11.2 Vitamins 1855

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ESSENTIALS The vitamins are a disparate group of organic compounds that are required in small amounts (mg or µg per day) for the maintenance of normal health and metabolic integrity. Four vitamins (A, D, E, and K) are lipid soluble, while the others are water-soluble. Determining how much of any particular vitamin is required for health is not straightforward, a standard technique being to deprive volunteers of the vitamin in question until there is detectable meta- bolic change and then replete with graded doses of the vitamin until normal metabolism is restored, with the reference intake (recom- mended daily intake or amount or recommended dietary allow- ance) set at 2× standard deviation above the average requirement. Deficiency leads to more or less specific signs and symptoms, and (assuming no bar to absorption or metabolism) restoring the vitamin to the diet will cure the deficiency disease. Effects of defi- ciency can be catastrophic and can cause, for example, blindness (vitamin A); rickets/osteomalacia (vitamin D); beriberi and Wernicke's encephalopathy (thiamine); pellagra (niacin); anaemia (vitamin B12 and folate); and scurvy (vitamin C). Excess of some vitamins can also cause disease. Several vitamins are used as effective and even life-saving therapies in inborn errors of metabolism, e.g. homocystinuria, methylmalonic acidaemia, pyridoxal (phosphate) responsive epilepsy syndromes, sideroblastic anaemia. They may overcome inherited defects in transporter function or have an activator or stabilizing role as cofac- tors for a mutant enzyme. Introduction The vitamins are a disparate group of organic compounds that are required in small amounts (mg or µg per day) for the maintenance of normal health and metabolic integrity. With two exceptions (vitamin D and niacin) they cannot be made in the body but must be provided in the diet. Deficiency leads to more or less specific signs and symp- toms, and (assuming no bar to absorption or metabolism) restoring the vitamin to the diet will cure the deficiency disease. Four vitamins (A, D, E, and K) are lipid soluble, while the others are water-soluble. The vitamins and their metabolic functions and deficiency signs are shown in Table 11.2.1. In some cases, different chemical forms of the vitamin show the same biological activity—in this case the different compounds are referred to as vitamers, and a generic descriptor is used to include all compounds that have the activity of the vitamin. Requirements and reference intakes of vitamins In order to determine requirements, volunteers have been deprived of the vitamin in question until there is a detectable metabolic change, then repleted with graded doses of the vitamin until normal metabolism is restored. This provides an estimate of the average re- quirement of the population group under investigation. To allow for individual variation in requirements, the reference intake is set at 2× standard deviation above the average requirement (Fig. 11.2.1). Assuming a normal distribution of requirements, this is an intake that is more than adequate to meet the requirements of 97.5% of the population. This reference intake is variously known as the re- commended daily intake or amount (RDI or RDA), the reference nutrient intake

(RNI), or the population reference intake (PRI). For some vitamins deficiency is more or less unknown, and an accept- able intake (AI) based on average intakes, which are obviously (more than) adequate, is used in place of a reference intake. An intake 2× standard deviation below the average requirement is adequate for only 2.5% of the population. Reference intakes of vitamins published by the UK, EU, and US authorities, and the UN Food and Agriculture Organization, are shown in Online Tables 11.2.1–11.2.4. If an individual has an intake below the reference intake, this does not imply deficiency. Indeed, if a population group has an average intake below the reference intake, this does not imply a problem: it is only when the average intake is below the average requirement that deficiency is likely. The lower graph in Fig. 11.2.1 shows the data plotted as the percentage of the population whose requirements have been met at any given level of intake, and therefore can be in- terpreted as the probability that any given intake is adequate to meet an individual person's requirement. Many inborn, and acquired disorders os metabolism that are - responsive to specific pharmocological vitamin supplementation are known. These may declare themselves for the first time in ado- lescence or adult life; inborn errors of B vitamin matabolism and transport often require supraphysiological doses. 11.2 Vitamins Tom R. Hill and David A. Bender

SECTION 11 Nutrition 1856 Several of the vitamins are toxic in excess. For these, a toler- able upper level (TUL) of habitual intake is established from the highest level of intake at which there is no detectable sign of tox- icity, with a safety factor to ensure that no-one will receive an ex- cessive intake. TULs published by the US Institute of Medicine and the European Food Safety Authority are shown in Online Table 11.2.5. Vitamin A Vitamin A is a generic term used to designate any compound possessing the biological activity of retinol (Fig. 11.2.2). The main dietary sources of retinols are liver, kidney, egg yolk and butter; β-carotene is mainly found in green leafy vegetables and carrots. Until recently the term 'retinol equivalents' (Res) was used to convert all sources of preformed retinol and provitamin A caroten- oids in the diet into a single unit: nutritionally, 1 μg RE = 1 μg of all- trans-retinol = 2 μg of supplemental (in oil) all-trans-β-carotene = 6 μg of dietary all-trans-β-carotene = 12 μg of other dietary pro- vitamin A carotenoids. When defining RE it was assumed that the efficiency of absorption of provitamin A carotenoids was rela- tively good. Recent studies document, however, that absorption of carotenoids is much lower and appears to be quite variable Functions Vitamin A, its analogues, and its metabolites function in vision (Fig. 11.2.3), cell differentiation, embryogenesis, the immune re- sponse, reproduction, and growth. Carotenoids also have a variety of different actions, including possible antioxidant activity, immune- enhancement, inhibition of mutagenesis and transformation, and reduced risk of age-related macular degeneration and cataracts, decreased risks of some cancers, and decreased risk of cardiovas- cular events. Deficiency Vitamin A deficiency is common in the developing world but is rare in developed countries, where severe deficiency associated with malnutrition causes night blindness and xerophthalmia— Bitot's spots, xerosis conjunctiva, and keratomalacia. At least 50% of young children in sub-Saharan Africa and South Asia are vitamin A deficient, with night blindness being just one of the stages where vitamin A deficiency reduces the ability to see. The other deficiency diseases are the result of abnormal func- tioning of epithelial cell on surface of the eye. In resource-rich countries, vitamin A deficiency is mainly seen in patients with fat malabsorption. Other consequences of vitamin A deficiency include impaired cell differentiation and development; replacement of mucus- secreting cells with keratin-secreting cells; reduced immunity to Table 11.2.1 The vitamins Vitamin Functions Deficiency disease A Retinol β-carotene Visual pigments in the retina; regulation of gene expression and cell

differentiation; (β-carotene is an antioxidant) Night blindness, xerophthalmia; keratinization of skin D Calciferol Maintenance of calcium balance; enhances intestinal absorption of Ca2+ and mobilizes bone mineral Rickets = poor mineralization of bone; osteomalacia = bone demineralization E Tocopherols tocotrienols Antioxidant, especially in cell membranes Extremely rare—serious neurological dysfunction K Phylloquinone menaquinones Coenzyme in formation of γ-carboxy-glutamate in proteins of blood clotting and bone matrix Impaired blood clotting, haemorrhagic disease B1 Thiamin Coenzyme in pyruvate and α-keto-glutarate dehydrogenases, and transketolase; role in nerve conduction Peripheral nerve damage (beriberi) or central nervous system lesions (Wernicke-Korsakoff syndrome) B2 Riboflavin Coenzyme in oxidation and reduction reactions; prosthetic group of flavoproteins Lesions of corner of mouth, lips, and tongue, seborrhoeic dermatitis B3 Niacin Nicotinic acid nicotinamide Coenzyme in oxidation and reduction reactions, functional part of NAD and NADP Pellagra—photosensitive dermatitis, depressive psychosis B5 Pantothenic acid Functional part of CoA and acyl carrier protein fatty acid synthesis and metabolism Peripheral nerve damage (burning foot syndrome) B6 Pyridoxine pyridoxal pyridoxamine Coenzyme in transamination and decarboxylation of amino acids and glycogen phosphorylase; role in steroid hormone action Disorders of amino acid metabolism, convulsions B7 Biotin Coenzyme in carboxylation reactions in gluconeogenesis and fatty acid synthesis Impaired fat and carbohydrate metabolism, dermatitis B9 Folic acid Coenzyme in transfer of one-carbon fragments Megaloblastic anaemia B12 Cobalamin Coenzyme in transfer of one-carbon fragments and metabolism of folate Pernicious anaemia = megaloblastic anaemia with degeneration of the spinal cord. C Ascorbic acid Coenzyme in hydroxylation of proline and lysine in collagen synthesis; antioxidant; enhances absorption of iron Scurvy—impaired wound healing, loss of dental cement, subcutaneous haemorrhage

11.2 Vitamins 1857 viral infection; impaired reproduction (male and female); abnormal growth; reduced ferritin synthesis; loss of appetite, reduced growth, severe weight loss, death. Meta-analysis of trials of vitamin A supplementation given to pre- school children in populations with endemic vitamin A deficiency has shown a weighted average mortality reduction of 11%. Requirements and criteria of adequacy Current estimates of vitamin A requirements are based on the in- take required to maintain a reserve concentration of at least 20 µg retinol/g of liver tissue. This concentration is adequate to main- tain normal plasma concentrations of retinol and protect against a vitamin A deficiency for approximately 4 months while the person consumes a vitamin A-deficient diet. The estimated average re- quirement (EAR) of preformed vitamin A required to achieve an adequate body reserve in men more than 19 years is 625 µg RAE/ day, and for women is 500 µg RAE/day. The recommended dietary allowance (RDA) for vitamin A is set using a coefficient of variation (CV) of 20% and the EAR for adequate stores of vitamin A. Higher levels of intake Several adverse effects have been reported at intakes of preformed vitamin A above the population reference intake. Acute toxicity can cause nausea, vomiting, vertigo, drowsiness, and blurred vision. Chronic toxicity can manifest with bone and muscle pain, visual impairment, headache (with increased cerebrospinal fluid pressure, pseudotumour cerebri), ataxia, alopecia, yellowing (carotenaemia) and peeling of the skin, hyperlipidaemia, and hepatotoxicity. Based on hepatotoxicity (in all adults) and teratogenicity in women of childbearing age, the tolerable upper intake levels (UL) 100 90 80 70 60 50 40 30 20 10 0 Frequency Intake to meet criterion of requirement Intake to meet criterion of requirement Percentage of population Average requirement Mean + 2 SD reference intake Mean - 2 SD threshold intake Average requirement Mean + 2 SD reference intake Mean - 2 SD threshold intake Fig. 11.2.1 The derivation of reference intakes of

nutrients from the distribution around the observed mean requirement; plotted here as a cumulative distribution curve, enabling estimation of the probability that a given level of intake is adequate to meet an individual’s requirement.

SECTION 11 Nutrition 1858 for preformed vitamin A (retinol and retinyl esters) has been set at 3000 µg RE/day for adults by both European Food Safety Authority (EFSA) and the Institute of Medicine (IOM), with correction for dif- ferences in basal metabolic rate compared to adults using scaling according to body surface area (body weight × 0.75) (Table 11.2.2). All-trans retinoic acid is used parenterally to induce apoptosis and remission in promyelocytic leukaemia. Isotretinoin (13-cis-retinoic acid) is widely used for severe acne and sometimes also to prevent certain skin cancers, especially those related to sunlight exposure. Vitamin D The term ‘vitamin D’ was given during the early 1920s to a group of closely related secosteroids with antirachitic properties. The two main dietary forms of vitamin D in foods are cholecalciferol (vitamin D3, derived from animals) and ergocalciferol (vitamin D2, derived from plants). Both chole- and ergo-calciferol are also formed by photoirradiation from their precursors 7-dehydrocholesterol in vertebrates and ergosterol in some fungi. The chemical structures of vitamin D2 and vitamin D3 differ only in their side chain at C-17, which in vitamin D2 has a double bond and an additional methyl group (Fig. 11.2.4). Functions As shown in Fig. 11.2.5, vitamin D undergoes 25-hydroxylation in the liver, then 1-hydroxylation in the kidney to yield the active hor- mone, calcitriol (1,25-dihydroxy-vitamin D). The main biological role of 1,25(OH)2D3 is to promote intestinal calcium absorption. In addition, it increases the absorption of other essential minerals across the intestine, such as phosphorus, zinc, and manganese and enhances the net renal reabsorption of calcium and phosphorus. 1,25(OH)2D3 is thus a major regulator of calcium homeostasis, and it also has important modulatory roles in other organ systems, including the endocrine glands, the immune system, the cardiovas- cular system, and the reproductive and nervous systems. The biological actions of 1,25 (OH)2 D3 in target tissues are me- diated either through, (i) a nuclear vitamin D receptor (VDR), which once complexed with 1,25 (OH)2 D3 and retinoic acid recep- tors (RXR) can regulate gene expression (genomic effects), or (ii) intracellular signalling pathways activated through putative plasma membrane receptors (nongenomic effects). Deficiency The serum or plasma concentration of 25(OH)D is considered to be the best index of vitamin D nutritional status because it closely reflects the amount produced in the skin and ingested in the diet, and meas- urement of 25(OH)D is used routinely for the detection of vitamin D deficiency. Vitamin D deficiency (defined by a 25(OH)D concentra- tion <25 nmol/litre) increases the risk of rickets in children and osteo- malacia in adults, processes in which the bone matrix (osteoid) fails to mineralize. Vitamin D deficiency can also result in immunosuppres- sion and muscle weakness and may increase the risk of colon cancer. Requirements and criteria of adequacy Establishing dietary requirements for vitamin D is difficult be- cause sunlight makes a very significant contribution to vitamin D status. Recent attempts to define vitamin D requirements have been based on the dose–response relationship between oral vitamin D and circulating 25(OH)D concentrations. Using both data from epidemiological and intervention studies, the Institute of Medicine established a population 25(OH)D concentration of 40 nmol/litre and 50 nmol/litre as the basis for setting an estimated average require- ment of 10 µg/day and a recommended daily allowance (RDA) of 15 µg/day, respectively, in people aged 1–70 years. In the United Kingdom, the Scientific Advisory Committee on Nutrition es- tablished a reference nutrient intake (RNI) of 10 µg/day for the majority of children and adults based on achieving a population 25(OH)D concentration of 25 nmol/litre. Higher levels of intake Very high intakes of vitamin D from supplements lead to hyper calcaemia and

calcification of soft tissues. Sunlight exposure does not lead to excessive formation of vitamin D. It has been suggested that the concentration of previtamin D in the skin of Caucasians reaches an equilibrium within 20 min of UVB exposure, with any excess 7-dehydrocholesterol being converted to inactive metabol- ites such as tachysterol and lumisterol, hence UVB exposure beyond the minimal erythemal dose does not increase vitamin D produc- tion further. Vitamin E The chemistry of vitamin E is complex because there are eight struc- turally related forms—four tocopherols (α-, β-, γ- and δ-) and four tocotrienols (α-, β-, γ- and δ-)—that are produced at various levels and in different combinations by all plant tissues and in some Fig. 11.2.2 Vitamin A and the major provitamin A carotenoids.

11.2 Vitamins 1859 H3C H3C H3C H3C +H3N H3C H3C H3C H3C H3C CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH2OH CH2OH HC=O 11-cis-retinol All-trans-retinol All-trans-retinaldehyde 11-cis-retinaldehyde Lysine residue in opsin C=O C=O C=O NH NH NH HC N H Rhodopsin (visual purple) 10-15 sec Photorhodopsin 45 psec 30 nsec 75 µsec 10 msec minutes Inactive phosphodiesterase Active phosphodiesterase GTPase Pi Na+ channel open Na+ channel closed Bathorhodopsin Lumirhodopsin Metarhodopsin I Metarhodopsin II Metarhodopsin III Opsin cGMP 5'GMP Transducin-GTP Transducin-GDP GTP GDP C=O H C N LIGHT Fig. 11.2.3 The role of retinaldehyde in the visual cycle. Table 11.2.2 Tolerable upper levels of habitual intake of preformed retinol Tolerable upper limit µg/day Reference intake µg/day Ratio Infants 900 350 2.6 1–3 years 1800 400 4.5 4–6 years 3000 500 6.0 6–12 years 4500 500 9.0 13–20 years 6000 600–700 8.6–10 Adult men 9000 700 12.9 Adult women 7500 600 12.5 Pregnant women 3000 700 4.3

CH3 CH2 HO CH2 HO Vitamin D2 ercalciol (ergocalciferol) Vitamin D3 calciol (cholecalciferol) Slow thermal isomerization H3C OH HO LIGHT LIGHT 7-Dehydrocholesterol Previtamin D Tachysterol OH Fig. 11.2.4 The synthesis of vitamin D in the skin. The structure of ergocalciferol (vitamin D2) is shown in the yellow box. CH2 CH2 CH2 CH2 COO- HO OH CH2 HO HO CH2 HO OH Calciol 25-hydroxylase Calcidiol 1-hydroxylase Calciol (cholecalciferol) Calcidiol (25-hydroxycholecalciferol) 24-Hydroxycalcidiol Calcitetrol Calcitroic acid Calcitriol (1 ,25-dihydroxycholecalciferol) OH OH OH OH Calcidiol 24-hydroxylase Calcidiol 24-hydroxylase Calcidiol 1-hydroxylase OH OH HO HO OH Fig. 11.2.5 The metabolism of vitamin D to yield its active metabolite calcitriol (1,25-dihydroxy vitamin D) and its inactivation.

11.2 Vitamins 1861 cyanobacteria. The main dietary sources are oils (e.g. olive, sunflower), meat, eggs, and leafy vegetables. All forms of vitamin E are amphi- pathic molecules with the general structures shown in Fig. 11.2.6. Functions Vitamin E (as α-tocopherol) is an indispensable component of biological membranes with membrane-stabilizing properties and high antioxidant activity. The overall mechanisms of lipid peroxidation and antioxidant protection in biological and food systems have been extensively reviewed. The antioxidant activity of chain-breaking antioxidants is determined by how rapidly they scavenge free radicals, the ease of hydrogen transfer from an anti- oxidant to a free radical and the difference in the standard one- electron reduction potentials. Vitamin E, in addition to having a protective role in the oxidative modification of LDL, may affect or limit the progression of atherosclerosis and several other con- ditions in ways that are unrelated to its antioxidant activity. The other vitamers have lower biological activity than α-tocopherol (see Online Table 11.2.6). Deficiency Vitamin E deficiency is seen rarely in clinical practice, but there may be a risk of vitamin E deficiency in premature infants because the placenta

does not transfer α-tocopherol to the fetus in adequate amounts. When it occurs in older children and adults, it is usually a result of lipoprotein deficiencies or a lipid malabsorption syndrome. These include patients with abetalipoproteinaemia or homozygous hypobetalipoproteinaemia, those with cholestatic disease, and pa- tients receiving total parenteral nutrition. There is also an extremely rare autosomal recessive neurodegenerative disease (ataxia with vitamin E deficiency, AVED) in which primary vitamin E deficiency occurs in the absence of lipid malabsorption as a result of mutations in the gene for α-tocopherol transfer protein (α-TTP). Clinical manifestations of vitamin E deficiency include neuro- logical syndromes (ataxia, hyporeflexia, loss of proprioception, skeletal myopathy) and anaemia due to haemolysis. Requirements and criteria of adequacy There is little consensus as to the threshold concentration of plasma or serum α-tocopherol at which people can be defined as having either an inadequate or acceptable vitamin E status. The Food and Nutrition Board (2000) set an EAR of 12 mg/d of α-tocopherol for all adults aged over 19 years, with an RDA of 15 mg/day, assuming a coefficient of variation of 10%. In Europe, the Scientific Committee for Food (1993) did not set a PRI for vitamin E on the basis that there is no evidence of deficiency from a low intake. Higher levels of intake The tolerable upper intake level (UL) is 1000 mg/d, based on studies showing haemorrhagic toxicity in rats and in the absence of human dose–response data. The Scientific Committee for Food (1993) proposed that the intake should not exceed 2000 mg α-tocopherol equivalents per day. Vitamin K The term ‘vitamin K’ describes several related compounds that have in common a 2-methyl-1,4-naphthoquinone ring system, but differ in the length and degree of saturation of their isoprenoid side chain at the 3-position. Three vitamin K compounds have biological ac- tivity: phylloquinone, (vitamin K1), menaquinones (vitamin K2), and menadione (vitamin K3; see Fig. 11.2.7). Vitamin K1 is found mainly in green vegetables, with particularly high levels in broccoli, Brussels sprouts, kale, and spinach. CH3 CH3 CH3 CH3 CH3 O CH3 CH3 O CH3 CH3 O CH3 O HO HO CH3 CH3 CH3 CH3 CH3 O O HO HO HO CH3 CH3 O HO H3C H3C H3C H3C CH3 CH3 O HO H3C α-Tocopherol β-Tocopherol γ-Tocopherol δ-Tocopherol α-Tocotrienol β-Tocotrienol γ-Tocotrienol δ-Tocotrienol Fig. 11.2.6 The vitamin E vitamers.

SECTION 11 Nutrition 1862 Functions Vitamin K acts as a cofactor for a carboxylation reaction that trans- forms selective glutamate residues to γ-carboxyglutamate (Gla) res- idues in proteins. The reaction is catalysed by the microsomal enzyme vitamin K-dependent γ-glutamyl carboxylase, which in turn is linked to a cyclic pathway known as the vitamin K epoxide cycle (Fig. 11.2.8). The resultant Gla residues increase the affinity of the vitamin K- dependent proteins for calcium ions. Prothrombin and other proteins of the blood clotting system (Fig. 11.2.9), as well as certain bone matrix proteins, contain Gla and thus require vitamin K for their synthesis. Deficiency Newborn infants are at serious risk of haemorrhage because of poor placental transfer of vitamin K, lack of intestinal bacteria, and the low vitamin K content in breast milk. For this reason, vitamin K is routinely administered prophylactically at birth in many coun- tries. The risk of bleeding is greatest in prematurely born infants, in breast-fed infants, and in those with gastrointestinal conditions that impair vitamin K absorption. In normal infants, plasma pro- thrombin concentrations and those of the other vitamin K-de- pendent factors are approximately 20% of adult values at birth. Normal or near-normal blood coagulation is usually maintained in older children and adults and clinical deficiency is rare. Several factors protect adults from a lack of vitamin K, including widespread distribution of vitamin K in plant and animal tissues, the vitamin K cycle, which conserves the vitamin, and the microbiological flora of the normal gut, which synthesizes menaquinones. However, subclinical vitamin K deficiency in extrahepatic tissues, particularly in bone, is not uncommon in the adult population. Requirements and criteria of adequacy A large review,

including 11 different studies, reported that phyllo- quinone intake ranged from 60 to 210 µg/day with an average intake of approximately 80 µg/day for younger adults (<45 years) and ap- proximately 150 µg/day for older adults (>55 years). Healthy indi- viduals with a phylloquinone intake of 80 µg/day show no signs of CH3 R CH2 CH2 CH2 CO2 O2 OH OH CH3 R O O O CH3 R O O H2C—COO- HC—COO- -OOC—CH—COO- NH–HC–C=O Glutamate residue Vitamin K hydroquinone NADP+ NADPH Disulfide Vitamin K epoxide Sulfydryl Disulfide Sulfydryl Vitamin K quinone Glutamate carbanion Glutamate carboxylase Quinone reductase Vitamin K quinone reductase Vitamin K epoxide reductase γ-Carboxyglutamate residue NH–HC–C=O HN–CHC=O – Fig. 11.2.8 The role of vitamin K in γ-carboxyglutamate synthesis. O O Phylloquinone (vitamin K1) Menaquinone (vitamin K2) Menadiol (vitamin K3) Menadiol diacetate (acetomenaphthone) 3 n CH3 O O CH3 OH OH CH3 CH3 CH3 C=O O CH3 C=O O Fig. 11.2.7 Vitamin K vitamers. Menadione and menadiol diacetate are synthetic compounds that are converted to menaquinone in the liver.

11.2 Vitamins 1863 deficiency, suggesting that this level is probably adequate for most of the adult population. The most recent guideline (AI) for vitamin K intake in the United States for adults (aged 19 years and older) is 120 µg/day for men and 90 µg/day for women. In Europe, the Scientific Committee on Food (SCF) made no recommendation for a PRI for vitamin K but considered that an intake of 1 µg/kg body weight/day appears to be adequate and would be provided by a normal diet. Higher levels of intake In a few human studies there is no evidence of adverse effects as- sociated with supplementary intakes of vitamin K in the form of phylloquinone of up to 10 mg/day (more than two orders of mag- nitude higher than AI) for limited periods of time. These limited data are supported by experimental animal studies in which no ad- verse effects were observed after daily administration of extremely high doses (2000 mg/kg body weight) for 30 days. However, high intakes of phylloquinone can negate the effects of the anticoagulant warfarin. The synthetic form of vitamin K, menadione, can interfere with the function of glutathione, one of the body’s natural antioxi- dants, resulting in oxidative damage to cell membranes. Vitamin B1 (thiamine) Dietary thiamine is mainly found in legumes, brown rice, and cer- eals made from whole grains. It is very low in white (polished) rice or wheat flour, and denatured by the cooking, baking, and canning of foods. Functions Thiamine has a central role in energy-yielding metabolism. As thia- mine diphosphate (Fig. 11.2.10) it provides the coenzyme for three multienzyme complexes catalysing the oxidative decarboxylation of pyruvate, α-ketoglutarate and branched-chain keto-acids derived from the branched-chain amino acids, as well as the coenzyme for transketolase in the pentose phosphate pathway of carbohydrate metabolism. Thiamine triphosphate has a role in nerve conduction, acting to phosphorylate a membrane sodium ion transporter. Deficiency Thiamine deficiency, most commonly found in populations where the diet consists mainly of polished rice or milled white cereals, leads to impaired carbohydrate metabolism and the develop- ment of lactic and pyruvic acidosis. It can result in three distinct conditions: 1. Beriberi, chronic peripheral neuritis, which may or may not be associated with heart failure and oedema. 2. Acute pernicious beriberi, in which heart failure and metabolic abnormalities predominate, with little evidence of peripheral neuritis. 3. Wernicke’s encephalopathy with Korsakoff’s psychosis, which is associated especially with alcohol and narcotic abuse, and is due to central nervous system lesions. Treatment of beriberi and Wernicke’s is with parenteral (if the pa- tient is critically ill) followed by oral thiamine Surface adsorption or kallikrein Factor XII Factor XI Factor IX Factor VIII Factor X Factor V Prothrombin Fibrinogen Fibrin Thrombin Active factor X Active factor VIII Active factor IX Active factor XI Active factor XII Thromboplastin +Factor VII Injury Fig. 11.2.9 The intrinsic and extrinsic clotting factor cascades. H3C H3C N N N NH2 Thiamine Thiamine diphosphate NH2 CH3 CH3

CH2·CH2OH CH2 H2 ·C ·O—P—O—P—O- O- –– – – –– O- O O C—N H2 C—N + H2 S S N + Fig. 11.2.10 Thiamine and the coenzyme thiamine diphosphate.

SECTION 11 Nutrition 1864 Requirements and criteria of adequacy The activation of erythrocyte transketolase by added thiamine di- phosphate is the most widely used criterion of adequacy; an activa- tion coefficient of more than 1.25 is considered to reflect deficiency, and less than 1.15 adequate status. The reference intake is 100 µg/MJ (0.5 mg/1000 kcal) energy intake. There is no evidence on which to set upper levels of thiamine intake. Vitamin B2 (riboflavin) Riboflavin is found in many foods including milk and eggs, meat and fish, green vegetables, and fortified bread and cereals. Functions Riboflavin provides the coenzyme of many enzymes involved in energy-yielding metabolism, both as riboflavin itself and also as riboflavin monophosphate and flavin adenine dinucleotide (FAD, see Fig. 11.2.11). The flavin coenzymes undergo either single- electron reduction, forming a semiquinone radical, or a two-electron reduction (see Online Fig. 11.2.1). In the mitochondrial electron transport chain, they therefore provide a link between the obliga- tory two-electron reactions of nicotinamide adenine dinucleotide (NAD) and the single-electron reactions of cytochromes and non haem iron proteins. Deficiency Riboflavin deficiency is widespread in developing countries, but des- pite its central role in metabolism, deficiency is rarely fatal. This is partly because the vitamin is widespread in foods, such that most diets will provide minimally adequate amounts, and also because in deficiency there is very efficient recycling of riboflavin released by the turnover of enzymes; only a small amount is catabolized or excreted. In resource-rich countries riboflavin deficiency may be seen in an- orexia nervosa, patients with malabsorption, and in rare inborn errors of metabolism (e.g. glutaric acidaemia type 1, multiple acyl-coenzyme A dehydrogenase deficiency, riboflavin transporter deficiencies). Deficiency is characterized by lesions of the margin of the lips (cheilosis) and corners of the mouth (angular stomatitis), painful des- quamation of the tongue, and seborrhoeic dermatitis with filiform ex- crescences. There is resistance to malaria in deficiency, partly because of a high requirement of the parasite for riboflavin, and partly because in deficiency erythrocyte membranes are inadequately protected against oxidative damage, leading to membrane fragility and exposure of vul- nerable stages of parasite development to the host’s immune system. Requirements and criteria of adequacy The activation of erythrocyte glutathione reductase by FAD is the most widely used criterion of adequacy; an activation coefficient of more than 1.7 indicated deficiency. Normal values of the activation coefficient are seen in people whose intake is between 1.2–1.5 mg/day. There is no evidence on which to set upper levels of riboflavin intake. Vitamin B3 (niacin) The generic descriptor niacin, which is found in many foods, is used for two vitamers: nicotinic acid and nicotinamide, although in the United States niacin is generally used to mean the acid, with niacinamide for the amide. Functions Niacin provides the nicotinamide ring of the coenzymes NAD and NADP (nicotinamide adenine dinucleotide phosphate), which function as electron acceptors in a wide variety of oxidation and re- duction reactions (Fig. 11.2.12). In addition, NAD is the source of ADP-ribose for ADP-ribosylation of enzymes to modify their ac- tivity, and poly-adenosylation of breakage points in DNA, initiating the DNA repair mechanism. Fig. 11.2.11 Riboflavin and the flavin coenzymes. CH2-O–P–O–P–O–CH2 OH OH OH O O Nicotinamide adenine dinucleotide (NAD) Nicotinamide Nicotinic acid N COOH CONH2 CONH2 Oxidized coenzyme (NAD+ or NADP+) Reduced coenzyme (NADH or NADPH) CONH2 Phosphorylated in NADP

- H+ N N XH2 X H H N N CONH2 O O N N N N NH2 OH OH OH –– – – –– Fig. 11.2.12 Niacin vitamers and the nicotinamide nucleotide coenzymes.

11.2 Vitamins 1865 Deficiency Pellagra, due to dietary deficiency of niacin and tryptophan, can be seen in resource-poor countries where the diet is based on untreated corn, and this was a major public health problem in the southern United States during the first half of the 20th century for the same reason. Treating corn with alkali, as is done in the preparation of tortillas, increases the bioavailability and absorption of niacin and prevents pellagra. Enriching processed flour with niacin and other B-vitamins eradicated dietary pellagra in the United States. Pellagra can also occur in alcoholics, patients with anorexia nervosa or malabsorption, carcinoid syndrome (where tryptophan is metabolized to 5-OH tryptophan and serotonin instead of to nico- tinic acid), with prolonged use of isoniazid (and some other drugs), and in rare inherited metabolic conditions (e.g. Hartnup disease). Pellagra is characterized by a sun-burn like dermatitis (Fig. 11.2.13), depressive psychosis, and diarrhoea, and (un- treated) it is commonly fatal. Requirements and criteria of adequacy Niacin is not strictly a dietary essential since it can be formed from the essential amino acid tryptophan, and it is likely that normal in- takes of tryptophan can meet niacin requirements; 60 mg of trypto- phan is equivalent to 1 mg of preformed niacin. The usual criterion of adequacy is measurement of urinary excretion of niacin metabol- ites, although the ratio of NAD:NADP in erythrocytes has also been used. Neither is wholly satisfactory. Because NAD and NADP act as cosubstrates and are not tightly bound to enzymes, there is no en- zyme activation assay for niacin status. The average requirement is 1.3 mg niacin equivalents (mg preformed niacin + 1/60 mg trypto- phan)/MJ energy intake, giving a reference intake of 1.6 mg/MJ. Upper levels of intake High intakes of nicotinic acid can lead to vasodilatation and flushing, and also (especially with sustained-release preparations used to treat hyperlipidaemia) to liver damage. The European Food Safety Authority has set an upper level of 10 mg nicotinic acid/day. Nicotinamide does not cause flushing or liver damage. It has been used in relatively high doses for prevention trials of type I diabetes mellitus; EFSA has set an upper level of 12.5 mg/kg body weight/day, equivalent to c.900 mg/day for an adult. Vitamin B6 There are six vitamers of vitamin B6: pyridoxal, pyridoxine, pyridoxamine, and their phosphates; all are converted to the active coenzyme pyridoxal phosphate in the body (Fig. 11.2.14). They are predominantly found in plant foods. Functions Pyridoxal phosphate has a major role in amino acid metabolism, acting as the coenzyme for transamination and decarboxylation. Decarboxylation products of amino acids include several neuro- transmitters. Pyridoxal phosphate is also the coenzyme for glycogen phosphorylase in liver and muscle, and has a role in modulating the actions of steroid hormones, acting to release hormone-receptor complexes from DNA binding. Deficiency Acquired deficiency of vitamin B6 occurred when infants fed an overheated milk formula developed severe seizures responsive to vitamin B6: liberated lysine reacted with endogenous vitamin, to generate pyridoxyllysine, which has antivitamin activity. Deficiency of pyridoxal 5’-phosphate principally causes peripheral neuropathy in adults, most often due to drugs such as isoniazid, hydralazine and penicillamine that form complexes with the active B6 vitamer. Several important inherited defects causing vitamin B6 defi- ciency are now known. These occur principally in infants and chil- dren in whom seizures and (sometimes) dystonia are dominant clinical features. These generally respond well to vitamin B6 (pyri- doxine hydrochloride), but some patients with particular defects of B6 activation will require pyridoxal 5-phosphate supplementation, which must be given parenterally. Other effects of vitamin B6 de- ficiency include white matter disease, sideroblastic anaemia, dis- turbed amino acid profiles, hypoglycaemia and hypophosphatasia. Requirements and criteria of adequacy Two enzyme assays are widely used to assess vitamin B6 status; acti- vation of erythrocyte aspartate and alanine transaminases by pyri- doxal phosphate. In addition, plasma concentrations of pyridoxal phosphate and urinary excretion of the metabolite pyridoxic acid are

used. The metabolism of two amino acids, tryptophan and methio- nine, are also vitamin B6 dependent, and after a loading dose of 2–5 g of the amino acid, abnormal metabolites are excreted in the urine. Because of the central role of vitamin B6 in amino acid metab- olism, requirements depend on protein intake; the average require- ment is 13 µg/g dietary protein, and reference intakes are based on 15–16 µg/g protein. Upper levels of intake Pyridoxine supplements have been widely recommended for the premenstrual syndrome and as an anti-emetic. Daily doses of sev- eral grams cause frank sensory neuropathy and injury may occur at 50–200 mg. The Institute of Medicine set a daily maximum of 100 mg but the European Food Safety Authority has taken a more precau- tionary approach, and set an upper level of 25 mg/day. More generous supplements are recommended for individual inborn diseases such as homocystinuria, sideroplastic anaemia and pyridoxine-sensitive seiz- ures (see further reading and Chapters 12.1 and 12.2). Fig. 11.2.13 A pellagra-like scaling, crusted dermatitis in a butterfly distribution in a patient with Hartnup disease. From Galadari E, Hadi S, Sabarinathan K (1993). Hartnup disease. Int J Dermatol, 32, 904,

 Vitamin B12 The structure of vitamin B12 is shown in Fig. 11.2.15. Several com- pounds related to vitamin B12 occur in plants, bacteria, and algae, but have no vitamin activity, and many have antivitamin activity. The only sources of true vitamin B12 are animal foods, although supplements prepared by bacterial fermentation are available for vegetarians. Functions There are two vitamin B12-dependent enzymes: methionine synthetase and methylmalonyl CoA mutase. The methionine synthetase reaction is central to the function of folate, and vitamin B12 deficiency leads to secondary folate deficiency (see Online Fig. 11.2.6 and Chapter 22.6.6). The reaction of methylmalonyl CoA mutase is shown in Online Fig. 11.2.2. Deficiency Dietary deficiency of vitamin B12 occurs only in strict vegetarians who eat no food of animal origin. Pernicious anaemia (megalo- blastic anaemia with spinal cord degeneration) occurs as a result of failure to absorb the vitamin. The megaloblastic anaemia is due to secondary folate deficiency, and the irreversible nerve damage to lack of methionine in the central nervous system as a result of im- paired activity of methionine synthetase (see Online Fig. 11.2.6). Absorption of vitamin B12 from foods requires the action of gastric acid to release the vitamin from protein binding, followed by binding to intrinsic factor, a protein secreted by the gastric parietal cells. Binding to intrinsic factor is essential for absorption of the vitamin in the small intestine. Classical pernicious anaemia is an auto-immune disease. Patients who form antibodies against gastric parietal cells can be treated with oral intrinsic factor, whereas those who secrete anti-intrinsic factor antibodies require parenteral vitamin B12 (Chapter 22.6.6). Requirements and criteria of adequacy The total body pool of vitamin B12 is around 2.5 mg, with a minimum desirable body pool of 1 mg, and about 0.1% of the body pool is lost daily, giving an average requirement for replacement of 1–2.5 µg/day and reference intakes of 1.4–2.0 µg. A significant amount of vitamin B12 is secreted in the bile and re-absorbed bound to intrinsic factor, hence requirements for people who do not secrete intrinsic factor or secrete anti-intrinsic factor antibodies are considerably higher. The assessment of vitamin B12 status is by measurement of the plasma concentration of the vitamin by radio-ligand binding assay using intrinsic factor as the binding protein. Urinary excretion of methylmalonic acid indicates deficiency. The absorption of the vitamin can be assessed by the Schilling test, in which an oral dose of radioactively labelled vitamin B12 is given together with paren- teral administration of a flushing dose of 1 mg of nonradioactive vitamin to saturate body reserves. Urinary excretion of the radio- active vitamin is measured as an index of absorption. There is no evidence on which to set upper levels of vitamin B12 intake. Folate (Vitamin

B9) The structure of folic acid (tetrahydrofolic acid) is shown in Fig. 11.2.16. Many plant and animal foods, particularly leafy vegetables and liver, contain a variety of one-carbon substituted derivatives of folic acid, collectively known as folates (see Online Fig. 11.2.3), and they may HO–C H2 CH3 Pyridoxine Pyridoxal Pyridoxal phosphate Pyridoxamine Pyridoxamine phosphate CH2NH2 Pyridoxine phosphate H2 CH3 CH2OH CH2OH OH OH N O—P–O–C O—P–O–C O—P–O–C O- Kinase Phosphatase Kinase 4-Pyridoxic acid Phosphatase Kinase Phosphatase Oxidase Oxidase Oxidase Transaminases O- – – H2 CH3 N OH CH3 N OH O- O- – – H2 O- O- – – N HO–C H2 CH3 COO- OH N HO–C H2H2C—NH2 CH3 OH N HO–C H2 CH3 HC O HC O OH N Fig. 11.2.14 Interconversion of the vitamin B6 vitamers.

11.2 Vitamins 1867 have up to seven additional glutamate residues. The extent to which the various folates in food are absorbed varies. In order to permit calcula- tion of folate intake the dietary folate equivalent (DFE) has been defined as 1 µg mixed food folates or 0.6 µg folic acid. On this basis, total DFE intake = µg mixed food folates + 1.7 x µg (synthetic) folic acid. Functions Folate functions in the transfer of single carbon units in the catab- olism of a variety of compounds and the synthesis of serine, me- thionine, thymidine monophosphate and purines (see Online Fig. 11.2.4). Much folate is methylated during absorption, and me- thyl folate is the main form of the vitamin in the circulation. The re- duction of methylene folate to methyl folate is irreversible, and free folate can only be released by the reaction of methionine synthetase, which is vitamin B12-dependent. Vitamin B12 deficiency therefore leads to functional folate deficiency, since the vitamin is trapped as unusable methyl folate. For further discussion see Chapter 22.6.6. Because of the role of folate in synthesis of purine and pyrimidine nucleotides, folate antagonists are used in cancer chemotherapy. Deficiency Adults eating a normal diet in developed countries in which many foods (typically cereals and grains) are routinely fortified with folic acid rarely develop dietary folate deficiency. However, folate deficiency can arise in those who consume a poor diet (e.g. chronic alcohol misuse, anorexia nervosa), have malabsorption, take drugs that interfere with folate metabolism (e.g. methotrexate, phenytoin), or have increased folate requirements (e.g. pregnancy, lactation, chronic haemolytic an- aemia, widespread exfoliative skin diseases, haemodialysis). The most obvious clinical feature of folate deficiency is macrocytic anaemia. Other manifestations include mouth ulcers and (possibly) neurocognitive changes, although the latter are more commonly at- tributed to vitamin B12 deficiency. Requirements and criteria of adequacy Depletion/repletion studies using folic acid suggest an average re- quirement of 80–100 µg/day, and studies of the excretion of folate metabolites on a folate-free diet suggest a requirement for replace- ment of 80 µg/day. Because of uncertainty over both the various forms of folate in foods, and their relative biological availability and activity, reference intakes allow a wide margin of safety and are based on an allowance of 3 µg/kg body weight (and hence 210 µg/ day for a 70 kg adult). Folate status can be assessed by measurement of serum or erythro- cyte folate, by either radio-ligand binding or microbiological growth assays. Functional folate status can be assessed by measurement of the urinary excretion of formiminoglutamate (FIGLU) after a test dose of histidine: as shown in Online Fig. 11.2.5, FIGLU is an inter- mediate in histidine catabolism, and its onward metabolism to glu- tamate is folate-dependent. Rapidly dividing cells can use either preformed thymidylate (TMP) for DNA synthesis, or can synthesize it de novo from dUMP in a folate-dependent reaction. Stimulated lymphocytes incubated with [3H]TMP will incorporate it into DNA, but if they have ad- equate folate status and are provided with dUMP, they will form nonradioactive TMP, so reducing the amount of radioactivity in- corporated into DNA. Aside from addressing any underlying cause, folate deficiency is typically treated with oral folic acid (1–5 mg

daily), which is gener- ally adequate even in the presence of malabsorption. Supplementing Folate intake Supplements of folic acid of 400 µg/day started before concep- tion reduce the incidence of spina bifida and other neural tube de- fects by at least 50%. Similar supplements also reduce the plasma concentration of homocysteine, which is an independent risk factor for atherosclerosis and coronary heart disease (see Online Fig. 11.2.6). In order to reduce the incidence of neural tube defects, some coun- tries have introduced mandatory fortification of flour with folic acid. However, intakes in excess of 1000 µg/day may mask the megaloblastic anaemia in people with vitamin B12 deficiency due to atrophic gastritis, and there is some evidence that high intakes of folate may accelerate the transformation of benign intestinal polyps to cancer. In addition, folic Fig. 11.2.15 Vitamin B12. Four coordination sites of the central cobalt atom are chelated by the nitrogen atoms of the corrin ring, and one by the nitrogen of the dimethylbenzimidazole nucleotide. The sixth coordination site may be occupied by CN– (cyanocobalamin), OH (hydroxocobalamin), H2O (aquocobalamin), –CH3 (methylcobalamin), or 5’deoxyadenosine (adenosylcobalamin). H2N H2 C H2 CH2 CH2 (Glu)n Tetrahydrofolate (THF) C = O C N N N HN O H H N H N H COO CH Fig. 11.2.16 Folic acid (tetrahydrofolate).

SECTION 11 Nutrition 1868 acid antagonizes the action of some antiepileptic medication. An upper level of intake is set at 1000 µg of folic acid/day for adults. Biotin (vitamin B7) Biotin (Fig. 11.2.17) is widely distributed on foods and also synthesized by intestinal flora, although it is not known to what ex- tent this bacterial biotin is absorbed. Functions Biotin functions to transfer carbon dioxide in a few carboxylation re- actions, forming protein-bound carboxy-biocytin (see Fig. 11.2.17). It also has a role in regulating the cell cycle by biotinylation of his- tones and other proteins. Deficiency Because biotin is widely distributed in foods, deficiency is unknown except among people maintained on total parenteral nutrition for prolonged periods, or people who eat abnormally large amounts of uncooked egg white, which contains the protein avidin that binds biotin and renders it unavailable for absorption. Avidin is denatured when eggs are cooked, and cooked eggs are a rich source of the vitamin. Deficiency leads to impaired fatty acid synthesis and fine scale dermatitis and alopecia. Requirements There is no evidence on which to base reference intakes for biotin. Average intakes are between 10 and 200 µg/day, and these are ob- viously more than adequate to meet requirements. There is no evi- dence on which to base upper levels of intake. Pantothenic acid (vitamin B5) Pantothenic acid is widely distributed in foods—indeed, the name means ‘from everywhere’. Functions Pantothenic acid has a major role in energy-yielding metabolism as the functional moiety of coenzyme A (Fig. 11.2.18) and in the syn- thesis of fatty acids as the prosthetic group of acyl carrier protein. Deficiency Prisoners of war in the Far East in the 1940s showed, among other deficiency diseases, a new condition of paraesthesia and severe pain in the feet, which was tentatively ascribed to pantothenic acid defi- ciency, although no specific trials of pantothenic acid were carried out—they were repleted with yeast extract and other rich sources of vitamins. Other than that, pantothenic acid deficiency has only been observed in experimental studies using antivitamin antimetabolites in which deficiency led to neuromotor defects and mental depres- sion (probably due to defective synthesis of acetylcholine), gastric disturbances, and impaired synthesis of steroids. Requirements There is no evidence on which to base reference intakes for panto- thenic acid. Average intakes are between 3 and 7 mg/day, and these are obviously more than adequate to meet requirements. There is no evidence on which to base upper levels of intake. Vitamin C (ascorbic acid) Ascorbic acid (Fig. 11.2.19) is a vitamin for only a few vertebrates, including human beings and other primates: other species synthesize it as an intermediate in the gulonolactone pathway of carbohydrate metabolism. Those species that require

it in the diet have suffered loss of the enzyme gulonolactone oxidase. Ascorbic acid and the oxidized forms, monodehydroascorbate and dehydroascorbate, all have vitamin activity. It is found in citrus fruits, tomatoes, potatoes, and a range of other fruits and vegetables. Functions Ascorbic acid has specific roles in two groups of enzymes: a) Copper-containing hydroxylases, including dopamine β-hydroxylase in noradrenaline and adrenaline synthesis and peptidylglycine hydroxylase, which are involved in postsynthetic modification and activation of certain peptide hormones. In O HN NH O S H N C O CH NH CH NH HN NH O N S HN NH S Biotin Biotinyl lysine (biocytin) Carboxybiocytin -OOC— C O- – – –—— – – – – – O C –—— –—— C O –—— O C –—— O Fig. 11.2.17 Biotin, biocytin (ε-amino biotinyllysine) and carboxy-biocytin. H2 CH2 CH2 NH C=O CHOH H3C–C–CH3 -O–P–O–P–O–CH2 CH2 O O O- N N N N NH2 O O OH O – –– – – – – – – – – – – – – O- - O P O = C—NH—C ·C · H2 (Cysteamine) Coenzyme A (CoASH) (Pantothenic acid) SH -SH group forms thioesters with fatty acids —— O —— Fig. 11.2.18 The role of pantothenic acid in the structure of coenzyme A.

11.2 Vitamins 1869 these enzymes the copper is oxidized in the reaction, and ascor- bate is specifically required to reduce it to restore activity. b) α-Ketoglutarate-linked iron-containing hydroxylases, including pro- line and lysine hydroxylases involved in collagen synthesis. In these enzymes the reactive iron undergoes accidental oxidation in some reaction cycles as a result of binding and activating oxygen, and as- corbate is specifically required to reduce it back to restore activity. Ascorbate also acts as a general antioxidant, acting nonenzymically to reduce reactive oxygen species and the tocopheroxyl radical formed by oxidation of vitamin E. Deficiency Historically, scurvy, due to vitamin C deficiency, occurred at the end of winter when there was limited availability of fresh fruit and veget- ables. In Britain it is most often seen in the isolated elderly poor. It is characterized by capillary fragility and subcutaneous petechial haem- orrhages (Fig. 11.2.20). At a later stage there is bleeding of the gums and loss of dental cement with tooth loss. Impaired collagen cross- linking leads to poor wound and fracture healing, bone pain with demineralisation and osteoporosis: scars are thin and weak and may dehisce spontaneously. Scurvy with florid osteoporosis occurs in pa- tients from South Africa with secondary haemochromatosis due to excess iron ingestion from local craft (Kaffir) beers (Chapter 12.7.1). Requirements and criteria of adequacy Depletion/repletion studies with measurement of scar tissue formation after surgical wounding give an average requirement for vitamin C of 20 mg/day, leading to a reference intake of 30 mg/day. Measurement of the plasma concentration of the vitamin, which indicates when there is surplus vitamin available to be transported between tissues, gives a reference intake of 40 mg/day, as does measurement of the rate turnover of the whole-body ascorbate pool during depletion using radioactive or stable isotopically labelled vitamin. However, the rate of turnover decreases during depletion, and depends on the initial size of the body pool. Extrapolating back from depletion to normal status gives reference intakes of 60–80 mg/day. Saturation of neutrophils with vitamin C gives a reference intake of 90 mg/day. Measurement of total leukocyte vitamin C cannot be used as an index of status without a differential leukocyte count, since different classes of leukocytes are saturated with the vitamin at different concentrations. Higher levels of intake At intakes above about 100 mg/day, the body’s capacity to metabolize vitamin C is saturated and any further intake is excreted unchanged in the urine. However, the absorption of inorganic iron salts requires reduction to Fe^{2+} in the intestinal lumen, and intakes of 25–1000 mg of vitamin C together with inorganic iron (be it in supplements or foods) maximizes absorption. This is a potential hazard of high in- takes of the vitamin by people with a genetic failure of the regulation of iron absorption (haemochromatosis, Chapter 12.7.1). Similarly,

relatively high intakes of vitamin C with meals reduces the non enzymic formation of nitrosamines from dietary amines and nitrite. There is, however, little evidence to support the use of high doses of vitamin C to prevent or cure the common cold, or other illnesses. High concentrations of ascorbate can react with proteins, glycating them in the same way as occurs with glucose in poorly controlled diabetes mellitus, and there is some evidence of increased risk of car- diovascular disease in people with diabetes who consume high doses of vitamin C. Upper levels of intake for adults are set at 2000 mg/day. FURTHER READING Azzi A, Stocker A (2002). Vitamin E: non-antioxidant roles. Prog Lipid Res, 39, 231–55. Balasubramaniam S, Christodoulou J, Rahman S (2019). Disorders of Riboflavin Metabolism. J Inherit Metab. Dis, 42, 608–19. Bailey LB, Gregory JF, 3rd (1999). Folate metabolism and require- ments. J Nutr, 129, 779–82. Bates CJ (1987). Human requirements for riboflavin. Am J Clin Nutr, 46, 122–3. Bates CJ (1987). Human riboflavin requirements, and metabolic con- sequences of deficiency in man and animals. World Rev Nutr Diet, 50, 215–65. Bates B, et al. (eds) (2010). National diet and nutrition survey: headline results from years 1 and 2 (combined) of the rolling programme (2008/ 2009–2009/10). Department of Health, London. Bender DA, Bender AE (1986). Niacin and tryptophan metabolism: the biochemical basis of niacin requirements and recommendations. Nutrition Abstracts and Reviews (Series A), 56, 695–719. Balasubramaniam S, Christodoulou J, Rahman S, (2019). Disorders of Riboflavin Metabolism. J Inherit Metab Dis, 42, 608–19. Bender DA (1989). Vitamin B6 requirements and recommendations. Eur J Clin Nutr, 43, 289–309. Bender DA (1996). Tryptophan and niacin nutrition—is there a problem? Adv Exp Med Biol, 398, 565–9. Bender DA (1999). Non-nutritional uses of vitamin B6. Br J Nutr, 81, 7–20. Bender DA (2003). Nutritional Biochemistry of the Vitamins, 2nd edi- tion. Cambridge University Press, Cambridge. Benzie IF (1999). Vitamin C: prospective functional markers for defining optimal nutritional status. Proc Nutr Soc, 58, 469–76. O O O CH2OH CH2OH CH2OH HO–CH HO–CH HO–CH O OH O O O O OH Ascorbate Monodehydroascorbate (semidehydroascorbate) Dehydroascorbate OH O Fig. 11.2.19 Vitamin C. Fig. 11.2.20 Perifollicular purpura (with positive Hess’s sign from dressing) in teenage vagrant with scurvy. From Lewis-Jones S (ed) (2010). Paediatric Dermatology (Oxford handbooks in paediatrics). By permission of Oxford University Press.

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