Molecular Basis of Human Nutrition

LIFELINES

MOLECULAR BASIS OF HUMAN NUTRITION

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SERIES EDITOR'S PREFACE

Teaching programmes in universities now are generally arranged in collections of discrete units. These go under various names such as units, modules, or courses. They usually stand alone as regards teaching and assessment but, as a set, comprise a programme of study. Usually around half of the units taken by undergraduates are compulsory and effectively define a 'core' curriculum for the final degree. The arrangement of teaching in this way has the advantage of flexibility. The range of options over and above the core curriculum allows the student to choose the best programme for her or his future.

The Lifeline series provides a selection of texts that can be used at the undergraduate level for subjects optional to the main programme of study. Each volume aims to cover the material at a depth suitable to a particular level or year of study, with an amount of material appropriate to around one-quarter of the undergraduate year. The concentration of life science subjects in the Lifeline series reflects the fact that it is here that individual topics proliferate.

Suggestions for new subjects and comments on the present volumes in the series are always welcomed and should be addressed to the series editor.

John Wrigglesworth
King's College London

PREFACE

This book is aimed at first or second year undergraduates, or taught master's students, who are studying nutrition as part of a degree in molecular life sciences, health sciences or medicine, including single honours nutrition students. It is intended to supplement the larger nutrition textbooks with greater emphasis on the molecular and metabolic basis of nutrition. It focuses on the biochemical functions of the essential nutrients and the physiological consequences of deficient and excessive intakes. These are described within the context of normal human diets and the requirements for health. Consideration is also given to the other biologically active materials within foods, and to the role of diet in multifactorial diseases. The book focuses on human nutrition, although there are instances where comparisons with, or examples from, the nutrition of other mammalian species will be mentioned to help in the understanding of basic nutritional principles.

It is assumed that readers will have studied, or will be studying concurrently, first year undergraduate modules in general biochemistry and mammalian physiology. The book is based on our experience of many years of research and teaching in nutrition.

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INTRODUCTION

1

What we eat has an enormous impact on our health. Nutritional deficiencies in developing countries are responsible for the major causes of blindness and brain damage worldwide, contribute to high rates of childhood mortality and affect the capacity of adults to work. On the other hand, in the economically developed areas of the world, obesity is an increasing threat to health and the composition of food eaten has a strong influence on the risk of many chronic diseases such as stroke, coronary heart disease, cancer and dental caries. Recent mass outbreaks of food poisoning and the apparent transmission of bovine spongiform encephalopathy (BSE) to humans have highlighted how important a role food plays in the spread of new diseases. In this book, we attempt to explain the molecular basis of human nutrition by outlining the role of nutrients in the body, the consequences of deficient and excessive intakes, the mechanisms involved in diet-related disease and other hazards associated with food intake.

1.1 WHAT IS NUTRITION?

Nutrition can be defined as the process by which living matter acquires substances called nutrients for growth, repair and energy. However, this narrow definition does not adequately describe the effects of food intake on metabolic processes, as food also contains non-nutritive material. Non-nutritive material is more prevalent in food of plant origin. Some of these compounds exert pharmacological effects (e.g. caffeine in coffee). Indeed, many drugs are derived from plants. However, the body has the capacity to adapt to metabolize a wide variety of chemicals and generally converts them into forms which can be excreted. The science of human nutrition is better defined as being concerned with understanding the effects of food on the human body in both health and disease.

Nutrients and non-nutritive materials consist of chemical entities. The contribution a food makes to intake is a function of (i) the concentration of the chemical entity in the food; (ii) the amount consumed; and (iii) the frequency of consumption. For example, parsley contains a high concentration of vitamin C (approximately 1mg/g) but is only consumed in small amounts (no more than 5 g/serving) occasionally (perhaps

once a week), and therefore only contributes small amounts to the total weekly intake ($1 \times 5 \times 1 = 5$ mg/week). On the other hand, potatoes contain moderate amounts of vitamin C (0.15 mg/g) but are consumed frequently (say 4 occasions/week) in substantial amounts (typically 150 g/portion) so contribute substantially to total intake (90 mg/week). In order that comparisons can be made between individuals of different size, an adjustment can be made by dividing the intake by body weight. The term dietary exposure is used to express the intakes and this is normally expressed in relation to body weight:

Nutritional value = quantity × quality

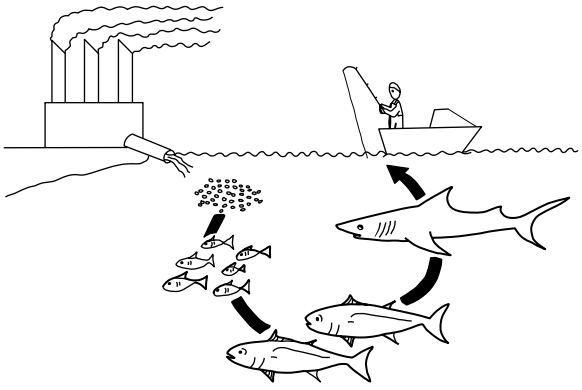
$$\text{Dietary exposure} = \frac{(\text{food chemical}) \times \text{daily food consumption}}{\text{body weight}}$$

Some compounds have the capacity to accumulate in the body. In the case of nutrients that can be stored, such as vitamin A, this means that a regular intake is not necessary. For example, 100 g of lamb's liver contains about 30,000 retinol equivalents (r.e.) which are sufficient to meet the requirements of an individual for about a month. On the other hand, a regular, low intake of a non-nutritive compound that accumulates in the body could be cumulatively toxic. For example, some fat-soluble pesticides such as DDT can accumulate in body fat. Furthermore, some compounds can accumulate up the food chain (Figure 1.1) with the highest levels being found in carnivorous animals at the top of the food chain. For example, the liver of the polar bear contains very high concentrations of vitamin A and whale meat can contain very high levels of toxic heavy metals.

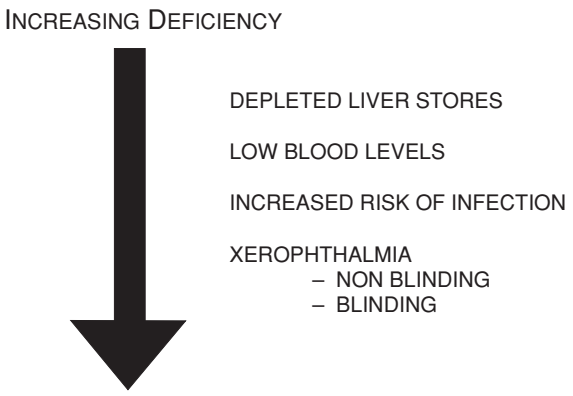
Fat-soluble nutrients and contaminants which are not readily excreted accumulate up the food chain

Nutrients can be subdivided into macronutrients (protein, fat, carbohydrates and the major minerals Na, K, Ca, Mg, Cl, P) and micronutrients (vitamins and trace minerals) which are needed in smaller amounts (mg or μg/d). The main role of macronutrients is to supply energy and structural material (proteins, membranes, teeth and bones) and to make compounds needed for normal metabolism (hormones, enzymes etc), whereas the main role of micronutrients is to act as cofactors required for normal metabolism. The specific roles of each nutrient and the consequences of deficiencies are discussed in the ensuing chapters.

• **Figure 1.1** Chemicals and fat-soluble nutrients can accumulate up the food chain



• **Figure 1.2** Relationship between decreasing intakes of vitamin A and indices of deficiency



■ 1.2 ESTIMATION OF NUTRIENT REQUIREMENTS

The aim of the process of estimating nutrient requirements is to prevent harm arising from a lack of the nutrient, but at the same time to safeguard against adverse effects arising from excessive intakes. The assessment of nutrient requirements depends heavily upon the criteria used. This is well illustrated by an experiment conducted in rats fed varying intakes of vitamin A. It was possible to prevent the major signs of vitamin deficiency (blindness, sterility, altered cell division) with 5 μg/d of vitamin A, but greater amounts were required for a normal visual threshold (8 μg/d), while for normal liver storage of the vitamin an intake of 24 μg/d was required. Even higher intakes are required for optimum growth and reproduction. The same pattern can be seen in humans by observing the stages of vitamin A deficiency (Figure 1.2). Tissue stores become depleted and an increased risk of infection occurs before clinical signs and symptoms of deficiency are observed.

Clinical signs are what can be observed whereas symptoms are what the patient reports

The three main methods used to estimate human nutrient requirements are: 1) determination of the amount required to prevent or cure a deficiency disease, 2) determination of the amount required to maintain a nutrient balance, and 3) determination of the amount needed to optimize biochemical processes that are dependent on the nutrient. Each of these methods can give different results. Clinical deficiencies are usually only apparent when deficiency is severe, and so estimates of requirements using this method tend to be lower than for the other methods.

The amount that is sufficient to cure or prevent a deficiency disease is sometimes referred to as the **minimal requirement**; however, an intake that is adequate to prevent or cure the classical deficiency disease but still results in functional impairments is regarded as suboptimal. This is well illustrated by reference to vitamin C. Experiments carried out on a small number of conscientious objectors to military service in the Second World War in Sheffield showed that a daily intake of 10 mg of vitamin C was sufficient to prevent and cure the deficiency disease scurvy. However, an intake of 20 mg/d was required to support normal wound healing. Moreover, later studies conducted on a large number of subjects showed that an intake of 30 mg/d decreased the risk of gingivitis (inflammation of the gums). It should be noted that one of the

The amount of a nutrient required to prevent/cure a deficiency disease is regarded as the minimal requirement

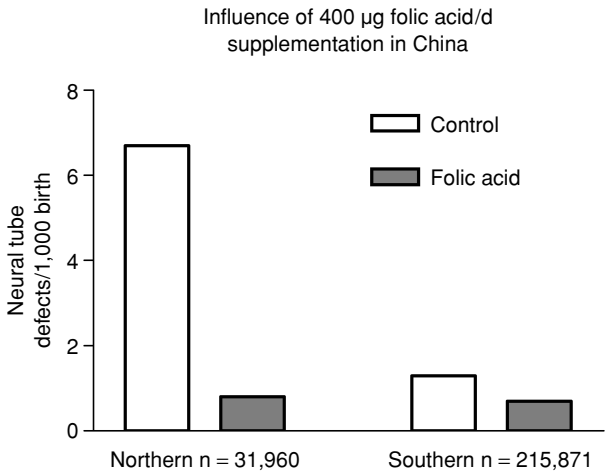
features of scurvy is inflammation of the gums, which become purplish and spongy and bleed. Consequently an intake of 10 mg/d of vitamin C is regarded as suboptimal and higher intakes are needed to maintain optimal wound healing and protection against gingivitis.

The second method is to determine the intake that will allow the body to maintain a balance between intake and utilization. However, this approach has some limitations because the body can adapt to low intakes of some nutrients, and thus maintain a balance over quite a wide range of intakes. This is well illustrated by a study of experimental scurvy conducted on prisoners in the Iowa State Penitentiary, USA. The subjects were put on a vitamin C-deficient diet and injected with a radioactively labelled form of the vitamin so that the rate of utilization of vitamin C and the size of the body pool could be estimated. It was observed that as the body pool of vitamin C became depleted, so the rate of its utilization decreased such that the turnover of vitamin C was 3 per cent of the body pool size: when the pool size was 1,500 mg the rate of turnover was about 30 mg/d, whereas when the pool size was 300 mg the turnover was only 9 mg/d. Similar adaptations occur on low intakes of protein, where the catabolism of amino acids to urea is suppressed, and on low energy intakes, where energy expenditure decreases. Thus for vitamin C the Reference Nutrient Intake (RNI–see p.5) is based on the amount needed to maintain an adequate pool size, as indicated by the circulating concentration. However, it can be argued that intake is adequate only when it saturates the body pool (in the case of a nutrient where excess intakes are excreted) or when it enables storage of the nutrient in the body. For example, estimates of the dietary requirement for vitamin A are based on the capacity of the liver to store more than 20 μg/g.

The third method uses functional indices that relate to the biochemical role of the nutrient. This approach can be applied to many vitamins which are coenzymes in metabolic reactions. For example, a deficiency of vitamin B_{12} results in elevations of plasma homocysteine and methyl malonic acid concentrations because the vitamin is a cofactor for methionine synthase and methyl malonyl mutase. Consequently, the amount of vitamin B_{12} required to normalize plasma concentrations of these metabolites can be used to assess requirements.

A major weakness of these three methods is that they do not take into account potential health benefits/risks that may result from intakes greater than those that fulfil the criteria for assessing requirements. For example, an increased intake of 400 μg/d folic acid on top of the normal dietary intake in the first trimester of pregnancy has been shown to decrease the risk of a woman giving birth to a child with a neural tube defect. On the other hand, high intakes of folic acid may increase the risk of spontaneous abortion in a pregnancy already affected by a neural tube defect. However, women who give birth to infants with neural tube defects do not show any of the classical signs of folate deficiency, and their dietary intake does not differ from women who give birth to healthy babies. One interpretation is that folic acid is exerting a pharmacological effect in those susceptible to having an affected pregnancy. It also raises the question as to whether folic acid really prevents neural tube defects or whether it makes the abortion of an affected foetus more likely. It therefore raises the issue of whether all women should be advised to take additional folic acid in early pregnancy. Questions such as these can only be resolved by large controlled trials where subjects are allocated either an active or placebo

• **Figure 1.3** Influence of folic acid supplementation on the outcome of pregnancy (*Source*: adapted from Berry *et al.*, 1999)



treatment and the outcome observed. The results of such trials showed that folic acid supplementation improved the outcome of pregnancy (i.e. that there were fewer pregnancies affected by neural tube defects) but that the protective effect was greater where the habitual intake of folate was lowest.

■ 1.2.1 DIETARY REFERENCE VALUES

The generic term Dietary Reference Values (DRV) is used to describe a series of values which relate to estimates of the nutritional needs of groups of individuals and populations. They include the following: Estimated Average Requirement (EAR), Recommended Dietary Allowances (RDA), Reference Nutrient Intake (RNI), Lower Reference Nutrient Intake (LRNI), Safe Intake and Tolerable Upper Intake Level. DRVs are also used to describe the desirable proportions of food energy derived from fat, saturated fatty acids and carbohydrate, and the desirable intake of dietary fibre in order to prevent diet-related disease (the scientific basis for these recommendations is discussed in Chapter 9).

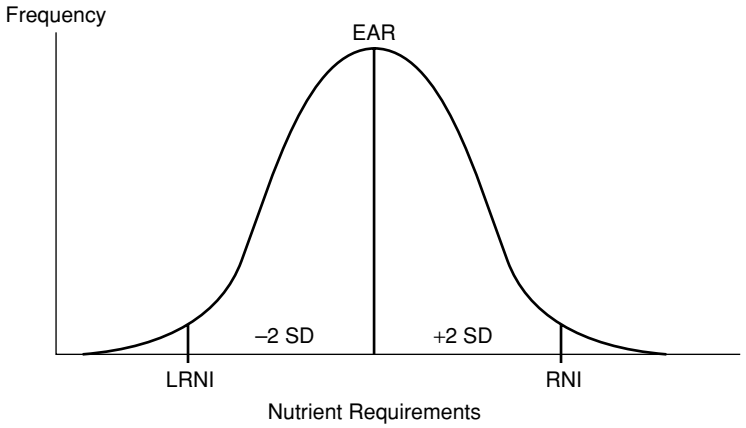
Dietary Reference Values (DRV) is a generic term used to describe estimates of nutritional needs and dietary recommendations for groups of individuals and populations

The EAR is generally based on the amount that prevents deficiency and normalizes physiological and biochemical processes associated with a lack of the nutrient, as described above. However, for some nutrients deficiency disease is unknown among individuals following self-selected diets, so estimates of Safe Intake are made on the basis of the intakes in populations that are in good health (e.g. for vitamin E).

There is significant variation between individuals in nutrient requirements. Consequently, when setting the RNI or RDA, which are supposed to cover the nutrient requirements of almost all individuals, an allowance for individual variability is added on to EAR to ensure that the needs of individuals with above average requirements are met. The exception to this rule is for food energy where a positive energy balance would lead to weight gain. It should be noted that the available experimental data may not always give an accurate estimate of the true variability because it is often based on observations of a small number of healthy young subjects.

The assumption underlying the estimation of nutrient requirements is that the distribution of individual requirements within a population follows a normal distribution

• **Figure 1.4** Hypothetical distribution of nutrient intakes taken from the Dietary Reference Values Report



(Figure 1.4). Thus there will be equal numbers of subjects with requirements below and above the EAR. In a normal distribution, adding 1.96 times the standard deviation to the mean value embraces all values except for the top 2.5 per cent of the population. The RNI is usually estimated by adding 2 standard deviations to the EAR (2 is an approximation of 1.96). This means that RNI is estimated to meet the requirements of 97.5 per cent of the population. There are, however, a few exceptions where this approach is not used, particularly where the nutrient is relatively toxic in excess (e.g. vitamin A). RNIs are often estimated in relation to body weight: the RNI for different age groups can be estimated by multiplying the RNI expressed in mg nutrient/kg body weight by the average body weight for each age group. For some nutrients, RNIs are expressed in relation to energy intake, for example in mg/kJ. This is because the requirement is linked to energy expenditure (for example, for thiamin, riboflavin and niacin). Additional allowances are also made for pregnancy and lactation.

Genetic and environmental factors cause variations in requirements. Gene polymorphisms are common variations in the gene encoding for a protein that result in altered but not entirely defective functioning of that protein. For example, about 10 per cent of the population carry the C677T polymorphism for the enzyme methyltetrahydrofolate reductase (MTHFR), which is a critical enzyme in folate metabolism, catalysing the conversion of 5, 10-methylene-tetrahydrofolate to 5-methyl-tetrahydrofolate. The MTHFR C677T polymorphism decreases MTHFR activity and thus increases the rate of utilization of plasma folate. There are also common polymorphisms of the 1, 25 $(OH)_2$ vitamin D receptor which influence sensitivity to vitamin D.

Environmental effects on nutrient requirements include factors such as stress, alcohol intake and cigarette smoking. For example, cigarette smoking increases the rate at which vitamin C is used by the body and consequently smokers have a higher requirement for the vitamin than non-smokers. Parasitic infestations (such as malaria, hookworm, giardiasis) which are common in many developing countries can also affect requirements because they either interfere with the absorption of nutrients or accelerate the rate at which the nutrients are used or lost from the body. Giardiasis is a common intestinal parasitic infection caused by the amoeba *Giardia lamblia*. It is prevalent in developing countries

and results in decreased absorption of fat-soluble vitamins, particularly β-carotene (provitamin A). Infestation with hookworm, which is also prevalent in developing countries, results in an increased loss of iron due to bleeding into the gut. Malaria, which is a major public health problem in tropical countries, causes an increased turnover of red blood cells and, therefore, increases the requirement for nutrients associated with blood formation (iron, folate and vitamin B_{12}). Human immunodeficiency virus (HIV) infection can increase the risk of opportunistic infections of the gut that can result in the decreased absorption of several micronutrients.

For food labelling purposes, an average recommended daily allowance (RDA) figure is used. This is usually based on the RNI for an adult. However, there has been much confusion caused by the terms RDA and RNI. They were derived to be benchmarks by which to compare groups of individuals rather than to assess whether an individual has an adequate or inadequate intake of a nutrient. The terms are often misunderstood, for example, by journalists who suggest that the RNI is the minimum requirement. If an intake is above the RNI, then it is extremely unlikely that it will be inadequate. However, an individual may have an intake which is below the RNI but which is still perfectly adequate to meet their individual requirement. The Lower Reference Nutrient Intake (LRNI) is 2 standard deviations below the estimated average requirement. This can be used as a benchmark to assess whether an individual's habitual intake is likely to be in the range where their requirement may not be met.

Because the body requires a certain amount of a nutrient to function properly, it does not follow that greater amounts will necessarily improve health. Many nutrients can be purchased as supplements in health food shops and there have been cases of individuals consuming excessive amounts which have resulted in harm and even death, especially for vitamins A and D, and iron. Consequently, there has been a need to define safe upper limits for supplement use. The approach employed is to observe the lowest dose at which toxic effects occur and then allow a safety margin.

Small amounts of micronutrients are essential but excessive intakes can be toxic

■ 1.2.2 MEASUREMENTS OF TOXICITY

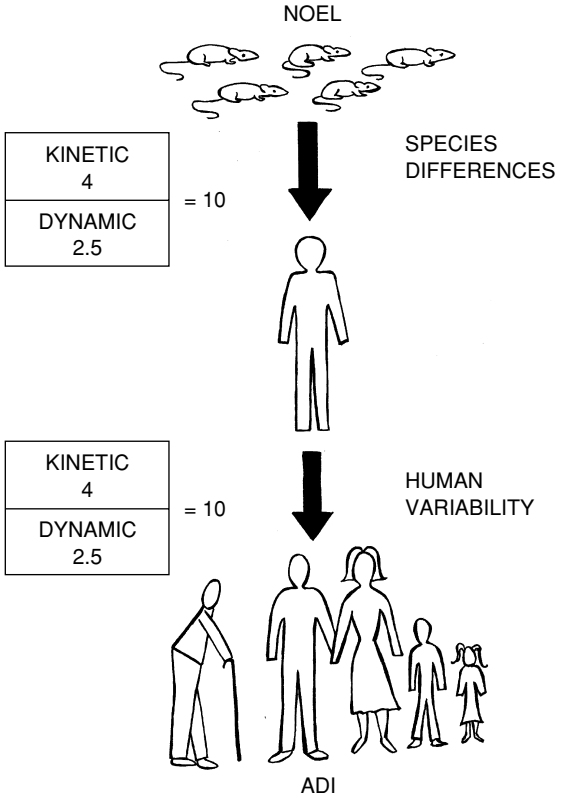
The Swiss sage Paracelsus recognized that plants could be foods, drugs or poisons, and that it was the dose that made the difference. Toxicity can be defined as the ability of a substance to cause harm when tested in isolation. All substances are toxic if sufficient amounts are consumed: whether a substance is a hazard (i.e. causes harm in practice) depends on the dose consumed, the timing and duration of exposure, the extent to which the compound can be metabolized and excreted and other factors that affect the sensitivity of the host such as age, gender and physiological state.

The nature of scientific investigation involves hypothesis testing, where a hypothesis is stated and an experiment designed to test the hypothesis. The statistical methods used in the testing of hypotheses are more robust at detecting significant differences than determining equivalence. Consequently, it is easier to demonstrate toxicity than to determine safety, which is the absence of potentially harmful effects. In order to assess toxicity, animals (usually mice and rats) are initially fed the test compound from high to low intakes in order to induce harmful effects. The lowest dose that induces adverse effects is then used to design long-term dietary exposure studies, often focusing on the organs where harm is observed in the acute test (this is called a target organ study). In

these long-term studies, the aim is again to find the lowest intake of the compound that causes harm. This intake is termed the Lowest Adverse Effects Level (LOEL) and is expressed in mg/kg body weight. The intake below this is called the No Adverse Effects Level (NOEL). This figure is not likely to be precise but only an estimate depending on the number of dose levels used in the study.

In calculating a safe intake from the NOEL, several allowances are made to give a safety margin. An allowance is made for the variations in: 1) toxicokinetics, which are the properties which determine the delivery of the chemical to the target organ and the duration and extent of exposure, and 2) toxicodynamics, which are the properties which determine the response of the target organ to the chemical. In practice, the variability in toxicokinetics is usually taken as fourfold and that of toxicodynamics as two-and-a-half-fold. So if the NOEL value is divided by 10 (an approximation of the product of toxicokinetics and toxicodynamics) an estimated safe intake can be derived for the species in which the tests are conducted. However, if the results are to be extrapolated from animals to humans, a further safety factor is built in and this involves dividing the estimated safe intake by another factor of ten (again allowing for toxicokinetic and toxicodynamic variation) to yield an intake, usually expressed in mg/kg body weight. This is used as the basis for calculating the acceptable daily intake (ADI) (Figure 1.5).

• **Figure 1.5** Safety factors used in calculating acceptable daily intakes (ADI) from no observed effect level (NOEL) in animals



The ADI is defined as the amount of a chemical, expressed on a mg/kg body weight basis, that can be safely ingested each day over a lifetime. Daily intakes for men and women can then be calculated by multiplying by average body weight: the assumption generally used is that men weigh 60 kg and women weigh 50 kg (although this is considerably lower than actual average weights in the UK which are nearer 76 and 66 kg respectively). ADIs are set for food additives, which are intentionally added to food for a defined purpose during processing, and contaminants, which may be artificial or naturally occurring.

Variability in toxicokinetics and toxicodynamics is well illustrated by reference to the effects of alcohol. Anecdotal evidence suggests that women get drunk more easily than men and it has been proven that women are more likely to develop cirrhosis of the liver as a consequence of alcohol abuse. In men of all age groups and postmenopausal women, there is some oxidation of alcohol in the stomach prior to delivery to the liver (target organ) whereas this does not occur in women of reproductive age. Furthermore, because women contain more body fat than men, the distribution of alcohol in the body is different. This results in the same dose of alcohol/kg body weight, resulting in a higher blood alcohol concentration in women than men: these are all toxicokinetic effects. The effect blood alcohol has on the liver will depend on the size of the liver and its sensitivity to harmful effects: these are toxicodynamic effects. For example, the toxic effects of alcohol will be greater in an individual with an impaired capacity to metabolise alcohol or with some other pre-existing disorder such as chronic viral hepatitis. It is known that the livers of women are on average smaller than those of men and that they are more sensitive to the toxic effects of alcohol.

The risk of harm is regarded as neglible providing the ADI is not exceeded. If the ADI is occasionally exceeded, this is not of concern because of the large safety margin and because the ADI is set for long-term exposure. However, an ADI is not appropriate for compounds that can accumulate in the body. Several minerals such as arsenic, lead and mercury are cumulatively toxic, as are a large number of fat-soluble organochlorine compounds. Food of animal origin is generally not a source of toxic material unless the animal has accumulated a toxic substance from the food chain. As it is difficult to define safe intakes for such cumulatively toxic compounds, a Provisional Tolerable Weekly Intake (PTWI) expressed in mg/kg body weight is set. The PTWI is normally estimated by assessing how much of a given dose of the chemical is retained and estimating the rate of turnover of the compound. In some cases, the levels of compounds are irreducible (e.g. PCBs in oily fish) and so a more pragmatic view is taken which aims to set the PTWI as reasonably low as is achievable.

Non-nutritive material is more prevalent in foods of plant origin. Foods of plant origin are also the main source of potentially toxic material. For example, hydrogen cyanide is released by hydrolysis of cyanogenic glycosides, which are found in cassava, apricot kernels, linseed and butter beans. This is acutely toxic. Although there have been deaths resulting from individuals eating apricot kernels, acute cyanide toxicity is uncommon because cooking destroys most of the hydrogen cyanide and the small amounts present in apple pips are not sufficient to cause harm.

Plant foods contain a variety of potentially pharmacologically active substances, but food processing decreases dietary exposure and the effects are spread over a variety of receptors so that many of the pharmacological effects are balanced out. However, there can be synergistic interactions between pharmacologically active substances in food and

drugs. For example, tyramine, which is a bacterial metabolite of the amino acid tryptophan, has a serious blood pressure raising effect in patients taking anti-depressant drugs that inhibit monoamine oxidase. Patients taking these drugs have to avoid sources of tyramine such as cheese, pickled fish and meat extracts. There are many such interactions with drugs and warnings are given on the data sheet for the drug. For example, terfenidine, a drug used to treat hay fever, was withdrawn from over-the-counter sales when it was discovered to interact with flavonoids in grapefruit juice and cause heart arrhythmias. On the other hand, some non-nutritive compounds may have beneficial effects on health by acting as antioxidants and cancer blocking agents (see Chapter 10).

1.2.3 DIETARY GUIDELINES

Dietary guidelines have three primary aims: to provide a diet that meets the requirement for all nutrients; to avoid diet-related diseases such as obesity, cardiovascular disease, dental caries and cancer; and to prevent the transmission of foodborne diseases such as food poisoning and zoonoses including variant Creutzfeldt-Jakob disease. A detailed discussion of the risks and mechanisms relating to these conditions is given in Chapters 9 and 10. Dietary guidelines can be further divided into those which are aimed at the population, those that are given to caterers and the food industry, and those that are targeted at the individual. The latter are often known as food-based dietary guidelines. All dietary guidelines involve a risk/benefit analysis and to be successful they need to take into account normal human behaviour and recognize that the intake of food has an important social and cultural role.

The process by which dietary guidelines are derived is generally through consensus reports. These reports are written by committees of experts given specific terms of reference. Expert committees have been criticized because of the nature of the selection of their membership. Cronyism is the term used to describe the situation where committee members are selected from colleagues of one or two leading workers in the field. Stakeholders may also influence committee membership in order to ensure that their views are expressed. Experts who have links with industry, and lobby groups, are regarded as having a vested interest. This can lead to bias and the process has been criticized for lacking transparency and openness. An effort has been made to make the working of expert committees more open. However, this does tend to make the process more political and vulnerable to a different form of lobbying. More recently, the technique of systematic review has been applied to the development of dietary guidelines. In this process, strict rules are laid down concerning the admissibility of evidence. Systematic reviews were primarily developed for evaluating different treatment strategies and not for dealing with uncertainty. While this approach is an improvement, dietary guidelines should not be regarded as being written on tablets of stone.

The main focus of recent dietary guidelines has been to prevent obesity, cardiovascular disease, cancer and dental caries. All dietary guidelines advocate maintaining energy balance by matching energy intake with energy expenditure. Most dietary guidelines recommend that total fat intake should be decreased so that it provides between 25 and 35 per cent of energy, and that carbohydrate consumption should be increased to between 50 and 60 per cent of energy intake. These guidelines also recommend that intake of saturated fatty acids should not exceed 10 per cent of dietary energy, that intake of salt

Table 1.1 Dietary reference values from the UK Dietary Reference Values Report and the Eurodiet Consensus Conference

	UK DRV	*EURODIET*
Protein % energy	8–10	10–15
Fat % energy	35	<30
of which		
saturated fatty acids	10	<10
polyunsaturated fatty acids	6	4–8
trans fatty acids	<2	<2
Carbohydrates % energy	50	>55
of which non-milk extrinsic sugars	11	–
Dietary fibre g/d	18†	>25
Sodium chloride g/d	<6	<6

Note: †Expressed in terms on non-starch polysaccharide: approximately 20 g NSP is equivalent to 30 g dietary fibre.
Sources: Department of Health (1991; 1994); Proceedings of the European Conference (2000).

should be reduced to around 6 g/d and that intakes of dietary fibre (or non-starch polysaccharides) and potassium should be increased. Current UK DRVs and those proposed by the Eurodiet Consensus Conference are shown in Table 1.1. There is much dispute regarding the recommendations with regard to sugar. However, there is a consensus that the frequent consumption of sugar-containing snacks should be limited to no more than four eating occasions/day in order to help prevent dental caries. The scientific basis for these recommendations is given in Chapter 9.

Food-based dietary guidelines have been developed in order to translate the numerical DRVs into foods that make up the typical diet. These are often illustrated as a food pyramid or food on a plate showing the relative proportions of the major food groups that should make up a balanced diet. Replacing fatty meat and meat products, with lean meat and fish, is emphasized, as is using dairy products with a decreased fat content, and using vegetable oils sparingly in place of animal fats. In order to increase the intake of carbohydrate, an increased intake of starchy foods, preferably wholegrain cereals, is advocated rather than an increase in sugar consumption. One of the practical dietary guidelines has been to increase the recommended consumption of fruit and vegetables to five portions per day.

SUMMARY

- Nutrition is the effect of food intake on the human body in health and disease.
- Nutrient requirements vary according to age, gender, physiological state, genetic and environmental factors.
- Adaptation to low intakes of nutrients occurs.
- Excessive intakes of some vitamins and minerals can cause poisoning.
- Food contains both potentially toxic and beneficial non-nutritive material.
- Diet affects the risk of cardiovascular disease, cancer, diabetes and dental caries.
- Dietary Reference Value is the term used to describe estimates of the nutritional needs of groups of individuals and populations.

FURTHER READING

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ENERGY

2

2.1 ENERGY CONTENT OF FOODS

The human body obtains energy from four classes of nutrients: fats, carbohydrates, proteins and, for some people, alcohol. During digestion the macromolecules are hydrolysed to their monomers: fatty acids and glycerol from fats, monosaccharides from carbohydrates and amino acids from proteins. These monomers can then be taken up from the circulation by tissues and oxidised to generate ATP. Many tissues are able to utilize any or all of these molecules as fuel, although some show a marked preference or even an obligatory requirement for particular substrates (see Chapters 3, 4 and 5).

Energy can be obtained from fats, carbohydrates, proteins and alcohol

2.1.1 GROSS ENERGY

Complete oxidation of these molecules yields carbon dioxide, water and oxides of nitrogen and sulphur, and liberates a certain amount of energy. The amount of energy generated by complete oxidation of a foodstuff is known as its gross energy content. This can be measured in a bomb calorimeter, in which the energy generated after igniting a known amount of the foodstuff in an atmosphere of pure oxygen is transferred to a known amount of water and the temperature rise in the water is measured. Precise determination of gross energy values in this way is relatively tedious, and most nutritional work nowadays utilizes a simpler instrument known as a ballistic bomb calorimeter. Here, the heat is transferred simply to the heavy metal casing of the combustion chamber, and the maximum temperature rise in the casing is measured. The instrument is calibrated by burning a similar amount of a standard substance, usually benzoic acid or sucrose, under the same conditions.

Gross energy is measured by bomb calorimetry

Representative values for the gross energy content of the major nutrients are shown in Table 2.1. If the nutrient composition of a foodstuff, or indeed a whole diet, is known then its gross energy content can be calculated as the algebraic sum of the gross energy contents of the individual nutrients.

Because the energy content of foods is measured by calorimetry, the results have generally been expressed in the traditional units of heat: calories. The word calorie has

Table 2.1 Gross energy content of major nutrients

	kJ/g	*kcal/g*
Carbohydrates		
Monosaccharides	15.7	3.75
Disaccharides	16.6	3.95
Polysaccharides	17.4	4.15
Polyols	8.3	2.00
Fats		
Average	39.1	9.3
Palmitic acid	27.5	6.1
Oleic acid	31.6	7.5
Linoleic acid	30.8	7.4
Proteins		
Average	22.9	5.4
Glycine	13.0	3.1
Phenylalanine	28.1	6.7
Ethanol	29.8	7.1

become so closely identified with this use in the public consciousness that it is now used colloquially as a synonym for the energy derived from food. However, from a scientific point of view it is important to recognise the equivalence of different forms of energy, and the accepted unit of energy is the joule. Thus, energy values are now always quoted in joules, although it is still useful in nutritional literature to quote equivalent values in calories as additional information; 1 calorie equals approximately 4.18 joules. Joules and calories are rather small units for measuring nutritionally significant amounts of food, so values are normally expressed in kilojoules (kJ) or kilocalories (kcal, sometimes abbreviated as Cal).

1 calorie = 4.18 joules

■ 2.1.2 DIGESTIBLE ENERGY

Digestible energy means the amount of energy from food actually absorbed by the body through the digestive tract. It is measured by subtracting the gross energy content of the faeces from the gross energy content of the food consumed.

Classic experiments by Atwater and others have measured the digestibility of pure nutrients. Alcohol is essentially 100 per cent absorbed. Glucose, sucrose and starch are at least 99 per cent digestible, which is why they are called available carbohydrates. Dietary fibre, or non-starch polysaccharide, is classically considered to have a digestibility of zero, although the fermentation of some non-starch polysaccharides in the large intestine means that a digestibility value of around 50 per cent may be more appropriate (see Chapter 4). The digestibility of fat is approximately 95 per cent, although there is some variation between different fats (see Chapter 5). The true digestibility of most animal proteins is also around 95 per cent, whereas the true digestibility of some plant proteins can be as low as 80 per cent. (See p. 39 in Chapter 3 on protein for a definition of true and apparent digestibility). Moreover, the addition of endogenous protein losses from the gut means that the apparent digestibility of mixed proteins in a typical Western diet is usually about 92 per cent, and it can be even lower in predominantly plant-based diets (see Chapter 3).

Digestible energy content can be predicted by applying these digestibility factors to the gross energy content of each component in a foodstuff or a diet. There is some evidence that large amounts of dietary fibre can inhibit the absorption of other components of a diet, but the effect appears to be very small.

2.1.3 METABOLIZABLE ENERGY

Metabolizable energy is the amount of energy potentially available to the body to do work such as ATP synthesis. This is the conventional way of describing the energy content (or calorie content) of a diet or a foodstuff. It is measured by subtracting the gross energy content of the urine from the digestible energy intake. In humans, the difference between digestible and metabolizable energy values is due almost entirely to the energy content of the urinary urea. In other words, it arises because amino acids are not completely oxidized in the body to carbon dioxide, water and nitrogen oxides. Nitrogen is excreted in the form of urea, and this represents energy which is not available to the body. Hence although the gross energy value of most proteins is around 22.9 kJ/g (5.4 kcal/g), their metabolizable energy values are around 16.7 kJ/g (4.0 kcal/g).

For ruminant animals there is also a significant loss of energy in the breath in the form of methane which is produced during bacterial fermentation in the rumen, and this causes a somewhat greater difference between digestible energy and metabolizable energy values.

In practice, when constructing a table of food composition values or when analysing a diet, the metabolizable energy content is predicted from the amounts of protein, fat, alcohol and available carbohydrate present, multiplied by the average metabolizable energy value of each component. These average metabolizable energy values are often known as Atwater factors, and are shown in Table 2.2.

The energy values shown in tables of food composition are metabolizable energy values

2.2 SOURCES OF ENERGY

Most foodstuffs contain a mixture of protein, fat and carbohydrate, as well as water. It is therefore somewhat misleading to refer to a particular foodstuff as a protein or a carbohydrate (except sugar), although it is appropriate in the case of oils and some fats. Since the Atwater factors for protein and carbohydrate are quite close to each other, the main determinant of the energy content per unit dry weight is the fat content. For pure fats this value will be 37 kJ/g (9 kcal/g), while for low fat foods it will be close to 17 kJ/g (4 kcal/g). In fact, even foods which are considered to have a high fat content, such as chocolate, peanuts and potato crisps, rarely exceed a value of 25 kJ/g (6 kcal/g).

The other major determinant of energy density (energy content per unit mass) is the water content. Foods with a high starch content often have a high water content as well.

Table 2.2 Average metabolizable energy values for macronutrients, or Atwater factors

	kJ/g	*kcal/g*
Available carbohydrate	16	3.75
Fat	37	9
Protein	17	4
Ethanol	29	7

Source: *McCance and Widdowson's The Composition of Foods* (2002).

Table 2.3 Contribution of macronutrients to food energy consumption in representative groups of countries

	% Energy from		
	Protein	*Carbohydrate*	*Fat*
Most affluent	11.5	53.0	35.7
Intermediate	10.4	67.5	22.1
Least affluent	10.1	74.7	15.2

Note: Data calculated from Food Balance Sheets (United Nations Food and Agriculture Organization).

The energy density of food is determined mainly by its fat and water contents

Thus bread is 40 per cent water and 50 per cent carbohydrate, giving an energy density of 9 kJ/g (2.2 kcal/g). Boiled rice is 70 per cent water and 6 kJ/g (1.4 kcal/g), potatoes are 80 per cent water and 3 kJ/g (0.7 kcal/g) and cabbage is 90 per cent water and 1 kJ/g (0.25 kcal/g).

The same analysis may be applied to the diet as a whole. Because of the dominant effect of water content, the most useful way of describing the proportions of the major nutrients in a diet is to refer to their contribution to the energy content of the diet. This also corrects for the effect of total energy intake, allowing qualitative comparisons between diets to be made. In particular, recommendations concerning the amount of fat in the diet are usually framed in terms of the proportion of energy coming from fat.

Table 2.3 shows the proportions of energy coming from the major nutrients in typical diets from different parts of the world, arranged in groups according to their affluence. The diets of people in the world's poorest countries tend to be dominated by carbohydrate, mainly from starchy staple foods. When economic constraints are removed, and people have access to a greater range of foods, they choose a much higher proportion of fat, while the amount of protein consumed varies over a much smaller range.

Clearly, energy requirements can be met by a wide range of diets. The specific requirement for protein appears to be met by most normal diets, with the possible exception of some diets of very low digestibility which may not meet the requirements of young infants in developing countries. Some tissues have an absolute requirement for glucose as a fuel (see Chapter 4), but the body can synthesize glucose from most amino acids or from glycerol. Since diets with a low carbohydrate content (such as the traditional Inuit diet) tend to be high in protein, dietary carbohydrate deficiency has never been observed. The minimum requirement for essential fatty acids is also small, amounting to around 1 per cent of dietary energy. In practical terms, however, very low fat diets are usually inadequate because of limited absorption of fat-soluble vitamins (see Chapter 5). Low fat, high carbohydrate diets also tend to be very bulky, particularly as they are likely to have a high water content. Cases have been reported where infants are unable to consume enough of such a bulky diet to meet their energy requirements, leading to protein–energy malnutrition.

■ 2.3 ENERGY EXPENDITURE

Within the body, the macronutrients are oxidized by a variety of biochemical pathways, and the energy released in this overall oxidative process is used mainly to synthesize ATP from ADP and inorganic phosphate. The ATP is then utilized to drive biosynthetic

reactions, to maintain electrochemical gradients across membranes, and to perform mechanical work via contractile proteins. The efficiency with which ATP synthesis and hydrolysis is coupled to these reactions is not particularly high, so that around 75 per cent of the energy is lost as heat. The total amount of heat produced plus the amount of useful work done is called the energy expenditure.

Energy expenditure can be measured by either direct or indirect calorimetry. Strictly speaking, direct calorimetry measures heat loss rather than heat production, and because of cyclic changes in body temperature these two processes are not always in phase. Thus, direct calorimetry can only be used to assess heat production over periods of at least 24 hours, and since calorimeter chambers are usually rather small this may not be very pleasant for the subject. Hence direct calorimetry is mainly used in the study of temperature regulation.

■ 2.3.1 INDIRECT CALORIMETRY

Indirect calorimetry involves measuring the amounts of oxygen consumed and carbon dioxide produced by respiration. Table 2.4 shows the average amounts of oxygen consumed and carbon dioxide produced per gram of each of the major nutrients, although clearly there will be small differences depending on the exact composition of the substrate, particularly in the case of fats. However, it can be seen that the amount of heat produced per unit oxygen consumed is virtually the same (approximately 20 kJ/l O_2; 4.9 kcal/l O_2) for all substrates. Hence for practical purposes it is sufficient to measure the rate of oxygen consumption in order to calculate energy expenditure.

Energy expenditure is usually measured by indirect calorimetry. This involves measuring oxygen consumption

The ratio of the amounts of carbon dioxide produced to the amount of oxygen consumed is known as the Respiratory Exchange Ratio (RER, sometimes also called the respiratory quotient), and this varies from 0.7 when pure fat is being oxidized to 1.0 when pure carbohydrate is being oxidized. The amount of amino acids being oxidized can be calculated from measurements of urinary nitrogen excretion, so that when this is combined with measurements of gas exchange it is possible to calculate the amounts of each of the three major nutrients being oxidized (see Box 2.1).

Oxygen consumption can be measured in a number of different ways. The simplest is for the subject to breathe through a mouthpiece into a large bag, called a Douglas bag, for a known period of time, after which the volume of gas exhaled and its oxygen content can be measured. The oxygen content of the inspired air will be that of the atmosphere (20.9 per cent at sea level), so this is sufficient information to calculate oxygen

Table 2.4 Average amounts of oxygen consumed and carbon dioxide produced during the oxidation of metabolic fuels

Nutrient	*O_2 consumed (l/g)*	*CO_2 produced (l/g)*	*RER (CO_2/O_2)*	*Energy released (kJ/g)*	*Energy/O_2* (kJ/l)
Carbohydrate	0.83	0.82	1.0	17.5	21.1
Fat	1.98	1.40	0.71	39.1	19.8
Protein	0.96	0.78	0.81	18.5	19.3
Alcohol	1.43	0.97	0.66	29.8	20.4

■ BOX 2.1 USE OF DATA FROM INDIRECT CALORIMETRY TO CALCULATE ENERGY EXPENDITURE, RESPIRATORY EXCHANGE RATIO AND THE AMOUNTS OF THE THREE MAJOR NUTRIENTS BEING OXIDIZED

In one day: oxygen consumption (VO_2) = 600 l
carbon dioxide production (VCO_2) = 525 l
urinary nitrogen excretion (N_U) = 11 g

It is assumed that no alcohol is being metabolized;

Then respiratory exchange ratio = VO_2/VCO_2

$= 525/600$

$= 0.875$

Energy expenditure, using the formula of Brockway (1987):

$EE = 16.58\ VO_2 + 4.51\ VCO_2 - 5.90\ N_U$ kJ

$= 16.58 \times 600 + 4.51 \times 525 - 5.90 \times 11.0$ kJ

$= 9948 + 2368 - 65$ kJ

$= 12251$ kJ

Carbohydrate oxidation, using the formula of McNeill (2000)

$= 4.707\ VCO_2 - 3.340\ VO_2 - 2.714\ N_U$ g

$= 4.707 \times 525 - 3.340 \times 600 - 2.714 \times 11$ g

$= 2471 - 2004 - 30$ g

$= 437$ g

Fat oxidation, using the formula of McNeill (2000)

$= 1.786\ VO_2 - 1.778\ VCO_2 - 2.021\ N_U$ g

$= 1.786 \times 600 - 1.778 \times 525 - 2.021 \times 11$ g

$= 1072 - 933 - 22$ g

$= 113$ g

consumption and hence energy expenditure. The most widely used formula for this purpose is known as the Weir formula

$$\text{energy expenditure (kJ/min)} = V(4.376 - 0.209 \cdot O_E)$$

where V is the volume of breath exhaled per minute, reduced to standard temperature and pressure, and O_E is the percentage oxygen content of the expired gas (see Box 2.2 for a worked example).

■ **BOX 2.2 CALCULATION OF ENERGY EXPENDITURE WHILE STANDING FROM MEASUREMENTS OF OXYGEN CONSUMPTION ALONE, USING A DOUGLAS BAG**

The subject breathed into the Douglas bag for exactly 7 minutes. The volume of gas collected was 73.9 l, and its oxygen content was 17.4 per cent. The temperature of the gas was 23 °C, and atmospheric pressure was 688 mm Hg.

The gas volume is first reduced to STP, using a factor derived from standard tables for air saturated with water vapour. For this temperature and pressure the factor is 0.8092, so the volume at STP is $73.9 \times 0.8092 = 59.8$ l.

Dividing by 7 minutes,

$$V = 59.8 / 7$$

$$= 8.54 \text{ l/min}$$

$$O_E = 17.4$$

Using the formula of Weir (1949):

$$\text{Energy expenditure} = V \times (4.376 - 0.209 \times O_E)$$

$$= 8.54 \times (4.376 - 0.209 \times 17.4)$$

$$= 8.54 \times (4.376 - 3.637)$$

$$= 8.54 \times 0.739$$

$$= 6.31 \text{ kJ/min (1.51 kcal/min)}$$

A full Douglas bag is rather cumbersome to carry around, and even a 100 l bag fills quite rapidly during any form of exercise, so more portable apparatus has been developed for measuring energy expenditure during non-sedentary activities. Examples are the Kofranyi-Michaelis respirometer, which monitors expired volume continuously and collects a small sample of the expired gas; and the Oxylog, which monitors both expired volume and oxygen content of expired gas continuously. These techniques have allowed the energy costs of a wide range of activities to be determined (see Table 2.5). Such

Table 2.5 Representative values for energy expenditure during a range of activities (values are expressed as multiples of basal metabolic rate)

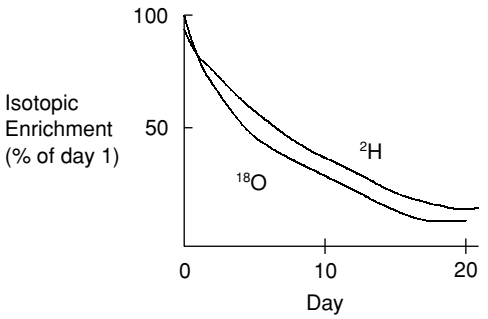
Activity	*Multiple of BMR*
Sitting	1.2
Standing	1.4
Walking	3.2
Walking up stairs	6
Running	8
Office work	1.5
Labouring	4

values can then be used in combination with a diary recording the activities performed, say every five minutes, to estimate a person's energy expenditure over a whole day.

Experimental subjects may find the use of a mouthpiece (or a mask) uncomfortable, and may prefer a ventilated hood. This involves placing the subject's head inside a hood, box or small tent attached to a pump which draws room air at a known rate past the subject's face and then through the sensors of oxygen and carbon dioxide analysers. This technique can only be used if the subject remains in one place. Nevertheless, it is currently the method of choice for clinical investigations and short-term metabolic studies.

■ BOX 2.3 CALCULATION OF ENERGY EXPENDITURE USING DOUBLY LABELLED WATER

The subjects consume a single dose of $^{2}H_{2}{}^{18}O$, and urine samples are collected over the next 20 days. The isotopic enrichment of urinary water is measured by isotope ratio mass spectrometry.



From these graphs' rate constants are calculated for the rate of change of enrichment of oxygen (k_O) and hydrogen (k_D). Then the rate of production of CO_2 (R_{CO_2}) is given by:

$$R_{CO_2} = 0.5N(k_O - k_D)$$

where N is the total body water content.

Typical values are N = 2000 mol, k_O = 0.110/d, k_D = 0.088/d

Thus $R_{CO_2} = 0.5 \times 2000 \times (0.110 - 0.088) = 22$ mol/d

To convert this to a value for energy expenditure requires information on the respiratory exchange ratio. It is usually assumed that this can be calculated from the amounts of protein, fat and carbohydrate consumed during the experimental period. A typical value for respiratory exchange ratio on a mixed diet would be 0.85. This corresponds to a value of 23.9 kJ per litre of CO_2 produced, or 534 kJ per mole.

Thus energy expenditure = $22 \times 534 = 11760$ kJ/d

Note: this is a very simplified version of the calculation – there are a number of other correction factors that have to be applied in practice.

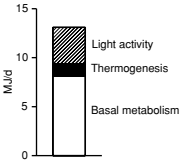
For longer-lasting metabolic studies, where the subject needs to be able to carry out normal daily activities, calorimeters the size of a whole room have been constructed. Again the principle is simply to draw air through the room and to monitor continuously the oxygen and carbon dioxide content of the air that leaves the room. A subject can stay in the room for several days, receiving known amounts of food. This allows extremely accurate balances of fat, carbohydrate and protein, as well as energy, to be calculated.

Confining an experimental subject to a single room for several days does not allow the true energy expenditure of free-living people to be measured. One method which has recently been developed in an attempt to achieve that objective is known as the doubly labelled water method. This requires the subjects to ingest a single dose of water which has been labelled with two stable (i.e. non-radioactive) isotopes, deuterium (^{2}H) and ^{18}O. Samples of a body fluid (usually either saliva or urine) are then collected at intervals over several days, the enrichment of both isotopes is measured and their rate of change with time is calculated, in both cases as complex curvilinear functions. The rate of loss of ^{2}H depends on the rate at which water is being lost, while the rate of loss of ^{18}O depends on the rate of loss of water and carbon dioxide, so that the difference between the two disappearance rates allows the rate of carbon dioxide production to be calculated. This in turn allows energy expenditure to be calculated if the proportions of the different fuels being oxidized is known, and this is usually assumed to be the same as the composition of the diet.

■ 2.3.2 COMPONENTS OF ENERGY EXPENDITURE

It is convenient to consider energy expenditure as consisting of a basal component plus various increments related to physical activity, eating, keeping warm and the response to drugs and hormones. The heat produced by these incremental components is sometimes known as thermogenesis.

Figure 2.1 Components of daily energy expenditure in an 80 kg young male



The basal metabolic rate is defined as the energy expenditure of a person lying down at complete physical and mental rest in a thermoneutral environment at least twelve hours after eating, drinking or smoking. This can be difficult to achieve in practice, and most experimental determinations are more correctly known as the resting metabolic rate. This is a measure of the energy required for normal metabolic reactions, including the turnover of protein and RNA, the maintenance of cellular sodium and potassium gradients, muscle and vascular tone, breathing, heartbeat, etc.

The major determinants of basal metabolic rate are body size and composition. Adipose tissue has a much lower metabolic rate per unit mass than lean tissue, and this is largely because so much of the adipose tissue mass consists of relatively inert deposits of triacylglycerol. Age and sex also affect basal metabolic rate. This is mainly due to their effects on body size and composition, although in children there is also a component associated with the energy cost of growth. There also appears to be a genetic component, since there are reports of differences in metabolic rate of up to 10 per cent between individuals of apparently similar body size and composition, but no genes have yet been identified which account for a consistent or significant proportion of this variation. On the other hand, there is no shortage of suggestions for possible mechanisms leading to different metabolic rates, including differences in the rate of protein turnover, the efficiency of Na:K ATPase, or the activity of various futile metabolic cycles.

The increment due to physical activity includes both the work done and the heat produced by muscular contraction. It can account for 20–40 per cent of daily energy expenditure. Clearly it varies with the intensity of the exercise or work, but it is also affected by the person's body weight whenever the activity involves moving that weight.

The ingestion of food causes a temporary increase in metabolic rate which may amount to about 10 per cent of the energy content of the meal. This is caused by a variety of processes, including the activity involved in eating and the energy costs of digesting, absorbing and transporting the nutrients and the associated changes in blood flow. However, the major component is the energy utilized in synthesizing and storing glycogen, triacylglycerol and protein. The size of this increment is affected by the composition of the meal, with protein intake causing a slightly greater increase than either fat or carbohydrate intake. For this reason the increment used to be known as the specific dynamic action of protein, although it is now given the more general name of the thermic effect of food or the heat increment of feeding.

Some energy may need to be expended to maintain normal body temperature. Quite a lot of heat is generated inevitably as a by-product of normal metabolic processes, as has been mentioned, but if more heat is needed it can be generated by either non-shivering or shivering thermogenesis. Non-shivering thermogenesis may involve a degree of uncoupling of electron transport from ADP phosphorylation under the influence of a mitochondrial protein named thermogenin. This is an important process in small mammals and human infants, where it occurs particularly in brown adipose tissue. It occurs to a lesser extent in adult human beings, where it tends to be mainly associated with skeletal muscle. Keeping cool by sweating also involves a small increase in energy expenditure.

Many common pharmacological agents cause energy expenditure to rise, including alcohol, nicotine, theophylline and caffeine. Thyroid hormone causes an increase in metabolic rate, as do catecholamines, which may mediate the acute effects of psychological stress on energy expenditure. Cytokines such as tumour necrosis factor and the interleukins may have a similar effect, and thus be responsible for the increase in metabolic rate which occurs in response to infectious, traumatic and inflammatory illnesses.

■ 2.4 ENERGY REQUIREMENTS

An adult person needs to consume just enough food energy to balance their energy expenditure and thus maintain energy balance, hence recommendations for energy intake are based on estimates of energy expenditure. It is clearly impractical to measure every individual's energy expenditure, but there are sufficient data in the literature to allow the development of equations which predict the average energy expenditure of groups of people.

The current recommendations of the authorities in the UK, and indeed the international recommendations of the United Nations Organisation are based on the work of Schofield *et al.* This involves firstly the prediction of basal metabolic rate from body weight, age and sex, using the equations listed in Table 2.6. The result is then multiplied by a ratio known as the physical activity level. This ratio varies from 1.4 to 1.9, depending on the amount of energy likely to be expended in occupational and recreational activities (see Table 2.7). For children, the recommendations also take into account the additional energy costs of growth. For pregnant and lactating women, additional amounts of energy are recommended to allow for the growth of the foetus and the synthesis and

Energy requirements can be estimated from predicted energy expenditure

Table 2.6 Equations for predicting basal metabolic rate (BMR) from body weight (W) measured in kg

	BMR (MJ/d)
Males	10 – 17y BMR = 0.074W + 2.754
	18 – 29y BMR = 0.063W + 2.896
	30 – 59y BMR = 0.048W + 3.653
Females	10 – 17y BMR = 0.056W + 2.898
	18 – 29y BMR = 0.062W + 2.036
	30 – 59y BMR = 0.034W + 3.538

Source: Dietary Reference Values for Food Energy and Nutrients for the United Kingdom (2001).

Table 2.7 Physical activity levels for adults

Non-occupational	*Occupational activity*					
Activity	*Light*		*Moderate*		*Heavy*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*
Non-active	1.4	1.4	1.6	1.5	1.7	1.5
Moderately active	1.5	1.5	1.7	1.6	1.8	1.6
Very active	1.6	1.6	1.8	1.7	1.9	1.7

Note: These represent the ratio of total energy expenditure to basal metabolic rate.
Source: Dietary Reference Values for Food Energy and Nutrients for the United Kingdom (2001).

secretion of breast milk (see Box 2.4), although there is evidence that metabolic adaptations reduce the expected energy costs of these processes.

■ 2.5 ENERGY BALANCE

Energy balance is defined as the difference between energy intake and expenditure. If intake is greater than expenditure balance is said to be positive, and this leads to net deposition of energy, usually in the form of triacylglycerol in adipose tissue. A negative balance means expenditure is greater than intake, and leads to loss of tissue. Children need to be in modestly positive energy balance during periods of growth, but most people maintain a zero balance most of the time. Obese people tend to be in positive balance for a relatively short time (the so-called active phase of obesity), then maintain balance at a new, stable body weight.

The fact that body weight remains relatively stable in many people (varying less than 1 kg over a one year period) suggests that quite powerful mechanisms exist to control either intake or expenditure, or both. On the other hand, an increasing proportion of the population is becoming obese, which suggests that recent changes in lifestyle have perturbed these normal regulatory mechanisms. For such people to lose weight requires them to achieve negative energy balance. It may require very considerable effort to decrease energy intake and/or increase expenditure sufficiently to overcome the control

■ **BOX 2.4 EXAMPLE OF CALCULATION OF ESTIMATED AVERAGE ENERGY REQUIREMENT OF A GROUP OF BREAST-FEEDING WOMEN**

Age: 25 years
Weight: 60 kg
Occupational activity: Moderate
Non-occupational activity: Non-active
Basal metabolic rate (from Table 2.6)

$$\text{BMR} = 0.062W + 2.036 \text{ MJ/d}$$
$$= 0.062 \times 60 + 2.036 \text{ MJ/d}$$
$$= 3.720 + 2.036 \text{ MJ/d}$$
$$= 5.756 \text{ MJ/d}$$

Physical activity level (from Table 2.7) = 1.5;
Hence total energy expenditure

$$= 5.756 \times 1.5 \text{ MJ/d}$$
$$= 8.63 \text{ MJ/d}$$

Add increment for lactation (from Dietary Reference Values)

$$= 2.0 \text{ MJ/d}$$

Hence estimated average energy requirement

$$= 8.63 + 2.0 \text{ MJ/d}$$
$$= 10.6 \text{ MJ/d}$$

mechanisms which normally act to minimize changes in energy balance. This is one reason why obese people tend to regain weight after losing it by dieting.

It is generally accepted that energy balance is regulated mainly by changes in energy intake. Numerous mechanisms have been demonstrated both in humans and animals by which hunger and satiety are affected by metabolites, particularly glucose or amino acids, or hormones in such a way as to tend to regulate energy intake. For example, much interest currently concerns the hormone leptin which is secreted by adipose tissue and acts on the hypothalamus to suppress appetite. Unfortunately, in humans there are also numerous social, psychological and emotional factors which also affect eating behaviour, and these often seem to override the physiological control mechanisms and disturb energy balance. The unprecedented increase in obesity over the past decade has been attributed to an obesogenic environment, where food is in abundance and physical activity is minimized (e.g. the use of cars, computers and watching television).

■ **BOX 2.5 CONSEQUENCES OF FAILURE TO CONTROL ENERGY BALANCE**

The average intake of adult males in the UK is around 10 MJ per day. If energy intake exceeded energy expenditure by just 10 per cent, this would result in a positive energy balance of 1 MJ per day. Over a year this would amount to 365 MJ which would be stored as fat. The energy cost of storing 1 kg fat is about 42 MJ so this would be estimated to lead to an accumulation of 8.7 kg fat, and as body fat contains about 25 per cent water this would lead to a weight gain of about 11.6 kg. However, in practice weight gain is likely to be less than this because more energy has to be expended in carrying around the extra weight. Furthermore, basal metabolic rate increases slightly with increasing energy intake.

Some components of energy expenditure also act to minimize, though not prevent, perturbations in energy balance. Thus postprandial thermogenesis increases with meal size, acting to dissipate some of the excess energy consumed. Any tissue which is laid down increases the overall basal metabolic load of the body, and increases the energetic cost of moving the body.

In small mammals there is good evidence of further adaptive changes in energy expenditure. Thus when rats are over-fed they show a considerable increase in energy expenditure, mediated largely by an increase in non-shivering thermogenesis in brown adipose tissue. This lasts for as long as the overfeeding continues, and in some cases completely prevents additional weight gain. Although there is some evidence for similar adaptive changes in humans, it is far from conclusive.

Attempts to induce a negative energy balance in order to lose weight focus on reducing energy intake. Hundreds of different approaches to dieting have been proposed, many of which work for at least some people. However, they only work if they succeed in decreasing energy intake, since energy from one nutrient or foodstuff is just as fattening as the same amount of energy from any other nutrient or foodstuff. The only difference between different diets is the way in which the energy intake is reduced, and the way in which the desire to overeat is controlled. There are also some drugs which can help to suppress appetite, including amphetamines, fenfluramine and diethylpropion. These all have undesirable side-effects, including addiction in some cases, and most tend to become less effective with repeated use.

Decreased energy expenditure is an important cause of weight gain. However, there is less scope for losing weight by increasing energy expenditure. It is difficult to sustain increased levels of physical activity to an extent that will achieve more than about a 10 per cent increase in energy expenditure. This will not achieve an encouraging rate of weight loss, although it may be useful in maintaining a stable weight after the desired weight loss has been achieved, and it does have a beneficial effect on the cardiovascular system and decreases the risk of developing Type II diabetes (see Chapter 9). There is considerable research activity devoted to finding a drug which will increase metabolic rate, with much of the current focus being on β_3-adrenergic agonists, but so far none has been found which is sufficiently safe and effective.

SUMMARY

- Energy is derived from the oxidation of protein, fat, carbohydrate and alcohol by reactions that are coupled to the synthesis of ATP.
- Metabolizable energy is the amount of energy that is available to the body for ATP synthesis, after correcting for urinary and faecal losses.
- Fat has a metabolizable energy value of 37 kJ/g, carbohydrate 16 kJ/g, protein 17 kJ/g and alcohol 29 kJ/g.
- Energy expenditure is usually measured by indirect calorimetry, which involves measuring oxygen consumption and carbon dioxide production.
- The main components of energy expenditure are basal metabolic rate, thermogenesis and physical activity.
- Energy requirements are derived from measurements of energy expenditure needed to maintain energy balance. Energy requirements for groups of people can be predicted from their age, weight, sex and physical activity level.

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PROTEIN

3

3.1 THE NEED FOR PROTEIN

Protein is a major component of all living cells, and thus of the human body. It makes up about 17 per cent of the weight of an average adult, making it the second biggest component after water. It forms the building blocks of tissues, enzymes and chemical messengers (see Table 3.1). The need for protein during growth is self evident – it is needed to make up new tissue. What is not so obvious is the need for protein in a non-growing adult. A certain amount of tissue protein is broken down to amino acids each day; some of these amino acids are oxidized or irreversibly converted to other compounds. Protein is also lost from the body as dead skin, hair, nails and intestinal secretions. Thus dietary protein is needed to replace that which is lost.

Protein is an inevitable component of any diet based on the consumption of other organisms. Although it is possible to extract purified products containing just fat or just carbohydrate, as soon as one consumes any cellular material there is protein present.

Table 3.1 Functions of proteins within the body

Function	*Examples*
Catalysis	Enzymes
Storage and transport	Ferritin
	Haemoglobin
	Amino acid transporters
Structure	Collagen
	Elastin
Contraction	Actin
	Myosin
Communication	Hormones
	Receptors

Note: This list is not exhaustive, but illustrates some of the range of functions for which proteins are responsible.

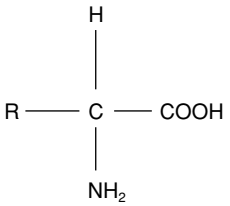
Thus it is very unusual to find a diet that is very low in protein, and it is consumed in adequate amounts by most people.

■ 3.2 PROTEIN CHEMISTRY

Proteins are macromolecules made up of chains of amino acids joined together by peptide bonds. There are 20 different amino acids which can be incorporated into proteins, although some of them can be chemically modified after incorporation, so that hydrolysis of a mature protein can yield in excess of this number.

Amino acids can be represented by a common formula (see Figure 3.1). The R group is different for each different amino acid, and this affects not only the chemical and physical properties of the amino acid but also the structure and function of the protein which contains it (see Table 3.2).

• **Figure 3.1** The common formula for amino acids



Since different proteins contain different proportions of the different amino acids, their elemental composition will each be slightly different. However, they will all contain carbon, hydrogen, oxygen and nitrogen, and most will also contain sulphur. The most useful feature of this composition from a nutritional point of view is the nitrogen content. This distinguishes protein from the other major components of both tissues and foodstuffs – water, fat and carbohydrate do not contain nitrogen. This means that if we want to measure the protein content of a food, or of a sample of tissue, all we have to do is to measure the nitrogen content. This is very useful because different proteins have such a wide variety of physical and chemical properties that it would be difficult to separate them all and measure them in any other way.

Proteins contain nitrogen as well as carbon, hydrogen and oxygen

The nitrogen content is also important in metabolic terms. Once the protein from food has entered the body it is broken down and metabolized to a variety of other substances, and these are excreted in various different forms, but again the feature which distinguishes them as end products of protein metabolism is the nitrogen content. So for practical reasons we tend to measure nitrogen metabolism, and this becomes synonymous with protein metabolism.

■ 3.2.1 MEASUREMENT OF PROTEIN CONTENT

The protein content of foodstuffs is usually measured by determining the nitrogen content using the Kjeldahl method. This can be used to measure the total nitrogen content of tissue samples, or urine, faeces or other physiological specimens. The method involves digesting the sample for several hours in hot concentrated sulphuric acid. The digestion rate can be increased by the addition of catalysts, and an inert solute to raise the boiling point. The carbon and hydrogen are oxidized to carbon dioxide and water, while the

Nitrogen is measured by the Kjeldahl method which converts amino nitrogen into ammonia

Table 3.2 Structure of amino acids

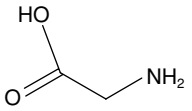
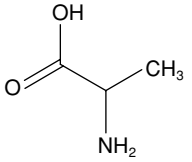
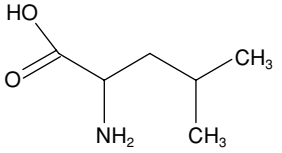
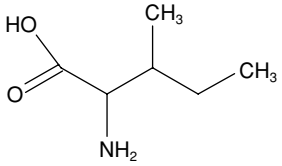
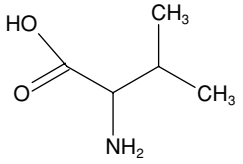
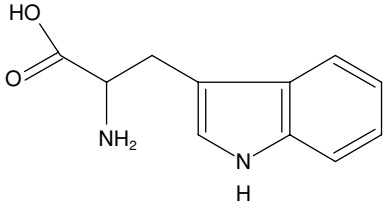
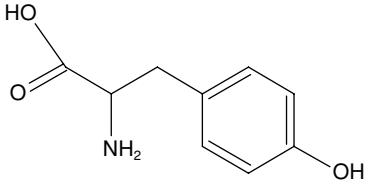
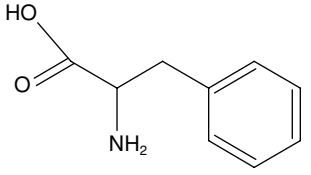
Common feature	*Name*	*Structure*
Aliphatic side chains	Glycine	
	Alanine	
Branched chain amino acids	Leucine	
	Isoleucine	
	Valine	
Aromatic side chains	Tryptophan	
	Tyrosine	
	Phenylalanine	

Table 3.2 ***(con't)***

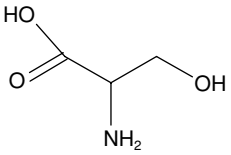
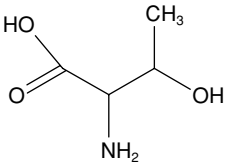
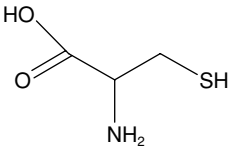
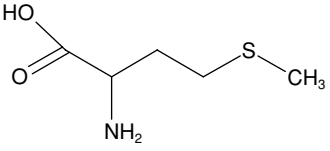
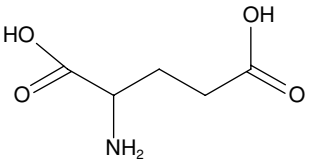
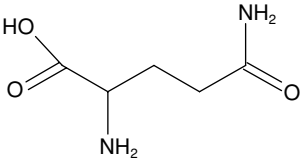
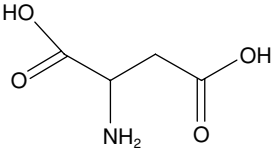
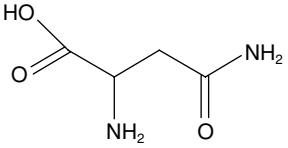
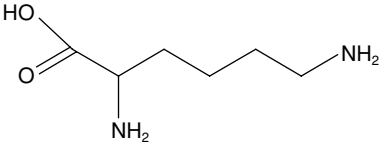
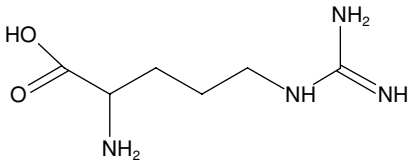
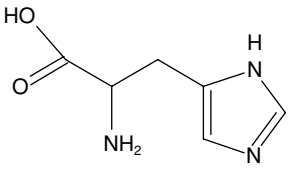
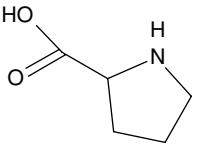
Common feature	*Name*	*Structure*
Hydroxy side chains	Serine	
	Threonine	
Sulphur containing amino acids	Cysteine	
	Methionine	
Acids and amides	Glutamic Acid	
	Glutamine	
	Aspartic Acid	
	Asparagine	
Basic side chains	Lysine	

Table 3.2 ***(con't)***

Common feature	*Name*	*Structure*
	Arginine	
	Histidine	
Imino acids	Proline	

nitrogen is reduced to ammonia. The amount of ammonia produced can then be measured by a variety of colorimetric or titrimetric methods.

The measured nitrogen content is then converted to a protein content on the basis that the average nitrogen content of protein is 16 per cent. Most people find it easier to multiply than to divide, so instead of dividing by 0.16, nitrogen content is multiplied by 6.25 to give protein content.

There are three limitations to this method for determining the protein content of a food:

1 It measures all the nitrogen, including that in molecules other than protein. For example, it would include nucleic acids. These make up no more than 1–2 per cent of the nitrogen in most foods, and so can be ignored, but there are exceptions such as mushrooms, in which 60 per cent of the nitrogen is non-protein nitrogen.
2 Not all the nitrogen gets converted to ammonia by the Kjeldahl method. This mainly applies to compounds in which the nitrogen is bonded to oxygen (which doesn't include the nitrogen in protein). In any case, it is only a very small proportion of the nitrogen in foodstuffs, and can safely be ignored.
3 Not all proteins contain exactly 16 per cent N. For example, cereals contain rather more, so for wheat flour the figure is N × 5.70. On the other hand milk contains rather less, so for milk and milk products the figure is N × 6.38.

The value obtained from Kjeldahl N × 6.25 is referred to as the **crude protein** content of the food. This term does not imply any imprecision or inaccuracy in the measurement – indeed it is a very precise definition – but it simply recognizes that it is not a true measure of the protein content. However, other biochemical methods for measuring

protein content such as those based on the biuret reaction tend not to be appropriate for most foodstuffs, where it may be difficult to extract the protein quantitatively from a complex matrix and where the proportions of different amino acids may vary widely between the different food proteins.

Crude protein = N × 6.25

■ 3.3 FOOD SOURCES

Virtually all the food we consume, both plant and animal, contains some protein. Some foods are considered as 'protein foods', which means that they contain a relatively high concentration of protein. The main examples are meat, fish, milk, cheese, eggs and legumes, especially soya beans. However, the importance of any food as a source of any nutrient also depends on the amount of that food that is eaten, so foods that we eat a lot of are important sources of many nutrients.

On a worldwide basis by far the most important sources of protein are cereals. It is worth noting that, for a diet based on cereals, if people are able to consume enough to satisfy their energy needs they will also have consumed enough to satisfy their protein needs. This does not apply to diets based on starchy roots such as cassava and plantains, which have a much lower ratio of protein to energy, so that people need to eat significant quantities of other protein sources such as beans, cereals or animal products as well.

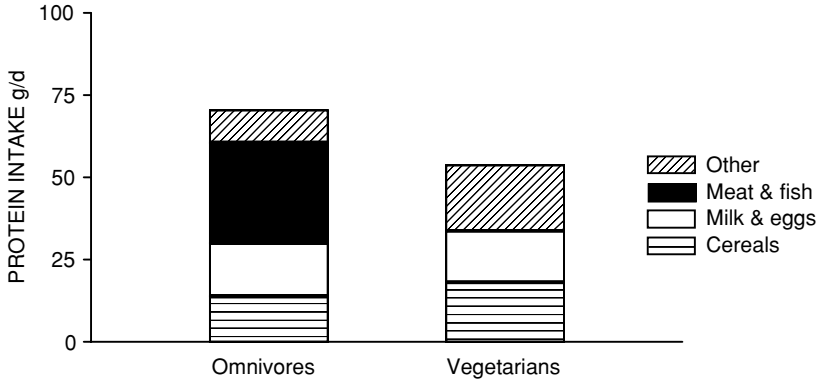
Cereals are major sources of protein in human diets

The major sources of protein in the diets of women following an omnivorous or vegetarian diet living in the UK are shown in Figure 3.2.

Note that meat is the biggest source of protein in the average diet in the UK, in common with other developed countries. Protein intakes are lower in vegetarians but a higher contribution is derived from cereals and other plant-based foods. In vegan diets, cereals and pulses both provide about one-third of the intake. However, the total protein intake of vegans and vegetarians is only slightly lower than that of omnivores.

Adults in this country eat on average 73 g protein per day (men 85 g, women 62 g). However, the most useful way to look at quantity is as a proportion of energy, to take account of differences in total food intake. In almost all diets around the world this proportion is between 10 and 15 per cent, with relatively small differences between poorer

• **Figure 3.2** Sources of dietary protein in omnivore and vegetarian women in the UK (*Source*: Adapted from Reddy S and Sanders TAB, 1990)



countries and richer ones. In the UK the average protein intake in men is 14.1 per cent of energy, while for women it is 15.2 per cent. The proportion increases slightly with age, as energy intake falls. It has also been increasing slightly over recent years, again as energy intake has fallen. Finally, there is a small social class gradient in the UK, from approximately 14.7 per cent in the highest social class A to 14.3 per cent in social class D.

Human diets contain a huge variety of different proteins, but from a nutritional point of view differences in their biochemical functions are not particularly important. Of much greater importance is the proportions of the various amino acids which they contain, and the digestibility of the protein within the human gut. These two properties determine the **quality** of the protein (see below), which must be considered when evaluating whether a given quantity of protein will satisfy nutritional needs.

■ 3.4 DIGESTION, ABSORPTION AND METABOLISM

The classical view is that proteins are hydrolysed in the stomach and small intestine to amino acids, which are then absorbed from the small intestine. These free amino acids then circulate in the bloodstream to all the organs and tissues of the body, where they are metabolized. This is a reasonable description of the overall process, although it is now clear that the uptake of small peptides, 2–5 amino acids long, is also quite important.

Proteins are digested in the gut and enter the circulation as a mixture of free amino acids

■ 3.4.1 DIGESTION

The stomach secretes a series of enzymes which are collectively known as pepsins. These enzymes have different pH optima ranging from just below neutral, corresponding to the conditions within the stomach immediately after a meal, to pH 1.2, as would be found there several hours later. They begin the process of breaking the proteins up into smaller peptides by hydrolysing peptide bonds adjacent to phenylalanine, tyrosine and leucine residues.

Most protein digestion occurs in the small intestine by the action of enzymes which are secreted by the exocrine pancreas. Table 3.3 shows the specific sites of secretion of each of these enzymes.

Table 3.3 Digestive proteolytic enzymes

Enzyme	*Zymogen*
Stomach	
Pepsin	Pepsinogen
Pancreas	
Trypsin	Trypsinogen
Chymotrypsins	Chymotrypsinogens
Elastase	Proelastase
Carboxypeptidases	Procarboxypeptidases
Small intestine	
Enterokinase	–
Aminopeptidases	–

These enzymes are synthesized as inactive proenzymes, or zymogens, in order to avoid them hydrolysing the proteins of the cells in which they are synthesized. They are activated only after being secreted into the duodenum. This activation involves cleaving off a terminal peptide which prevents the normal folding of the mature polypeptide chain. Thus pepsinogen is activated by hydrochloric acid in the stomach. Trypsinogen is activated by enteropeptidase (enterokinase), an enzyme secreted by the small intestine. Trypsin then activates all the other proteolytic enzymes.

There are several factors such as the tertiary structure of the protein and the degree of cross-linking of the peptide chains which can affect the rate of digestion of proteins. Indigestible cell walls may physically hinder the access of digestive enzymes to some plant proteins. Antinutrients such as tannins and trypsin inhibitors (found in raw beans) can inhibit protein digestion either by binding to the digestive enzymes or by forming insoluble complexes with the protein substrate. This results in reduced protein digestibility as well as abdominal discomfort if consumed in large quantities. Digestibility can often be improved by cooking, particularly extended boiling in water which denatures trypsin inhibitors and leaches out tannins. The foodstuffs which most commonly display low digestibility are the legumes, including soya beans.

■ 3.4.2 ABSORPTION

The products of digestion by the pancreatic enzymes are mainly small peptides. The final stage of digestion to free amino acids is carried out by aminopeptidases in the cells lining the small intestine (enterocytes). This hydrolysis may occur just before the amino acids are transported into the cell, or it may occur within the cell. Experiments *in vitro* have indicated that small peptides may actually be transported into these cells rather faster than free amino acids.

Amino acids and small peptides can enter the enterocyte both by passive diffusion and by active transport. The specificities and mechanisms of the amino acid transport systems in the gut appear to be broadly similar to those of the systems which are found in other tissues, particularly the brush border of the kidney tubule (see Table 3.4). The amino acids may then be metabolized within the cell, but the majority diffuse down a concentration gradient into the portal circulation.

■ 3.4.3 METABOLISM

The amino acids which are derived from dietary protein mix with the pool of free amino acids within the body, and can be considered as having three possible metabolic fates. They can be used for protein synthesis, they can be oxidized to urea, carbon dioxide and water, or they can be converted to a variety of other small molecules (see Figure 3.3).

3.4.3.1 Protein synthesis

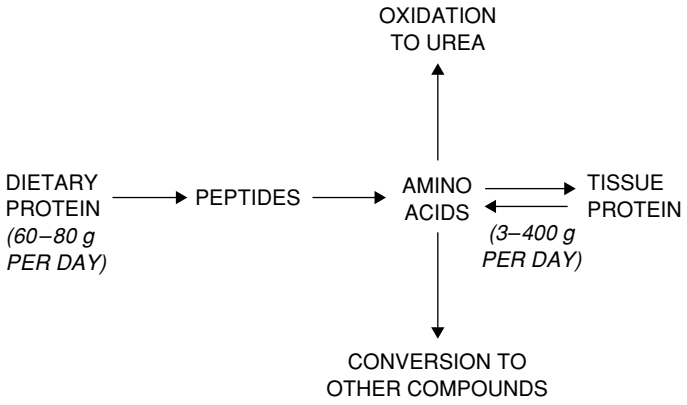
Even in the non-growing adult there is always some protein being synthesized from amino acids, and this is matched by an equivalent amount of protein being broken down to amino acids. This phenomenon of protein turnover can be demonstrated by feeding isotopically labelled amino acid and observing that a significant proportion of the label is retained in body proteins even though the amount of nitrogen going in as food protein is closely matched by the amount of nitrogen excreted as urea.

Protein turnover means the continual breakdown and resynthesis of tissue proteins

Table 3.4 Intestinal amino acid transport systems

System	*Sodium dependence*	*Preferred amino acids*
A	yes	alanine, serine, glycine, methionine, proline
L	no	leucine, isoleucine, valine, methionine, phenylalanine, tyrosine, tryptophan, histidine
ASCP	yes	alanine, serine, cysteine, proline
Ly	yes	lysine, histidine, arginine, ornithine
x_A^-	yes	aspartate
x_G^-	yes	glutamate
x_C^-	no	aspartate, glutamate, cysteine
y^+	yes	lysine, arginine, histidine
β	yes	β-alanine, taurine
$b^{0,+}$	no	lysine, leucine
Gly	yes	glycine, sarcosine
N	yes	histidine, glutamine, asparagine
imino	yes	proline

• **Figure 3.3** Metabolic fates of ingested protein



The difference between the rates of protein synthesis and breakdown determines whether the mass of protein in the body increases, for instance during growth, or decreases, for instance during wasting diseases. Nutrient intake is one factor which can affect rates of protein synthesis and breakdown, with both tending to decrease if protein or energy intakes are inadequate. However, protein turnover does continue even if intake is zero. In this case an obligatory level of protein breakdown occurs, releasing amino acids of which a proportion can be recycled to maintain protein synthesis.

Protein synthesis is quantitatively the biggest process for disposal of amino acids. It has been shown that an adult synthesizes 3–400 g protein each day, even though intake may be only 60–80 g per day. The rates of protein synthesis and breakdown are always very close. Even the most rapidly growing young infant would only be depositing protein at a net rate of approximately 10 g per day, while he or she is turning over 50–100 g protein per day.

3.4.3.2 Oxidation

Ultimately, all the amino acids that enter the body will be disposed of by oxidation. Some will be retained as tissue protein for a time, but this is matched by an equal amount of amino acids being released from tissue protein to be oxidized.

The amino acid can be considered in two parts, as a carbon skeleton and an amino group. The amino group is oxidized to urea in the liver; the urea then circulates to the kidney, where it is excreted. In fact the rate of urea production is somewhat greater than the rate of urea excretion in the urine: the difference is called urea salvage. This occurs in the large intestine where urea can be hydrolysed to ammonia by bacteria. This ammonia diffuses back into the circulation, and can be reutilized for the synthesis of non-essential amino acids.

Amino acids are catabolized to urea, carbon dioxide and water, with the release of energy

The carbon skeleton of the amino acid is oxidized to carbon dioxide and water, with the release of energy as ATP. Thus amino acids form one of the major fuel sources for the liver, in particular. Moreover one particular amino acid, glutamine, is the major fuel for the gut and for white blood cells.

Under certain circumstances, such as starvation, diabetes or a high fat diet, the body may need to synthesize glucose from amino acids rather than oxidizing them directly. Experiments with diabetic dogs fed on single amino acids have shown that most of the amino acids can be converted to glucose, and are therefore classified as **glucogenic**. However, leucine and lysine cannot be converted to glucose, and under these circumstances they give rise to acetoacetic acid, so they are classified as **ketogenic**. This classification can be related to the pathways by which the amino acids are catabolized. The ketogenic amino acids are those that are metabolized only to acetyl CoA, while those that are metabolized to TCA cycle intermediates are glucogenic. Tryptophan, methionine and cysteine produce pyruvate and so can be either ketogenic or glucogenic. Phenylalanine and tyrosine are metabolized to fumarate plus acetoacetate and are thus both ketogenic and glucogenic, as is isoleucine, which is metabolized to acetyl CoA plus succinyl CoA.

3.4.3.3 Other metabolic pathways

The third possibility is that some amino acids can be metabolized to other molecules such as hormones and nucleic acids, including those shown in Table 3.5.

Some amino acids will also be converted to other amino acids in order to supply the appropriate balance of substrates for protein synthesis. Again, the amino group and the

Table 3.5 Examples of other molecules to which amino acids may be converted

Amino acid	*Product*
Arginine	Creatine, NO
Aspartate	Nucleic acid bases
Glutamine	Nucleic acid bases
Glycine	Creatine, haem, bile acids
Lysine	Carnitine
Methionine	Creatine
Tryptophan	5-hydroxytryptamine, nicotinic acid
Tyrosine	Catecholamines, thyroid hormones, melanin

carbon skeleton must be considered separately. The amino group can be transferred from almost any amino acid to almost any other by the action of transaminase enzymes. The only amino acids which don't appear to participate in transamination reactions are lysine and threonine.

The situation with the carbon skeletons is more complicated. There are some amino acids whose carbon skeletons can be made from other amino acids, or indeed from other metabolic intermediates which may be derived from carbohydrate or fat. These are known as **non-essential** or dispensable amino acids. Amino acids whose carbon skeletons cannot be made from other dietary constituents are known as **essential** or indispensable amino acids, and these must be supplied in adequate quantities by the diet.

Essential amino acids are those whose carbon skeletons cannot be synthesized in the human body

■ 3.5 CLASSIFICATION OF AMINO ACIDS AS ESSENTIAL OR NON-ESSENTIAL

This concept arose originally from a series of classic nutritional experiments by W.C. Rose in the 1930s. In the first series he fed young, rapidly growing rats on purified diets containing adequate amounts of fat, carbohydrate, vitamins and minerals together with mixtures of all the 20 amino acids which were known to be present in proteins. He then removed one amino acid at a time from the diet. Two types of response were observed. For some amino acids the removal made no difference – the rats continued to grow at the same rate. These amino acids could thus be described as non-essential (see Table 3.6). For others the response was dramatic – the rats stopped growing, then lost weight, lost appetite, and eventually died. These amino acids were described as essential. The result of removing arginine was somewhat ambiguous, as the rats still grew but at a much reduced rate.

Further experiments showed that rats could synthesize the non-essential amino acids themselves, however they could not synthesize the essential amino acids, so that when one of these was excluded from the diet they could not synthesize any protein, since

Table 3.6 Essential and non-essential amino acids for the rat and humans

Essential		*Non-essential*	
Rat	*Man*	*Rat*	*Man*
Leucine	Leucine	Tyrosine*	Tyrosine*
Valine	Valine	Cysteine†	Cysteine†
Threonine	Threonine	Aspartic acid	Aspartic acid
Methionine	Methionine	Asparagine	Asparagine
Phenylalanine	Phenylalanine	Glumatic acid	Glumatic acid
Lysine	Lysine	Glutamine	Glutamine
Histidine		Alanine	Alanine
Arginine		Proline	Proline
		Glycine	Glycine
		Serine	Serine
			Histidine
			Arginine

Notes:
*can be synthesized from phenylalanine
†can be synthesized from methionine

virtually all tissue proteins have to contain some of each amino acid. Protein breakdown and amino acid oxidation continued, leading to a continual loss of tissue protein. The rats were able to synthesize arginine, but at a limited rate which was clearly not sufficient to allow optimum growth.

Rose went on to do similar feeding experiments in human volunteers, and found that the two species had slightly different nutritional needs. In these studies he used the **nitrogen balance** technique rather than the growth response as the criterion for adequacy of the diets. This means that he measured the intake and excretion of nitrogen over a period of several days. For an adult on an adequate diet one would expect intake and excretion to be equal. If intake is greater than excretion (positive balance) tissue protein must be being deposited, as occurs during growth. On the other hand if excretion is greater than intake (negative balance) this means that there is a net loss of tissue protein, and indicates that the diet is inadequate.

Rose started with a mixture of the ten essential amino acids from his work on the rats. The volunteers maintained nitrogen balance on this, showing clearly that the other ten amino acids were also non-essential for humans. He then removed each in turn. Removing histidine or arginine made no difference – nitrogen balance was maintained, showing that histidine and arginine are non-essential for humans. But for each of the other amino acids, the volunteers immediately went into sustained negative nitrogen balance as soon as it was removed from their diet. Interestingly, they also complained of symptoms such as fatigue, irritability and loss of appetite. It should be noted that cysteine can only be synthesized from methionine, so the requirements for these two amino acids are normally considered together. The same applies to tyrosine, which can only be synthesized from phenylalanine. Hence cysteine and tyrosine are sometimes referred to as semi-essential amino acids.

Recent work has suggested that there are some conditions involving rapid growth or the recovery from certain illnesses in which the body's capacity to synthesize arginine, histidine, glycine or glutamine can be inadequate, and nitrogen balance can improve when one or other of these amino acids is given in the diet. Thus these amino acids are sometimes classified as conditionally essential.

■ 3.6 PROTEIN QUALITY

Protein quality means the efficiency with which dietary protein is utilized within the body

Protein quality may be defined as the efficiency with which a dietary protein can be utilized by the body. It has two main components: digestibility (i.e. the proportion of ingested protein that is actually absorbed from the gut), and essential amino acid composition relative to requirement.

The best way to understand protein quality is to see how it is measured. There are two main approaches – the so-called biological and chemical methods.

■ 3.6.1 BIOLOGICAL METHODS FOR ASSESSING PROTEIN QUALITY

These involve feeding a group of people or animals on a diet containing a set amount of the test protein for a period of days and measuring an appropriate biological response. The most useful method is called **Net Protein Utilization** (**NPU**). This is defined as the increase in nitrogen retention per unit increase in nitrogen intake, and is commonly abbreviated to

$$\text{NPU} = \text{nitrogen retained/nitrogen intake}$$

Outlines of the methods for measuring NPU using experimental animals or human volunteers are given in Boxes 3.1 and 3.2.

■ BOX 3.1 MEASUREMENT OF NET PROTEIN UTILIZATION (NPU) USING EXPERIMENTAL ANIMALS

To measure NPU, two diets are formulated with the test protein as the sole source of protein; only the concentration of protein differs between the two diets. The diets are then fed to matched groups of experimental animals, usually rats. Nitrogen retention can be determined as the difference in carcass nitrogen content between the beginning and the end of the test period:

$$\text{N retention} = B - B_0$$

where B_0 and B are the body nitrogen contents of the rats at the beginning and end of the test period respectively. Hence the difference in nitrogen retention attributable to the two diets

$$= (B_X - B_0) - (B_Y - B_0)$$

$$= B_X - B_Y$$

where B_X and B_Y are the final body nitrogen contents of rats fed on diets X and Y. NPU is defined as the difference in nitrogen retention divided by the difference in nitrogen intake on the two diets:

$$\text{NPU} = (B_X - B_Y)/(I_X - I_Y)$$

where I_X and I_Y are the intakes of protein on diets X and Y.
The levels of protein usually chosen for X and Y are 0 and 10 per cent respectively.

The two main components of protein quality, digestibility and essential amino acid composition, can be measured separately. **Digestibility** is defined as the amount absorbed expressed as a proportion of intake, a definition which applies to any nutrient. The amount absorbed can be calculated by subtracting the amount excreted in the faeces from the amount consumed, i.e.:

$$\text{N digestibility} = \text{N absorbed/N intake}$$

$$= (I - F)/I$$

where I is nitrogen intake and F is faecal nitrogen. This is actually the definition of apparent digestibility, and needs be corrected for endogenous losses – intestinal secretions, bacterial cells and intestinal mucosal cells which are sloughed off by the passage of digesta:

$$\text{True N digestibility} = \frac{(I - I_k) - (F - F_k)}{(I - I_k)}$$

where I_k and F_k are the intake and faecal excretion of nitrogen on a protein-free diet. This formula simplifies to:

$$\text{True N digestibility} = \frac{I - (F - F_k)}{I}$$

True digestibility is apparent digestibility corrected for endogenous losses

so long as I_k is zero.

If NPU is now divided by digestibility we get a quantity which is known as the **biological value** (BV). This is defined as the increase in nitrogen retention per unit increase in nitrogen absorbed. It is generally assumed to be mainly a reflection of how well the pattern of amino acids absorbed from the gut matches the requirement for tissue deposition.

■ BOX 3.2 MEASUREMENT OF NET PROTEIN UTILIZATION USING HUMAN VOLUNTEERS

It is possible to calculate nitrogen retention from measurements of intake and excretion during a balance period of five days on a diet containing the test protein as sole nitrogen source. The major routes of nitrogen excretion are urine and faeces, so that

$$\text{nitrogen retention} = I - U - F$$

where I is nitrogen intake and U and F are urinary and faecal nitrogen excretion respectively. NPU is defined as the difference in nitrogen retention divided by the difference in nitrogen intake:

$$NPU = (I_X - U_X - F_X) - (I_Y - U_Y - F_Y)/(I_X - I_Y)$$

where the subscripts refer to intake and excretion on two diets X and Y.

■ 3.6.2 CHEMICAL METHODS FOR ASSESSING PROTEIN QUALITY

In order to avoid the need for numerous biological assays a number of *in vitro* procedures have been developed for predicting aspects of protein quality. Digestibility is usually measured by incubating the test protein with a mixture of proteolytic enzymes, including porcine trypsin, chymotrypsin and intestinal peptidase, and sometimes bacterial proteases. Digestibility can then be determined from the rate at which the pH falls, and this is usually quantified by measuring the rate at which standard alkali has to be added to keep the pH constant.

The adequacy of the amino acid composition of a protein can be assessed by comparing it with an estimate of essential amino acid requirements. The requirements are based on experiments to determine the amounts of essential amino acids needed by pre-school children to achieve optimal nitrogen retention. The resulting pattern of essential amino acid requirements is known as the reference protein, and the result of comparing the amino acid composition of a dietary protein with the reference protein is known as the **amino acid score**.

$$\text{Amino acid score} = \frac{\text{mg amino acid per g test protein} \times 100}{\text{mg amino acid per g reference protein}}$$

Applying this formula to each essential amino acid in turn will produce a series of eight figures. The lowest figure represents the amino acid score of the protein as whole, and generally predicts the biological value quite well.

The amino acid with the lowest score is called the **(first) limiting amino acid**, because it limits the value of the protein. The limiting amino acid is defined as the essential amino acid which is present in the smallest quantity in relation to its requirement, though it is not necessarily the essential amino acid that is present in the lowest absolute amount. Once the limiting amino acid has all been utilized within the body, the remaining amino acid mixture is incomplete, so no more tissue protein can be synthesized.

The limiting amino acid is the essential amino acid that is present in the smallest quantity in relation to its requirement

In practice there are only two or three amino acids that are ever limiting in normal foodstuffs. For cereals it is usually lysine, while for legumes and for most other important protein sources it is methionine. Tryptophan is usually the next limiting amino acid, or occasionally threonine.

In reality, of course, people do not usually consume only a single source of protein. When a whole diet is analysed the amino acid score is rather greater than that of its individual constituents. This is because of the phenomenon of mutual supplementation, whereby a relative shortage of one amino acid in one food is made good by a relative excess of that amino acid in another food. For example, rice is limited by its lysine content while beans are limited by their methionine content. But if they are mixed together, for example in a diet based on rice plus a relish made from beans, there is enough lysine in the beans to make up for what is missing in the rice, and enough methionine in the rice to make up for what is missing in the beans.

For virtually all diets around the world, the amino acid composition is not a limiting factor for adults or older children, but for younger children it can be a significant consideration in some cases, because of their relatively higher requirements for essential amino acids for growth. On the other hand, protein digestibility is a significant factor for many diets around the world. Many vegetable protein sources, particularly legumes and wholegrain cereals, which are the major sources of protein on a worldwide basis, have quite low protein digestibilities. They are very low if they are uncooked, because of antinutrients, but even when they are cooked they may be only 70–80 per cent digestible.

In normal mixed diets protein quality is mainly determined by digestibility

■ 3.7 PROTEIN REQUIREMENTS AND RECOMMENDED INTAKES

The protein intake of an adult is judged to be adequate if the person is able to maintain nitrogen balance, i.e. if the excretion of nitrogenous compounds from the body is equal to the intake of nitrogen, so that the body is neither gaining nor losing nitrogen. For a child the diet must also allow growth at an optimal rate.

Protein requirements are based on the maintenance of nitrogen balance or optimal growth rates

It should be noted that the measurement of nitrogen balance is not simple, and there is a tendency for intake to be overestimated and for excretion to be underestimated, generally because of incomplete collection from the subject. There are many different routes by which nitrogen is lost from the body; as well as urine and faeces nitrogen is lost in sweat, skin, hair, nails, saliva, menstrual blood and semen, and some of these are

quite hard to collect reliably. Moreover, even on a constant diet excretion fluctuates by at least one or two grams of nitrogen per day, so that balance may change between positive and negative from day to day. Thus a period of at least four days is needed to make a reliable estimate of nitrogen balance. Nevertheless, no better way of judging the adequacy of protein intakes has yet been established.

One way of trying to predict protein requirements is to measure the loss of nitrogen in subjects fed on a protein-free diet. This endogenous loss amounts to approximately 57 mg N per kg body weight per day for normal adults, equivalent to 0.36 g protein per kg per day. However when people are fed this amount of high quality protein they go into sustained negative nitrogen balance. This is because urinary and faecal nitrogen excretion increase as dietary protein intake increases, so they are higher on an intake of 0.36 g protein/kg/d than on a protein-free diet. In fact it requires an intake of approximately 0.63 g of good quality protein per kg per day on average to maintain nitrogen balance in adults. Thus after making allowances for individual variation in protein requirements, the recommended intake, which should be enough to cover the requirements of virtually all individuals, is usually taken as 0.75 g of good quality protein per kg per day for adults. This figure has to be adjusted upwards if protein quality is low.

For children, similar considerations apply when predicting maintenance requirements. The increment for growth can be calculated from the average rate at which protein is deposited in the body, but again this leads to a figure which is too low to sustain adequate growth rates when tested experimentally. This may be because growth does not normally occur linearly: there are periods of rapid growth interspersed with periods of little or no growth. Thus tables of recommended protein intakes for children at various ages are based on a few experimental observations with interpolation between these points. For infants under 6 months the recommendations are based on the nitrogen content of breast milk.

From a practical point of view, normal diets supply considerably more protein than is implied by the recommended intakes. For example, the estimated average requirement for energy in a moderately active 74 kg adult male is 10.6 MJ/d, and the recommended intake of protein for this person would be 56 g/d, representing 8.7 per cent of the energy intake. But people in the UK actually consume around 15 per cent of their dietary energy as protein. This proportion has increased from about 12 per cent of the energy in the 1970s, mainly because of a decline in the intake of starchy and cereal-based foods such as bread rather than an increase in the absolute protein intake. The trend has been for a decline in the consumption of fatty meats (beef and lamb) and an increase in lean meat such as poultry. Protein intakes are lower in UK vegetarians and vegans (on average 12 per cent of energy intake) but still adequate to maintain a nitrogen balance. Alcoholics are at risk of having an inadequate intake of protein because they derive such a high proportion of their dietary energy from alcohol which dilutes the contribution made by other nutrients. In fact very few diets around the world supply less than 10 per cent of energy as protein, so protein deficiency is not likely to occur if energy intakes are adequate. The diets of children suffering from protein energy malnutrition are usually found to be lacking in energy and many other nutrients rather than being specifically deficient in protein. There is currently no agreement regarding the upper limits to protein intakes.

SUMMARY

- Proteins are macromolecules that are synthesized from 20 different amino acids.
- The protein content in food is measured by analysing its nitrogen content.
- Dietary protein comes from both plant and animal sources.
- Proteins enter the body as a mixture of amino acids which are then used to synthesize tissue proteins or are oxidized to carbon dioxide, water and urea with the production of energy.
- There are eight essential amino acids that must be supplied in the diet.
- Protein quality is a measure of the efficiency with which dietary protein is utilized.
- Protein is required in amounts that will maintain nitrogen balance in adults and support optimal growth in children.

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4 CARBOHYDRATE

4.1 INTRODUCTION

Carbohydrates consist of sugars, starch and non-starch polysaccharides (dietary fibre)

Carbohydrates are a diverse group of substances which fall into three main groups: sugars, starch and non-starch polysaccharides (dietary fibre). Apart from lactose they are derived almost exclusively from food of plant origin. Plants use the energy from sunlight to synthesize sugars via the process of photosynthesis. The sugars may then be converted to starch for storage or non-starch polysaccharides which form the major structural components of the plant.

Carbohydrate is a major source of energy in most human diets. When there is insufficient carbohydrate in the diet to meet the body's obligatory requirement for glucose (see p 54) it can be synthesized by the process of gluconeogenesis from amino acids (particularly alanine and glutamine), lactic acid or glycerol, though not from fatty acids or alcohol.

Glucose cannot be synthesized from fatty acids in humans

Apart from being absorbed and metabolized within the body, carbohydrates can be fermented by bacteria in the mouth and in the large intestine, and these are areas of considerable nutritional significance. Fermentation of soluble carbohydrates in the mouth produces lactic acid which dissolves the enamel of the teeth, leading to dental caries. In the large intestine, fermentation of carbohydrates which have escaped digestion and absorption in the small intestine results in faecal bulking and the formation of short chain volatile fatty acids and gases such as hydrogen, carbon dioxide and methane. It has been argued that some of the effects of colonic bacteria may influence the risk of diseases of the large bowel, particularly cancer (see Chapter 9). It should be noted that most herbivorous species derive the majority of their energy from bacterial fermentation of non-starch polysaccharides. In some species such as the horse and rabbit, this fermentation is also in the hind-gut, but in many others, including cows and sheep, there is a separate organ called the rumen in which fermentation occurs before the digesta passes into the stomach (abomasum) and the intestines.

4.2 CLASSIFICATION

Carbohydrates have a general molecular formula $(CH_2O)_n$, although many carbohydrates do not quite fit this formula. The following is a strict chemical definition:

> The polyhydroxyaldehydes, -ketones, -alcohols, acids, their simple derivatives and their polymers having polymeric linkages of the acetal type.

In reality the best way to understand what carbohydrates are is to consider a classification based on their nutritional significance. This is summarized in Table 4.1.

Table 4.1 Classification of dietary carbohydrates

	Component	*Examples*
Sugars	Monosaccharides	Glucose
		Fructose
	Disaccharides	Sucrose
		Lactose
		Maltose
	Sugar alcohols	Sorbitol
		Lactitol
		Xylitol
		Isomalt
		Maltitol
	Oligosaccharides	Raffinose
		Stachyose
		Fructo-oligosaccharides
		Maltodextrins
Polysaccharides	Starch	Amylose
(complex carbohydrates)		Amylopectin
	Glycogen	
	Non-starch polysaccharides	Cellulose
	(dietary fibre)	Hemicellulose
		Pectin
		Gums
		Lignin

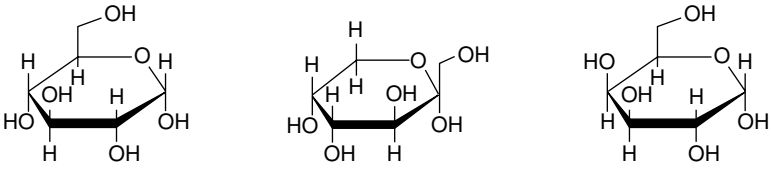
A distinction is sometimes made between simple and complex carbohydrates. This is not very helpful because complex carbohydrates include both starch and non-starch polysaccharides, which have very different physiological and nutritional properties.

4.2.1 MONOSACCHARIDES

These are sugars containing 3–7 carbon atoms. Many phosphorylated derivatives are found within the cell as metabolic intermediates. They can be synthesized from most amino acids though not from fatty acids.

The pentoses (ribose and deoxyribose) are very important as components of nucleic acids, but the amounts supplied in the diet are very small. The only free monosaccharides found in significant quantities in food are the hexose sugars, glucose and fructose (see Figure 4.1).

• **Figure 4.1** Structures of monosaccharides



4.2.1.1 Glucose

Glucose is of central importance because (i) it is the free sugar that is transported in the blood as a fuel for cells and tissues; (ii) it is the basic unit from which glycogen, the storage polysaccharide in animals, is built; and (iii) it is also the basic unit from which starch, the storage polysaccharide in plants is built, and is thus the ultimate product of starch digestion, so it is the form in which most of our dietary carbohydrate enters the circulation. It is also a sub-unit of the structure of the two most common dietary sugars, lactose and sucrose, again adding to the amount of carbohydrate that arrives in the body in this form.

On the other hand, little free glucose is found naturally in foods – some is present in fruits such as grapes and in honey. Athletes often take glucose tablets as a rapid source of energy, although it is certainly absorbed no faster than disaccharides, and only a little faster than starch. Most sports drinks now contain low molecular weight glucose polymers because they release glucose rapidly but have a lower osmolarity than glucose and so promote rehydration.

Glucose is also known as dextrose, particularly in hospitals where it is used in intravenous fluids to maintain blood glucose, for example in shock, and as the main energy source in total parenteral nutrition. In the food industry glucose usually refers to glucose syrups, which are made from partially hydrolysed starch. Pure glucose is again known as dextrose and may be used as a food ingredient or additive since it has useful textural properties and is only about 75 per cent as sweet as sucrose.

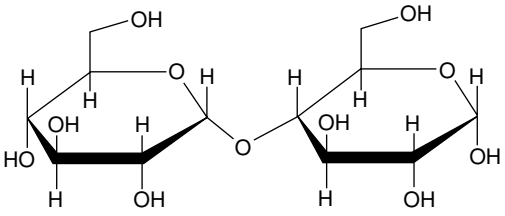
4.2.1.2 Fructose

Fructose is the commonest free monosaccharide in the diet, coming mainly from fruit, although much of the sugar in many fruits is actually sucrose. Fructose is also known as laevulose.

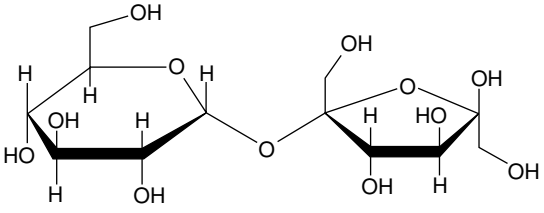
Fructose is absorbed relatively slowly from the gut and is metabolized in the liver to glucose derivatives, entering the main glycolytic/gluconeogenic pathway as dihydroxyacetone. It is almost twice as sweet as sucrose, so that less needs to be used to achieve the same sweetening effect. Because of this, as well as its slow absorption and non-insulin dependent metabolism, fructose is used to sweeten specialist diabetic products. However, an excessive intake can lead to diarrhoea caused by the high osmotic pressure it exerts.

In the food industry fructose is usually used in combination with glucose, for example as invert sugar, which is obtained by hydrolysing sucrose to give a 50/50 mixture of glucose and fructose. This mixture does not crystallize, it absorbs water, and is sweeter

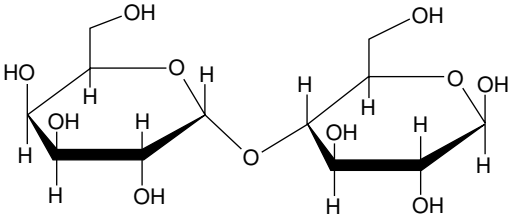
• **Figure 4.2** Common dietary disaccharides



Maltose (glucosyl-glucose)



Sucrose (glucosyl-fructose)



Lactose (galactosyl-glucose)

than sucrose. Alternatively fructose rich syrups can be produced by hydrolysing corn starch to glucose, then inverting about half the glucose to fructose.

■ 4.2.2 DISACCHARIDES

4.2.2.1 Sucrose

This disaccharide consisting of one glucose and one fructose residue is by far the most common sugar in our diet. Average intake in the UK is around 80 g/day, amounting to around 30 kg in a year. This has declined, however, from a peak of around 50 kg per year in the early 1970s. Less than half is bought as table sugar, with increasing amounts coming from manufactured products and soft drinks.

Sugar has been a major food in the UK only since the latter part of the nineteenth century. It used to be all imported from sugar cane, whereas now most is grown here as beet, making it much cheaper. Sugar consumption tends to rise as countries become more affluent, though it appears never to reach more than 20 per cent of energy intake. Current intakes are around 14 per cent of energy, and it is recommended that this should fall to less than 10 per cent, mainly because of its effects on the teeth.

Table sugar is one of the purest chemicals readily available, being 99.95 per cent sucrose, though even the most unrefined brown sugars contain over 98 per cent sucrose. In this

form it is clearly 'empty calories', though it is almost always taken as part of a composite dish which does provide other nutrients.

The main health problem caused by sucrose is dental caries. It is estimated that dental caries becomes prevalent in societies when the intake of sugar exceeds 10 kg per head/year. However, the impact of sugar intake on dental caries is dependent on the presence of dental plaque and the effects are mitigated by exposure to fluoride (see Chapter 9). Moreover, the frequency of intake is probably more important with regard to risk of caries than total intake, though the two are strongly associated.

There is also concern that high sugar diets are more likely to promote overconsumption of energy and hence obesity, though there is little direct evidence to support this. The consumption of sugar-containing carbonated beverages has been associated with the risk of excess weight in childhood when compared with consumption of low-calorie drinks.

Over the years there have also been concerns about the adverse metabolic effects of high sugar consumption, based mainly on animal research, which has shown high concentrations of insulin in the blood, or damage to the liver or kidneys. But the relevance of these findings is questionable as the studies were of diets very high in sugar. There is no evidence that sugar causes diabetes. Furthermore, current dietary advice for diabetics is that it can be consumed in moderation.

The two most common sugars in the diet are the disccharides sucrose and lactose

4.2.2.2 Lactose

The only other common sugar in our diet is lactose, a disaccharide composed of one glucose and one galactose residue. Average consumption in the UK is estimated to be approximately 15 g/d.

Lactose occurs naturally only in milk, at a concentration of 5 per cent in cow's milk and 7 per cent in human milk. It is present in products made with whole or skimmed milk, but many traditional dairy products exclude the water-soluble fraction. Thus cream contains about half as much lactose as milk, and butter contains virtually none. When cheese is made, some lactose is fermented to lactic acid, and what is left is discarded in the whey fraction. The exception is cottage cheese, which contains a little lactose; there is also some in cheese spreads. Yoghurt also involves fermentation, but only about 25 per cent of the lactose is fermented, and since extra lactose is often added to start the fermentation it may end up with a higher content than whole milk.

Lactose is less sweet than sucrose, and hence is a useful food ingredient, either by itself or with protein in the form of dried skimmed milk. In the newborn, lactose plays an important role in promoting the growth of *Lactobacillus bifidus* in the gut.

4.2.2.3 Maltose

Maltose is a minor component of the diet. It consists of two glucose residues, and occurs mainly as an intermediate of starch digestion. It is found in malted cereal products, having been formed by the partial hydrolysis of starch as the seed grains are allowed to sprout.

■ 4.2.3 OLIGOSACCHARIDES

Sugars containing 3–20 monosaccharide units are known as oligosaccharides. Glucose polymers and maltodextrins are widely used in processed foods. There are a number of non-digestible oligosaccharides (NDO). The most notorious are the trisaccharide raffinose

and the tetrasaccharide stachyose, which are found in quite large quantities in legumes (peas and beans), especially soya beans. They are not digested by the enzymes in the mouth or in the small intestine, but can be rapidly fermented by bacteria in the colon, producing the gases carbon dioxide, hydrogen and methane as well as volatile fatty acids. This causes discomfort as well as flatulence, and tends to limit the consumption of legumes by infants and young children who could otherwise benefit from such supplementary protein sources. The content of oligosaccharides can be significantly reduced by soaking and cooking. Inulin is a fructo-oligosaccharide found in Jerusalem artichokes and onions and is responsible for the flatulence which is an effect of eating these foods. Human milk contains NDO in the form of galactooligosaccharides. These are believed to be the *Bifid* factor that promotes the growth of *L. bifidus* in the infant.

■ 4.2.4 POLYSACCHARIDES

4.2.4.1 Starch

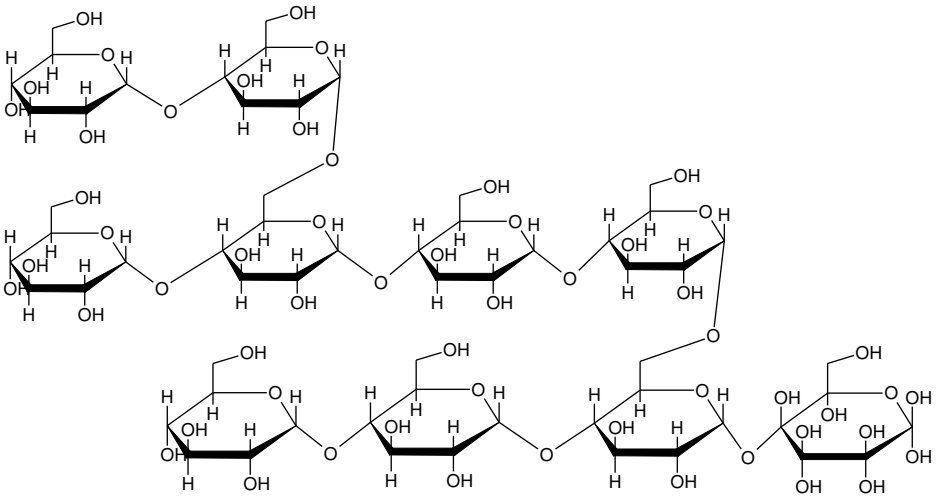
Starch makes up more than half the carbohydrate in the diets of even the most affluent countries, and much more in those of poorer countries. Average intakes in the UK are around 130 g/day. The major sources of starch are the traditional staple foods such as cereals, roots and tubers, where it has been deposited in the plant's storage organs.

Starch is a polymer of glucose and is found in plants

Starch is a mixture of two types of molecule, usually 20–30 per cent amylose and 70–80 per cent amylopectin. Both are made entirely of glucose sub-units. In amylose these are linked by $1–4_{\alpha}$ bonds in one long straight chain which tends to adopt a helical structure. Amylopectin includes both $1–4_{\alpha}$ and $1–6_{\beta}$ links, giving a branched structure (see Figure 4.3). This structure offers more free ends from which amylase enzymes can work, so amylopectin is more rapidly digested.

Raw starch is enclosed in granules which are insoluble and not easily digested. Hence starchy foods need to be cooked before eating. The application of heat and moisture causes the process of gelatinization, by which the granules swell and burst, making the starch

• **Figure 4.3** Structure of amylopectin



soluble and readily digestible. If cooked starch is then allowed to cool, some of the amylose will adopt a crystalline structure, with neighbouring molecules aligned in the same plane forming hydrogen bonds. This so-called retrograded amylose is then somewhat less readily digested by amylase enzymes.

4.2.4.2 Glycogen

Glycogen is a polymer of glucose and is found in animals

Carbohydrate is stored in animals as glycogen, a molecule with a similar structure to amylopectin. There is very little glycogen in the human diet since it is rapidly lost by glycolysis after death, but oysters eaten live do contain 6 per cent glycogen.

The adult human body can store about 90 g glycogen in the liver plus 350 g in muscle. Thus the total carbohydrate store is equivalent to approximately 1,700 kcal (7 MJ), which is barely one day's energy expenditure. Glycogen is stored with twice its own weight of water, so it would be very heavy to carry much greater carbohydrate stores. Liver glycogen is used to keep blood glucose levels constant (in order to keep the brain functioning) during a short-term fast, for example between meals, and is replenished after the next meal. Muscle glycogen can't release glucose into the bloodstream, so is only used locally to fuel exercise. It becomes depleted after heavy or prolonged exercise, and so has to be repleted afterwards from dietary carbohydrate.

Athletes have learned that if muscles are depleted of glycogen, by exercising to exhaustion, and a low carbohydrate diet is consumed for the next 1–3 days, and after this a high carbohydrate diet is then eaten the muscles will deposit more glycogen than normal. This temporary supercompensation phenomenon is known as glycogen loading, and can enhance the athlete's performance during an event such as a marathon run immediately afterwards.

■ 4.2.5 DIETARY FIBRE (NON-STARCH POLYSACCHARIDES)

These terms are used more or less interchangeably to cover several different classes of substances which share the common feature of being indigestible by the enzymes of the human gut. They are all derived from plants, where they have mainly structural and protective functions. Indeed, the original definition of dietary fibre referred specifically to plant cell walls. The term 'unavailable carbohydrate' is also sometimes used, though the older term 'roughage' is now considered unscientific.

The confusion generated by the different terminology is exacerbated by the existence of several different analytical techniques for their measurement, all of which produce different values. In food tables in the UK values for dietary fibre are obtained using the Southgate method (Southgate, 1969), while those for non-starch polysaccharides are obtained using the Englyst method (Englyst *et al.*, 1982). Values for dietary fibre are generally about 50 per cent higher than values for non-starch polysaccharide content of the same food. The AOAC method is now being introduced for food tables; this gives slightly higher values than the Englyst method because it includes non-digestible oligosaccharides (AOAC, 2000).

Unavailable carbohydrate includes celluloses, hemicelluloses, pectic substances and lignin

4.2.5.1 Celluloses

These are high molecular weight polymers of glucose joined by $1–4_{\beta}$ links and arranged in long straight chains, with much hydrogen bonding between adjacent molecules. This

makes them physically strong and very insoluble: they need to be dispersed in concentrated sulphuric acid which is then diluted to achieve hydrolysis. Cellulose is characteristically present in all plant cell walls, though it is not necessarily the major component. Celluloses are not digested by amylase, but bacterial cellulases will degrade them. Thus they are extensively fermented in the rumen, though not to any great extent in the human colon.

4.2.5.2 Hemicelluloses

This is a heterogeneous group of non-cellulosic polysaccharides that are insoluble in water but soluble in alkaline solutions of various strengths. It includes polymers of a number of sugars other than glucose, often including uronic acids. They undergo limited fermentation in the colon.

4.2.5.3 Pectic substances

These are characteristically found in fruits, but also in most legumes and in some cereals (e.g. oats). They are soluble in hot water, and are known to food scientists and home economists as thickening and gelling agents. Some are extracted to be used as food additives for these purposes, and may be given specific names including gums, such as guar and tragacanth, and mucilages, such as ispaghula. Alginates are similar substances extracted from algae. All are extensively fermented in the colon.

4.2.5.4 Lignins

Lignins are classically included as fibre, although chemically they are not carbohydrates but polymers of aromatic alcohols. They are the secondary thickening of plant stems, which is deposited as plants get older. Lignin may become covalently bonded to other polysaccharides, making analysis more difficult and impeding bacterial fermentation. They are chemically and nutritionally very inert.

■ 4.2.6 SUGAR ALCOHOLS

These are found in nature, but are also synthesized commercially for use as sweeteners e.g. isomalt, xylitol and sorbitol; they are also referred to as polyols. They are generally poor substrates for bacterial fermentation in the mouth and thus do not cause acid formation and dental caries. Isomalt and xylitol are used in tooth-friendly sweets and chewing gum. Most polyols are not absorbed in the small intestine and thus enter the colon where they are fermented to varying extents to yield short chain fatty acids and gas. There is a limit to the amounts that can be consumed because they increase osmotic pressure and can cause diarrhoea if consumed in excess.

■ 4.3 CARBOHYDRATE INTAKE

The average intake of carbohydrate in the UK is 250 g/d, representing 42 per cent of energy intake. This consists of 100 g sugars, 130 g starch and 20 g fibre. Bread accounts for one quarter of the available carbohydrate, and other cereal products for another quarter, while potatoes account for another 10 per cent. Half the fibre also comes from cereal products, and most of the rest comes from vegetables, particularly legumes, with less than 10 per cent coming from fruit.

Carbohydrate forms an even greater proportion of the diet in poorer countries, since as people become more affluent they tend to replace carbohydrate with fat. Thus carbohydrate accounts for nearly 80 per cent of energy in African diets as a whole, and at least 65 per cent in Caribbean diets, but less than 50 per cent in European and North American diets. Starch is always the major carbohydrate, and much of it is from 'staple foods' (the most abundant item in the average diet of a community). On average 85 per cent of carbohydrate comes from staple foods in developing countries, compared with 62 per cent in developed countries.

Starch is the most abundant carbohydrate in all human diets

■ 4.4 DIGESTION AND ABSORPTION

Starch digestion begins in the mouth with the action of the salivary amylase, ptyalin. It then ceases in the stomach because of the low pH. Most digestion then occurs in the duodenum, where the pH rises again and pancreatic amylase is secreted. This enzyme breaks alternate $1–4_{\alpha}$ bonds, producing maltose, maltotriose and limit dextrins, which are small oligosaccharide remnants from the branching points in amylopectin molecules.

The products of luminal digestion are hydrolysed further at the brush border of the intestinal mucosa, where glucosidases can hydrolyse the dextrins and maltase hydrolyses the maltose to glucose. Glucose is then absorbed both by diffusion and by an active transport mechanism which requires sodium and ATP. From the mucosal cells glucose can diffuse down a concentration gradient into portal blood.

There are similar disaccharidase enzymes, sucrase and lactase, in the mucosal membrane to hydrolyse sucrose and lactose to their constituent monosaccharides, and these are absorbed by the same mechanisms as glucose.

Absorption of sugars is normally very efficient, except in the case of acquired lactose intolerance. In many people, particularly those of African, Asian or Middle Eastern ethnic origin, lactase activity is lost after the ages of early childhood. This is not surprising, since until recently (in evolutionary terms) it was rare for anyone other than infants and young children to drink milk. The consequences of lactose intolerance are that ingested lactose stays in the lumen of the gut, drawing water in. Some is fermented to lactic acid, drawing more water in which causes diarrhoea, and gases (hydrogen and methane) which are responsible for flatulence, distension and pain. Thus individuals who are lactose intolerant learn to avoid consuming more than a small amount of milk, even though this deprives their diet of a valuable source of calcium and protein.

■ 4.4.1 RESISTANT STARCH

Cooked starch has classically been considered to be rapidly and completely digestible, but recent work has focused attention on differences in the rate and extent of digestion of starch in different foodstuffs. Digestibility can be measured by incubating the food *in vitro* with pancreatic amylase, and this has revealed that most cooked starch is completely hydrolysed within 20 minutes, and is thus classified as readily digestible starch. Even milled raw cereals (flour), together with a proportion of the starch in pasta, are completely digested within two hours, and this fraction has been called slowly digestible starch.

Any starch that is undigested after two hours is called resistant starch. This includes raw cereal grains and other seeds that have been only partly milled, in which significant

amounts of starch are still enclosed in indigestible, fibrous seed coats which prevent the access of digestive enzymes. It also includes raw potato and banana starch which is enclosed in indigestible granules. The third category of resistant starch is the retrograded amylose which forms when cooked potato or cereal starch is allowed to cool and recrystallize. It should be noted, however, that the resistant starch content of the starch in most foods is considerably less than 5 per cent, so that starch can still be considered to be at least 95 per cent digestible.

The digestibility of starch in human diets is around 95 per cent

■ 4.4.2 FERMENTATION OF FIBRE IN THE COLON

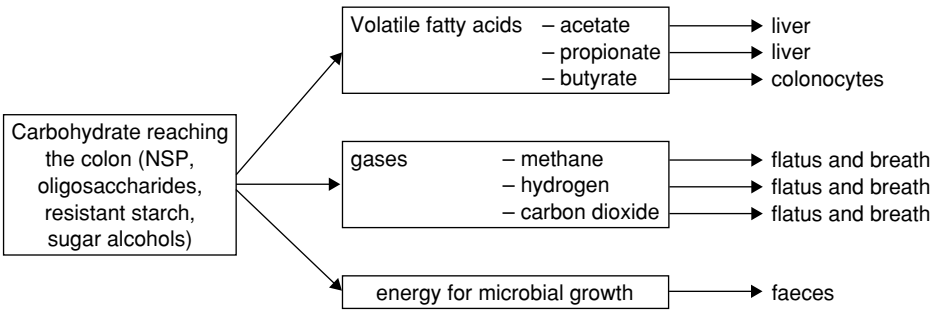
The non-starch polysaccharides, together with any resistant starch and undigested oligosaccharides, pass through the small intestine and into the colon. Here there is a massive population of bacteria which are able to ferment many types of carbohydrate. Soluble carbohydrates such as pectin can be completely fermented, whereas insoluble polysaccharides such as cellulose undergo very limited degradation, especially if they are also associated with lignin.

The main products of fermentation are the short chain fatty acids acetate, propionate and butyrate, together with the gases carbon dioxide, hydrogen and methane. The proportions of the different products formed depends on the nature of the substrates entering the colon and the proportions of the different bacteria present. For example, the fermentation of starch produces a high proportion of butyrate while pectin produces very little butyrate.

Fermentation of undigested carbohydrate in the colon produces acetate, propionate, butyrate, CO_2, H_2 and CH_4

The short chain fatty acids are absorbed from the colon. Propionate is metabolized to release energy, or for gluconeogenesis, in the liver, while acetate is used as a fuel both by the liver and peripheral tissues. Butyrate is the preferred fuel substrate for colonocytes, where it is metabolized to acetoacetate and β-hydroxybutyrate. Thus a considerable proportion of the energy from unavailable carbohydrates may actually be available to the body, and data from studies feeding mixed sources of fibre have suggested that a metabolizable energy value of 8 kJ/g (2 kcal/g) may be appropriate.

• **Figure 4.4** Fermentation of unavailable carbohydrates in the colon



The gases which are produced during colonic fermentation may also be absorbed across the wall of the colon and ultimately expired in the breath. Indeed measurement of increased levels of hydrogen in the breath can be used to indicate the arrival of unavailable

carbohydrate in the colon. However when the capacity of the colon to absorb gases is exceeded the excess is passed as flatus.

4.5 METABOLISM OF A GLUCOSE LOAD

Glucose is used in the body for energy, or stored as glycogen or converted to fat

Most carbohydrate enters the bloodstream as glucose for transport to the tissues, where it has three possible metabolic fates: it can be used for energy, stored as glycogen in the liver and muscles, or converted to fat.

4.5.1 FUEL

Glucose can be metabolized as a source of energy via glycolysis and, so long as the supply of oxygen is adequate, the tricarboxylic acid cycle. If there is insufficient oxygen, entry to the tricarboxylic acid cycle is blocked and the end-product of glycolysis, pyruvate, is converted to lactate.

Most tissues will utilize glucose as an energy source after a meal, then switch progressively to fatty acids. The main exception is the liver, which oxidizes very little glucose. Its main fuels are short chain fatty acids and amino acids. In contrast, some tissues have an obligatory need for glucose. In the case of the brain, which is the biggest user of circulating glucose, this is because the fatty acids can't get across the blood-brain barrier. Tissues such as the lens of the eye and the red blood cells are unable to oxidize fatty acids because they have no mitochondria. In other cases, such as the kidney medulla and the skin, fatty acids cannot be oxidized because of poor oxygen delivery.

4.5.2 STORAGE AS GLYCOGEN

Glycogen is stored in muscle, to replace what has been used for exercise, and in the liver, for subsequent use to maintain blood glucose. It should be noted that most glycogen synthesized in the liver after a meal is made from lactate, via a so-called indirect pathway which involves the enzymes of gluconeogenesis. This is because the affinity of glucokinase for glucose is very low, so that the liver does not take up significant amounts of glucose from the circulation unless the glucose concentration exceeds 15 mM. This allows tissues such as the brain to have priority in taking up glucose.

4.5.3 CONVERSION TO FAT

Glucose can be converted to fatty acids and glycerol phosphate in both liver and adipose tissue, and these components are made into triacylglycerols. Triacylglycerols which are synthesized in the liver are secreted as very low density lipoproteins and transported to adipose tissue for storage. Recent evidence suggests that very little fatty acid is synthesized *de novo* in humans, and that most of the fat that is stored comes from dietary fat, but this may simply reflect the relatively high fat content of the mixed diets which most people consume.

4.5.4 CONTROL OF BLOOD GLUCOSE

Clearance of glucose is under the control of the hormone insulin, which is secreted in response to glucose absorption. Insulin facilitates both glucose transport and its utilization in muscle and adipose tissue, and suppresses gluconeogenesis in the liver.

Postabsorbtively, insulin levels fall, preventing glucose uptake into muscle and adipose tissue, thereby ensuring that it is available for uptake by the brain.

4.6 EFFECTS OF UNAVAILABLE CARBOHYDRATE INTAKE ON HEALTH

Many epidemiological studies have shown an inverse relationship between habitual fibre intakes and the incidence of certain diseases, notably coronary heart disease, colon cancer, diverticular disease, appendicitis, gallstones, varicose veins, hiatus hernia, haemorrhoids, obesity and diabetes. In many cases increased fibre intake is also beneficial in their treatment. These are all multifactorial diseases: fibre content is only one aspect of the diet that may be involved in their aetiology, and other environmental and genetic factors are also involved. Some of the mechanisms by which dietary fibre may influence the development of these diseases are set out below.

4.6.1 FOOD INTAKE

Food intake tends to be reduced on bulky, high fibre diets. One possible mechanism is that such diets require more chewing, causing more saliva and more gastric juice to be secreted, which in turn causes greater stomach distension and slower gastric emptying, and thus an earlier or greater feeling of satiety. It may also be that high fibre diets are less tasty than diets with a higher concentration of fat and sugar, and thus less likely to induce overeating, or that too much fibre causes bloating and flatulence, and the discomfort puts people off eating too much.

Fibre tends to delay gastric emptying and slow down glucose absorption

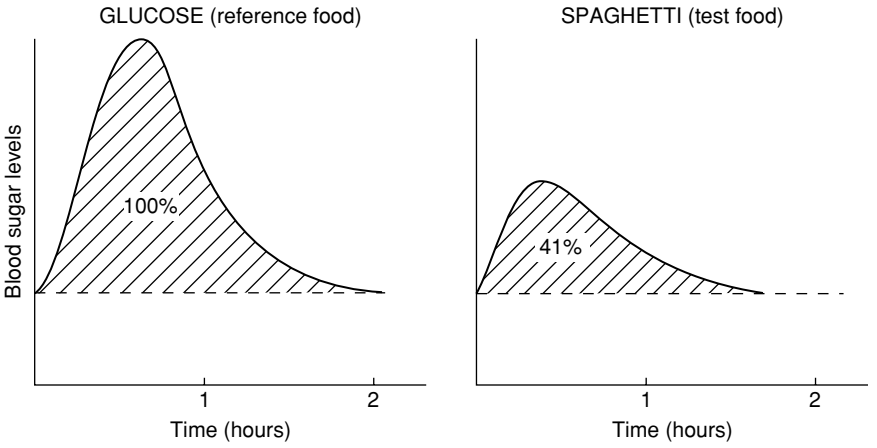
4.6.2 GLUCOSE ABSORPTION

The presence of fibre reduces the rate of gastric emptying, so food enters the small intestine more slowly and thus glucose is absorbed more slowly. Also, once the digesta reaches the small intestine the higher viscosity caused by soluble fibres, especially gums, slows the diffusion of nutrients to the gut wall, so again glucose is absorbed more slowly. The presence of intact remnants of plant cell walls may also inhibit the access of digestive enzymes to starch, thereby slowing its digestion. The decreased rate of glucose absorption is useful for treating Type II diabetes. It has also been suggested that this may help prevent diabetes and heart disease, by reducing insulin secretion. Periodic high peaks of insulin secretion are thought to contribute to the aetiology of both diseases.

The term 'glycaemic index' is now used to describe the rate and extent of the rise in blood glucose following a meal (see Box 4.1). The glycaemic index of a food is defined as the ratio of the area under the blood glucose curve following ingestion of a portion of that food containing 50 g of available carbohydrate to the area under the blood glucose curve following the ingestion of a portion of white bread or glucose containing the same amount of available carbohydrate. As well as its soluble fibre content, the glycaemic index of a food is affected by its content of sugar (since on digestion sucrose produces only half as much glucose as the same amount of starch), the degree of gelatinization of starch, and the presence of any structural components that may hinder the access of digestive enzymes. It is also affected by the other components, including protein and fat, within the food or meal.

BOX 4.1 CALCULATION OF GLYCAEMIC INDEX

Glycaemic index is determined by feeding healthy volunteers a portion of the food being tested containing 50 g of glucose and measuring blood glucose concentration at 15 minute intervals for the next two hours. A blood glucose curve such as the ones below is then drawn, and the area under the curve is calculated. On another occasion the same volunteers are fed a portion of spaghetti containing 50 g of available carbohydrate and the same measurements are made. Glycaemic index is calculated as the ratio of the area under the second blood glucose curve to that of the first. In the example shown the glycaemic index is 41 per cent.



■ 4.6.3 FAECAL BULK

The presence of undigested carbohydrate residues draws water into the lumen of the large intestine, considerably increasing faecal mass. This also increases the rate at which the faeces pass through the colon, i.e. it decreases the transit time. This helps to relieve constipation, which is important in itself for many people, and it also helps to prevent other diseases which may be caused by the high intra-abdominal pressure which results from straining to void small hard faeces. These diseases include hiatus hernia, haemorrhoids and varicose veins, which may result from inhibition of the venous return from the legs by high intra-abdominal pressure. The greater faecal mass also helps to dilute potential carcinogens and other toxins, and the more rapid transit through the colon reduces the length of time for which they are in contact with the intestinal wall, thereby reducing the risk of colon cancer. Some of the sources of dietary fibre (e.g. pectin and β-glucans) are able to bind to bile acids, preventing their reabsorption and promoting their excretion in faeces. To compensate for the increased loss of bile acids in faeces, further bile acids are synthesized from cholesterol in the liver, and the reduction in the hepatic cholesterol pool causes an upregulation of LDL receptors which results in a reduction in plasma cholesterol concentration (see Chapter 9 for further discussion on the regulation of plasma cholesterol concentrations).

Fibre increases faecal bulk and decreases transit time

4.6.4 BACTERIAL FERMENTATION

As described earlier there is a large mass of bacteria within the colon which utilizes undigested carbohydrate as its main energy source. These bacteria can detoxify some carcinogens. The butyric acid produced by bacterial fermentation tends to stimulate cell division in the gut mucosa, but apparently without stimulating neoplastic growth. Another product of bacterial fermentation is propionic acid, some of which is absorbed and can inhibit cholesterol synthesis in the liver. However, acetic acid which is also produced from some substrates stimulates cholesterol synthesis.

Finally it should be noted that some of these effects are not confined to dietary fibre but also apply to resistant starch and oligosaccharides. Consequently, dietary advice now focuses on promoting the health benefits of foods rich in complex carbohydrates rather than specifically advocating dietary fibre.

SUMMARY

- Dietary carbohydrates fall into three main groups: sugars, starch and non-starch polysaccharides (dietary fibre).
- The main sugar in the diet is sucrose which accounts for around 14 per cent of energy intake. Sucrose intake should be limited because of its deleterious effect on dental health.
- Starch is a polymer of glucose which accounts for over a quarter of our energy intake.
- Dietary fibre refers to a series of substances that are not digested in the human small intestine, including cellulose and hemicellulose, gums and pectins.
- Available carbohydrates enter the body as glucose which can be oxidized to produce energy, stored as glycogen or converted to fat.
- Unavailable carbohydrates remain in the intestine, and some can be fermented by colonic bacteria to produce volatile fatty acids and gases.
- A high intake of complex carbohydrates and dietary fibre has a number of health benefits.

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