SECTION 11
Nutrition

- 11.1 Nutrition Macronutrient metabolism 1839
- 11.2 Vitamins 1855
- 11.3 Minerals and trace elements 1871
- 11.4 Severe malnutrition 1880
- 11.5 Diseases of affluent societies and the need f
- 11.6 Obesity 1903
- 11.7 Artificial nutrition support 1914

11.1 Nutrition Macronutrient metabolism 1839

11.1 Nutrition: Macronutrient metabolism 1839

ESSENTIALS Food intake is sporadic and, in many cultures, occurs in three daily boluses. At the same time, energy expenditure is continuous and can vary to a large extent independently of the pattern of energy intake, although fixed or predictable demands (e.g. through occupation) means that in most persons food intake and energy expenditure are soon balanced. The body has developed complex systems that direct excess nutrients into storage pools; as they are needed, they also regu- late the mobilization of nutrients from these pools. Analogous to the fuel tank of a car and the throttle that regulates fuel oxida- tion, supply and need are closely linked, except that in the vehicle there is just one fuel and just one engine. In contrast, in humans there are three major nutrients and a variety of tissues and organs, each of which may have its own preferences for fuels that vary with time. Carbohydrate, lipid, and protein (the latter a source of amino acids) are the three types of energy supply that are stored variably and assimilated from food each day. That we can carry on our daily lives without thinking about whether to store or mo- bilize fuels, and which to use, attests to the remarkable efficiency and refinement of these systems of metabolic control. Overview of metabolism The body requires energy for chemical and mechanical work in order to maintain homeostasis; functions including maintenance of ionic gradients, transport, biosynthesis, heat generation, and loco- motion. This energy is derived from three groups of energy-rich substrates: carbohydrates, lipids, and amino acids. Multiple groups are utilized because they all have chemical and thermodynamic ad- vantages and disadvantages, and together they provide energy under widely varying conditions and demands. All three nutrient groups exist in large, energy-rich macromolecular storage forms. The prin- cipal macronutrient stores are listed in Table 11.1.1 and are related to daily fluxes of energy substrates in the body. For energy mobilization these are sequentially broken down into less energy-rich metabolites, the energy liberated being captured by intermediary reduction-oxidation molecules which carry the energy to a common pathway of oxidation linked to the phosphorylation of ADP to ATP. Hence, the energy is used to synthesize ATP, the common energy carrier to which most energy-requiring biological processes are linked. At a whole-body level, this process is termed ‘catabolism’. Conversely, in energy-rich states when energy intake exceeds expenditure, these metabolic pathways can be reversed, whereby ingested nutrients from all three groups are assembled into large storage macromolecules (‘anabolism’) (Fig. 11.1.1). Lipids (fats) are the most energy-dense metabolic fuels

(c.37 kJ/g). The storage form of lipids for energy provision is triacylglycerol (TAG), which comprises three fatty acids esterified to a glycerol backbone. Being highly hydrophobic and reduced, TAGs are very energy dense and a highly efficient energy store. However, TAGs are relatively slow to mobilize, must be oxidized to yield energy and cannot provide energy anaerobically, and the nonesterified fatty acids (NEFAs) from which they are assembled are amphipathic (detergent-like) and hence potentially toxic in high concentra- tions. Furthermore, fatty acids cannot be converted into carbohy- drates or proteins, limiting their metabolic flexibility. Carbohydrates such as glucose are less reduced and more soluble than lipids and hence contain only about half the energy density of fats (c.17 kJ/g), but they are nontoxic, quickly mobilized/utilized, and can provide some energy anaerobically. They are stored as the glucose polymer glycogen. Glycogen, as a polar molecule, is stored with water (about three times its own weight), so its low energy density makes this an inefficient energy store, and only limited amounts are synthesized (Table 11.1.1). Carbohydrates are able to supply intermediary metabolites to maintain pathway integrity (anaplerosis) in contrast to lipids, oxi- dation of which leads to depletion of intermediary metabolites (cataplerosis): hence some carbohydrate is always required for me- tabolism to proceed efficiently (captured in the old aphorism ‘fat burns in the fire of carbohydrate’). Proteins (polymers of amino acids) have similar energy content to carbohydrates (c.17 kJ/g), but each protein has a specific function and they are not used as dedicated energy stores. In catabolic states of carbohydrate deple- tion (e.g. starvation), however, proteins are broken down to their constituent amino acids for conversion into glucose for energy and anaplerosis—hence proteins constitute a virtual carbohydrate store. 11.1 Nutrition: Macronutrient metabolism Keith N. Frayn and Rhys D. Evans

SECTION 11 Nutrition 1840 Whole body metabolic strategy therefore comprises breaking down large macronutrient storage molecules (TAGs, glycogen, protein—by lipolysis, glycogenolysis and proteolysis respectively) into smaller energy-rich substrates (NEFAs, glucose, amino acids) with distinct characteristics and roles. In the next stage of metab- olism these small substrates are converted into a common fuel, acetyl-CoA (by β-oxidation, glycolysis, and amino acid metabolism, respectively). In the final stage of metabolism the acetyl-CoA is fully oxidized by the tricarboxylic acid (TCA) cycle into carbon dioxide within the mitochondria. The step-wise release of energy from these pathways is carried as a hydride (H-) ion by NAD+ and FAD as their reduced forms, NADH and FADH2: these redox carriers are then reoxidized by the electron transport chain, the energy derived being used to phosphorylate ADP to ATP (oxidative phosphorylation). By contrast, in anabolism these pathways are reversed, chemical energy being used to synthesize complex energy-rich storage macromol- ecules from simple precursor substrates. Three key features of metabolism impact metabolic strategy and energy provision: • Most energy stored in the body is in the form of lipid (TAGs); • This lipid cannot be converted to carbohydrate; and • All tissues require some glucose for normal metabolic func- tioning, and some tissues (glycolytic, lacking mitochondria, such as erythrocytes) have an absolute requirement for glucose, or cannot utilize NEFAs (brain). Since very little carbohydrate is stored (c.100 g hepatic glycogen; <1 day if sole fuel), in catabolic states glucose is rapidly depleted and alternative mechanisms are required to provide or replace glu- cose: under these conditions, breakdown of protein to amino acids, and then conversion of these to glucose by gluconeogenesis, becomes an essential pathway. Indeed, the ability of the body to divert protein from its primary (e.g. contractile) function to a secondary function of glucose provision has been the adaptation that has allowed such limited stores of the energy density-inefficient glycogen to be per- mitted. Another mechanism is ketogenesis, whereby the liver con- verts TAG-derived NEFAs into small, soluble (nonamphipathic) ketone bodies, which

can be utilized by many tissues, including brain, hence acting as a ‘glucose-sparing’ substrate. Hence during conditions of energy repletion, energy in ex- cess of current requirements is stored in a tissue-specific manner (lipid as TAGs principally in adipose tissue; carbohydrate as glycogen in most tissues but specifically in liver for glucose re- lease to maintain blood glucose concentration; amino acids ‘vir- tually’ in labile proteins, e.g. muscle). In subsequent periods of limited energy ingestion (postabsorptive, fasted) this substrate resource can be mobilized in a regulated fashion and directed to specific tissues according to their metabolic requirement. These pathways are illustrated schematically in Fig. 11.1.2. Table 11.1.1 The principal macronutrient stores Macronutrient Total amount in body Energy equivalent (MJ) Days’ supply if the only energy source Daily intake (g) Daily intake as percentage of store Carbohydrate 0.6 kg 8.5 <1 300 60 Free glucose 12 g Liver glycogen 100 g Muscle glycogen 500 g Fat (triacylglycerol) 12–18 kg 550 56 100 0.7 Circulating in plasma 5 g Stored in adipocytes 12–18 kg Protein and amino acids 12 kg 200 (20) 100 0.8 Free amino acids 100 g Protein 12 kg Note: These are very much typical rounded figures. Days’ supply is the length of time for which this store would last if it were the only fuel for oxidation at an energy expenditure of 10 MJ/day: the figure for protein is given in parentheses since protein does not fulfil the role of an energy store in this way. Energy-rich substrates: • Carbohydrates • Lipids • Proteins Complex molecules: • Polysaccharides • Lipids • Nucleic acids • Proteins Energy-poor end-products: • CO2 • H2O • NH3 Precursor molecules: • Amino acids • Hexoses • Fatty acids ANABOLISM CATABOLISM chemical energy • ATP • NAD(P)H Fig. 11.1.1 Anabolism and catabolism. Anabolism refers to the synthesis of complex molecules from simpler ones, and in the context of metabolism refers to energy storage within carbohydrate, lipid and protein macromolecules; catabolism refers to the breakdown of molecules to smaller ones which contain less energy; the energy difference is released and used for biological work (including providing the energy for anabolism). Biological energy is carried in the form of ‘high energy’ phosphate groups (e.g. ATP) and as electrons (hydride ions, e.g. NADH).

11.1 Nutrition: Macronutrient metabolism 1841 Carbohydrate metabolism in the postabsorptive and postprandial states Pathways of glucose metabolism Glucose is a ubiquitous sugar which may be derived from dietary carbohydrate or synthesized in the body. As noted here already, it is stored in polymeric form as glycogen: this removes the osmotic problems that would arise if it were stored in cells as free sugars. Glucose, as a polar molecule, cannot cross membranes composed of phospholipid bilayers by diffusion, and a family of glucose trans- porter proteins, expressed in a tissue-specific manner, facilitates its movement in and out of cells. Within cells, the first step of glu- cose metabolism is always phosphorylation to glucose 6-phosphate, brought about by a member of a family of enzymes (‘hexokinases’— the form expressed in liver and pancreatic β-cells is generally known as glucokinase) again expressed in a tissue-specific manner. Phosphorylation ensures that the molecule does not diffuse again out of the cell. Glucose (molecular formula $C_6H_{12}O_6$) is broken down by the pathway of glycolysis to pyruvate ($C_3H_4O_3$, showing that H has been lost relative to C and O; i.e. this is a partial oxidation). A small amount of ATP is generated by so-called substrate-level phosphor- ylation, as opposed to the oxidative phosphorylation pathway men- tioned earlier: indeed, this is a cytosolic pathway and can occur even in cells that lack mitochondria. Pyruvate, as described next, may be reduced to lactate ($C_3H_6O_3$, so exactly half a glucose molecule with no redox changes). Pyruvate can also enter mitochondria where it can be a substrate for the enzyme complex known as pyruvate de- hydrogenase (pyruvate dehydrogenase complex, PDC). PDC not only further oxidizes pyruvate, but also removes one carbon, re- sulting in the formation of acetyl-CoA which, as described earlier, can be fully oxidized in the TCA cycle. The

pathway of glucose synthesis, gluconeogenesis, occurs primarily in liver cells and is basically a reversal of glycolysis al- though with some specific steps, circumventing energy-yielding and largely irreversible steps of glycolysis. The major substrate for gluconeogenesis under most conditions is lactate. Amino acids whose carbon skeletons can be converted to lactate or pyruvate (discussed later) can also contribute, as can the glycerol released from lipolysis of TAGs in adipose tissue. Note that glucose may be broken down to lactate in red blood cells, for instance: the lactate may be transferred via the bloodstream to the liver where it is used glucogenic amino acids (≥3C) ketogenic amino acids (≡2C) glucose (6C) pyruvate (3C) GLYCOGEN acetyl-CoA(2C) 2CO2 nonesterified fatty acids (x x 2C) TRIACYLGLYCEROL 5C-sugars NADPH ketone bodies PDH e- O2 ADP ATP H2O PROTEIN CoA TCA cycle NADH NAD+ e- CO2 WORK lactate 1 2 3 4 5 6 7 8 9 10 Fig. 11.1.2 Stages of metabolism. Flux in a downward direction is catabolic (energy-yielding) while upward flux denotes energy storage, hence is anabolic. In the first stage of energy mobilization, large storage macromolecules are broken down to smaller, energy-rich, substrates (NEFAs, glucose, amino acids). In the second stage, these small energy-rich substrates are converted into the common 'fuel' for oxidation, acetyl-CoA. While these pathways can be reversed in order to store excess energy (anabolism), in the case of carbohydrates the conversion of pyruvate to acetyl-CoA by pyruvate dehydrogenase (PDH) is essentially irreversible, therefore lipids (which are assemblies of two carbon groups themselves derived from acetyl-CoA) cannot be converted into pyruvate, and hence carbohydrates. In the third stage of energy mobilization, the acetyl-CoA is fully oxidized by the tricarboxylic acid (TCA) cycle; the energy released is carried by electron transporters down the electron transport chain and converted into ATP by oxidative phosphorylation. 1. esterification 2. lipolysis 3. glycogenesis 4. glycogenolysis 5. protein synthesis/ proteolysis 6. lipogenesis 7. β-oxidation 8. gluconeogenesis 9. glycolysis 10. pentose phosphate pathway.

SECTION 11 Nutrition 1842 to make new glucose. This cycle is sometimes called the Cori cycle. It does not result in irreversible loss of glucose from the body. That occurs after the action of PDC, as acetyl-CoA can no longer be re- converted to glucose. Glycogen synthesis starts with glucose 6-phosphate and involves sequential polymerization of glucose units on a protein backbone (glycogenin). Glycogenolysis involves the reverse: sequential re- moval of glucose units. In most tissues this will result in glucose 6-phosphate that can enter the pathway of glycolysis. In the liver specifically (and to some extent in kidney, especially during star- vation) the enzyme glucose 6-phosphatase may convert glucose 6- phosphate to glucose: thus, glucose released from glycogenolysis or produced by gluconeogenesis may be released into the bloodstream to maintain blood glucose concentrations in the postabsorptive or the fasting state. Breakdown of glucose as far as acetyl-CoA can also be part of a synthetic process. Acetyl-CoA produced from glucose is the starting point for the pathways of lipid synthesis: lipogenesis, which usu- ally refers to the synthesis of fatty acids from glucose, and choles- terol synthesis. These pathways, like most biosynthetic pathways, are cytosolic, and the acetyl-CoA must be transferred out of the mitochondria. One further pathway of glucose metabolism will be mentioned briefly: the pentose phosphate pathway. This involves the metab- olism of glucose 6-phosphate through a complex series of reactions that generate pentose sugars, used in nucleic acid synthesis, and also reducing power in the form of NADPH. NADPH is used in many biosynthetic pathways such as lipogenesis. Lactate and ethanol metabolism Glycolysis requires an electron acceptor, and NAD+ acts in this role, becoming reduced to NADH; however, the NAD+ must be replenished for glycolysis to continue. In the aerobic state this is achieved by oxidizing NADH back to NAD+ in the electron trans- port chain,

with useful energy yield. However, in the absence of oxygen the electron transport chain is inhibited and the NADH is reoxidized back to NAD+ by linking this to the reduction of pyru- vate to lactate, as just described, by lactate dehydrogenase (LDH). Hence lactate (instead of pyruvate) accumulates but NADH does not, and NAD+ is replenished; glycolysis proceeds, providing limited ATP production by substrate-level phosphorylation (anaerobic metabolism) (Fig. 11.1.3). This is a true fermentation pathway: ‘homolactic fermentation’. Lactate is produced by tissues lacking mitochondria (and hence electron transport chains, e.g. red blood cells) and physiologically by oxidative tissues in the presence of oxygen, where it likely rep- resents a redox buffering mechanism, but excessive lactate produc- tion is associated with the hypoxic (and ischaemic) state. However, the lactate contains considerable energy (more than pyruvate as it is further reduced), and when oxygen availability is restored and oxi- dative metabolism is again possible, it makes an excellent substrate, being converted back to pyruvate (LDH being near-equilibrium) for subsequent oxidation via the TCA cycle (e.g. in myocardium). Furthermore, lactate is a principal substrate for gluconeogenesis as discussed above. This Cori cycle is constitutive (lactate being con- stantly produce by glycolytic tissues such as erythrocytes). However, since the concentration of lactate in the blood is dependent not only glucose pyruvate lactate acetaldehyde ethanol acetate acetyl-CoA ATP ADP NAD+ NADH NAD+ NADH ATP ADP CO2 NADH NAD+ NAD+ CO2 glycolysis 1 2 3 4 Fig. 11.1.3 Fermentation reactions. Glucose is split to pyruvate by glycolysis, with small amounts of ATP formed. In the absence of oxygen or a functioning TCA cycle, NAD+ must be regenerated to allow glycolysis to continue. In humans (black lines) this is achieved by lactate production; the lactate can be used to resynthesize glucose by gluconeogenesis or oxidized when oxygen becomes available. In yeasts (orange lines), NAD+ regeneration is achieved by ethanol formation. Metabolism of ethanol by humans alters the NAD+:NADH ratio with significant effects on metabolism. Pyruvate dehydrogenase (red) common to both. 1. pyruvate dehydrogenase 2. lactate dehydrogenase 3. alcohol dehydrogenase 4. acetaldehyde dehydrogenase.

 on peripheral tissue production (e.g. hypoxic/ischaemic muscle) but also on hepatic disposal (uptake and gluconeogenesis), hep- atic blood flow and liver function must both be considered when interpreting hyperlactataemic states. Certain organisms, such as yeasts, have an alternative strategy to regenerate NAD+ for glycolysis—alcoholic fermentation. Here, the pyruvate is decarboxylated to acetaldehyde with carbon dioxide evolved, and acetaldehyde is then reduced to ethanol; the alcohol dehydrogenase enzyme responsible is linked to the oxidation of NADH, regenerating NAD+ and glycolysis continues. The ethanol accumulates and inhibits competing microorganisms. When ethanol is ingested by humans, its metabolism has multiple effects as a result of this link to the NAD+:NADH ratio (redox potential). Following absorption, ethanol is oxidized to acetaldehyde by alcohol dehydrogenase, and acetaldehyde is further oxidized to acetate by aldehyde dehydrogenase; both these enzymes are linked to NAD+ and generate NADH (and potentially reactive oxygen species). The acetate is converted into acetyl-CoA, providing an abundant energy source. However, the high levels of NADH inhibit the oxidation of lactate to pyruvate, limiting the availability of lactate as a precursor for gluconeogenesis (and causing a mild metabolic lactic acid- osis). In addition, the NAD-dependent malate shuttle is inhibited, limiting availability of alanine also as a gluconeogenic substrate. The result is decreased gluconeogenesis and potentially hypoglycaemia. Furthermore, the TCA cycle and fatty acid β-oxidation are inhibited, while lipogenesis is increased (increased acetyl-CoA), leading to hepatic lipid (TAG) accumulation and alcoholic fatty liver. Glucose metabolism in the postabsorptive state (overnight-fasted) In the overnight-fasted (postabsorptive)

state, no glucose enters the plasma from the small intestine. Glucose enters and leaves the plasma at about 2 mg/kg body weight per min (200 g/24 h). About one-half of this will be consumed by the brain. Of the remainder, a considerable proportion will be utilized by blood cells and periph- eral tissues by anaerobic glycolysis, thus returning lactate to the liver for reconversion to glucose (Fig. 11.1.4). This is the Cori cycle. Glucose is produced by hepatocytes from glycogen breakdown and from gluconeogenesis. Net glycogen breakdown is stimulated by the relatively low insulin/glucagon ratio after overnight fasting. The major substrates for gluconeogenesis are pyruvate, derived from lactate (released from blood cells and peripheral tissues) and alanine (from proteolysis), and glycerol (from lipolysis). The pathway of gluconeogenesis predominates over that of glycolysis, again because of the relatively low insulin/glucagon ratio. Glucose metabolism after a meal When a meal enters the system (the postprandial state), this pattern of metabolism changes rapidly. About 12 g of free glucose are present in the circulation and extravascular space. Typically, a single meal Brain Insulin Insulin Glycogen Muscle Glycogen + + + + – – Insulin Insulin Insulin Insulin Insulin Insulin Liver Adipose tissue + Glucose Small intestine Glucose + G6P Pyruvate, Lactate Pyruvate, Lactate Lactate CO_2 CO_2 CO_2 GLUT4 GLUT4 GLUT2 GLUT2 GLUT2 GLUT3 G6P Pancreas GLUT2 Glucose Fig. 11.1.4 Overview of carbohydrate metabolism. Pathways in the liver shown as regulated by insulin are probably controlled by the insulin/glucagon ratio (high in the fed state, low in fasting). In muscle, contraction is an important stimulus for glycogen breakdown and glycolysis. Adrenaline also contributes. Not shown is the significant glucose uptake by red blood cells and other glycolytic tissues, returning lactate to the liver (Cori cycle). GLUT2 is the high-Km non-insulin-regulated glucose transporter (i.e. the glucose flux is determined by concentration), GLUT3 is the low-Km brain glucose transporter (the glucose flux is relatively independent of concentration within the normal range), and GLUT4 the insulin-regulated glucose transporter (insulin brings about movement of GLUT4 to the cell surface from intracellular vesicles). G6P is glucose 6-phosphate.

 will provide about 100 g of glucose, entering the circulation over perhaps 60 min. In order to minimize variations in plasma glucose concentration, coordinated mechanisms come into play to suppress the production of endogenous glucose and to increase the rate of re- moval of glucose from the circulation. Much of the incoming glucose may be taken up by hepatocytes as described earlier, but some enters the systemic circulation and stimulates pancreatic insulin secretion (and somewhat suppresses glucagon secretion). Insulin is liberated into the portal vein. Thus, the liver is exposed to high concentrations of glucose (from the small intestine) and insulin. The net effect is to reverse glycogenolysis, so that glycogen synthesis begins. In addition, gluconeogenesis is sup- pressed and glycolysis favoured (Fig. 11.1.4). Hepatocyte glucose output is therefore rapidly suppressed and converted to an uptake of glucose. At the same time, utilization of glucose by insulin-sensitive peripheral tissues such as skeletal muscle and adipose tissue is in- creased. The main mechanism of this short-term change is the re-cruitment of the insulin-regulated glucose transporter GLUT4 to the cell membrane (Fig. 11.1.4). However, the decrease in concen- tration of plasma NEFAs (see following paragraphs) will also remove inhibition of glucose uptake caused by fatty acid oxidation. Within muscle, glycolysis and glycogen synthesis will be stimulated by in- sulin. In adipose tissue, increased glucose uptake provides glycerol 3-phosphate (formed from glycolysis) for esterification of fatty acids (see following paragraphs). Thus, insulin is the key regulator of the rapid changes that occur in glucose metabolism in the postprandial state: it brings about glucose storage as glycogen, and promotes the utilization of glucose at the expense of fatty acids. Lipid metabolism in the postabsorptive and postprandial states As discussed earlier, lipids are stored primarily as TAGs in adipo- cytes. When

energy is required in other tissues, TAGs are hydrolysed by enzymes (lipases) within adipocytes, and NEFAs are transported through the circulation, bound to albumin as they are not in them- selves water-soluble, to those tissues that can take them up and use them (Fig. 11.1.2). This is the pathway of fat mobilization. However, adipocyte TAG stores remain relatively constant in amount over many years (if body weight is stable), showing that there must also be matching pathways for deposition of TAGs in adipocytes (fat storage). In principle adipocyte TAGs could arise from direct uptake of plasma NEFAs, by uptake of plasma TAGs, and by de novo syn- thesis of fatty acids from glucose or amino acids within the adipo- cytes by the pathway of lipogenesis. The first of these pathways, direct uptake of NEFAs, can be demonstrated by tracer methods but does not achieve net fat storage, as the NEFAs will have arisen from adipo- cyte TAG stores. It has been suggested that this pathway may serve to redistribute lipids between adipose depots. Uptake of fatty acids from plasma TAGs (rather than uptake of the TAGs themselves) is, how- ever, an important pathway, and indeed the predominant pathway for fat storage in humans. It will be considered further next. The last of these options, de novo synthesis of glucose from glucose or amino acids, can be demonstrated to occur, but much evidence points to this being a very minor pathway for adipose tissue lipid deposition in humans. (It may be more prominent in rodents, which typically consume a low-fat, high-carbohydrate diet.) There is also the pos- sibility of lipogenesis in the liver with export of TAG-fatty acids to adipose tissue. This pathway undoubtedly contributes to lipid storage but is small quantitatively under most conditions. The major path- ways of fat metabolism are summarized in Fig. 11.1.5. Triacylglycerols in the circulation TAGs are not water-soluble—this is one reason that they are such an efficient form of energy storage. However, this poses problems when they must be transported through the plasma. Evolution has solved this problem by the development of lipoproteins, submicroscopic lipid droplets in which a core of neutral lipid (TAGs or cholesteryl esters) is stabilized by a surface monolayer of amphipathic phospho- lipids. This is an oil-in-water emulsion and is highly analogous to the stable lipid droplets in milk. Plasma lipoproteins are heterogeneous and are usually classified by their density—essentially, the greater the core lipid content per particle, the less dense the particle (lipid being less dense than water), and this enables different fractions to be separated in an ultracentrifuge. The main lipoprotein carriers of TAGs in the circulation are known as the TAG-rich lipoproteins: chylomicrons, secreted from the small intestine and transporting dietary lipid, and very low- density lipoprotein (VLDL) particles secreted from the liver, trans- porting endogenous TAGs (i.e. lipid from hepatocytes). In the postabsorptive state, chylomicron-TAG secretion is virtually zero. Secretion of VLDL is a means of exporting lipid from the liver to peripheral tissues. Insulin -

- Insulin

- Catecholamines NEFA Chylomicrons (via lymphatics) CO2 LPL LPL TAG TAG HSL, ATGL FA Muscle, myocardium renal cortex etc Small intestine Adipose tissue Ketone bodies & CO2 VLDL NEFA Insulin +

- Insulin Liver Fig. 11.1.5 Overview of fat metabolism. Dietary triacylglycerols (TAGs) enter the circulation in the form of chylomicrons. Fatty acids are taken up by tissues through the action of the enzyme lipoprotein lipase (LPL). Adipose tissue is the major TAG store. TAGs are mobilized in times of energy demand by the enzymes adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL; for more detail see Fig. 11.1.6), liberating nonesterified fatty acids (NEFAs) into the circulation, from where they may be taken up by

several tissues and used for synthesis of new TAGs and for oxidation. Major points of hormonal regulation are shown (italic).

11.1 Nutrition: Macronutrient metabolism 1845 Direct uptake of TAGs from plasma only occurs in small amounts when whole lipoprotein particles are taken into cells by receptor- mediated pathways. No TAG transporter protein has been identi- fied. Instead, the main route for cellular uptake of plasma TAGs is hydrolysis within the capillaries to release fatty acids that may be taken up by simple diffusion across the phospholipid bilayer, or by carrier-mediated diffusion. As with glucose transport, there are sev- eral fatty acid transport proteins, although rather more disparate than the GLUT family of glucose transporters. Hydrolysis of lipoprotein TAGs in the capillaries of many tissues is mediated by the enzyme lipoprotein lipase, situated in the ca- pillaries and bound to the capillary endothelial cells. This occurs in skeletal muscle and heart, adipose tissue, mammary glands, and other tissues that use fatty acids, although not the liver. (In the liver there is a related enzyme, hepatic lipase.) Lipoprotein lipase acts on the circulating TAG-rich particles to liberate fatty acids which may be taken up by the parenchymal cells (muscle fibres, adipocytes, and so on). Adipose tissue lipoprotein lipase is upregulated by insulin, giving that tissue a special role in clearance of dietary lipid from the chylo- microns in the postprandial state. In the postabsorptive state, muscle lipoprotein lipase is likely to predominate as the site of removal of TAGs from the VLDL particles. Muscle lipoprotein lipase expression is upregulated in response to physical activity, and during fasting. The fatty acids can then be used as an oxidative fuel by the muscle. In this process, VLDL particles lose their TAG core and become rela- tively enriched with cholesterol and phospholipids. After several cycles through such capillary beds, they shrink to become simple particles with a core of cholesteryl ester and an outer phospholipid shell: these are known as low density lipoprotein (LDL) particles, the main carrier of cholesterol in the circulation. Fat mobilization, nonesterified fatty acids and ‘energy transport’ from adipose to other tissues Lipid is mobilized from adipose tissue stores in the form of NEFAs (Fig. 11.1.2, Fig. 11.1.5). The adipocyte has a central droplet of TAGs, which is hydrolysed by intracellular enzymes (Fig. 11.1.6), releasing glycerol and NEFAs. Fat mobilization is stimulated by cat- echolamines but powerfully suppressed by insulin (see Fig. 11.1.5). Thus, fat mobilization is active in the postabsorptive state when in- sulin levels are low, and there is a call upon the body’s fat stores. It is also activated during exercise, mainly by catecholamine stimulation. Atrial natriuretic peptide (ANP), released from the heart during ex- ercise, also stimulates lipolysis. The turnover of NEFAs in the plasma is rapid. They are the major oxidative fuel in muscle after overnight fast. In the liver, fatty acids are both a fuel for oxidation and a sub- strate for synthesis of TAGs that will be exported as VLDL.
A typical concentration of nonesterified fatty acids in the plasma after over- night fast is 500 μmol/litre, one-tenth that of glucose, but because of their rapid turnover, their larger molecular mass and more reduced state fatty acids account for about twice the energy turnover of glu- cose in the circulation. Disposition of dietary fat Dietary fat is almost entirely (typically 95% or more) in the form of TAGs. A typical meal might contain 30 to 40 g of lipid. The typ- ical plasma TAG concentration in a healthy subject is 1 mmol/litre, confined to the vascular space; this means that about 3 g of TAGs is present in the circulation. Therefore, as in the case of glucose, the amount in a meal could overwhelm the system unless coordinated mechanisms come into play to ensure its rapid dispersion. Dietary TAG is digested in the stomach and small intestine and packaged by the enterocytes of the duodenum and proximal je- junum into chylomicrons, which enter the circulation via the lymph- atics (Fig. 11.1.5). Therefore, unlike other nutrients absorbed from TAG Perilipin FA FA FA DAG ATGL CGI-58 MAG Glycerol MGL HSL Fig. 11.1.6 Fat mobilization in adipocytes. The

pathway of adipocyte lipolysis is mediated by a series of three enzymes which progressively remove NEFAs from stored TAGs. Adipose triglyceride [triacylglycerol] lipase (ATGL) is active against TAGs, whereas hormone-sensitive lipase (HSL) is active mainly against diacylglycerols (DAGs), with some activity against TAGs also. Monoacylglycerol (MAG) lipase (MGL) acts to release free glycerol together with one NEFA. Free glycerol is exported from the adipocyte and will eventually be taken up by the liver. The pathway of adipocyte lipolysis is highly regulated. HSL is activated on a very short-term basis by reversible phosphorylation by protein kinases A and G, brought about by changes in the intracellular concentrations of cyclic AMP and cyclic GMP. The regulation of ATGL is less direct. ATGL has an essential coactivator protein called CGI-58 (comparative gene identification member 58). There is additional regulation at the surface of the lipid droplets where these lipases act. The lipid droplet is coated with specific proteins, a major one of which in the adipocyte is perilipin 1. Perilipin 1 is itself subject to phosphorylation, under the same conditions as HSL, and this appears to cause a conformational change that allows lipases to access the lipid droplet. CGI-58 is bound to perilipin in the unstimulated state, but released, and hence is free to activate ATGL, upon perilipin phosphorylation. The figure shows a lipid droplet surrounded by perilipin. Upon phosphorylation of perilipin, and also of HSL, a conformational change in perilipin (i) allows the lipases access to the lipid droplet and (ii) allows CGI-58 to dissociate and thus to activate ATGL. N.B. The lipases act much closer to the surface of the lipid droplet than is shown here. Fatty acids (FA on diagram) may be released from the cell for transport to other tissues, although a proportion is always re-activated (thio-esterified to CoA) and re-esterified to form TAGs. Largely reproduced from Gurr MI, Harwood JL, Frayn KN, Murphy DJ, Michell RH. Lipids: Biochemistry, Biotechnology and Health (Lipid Biochemistry: an Introduction, 6th edn), 2016 (Wiley, Oxford).

SECTION 11 Nutrition 1846 the small intestine, they bypass the liver on first passage. The chylo- microns also carry other lipid constituents of food, including choles- terol and fat-soluble vitamins. In the circulation their fate is similar to that of VLDL particles, although the tissue-specific regulation of lipoprotein lipase ensures that adipose tissue (where lipoprotein lipase is upregulated by insulin) is a major site of clearance of their TAGs. The pathway of TAG synthesis from fatty acids in adipocytes, as in the liver, is stimulated by insulin. Therefore, there is a short and energy-efficient pathway for storage of dietary fatty acids in adipose tissue (Fig. 11.1.5). The half-life of chylomicron-TAGs in the circu- lation is about 5 min. After hydrolysis of most of the TAGs, the rem-nant particles are removed by receptors in the liver and other tissues. Thus dietary cholesterol, which remains in the remnant particles along with fat-soluble vitamins, is transported mainly to the liver. Provided that a meal contains carbohydrate or protein, stimu- lation of insulin secretion will rapidly suppress the mobilization of adipose tissue TAG stores, and concentrations of NEFAs in the plasma fall after a meal. Therefore, utilization of fatty acids by tis- sues such as skeletal muscle and liver will be decreased simply by lack of availability. This reduces competition for oxidation in muscle, further increasing glucose utilization. In liver, the lack of NEFAs is likely to decrease the secretion of VLDL-TAGs. Within the liver, insulin powerfully stimulates esterification of fatty acids (for TAG synthesis) at the expense of oxidation of fatty acids (see following paragraphs). Interrelationships between carbohydrate and lipid metabolism Links between carbohydrates and lipids Carbohydrates and lipids are our main energy fuels. Oxidation of each of them is regulated by how much we ingest, our physical activity level and many other factors. However, it should not be surprising that the metabolic fates of these two important fuels are also intertwined metabolically. As noted earlier, in mammals lipids cannot be converted to glucose in a net sense.

Glucose can, however, be converted to lipid. Acetyl-CoA produced by PDC leaves the mitochondrion (it is transported across the mitochondrial membrane as citrate), and is then a substrate for the pathway of de novo lipogenesis, which begins with the enzyme acetyl-CoA carboxylase, forming malonyl-CoA. Principal among the way these fuels interact is carbohydrate- induced insulin secretion. Insulin, as outlined earlier (Fig. 11.1.5), acutely suppresses the release of NEFAs from adipose tissue. Therefore, when carbohydrate is readily available, lipid stores are conserved. In the longer term, ingestion of a high-carbohydrate diet will induce enzymes of lipid synthesis and downregulate enzymes of fatty acid oxidation, through insulin- and carbohydrate-response elements in the promoter regions of the relevant genes (see para- graph on ‘Regulation of macronutrient flux’). Glucose–fatty acid cycle Beyond this, there are specific cellular mechanisms that regulate the relative oxidation of carbohydrate and lipid. These probably operate in several tissues, although they have been most studied in skeletal and heart muscle and in liver. In 1963, Philip Randle and colleagues described the glucose–fatty acid cycle, which encompasses one aspect of this mutual relationship between carbohydrate and lipid oxidation. It is summarized in Fig. 11.1.7. The concept was based upon observations that availability of fatty acids reduced the oxi- dation of glucose in skeletal and cardiac muscle. This basic obser- vation has been confirmed many times both in vitro and in vivo. The glucose–fatty acid cycle describes both the normal interplay between fat and carbohydrate oxidation, and also pathological situ- ations involving excess availability of lipids and insulin resistance (e.g. type 2 diabetes and obesity). Glucose and the regulation of fatty acid oxidation An additional mechanism was first described in 1977 by Denis McGarry and Daniel Foster. They were following up a long-standing observation that the generation of ketone bodies by the liver was suppressed by insulin. They showed that malonyl-CoA, the first committed intermediate in the pathway of de novo lipogenesis (pro- duced by acetyl-CoA carboxylase; see earlier), strongly inhibits fatty acid oxidation. This inhibition is mediated via the enzyme carnitine palmitoyltransferase-1 in the mitochondrial membrane. Carnitine palmitoyltransferase-1 is responsible for the transport of fatty acids from the cytoplasm to the mitochondrion for β-oxidation. Acetyl- CoA carboxylase is activated by insulin (both by increased gene transcription and by reversible dephosphorylation). Hence, in a carbohydrate-replete state, malonyl-CoA will be formed and fatty acid oxidation inhibited (Fig. 11.1.7). This is now recognized as a widespread regulatory mechanism. There are two isoforms of acetyl-CoA carboxylase. Acetyl-CoA carboxylase 1, expressed in lipogenic tissues such as liver and adi- pose tissue, is involved in de novo fatty acid synthesis. Acetyl-CoA carboxylase 2 is expressed more in tissues oxidizing fatty acids such as heart and skeletal muscle and is thought to produce malonyl-CoA for regulatory, rather than synthetic, purposes. Muscle carnitine palmitoyltransferase-1 is more sensitive to inhibition by malonyl- CoA than is the liver enzyme. The ability of glucose to inhibit the oxidation of fatty acids in muscle has been clearly demonstrated in vivo, and has been termed the ‘reverse glucose–fatty acid cycle’. Protein and amino acid metabolism and their regulation The body pools of protein and amino acids, and their turnover, are summarized in Fig. 11.1.8. Insulin exerts a net anabolic effect on body protein, mainly in skeletal muscle, whereas thyroid hormones and cortisol are generally catabolic. Anabolism is also stimulated by anabolic steroids, by physical training, and during growth by the insulin-like growth factors (IGF-1; IGF-2). Dietary protein, digested in the small intestine and absorbed as free amino acids and short peptides, enters the portal vein. Enterocytes of the small intestine remove some amino acids, espe- cially glutamine, for use as an oxidative fuel. The remaining products of digestion next enter the liver, where further preferential extrac- tion occurs. Amino acid oxidation is, under most circumstances, the major oxidative pathway in the liver—about 60% of incoming amino acids may be directed into immediate oxidation. The rate of

11.1 Nutrition: Macronutrient metabolism 1847 hepatic protein synthesis is also high, and since much of the pro- tein is secreted (e.g. albumin), this represents a net loss of amino acids from the liver (perhaps a further 20% of the incoming amino acids). The remaining mixture of amino acids, around 20% of those absorbed, enters the systemic circulation. This mixture is enriched in the branched-chain amino acids (BCAA) leucine, isoleucine, and valine, which have a special role in muscle. BCAA make up approxi- mately one-third of all amino acids in the body; while the other amino acids are metabolized principally in the liver, these essen- tial amino acids are metabolized in peripheral (nonhepatic) tissue, especially skeletal muscle. Amino acids must be synthesized, obtained from the diet or de- rived from proteolysis (although no dedicated protein exists whose sole function is to supply amino acids for energy). 'Nonessential' amino acids can be synthesized from intermediary metabolites (or from other amino acids); 'essential' amino acids cannot be synthesized by humans and therefore must be obtained from the diet. 'Conditionally essential' amino acids can be synthesized in only limited amounts, and this must be supplemented by the diet in states of rapid protein synthesis (e.g. growth). Free amino acids (dietary, synthetic, proteolytic) constitute a soluble amino acid pool; this is quantitatively small, but dynamic. From this pool, amino acids are used for biosynthetic functions as well as degradation for energy production, their carbon skeletons entering the common metabolic pool of intermediary metabolites shared with carbohydrate and lipid metabolism. While amino acids are used to synthesize proteins, proteins are broken down to amino acids, this constituting the protein turnover rate (Fig. 11.1.8), which varies between individual proteins. For a protein to be useful as a source of amino acids for energy production, Fig. 11.1.7 The glucose–fatty acid cycle. When glucose and insulin concentrations are high, release of nonesterified fatty acids (NEFAs) from adipose tissue is suppressed, and glucose utilization predominates in insulin-sensitive tissues such as skeletal muscle—its uptake is stimulated by GLUT4. In addition, glucose metabolism inhibits NEFA oxidation: stimulation of acetyl-CoA carboxylase (ACC; 1 in image) produces malonyl-CoA which inhibits uptake of fatty acyl-CoA (FA-CoA) into the mitochondrion by inhibiting carnitine palmitoyl-transferase-1 (CPT-1; 2 in image), hence β-oxidation of fatty acids is inhibited. In the fasting state (glucose and insulin concentrations are low), insulin-mediated inhibition of adipose tissue lipolysis is decreased, and NEFA utilization predominates, reinforced by inhibitory effects of fatty acids and their products of β-oxidation on glucose uptake and oxidation. This may have pathological significance, in that states in which NEFA concentrations tend to be high (e.g. type 2 diabetes mellitus) will be associated with resistance of glucose utilization to insulin. Protein 100 g/day 10 kg protein ? 100 g amino acids Nucleotides, hormones etc CO2 plus urea, NH3, equivalent to protein 100 g/day 300 g/day 300 g/day Fig. 11.1.8 The body pools of protein and free amino acids and their turnover. Numbers are approximate.

SECTION 11 Nutrition 1848 its turnover rate must be relatively high, and there must be a rela- tively large amount of it in the body. Dietary amino acids surplus to synthetic requirements (for proteins, nucleotides, hormones, neurotransmitters, creatine, porphyrins, sphingolipids) are utilized directly for energy pro- duction. Although many amino acids exist in vivo (20 'standard' amino acids are coded for in proteins, but there are others that are not used for peptide bond formation), and some have indi- vidual amino acid metabolic pathways, most follow a common biochemical route to yield their energy. Amino acids comprise a central (α-) carbon bonded to a carboxyl, amino, hydrogen and side chain ('R group') group—hence they contain C, H, O atoms, like carbohydrates and lipids, but also a distinguishing N-atom. The common feature of amino acid metabolism is removal of the amino-N group (deamination), which is excreted as urea or ammonia

(or incorporated into certain biomolecules), followed by utilization of the remaining carbon skeleton (α-keto acid; 2-oxoacid) (Fig. 11.1.9). The fate of the 2-oxoacid carbon skeleton depends on where it enters the common metabolic pool of inter- mediary metabolism. Nitrogen disposal Deamination of amino acids is achieved by two types of reaction which function in a complementary manner (Fig. 11.1.10). The first is transamination, in which the amino group from one amino acid is transferred to another 2-oxoacid (carbon skeleton), forming its corresponding amino acid (i.e. amino acid-1 + 2-oxoacid-2 ↔ 2- oxoacid-1 + amino acid-2). The enzymes responsible for transamin- ation reactions are aminotransferases (transaminases), all of which contain pyridoxal phosphate, a derivative of vitamin B6, in their ac- tive centres. Aminotransferases are widespread in most tissues and are near-equilibrium, hence readily reversible. Each is specific for a limited number of amino acids, but most utilize 2-oxoglutarate (α- ketoglutarate) as the amino (N) acceptor, producing the carbon back- bone of the donor amino acid together with glutamate (amino acid + 2-oxoglutarate → 2-oxoacid + glutamate). Hence 2-oxoglutarate and glutamate are central to amino acid catabolism as these reactions ‘funnel’ the various amino acids into glutamate (and note that 2- oxoglutarate is common to the TCA cycle, and its utilization by this pathway depletes TCA intermediates—cataplerosis). Alanine aminotransferase (ALT) transfers the amino group of ala- nine to 2-oxoglutarate, forming pyruvate and glutamate. Aspartate aminotransferase (AST) transfers the amino group of aspartate to 2-oxoglutarate, forming oxaloacetate and glutamate—however, this enzyme usually works in the reverse direction, its function being to convert glutamate (derived from amino acid funnelling, de- scribed earlier) into aspartate, which is required to donate a second urea N-atom to the urea cycle. Since ALT and AST are both intra- cellular enzymes and widespread, necrosis of many tissues causes them to increase in plasma; they are commonly used to diagnose hepatocellular damage. The second type of reaction responsible for amino acid de- amination is oxidative deamination. Since most amino acids have been deaminated (funnelled) into glutamate by transamination, glutamate is the only amino acid that undergoes direct, oxida- tive, deamination, by glutamate dehydrogenase, regenerating 2-oxoglutarate and producing ammonia (NH_3). Unusually for a highly regulated enzyme, glutamate dehydrogenase is revers- ible, and can use NAD^+ or $NADP^+$ as electron acceptors. In the ‘forward’ direction of deamination (catabolic, amino acid break- down), it uses NAD^+, but in the ‘reverse’ direction of amination of 2-oxoglutarate to glutamate (anabolic, amino acid synthesis) it uses NADPH, reflecting the different roles of these cofactors as redox energy carriers in different metabolic states. Hence, aminotransferases (transamination) and glutamate dehydrogenase (oxidative deamination) work together to produce ammonia for detoxification to urea in the urea cycle, and carbon skeletons for further intermediary metabolism (Fig. 11.1.10). The urea cycle occurs in the liver (the pathway is partially pre- sent in kidney, and also in the brain, but this is not a significant site of blood urea production.) Urea ($CO(NH_2)_2$) contains two ni- trogen atoms: one derives from ammonia (produced by oxidative deamination of glutamate, described earlier), the other derives from AST (also from glutamate; Fig. 11.1.10); the body excretes nitrogen with minimal carbon (and energy) loss. Because urea is very water- soluble, much nitrogen can be excreted for relatively little water loss, an important adaptation in terrestrial animals. Urea lacks toxicity at physiological concentrations; it is (neuro)toxic only in extremely high concentrations, for example those seen in untreated renal failure, but considerably less so than ammonia. Besides urea formation, there is another route of ammonia excre- tion. In peripheral tissues (e.g. muscle) ammonia may be formed by the oxidative deamination of glutamate (by glutamate dehydro- genase). This reaction, in combination with the aminotransferases, can be seen to capture amino nitrogen from several amino acids. However, blood ammonia concentrations are very low (it is

highly toxic) and instead it is exported by being fixed in the amido (side chain) group of glutamine by the enzyme glutamine amino acid carbon skeleton (2-oxoacid) TCA intermediates (≥ 3 C; glucogenic) acetyl-CoA acetoacetyl-CoA (≡2C; ketogenic) glucose CO_2+ H_2O + ATP ketone bodies fatty acids deamination NH_3 urea urea cycle 3 1 2 Fig. 11.1.9 Amino acid metabolism. In order to yield energy, amino acids must have their α-amino group removed (deamination). This is achieved by transamination and oxidative deamination (see Fig. 11.1.10). The resulting ammonia is converted to urea (urea cycle) in order to decrease its toxicity. The remaining carbon skeleton (2-oxoacid; 'α-keto acid') enters the common metabolic pool of intermediary metabolites for immediate oxidation, or conversion into glucose (glucogenic amino acids; blue) or lipids (ketogenic amino acids; green) for subsequent oxidation.

11.1 Nutrition: Macronutrient metabolism 1849 synthetase: hence glutamine is carrying two nitrogen atoms. In liver, the enzyme glutaminase removes the amido nitrogen of glutamine as ammonia for rapid incorporation into urea. In the kidney, glutaminase also removes the amido group of glutamine to form ammonia (and glutamine; glutamate dehydrogenase then deaminates this to form another ammonia), but here the resulting ammonia is excreted directly into the urine as a urinary buffer. There is also a supply of ammonia from the small intestine. Metabolism of carbon skeleton Following amino acid deamination, the remaining 2-oxoacid enters the common metabolic pool. All amino acid carbon skeletons ultim- ately yield just seven products of intermediary metabolism: pyru- vate, 2-oxoglutarate, succinyl-CoA, fumarate, oxaloacetate, acetyl-CoA, and acetoacetyl-CoA. The first five of these represent at least three carbons, hence amino acids producing these metab- olites can be used for glucose synthesis ('glucogenic'). The acetyl-CoA and acetoacetyl-CoA, however, yield two carbon groups or equivalent, and amino acids which produce them cannot be used for gluconeogenesis (Fig. 11.1.9)—they can be directly oxidized in the TCA cycle, undergo lipogenesis or be used to synthesize ketone bodies ('ketogenic'). The glucogenic amino acids therefore confer on proteins the property of acting as a carbohydrate reserve in states such as starvation. Intertissue amino acid flux Considerable flux of amino acids occurs between tissues as part of intermediary metabolism. Liver is the site of both ureagenesis (amino-N metabolism) and gluconeogenesis (carbon skeleton me- tabolism), and diet-derived amino acids enter the liver through the portal circulation for immediate processing. However, many amino acids are derived from endogenous proteolysis in many peripheral (nonhepatic) tissues. Amino acid transport from peripheral tissues to the liver for catabolism involves transport of both the N-group (for deamination and excretion) and the carbon skeleton (for oxida- tion/glucose synthesis) (Fig. 11.1.11). Hence, amino acids released from proteolysis in peripheral tissues must transfer their amino nitrogen to the liver. This re- sults in considerable interaction between the pathways of amino acid, carbohydrate, and fat metabolism. Measurements of arterio- venous differences across muscle and adipose tissue show that the release of the amino acids alanine and glutamine predomin- ates. Since glutamine carries two nitrogens it is, under most cir- cumstances, the predominant nitrogen carrier. Arteriovenous difference measurements across the splanchnic bed (by cath- eterization of the hepatic vein) show an almost identical pattern for uptake: removal of alanine and glutamine far exceeds that of other amino acids. Therefore, amino acids in tissues including muscle must transfer their amino nitrogen to alanine (by trans- amination with pyruvate) and glutamine (formed by glutamine synthetase from glutamate, itself arising by transamination with 2-oxoglutarate). It is important that the 2-oxoacid acceptors, pyruvate and 2-oxoglutarate, are common metabolic intermedi- ates and thus readily available. All three BCAA are transaminated by a single branched-chain aminotransferase, and the resulting branched-chain 2-oxoacids undergo

oxidative decarboxylation (branched-chain α-ketoacid de- hydrogenase (BCKD) complex). Branched-chain amino acids ab- sorbed from the diet are not removed from the portal circulation by the liver (therefore avoid the hepatic first pass effect of other amino acids) and appear in high concentration in the blood from the splanchnic bed; furthermore, branched-chain amino acids may amino acid 2-oxoglutarate glutamate NH3 urea CO2 transamination oxidative deamination urea cycle carbon skeleton (2-oxoacid) intermediary metabolism aspartate transamination glutamate 2-oxoglutarate OAA aminotransferase glutamate dehydrogenase aspartate aminotransferase
Fig. 11.1.10 Amino acid deamination. Multiple amino acids are ‘funnelled’ into one amino acid, glutamate, which acts as the universal donor of the α-amino group. Transamination reactions, catalysed by aminotransferase enzymes (transaminases), are responsible for the funnelling of most amino acids into glutamate; the remaining 2-oxoacid (carbon skeleton) can then be used for energy generation. These transamination reactions occur both in tissues of amino acid supply (e.g. muscle) and in the site of urea synthesis (liver); alanine is used for amino acid transport and therefore an important aminotransferase is alanine aminotransferase (ALT), yielding the 2-oxoacid pyruvate. Aspartate aminotransferase (AST) also utilizes glutamate for deamination. Glutamate provides both nitrogen atoms for the urea cycle (urea: CO(NH2)2) and is the only amino acid to undergo direct (oxidative) deamination by glutamate dehydrogenase. OAA, oxaloacetate.

SECTION 11 Nutrition 1850 also have a role as nutrient signals. Hence, branched-chain-amino acids act as a major source of nitrogen in skeletal muscle to maintain pools of glutamine, glutamate, and alanine (branched-chain amino acid transferase activity is significantly higher than BCKD activity). Much of the alanine released from skeletal muscle comes from transamination of pyruvate formed in glycolysis. Within the liver, the amino group can be transferred further (e.g. to oxaloacetate, forming aspartate, which is one of the immediate donors of nitrogen to the urea cycle). The pyruvate thus formed may be a substrate for gluconeogenesis, producing glucose that can be recycled to periph- eral tissues. This metabolic cycle has been called the glucose-alanine cycle. It closely parallels the Cori cycle (see Fig. 11.1.4). An important aspect of the large depot of muscle protein is that it represents a potential source of synthesis of new glucose during fasting. In that situation, while the brain continues to require glu- cose for oxidation, and as glycogen reserves are depleted, new glu- cose can only be formed from glycerol, released in adipose tissue lipolysis, and from amino acids. Regulation of macronutrient flux The need for the coordinated control of nutrient storage, mobiliza- tion, and flux between tissues and along the many metabolic path- ways, is met by a complex series of control mechanisms. These may be viewed on several levels. The simplest involves the effects of sub- strate concentration, and is dependent upon the kinetic properties of enzymes and transport proteins. The next level involves more specific interaction of nutrients, or pathway intermediates, with enzymes, usually through allosteric effects (binding of the effector alters the conformation of the en- zyme and hence its catalytic properties). There are many examples in the metabolism of carbohydrate, fat, and protein. The enzyme 6-phosphofructo-1-kinase in the glycolysis pathway is a good ex- ample. This enzyme is subject to allosteric regulation by many com- pounds that relate to the energy status of the cell. For instance, it is activated by AMP (indicating energy shortage) and inhibited by ATP. Such mechanisms undoubtedly provide important fine tuning of flux along various pathways, entirely in accord with the modern view that control of flux does not reside in certain rate-limiting steps but is distributed among many steps along a pathway. Related to this, the enzyme AMP-activated protein kinase (AMPK) re- sponds to the cellular energy status and regulates several metabolic pathways accordingly (see ‘Further reading’). These mechanisms operate essentially within tissues. However, the coordination of

nutrient metabolism requires considerable interaction between tissues and organs. This coordination is largely brought about by the hormonal and nervous systems. Certain hor- mones play a particularly important role in regulation of macronu- trient flux (Table 11.1.2). The role of the nervous system in metabolic glucose glucose Liver Intestine Kidney Muscle glucose alanine alanine alanine pyruvate AA AA BCAA BCAA urea urea urea NH3 NH3 NH3 glutamine glutamine glutamate glutamate glutamine pyruvate NH3 2-oxoglutarate 2-oxoglutarate 2-oxoglutarate 2-oxoacid PROTEIN NH3 PROTEIN CO2 + H2O Fig. 11.1.11 Intertissue amino acid flux. Amino acids are provided from the diet and by amino acid turnover from labile protein pools. In catabolic states where amino acids are required for energy (glucose) provision, muscle proteolysis and transamination yield alanine and glutamine for export (muscle is the major source of amino acids during starvation and is shown here for clarity). Alanine is transported to the liver, where it is deaminated, and its carbon skeleton (pyruvate) used for gluconeogenesis; the glucose produced is used by brain, or recycled to the muscle to facilitate further nitrogen transport (glucose-alanine cycle), while the nitrogen is converted to urea for renal excretion. Glutamine exported from peripheral protein sources is transported to several tissues, including kidney, where it is deaminated to yield free ammonia, an important urinary buffer. AA, amino acids; BCAA, branched-chain amino acids.

11.1 Nutrition: Macronutrient metabolism 1851 Table 11.1.2 Major hormonal effects on intermediary metabolism Hormone Origin Target tissue Major metabolic effects Comments Insulin Pancreatic islets (β-cells) Liver Stimulation of glycogen synthesis/suppression of glycogen breakdown Regulates glucose storage in liver Stimulation of glycolysis/suppression of gluconeogenesis Regulates hepatic glucose output Suppression of fatty acid oxidation/ketogenesis Via malonyl-CoA Stimulation of triacylglycerol synthesis Stimulation of cholesterol synthesis Skeletal muscle Stimulation of glucose uptake Via recruitment of GLUT4 (see Fig. 11.1.4) Stimulation of glycogen synthesis Net protein anabolic effect Suppression of protein breakdown may be more important than stimulation of protein synthesis Adipose tissue Activation of triacylglycerol removal from plasma Via lipoprotein lipase Suppression of fat mobilization Via intracellular lipases (see Fig. 11.1.6) Glucagon Pancreatic islets (α-cells) Liver Stimulation of glycogen breakdown/suppression of glycogen synthesis In effect the regulation is via the insulin/glucagon ratio Stimulation of gluconeogenesis/suppression of glycolysis Stimulation of fatty acid oxidation/ketogenesis Somatostatin δ-Cells in pancreatic islets and in gastrointestinal tract; some neuroendocrine neurons in brain Cells secreting other peptide hormones; acid-producing parietal cells of stomach Indirect, via inhibition of secretion of insulin, glucagon, growth hormone and other peptide hormones; and via inhibition of gastric acid secretion Somatostatin or analogues are used to treat growth hormone excess ‘Incretins’ K and L cells in gastrointestinal tract α- and β-Cells of pancreatic islets Indirect, via increasing the effect of ingested carbohydrate on insulin secretion (hence the name ‘incretin’); and reducing glucagon secretion The name ‘incretins’ covers at least two peptide hormones, glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (also known as: glucose-dependent insulinotropic polypeptide or GIP). Analogues, or small molecules that block the proteolytic breakdown of incretins, now used in treatment of type 2 diabetes Adrenaline Adrenal medulla Adipose tissue Stimulation of fat mobilization Via intracellular lipases (see Fig. 11.1.6) Skeletal muscle Stimulation of glycogen breakdown Acts in concert with muscle contraction Tri-iodothyronine Thyroid All oxidative tissues Increase in basal metabolism Cortisol Adrenal cortex Liver Stimulation of gluconeogenesis Skeletal muscle Generally catabolic effect on protein Adipose tissue Promotes site-specific fat deposition (central depots) and fat mobilization

(peripheral depots) Growth hormone Anterior pituitary Liver Stimulation of gluconeogenesis Direct effect: other effects are mediated indirectly via insulin-like growth factors Adipose tissue Stimulation of fat mobilization This is an acute effect: chronically, growth hormone promotes mobilization from central fat depots Insulin-like growth factors (IGF) I and II Liver (IGF-I) and other tissues (both) Several Generally insulin-like acute effects on metabolism Physiological role is probably longer-term effects on growth Leptin Adipose tissue Hypothalamus Suppression of appetite; possibly stimulation of energy expenditure Latter effect prominent in rodents, may not occur in humans; low leptin levels (signalling starvation) more important than high levels signalling excess. Recombinant leptin has been used to treat the rare genetic condition of leptin deficiency Reproductive system Signals sufficient fat stores for reproduction to be possible As with effects on hypothalamus, low leptin may be a signal of starvation

SECTION 11 Nutrition 1852 regulation is often difficult to assess. Although the effects of adren- aline are properly regarded as hormonal, liberation of noradrenaline from sympathetic nerve endings in tissues may bring about iden- tical effects and can be difficult to distinguish. The somatic nervous system (motor neurons innervating skeletal muscle) has clear effects (e.g. stimulation of breakdown of muscle glycogen linked to muscle contraction). The autonomic nervous system probably plays mul- tiple roles, but some are indirect (e.g. regulation of blood flow and cardiac output), thus affecting delivery of substrate to tissues, and regulation of the secretion of pancreatic hormones. The effects of hormones are mediated in many ways, but these may be divided into acute effects (usually acting within seconds or minutes), often brought about through reversible phosphorylation or dephosphorylation of enzymes, and longer-term effects (hours or days), brought about by regulation of gene expression. The former are usually exerted through binding to cell surface receptors linked to a variety of second-messenger systems, the latter through nuclear receptors (e.g. for glucocorticoids and thyroid hormones; for more details see Chapter 13.1). However, the distinction is not absolute (e.g. insulin brings about both acute and longer-term effects through binding to the same cell surface receptor). Until recently it was considered that there was a complete distinction between hormones and substrates (or metabolites). One obvious distinction is in typical concentrations in plasma. Table 11.1.3 Some G-protein-coupled receptors (GPCRs) that respond to nutrients and related metabolites GPCR number Other names Gene name Ligand Tissue expression (major tissues) Physiological role and comments GPR40 FFA1, FFAR1 (free fatty acid receptor 1) FFAR1 Long-chain fatty acids (C12–C16) Pancreatic β-cells Potentiates glucose-stimulated insulin secretion GPR41 FFA3, FFAR3 FFAR3 Short-chain fatty acids Adipose tissue, gastrointestinal (GI) tract (enteroendocrine cells) Stimulation of leptin production; stimulation of gut hormone secretion GPR43 FFA2, FFAR2 FFAR2 Short-chain fatty acids Adipose tissue, GI tract (enteroendocrine cells) Adipogenesis, reduction of lipolysis; stimulation of gut hormone secretion GPR70 Taste receptor 1, T1R1 TAS1R1 L-amino acids Taste cells, GI tract, pancreatic islets GPR71 Taste receptor 2, T1R2 TAS1R2 Sugars, artificial sweeteners Taste cells, GI tract, pancreatic islets TAS1R1 and TASR2 act as heterodimers with TASR3 to act as receptors for umami and sweet tastes, respectively Taste receptor 3, T1R3 TAS1R3 See comments on T1R1, T1R2 Taste cells, GI tract, pancreatic islets GPR81 HCAR1 (hydroxycarboxylic acid receptor 1) Lactate Adipocytes System by which lactate reduces adipocyte lipolysis; may act as a paracrine amplifier of insulin action on lipolysis (since insulin increases adipocyte lactate production) GPR109A HM74A, NIACR1 HCAR2 (hydroxycarboxylic acid receptor 2) Probably 3- hydroxybutyrate (ketone body) Adipocytes Identified initially as the receptor for nicotinic acid (a component of the B- vitamin niacin), used in large doses to treat high triacylglycerol concentrations. Only known

metabolic function is to suppress adipocyte lipolysis. Since 3-hydroxybutyrate is a product of hepatic fatty acid oxidation, this could provide a feedback loop GPR109B HCAR3 3-hydroxyoctanoic acid (intermediate of fatty acid oxidation) Adipocytes Reducing lipolysis when fat oxidation is already high (e.g. in pathological situations) GPR119 Oleoylethanolamide receptor GPR119 Oleoylethanolamide and other lipids containing oleic acid, e.g. 2-oleoyl glycerol Pancreatic β-cells, GI tract Oleoylethanolamide has appetite-suppressing activity (although not entirely via GPR119). It is related to the endogenous cannabinoids. 2- monoacylglycerol stimulation in the GI tract may enhance GLP-1 secretion (together with GPR40) GPR120 FFAR4 n-3 Fatty acids Macrophages, GI tract, adipose tissue, brain (hypothalamus) Has been suggested to modulate anti- inflammatory effects of n-3 fatty acids. Human genetic variation associated with obesity and insulin resistance GPR131 GPBAR1 (G protein-coupled bile acid receptor 1), TGR5 GPBAR1 Bile acids Liver, adipose tissue, GI tract, gall bladder Regulates gall bladder filling with bile, gut motility, and secretion of GI tract hormones

11.1 Nutrition: Macronutrient metabolism 1853 For instance, insulin is major regulator of glucose metabolism (see earlier) and yet insulin concentrations in plasma are typic- ally 10–100 pmol/l, whereas glucose concentrations might be 5–10 mmol/litre (a difference of about eight orders of magnitude). However, in recent years it has been appreciated that many nutri- ents and their metabolites also regulate metabolic pathways rap- idly by signalling through receptors that were once thought to be receptors for hormones and neurotransmitters. In particular, this applies to signalling through the G protein-coupled receptors (GPCRs). A variety of compounds that we recognize as nutrients or related metabolites is now known to signal through specific GPCRs. This adds a further level of control of metabolic pathways according to nutrient and metabolite availability. These actions are usually rapid (many mediated via alteration of cellular cyclic AMP concentrations) and so are complementary to the longer- term effects of nutrients and metabolites exerted on gene expres- sion, as discussed next. Some examples of nutrients and their metabolites and the GPCRs through which they may act are given in Table 11.1.3. A further level of coordination is through the effects of nutri- ents themselves, or important cellular components such as chol- esterol, upon gene expression (summarized in Table 11.1.4). This can be seen as a longer-term mechanism to ensure that metab- olism is appropriate to the diet being ingested and the lifestyle followed. A variety of nutrient response elements are known in the promoter regions of genes for enzymes concerned with substrate metabolism. Particular examples are the carbohydrate-response element (which upregulates expression of genes for glucose metabolism such as pyruvate kinase in the glycolysis pathway, and lipogenic genes), the sterol response element (by which insulin activates lipogenic gene expression, as in Table 11.1.4, and cellular sterols downregulate ex- pression of the low density lipoprotein receptor and the enzymes of cholesterol biosynthesis) and response elements for fatty acid de- rivatives. Fatty acids affect gene expression through a family of tran- scription factors known as the peroxisome proliferator-activated receptors, summarized in Table 11.1.4. The expression of many genes is also regulated by insulin. Table 11.1.4 Mechanisms by which nutrients regulate expression of genes involved in macronutrient metabolism Stimulus Transcription factor Examples of proteins whose expression is regulated at the mRNA transcription level Comments Glucose Carbohydrate-response element binding protein Pyruvate kinase (liver isoform) (+) Acetyl-CoA carboxylase 1 (+) Fatty acid synthase (+) SREBP-1c (see next) (+) Insulin (in the pancreatic β-cell) (+) Insulin Various, binding to a variety of insulin response elements (see ‘Further reading’) GLUT 1, 2, 3, 4 (glucose transporters) (+) Hexokinase, glucokinase (+) Glyceraldehyde-3-phosphate dehydrogenase (+)

Glucose-6-phosphatase (–) Acetyl-CoA carboxylase 1 (+) Fatty acid synthase (+) SREBP-1c (+) Glycolysis and lipogenesis are activated, gluconeogenesis suppressed; see ‘Further reading’ for more information Cholesterol (and insulin) Sterol regulatory element binding proteins (SREBP) SREBP-1c: acetyl-CoA carboxylase 1 (+) Fatty acid synthase (+) Stearoyl CoA desaturase (+) SREBP2: LDL receptor (+) HMG CoA synthase (+) HMG CoA reductase (+) The two major isoforms, SREBP-1c and SREBP2 respectively, regulate lipogenesis (in response to glucose and insulin) and cellular cholesterol homeostasis (in response to cellular sterol levels; low sterol levels allow mature SREBP2 to migrate to the nucleus) Fatty acids Peroxisome proliferator- activated receptors (PPARs): PPARα PPARδa PPARγ (Liver): Apolipoproteins; enzymes of peroxisomal fatty acid oxidation Enzymes of mitochondrial oxidation Adipocyte differentiation factors Adipose tissue FABP (also known as aP2) Lipoprotein lipase Adiponectin PPARs act as transcription factors as heterodimers with the retinoid-X receptor; the endogenous ligand is unclear:
it might be a fatty acid (weak affinity) or a fatty acid derivate (e.g. a prostaglandin) (higher affinity) Target for the fibrate lipid-lowering drugs Effects have been documented in adipose tissue, skeletal muscle, and heart; clinical use of agonists uncertain Target for the thiazolidinedione insulin-sensitizing agents Amino acids Mammalian (or mechanistic) target of rapamycin (mTOR); Activating transcription factor 4 (ATF4) IGFBP-1 (–) Asparagine synthase (–) Amino acid transporters (–) (especially neutral amino acid transport system A; cationic amino acid transporter CAT-1) Induction of IGFBP-1 (binds IGF-1) when amino acid supply is restricted limits growth; molecular mechanisms are described in ‘Further reading’ Note: (+), indicates gene induction; (–), gene suppression. a Also known as PPARβ, NUC 1, FAAR (fatty-acid activated receptor). FABP, fatty acid binding protein; GLUT, glucose transporter; HMG, 3-hydroxy-3-methylglutaryl; IGF, insulin-like growth factor; IGFBP, IGF binding protein.

 FURTHER READING Blad CC, Tang C, Offermanns S (2012). G protein-coupled receptors for energy metabolites as new therapeutic targets. Nat Rev Drug Discov, 11, 603–19. Feige JN, et al. (2006). From molecular action to physiological out- puts: peroxisome proliferator-activated receptors are nuclear recep- tors at the crossroads of key cellular functions. Prog Lipid Res, 45, 120–59. Frayn KN, Evans RD (2019). Human metabolism: a regulatory perspec- tive, 4th edition. Wiley/Blackwell, Oxford. He W, et al. (2012). Mitochondrial sirtuins: regulators of protein acyl- ation and metabolism. Trends Endocrinol Metab, 23, 467–76. Howell JJ, Manning BD (2011). mTOR couples cellular nutrient sensing to organismal metabolic homeostasis. Trends Endocrinol Metab, 22, 94–102. Jeon T-I, Osborne TF (2012). SREBPs: metabolic integrators in physi- ology and metabolism. Trends Endocrinol Metab, 23, 65–72. Kersten S (2014). Physiological regulation of lipoprotein lipase. Biochim Biophys Acta, 1841, 919–33. Krycer JR, et al. (2010). The Akt-SREBP nexus: cell signaling meets lipid metabolism. Trends Endocrinol Metab, 21, 268–76. Lass A, et al. (2011). Lipolysis—a highly regulated multi-enzyme com- plex mediates the catabolism of cellular fat stores. Prog Lipid Res, 50, 14–27. Liu Z, Barrett EJ (2002). Human protein metabolism: its meas- urement and regulation. Am J Physiol Endocrinol Metab, 283, E1105–12. Li X, Sun K (2018). Regulation of lipolysis in adipose tissue and clin- ical significance. Adv Exp Med Biol, 1090, 199–210. Long YC, Zierath JR (2006). AMP-activated protein kinase signaling in metabolic regulation. J Clin Invest, 116, 1776–83. Nakamura MT, Yudell BE, Loor JJ (2014). Regulation of energy me- tabolism by long-chain fatty acids. Prog Lipid Res, 53, 124–44. Newman JC, Verdin E (2014). Ketone bodies as signalling metabolites. Trends Endocrinol Metab, 25, 42–52. Poupeau A, Postic C (2011). Cross-regulation of hepatic glucose me- tabolism via ChREBP and nuclear receptors. Biochim Biophys Acta, 1812, 995–1006. Rosenbaum DM, Rasmussen SGF, Kobilka BK

(2009). The structure and function of G-protein-coupled receptors. Nature, 459, 356–63. Shimano H, Sato R (2017). SREBP-regulated lipid metabolism: convergent physiology—divergent pathophysiology. Nat Rev Endocrinol, 13, 710–30. Thorens B, Mueckler M (2010). Glucose transporters in the 21st cen- tury. Am J Physiol Endocrinol Metab, 298, E141–5. Uyeda K, Repa JJ (2006). Carbohydrate response element binding pro- tein, ChREBP, a transcription factor coupling hepatic glucose util- ization and lipid synthesis. Cell Metabolism, 4, 107–10. Wang H, Eckel RH (2009). Lipoprotein lipase: from gene to obesity. Am J Physiol Endocrinol Metab, 297, E271–88. Wong RH, Sul HS (2010). Insulin signaling in fatty acid and fat synthesis: a transcriptional perspective. Curr Opin Pharmacol, 10, 684–91. Wu G (2009). Amino acids: metabolism, functions, and nutrition. Amino Acids, 37, 1–17. Zechner R, et al. (2012). FAT SIGNALS—lipases and lipolysis in lipid metabolism and signaling. Cell Metab, 15, 279–91. Zhang BB, Zhou G, Li C (2009). AMPK: an emerging drug target for diabetes and the metabolic syndrome. Cell Metab, 9, 407–16.

11.2 Vitamins 1855

11.2 Vitamins 1855

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 Ca^{2+} 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 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, Copyright © 2007, John Wiley and Sons.

SECTION 11 Nutrition 1866 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 oxi- dized 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 Fe2+ 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.

SECTION 11 Nutrition 1870 Bonham MP, et al. (2009). Estimation of the dietary requirement for vitamin D in free-living adults >=64 years. Am J Clin Nutr, 89, 1366–74. Butterworth RF (1982). Neurotransmitter function in thiamine defi- ciency. Neurochem Int, 4, 449–65. Carmel R (2000). Current concepts in cobalamin deficiency. Annu Rev Med, 51, 357–75. Cashman KD, et al. (2008). Estimation of the dietary requirement for vitamin D in healthy adults. Am J Clin Nutr, 88, 1535–42. Dakshinamurti K, Chauhan J (1989). Biotin. Vitam Horm, 45, 337–84. Englard S, Seifter S (1986). The biochemical functions of ascorbic acid. Annu Rev Nutr, 6, 365–406. European Food Safety Authority (EFSA) (2006). Tolerable upper intake levels: vitamins and minerals. Scientific Panel on Dietetic Products, Nutrition and Allergies. European Food Safety Authority (EFSA) (2012). Tolerable upper in- take levels for vitamins and minerals. Scientific Committee on Food, Scientific Panel on Dietetic Products, Nutrition and Allergies. Ferland G (2001). Vitamin K. In: Bowman BA, Russel RM (eds) Present knowledge in nutrition, 8th edition, pp. 164–72. ILSI Press, Washington, DC. Froese DS, Fowler B, Baumgartner MR (2019). Vitamin B12, folate, and the methionine remethylation cycle-biochemistry, pathways, and regulation. J Inherit Metab Dis, 42, 673–85. Henderson L, et al. (2000). The national diet & nutrition survey: adults aged 19 to 64 years. Vitamin and mineral intake and urinary analytes. HMSO, London. Holick MF (1994). McCollum award lecture: vitamin D—new hori- zons for the 21st century. Am J Clin Nutr, 60, 619–30. Hommes FA (1986). Biotin. World Rev Nutr Diet, 48, 34–84. Huemer M, Baumgartner MR (2019). The clinical presentation of cobalamin-related disorders: From acquired deficiencies to inborn errors of absorption and intracellular

pathways. J Inherit Metab Dis, 42, 686–705. Institute of Medicine (2000). Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids. National Academy Press, Washington, DC. Jiang Q, et al. (2001). γ-Tocopherol, the major form of vitamin E in the US diet, deserves move attention. Am J Clin Nutr, 74, 712–22. Kril JJ (1996). Neuropathology of thiamine deficiency disorders. Metab Brain Dis, 11, 9–17. Lal H, Pandey R, Aggarwal SK (1999). Vitamin D: non-skeletal actions and effects on growth. Nutr Res, 19, 1683–718. Leon del-rio A (2019). Biotin in metabolism, gene exression and human disease. J Inherit Metab Dis, 42, 647–54. Marcé-Grau A, Martí-Sánchez L, Baide-Mairena H, Ortigoza-Escobar JD, Pérez-Dueñas B (2019). Genetic defects of thiamine transport and metabolism: A review of clinical phenotypes, genetics, and functional studies. J Inherit Metab Dis, 42, 581–97. Merrill AH, Jr., Henderson JM (1987). Diseases associated with defects in vitamin B6 metabolism or utilization. Annu Rev Nutr, 7, 137–56. Morrissey P, Hill TR (2009). Fat soluble vitamins and vitamin C in milk and milk products. In: Fox PF, McSweeney P (eds) Advanced dairy chemistry-3. lactose, water, salts and minor constituents, pp. 527–89. Springer, New York. Neuzil J, Weber C, Kontush A (2001). The role of vitamin E in athero- genesis: linking the chemical, biological and clinical aspects to the disease. Atherosclerosis, 157, 257–83. O'Callaghan B, Bosch AM, Houlden H (2019). An update on the gen- etics, clinical presentation, and pathomechanisms of human ribo- flavin transporter deficiency. J Inherot Metab Inherit Dis, 42, 598–607. Pellagra (2000). Prevention and Cure of Review 32 pages. Wolrd Health Organization. https://www.who.int/nutrition/publications/ en/pellagra_prevention_control.pdf Pope S, Artuch R, Heales, Rahman S (2019). Cerebral folate deficiency: analytical tests and differential diagnosis. J Inherit Met Diseases, 42, 655–72. Prentice A, Goldberg G, Schoenmakers I (2008). Vitamin D across the lifecycle: physiology and biomarkers. Am J Clin Nutr, 88, 500S–505S. Pryor WA (2000). Vitamin E and heart disease: basic science to clinical intervention trials. Free Radical Biology and Medicine, 28, 141–64. Rahman S, Baumgartner M (editors) (2019). B Vitamins; Small Molecules, big effects. J Inherit Metabol Dis, 42, 579–80. Ross C, et al. (2010). Dietary reference intakes for calcium and vitamin D. Institute of Medicine, Washington, USA. Scientific Advisory Committee on Nutrition. Vitamin D and Health Report. Crown copyright. Available online: https://www.gov.uk/ government/publications/sacn-vitamin-d-and-health-report (ac- cessed on 14 April 2019). Scott J, Weir D (1994). Folate/vitamin B12 inter-relationships. Essays Biochem, 28, 63–72. Shea MK, Booth SL (2008). Update on the role of vitamin K in skeletal health. Nutr Rev, 66, 549–57. Shearer MJ (2000). Role of vitamin K and Gla proteins in the patho- physiology of osteoporosis and vascular calcification. Curr Opin Clin Nutr Metab Care, 3, 433–8. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (1998). Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin and choline. National Academy Press, Washington, DC. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (2000). Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids. National Academy Press, Washington, DC. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (2001). Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, sil- icon, vanadium and zinc. National Academy Press, Washington, DC. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (2001). Dietary reference intakes for calcium and vitamin D. National Academy Press, Washington, DC. Tahiliani AG, Beinlich CJ (1991). Pantothenic acid in health and dis- ease. Vitam Horm, 46, 165–228. Tucker JM, Townsend DM (2005). Alpha-tocopheropl: roles in preven- tion and therapy of human disease. Biomed Pharmacother, 59, 380–7.

Vallerand IA, Lewinson RT, Farris MS, et al. (2018). Efficiency and adverse events of oral isotretinoin for acne: a systematic review.
Br J Dermatol, 178, 76–85. Various authors (1999). Symposium proceedings: nutrition, biochemistry and molecular biology of biotin. J Nutr, 129, 476s–503s. Wagner KH, Kamal-Eldin A, Elmadfa I (2004). Gamma-tocopherol- an underestimated vitamin? Ann Nutr Metab, 48, 169–88. Wang S (2009). Epidemiology of vitamin D in health and disease. Nutr Res Rev, 22, 188–203. Wang ZY, Chen Z (2000). Differentiation and apoptosis induction theraphy in acute promyelocytic leukaemia. Lancet Oncology, 1, 101–6. Wilson MP, Plecko B, Mills PB, Clayton PT (2019). Diseases affecting Vitamin B6 metabolism. J Inherit Metab Dis, 42, 629–641. Ziegler M (2000). New functions of a long-known molecule. Emerging roles of NAD in cellular signaling. Eur J Biochem, 267, 1550–64. Zubaran C, Fernandes JG, Rodnight R (1997). Wernicke-Korsakoff syndrome. Postgrad Med J, 73, 27–31.

11.3 Minerals and trace elements 1871

11.3 Minerals and trace elements 1871

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, Cu^{1+}, and predominant cupric, Cu^{2+}) 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.
FURTHER READING Clayton PT (2017). Inherited disorders of transition metal metab- olism: an update. J. Inherit Metab Dis, 40, 519–29. European Food Safety Authority (2017). Dietary Reference Values for Nutrients Summary report. https://www.efsa.europa.eu/en/ supporting/pub/e15121

Ferreira CR, Gahl WA (2017). Disorders of metal metabolism.
Transl Sci Rare Dis, 2(3–4), 101–39. Institute of Medicine (2006). Dietary Reference Intakes—the essen- tial guide to nutrient requirements. The National Academies Press, Washington, DC. http://iom.nationalacademies.org/reports/2006/ dietary-reference-intakes-essential-guide-nutrient-requirements.aspx Institute of Medicine. http://iom.nationalacademies.org/Reports.aspx?searchQuery=DRI Institute of Medicine. http://nationalacademies.org/hmd/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx Kumar N (2006). Copper deficiency myelopathy (Human Swayback). Mayo Clinic Proceedings, 81, 1371–84. Livingstone C (2018). Manganese provision in parenteral nutrition: an update. Nutrition and Clinical Practice, 33, 404–8. Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy (1991). Report on Health and Social Subjects 41. Dietary reference values for food energy and nutrients for the United Kingdom. HMSO, London. SACN updates and position statements. https://www.gov.uk/government/collections/sacn-reports-and-position-statements Tuschl K, Clayton PT, Gospe SM Jr, Mills PB (2017). Dystonia/ Parkinsonism, Hypermanganesemia, Polycythemia, and Chronic Liver Disease. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A (eds). GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle. Yao Y, Pei F, Kang P (2011). Selenium, iodine, and the relation with Kashin-Beck disease. Nutrition, 27(11-12), 1095–100.

11.4 Severe malnutrition 1880

11.4 Severe malnutrition 1880

ESSENTIALS Severe malnutrition is the consequence of systemic deficiency of energy and nutrients over a prolonged period: in children de- velopment is stunted and the individual is at risk of fatal (often clinically ‘silent’) infection and other illnesses. It is a medical and societal emergency: mortality is high, despite attempts to provide appropriate care. When severe malnutrition affects several individuals in a society, it reflects a state in which basic needs and justice are not met. Severe malnutrition may also result from clinical disorders affecting a single person with gastrointestinal disease, poor appetite, or reduced food intake for other reasons. Classification The World Health Organization has produced guidelines for facility- based care of patients suffering severe malnutrition. Prompt clas- sification into groups of differential risk assists in the identification of those requiring the most immediate clinical care (severe acute malnutrition, defined as weight for height more than three standard deviations below the reference mean, a mid upper-arm circumfer- ence of less than 115 mm, or the presence of oedema of both feet) and in monitoring the outcomes of intervention. Low height for age indicates long-term malnutrition or poor health (stunting); low weight for height or low mid upper-arm circumference indicate re- cent or continuing severe weight loss (wasting); low weight for age implies stunting and/or wasting. Prevention Malnutrition is a preventable condition and the early identification of those at risk (e.g. by regular weighing) and the implementation of interventions (e.g. advice and demonstration of best practice in child care and feeding) which correct underlying problems and pre- vent further deterioration is central to strategies for effective care. Childhood malnutrition is a clinical problem for the individual, but also a symptom of ineffective public health policy. Aside from feeding, important aspects are to recognize and treat infection, immunize against infection, enhance the child-rearing skills of the parents, and strengthen general hygienic practices, especially for water and sanitation. Severe acute malnutrition Severe malnutrition results from the interaction of three distinct but related processes: (1) reductive adaptation, which is a general response to preserve essential function that takes place when the demands of the body for energy and nutrients are not adequately met; (2) inflammatory/immune responses and healing, which are impaired as a result of reductive adaptations; (3) specific nutrient deficiencies, when failure because of marginal diet to correct exces- sive losses of nutrients (e.g. through diarrhoea and vomiting) leads to major imbalances. These combine to put the child at risk of the deadly triad of infection, hypothermia,

and hypoglycaemia, often compounded by marked fluid and electrolyte disturbances. Sick malnourished individuals have no appetite for food, with loss of appetite being an important protective mechanism against consuming food which is likely to stress the systems of the body. Attempts (well meaning) to force feed are dangerous: the poten- tially fatal ‘recovery syndrome’ (manifest as heart failure, progressing to circulatory collapse, often with severe secretory diarrhoea) must be avoided. Aside from the provision of a sympathetic and quiet environment during treatment, key aspects of management in- clude: (1) resuscitation—management of infection, fluid, and electro- lyte imbalances, and shock, also treatment of vitamin A deficiency; (2) stabilization—give small frequent meals (every 3–4 h throughout 24 h; 100 kcal/kg per day; 1–1.5 g protein/kg per day), add specific nutrients to food to correct deficiency (potassium, magnesium, folic acid, zinc, copper, multivitamin), treat infections, transfuse for se- vere anaemia, treat skin lesions, exclude tuberculosis; (3) weight gain (rapid catch-up growth)—ad libitum intake, continue with micronu- trient supplements, add supplemental iron. Introduction Severe malnutrition occurs in societies that are not able to meet basic needs for healthcare and survival. It is characterized by under- development, poverty and deprivation, an insanitary environment, frequent infections, and food that is poor in quality or limited in availability. A series of vicious cycles operate within individuals and across generations, limiting the ability of vulnerable groups, families, 11.4 Severe malnutrition Alan A. Jackson

 and individuals to cope with the harsh realities of a hostile environ- ment, either through the exigencies of nature or a human unwill- ingness to share the available resources with greater equity. Across the globe, severe malnutrition is a common condition during child- hood. It is most prevalent among the poorest in developing coun- tries, but it is also found with uncomfortable frequency among the most deprived of every society, including those in Europe and North America. It is a frequent aspect of clinical medicine in patients who, for any reason, have a loss of appetite or a reduction in food intake. The same principles of management and care apply wherever the problem is found. Malnutrition at any age impairs the ability to perform and function. Children with severe malnutrition are at risk of life- threatening diseases, which require urgent attention. More in- sidiously, malnutrition during childhood stunts development and leaves a scar that remains for the rest of that person’s life. This lost potential can express itself as an increased risk of ill health, as im- paired intellectual development leading to poor school perform- ance, or in limited physical development leading to poorer work performance. Once part of an individual’s potential for develop- ment has been lost, the clinical and social implications tend to be cumulative. On a global scale, the sum total of the loss of indi- vidual capability represents a fundamental brake on aspirations for social and economic development. Most recent estimates indicate that globally, 45% of the disease burden for children under 5 years of age can be attributed directly or indirectly to malnutrition, at least 3 million deaths and 6% of total global disability-adjusted life years (DALYs). This burden is not spread evenly between different parts of the world. For the worst-affected countries, as many as 50% of children under 5 have malnutrition, which is severe enough to threaten life, with the highest prevalence in sub-Saharan Africa and the greatest numbers in Southeast Asia. This is representative of the day-to-day situation, and is not a peculiarity of special emer- gencies. There are at least 150 million children in the world for whom severe deprivation, indexed as stunting or survival on less than $2/day, has limited their potential for normal physical and neurocognitive development. Notwithstanding the large number of children with severe mal- nutrition, over the past 20 years there has been a shift to the right of the curve for the distribution of the height and weight of children, indicating a general success for specific

interventions. Thus, change is possible, and when suitable measures are put in place sustained improvement can be achieved. However, there is absolutely no basis for complacency, as recent figures suggest a slowing down, or even a reversal, of this improvement. This may relate to an inability to con- trol infections effectively, with tuberculosis, malaria, and diarrhoea continuing to play a major role and the HIV epidemic making a sig- nificant contribution. The world's population continues to increase, so an improvement in percentage terms does not necessarily mean a decrease in the absolute numbers of malnourished people across the globe. Severe malnutrition is a late stage in a process where an individual has had inadequate access to sufficient energy and nutrients for a period of time. During this time, the function of the body changes until a point is reached where severely malnourished children are significantly different from normal children in their response to medical treatment. This stage differentiates those who might be readily treated in a community setting from those who require more skilled care in a facility. If this group is treated in the same way as normal children, they will very likely die. Based upon best practice, mortality would be expected to be around 5 to 10%, but in many centres, case mortality has remained unchanged for 50 years, around 40 to 50%. Sometimes, this can be attributed to poor case management, with four major errors in care occurring in about 80% of centres (Table 11.4.1). However, frequently, the organization of systems of care is poor or the availability of simple, basic resources are limited or insecure. The World Health Organization (WHO) has produced guidelines for community and facility-based care with effective facility-based treatment using a 10-step approach (Fig. 11.4.1). During the early period of care, the order in which different aspects of treatment are carried out is critical for a successful outcome. A central feature is that, as a first step, the body's cellular machinery has to be repaired Table 11.4.1 The case mortality for complicated severe malnutrition has failed to improve because of four major errors of management 1. The assumption that a low plasma albumin concentration is the basis of oedema and can be effectively treated with a high-protein diet 2. The use of diuretics for the treatment of oedema 3. Early use of iron supplements to treat anaemia 4. Failing to differentiate that the acute illness should be managed before any attempts to correct weight loss From Schofield C and Ashworth A (1996). Why have mortality rates for severe malnutrition remained so high? Bulletin of the World Health Organization, 74, 223–9. Activity Treat or prevent: hypoglycaemia hypothermia dehydration Treat Infection Correct electrolyte imbalance Correct micronutrient deficiencies Begin feeding Increase feeding to recover lost weight ('catch-up growth') Stimulate emotional and sensorial development Prepare for discharge Follow-up Initial treatment Rehabilitation weeks 7–26 weeks 2–6 days 3–7 days 1–2 with iron without iron Fig. 11.4.1 WHO recommendations for the 10-step approach to the management of severe malnutrition.

SECTION 11 Nutrition 1882 if function is to be restored. Silent infections are common. There have been unusual losses of nutrients from the body, which cannot be corrected adequately on a standard diet. The damaged systems of the body are not able to cope with excess energy or further stress. Effective treatment requires the ordered correction of the underlying problems before any attempts are made to correct the tissue deficits. Clinical syndromes Severe malnutrition can present with an array of clinical symptoms and signs, which depend upon the duration of the illness, the extent of coinfection, the particular pattern of nutrient deficiencies and metabolic disturbances, and other associated complications such as diarrhoea and vomiting with attendant disturbances in fluid and electrolytes (Table 11.4.2). All descriptions of the condition empha- size one or other feature of the presentation. The archetypal descrip- tive terms for childhood malnutrition—kwashiorkor, marasmus, or marasmic kwashiorkor—were originally used to

characterize clin- ical syndromes. The first description of the kwashiorkor syndrome emphasized the development, location, and timing of the skin lesion, with pro- gression from friable hyperpigmented skin, which stripped to re- veal hypopigmented skin, which ulcerated easily to provide a ready portal for infection—lesions distinct from pellagra. Other features such as abnormal affect and hepatomegaly were noted, but were less remarkable. Placing emphasis upon variability in clinical presenta- tion has made comparison difficult and encouraged the idea that the underlying pathophysiology, and hence its treatment, differs in important ways between locations. This has diverted attention from similarities in the fundamental changes that take place across the range of clinical presentations. The function of the body is controlled through the integration of many systems. A fault in any one has implications for the function of all the others. Thus, there is the need for adequate amounts of energy, energy-generating nutrients (carbohydrate, lipid, and pro- tein), minerals, and a range of micronutrients for the body to func- tion effectively in a harmonized way. Lack of any one component, or an imbalance, leads to deranged handling of other components. By adopting an agreed classification, relevant comparisons have been drawn, and it is clear that the range of clinical features represent varying manifestations of a clinical disorder with the interaction of qualitative and quantitative factors. The quantitative change results from an inadequate intake of food and leads to a wasting syndrome, classically marasmus, with the progressive loss of tissue, especially marked for subcutaneous fat and muscle. The result is a thin ap- pearance, with pinched features, thin arms and legs, and a scaphoid abdomen. Qualitative changes are usually associated with unusual losses of nutrients from the body, for example, through diarrhoea or infection, reordered metabolism to deal with metabolic stress, or the toxic effects of a range of noxious exposures. The end result of this process is likely to be the loss of cellular integrity and control, leading to oedema. Classification An effective classification differentiates those at greatest risk, guides suitable interventions, and helps determine the extent to which interventions have successfully corrected the problem. The more severely malnourished an individual, the greater the risk of com- plications, and the risk of an adverse outcome is related to the se- verity of the weight deficit or the extent to which normal function is deranged. The term ‘severe acute malnutrition’ (SAM) has been introduced to differentiate those who are in need of immediate clin- ical care associated with wasting, from the more chronic problems associated with stunting. These changes can all be marked either quantitatively or qualitatively. SAM is defined as severe wasting (a score of less than –3 standard deviations weight for height, or on screening a mid upper-arm circumference of less than 115 mm), or the presence of oedema of both feet, or clinical signs of severe malnutrition (Table 11.4.3). Recently, WHO/UNICEF introduced guidance on the identification of severe malnutrition and the use in practice of the new WHO growth standards for infants and children from 6 months to 5 years of age. Quantitative measures indicate the extent to which the expected pattern of growth in height and weight has not been achieved: low height for age, low weight for height, and low weight for age. Low height for age (shortness or stunting) is indicative of longer-term malnutrition or poor health. Low weight for height (thinness or wasting) implies recent or continuing current severe weight loss. Low weight for age (insufficient weight relative to age) implies stunting and/or wasting. Weight is more easily measured than height, and assessing weight for age is the simplest way of excluding severe malnutrition in the absence of oedema. Weight for age is in- fluenced by both height for age and weight for height. Where de- privation is common, there is a high prevalence of low height for age. Weight for age is more strongly influenced by stunting than by wasting, and requires broader public health approaches for its al- leviation, being unlikely to respond in the short term to aggressive Table 11.4.2 Important clinical features to enable immediate clinical decisions for emergency management of severe

malnutrition Feature Details/relevance Anthropometry Stunting, wasting, presence of pitting oedema Gastrointestinal History of anorexia, poor appetite, vomiting, diarrhoea. Appearance of mouth. Distended or scaphoid abdomen, with succussion splash Liver Degree of enlargement, jaundice, petechiae Cardiovascular Circulatory collapse, anaemia, shock (depleted intravascular volume, cold hands and feet, weak radial pulse, diminished consciousness) ± signs of 'dehydration' (sunken eyes, sunken fontanelle, decreased skin turgor) Infection Hypothermia, fever, localizing signs (respiratory distress, broken skin, mouth, ears) Specific deficiencies Eye signs of xerophthalmia, vitamin A

11.4 Severe malnutrition 1883 clinical intervention. Around one-third of stunting is present at birth, but the prevalence starts to increase at around 3 months of age, and the progression of stunting slows down at around 3 years of age, after which mean heights run below but parallel to the reference. Weight for height has the advantage that it can be used when age is not known reliably and suggests recent severe weight loss, indicating those children who are most likely to benefit from im- mediate aggressive nutritional intervention and support. The rate at which weight improves is used to assess progress during recovery, and success of care is indicated by the achievement of a weight that is appropriate for the individual's height. The measurement of mid upper-arm circumference provides simple, robust indication of the degree of wasting in this age group and is recommended in screening for SAM. In places where SAM is common there is the need to differentiate those who can be effectively and reliably managed by super- vised care in the community, and those who require the level of care that can only be provided in a facility. This differentiation is made using qualitative criteria on the basis of appetite, the presence of oe- dema, or other identifiable serious comorbidity. Qualitative criteria are more difficult, because of their variability and uncertainty about whether they mark any particular pathophysiological process. It has been agreed that the presence of pitting oedema is the archetype of qualitative change, identified as kwashiorkor in the Wellcome classi- fication and now called oedematous malnutrition. In milder forms, oedema might be restricted to the limbs, but in more severe forms it embraces the entire body. Obtaining a reliable measure of body weight is difficult in the presence of oedema, because of the uncer- tain contribution of oedematous fluid. The overall appearance might be of a child who superficially appears full, but has evident wasting below the oedema when examined carefully with the clothes re- moved. The extent of poor appetite or anorexia may be elicited by history, but a formal appetite test should be carried out if there is any uncertainty. Multiple infection is common and often silent, so that specific sites of infection may be difficult to identify or localize. A high index of suspicion is required for the presence of silent infections, which should be presumed to be present. Infection is not part of the diag- nostic criteria. Natural history and clinical presentation Inadequate nutrition slows the pace of growth and development and the greater the severity of the limitation or insult, or the longer its duration, the greater the difference between the achieved development and that expected. The stress of an insult of greater se- verity evokes a metabolic response that is associated with a loss of body weight and a reordering of function, so that resources and effort devoted to growth and development are diverted to maintain the integrity of the individual. The nutritional health of the infant is critically determined by how well prepared the mother was to carry the pregnancy, and the effectiveness with which breastfeeding is established and maintained. During pregnancy and for the first months of life, the infant is totally dependent upon the mother for its nutrient supply. During early pregnancy, there is the elaboration of structure in the embryo and maturation of function in the fetus. The last trimester is of critical importance as it is when the fetus accumulates effective reserves of nutrients, helping survival and

facilitating development during the first year of life. The fetus ac- cumulates reserves of energy, as subcutaneous lipid, and of min- erals and vitamins, such as iron, zinc, copper, vitamin A, riboflavin, and pyridoxine, in liver and muscle. At birth, the relative protection of the intrauterine environment is replaced by the many hazards of the external world. Gastrointestinal and respiratory infections are among the serious dangers to survival, and breastfeeding pro- vides effective protection from both. Even in affluent societies, breastfeeding provides the infant with a level of protection against ill health that identifies effective breastfeeding as a singularly im- portant feature in any rational policy in public health nutrition. There is a massive increase in the risk of ill health for infants who are not breastfed during the early months of life. This risk is mag- nified enormously for infants exposed to unsanitary environments with limited access to healthcare. Anything that limits the growth of the fetus, impairs its development, or causes it to be delivered early will limit its ability to cope with extrauterine life, and increase the risk of problems, infections, and malnutrition. There is en- hanced mother–infant bonding and emotional development with breastfeeding, and other special benefits include the remarkable bio- availability of energy and nutrients, the presence of nonnutritional factors, protective factors, and growth factors. Screening: Identification and prevention Malnutrition is a preventable condition, and the early identification of those at risk and the implementation of interventions that correct underlying problems and prevent further deterioration are central to strategies for effective care. Early growth failure can be detected by regular weighing, as an integral part of immunization and other health programmes. A series of plotted weights is most valuable, and intervention is required for those whose weight crosses two Table 11.4.3 Classification of malnutrition. The diagnoses are not mutually exclusive Moderate malnutrition Severe malnutrition Symmetrical oedema No Yes (oedematous malnutrition)a Weight for height SD score between –3 and –2b (70–79%)c SD score below –3 (<70%) (severe wasting)d Height for age SD score between –3 and –2 (85–89%) SD score below –3 (<85%) (severe stunting) Mid upper-arm circumference Below 125 mm Below 115 mm a This includes kwashiorkor and marasmic kwashiorkor in older classifications. To avoid confusion with the clinical syndrome of kwashiorkor, which includes other features, the term ‘oedematous malnutrition’ is preferred. b Below the WHO growth standard; the SD score is defined as the deviation of the value for the individual from the median value for the reference population, divided by the standard deviation of the reference population. c Percentage of the median WHO growth standard. d This corresponds to marasmus (without oedema) in the Wellcome clinical classification, and to grade III malnutrition in the Gomez system. To avoid confusion the term severe wasting is preferred.

 growth centiles on successive measurements. If measurements are only available for a single time point, then height for age, weight for height, or mid upper-arm circumference provides an indication of any past or ongoing growth failure. Advice and demonstration of best practice in child care and feeding may be sufficient to cor- rect a mild degree of growth failure, but persistent or more severe growth failure requires closer investigation to exclude underlying problems. Poor anthropometry, with a history of poor appetite and weight loss, should always be taken very seriously and pursued until a cause has been identified and corrected. Severe malnutrition is a medical emergency. Childhood malnutrition is a clinical problem for the individual, but is also a symptom of ineffective public health policy. Targeted interventions should address the immediate needs of the child, but should also embrace broader considerations. For the child, there is the need to effectively immunize against infection, recognize and treat infection in a timely way, and ensure an effective period of nu- tritional support following infection. For the family, there is the need to enhance the child-rearing skills of the parents, create a stimu-

lating environment, acquire and practice simple skills in hygiene and food preparation, and strengthen family dynamics and coping strategies. For the community, there is the need to improve the eco- nomic base of households, increase food purchasing power, increase food security or household food availability, and treat specific nu- trient deficiencies. Sound hygienic practices have to be strengthened at the group or household level, and where necessary, the amount and quality of water and the safe and effective removal of solid waste improved. Each activity can exert a beneficial effect on growth and development. Any one might be relatively easy to introduce, but the real difficulty is to ensure that all are sustained. The need is for a fun- damental change in the health culture and the creation of a frame- work of behaviour in which development activities become rooted and take place as a matter of course. A failure to establish and main- tain an effective system of healthcare leads to a progressive deteri- oration in the clinical state of the most vulnerable infants, leading eventually to severe malnutrition. The World Bank has identified the severe limitation this places on national development, and the need to have effective interventions before 2 years of age if this critical po- tential is not to be lost. Aetiology and pathophysiology Children may become malnourished simply because there is not enough food available. Community-based interventions place em- phasis on providing adequate amounts of food of high nutritional value, if necessary as ready-to-use therapeutic-foods, but sick mal- nourished individuals have no appetite for food. It seems paradox- ical that a child who has obviously lost weight and needs to eat may refuse food even when it is readily available. If food is forced, there is the possibility that the child will become worse, or even die. In managing severe malnutrition, appetite is one of the most important symptoms. A loss of appetite is an important protective mechanism against consuming food, which is likely to stress the systems of the body. In experimental studies, there are two major biological reasons why appetite is lost: a deficiency of a specific nutrient and infection. Severe malnutrition is a disorder that results from the interaction of three distinct but related processes, each of which appears to be related directly to the food consumed, but none of which can be easily understood simply by a consideration of food: • reductive adaptation • inflammatory and immune responses • specific nutrient deficiencies Food helps meet the many needs for normal function, growth, and development in childhood, but also the ability to cope with environ- mental challenge. A diet that is adequate, but marginal under normal circumstances, is inadequate for the increased demands during re- covery from frequent intercurrent illness with the double burden of the need to catch-up growth and to make good the unusual losses of nutrients during the infective episode itself. The time available for successful convalescence before the next bout of infection is too short to adequately make up the deficit. Reductive adaptation: Failure to meet the body’s usual demands for macronutrients Reductive adaptation takes place when the demands of the body for energy and nutrients are not adequately met by the dietary intake. The general features are similar, regardless of the basis for the inadequate intake. It is a general response to preserve essential function, but car- ries a cost. Normal metabolism takes place within a highly regulated environment, through the control and integration of exchange and turnover among cells and tissues. For the cellular machinery of the body to remain functionally intact and operationally effective, it re- quires a constant supply of energy and other nutrients. An estimated one-third of resting energy expenditure may be consumed through the synthesis and degradation of macromolecules such as protein, and a further one-third is associated with the movement of material across membranes (e.g. through the pumping activity of the sodium/ potassium pump, Na+,K+-ATPase). These processes represent the in- ternal work of the body at cellular level and underlie the functioning of all the organs and tissues. They take place continuously, and the total activity can be measured as energy

expenditure. As food con- sumption is intermittent, the processes are independent of the im- mediate food intake. However, a sustained lack of food leads to progressive impairment of the cellular machinery as damage due to the wear and tear of normal use can no longer be replaced effectively. Structure When food consumption is significantly reduced, metabolic pro- cesses continue to enable the body to function, and the energy to support these processes is derived from reserves within the body. The body is in negative energy balance, and tissue mass cannot be maintained, leading to loss in weight. The losses are uneven between tissues, with major losses in subcutaneous fat and muscle, and rela- tive preservation of the metabolically more active visceral tissues. One important consequence is that heat generated by muscle is reduced, and at the same time, insulation in the skin is impaired leading to greater heat loss. The altered body composition under- lies all anthropometric methods that are used to assess nutritional status. In addition to the changes in mass, efficiencies in the utiliza- tion of energy have to be found. Function Efficiencies are achieved by reducing the amount of work carried out by the body. External work is reduced by decreasing physical

 activity. Internal work is reduced by decreasing cellular metabolic activity, with subsequent effects upon tissue function. Significant efficiencies might be achieved for the major energy-consuming processes such as membrane pumping, protein turnover, and cel- lular replication. The relative distribution of potassium in the intra- cellular space and sodium in the extracellular space is fundamental to maintaining the chemical environment of cells. As potassium tends to leak out of the cell and sodium tends to leak into the cell, for the cell membrane to maintain the effective partitioning of elec- trolytes requires that sodium is pumped out of the cell in exchange for potassium, consuming ATP. The cell membrane tends to be- come more ‘leaky’ in malnutrition as its lipid composition changes, and the Na+,K+-ATPase is down-regulated as one way in which to reduce energy expenditure. Therefore, compared with normal, all people with malnutrition have reduced intracellular potassium and increased intracellular sodium, hence decreased total body potas- sium and increased total body sodium, which is not necessarily identified on standard biochemical tests. The ability to maintain protein synthesis is fundamental but energetically expensive; en- ergetic efficiency requires a reduction in protein synthesis, which is not divided equally among tissues. Liver normally accounts for about 25% of protein synthesis, with the synthesis of nutrient trans- port proteins playing a critical role in the delivery of lipid, minerals, and vitamins to the other tissues. Reduced synthesis of nutrient transport proteins may save energy, but at the cost of reduced de- livery to peripheral tissues (e.g. limited synthesis of apolipoproteins limits the delivery of lipid to peripheral tissues and enhances the accumulation of lipid in liver). Cellular replication is energetic- ally demanding, requiring the ready availability of all nutrients. A reduction in cellular replication provides efficiencies in energy and nutrient use but impairs the function of systems critically de- pendent upon cellular replication: the skin, gastrointestinal tract, respiratory tract, and immune system. Functional and metabolic cost of reductive adaptation The function of the cells in all tissues is affected by reductive adap- tation. With relative protection of more vital functions, the cost is a reduction in those functions that are not immediately vital, but which provide the functional reserve capability that enables the metabolic flexibility to respond to a changed internal environment or a challenge from the external environment. As a consequence, changes that would be readily managed in the normal state present a metabolic stress in the reductively adapted state. What would nor- mally be a modest challenge can induce a major metabolic perturb- ation. Reductive adaptation represents the loss of reserve capacity, which leads to increased metabolic brittleness and vulnerability. The cellular

machinery is no longer capable of responding effect- ively to the usual challenges. There is a change in the function of all systems. Gastrointestinal tract There is loss of mucosa and submucosal tissues, loss of gastric acidity, and a reduced capacity for digestion and absorption. This leads to impaired bioavailability of nutrients from food, decreased transit time, and predisposition to small bowel bacterial overgrowth. An impaired ability to repair and maintain the integrity of the endo- thelium predisposes to bacterial translocation and overexposure to endotoxins. Skin The skin wastes, loses its ability to retain heat, and readily becomes breached and infected. Immune system There is increased exposure to pathogens and a decreased capacity to respond (inflammation and immune response—see following paragraphs). Liver There is downregulation of synthetic and excretory processes. The reduced functional reserve makes it more difficult to maintain glucose homeostasis in the face of increased bacterial exposure. Intermediary metabolism is impaired, and transport proteins for the delivery of lipid, vitamins, and minerals to other parts of the body are reduced. The formation of clotting factors is impaired. Reduced bile and bile salt formation affect digestion. Metabolism and clear- ance of drugs, toxins, and xenobiotics is also reduced. Cardiovascular system A reduction in the functional reserve of the heart, slower pulse, and increased circulation time make heart failure more likely if excess fluid is given intravenously. There is poor circulatory control, with a tendency to reduced intravascular volume with an expanded inter- stitial fluid space. Iron is an integral part of haemoglobin in red blood cells, involved in the transport of oxygen from the lungs to the tissues. The mass of red cells is related to the amount of oxygen that has to be trans- ported, which, in turn, relates to the mass of active lean tissue. As part of reductive adaptation, there is a decrease in the lean tissue of the body with an associated decrease in the red cell mass. The iron that is released from haemoglobin is not required immediately for the formation of more red cells. The level of iron in the body is controlled by the rate at which it is absorbed from the gastrointes- tinal tract, as, once in the body, there are no recognized mechan- isms through which iron can be lost. The iron released from red cells therefore cannot be excreted and is placed into storage. Free iron is highly reactive and acts as a focus for uncontrolled excess generation of free radicals, thereby damaging other cellular components. Excess iron is stored in the liver, bound to ferritin. A demand for ferritin synthesis is energetically expensive and diverts amino acids from the formation of other proteins. As part of reductive adaptation, the ability to effectively sequester iron in a chemically quiescent state is impaired. Renal There is decreased functional capacity of the kidney, with an im- paired ability to concentrate, dilute, or acidify urine. Muscle Muscle mass is reduced, and muscle function impaired by reduced potassium, which together lead to reduced generation of heat. Brain Brain function is relatively well preserved. Nevertheless, there is blunting of higher functions with decreased mentation, apathy, and depression, and impaired control of hormonal and integrative re- sponses. There is a decrease in activity, poor work performance, and

 a decrease in discretionary activities, which together contribute to a slowing of learning. Infection: The inflammatory and immune responses Survival in a potentially hostile world requires effective nonspecific and specific defence mechanisms. Nonspecific physical barriers (skin and mucous membranes) and chemical protection (gastric acidity, secretions such as tears and mucins) depend upon cellular replication, which is less well maintained during reductive adapta- tion, and even minor damage leads to a breach that is not repaired. Local damage with bacterial invasion usually elicits local inflamma- tion, a systemic or acute-phase response, and a specific immune re- sponse. The mounting, coordination, and regulation of an effective response require energy, increased cellular replication, and pro- tein synthesis. The changes in hormones

and cytokines associated with reductive adaptation impair the establishment and control of normal inflammatory and immune responses. The localized signs of tissue damage or infection—enlarged lymph nodes, enlargement of the spleen or liver, and the normal features of the acute-phase response (fever, rapid pulse, and respiration)—are blunted or lost in malnutrition, making diagnosis more difficult. Loss of appetite is a central feature of a more severe acute-phase response, as the body raids its own tissues for the nutrients it re- quires to satisfy this unusual demand. There is a shift from the usual pattern of protein synthesis, with less emphasis on growth. As muscle wastes, the amino acids are made available for the syn- thesis of proteins for the immune system, and the liver shifts from synthesizing large amounts of nutrient transport proteins to the for- mation of acute-phase response proteins, which limit cell damage and help repair. Intravascular albumin is redistributed to the third space, leading to a reduced plasma albumin concentration. A low plasma albumin is frequently seen in malnourished people and is indicative of ongoing infection rather a dietary deficiency of protein. Correcting the problem requires that the underlying infection be effectively treated, not that dietary protein be increased. The cells of the inflammatory and immune systems increase their utilization of glucose, with increased gluconeogenesis from amino acids.
A feature of the acute-phase response is a profound change in the handling of micronutrients. There is a block in the absorption of iron. Net tissue breakdown releases components for which there is no immediate use. The circulating concentrations may be reduced (iron and zinc, which are sequestered in the liver), or increased (copper), and there may be increased losses from the body in urine or stools (zinc and vitamin A). In childhood, diarrhoea is a frequent accompaniment of infection, which adds an excessive loss of nutrients from the body, especially potassium, magnesium, zinc, and vitamin A. Specific nutrient deficiencies Deficiency of specific nutrients is the most difficult aspect of severe malnutrition to manage effectively. Whereas in classical deficiency states, inadequate dietary intake is usually the major underlying cause, in severe malnutrition, it is the failure to correct excessive losses of nu- trients, which leads to major imbalances. Major losses of intracellular nutrients can be difficult to identify reliably, for three reasons: • Losses of intracellular content may not be readily identified using standard biochemical tests on blood (e.g. potassium). • Bone acts as a very effective buffer for many nutrients and there- fore severe total body depletion can develop without obvious bio- chemical change or loss of function (e.g. magnesium). • During an inflammatory response, redistribution of nutrients within the body makes standard tests for nutrient deficiency very difficult to interpret (e.g. vitamin A, zinc, or iron).
Infection causes an unbalanced loss of nutrients, which may be ob- vious in association with diarrhoea and vomiting, or may be more subtle as in the increased urinary losses of vitamin A and zinc which are an integral feature of the acute-phase response. For an individual consuming a diet that is marginal in one or other nutrient, increased losses may make the critical difference to achieving balance, which cannot be restored unless additional nutrients are provided during the convalescent period. All cellular functions are likely to be af- fected to a greater or lesser degree by specific deficiencies, but one process that is of special importance is the ability to cope with free radicals or oxidation-induced cell damage. Antioxidant protection In severe malnutrition, there is a major imbalance between the po- tential for damage induced by free radicals and protective antioxi- dant systems. Infection, oxidative burst, and free iron all contribute to an increased potential for damage. Mortality is greatest in those with an obvious impairment of the antioxidant defences. Children with oedematous malnutrition have severely reduced concentra- tions of glutathione in blood, and mortality is highest in those with impaired activity of glutathione peroxidase. Although the pattern varies with location, deficiencies of micronutrients are common and result in impaired cell function and membrane damage. The many layers of antioxidant

protection, which are specific for each compart- ment of the cell, provide a measure of safety. However, the system is potentially vulnerable to deficiencies or limitations in multiple micronutrients (e.g. niacin, folate, thiamine, riboflavin, cobalamin, ascorbic acid, carotenoids, tocopherol, selenium, zinc, copper, mag- nesium). A deficiency might not be readily identifiable, either clin- ically or biochemically, and a high index of suspicion is required. Oedema Oedema reflects an inability to maintain the correct distribution of fluid in the intracellular space, the vascular space, and the inter- stitial space, and is a final common pathway representing a loss of metabolic control. Incorrect approaches to the management of oedema—the use of diuretics or of high-protein diets—are among the commonest reasons for increased mortality. The rationale be- hind the incorrect approach to management presumes that oedema is simply the consequence of hypoalbuminaemia, itself the result of inadequate dietary protein. There are profound perturbations of protein metabolism in kwashiorkor, but these are due to concurrent infection, loss of appetite, and increased losses of nitrogen in stools rather than a diet deficient in protein. A low plasma albumin usu- ally indicates an acute-phase response to an unrecognized infection. Treatment with a high-protein diet or infusions of albumin does not correct the oedema, but does increase mortality. A low plasma con- centration of albumin might contribute to formation of oedema, but is seldom the sole or primary cause. Although diuretics exert a direct effect on cell membranes, giving a diuretic is less likely to be effective if the intravascular space is reduced. Diuretics that lead to increased

 urinary losses of potassium make the underlying problem of a defi- ciency of body potassium even worse. The normal distribution of water between the different body com- partments is tightly controlled through several interlinked factors. Disruption of one or more of these factors may lead to the develop- ment of oedema, and will need to be corrected for the oedema to be effectively cleared (Table 11.4.4). Potassium deficiency leads to retention of sodium. Altered mem- brane structure and reduced activity of Na+,/K+-ATPase allows intracellular potassium to fall and intracellular sodium to rise. All malnourished individuals should be presumed to be deficient in potassium and to have excess intracellular sodium, regardless of the composition of the plasma measured on routine biochem- istry. Indeed, plasma sodium concentrations might be low and it is tempting to give extra sodium, which is absolutely the wrong thing to do. There is more than enough sodium in the body, but it is in the wrong place. A direct approach that seeks to correct the disordered biochemistry is less likely to succeed than an approach which recognizes that the fundamental problem is disordered cel- lular function. Similar factors lead to cellular damage in any severely undernourished person, and by treating the malnutrition and re- pairing the metabolic machinery of the cells of the body, oedema will be effectively treated. What is required are generous supplements of potassium and correction of the underlying membrane dysfunction, which enables fluid and electrolyte balance to be restored. There is a close metabolic interdependence of potassium and magnesium, both of which are readily lost from the body in diarrhoea. It is ex- tremely difficult to correct potassium deficiency in the presence of an associated magnesium deficiency, or to correct a magnesium deficiency in the face of a potassium deficiency. They have to be cor- rected together. Principles of facility-based care Phases of treatment: The 10 steps (See Fig. 11.4.1 and Table 11.4.5.) One of the important reasons why mortality from malnutrition has not been reduced in many centres is because the primary ob- jective of treatment has been to try to correct the obvious weight deficit. In attempting to replace the lost tissue as soon as possible, generous intakes of food have been provided, encouraged, and even forced. If appetite is poor, or anorexia is a feature, then generous force-feeding by nasogastric tube has

been used. This can be very dangerous. The 10-step approach to treating malnutrition clearly identifies that treatment must be divided into different phases: the cellular machinery has to be repaired before it can be used to enable tissue growth. Two clinical features that are directly related to specific nutrient deficiencies and are particularly difficult to manage are oedema and persistent diarrhoea. Any specific nutrient deficiency impairs cel- lular function and increases the risk of infection. Infection increases nutrient losses through tissue wasting as an intrinsic feature of the acute-phase reaction and as vomitus or diarrhoea. Increased gen- eration of free radicals is part of the body's attempts to deal with infecting organisms, and deficiencies of specific micronutrients dir- ectly impair the ability to cope with free-radical generation. Even if an individual recovers from an infection, nutrients which have been Table 11.4.4 Major factors that contribute to the development of pitting oedema in severe malnutrition Hypoalbuminaemia Associated with impaired protein metabolism, infection or stress, impaired hepatic function, toxic damage Salt and water retention Potassium deficiency, phosphate deficiency, acid–base imbalance, impaired renal function Impaired membrane function Altered composition (phospholipid composition and fatty acid profile). Impaired or downregulation of Na+K+- ATPase. Free-radical-induced damage Table 11.4.5 Outline clinical management of severe malnutrition

1. Resuscitate Manage infection, fluid and electrolyte imbalance and shock: oxygen, glucose, reduce heat loss, give antibiotics, maintain circulation, treat vitamin A deficiency
2. Stabilize Control energy and protein intake at maintenance: 400 kJ/kg/day (100 kcal/kg/day), 1–1.5 g protein/kg/day Small frequent meals: eight meals every 3 h, or six meals every 4 h, throughout 24 h Correct deficiencies of specific nutrients by addition to food: potassium (4 mmol/kg/day), magnesium (0.4 mmol/kg/day), folic acid (1 mg/day), zinc (2 mg/kg/day), copper (0.3 mg/kg/day), multivitamin supplement Treat bacterial infection: broad spectrum antibiotics, cotrimoxazole or ampicillin with gentamycin Treat small bowel overgrowth with metronidazole Treat helminth infections with mebendazole Transfuse for severe anaemia Topical treatment and care for skin lesions Exclude tuberculosis and HIV Give sensory stimulation and emotional support
3. Weight gain (rapid catch-up growth) Ad libitum intake to achieve at least 600 kJ/kg/day (150 kcal/kg/day), 4 g protein/kg/day Continue with micronutrient supplements Add supplemental iron Give sensory stimulation and emotional support

 depleted from the body are not easily replaced. This has two im- portant effects. First, the individual is deficient in a specific nutrient and carries the specific and general features of the deficiency, im- portantly loss of appetite. Secondly, if the deficiency is severe it may be very difficult for it to be corrected by consuming a normal diet without the addition of specific nutrient supplements. Under this circumstance, poor appetite, persistent reductive adaptation, and continued risk of further infection are maintained. If energy is provided in excess of the requirements for mainten- ance, there are few ways in which it can be excreted or handled meta- bolically. Any significant excess is deposited as new tissue, either as cells or as cells filled with fat. There is a considerable underlying drive to form new cells, but in addition to energy this requires the availability of all the nutrients contained within the cell structure. When specific deficiencies have not been corrected individual nu- trients are limiting for cell formation and it is not possible to handle the excess energy through the formation of new tissue. The excess energy creates a very serious metabolic upset (see 'Recovery syn- drome', later). Therefore, during the period when nutrient deficien- cies are being corrected and infections treated, it is important to

give sufficient energy to cover the needs of the body, but not so much that the body is forced to make new tissue. This is the basis for identifying the different phases of treatment: first to repair the machinery and gain control of metabolism by providing only enough energy to satisfy the needs for maintenance, but not enough to drive growth. Managing reductive adaptation, specific nutrient deficiencies, infec- tion, and free-radical-induced membrane and cellular damage lie at the heart of the problems associated with immediate care during the resuscitation period. A loss of appetite is an important protective mechanism limiting food consumption, which is likely to stress the systems of the body. Hence the loss of appetite is a cardinal sign of an underlying meta- bolic problem that is ongoing. If the problem is identified and cor- rected, then appetite is restored very quickly. Severely malnourished children may have a profound loss of appetite due to a combination of infection and deficiencies of specific nutrients, which interact to make the problem worse. Correcting the loss of appetite is central to effective care. The restoration of appetite marks the restoration of metabolic control and is a key component of therapy and a marker of progress. Once the emergency treatment required to resuscitate the child has been completed, the emphasis of care is to treat the underlying problems that are associated with a loss of appetite. Resuscitation Severely malnourished children present a medical emergency be- cause of two sets of problems: the deadly triad of infection, hypo- thermia, and hypoglycaemia, and marked fluid and electrolyte disturbances (Table 11.4.5). The deadly triad: Hypoglycaemia, hypothermia, and infection Brain cells are absolutely dependent upon a regular supply of glucose and oxygen to maintain the availability of ATP. Death occurs within 5 min if the supply of either is impaired, through poor circulation, reduced respiration, or low blood glucose. The glucose required is either made in the liver or taken in the diet. Reductive adaptation limits the capacity for glucose formation and delivery, and a regular dietary supply is required if blood concentrations are to be main- tained. The availability of glucose for the brain can be impaired if there is competition from other tissues or functions (e.g. in order to maintain body temperature or to deal with infection). Malnourished individuals generate less heat and have reduced thermal insulation and therefore cool rapidly when exposed. Any attempt to generate more heat consumes glucose and other energy-providing fuels. A normal effective response to infection is a burst of activity in white blood cells, which places heavy demands on available glucose, com- peting with the brain and leading to hypoglycaemia, and increasing the rate of heat loss leading to hypothermia. Therefore, the triad of hypoglycaemia, hypothermia, and infection indicates a very serious situation in which the body is no longer able to adequately main- tain the supply of glucose to support essential functions. The treat- ment is to increase the supply by giving oral or intravenous glucose, reducing competing demands through decreasing the amount of heat lost, and by effectively treating infections. To deliver glucose and oxygen to the brain effectively requires an adequate circulation, which is compromised by intravascular dehydration. The correction of dehydration is closely associated with the correction of electro- lyte imbalances, with energy homeostasis, and with normal cellular function. Care has to be taken to ensure that each is corrected in concert with the other to ensure that imbalances do not arise. All malnourished individuals are deficient in potassium and carry ex- cess sodium. Specific micronutrients: Vitamin A, zinc, and iron Iron is highly reactive chemically, and fulfils many important func- tions related to the generation of energy for normal cellular function. High reactivity, if not adequately controlled, carries the potential for cell damage. Red cell mass reduces in malnutrition as the lean body mass decreases. The iron is not used for further haemoglobin forma- tion and cannot be excreted, so has to be stored innocuously, as any unbound iron is liable to increase oxidative cell damage. In severe malnutrition, there is increased stored iron and free iron. The avail- able iron is not used for haemoglobin formation, and giving iron

supplements to treat anaemia simply adds to the load, stresses the system further, and increases mortality, especially in the presence of infection such as malaria. Initially, it is more important to repair and restore the capacity to cope with free radicals by improving vitamin and trace element status. Later, when the acute problems have been resolved, the iron will be removed from storage and used to form new tissue. As stored iron is used up, supplemental iron will have to be provided to keep pace with the rate of tissue demand. Blindness and other eye signs of overt vitamin A deficiency are common in many parts of the world. Less obvious changes lead to impaired integrity of mucosal surfaces in the gastrointestinal and respiratory tracts, lowering resistance to gastroenteritis and respira- tory infections. During infection, vitamin A is lost from the body, severe deficiency may develop rapidly, and the eye signs often deteri- orate during early treatment. In areas where vitamin A deficiency is common, a large dose of vitamin A given very early in the treatment is an urgent necessity. Zinc is required for the function of a wide range of enzymes, and a deficiency has widespread effects. A shortage of zinc impairs the rep- lication of cells such as the gut mucosa, leading to further mucosal damage and increased diarrhoea. Zinc deficiency leads to diarrhoea, and diarrhoea leads to zinc deficiency. Similar changes take place in damaged skin leading to ulcerated skin which is readily damaged with mild trauma.

11.4 Severe malnutrition 1889 Persistent diarrhoea Many malnourished children have diarrhoea, which can take time to settle. The diarrhoea may be infective in origin or have an in- fective component, due to viruses, bacteria, fungi, or helminths. However, diarrhoea that has persisted for any time will also have an element due to specific nutrient deficiencies (zinc and vitamin A) or chemical injury (bile salt deconjugation). With continued diar- rhoea, there are ongoing losses of nutrients. Few bacteria exist in the healthy small intestine, but small bowel overgrowth develops readily in malnutrition, due to a combination of gastric achlorhydria, re- duced motility (potassium and magnesium deficiency), leading to bile salt deconjugation, damaged mucosa, and bacterial transloca- tion. For the bowel to repair and re-establish its resistance requires adequate nutrients, especially zinc, vitamin A, and folates. Thus, the effective treatment of chronic diarrhoea requires a three-pronged approach: correction of potassium deficiency, treatment of bacterial overgrowth (with metronidazole), and effective repletion of specific nutrient deficiencies (such as zinc, vitamin A, and folate). Management The objectives of the resuscitation phase are to stabilize vital func- tions, by giving oxygen, supporting respiratory and cardiac func- tions, and correcting fluid imbalance, to ensure that adequate amounts of glucose are delivered to the brain. Body temperature must be maintained by maintaining glucose supply to the system, limiting heat loss through the skin, and starting to control infection. As the capacity for the body to carry out metabolic functions is im- paired, external support has to be supplied regularly on a 24-h cycle. The regular intake of small amounts over 24 h (especially at night) is a very effective way of achieving this (Table 11.4.5). All infections must be treated. Specific nutrient deficiencies must be corrected, but no iron or extra sodium should be provided. The metabolic state must be controlled by limiting the intake of energy and protein to that required to maintain body weight, and ensuring that there is no excess (see following paragraphs). These steps will enable the re- pair of the metabolic machinery and allow cellular function to move towards normal. The response to a successful intervention will be a return of appetite; the patient will feel better, and smile. Recovery syndrome Limited availability of one or more nutrients leads to competition between all cells for the little available. Some nutrients become rela- tively more deficient, upsetting the balanced function between tis- sues, and the clinical signs of a deficiency become more obvious. There is a similar explanation for why the clinical signs of a deficiency are not always apparent, even though the

body might be particularly deficient. During reductive adaptation, the demand for nutrients is decreased, and the signs of a deficiency are masked. Signs of de- ficiency become exposed in rapidly dividing tissues, when the de- mand for nutrients is greatest. Vitamin A and zinc are examples, but the same principles apply to many other nutrients, especially the B vitamins. The recovery or refeeding syndrome develops when indi- viduals who have undergone reductive adaptation are suddenly pro- vided with a relative excess of food. Excess energy drives metabolism while specific nutrient deficiencies are inadequately corrected, and the metabolic machinery is still compromised. The syndrome may vary in its details, but consists of left- and right-sided heart failure associated with an overloaded circulation. This may progress to vas- cular collapse with abdominal distension as the circulating vascular volume is poured into the bowel as profound secretory diarrhoea. The first sign of the onset of the recovery syndrome is an increase in pulse and respiratory rate. If food continues to be consumed at the same rate, the load on the heart will progress to heart failure. This is a medical emergency, and it is vitally important that the food intake is reduced or stopped. If the changes are identified early and are rela- tively mild, then food intake should be reduced. If the condition has advanced and is severe, then it may be necessary to stop all food for 12 to 24 h. The problem will then resolve. Replacing lost weight The ultimate objective of treatment is to replace the lost tissue. Cellular hypertrophy and hyperplasia are critically dependent upon and limited by the available energy and nutrients. For tissue of average composition, the formation of 1 g tissue requires 20 kJ of energy. A normal 1-year-old infant gains 1 g/kg body weight per day, but for catch-up weight gain during recovery from malnutrition, it is possible to form tissue at up to 20 g/kg per day, by consuming an add- itional 400 kJ/kg per day. Achieving this requires an energy-dense diet, which is consumed throughout the 24 h of the day. Energy is necessary but not sufficient for new tissue formation. The nutrients needed for the formation of cell membranes and protoplasm are re- quired in adequate amounts and suitable proportions. As the lean body mass grows it has an increased need for oxygen, and the red blood cell mass increases. Iron is taken out of storage to form new red cells, and eventually these stores are depleted with the need to add supplemental iron to the diet. There is an increased demand for amino acids to meet the needs of new tissue formation. It is safe to allow quite large intakes of protein. As the amino acids are deposited in tissue and do not accumulate in the free form, there is no risk of toxicity. However, meeting the pattern of amino acids required by the body will require the endogenous biosynthesis of relatively large amounts of the ‘nonessential’ amino acids in the body, which in itself will require the generous availability of minerals and vitamins. Important general aspects of care The physical care that is provided to correct the biochemical, meta- bolic, and infective problems is critical for success. However, there is also a need to address the broader needs of the child for healthy development. In part, this is provided by creating a warm, caring environment; in part, by suitably structured activities that provide an appropriate level of stimulation to encourage brain function to recover and develop. All aspects of care need skill and sympathy. The severely mal- nourished child is desperately sick and must be nursed as a crit- ically ill child with minimum physical disturbance. With correct treatment, progress can be very rapid, and it is desirable to involve the parents and siblings, to encourage and demonstrate preferred childcare practices. This will facilitate the transfer between hos- pital and home, and make it more likely that the practices become embedded. Less seriously ill children can be effectively managed as outpatients, using the same principles and approach to the man- agement decisions.

 FURTHER READING Black RE, et al.; Maternal and Child Undernutrition Study Group (2008). Maternal and child undernutrition: global and regional ex- posures and health

consequences. Lancet, 371, 243–60. Black RE, et al.; Maternal and Child Nutrition Study Group (2013). Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet, 382, 427–51. de Onis M, et al. (2007). Comparison of the WHO child growth stand- ards and the CDC 2000 growth charts. J Nutr, 137, 144–8. Grantham-McGregor S, et al. (2007). Developmental potential in the first 5 years for children in developing countries. Lancet, 369, 60–70. Picot J, et al. (2012). The effectiveness of interventions to treat severe acute malnutrition in young children: a systematic review. Health Technol Assess, 16, 1–316. Ricci C, et al. (2018). Determinants of undernutrition prevalence in children aged 0-59 months in sub-Saharan Africa between 2000 and 2015: a report from the world bank database. Public Health Nutr, 11, 1–9. doi: 10.1017/S1368980018003415 UNICEF/WHO/WBG (2015). Levels and trends in child malnutrition. Joint child malnutrition estimates. Key findings of the 2016 edition. UNICEF, WHO, WBG; New York. Valid International (2006). Community-based Therapeutic Care: A Field Manual. https://www.fantaproject.org/sites/default/files/re- sources/CTC-Field-Manual-Oct2006-508.pdf Waterlow JC (2006). Protein-energy malnutrition. Smith-Gordon, London. WHO (1995). Physical status: the use and interpretation of anthropom- etry. Report of a WHO Expert Committee, WHO Technical Report Series 854. World Health Organization, Geneva. WHO (1999). Management of severe malnutrition: a manual for physi- cians and senior health workers. World Health Organization, Geneva. WHO (2013). Guideline. Updates on the management of severe acute malnutrition in infants and children. World Health Organization, Geneva. WHO/UNICEF (2000). Management of the child with a serious infec- tion or severe malnutrition: guidelines for care at the first-referral level in developing countries. World Health Organization, Geneva. WHO/UNICEF (2009). WHO child growth standards and the identi- fication of severe acute malnutrition in infants and children. A joint statement by WHO and UNICEF, 2009. World Health Organization, Geneva. World Bank (2006). Repositioning Nutrition as Central to Development: A Strategy for Large Scale Action. Directions in Development. World Bank, Washington, DC. https://www.intf.org

11.5 Diseases of affluent societies and the need f

11.5 Diseases of affluent societies and the need for dietary change 1891

ESSENTIALS Nutritional problems of many countries depend increasingly upon the stage of technical and economic development rather than geo- graphical location. People in affluent societies have ready access to food all year round. Traditional dietary patterns are being eroded and in many affluent societies replaced by diets which are higher in fats and/or free sugars and consequently more energy dense. Obesity is the most obvious and important nutritional disease in affluent soci- eties, with comorbidities including type 2 diabetes, coronary heart disease, hypertension, some cancers, gallstones, osteoarthritis, and obstructive sleep apnoea. Obese people may also be disadvantaged by social, economic, and psychological effects. Particular dietary constituents promote or protect against coronary heart disease by their effect on cardiovascular risk factors, and some promote or pro- tect against various cancers. While those at the highest personal risk are likely to show the greatest individual benefit from dietary and lifestyle changes, national rates of nutrition-related diseases will best be reduced if changes are made by the population at large. The main purpose of such recom- mendations is to reduce the risk of morbidity and mortality in those who are in the prime of life. Even greater reduction in morbidity and mortality and an improvement in life expectancy may occur in suc- ceeding generations if they have reduced lifetime exposure to risk factors related to lifestyle. Many different dietary patterns are compatible with widely ac- cepted nutritional recommendations for overnourished societies. More recent recommendations include a wider acceptable range of macronutrient intakes than had previously been suggested. There are multiple sources of nutritional advice, not all based on sound science. The following statements are representative of universally accepted advice: • Energy balance is essential for body weight control, hence energy- dense foods high in fat and sugars should be restricted to avoid excess weight gain • Wide ranges of fat (25–40% total calories) and carbohydrate (45– 60% total calories) intakes are acceptable provided appropriate food sources predominate • Saturated fat and trans-unsaturated fat intake should together provide less than 10% total energy, the remainder being from cis mono- and polyunsaturated fat • Vegetables, fruit,

and pulses (which are also sources of protein) and whole-grain cereals should provide most of the carbohydrate • Intake of salt and foods rich in salt should be reduced so that so- dium intake is below 100 mmol/d (6 g NaCl) • Alcohol should be consumed in moderation (1 to 2 drinks/day) by those who choose to drink All dietary patterns should include a wide variety of foods to en- sure a nutritionally adequate diet Introduction The current nutritional problems of many countries depends more upon the stage of technical and economic development than geo- graphical location (Table 11.5.1). Until about 10 000 years ago our ancestors were hunter-gatherers, most of whom collected a variety of plant foods, but also ate meat and fish. They ate little or no salt, alcohol, milk (other than breast milk), cereal, and no free sugar apart from honey. Studies of contemporary hunter-gatherers suggest that malnutrition was uncommon unless illness or injury supervened, and that the noncommunicable diseases (NCDs) of affluent societies were rare. However, the facts that life expectancy was short and that today's food supply bears little resemblance to the food consumed by our ancestors suggest that the diet of hunter-gatherers does not ne- cessarily provide indicators as to appropriate dietary practices in the 21st century. Furthermore, a hunter-gatherer type diet would not be sustainable today. In most parts of the world hunter gatherers acquired a more set- tled existence and became predominantly agriculturists and pastor- alists. Where traditional dietary patterns based on a variety of food sources were retained, diet-related NCDs and premature mortality from them remained relatively uncommon. However where there has been reliance on a single staple food which may lack essential nutrients or fail, malnutrition may result. A similar situation may occur, in developing countries where many people live in urban slums or periurban shanties, often in overcrowded insanitary ac- commodation, or in relatively affluent societies where poverty and affluence may co-exist. People have lost contact with the land and their food traditions. Food is expensive. Mothers of young chil- dren are required to go out to work and often cannot breastfeed. Undernourished young children are susceptible to infectious diseases
11.5 Diseases of affluent societies and
the need for dietary change J.I. Mann and A.S. Truswell

 and may develop marasmus. Some adults are excessively lean, others become obese, and excessive intake of alcohol is frequent. A totally different situation prevails among the prosperous people in affluent societies, especially when traditional dietary practices have been abandoned or modified and increasingly among the affluent in developing countries. They have access to a wide variety of safe, relatively cheap foods all year round. The environment is generally conducive to the consumption of a diet which is typically high in fats and or free sugars and dense in energy. Among such societies deaths from infectious diseases are infrequent, life expectancy has increased, and noncommunicable diseases, many linked in some way to in- appropriate nutrition, are the major causes of premature death and ill health. Malnutrition occurs mainly in frail elderly people and the sick. Approaches to the study of nutrition-related diseases The nutritional component of noncommunicable diseases is more difficult to study than classical nutrition deficiency diseases because noncommunicable diseases develop slowly and are multifactorial. The practice of evidence-based medicine ideally requires that an inter- vention recommended for the treatment or prevention of a disease should be proved to be of benefit in one or more randomized con- trolled trials. The evidence for the benefit of an intervention may be strengthened by the aggregation of the results of like studies in a meta- analysis. However, trials involving nutritional interventions and clinical endpoints are much more difficult to undertake than those involving drugs. It is possible to study the effects of a food component given as a pharmaceutical (e.g. antioxidant nutrients given as a tablet), and some trials have been

undertaken to study the effects of dietary manipulations on relatively common nutrition-related diseases (e.g. diabetes, hyper- tension). Clinical trials to demonstrate the effect of various dietary measures on the risk of coronary heart disease have been undertaken and have generated meaningful results when considered in aggregate, but the magnitude and duration of trials required to demonstrate the ef- fect of dietary change on cancer are such that few have been attempted. Much research involving the role of diet in chronic degenerative disease has centred around the effects of diet on modifying risk fac- tors rather than the disease itself. For many chronic diseases there are biochemical or clinical markers of risk. High plasma cholesterol is an important risk factor for coronary heart disease, for example, and high blood pressure is a major risk factor for strokes. Innumerable studies have examined the role of different nutrients and foods on plasma cholesterol, blood pressure, or other risk factors. Such studies are easier to undertake and cheaper than population-based studies because far fewer people are studied over a relatively short period of time. They have shown which foods lower cholesterol and so should help protect against coronary heart disease. Epidemiological studies have also played a pivotal role in establishing the role of nutritional factors as determinants of NCDs and the poten- tial of dietary modification in risk reduction. The first clue to the as- sociation between a food, or nutrient, and a disease often comes from observing striking differences in disease incidence between countries (or groups within a country) that correlate with differences in nutri- tional intake. Sometimes, dietary changes over time in a single country have been found to coincide with changes in disease rates. Such obser- vations give rise to hypotheses about possible diet–disease links, ra- ther than proof of causation, because many potential causative factors may be confounded by parallel dietary changes. Case–control studies have sometimes been used as a rapid and inexpensive way of testing hypotheses. These have been of value when comparing biochemical markers of nutrient intakes in the blood of people with (cases) and without (controls) various diseases, but they are of limited value when nutrient intake has been determined by recall of dietary intake. Prospective or cohort studies avoid the biases involved in asking people to recall past eating habits as information about food intake and other characteristics are collected well before onset of the disease. These have played a key role in identifying nutritional factors involved in coronary heart disease and cancer, but even strong nutrient or food and disease associations can be explained by confounding (i.e. the as- sociation between the nutritional factor and some other disease deter- minant). Sometimes the confounding can be quantified, but it is never possible to be absolutely certain that it has not been explained by some other factor which has not been measured, viz residual confounding. Given the difficulty in establishing casual associations between nutrients or individual foods and disease states, a decision as to whether or not to recommend dietary change needs to be based on a portfolio of evidence when evidence from randomized controlled trials is not available. Such evidence might include consistent and strong associations in longitudinal studies, biological plausibility, and corroborative experimental evidence in animals and humans. Obesity Obesity (see also Chapter 11.6) is the most obvious and important nutrition-related disease in affluent societies, its comorbidities Table 11.5.1 Nutrition issues at different stages of technical and economic development Hunter-gatherers Occasional seasonal hunger Malnutrition uncommon General nutritional health good No obesity No hypertension Low serum cholesterol Peasant agriculturists Single crop staple Clinical disorders may result from single or multiple nutrient deficiencies Hypertension may occur Obesity rare Urban slum and periurban shanty town dwellers Inadequate breastfeeding Inadequate food security Diarrhoea and other infective disorders, especially in young children Marasmus Obesity and alcoholism may occur Affluent societies Energy-dense diets, high in fats and sugars Physical inactivity Obesity, coronary

heart disease, and hypertension common Malnutrition may occur in frail elderly and sick people

11.5 Diseases of affluent societies and the need for dietary change 1893 including type 2 diabetes, coronary heart disease, hypertension, some cancers, gallstones, osteoarthritis, and obstructive sleep ap- noea. Obese people may also be disadvantaged by social, economic, and psychological effects. The psychological well-being of children may be particularly affected, and childhood obesity has recently been recognized as a risk factor for fractures in children. Most of the adverse consequences of obesity are appreciably reduced by weight loss, though gallstone formation may not be reduced. Although the genetic component of obesity is acknowledged, its dramatic increase in virtually all westernized countries and many developing countries in recent years provides ample evidence of overwhelming environmental factors. Physical inactivity is an im- portant cause, but frequent consumption of large portions of readily available energy-dense foods (high in fats and/or sugars) which contribute to an energy intake in excess of expenditure probably accounts for much of the global increase in obesity. Frequent con- sumption of sugar-sweetened soft drinks (and fruit juice) appears to enhance excessive weight gain, especially among children. Whole- grain cereals and cereal products, nonstarchy vegetables, and dietary fibre help to reduce the energy density of the diet, promote satiety, and thus reduce the risk of inappropriate weight gain. Current pharmaceutical measures have little to offer in the man- agement of obesity. While bariatric surgery results in weight loss and reduction of comorbidities for some obese people, it seems unlikely that the epidemic of obesity will be reversed unless the environ- ment in which we live is made more conducive to appropriate food choices and more opportunities for physical activity are provided. Such measures will also facilitate attempts by individuals to achieve weight reduction. Reducing the obesogenic environment requires commitment from national and local governments. Despite all of the aforementioned points, there is some cause for optimism in that obesity rates are relatively low among those of a higher socioeconomic status, and the increase in rates of childhood obesity appears to have been halted in countries where preventative measures have been implemented. Coronary heart disease The totality of evidence from experimental, epidemiological, and clinical trial data provide strong evidence for the role of nutritional factors in the aetiology of coronary heart disease and the potential for dietary modification to reduce cardiovascular morbidity and mortality in the population as a whole, in individuals at high risk, and in those who have already experienced a cardiovascular event. Prospective and experimental studies suggest a variety of foods and nutrients that may be involved (Table 11.5.2). Foods that in- crease the risk of coronary heart disease when consumed in large amounts probably do so because they are rich in saturated or trans- unsaturated fatty acids. ‘Protective’ foods contain several different nutrients that may reduce cardiovascular risk. Vegetable oils and nuts contain several potentially ‘protective’ fatty acids (linoleic and oleic acids). Oily fish is rich in very long-chain polyunsaturated fatty acids (eicosapentaenoic and docosahexaenoic acids). Fruit and vegetables are good sources of antioxidant nutrients, folate, potas- sium, and other biologically active substances. Whole-grain cereals are good sources of dietary fibre as well as of some unsaturated oils. Data presented in Table 11.5.3, derived from well-known pro- spective studies of cardiovascular disease, provide an indication of the extent of the potential cardioprotection and risk afforded by some foods and nutrients. Each of the foods and nutrients listed in Tables 11.5.2 and 11.5.3 has an appropriately favourable or adverse ef- fect on one or more of the cardiovascular risk factors (Table 11.5.4). As the global prevalence of obesity increases, risk factors associated with excess adiposity (notably dyslipidaemia, dysglycaemia, inflam- mation) contribute increasingly as ‘causes’ of coronary heart disease. Thus, it may be appropriate to also consider nutrition-related causes of obesity as causes

of coronary heart disease. The strongest evidence for recommending dietary change to re- duce risk of coronary heart disease relates to replacing an appreciable proportion of dietary saturated fat with polyunsaturated fatty acids. Systematic reviews and meta-analyses of both prospective cohort studies and randomized controlled trials suggest a reduction in car- diovascular events which, in the case of the randomized controlled trials, is proportional to the reduction in total and low-density lipo- protein (LDL) cholesterol achieved and comparable with benefit predicted from epidemiological data. LDL cholesterol appears to be a key risk factor for coronary heart disease, and a similar ‘dose re- sponse’ benefit in terms of cardiovascular risk reduction is seen when LDL cholesterol is lowered by means of statin drugs. It is unclear why meta-analyses do not show similar cardioprotection when saturated fatty acids are replaced by monounsaturated fats or carbohydrate, Table 11.5.2 Foods and nutrients which may protect against or promote coronary heart disease Protective Promoting Foods Nutrients Foods Nutrients • Fruits • Vegetables • Antioxidant nutrientsa, folatea • Dietary fibre (nonstarch polysaccharide) • High-fat dairy products • Fatty meats Saturated fatty acids (especially myristic and palmitic acids) Whole-grain cereals • Dietary fibre (nonstarch polysaccharides) • Unsaturated fatty acids Eggs Dietary cholesterol Vegetable oils (e.g. sunflower, safflower, olive, and canola) Unsaturated fatty acids (linoleic, oleic, α-linolenic) Some margarinesb, cooking oils, confectionery, and manufactured foods • Trans-unsaturated fatty acids • Saturated fatty acids Oily fish Eicosapentaenoic and docosahexaenoic acids Nuts Unsaturated fatty acids (oleic, linoleic), vitamin Ea Alcohol (moderate amounts only) a When present in foods, not supplements. b When containing appreciable quantities of trans-unsaturated fatty acids.

SECTION 11 Nutrition 1894 although it may be relevant that monounsaturated fat replacement was undertaken in only a small number of trials, and trials involving carbohydrate replacement did not emphasize the need to consume minimally processed carbohydrate-containing foods rich in dietary fibre which would be more likely to be cardioprotective than rapidly digested carbohydrate. It is noteworthy that the reduction in coronary heart disease which has been occurring in most Western countries since the 1970s has paralleled the reduction in saturated and increase in polyunsat-urated fats, although improved medical management of the disease and its risk factors and reduction in smoking in some sections of the populations will also have contributed to the trend. Trials that have examined potential benefits of dietary manipulations other than those designed to lower plasma cholesterol suggest that fur- ther clinical benefit might accrue from favourable changes in other risk factors, but the evidence is less conclusive. Consumption of oily fish two or more times per week, or a small amount of fish oil taken as a supplement, has been shown to reduce cardiovascular death in those with pre-existing coronary artery disease. Although increased intakes of vegetables and fruit may confer a cardioprotective effect, there is no convincing evidence from clinical trials of benefit asso- ciated with the use of antioxidant nutrient supplements. The role of margarines rich in plant sterols and stanols, which may further lower dietary cholesterol by preventing absorption and reabsorption of dietary cholesterol, is yet to be established with certainty. Community programmes aiming to change diet along the lines indicated here have been shown to reduce cardiovascular risk fac- tors and one, the North Karelia Project in Finland, has shown that cardiovascular disease mortality in the intervention county de- creased to a greater extent than might have been expected on the basis of experience in other Finnish counties. The availability of appropriate food choices at reasonable cost is an essential compo-nent of any programme aimed at reducing cardiovascular risk, since rates are highest in people of the lowest socioeconomic status. While those at the highest personal risk are likely to show the

greatest indi- vidual benefit from dietary and lifestyle changes, national coronary heart disease rates will best be reduced if changes are made by the population at large. The main purpose of such recommendations is to reduce the risk of morbidity and mortality from coronary heart disease in those who are in the prime of life. Even greater reduction in morbidity and mortality and an improvement in life expectancy may occur in succeeding generations if they have reduced lifetime exposure to risk factors related to lifestyle. Hypertension and stroke Salt (sodium chloride) Three dietary factors are well established as raising blood pressure. The longest known is salt, sodium chloride. In a few isolated com- munities salt was not available until recently, and there high blood pressures were rare or absent. Usual sodium intakes of around 150 mmol/(8.8 g NaCl) or more per day are about six times more than the physiological requirement (human milk contains only 7 mmol sodium/litre). Salt used to be important for preserving food before canning, re- frigeration and rapid transport, and people are now habituated to its flavour in foods like bread. The relationship between sodium intake Table 11.5.3 Age adjusted relative risk of coronary heart disease according to quintile of intake of certain foods or nutrients Study population Relative risk according to quintile of intake p for trend 1 2 3 4 5 43 757 male health professionals (40–75 years) Total dietary fibre (Rimm et al., 1996) 1.00 0.97 0.91 0.87 0.59 <0.001 75 521 female nurses (38–63 years) Whole-grain consumption (Liu et al., 1999) 1.00 0.87 0.82 0.72 0.67 <0.001 84 136 female nurses (30–55 years) Nuts <0.001 (Bernstein et al., 2010) 1.00 0.73 0.91 0.76 0.68 43 757 male health professionals (40–75 years) Trans fatty acids (Ascherio et al., 1996) 1.00 1.24 1.33 1.40 1.57 <0.001 Table 11.5.4 Some effects of nutrients which promote or protect against coronary heart disease on cardiovascular risk factors Nutrient Effect Promoting Saturated fatty acids ↑ total and LDL cholesterol ↑ thrombogenesis ↓ insulin sensitivity Trans-unsaturated fatty acids ↑ total and LDL cholesterol and Lp(a) Dietary cholesterol (when taken in large amounts) ↑ total and LDL cholesterol Protective Dietary fibre ↓ total and LDL cholesterol ↑ insulin sensitivity Antioxidant nutrientsa ↓ oxidation of LDL Unsaturated fatty acidsb ↓ total and LDL cholesterol ↓ arrhythmias, thrombogenesis ↑ increase; ↓ decrease a When consumed in fruits and vegetables, rather than supplements b C18:1, n-9: oleic acid C18:2, n-6; linoleic acid C18:3, n-3; α-linolenic acid C20:5, n-3: eicosapentaenoic acid C22:6, n-3; docosahexaenoic acid

11.5 Diseases of affluent societies and the need for dietary change 1895 and blood pressure cannot be studied by asking people to recall dietary intake of salt. Most of the salt consumed (c.85%) is added at the time of manufacture, rather than during food preparation or at the table, hence 24-h urinary sodium excretion rather than dietary intake measurements are needed to accurately assess salt intake, al- though sodium measurements in spot urine samples are considered to be adequate for assessing intakes of populations. Sodium excretion (reflecting intake) and blood pressures fluc- tuate markedly, and some individuals are more salt-sensitive than others. Nevertheless, surveys within one country (e.g. the 1986–1987 British National Dietary and Nutrition Survey) and internationally (the Intersalt Study involving 10 000 people in 32 countries) have shown a clear relationship between urinary so- dium and blood pressure, and a Finnish cohort study found an increased risk of cardiovascular disease in those who had high 24-h urinary sodium. There is strong confirmation from carefully controlled primate research that salt is causally related to essential hypertension. Blood pressure rose significantly over an 18-month period when salt was added to the diet of chimpanzees that nor- mally eat a vegetarian and fruit diet, and fell again when the salt was stopped. Several controlled clinical trials in humans have shown that when salt intakes are reduced to around 70 mmol/litre, blood pressure falls more in people with mild to moderate hyper- tension. Salt restriction can contribute to the treatment of hyper- tension, but

major dietary change is needed because so much is derived from manufactured food, emphasizing unprocessed foods and low-salt bread (ordinary bread contains over 100 times more salt than wheat flour). Weight reduction Overweight and obese people have higher blood pressures than those who are lean and, if they lose weight, blood pressure falls even if the usual salt intake is maintained. An Australian clinical trial showed that weight reduction (maximum loss 7.4 kg) compared favourably with metoprolol in the treatment of mild hypertension, and diet was associated with an improved plasma lipid profile not seen on the drug. Alcohol Alcohol intake is emerging as the third of the important envir- onmental factors associated with raised blood pressure. In epi- demiological studies, blood pressure, especially systolic, increases progressively when reported alcohol intake increases above three drinks per day. Several intervention studies have shown that reduc- tion of alcohol intake can produce an appreciable reduction in blood pressure among hypertensive heavy drinkers. For example, one trial showed that replacing standard beer (5% alcohol) with a reduced- alcohol beer (0.9% alcohol) produced a reduction in alcohol intake from 450 to 64 ml/week and a significant fall in blood pressure. Other factors Other components that may lower blood pressure are not as clearly established. Potassium, probably acting as an antagonist to sodium, has been shown in controlled trials to lower blood pressure modestly, but this was when given in pharmacological doses. Potassium may have been one of the operative factors in the Dietary Approaches to Stop Hypertension (DASH) trials that have shown an appreciable blood pressure lowering effect of substantial quantities of fruits and vegetables. In these trials the addition of low-fat dairy foods pro- duced additional blood pressure lowering, but the effects of calcium have been less marked in controlled trials. Blood pressure is an important determinant of ischaemic stroke and cerebral haemorrhage, so that all the nutritional determinants of hypertension may be regarded as relevant to their cause. In add- ition, prospective studies have consistently demonstrated that fruit and vegetables protect against ischaemic stroke. Although it appears that most categories of fruit and vegetables are protective, the effect is particularly striking for cruciferous vegetables, green leafy veget- ables, and citrus fruits. Diabetes mellitus and the metabolic syndrome Rates of type 2 diabetes have escalated in most affluent societies to the extent that the condition is considered to have reached epidemic proportions in many countries. The precise nature of the metabolic syndrome is not clearly understood, and some have questioned whether it should be regarded as a clinical entity. Nevertheless, the constellation of abnormalities (including abdominal obesity, hyper- glycaemia, raised blood pressure, dyslipidaemia, and increased in- sulin levels, which constitute the ‘syndrome’), does identify people likely to develop type 2 diabetes and who are at appreciably increased risk of cardiovascular disease. Where information is available, it ap- pears that the frequency of the ‘syndrome’ has also increased and that risk factors are the same as for type 2 diabetes. Epidemiological evidence suggests that type 2 diabetes is un- common in people eating a range of ‘traditional diets’ high in fresh fruit, vegetables and minimally processed cereals, and relatively low in fat, especially saturated fat. Diabetes prevalence seems to increase rapidly when traditional lifestyles are exchanged for the Western way of life, particularly when such transitions occur over a short time span. Such changes are occurring in China and India, where type 2 diabetes has already created an enormous public health problem. Similar findings had been noted earlier in Micronesians, Polynesians, American Indians, and Aboriginal Australians, as well as in Asian Indian immigrants to Fiji, South Africa, the United Kingdom, and Mauritius and among Chinese in Singapore, Taiwan, Hong Kong, and Mauritius. The change from traditional to a Western way of life is gener- ally associated with a reduction in physical activity and an increase in the energy density of the diet, resulting from increased intakes of fats and sugars, with the resultant energy imbalance leading to increasing rates of overweight

and obesity. Lack of physical ac- tivity and increasing degrees of obesity (especially abdominal adi- posity) have consistently been shown in longitudinal studies to be associated with the risk of developing type 2 diabetes. Globally and nationally, rates of type 2 diabetes have increased in parallel with increasing obesity. Genetic determinants of diabetes should not be underestimated, but they clearly cannot explain the exponential in- crease in so many countries. While any cause of energy imbalance leading to excessive weight gain will increase the risk of type 2 diabetes, there is less certainty re- garding the role of individual macronutrients in the aetiology. Excess sucrose has not been clearly established as an important dietary factor, except when high intakes contribute to an increase in energy density. However excessive energy intakes though sugar-sweetened

 beverages have been implicated as a cause of type 2 diabetes inde- pendent of an effect on body fatness. A high intake of saturated fatty acids increases insulin resistance, an underlying abnormality in type 2 diabetes and the metabolic syndrome, independently of an effect of excess adiposity, hence sat- urated fats are regarded as a probable contributor. One large pro- spective study of health professionals in the United States of America has found that a high intake of low glycaemic index foods tends to protect against type 2 diabetes and that this effect is independent of other individual dietary attributes. A high intake of dietary fibre has been shown to enhance insulin sensitivity in insulin-resistant indi- viduals, so that foods rich in dietary fibre and with a low glycaemic index are probably protective. Thus, it seems most likely that a com- bination of factors is responsible. Although we do not fully understand the complex mechanisms by which genes and environment interact to result in type 2 diabetes, randomized controlled trials among individuals with impaired glu- cose tolerance carried out in Finland, the United States, China, and India provide strong support for the suggestion that lifestyle modi- fication can help to prevent or at least appreciably delay the onset of type 2 diabetes. Interventions in the Finnish Diabetes Prevention Study (Box 11.5.1) resulted in an approximately 60% reduction in rate of progression from impaired glucose tolerance to type 2 dia- betes, a benefit which has persisted for well beyond the six-year dur- ation of the Study. Of particular interest is the fact that remarkably few of those individuals who complied with at least four of the five target interventions progressed from impaired glucose tolerance to type 2 diabetes. The benefits appear to accrue principally from re- duction in excess body fat rather than a change in any of the indi- vidual nutrients. The United States, Chinese, and Indian studies have reported comparable results. Similar lifestyle interventions have been shown to increase insulin sensitivity in insulin-resistant individuals prior to the development of impaired glucose tolerance or diabetes. Convincing randomised controlled trial evidence has shown that appreciable weight reduction (around 15kg), especially when achieved relatively soon after diagnosis can result in remission of established type 2 diabetes even in those already on drug treatment. It is yet to be established for how long remission can be sustained. Less marked weight loss and appreciable dietary change (high in- takes of dietary fibre, especially soluble forms, low glycaemic index, minimally processed wholegrain foods and reduced saturated fats) even in the absence of appreciable weight loss, can improve gly- caemic control (often with reduced requirements for hypoglycaemic drug treatment) and cardiovascular risk factors in those with type 2 diabetes regardless of the duration of the disease. Although diet is important in the management of type 1 diabetes, nutritional factors do not appear to have contributed to the aeti- ology of the disease to the same extent as for type 2 diabetes. Genetic and other environmental factors are believed to be more important. Some studies have suggested, however, that infants who have been breastfed may have a reduced risk of type 1 diabetes in later life, and this observation could be linked with immune mechanisms

known to be associated with this condition. Cancers The development of cancer involves several stages and occurs over a long period of time. Nutritional factors may operate at one or more of these stages, but given the time scale of cancer development it is hardly surprising that few data from intervention trials are available, and data relating dietary factors to various cancers are principally derived from epidemiological associations and animal experiments. Causal factors Despite the difficulty in assessing dietary intake over the prolonged period during which cancer develops, it has been estimated that about one-third of all cancers in Western countries may be asso- ciated with diet. The dietary and nutritional factors that may play a role in human cancer are listed in Table 11.5.5. Restriction of total energy intake, provided that nutrient requirements are met, has been clearly shown to reduce the risk of cancer in experimental animals, and obesity in humans is one of the most powerful and consistent epidemiological associations with cancers. Obesity is as- sociated with insulin resistance and increased levels of inflamma- tory markers and insulin-like growth factors, which may increase cancer risk. These effects are reversed by weight loss. High intakes of total fat are strongly correlated with colorectal, breast, prostatic, and pancreatic cancer in ecological (between coun- tries) studies. The effects of alcohol as a risk factor for breast cancer as well as cancer of the mouth, larynx, and pharynx are consistent and strong. Alcohol probably increases the risk of liver cancer because large intakes lead to cirrhosis of the liver, which is associated with liver cancer, regardless of cause. High intakes of red meat have been associated with an increased risk of colon cancer. Processed meats (the definition of which differs in different countries) have also been linked with colorectal cancer. Haem rather than iron per se is one possible explanation since it is susceptible to endogenous nitrosation by bacterial flora in the colon, and nitroso compounds can increase the likelihood of neoplastic change. Such effects are not seen with fish or poultry, which appear to be protective against colorectal cancer. Other clearly established nutrition-related promoters of cancers tend to operate regionally: salt and salted fish increase the risk of stomach and nasopharyngeal cancer in Japan and China, and maté, consumed at high temperatures in Brazil, is an important cause of oesophageal cancer. Protective factors Vegetables and fruit are generally accepted as important protective factors, particularly against lung, stomach, and colorectal cancers. Antioxidants (especially vitamin C, vitamin E, carotenoids, and Box 11.5.1 Lifestyle modifications, targets for the intervention group in the Finnish Diabetes Prevention Study • Weight loss of 5–7% initial body weight or a weight loss of 5–10 kg depending upon degree of obesity. • Reduce total and saturated fat by encouraging low-fat dairy and meat products. • Prefer unsaturated soft margarines and vegetables oils rich in mono- unsaturated fatty acids. • Increase whole grains, vegetables, and fruit. • Physical activity, at least moderate intensity for a minimum of 30 minutes daily.

 flavonoids), glucosinolates (found in brassica vegetables), sulphur components (in Allium species—onions and garlic) and folates have all been shown to have anticancer properties, which may explain the protective effects that have been demonstrated mainly in case– control studies. Possibly of even greater importance is the protection (particu- larly against colorectal cancer) conferred by dietary fibre (nonstarch polysaccharide) present in many minimally processed cereal foods, as well as fruits and vegetables. Dietary fibre and resistant starches escape digestion in the small intestine and are fermented in the large bowel by the colonic microbial flora. Short-chain fatty acids are pro- duced, one of which, butyric, is an antiproliferative agent. Dietary fibre may further reduce the risk of large-bowel cancer by increasing stool bulk and decreasing transit time, which in turn reduces the op- portunity for colonocytes to be in contact with carcinogens. While there is renewed interest in

the potential protective ef- fects of selenium, tomatoes, and lycopene against prostate cancer, and possible protection of folate and calcium against cervical and colorectal cancers, respectively, it seems likely that reducing rates of obesity may have a more marked effect on reducing nutrition-related cancers than modifying intakes of individual nutrients or foods. Dental caries Archaeological evidence shows that in ancient times dental caries was exceptionally rare in young people. In a recent survey of children's dental health in the United Kingdom the overall preva- lence of dental caries was 43% and the average number of decayed missing and filled teeth among 12-year-olds (permanent teeth) was 0.8. Among adults in the United Kingdom there appears to be an improvement. The Adult Dental Health Survey 2009 reported that in the 85 plus age group, 30% were edentulous (compared with al- most 80% in 1988). In the 75–84-year-old group 15% are edentu- lous and only 5% of those aged 65–74 years. The extent to which dental caries contributes to ill health throughout the life course has resulted in the condition being considered as a major chronic non- communicable disease. Several strands of evidence suggest a nutritional cause. Dental caries once had a very low prevalence among the indigenous populations of many countries where unrefined foods form the bulk of the diet (e.g. China, Uganda), and this increased rapidly within a few years of the addition of sugar and other refined foods. A similar change has been shown experimentally in monkeys. In a classical experiment carried out in a Swedish mental hospital, vo- lunteers given toffee apples, chocolate, and caramel in addition to their controlled diet had a 13-fold greater number of tooth surfaces becoming carious each year, compared with those eating the con- trolled diet alone. A 2013 meta-analysis of cohort, population and cross-sectional studies, and a small number of intervention trials conducted on behalf of the World Health Organization (WHO), found evidence of moderate quality that caries is lower when free sugars intake is less than 10% total energy and some evidence of a further reduction when intakes are below 5%. Although fluoride in the water at one part per million or in toothpaste can appreciably reduce the risk of dental caries, the association between free sugars and dental caries remains even in areas where fluoridated water is consumed. Diverticular disease of the colon The first suggestion that deficiency of dietary fibre may be impli- cated in the aetiology of diverticular disease of the colon came from geographical variations and trends over time in several countries which were compatible with a causative link with low-fibre diets, but such associations could also be explained by several alternative dietary and other environmental influences. The best-documented evidence comes from comparisons of asymptomatic groups of vege- tarians and meat eaters who volunteered to undergo radiological imaging. Radiological diverticular disease was found more fre- quently among omnivores than vegetarians, who had appreciably higher intakes of dietary fibre. Furthermore, when comparing in- dividuals with and without diverticular disease, in both the vege- tarian and nonvegetarian groups those with diverticular disease had appreciably lower intakes of dietary fibre than those with no evidence of diverticula. An increase in dietary fibre intake is widely recommended to patients with symptomatic diverticular disease, a treatment justified by the findings of some (but not all) controlled clinical trials. Table 11.5.5 Nutritional associations of various cancers Factor Causal (↑) Cancers Protective (↓) Obesity ↑ Postmenopausal breast, colorectum, endometrium, gallbladder, kidney, oesophagus, pancreas, prostate Processed and red meat ↑ Colorectum Alcohol ↑ Liver, breast, mouth, larynx, pharynx, oesophageal Salt ↑ Stomach Salted fish (Cantonese style) ↑ Nasopharynx Hot drinks (maté) ↑ Oesophagus Vegetables ↓ Colorectum, oesophagus, stomach Fruits ↓ Lung, stomach, oesophagus Nonstarch polysaccharide/dietary fibre ↓ Colorectum Selenium ↓ Prostate

SECTION 11 Nutrition 1898 Plausible theories concerning pathogenesis have been suggested; small, hard faeces associated with a fibre-deficient diet lead to nar- rowing of the colon and the formation of closed segments in which pressure increases. Additional work is needed by colonic muscles to provide the pressure to move the more solid faeces, producing muscular hypertrophy in addition to diverticula at sites of weakness where blood vessels penetrate the muscular coat. Constipation and the irritable bowel syndrome Ninety-nine per cent (99%) of a large population sample studied in the United Kingdom reported that they defecated at least three times per week but perceived constipation as a frequent com- plaint. Approximately 3% of all prescriptions written in the United Kingdom's National Health Survey were for purgatives and laxatives, at a cost of around £4 000 000, and many times this amount must have been spent in over-the-counter purchases. In another survey, 6% of people aged 18 to 80 years described straining when passing stools. By contrast, constipation is uncommon in populations with a high intake of dietary fibre. In Britain, stool weights in omnivores are usually around 100 g (with a very wide range), whereas in vegetarians with a high fibre in- take, the average stool weight is over 200 g. Furthermore, vegetarians and omnivores with high average daily fibre intakes have transit times of less than 75 h and rarely report constipation, whereas those with lower fibre intakes have transit times ranging from 20 to 124 h and frequently complain of constipation. Controlled clinical trials con- firm that increasing dietary fibre (especially that derived from cereals) relieves the symptoms of constipation. Diets rich in dietary fibre are widely recommended in the treatment of irritable bowel syndrome, despite the absence of good evidence from formal clinical trials. Osteoporosis Osteoporosis is an important cause of morbidity among elderly people, especially women, and the incidence of osteoporotic frac- tures is increasing steadily as people are living longer. The aetiology of osteoporosis is complex; women have a lower peak bone mass in their twenties than men and lose bone rapidly after the meno- pause in association with a decline in oestrogens. Women lose ap- proximately one-half their trabecular bone and one-third of their cortical bone, while men lose one-third of their trabecular bone and one-fifth of their cortical bone. Genetic factors influence peak bone mass and bone loss. These may operate by some established risk factors: family history of osteoporosis, short stature, early meno- pause, white or Asian race, and leanness. However, there are also environmental factors, including cigarette smoking, excessive salt and alcohol intakes, and lack of vitamin D, especially in housebound people with little sun exposure. The role of dietary calcium has been uncertain but there is now convincing evidence that the best way of avoiding osteoporotic fractures in later life is to achieve optimal skeletal mass for one's genetic potential and to retain this as long as possible. The best means of doing so is by ensuring lifelong adequate consumption and maximum absorption and retention of calcium. The need for substantial amounts of dietary calcium, in conjunc- tion with adequate vitamin D, is particularly important during the periods of growth, pregnancy, lactation, and in the postmenopausal years. Fruit, vegetables, and adequate physical activity have also been identified as protective factors. Other diseases Gallstones, appendicitis, haemorrhoids, varicose veins, and hiatus hernia all occur frequently in developed countries and rarely in developing countries, but the evidence linking these diseases to a nutritional cause is tenuous. Gallstones are undoubtedly associated with obesity. Both gall- stones and appendicitis are more common in omnivores than vegetarians, and there are some rather indirect data suggesting an association with diets high in sugars and deficient in dietary fibre. The addition of bran to the diet can make bile less saturated, and experimentally induced gallstones in animals tend to be reduced if fibre-rich foods rich are given. Historical studies provide interesting information; appendicitis rates were compared in two matched groups of South African whites, the privileged group living in uni- versity halls of residence and the other living in

establishments for the indigent, where the diets contained more fibre. Annual rates were 7.8/1000 and 1.8/1000, respectively. Of course, factors other than diets might explain this, but the rates were similar to those found in an almost identical study in Bristol (7.6/1000 in a fee- paying boarding school and 0.8/1000 in an orphanage). The case for dietary change Nutrition research often generates results that may be translated by researchers, self-styled ‘experts’, or the media into potentially confusing and conflicting messages. It is therefore important for governments who develop food and nutrition policies, for doctors and others involved in health and nutrition education, and for con- sumers to have authoritative recommendations that represent con- sensus opinions of nutrition scientists. Dietary or nutrient reference values define intakes of nutrients which are required for growth and maintenance of health and considered to reduce the risk of chronic diseases. These recommendations are intended for policy makers and health professionals who recommend diets for populations, special groups of people within populations, and individuals. Such reference values are unhelpful to the population at large. For the general public, dietary guidelines have been developed to translate reference values into practical advice. Dietary fat Reference values for macronutrients were initially centred around the evidence showing that alteration of dietary fat intake from that typical of most Western countries would be expected to reduce population and individual risk of coronary heart disease. Restriction of saturated fatty acids and trans-unsaturated fatty acids to no more than 10% total energy has been a consistent feature of all sets of national and inter- national reference values. Some have suggested an even lower propor- tion of total energy from these fatty acids for populations, groups, or individuals considered to be at increased risk of coronary heart dis- ease. Until relatively recently recommendations regarding dietary fat included a restriction on total fat intake, typically to less than 30%

 total energy. However, increasing evidence relating to the benefits of replacing saturated with unsaturated fatty acids has (other than trans-unsaturated fatty acids) resulted some countries including the Nordic group of countries suggesting an appreciably higher accept- able upper limit, around 40% total energy (Table 11.5.6). While an increase in unsaturated fatty acids (with a cis- configuration) is associated with a reduced risk of coronary heart disease, the potential contribution of total fat to the energy density of the diet appears to be the continuing justification for the World Health Organisation’s recommendation for continuing the recom- mendation to restrict total fat. There is evidence that high fat diets may promote and perpetuate excessive weight gain and obesity in individuals and populations but the extent to which this should be reflected in a restriction of total fat intake especially as it relates to populations rather than individuals remains a matter of opinion. The lower limit of fat intake in some recommendations is based on the minimum requirement considered to ensure an adequate in- take of fat-soluble vitamins, and the fact that there is no evidence of untoward effects in some Asian and African populations who traditionally consume low-fat diets. Dietary carbohydrate About 50 g of carbohydrate daily is required to avoid ketosis, but many populations maintain an adequate nutritional status when carbohydrate provides up to 80% total energy. Most Western societies are unaccustomed to a high carbohydrate intake and are reluctant to accept substantial increases. WHO and most countries recommend a relatively wide range of acceptable intakes, recog- nizing that source of carbohydrate is likely to be more important than the proportion of total energy provided by carbohydrate (Table 11.5.6). A high intake of free sugars (principally sucrose and, in the United States, high-fructose corn syrup) increases the risk of obesity by increasing the energy density of the diet, or simply by increasing total energy intake (and energy imbalance) when sugary drinks are consumed in excess. Sugars are also associated

with dental caries and in large amounts may enhance the metabolic derangements in people with insulin resistance. Foods with a high intake of free sugars are frequently nutrient poor (i.e. contain rela- tively few essential nutrients), so limiting such foods has no adverse nutritional consequences. Limiting free sugar intake of individuals to below 10% total energy is widely recommended and WHO has suggested that further reductions may be associated with additional benefits. On the other hand, intrinsic sugars (i.e. those incorpor- ated into the natural structure of foods, like fruits), milk sugars, and starches are not restricted and generally provide the balance of dietary energy not provided by protein, fat, and free sugars. Similar advice has been offered by the Specialist Advisory Committee on Nutrition (SACN) in the United Kingdom in their 2015 report (Carbohydrates and Health). They suggest that population average intakes of total carbohydrate should be around 50% total energy and free sugars around 5% total energy. There has been much discussion regarding the most appropriate carbohydrate-containing foods. Intact fruit and vegetables and minimally processed cereals and grains tend to be rich sources of dietary fibre, essential micronutrients, and some essential fatty acids. The SACN Report suggests that population average intake of fibre should be about 30 g/day, an appreciable increase from current levels. Cooked dried beans, chickpeas, and some whole-grain products are rich sources of dietary fibre and resistant starch, which having largely avoided digestion in the small intestine enter the colon in a largely undigested state. Resistant starch, oligosaccharides, and some com- ponents of dietary fibre (e.g. gum, pectins, mucilages) undergo fer- mentation that leads to the production of fatty acids, which provide a fuel source (via conversion to glucose in the liver) and may also re- duce the risk of colon cancer because of their antiproliferative effects. Other components of dietary fibre remain largely intact and act as stool-bulkers (e.g. cellulose and hemicellulose). Thus, a wide variety of fruits and vegetables, whole grains, and minimally processed cer- eals are particularly appropriate sources of carbohydrate. Some fruits, white rice and hot cooked potato are largely digested in the small intestine and provide an immediate or fairly rapid source of energy, depending upon the speed of digestion. Free or added sugars in jams and manufactured foods (e.g. confectionery prod- ucts) or added by the consumer to food and beverages are also rapid sources of energy, but increase energy density and promote obesity, so that foods rich in them should be restricted by most people. The glycaemic response following the ingestion of a specified amount of carbohydrate in a food, expressed as a percentage of the glycaemic response following a similar amount of glucose (glycaemic index), has been suggested as a useful approach to identifying the most ap- propriate carbohydrate-containing food choices (i.e. those with a low glycaemic index are particularly appropriate). While this is of some value in comparing different varieties of similar foods (e.g. different Table 11.5.6 Nutrient intake goals as recommended by WHO and FAO and in the United Kingdom (unless otherwise stated, the goals are expressed as percentage total energy) WHO/FAOa (2003) Nordicb (2012) Total fat 15–30% 25–40% Saturated fatty acids (SFA) <10% <10% Cis polyunsaturated fatty acids 6–10% 5–10% n-6 PUFA 5–8% c n-3 PUFA 1–2%

> 1%d Cis monounsaturated fatty acids By differencee 10–20% <1% As low as possible Dietary cholesterol (mg/day) <300 mg/day c Total carbohydrate 50–75%g 45–60% Free sugarsf <10% <10% Dietary fibre (NSP) 25 g/dayg 25–35 g/day Protein 10–15% 10–20% Sodium chloride <5 g/day c Potassium c Fruit and vegetables 400 g/day 400 g (5 portions) a Source: WHO (2003). Diet, Nutrition and the Prevention of Chronic Diseases. Report of a joint WHO/FAO Expert

> Consultation, Technical Series Report 916, World Health Organization, Geneva. b Nordic Council of Ministers. Nordic Nutrition Recommendations 2012. Main conclusions of the NNR. Online . Copenhagen: 2013. c No specific recommendation. d Mainly from oily fish. e Total fat (SFA & PFA & TFA). f All monosaccharides and disaccharides added to foods by manufacturer, cook, or consumer, plus sugars naturally present in honey, syrups, and fruit juice. g WHO/FAO Scientific Update on CHO (Nishida et al., 2007).

SECTION 11 Nutrition 1900 types of bread) there are several limitations, including that some low glycaemic index foods, especially those containing fat and sugars, may be very energy dense despite having a low glycaemic index (e.g. ice cream) and that there is considerable inter-and intraindividual variation in glycaemic response to foods. Synthetic forms of dietary fibre or fibre extracted from plant material favourably influence cardiometabolic risk factors but there is as yet no corroborative epi- demiological evidence that they have an effect on clinical outcomes comparable with those convincingly demonstrated for dietary fibre naturally found in foods. Dietary protein Dietary protein, the most fundamental macronutrient, has been largely taken for granted in affluent societies. The mixture of foods in the diets of Britain and similar countries provide dietary protein that contributes around 15% dietary energy across genders, occupa- tions, and socioeconomic levels, against nutrient reference amounts of 10% of energy. Protein-containing foods are also good sources of critical nutrients iron, calcium, and zinc. There is only one main subdivision of dietary proteins: animal source and plant source pro- teins. The constituent amino acid patterns are somewhat nearer to human requirements in meats and dairy products. Vegetarians (who consume dairy products) should have no difficulty to achieving ad- equate intakes. The diet of vegans whose protein intake is derived solely from plant sources requires more careful planning, but they have compensatory health advantages of less obesity and eating less saturated fat. Protein intake can be critical in old people. In Australia and New Zealand, the 2005 recommended dietary intake moves up at age 70 plus from 46 to 57 g per day in women and from 64 to 81 g/d in men. In old people dietary protein appears to be used less efficiently. There is increased splanchnic extraction and declining anabolic response to ingested protein. To help prevent sarcopenia, loss of muscle with ageing, the PROT-AGE international committee of geriatricians rec- ommend protein intake should be 1.0–1.2 g/kg (i.e. 65–78 g/d for a 65 kg woman or man). The usual daily pattern of our protein intake is to eat the bulk of it at one meal (dinner) of the day (with meat, fish, or beans). Most modern breakfasts provide some cereal, coffee, and a little milk, so much less than a third of the daily protein intake. It may be better for muscle maintenance to add a protein source at breakfast. Overall diet The appreciation that a wider range of macronutrients than was pre- viously recommended is appropriate for reducing the risk of many chronic diseases enables the translation of nutrition recommenda- tions into many acceptable dietary patterns which are diverse as those traditional to Mediterranean countries, where intake of unsaturated vegetable oils is relatively high, and to some Asian countries where diets relatively high in carbohydrate are consumed. Although a var- iety of carbohydrate intakes is acceptable, a very low carbohydrate high-fat diet is not included among the acceptable dietary patterns. The suggestion by some nutritionists and other health profes- sionals that populations and individuals at high risk of obesity and type 2 diabetes (or those who have already the disease) should be on very low carbohydrate diets (less than 20% total energy) is based principally on deleterious effects

on lipids and measure of carbo- hydrate metabolism observed when diets high in rapidly digested and absorbed carbohydrates are compared with lower carbohydrate intakes. Such untoward effects do not occur when diets are rich in vegetables, fruit, and minimally processed cereals. It has also been claimed that low carbohydrate diets, which tend to be relatively high in fat and protein, are associated with greater weight loss than Mediterranean-type diets or diets with a higher pro- portion of calories from carbohydrate. This is only true in short term studies. Macronutrient distribution is not an important determinant of long-term weight loss and diets with a higher carbohydrate con- tent may be more likely to facilitate weight maintenance. Not only is there no information about long-term clinical benefit of very low carbohydrate diets which are typically high in fat often saturated fat, there are also no data regarding their safety. Low carbohydrate diets have not been endorsed by expert committees or appropriately qualified government and nongovernment bodies. While appropriate distribution of macronutrients and good food choices might be expected to reduce cardiovascular risk, improve bowel function, and reduce the risk of certain cancers and other dis- eases of the large bowel, the importance of ensuring energy balance cannot be overstated. Obesity and its comorbidities, especially type 2 diabetes, account for a public health problem of enormous mag- nitude throughout the world. Increasing carbohydrate-containing bulking foods rich in dietary fibre at the expense of saturated fat is likely to enhance satiety. Such positive advice, along with the re- commendations to reduce frequent consumption of large portions of all energy-dense foods and sugary drinks, is likely to help reduce excessive energy intake. Increasing energy output by increasing physical activity may contribute to public health measures de- signed to stem the tide of the global obesity epidemic, but to a lesser extent than dietary measures. There is increasing recognition of the need to consider sustainability issues when making nutrition recommendations. Reference intakes for vitamins and minerals Reference nutrient intakes (adequate for most individuals) are pro- vided for vitamins and minerals by official bodies, such as the Institute of Medicine (IOM). They are set at a level of two standard deviations above the average of all individual requirements, so that requirements for the vast majority in the population are assured. Clinical vitamin deficiencies, discussed in detail in Chapter 11.2, are uncommon in affluent societies except in at-risk subgroups within populations. For example, immigrants who have migrated from sunny tropical regions to cloudy high-latitude countries may be at risk of vitamin D defi- ciency; strict vegetarians (who consume no animal or dairy prod- ucts) may become deficient in vitamin B12, and disadvantaged groups (especially the very young, pregnant, and lactating women, and older people) may have generally inadequate intakes. By contrast, inappropriate intakes of certain minerals and other nutrients are fairly common. Many groups are particularly vul- nerable to iron deficiency due to high physiological requirements (infants and toddlers, adolescents, pregnant women), high losses (menstruating women), or poor absorption (older people and those consuming foods high in inhibitors of absorption, such as fibre and tannin in tea). Vegetarians are also at increased risk of iron defi- ciency, even when total intake of iron appears to be adequate, since nonhaem iron from plant foods is less bioavailable than haem iron from animal sources. Bioavailability is enhanced by the consump- tion, at the same time, of foods rich in vitamin C. Iodine and selenium are deficient in soils in various parts of the world. Clinical selenium deficiency has only been reported from

 China, although the consequences of lesser degrees of selenium defi- ciency have yet to be established with certainty, especially in regions where soils are known to be deficient. Endemic iodine deficiency is widespread, especially in the Himalayas and the Andes, and clin- ical deficiency states are largely

avoided by the use of iodized salt and sanitizers containing iodine used by the dairy industry. In New Zealand, where goitre due to iodine deficiency had virtually been eliminated, mild iodine deficiency appears to be reoccurring pos- sibly as a result of reduced use of iodized salt and the introduction by the dairy industry of alternative sanitizers. Young women often have insufficient calcium to help achieve peak bone mass, and older women may have an inadequate intake to help reduce an age-related bone loss. Excessive intakes of salt (sodium chloride), to such an extent that it probably contributes to hypertension and its consequences, are common throughout the world. Targets for reduction may be more important than reference nutrient intakes for sodium. An intake of 100 mmol/day (2.3 g sodium/day, roughly equal to 6 g NaCl), a level currently exceeded in most countries, are considered to be an appro- priate maximum. Reference nutrient intakes need to be reviewed when new research becomes available. In the 1990s, a value of 200 µg/day for folate was widely recommended. It is now acknowledged that intakes of 400 µg/day can appreciably reduce the risk of neural tube defects. Most countries have altered their recommended intake to 400 µg/day. The case for increasing the recommended intakes of other nutrients be- yond established requirements in order to reduce the risk of chronic diseases is less clear-cut. Prospective cohort studies suggested that high intakes of several antioxidant nutrients can reduce cardiovas- cular disease, but these findings have not been replicated in large randomized controlled trials in which these nutrients were given as supplements. It is conceivable that these micronutrients are only protective when consumed as food constituents rather than as sup- plements such that it is not possible to specify optimal intakes in terms of reducing the risk of chronic disease. Much current interest centres around optimum dietary intakes of vitamin D, long known to be critically important in prevention and treatment of rickets and osteomalacia. Many nonbone actions of vitamin D have now been recognized and there is experimental and epidemiological evidence that vitamin D might protect against osteoporosis, some cancers, hypertension, type 1 diabetes, multiple sclerosis, and tuberculosis. Further research including clinical trials are needed before firmly establishing the most appropriate intakes and form in which this vitamin is most appropriately consumed.
Implementing nutrition recommendations Substantial changes in what have become traditional eating habits of many affluent societies are required in order to achieve the ad- vised changes in distribution of macronutrients and recommended intake of all essential micronutrients.
A multipronged approach is necessary if there is to be a real chance of achieving dietary change. At the policymaking and government level there needs to be a ser- ious commitment to enabling the population as a whole to make appropriate food choices. Fatty cuts of meat, high-fat products (e.g. meat pies), and convenience foods (e.g. fish and chips, burgers) are relatively inexpensive and therefore frequently eaten by those of lower socioeconomic status who have the highest rates of coronary heart disease. Policies are required which ensure that more appro- priate food choices are available at reasonable cost. This is not easy to achieve in many Western countries, where farmers may have con- siderable political influence, and subsidies may be available for some high-fat dairy products such as butter and cheese. Governments and intergovernmental agencies also have the re- sponsibility for ensuring that food labels and health claims are ac- curate, interpretable, and likely to facilitate health-promoting food choices, a particularly important issue given the increased con- sumption of packaged food. In countries in transition where poverty (undernutrition) and affluence (overnutrition) coexist, achieving appropriate food choices for the population as a whole presents an even greater challenge. Dietary guidelines are necessary to provide clear directions to individuals and families who wish to aim for a healthy diet pat- tern. These guidelines vary slightly from country to country, but some are almost universal (see Box 11.5.2). Others are less consistent (see Box 11.5.3). The public also need education re- garding

food groups and the nutrients they contain, the inter- pretation of food labels, the meaning of health claims, and the methods of food preparation. The increased use of convenience and packaged food has meant that many people no longer possess basic cooking skills. They also need (and usually want) to know the merits and demerits of obtaining certain essential micronu- trients by taking supplements or fortified food products rather than conventional foods. Doctors are frequently asked to give nutritional advice but may lack the necessary expertise. Dietitians, nutritionists, and appropriately trained practice nurses play an invaluable role in providing the public with practical advice to facilitate changes from the typical Western diet, as well as providing instruction re- garding therapeutic diets for those with diseases requiring spe- cific diet therapy. The enormous potential for dietary change to reduce the effects of a wide range of diseases should encourage physicians to approach the nutritional management of their pa- tients with enthusiasm. Box 11.5.2 Dietary guidelines for which there is almost complete agreement 1 Eat a nutritionally adequate diet composed of a variety of foods. 2 Eat less of foods rich in saturated fat and use mono- and polyunsatur- ated fats instead. 3 Adjust energy balance for body weight control: energy-dense foods high in fat and sugars should be restricted and exercise increased to avoid excess weight gain. 4 Eat more of a variety of vegetables, fruits, and whole grains. 5 Reduce intake of salt and foods rich in salt. 6 Drink alcohol in moderation, if you do drink. Box 11.5.3 Additional dietary guidelines in some countries 1 Recommendation regarding sugar and sugary foods may vary from ‘no increase’ to ‘decrease’. 2 Drink plenty of fluids each day. 3 Make sure you get enough calcium or milk. 4 Eat foods containing iron. 5 Drink fluoridated water. 6 Preserve the nutritive value of food (by good food preparation). 7 Eat three good meals a day.

 FURTHER READING Ascherio A, et al. (1996). Dietary fat and risk of coronary heart dis- ease in men: cohort follow up study in the United States. BMJ, 313, 84–90. Bauer J, et al. (2013). Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc, 14, 542–59. Bernstein AM, et al. (2010). Major dietary protein sources and risk of coronary heart disease in women. Circulation, 122, 876–83. FAO/WHO Scientific Update on Carbohydrates in Human Nutrition (2007). Eur J Clin Nutr, 61(Suppl 1), S132–S137. Food and Nutrition Board, Institute of Medicine (1998/2011). Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, (1998); and Dietary Reference Intakes for Calcium and Vitamin D (2011). National Academies Press, Washington DC. https://www.nap.edu. Lean M, et al. (2018). Primary care-led weight management for remis- sion of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet, 391, 541–51. Liu S, et al. (1999). Whole-grain consumption and risk of coronary heart disease: results from the Nurses’ Health Study. Am J Clin Nutr, 70, 412–19. Mann J, Truswell AS (eds) (2017). Essentials of human nutrition, 5th edition. Oxford University Press, Oxford. Mann J, et al. (2014). Low carbohydrate diets: going against the grain. Lancet, 384, 1479–80. Mann J, et al. (2015). Diverging global trends in heart disease and diabetes: implications for dietary guidelines. Lancet Diabetes Endocrinol, 3, 584–5. Moynihan PJ, Kelly SA (2014). Effect on caries of restricting sugars intake: systematic review to inform WHO guidelines. J Dent Res, 93, 8–18. Nordic Council of Ministers (2012). Nordic Nutrition Recommendations 2012. Main conclusions of the NNR, Copenhagen. https://norden. diva-portal.org/smash/get/diva2:704251/FULLTEXT01.pdf Reynolds, A, Mann, J, Cummings, J, Winter, N, Mete, E, Te Morenga, L (2019). Carbohydrate quality and human health: A series of system- atic reviews and meta-analyses. Lancet. Advance online publication. doi: 10.1016/S0140-6736(18)31809-9. Rimm EB, et al. (1996). Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. JAMA, 275, 447–51. Schwab U, et al. (2014).

Effect of the amount and type of dietary fat on cardiometabolic risk factors and risk of developing type 2 diabetes, cardiovascular diseases, and cancer: a systematic review. Food Nutr Res, 58. doi: 10.3402/fnr.v58.25145. eCollection 2014. Scientific Advisory Committee on Nutrition (SACN) (2015). Carbohydrates and health. The Stationery Office Limited, London. Te Morenga L, Mallard S, Mann J (2013). Dietary sugars and body weight: systematic review and meta-analyses of randomised con- trolled trials and cohort studies. BMJ, 346, e7492. Truswell AS (2010). Cholesterol and beyond: the research on diet and coronary heart disease 1900–2000. Springer, Dordrecht, Heidelberg, London. U.S Department of Agriculture (2015). Scientific Report of the 2015 Dietary Guidelines Advisory Committee. United States Department of Agriculture, Washington, DC. https://health.gov/dietaryguidelines/ 2015-scientific-report/ WHO (2003). Diet, nutrition and the prevention of chronic diseases. WHO Technical Report Series 916. World Health Organization, Geneva.

11.6 Obesity 1903

11.6 Obesity 1903

ESSENTIALS Obesity is defined as an excess of body fat that is sufficient to affect health adversely. While the quantification of fat mass is usually only performed in the research setting, body mass index (weight in kg/ height in metres2) is a useful surrogate marker for fat mass. Using the World Health Organization definition of a body mass index more than 30 kg/m2 to define obesity, 30% of Americans, and 10 to 20% of Europeans are classified as obese, with the prevalence rising in many developing countries. As body mass index increases, so does the relative risk of type 2 diabetes, hypertension, and cardiovascular disease. As such, obesity is associated with disability, mortality, and substantial health costs. At an individual level, severe obesity can be associated with sleep disturbance and respiratory difficulties, joint and mobility disorders, as well as considerable social stigma which can affect quality of life, educational attainment, and employment opportunities. Management of patients with severe obesity is a challenge, but success is enhanced by a sympathetic approach from the physician, with realistic weight loss goals and monitoring of the effects of treat- ment. Interventions include (1) low-calorie diets which often aim to provide a 600 kcal/day (2.5 MJ/day) energy deficit, based on es- timated energy requirements; (2) motivational and behavioural ap- proaches to implement and sustain changes in eating and activity behaviour; (3) drug treatment—which should be regarded as a thera- peutic trial and stopped if weight loss is not apparent after one to two months; (4) surgery—an option for people with morbid obesity/ obesity with associated complications. Introduction Obesity is frequently considered to be a ‘modern’ disease—a re- flection of the excesses of urbanized society. However, descriptions of obese individuals in medical texts from many of the ancient civilizations, suggest that, throughout history, certain individ- uals have harboured the tendency to store excess energy as fat. Hippocrates recognized that obesity posed a threat to health when he wrote that, ‘sudden death is more common in those who are naturally fat than in the lean’. Galen elaborated upon earlier descrip- tions of the obese state, distinguishing between different degrees of obesity; ‘moderate’ or common obesity and ‘immoderate’ or morbid obesity. Many Greek and Roman physicians documented some of the clinical complications associated with obesity, including reduced frequency of menses and infertility. The first known description of obesity and sleep apnoea dates from Roman times; Dionysius, the tyrant of Heraclea of Pontius who reigned from about 360 bc, was described as ‘an enormously fat man who frequently fell asleep’. The obesity-related changes in respiratory function, which are most prominent during sleep, are now recognized as the obesity–hypoventilation or Pickwickian syndrome. Definition of obesity as a medical disorder The recognition that obesity represents a serious medical disorder at a population level came with pooled life insurance data from the United States of America, showing that increasing degrees of overweight and obesity were important predictors of decreased longevity, much of which was attributed to cardiovascular dis- ease. Subsequently, several epidemiological studies, including the Framingham Study and the Build and Blood Pressure Study, have shown that the adverse effects of

excess weight tend to be delayed, sometimes for 10 years or longer. These observations led to the rec- ognition that obesity should be defined as a disorder in which excess body fat has accumulated such that health may be adversely affected. We now recognize that obesity is associated with substantially in- creased mortality from cardiovascular and cerebrovascular disease, type 2 diabetes, and certain cancers. Obesity is also associated with increased morbidity from musculoskeletal, gastrointestinal, psychi- atric, and reproductive diseases (Table 11.6.1) and is associated with lowered quality of life, self-esteem, and socioeconomic performance. The precise measurement of body fat is challenging and accurate methods are not applicable to large populations, hence surrogate markers such as the body mass index (BMI—weight in kilograms divided by the square of the height in metres) are most often used to define obesity in population studies and in the clinic. The underlying assumption is that most variation in weight for persons of the same height is due to fat mass. A World Health Organization Expert 11.6 Obesity I. Sadaf Farooqi

SECTION 11 Nutrition 1904 Committee has proposed a classification of overweight and obesity (Table 11.6.2) using BMI. Worldwide prevalence of obesity Obesity, defined as a BMI of more than 30 kg/m2, is a common condi- tion in Europe and the United States of America—20% of American men and about 25% of American women are obese. In Southeast Asia and the Middle East a dramatic rise is being seen in all popu- lations. Figure 11.6.1 shows the prevalence of obesity in high, low, lower-middle, and upper-middle income countries. In children the relationship between BMI and body fat varies markedly with age and with pubertal maturation. BMI percentile charts using national BMI reference data facilitate the graphical plotting of serial BMI measurements in individual patients. The International Obesity Task Force (IOTF) has recommended the use of BMI data derived from six countries, which extrapolate risk from the adult experience to children. These age- and gender-specific BMI cut-offs (overweight as approximately 91st percentile or greater and obesity as approximately 99th percentile or greater) allow the com- parison of obesity prevalence in different populations. Using these criteria, it is clear that the prevalence of overweight and obesity in childhood is a global concern, and—as shown in Fig. 11.6.2—the prevalence of overweight preschool children is greatest in lower- middle- and upper-middle-income countries. Although there is no accepted definition for severe or morbid obesity in childhood, a BMI of more than 2.5 standard deviations from the mean (weight off the chart) is often used in specialist centres, and the crossing of major weight percentile lines upwards is an early indication of risk of severe obesity. Aetiology of obesity Humans, like other mammals, are able to regulate their body weight over long periods of time despite day-to-day variation in the amount of calories consumed and in levels of energy expenditure. However, this homeostatic regulation of energy balance is easily overwhelmed by external stimuli. Body weight is determined by an interaction between genetic, en- vironmental, and psychosocial factors acting through the physio- logical mediators of energy intake and expenditure. By definition, obesity results from an imbalance between energy intake and en- ergy expenditure and, in any individual, excessive caloric intake or low energy expenditure, or both, may explain the development of obesity. A third factor, nutrient partitioning, a term reflecting the propensity to store excess energy as fat rather than lean tissue, may contribute. Environmental factors The increasing prevalence of obesity worldwide (an approximate doubling in the last 30 years), the inverse relationship between obesity and socioeconomic class, and the secular trend towards increasing obesity in developing countries associated with urban- ization, provide clear evidence of the environmental influences on weight gain. The adoption of relatively sedentary lifestyles due to reduced physical activity at work and in leisure time coupled

with an abundance of easily available, energy-rich, highly palatable foods represents a nutrition transition (see http://www.hsph.harvard.edu). Interestingly, some recent analyses of trends in obesity preva- lence have suggested a decline or stabilization of obesity preva- lence. However, many countries have either increasing (China) or decreasing (European countries) birth rates, so the potential global impact of these estimations is not readily predictable. Recent studies show that second generation migrants to the United States from all ethnic groups are heavier than their parents who migrated, but that people from some ethnic groups are more likely to gain weight than others on transitioning to a more obesogenic environment, sug- gesting that in addition to strong environmental drivers, genetic fac- tors play a role in influencing obesity susceptibility. The two priority areas for public health strategies aimed at preventing obesity are increasing physical activity and improving the quality of the available diet within a community. However, such strategies must address the need to improve the population's under- standing of the nature of obesity and its management and reduce exposure to an environment that promotes obesity.
Genetic factors In any environment, whether energy rich or energy lacking, there is considerable individual variation in body weight and fat mass. There is considerable evidence from family, twin, and adoption Table 11.6.1 Medical complications associated with obesity Type 2 diabetes 90% of type 2 diabetics have a BMI of >23 kg/m2 Hypertension 60–80% of hypertension is linked to excess weight Coronary artery disease (CAD) and stroke 3.6-fold risk of CAD for each unit change in BMI Respiratory effects Neck circumference of >43 cm in men and >40.5 cm in women is associated with obstructive sleep apnoea, daytime somnolence, and development of pulmonary hypertension Cancers 10% of all cancer deaths among nonsmokers are related to obesity (30% of endometrial cancers) Reproductive function 6% of primary infertility in women is attributable to obesity Impotency and infertility are frequently associated with obesity in men Osteoarthritis (OA) Frequent association in older people with increasing body weight Liver disease Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH); 40% of NASH patients are obese Gallbladder disease Threefold risk of gallbladder disease in women Table 11.6.2 Cut-off points proposed by a World Health Organization Expert Committee for the classification of overweight and obesity BMI WHO classification <18.5 Underweight 18.5–24.9 Normal weight 25–29.9 Overweight 30.0–39.9 Obesity 40.0 or greater Morbid obesity

Uruguay 26.7 United States of America 33.7 United Kingdom28.1 United Arab Emirates 37.2 Trinidad and Tobago 31.1 Switzerland 19.4 Sweden 20.5 Spain 23.7 Slovenia 25.1 Slovakia 25.7 Singapore 6.2 Saudi Arabia 34.7 Saint Kitts and Nevis 28.3 Russian Federation 24.1 Republic of Korea 5.8 Qatar 42.3 Portugal 20.1 Poland 25.2 Oman 30.9 Norway 23.1 New Zealand 29.2 Netherlands 19.8 Malta 26.6 Luxembourg 23.1 Lithuania 25.9 Latvia23.7 Kuwait 39.7 Japan 3.3 Italy 21.0 Israel 25.3 Ireland 25.6 Iceland 22.8 Greece 22.9 Germany 20.1 France 23.9 Finland 20.6 Estonia 22.6 Equatorial Guinea 17.5 Denmark 19.3 Czech Republic 26.8 Cyprus 23.8 Croatia 23.3 Chile 27.8 Canada 28.0 Brunei Darussalam 18.1 Belgium 20.2 Barbados 31.3 Bahrain 35.1 Bahamas 36.2 Austria 18.4 Australia 28.6 Antigua and Barbuda 30.9 Andorra 29.5 0% 50% 20% 10% 30% 40% Zimbabwe 10.5 United Republic of Tanzania 7.1 Uganda 4.9 Togo 7.5 Tajikistan13.6 Somalia 4.6 Sierra Leone 7.6 Rwanda 4.0 Niger 4.3 Nepal 3.3 Myanmar 2.9 Mozambique 5.3 Mali 6.8 Malawi 5.3 Madagascar 5.4 Liberia 6.6 Kenya 7.0 Haiti 11.9 Guinea-Bissau 7.2 Guinea 6.8 Gambia 10.9 Ethiopia 4.0 Eritrea 4.1 Democratic Republic of the Congo 4.4 Democratic People's Republic of Korea 2.4 Comoros 6.6 Chad 8.1 Central African Republic 5.1 Cambodia 3.2 Burundi 2.6 Burkina Faso 6.3 Benin 9.3 Bangladesh 3.6 Afghanistan 2.9 0% 50% 20% 10% 30% 40% High-income (a) Low-income Fig. 11.6.1 Age-standardized prevalence of obesity (percentage with BMI

>30 kg/m2) in adults aged 18 years and over, by individual country and World Bank Income group, 2014. Reprinted from Global status report on noncommunicable diseases 2014, Copyright © World Health Organization 2014.

SECTION 11 Nutrition 1906 Zambia 8.9 Yemen 17.2 Viet Nam 3.6 Vanuatu 35.4 Uzbekistan 15.5 Ukraine 20.1 Timor-Leste 2.2 Syrian Arab Republic 23.5 Swaziland 17.7 Sudan 7.5 Sri Lanka 6.5 South Sudan 7.5 Solomon Islands 27.7 Senegal 9.8 Sao Tome and Principe 12.3 Samoa 43.4 Republic of Moldova 14.9 Philippines 5.1 Paraguay 16.3 Papua New Guinea 27.9 Pakistan 5.4 Nigeria 11.0 Nicaragua 17.1 Morocco 22.3 Mongolia 16.7 Micronesia (Federated States of) 37.2 Mauritania 9.7 Lesotho 14.2 Lao People's Democratic Republic 3.5 Kyrgyzstan 14.4 Kiribati 40.6 Indonesia 5.7 India 4.9 Honduras 18.2 Guyana 22.9 Guatemala 18.6 Ghana 12.2 Georgia 20.8 El Salvador 21.8 Egypt 28.9 Djibouti 9.6 Côte d'Ivoire 9.2 Congo 11.0 Cameroon 11.4 Cabo Verde 13.0 Bolivia (Plurinational State of) 17.1 Bhutan 6.7 Armenia 19.5 0% 50% (b) 20% 10% 30% 40% Venezuela (Bolivarian Republic of) 24.8 Tuvalu 40.3 Turkmenistan 20.1 Turkey 29.5 Tunisia 27.1 Tonga 43.3 the former Yugoslav Republic of Macedonia 19.6 Thailand 8.5 Suriname 26.1 South Africa 26.8 Seychelles 26.3 Serbia 19.5 Saint Vincent and the Grenadines 24.3 Saint Lucia 26.9 Romania 21.7 Peru 21.1 Panama 26.8 Palau 47.6 Niue 43.2 Nauru 45.6 Namibia 18.9 Montenegro 20.0 Mexico 28.1 Mauritius 17.9 Marshall Islands 42.8 Maldives 7.9 Malaysia 13.3 Libya 33.1 Lebanon 31.9 Kazakhstan 23.4 Jordan 30.5 Jamaica 27.2 Iraq 23.8 Iran (Islamic Republic of) 26.1 Hungary 24.0 Grenada 26.2 Gabon 17.6 Fiji 36.4 Ecuador 18.7 Dominican Republic 23.9 Dominica 25.8 Cuba 25.2% Costa Rica 24.3 Cook Islands 50.8 Colombia 21.0 China 6.9 Bulgaria 23.2 Brazil 20.0 Botswana 22.4 Bosnia and Herzegovina 17.9 Belize 22.5 Belarus 23.4 Azerbaijan 22.5 Argentina 26.3 Angola 10.2 Algeria 24.8 Albania 17.6 0% 50% 20% 10% 30% 40% Low-middle-income Upper-middle-income Fig. 11.6.1 Continued

11.6 Obesity 1907 studies that genetic factors contribute to this variability. Heritability estimates can change over time and can differ between populations. Recent studies in a UK sample of 5092 twin pairs aged 8–11 years growing up during a time of dramatic rises in obesity, confirmed substantial heritability for BMI and waist circumference (77% for both), while there was a very modest shared-environment effect, and the remaining environmental variance was unshared. Interestingly, similar heritability estimates have been found when studying mono- zygotic and dizygotic twins who were reared together and apart and in adoption studies, where adopted children were discovered to have body sizes that were more similar to those of their biological parents than their adopted parents. Recently, genome-wide association have led to the identification of multiple genomic regions/loci that are strongly associated with increased BMI and/or obesity. However, to date, the common vari- ants that have been identified explain less than 5% of the heritability of increased BMI. It is likely that rare variants that are more highly penetrant will explain more of the missing heritability of obesity. Programming and epigenetics Recent evidence suggests that undernutrition of the fetus during intrauterine development can influence the later onset of obesity, hypertension, and type 2 diabetes, independent of genetic factors. Such a phenomenon suggests the possibility of long-term program- ming of genetic expression as a consequence of altered intrauterine growth. The influence of maternal diet and other factors on the regu- lation of genes in their offspring, referred to as epigenetics, is the focus of much current research. Hypothalamic circuits regulating energy homeostasis Energy homeostasis is tightly regulated, with the hypothalamus playing a pivotal role in integrating signals from adipose tissue stores, such as leptin, and short-term meal-related signals from the gut

(peptide-YY, glucagon like peptide-1 (GLP-1), cholecysto- kinin, and ghrelin; see Fig. 11.6.3). The hypothalamus integrates these sensory inputs, compares those inputs to ‘set-points’ for en- ergy homeostasis, and then initiates a set of responses by activating autonomic, endocrine, and behavioural outputs that aim to maintain these set-points (homeostasis). Leptin stimulates the expression of pro-opiomelanocortin (POMC), which is cleaved by prohormone convertases to yield the melanocortin peptides, which act as Prevalence of overweight in children aged under 5 years, by WHO region and World Bank income group, comparable estimates, 2013 14% 12% 10% 8% 6% 4% 2% 0% AFR AMR SEAR EUR EMR WPR Low- income Low- middle- income Upper- middle- income High- income Fig. 11.6.2 Prevalence of overweight in children under 5 years by World Health Organization (WHO) region and World Bank income group (estimates in 2013). AFR, African region; AMR, region of the Americas; SEAR, Southeast Asia region; EUR, European region; EMR, Eastern Mediterranean region; WPR, Western Pacific region. Reprinted from Global status report on noncommunicable diseases 2014, Copyright © World Health Organization 2014. Hypothalamus Leptin Insulin Pancreas Adipose tissue GI tract Ghrelin PYY GLP-1 CCK Vagus nerve Nutrients (glucose, fatty acids, etc.) Fig. 11.6.3 Interactions between the hypothalamus, adipose tissue, and gastrointestinal tract. CCK, cholecystokinin; GI, gastrointestinal; GLP-1, glucagon like peptide-1; PYY, peptide-YY.

SECTION 11 Nutrition 1908 suppressors of feeding through the melanocortin 4 receptor (MC4R). This is a key circuit in the regulation of body weight, but numerous other pathways involving the mesolimbic system, the hindbrain, and orbitofrontal cortex influence eating behaviour (Fig 11.6.4). Clinical history, examination, and investigation For the assessment of severely obese patients, the consultation room should be properly equipped with larger than average chairs, access for wheelchairs for patients with mobility problems, and medical equipment of appropriate size (examination couch, blood pressure cuff, weighing scales, stadiometer (for measurement of height), and tape measure). In addition to a general medical history, a specific weight his- tory should be taken, carefully establishing the age of onset (clinical photographs are helpful here), as it is useful to distinguish obesity that began in childhood (stronger genetic component) from that occurring later in life either in relation to specific physiological ‘crit- ical periods’ such as pregnancy, illness, or concomitant medications. A history of previous treatment for obesity, diet, and levels of phys- ical activity should be noted. The assessment of severely obese children and adults should include screening for potentially treatable endocrine and neuro- logical conditions and identifying genetic conditions so that ap- propriate genetic counselling and, in some cases, treatment can be instituted. In most patients, these specific causes can be excluded by a careful clinical history (Box 11.6.1), examination, and inves- tigations (Table 11.6.3), which should also address the potential hidden complications of severe obesity such as sleep apnoea, cor- onary heart disease, type 2 diabetes, gynaecological abnormalities, osteoarthritis, gallstones, and stress incontinence. Height should be measured accurately using a stadiometer and weight measured by accurate scales in light clothing. BMI does not distinguish between excess fat and lean body mass, hence waist cir- cumference (or waist-to-hip ratio), which is a predictor of metabolic complications, should be measured. Ethnicity should be taken into consideration as individuals from some groups (e.g. South Asians) have a greater metabolic risk than would be expected for their BMI and waist circumference. Waist circumference is taken as the mid- point between the lower rib margin and the iliac crest. An examination of the skin is important: thin, atrophic skin is a feature of excess corticosteroids; acanthosis nigricans (pigmented ‘velvety’ skin creases, especially in the axillae) suggests insulin re- sistance; severe hirsutism in women may indicate polycystic ovary syndrome.

A neck circumference of more than 43 cm indicates a likelihood of obstructive sleep apnoea. Clinicians should use laboratory testing to evaluate overweight and obese patients who may be at high risk for cardiovascular dis- ease and type 2 diabetes. Some useful tests to consider are fasting plasma glucose or 2-h postprandial glucose levels and serum lipid levels. Thyroid-stimulating hormone (TSH) may be helpful in excluding hypothyroidism. Urinary free cortisol can be obtained if hypercortisolism is suspected clinically. Fig. 11.6.4 Several single-gene defects that disrupt the molecules in the leptin–melanocortin pathway cause severe obesity (indicated by *). Leptin is released from adipose tissue to act on receptors expressed on the surface of distinct populations of neurones in the arcuate nucleus of the hypothalamus. Leptin stimulates a neuropeptide called pro-opiomelanocortin (POMC), which is then cleaved by the enzyme prohormone convertase 1 (PC1) to yield the melanocortin peptides. Leptin inhibits the expression of neuropeptide Y (NPY) and agouti-related peptide (AgRP). Both sets of neurons project to synapse, with second-order neurons expressing the melanocortin 4 receptor (MC4R), ultimately leading to an inhibition of food intake.

 Other tests to consider depend on clinical assessment and include ultrasonography for hepatic steatosis, gallstones, and the polycystic ovary syndrome; electrocardiography in patients at high risk for car- diovascular disease; polysomnography for patients with possible sleep apnoea; and head CT or MRI when pituitary or hypothalamic disorders are suspected. Genetic testing is needed to confirm the diagnosis in patients with rare genetic disorders. The measurement of serum leptin is not recommended as a routine examination, but should be undertaken in cases of severe early onset obesity, since, although it is rare, congenital leptin deficiency is a potentially treat- able disorder. Genetic obesity syndromes Classically, patients affected by genetic obesity syndromes have been identified as a result of their association with developmental delay, dysmorphic features, or other developmental abnormalities. More recently, several single-gene disorders resulting from disruption of the hypothalamic leptin–melanocortin signalling pathway have been identified. In these disorders, obesity itself is the predominant presenting feature, although frequently accompanied by character- istic patterns of neuroendocrine dysfunction that will only become apparent on investigation. Mutations in several of these molecules cause severe obesity associated with specific neuroendocrine abnor- malities (Table 11.6.4). One rare genetic disorder, leptin deficiency, is entirely treatable with daily subcutaneous injections of recom- binant human leptin, and another, MC4R deficiency, is relatively common, with a population prevalence of 1 in 1000 unselected indi- viduals and 1 in 100 obese people. For the purposes of clinical assessment, it remains useful to cat- egorize the genetic obesity syndromes as those with dysmorphism and/or developmental delay, and those without these features. There are about 30 Mendelian disorders with obesity as a clinical feature but often associated with mental retardation, dysmorphic features, and organ-specific developmental abnormalities: the commonest of these are listed in Table 11.6.5. Approach to the treatment of obesity The recommendation to treat obesity is based on evidence that re- lates obesity to increased mortality and the results from randomized controlled trials, which demonstrate that weight loss reduces the risk of many metabolic complications. Professional, governmental, Box 11.6.1 History • Age of onset—use of growth charts and family photographs. Early onset (<5 years of age) suggests a genetic cause. • Duration of obesity—short history suggests endocrine or central cause. • A history of damage to the CNS (e.g. infection, trauma, haemor- rhage, radiation therapy, seizures) suggests hypothalamic obesity with or without pituitary growth hormone deficiency or pituitary hypothyroidism. A history of morning headaches, vomiting, visual disturbances, and excessive urination or drinking also suggests that the obesity may be caused by

a tumour or mass in the hypothalamus. • A history of dry skin, constipation, intolerance to cold, or fatigue sug- gests hypothyroidism. Mood disturbance and central obesity suggests Cushing's syndrome. Frequent infections and fatigue may suggest ACTH deficiency due to POMC mutations. • Hyperphagia—often denied, but a sympathetic approach is needed and responses to specific questions, such as waking at night to eat or demanding food very soon after a meal, suggest hyperphagia. If se- vere, especially in children, suggests a genetic cause for obesity. • Developmental delay—milestones, educational history, behavioural disorders. Consider craniopharyngioma or structural causes (often relatively short history) and genetic causes. • Visual impairment and deafness can suggest genetic causes. • Onset and tempo of pubertal development—onset can be early or delayed in children and adolescents. Primary hypogonadotropic hypogonadism or hypogenitalism associated with some genetic disorders. • Family history—consanguineous relationships, other children affected, family photographs useful. Severity may differ due to environmental effects. • Treatment with certain drugs or medications. Glucocorticoids, sulphonylureas, oral contraceptives, antidepressants, and antipsychotics.
Table 11.6.3 Key points in the examination and investigation of an obese patient Examination Height, weight—calculate BMI Blood pressure Waist circumference Neck circumference Acanthosis nigricans Body fat distribution Secondary sexual characteristics Any evidence of cardiac disease Signs of hyperlipidaemia Signs of thyroid disease Ophthalmic evidence of diabetes or sustained hypertension Investigations Fasting and postprandial blood glucose Fasting lipid profile Strip test for urine glucose and protein Free thyroxine and thyroid-stimulating hormone Table 11.6.4 Obesity syndromes in the absence of developmental delay Name of syndrome Clinical characteristics Alstrom Progressive nephropathy, photophobia, retinitis pigmentosa, deafness, diabetes mellitus due to marked insulin resistance Leptin Severe hyperphagia, frequent infections, hypogonadism Prohormone convertase 1 Neonatal diarrhoea, postprandial hypoglycaemia, multiple endocrine abnormalities Leptin receptor Severe hyperphagia, frequent infections, hypogonadism POMC Isolated ACTH deficiency, hypopigmentation MC4R Increased linear growth, severe hyperinsulinaemia, 'big-boned' appearance ACTH, adrenocorticotropic hormone; MC4R, melanocortin 4 receptor; POMC, pro-opiomelanocortin.

 and other bodies have drawn up guidelines for obesity management and it is advisable to seek out the latest national and international guidelines as newer evidence is incorporated. These strategies pro- vide useful evidence-based guidance for clinical management, but it is important to remember that an individually tailored approach is often required and that any treatment programme for obese pa- tients should address weight reduction and the maintenance of the lowered weight and take account of individual circumstances. Goals of weight loss Achievement of normal or ideal body weight is not a necessary goal in the management of obesity and is rarely reached in practice. There is evidence from epidemiological studies of intentional weight loss that modest weight loss, of the order of 5 to 10% from presenta- tion weight, is associated with clinically worthwhile reductions in comorbidities, such as hypertension, dyslipidaemia, and diabetes risk (Table 11.6.6). In some patients, particularly in those with se- vere comorbidity, prevention of weight gain may be a reasonable aim of treatment. Weight loss should be approached incrementally, with new goals for weight loss negotiated with the patient once the ori- ginal target has been achieved. Dietary management Many dietary approaches have been advocated for the treatment of obesity. Recent evidence-based reviews support the use of low- calorie diets as being most likely to be effective for modest weight loss. A review of 48 randomized control trials shows that an average weight loss of 8% of the initial body

weight can be obtained over 3 to 12 months with a low-calorie diet. Such a treatment may require a period of supervision for at least 6 months. The weight-reducing dietary regimen should initially provide a 600 kcal/day (2.5 MJ/day) energy deficit, based on estimated en- ergy requirements. After 6 months, the rate of weight loss usually declines and a further adjustment of calorie intake may be indi- cated at this stage. The use of very low-calorie diets can be con- sidered, ideally under close supervision as preparations must provide a minimum of 400 kcal (1.7 MJ) per day for women and 500 kcal (2.1 MJ) per day for men. Evidence from randomized trials confirms that over the longer term (more than a year), weight loss following very low-calorie diets is no different from that obtained with low-calorie diets. Behavioural therapy and exercise Behavioural approaches aim to help people to implement and sus- tain changes to their eating and activity behaviour. There is evi- dence that combining a behavioural approach with more traditional dietary and activity advice leads to improved short-term weight loss. In general, weight loss with these approaches is modest (about 4 kg or 4% of body weight on average). Although modest physical activity has undoubted health bene- fits and can contribute to weight loss, it is not usually advocated as a sole treatment option. Many studies, however, do suggest that it can be helpful to improve weight loss maintenance once weight loss has been achieved. The results from randomized controlled trials suggest that a combination of diet and exercise generally produces more weight loss than diet alone. The optimal approach should be a high-quality diet to which patients will adhere, accompanied by an exercise prescription describing frequency and intensity of exercise with a minimum of 150 min moderate weekly activity. The type of physical activity (e.g. aerobic versus resistance) does not seem to af- fect overall weight loss. Table 11.6.5 Obesity syndromes with developmental delay Name of syndrome Gene/genetic region involved Clinical characteristics Prader–Willi Deletion or uniparental maternal disomy of chromosome 15q11.2–-q12 Hypotonia, short stature, hypogonadotropic hypogonadism, feeding difficulties <2 years of age, then hyperphagia with pica behaviour Bardet–Biedl Mutations in multiple genes affect the function of cilia Polydactyly, retinitis pigmentosa, and hypogonadism are consistent features Fragile X Unstable expansion of trinucleotide repeats in the FMR1 gene Moderate to severe developmental delay, macro-orchidism, prominent jaw, and high-pitched jocular speech Cohen COH1 mutations Microcephaly, characteristic facial features, progressive retinochoroidal dystrophy, myopia, and a cheerful disposition Albright hereditary osteodystrophy GNAS1 mutations Short stature, round facies, brachydactyly, and ectopic soft tissue ossification (osteoma cutis), variable hormone (TSH, PTH) resistance, short fourth metacarpal BDNF/TrkB deficiency Mutations/deletions in BDNF or its receptor TrKB Delayed speech and language development, impaired short-term memory, and loss of nociception BDNF, brain-derived neurotrophic factor; PTH, parathyroid hormone; TrkB, neurotrophic tyrosine kinase, receptor, type 2; TSH, thyroid-stimulating hormone. Table 11.6.6 Potential health benefits that may accrue from the loss of 10 kg from the initial body weight Mortality 20–25% fall in total mortality 30–40% fall in diabetes-related deaths 40–50% fall in obesity-related cancer deaths Blood pressure c.10 mm Hg fall in both systolic and diastolic values Diabetes

> 50% reduction in risk of developing diabetes 30–50% fall in fasting glucose 15% fall in haemoglobin A1c Lipids 10% fall in total cholesterol 15% fall in LDL cholesterol 30% fall in triglycerides 8% increase in HDL cholesterol HDL, high-density lipoprotein; LDL, low-density lipoprotein.

11.6 Obesity 1911 Two large randomized clinical trials—the Look AHEAD and the Diabetes Prevention Programme—support the use of intensive weight loss programmes with face-to-face (group or individual) sessions. The delivery of such programmes is often expensive and a useful alternative is the use of commercial programmes to deliver advice within communities. A meta-analysis comparing named diets and several comparisons of diets with different amounts of fat/carbohydrate/protein have found that there was no significant difference between diets in terms of weight loss achieved. A key goal is identifying a diet that a particular patient finds that they can adhere to. Drug therapy General principles While intervention programmes that focus on supporting people to change their diet and/or levels of physical activity can be effective in inducing weight loss in the short to medium term in some people, they lose efficacy in the long term. In addition to the focus on pre- vention of obesity, treatment of obese patients, preferably at a stage before complications has emerged, is therefore an important priority. Previous antiobesity drugs targeted cannabinoid signalling (rimonabant), noradrenergic (phentermine), serotoninergic signalling (fenfluramine, dexfenfluramine), and reuptake (sibutramine). These compounds were moderately effective but, as with many centrally acting agents, at the expense of many off-target effects, reflecting lack of specificity of the neural targets. The use of obesity drugs should follow the same principles as for any condition and be prescribed after assessment of the potential benefits and risks with appropriately informed patients, and with medical monitoring of the results of treatment. Some healthcare providers still believe that a short course of drug treatment might 'cure' obesity or that efficacy is measured only by ever-continuing weight loss. These ideas are inconsistent with the known biology as people who become obese have a persistent tendency both to defend their excess weight and to continue to gain extra body fat. Effective management must be lifelong and focused on weight loss mainten- ance in a similar fashion to the effective treatment for hypertension or diabetes. Starting drug treatment should always be regarded as a therapeutic trial and stopped if weight loss is not apparent after 1 or 2 months. The initiation of drug treatment will depend on the physician's judgement about the risks to an individual from continuing obesity. A drug should not be considered ineffective because weight loss has stopped, provided that the lowered weight is maintained. However, continuation of the drug should depend on the balance between the health benefits of maintained weight and the potential adverse ef- fects of the drug. Particular drugs Orlistat Orlistat inhibits pancreatic and gastric lipases, thereby decreasing the hydrolysis of ingested triglycerides. It produces a dose-dependent reduction in absorption of dietary fat that is near maximum at a dose of 120 mg, three times daily. It leads to 5 to 10% weight loss in 50 to 60% of patients, and in clinical trials the loss (and related clinical benefit) is largely maintained up to at least 4 years. Adverse effects of orlistat are predominantly related to malabsorption of fat. These include loose or liquid stools, faecal ur- gency, and oily discharge; they can be associated with malabsorption of fat-soluble vitamins. As the consumption of a high-fat meal will inevitably lead to severe gastrointestinal symptoms, it is possible that some of the weight loss with orlistat treatment results from an 'Antabuse effect', leading to behavioural change. Sibutramine Sibutramine inhibits the reuptake of noradrenaline and serotonin, promoting, and prolonging satiety. It may also have an enhancing effect on thermogenesis through the stimulation of peripheral noradrenergic receptors. Adverse effects include nausea, dry mouth, rhinitis, and constipation. It produces 5 to 10% weight loss in 60 to 70% of patients, which in clinical trials is well maintained for at least 2 years. The noradrenergic action increases heart rate by 1 to 2 beats/min and attenuates the fall in blood pressure expected with weight loss. Some patients, especially if they fail to lose weight, may record a rise in their blood pressure; it is therefore essential to monitor blood pressure during treatment. Recent concerns about increased cardiovascular

morbidity as- sociated with Sibutramine have led to prescribing restrictions, par- ticularly relevant to those patients with established cardiovascular disease. Current guidelines in Europe and the United States vary and physicians should consult local guidelines where available. Newer centrally acting antiobesity drugs Over the last few years, certain weight loss drugs have been ap- proved by the US Food and Drug Administration (FDA) and other regulators, expanding the number of options available to physicians seeking to treat patients with severe obesity and/or obesity with complications. Lorcaserin, a selective 5HT2cR agonist with limited activity at the other serotonin receptors, leads to weight loss, lowers blood pres- sure, total cholesterol, low-density lipoprotein cholesterol, and tri- glycerides, although concerns about potential cardiac valvulopathy and cancer risk remain. Adverse effects include headache, nausea, fatigue, and dizziness. An extended release combination of the anticonvulsant topiramate (which modulates GABA-ergic transmission and inhibits carbonic anhydrase) and phentermine, which increases central noradren- aline levels, is also approved in some countries. Topiramate is asso- ciated with fetal toxic effects and a pregnancy test before and during therapy is recommended. Bupropion, a dopamine and noradrenaline reuptake in- hibitor, has anorexigenic properties resulting in modest weight loss. The effectiveness of bupropion is increased (and thus the dose can be reduced) when combined with the opioid receptor antagonist naltrexone, resulting in the combination product, naltrexone-bupropion. The synthetic GLP-I receptor agonist liraglutide, effective in the treatment of type 2 diabetes, has been approved for the treatment of obesity alone by the FDA. Nausea remains a significant problem in many, but those who can tolerate the dug do well. Several other gut peptide analogues, gut hormone receptor agonists, and cen- trally active compounds are currently being studied in clinical trials.

SECTION 11 Nutrition 1912 More recently a potent melanocortin receptor agonist, RM-493, has been administered as part of a phase 1b proof-of-concept clinical trial in obese patients, including one cohort with heterozygous loss of function mutations in MC4R where there was promising weight loss after four-weeks. If this compound moves forward, this may be one of the first examples of a personalized medicine approach for treating obesity in people with a genetically characterized subtype of obesity. Surgical treatment of obesity Randomized controlled trials confirm that surgery for obesity is an effective option for carefully selected patients with severe obesity (BMI >40 kg/m2 or BMI >35 kg/m2 with comorbid conditions). The nature of the surgical procedures necessitates long-term hospital follow-up for such patients. The initial findings from the Swedish Obese Subjects study of severely obese subjects (those with a BMI

> 40. indicate that weight loss of approximately 30 kg over 2 years is associated with a 60% reduction in plasma insulin, a 25% decrease in plasma glucose and triglycerides, and a 10% reduction in blood pressure with associated effects on the risk of cardiovascular disease. Poor health-related quality of life was dramatically improved after gastric restriction surgery, while only minor fluctuations in health-related quality of life were observed in people treated by conven- tional dietary methods. Most surgical treatment is now carried out laparoscopically. Some procedures are commonly used, each having its own risks and benefits which need to be considered carefully on an

individual basis. Laparoscopic gastric banding This operation involves gastric restriction with the creation of a small compartment (<20 ml) by either a combination of vertical stapling and a constrictive band opening, or a gastric band pinching off a small proximal pouch. A modification of the latter procedure is an inflatable gastric band attached to a subcutaneous reservoir which allows access by a hypodermic syringe to inject or withdraw fluid, thereby tightening or enlarging the band width. This method mainly works by restricting how much food patients can eat. The average weight loss is around 15 to 20% of body weight, although some weight regain occurs over time. Morbidity and mortality are relatively low (mortality <0.2%), but patients do need to return for band adjustments. Gastric bypass This involves creating a small-volume gastric pouch and produ- cing a Roux-en-Y diversion so that food bypasses the duodenum and upper jejunum. This works by both restricting food intake and causing a modest degree of malabsorption. Weight loss is generally greater than with the band. Operative mortality is less than 0.2% for laparoscopic procedures and 0.5% for open procedures. Duodenal switch and sleeve gastrectomy A variant of the older biliopancreatic diversion, this involves a partial (sleeve gastrectomy) and bypass of a long loop of jejunum. Weight loss is greatest with this procedure, but malabsorption is more likely and patients need careful follow-up and attention to their diet, vitamin, and mineral supplementation. Concluding remarks As the prevalence of obesity is rising, we are seeing more and more patients with severe obesity. It is important to have a practical ap- proach to the investigation and management of these patients who have considerably increased morbidity and mortality. The clinical evaluation of severely obese patients will become increasingly so- phisticated, and novel biochemical and molecular genetic diagnos- tics will need to be combined with the more traditional nutritional and behavioural approaches to optimize treatment for individual patients. FURTHER READING Allison DB, et al. (1996). The heritability of body mass index among an international sample of monozygotic twins reared apart. Int J Obes Relat Metab Disord, 20, 501–6. Berrington de Gonzalez A, et al. (2010). Body-mass index and mor- tality among 1.46 million white adults. N Engl J Med, 363, 2211–19. Bray GA, et al. (2016). Management of obesity. Lancet, 387, 1947–56. Feinleib M (1985). Epidemiology of obesity in relation to health haz- ards. Ann Intern Med, 103, 1019–24. Gadde KM, et al. (2011). Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associ- ated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet, 377, 1341–52. Gautron L, Elmquist JK, Williams KW (2015). Neural control of en- ergy balance: translating circuits to therapies. Cell, 161, 133–45. Gray LJ,

et al. (2012). A systematic review and mixed treatment com- parison of pharmacological interventions for the treatment of obesity. Obes Rev, 13, 483–98. Greenway FL, et al. (2010). Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet, 376, 595–605. Khera R, et al. (2016). Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. JAMA, 315, 2424–34. Locke AE, et al. (2015). Genetic studies of body mass index yield new insights for obesity biology. Nature, 518, 197–206. Look AHEAD Research Group (2014). Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. Obesity (Silver Spring), 22, 5–13. Ogden CL, Carroll MD, Flegal KM (2012). Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. JAMA, 307, 483–90. Ogden CL, et al. (2014). Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA, 311, 806–14. Pi-Sunyer X, et al. (2015). A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med, 373, 11–22. Pilitsi E, et al. (2019). Pharmacotherapy of obesity: available medica- tions and drugs under investigation. Metabolism, 92, 170–92. Popkin BM (2006). Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases. Am J Clin Nutr, 84, 289–98. Puhl R, Brownell KD (2001). Bias, discrimination, and obesity. Obes Res, 9, 788–805.

11.6 Obesity 1913 Singh GK, Lin SC (2013). Dramatic increases in obesity and over- weight prevalence among Asian subgroups in the United States, 1992–2011. ISRN Prev Med, 2013, 898691. Smith SR, et al. (2010). Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med, 363, 245–56. Sorensen TI, et al. (1989). Genetics of obesity in adult adoptees and their biological siblings. BMJ, 298, 87–90. Tan T, Bloom S (2013). Gut hormones as therapeutic agents in treatment of diabetes and obesity. Curr Opin Pharmacol, 13, 996–1001. Thomas DM, et al. (2014). Dynamic model predicting overweight, obesity, and extreme obesity prevalence trends. Obesity (Silver Spring), 22, 590–7. van der Klaauw AA, Farooqi IS (2015). The hunger genes: pathways to obesity. Cell, 161, 119–32. Wardle J, et al. (2008). Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environ- ment. Am J Clin Nutr, 87, 398–404. Yanovski SZ, Yanovski JA (2014). Long-term drug treatment for obesity: a systematic and clinical review. JAMA, 311, 74–86.

11.7 Artificial nutrition support 1914

11.7 Artificial nutrition support 1914

ESSENTIALS The prevalence and relevance of undernutrition in affluent societies is often unrecognized, but nutritional status significantly impacts out- comes in all disease states. Nutrition screening identifies patients at risk of undernutrition and should be carried out in hospitals and community: its components comprise past weight loss, current body mass index, and likely fore- seeable nutritional challenges. A body mass index less than 18.5 kg/m2;
weight loss of more than 10% over 6 months; or BMI of less than 20 kg/m2 with weight loss of more than 5% over 6 months, are all indicative of undernutrition. Nutrition support is indicated for malnourished patients or those at risk of undernutrition in view of inadequate oral intake or malabsorption. Timing of the intervention depends on the pre- existing nutritional status and the likelihood of restoring adequate intake. Nutrient requirements are calculated using weight-based formulae for basal energy and protein requirements, with additional factors for physical activity, severity of illness, or desired weight gain. Increased requirements due to disease are often counterbalanced by reduced activity. Institutional provision of food (in a conducive environment) of appropriate quantity, texture, temperature, and variety, with encouragement and assistance to eat, may obviate the requirement for artificial nutrition support. Artificial nutrition support can be provided in the form of oral nu- tritional supplements, or enteral or parenteral tube feeding. Enteral feeding is physiologically preferable to parenteral nutrition as it maintains gut integrity, stimulates hormonal regulation of metab- olism and gastrointestinal functions, and delivers nutrients to the liver via the portal circulation. Tube feeding can be associated with significant complications re- lating to the means of access or delivery of nutrients. It is easy to overfeed with parenteral nutrition, especially in catabolic patients who are unable to utilize excess protein or energy. The potential risks of the route of feeding need to be balanced against the benefits for any individual, which influences the timing of the intervention. Tube feeding is only instituted where oral feeding is impossible or inadequate and hence benefits are unclear due to the ethical im- possibility of randomized trials in this setting. However, oral nutrition supplementation in selected patient groups is associated with signifi- cant reduction in both morbidity and mortality. A multiprofessional team is required to coordinate and monitor the necessary support for patients fed artificially in hospital and the community. Patients can receive artificial nutrition support indefin- itely in the community. Outcomes of intestinal transplantation have improved significantly over recent years,

but due to excellent long- term outcomes on home parenteral nutrition, this is usually con- sidered only where there are life-threatening complications of such treatment. Introduction In affluent societies where food is plentiful the extent of under nutrition is poorly recognized, affecting more than 10% of all adults over the age of 65 years in the community, and around 40% of all hospital inpatients or elderly care home residents. Undernutrition usually arises from social or disease-related factors, and in turn has profound implications for the progression of illness and outcome of treatment by altering physiological responses and having effects on immunity and healing as well as psychology, motivation, and social interaction. Chronic illness often increases nutritional require-ments, but this is often balanced by a reduction in physical activity. The associated anorexia or inability to feed orally usually contrib- utes more significantly to undernutrition and is directly amenable to intervention by nutrition support. Nutritional screening and assessment of nutritional status Weight is easier to lose than regain, and although weight may be ul- timately restored, the body composition takes longer to normalize as initial weight gain comprises significant fluid and fat components rather than lean mass. The risk of undernutrition related complica- tions therefore relates to the disease trajectory as well as the current nutritional status. These components—prior weight loss, current nutritional status, and pending threats to nutritional intake—are combined into a nutrition 'risk score', and such scores are routinely 11.7 Artificial nutrition support Jeremy Woodward

11.7 Artificial nutrition support 1915 used in clinical practice to identify patients requiring nutritional op- timization (Fig. 11.7.1). History A nutrition history will include the nature of the baseline diet—not only for vegans and vegetarians who may be lacking in haem iron and vitamin B12, but also for poor fresh fruit and vegetable intake (vitamin C and folic acid) and dairy avoidance (calcium), or other dietary restrictions due to intolerances, dislikes, or fads. Excessive alcohol intake can be associated with thiamine and folic acid deficiency. Oral conditions may make ingestion painful; abdominal symp- toms such as nausea, bloating or pain can reduce intake and patients may not admit to (or even be aware) of significant changes in appe- tite. Medication side effects may alter dietary intake and a variety of conditions can lead to taste disturbances. Psychosocial circumstances can have a profound impact on oral intake—for instance, in depres-sion, bereavement, social isolation, impaired mobility, or poverty. Fig. 11.7.1 The 'Malnutrition Universal Screening Tool' (MUST)—an example of an algorithm for screening and identification of malnutrition and the appropriate actions to be taken based on risk score. This tool is reproduced with kind permission of BAPEN—British Association for Parenteral and Enteral Nutrition.

SECTION 11 Nutrition 1916 Examination Patients may not have weighed themselves or be aware of weight loss, but clinical features may be present such as prominent cheek- bones, muscle wasting, redundant skin folds, and concave abdomen. Ill-fitting clothing, belt notches, and loose rings on fingers provide additional clues. Many of these signs are apparent even in obese in- dividuals who remain overweight despite recent weight loss. Signs of specific nutritional deficiencies (see Chapters 11.2 and 11.3) may be identified, particularly in hair, eyes, skin, nails, teeth, and tongue. Body mass index, and its limitations The ratio of weight (in kg) to the square of the height (in m2) is known as the body mass index (BMI) and provides a useful indication of nutritional status. It may, however, be misleading, for instance in younger patients, those with skeletal deformity due to cerebral palsy, or elderly patient with osteoporosis. A BMI of less than 18.5 kg/m2 is considered indicative of undernutrition, as is weight loss of more than 10% over 6 months or a BMI of less than 20 kg/m2 in associ- ation with weight loss of more than 5% over 6 months. In children the use of

centile charts is valuable as sustained undernutrition leads to reduced height velocity and failure to meet predicted height. The major drawback of using BMI for nutritional assessment is that it is affected by changes in body composition, with clinically important changes in lean body mass being masked by shifts in fluid distribution and adipose tissue. The entity of sarcopenic obesity—overweight individuals with reduced muscle mass or function—has recently been described associated with ageing or inflammatory pathology and highlights the weakness of using body mass alone without considering its components. Bio-impedance measurement can provide measurements of extra- cellular water and estimates of fat-free mass from which lean body mass can be calculated, but validation in disease settings is still re- quired. Sequential measurements of mid-upper arm circumference and triceps skin fold thickness using a tape measure and callipers can provide estimates of changes in lean body mass, and hand-grip dynamometry measurements are a useful surrogate of changes in functional muscle mass. Used at a single point in time, however, wide reference ranges make these tools unreliable for nutritional assessment. Dual energy X-ray absorptiometry (DEXA) and volu- metric analysis of CT scans are becoming more widely available as tools for measuring body composition. Indications for artificial nutrition support Undernutrition can be prevented in patients at risk by simple meas- ures to optimize appetite such as reducing symptoms such as pain or nausea that lead to anorexia. The range of menus and the presen- tation and temperature of meals in hospital affect the amount con- sumed, as well as limiting interruptions at mealtimes or ‘nil by mouth’ orders. Institutional catering needs to accommodate the require- ments of patients with altered feeding patterns, such as after upper gastrointestinal surgery or with dysmotility, and older people often prefer to snack rather than take large meals. Patients with disabil- ities may require assistance with eating and sufficient staff and time are required to provide this. Food texture may need to be altered— pureed or liquid diets benefit patients with oesophageal strictures or gastroparesis, whereas thickening fluids with starch reduces the risk of pulmonary aspiration in neurological causes of dysphagia. Artificial nutrition support is required if such measures are in- effective in maintaining sufficient oral intake. If swallowing is in- tact and palatability is acceptable then oral nutrition supplements can be provided. Unconscious patients, those unable to swallow or with upper gastrointestinal obstruction can receive enteral nutrition support if intestinal function is preserved. Access can be achieved by pernasal or transabdominal feeding tubes to the stomach or in- testine. Patients without adequate intestinal function require total or partial parenteral nutrition support via an intravenous catheter. Common indications for enteral and parenteral artificial support are given in Tables 11.7.1 and 11.7.2. The timing of nutritional support interventions depends on the pre-existing nutritional status of the patient and likely subsequent events. It has proven difficult to demonstrate any benefit for short term artificial nutrition support, but it is equally challenging to predict when a patient will become nutritionally independent. Table 11.7.1 Common indications for enteral nutrition support Impaired conscious level Head injury Ventilated patients in critical care setting Cerebrovascular disease Neurological dysphagia Motor neuron disease Cerebrovascular disease Multiple sclerosis Bulbar palsy Cerebral palsy Upper gastrointestinal obstruction Head and neck cancer Oesophageal cancer Gastric cancer Gastric outlet obstruction—benign or malignant Dysmotility Severe oesophageal dysmotility Gastroparesis Related to treatment modalities Prior to chemoradiation therapy for head and neck cancer Post complex upper gastrointestinal surgery (i.e. Whipple’s procedure, oesophagectomy) Inability to meet nutritional requirements orally Malabsorption Borderline short gut Anorexia secondary to chronic illness Respiratory disease (i.e. cystic fibrosis) Table 11.7.2 Common indications for parenteral nutrition support Enteric dysmotility Hirschsprung’s disease Visceral neuropathy Visceral myopathy Systemic sclerosis Radiation

enteritis Postoperative ileus Intestinal obstruction Malignancy – Gastrointestinal – Metastatic ovarian or peritoneal – Metastatic breast Sclerosing peritonitis Postsurgical adhesions Mucosal disease Microvillous inclusion disease Autoimmune enteropathy Refractory coeliac disease

11.7 Artificial nutrition support 1917 However, the benefits of early nutrition support have been clearly demonstrated in a variety of settings and the timing of intervention therefore requires an individual assessment balancing the benefits of early intervention against its cost and risks. Estimating nutrition requirements Energy Energy expenditure under basal conditions reflects physiological cellular metabolism and therefore correlates with body mass. Derivative equations based on weight and corrected for age and gender provide estimates of energy consumption that adequately match measurements based on oxygen uptake and CO_2 production (indirect calorimetry) for most clinical purposes. Additions are re- quired for activity and the thermal effect of food. Disease states such as burns, sepsis, or trauma increase energy expenditure, but this is usually compensated for by reduced physical activity and overall may equate to an increase of only 10–20% over resting energy ex- penditure. Corrections also need to be made for patients with oe- dema or obesity and energy requirements in these circumstances may be based on a proportion of body mass or ideal body weight. Most hospital patients' requirements lie within the range of 25–40 kcal/kg per day (105–168 kJ/kg per day). Fluid Fluid balance must be considered a part of the nutritional require- ments, and nutrition and hydration should be considered together. Most hospitalized patients require 30–35 ml/kg per day, with add- itions to replace losses. Fluid losses from the kidneys—with diabetes insipidus or when recovering from acute tubular necrosis—can be excessive and obligatory, while volumes of 10 litres a day can be lost from the gastrointestinal tract via a proximal jejunostomy or enterocutaneous fistula. Fluid restriction is indicated in overloaded states or in renal or cardiac failure and diluents for intravenous drugs and line flushes can reduce the fluid allowance available for the feed in ill patients. Most enteral feeds provide 1 kcal/ml but specialized feeds with up to 2 kcal/ml are available for such circumstances. Electrolytes Average requirements for sodium and potassium are of the order of 1 mmol/kg per day for most adults. However, significant losses of sodium and other electrolytes can occur through the gastrointes- tinal tract (Table 11.7.3), and potassium deficits may also be large in patients receiving thiazide diuretics, during recovery of metabolic acidosis, and during refeeding of severely underweight individuals. Phosphate requirements increase greatly during refeeding from a baseline of approximately 0.3 mmol/kg per day. Feeds with minimal electrolyte content are required in oliguric renal impairment where solute clearance is reduced, but the com- monest cause of excessive electrolyte administration in hospitals is the inappropriate use of normal (0.9%) saline, which contains 154 mmol/litre of sodium, and salt-rich colloid solutions for main- tenance fluid requirements. Macronutrients Protein Protein is required to meet obligatory catabolic losses (minimal requirement) and to stimulate protein synthesis (optimal require- ment). The World Health Organization (WHO) recommendation of minimal requirement is 0.75 g protein/kg per day (0.12 g N/kg per day) based on nitrogen balance studies on a protein-free diet (Fig. 11.7.2). Increasing the dietary protein intake will increase pro- tein synthesis in depleted patients as long as sufficient calories are taken, and the optimal calorie:nitrogen ratio may vary depending on the disease state. Although net protein synthesis can be achieved by increasing dietary protein in undernourished patients, the same is not true in the catabolic state induced by sepsis, burns, or trauma, where excess amino acids can exert detrimental effects. Intakes of above 1.5 g protein/kg per day (>0.24 g N/kg per day) are not gener- ally recommended. Amino acids have physiological roles beyond protein synthesis and individual amino acid levels vary significantly between dif-

ferent disease states. Most artificial feeds provide standard amino acid solutions that do not cater for such differences and may result in relative imbalances of amino acid that could compromise amino acid utilization. Histidine levels are low in renal impairment, and branched chain amino acids (valine, leucine, isoleucine) are reduced in chronic liver disease. Glutamine is significantly depleted in crit- ical illness and improvement in nitrogen balance has been demon- strated with supplementation. An important demonstration of amino acid imbalance affecting protein synthesis is the (diagnostic) rise in blood urea associated with an upper gastrointestinal haemorrhage. While previously thought to be associated with an excess nitrogen load absorbed from the protein in the ingested blood, it appears that the cause is the lack of isoleucine residues in haemoglobin that leads to a relative deficiency of isoleucine in the circulation which thereby inhibits protein synthesis. The rise in urea is endogenous, due to the ongoing breakdown of protein without utilization of resultant amino acids in protein synthesis, and can be abrogated by simultan- eous isoleucine infusion. Table 11.7.3 Electrolyte composition of gastrointestinal fluids (in order to calculate replacement of losses) Fluid Na+ (mmol/litre) K+ (mmol/litre) HCO_3^- (mmol/litre) Cl^- (mmol/litre) Volume (/24 h) Gastric juice 60 15 – 90 2500 Pancreatic juice 140 5 90 75 1500 Bile 140 5 35 100 500 Small intestinal contents 100 10 25 100 1000 (Succus entericus) Diarrhoea 60 30 45 45

 Carbohydrate Carbohydrates should make up 50–65% of calories in a healthy diet. In excess of 5 g/kg per day, glucose is stored as glycogen up to a max- imum storage capacity of 15 g/kg. Continued administration of glu- cose results in lipid synthesis and hepatic steatosis. Maximal glucose oxidation rates are frequently lower in disease states due to insulin resistance and excessive glucose administration can therefore result in hyperglycaemia. Lipid The lower limit constraint on lipid provision is the need for essential fatty acids (linoleic and α-linolenic acids), which can be provided in 3–4.5% of the total energy requirements as fat. Lipid is used in artificial nutrition to provide the energy that cannot be supplied as carbohydrate due to the limit of glucose oxidation. The amount of CO_2 produced by oxidation of lipid is 30% less than that of glucose, which could theoretically help patients with respiratory failure or weaning from a ventilator, but clinical benefits are small in practice. Micronutrients Vitamins A balanced diet provides sufficient vitamins in most cases. There are no body stores of the water-soluble B vitamins, which can be de- ficient in a variety of different disease states including alcoholism, recurrent vomiting, and diabetes. Vitamin B12 is only present in animal dietary sources and therefore those following a vegan diet are prone to deficiency. Vitamin deficiencies can have profound ef- fects on cellular metabolism and few vitamins are toxic in excess, hence vitamin levels in commercial feed preparations generally ex- ceed estimated requirements. This excess helps to compensate for the degradation of some vitamins that occurs in solution—vitamin A and riboflavin are photosensitive (hence the need to protect hanging parenteral nutrition solutions from the light), thiamine reacts with preservatives required to maintain shelf life in paren- teral nutrition, and vitamins C and E are ineffective when oxidized. The latter is used in excess in parenteral nutrition to prevent lipid peroxidation. Vitamin K is normally not required in artificial nutrition, due to enteric bacterial synthesis, and its addition could affect therapeutic anticoagulation. Biotin (vitamin B7) and pyridoxine (vitamin B6) are also made by enteric bacteria. The latter has been associated with a reversible toxic neuropathy if taken in excess. Fat soluble vitamins— A, D, and E—can be provided in a water-miscible solution in paren- teral nutrition. Minerals and trace elements In contrast to vitamins, toxicity is associated with excess delivery of some trace elements. The enterocyte regulates iron uptake and rela- tively small amounts of trace elements

are absorbed from the intestine, hence overadministration is more likely to occur with parenteral than with enteral nutrition. Manganese and copper undergo biliary ex- cretion and accumulation can occur in parenterally fed patients with cholestasis: basal ganglia deposition can be detected on brain MRI scanning, but neurological effects are rarely reported. Chromium is excreted through the kidneys and can accumulate in renal failure, but toxic effects have not been reported. Zinc is lost through the intestine in high output states and in wound exudates leading to requirement for supplementation. Selenium plays a key role in cellular redox main- tenance as a cofactor in glutathione peroxidase and some authorities recommend supplementation in critical illness. Analysis of trace element levels in the blood can be inaccurate and affected by the acute-phase response and serum albumin con- centration, and interpretation of low levels is always complicated by the possibility that it reflects a physiological response to acute illness such as in the case of iron sequestration in infection. Complications of artificial nutrition support The ease with which full nutrition requirements can be delivered by artificial means results in a risk of ‘refeeding syndrome’ on initiating feeding in chronically undernourished patients. Features include elec- trolyte imbalance (hypokalaemia, hypophosphataemia, hypomagnes- aemia) and an associated risk of cardiac arrhythmia and sudden death, hyperglycaemia, and fluid shifts that can precipitate heart failure. The rapid depletion of thiamine—an essential cofactor of pyruvate decarboxylase—results in inhibition of glycolysis on refeeding and damage to glucose dependent cells such as neurons, the clinical pres- entation of Wernicke–Korsakoff syndrome. This is preventable by the administration of high-dose intravenous thiamine prior to refeeding (or glucose administration) in patients considered at risk. Other complications of artificial nutrition support are specific to the route of delivery. Access devices in common use, with their ad- vantages and disadvantages are listed in Table 11.7.4. 0.5 0.4 0.3 0.2 0.1 Nitrogen intake (g/kg/day) Nitrogen balance (mg/kg/day) 200 160 120 80 40 40 80 120 160 200 + − Severe nutritional depletion Moderate nutritional depletion No nutritional depletion No nutritional depletion: Severe injury Fig. 11.7.2 Relationship of nitrogen intake and nitrogen balance in patients receiving sufficient energy. Normal subjects reach nitrogen balance at approximately 0.1 g/kg/day nitrogen intake; positive nitrogen balance can be achieved in malnourished patients. Severe illness (trauma, sepsis, burns) results in net catabolism. Patients with a combination of depletion and severe illness react in an intermediate fashion. Reprinted from Clinical Nutrition, Vol. 1. Elia M, ‘The effects of nitrogen and energy intake on the metabolism of normal, depleted and injured man: Considerations for practical nutritional support’, pp. 173–92, Copyright © 1982, with permission from Elsevier.

11.7 Artificial nutrition support 1919 Table 11.7.4 Types of enteral and parenteral access devices in common use Type of tube Description Use Advantages Disadvantages Enteral (EN) Nasogastric Fine-bore (6–8 F) polyurethane tube; can be secured with a nasal bridle—a loop of tape around the nasal septum Short-to-medium term intragastric feeding due to inability to swallow, nutritional supplementation; bolus or infusion feed Bedside placement without sedation; well tolerated Risk of malposition; difficult to manage in confused patients Nasojejunal Fine-bore polyurethane tube with tip passed into distal duodenum/proximal jejunum Inability to swallow complicated by gastro-oesophageal reflux or gastroparesis; gastric outlet obstruction; acute severe pancreatitis Can be placed noninvasively at bedside; accurate delivery into proximal intestine. Infusion feed only May require endoscopy or fluoroscopy for placement; easily displaced PEG (percutaneous endoscopically placed gastrostomy) Tube passed through abdominal wall into stomach using an endoscopic technique (‘push’ or ‘pull’). Retained internally by balloon or internal bumper/disc. Available in sizes up to 24 F Long-term intragastric feeding; mucositis due to head and neck cancer

therapy; palliative venting use in terminal intestinal obstruction Difficult to displace; reliable in long-term use; can be exchange for skin level (‘button’) device, ideal for ambulant or younger patients Requires endoscopic placement and endoscopy to change tube. Early complications include peritonitis, bleeding, PEG site infection. Late complications include overgranulation of the PEG site and ‘buried’ bumper (see Fig. 11.7.3) RIG (radiologically placed gastrostomy) Radiologically placed transabdominal gastrostomy tube Intragastric feeding where endoscopic placement is not possible due to risks of endoscopy or anatomical considerations Can be a safer option than standard PEG in some patients Requires gastric insufflation through a nasogastric tube which may not always be possible to place. Some centres report higher numbers of significant complications with RIGs than PEGs PEG-J (PEG with jejunal extension) Transgastric tube with tip positioned in distal duodenum/proximal jejunum through existing PEG tube Long-term intestinal feeding where gastric feeding is not available due to gastric dysfunction o outlet obstruction Minimally invasive route for long- term postpyloric feeding Jejunal tube can reflux back into the stomach DPEJ (direct percutaneous enteroscopic jejunostomy tube) PEG tube placed endoscopically into the jejunum Long-term intestinal feeding Reliable for long-term feeding Endoscopic placement not always possible. High risk of complications including pain and volvulus (given single point of contact of intestine and abdominal wall) Surgical jejunostomy Feeding tube placed surgically into the jejunum Postoperative feeding in upper gastrointestinal surgery and liver transplantation Permits early enteral feeding in postoperative setting Not ideal for long-term use due to risk of displacement and adhesional obstruction Parenteral (PN) Midline catheter Short peripheral (22 G) cannula inserted into antecubital vein Short term parenteral nutrition support May allow effective peripheral nutrition support or supplementation without risks or delays of central venous access Limited range of available feeds due to the osmolality and pH considerations which usually limits use of this route to 2–3 days PICC (peripherally inserted central venous catheter) ‘Long-line’—tube placed via the cephalic vein into large central veins Short-to-medium term parenteral nutrition support (suitable for majority of inpatient PN episodes) Reduced risk of infection and generally preserves central access points Thrombophlebitis and thrombosis. Not practical for use at home or by patients Triple lumen venous catheter Multiple lumen direct puncture central venous catheter Fluid and drug delivery—central venous pressure monitoring Ease of access in critically ill patients High risk of local complications and infection. Should be discouraged for parenteral feeding except in time limited circumstances with a dedicated lumen to PN Tunnelled Hickman catheter Single or double lumen line tunnelled subcutaneously to the skin surface with a Dacron cuff for retention Medium-long-term parenteral nutrition support Low risk of infection if properly maintained; low risk of displacement once cuff is grown in Care needed with the external portion to avoid accidental displacement. Risk of exit site infection or mechanical dysfunction Implantable subcutaneous port device Line accessed via a hub placed in a subcutaneous pocket—no part of the device visible above skin level Long-term parenteral nutrition support Ideal for patients with active lifestyle—evidence of different rates of line infection compared to tunnelled lines is controversial Skin puncture required for every access; consequences of infection more significant than with tunnelled line—more difficult to replace. Limited lifetime of membrane depending on the frequency of puncture

SECTION 11 Nutrition 1920 Enteral Complications of access Incorrectly placed nasogastric tube can kill. Inadvertent intra pulmonary placement is the most frequent, but insertion into cra- nial, pleural, and peritoneal cavities has occurred. Feeding should only be initiated after confirmation of gastric placement by pH meas- urement of aspirated stomach contents (<5.5) or by radiography.

Interruptions due to frequent tube displacement causes a signifi- cant reduction in feed delivery—as little as 55% of prescribed feed in one study. This can be prevented by the use of a loop of tape that can be safely and simply passed around the nasal septum to secure the tube (‘nasal bridle’). Modern tube material does not cause sig- nificant erosion or irritation of the face, nares, or mucosal surfaces, even with long-term use, but difficulties in managing such tubes in the community make them undesirable for long-term use. Transabdominal feeding tubes are therefore used in preference in the community for enteral feeding. Percutaneous endoscopically guided (PEG) tubes are most frequently employed, but a variety of tubes can be placed endoscopically, radiologically, or surgically into the stomach or proximal intestine (Fig. 11.7.3). There is a high risk of death following placement due to cardiorespiratory complications in patients who are at high risk due to dysphagia and pre-existing pneumonia. Asymptomatic pneumoperitoneum is common after PEG insertion, but chemical peritonitis can result from feed leakage into the peritoneal cavity. Superficial infections at the PEG site should occur in less than 5% of cases: these are usually easily treated but should not be confused with chemical burns due to leakage of enteric contents. Skin swabs are rarely useful in suspected PEG site infection. Too much tension on the device can lead to erosion of the internal retaining bolster into the gastric mucosa and through the abdominal wall (‘buried bumper’), leading to blockage, external feed leakage and infection, and may only be apparent on attempted PEG removal. Complications of enteral feeding The role of the intestine in regulating nutrient uptake is demon- strated by the reduced metabolic complications of enteral compared (a) (c) (b) Fig. 11.7.3 (a) A range of endoscopically placed gastrostomy tubes—from left to right—bumper-retained gastrostomy; traction-removable bumper-retained gastrostomy; balloon retained gastrostomy; skin level ‘PEG-button’ device (balloon retained). (b) Endoscopic photograph of PEG tube with bumper in place in the stomach. (c) ‘Buried bumper’—the bumper of the gastrostomy has eroded into the gastric mucosa as a result of pressure necrosis and the mucosa has overgrown the bumper. A wire has been passed through the lumen of the tube to demonstrate its position.

 to parenteral feeding: nutritional deficiencies in patients fed appro- priately with commercial preparations are highly unusual. Patients who require enteral feeding often have impaired con- scious level or swallowing and are therefore at risk of pulmonary aspiration. Delayed gastric emptying—as frequently occurs in crit- ical illness—increases the likelihood of aspiration of stomach con- tents. Gastro-oesophageal reflux may be exacerbated rather than reduced by PEG feeding. Patients at risk should be fed by infusion pump rather than intermittent bolus and at a 30-degree tilt. Passage of a feeding tube beyond the pylorus is beneficial in cases of delayed gastric emptying or gastric outlet obstruction. Diarrhoea is common in enterally fed hospital patients and is often due to the concomitant use of antibiotics. Liquid feed emp- ties rapidly from the stomach compared to solids and can result in an osmolar load that precipitates fluid influx and intestinal hurry, and neuroendocrine mechanisms have been described that result in right colonic fluid secretion with nasogastric feeding. Constipation may be encountered more frequently in enterally fed patients in the community: fibre-supplemented feeds are available for such instances. Parenteral Complications of access Intravenous feed should not be delivered via peripheral cannulae due to the risk of thrombosis and thrombophlebitis, and available preparations are constrained by pH and osmolality requirements. Central venous access is required for longer-term parenteral nutri- tion but carries attendant risks of pneumothorax and haemothorax on placement. Peripherally inserted central lines can be used suc- cessfully for feed delivery, and arteriovenous fistulae for renal dia- lysis have also been used successfully in this setting. Infection

is the major hazard of intravenous feeding catheters and is reduced by dedicating a single lumen to the feed and employing strict aseptic precautions. Use of opiates, presence of a stoma, and frequent line access are risk factors for infection. Tunnelled or peripherally inserted lines should be used in preference to non- tunnelled central lines. Staphylococci, Gram-negative bacilli, and candida are common infecting organisms. Infection can present insidiously with low grade fever and result in complications by dissemination such as bacterial endocarditis, discitis, osteomyelitis, or fungal endophthalmitis. Catheter-related infections are infrequent in longer-term commu- nity parenteral nutrition, with infections occurring on average every 2 to 5 years. Venous thrombosis associated with frequent line replacement may limit options for access and require creative solutions such as direct translumbar or transhepatic caval access, intra-atrial access, or surgical reconstruction of venous anatomy. Complications of parenteral feeding Metabolic complications are more likely to arise as a result of paren- teral than enteral feeding for the following reasons: • Parenteral feeding bypasses the enterocyte which actively regu- lates uptake, metabolizes nutrients, and re-exports them via the portal circulation. • Insulin, glucagon, and incretin secretion (as well as that of other entero-endocrine hormones) that regulate metabolic processes and disposal of nutrients from the circulation are controlled by the presence or absence of nutrients in the gut. • Parenteral feeds cannot replicate the complexity of circulating nu- trient molecules, being constrained by requirements of chemical stability within the solution. The metabolic risks of parenteral nutrition have previously been overestimated due to the ease of overnutrition via this route and de- liberate ‘hyperalimentation’. Hyperglycaemia is especially common due to insulin resistance associated with critical illness and re- sults in increased infection and adverse outcomes. Imbalances of other nutrients may occur as a result of variable losses associated with the underlying condition and require regular monitoring and replacement. The gut derives a proportion of its nutrient requirements from the lumen rather than the bloodstream, hence parenteral nutrition may result in mucosal atrophy and impaired barrier function. Although physiological and anatomical changes have been described, adverse consequences due to bacterial translocation appear to be rare from this cause in clinical practice. Intestinal-failure-associated liver disease Hepatic complications are commonly described in patients receiving parenteral nutrition. Asymptomatic elevation of liver enzymes indi- cative of cholestasis occurs after about 4 weeks of feeding via this route, but can progress to profound jaundice and cirrhosis, espe- cially in children. Intestinal-failure-associated liver disease tends to progress more insidiously through hepatic steatosis to cirrhosis in adults. Causes are likely multifactorial, including a reduced portal inflow due to short bowel syndrome and lack of enteric stimula- tion of cholecystokinin release. Several factors associated with par- enteral feed have been implicated in both excess and deficiency (Table 11.7.5). Maintaining oral intake, even if contributing only minimally to nutrient requirements, using cyclical rather than con- tinuous feed, and keeping exogenous lipid delivery under 1 g/kg per day appears to reduce the risk of developing liver disease. The use of new lipid substrates containing fish oil and rich in omega-3 lipids appears to be preferable to the use of older soy-oil based preparation. Intestinal-failure-associated bone disease Metabolic osteopenia is common in intestinal failure requiring long-term parenteral nutrition. Prolonged bed rest, immobiliza- tion, and vitamin D malabsorption contribute prior to the initiation Table 11.7.5 Aetiological factors implicated in intestinal-failure- associated liver disease (IFALD) Cholestasis Steatosis Reduced enteral stimulation Excess provision of calories as carbohydrate or lipid Phytosterols present in soy-based formulae Choline deficiency Infection Carnitine deficiency Bacterial translocation Reduced very low-density lipoprotein synthesis Taurine deficiency Inadequate Glucagon secretion Methionine deficiency

 of parenteral nutrition. A low bone turnover state has been rarely described. Careful monitoring of bone density and treatment with intravenous bisphosphonates is often required. Long-term artificial nutrition support and intestinal transplantation Long-term artificial nutrition support Patients can receive oral, enteral, or parenteral nutrition support in the community. In the United Kingdom, the British Artificial Nutrition Survey (BANS) carries out an annual survey of the number of tube-fed patients. Approximately 350 per million British adults receive enteral tube feed in the community, compared to about 40 per million receiving parenteral nutrition at home. The latter has increased significantly over recent years due to improvements in homecare provision and a recognition of previous underutilization leading to patchy uptake across the United Kingdom. Quality of life is often adversely affected by the underlying dis- ease process more than the route of artificial nutrition support, but infusing feed overnight can minimize lifestyle disruption. Life ex- pectancy is also mostly dictated by the underlying disease process, with relatively few deaths attributed to failure of feeding or compli- cations of delivery. Ten-year survival on long-term home parenteral nutrition is approximately 59–71% in adults and 81% in children. The patients receiving enteral nutrition at home tend to be more eld- erly and infirm than those receiving parenteral nutrition and have a survival of around 25% at five years.

Intestinal transplantation Patients with irreversible intestinal failure who experience life-threatening complications of parenteral nutrition can be con- sidered for intestinal transplantation, which can be combined with other abdominal organs where required for reasons of asso- ciated organ failure or anatomical considerations. Multivisceral transplantation including liver, stomach, intestine, pancreas, and colon may be required for patients with complications of exten- sive portomesenteric thrombosis, or urgently in acute abdominal ischaemia. Transplantation of the ileocecal valve and a segment of colon along with intestine is now routine to improve fluid absorp-tion postoperatively. Most patients undergoing intestinal transplant can become in- dependent of artificial nutrition support, and survival rates are now equivalent to—or better than—those of other solid organ transplant operations (Fig. 11.7.4). However, the operation is currently not considered as a routine alternative to home paren- teral nutrition, which is associated with excellent long-term out- comes, although it may offer benefits in some cases. There is a realistic prospect that further improvements in the field will re- sult in better identification of cases that would benefit from earlier transplantation. Ethics of artificial nutrition support Nutrition and starvation evoke emotive responses, but although it is a basic human right not to be deprived of fluid or food, the same is

Patient three-year survival, including super urgent patients, following first intestinal transplant, by ITR group, for patients transplanted between 1 February 2006 and 31 December 2015 at Cambridge transplant unit MMV SB MVT Transplant type MMV MVT SB Total 12 100 90 80 70 60 50 40 30 20 10 0 0 1 2 Years post-transplant % patient survival 3 34 12 58 1 14 2 17 89 (43–98) 62 (32–69) 81 (42–95) 65 (60–77) No patients No deaths % Patients survival (95% confidence interval) Transplanted and follow-up data were extracted from the UK Transplant Registry on 14 April 2016

Fig. 11.7.4 Survival post intestinal transplant. SB, small bowel transplant; MVT, multivisceral transplant (stomach, pancreas, liver, intestine, colon); MMV, modified multivisceral transplant (stomach, pancreas, intestine, colon). Source: NHSBT, courtesy Cambridge University Hospitals NHS Foundation Trust, 2016 data.

 not true of artificial nutrition support which requires invasive tube placement that may be associated with risks of morbidity or mor- tality. Ethically, withdrawing or withholding artificial nutrition are considered equivalent, but in practice it is often difficult to cease feeding when established through a tube, and the progress of an underlying condition can be

affected by the continued delivery or withdrawal of feed. Institution of artificial nutrition support there- fore requires careful multidisciplinary discussion and appropriate patient and carer information in order to identify appropriate goals and expectations of feeding. Special situations in nutrition support Critical illness—burns, trauma, and sepsis The metabolic response to stress is characterized by hypermetabolism and rapid tissue catabolism with resulting insulin resistance and hyperglycaemia. Direct effects of inflammatory mediators and cyto- kines such as tumour necrosis factor–α and interleukins 1 and 6 are responsible. Protein loss can be rapid, particularly in the case of burns where exudates add to catabolic loss. Feeding during acute metabolic decompensation can be detri- mental and should be withheld during such time. Otherwise, early institution of feeding has been shown to be beneficial in most set- tings, with a graded increment to meet requirements and avoid overfeeding. Gastric stasis is common after severe burns and head injury and intestinal ileus may occur in circulatory failure requiring inotropic support. Prokinetic use may assist gastric emptying of en- terally delivered feed, but where gastric aspirate volumes remain high or increase during intragastric feeding, postpyloric or paren- teral feeding may avoid the risk of pulmonary aspiration and ensure adequate nutrient delivery. Avoidance of underfeeding is also important in critical illness and relies on appropriate recognition of the transition from a catabolic to anabolic phase. Attempts to reverse catabolism using inhibitors of inflammatory cytokines or anabolic agents have unfortunately been unsuccessful. Nutrients themselves may be used to modulate inflammatory responses, such as the use of lipid substrates enriched with omega-3 fatty acids, and encouraging results have been demon- strated in sepsis and postsurgery. Renal disease Renal failure results in wasting, electrolyte and fluid imbalances, and anorexia with attendant malnutrition. Patients undergoing dialysis lose protein into the dialysate—up to 10 g/day on haemodialysis and up to 15 g/day on peritoneal dialysis. Water-soluble vitamins are also lost in the dialysate and require replacement. Adequate pro- tein intake is essential to minimize catabolism of endogenous pro- tein. Specialized feeds with minimal electrolytes and reduced fluid volume are available for renal patients (Table 11.7.6). Parenteral nu- trients may be infused to replace losses at the time of dialysis. The use of reduced (but high-quality) protein feeds may delay the re- quirement for dialysis in renal failure but this should not be at the expense of inadequate nutrition support. Liver disease Malnutrition is common in patients with established liver dis- ease as a result of reduced appetite, altered carbohydrate and lipid metabolism, and (in severe cases) impaired urea synthesis from ammonia leading to increased muscle catabolism. Cholestasis also results in fat malabsorption. Glucose intolerance limits glu- cose intake and complex polysaccharides are required to provide a slow release of carbohydrates in view of diminished glycogen stores. The lack of carbohydrate stores in the liver makes patients prone to significant protein catabolism during fasting and there- fore periods without nutrient intake—even overnight—should be avoided. High protein feeds may precipitate encephalopathy in cirrhosis, but restricting protein is nutritionally undesirable and an intake of 1.2–1.5 g protein/kg per day is recommended. Optimization of the amino acid composition—by enriching with branched chain amino acids which are deficient in liver disease—can improve protein syn- thesis and result in improved survival for patients with end stage liver disease awaiting transplant. Table 11.7.6 Examples of disease-specific and therapeutic feeds designed to have disease modifying activity (‘nutraceuticals’) Composition Intended use Rationale Low protein, high essential amino acids, and histidine, low electrolytes, high calorie density Renal impairment Appropriate matching of amino acid composition to requirements may improve protein metabolism; low protein reduces urea synthesis; high calorie density allows fluid restriction Low protein, reduced aromatic and increased branched chain amino acids, low sodium Hepatic impairment Reduced risk of encephalopathy with low protein; appropriate amino acid mix

to allow optimal protein metabolism High lipid, low carbohydrate Pulmonary disease; weaning from artificial nutrition Reduced CO_2 production High lipid (especially monounsaturated fatty acids); low carbohydrate, high fructose Diabetes Reduced glycaemia, improved diabetic control Oligopeptides, medium chain triglycerides Severe pancreatic exocrine deficiency Reduced dependence on luminal digestion for absorption Arginine, n-3 fatty acids, nucleotides ‘Immune enhancing’—critical illness/perioperative nutrition Substrates for rapidly dividing cells such as lymphocytes and competitive inhibition of proinflammatory eicosanoid production may enhance immune response and reduce inflammatory response Glutamine Critical illness Glutamine levels severely depleted in critical illness; supplementation may improve nitrogen balance and act as fuel for rapidly dividing cells such as lymphocytes and enterocytes; maintaining immune responses and gut mucosal integrity

SECTION 11 Nutrition 1924 Gastrointestinal disease Nutrition support is required in gastrointestinal conditions that re- sult in impaired access to the gut, for instance as a result of proximal obstruction or dysmotility, or intestinal failure due to short bowel or mucosal disease. Liquid, oral, or enteral feeds may be used to induce remission in Crohn’s disease with equivalent efficacy to steroids. Patients with proximal enterocutaneous fistulae may have high fluid and nutrient losses from the fistula. Parenteral nutrition may be essential to provide nutritional and fluid intake and reduce effluent that may compromise wound healing. However, in patients with low output fistulae who are able to manage their fluid and nutrient re- quirements orally or enterally, there is no evidence to suggest that ‘gut rest’ and parenteral nutrition increase rates of fistula closure. In severe acute pancreatitis, nutrition requirements are increased by the systemic inflammatory response and there are theoretical concerns of stimulation of pancreatic secretion by enteral feeding. Enteral feeding is often limited by gastric stasis in severe cases and intrajejunal feeding is associated with lower complications than par- enteral nutrition in this setting.
Perioperative nutrition Malnourished patients undergoing surgery experience up to three times as many complications and a fourfold increase in mortality compared to well-nourished individuals. Patients may be starved for prolonged periods prior to surgery due to obstruction or after surgery as a result of ileus. Surgery should be delayed where feasible in severely malnourished patients to provide a minimum of 10 to 14 days of adequate perioperative nutrition. Starvation immediately prior to surgery results in increased in- sulin resistance and complications postoperatively, and the simple expedient of providing a 50 g carbohydrate load orally two hours prior to surgery can speed postoperative recovery. Early reintroduc- tion of oral feeding after routine abdominal surgery is feasible and results in more rapid rehabilitation than waiting for unreliable clin- ical signs of gastrointestinal function to return prior to feeding. Palliative care Terminal illness—whether due to benign or malignant disease—is frequently associated with poor nutritional status resulting from catabolic effects of the underlying disease and associated anor- exia. Limited observational evidence suggests that both length and quality of life can be maintained for a period of time in some such patients with good initial performance status by the appropriate use of nutrition support. Patients with intestinal obstruction due to slow growing malignancy may derive benefit from parenteral nutri- tion, particularly if associated with a venting gastrostomy to prevent vomiting. However, the use of artificial nutrition support in all such cases needs to be carefully considered to ensure that the benefits out- weigh the additional burdens of feeding and that valuable time is not wasted setting up artificial nutrition in hospital for minimal gain. Delivering a nutrition service The hospital nutrition support team A multiprofessional team comprising clinician, specialist nurse, dietitian, and pharmacist as its core members is required to provide the full range

of nutrition support services. By appropriate use of nu- trition support, reducing catheter-related complications, and moni- toring patients receiving parenteral nutrition, such teams have been shown to provide significant cost savings as well as providing high- quality clinical care. Cost-effectiveness of nutrition support Public health and social care expenditure relating to malnutrition in 2011–2012 in the United Kingdom was estimated at £19.6 billion, equivalent to 15% of the healthcare budget. Oral nutrition support has been demonstrated to reduce mortality by up to 24% in some hospital and community settings, and to reduce complications (odds ratio 0.29—confidence intervals 0.18–0.47) and lengths of hospital inpatients' stay. Modelling suggests that appropriate nutrition sup- port is highly cost-effective despite high initial outlays in nutrition screening and costs of supplements. Future developments An increased awareness of the critical importance of nutrition in clinical care is likely to improve the recognition of malnutrition and lead to the institution of appropriate preventive measures with sig- nificant benefits in all areas of clinical medicine. An unfortunate lack of adequately powered trials has limited the application of innovative nutritional interventions, including novel nutrient substrates, to modulate inflammatory responses or explore disease-specific feeds (Table 11.7.6), hence there is much potential still to be unlocked in the field of therapeutic nutrition. FURTHER READING Andrews PJ, et al. (2011). Randomised trial of glutamine, selenium or both to supplement parenteral nutrition for critically ill patients. BMJ, 342, d1542. Bozzetti F, et al. (2002). Central venous catheter related complications in 447 patients on home parenteral nutrition; an analysis of over 100,000 catheter days. Clin Nutr, 21, 475–85. Briet F, et al. (2004). Effect of feeding malnourished patients for 1 mo on mitochondrial complex 1 activity and nutritional assessment measurements. Am J Clin Nutr, 79, 787–94. Campbell SE, et al. (2002). Assessment of nutritional status in hospital in-patients. QJ Med, 95, 83–7. Cano NJM, et al. (2009). ESPEN guidelines for adult parenteral nutri- tion. Clin Nutr, 28, 359–479. Dibb M, Soop M, Teubner A, et al. (2017). Home parenteral nutrition: Three decades of experience from a single referral centre. Clin Nutr., 36(2), 570–76. Druml C, et al. (2016). ESPEN guideline on ethical aspects of artificial nutrition and hydration. Clin Nutr, 35, 545–56. Elia M (1982). The effects of nitrogen and energy intake on the me- tabolism of normal, depleted and injured man. Considerations for practical nutrition support. Clin Nutr, 1, 173–92. Elia M (2003). The MUST Report: Nutritional Screening of Adults: A Multidisciplinary Responsibility. Development and Use of the Malnutrition Universal Screening Tool (MUST) for Adults. A report by the malnutrition advisory group of the British Association for Parenteral and Enteral Nutrition. BAPEN, Redditch. https://www.bapen.org.uk/pdfs/must/must-report.pdf

 Elia M, et al. (2015). The Cost of Malnutrition in England and Potential Cost Savings from Nutritional Interventions. https://www.bapen.org. uk/pdfs/economic-report-full.pdf Gauderer MW, Ponsky JL (1981). A simplified technique for con- structing a tube feeding gastrostomy. Surg Gynecol Obstet, 152, 83–5. Harvey SE, et al. (2014). Trial of the route of early nutritional support in critically ill adults. N Engl J Med, 371, 1673–84. Hashimoto K, et al. (2015). Recent advances in intestinal and multivisceral transplantation. Adv Surg, 49, 31–63. Heyland DK (2000). Parenteral nutrition in the critically ill pa- tient: more harm than good? Proc Nutr Soc, 59, 457–66. Jeejeebhoy KN (2012). Malnutrition, fatigue, frailty, vulnerability, sarcopenia and cachexia: overlap of clinical features. Curr Opin Clin Nutr Metab, 15, 213–19. Kalm LM, Semba RD (2005). They starved so that others could be better fed: remembering Ancel Keys and the Minnesota experiment. J Nutr, 135, 1347–52. Keys A (1946). Human starvation and its consequences. J Am Diet Assoc, 22, 582–7. Lewis SJ, et al. (2001). Early enteral feeding versus 'nil by mouth' after gastrointestinal surgery: systematic review and meta-analysis of controlled trials.

BMJ, 323, 773–6. Ljungqvist O, et al. (2002). Modulation of post-operative insulin re- sistance by pre-operative carbohydrate loading. Proc Nutr Soc, 61, 329–36. Maple JT, et al. (2005). Direct percutaneous endoscopic jejunostomy: outcomes in 307 consecutive attempts. Am J Gastroenterol, 100, 2681–8. Matsumoto CS, Subramanian S, Fishbein TM (2018). Adult Intestinal Transplantation. Gastroenterol Clin North Am, 47(2), 341–54. Mayer K, et al. (2003). Parenteral nutrition with fish oil modulates cytokine response in patients with sepsis. Am J Respir Crit Care Med, 167, 1321–8. McWhirter JP, Pennington CR (1994). Incidence and recognition of malnutrition in hospital. BMJ, 308, 945–8. Planck L, et al. (2008). Nocturnal nutrition supplementation im- proves total body protein status of patients with liver cirrhosis: a randomised 12 month trial. Hepatol, 48, 557–66. Shaw JF, et al. (1987). Whole body protein kinetics in severely septic patients. Ann Surg, 205, 288–94. Stratton R, Smith T, Gabe S (2018). Managing malnutrition to im- prove lives and save money. BAPEN October 2018. www.bapen. org.uk/pdfs/reports/mag/managing-malnutrition.pdfUm adist, ut idunt vit eaquas peruptate labore pa volorum im qui underfe

SECTION 12 Metabolic disorders Section editor: Timothy M. Cox 12.1 The inborn errors of metabolism:
General aspects 1929 Timothy M. Cox and Richard W.E. Watts 12.2 Protein-dependent inborn errors of metabolism 1942 Georg F. Hoffmann and Stefan Kölker 12.3 Disorders of carbohydrate metabolism 1985 12.3.1 Glycogen storage diseases 1985 Robin H. Lachmann and Timothy M. Cox 12.3.2 Inborn errors of fructose metabolism 1993 Timothy M. Cox 12.3.3 Disorders of galactose, pentose, and
pyruvate metabolism 2003 Timothy M. Cox 12.4 Disorders of purine and pyrimidine metabolism 2015 Anthony M. Marinaki, Lynette D. Fairbanks,
and Richard W.E. Watts 12.5 The porphyrias 2032 Timothy M. Cox 12.6 Lipid disorders 2055 Jaimini Cegla and James Scott 12.7 Trace metal disorders 2098 12.7.1 Hereditary haemochromatosis 2098 William J.H. Griffiths and Timothy M. Cox 12.7.2 Inherited diseases of copper metabolism: Wilson’s disease and Menkes’ disease 2115 Michael L. Schilsky and Pramod K. Mistry 12.8 Lysosomal disease 2121 Patrick B. Deegan and Timothy M. Cox 12.9 Disorders of peroxisomal metabolism in adults 2157 Anthony S. Wierzbicki 12.10 Hereditary disorders of oxalate metabolism: The primary hyperoxalurias 2174 Sonia Fargue, Dawn S. Milliner, and
Christopher J. Danpure 12.11 A physiological approach to acid–base disorders: The roles of ion transport and
body fluid compartments 2182 Julian Seifter 12.12 The acute phase response, hereditary periodic fever syndromes, and amyloidosis 2199 12.12.1 The acute phase response and C-reactive protein 2199 Mark B. Pepys 12.12.2 Hereditary periodic fever syndromes 2207 Helen J. Lachmann, Stefan Berg,
and Philip N. Hawkins 12.12.3 Amyloidosis 2218 Mark B. Pepys and Philip N. Hawkins 12.13 α1-Antitrypsin deficiency and the serpinopathies 2235 David A. Lomas