

Functional food science and substrate metabolism

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Abbreviations: ALP, atherogenic lipoprotein phenotype; GI, glycaemic index; IDDM, insulin-dependent diabetes mellitus; IRS, insulin resistance syndrome; MCT, medium-chain triacylglycerol; NEFA, non-esterified fatty acids; NIDDM, non-insulin-dependent diabetes mellitus; P:S ratio, polyunsaturated : saturated fatty acid ratio; PUFA, polyunsaturated fatty acids; SCFA, short-chain fatty acids.

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Abstract

The present review addresses the role of food constituents in the aetiology of metabolic conditions and chronic diseases, mostly related to energy metabolism and substrate regulation, such as obesity and non-insulin-dependent diabetes mellitus. Second, attention is paid to malnutrition, a major cause of mortality and morbidity in developing countries, which may be a cause of concern in Europe because of the increasing number of elderly people in the population. Finally, the role of diet during exercise, a condition of enormous substrate demands, is evaluated. Based on a critical evaluation of the existing knowledge in the literature, implications for future research in relation to functional foods are discussed.

Functional foods: Substrate metabolism: Energy balance: Physical activity

1. Introduction

It is clear that with modern food and physical activity habits, the human metabolic regulatory mechanisms are challenged. There is a growing imbalance between food-related energy intake and physical activity-related energy expenditure. Also, the balance in macronutrient intake has changed dramatically over the past few decades. Therefore, a number of specific body functions, mostly related to energy metabolism and substrate regulation, are at risk.

A number of chronic diseases such as obesity, non-insulin-dependent diabetes mellitus (NIDDM) and osteoporosis can be identified as being directly related to changes in food intake and physical activity-related behaviour. At the same time, however, malnutrition thought of as a major cause of mortality and morbidity only in the developing countries, is a cause for concern in Europe, mainly because of the increasing number of elderly people in the population. There are also specific groups in whom undernutrition poses a particular problem, especially those with concurrent chronic or severe illness.

This chapter will briefly evaluate the metabolic changes, and the underlying specific metabolic conditions as well as the role of specific dietary components in the aetiology of the previously mentioned chronic diseases.

Of special interest is the relation between nutrition and physical performance. During physical stress such as exercise, the substrate demands are enormous. Nutrition plays a crucial role in this process. Therefore, a balanced diet with a carefully planned mix of food ingredients can play an important role in the level of performance. In this way well-designed and effective sports foods have been proven to be clear examples of functional foods.

2. Chronic diseases related to energy balance and substrate regulation

2.1. Obesity

Obesity is defined as an excessive accumulation of body fat. Its prevalence may vary in different populations between 5 and 50%, also depending on the definition of overweight (mild *v.* moderate *v.* severe obesity). A BMI (body weight

(kg)/height (m)²) between 25 and 30 kg/m² is defined as mild obesity (in USA: BMI > 27 kg/m²), a BMI in the range of >30–35 kg/m² is moderate obesity, and a BMI > 35 kg/m² is severe obesity (Björntorp & Brodoff, 1992). The high incidence of obesity in affluent societies is recognized as a major health problem (VanItallie, 1992). Obesity is associated with an increased risk of developing hypertension, insulin resistance, diabetes and cardiovascular disease. Apart from these major health hazards, obesity is thought to cause a great variety of health problems, some of which are listed in Table 1.

2.1.1. Genetic contribution to obesity. It has been recognized that there is an important genetic contribution to obesity. The fact that a sedentary lifestyle and high-fat

Table 1. Health disorders and other problems thought to be caused or exacerbated by obesity (Based on VanItallie, 1992 and Frayn, 1996)

Problems	Possible cause
Cardiovascular disease	Elevated LDL-cholesterol, decreased HDL-cholesterol, hypertriglycerolaemia, hypertension
Hypertension	May result indirectly from insulin resistance
Non-insulin-dependent diabetes mellitus	Insulin resistance
Gallstones	Increased cholesterol flux into bile (possibly related to insulin resistance and high insulin concentrations)
Impaired reproductive and sexual function	Decreased androgens, increased oestrogen production in adipose tissue
Reduced fertility (males)	
Polycystic ovary syndrome (females)	
Increased risk of breast and endometrial cancer	Increased oestrogen production in adipose tissue*
Osteoarthritis in weight-bearing joints	Excess weight bearing
Impaired self-image, depression, suicides	Psychological aspects of poor body image
Accidents	Loss of mobility

* Increased oestrogen production occurs because adipose tissue contains the enzyme aromatase, which converts androgens (e.g. testosterone) into oestrogens.

diet may predispose towards obesity, independent of genetics, has been equally well recognized and appreciated (Prentice & Jebb, 1995). The interaction of genetic predisposition and environmental factors is the most commonly accepted model for the genetics of human obesity (Bouchard & Perusse, 1993). The relative importance of these two factors in different populations may vary across studies. The heritability of obesity on the basis of studies of monozygotic twins raised together or apart has ranged from 20 to 60%. The best current estimate of heritability of body fat is 35% (Bouchard & Perusse, 1993). If another 15% is allocated for subjects who are predisposed to obesity when a 'Western high-fat' diet is consumed, then genetic inheritance can account for about 50% of the variation in percentage body fat (Campfield *et al.* 1997).

2.2.2. Regulation of energy balance. Obesity develops under conditions where energy intake exceeds energy expenditure. Much of the research in the obesity field has focused on the possible deviations in the different components of the energy balance equation. There is some evidence that a low resting energy expenditure may contribute to the development of obesity and that the metabolic rate during rest is, to some extent, genetically determined (Ravussin *et al.* 1988). Also, a blunted diet-induced thermogenesis response has been reported in obesity (Segal *et al.* 1990), but this has not been found consistently (D'Allesio *et al.* 1992). Thus, the relative importance of a low rate of energy expenditure in the development of obesity and the extent of individual differences in susceptibility to obesity remain controversial. A major difference in energy balance between lean and obese subjects is the increased energy expenditure in obese subjects, proportional to their increased fat-free mass, and as a consequence the proportionally increased energy intake (Prentice *et al.* 1986). Within the past decade, attention has been shifted to the investigation of the balances of the individual macronutrients, proteins, carbohydrates and fat, in the development of obesity. There are indications that subjects predisposed to obesity, or obese subjects, may have a diminished ability to oxidize fat, which would make them more susceptible to a positive fat balance on a high-fat diet (Zurlo *et al.* 1990; Blaak *et al.* 1994). These topics will be dealt with further in section 3.1. Extensive attention to the control of food intake is given in another paper in the present supplement (Bellisle *et al.* 1998).

2.2.3. Costs of obesity. The direct economic costs of obesity, defined as the costs related to diversion of resources to diagnosis and treatment of obesity as well as the treatment of obesity itself, have been estimated to vary between 2 and 5% of total health-care costs of various countries. In this calculation, only the costs of moderate and severe obesity (BMI > 30 kg/m²) are taken into account. The costs associated with mild obesity (BMI between 25 and 30 kg/m²) may also be substantial, since a large proportion of the adult population is involved. These costs comprise costs of health services (visits to general practitioners, consultation with medical specialists, medication; Seidell, 1997). In addition societal costs (loss of productivity, disability pensions, premature death), and personal costs (job discrimination, higher premiums to life

insurance companies) contribute substantially to health-care costs, but many issues of these costs are too fragmentary to allow calculation (Seidell, 1997). Thus, there is much direct information to show that obesity contributes significantly to health-care costs.

2.2. Insulin resistance syndrome

It has been recognized for many years that a number of adverse metabolic changes tend to cluster within individuals (Table 2). The underlying change appears to be a decrease in insulin sensitivity (insulin resistance) although cause and effect have never been properly disentangled. Nevertheless, plausible mechanisms have been described whereby development of insulin resistance can lead to the other aspects of the syndrome. Each of these changes has been shown independently to relate to risk of cardiovascular disease, and insulin resistance is a strong marker of risk of development of NIDDM (Reaven, 1995). The terms insulin resistance syndrome (IRS) or metabolic syndrome are now preferred to the original term syndrome X. This syndrome may be very prevalent. Some studies suggest that about 25% of non-diabetic adults manifest this syndrome (Reaven, 1995).

The concept of the IRS has been enormously helpful in understanding current patterns of chronic disease, especially CHD and NIDDM. As a risk factor for CHD it is probably greater in absolute terms than elevated cholesterol concentrations (Després, 1993). The characteristic dyslipidaemia of insulin resistance includes elevated fasting plasma triacylglycerol and depressed HDL-cholesterol concentrations. These changes are associated with a preponderance of small, dense LDL particles. This dyslipidaemia has been called the atherogenic lipoprotein phenotype (ALP) (Griffin & Zampelas, 1995). Postprandial triacylglycerol concentrations may be even more important than fasting plasma triacylglycerol concentrations. It has been suggested that the ALP results from exaggerated postprandial lipaemia associated with insulin resistance (Frayn, 1993).

Insulin sensitivity is usually measured as the ability of insulin to stimulate glucose disposal, usually by means of the hyperinsulinaemic, euglycaemic clamp procedure.

Table 2. Metabolic changes associated with insulin resistance syndrome

Glucose metabolism
Hyperinsulinaemia
Glucose intolerance
Lipid metabolism
Hypertriacylglycerolaemia
Exaggerated postprandial lipaemia
Decreased HDL-cholesterol concentrations
Preponderance of small, dense LDL particles
Other
Hypertension
Increased coagulation
Clinical correlates
Cardiovascular disease
NIDDM
Gout
Breast cancer

NIDDM, non-insulin-dependent diabetes mellitus.

Insulin is infused at a rate chosen to elevate the plasma insulin concentration by a predetermined amount, and glucose is infused at a variable rate, as necessary to maintain a constant plasma glucose concentration (hence the glucose concentration is 'clamped'). Under these conditions of constant glycaemia, glucose disposal must equal the rate of glucose entry into the plasma, which is known since it is being infused. (A correction can be made for endogenous glucose production by infusion of a glucose tracer.) Thus, the rate of glucose disposal from plasma at a predetermined insulin concentration is known, and may be used to compare different subjects. An alternative procedure involves mathematical modelling of the disappearance of glucose following its intravenous injection (Ader & Bergman, 1987).

However, these specialized procedures are unsuitable for large-scale epidemiological studies. A simple 'proxy' may be measurement of the fasting plasma insulin and glucose concentrations. These may be referred to a simple mathematical model which interprets them in terms of insulin secretion and insulin sensitivity (Matthews *et al.* 1985). Even the fasting plasma insulin concentration alone provides useful information, and elevated fasting plasma insulin concentrations have been shown to be associated (for instance) with development of CHD independently of other lipid markers (Després *et al.* 1996).

Although insulin sensitivity is measured in terms of glucose disposal, insulin resistance appears to affect many metabolic processes other than glucose disposal. Insulin resistance of multiple aspects of lipid metabolism may be the explanation for the characteristic dyslipidaemia of insulin resistance (Frayn, 1993). Thus, there must be some common change leading to multiple aspects of insulin resistance. The effects of insulin on metabolism are mediated through binding to specific receptors on cell surfaces. The intracellular domain of the insulin receptor possesses an intrinsic tyrosine kinase (EC 2.7.1.112) activity which is activated upon insulin binding, and this initiates the intracellular signalling chains leading ultimately to changes in enzyme expression and activity. In principle, insulin sensitivity might affect any one of the steps in these signal chains, which are themselves divergent for different aspects of insulin action. However, because insulin resistance, as commonly observed, affects so many diverse metabolic functions, it is likely that an early and common step is mainly affected. Attention has focused on events around the insulin receptor. One possible mechanism for widespread modulation of sensitivity to insulin might be a change in membrane fluidity caused by the incorporation into the membrane of different amounts of cholesterol or of phospholipids containing different fatty acids.

2.2.1. Features predisposing to the insulin resistance syndrome. The IRS may exist in apparently healthy individuals of normal body weight. There is evidence for a genetic component (Austin *et al.* 1990; Mitchell *et al.* 1996). However, it is most commonly associated with obesity, particularly obesity involving upper body fat distribution (often called visceral obesity).

Since obesity and fat distribution are themselves in part genetically determined (Bouchard, 1992), there may be a considerable genetic component to the IRS. Nevertheless, it

must also be strongly influenced by environmental factors including diet and activity level, because it is considered to have markedly increased in prevalence in recent years in Western countries. Development of the IRS may be the reason for the high incidence of CHD and NIDDM in immigrant people from the Indian sub-continent (McKeigue *et al.* 1991). This highlights both the possible genetic predisposition of some groups, and the effect of a change in lifestyle imposed on a susceptible genetic make-up.

Many of the features of the IRS shown in Table 2 could also be described as the effects of a sedentary lifestyle. Therefore, physical inactivity, development of obesity and genetic make-up probably interact with dietary factors to explain the high prevalence of the IRS in Western societies. A number of studies have indicated that about 50% of variation in insulin sensitivity amongst individuals is accounted for by variations in body fat content together with some measure of aerobic capacity (Bogardus *et al.* 1985).

2.3. Diabetes

Diabetes mellitus is a disease characterized by increased plasma glucose concentrations due to a reduced insulin action at its target tissues (insulin resistance) and/or an impaired insulin secretion. High glucose levels sustained for several years induce structural abnormalities in the walls of small arteries at the level of the retina and kidney and in the peripheral nerves; moreover, they contribute (directly and/or indirectly) to acceleration of the atherosclerotic process in the large arteries at the level of heart, brain, and lower limbs (Table 3).

Diabetes mellitus is classified into two large groups in relation to its clinical manifestations and aetiology (American Diabetes Association, 1997a). Type 1 or insulin-dependent diabetes mellitus (IDDM) usually develops in young lean individuals; it has an abrupt onset and requires insulin treatment to prevent the occurrence of a severe metabolic derangement that leads to death within a few days. This type of diabetes is due to an almost complete destruction of pancreatic β cells which represents a consequence of an autoimmune process. Therefore, IDDM is characterized by plasma insulin levels that are very low or even unmeasurable. Type II diabetes (NIDDM) usually develops in elderly individuals who are very often overweight; it has a very slow onset (it may be asymptomatic for several years) and does not necessarily require insulin treatment. It develops as a consequence of two metabolic derangements occurring together: (1) insulin resistance at the level of liver, muscle, adipose tissue; (2) impaired insulin secretion (which nevertheless is never completely

Table 3. Long-term diabetic complications and their possible health implications

Complications	Health implications
Retinopathy	Blindness
Nephropathy	Dialysis
Neuropathy	Foot ulcers, impotence
Macroangiopathy	Stroke, myocardial infarction, foot gangrene

suppressed). In relation to the balance between these two metabolic derangements, plasma insulin concentrations can be increased, normal or slightly decreased in comparison with non-diabetic individuals.

Nutrition has very important implications for diabetes in relation to aetiology, management and prevention of complications (Riccardi, 1994).

2.3.1. Aetiology. Different nutritional factors have been implicated in the aetiology of IDDM and NIDDM (WHO Study Group, 1994). For IDDM, two nutritional factors have been described in association with increased susceptibility to the disease. The first one is represented by a short duration of breast-feeding. It is not clear, so far, whether it is breast-feeding *per se* which has a protective effect on IDDM development or if an early introduction of dairy products and/or solid foods in the infant diet might have a predisposing effect. However, since duration of breast-feeding and age at introduction of dairy products and/or solid foods are highly correlated, it is difficult to dissect the independent effect of each of them on the risk of IDDM. The second nutritional factor linked with IDDM is represented by consumption of *N*-nitroso compounds (chemically related to streptozotocin, a well-known β -cell toxin). Studies in laboratory animals and ecological surveys in man have shown an increased risk of developing IDDM when *N*-nitroso compounds are consumed both by the parents at the time of conception and by the progeny during infancy. Further studies are needed, particularly intervention trials in human subjects, before the link between these dietary factors and IDDM is fully established (Virtanen & Aro, 1994).

In relation to the aetiology of NIDDM a large body of evidence indicates obesity, particularly the visceral type, as an important cause of NIDDM (WHO Study Group, 1994). It is now generally accepted that both degree and duration of obesity are associated with an increased risk of NIDDM. Moreover, visceral adiposity represents a risk factor for the development of NIDDM independently of the degree of overweight. As a matter of fact, obesity, particularly visceral obesity, induces resistance to the action of insulin at its target tissues (probably due to high non-esterified fatty acid (NEFA) concentrations) thus deteriorating glucose tolerance in the presence of an impaired insulin secretion (this might also be secondary to high NEFA concentrations). Weight reduction can lower the risk of NIDDM and, in persons already affected by the disease, it can ameliorate insulin sensitivity and glucose tolerance.

Dietary factors for treating diabetes should be able to limit glycaemic excursions, which are difficult to keep under control, even with the use of the available glucose lowering medications, and which negatively affect the overall blood glucose control. In addition, the diabetes diet should be able to improve the cardiovascular risk profile by reducing plasma lipid levels and blood pressure values, which are often elevated in diabetic patients. This aim can be achieved by dietary measures that are in principle identical to those recommended for the non-diabetic population (Riccardi & Rivellese, 1991; Diabetes and Nutrition Study Group EASD, 1995). Nutritional factors that might possibly play a role in the aetiology of NIDDM are: (1) a low consumption of fibre-rich foods; (2) a low

consumption of fish; (3) a high consumption of fat, particularly the saturated type. Two recent epidemiological studies indicate that low-glycaemic-index (GI) diets (low glycaemic load) might protect against the development of NIDDM (Salmerón *et al.* 1997*a, b*). However, so far none of these nutritional factors has been unequivocally proven as being implicated in the aetiology of NIDDM (Virtanen & Aro, 1994; Storlien *et al.* 1996).

2.4. Undernutrition

2.4.1. Definition. A condition of undernutrition or malnutrition occurs due to consumption of a diet deficient in one or more food constituents (specific undernutrition), or insufficient consumption of an otherwise adequate diet (general undernutrition). This statement is not a tautology; it makes the point that the adequacy of a diet, the extent to which it meets the requirements, can only be defined in terms of functions of the consumer: growth, health, activity etc. (Waterlow, 1992).

Nutritional deficiency results from an imbalance between the body's requirements for nutrients and energy and the supply of these substrates of metabolism. Specific undernutrition is usually associated with biochemical changes preceding the clinical sign, thus allowing the early diagnosis of subclinical or impending deficiency. A general undernutrition is reflected by failure to grow or by loss of weight. It results usually from a quantitatively inadequate intake. The two conditions may or may not coexist.

2.4.2. Present position. Despite the extensive understanding of human nutritional requirements, malnutrition (undernutrition) is one of the main causes of morbidity and mortality in developing regions of the world, especially in young children. In technologically advanced societies undernutrition no longer constitutes a major hazard to health, but occurs in especially vulnerable groups in various ways. Some of these are related to the introduction and widespread use in recent years of techniques such as parenteral feeding and renal dialysis, or other treatments in the frame of artificial nutrition. Ageing, chronic alcoholism, drug abuse or even the medically supervised use of drugs, and food faddism may lead to deficiency disease states.

2.4.3. Pathophysiology and adaptive responses. Undernutrition may develop gradually (days or months). This process allows a series of metabolic and behavioural adjustments that result in decreased nutrient demand. If the supply of nutrients becomes persistently lower than that to which the body can adapt, a critical situation supervenes. Metabolic equilibrium can also be disrupted in aged individuals during the progression of a disease or as a result of inadequate therapeutic measures (Torún & Viteri, 1988).

2.4.4. Body composition. An undernourished individual differs in two ways from a normal subject: in the relative proportions of the various organs and tissues, and in the chemical composition of the body.

In malnutrition there is a preferential loss of muscle tissue which in the resting state has a low metabolic activity, while organs with high rates of activity are relatively well preserved. It is generally accepted that in undernutrition the proportion of extracellular water is increased. This is in

contrast to the condition of severe malnutrition in which excess extracellular fluid is only measurable in about 50 % of the cases. A decreased share of intracellular water is consistently found in malnutrition and undernutrition. This is important considering the recent hypothesis concerning the regulatory role of the cellular hydration state (Häussinger *et al.* 1993). Therefore, the measurement of the distribution of body water is fundamental to understanding the changes in body composition that occur in undernutrition.

It is not inconceivable that undernutrition is associated with intracellular K or Mg depletion, while moderate decreases of these cations might be observed in serum. Ca and P have received very little attention. It seems reasonable to assume that Ca deficiency may well occur in undernutrition. The intracellular Ca concentration is about 1000 times lower than the extracellular; the constancy of the cytoplasmic Ca concentration is of great importance, since it plays a fundamental role in the integrated control of membrane permeability, the cellular response to stimulation and intracellular signalling. There seems to be a clear case for studies on the possibility of P deficiency in undernutrition.

Nevertheless, in the case of muscle wasting, total body K might be decreased. The low insulin action and diminished intracellular energy substrates reduce the availability of ATP and phosphocreatine. This process probably alters the cellular exchange of Na and K, leading to K loss and increased intracellular Na. Water accompanies the Na influx, and although total body intracellular water, as mentioned, is decreased because of losses in lean body mass, there may occasionally be intracellular overhydration. These alterations in cell electrolytes may explain, at least in part, the increased fatigability and reduced strength of skeletal muscle.

2.4.5. Geriatric undernutrition. At present, about 12.5 % of the population are over 65 years of age; and in the next 25 years the number of 80-year-old individuals may grow to over 20 %. Nutrition and ageing research yields several unique challenges. Undernutrition may be common among older persons (morbid consequences) due

Table 4. Prevalence of risk factors for protein–(energy) undernutrition in the population of 65 years and older (Adapted from Miller *et al.* 1995)

Risk factor	Prevalence (%)
Social factors	
poverty	15
isolation	30
Psychological factors	
depression	3–6
dementia	5
widowed	35
Physical factors	
impaired mobility	8
needs help with shopping, meal preparation, feeding	20
visual deficit	8
poor dentition	20
chewing difficulty	35
Functional impairment	
impaired instrumental ADL	4
impaired basic ADL	8

ADL, activities of daily living.

to under-consumption of macro- and micronutrients, protein malnutrition being frequently observed, and deficiencies in the amino acids, glutamine and arginine, should be considered.

Changes in nutrient digestion, absorption or metabolism may contribute to undernutrition though the nutrients are within the recommended limits for the general public. Ageing is associated with impaired immune responses and increased infection-related morbidity. Protein undernutrition impairs, especially, cell-mediated immunity. Previous studies substantiate the hypothesis that an optimum intake of nutrients (protein) leads to a striking reduction of protein-deficiency-induced cardiac failure and decreases the risk of infection. These findings are of considerable clinical and public health importance (Chandra, 1992; Miller *et al.* 1995).

Several factors common among older adults have been shown to increase the risk of undernutrition (Table 4). The prevalence of risk factors for protein (energy) undernutrition in the elderly population ranges between 2 and 69 %.

Despite the common occurrence of protein–energy undernutrition in older persons, its presence is rarely recognized and even when it is observed, it is often not treated (Move & Bohmer, 1991). In Table 5 the major conditions that appear to be secondary to the development of undernutrition are listed.

2.5. Conclusions and further research

Obesity. Obesity is a major health hazard, associated with a great variety of health problems. The research with respect to body-weight regulation has shifted from the study of possible abnormalities in the energy balance equation towards the study of the individual macronutrients. These concepts, conclusions and recommendations for further research will be further discussed in section 3.

Insulin resistance syndrome. The IRS may be an important conceptual link between obesity, NIDDM and cardiovascular disease. Insulin resistance of severity comparable with that of NIDDM is thought to be present in 25 % of non-diabetic individuals. The IRS is associated with a characteristic dyslipidaemia, the ALP. Impaired lipid metabolism in the postprandial period (exaggerated postprandial lipaemia) may be the link between insulin resistance and the ALP.

The present knowledge base is lacking in several important areas.

What is the basis for the IRS in people of normal body weight? (This will require epidemiological and genetic studies.)

Table 5. Effects of protein undernutrition in ageing (Adapted from Morley, 1995)

Decubitus ulcers
Infection
Immune dysfunction (decreased CD4+, CD8+)
Falls
Euthyroid sick syndrome
Anaemia (decreased maximum breathing capacity)
Decreased bone mass
Decreased glomerular filtration rate
Weight loss

How prevalent is the ALP in non-obese, non-diabetic subjects?

The ALP has been described as a genetic condition, and yet it also appears to be a secondary consequence of the IRS. Can the genetic and environmental components be dissected?

Diabetes. Diabetes can be classified on the basis of its clinical manifestations and aetiology into type 1 or IDDM, due to almost complete destruction of the pancreatic β -cells as a consequence of an auto-immune process, and type 2 or NIDDM, associated with insulin resistance and impaired insulin secretion. Two nutritional factors linked with IDDM are the duration of breast-feeding and the consumption of *N*-nitroso-compounds during infancy and by the parents at the time of conception. Further studies are required, in particular intervention trials in human subjects, before the link between these dietary factors and IDDM is fully established. Type 2 diabetes is associated with ageing and obesity, particularly visceral obesity. Further research is necessary to elucidate the mechanisms behind the impaired insulin resistance, in particular in relation to obesity and intermediary carbohydrate and fat metabolism.

Undernutrition. Undernutrition is an important risk factor, being the main cause of morbidity and mortality in developing regions, especially in children. In the Western world, undernutrition occurs in some vulnerable groups especially in the elderly as outlined in section 2.4. The physiology of undernutrition related to various organ functions and its influence on immunity as well as recommendations for further research are outlined in section 3.1.8.

Protein undernutrition, in particular, impairs immunity. Furthermore, with the development of undernutrition, changes occur in the extra- and/or intracellular concentrations of K, Mg and Ca, leading to a shift in extra- and/or intracellular fluid and control of membrane permeability and intracellular signalling. Muscle wasting is frequently observed and the observed shift in muscle electrolytes may explain the reported fatigability and reduced strength.

3. Metabolic conditions related to these chronic diseases

3.1. Body-weight control

3.1.1. Energy balance, macronutrient balance and body-weight regulation. According to the classical energy balance equation, obesity develops when the equilibrium between energy intake and energy expenditure shifts towards a positive balance. The excess energy is stored in the form of triacylglycerol.

More recently, evidence has accumulated that energy balance can only be achieved in the case of macronutrient balance and interest has shifted to an investigation of the balances of the different macronutrients, carbohydrates, fats and proteins, in the aetiology of obesity (Blaak & Saris, 1995; Frayn, 1995; Hill & Prentice, 1995; Flatt, 1996). Achievement of macronutrient balance requires that the net oxidation of each nutrient equals the average amount of the same macronutrient in the diet. Oxidation of the different macronutrients appears to take place in a hierarchical manner, some substrates being more readily

oxidized than others. Oxidation of carbohydrates and proteins tends to vary in response to the recent intake of each fuel in an autoregulatory manner. Adjustments in carbohydrate oxidation are capable of efficiently maintaining carbohydrate balance in the face of large changes in carbohydrate intake. Many experiments confirm this carbohydrate-driven autoregulation (Hill & Prentice, 1995; Flatt, 1996). In contrast, in the shorter term fat intake does not promote its own oxidation when carbohydrate content is constant. It has been demonstrated that over a 9 h period the same amounts of fat, carbohydrate and protein are oxidized whether or not the test meal is supplemented with extra fat (Schutz & Jéquier, 1989). The underlying mechanisms between the differences in macronutrients may be related to the characteristics of the macronutrient stores. This theory fits in the framework described by Flatt (1996) and is based on the fact that the carbohydrate stores of the body are limited (illustrated in Table 6) and are only capable of covering oxidation for a few days, which requires a tight metabolic control of carbohydrate balance. In contrast, the capacity for fat storage is enormous (Table 6), which implies that rapid adjustment of fat oxidation to intake is not necessary. When a diet high in fat is consumed over longer periods of time, the inability to acutely adjust fat oxidation will result in a positive energy balance and expanding fat stores and obesity. This will in turn result in an increased NEFA release from the expanded fat stores and an increased fat oxidation, until a situation of fat balance is again reached. Recent studies indicate that subjects predisposed to obesity, or obese subjects, may have a diminished ability to oxidize fatty acids (Zurlo *et al.* 1990; Blaak *et al.* 1994), which would make them even more susceptible to positive fat balance on a high dietary fat intake. However, further long-term well-controlled studies have to be performed in different types of subjects to obtain more information on the long-term effect of carbohydrate-fat exchange on energy expenditure and substrate utilization.

The size of the protein pool, in relation to daily intake, may lead one to predict that the regulation of protein balance would resemble more the regulation of fat than carbohydrate balance, whereas the opposite is true. In this respect, it may be more realistic to think in terms of the body's free amino acid pool since most of the body's protein pool is in a relatively inert form (Frayn, 1995).

Also, in several studies it has been shown that the carbohydrate:fat ratio of the diet may affect food intake. It has been shown that over a 2-week period compensation is less accurate when the diet has been diluted by removal of fat than by removal of carbohydrates (Lissner *et al.* 1987). There is now substantial evidence which shows that high-fat diets undermine the body's ability to regulate energy intake

Table 6. Macronutrient reserves and daily and annual macronutrient intake (Data from Flatt, 1996)

	Carbohydrate	Fat	Protein
Intake (kg/year)	100	35	35
Body content (kg)	0.5	20	12
Intake (kg/d)	0.3	0.1	0.1
(% body content)	60	0.5	1.0

in line with requirements and that they induce high-fat overfeeding. Several reports on the relationship between diet and the prevalence of obesity show that a higher fat intake is associated with a higher BMI (Gibney *et al.* 1987; Miller *et al.* 1990; Lovejoy & DiGirolamo, 1992). There remains a debate as to whether high-fat overfeeding is a passive overconsumption simply due to an energy density effect or whether carbohydrates play a specific role in inhibiting food intake (macronutrient effect; Flatt, 1996). As mentioned earlier, Flatt's glycogenostatic hypothesis argues that the body's different storage capacities for carbohydrates and fats result in mechanisms which give priority to the maintenance of stable glycogen levels, and that changes in these glycogen stores provide the primary feedback signal to regulate appetite (Flatt, 1996). In contrast, studies by Prentice and colleagues (Prentice & Poppit, 1996) showed that high-fat hyperphagia was eliminated when diets were manipulated to have the same energy density. Further studies are necessary to elucidate this issue.

In the whole debate on the interaction of the carbohydrate:fat ratio of the diet and energy metabolism, less attention has been paid to possible differences of various types of carbohydrates and fats in the regulation of energy and macronutrient balance.

3.1.2. Type of carbohydrates. Monosaccharides, disaccharides and starch are defined as 'digestible' carbohydrates because they are digested and absorbed in the human small intestine. A second category of carbohydrates, defined as 'non-digestible', (i.e. dietary fibre) cannot be digested by intestinal enzymes. This latter category of carbohydrates, including a fraction of starch called resistant starch, may still have an important nutritional role because of their inhibitory effects on food intake (Blundell & Burley, 1987) and their possible role in weight management (Blundell & Burley, 1987; Hamilton & Anderson, 1992). This paragraph will further focus on the metabolic effects of digestible carbohydrates, also called glycaemic carbohydrates (Food and Agriculture Organization/World Health Organization, 1998).

The ingestion of different types of digestible carbohydrates may lead to varying metabolic postprandial responses, which implies the possibility that different types of carbohydrates have varying effects on thermogenesis and substrate utilization. Indeed, differences in postprandial thermogenesis among various types of digestible carbohydrate have been reported, with sucrose and fructose being more thermogenic than glucose and readily-digestible starch (Tappy *et al.* 1986; Blaak & Saris, 1996). Additionally, carbohydrate oxidation, glycogen formation and the decrement in lipid oxidation have been reported to be higher after fructose than glucose ingestion. The higher thermogenic response with sucrose and fructose ingestion may be ascribed to differences in post-ingestive substrate utilization and is probably related to particularities of fructose metabolism in the liver. The higher increase in post-ingestive carbohydrate oxidation with fructose and sucrose compared with glucose may be explained by the finding that fructokinase (*EC* 2.7.1.4), responsible for fructose phosphorylation, is about ten times as active as the combined activities of glucokinase (*EC* 2.7.1.2) and hexokinase (*EC* 2.7.1.1), required for glucose phosphorylation

(Blaak & Saris, 1996). Despite an increased carbohydrate oxidation with fructose, leaving less fructose available for storage, it has previously been reported that fructose is also a better substrate for hepatic glycogen synthesis (Nilsson & Hultman, 1974). Moreover, glycogen formation from fructose requires more energy than glycogen formation from glucose and starch, and may therefore be of importance in the higher thermogenic response with fructose and sucrose as compared with glucose and starch (Blaak & Saris, 1996).

Furthermore, acute thermogenesis studies showed no differences in thermogenesis after ingestion of an easily-digestible maize starch and glucose (Blaak & Saris, 1996) or cooked manioc starch and glucose (Ritz *et al.* 1991), indicating that there are no differences in the thermogenic efficiency with which the body handles available carbohydrates with varying chain lengths. All the previously mentioned studies are acute experimental studies. Evidence for differences in the effects of digestible carbohydrates on long-term energy expenditure and substrate utilization is lacking.

As indicated earlier the carbohydrate:fat ratio of the diet has a distinct effect on appetite regulation. In the current literature there are no indications that various types of digestible carbohydrates may differ in their effects on food intake or energy intake. However, it is a popular belief that starches and mono- and disaccharides may have varying effects on energy intake and that the attractiveness of 'simple'-sugar-rich foods may promote overeating and may thereby contribute to the development of obesity (Yudkin, 1988). In man, taste preferences for both fat and sugar have been investigated. Studies examining sweetness have not revealed any difference in sensory functioning between normal-weight and obese individuals (Grinker, 1978). In addition, several studies indicated a negative relationship between preference for sweet taste and degree of body fatness and a strong positive relationship between body fatness and preferences for fatty foods (Drewnowski *et al.* 1985, 1992). This seems consistent with reports on the relationship between diet and the prevalence of obesity, showing that a higher fat intake is associated with a lower carbohydrate and sugar intake, which is in turn associated with a higher BMI (Gibney *et al.* 1987; Miller *et al.* 1990; Lovejoy & DiGirolamo, 1992; Bolton-Smith & Woodward, 1994). In summary, it can be said that the available literature indicates a closer regulation of carbohydrate compared with fat balance and that there is no conclusive evidence indicating differences in the effects of different types of digestible carbohydrates on long-term energy and substrate balance.

3.1.3. Type of fat. As for the type of carbohydrate, the impact of type of fat on substrate metabolism and balance is often ignored. Modifications in dietary fat profile may affect body weight and adiposity through changes in partitioning between oxidation and storage and/or alterations in membrane structure (Pan *et al.* 1994).

Significant differences were observed in oxidation of stearate, oleate and linoleate with the oxidation rates for oleate sixteen times as high as for stearate (Jones *et al.* 1985). Furthermore, a low polyunsaturated:saturated fatty acid (P:S) ratio of the diet was associated with an increased basal fat oxidation, and a lower contribution of fat to the

thermic effect of feeding than a diet with a high P : S ratio in man, suggesting that the long-chain fatty acid composition of dietary fat modulates the oxidation of fat and carbohydrate after chronic feeding and after meal feeding (Jones & Schoeller, 1988). Another study showed that obese subjects consuming low P : S ratio diets exhibited a reduced contribution of fat oxidation to the thermogenic response, compared with lean individuals consuming low or high P : S ratio diets (Jones *et al.* 1992). Postprandial thermogenesis has been reported to be higher after a medium-chain-triacylglycerol meal than after a long-chain-triacylglycerol meal, indicating that besides the long-chain fatty acid composition of the diet the chain length of the fatty acid may be important in determining its metabolic effect (Seaton *et al.* 1986). Although these results indicate that the type of fatty acid may affect energy expenditure and substrate utilization, more (long-term) research is needed for these effects to result in nutritional implications.

3.1.4. Alcohol. The role of alcohol in human energy metabolism and human obesity is still a matter of debate. The consumption of excessive amounts of alcohol is usually discouraged because this may be a causal factor in the development and maintenance of obesity. The issues that receive most attention in the literature are whether alcohol is as efficiently used as an energy source as other macronutrients, i.e. carbohydrates and fats, and whether alcohol is added to, or substituted for, non-alcoholic energy in the diet. Several studies suggest that alcohol consumption may increase the risk of a positive energy balance and overweight (MacDonald *et al.* 1993; Tremblay *et al.* 1995). However, other epidemiological surveys show a negative association between alcohol consumption and adiposity and body weight (Colditz *et al.* 1991; MacDonald *et al.* 1993). Numerous studies have shown that the efficiency of use of alcohol for the maintenance of metabolizable energy is the same as for carbohydrates (Westrate *et al.* 1990; MacDonald *et al.* 1993; Sonko *et al.* 1994), whereas others have shown that ingested ethanol is less efficiently used as an energy source (Suter *et al.* 1992; MacDonald *et al.* 1993; Klesges *et al.* 1994). Other studies have shown that alcohol may have a fat-sparing effect (Suter *et al.* 1992), indicating that when consumed in excess this may promote fat gain, especially upper body fat. Although results remain controversial, alcohol does not seem to be a major determinant of body weight when consumed in moderate amounts, suggesting that replacing a moderate amount of energy from carbohydrates and fats with alcohol in non-alcoholics is not expected to decrease energy retention significantly or to be useful as an adjuvant in weight-reducing regimens.

3.1.5. Macronutrient replacement. Macronutrient substitutes are ingredients which are added to foods to replace macronutrients such as various digestible carbohydrates and fats in volume and in their technological functions (Finley & Leveille, 1996). The replacement may help the consumer to achieve dietary objectives, e.g.:

- reduced energy intake for reduction of body weight or maintenance of a normal body weight;
- reduced and modified fat intake (reduced cholesterol and saturated fat intake);

- reduction of the risk of developing dental caries by replacing sugars with polyols.

Carbohydrate replacement. Carbohydrates such as sucrose and glucose are bulking agents in foods such as chocolate, candies, cookies and cakes. Their replacement can be achieved by using a carbohydrate of similar or lower sweetness and similar taste but different physiological properties (e.g. reduced absorption and digestibility in the small intestine). In this respect polyols (sugar alcohols) have to be mentioned first (Bär *et al.* 1994). Complex polymeric carbohydrates e.g. polydextrose or inulin in combination with intensive sweeteners are the second group of bulking agents which can replace sugars in special cases (Finley & Leveille, 1996).

Metabolic studies of polyols have been reviewed elsewhere (Schiweck & Ziesentz, 1996) and can be summarized as follows: monosaccharide-derived polyols are more slowly absorbed from the small intestine than glucose. The absorption is thought to take place by means of passive diffusion along a concentration gradient. The rate of absorption differs among the polyols. Erythritol is well but not totally absorbed, whereas mannitol, sorbitol and xylitol are absorbed only slowly and incompletely. The absorbed part of the polyol is either excreted unchanged, mainly in the urine as in the case of erythritol and mannitol, or is converted to fructose by specific dehydrogenases, as found for sorbitol and, partly, mannitol. Xylitol is oxidized to xylulose by a polyol dehydrogenase and then enters the normal pentose pathway after phosphorylation by D-xylulokinase.

The disaccharide alcohols isomalt, lactitol and maltitol are hydrolysed at varying rates from slow and partial hydrolysis to almost none by the various glycosidases located in the small intestine. Hydrogenated starch hydrolysates also contain di- and oligomeric polyols which are hydrolysed to glucose, sorbitol and maltitol.

Most polyols have practically no impact on blood glucose concentrations and only a moderate influence, if any, on postprandial serum insulin profile. In the case of maltitol and hydrogenated starch hydrolysates substantially higher glycaemic responses were found (Felber *et al.* 1987).

Significant amounts of ingested polyols reach the large intestine and the colon, where they are readily fermented by micro-organisms to H₂, CO₂, CH₄ and short-chain fatty acids (SCFA). The latter lower the pH of the gut content and may, thereby, influence the composition of the colonic microbial flora.

The most recent assessment of the energy value of polyols was that of the Expert Scientific Panel of the Life Sciences Research Office of the Federation of American Societies for Experimental Biology (1994). According to that evaluation the following energy values were given: mannitol 6.7 kJ/g, lactitol 6.7–9.2 kJ/g, isomalt approximately 8.4 kJ/g, sorbitol 7.5–13.8 kJ/g, xylitol approximately 10 kJ/g, maltitol and hydrogenated starch hydrolysates 11.7–13.4 kJ/g.

Fructose as a replacer for glucose and sucrose should be mentioned in this context as a sweetener for diabetics, due to its low GI and low insulin response. Nutritional aspects are reviewed elsewhere (Bowman & Forbes, 1993). Whilst attention has been paid mainly to the use of polyols as sugar

Table 7. Polysaccharides as fat replacers (mimic fat)

Starches	unmodified modified maltodextrins
Further types	cellulose inulin β -glucan pectin resistant starch gums (xanthan, guar etc.)

replacers, a number of carbohydrates (including polyols) may also act to partly or totally mimic fat in food (as stabilizers and thickeners), i.e. as fat replacers. Carbohydrates relevant in this aspect are summarized in Table 7.

The degree of digestion and absorption of these carbohydrates in the small intestine varies according to the type of carbohydrate. All poorly digestible carbohydrates have in common the fact that the part which is not absorbed in the small intestine reaches the large intestine and is there fermented, to a greater or lesser extent, by the colonic microflora to SCFA and gases (H_2 , CO_2 , CH_4). Due to the increase in substrate reaching the large intestine and the production of SCFA there is also an increase in the osmotic load in the large intestine leading to an increase of water within the gut content. These circumstances might be noticeable for the host by e.g. an increase in flatulence (gas) or soft-to-watery stools. Certain advantages with respect to bacterial composition (e.g. bifidogenic effects) or the properties of some SCFA (e.g. butyric acid and its possible preventive effects with respect to colon cancer) should be taken into account as well (Scheppach, 1994), but to clarify this, or other positive effects on health, further research work is required.

Fat replacement. Generally, fat replacers are ingredients that are designed to replace all or part of the fat which is normally in a food without influencing the taste and texture quality of the food products (Jones, 1996). There are three categories of such fat replacers as indicated in Table 8.

As fat mimics are carbohydrate- or protein-based ingredients, at least 20 kJ/g less energy is provided compared with fat. Some of the carbohydrate replacers mentioned provide even less than 16 kJ/g, making them an important tool in recipes for energy-reduced foods. Their metabolism has already been described.

Fat substitutes are physically similar to fats and oils and therefore heat-stable. In the case of sucrose polyesters there are up to eight fatty acids (8–22 C atoms, saturated or

unsaturated) per sucrose molecule (Food and Drug Administration, 1996). The resulting molecules are too big to be split by lipases and are therefore neither digested nor appreciably absorbed. The small amount of material that is absorbed is metabolized to sucrose and fatty acids that are further metabolized normally in the body. These sucrose polyesters pass intact through the colon and are not used as a substrate for the bacterial microflora. The hydrophobic properties of these sucrose polyesters have influence on other hydrophobic substances in the gastrointestinal tract. For example fat-soluble vitamins are not well absorbed and cholesterol is removed in the faeces in the same way. Due to the fact that these sucrose polyesters pass through the small intestine undigested, gastrointestinal effects such as flatulence and soft stools occur in some people.

Low-energy fats are true triacylglycerols with a new lipid structure. Triacylglycerols may be composed of mixtures of long-chain saturated fatty acids and SCFA esterified on a glycerol backbone. It is stated that their available energy is approximately 20 kJ/g (Finley *et al.* 1994). This reduced energy content is based on the poor absorption of stearic acid and the lower energy value of SCFA compared with long-chain fatty acids which normally occur in fats. SCFA are rapidly absorbed and converted to CO_2 . Stearic acid in the 1- and 3-positions of the triacylglycerol would be hydrolysed by lipases. Free stearic acid would be poorly absorbed and stearic acid in the 2-position would be likely to remain on the glycerol and absorbed as monoacylglycerol, and further be converted to oleic acid (50% of the absorbed stearic acid).

Another example of a low-energy fat is a triacylglycerol prepared by the esterification of glycerol with capric, caprylic, and behenic acids resulting in caproacrylobehenin (Life Sciences Research Office/Federation of American Societies for Experimental Biology, 1991). Due to the limited intestinal absorption of behenic acid and the lower energy yield from capric and caprylic acids, an energy value of 20 kJ/g has been stated. This triacylglycerol is digested, absorbed, and metabolized by the usual pathways of triacylglycerol metabolism. Its medium-chain fatty acid component is readily absorbed. The long-chain component, behenic acid, is absorbed more slowly and less completely.

An alternative to fat replacement is fat-binding. Dietary fat might be sequestered by binding to an appropriate non-absorbed material. Derivatives of chitin such as chitosan have been shown to reduce plasma cholesterol concentrations in animals (Sugano *et al.* 1988), probably by binding of bile acids and interruption of the entero-hepatic circulation, but not to affect body weight. These derivatives of chitin and similar products are being widely marketed for human weight reduction, but we are not aware of scientific evidence of their efficacy. Their effectiveness might be estimated by comparison with the pharmacological agent tetrahydrolipstatin which is an inhibitor of pancreatic lipase (EC 3.1.1.3). This agent can lead to useful weight loss (typically a few kg greater than placebo) in controlled studies, although its usefulness is limited by unwanted side-effects of fat malabsorption and by reduction in absorption of fat-soluble vitamins (Drent & Van der Veen, 1993).

The idea of preventing absorption of dietary fat or fat replacement is appealing because it could, in principle,

Table 8. Categories of fat replacers

Fat mimics	microparticulated proteins \pm carbohydrates e.g. cellulose modified starches gums inulin polyols polydextrose
Fat substitutes	sucrose polyesters
Low-energy fats	triacylglycerols

mitigate many adverse features of metabolic diseases. First, energy intake would be reduced, helping with body-weight control. The limited number of controlled experiments that have been conducted with low-fat foods indicate that they may possibly help to reduce fat intake (Jones, 1996), although it also has been suggested that the 'fat-free foods' may actually cause consumers to increase consumption (Rolls & Shide, 1992). Thus, more information on population-based consumption is needed to assess the impact of such foods in reaching the goal of fat reduction. Second, there would be a direct reduction of postprandial lipaemia, and given the evidence reviewed earlier (section 2.2) linking postprandial lipaemia with the ALP, this is likely to be beneficial in terms of cardiovascular risk.

3.1.6. Dietary components stimulating thermogenesis. The most important mechanism controlling thermogenesis is the activity of the sympathetic nervous system. The pharmacological approach to enhance metabolic rate has centred on the development of novel β_3 adreno-receptor agonists (Stock, 1989). However, 'natural' ingredients of food can also interact with the adrenergic system for thermogenic stimulation. Minor food constituents such as caffeine and associated methylxanthines in coffee and tea have a profound effect on metabolic rate.

Also other minor constituents, such as spices, have thermogenic properties. Inclusion of these types of 'natural' food ingredients into food products could be a viable approach in stimulating energy expenditure to keep energy balance and thus body weight within acceptable limits.

Methylxanthines: caffeine, theophylline and theobromine. Caffeine and other methylxanthines are alkaloids derived from at least sixty-three species of plants, including the familiar coffee bean, the tea leaf and the cocoa bean.

Most human societies use caffeine regularly, most often in beverages, for its stimulant effect and flavour. Caffeine contents of beverages vary, depending on the plants they were made from and the food technological methods applied.

The caffeine in cola soft drinks is added, using the purified compound that is obtained from the decaffeination of coffee beans. The Food and Drug Administration lists caffeine as a multipurpose generally recognized as safe (GRAS) substance that may be added to foods and beverages. It has been known since 1915 that ingestion of caffeine provokes an increase in the metabolic rate and subsequent investigations have confirmed this original observation (Acheson *et al.* 1980). Current theories attempting to explain the diverse pharmacological actions of dietary methylxanthines, favour their actions as antagonists of adenosine-inhibitory effects on noradrenaline-induced cyclic AMP formation. The net result is an elevated cellular level of cyclic AMP, a critical intracellular mediator for the actions of catecholamines on thermogenesis. In a study by Dulloo *et al.* (1989), the effect of normal caffeine consumption on thermogenesis was studied. Single-dose oral administration of 100 mg caffeine (equal to a small cup of coffee) increased the metabolic rate by 3–4% over 150 min. Measurements of energy expenditure in a room respiration chamber indicated that repeated caffeine administration (100 mg) at 2 h intervals over a 12 h daytime period, increased energy expenditure by about 10%. Comparable results have been found by other groups. Acheson *et al.* (1980)

also observed an increase in fat oxidation, mediated by an increased lipolysis leading to higher blood NEFA levels. In a double-blind placebo-controlled study in moderate habitual coffee drinkers, Astrup *et al.* (1989) found increases in energy expenditure of 38.5, 30.1 and 136 kJ/h with 100, 200, 400 mg caffeine ingestion respectively. These effects were positively correlated to plasma caffeine response. In contrast, no significant correlations were found for plasma responses of theophylline and theobromine.

It is suggested that most people develop caffeine tolerance due to a decrease in the inhibitory effect on adenosine. However, in the study of Dulloo *et al.* (1989) habitual caffeine intake of the subjects was 250–500 mg/d. In the study of Astrup *et al.* (1989) habitual intake of caffeine was 100–200 mg/d. Although a certain degree of tolerance to the thermogenic effect of caffeine may have been developed, these results suggest that a substantial effect remains during moderate daily caffeine consumption.

Pungent ingredients of ginger and spices. Ginger is extensively used as a flavouring additive in foods, beverages and confectionery. Ginger is known for its apparent ability to subjectively warm the body.

The pungent principles of ginger are present as two phenylalanine-derived homologous series: the gingerols and shogaols (Eldershaw *et al.* 1992). In a number of spices such as hot chillies, the compounds capsaicin and dihydrocapsaicin have been isolated and found to have thermogenic effects in isolated perfused rat hindlimb (Cameron-Smith *et al.* 1990).

From the ginger components it turned out that gingerol especially induces thermogenesis. Interestingly, this effect was not inhibited by α - or β -adrenergic antagonists, suggesting that neither adrenergic receptors nor secondary catecholamine release was responsible for the observed effects.

Gingerols, shogaols and capsaicinoids have some similarities in terms of both structure and function. All contain the 4-methoxy, 3-hydroxy phenylvanillyl moiety as well as a carbonyl-containing allyl side-chain. Each group of homologues is responsible for the pungent taste of the parent plant.

The only human study on the thermogenic effects of spices was performed by Henry & Emery (1980) with chilli (component: capsaicin) and mustard (component: allyl isothiocyanate). Subjects were given test meals with or without 3 g mustard sauce and 3 g chilli sauce. Diet-induced thermogenesis over a 3 h period was 25% higher after the spiced meal. This is a substantial increase in thermogenesis compared with other thermogenic substances. Further research is needed to investigate the role of spicy ingredients in human nutrition and the metabolic origins of their effect on diet-induced thermogenesis. The thermogenic properties are substantial. However, detailed human research on tolerance and identification of active compounds and metabolic interactions is lacking. Recently, also the catechin teoline, purified from tea leaves, showed thermogenic effects that are synergistic with caffeine (Dulloo *et al.* 1996).

3.1.7. Physiological and metabolic consequences of undernutrition. In undernutrition certain functions are affected and some nutrient reserves decrease, making

the undernourished individual more susceptible to injuries that a well-nourished individual can withstand with little repercussion.

Cardiovascular and renal functions. In severe undernutrition cardiac work decreases, as does functional reserve, and central circulation takes precedence over peripheral circulation. Cardiovascular reflexes are altered, leading to postural hypotension and diminished venous return. Haemodynamic compensation occurs primarily from tachycardia rather than from increased stroke volume. Renal plasma flow and glomerular filtration rates may be reduced as a consequence of the decreased cardiac output, but water clearance and the ability to concentrate and acidify urine appear to be unimpaired.

Gastrointestinal functions. Impaired intestinal absorption of lipids and disaccharides and a decreased rate of glucose absorption occur only in severe protein deficiency. The greater the protein deficit, the greater the functional impairment.

Although the average protein requirement may not differ with advancing age, at least certain categories of elderly people have difficulties maintaining N balance when consuming the recommended daily amount (0.8 g/kg per d) (Young, 1992). To assess more accurately the needs of the elderly, they are usually evaluated in two age groups (65–75 years and 76 years and older). Distinctions are also made between healthy elderly people and those with chronic disease (Durnin, 1992; Morley, 1995). Due to the diminished efficiency of protein utilization in the elderly, the prudent dietary recommendations should ensure a minimum intake of 0.9 g/kg.

A decrease in gastric, pancreatic, and bile production is also observed, with normal to low enzyme and conjugated bile acid concentrations. These alterations further impair the absorptive functions. Nevertheless, the ingestion of nutrients in high, therapeutic amounts usually allows for their uptake in sufficient quantity to permit nutritional recovery. Undernourished elderly people are prone to have diarrhoea probably due to irregular intestinal motility and gastrointestinal bacterial overgrowth.

The immune system. The major defects are seen only in severe undernutrition. This seems to involve T-lymphocytes and the complement system. A marked depletion of lymphocytes from the thymus and atrophy of the gland occur. In addition, cells from the T-lymphocyte regions of the spleen and lymph nodes are depleted, probably owing to decreases in thymic factors. The production of several complement components, the functional activity of the complement system assessed by both the classic and alternative pathways, and the opsonic activity of serum are depressed. These deficiencies may explain the high susceptibility of severely undernourished patients to Gram-negative bacterial sepsis. Phagocytosis, chemotaxis, and intracellular killing are also impaired, partly due to the defects in opsonic and complement functional activities. The B-lymphocyte areas of spleen and lymph nodes and the circulating levels of B-cells and immunoglobulins are relatively normal, but there may be defects in antibody production, such as secretory immunoglobulin A.

The overall consequences of all these alterations in severe undernutrition are a greater predisposition to infections and

complications of otherwise less important infectious diseases. The defects in immune functions disappear with nutritional rehabilitation (Chandra, 1992).

3.1.8. Conclusions and further research. There seems to be a consensus view that a high-fat diet, resulting in a positive energy and fat balance, is an important risk factor in the aetiology of obesity. However, more information is necessary to elucidate whether (moderate) manipulation of the macronutrient content of the diet may affect body weight. In theory, epidemiological studies would be the best way to study these relationships. However, in this type of study there are too many variables that cannot be controlled. For this reason, long-term controlled intervention studies where the carbohydrate : fat ratio and types of carbohydrate and fat are manipulated would be more suitable. These studies have to cover at least 6 months, since changes in body weight are likely to be small. In this type of study acute experimental mechanistic studies can be included at several time points since more mechanistic research is necessary to elucidate the regulation of carbohydrate and fat balance within the body.

In the latter studies, attention has to be focused on the issue of whether the different storage capacities for carbohydrate and fat within the body give rise to a specific role of carbohydrate (stores) in the regulation of appetite (Flatt's theory) or whether the obesity-promoting effect of a high-fat diet is simply a passive overconsumption effect due to the high energy density of the diet. In mechanistic studies regarding the regulation of carbohydrate and fat balance, the type of fat or carbohydrate also has to be taken into account, since mechanisms behind the relationship of type of fat or carbohydrate and energy metabolism or substrate utilization are largely unknown. More specifically, mechanisms behind the increased sucrose-induced thermogenesis and decrement in fat oxidation and mechanisms behind the impact of the P : S ratio of the diet on fat oxidation require further study, since these metabolic effects may have important consequences for energy and macronutrient balance. Mechanistic studies have to include techniques for studying intermediary and tissue metabolism in man (stable-isotope techniques, tissue balance studies, tissue biopsies, microdialysis), since only these types of studies will add information to the existing knowledge of body-weight regulation in man.

With respect to alcohol, more mechanistic research is necessary to elucidate whether alcohol is handled in the body according to the law of thermodynamics (Macdonald *et al.* 1993). Additionally, long-term controlled experimental studies are necessary to study the relationship between alcohol consumption and body weight *per se* without confounding variables. However, it does not seem realistic to regard addition or substitution of alcohol in the diet in the concept of future functional foods.

With respect to their digestion, most of the macronutrient replacers discussed herein do have in common that they are not, or are only partially, hydrolysed and absorbed in the small intestine. They are partially or completely fermented in the large intestine by the colonic flora. As a result, these macronutrients provide less energy to the body than completely absorbed and metabolized substrates. This makes them an important tool in the development of

energy-reduced foods and an important tool to achieve a balanced energy and fat intake or a reduction in energy and fat intake. More research has to be performed to investigate the long-term effect of these macronutrient replacers, in particular the fat replacers, on energy and fat balance and on body-weight control. Attention has to be paid to the suggestion that consumption of fat- or energy-reduced foods may be compensated by an increased total food intake, resulting in similar energy intake.

Due to the very limited absorption of the carbohydrate- and fat-replacers in the small intestine, the substances are fermented mostly in the large intestine thereby increasing the amount of SCFA produced. The energy content provided by the different fermented carbohydrates as well as the impact of SCFA like butyric and propionic acids on health may be a field of further research.

A number of plant ingredients can be identified which elevate the diet-induced thermogenesis after ingestion. This elevation is mainly mediated by a prolonged activation of the sympathetic nervous system leading to an increased catecholamine release from the sympathetic nerve endings or an inhibitory effect on the action of adenosine. Both lead to an increase in cyclic AMP essential for the cellular increase in metabolism. However, other unknown mechanisms must also be involved since adrenergic blockade does not counteract the thermogenic properties of some ingredients.

From the group of methylxanthines caffeine seems to be the most potent in thermogenic response after ingestion of a normal dose of 100 mg (+3–4%). Another interesting group is the pungent ingredients from spices, such as ginger, chilli and mustard. With the increased interest in the non-nutrient compounds such as polyphenols in plants, it is clear that more ingredients that can increase thermogenesis will be discovered. Some of the known ingredients have already shown efficacy in the treatment of overweight subjects.

Undernutrition affects cardiovascular, renal and gastrointestinal functions. Impaired intestinal absorption of nutrients occurs only in severe conditions, yet in certain categories of elderly people, maintenance of N balance is difficult with the recommended daily amount. The immune system is apparently depressed in (severe) undernutrition. The defects in immune functions disappear with adequate nutritional rehabilitation.

In the field of undernutrition, the following points may need further research: (1) development of analytical methods (bioassay) and identification of biomarkers may help in making estimates of nutritional status and of nutrient requirements; (2) suitable animal and *in vitro* cell (cell culture) models would facilitate the investigation of metabolic handling of essential substrates (absorption, transport, receptor sites); (3) nutrient interactions are an essential focus of future studies because of alterations caused by the ageing process; (4) nutrient mechanisms that have an impact on genetic expression or immunological function should be examined with modern methods of molecular biology and immunology. Special interest should be directed to appraise post-translational modifications related to various proteins, diets or indispensable substrates.

3.2. Insulin resistance/sensitivity

3.2.1. Introduction. As reviewed earlier, the strongest factor predisposing to insulin resistance is obesity, particularly of the upper body. Therefore nutritional influences on body weight will also have a profound effect on insulin sensitivity. Since abdominal obesity is an even stronger predisposing factor, specific nutritional influences on body fat distribution are important. However, they are not clearly understood. Although the concept of the 'beer belly' is widespread, studies of the effect of alcohol on fat distribution have been conflicting (reviewed by Macdonald *et al.* 1993). More research is needed on this point. There is some evidence from animal studies that saturated fats may lead to intra-abdominal fat accumulation and that *n*-3 polyunsaturated fatty acids (PUFA) may protect against this (Hill *et al.* 1993), but no data on this point in human subjects are available. There is indirect evidence that a high dietary fat intake is associated with visceral obesity in women (Nicklas *et al.* 1995). On the whole, the most consistent explanation for the accumulation of intra-abdominal fat is an interaction between lifestyle, including stress factors, and excessive energy intake leading to obesity (Björntorp, 1991a). Thus, again, relevant dietary factors are those predisposing to obesity.

3.2.2. Dietary carbohydrates. In rats, feeding a fructose-enriched diet induces insulin resistance (reviewed in Frayn & Kingman, 1995). There is no clear evidence for this effect in human subjects at realistic levels of fructose intake.

High-carbohydrate, low-fat diets are consistently found, at least in the short term, to raise plasma triacylglycerol concentrations (see p. S66) and also plasma insulin concentrations (Hollenbeck & Coulston, 1991). This is not surprising in view of the potentiation of insulin secretion by carbohydrates, but it has been interpreted as an adverse change indicative of insulin resistance (Hollenbeck & Coulston, 1991). This may be an over-interpretation: there is no prospective evidence that such diets have adverse consequences on insulin sensitivity or CHD. Their well-documented beneficial effect on body-weight regulation (reviewed earlier) is likely to outweigh any possible direct adverse effect on insulin sensitivity.

A reduction in the GI of the diet may improve insulin sensitivity. This has been shown indirectly by an improvement in glycaemic control observed in many studies of low-GI diets in NIDDM (Brand Miller, 1994), and directly in patients with CHD (Frost *et al.* 1996).

3.2.3. Dietary fat. Clearly excessive intake of fat will lead to obesity, and possibly specifically visceral obesity, and thus to development of the IRS. Of more interest are specific effects of the quality of dietary fat. There is considerable evidence in experimental animals that saturated fat in the diet may lead to insulin resistance (Vessby, 1995). The effects of saturated fat may be reversed by the addition of *n*-3 PUFA (Vessby, 1995; Storlien *et al.* 1996). The mechanism is likely to relate to a change in membrane fluidity affecting processes around the insulin receptor and recruitment of glucose transporters to the membrane.

In man there is indirect evidence for the same effect. The phospholipid-fatty acids of skeletal muscle biopsies show a relationship to insulin sensitivity measured *in vivo*: a more

saturated fatty acid pattern is associated with insulin resistance and a high prevalence of PUFA is associated with increased insulin sensitivity (Storlien *et al.* 1996). Similar findings have been made with respect to plasma cholesteryl-ester fatty acids (Vessby *et al.* 1994). Since these fatty acid patterns reflect long-term dietary intake, a link between saturated fat in the diet and insulin resistance is reasonably firmly established (Fig. 1). Prospective studies of dietary fat change and insulin sensitivity in human subjects have not been conclusive, perhaps because periods of study have not been long enough (Storlien *et al.* 1996). Thus, it would be premature at this stage to make any functional claim for an effect of dietary PUFA on sensitivity to insulin.

3.2.4. Niacin and insulin sensitivity. A common metabolic mechanism in insulin resistance may be an elevated concentration of NEFA in the plasma (Frayn *et al.* 1996). Nicotinic acid (one form of niacin: the other is nicotinamide) exerts a powerful suppressive effect on adipocyte lipolysis and thus NEFA release, and has been used as an effective hypolipidaemic agent (Farmer & Gotto, 1995). However, it has a number of side-effects (Farmer & Gotto, 1995). Over-the-counter niacin preparations are popular in the USA. Their long-term safety and efficacy have not been properly evaluated. It might be predicted that a short-term reduction in NEFA concentrations could improve insulin

sensitivity, but in the longer term consistent entrapment of fatty acids in adipocytes might lead to obesity with adverse effects on insulin sensitivity. This may not happen in practice because a well-known aspect of nicotinic acid action is a marked 'rebound' of plasma NEFA levels between doses.

3.2.5. Minerals. Some minerals have been associated with insulin sensitivity.

Chromium. Cr may form a complex with nicotinic acid in plasma which has been called the glucose tolerance factor and may be associated with improved glucose tolerance (Mertz, 1993). It has been suggested that Cr deficiency might underlie the IRS (Mertz, 1993).

Vanadium. Inorganic and organic compounds containing V, such as vanadyl sulfate and vanadate, have an insulin-like effect both *in vitro* and *in vivo* (Shechter, 1990). V is available as an over-the-counter preparation in some Southern American countries. As in the case of Cr supplementation, there are no prospective human data on safety or efficacy.

Magnesium. There is a large body of evidence showing low plasma and intracellular Mg concentrations in diabetes. It is not clear whether these low levels represent Mg deficiency although it has been suggested that supplemental dietary Mg may be beneficial both in improving glycaemic control and in reducing the complications of diabetes (White & Campbell, 1993). In non-diabetic subjects low dietary Mg intake has been linked with a number of aspects of cardiovascular disease including insulin resistance (Ma *et al.* 1995).

3.2.6. Conclusions and further research. Insulin sensitivity is closely related to body fat content and body fat distribution. Thus, factors leading to obesity will increase insulin resistance, and those leading to upper-body or visceral obesity will have a greater influence. There are direct and indirect pieces of evidence that diets based on low-GI foods may improve sensitivity to insulin. The evidence linking saturated fat in the diet and insulin resistance appears to be reasonably firm, based on cross-sectional studies, although it has not been proven in long-term intervention studies. Critical areas for future research are as follows. (1) Long-term prospective studies of the effects of high-carbohydrate, low-fat diets on insulin sensitivity and on plasma triacylglycerol concentrations (see p. S20) are needed in view of suggestions that such diets might be harmful in these respects. These studies need to be conducted in subjects with a range of sensitivities to insulin (e.g. relatives of those with diabetes) and from different ethnic backgrounds, to illuminate potential gene-nutrient interactions. The potential of low-GI foods to improve insulin sensitivity needs further investigation. (2) Long-term prospective studies of the effects of manipulation of the quality of dietary fatty acids on insulin sensitivity are also required to investigate whether insulin resistance can be ameliorated by dietary means. Properly controlled studies of micronutrient and mineral supplementation (niacin, Cr, V and Mg) in insulin resistance are required.

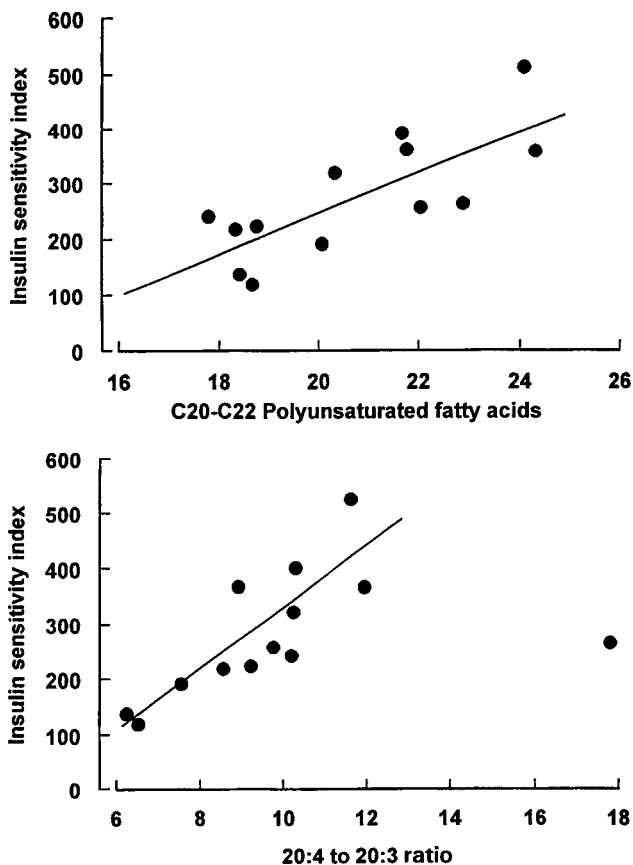


Fig. 1. Relationships between insulin sensitivity and the fatty acid composition of skeletal muscle phospholipids in normal men. The insulin sensitivity index was derived from a glucose clamp study; units are mg/m^2 per min. Redrawn with permission from Borkman *et al.* (1993).

3.3. Blood glucose control

3.3.1. Introduction. One of the characteristics of untreated diabetes is hyperglycaemia. This is not only the

cause of a large proportion of the symptoms that heavily affect the quality of life of these patients but represents also the primary cause of the long-term specific complications of diabetes (retinopathy, nephropathy, neuropathy) and is an important contributor to the excess risk of cardiovascular disease (The Diabetes Control and Complications Trial Research Group, 1993). High blood glucose concentrations (but below the diagnostic level of diabetes) may also represent a cardiovascular risk factor in the general population. This has been particularly substantiated in individuals with impaired glucose tolerance (characterized by mildly elevated postprandial and normal fasting blood glucose concentrations), but there are some indications that even within the normal population blood glucose values in the upper part of the normal range might represent a cardiovascular risk factor (Gerstein & Yusuf, 1996). A recent contribution has shown that near optimal blood glucose control is able to prevent most cases of microvascular complications occurring in diabetes (Stamler *et al.* 1993), indicating that preventive strategies to control blood glucose level may reduce the occurrence of chronic complications in diabetes.

In order to evaluate the effects of diet on blood glucose control, it is not sufficient to measure blood glucose concentrations in the fasting state since large fluctuations can occur throughout the day, particularly in patients with IDDM. Therefore, reliable information on blood glucose control needs to be based not only on fasting but also on postprandial evaluation of blood glucose concentrations; pre- and postprandial measurements can also be repeated at each meal. An additional useful marker of glucose control is the measurement of glycated haemoglobin, as it represents an integrated measure of blood glucose control during the preceding 2–3 months or, alternatively, fructosamine which reflects blood glucose levels during the previous 2–3 weeks. Relevant indices of blood glucose control are listed in Table 9, and any evaluation of functional foods in facilitating normoglycaemia needs to focus on these variables (American Diabetes Association, 1997b).

Measurements of plasma insulin concentrations and insulin sensitivity are also relevant to evaluate the effects of foods on glucose metabolism but they have been considered earlier.

The most powerful measure to improve blood glucose control in overweight diabetic patients is weight reduction. This is particularly effective in NIDDM patients who are very often (70–80%) overweight, a condition which has a major impact on insulin resistance and, consequently, on

plasma glucose levels. However, in IDDM patients, also, the presence of overweight (occurring in about 30% of cases) impairs the hypoglycaemic effect of exogenously administered insulin, thus hampering the achievement of optimal blood glucose control (Diabetes and Nutrition Study Group EASD, 1995; American Diabetes Association, 1996). However, dietary composition can also affect blood glucose control, particularly in the postprandial period, as discussed in the next paragraphs.

3.3.2. Nutritional influence on fasting and postprandial blood glucose levels. Although closely related, fasting and postprandial blood glucose levels are regulated by mechanisms that are, to some extent, different; in fact, while postprandial blood glucose concentrations are largely dependent on meal composition, fasting values are only minimally influenced by the amount and/or rate of glucose absorption during the previous meal, and reflect the rate of glucose production in the liver (the two key processes being glycogenolysis and gluconeogenesis).

Among the various dietary constituents, the one with the strongest influence on blood glucose levels in the postprandial period is the amount of digestible carbohydrate in the diet. Digestible carbohydrates include monosaccharides (glucose, fructose), disaccharides (sucrose, lactose) and polysaccharides (starch), which are digested and absorbed in the human intestine, thus contributing to the glucose inflow to the bloodstream (Table 10) (Asp, 1996). In diabetic patients, postprandial blood glucose levels are directly related to the amount of digestible carbohydrate in the diet and although they may be regulated by appropriate pharmacological treatment this is not always feasible or fully successful (Perrotti *et al.* 1984). Therefore, diets with a very high content of digestible carbohydrate are not without problems in the treatment of diabetic patients, particularly those with IDDM who have a severely impaired endogenous insulin secretion and are therefore more susceptible to exogenous influences on blood glucose metabolism. On the other hand, a drastic reduction in the intake of digestible carbohydrates is not feasible since in a weight-maintaining diet, this reduction should be compensated by an increase in protein or fat intake. Very high intakes of both protein and fat are not recommended because of their possible untoward effects on the development of chronic diabetic complications (Diabetes and Nutrition Study Group EASD, 1995). Therefore, it is important to identify food characteristics able to reduce the impact of digestible carbohydrates on postprandial blood glucose levels.

The glycaemic index. The GI is defined as the incremental blood glucose area after the test product has been ingested, expressed as a percentage of the corresponding area after a carbohydrate-equivalent amount of white bread (Jenkins *et al.* 1981).

The ratio between mono-, di- and polysaccharides is no longer regarded as important in relation to the effects on postprandial blood glucose since amylase and disaccharidase activities in the human duodenum are sufficient to hydrolyse starch and disaccharides within minutes. The meal content of protein and fat, although able to influence postprandial glucose values, has limited clinical significance because the magnitude of these effects is rather small. More important are all dietary factors able to delay the

Table 9. Relevant measures of blood glucose control

Fasting blood glucose
Postprandial blood glucose
Daily blood glucose profile*
Glycated haemoglobin†
Fructosamine†
Oral glucose tolerance test‡

* Several blood glucose measurements performed throughout the day either by conventional laboratory methods or by strips read on a reflectometer.

† Only in diabetic patients.

‡ Only in non-diabetic individuals or in patients with a milder form of diabetes.

Table 10. Main food carbohydrates and their digestibility in the small intestine (From Asp, 1996)

	Monomers	Digestibility
Monosaccharides		
Glucose		+
Fructose		+*
Galactose		+
Disaccharides		
Sucrose	glucose, fructose	+†
Lactose	glucose, galactose	+†
Oligosaccharides		
α -Galactosides, e.g. raffinose, etc.	galactose, glucose, fructose	-
Fructooligosaccharides	fructose, glucose	-
Maltooligosaccharides	glucose	+
Polysaccharides		
Starch		
amylose	glucose	+
amylopectin		(-)*
modified starches		
NSP		
cellulose	glucose	
hemicelluloses	galactose	
pectins	glucose	
β -glucans	mannose	
gums	arabinose	
mucilages	xylose	-
algal polysaccharides	rhamnose	
uronic acids		
fructans	fructose	
'New' carbohydrate food ingredients		
Inulin	fructose	-
Polydextrose	glucose	-
Polyols	various sugar alcohols	(+)
Pyrodextrins	glucose	(-)

* Limited in some individuals when ingested without glucose.

† Except in disaccharidase deficiency.

‡ Resistant starch is indigestible.

process of digestion and/or absorption of carbohydrates in the intestine, thus reducing the glycaemic response to carbohydrate-rich foods (Table 11).

Due to the variety of factors that influence the glycaemic impact of a meal, it is not possible to predict the glycaemic response of each food on the basis of its physical and chemical characteristics (Parillo & Riccardi, 1985). Therefore, it is necessary to test carbohydrate-rich foods *in vivo* to evaluate their glycaemic response, thus allowing the selection of low-GI foods. Although the procedure used for GI determination varies in different laboratories and needs to be standardized (Food and Agriculture Organization/World Health Organization, 1998), it allows the classification of carbohydrate-rich foods into broad categories (high, medium and low glycaemic responses) (Riccardi & Rivellese, 1987). *In vitro* methods for the prediction of the glycaemic response to starchy foods seem promising (Granfeldt *et al.* 1992); however, no methods are at hand to predict the glycaemic impact of foods containing low-molecular-mass carbohydrates.

It is now well documented that a diet preferentially containing low-GI foods improves the metabolic control in diabetic patients and has a number of other possible metabolic benefits. In fact, such a diet has been reported to lower the day-long blood glucose profile, reduce glycated haemoglobin or fructosamine, and improve glucose tolerance. In addition, in some studies, fasting blood glucose levels were decreased in diabetic subjects (Brand-Miller, 1994). Moreover, low-GI diets have also been shown to have beneficial effects on blood lipid metabolism and other cardiovascular risk factors (for review, see Björck, 1996; Food and Agriculture Organization/World Health Organization 1998). As to the mechanism of these beneficial effects, the slow rate of digestion and absorption *per se*, i.e. the GI features, may be important. In addition, low-GI foods may be more efficient in suppressing NEFA concentrations between meals, leading to an improved tissue uptake of glucose when the second meal is ingested 4 h later (Jenkins *et al.* 1982).

Cumulative effects of low-GI foods, extending beyond the improved insulin economy in the acute prandial phase, may also stem from a more extensive colonic production of SCFA, since such foods are frequently richer sources of indigestible carbohydrates. Generation of SCFA through fermentation might, thus, explain improvements seen in fasting blood glucose and glucose tolerance at breakfast when preceded by a low-GI evening meal (Thorburn & Proietto, 1993).

Effect on fasting glucose. The knowledge of nutritional factors influencing blood glucose metabolism in the fasting state is scarce. Liver glucose production, the major determinant of fasting glucose levels, is under the control of insulin and therefore not adequately suppressed when insulin resistance is present; thus nutritional factors influencing fasting plasma glucose concentrations are primarily those acting on insulin resistance. In this line it is well known that a diet with a very high fat and a very low carbohydrate content increases the production of ketone bodies, therefore impairing insulin sensitivity and elevating blood glucose levels, particularly in the fasting state. However, the relevance of this phenomenon in everyday life is questionable since such an extreme nutritional condition rarely occurs.

In relation to different dietary fats there are some indications that saturated fat could impair insulin sensitivity, thus increasing blood glucose levels. More controversial are the effects of polyunsaturated fats; in fact it seems that while *n*-6 PUFA could decrease blood glucose concentrations, *n*-3 PUFA (if consumed in large amounts) could have a hyperglycaemic effect. However, the influence of dietary fat composition on blood glucose control has limited clinical significance because it is small and has still to be properly documented in randomized controlled intervention trials of sufficiently large sample size (Rivellese *et al.* 1996).

Non-digestible carbohydrates (resistant starch, NSP, and oligosaccharides) escape digestion in the small intestine and are fermented by colonic bacteria in the large bowel generating SCFA (see p. S19). These metabolites could influence liver glucose production and, thus, the fasting glucose concentration.

Table 11. Properties of carbohydrate foods that can be utilized to modify the postprandial blood glucose response (the glycaemic index)

Chemical structure of the digestible carbohydrate	Physical structure of carbohydrates
Monomeric composition Amylose : amylopectin ratio	Degree of gelatinization Starch–lipid and starch–protein interactions Retrogradation Viscous properties of dietary fibre
	Food form Botanical integrity (cells and/or tissue) Physical structure, e.g. pasta
	Other food components/supplements Viscous dietary fibre Organic acids Amylase inhibitors

Finally, alcohol intake also has significant, although conflicting, clinical effects on plasma glucose levels. In fact, alcohol intake acutely suppresses hepatic glucose production thus lowering plasma glucose levels. Conversely, if habitually consumed in large amounts it impairs insulin sensitivity, thus impairing glucose tolerance and increasing plasma glucose levels.

3.3.3. Food properties determining the glycaemic index. As already mentioned, dietary carbohydrates represent the major dietary constituent influencing blood glucose control. However, the impact of dietary carbohydrates on glucose metabolism depends not only on the amount consumed, as believed in the past, but also on some specific food properties which can profoundly influence the metabolic effects (Parillo *et al.* 1985) (Table 12). These properties are a consequence not only of the ratio indigestible : digestible carbohydrates, but also of the food structure and of some specific physico-chemical characteristics of carbohydrates present in the food. This section will try to illustrate the importance of these properties in relation to the metabolic effects of different dietary carbohydrates.

Table 12 lists some important properties of carbohydrate foods that can be utilized for the production of functional foods with a reduced postprandial blood glucose response, i.e. a low GI. It should be noted in this context that major sources of carbohydrates such as potatoes and bread are characterized by high GI values.

Raw starch granules. Plant cells store starch in semi-crystalline granules with variable size and structure. Raw starch granules are slowly digested by amylases. Cereal starches with an A pattern on X-ray diffraction analysis display a rather high digestibility in the small intestine, whereas B-type granules, e.g. from potatoes or high-amylose maize starch, are mainly indigestible (Langkilde & Andersson, 1994). Formulas with raw maize starch have been utilized to provide extremely slow-release carbohydrates to children with glycogen storage disease, making it possible to avoid repeated tube-feeding during the night. The potential of raw starch in producing low-GI foods is limited to products produced below the gelatinization or melting temperature of starch granules.

Gelatinization and retrogradation. Heating of starch in excess water results in swelling, leakage (especially of amylose), and eventually disintegration of the granule

structure rendering the starch soluble or dispersible in water. This process is called gelatinization and occurs at different temperatures for different starches, usually between 60 and 80°. Dispersed or soluble starch is highly susceptible to salivary and pancreatic amylase, which is present in excess in relation to the final hydrolysis and absorption at the brush-border level. When, for example, rolled cereals are produced under mild enough conditions the starch may be only partly gelatinized. A very low degree of gelatinization, however, is required to lower the GI of such products significantly (Granfeldt *et al.* 1995).

Retrogradation is the process of recrystallization of starch from a solution. This occurs especially during slow cooling; amylose forms dense crystals resistant to amylase action, and staling of bread is related to retrogradation of amylopectin. Amylose retrogradation is a well-documented mechanism for resistant starch formation, but its effect on the GI is incompletely understood.

Amylose : amylopectin ratio. Amylose, the virtually unbranched form of starch, forms double helices with about six glucose residues per turn. The interior of the helices can accommodate the hydrophobic end of polar lipids, forming inclusion complexes with reduced availability of the amylose for enzymic hydrolysis (Holm *et al.* 1986). This, and the propensity of retrogradation, are factors behind the usefulness of high-amylose starch varieties for production of foods with low GI and/or high resistant starch content.

Cellular structure. Legumes such as beans have low GI and comparatively high resistant starch content. A main feature behind these properties is intact cell walls forming physical barriers to starch digestion even after boiling (Wursch *et al.* 1986). A rather high amylose content may contribute as well. Preservation of the intact cell structure is essential for keeping these properties in processed foods.

Table 12. Properties of food carbohydrates modifying their effects on glucose metabolism

Rate of absorption
Type of absorbed monomers
Extent of absorption
Extent and rate of colonic fermentation
Site and metabolites of colonic fermentation

Gross structure. The presence of intact grains in bread and other cereal products has been demonstrated to be a main determinant of the GI as well as a source of resistant starch (Jenkins *et al.* 1986; Björck *et al.* 1996). Pasta is another well-documented group of low-GI foods in which structural effects are important. In this case a protein network is responsible for the slow enzymic hydrolysis of the starch. At least in some studies, the maintenance of an intact botanical structure also reduces GI features of fruit products (Haber *et al.* 1977).

Organic acids. Another factor influencing the glycaemic and insulinaemic impact of foods is the presence of organic acids produced on fermentation of foods e.g. sourdough baking. The acids appear to differ in gastrointestinal effect, and whereas some may reduce the rate of starch digestion, others reduce the gastric emptying rate (Liljeberg & Björck, 1996). Thus, fermentation processes represent one way of reducing the GI of carbohydrate foods.

Amylase inhibitors. The presence of certain antinutrients such as phytate, polyphenols, and lectins has been discussed in relation to the low-GI features of legumes (Thompson *et al.* 1987). However, due to other effects such factors can hardly be used for optimizing starch properties in food products.

Glucose:fructose:galactose ratio. Fructose occurs in free form in fruits, berries and honey, as part of sucrose and in high-fructose syrups. Its use as a sweetener is based on its high sweetness, at least under certain conditions. The low glycaemic response (GI about 20% of glucose) has made fructose an alternative sweetener for use in diabetic diets (see also section 3.1.6.). The low-GI features of fructose probably explain the moderate GI range of certain fruits and the fact that sucrose has a moderate GI.

The main concern about fructose as a sweetener has been the possibility that it induces elevated triacylglycerol concentrations, relevant in diabetic patients and individuals with the IRS (Truswell, 1994).

The absorption capacity for fructose is limited when given alone (Truswell *et al.* 1988). Together with glucose, however, which is the normal situation in foods or diets, the absorption is improved and intolerance problems avoided.

Galactose is part of lactose, but significant amounts of free galactose are found only in fermented milk products, due to the preferential utilization of glucose by the microorganisms.

3.3.4. Indigestible carbohydrates and glucose metabolism: possible mechanisms of action. The main types of indigestible carbohydrates are: dietary fibre (NSP), resistant starch and oligosaccharides. Although not the determinant of low-GI features *per se*, many low-GI foods are rich sources of these carbohydrates. The possible effects of indigestible carbohydrates on glucose metabolism may be related to different upper gastrointestinal events e.g. reduced motility and/or absorption of carbohydrates due to viscous properties of dietary fibre components or a reduced rate of carbohydrate digestion and/or absorption due to entrapment of the substrate within a fibre matrix at cell or tissue level. However, the SCFA produced on colonic fermentation of indigestible carbohydrates are increasingly being discussed in relation to systemic effects on glucose and lipid metabolism (Cummings & Macfarlane, 1991). Thus,

carbohydrate fermentation has been reported to enhance suppression of hepatic glucose production and NEFA levels in man, leading to lowered fasting blood glucose and improved glucose tolerance (Thorburn & Proietto, 1993). Few studies are, however, available on this topic.

NSP. Among the nutritional factors able to influence blood glucose levels, dietary fibre is certainly the one that has been most extensively studied. NSP constitute the main part of dietary fibre in most foods, the daily average amount in European diets being about 20 g/d (Cummings, 1993). Plant cell walls are the main source of naturally occurring NSP, such as cellulose, hemicellulose and pectic substances, although storage polysaccharides such as inulin and guar gum, as well as exudate gums, are also indigestible polysaccharides included in dietary fibre. A large body of evidence clearly shows that a diet consisting of a high consumption of fibre-rich foods of natural origin induces lower blood glucose levels particularly in the postprandial period in comparison with a diet containing the same amount of digestible carbohydrate but not rich in fibre (Riccardi & Rivellese, 1991). More controversial is the issue of whether dietary fibre represents the marker or the cause of a low glycaemic response (Nuttal, 1993). It is now clear that more important than the amount of fibre is the interaction between fibre and carbohydrates within foods. The presence of cells with intact walls composed of fibre polysaccharides is important as they are able to encompass carbohydrates, slowing their accessibility and thus their digestibility.

As already mentioned, soluble viscous types of NSP are those affecting the postprandial glucose and insulin response after a meal. This has been demonstrated repeatedly for a large number of such polysaccharides when added to meals or incorporated into foods. The effect is related to viscosity, which inhibits mixing and diffusion in the intestinal tract and possibly delays gastric emptying, and which can be abolished by hydrolysis with loss of viscosity. A main obstacle in utilizing these properties to design functional foods lies in the organoleptic limitations to include enough viscous polysaccharides. The importance of viscosity in conditioning the GI of food naturally rich in soluble fibre, however, has been questioned. Even in products with high fibre content, e.g. flaked oats or bread with oat flour, structural properties seem more important in obtaining low-GI products. However, even if this is the case, the importance of fibre in conditioning the structural properties of foods (thus influencing the GI) cannot be neglected.

In addition to their effects on the postprandial blood glucose response, NSP act as the fermentation substrate for colonic bacteria with production of SCFA which might influence liver glucose production.

Resistant starch. Resistant starch, defined as starch and hydrolysis products thereof that are not absorbed in the small intestine, has emerged as a main substrate for the human intestinal microflora. Although the present intake in Europe seems low, about 4 g/d only (Dysseler & Hoffem, 1994), there is considerable potential for increasing it by providing food with elevated resistant starch content.

Three main forms of resistant starch have been identified: (1) physically enclosed starch, (2) resistant B-type starch granules and (3) retrograded amylose (Englyst *et al.* 1992).

Chemically modified food starches and pyrodextrin are other forms that may contribute in processed foods. Methods for determination of resistant starch are designed to estimate the starch residue after treatment of the sample with enzymes simulating normal starch digestion in the small intestine. A critical step, not yet fully solved with any one of the suggested methods, is simulation of the normal disintegration of foods by chewing. This is essential to recover the physically enclosed fractions of resistant starch.

The main interest in resistant starch stems from its properties as a fermentation substrate. Studies with human faecal flora *in vitro* have indicated a high yield of butyrate from resistant starch, which has been supported by some human *in vivo* data (Scheppach *et al.* 1988). The site, extent and SCFA pattern of fermentation of resistant starch from various sources need further study. There seems to be considerable potential for designing resistant-starch-containing foods for specific effects on colonic health (for review, see Asp & Björck, 1992; Asp *et al.* 1996).

Oligosaccharides. The main types of indigestible oligosaccharides in foods and food ingredients are:

- (1) α -galactosides (raffinose, stachyose, verbascose) found mainly in legumes;
- (2) fructans (fructo-oligosaccharides, inulin);
- (3) galacto-oligosaccharides (derived from lactose); and
- (4) pyrodextrins and cyclodextrins.

The present interest in oligosaccharides stems from their properties as low-energy more-or-less sweet bulk substances (see section 3.1.6.) and their effects as fermentation substrates producing metabolites with local and/or systemic effects, as well as prebiotics promoting desirable intestinal micro-organisms (Mitsuoka *et al.* 1986).

Fructans have been studied most extensively and shown to promote bifidobacteria with a concomitant inhibition of other species such as bacteroides and clostridia. *In vitro* studies have indicated a potential to inhibit pathogens. Other potentially beneficial effects include lower activities of hydrolytic and reductive enzymes thought to be involved in colonic carcinogenesis. A comparatively high yield of butyrate has been reported, which is also of interest in this context.

Effects of fructans on lipid metabolism (decreased plasma triacylglycerol and cholesterol concentrations) have been demonstrated in rats. Human data are still scarce, however, and the potential of oligosaccharides to reduce plasma lipids in man needs further exploration. With respect to glucose metabolism, a daily supplementation with oligofructose at 8 g/d for 14 d significantly reduced fasting blood glucose in type II diabetics (Yamashita *et al.* 1984).

Whereas fructo-oligosaccharides are being studied extensively, the potential of other indigestible oligosaccharides for prebiotic or systemic effects needs further exploration.

Metabolic effects of short-chain fatty acids. An important mechanism by which food characteristics may influence glucose metabolism is represented by intestinal fermentation of carbohydrate in the large bowel which may play a role in modulating glucose metabolism through the production of SCFA. All carbohydrates (particularly fibre, oligosaccharides and resistant starch) escaping digestion

and absorption in the small intestine, pass to the large bowel for subsequent bacterial fermentation. There is some evidence, mainly from *in vitro* studies, that the proportion of the various SCFA (acetate, propionate, butyrate) formed during fermentation differs depending on the specific carbohydrate acting as substrate, with concomitant differences in physiological effects (Macfarlane & Cummings, 1991).

Several studies show that dietary supplementation of propionic, acetic and lactic acids may diminish the post-prandial glucose and insulin response (Brighenti *et al.* 1995; Liljeberg & Björck, 1996). Such effects are probably mediated by mechanisms in the upper gastrointestinal tract, such as inhibition of gastric emptying or inhibition of digestive enzymes. Furthermore, long-term propionate administration has been shown to lower the fasting glucose concentration (Venter *et al.* 1990), an effect possibly related to inhibition of glucose release from the liver.

In spite of extensive fermentation, lactulose was demonstrated in one study (Jenkins *et al.* 1991) to increase plasma cholesterol levels in healthy subjects. The high yield of acetate obtained on fermentation of this substrate was suggested as an explanation.

The gross energy values for SCFA range from 15 kJ/g for acetate to 25 kJ/g for butyrate. Of this, 75–85 % is metabolizable. The true energy value of fermented carbohydrate is dependent on the yield of SCFA as well as the fractions used for biomass and combustible gas production. Resistant starch, for example, has been estimated to provide about 8.4 kJ/g fermented substrate (Livesey, 1994).

3.3.5. Conclusions and further research. The recent progress in understanding mechanisms determining both rate and extent of carbohydrate absorption have provided tools for designing foods with specific nutritional effects. One such tool is represented by the GI concept, and accumulating data have demonstrated facilitated control of blood glucose concentrations in diabetes with diets characterized by low-GI foods. Some recent epidemiological data also suggest the hypothesis that low-GI foods could be protective against NIDDM. The importance of blood glucose levels for protein glycosylation implies a potential role in ageing. Further, low-GI foods may help to reduce plasma cholesterol concentrations and insulin resistance, and thus be of more general importance in defeating the metabolic syndrome.

The emerging knowledge of properties important for the rate and site of fermentation of indigestible carbohydrates, as well as properties of various fermentation products, lays the ground for designing foods with optimal prebiotic effects, with the potential of influencing also metabolic variables through absorbed fermentation products.

However, proper clinical testing (also long term) is required before the functional properties of foods active on glucose metabolism can be fully assessed.

The European study group on diabetes (EASD) recommended in 1995 an increased use of low-GI foods in diabetes. Recently, a report (Food and Agriculture Organization/World Health Organization, 1998) recommended that the bulk of carbohydrate-containing foods consumed should be those rich in NSP and with low GI. The lack of variety of such

foods on the market, not least regarding cereal foods, makes the development of products with low GI a priority area for functional food development.

3.4. Plasma triacylglycerols

3.4.1. Introduction. An association between fasting plasma triacylglycerol concentrations and development of CHD has been recognized for decades. However, there has been some controversy over the nature of the link. In multivariate statistical analyses fasting plasma triacylglycerol concentrations have often been non-significant contributors compared with plasma HDL-cholesterol concentrations, with which they are strongly negatively related. More recently, however, meta-analysis has shown that elevation of the fasting plasma triacylglycerol concentration is a risk factor for development of CHD even when adjusted for plasma HDL-cholesterol (Hokanson & Austin, 1996). In fact, the combination of elevated plasma triacylglycerol and depressed HDL-cholesterol concentrations is a particularly strong risk marker for CHD. This is the typical dyslipidaemia associated with insulin resistance.

In the fasting state the plasma triacylglycerol originates from the liver, which secretes VLDL particles containing triacylglycerol. The triacylglycerol in these particles is hydrolysed by the enzyme lipoprotein lipase (*EC* 3.1.1.34) in peripheral tissues which include adipose tissue, skeletal muscle and myocardium. As the particles shrink they may be taken up by receptors or they may remain in the circulation, becoming smaller and more cholesterol-enriched as they lose further triacylglycerol until they are classed as LDL particles.

After a meal containing fat, dietary triacylglycerol is packaged within the enterocytes into chylomicron particles, which are released into the plasma via the lymphatics. The metabolism of chylomicron particles is similar to that of VLDL but they are a better substrate for lipoprotein lipase, and their triacylglycerol is rapidly removed before their remnants are taken up by receptors. Since the 1940s it has been realized that postprandial triacylglycerol concentrations may be related to CHD. It is now recognized that the magnitude and duration of elevated postprandial triacylglycerol concentrations (postprandial lipaemia) is a strong marker of CHD risk, far stronger, at least in some groups, than the fasting triacylglycerol concentration (Griffin & Zampelas, 1995). The inverse relationship between plasma triacylglycerol and HDL-cholesterol concentrations may be explained by events in the postprandial period (Frayn, 1993). Increased postprandial lipaemia, i.e. prolonged residence of triacylglycerol-rich particles in the circulation, leads to the exchange of their triacylglycerol for the cholesterol esters of HDL and LDL particles, leading to loss of HDL-cholesterol. Thus, low HDL-cholesterol concentrations may be a marker of impaired postprandial triacylglycerol metabolism. Loss of cholesterol esters from LDL particles makes them smaller and denser, thus accounting for the third component of the ALP (see section 2.2.).

Dietary components may affect fasting triacylglycerol concentrations mainly through changes in the rate of hepatic VLDL-triacylglycerol secretion. The fasting triacylglycerol concentration is one determinant of the postprandial

lipaemic response, perhaps because VLDL particles containing endogenous triacylglycerol compete with the chylomicrons for clearance by lipoprotein lipase. Therefore lowering of fasting triacylglycerol concentrations will usually also reduce postprandial lipaemia. Other dietary components may affect postprandial lipaemia more directly.

3.4.2. Dietary carbohydrates. When a low-fat, high-carbohydrate diet is introduced, a consistent change is an elevation of fasting (and in some studies postprandial) triacylglycerol concentrations (reviewed in Frayn & Kingman, 1995). This has led to the belief that such diets may be adverse in terms of their effects on blood lipids and thus CHD (Hollenbeck & Coulston, 1991). However, there is no evidence that this is so; rather, their beneficial effects on body weight are probably predominant. The effect on plasma triacylglycerol concentrations may be specifically to increase the proportion of large, buoyant VLDL particles and this might be a beneficial change since such particles are not major precursors of LDL. However, this is controversial and this area needs further work.

Ingestion of fructose in large amounts (e.g. 50 g) also has a marked effect in potentiation of postprandial lipaemia. The mechanism is thought to be potentiation of hepatic lipogenesis and thus VLDL secretion, although impairment of plasma triacylglycerol clearance has also been suggested (reviewed in Frayn & Kingman, 1995). Again, further work is needed to elucidate the mechanism of this effect and its implications.

3.4.3. Dietary fat. Diets enriched in *n*-3 PUFA lead consistently to lower fasting plasma triacylglycerol concentrations (Nestel, 1990). Other than this the effects of dietary fat quality are more on plasma cholesterol than on fasting triacylglycerol concentrations (reviewed by Hornstra *et al.* 1998).

Of more interest are dietary factors which may affect postprandial lipaemic responses, since this is an important determinant of the dyslipidaemia of the IRS. The greater the amount of fat eaten, the greater will be the lipaemic response. Again, different qualities of dietary fat affect this response, and in particular *n*-3 PUFA have a strong effect in diminishing postprandial lipaemia (Griffin & Zampelas, 1995). PUFA of the *n*-6 series lead to lesser postprandial lipaemia than saturated fatty acids, but the effects of monounsaturated fatty acids are not clear (Griffin & Zampelas, 1995): more research is needed in this area.

3.4.4. Conclusions and further research. Both fasting and postprandial plasma triacylglycerol concentrations are markers of risk of CHD. They are potentially modifiable by nutritional means. The short-term influence of a low-fat, high-carbohydrate diet is to increase plasma triacylglycerol concentrations. Whilst this had led to speculation that such diets may be disadvantageous in terms of CHD risk, it could also be argued that if such diets lead to weight loss they will be beneficial. The quality of dietary fat may be an important influence. Supplementation with long-chain *n*-3 PUFA reduces fasting and postprandial triacylglycerol concentrations, but the effects of other unsaturated fatty acids in this respect are not well documented.

Critical areas for future research are as follows. It is critically important that long-term (at least 6 months) studies of the effects of low-fat, high-carbohydrate diets

on plasma lipid constituents are carried out. The confusion which presently reigns over the effects of such diets is preventing their widespread acceptance (or avoidance). Important questions to be answered by such studies are:

- (1) Is the elevation of plasma triacylglycerol concentration on a high-carbohydrate diet transient?
- (2) What is the nature of the elevation of plasma triacylglycerol concentrations (large, buoyant or small, denser VLDL particles) and what is its impact on other lipid constituents (e.g. the density distribution of LDL particles)?
- (3) Is it reasonable to apply conclusions from epidemiological studies to the effects of dietary manipulation within individuals (e.g. an elevated plasma triacylglycerol concentration may be a risk factor for CHD in epidemiological terms, but does elevation of plasma triacylglycerol by dietary means confer equivalent risk?). (This will require prospective studies lasting at least 5 years with hard end-points such as incidence of CHD.)
- (4) Do beneficial effects of such diets on body-weight regulation outweigh direct effects on plasma lipid constituents?

Studies are needed of the effects of replacement of saturated fatty acids with monounsaturated fatty acids and *n*-6 PUFA, on plasma triacylglycerol concentrations, both fasting and postprandial. Any such effects must be related to changes in sensitivity to insulin and genetic factors (see section 3.2.).

Research is needed into factors acutely affecting postprandial lipaemia, including dietary fructose or sucrose, and the effects of different types of dietary fat.

4. Nutrition, substrate metabolism and physical performance

4.1. Introduction

The most important metabolic characteristic of physical exercise is the increased need for energy. Training or competition will increase the daily expenditure by 2–>4 MJ/h depending on duration and intensity.

Athletes must adapt their food consumption to meet the energy needs. This increased food intake should be well balanced, with respect to the macro- and micronutrients. However, this is not always simple. Many specific athletic events may be characterized by extremely high exercise intensities. Running a marathon, for example, costs about 10–12 MJ. Depending on the time needed to finish, this may induce an energy expenditure of approximately 3 MJ/h in a recreational athlete and 6 MJ/h in the elite athlete who finishes in approximately 2–2.5 h. A professional cycling race, such as the Tour de France, costs about 28 MJ/d, a value which will be increased to approximately 36 MJ/d when cycling over several mountain passes (Saris *et al.* 1989).

Compensating for such high expenditures by ingesting normal solid meals will pose a problem to any athlete involved in such competitions, since digestion and absorption processes will be impaired during intensive physical

activity. These problems are not exclusively restricted to competition days. During intensive training days the values for energy expenditure are impressive as well. In such circumstances athletes tend to ingest a large number of 'in-between meals', often composed of energy-rich snacks, which can be low in protein and micronutrients. As such, their diet may become imbalanced. Especially adapted foods and fluids which are easily digestible and rapidly absorbable may solve this problem. During endurance sports activity the body will use its own energy stores (fat stored as adipose tissue-triacylglycerol and carbohydrate stored as glycogen in liver and muscle). Additionally, small amounts of functional proteins (in the liver, gastrointestinal tract and muscle) will be broken down due to mechanical and metabolic stresses. These losses have to be compensated by supply of the necessary nutrients. At the same time heat will be produced, which to a large extent will be eliminated by production and evaporation of sweat. As a result, fluids and electrolytes will be lost (Brouns *et al.* 1992).

Large sweat losses may pose a risk to health by inducing severe dehydration, impaired blood circulation and heat transfer, leading to heat exhaustion and collapse (Sawka & Pandolf, 1990; Maughan & Noakes, 1991). Insufficient replacement of carbohydrate may lead to hypoglycaemia, central fatigue and exhaustion (Wagenmakers *et al.* 1991). Inadequate protein intake induces protein loss, especially of muscle and consequently a negative N balance and a reduced performance (Lemon, 1991).

These observations show that increased needs for specific nutrients should be met according to the level of daily physical activity and exercise. These requirements depend on the type, intensity and duration of the physical effort. Depending on these factors, specific nutritional measures and dietary interventions can be taken, particularly in the phases of preparation, competition and recuperation.

Some groups of athletes compete in sport events where a low body weight forms a prerequisite to perform well or to compete in a certain weight category. These athletes are on the one hand training frequently and intensively, but on the other hand they have to maintain a low body weight. The low energy intakes may in these situations lead to a low intake of essential nutrients such as protein, Fe, Ca and vitamins; the required carbohydrate intake to balance the carbohydrate used in training may also be marginal (Van Erp-Baart *et al.* 1989a,b). This aspect should receive special attention.

In the next paragraphs sports nutritional aspects, specifically those related to the macro- and micronutrients which make up the daily nutrition of individuals involved in heavy physical work or exercise, will be described (for review, see Brouns, 1993).

4.2. Carbohydrates

Carbohydrate is the most important nutrient for high-intensity performance. Energy release from carbohydrate is up to three times as fast as from fat. However, carbohydrate stores in the form of liver and muscle glycogen in the body are small. This limits the duration of high-intensity exercise. Apart from decreasing performance, carbohydrate depletion

induces an increased utilization of protein for energy production (Wagenmakers *et al.* 1991). This results in the production of NH_3 , which may enhance fatigue. Carbohydrate ingestion during exercise induces sparing of the body's carbohydrate stores, reduction of protein utilization and NH_3 production, and a delay of fatigue or improvement of performance (Costill, 1988; Coyle, 1991a,b; Wagenmakers *et al.* 1991). Adequate carbohydrate ingestion between training sessions or intense performance is of utmost importance to avoid progressive glycogen depletion and resulting fatigue development or overtraining. Carbohydrate sources to be used during exercise should be rapidly absorbable, i.e. have a high GI, and should be combined with sufficient fluid intake.

Factors that determine whether foods are 'fast or slow' carbohydrate sources have been reviewed earlier. Food properties such as particle size, integrity of cellular structure, dietary fibre content, presence of organic acids, etc. determine the rate at which the carbohydrates are absorbed. The differences between starch-containing products disappear when the starch is extracted from the original source and is ingested as pure starch. Glucose, sucrose and maltodextrins (glucose polymers) solubilized in water are all absorbed at similar rates and lead to equal oxidation rates (Coyle, 1991b; Hawley *et al.* 1992). Exceptions are fructose and galactose which are absorbed relatively slowly and also have lower oxidation rates than the aforementioned carbohydrate sources. The effects of training and dietary factors in the modulation of muscle glycogen as well as substrate utilization have recently been reviewed (Harreaves, 1995; Brouns, 1997a).

4.3. Fat

Fat is a 'slow' energy source (Newsholme & Start, 1973). When using fat as a prime energy source, athletes can only work at 40–60% of their maximal capacity. Nevertheless, increased fat utilization, as a result of training, reduces the use of carbohydrate from the stores in the body, and thus will influence carbohydrate availability and fatigue (Björntorp, 1991b). The idea that high-fat diets lead to adaptations which enhance fat oxidation during exercise in favour of glycogen sparing and performance capacity has been shown in animals. However, there is currently no evidence that this is also the case in human subjects. This topic has been reviewed by Brouns & van der Vusse (1998) and Jeukendrup *et al.* (1998).

Recently a number of studies have focused on the effect of medium-chain triacylglycerol (MCT) ingestion on substrate oxidation and performance. The results show that MCT is rapidly absorbed and oxidized. However, MCT oxidation does not lead to an increase in total fat oxidation, nor to a sparing of muscle glycogen. Additionally it was shown that the amount of MCT which can be consumed without causing gastrointestinal upset is <30 g. From these data it was concluded that MCT is a rapidly available energy source for athletes but that its consumption does not lead to measurable performance benefits (Jeukendrup *et al.* 1996).

Daily fat intake in athletes should be relatively low, 20–30% energy, allowing for an increase in the proportion

of carbohydrate in the diet in favour of restoring tissue glycogen levels after the daily training or competition sessions (Björntorp, 1991b; Coyle, 1991a,b). From a general health point of view, saturated fat sources should be avoided and vegetable-, fish- and plant-oil-based foods should be promoted.

4.4. Protein

Protein is needed for muscle growth, repair of tissues and enzymic adaptations. The protein requirement of athletes is increased and, according to present knowledge, amounts to approximately 1.2–1.8 g/kg body weight (Lemon, 1991a,b). The reason for this increase is an enhanced utilization of amino acids in oxidative energy production during physical exercise, a process which is known to be intensified at higher work levels and in a state of carbohydrate store depletion (Wagenmakers *et al.* 1991). Generally, however, the increased protein requirement is covered by an increased food intake to cover the daily energy needs.

Studies carried out during the Tour de France, for example, have shown that the mean daily energy intake amounted to <24 MJ (6000 kcal) (Saris *et al.* 1989; Van Erp-Baart *et al.* 1989a). Since the daily protein consumption (% of energy intake) remained the same, the cyclists ingested >3 g protein/kg body weight per d, more than enough to cover the increased requirement.

However, there are examples of athletes who may need to be protein-supplemented or need to increase the protein density of the diet. Athletes who ingest low-energy diets will generally have low protein intakes, which may not compensate for the net N loss from the body and will influence synthetic processes and training adaptations. To these categories belong, amongst others, body builders, athletes who have to fit into certain weight categories, gymnasts, dancers and female long-distance runners, and under certain circumstances vegetarian athletes (Van Erp-Baart *et al.* 1989a). Protein supplements such as milk and vegetable-protein hydrolysates may be useful in these cases. However, one should keep in mind that protein intake and/or supplementation above levels normally required (1.2–1.8 g/kg body weight) will not enhance muscle growth or performance (Lemon, 1991a,b).

The use of single amino acids, such as arginine, ornithine, tryptophan and branched-chain amino acids to influence metabolic pathways involved in fatigue development and hormone production, needs further research to make definite statements, especially because data on the safety aspects of high intakes of single amino acids in exercising athletes are generally lacking. Although amino acids, when supplied intravenously in high dosages, have been observed to enhance hormone release, there are no indications that this is also the case after oral ingestion of amounts which are normally present in supplements. Recently the ingestion of glutamine has been proposed as a means of supporting the immune competence of athletes involved in intense daily training. In addition, positive effects of branched-chain amino acid ingestion on the aetiology of central fatigue as well as on immune variables have recently been suggested. However, the currently available scientific data do not allow us (yet) to make

any claim in these respects (van Hall *et al.* 1995; Klarlund Pedersen & Rohde, 1997).

4.5. Fluid and electrolytes

During prolonged physical exercise an adequate supply of fluid is of prime concern for the performance capacity as well as the health status of the athlete, especially when performing in the heat. Progressive fluid loss from the body, by means of sweating and breathing and in endurance events also by diarrhoea, is associated with a decreased blood flow through the extremities, a reduced plasma volume and central blood volume, a reduction in sweating and heat dissipation, and under circumstances of high intensity work in the heat, with heat stroke and collapse (Sawka & Pandolf, 1990; Maughan, 1991; Maughan & Noakes, 1991).

Dehydration of >1.5 litres is known to reduce the O₂ transport capacity of the body and to induce fatigue. Appropriate rehydration is known to counter these effects and to delay fatigue (Sawka & Pandolf, 1990; Maughan, 1991; Maughan & Noakes, 1991). In contrast to plain water, the addition of Na and carbohydrate (up to 80 g/l) to rehydration drinks is known to stimulate water absorption (Maughan, 1991; Maughan & Noakes, 1991), as well as to supply energy. Addition of other electrolytes should generally not exceed the levels of loss with whole-body sweat (Brouns *et al.* 1992). Sport rehydration drinks should not be hypertonic because this reduces the rate of net water absorption (Maughan, 1991). Recently the importance of inclusion of a high amount of Na in post-exercise rehydration beverages has been underlined by Maughan *et al.* (1997). Aspects of dehydration and rehydration have recently been reviewed by Brouns (1997b).

4.6. Minerals

Exercise is known to be associated with increased mineral losses, through sweating during exercise and through urine in the post-exercise phase (Costill, 1988). In general, athletes may develop an impaired mineral status in cases of poor selection of food items which may lead to an inappropriate intake of some minerals, compared with the daily losses. Impaired Fe, Zn and Mg status are known to induce malperformance and muscle weakness and are often associated with the occurrence of muscle cramp. The latter needs further research to validate the direct influence of mineral deficits. As with most nutrients, mineral intake depends on the quality of the diet and the amount of energy consumed (Van Erp-Baart *et al.* 1989b). Therefore, athletes consuming low-energy diets may be at risk of marginal mineral intake, especially of Zn, Fe and Mg (Clarkson, 1991). Vegetarian athletes are especially prone to Fe deficiency. In these cases the ingestion of a daily supplement may be recommended.

4.7. Trace elements

The importance of an adequate trace element status for athletic training, performance and recovery has only received attention relatively recently (Kieffer, 1986). As

with minerals, trace elements are increasingly lost as a result of intensive physical training. Trace-element losses with sweat (Cu) and urine (Cr) may exceed the daily recommended intakes. The diet itself may strongly affect these losses. High carbohydrate intakes, especially of high-GI carbohydrates, are known to enhance losses of Cr, whereas diets rich in dietary fibre, often consumed by endurance athletes and vegetarians, are known to reduce trace-element absorption. Since science has become aware of the fact that exercise leads to enhanced tissue and cell damage, the importance of Se, which acts within the free-radical scavenging processes, has received attention. Much research is needed in this field, but it is considered that supplementation with amounts not exceeding the recommended safe daily intakes will contribute to adequate daily intakes in athletes.

4.8. Vitamins

Vitamins belong among the nutrients which have received the most attention. Vitamins are essential co-factors in many enzymic reactions involved in energy production and in protein metabolism. Any shortage of a vitamin is therefore linked to sub-optimal metabolism, which in the long term will result in decreased performance or even illness (Van der Beek, 1985). Additionally, some of the vitamins act as antioxidant substances and therefore have a protective role for tissue and cell integrity, which may be threatened in the case of metabolic stress (Bendich, 1991).

Vitamin supplementation has, thus, been shown to restore performance capacity in cases of a vitamin deficit and also to reduce tissue damage due to free radicals (Bendich, 1991; Brouns, 1993). Vitamin supplementation with quantities exceeding those needed for optimal blood levels has never been shown to improve performance (Van der Beek, 1985). As with minerals and trace elements, athletes involved in intensive training, but consuming low-energy diets, are the most prone to marginal vitamin intakes. In general it can be concluded that vitamin restoration of energy-dense processed foods for supplementation with preparations will not enhance performance but may, in athletic populations, contribute to adequate daily intakes.

Daily intake of a low-dose vitamin preparation or nutrient preparations, supplying not more than the recommended daily intake or safe intake, may be advisable in periods of intensive training or in any situation where athletes abstain from a normal diet, such as during periods of limited food intake combined with intensive training (especially in females and in athletes who have to fit into certain weight categories).

4.9. Ergogenic supplements

Substances such as creatine, caffeine, L-carnitine, aspartate, NaHCO₃, bee pollen, specific amino acids, etc. have recently received scientific attention due to their possible influence on performance, fatigue and recovery. In many cases such substances need further research to come to conclusive scientific evidence and recommendations (Brouns, 1993).

In the case of L-carnitine, for example, it has long been suggested that the oral intake of this compound leads to

improved fat oxidation which may improve athletic performance and reduce body-fat levels (Wagenmakers, 1991). These suggestions were based on *in vitro* studies. However, more recent and well-controlled human studies showed no change in muscle carnitine content after L-carnitine supplementation, nor effects on fat oxidation and performance.

The intake of bee-pollen preparations and of royal jelly has been said to initiate allergic responses in susceptible athletes, which may lead to anaphylactic shock and even death. Since there is no evidence for any performance effects of bee pollen its use by athletes should be discouraged.

Recently a number of publications have appeared with respect to creatine. The use of creatine has so far been shown to be safe and to enhance physical performance in events lasting 30 s–3 min as well as in the case of repetitive sprinting. Creatine supplementation (four doses of 5 g/d for 4–6 d) has been shown to increase the muscle total creatine content in most but not all subjects. It is hypothesized that this effect causes a better ATP transfer from mitochondria to cytosol by the creatine shuttle. This results in a reduced formation of lactic acid and NH₃ at a given work load and improved performance at a freely-chosen maximal work-load (Balsom *et al.* 1994). Creatine is a clear example of a new functional food ingredient.

Since there is a growing awareness of functional food ingredients which may affect athletic performance and health status positively, there will be a significant increase in the number of scientific studies needed to obtain evidence to support any functional claim. This development will be stimulated with the increasing knowledge about nutritional substances, which are involved in the different metabolic pathways, including brain metabolism. Judgement of the role of food-derived substances as being nutritional or pharmacological, requires research and optimal interaction between science and the food industry.

4.10. Conclusions and further research

Oral rehydration products for athletes were one of the first categories in the segment of functional foods and drinks for which scientific evidence was obtained on all levels of functionality: rapid gastric emptying, fast intestinal absorption, improved water retention, improved thermal regulation and improved physical performance and delayed fatigue.

Generally, research on nutrition for athletes has shown that the exercise-induced stress on the human body depends on the duration, intensity and type of exercise. Intense endurance exercise is characterized by changes in the functionality of the gastrointestinal system. This leads to the fact that nutrient and fluid supply during endurance exercise cannot be realized by ingestion of normal meals. Liquid food formulas, established to deliver fluid and energy-providing nutrients in a convenient way and easily digestible form, have been shown to be of benefit to athletes. Exercise-induced losses of N, minerals, vitamins and trace elements should be replenished by ingesting larger amounts of high-quality food with normal meals. However, this may be problematic in all cases where low-energy diets are combined with intense training or in the case of multiple-day competitions such as cycling tours. The use of special meals or food products and micronutrient

supplementation will help ensure adequate intakes under these conditions.

The ever increasing amount of daily high-intensity training leads to a high stress on the metabolic machinery, the musculo-skeletal system and the hormonal system. There is a growing awareness that the supply of food ingredients or food-derived substances may interact with the biochemical and physiological systems involved with physical and mental performance, as well as with recovery from intensive training and hence with the physical well-being and health of the athlete. Therefore it is emphasized that future studies are directed to the following goals:

- (1) to define the safety or toxicity of promising functional food substances or formulas, to be taken shortly before, during or after exercise. This should be realized with respect to short-term, single dosage intake, as well as long-term chronic intake;
- (2) to define the functionality of these substances in terms of their influence on factors limiting performance and recovery;
- (3) to support any claim made with respect to such improvements.

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