11.3 Minerals and trace elements 1871

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ESSENTIALS The essential minerals, calcium, phosphorus, potassium, sulphur, so- dium, chlorine, and magnesium (macrominerals) and trace elements chromium, copper, fluorine, iodine, magnesium, manganese, mo- lybdenum, phosphorus, selenium, and zinc, have diverse and critical functions in human metabolism. Dietary sources and the intake requirements for macrominerals and trace elements for optimal physiological well-being have been established, and the upper range of intake has been also been set so that unwanted or even toxic effects can be avoided. Deficiency of certain trace elements contributes importantly to the global burden of illness and mortality, especially in infants under the age of five years. Latterly also, especially in high- and middle- income regions, there has been burgeoning public and commercial interest in the role of, and requirements for, minerals and trace elem- ents in health and disease. An up-to-date familiarity with the scien- tific basis of mineral and trace element physiology is therefore critical for maintaining good standards of clinical practice and to inform the best standards of nutritional advice, especially in the treatment of severe illnesses associated with deficiency or toxic excess of one or more macrominerals or trace elements. Introduction Around 4% of body weight is made up of mineral elements, of which seven are required in larger amounts: calcium, phosphorus, potassium, sulphur, sodium, chlorine, and magnesium. In health these are required in amounts of g/day and may be referred to as the macrominerals. They are present principally in body fluids (typic- ally as electrolytes) and as structural components of tissues. The remaining element are required in amounts less than 100 mg/day and are termed trace minerals/elements: iron, zinc, copper, iodine, manganese, molybdenum, selenium, and chromium. Cobalt is required only as preformed vitamin B12. Fluorine is not essential but is beneficial as fluoride. Lithium is used to treat bipolar disorder. Some other elements may prove to be essential to humans (based on their role in other organisms): aluminium, arsenic, boron, bromine, cadmium, germanium, lead, nickel, rubidium, silicon, tin, and vanadium. They would be required in amounts less than 1 mg/day and are therefore sometimes referred to as ultratrace elements. Most of the other elements may be found in the human body, in amounts that depend on the environment, but have no known func- tion and may be toxic (e.g. mercury). The essential trace elements function as part of enzyme reac- tions, either as a constituent part of the enzyme, the metalloen- zymes, or as activators of enzyme

systems (where they are more loosely bound). They have a structural and catalytic role in gene expression. Other functions include the storage and transport of substrates as metalloproteins (e.g. zinc + insulin in secretory vesicles in the β cells of the pancreas). Their essentiality arises from their individual chemistry, which determines their specific roles. In general, the more soluble the mineral or trace element, the better it is absorbed in the gut. Uptake is usually controlled (i.e. via transport proteins), except when intakes are very high. All elements may be toxic in excess; intake may be via the gut, skin, or lungs. Excretion is usually minimal when the element is present in the body bound to protein(s), hence the risk of toxicity. Normal loss of these elements is mainly via desquamation (and bile), though chelating agents can be administered in the case of copper toxicity (e.g. in Wilson's disease) in order to promote excretion in the urine (and phlebotomy is used to deplete the body of excess iron in hemochromatosis). Primary deficiencies occur widely in the cases of iron and iodine, and, in some groups, zinc and selenium. Secondary deficiencies may occur due to excess losses from the body (urine, blood, diar- rhoea), or due to malabsorption, gut surgery, alcohol abuse, and other clinical conditions. It is possible that suboptimal status of minerals and trace elem- ents could be involved in the development of degenerative diseases such as coronary heart disease, cancer, and osteoporosis. However, it is currently difficult to investigate this due to the lack of good methods for assessing status and hence determining requirements of some minerals and trace elements, and the complex interactions possible between them and other minerals, nutrients, and non- nutrients in the diet. 11.3 Minerals and trace elements Katherine Younger

SECTION 11 Nutrition 1872 Chromium Chromium exists in nature in several valence states, trivalent (re- ducing) being the most stable in biological systems. Hexavalent chromium is a strong oxidizing agent and is carcinogenic. Trivalent chromium was established as an essential nutrient in 1977 when the diabetic signs of a patient on TPN were reversed by supplemental chromium. Chromium's main role appears to be the regulation of insulin, normalizing its secretion in both hyper- and hypogly- caemia such that blood glucose concentrations are normalized, and having no effect where glucose tolerance is normal. Lipid pro- files are also improved following normalization of insulin function. Supplemental chromium increases insulin binding and increased numbers of insulin receptors, and may be involved in the phosphor- ylation and dephosphorylation of insulin receptor proteins. Deficiency in humans is rare; the clinical signs and symptoms include impaired plasma glucose utilization and increased insulin requirements, weight loss, neuropathy, elevated plasma fatty acids, and abnormalities in nitrogen metabolism. The richest dietary sources of chromium are brewer's yeast, spices such as black pepper, mushrooms, prunes, raisins, nuts, asparagus, beer, and wine. Stainless steel vessels can contribute chromium to acidic foods. Absorption of chromium is inversely related to dietary intake at normal intakes of 10–40 μg/day, via a saturable passive diffusion process in the small intestine; absorption is promoted by ascorbic acid. It is transported in the blood mainly bound to trans- ferring, and excreted mainly in the urine. There is no satisfactory measure of chromium status, thus set- ting recommended dietary intakes is problematic. The UK dietary reference value (DRV) merely recommends safe and adequate intakes of more than 25 μg/day for adults and 0.1–0.2 μg/kg/day for children and adolescents. The US Institute of Medicine (IOM) has set adequate intakes (AI) ranging from 0.2 μg/day in infants up to 35 μg/day in adult men, 25 μg/day in adult women, 35 and 45 μg/ day in pregnant and lactating women, respectively. In contrast, the European Food Safety Authority (EFSA) has not set any recom- mendations due to lack of evidence. Similarly, there is insufficient evidence on which to base upper intake levels (UL), though there is World Health Organization (WHO) guidance that

chromium sup- plementation should not exceed 250 μg/day. Copper This essential transition metal can switch between redox states (cu- prous, Cu1+, and predominant cupric, Cu2+) forming a catalytic centre in several enzymes, notably cytochrome oxidase in the inner mitochondrial membrane, dopamine β-hydroxylase required for the synthesis of noradrenaline, Cu/Zn superoxide dismutase which protects cells from oxidative damage, and lysyl oxidase which hy- droxylates some of the ε-amino groups of elastin thereby enabling crosslinking which is essential for the integrity of connective tissue. Copper is therefore required for infant growth, immune function, bone strength, red and white blood cell maturation, and iron, chol- esterol, and glucose metabolism. The human body contains be- tween 50 and 150 mg, mostly bound to proteins. Liver stores are particularly important in newborn babies (being 5–10-fold more concentrated than in adults), in order to provide copper for growth while intakes are low. Preterm infants are therefore at risk of copper deficiency since their liver stores are inadequate, and cow's milk is a poor source of copper. In the plasma, more than 60% of copper is bound to caeruloplasmin, which functions as a ferroxidase enzyme. Iron crosses cell mem- branes in the Fe 2+ (ferrous) form and is oxidized by caeruloplasmin to the Fe 3+ (ferric) form in order to bind to its transport protein, transferrin. Copper deficiency (rare) therefore causes hypochromic anaemia; other symptoms include neutropenia and bone abnormal- ities (and in an inherited copper deficiency disease, Menkes syn- drome, characteristic hypopigmentation, and pili torti). In adults, copper deficiency also causes myelopathy and hence spastic gait and peripheral neuropathy similar to that seen in vitamin B12 deficiency (subacute combined degeneration of the spinal cord). High levels of dietary zinc are known to adversely affect copper absorption and bioavailability via the induction of the protein metallothionein in the intestinal epithelial cells, which inhibits up- take into the blood. Copper absorption may also be inhibited by dietary ferrous iron, sucrose, fructose, animal proteins, S-amino acids, and histidine. High dietary amounts of ascorbic acid sup- plements, molybdenum, calcium, and/or phosphorus and cad- mium have been shown to adversely affect copper absorption and bioavailability. The richest dietary sources of copper are organ meats, seafood, nuts, seeds, and whole grains. Drinking water distributed via copper piping can add 1.0 mg/day to intakes in acid and soft water areas. Absorption of copper depends on dietary intake, shown to range from 56% at low intakes (0.78 mg/day) to 12% at high intakes (7.53 mg/day); on typical EU diets, average absorption is 30–40%. Copper balance can therefore be achieved over a broad range of intakes, mainly by regulating excretion in bile (the major route of excretion). Recommended intakes for copper have been set: for adult males and females the UK DRV reference nutrient intake (RNI) is 1.2 mg/day, and the IOM recommended daily allowance (RDA) is 900 μg/day. Chronic copper toxicity can arise due to high levels in drinking water, and causes liver, kidney, and brain damage, probably due to oxidation. Acute copper toxicity causes gastrointestinal disturb- ances. The IOM have set the UL for adults at 10 mg/day, whereas the EFSA figure is 5 mg/day. People with Wilson's disease (an autosomal recessive disease of copper storage, incidence 1 in 30 000 worldwide), if untreated (with a chelating agent), accumulate copper in the liver, the cornea (Fig. 11.3.1) and the central nervous system, leading ultimately to hepatic failure and death (Chapter 12.7.2). There may also be a genetic component in many cases of Indian childhood cirrhosis, arising from consumption of milk that has been boiled and stored in copper and brass containers. Neurodegenerative diseases such as Alzheimer's and human prion disease have been associated with disruptions in copper metabolism. Mutations in the Cu/Zn superoxide dismutase gene are seen in 20% of familial cases of motor neurone disease, though it is not clear how this causes the progressive muscle weakness and atrophy; ditto in Down's syndrome, where there is an extra copy of this enzyme on the extra chromosome 21.

11.3 Minerals and trace elements 1873 Fluorine Fluorine, as the highly soluble fluoride ion, has gained notoriety in recent years as a public health issue. It is beneficial in bones and teeth, forming calcium fluorapatite, and in teeth also fluorhydroxyapatite, which together with fluoride's bacteriostatic effect, helps prevent dental caries. However, fluoride is toxic in excess, causing fluorosis, hence public concern. Fluorosis is dose-related, the effects ranging from mere mottling of the teeth (endemic in areas such as parts of Africa, China, and India where fluoride levels in water are naturally high, i.e. over 10 mg/litre; see Fig. 11.3.2), through to calcification of the ligaments and tendons causing crippling skeletal fluorosis (ex- tremely rare in the developed world, seen only when excess intakes, i.e. over 10 mg/day are consumed over at least 10 years, or in cases of industrial poisoning; see Fig. 11.3.3). Both EFSA and IOM have derived an AI for fluoride. The EFSA AI for adult males is 3.4 mg/day and 2.9 mg/day for adult females (with a UL for adults of 0.12 mg/kg body weight/day); the corresponding IOM AIs are 4.0 and 3.0 mg/day (UL 10 mg/day). If fluoridated, the public water supply is generally fluoridated at levels up to 1 mg/litre, and it should be noted that there is a narrow margin between bene- ficial intakes and the levels that cause fluorosis. Iodine Iodine, I_2, is a nonmetallic blue-black solid halogen that sublimes to form a violet gas. Iodine can exist in various oxidation states, the commonest being –1 (iodide), +5 (iodates) and + 7 (periodates). Iodine is the only mineral element that is an essential component of hormones, that is, the thyroid hormones thyroxine (T4) and the more active triiodothyronine (T3). These appear to bind to nu- clear receptors in cells, affecting gene expression in brain cells, pi- tuitary, liver, heart, and kidney cells, stimulating enzyme synthesis, oxygen consumption, and hence metabolic rate overall. Heart rate, respiratory rate, substrate mobilization, and oxidation, and other physiological activities are all involved. Hypothyroidism and hyper- thyroidism are the terms used to describe under- and overproduc- tion of thyroid hormones, respectively. Iodine probably also has other functions since it is concentrated from the blood by the sal- ivary glands, the gastric mucosa, the choroid plexus (brain) and the lactating mammary gland. Iodine is required for the development of the nervous system during the first trimester of pregnancy. Iodine may also have antibiotic and anticancer roles. Functional indicators of iodine status are provided by serum levels of thyroid stimulating hormone (TSH, most sensitive), T4, and T3. Iodine deficiency disorders (IDD) are some of the most preva- lent nutritional deficiencies worldwide. In the fetus it causes severe brain damage (cretinism: IQ as low as 20, hearing and speech de- fects, characteristic physical abnormalities) or hypothyroidism with less severe brain damage, both with stunted growth. In young children and adolescents, iodine deficiency causes hypothyroidism (high TSH with very low T3 and T4, causing lethargy, weakness, weight gain, poor concentration, oedema, myalgia, myxoedema, de- layed tendon reflexes, slow heart rate) and intellectual and growth retardation, while in adolescents and adults it causes goitre and hypothyroidism. The hypothyroidism is also associated with other mineral deficiencies: zinc, iron, copper, and the metabolic disrup- tion caused by IDDs affects the metabolism of many other nutrients, notably vitamin A. Fig. 11.3.1 Kayser–Fleischer ring: deposit of copper (brown, golden, or reddish-green) in Descemet's membrane of the cornea. Reproduced from Bloom S, Webster G, Marks D (2011). Oxford handbook of gastroenterology and hepatology, 2nd edition with permission from Oxford University Press. (a) (b) Fig. 11.3.2 Dental fluorosis: (a) mild and (b) severe. (a) By Dozenist (CC BY-SA 3.0, https://creativecommons.org/licenses/by-sa/3.0).

SECTION 11 Nutrition 1874 Goitre is an enlargement of the thyroid gland, due to hyperplasia and an excess of colloid in the follicles (the gland is stimulated to grow by TSH in an attempt to extract iodide from the blood; see Fig. 11.3.4). Goitre is ultimately harmful since, if large enough, the

thyroid gland presses on the windpipe and gullet. Iodine deficiency is also associated with decreased fertility, increased rates of stillbirth and spontaneous abortion, perinatal and infant mortality. It has been estimated that over 1 billion live in iodine-deficient areas, mostly in Africa and Asia. The WHO has identified iodine de- ficiency as the main cause of preventable brain damage worldwide. Iodine supplementation in the form of iodized salt or iodized oil injections can reverse many of the deficiency symptoms in adults and older children, including goitre and mental deficiency (to some extent) and hypothyroidism. However, cretinism is irreversible. Goitrogens are another factor associated with iodine deficiency. They are organic substances (glucosides) containing sulphur (thio- cyanates, isothiocyanates) which interfere with the uptake of iodide by the tissues, causing goitre. Active goitrogens may be released from progoitrogens by plant enzymes, or in animal tissues. Foods containing goitrogens or progoitrogens include cassava (a staple in much of Africa, the progoitrogen hydrogen cyanide is removed by soaking in water), bamboo shoots, maize, sweet potatoes, lima beans, brassica vegetables (e.g. cabbage). Tobacco smoke contains thiocyanate and other antithyroid compounds. In addition, the amounts of Ca, F, Mg, and Mn ions in hard water may be goitrogenic. The best sources of iodine are seafoods (fish, shellfish, seaweed); milk is now a major source of iodine (though seasonal) since the introduction of iodine-supplemented cattle feed and salt licks, iod- inated casein (a lactation promoter), and teat dip containing iodo- phors (sterilization agents). Organic milk has been found to be lower in iodine content than conventional milk due to the restrictions of organic farming. The iodine content of cereals and grains is variable as the level is dependent on the iodine content of the soil (iodine is leached out of soil by high rainfall, glaciations, or soil erosion, hence inland/upland areas most deficient). In most European countries and the United States and Canada, iodine intake is maintained by the use of iodized table salt; without it, low intakes are of concern, particularly among young women. Fig. 11.3.3 Skeletal fluorosis. Reprinted from Indian Journal of Medical Specialties, Vol. 8, Gupta L, Zanwar A, Agarwal V, Skeletal fluorosis mimicking Diffuse Idiopathic Skeletal Hyperostosis, Pages 213–4, Copyright © 2017, with permission from Elsevier. Fig. 11.3.4 Goitre. From Wass JAH, Stewart PM, Amiel SA, Davies MJ (eds) (2011). Oxford textbook of endocrinology and diabetes, 2nd edn. By permission of Oxford University Press.

11.3 Minerals and trace elements 1875 Iodine is usually present in food and water as iodide or iodate (sol- uble), is rapidly absorbed in the intestine and circulates in the blood; excess is excreted in the urine (hence urinary levels are a useful in- dicator of recent iodine intake). Approximately 80% of circulating iodide is taken up by the thyroid glands; depending on the activity of the gland. Here, the iodide is oxidized to iodine which is then bound to tyrosine in thyroglobulin proteins to form monoiodotyrosine and diiodotyrosine, catalysed by thyroid peroxidase. These iodinated compounds are converted to triiodothyronine, T3, and thyroxine, T4 in the epithelial cells of the gland. T4, thyroxine, is then bound to a globulin to form thyroglobulin, for storage in the follicles of the gland until released into the blood (Chapter 13.3.1). Flavonoids (from many plants) and phenol derivatives (from soil) inhibit thyroid peroxidase and are therefore antithyroid. The enzymes responsible for forming T3 from T4 (in the liver, kidney, muscle, and pituitary) are the selenium-dependant deiodinases, and selenium and iodine deficiencies overlap in various places (e.g. China, Tibet, Zaire). Recommended intakes have been set for iodine: for adult men and women the UK DRV RNI for adults is 140 µg/day, the IOM RDA is 150 µg/day, rising to 220 µg/day in pregnancy and the EFSA have set an AI for adults at 150 µg/day, and 200 µg/day in pregnancy. Excess iodine intakes (>2 mg/day) can cause elevated TSH levels, possibly leading to hypothyroidism (Chapter 13.3.1). Consequently, ULs have been set, at 600 µg/day by the EFSA, 1.0 mg/day in the United

Kingdom and 1.1 mg/day by the IOM. In contrast, those with IDDs can develop hyperthyroidism when exposed to moderate doses of iodine. Some individuals are sensitive to iodine and may develop mild skin symptoms (at relatively low doses), in severe cases, leading to cardiovascular collapse, convulsions, and death. Magnesium Magnesium is unusual among the minerals in that, because it is an essential component of chlorophyll, the best dietary sources are plant-based (green vegetables, whole grains, and pulses). Processing reduces the magnesium content, so highly refined diets are low in magnesium. Fish and shellfish are intermediate sources and tap and bottled water also contribute (variable). The body contains approximately 25 g (1000 mmol) of magne- sium, mostly (50–60%) in bone, in combination with phosphate and bicarbonate. The rest is in the soft tissues where it is mostly in com- bination with protein. Serum magnesium (Mg^{2+}) is normally strictly maintained between 0.75 and 0.95 mmol/litre; it is involved with acid/base balance. Intracellular magnesium concentration is much higher, approximately 10 mmol/litre (maintained against a con- centration gradient). Mg^{2+} plays a role as cofactor in over 300 enzymic steps in intermediary metabolism: ATP synthesis, Coenzyme A, DNA replication, RNA transcription, protein synthesis, β- oxidation, and glycolysis. Mg^{2+} is an integral part of mitochondrial superoxide dismutase. Mg^{2+} is also involved with the maintenance of the potential difference across the membranes of nerves and muscles. Parathyroid hormone (PTH) release requires Mg^{2+}, hence calcium homeostasis depends on it; also K and Na homeostasis. Hypomagnesaemia is defined as a serum Mg^{2+} below 0.75 mmol/ litre and is often accompanied by hypocalcaemia. Magnesium homeostasis is maintained by control (of the ac- tive component) of absorption in the small intestine (efficiency is 20–70%) and excretion via the kidney (the principal regulator). Vitamin D may regulate absorption, phosphate (free and/or phos- phate groups in phytate) may inhibit absorption, and protein and fructose may enhance it. Frank magnesium deficiency only occurs secondary to other dis- eases (including endocrine disorders such as hyperparathyroidism and hyperthyroidism) which cause malabsorption or excess losses of Mg via muscle wasting, diarrhoea, vomiting, or urinary losses due to renal dysfunction. Prolonged fasting can also cause magnesium deficiency, as can proton pump inhibitors when used in combin- ation with diuretics. Hypomagnesaemia is particularly common in patients with alcoholism admitted to hospital, with causes including poor dietary intake, diarrhoea, acute pancreatitis, and urinary wasting due to tubular toxicity of alcohol. There are several rare genetic abnormalities of Mg status which lead to Mg deficiency, with features including reduced serum Mg^{2+} and red cell magnesium, hypocalcaemia, and hypocalciuria, hypo- kalaemia caused by excess potassium excretion, neuromuscular dysfunction, muscle weakness, tachycardia, ventricular fibrillation, and death. Suboptimal magnesium status has been associated with chronic diseases including cardiovascular disease, hypertension, eclampsia, pre-eclampsia, and osteoporosis, though this is controversial due partly to the lack of sensitive and reliable tools for assessing magne- sium status. However, there is concern that magnesium intakes (in the United States and Europe) are suboptimal, thus the IOM have raised the RDA for magnesium for adult men and women to 420 mg/day and 320 mg/day, respectively; the EFSA have set AIs of 320 and 300 mg/day for men and women, respectively, while the corres- ponding UK DRV RNIs are 300 and 270 mg/day. Magnesium salts have a laxative effect, and ULs have been set for supplemental magnesium (only) at 250 mg/day for adults by the EFSA and 350 mg/day by the IOM. Manganese Manganese is a transition element which can exist in 11 oxidation states, Mn^{2+} being the predominant form in biological systems. The human body contains about 15 mg of manganese, 25% of which is in the skeleton; relatively high concentrations are also present in the liver, pancreas, and intestine. Manganese is an essential cata- lytic cofactor for mitochondrial superoxide dismutase, arginase, and pyruvate carboxylase; it

is also an activator of several other en- zymes. It is therefore essential for amino acid, lipid, and carbohy- drate metabolism. Primary deficiency has not been reported in humans, probably due to the relative abundance of Mn in the food supply (whole- grain cereals, legumes, nuts, fruits, and dried tea are good sources, depending on the soil, also crustaceans and molluscs, while animal products are less good). One case of an individual fed a purified diet (accidentally) deficient in Mn has been reported, which caused weight loss, dermatitis, reduced growth of hair and nails, reddening of black hair, and lowered blood lipids. However, it is possible that deficiency may occur more widely in infants since breast (and for- mula) milks are low in manganese. Absorption (both active, hence regulated, and passive) occurs in the small intestine and is relatively inefficient (<10%), and may be

SECTION 11 Nutrition 1876 inhibited by phytate, calcium, and phosphate; also nonhaem iron due to competition for binding and absorption sites. Manganese is taken up from the blood by the liver and transported to extrahepatic tissues by transferrin and possibly α2-macroglobulin and albumin. Excretion is mainly in the bile. Manganese status cannot be usefully assessed, so only AIs have been set by the IOM, at 2.3 and 1.8 mg/day for adult men and women, respectively, and the adult EFSA at 3.0 mg/day. Manganese neuro- toxicity is caused by contaminated dust or fumes—'manganic madness'. Oral manganese can also be neurotoxic, an effect en- hanced by ethanol. Manganese toxicity with Parkinsonian features is a notorious complication of parenteral nutrition (Chapter 11.7): T1-weighted MR images show high-signal deposits in basal ganglia. ULs have been set by the IOM at 11 mg/day for adults; for lack of data, EFSA have not. Recessive defects in the SLC30A10 carrier dis- turb manganese homeostasis and cause hypermanganesaemia, dys- tonia, Parkinsonism, dementia, polycythaemia and later, cirrhosis. Prompt use of parenteral calcium edetate can give effective relief. Molybdenum Molybdenum is a transition metal that has five oxidation sates, of which Mo4+ and Mo6+ are the predominant species. In nature, it occurs only in the combined state or as the molybdate anion in solution. Molybdenum is an essential cofactor for several iron- and flavin-containing enzymes (e.g. xanthine oxidase/hydrogenase and aldehyde oxidase). Primary deficiency seems not to occur in humans, and there are no useful biomarkers of molybdenum status. A single case of possible deficiency has been reported in a patient on total parenteral nutrition lacking molybdenum for more than 12 months. Good dietary sources include milk, beans, cereals (especially the germ); water also contrib- utes to intakes. Absorption of molybdenum is efficient (40–100%); it is widely distributed in the body fluids, and is mainly excreted in the urine and bile. The IOM has set an RDA for adults at 45 μg/day (rising to 50 μg/ day in pregnancy and lactation), and the EFSA have set an AI for all adults at 65 μg/day. Molybdenum supplementation depletes body levels of copper, useful in the case of Wilson's disease where it has been used as a che- lating agent. Based on adverse reproductive effects in animals, ULs have been set by the IOM at 2 mg/day for adults, and the EFSA at 0.01 mg/kg body weight/day, equivalent to 0.6 mg/person/day for adults. Phosphorus Phosphorus is nonmetallic. It is highly reactive, so it is present in na- ture only in combined forms, predominantly with calcium in rock or bone. The commonest form of phosphorus in nature is as phosphate, PO42-. The body contains approximately 0.6–1.1% phosphorus (total 600–900 g)—mostly (85%) as hydroxyapatite (mineral) in bones and teeth, the rest is in the soft tissues where it takes part in most metabolic reactions. Half to two-thirds of the phosphorus in blood is in the erythrocytes. Fasting serum phosphate is normally 0.8– 1.4 mmol/litre, the concentration is controlled via urinary excre- tion. Serum PO42– ion has an important role in buffering (acid/base balance). In cells, phosphorus is important in the structure of nucleic acids (DNA, RNA) and

phospholipids (membranes). It is involved in cell energy metabolism as the energy-containing nucleotides ATP, ADP, AMP, GDP, GMP, and in the activation (by phosphorylation) of many proteins. This phosphorus can be recycled. Phosphorus is therefore essential for cell metabolism. Phosphorus homeostasis is determined by dietary intake, intes- tinal absorption, exchanges with bone and intracellular compart- ments and renal excretion (the main regulator); PTH and calcitonin both increase phosphate excretion. Since phosphorus is a major constituent of all cells, all-natural foods of plant or animal origin contain it, particularly the foods rich in protein (e.g. meats, especially organ meats, eggs, cheese, milk, fish, nuts, legumes, and whole grains which contain phytic acid). Fruit and vegetables are less good sources. Phosphates are also added during food manufacture (e.g. polyphosphates) which are added to processed meats (they retain water, increasing the weight of the meat); phosphoric acid is also present in 'cola' and other soft drinks (it is an acidulant, hence the deleterious effect on teeth). Absorption efficiency for inorganic phosphate ranges from 55 to 70% and appar- ently does not adapt in response to low or high intakes or require- ment (in contrast with calcium). Primary phosphorus deficiency is unknown, except in star- vation (Chapter 11.4). Inadequate phosphorus intake causes hypophosphataemia and consequent cellular dysfunction, manifest as anorexia, muscle weakness, bone pain, rickets, osteomalacia, de- bility, increased susceptibility to infection, paraesthesia, ataxia, con- fusion, and ultimately death. Secondary deficiency can be caused by chronic malabsorption. Also, in people consuming large amounts of aluminium hydroxide antacids, or calcium carbonate; these bind phosphate in the gut, so it cannot be absorbed. Phosphate metab- olism is also disrupted by diseases affecting the kidneys or bone. Several genetic diseases (of phosphate transport in the kidney) lead to phosphorus deficiency. Recommended intakes for phosphorus have been traditionally tied to those for calcium (equimolar, e.g. the UK DRV PRIs for adults). More recently, the IOM have set an RDA based on serum inorganic phosphate levels for all adults at 700 mg/day, rising to 1200 mg/day in pregnancy. The EFSA set an AI of 550 mg/day for adults based on the whole-body calcium to phosphorus ratio. Excess phosphorus intake causes hyperphosphataemia, causing secondary hyperparathyroidism, which leads to increased production of 1,25(OH)2D and consequent bone resorption to restore calcium homeostasis. Chronic secondary hyperparathyroidism eventually reduces bone mineral density and can result in ectopic calcification. However, this is only seen in patients with end-stage renal disease. As long as renal capacity is adequate, excess phosphate is excreted. Nevertheless, high phosphorus dosages have been reported to cause osmotic diarrhoea and mild gastrointestinal symptoms. There is concern that phosphate-containing food additives may induce secondary hyperparathyroidism and its consequent adverse effects in those consuming a diet high in processed food. However, no ULs have been determined due to lack of data. Selenium Selenium is a stable, nonmetallic element that occurs in four natural oxidation states (0, –2, + 4 and + 6). It combines with other elements

 to form selenides, selenites, and selenates, or with oxygen to form oxides and oxyacids. Selenium replaces sulphur to form many or- ganic selenium compounds, especially selenocysteine (SeCys), also selenomethionine (SeMet) in selenoproteins (which may also contain selenides). In populations, selenium nutritional status is strongly related to the Se content of soil; which is low in parts of China and Russia, New Zealand, and Northern Europe, whereas parts of the United States, Canada, and Colombia have high Se soil (causing toxicity in grazing animals). Selenium occurs in over 30 selenoproteins as selenocysteine, which is the active site. An important selenoprotein is glutathione peroxidase (GPx, contains 4 atoms of Se acting as a redox centre) which is a major component of antioxidant defence. There are sev- eral

different forms of GPx, occurring in different locations in the cell, and in different tissues, for example, cytosolic (GPx1), mem- brane (GPx4), extracellular (GPx3), and gastrointestinal (GPx2). They comprise about a third of total body Se. Other important Se en- zymes include the iodothyronine deiodinases (three isoforms, in the liver) which control levels of active thyroid hormone T3, converted from T4. Also, selenoprotein P in plasma protects endothelial cells against peroxynitrite (a pro-oxidant), and thioredoxin reductases (three isoforms) reduce nucleotides in DNA synthesis, regenerate antioxidant systems, maintain intracellular redox state, and regulate DNA expression by redox control of binding of transcription factors to DNA. Se is therefore required for intra- and extracellular antioxidant de- fence, cell division, and gene expression, immunocompetence, thy- roid metabolism and reproduction (in the male). Epidemiological evidence suggests that good Se status may protect against cancer (particularly prostate cancer), heart disease, and perhaps inflamma- tory conditions such as rheumatoid arthritis, ulcerative colitis, and asthma (although evidence is less convincing). Selenium deficiency causes poor growth, liver necrosis, degener- ation of striated muscle, capillary fragility, and myocardial damage. In China, Keshan disease, a cardiomyopathy seen in children and women of childbearing age (often fatal, causing insufficiency of cardiac function, cardiac enlargement, and abnormal rhythm) is associated with very low soil Se, low Se intakes (less than 12 µg/ day), and poor Se status, and can be corrected by Se supplemen- tation. However, other factors are probably involved since not all the features can be explained by Se deficiency and in (for example) New Zealand or Finland where intakes are only 15–40 µg/day, no such disease is found. The same is true for Kashin–Beck disease, an osteoarthropathy (causing osteochondropathy, enlarged joints, shortened fingers/toes and dwarfism) affecting mostly growing chil- dren, which is seen in parts of Siberia and China. Some patients on TPN develop symptoms similar to Keshan disease, which can be corrected by Se. Selenium deficiency may induce goitre (iodine deficiency) due to its role in deiodinases. Chronic low selenium intake reduces innate immunity via the selenoproteins. An apparent hierarchical response to Se deficiency exists with the brain, endocrine, and reproductive organs preferentially provided with and retaining more Se compared with other tissues. There may be genetic variation in metabolic requirements for Se, caused by polymorphisms in genes coding for selenoenzymes (analogous to MTHFR variants in the case of folate). This would explain the large individual variation in selenoenzyme activity observed in response to Se supplementation. Vitamin E and Se de- ficiencies are related; each ‘spares’ the requirement for the other, though differently in different species. Interestingly, Se deficiency appears to predispose to certain other diseases, notably viral infections (e.g. in Se-deficient mice), the normally harmless coxsackie virus becomes virulent, causing myo- carditis (virulence persists when virus then isolated and injected into Se-replete animals). Furthermore, a coxsackie virus has been found in Keshan disease patients. Other retroviral diseases could have developed under comparable circumstances (e.g. the crossing over from monkeys) and increased virulence of HIV in Se-deficient people in Zaire (and from them to other, healthy people), ditto new influenza strains in China. In addition, some human viruses (e.g. HIV, Coxsackie, hepatitis, measles) induce synthesis of viral selenoproteins, thus reducing Se availability for the host, which could thus reduce the host’s defence. The selenium content of food varies depending on the selenium content of the soil (e.g. cereals and grains <0.1 to >0.8 µg/g). Selenium may be added to animal feed resulting in improved Se content of animal-derived products. Brazil nuts are a particularly rich source of Se, containing 18–12 µg/g. Fish, shellfish, and offal are rich sources of Se, less rich are meat and eggs; however, the Se from animal sources is less bioavailable than that from plant sources. Losses occur during refining and cooking. Se is absorbed mainly in the small intestine. Organic forms of Se are more bioavailable than inorganic

(e.g. from water, dietary sup- plements). Plant sources, (containing a higher proportion of organic selenium compounds, especially SeMet) are better absorbed than animal sources (which contain sulphides, selenites, SeCys, and some SeMet). More than 90% of SeMet, the major dietary form of the element, is absorbed by the same mechanism as methionine itself. SeCys also appears to be well absorbed. In the blood, Se travels bound mainly to VLDL β-lipoprotein; smaller amounts are bound to albumin. The liver, kidney, heart, and muscle are the main target organs. In cells, Se can be bound to selenium-binding proteins, or it can be used to form selenocysteine which can then be incorporated into polypeptides (via a tRNA specific for SeCys, the '21st amino acid'). Methylation of selenium occurs in the liver prior to excretion by the kidneys, mainly as trimethylselenium ion. Se also leaves the body in faeces (bile, intestinal secretions, unabsorbed dietary Se), as shed skin, and in the breath, as dimethylselenide (volatile, garlic odour). In assessing Se status, dietary intake measurements using food tables are not useful due to variations in Se content of foods and bioavailability. Plasma Se reflects recent dietary intake while erythrocyte Se reflects longer-term intake. Whole blood, hair, and toenail Se can be used to assess changes in Se status. Functional indices are most useful in assessing status, for example, plasma, or (better) platelet GSx activity, together with thyroid and immune function tests (since these reflect different levels of Se status, i.e. optimal status may occur at Se intakes above what is required to saturate GSx activity). Recommended intakes have been set for Se: for adult men and women the UK DRV RNIs are 75 and 60 μg/day, respectively, the IOM RDA is 55 μg/day for adults and the EFSA AI is 70 μg/day for adults.

SECTION 11 Nutrition 1878 Of concern is the observation that blood Se in the United Kingdom has fallen by half in over the last 30 years, and current intakes are only half of the RNI (due partly to a change in the source of wheat for breadmaking from higher Se Canadian wheat to lower Se wheat). It is therefore possible that there is widespread covert suboptimal Se status in the United Kingdom (and elsewhere). The margin between beneficial and toxic intakes of Se is narrow, only 3- or 4-fold: the EFSA UL for adults is 300 μg Se/day, and that set by the IOM is 400 μg Se/day. Intakes over 850–900 μg/day cause chronic selenosis. The symptoms include brittle hair and nails, skin lesions, mottled teeth, foul body odour and breath (dimethyl sel- enide), and peripheral nerve changes. Selenite and SeCys are more toxic than SeMet, and much more toxic than other organic forms. Excess dietary Se interferes with the bioavailability of zinc, and may ameliorate the toxicity of heavy metals (e.g. mercury and methyl mercury in fish); conversely Se bioavailability is reduced by heavy metals and a high-sulphur diet. Excess Se also affects other nutrients positively (copper stores in the heart, liver, kidneys), or negatively (iron stores). Zinc This essential transition metal exists in biology almost exclusively in the Zn^{2+} state and is a cofactor (often acting as an electron ac- ceptor) in more than 300 different enzymes in all branches of metabolism; notably carbonic anhydrase in erythrocytes, Cu/ Zn superoxide dismutase, alcohol dehydrogenase, alkaline phos-phatase, aldolase, carboxypeptidase, RNA polymerase, and DNA polymerase. In addition, zinc is a stabilizing structural component of several proteins, including the insulin granules stored in the β cells of the pancreas, and the zinc 'finger proteins' involved in the regulation of gene transcription. It is also involved in recep- tors for thyroid hormones, steroid hormones, vitamins D and A, mediating their interactions with promoter regions on DNA. Zinc also functions as an antioxidant in vivo and it plays an important role in the immune system; it has long been regarded as beneficial for wound healing. Because Zinc is required for all aspects of normal metabolism, deficiency causes diverse symptoms: growth cessation and sexual and skeletal immaturity (in children and adolescents), a char- acteristic bullous-pustular dermatitis, alopecia, diarrhoea, in- creased

susceptibility to infection, loss of taste and appetite, and neuropsychiatric disturbances. Chronic zinc deficiency was first reported in remote areas of Iran, caused by a diet of mostly un- leavened bread which is high in phytate, binding cations in the gut and preventing their absorption. Zinc deficiency is widespread in children, and is particularly prevalent in South Asia, sub-Saharan Africa, and regions of Central and South America. Marginal zinc deficiency is more difficult to diagnose and may be associated with other micronutrient deficiencies, including iron. Zinc supple- mentation may improve growth and development in infants and young children, and improve the immune response, hence redu- cing morbidity due to diarrhoea and respiratory infections in chil- dren, particularly in developing countries. Low zinc status in poor urban women has also been associated with low birth weight and increased risk of preterm delivery. Because there is a major entero-hepatic circulation of zinc, patients suffering from malabsorption, including due to Crohn's disease, or liver disease, are at risk of zinc deficiency. A recessively inherited defect in zinc absorption, Acrodermatitis enteropathica, causes acute zinc deficiency, which manifests as bullous dermatitis of the feet, hands, and around the orifices (see Fig. 11.3.5), diarrhoea, failure to thrive, susceptibility to infection, and death in early life if not treated. Most (60%) of the approximately 2–4 g of zinc in the adult body is in muscle, 30% in bone and the rest distributed among the other tissues. The choroid and retina of the eye and male reproductive organs contain relatively high concentrations (semen concentra- tion is 100× that in blood plasma). Less than 0.1% is in plasma (mostly bound to albumin), thus plasma zinc is only of limited use as a measure of current status (and is reduced in any condition that affects plasma albumin levels). Zinc content of erythrocytes, leucocytes, and hair can be used as indicators of longer-term status, but are not sensitive to mild deficiency. High-protein foods are the best dietary sources of zinc; the concentration in meat is in direct proportion to the darkness in colour and provides most of the zinc intake in the developed world, along with milk, cheese, eggs, and whole-grain cereals (milling removes the zinc, but also the phytate which inhibits absorption). Other metals (iron, copper, cadmium) may impair zinc absorption by competing for uptake whereas dietary com- ponents that increase the solubility of zinc (organic acids, pro- tein, histidine, cysteine) enhance absorption. Zinc absorption is a regulated, carrier-mediated process (via metallothionein) and varies from 20–40% on mixed Western diets to only 10–15% on unrefined vegetarian diets, most of which is excreted in the bile, there being no apparent specific storage in the body. When intakes are raised, fractional absorption decreases and intestinal excre- tion increases, while urinary losses remain constant. At very high intakes, the excess zinc is lost via the hair. Recommended intakes have been set for zinc: for adult men and women the UK DRV RNIs are 9.5 and 7.0 mg/day, respectively, the IOM RDAs are 11.0 and 8.0 mg/day, and the EFSA RDAs give ranges of 9.4–16.3 and 7.5–12.7 mg/day.
Fig. 11.3.5 Acrodermatitis enteropathica. Reproduced from Lewis-Jones S (ed) (2010). Paediatric dermatology (Oxford Specialist Handbooks in Paediatrics) with permission from Oxford University Press.

 Zinc toxicity has been caused by consuming water or food stored in galvanized containers, or by overconsuming supplements, and ULs have been set by the IOM at 40 mg/day for adults, and by the EFSA at 25 mg/day. Consideration should be given to people with Menke's disease (a rare genetic defect in the uptake of copper from gut cells into the blood) who are susceptible to excess zinc intake which may further limit copper absorption.
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