Impaired glucose removal, elevated fatty acids, neuropathy, weight loss, glucose intolerance (disappears after Cr treatment)	Chrome ulcer, nasal septum perforation, chronic renal failure, lung cancer
Cu	Component of enzymes in Fe metabolism, involved in activity of cytochrome oxidase, tyrosinase, cerulo plasmin, lysine oxidase, ascorbate oxidase, SOD, amine oxidase	Organ meats, legumes, nuts, seafood/shellfish, seeds, wheat bran cereals, whole grain products, cocoa products, cheese	Anemia, retarded growth, osteoporosis, neutropenia, skeletal abnormalities, decreased pigmentation In premature infants: pallor, decreased pigmentation, superficial veins, skin lesions, diarrhea, neuronal abnormalities	GI distress, liver and renal damage, rheumatoid arthritis, gastric ulcers, cancers, epileptic episodes

	Functions	Food Source	Deficiency	Overload
Fe	Component of hemoglobin and numerous enzymes; prevents microcytic hypochromic anemia	Nonheme Fe: fruit, vegetables (lentils, beans), fortified bread, grain products/cereal Heme Fe: red meat, fish, poultry	Tiredness, weakness, dizziness; slow social and cognitive development; easy freezing; decreased immune function or increased susceptibility to infection; glossitis; anemia; tinnitus; headache; cardiac pain or failure	Hemochromatosis, migraine headaches, arthritis, high blood pressure, cancer, heart disease, genetic diseases, GI disorders, diarrhea, nausea, vomiting, constipation, diabetes, preeclampsia, organ damage (cirrhosis of the liver) neurodegeneration, lower IQ in children
Mn	Bone and amino acid formation; lipid, protein and carbohydrate metabolism; cofactor of metalloenzymes (e.g., SOD)	Nuts, legumes, tea, seeds, whole grains, seaweed, beans, peas, ginger, coffee	Weight loss, transient dermatitis, nausea, vomiting, changes in hair color and growth, delayed blood clotting, low cholesterol In neonates: disturbed calcification, demineralization (corrected by Mn supplementation)	Insomnia, depression, delusion, anorexia, arthralgia, weakness, neurotoxicity, mental disorders, muscle tremors
Mo	Cofactor for enzymes in catabolism of sulfur amino acids, purines, and pyridines; involved in electron transfer via, e.g., flavin adenine dinucleotide	Legumes, grain products, nuts, lentils, beans, organ meats, soybeans, cauliflower	Not observed in humans, due to TPN; rapid heart and respiratory rates, headaches, night blindness, coma due to genetic defects; severe neurological dysfunction characterized by cerebral atrophy, mental retardation, intractable seizures, and dislocation of ocular lenses	Gout-like syndrome (one reported case of acute supplemental Mb toxicity), insomnia, seizures, psychosis, hallucinations, renal insufficiency, weight loss, changes in liver and kidney
Ni	No clear biological function in humans; may serve as a cofactor of metalloenzymes	Grains, vegetables, legumes, meat, poultry, nuts, chocolate, drinking water	Not observed in humans Pigs and rats: delayed sexual maturity, rough coat, liver abnormalities	Irritation of the respiratory tract, nonspecific symptoms, pulmonary and GI toxicity, pneumonitis, edema, cancer

Appendix 8.1 (continued)

	Functions	Food Source	Deficiency	Overload
Se	Reproduction, thyroid gland function, DNA production, protects from damage caused by free radicals and infection, involved in brain functioning	Organ and muscle meats, seafood, whole grains, eggs, poultry (depending on soil Se content)	Osteoarthritis, dwarfing and joint deformation, muscle pain and tenderness, cardiomyopathy dyschromotrichia, macrocytosis, cancer, thyroid disease, heart disease (Keshan disease), infertility in male, arthritis (Kashin-Beck disease)	Loss of hair and nails, skin lesions and polyneuritis, alopecia, nail changes, garlic breath, nausea, diarrhea, skin rashes, irritability, metallic taste in the mouth, discolored teeth, nervous system problems
V	No biological function in humans identified; effect on insulin metabolism suggested	Mushrooms, black pepper, shellfish, parsley, dill seed, vegetable oils, fats, olives, seafood, beer wine, grains	Humans: no reported deficiency Goats: abortion, convulsion, bone malformation, early deaths	Abdominal cramps, diarrhea, hemolysis, increased blood pressure, fatigue, cancer V_2O_5 : conjunctivitis, rhinitis, pulmonary inflammation
Zn	Component > 300 enzymes, 2nd messenger, vital for growth/cell division, fertility, functioning of immune system, taste, smell, appetite, skin, hair, nails, vision	Oysters, crab, lobster, liver, poultry, cheese, fortified cereals, whole grains, red meats, legumes, dairy products	Anorexia nervosa, hypogeusia, retarded growth, delayed sexual maturation, impaired wound healing, skin lesions; defects in reproduction, taste, vision and smell; neurosensory, hormonal, immunological disorders; skin problems; mental irritability, emotional disorders and chronic diarrhea; loss of appetite and hair; impotence; hypogonadism in males, eye lesions	Reduced copper status, nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, headaches, altered Fe function, reduced immune function, reduced levels of high-density lipoproteins

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