# 09-19 Nutritional factors in disease

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692 • NUTRITIONAL FACTORS IN DISEASE Insets (Scaphoid abdomen) From Chandra A, Quinones-Baldrich WJ. Chronic mesenteric ischemia: How to select patients for invasive treatment. Sem Vasc Surg 2010; 23:21–28; (Koilonychia) Habif TP. Clinical Dermatology, 6th edn. Philadelphia: Saunders, Elsevier Inc.; 2016; (Gingivitis) Newman MG, Takei H, Klokkevold PR, et al. Carranza's Clinical Periodontology, 12th edn. Philadelphia: Saunders, Elsevier Inc.; 2015; (Corkscrew hairs) Bolognia JL, Jorizzo JL, Schaffer JV, et al. Dermatology, 3rd edn. Philadelphia: Saunders, Elsevier Inc.; 2012. Eyes Sunken eyes Pallor Jaundice Bitot spots (↓vitamin A; see Fig. 19.12) Hands Muscle wasting (dorsal interossei, thenar eminences) Finger clubbing Leukonychia (low albumin) Koilonychia (iron deficiency) Simple anthropometrics (see right) Body mass index Triceps skin fold thickness Waist circumference Legs Pitting oedema Ulcers Affect Fatigue Depression Dementia Mouth Pallor Angular stomatitis (↓B12, folate, iron) Glossitis (↓B12, folate, iron) Gingivitis, bleeding gums (↓vitamin C; see Fig. 19.14) Poorly fitting dentures Corkscrew hairs Gingivitis Koilonychia Scaphoid abdomen Clinical effects of short bowel syndrome after multiple resection in Crohn's disease

Skin Dry, flaky skin or dermatitis (see Fig. 19.13) Hair loss Specific abnormalities: Petechiae, corkscrew hairs (↓vitamin C) Dermatitis of pellegra (↓niacin)

Observation Signs of weight loss: Prominent ribs Muscle wasting ↓Skin turgor

Clinical examination in nutritional disorders

Clinical assessment and investigation of nutritional status • 693

Clinical assessment and investigation of nutritional status Important elements of the diet history Ask about weight • Current weight • Weight 2 weeks, 1 month and 6 months ago • Assessment of degree of change Ask about current food intake • Quantity of food and if any change • Quality of food taken • Whether normal food is

being eaten • Avoidance of specific food types (e.g. solids) • Any nutritional supplements • Reliance on supplements/tube feeding • Any change in appetite or interest in food • Any taste disturbance Ask about symptoms that interfere with eating • Oral ulcers or oral pain • Difficulties swallowing • Nausea/vomiting • Early satiety • Alteration in bowel

habit • Abdominal (or other) pain Ask about activity levels/performance status • Normal activity • Slightly reduced activity • Inactive < 50% of the time • Inactive most of the time Under-nutrition can go unnoticed in patients with multiple comorbidities. It is vital to be aware of under-nutrition as a potential reason for any acute medical presentation

or as a modifier of it. Early nutritional assessment is crucial and a dietary history provides useful information (especially when taken by a dietitian). Points to note include past medical and surgical history (e.g. abdominal or intestinal surgery), a drug history and a specific diet history. Evidence of recent weight loss and muscle wasting

should be sought. Simple, validated tools are available to screen patients for nutritional problems. Body composition reflects energy balance and is assessed by clinical anthropomorphic measurements. More sophisticated techniques may be used to assess body composition or functional capacity if required. 2 Body mass index (BMI) BMI wt kg

# ht m

( ) ( )2 Example: an adult of 70 kg with a height of 1.75 m has a BMI of 70/1.752 = 22.9 kg/m2 • BMI is a useful way of identifying under- or over-nutrition but cannot discriminate between lean body or muscle mass and fat mass • Fat mass is also subject to ethnic variation; for the same BMI, Asians tend to have more body fat than Europeans • If height cannot be determined (e.g. in older people or those unable to stand), measurement of the femoral length or 'knee height' is a good surrogate Measurement of knee height. 2 Measures of body composition and nutritional status Body composition • Anthropometry (see below) • Bioelectrical impedance • Dual X-ray absorptiometry (DXA) Muscle function and global nutritional status • Hand grip strength (dynamometer test) – poor grip associated with increased mortality Obesity and fat distribution (android vs gynoid) • Waist:hip ratio (circumferences measured midway between superior iliac crest and lower border of rib cage, and at greater trochanters, respectively) Body fat content and muscle mass • Triceps skinfold thickness (when combined with mid-/upper arm circumference estimates muscle mass) Triceps skinfold thickness. Lean patients 6–12 mm; obese patients 40–50 mm. Screening hospitalised patients for risk of malnutrition. Acute illnesses include decompensated liver disease, cancer cachexia or being kept 'nil by mouth'. Adapted from the British Association of Parenteral and Enteral Nutrition Malnutrition Universal Screening Tool (www.bapen.org.uk). Weight loss score Unplanned loss in 6 months < 5% 5 – 10%

> 10% = 0 = 1 = 2 BMI score 20 18.5 – 20 < 18.5 = 0 = 1 = 2 Acute disease score Acute illness with no nutritional intake for 5 days = 2 Total = 1 – Medium risk Total = 0 – Low risk Total ≥ 2 – High risk Total score • Routine clinical care • Repeat screen weekly • Document dietary intake for 3 days • Repeat screen weekly • Refer to dietitian/nutrition support team • Review plan weekly

694 • NUTRITIONAL FACTORS IN DISEASE energy is also required for thermal regulation, and expenditure is higher in cold or hot environments. The energy required for digestion of food (diet-induced thermogenesis; Fig. 19.2D) accounts for approximately 10% of total energy expenditure, with protein requiring more energy than other macronutrients. Another component of energy expenditure is governed by the level of muscular activity, which can vary considerably with occupation and lifestyle (Fig. 19.2C). Physical activity levels are usually defined as multiples of BMR. Energy intake is determined by the 'macronutrient' content of food. Carbohydrates, fat, protein and alcohol provide fuel for oxidation in the mitochondria to generate energy (as adenosine triphosphate (ATP); p. 49). The energy provided by each of these elements differs: • carbohydrates (16 kJ/g) • fat (37 kJ/g) • protein (17 kJ/g) • alcohol (29 kJ/g). Regulation of energy balance Energy intake and expenditure are highly regulated (Fig. 19.3). A link with reproductive function ensures that pregnancy is most likely to occur during times of nutritional plenty, when both mother and baby have a better chance of survival. Improved nutrition is thought to be the reason for the increasingly early onset of puberty in many societies. At the other extreme, anorexia nervosa and excessive exercise can lead to amenorrhoea (p. 654). Regulation of energy balance is coordinated

in the hypothalamus, which receives afferent signals that indicate nutritional status in the short term (e.g. the stomach hormone ghrelin, which falls immediately after eating and rises gradually thereafter, to suppress satiety and signal that it is time for the next meal) and the long term (e.g. the adipose hormone leptin, which increases with growing fat mass and may also link fat mass to reproductive function). The hypothalamus responds with changes in many local neurotransmitters that alter activity in a number of pathways that influence energy balance (Fig. 19.3), including hormones acting on the pituitary gland (see Fig. 18.2, p. 633), and neural control circuits that connect with the cerebral cortex and autonomic nervous system. Responses to under- and over-nutrition These complex regulatory pathways allow adaptation to variations in nutrition. In response to starvation, reproductive function is suppressed, BMR is reduced, and there are profound psychological effects, including energy conservation through lethargy. These adjustments can ‘defend’ body weight within certain limits. In the low-insulin state of starvation (see Fig. 20.5, p. 725), however, fuels are liberated from stores initially in glycogen (in liver and muscle), then in triglyceride (lipolysis in adipose tissue, with excess free fatty acid supply to the liver leading to ketosis) and finally in protein (proteolysis in muscle). In those with a high glucose requirement, such as neonates and women who are pregnant or breastfeeding, starvation can result in ketoacidosis associated with normal or low blood glucose (p. 365). In response to over-nutrition, BMR is increased, and extra energy is consumed in the work of carrying increased fat stores, so that body weight is again ‘defended’ within certain limits. In the high-insulin state of over-nutrition, excess energy is invested in fatty acids and stored as triglycerides; these are deposited principally in adipose tissue but they may also accumulate in the liver (non-alcoholic fatty liver disease; p. 882) and skeletal muscle. If hypothalamic function is abnormal (e.g. in those with Nutritional factors and disease Obtaining adequate nutrition is a fundamental requirement for the survival of every individual and species. The politics of food provision for humans are complex and constitute a prominent factor in wars, natural disasters and the global economy. In recent decades, economic success has been rewarded by plentiful nutrition unknown to previous generations, which has led to a pandemic of obesity and its consequences for health, yet in many parts of the world, famine and under-nutrition still represent a huge burden. Quality, as well as quantity, of food influences health, with governmental advice on healthy diets maximising fruit and vegetable intakes (Fig. 19.1). Inappropriate diets have been linked to diseases such as coronary heart disease and cancer. Deficiencies of vitamins or minerals lead to avoidable conditions, such as anaemia due to iron deficiency or blindness due to severe vitamin A deficiency. A proper understanding of nutrition is therefore essential in dealing with the needs of individual patients and in informing the planning of public policy. Physiology of nutrition Nutrients in the diet can be classified into ‘macronutrients’, which are eaten in relatively large amounts to provide fuel for energy, and ‘micronutrients’ (e.g. vitamins and minerals), which do not contribute to energy balance but are required in small amounts because they are not synthesised in the body. Energy balance The laws of thermodynamics dictate that energy balance is achieved when energy intake = energy expenditure (Fig. 19.2). Energy expenditure has several components. The basal metabolic rate (BMR) describes the obligatory energy expenditure required to maintain metabolic functions in tissues and hence sustain life. It is most closely predicted by fat-free mass (i.e. total body mass minus fat mass), which is lower in females and older people (Fig. 19.2B). Extra metabolic energy is consumed during growth, pregnancy and lactation, and when febrile. Metabolic Fig. 19.1 Proportion of key food groups recommended for a healthy, well-balanced diet. Crown copyright. Department of Health in association with the Welsh Government, the Scottish Government and the Food Standards Agency in Northern Ireland. Fruit and vegetables Food and drinks high in fat and/or

sugar Milk and dairy foods Bread, rice, potatoes, pasta and other starchy foods Meat, fish, eggs, beans and other non-dairy sources of protein



are broken down to monosaccharides before absorption from the gut (p. 768), and supply over half the energy in a normal, well-balanced diet (see Fig. 19.2A). No individual carbohydrate is an essential nutrient, as carbohydrates can be synthesised de novo from glycerol or protein. If the available carbohydrate intake is less than 100 g per day, however, increased lipolysis leads to ketosis (see Fig. 20.7, p. 730). Dietary guidelines do not restrict the intake of intrinsic sugars in fruit and vegetables or the sugars in milk. However, intake of non-milk extrinsic sugars (sucrose, maltose, fructose), which increase the risk of dental caries and diabetes mellitus, should craniopharyngioma; see Fig. 18.31, p. 687) or in rare patients with mutations in relevant genes (e.g. in leptin or melanocortin-4 receptors), loss of response to satiety signals, together with loss of adaptive changes in energy expenditure, result in relentless weight gain. Macronutrients (energy-yielding nutrients) Carbohydrates Types of carbohydrate and their dietary sources are listed in Box 19.1. The ‘available’ carbohydrates (starches and sugars) Fig. 19.2 Determinants of energy balance. A Energy intake is shown as national averages, highlighting the differences in sources of energy in different countries (but obscuring substantial regional variations). The targets are recommendations as a percentage of food energy only (Source: Dept of Health 1991). For WHO targets, see Box 19.4. In the UK, it is assumed that 5% of energy intake will be derived from alcohol. B Data for normal basal metabolic rate (BMR) were obtained from healthy men and women in various countries. BMR declines from middle age and is lower in women, even after adjustment for body size because of differences in fat-free mass. C Energy is required for movement and activity. Physical activity level (PAL) is the multiple of BMR by which total energy expenditure is increased by activity. D Energy is consumed in order to digest food. *Leisure or sport activity increases PAL by ~0.3 for each 30–60 minutes of moderate exercise performed 4–5 times per week. The UK population median for PAL is 1.6, with estimates of 1.5 for the ‘less active’ and 1.8 for the ‘more active’. Immobile Sedentary work Standing work Active leisure/ sport* Strenuous work Soldier Athlete 0.0 1.0 2.0 3.0 Physical activity level (PAL) Total energy expenditure Basal metabolic rate Male Female Energy expenditure = B Basal metabolic rate D Diet-induced thermogenesis C Physical activity A Dietary intake = food + alcohol 17% Protein 35% Fat 48% Carbohydrate 10% Protein 15% Fat 75% Carbohydrate 17% Protein 33% Fat 50% Carbohydrate UK target food intakes Current food intakes Energy intake Energy expenditure India UK 1 megajoule (MJ) = 239 kilocalorie (kcal) = energy stored in ~ 34 g fat 18 – 29 30 – 39 40 – 64 Age (years) • Higher with greater fat-free mass • Lower with ageing • Increases with cold, heat, fever • Higher in smokers

# Energy expenditure (MJ/day)

 Fig. 19.3 Regulation of energy balance and its link with reproduction. Ϩ indicates factors that are stimulated by eating and induce satiety. Ω indicates factors that are suppressed by eating and inhibit satiety. Eating behaviour Habit Hedonic response

to food Satiety Muscle Adipose tissue Energy expenditure/storage Fertility Neuro-endocrine responses (growth hormone, cortisol, thyroxine) Autonomic nervous system Reproductive hormones Adipose tissue Hypothalamus Stomach Pancreas Small bowel Ghrelin Leptin Insulin Peptide YY Oxyntomodulin Glucagon-like peptide-1 Pancreatic polypeptide 19.1 Dietary carbohydrates Class Components Examples Source Free sugars Monosaccharides Disaccharides Glucose, fructose Sucrose, lactose, maltose Intrinsic: fruits, milks, vegetables Extrinsic (extracted, refined): beet or cane sucrose, high-fructose corn syrup Short-chain carbohydrates Oligosaccharides Maltodextrins, fructo-oligosaccharides Starch polysaccharides Rapidly digestible Slowly digestible Resistant Cereals (wheat, rice), root vegetables (potato), legumes (lentils, beans, peas) Non-starch polysaccharides (NSPs; dietary fibre) Fibrous Viscous Cellulose Hemicellulose Pectins Gums Plants Sugar alcohols Sorbitol, xylitol Sorbitol: stone fruits (apples, peaches, prunes) Xylitol: maize, berry fruits Both used as low-calorie sugar alternatives be limited. Individuals who do not produce lactase (‘lactoseintolerant’) are advised to avoid or limit dairy products and foods with added lactose. Starches in cereal foods, root foods and legumes provide the largest proportion of energy in most diets around the world. All starches are polymers of glucose, linked by the same 1–4 glycosidic linkages. Some starches are digested promptly by salivary and then pancreatic amylase, however, producing rapid delivery of glucose to the blood. Other starches are digested more slowly, either because they are protected in the structure of the food, or because of their crystal structure, or because the molecule is unbranched (amylose). These differences are the basis for the ‘glycaemic index’ of foods. This is the area under the curve of the rise in blood glucose concentration in the 2 hours following ingestion of 50 g carbohydrate, expressed as a percentage of the response to 50 g anhydrous glucose. There is evidence linking high glycaemic index foods, particularly foods containing large amounts of sugars such as glucose, sucrose or fructose (e.g. in soft drinks) with obesity and type 2 diabetes



fat (i.e. from animal sources: butter, ghee or lard) with PUFA in the diet can lower the concentration of circulating low-density lipoprotein (LDL) cholesterol and may help prevent coronary heart disease. High intakes of trans fatty acids (TFAs; isomers of the natural cis fatty acids) reflect the use of oils that have been partially hydrogenated in the food industry. It is recommended that TFAs are limited to less than 2% of the dietary fat intake, as they are associated with cardiovascular disease. Changes in industrial practice in the UK and US have meant that TFA intake is now below 1%, with the residual amounts coming from milk as a result of ruminant digestion. Cholesterol is also absorbed directly from food in chylomicrons and is an important substrate for steroid and sterol synthesis, but not an important source of energy. Proteins Proteins are made up of some 20 different amino acids, of which nine are ‘essential’ (Box 19.2), i.e. they cannot be synthesised in humans but are required for synthesis of important proteins. Another group of five amino acids are termed ‘conditionally essential’, meaning that they can be synthesised from other amino acids, provided there is an adequate dietary supply. The remaining amino acids can be synthesised in the body by transamination, provided there is a sufficient supply of amino groups. The nutritive or ‘biological’ value of different proteins depends on the relative proportions of essential amino acids they contain. Proteins of animal origin, particularly from eggs, milk and meat, are generally of higher biological value than proteins of vegetable origin, which are low in one or more of the essential amino acids. When two different vegetable proteins are eaten together (e.g. a cereal and a legume), however, their amino acid contents are complementary and produce an adequate mix,

an important principle in vegan diets. Dietary recommendations for macronutrients Recommendations for energy intake (Box 19.3) and proportions of macronutrients (Box 19.4) have been calculated to provide a balance of essential nutrients and minimise the risks of excessive refined sugar (dental caries, high glycaemic index/diabetes mellitus), saturated fat or trans fat (obesity, coronary heart disease). Recommended dietary fibre intake is based on avoiding risks of colonic disease. The usual recommended protein intake for a healthy man doing light work is 65–100 g/day. The minimum requirement is around 40 g of protein with a high proportion of essential amino acids or a high biological value. (p. 932). Sugar alcohols (e.g. sorbitol) that are not absorbed form the gut and are used as replacement sweeteners can cause diarrhoea if eaten in large amounts. Dietary fibre Dietary fibre is plant food that is not digested by human enzymes in the gastrointestinal tract. Most dietary fibre is known as ‘non-starch polysaccharides’ (NSPs) (see Box 19.1). A small percentage of ‘resistant’ dietary starch may also pass unchanged into the large intestine. Dietary fibre can be broken down by the resident bacteria in the colon to produce short-chain fatty acids. This is essential fuel for the enterocytes and contributes to bowel health. The extent of flatus formed is dependent on the food source. Some types of NSP, notably the hemicellulose of wheat, increase the water-holding capacity of colonic contents and the bulk of faeces. They relieve simple constipation, appear to prevent diverticulosis and may reduce the risk of cancer of the colon. Other viscous, indigestible polysaccharides like pectin and guar gum are important in the upper gastrointestinal tract, where they slow gastric emptying, contribute to satiety, and reduce bile salt absorption and hence plasma cholesterol concentration. Fats Fat has the highest energy density of the macronutrients (37 kJ/g) and excessive consumption may be an insidious cause of obesity (see Fig. 19.2A). Free fatty acids are absorbed in chylomicrons (pp. 371 and 372; see Fig. 21.5, p. 768), allowing access of complex molecules into the circulation. Fatty acid structures are shown in Figure 19.4. The principal polyunsaturated fatty acid (PUFA) in plant seed oils is linoleic acid (18 : 2 ω6). This and α-linolenic acid (18 : 3 ω3) are the ‘essential’ fatty acids, which humans cannot synthesise de novo. They undergo further desaturation and elongation, to produce, for example, γ-linolenic acid (18 : 3 ω6) and arachidonic acid (20 : 4 ω6). These are precursors of prostaglandins and eicosanoids, and form part of the structure of lipid membranes in all cells. Fish oils are rich in ω3 PUFA (e.g. eicosapentaenoic (20 : 5 ω3) and docosahexaenoic (22 : 6 ω3), which promote the anti-inflammatory cascade of prostaglandin production and occur in the lipids of the human brain and retina. They inhibit thrombosis by competitively antagonising thromboxane A2 formation. Replacing saturated Fig. 19.4 Schematic representation of fatty acids. Standard nomenclature specifies the number of carbon atoms and indicates the number and position of the double bond(s) relative to the methyl (−CH3, ω) end of the molecule after a colon. CH3 COOH Polyunsaturated fatty acid, e.g. linoleic acid (18:2 ω6) CH3 COOH Monounsaturated fatty acid, e.g. oleic acid (18:1 ω9) CH3 COOH Saturated fatty acid, e.g. myristic acid (14:0 )

CH2 CH 19.2 Amino acids Essential amino acids • Tryptophan • Histidine • Methionine • Threonine • Isoleucine • Valine • Phenylalanine • Lysine • Leucine Conditionally essential amino acids and their precursors • Cysteine: methionine, serine • Tyrosine: phenylalanine • Arginine: glutamine/glutamate, aspartate • Proline: glutamate • Glycine: serine, choline

698 • NUTRITIONAL FACTORS IN DISEASE Disorders of altered energy balance Obesity Obesity is regarded as a pandemic, with potentially disastrous consequences for human health. Over 25% of adults in the UK were obese (i.e. BMI ≥ 30 kg/m2) in 2015, compared with 7% in 1980 and 16% in

1995. Moreover, almost 66% of the UK adult population are overweight (BMI ≥ 25 kg/m2), although there is considerable regional and age group variation. In developing countries, average national rates of obesity are low, but these figures may disguise high rates of obesity in urban communities; for example, nearly 25% of women in urban India are overweight. There is increasing public awareness of the health implications of obesity. Many will seek medical help for their obesity, others will present with complications of obesity, and increasing numbers are being identified during health screening examinations. Complications Obesity has adverse effects on both mortality and morbidity (Fig. 19.5). Changes in mortality are difficult to analyse due to the confounding effects of lower body weight in cigarette smokers and those with other illnesses (such as cancer). It is clear, however, that the lowest mortality rates are seen in Europeans in the BMI range 18.5–24 kg/m2 (and at lower BMI in Asians). It is suggested that obesity at age 40 years can reduce life expectancy by up to 7 years for non-smokers and by 13 years for smokers. Coronary heart disease (Fig. 19.6) is the major cause of death but cancer rates are also increased in the overweight, especially colorectal cancer in males and cancer of the gallbladder, biliary tract, breast, endometrium and cervix in females. Obesity has little effect on life expectancy above 70 years of age, but the obese do spend a greater proportion of their active life disabled. The Fig. 19.5 Complications of obesity. Pulmonary Exercise intolerance Obstructive sleep apnoea Asthma Gastrointestinal Gallstones Gastro-oesophageal reflux Non-alcoholic fatty liver disease Colon cancer Renal Glomerulosclerosis Renal cancer Musculoskeletal Ankle sprains Flat feet Tibia vara Osteoarthritis Back pain Psychosocial Eating disorders Poor self-esteem Body image disorder Social isolation and stigmatisation Depression Neurological Pseudotumour cerebri (idiopathic intracranial hypertension) Cardiovascular Hypertension Dyslipidaemia Coagulopathy Chronic inflammation Endothelial dysfunction Endocrine Insulin resistance Impaired fasting glucose or glucose intolerance Type 2 diabetes Precocious puberty Menstrual irregularities Polycystic ovary syndrome (females) Hormone-related cancers (breast, endometrium, prostate) 19.4 WHO recommended population macronutrient goals Nutrient (% of total energy unless indicated) Target limits for average population intakes Lower Upper Total fat

Saturated fatty acids

Polyunsaturated fatty acids

Trans fatty acids

Dietary cholesterol (mg/day)

Total carbohydrate

Free sugars

Complex carbohydrate

Dietary fibre (g/day): As non-starch polysaccharides

As total dietary fibre

Protein

19.3 Daily adult energy requirements in health Circumstances Daily requirements* Females Males At rest (basal metabolic rate) 5.4 MJ (1300 kcal) 6.7 MJ (1600 kcal) Less active 8.0 MJ (1900 kcal) 9.9 MJ (2400 kcal) Population median 8.8 MJ (2100 kcal) 10.8 MJ (2600 kcal) More active 9.6 MJ (2300 kcal) 11.8 MJ (2800 kcal) *These are based on a healthy target body mass index (BMI) of 22.5 kg/m2. For a female, height is 162 cm and weight 59.0 kg; for a male, height is 175 cm and weight 68.8 kg. Previous average recommendations of 8.1 MJ (1950 kcal, usually rounded up to 2000 kcal) for females and 10.7 MJ (2500 kcal) for males should continue to be used, as these fall within experimental error.



in the liver and muscle, and hence induce insulin resistance and promote type 2 diabetes. Recent research has also highlighted the importance of fat deposition within specific organs, especially the liver, as an important determinant of metabolic risk in the obese. Aetiology Accumulation of fat results from a discrepancy between energy consumption and energy expenditure that is too large to be defended by the hypothalamic regulation of BMR. A continuous small daily positive energy balance of only 0.2–0.8 MJ (50–200 kcal; < 10% of intake) would lead to weight gain of 2–20 kg over a period of 4–10 years. Given the cumulative effects of subtle energy excess, body fat content shows ‘tracking’ with age, such that obese children usually become obese adults. Weight tends to increase throughout adult life, as BMR and physical activity decrease (see Fig. 19.2). The pandemic of obesity reflects changes in both energy intake and expenditure (Box 19.5), although both are difficult to measure reliably. The estimated average global daily supply of food energy per person increased from approximately 9.8 MJ (2350 kcal) in the 1960s to approximately 11.7 MJ (2800 kcal) in the 1990s, but its delivery is unequal. For example, in India it is estimated that 5% of the population receives 40% of the available food energy, leading to obesity in the urban population in parallel with under-nutrition in some rural communities. In affluent societies, a significant proportion of this food supply is discarded. In the USA, men’s average daily energy intake reportedly rose from 10.2 MJ (2450 kcal) in 1971 to 11.0 MJ (2618 kcal) in 2000. Portion sizes, particularly of energy-dense foods such as drinks with highly refined sugar content and salty snacks, have increased. However, UK data suggest that energy intakes have declined (which may in part be due to deliberate restriction or ‘dieting’), but this is apparently insufficient to compensate for the decrease in physical activity in recent years. Obesity is correlated positively with the number of hours spent watching television, and inversely with levels of physical activity (e.g. stair climbing). It is suggested that minor activities such as fidgeting, also termed non-exercise activity thermogenesis (NEAT), may contribute to energy expenditure and protect against obesity. Susceptibility to obesity Susceptibility to obesity and its adverse consequences undoubtedly varies between individuals. It is not true that obese subjects have a ‘slow metabolism’, since their BMR is higher than that of lean subjects. Twin and adoption studies confirm a genetic influence on obesity. The pattern of inheritance suggests a polygenic disorder, with small contributions from a number of different genes, together accounting for 25–70% of variation in weight. Recent results from ‘genome-wide’ association studies of polymorphisms in large numbers of people (p. 45) have rise in obesity has been accompanied by an epidemic of type 2 diabetes (p. 732) and osteoarthritis, particularly of the knee. Although an increased body size results in greater bone density through increased mechanical stress, it is not certain whether this translates to a lower incidence of osteoporotic fractures (p. 1044). Obesity may have profound psychological consequences, compounded by stigmatisation of the obese in many societies. Body

fat distribution For some complications of obesity, the distribution rather than the absolute amount of excess adipose tissue appears to be important. Increased intra-abdominal fat causes ‘central’ (‘abdominal’, ‘visceral’, ‘android’ or ‘apple-shaped’) obesity, which contrasts with subcutaneous fat accumulation causing ‘generalised’ (‘gynoid’ or ‘pear-shaped’) obesity; the former is more common in men and is more closely associated with type 2 diabetes, the metabolic syndrome and cardiovascular disease (see Fig. 19.5). The key difference between these depots of fat may lie in their vascular anatomy, with intra-abdominal fat draining into the portal vein and thence directly to the liver. Thus many factors that are released from adipose tissue (including free fatty acids; ‘adipokines’, such as tumour necrosis factor alpha, adiponectin and resistin) may be at higher concentration Fig. 19.6 Risks of diabetes and cardiovascular disease in overweight and obese women. Data are from the Nurses’ Health Study in the USA, and mostly relate to Caucasian women. In some ethnic groups (e.g. South Asians, Native Americans) and in people with higher waist circumference, the metabolic complications are even more severe at a given level of body mass index.

Relative risk for cardiovascular disease < 21 21– 22.9 23– 24.9 25– 28.9

> “ 29

Relative risk for type 2 diabetes < 25 25 – 30

> “ 30 Normal weight Overweight Obese Body mass index (kg/m2)

19.5 Some reasons for the increasing prevalence of obesity – the ‘obesogenic’ environment Increasing energy intake • ↑ Portion sizes • ↑ Snacking and loss of regular meals • ↑ Energy-dense food (fat and sugars) • ↑ Affluence Decreasing energy expenditure • ↑ Car ownership • ↓ Walking to school/work • ↑ Automation; ↓ manual labour • ↓ Sports in schools • ↑ Time spent on computer games and watching TV • ↑ Central heating

700 • NUTRITIONAL FACTORS IN DISEASE Severity of obesity can be quantified using the BMI and waist circumference. The risk of metabolic and cardiovascular complications of obesity is higher in those with a high waist circumference; lower levels of BMI and waist circumference indicate higher risk in Asian populations (Box 19.7). A dietary history may be helpful in guiding dietary advice (p. 693) but is notoriously susceptible to under-reporting of food consumption. It is important to consider ‘pathological’ eating behaviour (such as binge eating, nocturnal eating or bulimia; p. 1204), which may be the most important issue to address in some patients. Alcohol is an important source of energy intake and should be considered in detail. The history of weight gain may help diagnose underlying causes. A patient who has recently gained substantial weight or has gained weight at a faster rate than previously, and is not taking relevant drugs (see Box 19.6), is more likely to have an underlying disorder such as hypothyroidism (p. 639) or Cushing’s syndrome (p. 666). All obese patients should have thyroid function tests performed on one occasion, and an overnight dexamethasone suppression test or 24-hour urine free cortisol if Cushing’s syndrome is

suspected. Monogenic and ‘syndromic’ causes of obesity are usually relevant only in children presenting with severe obesity. Assessment of the diverse complications of obesity (see Fig. 19.5) requires a thorough history, examination and screening investigations. The impact of obesity on the patient’s life and work is a major consideration. Assessment of other cardiovascular risk factors is important. Blood pressure should be measured with a large cuff, if required (p. 510). Associated type 2 diabetes and dyslipidaemia are detected by measurement of blood glucose or HbA1c and a serum lipid profile, ideally in a fasting morning sample. Elevated serum transaminases occur in patients with non-alcoholic fatty liver disease (p. 884). Management The health risks of obesity are largely reversible if identified and treated early. Interventions proven to reduce weight in obese patients also ameliorate cardiovascular risk factors. Lifestyle advice that lowers body weight and increases physical exercise reduces the incidence of type 2 diabetes (p. 743). Given the high prevalence of obesity and the large magnitude of its risks, population strategies to prevent and reverse obesity are high on the public health priority list for many countries. Initiatives include promoting healthy eating in schools, enhancing walking identified a handful of genes that influence obesity, some of which encode proteins known to be involved in the control of appetite or metabolism and some of which have an unknown function. These genes account for less than 5% of the variation in body weight, however. Genes also influence fat distribution and therefore the risk of the metabolic consequences of obesity, such as type 2 diabetes and fatty liver disease. A few rare single-gene disorders have been identified that lead to severe childhood obesity. These include mutations of the melanocortin-4 receptor (MC4R), which account for approximately 5% of severe early-onset obesity; defects in the enzymes processing propiomelanocortin (POMC, the precursor for adrenocorticotrophic hormone (ACTH)) in the hypothalamus; and mutations in the leptin gene (see Fig. 19.3). The latter can be treated by leptin injections. Additional genetic conditions in which obesity is a feature include Prader–Willi (see Box 3.8, p. 51) and Lawrence–Moon–Biedl syndromes. Reversible causes of obesity and weight gain In a small minority of patients presenting with obesity, specific causal factors can be identified and treated (Box 19.6). These patients are distinguished from those with idiopathic obesity by their short history, with a recent marked change in the trajectory of their adult weight gain. Clinical features and investigations In assessing an individual presenting with obesity, the aims are to: • quantify the problem • exclude an underlying cause • identify complications • reach a management plan. 19.6 Potentially reversible causes of weight gain Endocrine factors • Hypothyroidism • Cushing’s syndrome • Insulinoma • Hypothalamic tumours or injury Drug treatments • Atypical antipsychotics (e.g. olanzapine) • Sulphonylureas, thiazolidinediones, insulin • Pizotifen • Glucocorticoids • Sodium valproate • β-blockers 19.7 Quantifying obesity with BMI and waist circumference for risk of type 2 diabetes and cardiovascular disease BMI (weight in kg/height in m2) Classification1 Waist circumference2 Men < 94 cm Women < 80 cm Men 94–102 cm Women 80–88 cm Men > 102 cm Women > 88 cm 18.5–24.9 Reference range Negligible Mildly increased Moderate 25.0–29.9 Overweight Negligible Moderate Severe

> 30.0 Obese 30.0–34.9 Class I Moderate Severe Very severe 35.0–39.9 Class II – Very severe Very severe 40.0 Class III – Very severe Very severe 1Classification of the World Health Organisation (WHO) and International Obesity Task Force. The Western Pacific Region Office of WHO recommends that, among Asians, BMI > 23.0 is overweight and > 25.0 is obese. Lower cut-offs for waist circumference

> have also been proposed for Asians but have not been validated. 2When BMI is 35 kg/m2 , waist circumference does not add to the increased risk.



snacking, regular meals to encourage satiety, and substitution of sugar with artificial sweeteners) should be discussed. Regular support from a dietitian or attendance at a weight loss group may be helpful. Weight loss diets In overweight people, adherence to the lifestyle advice given above may gradually induce weight loss. In obese patients, more active intervention is usually required to lose weight before conversion to the ‘weight maintenance’ advice given above. A significant industry has developed in marketing diets for weight loss. These vary substantially in their balance of macronutrients (Box 19.8) but there is little evidence that they vary in their medium-term (1-year) efficacy. Most involve recommending a reduction of daily total energy intake of −2.5 MJ (600 kcal) from the patient’s normal consumption. Modelling data that take into account the reduced energy expenditure as weight is lost suggest that a reduction of energy intake of 100 kJ per day will lead to an eventual body weight change of about 1 kg, with half of the weight change being achieved in about 1 year and 95% of the weight change in about 3 years. Weight loss is highly variable and patient adherence is the major determinant of success. There is some evidence that weight loss diets are most effective in their early weeks and that adherence is improved by novelty of the diet; this provides some justification for switching to a different dietary regimen when weight loss slows on the first diet. Vitamin and cycling options for commuters, and liaising with the food industry to reduce energy, sugar and fat content and to label foods appropriately; taxes on high-sugar drinks have also been introduced in some countries. Unfortunately, ‘low-fat’ foods are often still energy-dense, and current lifestyles with labour-saving devices, sedentary work and passive leisure activities have much lower energy requirements than the manual labour and household duties of previous generations. Most patients seeking assistance with obesity are motivated to lose weight but have attempted to do so previously without long-term success. Often weight will have oscillated between periods of successful weight loss and then regain of weight. These patients may hold misconceptions that they have an underlying disease, inaccurate perceptions of their energy intake and expenditure, and an unrealistic view of the target weight that they would regard as a ‘success’. An empathetic explanation of energy balance, which recognises that some individuals are more susceptible to obesity than others and may find it more difficult to lose body weight and sustain this loss, is important. Exclusion of underlying ‘hormone imbalance’ with simple tests is reassuring and shifts the focus on to consideration of energy balance. Appropriate goals for weight loss should be agreed, recognising that the slope of the relationship between obesity and many of its complications becomes steeper with increasing BMI, so that a given amount of weight loss achieves greater risk reduction at higher levels of BMI. A reasonable goal for most patients is to lose 5–10% of body weight. The management plan will vary according to the severity of the obesity (see Box 19.7) and the associated risk factors and complications. It will also be influenced by availability of resources; health-care providers and regulators have generally been careful not to recommend expensive interventions (especially long-term drug therapy and surgery) for everyone who is overweight. Instead, most guidelines focus resources on short-term interventions in those who have high health risks and comorbidities associated with their obesity, and who have demonstrated their capacity to alter their lifestyle to achieve weight loss (Fig. 19.7). Lifestyle

advice Behavioural modification to avoid some of the effects of the ‘obesogenic’ environment (see Box 19.5) is the cornerstone of long-term control of weight. Adopting regular eating patterns and maximising physical activity are advised, with reference to the modest extra activity required to increase physical activity level (PAL) ratios (see Fig. 19.2C). Where possible, this should be incorporated in the daily routine (e.g. walking rather than driving to work), as this is more likely to be sustained. Alternative exercise (e.g. swimming) may be considered if musculoskeletal complications prevent walking. Changes in eating behaviour (including food selection, portion size control, avoidance of Fig. 19.7 Therapeutic options for obesity. Relevant comorbidities include type 2 diabetes, hypertension, cardiovascular disease, sleep apnoea, and waist circumference of > 102 cm in men or 88 cm in women. This is an approximate consensus of the numerous national guidelines, which vary slightly in their recommendations and are revised every few years. ↑Exercise Eating behaviour modification Treat cardiovascular risk factors Supervised low-calorie diet Drugs Surgery BMI cut-offs in absence of comorbidity

BMI cut-offs in presence of comorbidity 19.8 Low-calorie diet therapy for obesity Diet % Carbohydrate % Fat % Protein Comments Normal (typical developed country)

Moderate fat (e.g. Weight Watchers)

Maintains balance in macronutrients and micronutrients while reducing energy-dense fats Low carbohydrate (e.g. Atkins)

Induction of ketosis may suppress hunger High protein (e.g. Zone)

Protein has greater satiety effect than other macronutrients Low fat (e.g. Ornish)

 rimonabant (psychiatric side-effects) in recent years. Orlistat has been available for many years, and four drugs or drug combinations have recently been approved in the USA and two of these in Europe. There is no role for diuretics, or for thyroxine therapy without biochemical evidence of hypothyroidism. Drug therapy should always be used as an adjunct to lifestyle advice and support, which should be continued throughout treatment. Orlistat inhibits pancreatic and gastric lipases and thereby decreases the hydrolysis of ingested triglycerides, reducing dietary fat absorption by approximately 30%. The drug is not absorbed and adverse side-effects relate to the effect of the resultant fat malabsorption on the gut: namely, loose stools, oily spotting, faecal urgency, flatus and the potential for malabsorption of fat-soluble vitamins. Orlistat at the standard dose of 120 mg is taken with each of the three main meals of the day; a lower dose (60 mg) is available without prescription in some countries. Its efficacy is shown in Figure 19.8; these effects may be explained because patients taking orlistat adhere better to low-fat diets in order to avoid unpleasant gastrointestinal side-effects. The combination of low-dose phentermine and topiramate extended release has been approved in the USA; this results in weight loss of approximately 6% greater than placebo and benefits lipids and glucose concentrations. Concerns over teratogenicity of topiramate and cardiovascular effects of phentermine have so far supplementation is wise in those diets in which macronutrient balance is markedly disturbed. In some patients, more rapid weight loss is required, e.g. in preparation for surgery. There is no role for starvation diets, which risk profound loss of muscle mass and the development of arrhythmias (and even sudden death) secondary to elevated free fatty acids, ketosis and deranged electrolytes.

Very-lowcalorie diets (VLCDs) can be considered for short-term rapid weight loss, producing losses of 1.5–2.5 kg/week, compared to 0.5 kg/week on conventional regimens, but require the supervision of an experienced physician and nutritionist. The composition of the diet should ensure a minimum of 50 g of protein each day for men and 40 g for women to minimise muscle degradation. Energy content should be a minimum of 1.65 MJ (400 kcal) for women of height < 1.73 m, and 2.1 MJ (500 kcal) for all men and for women taller than 1.73 m. Side-effects are a problem in the early stages and include orthostatic hypotension, headache, diarrhoea and nausea. Drugs A huge investment has been made by the pharmaceutical industry in finding drugs for obesity. The side-effect profile has limited the use of many agents, with notable withdrawals from clinical use of sibutramine (increased cardiovascular events) and Fig. 19.8 Effects of orlistat (A), liraglutide (B) and bariatric surgery (C) on weight loss. For the bariatric surgery data, each obese subject undergoing surgery was matched with a control subject whose obesity was managed according to the standard of care for non-operative interventions. Note that the maximum weight loss achieved with orlistat and liraglutide was approximately 10 kg, and that the follow-up period is relatively short; surgery achieves much more substantial and prolonged weight loss. A, Data from Torgerson JS Hauptman J, Boldrin MS, et al. A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004; 27:155–161. B, Data from le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet; published online 22 Feb 2017. C, Data from Sjöström L, Narbro K, Sjöström D, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007; 357:741–752. Change in body weight (%) Control Banding Vertical banded gastroplasty Gastric bypass -2% -13% -18% -27% Placebo

- lifestyle Placebo
- lifestyle Liraglutide
- lifestyle Orlistat
- lifestyle p < 0.001

-40 -35 -30 -25 -20 -15 -10 -5 -40 -35 -30 -25 -20 -15 -10 -5

Change in body weight (%) -40 -35 -30 -25 -20 -15 -10 -5

A Change in body weight (%)

B

Years of follow-up Years of follow-up Years of follow-up C

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recent-onset diabetes and a BMI > 30 kg/m2. Only experienced specialist surgeons should undertake these procedures, in collaboration with a multidisciplinary team. Several approaches are used (Fig. 19.9) and all can be performed laparoscopically. The mechanism of weight loss may not simply relate to limiting the stomach or absorptive capacity, but rather in disrupting the release of ghrelin from the stomach or promoting the release of other peptides from the small bowel, thereby enhancing satiety signalling in the hypothalamus. Diabetes may improve rapidly precluded its

approval in Europe. The 5-HT2c inhibitor lorcaserin is also approved in the USA; it is moderately effective and has a relatively low rate of adverse effects. The combination of the opioid antagonist naltrexone and the noradrenaline (norepinephrine)/ dopamine re-uptake inhibitor bupropion is also effective. The main adverse effects are dry mouth and constipation. Finally, a higher dose of the injectable glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide (3 mg) is also approved for use and has been shown to reduce the risk of diabetes in patients with pre-diabetes. Drug therapy is usually reserved for patients with high risk of complications from obesity (see Fig. 19.7), and its optimum timing and duration are controversial. There is evidence that those patients who demonstrate early weight loss (usually defined as 5% after 12 weeks on the optimum dose) achieve greater and longer-term weight loss, and this is reflected in most guidelines for the use of drugs for obesity. Treatment can be stopped in non-responders at this point and an alternative treatment considered. Although life-long therapy is advocated for many drugs that reduce risk on the basis of relatively short-term research trials (e.g. drugs for hypertension and osteoporosis), some patients who continue to take anti-obesity drugs tend to regain weight with time; this may partly reflect age-related weight gain, but significant weight gain should prompt reinforcement of lifestyle advice and, if this is unsuccessful, drug therapy should be discontinued (see Fig. 19.8). Surgery ‘Bariatric’ surgery is by far the most effective long-term treatment for obesity (see Fig. 19.8 and Box 19.9) and is the only anti-obesity intervention that has been associated with reduced mortality. Bariatric surgery should be contemplated in motivated patients who have very high risks of complications of obesity (see Fig. 19.7), when extensive dietary and drug therapy has been insufficiently effective. It is usually reserved for those with severe obesity (BMI

> 40 kg/m2), or those with a BMI > 35 kg/m2 and significant complications, such as type 2 diabetes or obstructive sleep apnoea, although some evidence-based guidelines now suggest surgery can be considered at a lower weight in people with 19.9 Effectiveness and adverse effects of laparoscopic bariatric surgical procedures Procedure Expected weight loss (% excess weight) Adverse effects Gastric banding 50–60% Band slippage, erosion, stricture Port site infection Mortality < 0.2% in experienced centres Sleeve gastrectomy 50–60% Iron deficiency Vitamin B12 deficiency Mortality < 0.2% in experienced centres Roux-en-Y gastric bypass 70–80% Internal hernia Stomal ulcer Dumping syndrome Hypoglycaemia Iron deficiency Vitamin B12 deficiency Vitamin D deficiency Mortality 0.5% Duodenal switch Up to 100% Steatorrhoea Protein-calorie malnutrition Iron deficiency Vitamin B12 deficiency Calcium, zinc, copper deficiency Mortality 1% Fig. 19.9 Bariatric surgical procedures. A Laparoscopic banding, with the option of a reservoir band and subcutaneous access to restrict the stomach further after compensatory expansion has occurred. B Sleeve gastrectomy. C Roux-en-Y gastric bypass. D Biliopancreatic diversion with duodenal switch. A B C D Access port Oesophagus Gastric band Gastric sleeve Pylorus Resected stomach The small intestine is connected to the stomach pouch Unused portion of the small intestine Removed portion of stomach Biliopancreatic loop Digestive loop Duodenal switch 75–100 cm common loop

704 • NUTRITIONAL FACTORS IN DISEASE Clinical features In starvation, the severity of malnutrition can be assessed by anthropometric measurements, such as BMI (see p. 693 and Box 19.10). Demispan and mid-arm circumference measurements are most useful in monitoring progress during treatment. The clinical features of severe under-nutrition in adults are listed in Box 19.12. Under-nutrition often leads to vitamin deficiencies, especially of thiamin, folate and vitamin C (see below). Diarrhoea can lead to depletion of sodium, potassium and magnesium. The high mortality rate in famine situations is often due to outbreaks of infection, such as typhus or cholera, but the usual signs of infection may not be apparent. In advanced starvation, patients become completely inactive and may assume a flexed, fetal position. In the last stage of starvation, death comes quietly and often quite suddenly. The very old are most vulnerable. All organs are atrophied at necropsy, except the brain, which tends to maintain its weight. Investigations In a famine, laboratory investigations may be impractical but will show that plasma free fatty acids are increased and there is ketosis and a mild metabolic acidosis. Plasma glucose is low after surgery, particularly after gastric bypass, and although this may be attributed to severe energy restriction in the perioperative period, it is possible that increased release of incretin hormones such as GLP-1 may contribute to the improvement in glucose control. Complications depend on the approach. Mortality is low in experienced centres but post-operative respiratory problems, wound infection and dehiscence, staple leaks, stomal stenosis, marginal ulcers and venous thrombosis may occur. Additional problems may arise at a later stage, such as pouch and distal oesophageal dilatation, persistent vomiting, ‘dumping’ (p. 801), hypoglycaemia and micronutrient deficiencies, particularly of folate, vitamin B12 and iron, which are of special concern to women contemplating pregnancy; this should be delayed for at least 2 years following surgery. Cosmetic surgical procedures may be considered in obese patients after successful weight loss. Apronectomy is usually advocated to remove an overhang of abdominal skin, especially if infected or ulcerated. This operation is of no value for long-term weight reduction if food intake remains unrestricted. Treatment of additional risk factors Obesity must not be treated in isolation and other risk factors must be addressed, including smoking, excess alcohol consumption, diabetes mellitus, hyperlipidaemia, hypertension and obstructive sleep apnoea. Treatment of these is discussed in the relevant chapters. Under-nutrition Starvation and famine There remain regions of the world, particularly rural Africa, where under-nutrition due to famine is endemic, the prevalence of BMI of less than 18.5 kg/m2 (Box 19.10) in adults is as high as 20%, and growth retardation due to under-nutrition affects 50% of children. The World Health Organisation (WHO) reports that chronic under-nutrition is responsible for more than half of all childhood deaths worldwide. Starvation is manifest as marasmus (malnutrition with marked muscle wasting) or, when additive complications such as oxidative stress come into play, malnourished children can develop kwashiorkor (malnutrition with oedema). Growth retardation is due to deficiencies of key nutrients (protein, zinc, potassium, phosphate and sulphur). Treatment of these childhood conditions is not discussed in this adult medical textbook. In adults, starvation is the result of chronic sustained negative energy (calorie) balance. Causes are shown in Box 19.11. Causes of weight loss are considered further on page 785. 19.12 Clinical features of severe under-nutrition in adults • Weight loss • Thirst, craving for food, weakness and feeling cold • Nocturia, amenorrhoea or impotence • Lax, pale, dry skin with loss of turgor and, occasionally, pigmented patches • Cold and cyanosed extremities, pressure sores • Hair thinning or loss (except in adolescents) • Muscle-wasting, best demonstrated by the loss of the temporalis and periscapular muscles and reduced mid-arm circumference • Loss of subcutaneous fat, reflected in reduced skinfold thickness and mid-arm circumference • Hypothermia, bradycardia, hypotension and small heart • Oedema, which may be present without hypoalbuminaemia (‘famine

oedema') • Distended abdomen with diarrhoea • Diminished tendon jerks • Apathy, loss of initiative, depression, introversion, aggression if food is nearby • Susceptibility to infections (Box 19.13) 19.11 Causes of under-nutrition and weight loss in adults Decreased energy intake • Famine • Persistent regurgitation or vomiting • Anorexia, including depression and anorexia nervosa • Malabsorption (e.g. small intestinal disease) • Maldigestion (e.g. pancreatic exocrine insufficiency) Increased energy expenditure • Increased basal metabolic rate (thyrotoxicosis, trauma, fever, cancer, cachexia) • Excessive physical activity (e.g. marathon runners) • Energy loss (e.g. glycosuria in diabetes) • Impaired energy storage (e.g. Addison's disease, phaeochromocytoma) 19.10 Classification of under-nutrition in adults by body mass index (weight/height2) BMI (kg/m2) Classification

> 20 Adequate nutrition 18.5–20 Marginal < 18.5 Under-nutrition 17–18.4 Mild 16–17 Moderate < 16 Severe



average of 5% of their total body weight during that admission. In the older population, levels of under-nutrition and vitamin deficiencies parallel levels of independent living. In Scotland, 33% of those aged over 65 who are living in their own home are deficient in folic acid and 10% are deficient in vitamin C. The prevalence of vitamin deficiencies rises further in less independent groups in residential or nursing homes. Under-nutrition is poorly recognised in hospitals and has serious consequences. Physical effects include impaired immunity and muscle weakness, which in turn affect cardiac and respiratory function, and delayed wound healing after surgery with increased risks of post-operative infection. The under-nourished patient is often withdrawn and this may be mistaken for depressive illness. Engagement with treatment and rehabilitation can be adversely affected. Much of this can be avoided through better awareness of the prevalence of under-nutrition, prompt nutritional assessment and monitoring with appropriate intervention. Scoring systems, such as the MUST tool (p. 693), raise awareness across multidisciplinary teams, and encourage staff to assess and monitor food intake and weigh patients regularly. Causes are often complex (see Box 19.11). Social issues impact on food choices and may cause or exacerbate disease. Social isolation, low levels of disposable income and a lack of knowledge or interest in healthy eating may increase reliance on calorie-dense convenience foods of poor nutritional quality. In turn, the non-specific effects of chronic inflammation, infection or malignancy, as well as specific gastrointestinal disorders, may adversely affect appetite, reducing food intake. Patients may report avoidance of certain foods that exacerbate their symptoms (often fibre-rich, otherwise healthy foods). A loss of appetite is not specific to gastrointestinal disease and may be seen as a non-specific response to myriad other conditions or their treatments. The most common reported side-effects but albumin concentration is often maintained because the liver still functions normally. Insulin secretion is diminished, glucagon and cortisol tend to increase, and reverse T3 replaces normal triiodothyronine (p. 634). The resting metabolic rate falls, partly because of reduced lean body mass and partly because of hypothalamic compensation (see Fig. 19.2). The urine has a fixed specific gravity and creatinine excretion becomes low. There may be mild anaemia, leucopenia and thrombocytopenia. The erythrocyte sedimentation rate is normal unless there is infection. Tests of delayed skin hypersensitivity, e.g. to tuberculin, are falsely negative. The

electrocardiogram shows sinus bradycardia and low voltage. Management Whether in a famine or in wasting secondary to disease, the severity of under-nutrition is graded according to BMI (see Box 19.10). People with mild starvation are in no danger; those with moderate starvation need extra feeding; and those who are severely underweight need hospital care. In severe starvation, there is atrophy of the intestinal epithelium and of the exocrine pancreas, and the bile is dilute. It is critical for the condition to be managed by experts. When food becomes available, it should be given by mouth in small, frequent amounts at first, using a suitable formula preparation (Box 19.14). Individual energy requirements can vary by 30%. During rehabilitation, more concentrated formula can be given with additional food that is palatable and similar to the usual staple meal. Salt should be restricted and micronutrient supplements (e.g. potassium, magnesium, zinc and multivitamins) may be essential. Between 6.3 and 8.4 MJ/day (1500–2000 kcal/day) will arrest progressive under-nutrition but additional energy may be required for regain of weight. During refeeding, a weight gain of 5% body weight per month indicates satisfactory progress. Other care is supportive and includes attention to the skin, adequate hydration, treatment of infections and careful monitoring of body temperature, since thermoregulation may be impaired. Circumstances and resources are different in every famine but many problems are non-medical and concern organisation, infrastructure, liaison, politics, procurement, security and ensuring that food is distributed on the basis of need. Lastly, plans must be made for the future for prevention and/or earlier intervention if similar circumstances prevail. Under-nutrition in hospital It is a paradox that, in spite of record levels of access to food in the developed economies of the world, under-nutrition remains a serious issue in many sectors of society, particularly the elderly and less independent. While the scale of the problem does not match that seen in the developing world, the issues pertaining to poor or impaired health are similar. In the general UK population, 30% of those requiring acute admission to hospital show evidence of serious under-nutrition and 65% of those admitted will lose an 19.13 Infections associated with starvation • Gastroenteritis and Gram-negative sepsis • Respiratory infections, especially bronchopneumonia • Certain viral diseases, especially measles and herpes simplex • Tuberculosis • Streptococcal and staphylococcal skin infections • Helminthic infestations 19.14 WHO recommended diets for refeeding Nutrient (per 100 mL) F-75 diet1 F-100 diet2 Energy 315 kJ (75 kcal) 420 kJ (100 kcal) Protein (g) 0.9 2.9 Lactose (g) 1.3 4.2 Potassium (mmol) 3.6 5.9 Sodium (mmol) 0.9 1.9 Magnesium (mmol) 0.43 0.73 Zinc (mg) 2.0 2.3 Copper (mg) 0.25 0.25 Percentage of energy from: Protein

Fat

Osmolality (mOsmol/kg)

Dose 170 kJ/kg (40 kcal/kg) 630–920 kJ/kg (150–220 kcal/kg) Rate of feeding by mouth 2.2 (mL/kg/hr) Gradual increase in volume, 6 times daily 1F-75 is prepared from milk powder (25 g), sugar (70 g), cereal flour (35 g), vegetable oil (27 g) and vitamin and mineral supplements, made up to 1 L with water. 2F-100 (1 L) contains milk powder (80 g), sugar (50 g), vegetable oil (60 g) and vitamin and mineral supplements (no cereal).

 for small intestinal bacterial overgrowth (malabsorption of iron, folic acid and vitamin B12). Ileal resection Ileal resection (p. 810) may give rise to vitamin B12 deficiency and, rarely, to steatorrhoea and malabsorption of fat-soluble vitamins. Massive small bowel resection This may cause short bowel syndrome and intestinal failure, with impaired

ability to absorb fluids, electrolytes and macronutrients adequately without parenteral support. An approach to assisted nutrition in hospital patients Once the problems leading to under-nutrition have been recognised, it is important to make an individualised plan to address these issues specifically. In most cases, this means a decision to intervene to tackle and reverse nutritional difficulties. This may involve simply ensuring that adequate supplies of food are delivered and prepared regularly or that dentures fit properly, but may require an assessment of a patient's ability to swallow or of the intestine's ability to digest foods. This must include consideration of the potential for disruption of the normal physiology of absorption and digestion in the context of the patient's medical and surgical history. Whenever possible, it is best to use the most physiological means of feeding, reserving more invasive interventions for when normal physiological mechanisms of swallowing and digestion are impaired or absent. Enteral feeding is preferred to parenteral, provided the intestine is accessible and functioning. Refeeding syndrome In severely malnourished individuals, attempts at rapid correction of malnutrition switch the body from a reliance on fat to carbohydrate metabolism. Release of insulin is triggered, shifting potassium, phosphate and magnesium into cells (with water following the osmotic gradient) and causing potentially fatal shifts of fluids and electrolytes from the extracellular to the intracellular compartment. Rapid depletion of (already low) thiamin exacerbates the condition. Clinical features include nausea, vomiting, muscle weakness, seizures, respiratory depression, cardiac arrest and sudden death. The risks of refeeding are greatest in those who are most malnourished (especially chronic alcoholics), but even those who have gone without food for 5 days can be at risk and restitution of feeding should always be done slowly, with careful monitoring of serum potassium, phosphate and magnesium in the first 3–5 days. Oral nutritional supplements Poor appetite, immobility, poor dentition or even being kept 'nil by mouth' for hospital procedures all contribute to weight loss. As a first step, patients should be encouraged and helped to eat an adequate amount of normal food. Where swallow and intestinal function remain intact, the simplest form of assisted nutrition is the use of oral nutritional supplements. Most branded products are nutritionally complete (fortified with the daily requirements of vitamins, minerals and trace elements). They most often come in the form of liquid drinks but various formulations and textures exist, including 'shakes' and 'puddings' with a thicker consistency. They are cost-effective and very useful for people who may require just a small number of additional calories each day to maintain or gain weight in the short or longer term. However, in spite of their nutritional value, small volume and range of flavours, many people find them unpalatable or difficult to tolerate. of many prescription drugs are nausea and gastrointestinal disturbance. Surgical resection of the gastrointestinal tract can have major nutritional sequelae in the years following, ranging from intolerance of normal volumes of food to intestinal failure (where there is partial or complete failure of the intestine to perform its vital functions). There may be no single problem impacting on the intake of adequate nutrition but it helps to consider systematically where the problem(s) might lie (Box 19.15). Specific issues arising after intestinal surgery Gastrectomy or partial gastrectomy There may be a loss of gastric capacity, leading to intolerance of larger volumes of food and early satiety or vomiting. Vagotomy and gastroenterostomy may cause symptoms of dumping syndrome (p. 801), which can lead to food avoidance and weight loss. Many patients who have had gastric surgery will develop iron deficiency (and, less commonly, vitamin D and vitamin B12 deficiency) unless adequately supplemented post-operatively. Proximal small bowel surgery Those who have had roux-en-Y reconstruction or have blindending or excluded loops of small bowel are prone to small intestinal bacterial overgrowth. This may impair absorption of iron, folic acid and vitamin B12. Very rarely, it can cause hyperammonaemia and metabolic coma, in which bacterial metabolism of

amino acids leads to a lack of citrulline and impairment of the urea cycle. Pancreatic resection/Whipple's operation Without adequate post-operative supplementation, this can be a very serious insult to the digestive tract. There is loss of pancreatic exocrine function (causing steatorrhoea and malabsorption of protein, fats and fat-soluble vitamins), as well as the potential 19.15 Factors affecting adequacy of nutritional intake in hospitalised patients Factors affecting appetite • Altered taste • Nausea and/or vomiting • Non-specific effects of illness and/or drugs Issues of quantity • Is there enough food on the plate? • Social, cultural, financial, general and mental health issues may all be relevant, individually or in combination Getting the food from the plate to the mouth • Generalised reduced mobility • Reduced manual dexterity • Loss of limb function Difficulties chewing the food • Poorly fitting dentures • Pain in the oral cavity Specific problems with the gastrointestinal tract • Obstruction • Ischaemia • Inflammation • Malabsorption Cultural issues • Is the food provided appropriate to the patient's beliefs? More general evidence of self-neglect • Evidence of chronic coexisting illness • Evidence of mental health problems – low mood may be 'cause' or 'effect' in under-nutrition



device, which fixes the tube around the nasal septum. Although these devices are very effective, there is a risk of damage to the nasal septum (especially bleeding) if a patient persists in pulling forcibly on the tube. Gastrostomy feeding Gastrostomy is a more invasive insertion technique with higher costs initially. It is most suitable for when longer-term feeding (more than 4 weeks) is required. Gastrostomies are less liable to displacement than nasogastric tubes and the presence of the gastrostomy in the stomach allows for fewer feed interruptions, meaning that more of the prescribed feeds can be administered. Tubes were placed at the time of open surgery until the 1980s, when an endoscopic, minimally invasive technique was developed. A variety of techniques for radiological insertion have also been introduced subsequently. Both endoscopic and radiological gastrostomy insertion involve inflating the stomach, thus apposing it to the anterior abdominal wall. The stomach is then punctured percutaneously and a suitable tube placed (Fig. 19.10). Tubes vary in design but each has an internal retainer device (plastic 'bumper' or balloon) that sits snugly against the gastric mucosa, and an external retainer that limits movement. These retainers hold the gastric wall against the abdominal wall, effectively creating a controlled gastrocutaneous fistula that matures over 2–4 weeks. Radiological gastrostomy placement also utilises percutaneous 'stay sutures', which provide further temporary anchorage and assist in placement. There is no evidence to recommend one technique over another, although the radiological method has advantages in patients with cancers of the head and neck undergoing potentially curative therapy (less chance of tumour 'seeding') and in those with poor respiratory reserve (such as motor neuron disease) since there is no endoscope to compress the upper airways. Reported outcomes are broadly similar for both and the choice of technique should be based on indications and contraindications, operator experience and facilities available. Most important is rigorous patient assessment and selection prior to gastrostomy placement, which should be done by a multidisciplinary nutrition support team, and avoided when the procedure may be too hazardous or the benefits are outweighed by the risks (see Boxes 19.18 and Box 19.27 below). Post-pyloric feeding In patients with a high risk of pulmonary aspiration or gastroparesis, it may be preferable to feed into the jejunum (via a nasojejunal tube, gastrostomy with jejunal extension or direct placement into jejunum by radiological, endoscopic or laparoscopic means). Parenteral nutrition This is usually reserved for clinical situations where the absorptive functioning of the intestine is severely impaired. In

parenteral feeding, nutrition is delivered directly into a large-diameter systemic vein, completely bypassing the intestine and portal venous system. As well as being more invasive, more expensive and Enteral feeding Where swallowing or food ingestion is impaired but intestinal function remains intact, more invasive forms of assisted feeding may be necessary. Enteral tube feeding is usually the intervention of choice. In enteral feeding, nutrition is delivered to and absorbed by the functioning intestine. Delivery usually means bypassing the mouth and oesophagus (or sometimes the stomach and proximal small bowel) by means of a feeding tube (naso-enteral, gastrostomy or jejunostomy feeding). There are a number of theoretical advantages to enteral, as opposed to parenteral, feeding, which have achieved almost mythical status. These include: • preservation of intestinal mucosal architecture, gutassociated lymphoid tissue, and hepatic and pulmonary immune function • reduced levels of systemic inflammation and hyperglycaemia • interference with pathogenicity of gut micro-organisms. However, the areas in which advantage has been consistently proven are: • fewer episodes of infection • reduced cost • earlier return to intestinal function • reduced length of hospital stay. Complications The risks of enteral feeding are those related to tube insertion (Box 19.16) and diarrhoea (Box 19.17). Route of access Nasogastric tube feeding This is simple, readily available, comparatively low-cost and most suitable for short-term feeding (up to 4 weeks). Insertion of a nasogastric tube requires care and training (see Box 21.41, p. 805), as potentially serious complications can arise (Box 19.16). Patients with reduced conscious level may pull at tubes and displace them. This can be minimised in the short term by the use of a nasal ‘bridle’ 19.16 Complications of nasogastric tube feeding • Tube misplacement, e.g. tracheal or bronchial placement (rarely, intracranial placement) • Reflux of gastric contents and pulmonary aspiration • Interrupted feeding or inadequate feed volumes • Refeeding syndrome 19.17 Diarrhoea related to enteral feeding Factors contributing to diarrhoea • Fibre-free feed may reduce short-chain fatty acid production in colon • Fat malabsorption • Inappropriate osmotic load • Pre-existing primary gut problem (e.g. lactose intolerance) • Infection Management • Often responds well to a fibre-containing feed or a switch to an alternative feed • Simple antidiarrhoeal agents (e.g. loperamide) can be very effective 19.18 Complications of gastrostomy tube feeding • Reflux of gastric contents and pulmonary aspiration (same as nasogastric tube) • Risks of insertion (pain, damage to intra-abdominal structures, intestinal perforation, pulmonary aspiration, infection, death) • Risk of tumour ‘seeding’ if an endoscopic ‘pull-through’ technique is used in head and neck or oesophageal cancer patients • Refeeding syndrome

 impair gastrointestinal function, such that oral or enteral feeding is not possible for at least 7 days. Intestinal failure (‘short bowel syndrome’) Intestinal failure (IF) is defined as a reduction in the function of the gut below the minimum necessary for the absorption of macronutrients and/or water and electrolytes such that intravenous supplementation is required to support health and/or growth. The term can be used only when there is both: • a major reduction in absorptive capacity and • an absolute need for intravenous fluid support. IF can be further classified according to its onset, metabolic consequences and expected outcome. • Type 1 IF: an acute-onset, usually self-limiting condition with few long-term sequelae. It is most often seen following abdominal surgery or in the context of critical illness. Intravenous support may be required for a few days to weeks. less physiological than the enteral route, parenteral nutrition is associated with many more complications (Box 19.19), mainly infective and metabolic (disturbances of electrolytes, hyperglycaemia). Strict adherence to aseptic practice in handling catheters and careful monitoring of clinical (pulse, blood pressure and temperature) and biochemical (urea, electrolytes, glucose and liver function tests) parameters are necessary to

minimise risk to the patient (Box 19.20). The parenteral route may be indicated for patients who are malnourished or at risk of becoming so, and who have an inadequate or unsafe oral intake and a poorly functioning or non-functioning or perforated intestine or an intestine that cannot be accessed by tube feeding. In practice, it is most often required in acutely ill patients with multi-organ failure or in severely under-nourished patients undergoing surgery. It may offer a benefit over oral or enteral feeding prior to surgery in those who are severely malnourished when other routes of feeding have been inadequate. Parenteral nutrition following surgery should be reserved for when enteral nutrition is not tolerated or feasible or where complications (especially sepsis) Fig. 19.10 Percutaneous endoscopic gastrostomy (PEG) placement. A Finger pressure on the anterior abdominal wall is noted by the endoscopist. B Following insertion of a cannula through the anterior abdominal wall into the stomach, a guidewire is threaded through the cannula and grasped by the endoscopic forceps or snare. C The endoscope is withdrawn with the guidewire. The gastrostomy tube is then attached to the guidewire. D The guidewire and tube are pulled back through the mouth, oesophagus and stomach to exit on the anterior abdominal wall, and the endoscope is repassed to confirm the site of placement of the retention device. The latter closely abuts the gastric mucosa; its position is maintained by an external fixation device (see inset). It is also possible to place PEG tubes using fluoroscopic guidance when endoscopy is difficult (radiologically inserted gastrostomy). A B C D 19.20 Parameters for monitoring parenteral nutrition in hospital Parameter Monitoring requirement Electrolytes (sodium, potassium, magnesium) Bone profile (calcium, phosphate) Liver function tests (bilirubin, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transferase) Markers of inflammation (C-reactive protein, leucocyte count) Daily until stable and then 2–3 times per week Blood glucose At least twice daily until stable and then daily Cholesterol and triglycerides Weekly initially, reducing to every 3 months when stable 19.19 Complications of parenteral nutrition Intravenous catheter complications • Insertion (pneumothorax, haemothorax, arterial puncture) • Catheter infection (sepsis, discitis, pulmonary or cerebral abscess) • Central venous thrombosis Metabolic complications • Refeeding syndrome • Electrolyte imbalance • Hyperglycaemia • Hyperalimentation • Fluid overload • Hepatic steatosis/fibrosis/cirrhosis



following the acute insult but develop protein-energy malnutrition and significant weight loss, becoming seriously under-nourished over weeks to months. Stool volume is determined by oral intake, with higher intakes causing more diarrhoea and the potential for dehydration, sodium and magnesium depletion and acute renal failure. The absence of the ileum leads to deficiencies of vitamin B12 and fat-soluble vitamins. The absorption of various drugs, including thyroxine, digoxin and warfarin, can be reduced. Approximately 45% of patients will develop gallstones due to disruption of the enterohepatic circulation of bile acids, and 25% may develop calcium oxalate renal stones due to increased colonic absorption of oxalate (see Fig. 21.43, p. 810). Jejunostomy patients Patients left with a stoma (usually a jejunostomy) behave very differently, although stool volumes are again determined by oral intake. The jejunum is intrinsically highly permeable, and in the absence of the ileum and its net absorptive role, high losses of fluid, sodium and magnesium dominate the clinical picture from the outset. Dehydration, hyponatraemia, hypomagnesaemia and acute renal failure are the most immediate problems but protein-energy malnutrition will also develop. The jejunum has no real potential for adaptation in terms of absorption, so it is essential to recognise and address the issues of dehydration and electrolyte disturbance early and not

expect the problems to improve with time (Box 19.23). • Type 2 IF: far less common. The onset is also usually acute, following some intra-abdominal catastrophic event (ischaemia, volvulus, trauma or perioperative complication). Septic and metabolic problems are seen, along with complex nutritional issues. It requires multidisciplinary input (nursing, dietetic, medical, biochemical, surgical, radiological and microbiological) and support may be necessary for weeks to months. • Type 3 IF: a chronic condition in which patients are metabolically stable but intravenous support is required over months to years. It may or may not be reversible. Management IF is a complex clinical problem with profound and wide-ranging physiological and psychological effects, which is best cared for by a dedicated multidisciplinary team. The majority of IF results from short bowel syndrome (Box 19.21), with chronic intestinal dysmotility and chronic intestinal pseudo-obstruction accounting for most of the remainder. The severity of the physiological upset correlates well with how much functioning intestine remains (rather than how much has been removed). Measurement of the remaining small bowel (from the duodeno-jejunal flexure) at the time of surgery is essential for planning future therapy (Box 19.22). The aims of treatment are to: • provide nutrition, water and electrolytes to maintain health with normal body weight (and allow normal growth in affected children) • utilise the enteral or oral routes as much as possible • minimise the burden of complications of the underlying disease, as well as the IF and its treatment • allow a good quality of life. If the ileum and especially the ileum and colon remain intact, long-term nutritional support can usually be avoided. Unlike the jejunum, the ileum can adapt to increase absorption of water and electrolytes over time. The presence of the colon (part or wholly intact) further improves fluid absorption and can generate energy through production of short-chain fatty acids. It is therefore useful to classify patients with a short gut according to whether or not they have any residual colon. Jejunum–colon patients Those with an anastomosis between jejunum and residual colon (jejunum–colon patients) may look well in the days or initial weeks 19.21 Causes of short bowel syndrome in adults • Mesenteric ischaemia • Post-operative complications • Crohn’s disease • Trauma • Neoplasia • Radiation enteritis 19.22 Likely requirements for support according to length of intact residual small bowel Residual length of jejunum (cm) Oral fluid restriction Oral glucose/electrolyte solution Intravenous fluids Parenteral nutrition < 200 Yes Yes May avoid May avoid < 100 Yes Yes Yes May avoid < 75 Yes Yes Yes Yes 19.23 Management of short bowel patients (and ‘high-output’ stoma) Accurate charting of fluid intake and losses • Vital: oral intake determines stool volume and should be restricted rather than encouraged Dehydration and hyponatraemia • Must first be corrected intravenously to restore circulating volume and reduce thirst • Stool volume should be minimised and any ongoing fluid imbalance between oral intake and stool losses replenished intravenously Measures to reduce stool volume losses • Restrict oral fluid intake to ≤ 500 mL/24 hrs • Give a further 1000 mL oral fluid as oral rehydration solution containing 90–120 mmol Na/L (St Mark’s solution or Glucodrate, Nestlé) • Slow intestinal transit (to maximise opportunities for absorption): Loperamide, codeine phosphate • Reduce volume of intestinal secretions: Gastric acid: omeprazole 20 mg/day orally Other secretions: octreotide 50–100 µg 3 times daily by subcutaneous injection Measures to increase absorption • Teduglutide (a recombinant glucagon-like peptide 2) significantly reduces requirements for intravenous fluid and nutritional support

 19.27 Ethical and legal considerations in the management of artificial nutritional support • Care of the sick involves the duty of providing adequate fluid and nutrients • Food and fluid should not be withheld from a patient who expresses a desire to eat and drink, unless there is a medical contraindication (e.g. risk of aspiration) • A

treatment plan should include consideration of nutritional issues and should be agreed by all members of the health-care team • In the situation of palliative care, tube feeding should be instituted only if it is needed to relieve symptoms • Tube feeding is usually regarded in law as a medical treatment. Like other treatments, the need for such support should be reviewed on a regular basis and changes made in the light of clinical circumstances • A competent adult patient must give consent for any invasive procedures, including passage of a nasogastric tube or insertion of a central venous cannula • If a patient is unable to give consent, the health-care team should act in that person's best interests, taking into account any wishes previously expressed by the patient and the views of family • Under certain specified circumstances (e.g. anorexia nervosa), it is appropriate to provide artificial nutritional support to the unwilling patient Adapted from British Association for Parenteral and Enteral Nutrition guidelines (www.bapen.org.uk). include abdominal cramps and distension (seen in 50%), peristomal swelling, pain, nausea, vomiting and local injection site reactions. Since teduglutide stimulates proliferation of the intestinal epithelium, it should be avoided in those with a history of gastrointestinal malignancy in the past 5 years or a current malignancy. In those patients with a colon, a pre-treatment screening colonoscopy should be undertaken to detect and remove any polyps. Use of teduglutide is currently limited by high costs. Artificial nutrition at the end of life Rarely, assisted nutrition may not result in the expected outcomes of reversal of weight loss or improved quality and duration of life. It very seldom reverses other underlying health issues, although it may be used as a short term 'bridge' to help through a patient through a particular crisis. Such scenarios may present when someone is approaching the end of life, or in the face of weight loss due to advanced Small bowel and multivisceral transplantation Long-term intravenous nutritional support remains the mainstay of therapy for chronic IF but has its own morbidity and mortality. The 10-year survival for patients on long-term home parenteral nutrition is approximately 90%. The majority of deaths are due to the underlying disease process but 5–11% will die from direct complications of parenteral nutrition itself (especially catheterrelated sepsis). A minority of patients with chronic IF, for whom the safe administration of parenteral nutrition has become difficult or impossible, may benefit from small bowel transplantation (Box 19.24). The first successful small bowel transplant was carried out in 1988. The introduction of tacrolimus allowed a satisfactory balance of immunosuppression, avoiding rejection while minimising sepsis. Since then, over 2000 transplants have been performed worldwide. Survival rates continue to improve, for both isolated small bowel and multivisceral transplantation (small bowel along with a combination of liver and/or kidney and/ or pancreas), although major complications are still frequent (Box 19.25). Current 5-year survival rates are 50–80%, with better outcomes for younger patients and those receiving isolated small bowel procedures. Further developments in treatment of intestinal failure Teduglutide is a long-acting recombinant human GLP-2. It enhances intestinal absorption by: • increasing intestinal blood flow to the intestine • increasing portal blood flow away from the intestine • slowing intestinal transit times • reducing gastric acid secretion. In patients with short bowel syndrome and IF, the increased intestinal absorptive function induced by teduglutide can significantly reduce the volumes of parenteral fluids and nutrition required, and may allow some patients to regain independence of parenteral support. Recognised side-effects 19.26 Energy balance in old age • Body composition: muscle mass is decreased and percentage of body fat increased. • Energy expenditure: with the fall in lean body mass, basal metabolic rate is decreased and energy requirements are reduced. • Weight loss: after weight gain throughout adult life, weight often falls beyond the age of 80 years. This may reflect decreased appetite, loss of smell and taste, and decreased interest in and financial resources for food preparation, especially after loss of a partner. • BMI: less reliable in old age as

height is lost (due to kyphosis, osteoporotic crush fractures, loss of intervertebral disc spaces). Alternative measurements include arm demispan and knee height (p. 693), which can be extrapolated to estimate height. 19.25 Complications of small bowel/multivisceral transplantation • Sepsis: Enteric bacterial species Staphylococci Fungal species • Cytomegalovirus infection • Post-transplantation lymphoproliferative disease (PTLD) • Graft-versus-host disease • Acute and chronic rejection • Chronic renal impairment 19.24 Potential indications for small bowel transplantation Complications of central venous catheters • Central venous thrombosis leading to loss of two or more intravenous access points • Severe or recurrent line sepsis • Recurrent severe acute kidney injury related to dehydration Metabolic complications of parenteral nutrition • Parenteral nutrition-related liver fibrosis, cirrhosis and liver failure



Micronutrients, minerals and their diseases Vitamins Vitamins are organic substances with key roles in certain metabolic pathways, and are categorised into those that are fat-soluble (vitamins A, D, E and K) and those that are water-soluble (vitamins of the B complex group and vitamin C). Recommended daily intakes of micronutrients (Box 19.28) vary between countries and the nomenclature has become potentially confusing. In the UK, the ‘reference nutrient intake’ (RNI) has been calculated as the mean plus two standard deviations (SD) of daily intake in the population, which therefore describes normal intake for 97.5% of the population. The lower reference Fig. 19.11 Malnutrition in dementia – a vicious circle. From Volkert D, Chourdakis M, Faxen-Irving G, et al. ESPEN guidelines on nutrition in dementia. Clin Nutr 2015; 34:1052–1073. Intake↓ Cognitive impairment↑ Dementia Cognitive impairment Age-related changes and diseases Frailty Sarcopenia Weight loss Nutritional deficiencies 19.28 Summary of clinically important vitamins Vitamin Sources* Reference nutrient intake (RNI) Rich Important Fat-soluble A (retinol) Liver Milk and milk products, eggs, fish oils 700 µg men 600 µg women D (cholecalciferol) Fish oils Ultraviolet exposure to skin Egg yolks, margarine, fortified cereals 10 µg if > 65 years or no sunlight exposure E (tocopherol) Sunflower oil Vegetables, nuts, seed oils No RNI. Safe intake: 4 mg men 3 mg women K (phylloquinone, menaquinone) Soya oil, menaquinones produced by intestinal bacteria Green vegetables No RNI. Safe intake: 1 µg/kg Water-soluble B1 (thiamin) Pork Cereals, grains, beans 0.8 mg per 9.68 MJ (2000 kcal) energy intake B2 (riboflavin) Milk Milk and milk products, breakfast cereals, bread 1.3 mg men 1.1 mg women B3 (niacin, nicotinic acid, nicotinamide) Meat, cereals 17 mg men 13 mg women B6 (pyridoxine) Meat, fish, potatoes, bananas Vegetables, intestinal microflora synthesis 1.4 mg men 1.2 mg women Folate Liver Green leafy vegetables, fortified breakfast cereals 200 µg B12 (cobalamin) Animal products Bacterial colonisation 1.5 µg Biotin Egg yolk Intestinal flora No RNI. Safe intake: 10–200 µg C (ascorbic acid) Citrus fruit Fresh fruit, fresh and frozen vegetables 40 mg *Rich sources contain the nutrient in high concentration but are not generally eaten in large amounts; important sources contain less but contribute most because larger amounts are eaten. respiratory or cardiac failure, malignancy or dementia. In selected cases, a decision not to intervene may be appropriate. An intervention that merely prolongs life without preserving or adding to its quality is seldom justified, particularly if the intervention is not without risk itself. Such decisions are not taken lightly and careful scrutiny of each case is necessary. There should be a thoughtful and sensitive discussion explaining what artificial nutrition can and cannot achieve involving the multidisciplinary team looking after the patient as well as next of kin and, in some cases, legal representatives (Box 19.27). Nutrition and dementia Weight loss is seen commonly in people with dementia, and nutritional and eating problems are a significant source of

concern for those caring for them. It is appropriate to: • screen for malnutrition (e.g. MUST, see above) • assess specific eating difficulties (e.g. Edinburgh Feeding Evaluation in Dementia questionnaire) • monitor and document body weight • encourage adequate intake of food • use oral nutritional supplements. However, the evidence that artificial nutritional support beyond oral supplementation improves overall functioning or prolongs life in dementia is absent or weak. There may be specific circumstances where a trial of such feeding can be justified (see Box 19.27). Success is more likely in those with mild to moderate dementia, when a temporary and reversible crisis has been precipitated by some acute event. It is important to remember that there is strong evidence to avoid tube feeding in those with advanced dementia because this improves neither the quality nor the duration of life (Fig. 19.11).

712 • NUTRITIONAL FACTORS IN DISEASE Some vitamins also have pharmacological actions when given at supraphysiological doses, such as the use of vitamin A for acne (p. 1242). Taking vitamin supplements is fashionable in many countries, although there is no evidence of benefit. Toxic effects are most serious with high dosages of vitamins A, B6 and D. Investigation of suspected vitamin deficiency or excess may involve biochemical assessment of body stores (Box 19.32). Measurements in blood should be interpreted carefully, however, in conjunction with the clinical presentation. Fat-soluble vitamins Vitamin A (retinol) Pre-formed retinol is found only in foods of animal origin. Vitamin A can also be derived from carotenes, which are present in green and coloured vegetables and some fruits. Carotenes provide most of the total vitamin A in the UK and constitute the only supply in vegans. Retinol is converted to several other important molecules: • 11-cis-retinaldehyde is part of the photoreceptor complex in rods of the retina. nutrient intake (LRNI) is the mean minus 2 SD, below which would be considered deficient in most of the population. These dietary reference values (DRV) have superseded the terms RDI (recommended daily intake) and RDA (recommended daily amount). Other countries use different terminology. Additional amounts of some micronutrients may be required in pregnancy and lactation (Box 19.29). Vitamin deficiency diseases are most prevalent in developing countries but still occur in developed countries. Older people (Box 19.30) and alcoholics are at risk of deficiencies in B vitamins and in vitamins D and C. Nutritional deficiencies in pregnancy can affect either the mother or the developing fetus, and extra increments of vitamins are recommended in the UK (see Box 19.29). Darker-skinned individuals living at higher latitude, and those who cover up or do not go outside are at increased risk of vitamin D deficiency due to inadequate sunlight exposure. Dietary supplements are recommended for these ‘at-risk’ groups. Some nutrient deficiencies are induced by diseases or drugs. Deficiencies of fat-soluble vitamins are seen in conditions of fat malabsorption (Box 19.31). 19.31 Gastrointestinal disorders that may be associated with malabsorption of fat-soluble vitamins • Biliary obstruction • Pancreatic exocrine insufficiency • Coeliac disease • Ileal inflammation or resection 19.30 Vitamin deficiency in old age • Requirements: although requirements for energy fall with age, those for micronutrients do not. If dietary intake falls, a vitamin-rich diet is required to compensate. • Vitamin D: levels are commonly low due to reduced dietary intake, decreased sun exposure and less efficient skin conversion. This leads to bone loss and fractures. Supplements should be given to those at risk of falls in institutional care – the group at highest risk and most likely to benefit. • Vitamin B12 deficiency: a causal relationship with dementia has not been identified, but it does produce neuropsychiatric effects and should be checked in all those with declining cognitive function. 19.29 Nutrition in pregnancy and lactation • Energy requirements: increased in both mother and fetus but can be met through reduced maternal energy expenditure. • Micronutrient requirements: adaptive

mechanisms ensure increased uptake of minerals in pregnancy, but extra increments of some are required during lactation (see Box 19.32). Additional increments of some vitamins are recommended during pregnancy and lactation: Vitamin A: for growth and maintenance of the fetus, and to provide some reserve (important in some countries to prevent blindness associated with vitamin A deficiency). Teratogenic in excessive amounts. Vitamin D: to ensure bone and dental development in the infant. Higher incidences of hypocalcaemia, hypoparathyroidisim and defective dental enamel have been seen in infants of women not taking vitamin D supplements at > 50° latitude. Folate: taken pre-conceptually and during the first trimester, reduces the incidence of neural tube defects by 70%. Vitamin B12: in lactation only. Thiamin: to meet increased fetal energy demands. Riboflavin: to meet extra demands. Niacin: in lactation only. Vitamin C: for the last trimester to maintain maternal stores as fetal demands increase. Iodine: in countries with high consumption of staple foods (e.g. brassicas, maize, bamboo shoots) that contain goitrogens (thiocyanates or perchlorates) that interfere with iodine uptake, supplements prevent infants being born with cretinism. 19.32 Biochemical assessment of vitamin status Nutrient Biochemical assessments of deficiency or excess Vitamin A Serum retinol may be low in deficiency Serum retinyl esters: when vitamin A toxicity is suspected Vitamin D Plasma/serum 25-hydroxyvitamin D (25(OH)D): reflects body stores (liver and adipose tissue) Plasma/serum 1,25(OH)2D: difficult to interpret Vitamin E Serum tocopherol:cholesterol ratio Vitamin K Coagulation assays (e.g. prothrombin time) Plasma vitamin K Vitamin B1 (thiamin) Red blood cell transketolase activity or whole-blood vitamin B1 Vitamin B2 (riboflavin) Red blood cell glutathione reductase activity or whole-blood vitamin B2 Vitamin B3 (niacin) Urinary metabolites: 1-methyl-2-pyridone-5carboxamide, 1-methylnicotinamide Vitamin B6 Plasma pyridoxal phosphate or erythrocyte transaminase activation coefficient Vitamin B12 Plasma B12: poor measure of overall vitamin B12 status but will detect severe deficiency Alternatives (methylmalonic acid and holotranscobalamin) are not used routinely Folate Red blood cell folate Plasma folate: reflects recent intake but also detects unmetabolised folic acid from foods and supplements Vitamin C Leucocyte ascorbic acid: assesses vitamin C tissue stores Plasma ascorbic acid: reflects recent (daily) intake



is according high priority to prevention in communities where xerophthalmia occurs, giving single prophylactic oral doses of 60 mg retinyl palmitate (providing 200 000 U retinol) to pre-school children. This also reduces mortality from gastroenteritis and respiratory infections. Repeated moderate or high doses of retinol can cause liver damage, hyperostosis and teratogenicity. Women in countries where deficiency is not endemic are therefore advised not to take vitamin A supplements in pregnancy. Retinol intake may also be restricted in those at risk of osteoporosis. Acute overdose leads to nausea and headache, increased intracranial pressure and skin desquamation. Excessive intake of carotene can cause pigmentation of the skin (hypercarotenosis); this gradually fades when intake is reduced. Vitamin D The natural form of vitamin D, cholecalciferol or vitamin D3, is formed in the skin by the action of ultraviolet (UV) light on 7-dehydrocholesterol, a metabolite of cholesterol. Few foods contain vitamin D naturally and skin exposure to sunlight is the main source. Moving away from the equator, the intensity of UV light decreases, so that at a latitude above 50° (including northern Europe) vitamin D is not synthesised in winter, and even above 30° there is seasonal variation. The body store accumulated during the summer is consumed during the winter. Vitamin D is converted in the liver to 25-hydroxyvitamin D (25(OH)D), which is further hydroxylated in the kidneys to 1,25-dihydroxyvitamin D (1,25(OH)2D),

the active form of the vitamin (see Fig. 24.61, p. 1051). This 1,25(OH)2D activates specific intracellular receptors that influence calcium metabolism, bone mineralisation and tissue differentiation. The synthetic form, ergocalciferol or vitamin D2, is considered to be less potent than endogenous D3. Recommended dietary intakes aim to improve musculoskeletal health, preventing rickets and osteomalacia, enhancing muscle strength and reducing the risks of falls in the elderly. Adequate levels of vitamin D may also be important in non-musculoskeletal conditions and may improve immune function (p. 1309). Margarines are fortified with vitamin D in the UK, and milk is fortified in some parts of Europe and in North America. However, the combination of low dietary intake and limited sunlight exposure in the UK has led to recommendations that everyone over the age of 5 should take 10 µg of vitamin D daily. The individuals at highest risk of vitamin D deficiency are those who have limited exposure to sunshine. People who are confined indoors, those who habitually cover up their skin when outdoors and those with darker skins should take 10 µg of vitamin D per day all year round. Other groups may require such supplementation only in the winter months of October to March. The effects of vitamin D deficiency (calcium deficiency, rickets and osteomalacia) are described on page 1049. An analogue of vitamin D (calcipotriol) is used for treatment of skin conditions such as psoriasis. Excessive doses of cholecalciferol, ergocalciferol or the hydroxylated metabolites cause hypercalcaemia (p. 661). Vitamin E There are eight related fat-soluble substances with vitamin E activity. The most important dietary form is α-tocopherol. Vitamin E has many direct metabolic actions: • It prevents oxidation of polyunsaturated fatty acids in cell membranes by free radicals. • It helps maintain cell membrane structure. • It affects DNA synthesis and cell signalling. • It is involved in the anti-inflammatory and immune systems. • Retinoic acid induces differentiation of epithelial cells by binding to specific nuclear receptors, which induce responsive genes. In vitamin A deficiency, mucus-secreting cells are replaced by keratin-producing cells. • Retinoids are necessary for normal growth, fetal development, fertility, haematopoiesis and immune function. Globally, the most important consequence of vitamin A deficiency is irreversible blindness in young children. Asia is most notably affected and the problem is being addressed through widespread vitamin A supplementation programmes. Adults are not usually at risk because liver stores can supply vitamin A when foods containing vitamin A are unavailable. Early deficiency causes impaired adaptation to the dark (night blindness). Keratinisation of the cornea (xerophthalmia) gives rise to characteristic Bitot’s spots and progresses to keratomalacia, with corneal ulceration, scarring and irreversible blindness (Fig. 19.12). In countries where vitamin A deficiency is endemic, pregnant women should be advised to eat dark green, leafy vegetables and yellow fruits (to build up stores of retinol in the fetal liver), and infants should be fed the same. The WHO Fig. 19.12 Eye signs of vitamin A deficiency. A Bitot’s spots in xerophthalmia, showing the white triangular plaques (arrows). B Keratomalacia in a 14-month-old child. There is liquefactive necrosis affecting the greater part of the cornea, with typical sparing of the superior aspect. A, Courtesy of Institute of Ophthalmology, Moorfields Eye Hospital, London. B, From WHO. Report of a joint WHO/USAID meeting, vitamin A deficiency and xerophthalmia (WHO technical report series no. 5 W); 1976. A B

 • Wet (or cardiac) beri-beri causes generalised oedema due to biventricular heart failure with pulmonary congestion. In dry beri-beri, response to thiamin administration is not uniformly good. Multivitamin therapy seems to produce some improvement, however, suggesting that other vitamin deficiencies may be involved. Wernicke’s encephalopathy and wet beri-beri should be treated without delay with intravenous vitamin B and C mixture (Pabrinex, p. 1195). Korsakoff’s psychosis is irreversible and does not respond to thiamin

treatment. Riboflavin (vitamin B2) Riboflavin is required for the flavin co-factors involved in oxidation–reduction reactions. It is widely distributed in animal and vegetable foods. Levels are low in staple cereals but germination increases its content. It is destroyed under alkaline conditions by heat and by exposure to sunlight. Deficiency is rare in developed countries. It mainly affects the tongue and lips and manifests as glossitis, angular stomatitis and cheilosis. The genitals may be involved, as well as the skin areas rich in sebaceous glands, causing nasolabial or facial dyssebacea. Rapid recovery usually follows administration of riboflavin 10 mg daily by mouth. Niacin (vitamin B3) Niacin encompasses nicotinic acid and nicotinamide. Nicotinamide is an essential part of the two pyridine nucleotides, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which play a key role as hydrogen acceptors and donors for many enzymes. Niacin can be synthesised in the body in limited amounts from the amino acid tryptophan. Deficiency – pellagra Pellagra was formerly endemic among poor people who subsisted chiefly on maize, which contains niacytin, a form of niacin that the body is unable to utilise. Pellagra can develop in only 8 weeks in individuals eating diets that are very deficient in niacin and tryptophan. It remains a problem in parts of Africa, and is occasionally seen in alcoholics and in patients with chronic small intestinal disease in developed countries. Pellagra can occur in Hartnup's disease, a genetic disorder characterised by impaired absorption of several amino acids, including tryptophan. It is also seen occasionally in carcinoid syndrome (p. 678), when tryptophan is consumed in the excessive production of 5-hydroxytryptamine (5-HT, serotonin). Pellagra has been called the disease of the three Ds: • Dermatitis. Characteristically, there is erythema resembling severe sunburn, appearing symmetrically over the parts of the body exposed to sunlight, particularly the limbs and especially on the neck but not the face (Casal's necklace, Fig. 19.13). The skin lesions may progress to vesiculation, cracking, exudation and secondary infection. • Diarrhoea. This is often associated with anorexia, nausea, glossitis and dysphagia, reflecting the presence of a non-infective inflammation that extends throughout the gastrointestinal tract. • Dementia. In severe deficiency, delirium occurs acutely and dementia develops in chronic cases. Treatment is with nicotinamide, given in a dose of 100 mg 3 times daily orally or parenterally. The response is usually rapid. Within 24 hours the erythema diminishes, the diarrhoea ceases and a striking improvement occurs in the patient's mental state. Human deficiency is rare and has been described only in premature infants and in malabsorption. It can cause a mild haemolytic anaemia, ataxia and visual scotomas. Vitamin E intakes of up to 3200 mg/day (1000-fold greater than recommended intakes) are considered safe. Diets rich in vitamin E are consumed in countries with lower rates of coronary heart disease, although randomised controlled trials have not demonstrated cardioprotective effects of vitamin E or other antioxidants. Vitamin K Vitamin K is supplied in the diet mainly as vitamin K1 (phylloquinone) in the UK, or as vitamin K2 (menaquinone) from fermented products in parts of Asia. Vitamin K2 is also synthesised by bacteria in the colon. Vitamin K is a co-factor for carboxylation reactions: in particular, the production of γ-carboxyglutamate (gla). Gla residues are found in four of the coagulation factor proteins (II, VII, IX and X; p. 918), conferring their capacity to bind to phospholipid surfaces in the presence of calcium. Other important gla proteins are osteocalcin and matrix gla protein, which are important in bone mineralisation. Vitamin K deficiency leads to delayed coagulation and bleeding. In obstructive jaundice, dietary vitamin K is not absorbed and it is essential to administer the vitamin in parenteral form before surgery. Warfarin and related anticoagulants (p. 939) act by antagonising vitamin K. Vitamin K is given routinely to newborn babies to prevent haemorrhagic disease. Symptoms of excess have been reported only in infants, with synthetic preparations linked to haemolysis and liver damage. Water-soluble vitamins Thiamin (vitamin B1) Thiamin is widely

distributed in foods of both vegetable and animal origin. Thiamin pyrophosphate (TPP) is a co-factor for enzyme reactions involved in the metabolism of macronutrients (carbohydrate, fat and alcohol), including: • decarboxylation of pyruvate to acetyl-co-enzyme A, which bridges between glycolysis and the tricarboxylic acid (Krebs) cycle • transketolase activity in the hexose monophosphate shunt pathway • decarboxylation of α-ketoglutarate to succinate in the Krebs cycle. In thiamin deficiency, cells cannot metabolise glucose aerobically to generate energy as ATP. Neuronal cells are most vulnerable because they depend almost exclusively on glucose for energy requirements. Impaired glucose oxidation also causes an accumulation of pyruvic and lactic acids, which produce vasodilatation and increased cardiac output. Deficiency – beri-beri In the developed world, thiamin deficiency is mainly encountered in chronic alcoholics. Poor diet, impaired absorption, storage and phosphorylation of thiamin in the liver, and the increased requirements for thiamin to metabolise ethanol all contribute. In the developing world, deficiency usually arises as a consequence of a diet based on polished rice. The body has very limited stores of thiamin, so deficiency is manifest after only 1 month on a thiamin-free diet. There are two forms of the disease in adults: • Dry (or neurological) beri-beri manifests with chronic peripheral neuropathy and with wrist and/or foot drop, and may cause Korsakoff's psychosis and Wernicke's encephalopathy (p. 1195).



Folic acid is the stable synthetic form. Folate works as a methyl donor for cellular methylation and protein synthesis. It is directly involved in DNA and RNA synthesis, and requirements increase during embryonic development. Folate deficiency may cause three major birth defects (spina bifida, anencephaly and encephalocele) resulting from imperfect closure of the neural tube, which takes place 3–4 weeks after conception. The UK Department of Health advises that women who have experienced a pregnancy affected by a neural tube defect should take 5 mg of folic acid daily from before conception and throughout the first trimester; this reduces the incidence of these defects by 70%. All women planning a pregnancy are advised to include good sources of folate in their diet, and to take folate supplements throughout the first trimester. Liver is the richest source of folate but an alternative source (e.g. leafy vegetables) is advised in early pregnancy because of the high vitamin A content of liver (p. 712). Folate deficiency has also been associated with heart disease, dementia and cancer. There is mandatory fortification of flour with folic acid in the USA and voluntary fortification of many foods across Europe. There are now concerns that this may contribute to the increased incidence of colon cancer through promotion of the growth of polyps. Hydroxycobalamin (vitamin B12) Vitamin B12 is a co-factor in folate co-enzyme recycling and nerve myelination. Vitamin B12 and folate are particularly important in DNA synthesis in red blood cells (p. 943). The haematological disorders (macrocytic or megaloblastic anaemias) caused by their deficiency are discussed on pages 943–945. Vitamin B12, but not folate, is needed for the integrity of myelin, so that vitamin B12 deficiency is also associated with neurological disease (see Box 23.33, p. 944). Neurological consequences of vitamin B12 deficiency In older people and chronic alcoholics, vitamin B12 deficiency arises from insufficient intake and/or from malabsorption. Several drugs, including neomycin, can render vitamin B12 inactive. Adequate intake of folate maintains erythropoiesis and there is a concern that fortification of foods with folate may mask underlying vitamin B12 deficiency. In severe deficiency there is insidious, diffuse and uneven demyelination. It may be clinically manifest as peripheral neuropathy or spinal cord degeneration affecting both posterior and lateral columns ('subacute combined degeneration of the spinal cord'; p. 1138), or there may be cerebral manifestations (resembling dementia) or optic

atrophy. Vitamin B12 therapy improves symptoms in most cases. Vitamin C (ascorbic acid) Ascorbic acid is the most active reducing agent in the aqueous phase of living tissues and is involved in intracellular electron transfer. It takes part in the hydroxylation of proline and lysine in protocollagen to hydroxyproline and hydroxylysine in mature collagen. It is very easily destroyed by heat, increased pH and light, and is very soluble in water; hence many traditional cooking methods reduce or eliminate it. Claims that high-dose vitamin C improves immune function (including resistance to the common cold) and cholesterol turnover remain unsubstantiated. Deficiency – scurvy Vitamin C deficiency causes defective formation of collagen with impaired healing of wounds, capillary haemorrhage and reduced platelet adhesiveness (normal platelets are rich in ascorbate) (Fig. 19.14). Precipitants and clinical features of scurvy are shown Toxicity Excessive intakes of niacin may lead to reversible hepatotoxicity. Nicotinic acid is a lipid-lowering agent but at doses above 200 mg a day gives rise to vasodilatory symptoms (‘flushing’ and/or hypotension). Pyridoxine (vitamin B6) Pyridoxine, pyridoxal and pyridoxamine are different forms of vitamin B6 that undergo phosphorylation to produce pyridoxal 5-phosphate (PLP). PLP is the co-factor for a large number of enzymes involved in the metabolism of amino acids. Vitamin B6 is available in most foods. Deficiency is rare, although certain drugs, such as isoniazid and penicillamine, act as chemical antagonists to pyridoxine. Pyridoxine administration is effective in isoniazid-induced peripheral neuropathy and some cases of sideroblastic anaemia. Large doses of vitamin B6 have an antiemetic effect in radiotherapy-induced nausea. Although vitamin B6 supplements have become popular in the treatment of nausea in pregnancy, carpal tunnel syndrome and pre-menstrual syndrome, there is no convincing evidence of benefit. Very high doses of vitamin B6 taken for several months can cause a sensory polyneuropathy. Biotin Biotin is a co-enzyme in the synthesis of fatty acids, isoleucine and valine, and is also involved in gluconeogenesis. Deficiency results from consuming very large quantities of raw egg whites (> 30% energy intake) because the avidin they contain binds to and inactivates biotin in the intestine. It may also be seen after long periods of total parenteral nutrition. The clinical features of deficiency include scaly dermatitis, alopecia and paraesthesia. Folate (folic acid) Folates exist in many forms. The main circulating form is 5-methyltetrahydrofolate. The natural forms are prone to oxidation. Fig. 19.13 Dermatitis due to pellagra (niacin deficiency). The lesions appear on those parts of the body exposed to sunlight. The classic ‘Casal’s necklace’ can be seen around the neck and upper chest. From Karthikeyan K, Thappa DM. Pellagra and skin. Int J Dermatol 2002; 41:476–481.

 inadequate dietary intake of minerals or excessive loss from the body. Toxic effects have also been observed from selfmedication and disordered absorption or excretion. Examples of clinical toxicity include excess of iron (haemochromatosis or haemosiderosis), fluoride (fluorosis; p. 149), copper (Wilson’s disease) and selenium (selenosis, seen in parts of China). For most minerals, the available biochemical markers do not accurately reflect dietary intake and dietary assessment is required. Calcium and phosphorus Calcium is the most abundant cation in the body and powerful homeostatic mechanisms control circulating ionised calcium levels (pp. 661 and 1050). The WHO’s dietary guidelines for calcium differ between countries, with higher intakes usually recommended in places with higher fracture prevalence. Between 20% and 30% of calcium in the diet is absorbed, depending on vitamin D status and food source. Calcium requirements depend on phosphorus intakes, with an optimum molar ratio (Ca:P) of 1 : 1. Excessive phosphorus intakes (e.g. 1–1.5 g/day) with a Ca:P of 1 : 3 have been shown to cause hypocalcaemia and secondary hyperparathyroidism (p. 662). Calcium absorption may be

impaired in vitamin D deficiency (pp. 661 and 1050) and in malabsorption secondary to small intestinal disease. Calcium deficiency causes impaired bone mineralisation and can lead to osteomalacia in adults. The potential benefits of high calcium intake in osteoporosis are discussed on page 1048. Too much calcium can lead to constipation, and toxicity has been observed in 'milk-alkali syndrome' (p. 662). Dietary deficiency of phosphorus is rare (except in older people with limited diets) because it is present in nearly all foods and phosphates are added to a number of processed foods. Phosphate deficiency in adults occurs: • in patients with renal tubular phosphate loss (p. 405) • in patients receiving a prolonged high dosage of aluminium hydroxide (p. 419) • in alcoholics sometimes when they are fed with highcarbohydrate foods • in patients receiving parenteral nutrition if inadequate phosphate is provided. Deficiency causes hypophosphataemia (p. 368) and muscle weakness secondary to ATP deficiency. Iron Iron is involved in the synthesis of haemoglobin and is required for the transport of electrons within cells and for a number of enzyme reactions. Non-haem iron in cereals and vegetables is in Box 19.33. A dose of 250 mg vitamin C 3 times daily by mouth should saturate the tissues quickly. The deficiencies of the patient's diet also need to be corrected and other vitamin supplements given if necessary. Daily intakes of more than 1 g/day have been reported to cause diarrhoea and the formation of renal oxalate stones. Other dietary organic compounds There are a number of non-essential organic compounds with purported health benefits, such as reducing risk of heart disease or cancer. Groups of compounds such as the flavonoids and phytoestrogens show bioactivity through their respective antioxidant and oestrogenic or anti-oestrogenic activities. Flavonoids (of which there are a number of different classes of compound) are found in fruit and vegetables, tea and wine; phytoestrogens are found in soy products (with higher intakes in parts of Asia compared to Europe and the USA) and pulses. Caffeine from tea and coffee and carbonated beverages affects the nervous system and can improve mental performance in the short term, with adverse effects seen at higher intakes. Intake of non-carbonic organic acids (which are not metabolised to carbon dioxide), e.g. oxalates, may be restricted in individuals prone to kidney stones. Inorganic micronutrients A number of inorganic elements are essential dietary constituents for humans (Box 19.34). Deficiency is seen when there is Fig. 19.14 Scurvy. A Gingival swelling and bleeding. B Perifollicular hyperkeratosis. A and B, From Ho V, Prinsloo P, Ombiga J. Persistent anaemia due to scurvy. J New Zeal Med Assoc 2007; 120:62. Reproduced with permission. A B 19.33 Scurvy – vitamin C deficiency Precipitants Increased requirement Dietary deficiency • Trauma, surgery, burns, infections • Smoking • Drugs (glucocorticoids, aspirin, indometacin, tetracycline) • Lack of dietary fruit and vegetables for > 2 months • Infants fed exclusively on boiled milk Clinical features • Swollen gums that bleed easily • Perifollicular and petechial haemorrhages • Ecchymoses • Haemarthrosis • Gastrointestinal bleeding • Anaemia • Poor wound healing



disorder. Goitre is the most common manifestation, affecting about 200 million people (p. 648). In those areas where most women have endemic goitre, 1% or more of babies are born with cretinism (characterised by mental and physical retardation). There is a higher than usual prevalence of deafness, slowed reflexes and poor learning in the remaining population. The best way of preventing neonatal cretinism is to ensure adequate levels of iodine during pregnancy. This can be achieved by intramuscular injections with 1–2 mL of iodised poppy seed oil (475–950 mg iodine) to women of child-bearing age every 3–5 years, by administration of iodised oil orally at 6-monthly or yearly intervals to adults and children, or by provision of iodised salt for cooking. Zinc Zinc is

present in most foods of vegetable and animal origin. It is an essential component of many enzymes, including carbonic anhydrase, alcohol dehydrogenase and alkaline phosphatase. Acute zinc deficiency has been reported in patients receiving prolonged zinc-free parenteral nutrition and causes diarrhoea, mental apathy, a moist, eczematoid dermatitis, especially around the mouth, and loss of hair. Chronic zinc deficiency occurs in dietary deficiency, malabsorption syndromes, alcoholism and its associated hepatic cirrhosis. It causes the clinical features seen in the very rare congenital disorder known as acrodermatitis enteropathica (growth retardation, hair loss and chronic diarrhoea). Zinc deficiency is thought to be responsible for one-third of the world's population not reaching their optimal height. In the Middle East, chronic deficiency has been associated with dwarfism and hypogonadism. In starvation, zinc deficiency causes thymic atrophy; zinc supplements may accelerate the healing of skin lesions, promote general well-being, improve appetite and reduce the morbidity associated with the under-nourished state, and lower the mortality associated with diarrhoea and pneumonia in children. poorly absorbed but makes the greater contribution to overall intake, compared to the well-absorbed haem iron from animal products. Fruits and vegetables containing vitamin C enhance iron absorption, while the tannins in tea reduce it. Dietary calcium reduces iron uptake from the same meal, which may precipitate iron deficiency in those with borderline iron stores. There is no physiological mechanism for excretion of iron, so homeostasis depends on the regulation of iron absorption (see Fig. 23.18, p. 942). This is regulated at the level of duodenal enterocytes by hepcidin (a peptide secreted by hepatocytes in the duodenum). The expression of hepcidin is suppressed when body iron is low, leading to enhanced efflux of iron into the circulation. The normal daily loss of iron is 1 mg, arising from desquamated surface cells and intestinal losses. A regular loss of only 2 mL of blood per day doubles the iron requirement. On average, an additional 20 mg of iron is lost during menstruation, so pre-menopausal women require about twice as much iron as men (and more if menstrual losses are heavy). The major consequence of iron deficiency is anaemia (p. 940). This is one of the most important nutritional causes of ill health in all parts of the world. In the UK, it is estimated that 10% women are iron-deficient. Dietary iron overload is occasionally observed and results in iron accumulation in the liver and, rarely, cirrhosis. Haemochromatosis results from an inherited increase in iron absorption (p. 895). Iodine Iodine is required for synthesis of thyroid hormones (p. 634). It is present in sea fish, seaweed and most plant foods grown near the sea. The amount of iodine in soil and water influences the iodine content of most foods. Iodine is lacking in the highest mountainous areas of the world (e.g. the Alps and the Himalayas) and in the soil of frequently flooded plains (e.g. Bangladesh). About a billion people in the world are estimated to have an inadequate iodine intake and hence are at risk of iodine deficiency 19.34 Summary of clinically important minerals Mineral Sources1 Reference nutrient intake (RNI) Rich Important Calcium Milk and milk products, tofu Milk, boned fish, green vegetables, beans 700 mg2 Phosphorus Most foods contain phosphorus 550 mg2 Marmite and dry-roasted peanuts Milk, cereal products, bread and meat Magnesium Whole grains, nuts Unprocessed and wholegrain foods 300 mg men 270 mg women2 Iron Liver, red meat (haem iron) Non-haem iron from vegetables, wholemeal bread 8.7 mg 14.8 mg women < 50 years Zinc Red meat, seafood Dairy produce, wholemeal bread 9.5 mg men 7 mg women2 Iodine Edible seaweeds Milk and dairy products 140 µg Selenium Fish, wheat grown in selenium-rich soils Fish 75 µg men 60 µg women2 Copper Shellfish, liver Bread, cereal products, vegetables 1.2 mg2 Fluoride Drinking water, tea No RNI. Safe intake: 0.5 mg/kg Potassium Dried fruit, potatoes, coffee Fresh fruit, vegetables, milk 3500 mg Sodium Table salt, anchovies Processed foods, bread, bacon 1600 mg 1Rich sources contain the nutrient in high concentration but are not generally eaten in large amounts; important sources contain less but contribute most

because larger amounts are eaten. 2Increased amounts are required in women during lactation.

718 • NUTRITIONAL FACTORS IN DISEASE that daily salt intakes are kept well below 6 g. The roles of sodium, potassium and magnesium, along with the disease states associated with abnormal intakes or disordered metabolism, are discussed in Chapter 14. Other essential inorganic nutrients These include chloride (a counter-ion to sodium and potassium), cobalt (required for vitamin B12), sulphur (a constituent of methionine and cysteine), manganese (needed for or activates many enzymes) and chromium (necessary for insulin action). Deficiency of chromium presents as hyperglycaemia and has been reported in adults as a rare complication of prolonged parenteral nutrition. Copper metabolism is abnormal in Wilson's disease (p. 896). Deficiency occasionally occurs but only in young children, causing microcytic hypochromic anaemia, neutropenia, retarded growth, skeletal rarefaction and dermatosis. Further information Websites bapen.org.uk British Society for Parenteral and Enteral Nutrition; includes the MUST tool. bsg.org.uk British Society of Gastroenterology: guidelines on management of patients with a short bowel, enteral feeding for adult hospital patients and the provision of a percutaneously placed enteral tube feeding service. espen.org European Society for Parenteral and Enteral Nutrition: guidelines for adult parenteral nutrition; perioperative care in elective colonic and rectal/pelvic surgery; nutrition in dementia; acute and chronic intestinal failure in adults; and nutrition in cancer patients. nice.org.uk National Institute for Health and Care Excellence: guidance for nutritional support in adults. Selenium The family of seleno-enzymes includes glutathione peroxidase, which helps prevent free radical damage to cells, and monodeiodinase, which converts thyroxine to triiodothyronine (p. 634). North American soil has a higher selenium content than European and Asian soil, and the decreasing reliance of Europe on imported American food in recent decades has resulted in a decline in dietary selenium intake. Selenium deficiency can cause hypothyroidism, cardiomyopathy in children (Keshan's disease) and myopathy in adults. Excess selenium can cause heart disease. Fluoride Fluoride helps prevent dental caries because it increases the resistance of the enamel to acid attack. It is a component of bone mineral and some studies have shown anti-fracture effects at low doses, but excessive intakes may compromise bone structure. If the local water supply contains more than 1 part per million (ppm) of fluoride, the incidence of dental caries is low. Soft waters usually contain no fluoride, while very hard waters may contain over 10 ppm. The benefit of fluoride is greatest when it is taken before the permanent teeth erupt, while their enamel is being laid down. The addition of traces of fluoride (at 1 ppm) to public water supplies is now a widespread practice. Chronic fluoride poisoning is occasionally seen where the water supply contains > 10 ppm fluoride. It can also occur in workers handling cryolite (aluminium sodium fluoride), used in smelting aluminium. Fluoride poisoning is described on page 149. Pitting of teeth is a result of too much fluoride as a child. Sodium, potassium and magnesium Western diets are high in sodium due to the sodium chloride (salt) that is added to processed food. In the UK, it is suggested

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