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REVIEW

Physiological aspects of energy metabolism and gastrointestinal effects of carbohydrates

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The energy values of carbohydrates continue to be debated. This is because of the use of different energy systems, for example, combustible, digestible, metabolizable, and so on. Furthermore, ingested macronutrients may not be fully available to tissues, and the tissues themselves may not be able fully to oxidize substrates made available to them. Therefore, for certain carbohydrates, the discrepancies between combustible energy (cEI), digestible energy (DE), metabolizable energy (ME) and net metabolizable energy (NME) may be considerable. Three food energy systems are in use in food tables and for food labelling in different world regions based on selective interpretation of the digestive physiology and metabolism of food carbohydrates. This is clearly unsatisfactory and confusing to the consumer. While it has been suggested that an enormous amount of work would have to be undertaken to change the current ME system into an NME system, the additional changes may not be as great as anticipated. In experimental work, carbohydrate is high in the macronutrient hierarchy of satiation. However, studies of eating behaviour indicate that it does not unconditionally depend on the oxidation of one nutrient, and argue against the operation of a simple carbohydrate oxidation or storage model of feeding behaviour to the exclusion of other macronutrients. The site, rate and extent of carbohydrate digestion in, and absorption from the gut are key to understanding the many roles of carbohydrate, although the concept of digestibility has different meanings. Within the nutrition community, the characteristic patterns of digestion that occur in the small (upper) vs large (lower) bowel are known to impact in contrasting ways on metabolism, while in the discussion of the energy value of foods, digestibility is defined as the proportion of combustible energy that is absorbed over the entire length of the gastrointestinal tract. Carbohydrates that reach the large bowel are fermented to short-chain fatty acids. The exact amounts and types of carbohydrate that reach the caecum are unknown, but are probably between 20 and 40 g/day in countries with 'westernized' diets, whereas they may reach 50 g/day where traditional staples are largely cereal or diets are high in fruit and vegetables. Non-starch polysaccharides clearly affect bowel habit and so, to a lesser extent, does resistant starch. However, the short-chain carbohydrates, which are also found in breast milk, have little if any laxative role, although do effect the balance of the flora. This latter property has led to the term 'prebiotic', which is defined as the capacity to increase selectively the numbers of bifidobacteria and lactobacilli without growth of other genera. This now well-established physiological property has not so far led through to clear health benefits, but current studies are focused on their potential to prevent diarrhoeal illnesses, improve well-being and immunomodulation, particularly in atopic children and on increased calcium absorption.
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Introduction

All organisms require fuels to maintain their life cycles. For humans, carbohydrates are the major fuels, typically accounting for 45–70% of the total energy intake and expenditure. Despite their importance in energy metabolism, the energy values of some carbohydrates continue to be debated and are confused due to the existence of different energy systems, which are not entirely consistent with each other (for example, combustible, digestible energy (DE), metabolizable energy (ME), net metabolizable energy (NME) systems; general and specific Atwater systems). The choice of energy system is of considerable importance because it not only affects the energy values of carbohydrates, but also those of fats, proteins and alcohol (FAO,

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2003). In establishing the energy values of carbohydrates, it is not only necessary to consider their intrinsic physicochemical properties, but also their physiology, specifically, their digestibility, the end products of their metabolism and even the pathways by which they are metabolized. Since it is desirable to use the same energy system for all macronutrients, it is appropriate to consider at least briefly the energy values of carbohydrates, fats and proteins as a combined entity. Similarly, the role of carbohydrates in energy balance can only be adequately examined by considering the broader perspectives of energy homeostasis, which involve all macronutrients.

The site of carbohydrate breakdown in the gut, the rate and extent of breakdown, and the kinetics of absorption are key to understanding many other roles that carbohydrate plays beyond providing energy. In the large bowel, dietary carbohydrate interacts with a rich and diverse microbiota that produce end products unique to the body. This process of fermentation affects bowel habit, transit time, mucosal health, and also provides products to the portal and systemic circulation, thus effecting metabolism both within and beyond the gut.

In this paper, we have focused on areas where there has been progress since the 1997 consultation, or where there is substantial controversy. The implications for the glycaemic response and for conditions such as diabetes, obesity and cancer are dealt with in other papers in this expert review. The evidence reviewed is primarily from human studies.

Energy values of carbohydrates and other macronutrients

Figure 1, which is a modification of previous diagrams (Warwick and Baines, 2000; Livesey, 2001; FAO, 2003), shows the flow of energy through the body. It presents a conceptual framework for considering energy values of foods and individual macronutrients. The pathway begins with the combustible energy intake that depends on the physicochemical characteristics of ingested macronutrients, and not on physiological processes. There are then three subsequent consecutive steps, each of which depends on the previous one. Each of these depends on physiological processes: digestibility (relevant to DE), metabolizability (relevant to ME) and relative metabolic (bioenergetic) efficiency (relevant to NME). These are considered separately below.

Combustible energy

Combustible energy refers to the heat released during complete combustion of foodstuffs or macronutrients in the presence of O_2, to yield CO_2 and H_2O. The heat of combustion of amino acids/protein is reported in various ways, for example with S being in elemental form, as SO_3, or H_2SO_4. In the comprehensive analysis provided by Elia and Livesey (1992), the end products are H_2O (liquid), CO_2 (gas), N_2 (gas) and $H_2SO_4.115H_2O$. Combustible energy has also been called the heat of combustion, gross energy, intake energy and energy intake. Since some of these terms can be confused with DE and ME intake, the term combustible intake of energy (cIE) will be used in this paper, because it is self-explanatory and less likely to be misinterpreted or confused with other terms.

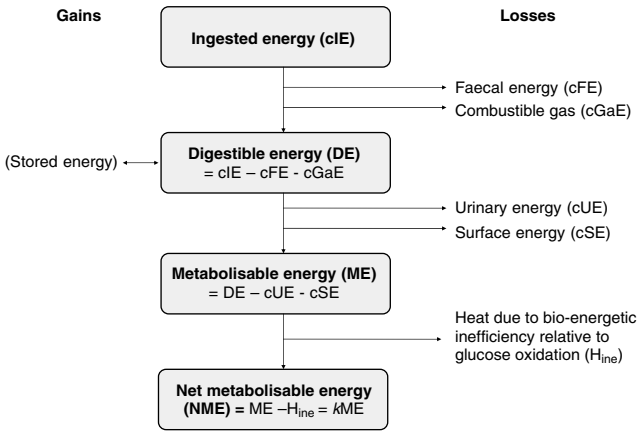

Figure 1 Diagram showing the flow of energy through the body. The abbreviations cIE, cFE, cGaE and cSE refer to combustible intake energy (cIE), combustible faecal (cFE), gaseous (cGaE) and surface energy (cSE), respectively. H_{ine} is the heat released as a result of metabolic inefficiency in performing metabolic and external work relative to glucose. The coefficient k reflects this metabolic efficiency. The equations shown in the diagram apply in states of nutrient balance. In situations where excess energy is deposited, metabolizable energy (ME) and net metabolizable energy (NME) of the diet includes the energy that would be made available through mobilization and oxidative metabolism of the stored energy.

The combustible energy values for hexose-based carbohydrates (kJ/g) are generally between 15.5 and 17.5 kJ/g (less than 15% difference) (Table 1) (Livesey and Elia, 1988; Elia and Livesey, 1992), and are more than twofold lower than those of typical fats. Since carbohydrates are more oxidized than fats (their carbon skeletons are linked to relatively more oxygen and less hydrogen), they generate less heat than fat when fully combusted with oxygen. The variability in heat of combustion of different hexose-based carbohydrates (kJ/g) is almost entirely determined by the number of glycosidic bonds, the formation of which is associated with loss of one molecule of water (water of condensation) per glycosidic bond (Elia and Livesey, 1992). When the heat of combustion of hexose-based carbohydrates is expressed as monosaccharide equivalents, the values are very consistent with each other (~15.7 kJ/g, rounded to 16 kJ/g). The value for glycogen is only approximately 1.3% greater than that of glucose (Elia and Livesey, 1992), the difference being due to the heat released during the breakdown of the glycosidic bonds (in living organisms, this is achieved through enzymatic hydrolysis of glycosidic bonds (heat of hydrolysis). Glucose monohydrate is unusual in being hydrated

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Table 1 The RQ (CO_2 production/O_2 consumption), combustible energy equivalents of CO_2 ($cEeqCO_2$) and O_2 ($cEeqO_2$), and the heat of combustion of the major macronutrients and specific carbohydrates[a]

	RQ	*$EeqO_2$ (kJ/l)*	*$EeqCO_2$ (kJ/l)*	*Heat of combustion (kJ/g)*
Macronutrients				
Carbohydrate	1.000	21.12	21.12	17.51
Fat	0.710	19.61	27.62	39.42
Protein	0.835	19.48	23.33	23.64
Alcohol	0.667	20.33	30.49	29.68
Specific carbohydrates				
Starch	1.000	21.12	21.12	17.48
Glycogen	1.000	21.12	21.12	17.52
Sucrose	1.000	20.97	20.97	16.48
Maltose	1.000	20.99	20.99	16.49
Lactose	1.000	21.00	21.00	16.50
Glucose	1.000	20.84	20.84	15.56
Galactose	1.000	20.84	20.84	15.56
Fructose	1.000	20.91	20.91	15.61
Glycerol	0.857	21.16	24.69	18.03
Erythritol	0.889	20.91	23.53	17.27
Xylitol	0.909	19.92	21.91	16.96
Sorbitol	0.923	20.89	22.71	16.71
Mannitol	0.923	20.89	22.71	16.71
Maltitol	0.960	20.87	21.74	16.98
Lactitol	0.960	20.87	21.74	16.98
Isomalt	0.960	20.87	21.74	16.98

Abbreviations: $EeqCO_2$, energy equivalents of CO_2; $EeqO_2$, energy equivalents of O_2; RQ, respiratory quotient.
[a]The values are based on the characteristics of the nutrients and are independent of whether they are endogenous or exogenous or whether they are given orally or intravenously. Based on Elia and Livesey (1992) and unpublished data.

and having a low-energy density (14.1 kJ/g), but when expressed as anhydrous glucose, the value becomes 15.6 kJ/g.

The heat of combustion of polyols (alcohol derivatives of sugars), as for other carbohydrates, depends on their composition and number of glycosidic linkages. For many the values are ~17.0 kJ/g (for example, 16.70–17.2 kJ/g for erythritol, isomalt, lactitol, maltitol, mannitol, sorbitol, xylitol) (Elia and Livesey, 1992; Livesey, 1992). Glycerol (triol), which is also a polyol, has a relatively high heat of combustion (18 kJ/g). The values for polysaccharides that reach the colon do not differ substantially from those for starch or glycogen (for example, 17.5 kJ/g for guar gum and solka-floc cellulose, 17.2 kJ/g for pectin, but as low as 15.5 kJ/g for psyllum gum and as high as 17.6 kJ/g for sugar beet fibre) (Livesey, 1992; Livesey and Elia, 1995). The mean values for non-starch polysaccharides (NSP) in cereals have been reported to be 17.5 (range 16.6–18.5) kJ/g, vegetables, 16.8 (range 16.6–17.9) kJ/g, and fruits 16.5 (range 14.9–17.3) kJ/g. Hydroxyl-propylmethyl cellulose, a chemically modified NSP, has a particularly high heat of combustion (22.0 kJ/g), which is due to the high heat of formation of the substituted side chains. The values for oligosaccharides, such as polydextrose, polyfructose and soya bean oligosaccharides are between 16.8 and 17.0 kJ/g. It is estimated that the average combustible energy of NSP in mixed conventional diets is approximately 17.0 kJ/g, compared to 15.7 kJ/g for carbohydrates (as monosaccharide equivalents) that are absorbed by the small bowel ('available carbohydrates').

The principles of thermodynamics imply that the heat released when carbohydrates are completely combusted in a bomb calorimeter in the presence of oxygen is the same as when the same quantity of carbohydrate is fully oxidized to H_2O and CO_2 by living organisms through a large series of metabolic steps. However, ingested macronutrients may not be made fully available to tissues, and the tissues themselves may not be able to fully oxidize substrates made available to them. Therefore, for certain carbohydrates, the discrepancies between combustible energy (cEI), DE, ME and NME may be considerable.

Digestible energy

It is obvious that substances that are not absorbed cannot be metabolized by human tissues. For the purposes of energy metabolism, digestibility is defined as the proportion of combustible energy that is absorbed over the entire length of the gastrointestinal tract. DE ($DE = cIE \times digestibility$) is estimated as the difference between the combustible energy present in ingested food and that present in faeces (+combustible gases, such as H_2 and CH_4 which are excreted).

$$DE = cIE - cFE - cGaE$$

The 'c' in cIE (combustible intake energy), cFE (combustible faecal energy) and cGaE (combustible gaseous energy) indicates that it is the heat of combustion that is being considered, thus avoiding confusion with DE, ME and NME values. DE is actually an 'apparent' energy value, because the flux of nutrients into and out of the colon is not unidirectional. For example, mucus is secreted into the large bowel (estimated to be 2–3 g/day, but in certain diseases affecting the large intestine, the amount may be considerably more). In addition, desquamated colonic cells are shed directly into the lumen of the colon, which may also receive desquamated cells from the small intestine. Some of the energy from these sources, which is not present in the diet, may be lost to faeces, reducing the apparent digestibility of the diet. Another problem concerns loss of energy in the form of combustible gaseous products (flatus + breath), which was neglected in early human studies. The result is that DE intake was slightly overestimated. However, this omission makes very little overall difference to DE intake because a relatively small amount of energy is lost in this way in humans. Whole body calorimetry studies over 24 h in healthy subjects have measured the excretion of H_2 and CH_4 (via flatus and breath) and found it to be small (usually <1 l/day) (Poppitt *et al.*, 1996; King *et al.*, 1998), with variable and sometimes an inverse relationship between H_2 and CH_4 excretion. This may correspond, very approximately, to about 3–5% of the

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combustible energy of the fermentable carbohydrates entering the colon (0.50–0.85 kJ/g, sometimes rounded up to 1 kJ/g of fermentable carbohydrate) and 0.3–0.5% of total combustible carbohydrate intake when 10% of it enters the colon as fermentable carbohydrate. Most H_2 and CH_4 are excreted in flatus, especially at high rates of net gaseous production, but a variable proportion is absorbed and excreted unchanged in breath (cf. definition of DE above, which involves absorption of gases produced during fermentation, which contributes to the overall 'digestibility' of energy).

It should be noted that the digestibility and DE values are mean values obtained in subjects without disease. It is recognized that digestibility, and therefore DE (kJ/g), vary between individuals and are affected by both age (for example, the fractional absorption of some macronutrients, is less in young infants than adults) and disease (malabsorption disorders). There may also be interaction between nutrients. For example, studies in rats suggest that guar gum and some pectin preparations induce substantial faecal fat loss, although quantitatively important interactions of a similar kind were not observed in humans (Rumpler *et al.*, 1998). One study in healthy volunteers showed that an increase in dietary fibre intake from 15 to 46 g/day, through addition of pectin to the diet, increased fatty acid excretion from 1.5 to 2.7 g/day (Cummings *et al.*, 1979). Another study reported a smaller increase in fatty acid excretion when dietary fibre intake was increased from 17 to 45 g/day through addition of wheat bran to the diet (Cummings *et al.*, 1976). The possibility that quantitatively greater interactions occur with novel fats cannot be excluded. Dietary fibre has also been repeatedly reported to increase N excretion, but at least some of this N originates from urea, which passes through the colonic mucosa to reach bacteria and which also enters the colon through the ileocaecal valve, which allows transfer of small intestinal fluid from the small to the large intestine. Fat and protein (non-nitrogenous component) in biomass are generally thought to be generated from fermentable carbohydrate. High intakes of fibre may also increase shedding of mucosal cells, containing some fat and protein) into the lumen of the gut.

For carbohydrates that are considered to be fully digested and absorbed by the small intestine (digestibility = 1.0; for example, glucose, fructose, lactose, sucrose and starch), DE is identical to cIE. For carbohydrates that are not absorbed at all, DE and digestibility are zero (although their cIE is similar to that of other types of carbohydrates (kJ/g)).

The DE of carbohydrate that reaches the colon ('unavailable carbohydrate') is lower than its cEI, partly because some are not fermented (faeces generally contain some of this carbohydrate) and partly because some of the products of fermentation are lost to faeces (for example, as bacterial biomass). Virtually, all the short-chain fatty acids (SCFAs) produced during fermentation are absorbed through the colon and metabolized by human tissues (butyrate is also actively metabolized by the colonic mucosa). Guar gum, which is completely fermented, contributes about 60% of its cIE to SCFAs; pectin, which is about 95% fermented contributes a little less of its energy to SCFAs; and other types of carbohydrates, which are poorly fermented (for example, Solka-floc) contribute very little of their energy to SCFAs (Livesey and Elia, 1995). For traditional foods (foods listed in the 1978 edition of *McCance and Widdowson's Composition of Foods* (Paul and Southgate, 1978), a general fermentability value of 70% seems reasonable (Livesey and Elia, 1995; FAO, 1998), since 30% of the NSP is excreted in faeces over a wide range of intakes. This is in agreement with intestinal balance studies and net production rates of SCFAs, which are almost entirely available for metabolism by human tissues (Livesey and Elia, 1995), with lower efficiency than glucose (H_{ine} is used to indicate the heat released as a result of this metabolic inefficiency relative to glucose). A schematic diagram (Figure 2) can help understand how standard reference values for DE (and ME) of NSP and other carbohydrates reaching the colon ('fibre') are established, assuming that 70% are fermented there. For historical reasons, values for the energy values of 'fibre' largely developed from meta-analyses of studies using either the AOAC (2002) or Southgate (1969) analytic procedures, which corresponds approximately to NSP + resistant starch (RS).

$$\begin{aligned} DE &= cIE - cFE - cGaE \\ &= 17.0 - 8.7 - 0.6 kJ/g \\ &= 7.7 kJ/g \end{aligned}$$

The value for cFE (8.7 kJ/g) is the sum of the cIE of unfermented carbohydrate (5.1 kJ/g or 30% of the total cIE of the carbohydrate entering the colon; Figure 2) and products of fermentation lost to faeces (mainly bacterial matter) (3.6 kJ/g). Another way of calculating the same result is to use a fractional intestinal balance approach. Since 70% of carbohydrate that reaches the colon is fermented, of which ~65% is transformed into SCFAs (~60%) plus gaseous energy (5%), then the following equation applies:

$$\begin{aligned} DE &= 17.0 \times 0.7 \times 0.65 \\ &= 7.7 kJ/g \end{aligned}$$

For simplicity, the figure assumes that 5% of the energy of fermented carbohydrate is lost as fermentation heat and another 5% as gaseous energy, although it is more likely to be 7 and 3%. The results also vary between subjects. For example, calculations based on balance studies carried out in six subjects who were studied in a metabolic unit and whole body calorimeter indicate that 3.8 ± 2.8% of fermentable energy (NSP + RS) was lost as gaseous energy (H_2 and CH_4) (Poppitt *et al.*, 1996). The values for individual types of fermented carbohydrate differ, partly because the proportion fermented varies and partly because products of fermentation also vary (that is, bacterial biomass plus gaseous products, which are excreted vs SCFAs, virtually all of which are absorbed and metabolized by human tissues) (Livesey and Elia, 1995).

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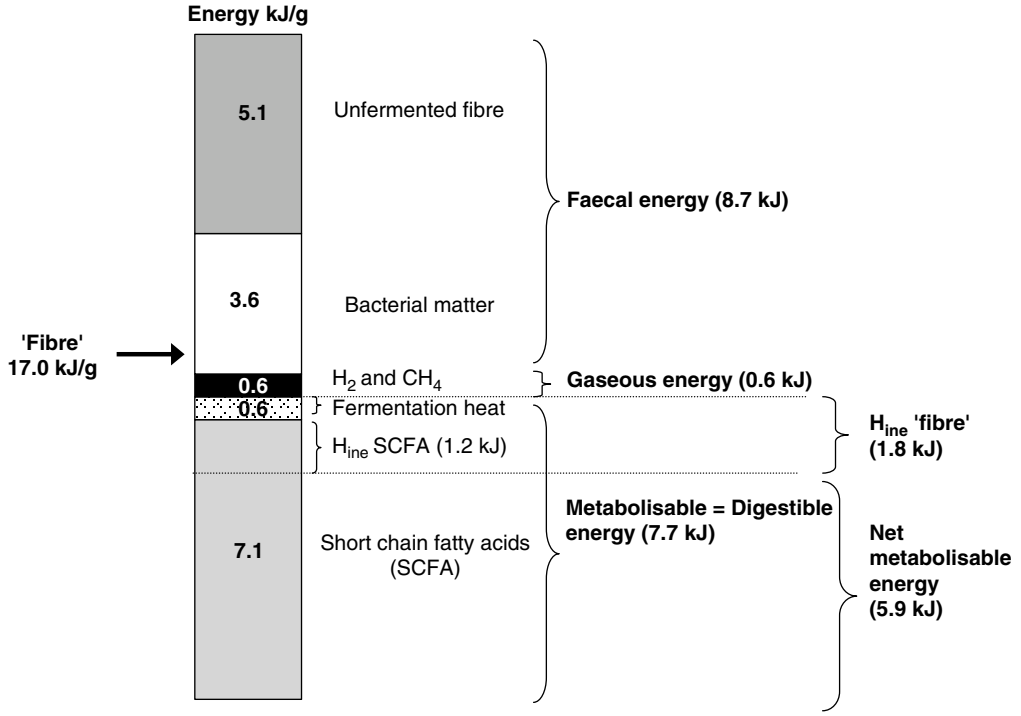

Figure 2 The fate of 'fibre' ingested with conventional foods. It is assumed that 70% is fermented, so that 5.1 kJ/g (30% of the combustible intake energy (cIE) is lost to faeces unchanged. Of the fibre that is fermented, 5% of the cIE energy is lost as gaseous products (H_2 and CH_4), and another 5% as heat of fermentation, which contributes to metabolizable energy. The majority (60% of cIE) is converted to short-chain fatty acids, almost all of which are absorbed and metabolized by human tissues, or lost to faeces (30% of cIE), mainly as bacterial biomass. Of the energy initially present in total fibre (fermentable and non-fermentable) 51.0% is lost to faeces, 3.5% to gaseous products and the remaining 45.5% accounts for metabolizable energy.

Similar calculation procedures to the above can be used to establish DE values of polyols. Like NSP, polyols are a heterogeneous group of substances (Bernier and Pascal, 1990; Japanese Ministry of Health, 1991; Livesey, 1992; FASEB 1994; Finley and Leveille, 1996) that have different physiological properties. For example, glycerol, like glucose, is fully absorbed (digestibility = 1.0), and therefore its DE is the same as its cEI (18.0 kJ/g). Although other polyols, such as isomalt, lactitol, maltitol and erythritol, have a cEI of 16.70–17.20 kJ/g, their DE values (11.0–16.61 kJ/g) are 65–97% of their cEI. In contrast, virtually, all the lactitol in food escapes digestion and absorption by the small bowel and finds its way into the large bowel, where about 60% of its cIE is converted to SCFAs, which are subsequently absorbed by the colon (cIE, 17.0 kJ/g; DE, estimated to be about 11.1 kJ/g (DE = 0.65cIE)). With the increasing use of different types of polyols in foods, it is becoming apparent that their digestibility, the extent to which they are absorbed by the small bowel and the extent to which they are subsequently metabolized by human tissues varies so much (see below) that it might be appropriate to use individual rather than generic energy values. A further potential complexity is that polyols may be handled differently by the gut (resulting in different digestibility and DE values) when taken in foods compared to drinks. However, food regulations normally prohibit the use of polyols in drinks. An exception is the use of erythritol, which is hardly metabolized once absorbed and hardly fermented when reaching the colon. An issue for further consideration is whether low-dose polyols should be used in drinks.

Metabolizable energy

By convention, the metabolizable dietary energy (ME) is measured at zero nitrogen and energy balance. In these circumstances, ME is the component of DE that produces heat during oxidative metabolism. It does not include energy that is lost to urine (combustible urinary energy (cUE; for example, urea, which is a partially combusted end product of protein metabolism or unmetabolized urinary polyols) or body surfaces (combustible surface energy (cSE; for example, desquamated cells, hair loss, perspiration), because this energy is not used in metabolism. Therefore, ME can be defined mathematically as follows:

$$ME = DE - cUE - cSE$$

Since DE = cIE–cGaE, the following also applies:

$$ME = cIE - cGaE - cUE - cSE$$

In normal healthy subjects, loss of surface energy is small and can be ignored. For many carbohydrates (for example,

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glucose, starch, NSP) there is also negligible loss of cIE to urine, and so cUE can also be ignored. Under these circumstances (which do not apply to many polyols), the following equation is valid

$$DE = ME$$

For carbohydrates that are fully absorbed and fully metabolized to CO_2 and H_2O ('available carbohydrates', for example, glucose, starch), the following equation also applies:

$$cIE = DE = ME$$

For other types of carbohydrates, ME is less than cIE, either because there is some loss of cIE to faeces (cFE) and/or urine (cUE), as in the case of some polyols. Polyols, which are often used as bulk-sweetening agents, have fewer detrimental effects on teeth, lower glycemic indices and lower ME values than conventional sweet sugars (for example, glucose, fructose, sucrose). The proportion absorbed by the small intestine varies considerably with the type of polyol (Bernier and Pascal, 1990; Livesey, 1992; Finley and Leveille, 1996), and tends to decrease with increasing molecular weight. As much as 35% of the energy of polyols can be accounted for in faeces (digestibility of energy, 65–100%; although polyols are fermented and not recovered in faeces, some of the products of this fermentation are recovered in faeces). In addition, a variable proportion of absorbed polyols is lost in urine. A detailed discussion about the extent of absorption and metabolism of polyols by bacteria in the human colon and by human tissues is beyond the scope of this paper. However, the following brief points illustrate the variability in their physiological handling. The small intestine absorbs only about 2–5% of lactitol, which is almost completely recovered in urine (95%), with little oxidation by human tissues (suggested by studies involving intravenous administration of C-labelled lactitol (Bernier and Pascal, 1990)). The small intestine absorbs ~25% of mannitol and, like lactitol, it is almost totally excreted in urine without metabolism by human tissues (again suggested by intravenous administration of labelled (Nasrallah and Iber, 1969) and unlabelled (Nasrallah and Iber, 1969) mannitol). In contrast, glycerol is completely absorbed and metabolized by human tissues, without excretion in urine. Sorbitol is absorbed to the extent of ~50%, of which the majority (~85%) is metabolized by human tissues (Finley and Leveille, 1996).

Most studies assessing ME of diets have been carried out in subjects close to N and energy balance. The DE and ME systems appear to overestimate DE and ME when energy intake is low, especially when accompanied by high NSP intake because apparent digestibility tends to be lower. Food energy values reflect the supply of energy and not whether it is spent. Some energy is deposited during growth and development of obesity. The combustible energy that is deposited in such situations corresponds to DE, which may not be made available to oxidative metabolism, if for example it is retained during the growing process. Some of it may not be made available even if it were mobilized and metabolized, because incompletely combusted products of metabolism, such as urea, are excreted in urine (for protein, DE > ME). However, when carbohydrate is mobilized, it is usually totally oxidized (combustible energy = DE = ME). The issue is discussed further below—'Calculating energy balance'.

DE and ME values may be influenced by genetic factors and disease. For example, although lactose is assigned a digestibility coefficient of 1.0, so that cIE = DE (also = ME), in subjects with lactose malabsorption (Matthews *et al*., 2005; Montalto *et al*., 2006) (due to genetic factors that can affect entire populations, or to damage of intestinal lactase by gastroenteritis or enteropathy), not all the lactose is hydrolyzed and absorbed by the small intestine. Some of it reaches the colon, where it is fermented to produce faecal matter and gaseous end products (both of which reduce DE and ME) and SCFAs, which are absorbed and metabolized by human tissues. Another example concerns fructose, which when ingested in small quantities is fully absorbed by the small intestine, but when ingested in large quantities, can reach the large bowel, where it is fermented (Truswell *et al*., 1988). This fermentation results in some loss of energy to faeces (cFE) (for example, as bacterial biomass), which again reduces its DE and ME values. Yet another example involves loss of glucose in the urine of diabetic patients (metabolizability of < 1.0; and ME < DE). Since DE and ME values vary between individuals and are affected by disease, the values in general use are based on average results obtained in 'healthy' subjects using doses of substrates that are likely to be ingested. Any errors in establishing DE values will not only affect ME values but also NME values, which is discussed next.

Net metabolizable energy

A criticism that has been raised against the ME system is that it fails to consider differences in the efficiency with which substrates supply biologically useful energy. The NME system is based on the concept of biological efficiency at the level of ATP and takes into account two specific processes, both of which have the effect of reducing metabolic efficiency. First, the heat of fermentation does not yield ATP to the host. Since this lowers the overall bioenergetic efficiency of the fermentable substrate, some workers have suggested using the term 'true metabolizable energy', which they have defined as ME minus the heat of fermentation (Bar, 1990; Bernier and Pascal, 1990). This approach, which is used in animal nutrition, differs from that in human nutrition, where the heat of fermentation is included in ME. Second, different fuels yield net ATP (ATP gain) with different bioenergetic efficiencies (Elia and Livesey, 1988, 1992; Blaxter, 1989). Those with lower efficiencies (for example, protein) will result in more heat production for the

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same useful metabolic or external physical work done than in those with higher efficiencies (that is, more heat is released for the same ATP gain). The NME system aims to make the energy values of all fuels equivalent at a biochemical level (isobioenergic). It does this by adjusting ME values to take into account differences in the energetic efficiency with which net ATP is generated. A theoretical approach, which is discussed first, has been found to agree remarkably well with an empirical approach based on measurements obtained by indirect calorimetry, which is discussed later.

The energy equivalent of ATP is the heat generated during oxidation of a substrate (ME) divided by the number of moles of ATP gained through specified oxidative metabolic pathways. To understand this, it is necessary to clarify four points (Elia and Livesey, 1988, 1992).

(1) Application of NME does not require an understanding of how ATP is generated, any more that than application of ME requires an understanding of the complex processes of digestion and fermentation, which are quantitatively poorly understood and variable.
(2) ATP gain does not mean that ATP accumulates: ATP has a small pool size with a very rapid turnover. Therefore, the term 'ATP gain' refers to the ATP made available to the body for metabolic or external work.
(3) Some pathways involve both production and utilization of ATP. For example, during glucose oxidation, one ATP is obligatorily used in the initial activation of glucose to glucose 6-phosphate and another for the conversion of fructose-6-phosphate to fructose-1,6-biphosphate. Therefore, two extra moles of ATP are produced than are gained. The term 'ATP gain' refers to the net gain of ATP (total ATP produced minus ATP utilized obligatorily during the oxidation of a substrate).
(4) ATP gain, which refers to the net provision of energy in the form of ATP, has to be distinguished from biochemical processes, including substrate cycling (for example, fatty acid-acetyl-CoA recycling or glucose-lactate recycling) that utilizes ATP. The two should not be confused because they are on different sides of the ATP balance equation (ATP gain = ATP utilized).

The NME system is based on the concept of relative metabolic efficiency. Although uncoupling of oxidative phosphorylation increases the amount of heat released per ATP gained, this affects all macronutrients, so that the ratio of metabolic efficiency between two macronutrients is expected to change much less than that associated with a single nutrient. This is confirmed quantitatively by theoretical models of progressive uncoupling (Livesey, 1984, 1986). By convention, the NME system expresses efficiency of nutrients relative to glucose, which is assigned an efficiency coefficient of 1.0 ($k_{glucose} = 1.0$)(Dutch Nutrition Council, 1987; Blaxter, 1989; Livesey and Elia, 1995).

$$k_{(nutrient)} = \text{kJ}(\text{ME}_{glucose})\text{ per ATP gain}/\text{kJ}(\text{ME}_{nutrient})\text{ per ATP gain}$$
$$= \text{ATP gain per kJ}(\text{ME}_{nutrient})/\text{ATP gain per kJ}(\text{ME}_{glucose})$$

The following equations show how the coefficient, $k_{nutrient}$, is related to its NME ($NME_{nutrient}$).

The lower the value of $k_{nutrient}$, the greater the metabolic inefficiency relative to glucose and the greater the amount of heat released for the same ATP gain (Livesey, 1984; Elia and Livesey, 1988, 1992; Livesey and Elia, 1995).

The term H_{ine} is the extra heat released as a result of metabolic inefficiency relative to glucose (that is, extra heat released for the same ATP gain). H_{ine} is therefore a component of total heat release.

$$\begin{aligned}\text{NME}_{nutrient} &= k_{nutrient} \times \text{ME} \\ &= \text{ME}_{nutrient} - ((1 - k_{nutrient}) \times \text{ME}_{nutrient}) \\ &= \text{ME}_{nutrient} - \text{H}_{ine}\end{aligned}$$

Since H_{ine} is the heat released as a result of the metabolic inefficiency (relative to glucose) ($H_{ine} = (1-k_{nutrient}) \times ME_{nutrient}$), $1-k_{nutrient}$ can be regarded as the metabolic inefficiency coefficient relative to glucose. The overall values for k (and therefore $1-k$) for carbohydrates fermented in the large bowel takes into account not only the relative metabolic inefficiency of oxidizing the products of fermentation (SCFAs are absorbed and oxidized by human tissues), but also the heat of fermentation, which is not associated with ATP gain to the host. Both of these elevate the overall energy equivalent of ATP gain relative to glucose, and decrease the overall value for $k_{nutrient}$ (or increase the inefficiency coefficient, $1-k_{nutrient}$), with a resulting increase in heat production (H_{ine}).

The metabolic efficiency with which fats are oxidized is 98% that of glucose, proteins about 80%, alcohol about 90%, SCFAs (direct oxidation) about 85–90%. Various scholars and committees have established theoretical values of efficiency of substrate oxidation relative to glucose from the stochiometry of metabolic pathways (summarized by G Livesey) with the following ranges: protein (Blaxter, 1971, 1989; Schulz, 1975, 1978; Flatt, 1978, 1980, 1987, 1992; Livesey and Elia, 1985; Life Sciences Research Office, 1994; Black, 2000), 0.78–0.85 (mean, 0.81); fat (Armstrong, 1969; Schulz, 1975, 1978; Flatt, 1978, 1980, 1987, 1992; Livesey and Elia, 1985; Blaxter, 1989; Black, 2000), 0.97–1.01 (mean 0.98); fermentable carbohydrate (British Nutrition Foundation, 1990; Life Sciences Research Office, 1994; Livesey, 2002), 0.74–0.75 (mean, 0.74); and mixed short-chain organic acids (Armstrong, 1969; Livesey and Elia, 1985; Dutch Nutrition Council, 1987; Livesey, 1992; Life Sciences Research Office, 1994), 0.83–0.87 (mean, 0.85). In the case of oxidation of SCFAs by human tissues, this means that about 10–15% more heat is released for a given ATP gain than when glucose is oxidized to yield the same ATP gain. However, in subjects ingesting 80 g protein and only 20 g 'fibre', the excess heat

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generated through bioenergetic inefficiency during protein oxidation is ~10-fold greater than during SCFA oxidation (~5-fold greater than the overall H_{ine} of fibre, which includes the heat of fermentation). This is mainly because more protein is oxidized than in SCFAs, and partly because the bioenergetic inefficiency in generating ATP is greater during protein oxidation than in SCFA oxidation. The inefficiency associated with the metabolism of NSP as a whole not only takes into account the bioenergetic inefficiency of oxidizing SCFAs but also the heat of fermentation (overall metabolic efficiency of fermentable NSP ~72.5% that of glucose). Even so, the heat released as a result of metabolic inefficiency relative to glucose (H_{ine}) remains quantitatively more important with protein than with NSP mainly because much more protein than NSP is usually ingested. However, in subjects ingesting large amounts of NSP and relatively little protein, as in some low-income countries, the heat released as a result of metabolic inefficiency associated with these two macronutrients can be almost equivalent.

To examine the validity of the NME system, theoretically calculated *k* coefficients were compared to those based on experimental observations obtained in human studies that involved calorimetry (for example, whole body 24 h calorimetry), N balances, and in some cases measurement of H_2 and CH_4 excretion (Livesey, 2001). In these studies, measurements of energy expenditure were undertaken in subjects given a control diet or a test diet, which differed from the control diet in that available carbohydrate was exchanged for a test substrate (for example, protein, which has a lower *k* coefficient than glucose). Test diets, which had lower k_{diet} coefficients than control diets, would be expected to be associated with greater energy expenditure (more heat production). The increased heat production (H_{ine}) on the test diet (after adjusting for energy and N balance) was used to calculate $k_{(nutrient)}$ ((ME–H_{ine})/ME), assuming that ATP gain remained unchanged under the conditions of the study, which involved undertaking a fixed pattern of physical activity in ambient temperatures of thermal comfort. The mean results obtained by the theoretical and experimental approaches are strikingly similar (Table 2). The same type of approach has been used to establish coefficients for *k* for the NME system in animals, and again the similarities between theoretical and experimental approaches are striking (Livesey, 2001). However, as is the case for DE and ME evaluation of foods, time-consuming studies cannot realistically be undertaken to establish efficiency values for large numbers of foods reported in food tables. Therefore, some of the recent developments and applications of the human NME system have relied heavily on the theoretical approach.

Detailed theoretical considerations about potential alternative pathways for generating ATP gain from the same substrate are beyond the scope of this paper (for example, cytosolic vs mitochondrial activation of SCFAs, net lipogenesis from glucose; Elia and Livesey, 1988; Livesey and Elia, 1995; and oxidation of alcohol with alcohol dehydrogenase or mixed function oxidase). However, alternative pathways are considered to have small effects on the overall energy equivalents of ATP. In addition, some processes may also operate only in unusual circumstances. For example, 24-h whole-body indirect calorimetry shows that it is unusual for individuals ingesting a western-type diet to achieve a non-protein respiratory quotient above 1.0, which would indicate net lipogenesis from carbohydrate (although persistent overfeeding with large amounts of carbohydrate can do this, for example, during nutritional repletion of malnourished subjects; Pullicino and Elia, 1991). The energy equivalent of ATP associated with low to moderate intake of alcohol was established using the pathway involving alcohol dehydrogenase, and its validity confirmed by calorimetry studies (Table 2).

Table 2 A comparison of experimentally obtained and theoretical values of metabolic efficiency of macronutrients relative to glucose ($k_{nutrient}$)[a]

Macronutrient (number of studies)	*Relative metabolic efficiency ($k_{nutrient}$)*	
	Experimentally obtained mean ± s.e.m.	*Theoretical*
Fat ($n=8$)	0.97 ± 0.01	0.98
Protein ($n=9$)	0.79 ± 0.02	0.80
Fermentable unavailable carbohydrate ($n=8$)	0.71 ± 0.09	0.76
Alcohol ($n=3$)	0.90 ± 0.04	0.90

[a]Based on Livesey (2001).

The NME system has been supported by many national committees in different countries, and the FAO has recommended that it should be considered for food labelling, for food tables and when calculating practical food needs from energy requirements. General values for the major macronutrients and specific values for different types of carbohydrates are shown in Table 3 (Livesey, 2003a), together with combustible digestible and metabolizable conversion factors.

Variability in energy values

DE, ME and NME values for specific carbohydrates do not necessarily apply in all circumstances. For example, in some individuals, carbohydrates may be totally metabolized by human tissues after complete absorption by the small intestine, whereas in others, they are incompletely digested and absorbed by the small intestine (for example, lactose malabsorption, which can be elicited more readily certain ethnic groups). In the latter situation lactose undergoes colonic fermentation, with some converted into cFE, cGaE and fermentation heat. The absorption and oxidation of SCFAs derived from fermentation of lactose is associated with higher energy equivalents of ATP (less ATP gain) than when lactose is hydrolyzed and oxidized directly by human

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Table 3 Energy values of macronutrients and specific carbohydrates in foods (kJ/g)[a]

	cIE	*DE*	*ME*	*NME*
Macronutrients				
Fat	39.3	37.4	37.4	36.6
Protein	23.6	21.7	16.8	13.4
Available carbohydrates[b]	15.7	15.7	15.7	15.7
'Fibre'/NSP	17.0	7.7	7.7	6.0
Alcohol	29.6	29.6	29.0	25.8
Specific carbohydrates				
Available carbohydrates				
Glucose monohydrate	14.1	14.1	14.1	14.1
Glucose	15.7	15.7	15.7	15.7
Fructose	15.7	15.7	15.7	15.2
Lactose	16.5	16.5	16.5	16.3
Sucrose	16.5	16.5	16.5	16.3
Starch	17.5	17.5	17.5	17.5
Fibre				
Fermentable 'fibre'	17.0	11.0	11.0	8.0
Non-fermentable 'fibre'	17.0	0.0	0.0	0.0
Resistant starch	17.5	11.4	11.4	8.8
Non-digestible oligosaccharides				
General, conventional foods	17.0	11.1	11.1	8.4
Isolated/synthetic				
Fructooligosaccharides	17.0	11.1	11.1	8.4
Synthetic polydextrose (5% glucose)	16.9	6.6	6.6	5.2
Inulin (pure)	17.5	11.4	11.4	8.8
Polyols				
Erythritol	17.2	16.6	1.1	0.9
Glycerol	18.0	18.0	18.0	16.6
Isomalt	17.0	11.6	11.2	8.9
Lactitol	17.0	11.1	10.7	8.2
Maltitol	17.0	13.4	13.0	11.5
Mannitol	16.7	12.3	8.1	6.3
Polyglycitol	17.1	13.5	13.2	11.6
Sorbitol	16.7	12.0	11.7	9.7
Xylitol	17.0	14.0	13.7	12.4

Abbreviations: cIE, combustible intake of energy; DE, digestible energy; ME, metabolizable energy; NME, net metabolizable energy; NSP, non-starch polysaccharides.
[a]Based on Livesey (2003a). The values for macronutrients have also been reported in Livesey (2001), with some trivial differences in the values for protein and alcohol. For available carbohydrates, see also Livesey and Elia (1988) and Elia and Livesey (1992). For fibre see text.
[b]Available carbohydrate (as monosaccharide equivalents) measured by direct analysis of sugars. When carbohydrate is measured 'by difference', the values increase by 1 kJ/g.

tissues. The overall result is that DE, ME and NME values for lactose, when there is lactose malabsorption, are lower than cIE, and lower than the usual values assigned to it, which assume that all lactose is absorbed from the small bowel (16.5 kJ/g for cIE, DE and ME values, and 16.3 kJ/g for the NME). However, this problem is likely to be a minor one, since individuals with lactose intolerance do not normally ingest large amounts of lactose because it can produce undesirable bloating effects and diarrhoea.

The standard DE, ME and NME values obviously overestimate the actual values in patients with malabsorption disorders to an extent that depends on the type of malabsorption disorder and its severity. In contrast, the standard values may underestimate the actual values when nutrients are given intravenously and made directly available to human tissues. This problem is addressed in detail elsewhere (Livesey and Elia, 1985, 1988). However, the energy value for glucose, which is usually the dominant energy source for intravenous nutrition, remains unaltered, but this may not be so for other types of carbohydrates that may be lost in urine to a variable extent.

Calculating energy balance

There is interest in estimating energy balance during growth, development of obesity and undernutrition, as well as during their treatment. The energy balance can be calculated from changes in body composition (Fuller *et al*., 1992; Heymsfield *et al*., 2005), which can provide estimates of fat and protein mass, and in some cases carbohydrate (glycogen stores are small, but can be measured accurately and precisely using nuclear magnetic resonance; Taylor *et al*., 1992; Casey *et al*., 2000). Energy balance can also be calculated from classic balance studies, which involve measurement of energy intake and energy expenditure. In calculating energy balance, it is important not to confuse the energy values of endogenous and exogenous fuels and also not to confuse different food energy systems (combustible, ME and NME systems; Table 4).

The ME and NME values of nutrients (kJ/g) that are mobilized from body stores and used for oxidation during weight loss are higher than the corresponding food energy values (Table 4), mainly because digestibility does not apply to the former but it does to the latter. For example, the ME values of fat in food is 37.4 kJ/g compared to the value of 39.3 kJ/g of stored fat, and for food protein 16.8 kJ/g compared to 18.4 kJ/g of tissue protein.

Using body composition techniques, the energy balance equations is

$$\begin{aligned}\text{Energy balance} &= \text{Energy stores}_{\text{time point 2}} - \text{energy stores}_{\text{time point 1}} \\ &= \text{energy}_{\text{time point 2}}(\text{carbohydrate} + \text{fat} + \text{protein}) \\ &\quad - \text{energy}_{\text{time point 1}}(\text{carbohydrate} + \text{fat} + \text{protein})\end{aligned}$$

The energy values for all macronutrients in this equation are the endogenous food energy values and not the exogenous food energy values (see Table 4 for combustible energy, ME and NME values). The body composition approach is usually only of value in long-term studies where there are large changes in body composition, which far outweigh measurement precision. In some such studies, the changes in glycogen stores are small and therefore they are either be ignored or estimated. The errors associated with this approach have been assessed (Elia *et al*., 2003).

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Table 4 cE, ME and NME, and content of macronutrients in food and in body stores

	'Food' energy			*Body stores*[a]		
	cE kJ/g	*ME kJ/g*	*NME kJ/g*	*cE kJ/g*	*ME kJ/g*	*NME kJ/g*
Fat	39.3	37.4	36.6	39.3	39.3	38.5
CHO[b]						
Available	15.7	15.7	15.7	15.7	15.7	15.9[c]
Unavailable	17.0	7.7	5.6	—	—	—
Protein	23.6	16.8	13.4	23.6	18.4	<14.7[d]
Alcohol	29.6	29.0	25.8	—	—	—

Abbreviations: cE, combustible energy; ME, metabolizable energy; NME, net metabolizable energy.
[a]The values indicated assume mobilization and oxidation of 'stored' macronutrients. The starting points are the body stores (which are lost during starvation), and as such represent a departure from food energy systems.
[b]CHO as monosaccharide equivalents.
[c]The value, which is higher than that of glucose, takes into account the heat of hydrolysis of glycogen and one extra ATP gained per glucosyl residue during oxidation of glycogen compared to oxidation of glucose.
[d]Protein breakdown involves both ATP-independent pathways (in which case the value of ~14.7 kJ/g applies) and ATP-dependent pathways (in which case the value <14.7 kJ/g applies).

The classic energy balance technique involves measurements of both total energy expenditure, using calorimetry (whole-body calorimetry) or tracer techniques (the doubly labelled water technique (Prentice, 1990) or the bicarbonate–urea method (Elia *et al*., 1995; Gibney *et al*., 1996, 2003; Paton *et al*., 1996, 2001; Tang *et al*., 2002; Elia, 2005) and energy intake.

The energy balance equation can be considered in terms of combustible energy or ME.

(i) Energy balance (combustible energy): cEstored = cIE–heat–cEnergy losses where cEnergy losses are the combined losses through faeces urine, body surfaces and gases (cFE + cUE + cSA + cGaE). cIE can be measured using bomb calorimetry, but can also be estimated (Table 3).
(ii) Energy balance (ME): MEstored = ME intake–heat

Since the following two equations apply,

$$\text{ME stored} = \text{NME}/k_{\text{stored}}$$
$$\text{ME intake} = \text{ME intake}/k_{\text{intake(diet)}}$$

the energy balance equation can also be expressed in relation to NME.

$$\text{Energy balance (NME): NME}/k_{\text{stored}} = \text{ME intake}/k_{\text{intake(diet)}} - \text{heat}$$

In these equations, the heat released (energy expenditure) is again measured by calorimetry in controlled laboratory conditions or by tracer techniques in free-living conditions. ME intake in this situation is obviously calculated from the exogenous food energy values (Table 4). Parenthetically, it should be noted that in short-term studies involving external work, not all of the heat produced is lost from the body (some is transiently retained in the body, causing an increase in body temperature).

Energy systems and food labelling

Food energy systems have evolved over time, as fundamental physiology of macronutrient metabolism was reviewed. For example, a value of 17 kJ/g (Atwater general factor) was assigned to the ME for total carbohydrate including 'fibre' (or unavailable carbohydrate) (this system also assigns values of 17 and 37 kJ/g of protein and fat, respectively) (Merill and Watt, 1973). There are physiological objections to this: not all carbohydrate that reaches the colon is fermented (some is excreted unchanged in faeces); some is converted to substances, such as combustible bacterial biomass in faecal matter and combustible gases, which are lost from the body. Therefore, more appropriate ME values for 'fibre'/NSP have been established (for example, ME of 7.7 kJ/g for that present in conventional foods (see section on Digestible energy), which can be rounded to 8 kJ/g and NME of 6 kJ/g). The same evolution of thought occurred with polyols. Regulatory agencies assigned a value of 17 kJ/g to polyols (as for other carbohydrates) because none was recovered in faeces. However, this did not agree with energy balance studies. Basic physiological considerations (confirmed by experimental studies) suggest that fermentation of polyols results in some loss of energy in faeces and gaseous products (as with 'fibre'). In addition, absorbed polyols are frequently lost in substantial quantities in urine. After further consultations within the European Union, polyols were assigned a general energy value of 10 kJ/g (European Communities, 1990). However, because of the variability in ME values for different polyols, European countries (for example, The Netherlands, France) as well as non-European countries (for example, the United States, Canada, New Zealand and Japan) have adopted or recommended a specific value for each polyol. An FAO consultation suggested that where one polyol represents a substantial source of energy in a product, use of a more specific factor may be desirable (FAO, 2003).

Three food energy systems have been widely promoted for use in food tables and for food labelling in different world regions: those that employ the Atwater-specific factors (Merill and Watt, 1973); those that employ the Atwater general factors (Merill and Watt, 1973; FAO/WHO/UNU, 1985) (17, 17, 37 kJ/g for carbohydrate, protein and fat, respectively); and those that employ NME factors (typically applied to polyols). The use of all these systems is a source of confusion, especially when factors from different systems are used in the same country. A further source of confusion is that in some countries, energy is expressed in relation to weight of carbohydrate, and in others in relation to weight of monosaccharide equivalents (~11% difference in the case of starch). There is also the issue of accuracy. A particular problem with the Atwater general system (Merill and Watt, 1973) is that it appears to overestimate the energy values of specific food items, to the extent of 0–30%. The bias is

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especially marked for food items containing a high proportion of 'fibre' and certain types of protein, both of which may be prominent in weight-reducing diets (Brown *et al.*, 1998). A modification of the Atwater general system that takes into account the presence of unavailable carbohydrate in foods (Livesey, 1991) has the advantage of overcoming the inaccuracy of the Atwater general system, while avoiding the complexity of the Atwater-specific system (Merill and Watt, 1973).

Terminological and methodological issues in carbohydrate analysis are also important, due to the varied nature of the techniques that are in use. These are dealt with in other papers in this consultation (for example, see Measurement of dietary carbohydrates for food tables and labelling by Englyst *et al.*, 2007). All carbohydrates can be determined by direct analysis. Carbohydrate 'by difference' (total carbohydrate−unavailable carbohydrate) requires assumptions about the fate of carbohydrates in the colon that cannot always be predicted because this will, for example in the case of starches, be dependent on the physical form of the food, cooking and cooling, the degree of ripeness and nature of the starch granule. Therefore, 'by difference methods' should not have a place in carbohydrate analysis. Compared to the direct method, the indirect method ('by difference') has the effect of increasing the cEI, DE, ME and NME values of available carbohydrates by ~1 kJ/g. As already suggested, the direct analysis is preferable (FAO, 1998), although this may pose practical problems in developing countries with poor access to analytical facilities. Finally, it should be remembered that food labelling applies to food items not diets, and that some foods may acquire different properties and different energy values before being ingested. For example, starch in potato can become resistant if it is cooked and allowed to cool before being ingested (Englyst and Cummings, 1987). In contrast, RS changes into ordinary of starch during the maturation of bananas, which occurs whilst their skins turn from green to yellow. Although these processes will affect DE, ME and NME values in different ways, food labelling cannot adequately take them into account.

The idea that bioenergetic inefficiency results in heat production is not new, since it was already in existence in early part of the twentieth century. It is also well known that agents such as 2,4-dinitrophenol, which uncouple oxidative phosphorylation, produce a considerable amount of heat. Therefore, measurement of energy expenditure (heat production) does not necessarily reflect useful metabolic or external work done. The idea of establishing bioenergetic equivalence of different macronutrients has obvious attractions to food labelling. The NME (but not the ME) system is based on the concept that macronutrients contribute equivalently to energy balance and energy requirements irrespective of food composition. The FAO acknowledges that the Atwater-specific and general systems do not take into account H_{ine}, which is relevant to calculations of energy requirements, and in the annexe of its report on food energy (FAO, 2003), it provides two tables to address this issue (Table 3.1 provides correction factors when ME intakes are being matched with requirements and Table 3.2 expresses food needs as the 'food NME requirement').

The current labelling of carbohydrates (and more broadly foods in general) is unsatisfactory because the ME system is used for some carbohydrates (usually the most abundant carbohydrates, such as starch and sucrose), but the NME system is used for polyols and polydextrose in many regions (and in the same regions that use the ME system). It would seem more logical to use the same energy system for all carbohydrates, and indeed for all other nutrients. It has been argued that since NME values are only ~96% of ME values (NME~ = 0.96 ME), it makes little difference which system is used (especially since energy intake cannot generally be assessed with an accuracy of less than 4%). On the other hand, values for specific foods can be affected by considerably more (up to 30%; for example, those rich in certain types of protein and 'fibre' are used for weight reduction). These errors may fall outside the range permitted by legislation in the European Union (Commission, 2006). In addition, by comparison with the NME system different diets of the same ME value can be constructed that would result in differences of 10–15% (for example, diets rich in NSP or protein, as for example energy-restricted diets in which normal protein intake represents a high proportion of energy). Therefore, it would seem sensible to use a consistent method that is sound at all levels, so that the consumer, the nutritionist and the researcher are not misled. In addition, it should be remembered that physiological considerations that make a difference of only a few percent have already been taken into account in devising food energy systems, for example DE of the diet is greater than ME by a few percent, which is similar to the extent to which ME is greater than NME. Furthermore, as indicated above, early inaccuracies in energy values for 'fibre'/NSP and polyols have been corrected, even though the changes make only a few percent difference to the total energy value of the diet. An early example of implementing small changes involves the Atwater energy factors that replaced the earlier Rubner factors, for example 2.5% difference for combustible energy of carbohydrate. Another argument is that errors associated with measurement of dietary intake and potential errors associated with the development of RS after cooking are sources of greater error than the use of the ME system instead of the NME system. This poses a problem for analysts and those compiling food composition tables, However, it is reasonable to suggest that food-labelling policy should aim to establish a system that avoids bias as far as possible using a practical user-friendly system. It has also been argued that an enormous amount of work would have to be undertaken to change the current ME system into an NME system. On the other hand, if an attempt is to be made to establish either a consistent ME or an NME system, some changes will be necessary. If this involves conversion to a consistent NME system, the additional changes may not be as great as anticipated, as the following three equations (round numbers) indicate.

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ME (Atwater general system) (Merill and Watt, 1973) = $37F + 17CHO_{total} + 17P$.

ME (modified Atwater general system) (Livesey, 1991) = $37F + 16CHO_{available}* + 8CHO_{unavailable} + 17P$.

NME (Livesey, 2001) = $37F + 16CHO_{available}* + 6CHO_{unavailable} + 13P$.

In these equations, ME and NME are in kJ, the coefficients are in kJ/g, and F, P and CHO are in g of fat, protein and carbohydrate, which may be available or unavailable (* = as monosaccharide equivalents).

The key issues are the extent to which the underlying physiological considerations are sound, the extent to which they should drive food-labelling policy and the extent to which food energy system(s) should become consistent within and between regional jurisdictions.

Carbohydrates, feeding behaviour and energy balance

The above discussion regarding energy values of carbohydrates and energy balance equations gives no indication about physiological processes that control voluntary food intake and energy expenditure in different environments. Do carbohydrates play a special role in processes that affect energy balance? Many theories of appetite regulation and energy homeostasis have been proposed, with carbohydrates playing a key role in several of them. None of these theories are universally accepted. Some have evolved over time and a few are continuing to do so. The literature is vast, and therefore only a brief overview of certain aspects of carbohydrates physiology will be discussed in this paper. Since there seems to be so much confusion and conflicting advice being given to the consumer about the types of foods that should be used for weight control and energy homeostasis, the origins of some concepts and the mechanisms involved are also discussed. This provides a platform for considering future research. It is worth emphasizing that despite the widespread use of a large number of diets that vary in macronutrient composition, there is continued growth of obesity and overweight. If a diet was associated with long-term compliance and overwhelmingly successful reduction in weight, a decrease in the prevalence of overweight and obesity might be expected. Several randomized and non-randomized controlled trials have reported weight reduction over several months when low fat (high-carbohydrate diets) are used. A review of four separate meta-analyses of low-fat vs control diets (or the relationship between the fat content of the diet and weight loss) (Astrup *et al*., 2002) reported greater weight loss with the low-fat diets, and one meta-analysis reported a dose–response relationship between reduction in percent dietary fat intake and weight loss. And yet, these results raise a conundrum, firstly because the meta-analyses consistently show weight loss (generally only slight to modest mean weight loss of ~2–3 kg), whereas in the general population there is progressive weight gain; and secondly because the percent fat intake in the United Kingdom (Henderson *et al*., 2003) and the United States (Centres for Disease Control and Prevention (CDC), 2004) appears to have decreased in recent years, while obesity and overweight have increased. Several questions arise from these simple observations. Would the growth of obesity have been greater if there was no decrease in the percent fat intake? Is the study population representative of the general population (for example, one meta-analysis included separate studies of patients with breast dysplasia, breast cancer and hypercholesterolaemia (Astrup *et al*., 2000))? Are confounding variables such as physical activity adequately controlled for? Is the dietary compliance under the study conditions of randomized controlled trials better than non-study conditions? If the studies had been extended over longer periods, would there have been a decrease in dietary compliance (for example, one systematic review included studies that lasted for only 3 weeks; Yu-Poth *et al*., 1999)? Are the effects of these diets mediated by energy density rather than macronutrient composition (low-fat diets, especially those rich in fibre tend to have a low-energy density)? Do the types of carbohydrates used in the diets of studies carried out over the past 20 or more years reflect those currently ingested (for example, carbohydrates in soft drinks and other food items have changed over time)? This section examines some of these issues from a physiological perspective, focusing on appetite regulation. It is of course recognized that there is considerable scope for interaction between feeding behaviour and other confounding factors that affect energy expenditure. This section does not aim to provide a detailed summary of the effectiveness or advantages and disadvantages of the large number of popular weight-reducing diets (reviewed elsewhere; Freedman *et al*., 2001), some of which may suit certain individuals more than others. It primarily aims to establish some links between physiology and clinical/public health nutrition, through examination of feeding behaviour, which has a key role in energy homeostasis. To do this, it is first necessary to place the scientific issues in perspective by considering the extent to which energy balance is regulated in man.

The extent to which energy balance is regulated

Figure 3 shows that the cumulative energy intakes of a reference male and reference female, both of which were established using the UK-recommended ME intakes (Department of Health, 1991). The figure indicates that 231 GJ (231 000 MJ) are ingested during a lifetime of 75 years by the reference male, and 196 GJ (196 000 MJ) by the reference female. Since the ME of stored fat is ~39.4 MJ/kg and that of fat-free tissue is ~3.8 MJ/kg (of which <0.1 MJ/kg is in the form of glycogen), it can be calculated that the total energy content of a 65 kg man (15% fat) is 0.594 GJ. This corresponds to 15.6% of the annual energy intake of a man

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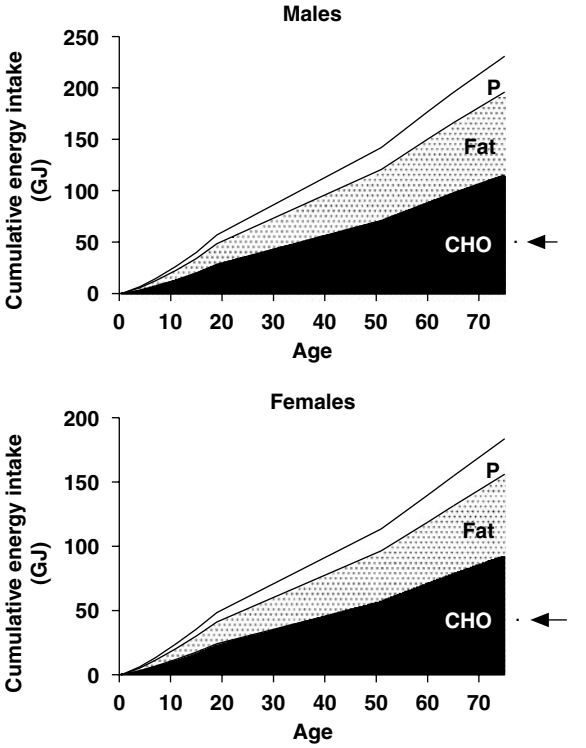

Figure 3 The cumulative energy intake (1 GJ = 1000 MJ) of reference male and female (based on reference nutrient intake; Department of Health, 1991) and its distribution between carbohydrate (CHO; 55% of total intake), fat (35% of total energy intake) and protein (P; 15% of total energy intake). The arrow points to a dot that corresponds to approximately 1% of the cumulative energy intake at 75 years, which if deposited, would double adult body weight and body mass index.

aged 20–50 years. An energy imbalance that halves the body mass index (BMI) from 20 to 10 kg/m^2 (barely compatible with life) and that halves body weight from 65 (15% fat; 7.25 kg fat) to 32.5 kg (1.54% fat or 0.5 kg fat) corresponds to only 0.49 GJ. This is equivalent to only 0.21% of the total ME intake over a lifetime (or 0.42% of the ME of carbohydrate intake over a lifetime). It is also equivalent to 0.26% of the intake during adult life, and 1.3% of the intake over 10 years of adult life (for example, between 30 and 40 years of age). The dot by the side of Figure 3 is scaled to correspond to approximately 1% of the final cumulative intake. These considerations suggest that any effective regulatory physiological system (without assumptions about the type or level of regulation or specific drivers used in regulation; Stock, 1999; Spiegelman and Flier, 2001; Liu *et al.*, 2003; Druce and Bloom, 2006) must achieve much better results than the small percentages indicated above, if good health is to be maintained. Similar calculations can be made for increments in body weight. An energy imbalance that doubles the BMI of a man (from 20 to 40 kg/m^2) and doubles body weight (from 65 kg (15% fat) to 130 kg fat (45% fat)) corresponds to 1.98 GJ, which is less than 1% of the total energy intake over a lifetime (less than 2% of carbohydrate intake), almost exactly 1% if this occurred during adult life, and 2.5% if it occurred over 30 years, between 20 and 50 years of age. Again, with a view to maintain good health, any effective regulatory system must achieve very much better results than these calculations indicate. The alarming increase in the number of grossly obese individuals in high-income countries, and to a lesser extent in low-income countries, argues against the operation of a tightly regulated physiological system(s) of long-term energy homeostasis to maintain optimal health in the modern environment. Short-term regulation of energy balance is probably less precisely regulated, perhaps reflecting an advantage during evolutionary development, to store excess energy when food is available for subsequent use when it is not readily available.

Carbohydrate-specific models of feeding behaviour

Carbohydrate-specific models of feeding behaviour have been prominent in the last 50 years. Many models established testable hypotheses, which have been examined, and through this examination new concepts about energy homeostasis have emerged. Mayer's original glucostatic theory (Mayer, 1955), which was published in 1955, suggested that regulation of energy balance predominantly involved short-term 'glucostatic' responses that could be modified by longer term 'lipostatic' responses. Russek (1963, 1976) went on to establish the hepatostatic theory in 1963 by postulating the presence of receptors in the liver. Other studies suggested that 6–12% fall in plasma glucose concentration predicts meal initiation in animals (Campfield and Smith, 1990; 2003) and humans (Campfield *et al.*, 1992; Campfield and Smith, 2003). Simple relationships do not necessarily prove causality, although infusions of glucose in animals to prevent the drop in circulating glucose concentrations were found to delay feeding behaviour. Irrespective of the regulatory mechanisms, there would be a clear advantage in coupling oxidative metabolism (energy expenditure) with feeding behaviour (energy intake). Over the last 25 years, arguments have been put forward that the oxidation (or deposition) of specific macronutrients, especially carbohydrates, have a disproportionately large effect on feeding behaviour. The arguments are set out below.

(1) Macronutrients have different propensities to being oxidized and stored. Alcohol is not stored at all, and therefore it has to be oxidized (very little is excreted unchanged). Protein is also readily oxidized, since little of it, if any, is accreted into the tissues of non-growing individuals in a range of pools with varying size, rates of turnover and 'lability'. Only a small proportion of ingested protein is retained during development of muscular hypertrophy from physical training and during development of obesity (obese individuals have more muscle to support the extra body, the heart hypertrophies as its cardiac output increases and organs may also enlarge). Carbohydrate stores, which are limited

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(<0.8 kg in the adult), increase after ingestion of a mixed meal (Elia *et al*., 1988), but much, if not all of the increased store, may be mobilized for oxidative purposes before the next meal. The increased post-prandial oxidation of carbohydrate contrasts with decreased oxidation of fat, which is the main storage form of energy (Elia *et al*., 1988). Fat too can be oxidized before the next meal, but excess energy intake over time is predominantly stored as fat, which has very large potential storage capacity, rather than carbohydrate, which has a limited storage capacity. Therefore, the oxidative hierarchy of fuels (alcohol, protein, carbohydrate and fat) is associated with the reverse hierarchy in storage, with carbohydrates occupying a fairly central position.

(2) A number of workers have attempted to examine the relative satiating efficiency of different macronutrients. They reported that protein is more satiating than carbohydrate, which in turn is more satiating than fat (alcohol is enigmatic in that it may actually stimulate appetite in some circumstances). This hierarchy was reported to occur at a community level, elucidated through surveys of dietary intake (de Castro and de Castro, 1989; de Castro, 1991) (a limitation of such studies is possible misreporting of dietary intake) and also at the laboratory level (Weststrate, 1992), where dietary intake is usually measured by the researchers. It has also been reported to occur at the level of nutrient balance in subjects ingesting an oral diet (Stubbs *et al*., 1995b) as well as in those receiving nutrients intravenously (Gil *et al*., 1991). The results of some of the macronutrient balance studies undertaken in metabolic centres do not appear to be simply due to differences in sensory cues. For example, in a study of men who were studied on three separate occasions so that they could receive a high carbohydrate (low fat), medium carbohydrate (medium fat), or low carbohydrate (high fat) diet, differences in sensory cues (taste, smell) were minimized by covertly manipulating the diets (Stubbs *et al*., 1995a). The proportion of energy from protein was kept constant across all diets, but the energy density decreased progressively as proportion of energy from carbohydrate increased. The subjects ate these covertly manipulated diets *ad libitum* while in a whole body calorimeter for 7 days. Average daily balances were 2.58, 0.77 and −0.27 MJ/day on the low-, medium- and high-carbohydrate diets, respectively. Carbohydrate appeared to be more satiating than fat. It also appeared that oxidation of carbohydrate and protein predicted the subsequent day's intake better than fat oxidation. The effects on energy balance persisted through the entire 7-day period of study, apparently without compensation as the study progressed. Other studies suggested that protein, which has even less 'storage capacity' than carbohydrate, is also more satiating than fat, and probably also more satiating than carbohydrate, especially when protein is ingested in large quantities (>1.2 MJ per meal) (Weststrate, 1992). From such studies, it appeared that macronutrients such as carbohydrate and protein, whose balance is most tightly regulated, exerted greater suppressive effects on subsequent energy intake than fat, the balance of which is not so tightly regulated.

(3) If the macronutrient hierarchy in satiation parallels the macronutrient hierarchy in oxidation (inversely with the hierarchy in storage), as several studies suggest, the possibility exists that the two are causally linked. In examining this hypothesis, it is necessary to consider at least two issues: (i) plausible mechanisms by which such effects might be mediated and (ii) whether the macronutrient hierarchy on satiety are independent of the energy density of the diet.

Potential mechanisms by which oxidation and storage are linked to feeding behaviour. A large number of potential mechanisms may be invoked in carbohydrate-specific models of eating behaviour. A basic consideration is whether the sensor is linked predominantly to storage of specific macronutrients (glycogen in the case of carbohydrate) or oxidation.

Flatt (1987) suggested that glycogen exerts a strong negative feedback on energy intake, giving rise to the glycogenostatic model of appetite regulation. The model, which was developed from observations in rodents, has its attractions because changes in carbohydrate stores can occur rapidly, from meal to meal, and are associated with changes in carbohydrate oxidation. Therefore, the model could provide a plausible physiological basis for feeding behaviour, which typically involves ingestion of carbohydrate as the major macronutrient. However, the model does not distinguish between liver, which is rapidly lost during starvation, and muscle glycogen, which appears to be depleted slowly compared to muscle rapidly depleted during fasting in which does not appear to be rapidly lost during starvation (rodents muscle glycogen appears to be depleted much faster during short-term starvation than in human). In addition, several human studies have examined the predictions of this model, and in some circumstances they were unable to confirm them. For example, changes in feeding behaviour induced by dietary manipulations that change carbohydrate stores, without necessarily altering energy balance, or *vice versa*, cannot be readily explained by the glycogenostatic theory (van Stratum *et al*., 1978; Shetty *et al*., 1994; Stubbs *et al*., 1995a, 1996; Snitker *et al*., 1997). Some of these studies found that oxidation of all three macronutrients are considerably better at predicting subsequent energy intake than carbohydrate alone (Stubbs *et al*., 1995b).

The putative signal(s) and sensor(s) associated with the glycogenostatic model have also not been identified.

Another approach is to examine the effect of blocking oxidative pathways, either individually or in combination. Friedman and Stricker (1976) proposed a model that was based on the balance between oxidation and storage of fuels. They established an integrative macronutrient model of

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feeding behaviour, which was consistent with pharmacological inhibition of metabolic pathways. However, the model does not specify the metabolic sensor(s), and therefore a number of general questions arise. How are fuel oxidation and/or storage detected? Can the oxidation of one fuel be distinguished from that of another (a necessary consideration in macronutrient-specific models) and how are signals integrated to influence feeding behaviour? Another basic issue is whether it is oxidation of fuels *per se* or oxidative phosphorylation (for example, ATP (or other related substances) that is primarily responsible for feeding behaviour. The use of drugs that uncouple oxidative phosphorylation, causing a major increase in oxidation of nutrients without an increase in ATP generation, could be used as tools for addressing this last issue. Dinitrophenol administration in humans was found to have a linear relationship with metabolic rate and weight loss, so that at a dose of 0.5 g/day it increased metabolic rate by about 50% and decreased body weight by almost 1 kg/week (Tainter *et al*., 1935; Harper *et al*., 2001). The use of dinitrophenol to treat obesity in the United States in the 1930s (Tainter *et al*., 1935; Harper *et al*., 2001) made some subjects very hungry during treatment. If this were a general effect, it would suggest that oxidation of fuels *per se*, was not responsible for providing feedback on energy intake, and that oxidative phosphorylation was more likely to be the cause. However, the information on the effects of dinitrophenol in humans is far from clear, since some subjects became less hungry during treatment, so that in reality there was no consistent overall effect on appetite. It is difficult to assess the significance of these briefly reported observations, partly because no measurements of dietary intake were made, and partly because dinitrophenol can cause a range of side effects which suppress appetite (for example, nausea, gastrointestinal symptoms, loss of taste (especially for salt and sweet), skin rashes and a variety of other symptoms) (Rabinowitch and Fowler, 1934; Tainter *et al*., 1935; Harper *et al*., 2001). In addition, uncoupling oxidative phosphorylation would not distinguish between carbohydrates and fat because both are uncoupled by dinotrophenol.

The effect of blocking specific oxidative pathways on eating behaviour has also been examined. For example, humans experience increased hunger when given 2-deoxyglucose (50 mg/kg body weight), which blocks glucose oxidation by competitively inhibiting phosphohexose isomerase (EC 5.3.1.9), an enzyme that catalyses one of the early steps of the glycolytic pathway (Thompson and Campbell, 1977; Welle *et al*., 1980; Thompson *et al*., 1982). When rats were given 2-deoxyglucose, a dose-dependent increase in food intake was observed (Friedman and Tordoff, 1986). When rats are given methyl palmoxirate, which blocks fat oxidation by inhibiting the transport of long-chain fatty acids across the inner mitochondrial membrane (necessary for mitochondrial fat oxidation), there was also an increase in food intake (Friedman *et al*., 1990). Separate sensory systems for detecting carbohydrate and fat oxidation have been identified through investigations that have combined surgical lesions of the nervous system and administration of pharmacological agents that inhibit either fat or carbohydrate oxidation (Titter and Calingasan, 1994). Some inhibitors of glucose oxidation act both centrally in the brain and peripherally (2-deoxyglucose), whereas others do not penetrate the blood–brain barrier, and therefore inhibit glucose oxidation only in peripheral tissues (for example, 2.5-anhydro-D mannitol). Investigations using such tools suggest that fatty acid oxidation is monitored peripherally, whereas glucose oxidation is monitored both peripherally and centrally. The area postrema and nucleus of the solitary tract receive signals from both systems (the vagus nerve relays signals from the periphery). However, lesions that destroy the sensory but not the motor nucleus abolishes mercaptoacetate (lipoprivic), but not the 2-deoxyglucose (glucoprivic)-induced feeding. It is not clear to what extent these distinct pathways, and their interactions, which have been identified in animals (Titter and Calingasan, 1994), also operate in humans.

Feeding behaviour and energy density. Several of the studies that established a satiating hierarchy of macronutrients did not control the energy density of the diet. Since high-carbohydrate/low-fat diets tend to be less energy dense than low-carbohydrate/high-fat diets, it is possible that energy density rather than a macronutrient hierarchy is responsible for many of the differential effects on satiety. If this were the case generally, macronutrient-specific models of feeding behaviour would decline in importance and give way to new alternatives, but perhaps complementary models of feeding behaviour. Few long-term physiological studies have been undertaken to address this specific issue, but two are noteworthy. The first is the study of van Stratum *et al*. (1978), which was already published at the time when the macronutrient hierarchy and glycogenostatic models of feeding behaviour were being actively explored. It reported that isoenergetically dense high-fat and high-carbohydrate diets had similar effects on energy intake over 2 weeks in 22 Trappistine nuns. The second study of Stubbs *et al*. (1996), involving men who were also studied over a period of 2 weeks, confirmed the results obtained on the Trappistine nuns. Both of these studies covertly manipulated the diets to conceal taste differences. A number of short-term studies (Johnstone *et al*., 1996; Stubbs *et al*., 1996), including those involving single preloads (Stubbs *et al*., 1996), found that there may still be some subtle macronutrient effects that are independent of energy density. Protein was still considered by some workers to be more satiating than other macronutrients when taken in doses of >1.2 MJ per meal (Weststrate, 1992), although even this was challenged by a recent short-term study with a crossover design (Raben *et al*., 2003). It measured the *ad libitum* intake of a high-protein, high-carbohydrate, high-fat and high-alcohol meals over a period of 5 h in the same subjects on separate occasions. The energy intake from the high-protein meal, which included

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~1.4 MJ from protein in men, did not differ significantly from the other meals, which had similar energy density and 'dietary fibre' content (although they differed in their sensory attributes, such as taste and after taste). There was also no difference in intake among the 10 women who consumed ~0.7 MJ of protein from the high-protein meal. This study did not covertly manipulate the meals to conceal taste. Nevertheless, all the above observations taken together raise questions about the predictive value of macronutrient-specific models of feeding behaviour, at least under laboratory conditions, which may not necessarily apply to free-living conditions, for reasons that will emerge later. Inevitably, attention is focused on the weight and energy density of foods, including ready-to-eat foods, which have recently flooded the market in developed countries.

Before considering these issues further, it is worth briefly reflecting on the likely limitations of physiological processes controlling feeding behaviour that place disproportionate importance on a single nutrient (for example, carbohydrate). Such a system would regulate energy balance poorly because it would be unable to adapt adequately to situations associated with changes in the proportions of different macronutrients in the food supply. Therefore, it is not surprising that specific macronutrient models of feeding behaviour were not found to be robust in some circumstances, particularly those involving covert manipulation of diets with the same energy density but different macronutrient composition (see above). In addition, pharmacological inhibition of both fat and glucose oxidation in animals were found to elicit a massive increase in food intake, compared to inhibition of either fat or carbohydrate oxidative pathways (Friedman and Tordoff, 1986). This suggests that the regulatory system is responsive to oxidation of both fat and carbohydrate, and that oxidation of each substrate compensates for the other, when the availability of one of them is reduced. Therefore, eating behaviour does not unconditionally depend on the oxidation of one nutrient, and indeed it would be surprising if it did. Furthermore, the satiating effect of the Eskimo diet (fat and protein) (Mowat, 1981) would argue against the operation of a simple carbohydrate oxidation or storage model of feeding behaviour to the exclusion of other macronutrients.

Energy density, weight of food and carbohydrates

Several reports suggest that under *ad libitum* feeding conditions (mainly under laboratory conditions), people tend to consume a fixed weight or volume of food (Duncan *et al*., 1983; Lissner *et al*., 1987; Tremblay *et al*., 1991; Tremblay, 1992; Poppitt, 1995; Rolls and Bell, 1999; Bell and Rolls, 2001). This implies that when foods or diets differ in energy density, energy intake will be affected. Indeed, it has been suggested that this is a major mechanism for determining energy intake at different stages of the life cycle (for example, compared to young adults, older adults reduce energy intake by largely decreasing the energy density of the food eaten). If satiety was mainly determined by the weight of food eaten, then those who consume high-energy density foods would be expected to feel satiated only after increased energy intake, whereas those consuming low-energy density foods would feel satiated despite lower energy intake. This argument has been promoted by several workers (Poppitt, 1995; Poppitt and Prentice, 1996; Prentice and Poppitt, 1996; Rolls and Bell, 1999). It is argued that in real-life energy dense foods tend to be more palatable and less satiating than foods with low-energy density. Typically, palatable snacks are energy dense, and those rich in both fat and available carbohydrates, which are rapidly digested and absorbed, are said to be particularly palatable (Drewnowski, 1998). Interestingly, available carbohydrate and fat also provide more NME per unit ME than does the diet as a whole or either protein or NSP or other carbohydrates fermented in the large bowel. Therefore, when using the ME system, high-fat, high-available carbohydrate foods (or diets) are more fattening than isoenergetic high-protein, high-fibre foods. In addition, foods of low-energy density (often rich in NSP and water) were less palatable in these studies.

An examination of 1032 foods revealed that the strongest predictors of energy density are water, which is negatively related to energy density, and fat (g per 100 g food), which is positively related to energy density (Stubbs *et al*., 2000). The carbohydrate and protein content of foods (g per 100 g food) are both positively related to energy density, but the association is much weaker than those obtained with fat or water (Figure 4). This weak relationship with carbohydrate is understandable because it is possible for foods containing a large proportion of energy from carbohydrate to have either a low-energy density (for example, vegetables) or high-energy density (some sweet snacks). Diet surveys do not generally report the energy density of the food eaten, and this precludes extensive analyses and interpretation of data

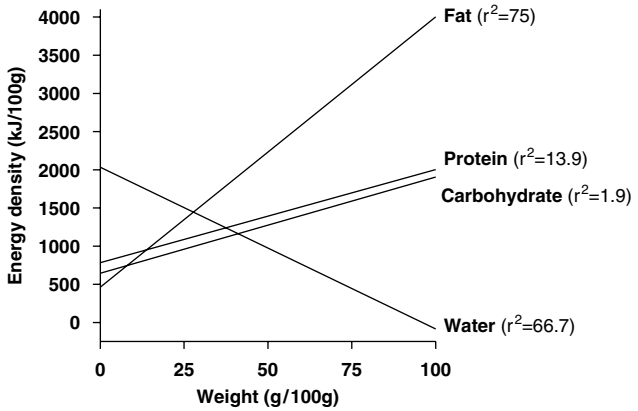

Figure 4 Relationship between energy density (outcome variable) and % weight of dietary macronutrients and water of 1032 ready-to-eat foods (Stubbs *et al*., 2000). The prediction equations are as follows: Energy density (ED) = 462.6 + (35.5 × fat); ED = 781.4 + (12.2 × protein); ED = 654.5 + (12.5 × carbohydrate); and ED = 2034–(21.2 × water). The values in parentheses, derived from regression are $r^2 \times 100$.

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in free-living conditions. However, below is a summary of some observations, including some in free-living conditions, which need to be taken into account in models of energy homeostasis in free-living conditions. The role of different types of carbohydrates on satiety, energy intake and energy balance are then considered in the light of these observations.

(1) The idea that energy intake and energy balance are largely determined by energy density or weight of food eaten has enormous implications for the control of feeding behaviour and energy balance, because it implies that normally energy intake is a secondary or passive manifestation of the drive to eat a constant weight of food. This would not be an ideal evolutionary strategy for survival. The energy density of the food eaten by our ancestors is likely to have varied from a low-energy density (berries, fruits) to high-energy density (fatty fish, animal meat and fat), depending on location, season and other environmental changes, including natural disasters. Too much reliance on weight of food eaten, rather than on energy eaten, would bring about poor regulation in energy homeostasis, at least in the long term.

(2) A recent epidemiological study (Ledikwe *et al.*, 2006) reported that US adults consuming a low-energy-dense diet are likely to consume more food by weight, and at the same time less energy intake (assessed by 24 h recall) than those consuming a higher energy-dense diet. Normal weight individuals were found to consume diets with a lower energy density than obese individuals, but causality is difficult to assess from the available information. This study is of course subject to potential problems associated with misreporting, which are briefly discussed below.

(3) If free-living individuals primarily eat a constant weight of food, with energy intake as a passive outcome, then the within-subject day-to-day coefficient of variation for weight of food ingested would be expected to be lower than that for energy intake. This was not found to be the case. In an analysis of 7-day-weighed food intakes in 73 subjects, the coefficients of variation were found to be slightly higher for weight of food ingested rather than energy intake (23 vs 21%, respectively, or 21 vs 20.5%, when drinks were added in the analysis) (Stubbs *et al.*, 2000; Stubbs and Whybrow, 2004). It would be valuable to know the extent to which coefficients of variation of ingested energy relative to ingested weight of food depended on the environmental conditions. Studies to address this issue are subject to the problem of misreporting of dietary intake. One review concluded that there is no accurate method of measuring dietary intake (Westerterp and Goris, 2002). Another extensive review (Livingstone and Black, 2003) expressed dietary energy intake per day as a fraction of energy expenditure measured by the doubly labelled water method. The results for 7-day-weighed food intake were variable according to the study. For example, in one study in women aged 60 years, the values were 1.07 ± 0.08 (s.d.) in unrestrained eaters and 0.94 ± 0.05 in restrained eaters (Bathalon *et al.*, 2000), whereas in another study (Kaskoun *et al.*, 1994) in 15 and 18-year-old males, the value was 0.77 ± 0.023.

(4) Laboratory studies have been undertaken in which diets with different energy densities are covertly manipulated to maintain the same palatability (Titter and Calingasan, 1994). In such environments, studies suggest that a large proportion of the variability in energy intake ($>40\%$) can be explained by energy density of the diet (Prentice and Poppitt, 1996; Rolls and Bell, 1999; Stubbs *et al.*, 2000) compared to only a much smaller proportion in free-living conditions (for example, only 7% according to one study; Stubbs and Whybrow, 2004). There are several possible explanations for the discrepancy between laboratory and free-living studies. (i) It is easier to covertly manipulate diets of different energy densities or macronutrient composition at the lower end of the energy density range. Studies that have varied the energy density of foods at constant palatability (Drewnowski, 1998) have used diets containing 2.5–4.4 kJ/g and compared them with diets containing 5.6–7.0 kJ/g. They have not extended to the higher energy density range. To give the readers a feel for the energy density of specific foods that can make up diets, here are some values: chocolate cake, hamburger and chips, which can make up a meal, fall in the range of 12–18 kJ/g; chocolate, decreases in the range of 22–24 kJ/g; raw vegetables and soft drinks ~ 2 kJ/g for; the full potential range is from 0 (water) to ~ 39 kJ/g (pure oil or fat). This means that the energy density (and the variety) of foods/diets in free-living conditions are more variable than those predetermined (lower values) in the laboratory. There is also some evidence that specific macronutrient effects are more likely to exert effects at the lower end of the energy density spectrum (Westerterp-Plantenga, 2001). (ii) Learned cues, which influence eating behaviour, are absent or dramatically reduced in laboratory studies, because such studies often use foods that are unfamiliar or covertly manipulated. (iii) Energy density is fixed in some laboratory conditions, but not usually in free-living conditions. (iv) Measurement of dietary intake is likely to be more accurate under laboratory than in free-living conditions. (iv) There appear to be a longer-term compensatory mechanisms for the increase in energy intake induced by *ad libitum intake* of high-energy-density foods (Stubbs *et al.*, 2004). A reduction in the weight of food eaten appears to be an important compensatory mechanism. (v) Some free-living studies have reported an association between energy density of the diet and increased intake. A recent study (de Castro, 2004) involving 952 subjects who provided 7-day food diaries, reported such a relationship, but found no relationship between energy density of the consumed

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food and body weight, height or BMI. Since high-energy density appears to be related to greater overall intake in the short term, the author suggested that there may be compensation over the long term with no net effect on body size. An alternative possibility is that increased activity may determine the energy density of the diet: large volumes of bulky diets may be less acceptable to individuals who require a lot of energy.

(5) Analyses of energy intake in free-living conditions using multiple regression models suggest that there are multiple determinants of energy intake, of which energy density is one, and percent energy from individual macronutrients, including carbohydrate, is another (Stubbs and Whybrow, 2004). From this and other works, it appears that macronutrients have effects on energy intake that are independent of the energy density of the food consumed. One study reported that specific macronutrients influence intake, when foods contain little water (high-energy density) and not when they contain a lot of water (low-energy density) (Westerterp-Plantenga, 2001). This could provide an explanation why laboratory studies, which have covertly manipulated diets at the lower end of the energy density range, have a strong predictive effect on energy intake.

(6) Substitution of sugar for artificial sweeteners offers a way of separating palatability from energy density of foods. But even here the effects are not clear-cut. For example, there is little epidemiological evidence to suggest that intense sweeteners are causally linked to BMI. In addition, most intervention studies with intense sweeteners are of short duration (less than 1 or 2 days, and often only a few hours), with the exception of a few studies, which suggested that the intense sweetener, aspartame, reduced energy intake in metabolic units (Porikos *et al*., 1977, 1982) or free-living conditions (Tordoff and Alleva, 1990a). Some short-term studies using drinks (Blundell and Rogers, 1994) or gum (Tordoff and Alleva, 1990b) suggested that intense sweeteners might actually stimulate appetite. One study found that aspartame-sweetened water transiently increased appetite in lean men, but aspartame-sweetened soft drinks suppressed appetite (Black *et al*., 1993; Black and Anderson, 1994). Other studies report that sweeteners have the same effect as water (Rogers *et al*., 1988; Rodin, 1990; Canty and Chan, 1991), whereas others report suppression of overall intake when compared with soft drinks containing sugar (Rolls, 1997). Yet, other studies suggest that there is an increased intake when an unpalatable food item is made more palatable by addition of a sweetener. Methodological problems are at least partly responsible for the variable results obtained. In addition, the responses to sweet foods and drinks depend on dietary restraint (Lavin *et al*., 1997) and they can be conditioned. Intense sweeteners may mimic the ingestive effects of sugars on satiety but not the post-ingestive effects. For example, animal studies suggest that initial dislike for a bitter taste of a sucrose octa acetate solution is reversed once the animals learn to associate this taste with positive post-ingestive effects (Sclafani, 1987, 2001). Finally, a 10-week study involving overweight men and women, who consumed 28% of their energy as sucrose (mostly as beverages), showed an increase in body weight (1.6 kg), which was not observed in a similar group of subjects who consumed artificial sweeteners (Raben *et al*., 2002).Overall it appears that intense sweeteners do not reliably affect appetite and energy intake, but more longer term studies in free-living conditions are required.

From the above, it appears that the control of appetite operates through a redundant system that does not rely overwhelmingly on one or two major factors, such as energy density or on a specific macronutrient. Rather it depends on multiple factors that can interact, compensate or override each other, depending on environmental exposures and their duration. Given the fundamental importance of eating for survival, this is not surprising. The factors that influence eating behaviours include sensory factors, diet composition and variety of available food items, eating environment and individual subject characteristics, such as age, habitual dietary intake and prior social conditioning. It has been difficult to establish the relative importance of these factors, which are likely to differ with the environmental setting, for example, developed or developing countries. However, it is clear that feeding behaviour is influenced by both nutritional and non-nutritional factors. In addition, it appears that there is a good defence against development of underweight (in the absence of disease) (Garrow, 1988), but less good defence against development of overweight (Blundell and Stubbs, 1999), especially in an environment where the availability of abundant and varied food is coupled with limited physical activity. This defence needs to be very tight because deposition if only 1% of the lifetime cumulative energy intake were deposited in the reference male or female (equivalent to the dot by the side of Figure 3), it would double adult body weight and BMI, and adversely affect health.

Effect of different types of carbohydrate on feeding behaviour and energy homeostasis

With this background, the role of different types of carbohydrates on eating behaviour might not be expected to have overwhelming effects on long-term energy homeostasis. The following summary based on intervention studies is generally consistent with this view.

Non-starch polysaccharides (dietary fibre). The majority of studies comparing the effects of carbohydrates on energy balance and weight loss have been undertaken with NSP in various forms, probably because there are several potential ways in which NSP might induce a negative energy balance.

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The following are potential mechanisms: compared to available carbohydrates, NSP has a lower energy density (kJ/g; see above); foods containing NSP are often made from whole grains or whole foods such as fruit and vegetables and are thus bulky with a low-energy density, which may promote satiety; some types of NSP are viscous and can delay gastric emptying, causing feelings of increased fullness and satiety; NSP affects the intestinal absorption of other macronutrients, such as fat, although there is little evidence for significant losses in this way in humans; and delayed colonic metabolism of NSP after meal ingestion may delay the onset of hunger before the next meal (although the possible role of SCFAs and other potential signals from the colon appear to have been little investigated in humans). Results of more than 50 studies have been summarized in several reviews (Blundell and Burley, 1987; Stevens, 1988; Burley and Blundell, 1990; Levine and Billington, 1994), but it is difficult to establish firm overarching conclusions that apply to all circumstances. There are several reasons for this: the type and amount of NSP used in different studies have varied; the intervention has sometimes involved administration of tablets of extracted NSP and at other times diets rich in NSP; the age and adiposity of the study population have varied; and study designs have varied from open trials to double-blind control trials. Nevertheless, it appears that dietary supplementation with extracted NSP to a level that can be tolerated has at best a modest effect in reducing body weight over a period of several months or longer. Bulky NSP-rich diets with a low-energy density might be expected to encourage weight loss, or prevent weight gain, by promoting satiety, but such diets are often less palatable and less likely to be consumed. Better modelling techniques of the available data, including dose–response curves (for example, studied by meta-regression), may shed further light on possible effects of NSP on energy intake and body weight.

Starch and sugars. A few short-term preload studies have examined the effects of different types of hexose-based sugars on appetite and found little difference between them. Comparisons between sugars and high glycaemic index (GI) starches using short-term preloading protocols or 7-day protocols (Mazlam, 2001) suggest no major differences in satiety. However, a study comparing a high-starch diet with a high-sucrose diet found that the *ad libitum* intake over 14 days was lower and weight loss greater with the high-starch diet than the high-sucrose diet, which scored better on palatability (Raben *et al*., 1997). Another study (Raben *et al*., 1994) found that exchange of digestible starch for RS in a meal reduced satiety as well as post-prandial glycaemia and insulinaemia. The authors acknowledged that the differences in satiety may be due to texture and palatability of the meal, but it can be difficult to separate the sensory properties of diets from their macronutrient composition. However, it appears from other studies that sensory-specific satiety is related more to the sensory characteristics of a food than to its macronutrient composition (Johnson and Vickers, 1993).

As indicated in section above, energy density (see section Energy density, weight of food and carbohydrates) is also a potentially confounding variable. There is a lack of long-term studies. The CARMEN multicentre trial (Saris *et al*., 2000) compared the effects of *ad libitum* intake of low-fat diets rich in either complex carbohydrates or simple carbohydrates. Body weight loss in the low-fat simple carbohydrate and low-fat complex carbohydrate groups did not differ significantly (0.9 and 1.8 kg, respectively). There were also no significant differences in circulating lipids. Since the distribution of complex carbohydrate between starch and NSP was not reported, it is not possible to assess the effects of starch vs sugars. Therefore, it appears that there is lack of convincing evidence from long-term studies that starch offers advantages over sugars in weight reduction.

Polyols. There appears to be little information on the effect of polyols relative to other carbohydrates on weight loss or on satiety and other appetite sensations. One study found that replacement of sucrose with increasing doses of isomalt (12, 24 and 48 g per day), which is mostly unavailable carbohydrate, resulted in weight loss of about 2 kg over a period of 12 weeks (Spengler and Boehme, 1984).

Low vs high glycaemic index (GI carbohydrates, foods and diets). Numerous reports have examined the role of different carbohydrates, foods and diets with varying GI on appetite and satiety (Raben *et al*., 1994; Anderson *et al*., 2002; Kaplan and Greenwood, 2002; Anderson and Woodend, 2003; Ball *et al*., 2003), and weight control (Pawlak *et al*., 2002; Raben, 2002; Ludwig, 2003; Warren *et al*., 2003). The overall results do not appear to be consistent, although many short-term studies (<1 day) suggest that low-GI carbohydrates and foods promote satiety. One review concluded that short-term feeding trials generally show an inverse association between GI and satiety, and medium-term clinical trials show less weight loss on high-GI (or high glycaemic load) diets compared to low-GI (or low glycaemic load) diets (Pawlak *et al*., 2002). However, the differences in weight between control and intervention groups were small. Another review (Pawlak *et al*., 2002) (presented as part of a debate) systematically examined 31 short-term studies (<1 day) and reported that in 15 of these, low-GI foods promoted satiety or reduced hunger, and in the remaining 16 low-GI foods either reduced or made no difference to satiety. Low-GI foods reduced *ad libitum* food intake in seven studies, but did not do so in eight other studies. The same systematic review examined results from 20 longer term studies (up to 6 months). Weight loss was favoured by the low-GI diets in four studies, by the high-GI diets in two studies and there was no significant difference between the low and high-GI diets in the remaining 14 studies. The average weight loss was only 1.5 kg on the low-GI diets and 1.6 kg on the high-GI diets. Not surprisingly, the author concluded that there was no evidence that low-GI foods were superior to high-GI foods for long-term weight control. The overall differences in

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results may relate not only to the duration of the studies, but also to the energy density and sensory attributes of foods or diets, as well as the age of subjects, which has ranged from the young age of pre-pubertal children (Warren *et al*., 2003) to that of elderly people . The sensory attributes of foods are particularly important in free-living studies, because poorly palatable diets are likely to be associated with poor compliance. The obligatory ingestion of a diet or a meal when used as a preload under short-term laboratory conditions may well produce different results when the same diet is promoted for longer term use under free-living conditions. Ingestion of such a diet is not obligatory in free-living conditions, and therefore a diet may show efficacy in laboratory conditions but not effectiveness in free-living conditions. In addition, a recent study (Alfenas and Mattes, 2005) examined the effect of consuming only low- or high-GI foods *ad libitum* in the laboratory for 8 days in either high (three foods per meal) or low (one food per meal) variety conditions. It appeared that differential appetite sensations and glycaemic responses to foods tested in isolation were not preserved under conditions of longer term *ad libitum* ingestion of mixed meals. The potential interactions between different foods are much greater in free-living conditions than in laboratory conditions. In summary, the evidence suggesting that low-GI foods favour weight loss is stronger in short-term than in long-tem studies. It would be valuable to examine dose–response curves, especially in the long term, partly because there are fewer long-term studies, and partly because they are more relevant to health.

Liquid vs solid carbohydrates. Several papers and reviews (Mattes, 1996, 2006; DiMeglio and Mattes, 2000) suggest that supplemental energy provided as carbohydrates in fluids is less precisely compensated than when solid foods are manipulated. The reasons for the difference in energy compensation are not clear but may involve the rate at which these are ingested (liquids can be ingested several times more rapidly than solid food items), their energy density and sensory attributes, and gastric emptying rates, which are generally faster for liquids than solids. Reactive hypoglycaemia may also be implicated. One short-term study lasting a few hours examined the effect of ingesting the same quantity of available carbohydrate at the same rate in the form of an apple, puree apple or juice without the cell wall material or 'fibre'. The juice was less satiating than the puree, which in turn was less satiating than the apple. These changes were associated with greater insulin responses, which peaked at 30 min (juice > puree > apple) and a greater subsequent rebound hypoglycaemia (also juice > puree > apple) from similar peak glucose concentrations (measured in venous rather than arterial blood, which could confound interpretation) (Haber *et al*., 1977). There are few long-term studies, but in 1958 Fryer (Fryer, 1958) reported the effects of supplementing the diet of 20 college students for 2 months with a carbohydrate-rich drink (1.8 MJ/day). Dietary compensation for the extra liquid energy intake was only about half complete by 2 months. Other studies (observational or epidemiological) have shown that the compensation that does occur displaces the intake of protein and micronutrients from the diet, the full significance of which is still somewhat uncertain. The above intervention trials are complemented by epidemiological studies, such as the Nurses' Health Study II in the United States (Schulze *et al*., 2004), which reported that higher consumption of sugar-sweetened beverages is associated with greater weight gain (4–5 kg over 4 years in those who increased consumption from one or fewer drinks per week to one or more drinks per day) and greater risk of type II diabetes. Conversely, weight gain was smaller among women who decreased their intake of sugar-sweetened drinks (0–1.5 kg over 4-year periods). Epidemiological studies in children (for example, US Growing Up Today Study; Berkey *et al*., 2004) also show a link between sugar-added beverages and weight gain. The link between soft drinks and childhood obesity has been reviewed recently (James and Kerr, 2005). Finally, a long-term intervention trial in England (The Christchurch obesity prevention project in schools (CHOPPS); James *et al*., 2004) reported that the results of a cluster randomized control trial involving 644 children aged 7–11 years. A focused educational program at school over a year reported the average 3-day consumption of carbonated drinks decreased by 0.6 glasses (average glass size 250 ml) in the intervention group and increased by 0.2 glasses in the control group, with the result that in the percentage of overweight and obese children at the end of the year increased by 7.5% in the control group and decreased by 0.2% in the intervention group. In summary, there is epidemiological, physiological evidence, as well as interventional evidence linking sugar-sweetened beverages and weight gain.

The need to expand the physiological evidence base

The early growth of the obesity epidemic in developed countries some 30 years ago was associated with ingestion of high-fat, low-carbohydrate diets. Many workers felt that the macronutrient composition of the diets had a large part to play in this, and physiological studies that varied the carbohydrate to fat ratios (without controlling for energy density or GI) in laboratory studies were consistent with this notion. However, the recent trend in many developed countries, such as the United States (Centres for Disease Control and Prevention (CDC), 2004) and the United Kingdom (Henderson *et al*., 2003), for a decrease in the proportion of dietary energy from fat and an increase from carbohydrate, has not prevented the growth in obesity and overweight, which has continued to rise unabated. It is possible that without this change an even greater rise would have occurred. These trends have also been associated with exposure to an increased variety of foods and drinks containing different types of carbohydrates, carbohydrate combinations, sweeteners and sweet-bulking agents. Advances in technology can

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modify the structures of carbohydrates, for example, starch to RS, and lead to the development of new types of carbohydrates or mimetics (substances that mimic carbohydrates). However, their functional effects and their interactions with other dietary components need systematic examination so that their overall effect on energy balance can be understood.

Consumer behaviour and demands have also grown, and they have strained the existing physiological evidence base. For example, the above discussion indicates that macronutrients (or particular types of macronutrients, such as sugars, starch or NSP) can themselves influence energy density, GI and palatability of foods, all of which have been implicated in feeding behaviour. However, some of the effects of these food attributes on feeding behaviour overlap with each other to an uncertain degree (Figure 5). They probably also interact with other factors, such as texture and viscosity, which can also be influenced by macronutrients (for example, viscosity can be increased by certain types of NSP, such as guar gum). Most studies on feeding behaviour have studied only one of these attributes, some have considered a couple, but there is a lack of studies that have considered the effects of three or more such attributes simultaneously. Therefore, a number of key questions arise, which emphasize the need for integrative research. To what extent is energy density linked with GI and palatability? To what extent is palatability linked to GI and energy density? How do different types of carbohydrates influence these attributes, and can artificial modification bring about predictable changes? There is also the issue about the extent to which feeding behaviour is causally linked to these food attributes, as opposed to being markers of some other functional and causal property or properties. It has been suggested that weight-reducing diets should avoid high glycaemic foods, on the basis that they might cause reactive hypoglycaemia, which in turn, it is argued, stimulates appetite, reduces satiety and makes weight loss more difficult (Agatston, 2003). Mention has already been made (see section Liquid vs solid carbohydrates') about the hypothetical role of reactive hypoglycaemia in mediating differences in satiety after ingestion of apple, puree and juice (Haber *et al*., 1977). However, the evidence base for this causal pathway is weak and further work at each one of these steps is required.

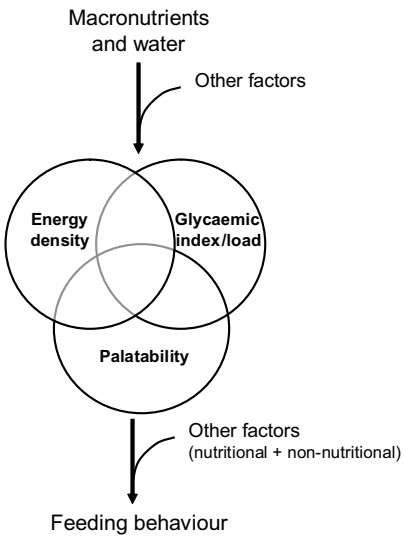

Figure 5 A model showing a possible pathway between intake of different macronutrients (and different subtypes, such as sugar, starch, polyols and fibre, in the case of carbohydrate) and feeding behaviour. Study of only one of the properties of foods (glycaemic index, energy density, palatability and others) is less informative than their simultaneous study, especially when linked to food and macronutrient composition.

Another issue concerns the energy system used in detailed metabolic studies, for example, studies that accurately assessed the effects of isoenergetic diets on *ad libitum* energy intake. Almost invariably the ME system has been used for this purpose (at least for the major macronutrients—fat, protein and carbohydrate absorbed by the small bowel). However, since this system can be considered to be flawed in relation to energy balance, a re-evaluation of the situation using the NME system is necessary, especially for those studies that have used large amounts of protein, fibre or other macronutrients that have a low bioenergetic efficiency. Diets that are isoenergetic in relation to the ME system are not necessarily isoenergetic in relation to the NME system (see sections Net metabolizable energy, and Energy systems and food labelling).

There is also a need to bridge the gap between short-term physiological studies that are undertaken in confined environments (laboratory studies) and longer term studies in free-living environments. Epidemiological approaches are useful in establishing associations, but they may have greater difficulty in separating causes from effects. For example, cross-sectional epidemiological studies on the role of sweeteners on weight control may be difficult to interpret because sweeteners may be preferentially used by those already overweight or obese, and this may mask any associations between sweeteners and weight loss. In addition, it should be remembered that sweeteners are used both as replacements for sugar and as supplements to sugar (for example, in several sugary soft drinks) in an attempt to promote a more prolonged and desirable after taste.

This discussion has placed much emphasis on physiological determinants of eating behaviour. However, there have been long-standing debates about the relative importance of physiology and psychology on feeding behaviour, and the boundary between them. Both are important, but their interactions and their independent contributions to feeding behaviour almost certainly vary with the environment. Social conditioning, social and environmental ambiance, and learned behaviour all play a role. Even the extent to which compensation occurs following supplementation may depend on whether the food is familiar to the consumer. Future research using a multidisciplinary approach is to be encouraged. Such an approach should also involve the

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ecologist, who is pre-occupied with why animals evolved with the behavioural programmes that control food intake. In contrast, the physiologist is pre-occupied with more immediate determinants of feeding behaviour. Both can provide important insights into mechanisms of eating behaviour and possible ways for combating over- and undernutrition.

Requirements for dietary carbohydrate

Using the brain's requirement of glucose as a basis for considering carbohydrate requirements, the Institute of Medicine has estimated the average requirement to be 100 g/day, and the Recommended Dietary Allowance to be 130 g/day day, for both men and women aged 19 years and above (Institute of Medicine, 2005). Estimated average requirement typically represents only 10–20% of total energy requirements, which vary according to weight and physical activity (FAO/WHO/UNU Expert Consultation, 2004). However, high-fat, high-protein diets are not considered healthy and many national and international bodies have set limits and ranges for carbohydrate intake based mainly on supplying energy needs for the individual that would not be supplied by recommended amounts of fat and protein. In its report 'Diet and Prevention of Chronic Diseases', WHO/FAO recommended that carbohydrate provides 55–75% of total energy (WHO, 2003). The upper limit is thought to allow adequate protein and fat intake, whereas the lower limit allows a maximum energy intake from fat of 30% and protein of 15%.

The partial replacement of carbohydrate with monounsaturated fats in diabetic diets has been seen to be beneficial (Garg, 1998). This has motivated European and UK diabetes associations to implement this advice for people with diabetes (Diabetes and Nutrition Study Group of European Association for the Study of Diabetes, 2000; Connor *et al*., 2003). They recommend that 40–60% of total energy should come from carbohydrate, and that carbohydrate plus monounsaturated fat should provide 60–70% of energy. This allows 20% of energy to come from monounsaturates.

WHO/FAO, and other bodies, also suggest that there should be a limit on the intake of free sugars at $<10\%$ of energy. This arises from the relation of sugar to dental caries, an increasing problem in the developing world, and that FAO/WHO 'considered that studies showing no effect of free sugars on excess weight have significant limitations' (Nishida *et al*., 2004). The 10% figure is given as a maximum, and one would expect therefore that sugar intakes on average would be less than this for populations as a whole.

Carbohydrate and physical performance

Carbohydrate feeding both before and during exercise can improve performance through a variety of mechanisms (Jeukendrup, 2004).

Carbohydrates in the large bowel

Quantitative aspects

The principal carbohydrates that reach the human large bowel are the NSP, RS, non-α-glucan oligosaccharides (short-chain carbohydrates), and some polyols and modified starches. In many populations of the world, there is primary low lactase activity in the small bowel.

The amount of these carbohydrates that arrive in the caecum is difficult to calculate because dietary intakes of most, except NSP, are largely unknown. NSP in the diet in European countries is between 11 and 33 g/day (Cummings and Frolich, 1993; Bingham *et al*., 2003) and all of this will reach the colon. Intakes of NSP in Mexicans are reported as 22 and 17 g/day in rural men and women, and 18 and 16 g/day in urban men and women (Sanchez-Catillo *et al*., 1997). In a West African village, intakes (corrected to 100% energy intake) were in the range of 25–28 g/day for men and 21–24 g/day for women, and 10–13 g/day in children of unspecified age, but sharing meals with adults (Hudson and Englyst, 1993). Other data, reported by Cassidy *et al*. (1994) give NSP intakes for Australia of 12–13 g/day, India 15–21 g/day, Ireland 9–11 g/day, Japan 11 g/day and the United States 12–17 g/day. Higher intakes may occur in vegetarians and populations with high intakes of fruit and vegetables such as some Pacific Islanders.

Resistant starch intakes are much more difficult to determine. This is because almost any handling of starchy foods from diet collections, that is mixing with water, heating, homogenization, freezing or cooling, will affect RS content. Present estimates for countries with westernized diets are in the range of 3–10 g/day (Champ *et al*., 2003; Goldring, 2004). Clearly this is very diet dependent. A couple of relatively unripe bananas will readily provide 20 g RS. A single biscuit made with potato flour would give 10 g. Estimates for developing countries for RS intakes are 9–10 to 30–40 g/day where starch intakes are high (Stephen *et al*., 1995). The amount of RS that escapes digestion also varies between people, partly dependent on transit time through the small bowel (Stephen *et al*., 1983; Silvester *et al*., 1995).

Modified starches are also likely to reach the colon because of their ether and ester bonds or increased cross-linking and substitutions. These starches are used in small amounts by the food industry for their functional properties and intakes are unlikely to be more than 2–3 g/day.

Almost no data have been reported of intakes of the non-α-glucan oligosaccharides or short-chain carbohydrates. Fructooligosaccharide and inulin intakes were estimated at between 1 and 10 g/day in European countries by Van Loo *et al*. (1995), but one must add to this the other oligosaccharides in beans, peas, non-wheat cereals and milk. Again, a meal containing 100 g of Jerusalem artichokes would provide 16–20 g of inulin, and babies living on breast milk will be getting 15 g/l of oligosaccharides (Miller and McVeagh, 1999). Average oligosaccharide intakes for westernized diets could, therefore, be in excess of 10 g/day.

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Polyols, such as lactitol, isomalt, maltitol, sorbitol, manitol, erythritol and xylitol, are mostly used as low-calorie substitutes for sugar in foodstuffs and confectionary. Daily intake of these carbohydrates is unknown but is likely to average only 2–3 g. However, people selecting sugar-free products including diabetics and those trying to lose weight may easily consume 20 g/day, so variation in intakes may well be great. Intakes are limited because of gastrointestinal intolerance (Lee *et al*., 2001). Even when intakes are known, the amount of these carbohydrates reaching the colon is difficult to calculate because their absorption varies between 2 and 90%, whereas some, such as erythritol, are almost completely excreted by kidney (Livesey, 2003b).

Overall, therefore, carbohydrate reaching the colon in people on westernized diets is probably in the range of 20–40 g/day, whereas in countries with high cereal intakes or higher intakes of fruit and vegetables, this could reach 50 g/day.

Virtually, all carbohydrate that enters the large bowel will be fermented by the commensal bacteria that live in the colon at densities of up to 10^{12}/g. The extensive fermentation of NSP has been known for many years (Cummings, 1981), while recovery of oligosaccharides from faeces is effectively nil (Cummings *et al*., 2001). Similar data are also available for RS with only very resistant retrograded starches partly surviving, the amount depending on colonic transit time, although occasional individuals are unable to digest some RS fractions (Cummings *et al*., 1996). Microcrystalline cellulose may resist fermentation because of its highly condensed structure, an observation that led to the belief that cellulose was not digested in the human gut. This is because microcrystalline cellulose was used in many early experiments of cellulose digestion. However, cellulose naturally present in the cell wall of food is completely fermented unless in association with large amounts of lignin. Other polysaccharides of the plant cell wall are also readily fermented, even when given in purified forms such as pectin or guar gum. This process is facilitated by the ability of these latter substances to form gels readily accessible to the microbiota.

Fermentation

Fermentation is an anaerobic process and, therefore, produces unique end products. These include principally the SCFAs acetate, propionate and butyrate (Cummings, 1995; Cummings *et al*., 1995). They are rapidly absorbed. Butyrate is the major energy source for the colonic epithelial cell, in contrast to glutamine for the small bowel and glucose for most other tissues. Butyrate also has differentiating properties in the cell, arresting cell division through its ability to regulate gene expression (Siavoshian *et al*., 2000). This property provides a credible link between the dietary intake of fermented carbohydrates, such as NSP, and protection against colorectal cancer (Bingham *et al*., 2003).

Propionate is absorbed and passes to the liver where it is taken up and metabolized aerobically. This molecule is not seen as having significant regulatory properties in humans, although it may moderate hepatic lipid metabolism (Todesco *et al*., 1991; Stephen, 1993). However, in ruminant animals, propionate is crucial to life because it is used to synthesize glucose in the liver.

Acetate is the major SCFA produced in all types of fermentation, the molar ratio of acetate:propionate:butyrate is around 60:20:20. Acetate is rapidly absorbed, stimulating sodium absorption and passes to the liver and then into the blood from where it is available as an energy source. Fasting blood acetate levels are about 50 μmol/l, rising 8–12 h later to 100–300 μmol/l after meals containing fermentable carbohydrate. Acetate is rapidly cleared from the blood with a half-life of only a few minutes and is metabolized principally by skeletal and cardiac muscle and the brain. Acetate spares free fatty acid oxidation in humans and its absorption does not stimulate insulin release. Another precursor of blood acetate is alcohol.

Fermentation also gives rise to the gases hydrogen and carbon dioxide. Much of the hydrogen is converted to methane by bacteria, and both hydrogen and methane are excreted in breath and flatus. Gas production, especially if rapid, is one of the principal complaints of people unused to eating foods containing significant amounts of fermentable carbohydrate. Another product of fermentation is microbial biomass or microbial growth (Stephen and Cummings, 1980). These bacteria are excreted in faeces and this is one of the principal mechanisms of laxation by NSP. Lactate is also produced from fermentation, usually during rapid breakdown of soluble carbohydrates such as oligosaccharides. Both D- and L-lactate are produced and both are absorbed. Some ethyl alcohol is produced during hind gut fermentation, although it is more characteristic of fermentation due to yeasts as in brewing and wine making.

Bowel habit

Carbohydrates in the colon have additional health benefits beyond providing energy through SCFA absorption. The best documented effect is that of NSP on bowel habit. Table 5 is a compilation of faecal weight data from around 120 papers published between 1932 and 1992 detailing 150 separate studies (Cummings *et al*., 2004). It shows the average increase in stool output expressed as grams of stool (wet weight) per gram of 'fibre' fed using weighted means from published data. Wheat bran as a source comes out as the most effective with raw bran at 7.2 g/g more effective than cooked bran, 4.4 ($P<0.05$), but has the disadvantage of containing 3% phytate—a known inhibitor of the absorption of divalent cations (calcium, magnesium, zinc and iron). Fruit and vegetables are remarkably effective, 6.0 g/g, and with wheat bran are well ahead of the rest. After fruit and vegetables comes psyllium at 4.0 g/g and then the league table progresses through oats 3.4, other gums and mucilages 3.1, corn 2.9, legumes (mainly soya) 1.5 and lastly pectin 1.3. The overall differences among the various sources of NSP are

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Table 5 Effect of NSP (dietary fibre) on bowel habit[a]

Source	N[b]	*Increase in stool weight (mean g/g 'fibre' fed)*	*Median*	*Range*
Raw bran	82	7.2	6.5	3–14.4
Fruit and vegetables	175	6.0	3.7	1.4–19.6
Cooked bran	338	4.4	4.9	2–12.3
Psyllium/ispaghula	119	4.0	4.3	0.9–6.6
Oats	53	3.4	4.8	1–5.5
Other gums and mucilages	66	3.1	1.9	0.3–10.2
Corn	32	2.9	2.9	2.8–3.0
Soya and other legumes	98	1.5	1.5	0.3–3.1
Pectin	95	1.3	1.0	0–3.6

Abbreviations: ANOVAR, analysis of variance; NSP, non-starch polysaccharides.
Difference among sources significant: ANOVAR: $F = 4.78$; $P < 0.001$.
[a]Modified and recalculated from Cummings *et al.* (2001, 2004).
[b]*N*, number of subjects involved in studies.

Table 6 Effect of RS on bowel habit

Source	N	*Amount fed (g/day)*	*Increase in stool weight (mean g/g RS fed)*
Potato RS_2	9	26.8	1.6
Banana RS_2	8	30.0	1.7
Wheat RS_3	9	17.4	2.5
Maize RS_3	8	19.0	2.7
Hylon VII RS_2	23	32	1.4
Hylon VII RS_3	23	32	2.2
Hylon VII	12	55	0.8
Mixed potato RS_2 and Hylon VII	8	40	0.9
Mixed food sources	11	39	1.8
Cornflakes	8	10	0
Hylon VII RS_2	14	28	1.0

Abbreviation: RS, resistant starch.
Overall weighted mean (s.e.m.) 1.5 g/g (0.24).
$N = 147$ diet periods in 11 studies.
For data sources see Figure 6.

statistically significant. These laxative properties of NSP are used in the prevention and treatment of constipation (Cummings, 1994).

Are any of the changes brought about by plant cell wall NSP unique? For most of them the answer is 'no', although the physical properties of NSP in the gut, especially gel function in the small bowel and surface effects in the large intestine, come closest. What has put the physiological and health effects of NSP into perspective has been the arrival on the nutritional scene in the last 20 years of RS and prebiotic carbohydrates (oligosaccharides).

Resistant starch shows some of the attributes of NSP in that it provides substrate for fermentation with the production of SCFA, but differs radically from NSP in not having physical properties that come from the plant cell wall, and RS is more the product of food processing rather than being an indicator of a healthy diet. RS, through its fermentability has mild laxative properties. Seven studies have reported accurate RS measurements in diet and have carried out adequate faecal collections (Table 6), from which it can be seen that the average increase in stool weight is 1.5 g/g RS fed. A meta-analysis including data from six of these seven studies (Tomlin and Read, 1990; van Munster *et al.*, 1994; Phillips *et al.*, 1995; Cummings *et al.*, 1996; Silvester *et al.*, 1997; Heijnen *et al.*, 1998; Hylla *et al.*, 1998) (excluding Tomlin and Read, 1990; because no error measurements are given in the paper) has been carried out and the results are given in Figure 6. This shows a highly significant overall increase in mean daily stool weight for the group of 41.1 g/day (± 5.4 g s.e.m.; $P < 0.001$), but no significant dose-response was found using meta-regression. It was not possible to distinguish from these data among the different types of RS. This puts RS very much towards the bottom of the league table of carbohydrates that affect bowel habit (Table 5) and a minor contributor compared with NSP from whole grain cereals, fruit, vegetables, psyllium, oats and corn. *In vitro* starch and RS are good sources of butyrate (Cummings, 1995), but these findings do not lead through to consistent changes in faecal butyrate output or molar ratios of SCFA (Flourie *et al.*, 1986; van Munster *et al.*, 1994; Phillips *et al.*, 1995; Cummings *et al.*, 1996; Heijnen *et al.*, 1998; Hylla *et al.*, 1998).

Clinical aspects

Irritable bowel syndrome (IBS) is one of the most common disorders seen in the gastroenterology clinic. It has two main presenting features, namely, abdominal pain and altered bowel habit. It is, however, a very diverse disease with no clear aetiology. While the cause is unknown, NSP has a useful role to play in the management of constipation-predominant IBS. However, wheat bran is not universally beneficial in this condition possibly because it is thought that a significant number of IBS patients are wheat intolerant without having the diagnostic features of coeliac disease (Nanda *et al.*, 1989; Francis and Whorwell, 1994; Snook and Shepherd, 1994). Furthermore, changing people onto significantly increased NSP intakes leads to excess gas production and IBS patients may have a gut that is unusually sensitive to gas (King *et al.*, 1998; Drossman *et al.*, 2002; Talley and Spiller, 2002; Longstreth *et al.*, 2006).

Colonic diverticular disease is another condition that benefits from carbohydrate in the diet, particularly NSP. A diverticulum is a pouch that protrudes outwards from the wall of the bowel and is associated with hypertrophy of the muscle layers of the large intestine, particularly the sigmoid colon. Diverticular disease is very common in industrial societies, the prevalence rising with age to about 30 percent of people over the age of 65 years. Many people with diverticula do not have symptoms, but those that do,

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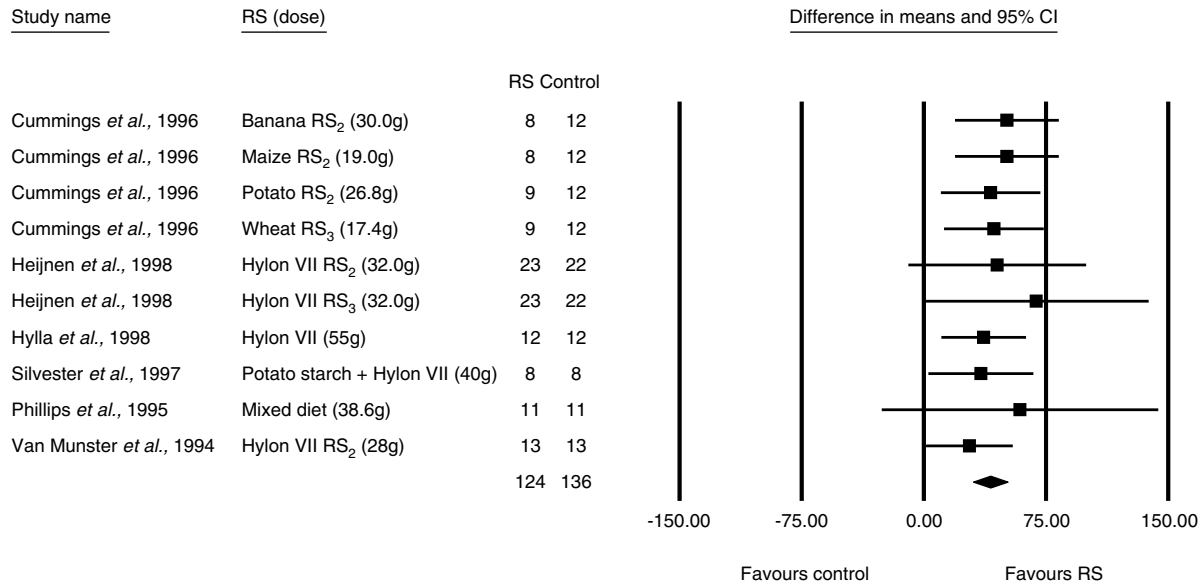

Figure 6 Meta-analysis (fixed effect model) of effect of various sources of resistant starch on bowel habit (stool weight). Point estimate +41.1 g/day; 95% CI: +30.5 to +51.7 g/day. The test of overall effect was highly significant ($P = <0.001$), and the test of heterogeneity was not significant ($I^2 = 0\%$; $P = 0.971$).

complain of lower abdominal pain and changes in bowel habit. High NSP-containing diets were introduced in the 1960s and their use revolutionized the management of this condition (Painter *et al*., 1972). Wheat bran is thought to be more effective than other sources of NSP or bulk laxatives, although bran is not a panacea and may aggregate gas production, feelings of abdominal distension and incomplete emptying of the rectum (Stollman and Raskin, 2004). The role of carbohydrate in the prevention of colorectal cancer is dealt with elsewhere in this consultation.

Prebiotics

Definition

'A prebiotic is a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one of a limited number of bacteria in the colon, and thus improves host health' (Gibson and Roberfroid, 1995). This use of the term 'non-digestible' in this context is meant to convey the idea of carbohydrates that are not digested and absorbed in the small intestine. As such it conflicts with the use of the term digestion referred to in the section on DE where 'digestibility is defined as the proportion of combustible energy that is absorbed over the entire length of the gastrointestinal tract.' (see below).

Physiology and microbiology

The main candidate prebiotics are all non-α-glucan oligosaccharides. They are present in the normal diet, as described above, at intakes of 5–10 g/day. Those that have been shown to be prebiotic are fructooligosaccharides, galactooligosaccharides and lactulose. The ability of fructooligosaccharides, galactooligosaccharides and inulin, when taken in relatively small amounts in the diet of around 5–15 g/day, to alter the composition of the flora to one dominated by bifidobacteria and lactobacilli is now well established (Gibson *et al*., 2004; Roberfroid, 2005).

Prebiotic carbohydrates are important because of the new concept of a healthy or balanced gut flora. A healthy, or 'balanced' microbiota is one that is predominantly saccharolytic and comprises significant numbers of bifidobacteria and lactobacilli (Cummings *et al*., 2004). This concept is based on a number of observations. The genera *Bifidobacterium* and *Lactobacillus* do not contain any known pathogens, and they are primarily carbohydrate-fermenting bacteria, unlike other groups such as bacteroides and clostridia that are also proteolytic and amino-acid fermenting. The products of carbohydrate fermentation, principally SCFAs are beneficial to host health, while those of protein breakdown and amino acid fermentation, which include ammonia, phenols, indoles, thiols, amines and sulphides, are not (Cummings and Macfarlane, 1991). Furthermore, lactic acid-producing bacteria such as bifidobacteria and lactobacilli play a significant role in the maintenance of colonization resistance, through a variety of mechanisms (Gibson *et al*., 2005). Equally importantly, the exclusively breast-fed neonate has a microflora dominated by bifidobacteria, which is part of the baby's defence against pathogenic microorganisms, and which is an important primer for their immune system. This microflora is nurtured by oligosaccharides in breast milk, which can be considered to be the original prebiotics.

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As already described, almost any carbohydrate that reaches the large bowel will provide a substrate for the commensal microbiota, and will affect its growth and metabolic activities. This has been shown for NSP (Stephen and Cummings, 1980), and will occur with other substrates such as RS, sugar alcohols and lactose. However, stimulation of growth by these carbohydrates is a nonspecific, generalized effect, that probably involves many of the major saccharolytic groups, and associated cross-feeding species in the large bowel (Macfarlane and Cummings, 1991). The selective properties of prebiotics relate to the growth of bifidobacteria and lactobacilli at the expense of other groups of bacteria in the gut, such as bacteroides, clostridia, eubacteria, enterobacteria, enterococci, and so on. In practice, studies show that such selectivity is variable, and the extent to which changes in the microbiota allow a substance to be called prebiotic have not been established. There are also qualitative aspects of the concept of selectivity. Some investigations have shown increases in other bacterial genera such as *Roseburia*, *Ruminococcus* and *Eubacterium*, with established prebiotics like inulin (Duncan *et al*., 2003; Langlands *et al*., 2004). Moreover, it is now recognized that many bacteria inhabiting the large bowel have not yet been identified and are difficult to culture routinely (Macfarlane and Macfarlane, 2004; Eckburg *et al*., 2005). One consequence of this is that we do not know what the global effects of prebiotics are on the structure of the microbiota. Furthermore, prebiotics can only enhance the growth of bacteria that are already present in the gut and the composition of the microbiota can be affected by a variety of other factors, such as diet, disease, drugs, antibiotics, age, and so on. Nevertheless, prebiotic carbohydrates do have dramatic effects on the gut flora. Does this lead to any health benefits?

Prebiotics should be laxative but as Table 7 and Figure 7 show (Ito *et al*., 1990; Gibson *et al*., 1995; Alles *et al*., 1996; Bouhnik *et al*., 1997; Castiglia-Delavaud *et al*., 1998; van Dokkum *et al*., 1999; Gostner *et al*., 2005), they are not significantly so. Meta-analysis of the studies in Table 7 show that overall there is no significant change in faecal weight when a wide range of sources and doses of oligosaccharides are studied. Most of these papers do, however, report a clear bifidogenic effect, so this alone does not affect bowel habit. Subjects often report increased flatulence and bloating, a sign that fermentation is occurring, but there is no change in SCFA profile or bile acid output. Studies in constipated subjects (Teuri and Korpela, 1998; Chen *et al*., 2000; Den Hond *et al*., 2000), report increases in stool weight, which is surprising and should be followed up.

Health benefits

The main potential health benefit of prebiotics should be in strengthening gut barrier function against infection. So far, however, few randomised controlled trial (RCT) have been done and those that have, in traveller's diarrhoea, IBS, inflammatory bowel disease and pouchitis, really do not show a clear benefit except, possibly, in well-being, although animal studies in inflammatory bowel disease are numerous and show reductions in inflammation. In antibiotic-associated diarrhoea, three RCT have been reported, in one of which there was a benefit in reducing episodes of diarrhoea in patients with *Clostridium difficile*-associated symptoms treated with metronidazole and vancomycin. Again, it is too early to draw conclusions from these studies. (see review by Macfarlane *et al*., 2006).

Table 7 Effects of prebiotics on bowel habit

Type	*Amount (g/day)*	N	*MDSW/g/day*		*Increase in stool weight (mean g/g 'fibre' fed)*
			Control	*Prebiotic*	
Oligomate 55 (GOS)	4.8	12	151	134	0
	9.6	12		151	0
	19.2	12		162	0.6
Oligofructose	15.0	8	134	154*	1.3
Inulin	15	4	92	123	2.1
Oligofructose	5	24	272	279	0
	15			264	0
TOS	10	8	105	80	0
Inulin	31	9	129	204*	2.4
Inulin	15	12	129	155	1.7
Oligofructose	15	12		108	0
GOS	15	12		158	1.9
Isomalt[a]	30	19	99	111	0.4

Abbreviations: GOS, galacto-oligosaccharides; gram/gram increase, gram increase in stool weight per day per gram prebiotic fed; MDSW, mean daily stool weight; *N*, number of subjects; TOS, transgalacto-oligosaccharide.
*Significantly different from control $P<0.05$.
[a]Proposed as a prebiotic but not established as one.
For data sources see Figure 7.

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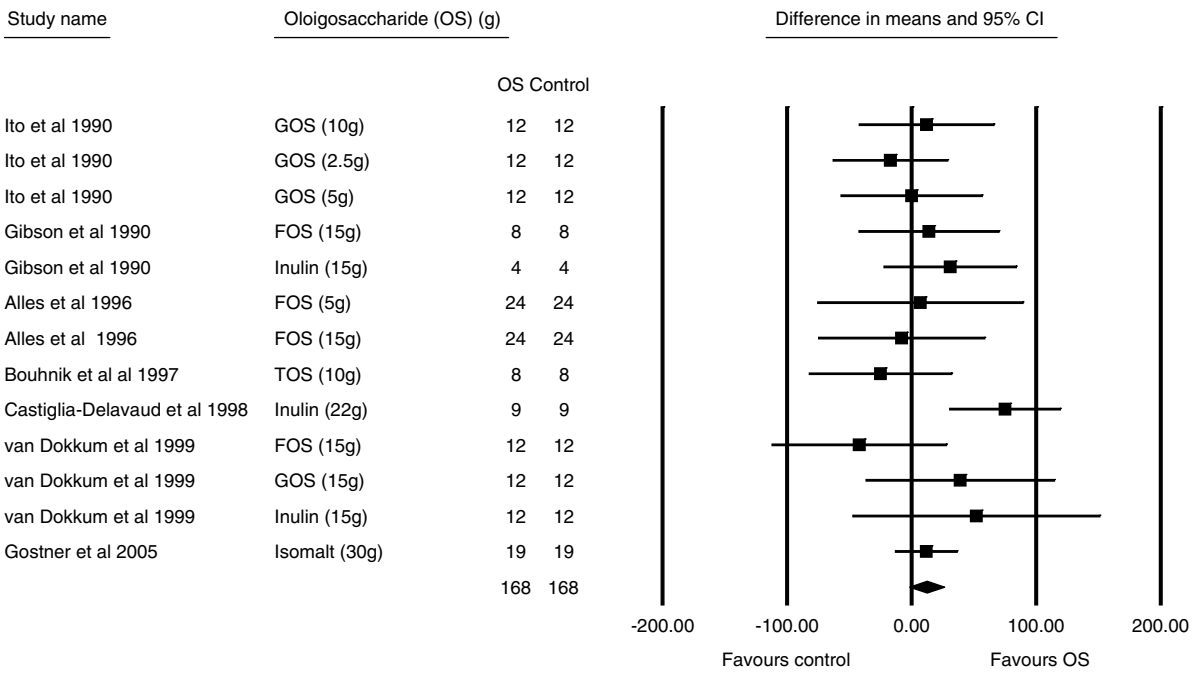

Figure 7 Meta-analysis (fixed effect model) of various prebiotic carbohydrates on bowel habit (stool weight). Point estimate +12.6 g/day; 96% CI: −1.5 to +26.6 g/day. The test of overall effect was not significant ($P=0.079$) and nor was the test of heterogeneity ($I^2=21.6\%$; $P=0.225$).

Table 8 Effect of prebiotics on calcium absorption in humans

Subjects	N	*Prebiotic*	*Study design*	*Absorption method*	*Result*
Adolescents, M 14–16 years	12	FOS 15 g	RCT feeding study. 9-day periods	^{44}Ca, ^{48}Ca	Fractional absorption increased from 48±17% to 60±17%
Adolescents, F 11–14 years	59	FOS 8 g FOS + inulin 8 g	Randomized crossover feeding study. 3-week periods	^{46}Ca, ^{42}Ca	FOS—effect FOS/inulin absorption increased from 32±10% to 38±10%
Adolescents, F/M 9–13 years	100	Mixed long- and short-chain inulin 8 g	1-year supplement to diet	^{46}Ca	Calcium absorption greater. Bone mineral density higher
M 20–30 years	12	Inulin 15 g, FOS 15 g, GOS 15 g	Randomized crossover feeding study. 21-day periods	^{44}Ca, ^{48}Ca	No effect on calcium or iron absorption
M	9	Inulin	Latin square feeding study. 28-day periods	Balance	Significant increase in absorption. No effect on magnesium, iron or zinc
Post menopausal women 50–70 years	12	FOS 10 g	RCT feeding study. 5-week periods	^{44}Ca and balance	No effect
Post menopausal women 55–65 years	12	TOS 20 g	RCT crossover. 9-day periods	^{44}Ca, ^{48}Ca	Ca absorption increased from 21±7% to 24±7%
8 men 7 women, 25–36 years	15	FOS 0.8–1.1 g	Absorption from fortified milk drinks	^{42}Ca, ^{43}Ca, ^{44}Ca	No effect

Abbreviations: FOS, fructo-oligosaccharides; TOS, transgalacto-oligosaccharides.
For data sources see Macfarlane *et al.* (2006).

An unexpected but potentially very important effect of prebiotics is that on calcium absorption and bone mineral density. Studies in animal models show clearly enhanced absorption of calcium, magnesium and iron with galacto-oligosaccharides, fructooligosaccharides and inulin, and prevention of osteopenia following gastrectomy and ovariectomy. Table 8 summarizes the studies in humans in which five out of eight show a benefit, most importantly,

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in adolescents. Possible mechanisms are discussed elsewhere (Macfarlane *et al*., 2006). How specific this effect on calcium absorption is to this class of fermented carbohydrate remains to be seen. Lactose has traditionally been thought to promote calcium absorption, although this is not a consistent finding (Zittermann *et al*., 2000).

Other possible health benefits of prebiotics are now being explored in many situations, facilitated by their safety and ease of use. A substantial literature is accumulating on prebiotics and cancer. However, much of the published work is in animals where the role of prebiotics looks to be beneficial, whereas human studies are mostly concerned with identification of early biomarkers of risk (Pool-Zobel, 2005). Prebiotics are now being added to follow-on feeds for infants (Fanaro *et al*., 2005), a practice which arises from the clear benefits to children of probiotics in preventing and ameliorating the symptoms of acute infectious diarrhoea, and in atopic disease. Their use to prevent necrotizing enterocolitis shows promise in animal models (Butel *et al*., 2002). Prebiotics clearly change the gut microbiota of infants and alter large bowel function, but large clinical trials are awaited. Another area of importance is lipid metabolism where prebiotic studies in animals have shown reduced blood levels of cholesterol and triglycerides and beneficial effects on fatty liver. Clinical trials in humans have not yielded such consistent results (Williams and Jackson, 2002; Beylot, 2005). However, the effects on hepatic lipid metabolism are worth further study. There is also great interest in prebiotics in the pet food and animal feed industry (Flickinger and Fahey, 2002), where improved control of gastrointestinal infection is reported and enhanced growth performance is seen in poultry especially. Other areas of interest include prebiotics and immunomodulation and the gut immune system, glycaemic control, behavioural effects, especially cognitive performance, and the enhancement of probiotic activity in synbiotics.

Prebiotics bring a new dimension to dietary carbohydrates, which might not have been predicted. Their ability to change the composition of the gut flora towards one that should protect against infection and their effect on calcium absorption are very important for public health. However, much work needs to be done in determining intakes of prebiotics in individuals and populations, on their mechanisms of action in the gut and potential effect on the immune system, inflammation and cancer.

Digestibility concepts

Within the nutrition community there is an awareness that the digestion (mechanical, chemical and enzymic breakdown) of food and absorption of products takes place in characteristically different regions of the gut. Of particular consequence has been the division of digestive processes into those that take place in the small bowel vs the large bowel. Small bowel digestion and absorption occurs for most nutrients, whereas the large bowel, through the versatility of its anaerobic bacteria, deals mainly with carbohydrates such as NSP, non-α-glucan short-chain carbohydrates (oligosaccharides), RS and polyols.

The end products of carbohydrate breakdown vary in different regions of the gut with sugars appearing in blood and insulin secretion stimulated after small bowel absorption, while from the colon the process of fermentation yields SCFAs, which metabolically are entirely different (Remesy *et al*., 1995). Other divisions within the gut are also valid, especially between duodenum/jejunum and ileum with, for example, iron being absorbed in the duodenum and upper jejunum and vitamin B12 in the terminal ileum. These patterns of digestion are significant for health and extend across the animal kingdom depending largely on the anatomy of the gut. For example, in ruminants, fermentation takes place primarily in the upper gut (the stomach and rumen).

Knowledge of the importance of this contrasting physiology linked to different regions of the gut has led to suggested classifications of nutrients, especially carbohydrates on the basis of the apparent site of their digestion and absorption. An example is fibre, originally the cell wall carbohydrates of plants such as cellulose, hemicellulose and pectin. However, as our understanding of carbohydrate digestion has increased, it has become clear that while regional differences in function occur, there is no such clarity in regional differences in carbohydrate digestion. Most carbohydrates can reach the colon, for example, lactose, polyols, short-chain carbohydrates, some starches and all NSP. For some of these, for example, polyols or starch, the amount can vary between meals and individuals, depending on factors such as dose and transit time (Stephen *et al*., 1983; Cummings and Englyst, 1991; Silvester *et al*., 1995; Cummings *et al*., 1996; Livesey, 2003b). To describe carbohydrates by the region of their digestion in the gut is, therefore, not an exact science.

Moreover, the gut acts as a single organ in digestion. Internal regulation of gut digestive processes occurs through neuro-endocrine loops between different regions. A classic example is the gastro-colic reflex, but much more intricate feedback occurs between regions of the gut (Cooke and Reddix, 1994; Nightingale *et al*., 1996; Camilleri, 2006).

Furthermore, as already indicated in the discussion of energy values of food, 'digestibility is defined as the proportion of combustible energy that is absorbed over the entire length of the gastrointestinal tract'. Other terms in use include 'true digestibility' (small bowel), 'fermentable' (large bowel) and 'apparent digestibility' (whole gut).

There is a strong case for looking at carbohydrate digestion as an integrated whole gut process. For the purposes of classifying food as carbohydrates, both their DE and digestion and absorption should be seen as a single integrated system. This is not to underestimate the importance of regional differences in these processes and their subsequent metabolic effects, but the digestion and classification of carbohydrate should be based on their chemistry

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while considering their digestion and digestibility, a whole gut approach should be used.

Conclusion

Being quantitatively the most important dietary energy source for most populations, carbohydrates have a special role to play in energy metabolism and homeostasis. The overview provided here deals with only selected physiological effects of energy metabolism and gastrointestinal effects of carbohydrates and their health implications. Several carbohydrate-specific theories of appetite regulation have been proposed but none are universally accepted, although high-carbohydrate, low-energy-density diets rich in fruit, vegetables and fibre are often recommended for weight reduction or prevention of weight gain. Appetite and hunger, which are of fundamental to survival, appear to have many layers of control, with one layer compensating or dominating another in some circumstances. The recent growth of overweight and obesity throughout the world is related to lifestyle changes, which have placed the human in the unusual situation (at least in evolutionary terms) of having to defend against a combination of persistent abundance of tasty food and reduced physical activity. There is a need to better understand the interaction between energy density, GI/load, palatability and other factors and their effects on feeding behaviour. At the same time, there is room to establish more rational national and international dietary energy systems and to consider greater application of the NME system, which has some advantages over the more commonly used, ME system.

The other physiological effects of many carbohydrates depend on the site, rate and extent of their digestion in and absorption from the gut. The majority of mono- and disaccharides, together with maltodextrins and most starch, are hydrolyzed by pancreatic enzymes in the small bowel and at the epithelial surface, and the resultant monosaccharide mixtures absorbed transported to the liver and then stored or metabolized. These carbohydrates are primarily energy yielding. The non-α-glucan oligosaccharides have other properties, in that they increase calcium absorption and some selectively modify the composition of the large bowel microbiota to one dominated by bifidobacteria and lactobacilli, known as the prebiotic effect. Studies to demonstrate proven health benefits of prebiotics are awaited.

The prebiotic carbohydrates, along with NSP, RS and some polyols, reach the large bowel where they are fermented. The principal end products, SCFA, are absorbed and provide a further energy source to the tissues. Fermentation benefits bowel habit, although the effects can be very small, and provides mechanisms that could be important in cancer prevention in the colon.

In the digestion of carbohydrates, the gut acts as an integrated organ with distinct regions of function. The nature of carbohydrate, both its chemical and physical properties, together with the physiological responses of absorption and secretion, local and visceral neuro-endocrine reflexes, enzyme section and microbial activity, determine the varied responses to carbohydrate in our diet.

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Conflict of interest

During the preparation and peer review of this paper in 2006, the authors and peer reviewers declared the following interests.

Authors

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Peer-reviewers

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References

Agatston A (2003). *The South Beach Diet*. Headline Book Publishing: London.

Alfenas RC, Mattes RD (2005). Influence of glycemic index/load on glycemic response, appetite, and food intake in healthy humans. *Diabetes Care* **28**, 2123–2129.

Alles MS, Hautvast JG, Nagengast FM, Hartemink R, Van Laere KM, Jansen JB (1996). Fate of fructo-oligosaccharides in the human intestine. *Br J Nutr* **76**, 211–221.

Anderson GH, Catherine NL, Woodend DM, Wolever TM (2002). Inverse association between the effect of carbohydrates on blood glucose and subsequent short-term food intake in young men. *Am J Clin Nutr* **76**, 1023–1030.

Anderson GH, Woodend D (2003). Effect of glycemic carbohydrates on short-term satiety and food intake. *Nutr Rev* **61**, S17–S26.

AOAC (2002). *AOAC Official Methods of AOAC International*, 17th edn. Gaithersburg, MD, USA.

Armstrong DG (1969). Cell bioenergetics and energy metabolism. In: Lenkeit W, Breiren D, Crassman E (eds). *Handbuch Der Tierernahrung*. Parey Publishing: Hamburg.

Astrup A, Buemann B, Flint A, Raben A (2002). Low-fat diets and energy balance: how does the evidence stand in 2002? *Proc Nutr Soc* **61**, 299–309.

Astrup A, Grunwald GK, Melanson EL, Saris WH, Hill JO (2000). The role of low-fat diets in body weight control: a meta-analysis of *ad libitum* dietary intervention studies. *Int J Obes Relat Metab Disord* **24**, 1545–1552.

Ball SD, Keller KR, Moyer-Mileur LJ, Ding YW, Donaldson D, Jackson WD (2003). Prolongation of satiety after low versus moderately high glycemic index meals in obese adolescents. *Pediatrics* **111**, 488–494.

Bar A (1990). Factorial calculation model for the estimation of the physiological caloric value of polyols. In: Hosoya N (ed). *Proceedings of the International Symposium on the Caloric Evaluation of Carbohydrates*. The Japanese Association for of Dietetic and Enriched Foods: Tokyo, pp 209–379.

Bathalon GP, Tucker KL, Hays NP, Vinken AG, Greenberg AS, McCrory MA *et al.* (2000). Psychological measures of eating behavior and the accuracy of 3 common dietary assessment methods in healthy postmenopausal women. *Am J Clin Nutr* **71**, 739–745.

Bell EA, Rolls BJ (2001). Energy density of foods affects energy intake across multiple levels of fat content in lean and obese women. *Am J Clin Nutr* **73**, 1010–1018.

Berkey CS, Rockett HR, Field AE, Gillman MW, Colditz GA (2004). Sugar-added beverages and adolescent weight change. *Obes Res* **12**, 778–788.

Bernier J, Pascal G (1990). Valeur energetique des polyols (surcres alcools). *Med Nutr* **26**, 221–238.

Beylot M (2005). Effects of inulin-type fructans on lipid metabolism in man and in animal models. *Br J Nutr* **93** (Suppl 1), S163–S168.

Bingham SA, Day NE, Luben R, Ferrari P, Slimani N, Norat T *et al.* (2003). Dietary fibre in food and protection against colorectal cancer in the European prospective investigation into cancer and nutrition (EPIC): an observational study. *Lancet* **361**, 1496–1501.

Black JL (2000). Modelling growth and lactation in pigs. In: Theodorou KM, France J (eds). *Feeding Systems and Feed Evaluation Models*. Wallingford, Oxon, UK, pp 363–391.

Black RM, Anderson GH (1994). Sweeteners, food intake and selection. In: Fernstrom JD, Miller GD (eds). *Appetite and Body Weight Regulation: Sugar, Fat and Macronutrient Substitutes*. Boca Raton, FL.

Black RM, Leiter LA, Anderson GH (1993). Consuming aspartame with and without taste: differential effects on appetite and food intake of young adult males. *Physiol Behav* **53**, 459–466.

Blaxter KB (1989). *Energy Metabolism in Animals and Man*. Cambridge University Press: Cambridge.

Blaxter KL (1971). Methods of measuring the energy metabolism of animals and interpretation of results obtained. *Fed Proc* **30**, 1436–1443.

Blundell JE, Burley VJ (1987). Satiation, satiety and the action of fibre on food intake. *Int J Obes* **11** (Suppl 1), 9–25.

Blundell JE, Rogers PJ (1994). Sweet carbohydrate substitutes (intense sweeteners) and control of appetite: scientific issues. In: Fernstrom JD, Miller GD (eds). *Appetite and Body Weight Regulation: Sugar, Fat and Macronutrient Susbstitutes*. Boca Raton, FL.

Blundell JE, Stubbs RJ (1999). High and low carbohydrate and fat intakes: limits imposed by appetite and palatability and their implications for energy balance. *Eur J Clin Nutr* **53** (Suppl 1), S148–S165.

Bouhnik Y, Flourie B, D'Agay-Abensour L, Pochart P, Gramet G, Durand M *et al.* (1997). Administration of transgalacto-oligosaccharides increases fecal bifidobacteria and modifies colonic fermentation metabolism in healthy humans. *J Nutr* **127**, 444–448.

British Nutrition Foundation (1990). Energy from complex carbohydrates. In: *BNF Task Force on Complex Carbohydrates in Foods*. Chapman and Hall: London.

Brown J, Livesey G, Roe M, Faulks R, Poppitt S, Wilkinson J *et al.* (1998). Metabolizable energy of high non-starch polysaccharide-maintenance and weight-reducing diets in men: experimental appraisal of assessment systems. *J Nutr* **128**, 986–995.

Burley VJ, Blundell JE (1990). Action of dietary fibre on the satiety cascade. In: Kritchevsky D, Bonfield C, Anderson JW (eds). *Dietary Fibre. Chemistry, Physiology and Health Effects*. Plenum Press: New York, NY.

Butel MJ, Waligora-Dupriet AJ, Szylit O (2002). Oligofructose and experimental model of neonatal necrotising enterocolitis. *Br J Nutr* **87** (Suppl 2), S213–S219.

Camilleri M (2006). Integrated upper gastrointestinal response to food intake. *Gastroenterology* **131**, 640–658.

Campfield LA, Smith FJ (1990). Transient declines in blood glucose signal meal initiation. *Int J Obes* **14** (Suppl 3), 15–31; discussion 31–34.

Campfield LA, Smith FJ (2003). Blood glucose dynamics and control of meal initiation: a pattern detection and recognition theory. *Physiol Rev* **83**, 25–58.

Campfield LA, Smith FJ, Rosenbaum M (1992). Human hunger: is there a role for blood glucose dynamics? *Appetite* **18**, 244.

Canty DJ, Chan MM (1991). Effects of consumption of caloric vs noncaloric sweet drinks on indices of hunger and food consumption in normal adults. *Am J Clin Nutr* **53**, 1159–1164.

Casey A, Mann R, Banister K, Fox J, Morris PG, Macdonald IA *et al.* (2000). Effect of carbohydrate ingestion on glycogen resynthesis in human liver and skeletal muscle, measured by (13)C MRS. *Am J Physiol Endocrinol Metab* **278**, E65–E75.

Cassidy A, Bingham SA, Cummings JH (1994). Starch intake and colorectal cancer risk: an international comparison. *Br J Cancer* **69**, 937–942.

Castiglia-Delavaud C, Verdier E, Besle JM, Vernet J, Boirie Y, Beaufrere B *et al.* (1998). Net energy value of non-starch polysaccharide isolates (sugarbeet fibre and commercial inulin) and their impact on nutrient digestive utilization in healthy human subjects. *Br J Nutr* **80**, 343–352.

Centres for Disease Control and Prevention (CDC) (2004). Trends in intake of energy and macronutrients—United States, 1971–2000. *MMWR Morb Mortal Wkly Rep* **53**, 80–82.

www.manaraa.com

Champ M, Langkilde A-M, Brouns F *et al*. (2003). Advances in dietary fibre characterization. 2. Consumption, chemistry, physiology and measurement of resistant starch; implications for food health and food labelling. *Nutr Res Rev* **16**, 143–161.

Chen H-L, Lu Y-H, Lin JJ, Ko L-Y (2000). Effects of fructooligosaccharide on bowel function and indicators of nutritional status in constipated elderly men. *Nutr Res* **20**, 1725–1733.

Commission E (2006). *Directive 90/496/EEC on Nutrition Labelling of Foodstuffs: Discussion Paper on Revision of Technical Issues*. Services for the European Commission.

Connor H, Annan F, Bunn E, Frost G, McGough N, Sarwar T *et al*. (2003). The implementation of nutritional advice for people with diabetes. *Diabet Med* **20**, 786–807.

Cooke HJ, Reddix RA (1994). Neural regulation of intestinal electrolyte transport. In: Johnson LR, Alpers DH, Christensen J, Jacobson ED, Walsh JH (eds). *Physiology of the Gastrointestinal Tract*. Raven Press, New York, pp 2083–2132.

Cummings JH (1981). Dietary fibre. *Br Med Bull* **37**, 65–70.

Cummings JH (1994). Non-starch polysaccharides (dietary fibre) including bulk laxatives in constipation. In: Kamm MA, Lennard-Jones JE (eds). *Constipation*. Wrightson Biomedical Publishing Ltd: Petersfield, UK, pp 307–314.

Cummings JH (1995). Short-chain fatty acids. In: Gibson GR, Macfarlane GT (eds). *Human Colonic Bacteria*. CRC Press: Boca Raton, FL, pp 101–130.

Cummings JH, Antoine JM, Azpiroz F, Bourdet-Sicard R, Brandtzaeg P, Calder PC *et al*. (2004). PASSCLAIM—gut health and immunity. *Eur J Nutr* **43** (Suppl 2), II118–II173.

Cummings JH, Beatty ER, Kingman SM, Bingham SA, Englyst HN (1996). Digestion and physiological properties of resistant starch in the human large bowel. *Br J Nutr* **75**, 733–747.

Cummings JH, Englyst HN (1991). Measurement of starch fermentation in the human large intestine. *Can J Physiol Pharmacol* **69**, 121–129.

Cummings JH, Frolich W (1993). *Dietary Fibre Intakes in Europe: A Survey Conducted by Members of the Management Committee of COST 92. Metabolic and Physiological Aspects of Dietary Fibre in Food*. Brussels.

Cummings JH, Hill MJ, Jenkins DJ, Pearson JR, Wiggins HS (1976). Changes in fecal composition and colonic function due to cereal fiber. *Am J Clin Nutr* **29**, 1468–1473.

Cummings JH, Macfarlane GT (1991). The control and consequences of bacterial fermentation in the human colon. *J Appl Bacteriol* **70**, 443–459.

Cummings JH, Macfarlane GT, Englyst HN (2001). Prebiotic digestion and fermentation. *Am J Clin Nutr* **73**, 415S–420S.

Cummings JH, Rombeau JL, Sakata T (1995). *Physiological and Clinical Aspects of Short-Chain Fatty Acids*. Cambridge University Press: Cambridge.

Cummings JH, Southgate DA, Branch WJ, Wiggins HS, Houston H, Jenkins DJ *et al*. (1979). The digestion of pectin in the human gut and its effect on calcium absorption and large bowel function. *Br J Nutr* **41**, 477–485.

de Castro JM (1991). Seasonal rhythms of human nutrient intake and meal pattern. *Physiol Behav* **50**, 243–248.

de Castro JM (2004). Dietary energy density is associated with increased intake in free-living humans. *J Nutr* **134**, 335–341.

de Castro JM, de Castro ES (1989). Spontaneous meal patterns of humans: influence of the presence of other people. *Am J Clin Nutr* **50**, 237–247.

Den Hond E, Geypens B, Ghoos Y (2000). Effect of high performance chicory inulin on constipation. *Nutr Res* **20**, 731–736.

Department of Health (1991). *Dietary Reference Values for Food, Energy and Nutrients for the United Kingdom*. HMSO: London.

Diabetes and Nutrition Study Group of European Association for the Study of Diabetes (2000). Recommendations for the nutritional management of patients with diabetes mellitus. *Eur J Clin Nutr* **54**, 353–355.

DiMeglio DP, Mattes RD (2000). Liquid versus solid carbohydrate: effects on food intake and body weight. *Int J Obes Relat Metab Disord* **24**, 794–800.

Drewnowski A (1998). Energy density, palatability, and satiety: implications for weight control. *Nutr Rev* **56**, 347–353.

Drossman DA, Camilleri M, Mayer EA, Whitehead WE (2002). AGA technical review on irritable bowel syndrome. *Gastroenterology* **123**, 2108–2131.

Druce M, Bloom SR (2006). The regulation of appetite. *Arch Dis Child* **91**, 183–187.

Duncan KH, Bacon JA, Weinsier RL (1983). The effects of high and low energy density diets on satiety, energy intake, and eating time of obese and nonobese subjects. *Am J Clin Nutr* **37**, 763–767.

Duncan SH, Scott KP, Ramsay AG, Harmsen HJ, Welling GW, Stewart CS *et al*. (2003). Effects of alternative dietary substrates on competition between human colonic bacteria in an anaerobic fermentor system. *Appl Environ Microbiol* **69**, 1136–1142.

Dutch Nutrition Council (1987). *The Energy Values of Polyols. Recommendations of the Committee on Polyols*. Nutrition Council: The Hague.

Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M *et al*. (2005). Diversity of the human intestinal microbial flora. *Science* **308**, 1635–1638.

Elia M (2005). Insights into energy requirements in disease. *Public Health Nutr* **8**, 1037–1052.

Elia M, Folmer P, Schlatmann A, Goren A, Austin S (1988). Carbohydrate, fat, and protein metabolism in muscle and in the whole body after mixed meal ingestion. *Metabolism* **37**, 542–551.

Elia M, Jones MG, Jennings G, Poppitt SD, Fuller NJ, Murgatroyd PR *et al*. (1995). Estimation of energy expenditure from specific activity of urine urea during lengthy subcutaneous $NaH^{14}CO3$ infusion. *Am J Physiol* **269**, E172–E182.

Elia M, Livesey G (1988). Theory and validity of indirect calorimetry during net lipid synthesis. *Am J Clin Nutr* **47**, 591–607.

Elia M, Livesey G (1992). Energy expenditure and fuel selection in biological systems: the theory and practice of calculations based on indirect calorimetry and tracer methods. *World Rev Nutr Diet* **70**, 68–131.

Elia M, Stratton R, Stubbs J (2003). Techniques for the study of energy balance in man. *Proc Nutr Soc* **62**, 529–537.

Englyst HN, Cummings JH (1987). Digestion of polysaccharides of potato in the small intestine of man. *Am J Clin Nutr* **45**, 423–431.

Englyst KN, S Liu, Englyst HN (2007). Nutritional characterisation and measurement of dietary carbohydrates. *Eur J Clin Nutr* **61** (Suppl 1), S19–S39.

European Communities (1990). Directive 90/496/EEC. Nutrition labelling for foodstuffs. *Off J Eur Commun* **L276**, 40–44.

Fanaro S, Boehm G, Garssen J, Knol J, Mosca F, Stahl B *et al*. (2005). Galacto-oligosaccharides and long-chain fructo-oligosaccharides as prebiotics in infant formulas: a review. *Acta Paediatr Suppl* **94**, 22–26.

FAO (1998). *Carbohydrates in human nutrition*. Report of a Joint FAO/WHO Expert Consultation. FAO Food and Nutrition Paper No. 66. FAO: Rome.

FAO (2003). *Food Energy—Methods of Analysis and Conversion Factors*. FAO: Rome.

FAO/WHO/UNU (1985). *Energy and Protein Requirements*. WHO: Geneva.

FAO/WHO/UNU (2004). *Human Energy Requirements. Food and Nutrition Technical Series 1*. FAO: Rome.

FASEB (1994). *The Evaluation of the Energy of Certain Sugar Alcohols Used as Food Ingredients*. Life Science Research Office: Bethesda, MD.

Finley JW, Leveille GA (1996). Macronutrient substitutes. In: Zeigler EE, Filer LJ (eds). *Present Knowledge in Nutrition*. ILSI Press: Washington, DC, pp 581–595.

Flatt JP (1978). The biochemistry of energy expenditure. In: Bray GA (ed). *Recent Advances in Obesity Research*. Newman Publications Limited: London, pp 221–228.

Flatt JP (1980). Energetics of intermediary metabolism. In: *Assessment of Energy Metabolism in Health and Disease. Report of the First ROSS*

www.manaraa.com

Conference on Medical Research. Ross Laboratories: Columbus, OH, pp 77–87.
Flatt JP (1987). The difference in the storage capacities for carbohydrate and for fat, and its implications in the regulation of body weight. *Ann N Y Acad Sci* **499**, 104–123.
Flatt JP (1992). Energy costs of ATP synthesis. In: Kinney JM, Tucker HN (eds). *Energy Metabolism: Tissue Determinants and Cellular Corollaries*. Raven Press: New York, pp 319–343.
Flickinger EA, Fahey Jr GC (2002). Pet food and feed applications of inulin, oligofructose and other oligosaccharides. *Br J Nutr* **87** (Suppl 2), S297–S300.
Flourie B, Florent C, Jouany JP, Thivend P, Etanchaud F, Rambaud JC (1986). Colonic metabolism of wheat starch in healthy humans. Effects on fecal outputs and clinical symptoms. *Gastroenterology* **90**, 111–119.
Francis CY, Whorwell PJ (1994). Bran and irritable bowel syndrome: time for reappraisal. *Lancet* **344**, 39–40.
Freedman MR, King J, Kennedy E (2001). Popular diets: a scientific review. *Obes Res* **9** (Suppl 1), 1S–40S.
Friedman MI, Ramirez I, Bowden CR, Tordoff MG (1990). Fuel partitioning and food intake: role for mitochondrial fatty acid transport. *Am J Physiol* **258**, R216–R221.
Friedman MI, Stricker EM (1976). The physiological psychology of hunger: a physiological perspective. *Psychol Rev* **83**, 409–431.
Friedman MI, Tordoff MG (1986). Fatty acid oxidation and glucose utilization interact to control food intake in rats. *Am J Physiol* **251**, R840–R845.
Fryer JH (1958). The effects of a late-night caloric supplement upon body weight and food intake in man. *Am J Clin Nutr* **6**, 354–364.
Fuller NJ, Jebb SA, Laskey MA, Coward WA, Elia M (1992). Four-component model for the assessment of body composition in humans: comparison with alternative methods and evaluation of the density and hydration of fat-free mass. *Clin Sci* **82**, 687–693.
Garg A (1998). High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. *Am J Clin Nutr* **67**, 577S–582S.
Garrow JS (1988). *Obesity and Related Diseases*. Churchill Livingstone: Edinburgh.
Gibney E, Elia M, Jebb SA, Murgatroyd P, Jennings G (1996). Total energy expenditure in patients with small cell lung cancer: results of a validated study using the bicarbonate-urea method. *Metabolism* **46**, 1412–1417.
Gibney ER, Murgatroyd P, Wright A, Jebb S, Elia M (2003). Measurement of total energy expenditure in grossly obese women: comparison of the bicarbonate-urea method with whole-body calorimetry and free-living doubly labelled water. *Int J Obes Relat Metab Disord* **27**, 641–647.
Gibson GR, Beatty ER, Wang X, Cummings JH (1995). Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin. *Gastroenterology* **108**, 975–982.
Gibson GR, McCartney AL, Rastall RA (2005). Prebiotics and resistance to gastrointestinal infections. *Br J Nutr* **93** (Suppl 1), S31–S34.
Gibson GR, Probert HM, Van Loo J, Rastall RA, Roberfroid M (2004). Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. *Nutr Res Rev* **17**, 259–275.
Gibson GR, Roberfroid MB (1995). Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J Nutr* **125**, 1401–1412.
Gil KM, Skeie B, Kvetan V, Askanazi J, Friedman MI (1991). Parenteral nutrition and oral intake: effect of glucose and fat infusions. *JPEN J Parenter Enteral Nutr* **15**, 426–432.
Goldring JM (2004). Resistant starch: safe intakes and legal status. *J AOAC Int* **87**, 733–739.
Gostner A, Schaffer V, Theis S, Menzel T, Luhrs H, Melcher R *et al.* (2005). Effects of isomalt consumption on gastrointestinal and metabolic parameters in healthy volunteers. *Br J Nutr* **94**, 575–581.
Haber GB, Heaton KW, Murphy D, Burroughs LF (1977). Depletion and disruption of dietary fibre. Effects on satiety, plasma-glucose, and serum-insulin. *Lancet* **2**, 679–682.
Harper JA, Dickinson K, Brand MD (2001). Mitochondrial uncoupling as a target for drug development for the treatment of obesity. *Obes Rev* **2**, 255–265.
Heijnen ML, van Amelsvoort JM, Deurenberg P, Beynen AC (1998). Limited effect of consumption of uncooked (RS2) or retrograded (RS3) resistant starch on putative risk factors for colon cancer in healthy men. *Am J Clin Nutr* **67**, 322–331.
Henderson L, Gregory J, Irving K, Swan G (2003). *The National Diet & Nutrition Survey: Adults Aged 19 to 64 Years. Energy, Protein, Carbohydrate, Fat and Alcohol Intake*. The Stationery Office: London.
Heymsfield SB, Lohman TG, Wang W, Going SB (2005). *Human Body Composition*, 2nd edn. Human Kinetics: Champaign, IL.
Hudson GJ, Englyst HN (1993). UK and some other countries. In: Cummings JH, Frolich W (eds). *Dietary Fibre Intakes in Europe*. CEC—Directorate General, Science, Research & Development: Brussels, pp 83–87.
Hylla S, Gostner A, Dusel G, Anger H, Bartram HP, Christl SU *et al.* (1998). Effects of resistant starch on the colon in healthy volunteers: possible implications for cancer prevention. *Am J Clin Nutr* **67**, 136–142.
Institute of Medicine (2005). *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Protein, and Amino Acids*. The National Academies Press: Washington, DC.
Ito M, Deguchi Y, Miyamori A, Matsumoto K, Kiluchi H, Matsumoto K *et al.* (1990). Effects of administration of galactooligosaccharides on the human faecal microflora, stool weight and abdominal sensation. *Microb Ecol Health Dis* **3**, 285–292.
James J, Kerr D (2005). Prevention of childhood obesity by reducing soft drinks. *Int J Obes (Lond)* **29** (Suppl 2), S54–S57.
James J, Thomas P, Cavan D, Kerr D (2004). Preventing childhood obesity by reducing consumption of carbonated drinks: cluster randomised controlled trial. *BMJ* **328**, 1237.
Japanese Ministry of Health and Welfare (1991). *Japanese Ministry of Health and Welfare Official Notice: Evaluation of the Energy Value of Indigestible Carbohydrates in Nutritive Foods*. Docket Number Ei-shin 71. Japanese Ministry of Health and Welfare: Tokyo.
Jeukendrup AE (2004). Carbohydrate intake during exercise and performance. *Nutrition* **20**, 669–677.
Johnson J, Vickers Z (1993). Effects of flavor and macronutrient composition of food servings on liking, hunger and subsequent intake. *Appetite* **21**, 25–39.
Johnstone AM, Stubbs RJ, Harbron CG (1996). Effect of overfeeding macronutrients on day-to-day food intake in man. *Eur J Clin Nutr* **50**, 418–430.
Kaplan RJ, Greenwood CE (2002). Influence of dietary carbohydrates and glycaemic response on subjective appetite and food intake in healthy elderly persons. *Int J Food Sci Nutr* **53**, 305–316.
Kaskoun MC, Johnson RK, Goran MI (1994). Comparison of energy intake by semiquantitative food-frequency questionnaire with total energy expenditure by the doubly labeled water method in young children. *Am J Clin Nutr* **60**, 43–47.
King TS, Elia M, Hunter JO (1998). Abnormal colonic fermentation in irritable bowel syndrome. *Lancet* **352**, 1187–1189.
Langlands SJ, Hopkins MJ, Coleman N, Cummings JH (2004). Prebiotic carbohydrates modify the mucosa associated microflora of the human large bowel. *Gut* **53**, 1610–1616.
Lavin JH, French SJ, Read NW (1997). The effect of sucrose- and aspartame-sweetened drinks on energy intake, hunger and food choice of female, moderately restrained eaters. *Int J Obes Relat Metab Disord* **21**, 37–42.
Ledikwe JH, Blanck HM, Kettel Khan L, Serdula MK, Seymour JD, Tohill BC *et al.* (2006). Dietary energy density is associated with energy intake and weight status in US adults. *Am J Clin Nutr* **83**, 1362–1368.
Lee A, Livesey G, Storey D, Zumbe A (eds). (2001). International symposium on low-digestible carbohydrates. *Br J Nutr* **85**, S1–S64.
Levine AS, Billington CJ (1994). *Appetite and Body Weight Regulation: Sugar, Fat, and Macronutrient Substitutes*. CRC Press: Boca Raton, FL.

www.manaraa.com

Life Sciences Research Office (1994). *The Evaluation of the Energy of Certain Sugar Alcohols used as Food Ingredients. Life Sciences Research Office, Federation of American Societies for Experimental Biology.* Bethesda, MD.

Lissner L, Levitsky DA, Strupp BJ, Kalkwarf HJ, Roe DA (1987). Dietary fat and the regulation of energy intake in human subjects. *Am J Clin Nutr* **46**, 886–892.

Liu YJ, Araujo S, Recker RR, Deng HW (2003). Molecular and genetic mechanisms of obesity: implications for future management. *Curr Mol Med* **3**, 325–340.

Livesey G (1984). The energy equivalents of ATP and the energy values of food proteins and fats. *Br J Nutr* **51**, 15–28.

Livesey G (1986). ATP yields from proteins, fats and carbohydrates and mitochondrial efficiency *in vivo*. In: Barry EM, Blondheim SH, Eliahou HE, Shafir E (eds). *Recent Advances in Obesity Research. V.* John Libbey: London, Paris.

Livesey G (1991). Calculating the energy values of foods: towards new empirical formulae based on diets with varied intakes of unavailable complex carbohydrates. *Eur J Clin Nutr* **45**, 1–12.

Livesey G (1992). The energy values of dietary fibre and sugar alcohols for man. *Nutr Res Rev* **5**, 61–84.

Livesey G (2001). A perspective on food energy standards for nutrition labelling. *Br J Nutr* **85**, 271–287.

Livesey G (2002). Thermogenesis associated with fermentable carbohydrate in humans, validity of indirect calorimetry, and implications of dietary thermogenesis for energy requirements, food energy and body weight. *Int J Obes Relat Metab Disord* **26**, 1553–1569.

Livesey G (2003a). Analytical issues in food energy and composition. Energy in food labeling—including regulatory and trade issues. Posited with FAO.

Livesey G (2003b). Health potential of polyols as sugar replacers, with emphasis on low glycaemic properties. *Nutr Res Rev* **16**, 163–191.

Livesey G, Elia M (1985). Food energy values for artificial feeds for man. *Clin Nutr* **4**, 99–111.

Livesey G, Elia M (1988). Estimation of energy expenditure, net carbohydrate oxidation and net fat oxidation and synthesis by indirect calorimetry. Evaluation of some errors with special reference to the detailed composition of fuels. *Am J Clin Nutr* **47**, 608–623.

Livesey G, Elia M (1995). Short chain fatty acids as an energy source in the colon: metabolism and clinical implications. In: Cummings JH, Rombeau JL, Sakata TT (eds). *Physiological and Clinical Aspects of Short Chain Fatty Acids*. Cambridge University Press: Cambridge, pp 1427–1482.

Livingstone MB, Black AE (2003). Markers of the validity of reported energy intake. *J Nutr* **133** (Suppl 3), 895S–920S.

Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC (2006). Functional bowel disorders. *Gastroenterology* **130**, 1480–1491.

Ludwig DS (2003). Dietary glycemic index and the regulation of body weight. *Lipids* **38**, 117–121.

Macfarlane GT, Cummings JH (1991). The colonic flora, fermentation and large bowel digestive function. In: Phillips SF, Pemberton JH, Shorter RG (eds). *The Large Intestine: Physiology, Pathophysiology and Disease*. Raven Press: New York, pp 51–92.

Macfarlane S, Macfarlane GT (2004). Bacterial diversity in the human gut. *Adv Appl Microbiol* **54**, 261–289.

Macfarlane S, Macfarlane GT, Cummings JH (2006). Prebiotics in the gastrointestinal tract. *Aliment Pharmacol Ther* **24**, 701–714.

Mattes R (2006). Fluid calories and energy balance: the good, the bad, and the uncertain. *Physiol Behav* **89**, 66–70.

Mattes RD (1996). Dietary compensation by humans for supplemental energy provided as ethanol or carbohydrate in fluids. *Physiol Behav* **59**, 179–187.

Matthews SB, Waud JP, Roberts AG, Campbell AK (2005). Systemic lactose intolerance: a new perspective on an old problem. *Postgrad Med J* **81**, 167–173.

Mayer J (1955). Regulation of energy intake and the body weight: the glucostatic theory and the lipostatic hypothesis. *Ann N Y Acad Sci* **63**, 15–43.

Mazlam N (2001). *Effect of Fat and Carbohydrate on Energy Intake and Macronutrient Selection in Humans*. PhD thesis, University of Aberdeen.

Merill AL, Watt BK (1973). *Energy Value of Foods: Basis and Derivation*. United States Department of Agriculture: Washington, DC.

Miller JB, McVeagh P (1999). Human milk oligosaccharides: 130 reasons to breast-feed. *Br J Nutr* **82**, 333–335.

Montalto M, Curigliano V, Santoro L, Vastola M, Cammarota G, Manna R *et al*. (2006). Management and treatment of lactose malabsorption. *World J Gastroenterol* **12**, 187–191.

Mowat F (1981). *People of the Deer*. Seal Books: Toronto.

Nanda R, James R, Smith H, Dudley CR, Jewell DP (1989). Food intolerance and the irritable bowel syndrome. *Gut* **30**, 1099–1104.

Nasrallah SM, Iber FL (1969). Mannitol absorption and metabolism in man. *Am J Med Sci* **258**, 80–88.

Nightingale JM, Kamm MA, van der Sijp JR, Ghatei MA, Bloom SR, Lennard-Jones JE (1996). Gastrointestinal hormones in short bowel syndrome. Peptide YY may be the 'colonic brake' to gastric emptying. *Gut* **39**, 267–272.

Nishida C, Uauy R, Kumanyika S, Shetty P (2004). The joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases: process, product and policy implications. *Public Health Nutr* **7**, 245–250.

Painter NS, Almeida AZ, Colebourne KW (1972). Unprocessed bran in treatment of diverticular disease of the colon. *BMJ* **2**, 137–140.

Paton NI, Angus B, Chaowagul W, Simpson AJ, Suputtamongkol Y, Elia M *et al*. (2001). Protein and energy metabolism in chronic bacterial infection: studies in melioidosis. *Clin Sci (Lond)* **100**, 101–110.

Paton NI, Elia M, Jebb SA, Jennings G, Macallan DC, Griffin GE (1996). Total energy expenditure and physical activity measured with the bicarbonate-urea method in patients with human immunodeficiency virus infection. *Clin Sci (Lond)* **91**, 241–245.

Paul AA, Southgate DAT (1978). *McCance and Widdowson's The Composition of Foods*, 4th edn. HMSO: London.

Pawlak DB, Ebbeling CB, Ludwig DS (2002). Should obese patients be counselled to follow a low-glycaemic index diet? Yes. *Obes Rev* **3**, 235–243.

Phillips J, Muir JG, Birkett A, Lu ZX, Jones GP, O'Dea K *et al*. (1995). Effect of resistant starch on fecal bulk and fermentation-dependent events in humans. *Am J Clin Nutr* **62**, 121–130.

Pool-Zobel BL (2005). Inulin-type fructans and reduction in colon cancer risk: review of experimental and human data. *Br J Nutr* **93** (Suppl 1), S73–S90.

Poppitt SD, Prentice AM (1996). Energy density and its role in the control of food intake: evidence from metabolic and community studies. *Appetite* **26**, 153–174.

Poppitt SD (1995). Energy density of diets and obesity. *Int J Obes Relat Metab Disord* **19** (Suppl 5), S20–S26.

Poppitt SD, Livesey G, Faulks RM, Roe M, Prentice AM, Elia M (1996). Circadian patterns of total 24-h hydrogen and methane excretion in humans ingesting nonstarch polysaccharide (NSP) diets and the implications for indirect calorimetric and D2 18O methodologies. *Eur J Clin Nutr* **50**, 524–534.

Porikos KP, Booth G, Van Itallie TB (1977). Effect of covert nutritive dilution on the spontaneous food intake of obese individuals: a pilot study. *Am J Clin Nutr* **30**, 1638–1644.

Porikos KP, Hesser MF, van Itallie TB (1982). Caloric regulation in normal-weight men maintained on a palatable diet of conventional foods. *Physiol Behav* **29**, 293–300.

Prentice AM (1990). The doubly-labelled water method for measuring energy expenditure. Technical recommendations for use in humans: a consensus report by the IDECG Working Group International Atomic Energy Agency NAHRES-4.

www.manaraa.com

Prentice AM, Poppitt SD (1996). Importance of energy density and macronutrients in the regulation of energy intake. *Int J Obes Relat Metab Disord* **20** (Suppl 2), S18–S23.

Pullicino E, Elia M (1991). Intravenous carbohydrate over-feeding: a method for rapid nutritional repletion. *Clin Nutr* **10**, 146–154.

Raben A (2002). Should obese patients be counselled to follow a low-glycaemic index diet? No. *Obes Rev* **3**, 245–256.

Raben A, Agerholm-Larsen L, Flint A, Holst JJ, Astrup A (2003). Meals with similar energy densities but rich in protein, fat, carbohydrate, or alcohol have different effects on energy expenditure and substrate metabolism but not on appetite and energy intake. *Am J Clin Nutr* **77**, 91–100.

Raben A, Macdonald I, Astrup A (1997). Replacement of dietary fat by sucrose or starch: effects on 14 d *ad libitum* energy intake, energy expenditure and body weight in formerly obese and never-obese subjects. *Int J Obes Relat Metab Disord* **21**, 846–859.

Raben A, Tagliabue A, Christensen NJ, Madsen J, Holst JJ, Astrup A (1994). Resistant starch: the effect on postprandial glycemia, hormonal response, and satiety. *Am J Clin Nutr* **60**, 544–551.

Raben A, Vasilaras TH, Moller AC, Astrup A (2002). Sucrose compared with artificial sweeteners: different effects on *ad libitum* food intake and body weight after 10 wk of supplementation in overweight subjects. *Am J Clin Nutr* **76**, 721–729.

Rabinowitch IM, Fowler AF (1934). Dinitrophenol. *Can Med Assoc J* **30**, 128–133.

Remesy C, Demigne C, Morand C (1995). Metabolism of short-chain fatty acids in the liver. In: Cummings JH, Rombeau JL, Sakata T (eds). *Physiological and Clinical Aspects of Short-Chain Fatty Acids*. Cambridge University Press: Cambridge, pp 171–190.

Roberfroid M (2005). *Inulin-Type Fructans. Functional Food Ingredients*. CRC Press: Boca Raton, FL.

Rodin J (1990). Comparative effects of fructose, aspartame, glucose, and water preloads on calorie and macronutrient intake. *Am J Clin Nutr* **51**, 428–435.

Rogers PJ, Carlyle JA, Hill AJ, Blundell JE (1988). Uncoupling sweet taste and calories: comparison of the effects of glucose and three intense sweeteners on hunger and food intake. *Physiol Behav* **43**, 547–552.

Rolls BJ (1997). Fat and sugar substitutes and the control of food intake. In: Rolls BJ, Anderson, GH, Steffen DG (eds). *Nutritional Implications of Macronutrient Substitutes*. New York Academy of Sciences: New York, NY, pp 180–193.

Rolls BJ, Bell EA (1999). Intake of fat and carbohydrate: role of energy density. *Eur J Clin Nutr* **53** (Suppl 1), S166–S173.

Rumpler WV, Baer DJ, Rhodes DG (1998). Energy available from corn oil is not different than that from beef tallow in high- or low-fiber diets fed to humans. *J Nutr* **128**, 2374–2382.

Russek M (1963). Participation of hepatic glucoreceptors in the control of intake of food. *Nature* **197**, 79–80.

Russek M (1976). Hepatic glucoreceptors in the short-term control of feeding. *Acta Physiol Pol* **27**, 147–156.

Sanchez-Catillo C, Grubb D, Solano ML, Franklin F, James WPT (1997). Non-starch polysaccharide intakes in Mexican villagers and residents of Mexico City. *Br J Nutr* **77**, 345–357.

Saris WH, Astrup A, Prentice AM, Zunft HJ, Formiguera X, Verboeket-van de Venne WP *et al*. (2000). Randomized controlled trial of changes in dietary carbohydrate/fat ratio and simple vs complex carbohydrates on body weight and blood lipids: the CARMEN study. The Carbohydrate Ratio Management in European National diets. *Int J Obes Relat Metab Disord* **24**, 1310–1318.

Schulz AR (1975). Computer-based method for calculation of the available energy of proteins. *J Nutr* **105**, 200–207.

Schulz AR (1978). Simulation of energy metabolism in the simple-stomached animal. *Br J Nutr* **39**, 235–254.

Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC *et al*. (2004). Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA* **292**, 927–934.

Sclafani A (1987). Carbohydrate-induced hyperphagia and obesity in the rat: effects of saccharide type, form, and taste. *Neurosci Biobehav Rev* **11**, 155–162.

Sclafani A (2001). Psychobiology of food preferences. *Int J Obes Relat Metab Disord* **25** (Suppl 5), S13–S16.

Shetty PS, Prentice AM, Goldberg GR, Murgatroyd PR, McKenna AP, Stubbs RJ *et al*. (1994). Alterations in fuel selection and voluntary food intake in response to isoenergetic manipulation of glycogen stores in humans. *Am J Clin Nutr* **60**, 534–543.

Siavoshian S, Segain JP, Kornprobst M, Bonnet C, Cherbut C, Galmiche JP *et al*. (2000). Butyrate and trichostatin A effects on the proliferation/differentiation of human intestinal epithelial cells: induction of cyclin D3 and p21 expression. *Gut* **46**, 507–514.

Silvester KR, Bingham SA, Pollock JR, Cummings JH, O'Neill IK (1997). Effect of meat and resistant starch on fecal excretion of apparent N-nitroso compounds and ammonia from the human large bowel. *Nutr Cancer* **29**, 13–23.

Silvester KR, Englyst HN, Cummings JH (1995). Ileal recovery of starch from whole diets containing resistant starch measured *in vitro* and fermentation of ileal effluent. *Am J Clin Nutr* **62**, 403–411.

Snitker S, Larson DE, Tataranni PA, Ravussin E (1997). *Ad libitum* food intake in humans after manipulation of glycogen stores. *Am J Clin Nutr* **65**, 941–946.

Snook J, Shepherd HA (1994). Bran supplementation in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* **8**, 511–514.

Southgate DA (1969). Determination of carbohydrates in foods. II. Unavailable carbohydrates. *J Sci Food Agric* **20**, 331–335.

Spengler M, Boehme K (1984). *Tolerance and Acceptance of Isomalt Study 26 report no. 13850, Wupperpal, Germany* (Rn Study 26, editor: Bayer AG Pharmaceuticals Division).

Spiegelman BM, Flier JS (2001). Obesity and the regulation of energy balance. *Cell* **104**, 531–543.

Stephen A (1993). Proprionate—sources and effect on lipid metabolism. In: Binder HJ, Cummings JH, Soergel KH (eds). *Short-Chain Fatty Acids. Falk Symposium*. Kluwer Academic Publishers, Dordrecht, pp 260–271.

Stephen AM, Cummings JH (1980). Mechanism of action of dietary fibre in the human colon. *Nature* **284**, 283–284.

Stephen AM, Haddad AC, Phillips SF (1983). Passage of carbohydrate into the colon. Direct measurements in humans. *Gastroenterology* **85**, 589–595.

Stephen AM, Sieber GM, Gerster YA, Morgan DR (1995). Intake of carbohydrate and its components—international comparisons, trends over time, and effects of changing to low-fat diets. *Am J Clin Nutr* **62**, 851S–867S.

Stevens J (1988). Does dietary fiber affect food intake and body weight? *J Am Diet Assoc* **88**, 939–942; 945.

Stock MJ (1999). Gluttony and thermogenesis revisited. *Int J Obes Relat Metab Disord* **23**, 1105–1117.

Stollman N, Raskin JB (2004). Diverticular disease of the colon. *Lancet* **363**, 631–639.

Stubbs J, Ferres S, Horgan G (2000). Energy density of foods: effects on energy intake. *Crit Rev Food Sci Nutr* **40**, 481–515.

Stubbs RJ, Harbron CG, Murgatroyd PR, Prentice AM (1995a). Covert manipulation of dietary fat and energy density: effect on substrate flux and food intake in men eating *ad libitum*. *Am J Clin Nutr* **62**, 316–329.

Stubbs RJ, Harbron CG, Prentice AM (1996). Covert manipulation of the dietary fat to carbohydrate ratio of isoenergetically dense diets: effect on food intake in feeding men *ad libitum*. *Int J Obes Relat Metab Disord* **20**, 651–660.

Stubbs RJ, Hughes DA, Johnstone AM, Whybrow S, Horgan GW, King N *et al*. (2004). Rate and extent of compensatory changes in energy intake and expenditure in response to altered exercise and diet composition in humans. *Am J Physiol Regul Integr Comp Physiol* **286**, R350–R358.

Stubbs RJ, Ritz P, Coward WA, Prentice AM (1995b). Covert manipulation of the ratio of dietary fat to carbohydrate and

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energy density: effect on food intake and energy balance in free-living men eating *ad libitum*. *Am J Clin Nutr* **62**, 330–337.
Stubbs RJ, Whybrow S (2004). Energy density, diet composition and palatability: influences on overall food energy intake in humans. *Physiol Behav* **81**, 755–764.
Tainter ML, Stockton AB, Cutting WC (1935). Dinitrophenol in the treatment of obesity. Final report. *JAMA* **105**, 332–337.
Talley NJ, Spiller R (2002). Irritable bowel syndrome: a little understood organic bowel disease? *Lancet* **360**, 555–564.
Tang NL, Chung ML, Elia M, Hui E, Lum CM, Luk JK *et al.* (2002). Total daily energy expenditure in wasted chronic obstructive pulmonary disease patients. *Eur J Clin Nutr* **56**, 282–287.
Taylor R, Price TB, Rothman DL, Shulman RG, Shulman GI (1992). Validation of 13C NMR measurement of human skeletal muscle glycogen by direct biochemical assay of needle biopsy samples. *Magn Reson Med* **27**, 13–20.
Teuri U, Korpela R (1998). Galacto-oligosaccharides relieve constipation in elderly people. *Ann Nutr Metab* **42**, 319–327.
Thompson DA, Campbell RG (1977). Hunger in humans induced by 2-deoxy-D-glucose: glucoprivic control of taste preference and food intake. *Science* **198**, 1065–1068.
Thompson DA, Welle SL, Lilavivat U, Penicaud L, Campbell RG (1982). Opiate receptor blockade in man reduces 2-deoxy-D-glucose-induced food intake but not hunger, thirst, and hypothermia. *Life Sci* **31**, 847–852.
Titter S, Calingasan NY (1994). *Neural Substrates for Metabolic Control of Feeding*. CRC Press: Boca Raton, FL.
Todesco T, Rao AV, Bosello O, Jenkins DJ (1991). Propionate lowers blood glucose and alters lipid metabolism in healthy subjects. *Am J Clin Nutr* **54**, 860–865.
Tomlin J, Read NW (1990). The effect of resistant starch on colon function in humans. *Br J Nutr* **64**, 589–595.
Tordoff MG, Alleva AM (1990a). Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight. *Am J Clin Nutr* **51**, 963–969.
Tordoff MG, Alleva AM (1990b). Oral stimulation with aspartame increases hunger. *Physiol Behav* **47**, 555–559.
Tremblay A (1992). Human obesity: a defect in lipid oxidation or in thermogenesis? *Int J Obes Relat Metab Disord* **16**, 953–957.
Tremblay A, Lavallee N, Almeras N, Allard L, Despres JP, Bouchard C (1991). Nutritional determinants of the increase in energy intake associated with a high-fat diet. *Am J Clin Nutr* **53**, 1134–1137.
Truswell AS, Seach JM, Thorburn AW (1988). Incomplete absorption of pure fructose in healthy subjects and the facilitating effect of glucose. *Am J Clin Nutr* **48**, 1424–1430.
van Dokkum W, Wezendonk B, Srikumar TS, van den Heuvel EG (1999). Effect of nondigestible oligosaccharides on large-bowel functions, blood lipid concentrations and glucose absorption in young healthy male subjects. *Eur J Clin Nutr* **53**, 1–7.
van Loo J, Coussement P, de Leenheer L, Hoebregs H, Smits G (1995). On the presence of inulin and oligofructose as natural ingredients in the western diet. *Crit Rev Food Sci Nutr* **35**, 525–552.
van Munster IP, Tangerman A, Nagengast FM (1994). Effect of resistant starch on colonic fermentation, bile acid metabolism, and mucosal proliferation. *Dig Dis Sci* **39**, 834–842.
van Stratum P, Lussenburg RN, van Wezel LA, Vergroesen AJ, Cremer HD (1978). The effect of dietary carbohydrate: fat ratio on energy intake by adult women. *Am J Clin Nutr* **31**, 206–212.
Warren JM, Henry CJ, Simonite V (2003). Low glycemic index breakfasts and reduced food intake in preadolescent children. *Pediatrics* **112**, e414.
Warwick PM, Baines J (2000). Point of view: energy factors for food labelling and other purposes should be derived in a consistent fashion for all food components. *Br J Nutr* **84**, 897–902.
Welle SL, Thompson DA, Campbell RG, Lilavivathana U (1980). Increased hunger and thirst during glucoprivation in humans. *Physiol Behav* **25**, 397–403.
Westerterp KR, Goris AH (2002). Validity of the assessment of dietary intake: problems of misreporting. *Curr Opin Clin Nutr Metab Care* **5**, 489–493.
Westerterp-Plantenga MS (2001). Analysis of energy density of food in relation to energy intake regulation in human subjects. *Br J Nutr* **85**, 351–361.
Weststrate JA (1992). *Effect of Nutrients on the Regulation of Food Intake*. Unilever Vlaardingen, The Netherlands.
WHO (2003). *Diet, nutrition and the prevention of chronic diseases*. Report of a Joint WHO/FAO Expert Consultation. WHO Technical Report Series No. 916. World Health Organization: Geneva.
Williams CM, Jackson KG (2002). Inulin and oligofructose: effects on lipid metabolism from human studies. *Br J Nutr* **87** (Suppl 2), S261–S264.
Yu-Poth S, Zhao G, Etherton T, Naglak M, Jonnalagadda S, Kris-Etherton PM (1999). Effects of the national cholesterol education program's step I and step II dietary intervention programs on cardiovascular disease risk factors: a meta-analysis. *Am J Clin Nutr* **69**, 632–646.
Zittermann A, Bock P, Drummer C, Scheld K, Heer M, Stehle P (2000). Lactose does not enhance calcium bioavailability in lactose-tolerant, healthy adults. *Am J Clin Nutr* **71**, 931–936.

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