Since the Second World War there has been a secular trend of increased overweight and obesity in societies where people have *ad libitum* access to Western-type diets (Royal College of Physicians, 1983; Gregory *et al.* 1990; White *et al.*, 1991; Department of Health, 1995). Over this time period the economic costs of obesity and the personal costs of being overweight (in terms of reduced quality of life, increased morbidity and mortality) have been well documented (Seidell, 1995). Throughout this period scientific efforts have intensified in attempting to understand the cause of overweight and obesity and in endeavours to produce effective approaches to sustained body-weight reduction. Ironically, the increased governmental, public health and biomedical research efforts aimed at understanding how to reverse current secular trends in body fatness have been accompanied by an escalation of those very trends. We have now reached the remarkable situation in the UK whereby more that half of the adult population has been categorized as collectively overweight and obese (Department of Health, 1995). By considering research trends in the area of human energy balance (EB) over the last two decades it should become apparent that current research has grown out of and built on the research that went before it. Several of the hypotheses of the 1970s and 1980s have been rejected as inoperable in human subjects in the light of the evidence that was collected to evaluate them. It is worth remembering that disproving an hypothesis does not reduce the importance it has made to scientific understanding. The very process of disproving the hypothesis actually advances science and leads to new avenues of investigation. It is unfortunate that the meticulous process of hypothesis-testing necessarily proceeds at a somewhat slower rate than the problem that we are trying to address: a large prevalence of excess body weight. However, considerable progress has been made over the last two decades in understanding the major factors most likely to alter EB in man and the types of model which are likely to explain how some people become overweight and obese. These insights have proved invaluable in helping us address current issues pertinent to the control of EB and in targeting key research areas for the future. In order to fully illustrate this point it is worth considering the direction of research into obesity and EB over the last couple of decades.

Recent trends in energy balance research

Throughout the 1970s a good deal of research effort was focused on exploring the possibility that obesity was characterized by a defect in a physiological mechanism which was thought to protect against weight gain. The mechanism was termed ‘adaptive thermogenesis’, and had been identified in rodents (Himms-Haagen *et al.*, 1978; Rothwell & Stock, 1979, 1983). Researchers had discovered, in rodents, a protein in brown adipose tissue which was capable of uncoupling oxidation and phosphorylation, the process whereby food energy can be converted to ATP for use by the body (Lin & Klingenberg, 1980; Klingenberg *et al.*, 1980). The uncoupling protein was responsible for liberating as heat some of the energy normally stored in high-energy phosphate bonds. Loss of heat from the body in this manner would reduce the efficiency of energy storage and so would prevent excess storage of body fat (Hervey & Tobin, 1983).

Between the 1950s and the 1980s a considerable number of dietary survey studies were conducted. Many studies suggested very large differences in self-reported energy intake (EI) of subjects with apparently similar lifestyles and body weights (e.g. Widdowson, 1936; Widdowson & McCance, 1936; Edholm *et al.*, 1970). Taken at face value these dietary intake studies suggested that some people apparently consumed large amounts of energy but remained lean, while others appeared to consume only small-to-moderate amounts of food and gain weight easily. These observations were interpreted as supporting the notion that people with a predisposition to obesity may have highly efficient mechanisms of energy storage (so-called ‘small eaters’) and so gain weight readily, while others may eat large amounts of food and still remain lean (so-called ‘large eaters’) (George *et al.*, 1989,
1991; Clark et al. 1995). Furthermore, at the time there was no independent, precise means of measuring free-living energy expenditure (EE), instead EE was estimated by use of activity diaries, which are imprecise. Studies that attempted to compare EI and EE by use of diary records suggested a very poor correspondence between EI and EE (Edholm et al. 1955, 1970). This further hinted that some people may be able to ingest energy in excess of requirements and remain lean, while others appeared to consume relatively small amounts of food and were overweight.

There was, therefore, a sound theoretical background and a mechanism for dissipation of energy identified in rodents. This was supported (as is often the case) by circumstantial evidence in human subjects. A good deal of research in human subjects therefore searched for (1) differences in thermogenic capacity between lean and obese subjects, (2) physiological and metabolic responses of self-reported large and small eaters, (3) evidence for an energy-dissipating mechanism in response to overfeeding and (4) energy-sparing physiological adaptations in relation to underfeeding. By the mid 1980s many data had accumulated and a number of patterns were beginning to emerge. The main findings of these research endeavours can be summarized as follows.

(a) Little evidence was found of quantitatively significant differences in rates of EE between the lean and the obese, once body size and composition are taken into account (Miller & Blyth, 1953; Halliday et al. 1979; Cunningham, 1980; Prentice et al. 1986, 1989, 1992; Garby et al. 1988). When excess energy is ingested, thin individuals gain proportionately more lean tissue; obese individuals gain proportionately more adipose tissue (Forbes et al. 1982, 1986, 1989; Forbes, 1987). Per gram of tissue gained the energy cost for adipose tissue gain is about six times greater than for lean tissue. Thus per unit of excess energy ingested, it is actually energetically more costly for the obese to gain weight. In order to do so, the obese must ingest more (not less) energy than the lean.

(b) There do not appear to be substantial differences in rates of whole body EE between different age, sex or ethnic groups, once body size and composition are taken into account (Gopalan et al. 1955; Tzankoff & Norris, 1977; Bernstein, 1983; Owen et al. 1986, 1987; Brunn et al. 1988; Lawrence et al. 1988). There is a notable exception to this body of data in that low BMR in Pima Indians predicts subsequent weight gain, although it has not been demonstrated that the weight gain is entirely attributable to a low BMR (Zurlo et al. 1990; Ravussin & Swinburn, 1993; Rising et al. 1996). Other factors could be involved.

(c) Very little evidence of adaptive thermogenesis was found in human subjects when the components of the energy equation (intake, expenditure and balance) were independently measured (Norgen & Durnin, 1980; Forbes et al. 1986; Ravussin et al. 1986). As James (1992) points out, studies that have supported the notion of luxuskonsumption (Widdowson, 1936; Widdowson & McCance, 1936; Miller et al. 1967; Sims, 1968; Sims et al. 1968, 1973; Sims & Horton, 1968; Edholm et al. 1970) have only inferred, not measured, the one unambiguously measurable outcome variable; that is, an increased rate of heat output from the body. However, some studies have demonstrated considerable inter-individual variability in the rate of weight gain, under the same conditions of overfeeding. This may, in part, reflect interindividual variations in partitioning the excess energy between fat and lean tissue, or inter-individual variation in EE due to physical activity (Forbes et al. 1986; Bouchard et al. 1988, 1990; Diaz et al. 1992).

(d) There is also very little evidence for adaptation of whole-body metabolic rate during chronic undernutrition that is independent of changes in metabolically active tissue. The estimated maximum change of resting metabolic rate under such conditions is 15% (Keys et al. 1950; Shetty, 1993). The major changes that occur under conditions of acute energy stress are changes in body size and composition, together with probable changes in behaviour in terms of physical activity.

Thus by the middle of the 1980s it was becoming apparent that the majority of studies in human beings do not support the concept of a flexible rate of EE which defends body weight against excesses or deficiencies in EI. Neither is there much evidence that obese subjects are characterized by an inherently low metabolic rate. Indeed, it has been repeatedly demonstrated that under standardized conditions the obese have higher absolute energy requirements than do the lean, due to the greater mass of metabolically active tissue (James et al. 1978; Rucker, 1978; Jequier, 1984; Prentice et al. 1986, 1989). Initially this created a paradox, because it had also been repeatedly demonstrated that the obese appear to consume less food energy than do the lean under conditions where their intake is being monitored or self-recorded (Spitzer & Rodin, 1981). The recent development of techniques that assess dietary compliance helped to resolve this paradox (Bingham & Cummings, 1985; Bingham et al. 1991). Use of urinary N as proxy marker for validity of dietary intake data suggested that people tend to under-report their EI during dietary survey studies (Bandini et al. 1990; Black et al. 1991). The obese, however, appear to systematically under-report their EI relative to expenditure of energy (estimated using doubly-labelled water), to a greater degree than do the lean (Durrant et al. 1982; Bingham et al. 1991; Black et al. 1991; Goldberg et al. 1991). These findings contradicted the notion that the obese actually require less energy or the same energy in order to maintain a stable body weight as do the lean. The findings of significant under-reporting of food intake in the obese, together with absolutely higher energy requirements, tend to support the contention that the obese actually consume less than their usual intakes of energy under the conditions of the studies concerned (Spitzer & Rodin, 1981; Durrant et al. 1982; Bandini et al. 1990). By the middle of the 1980s a number of conclusions were beginning to emerge about the nature of EB control in man. (1) The purported ability to raise or lower whole-body metabolic rate in order to adapt to fluctuations in the environmental supply of energy and nutrients (Rothwell & Stock, 1979, 1983; Sukhatme & Margen, 1982) is unlikely as a mechanism of EB homeostasis, since such metabolic
adaptation is limited in human subjects (James, 1992; Jequier, 1992; Prentice et al. 1992; Shetty, 1993). (2) It follows from (1) that a large component of the change in EB in human subjects is likely to centre on the control of energy and nutrient intake (Danforth, 1985; Le Magnen, 1985; Flatt, 1987; Prentice et al. 1989). (3) The development of obesity is primarily due to an excessive EI relative to energy requirements. Since the flexibility of EE in man is very limited, the development of obesity must therefore be due to a real hyperphagia and/or a gross decrease in EE through physical activity. (4) EI is somehow altered during the development of obesity and regulation may again be re-established at a higher level of body weight once stable obesity is established (e.g. Mayer, 1955; Blundell & Hill, 1986; Flatt, 1987).

A logical extension of detailed EE studies was to study the components of EI, EE and EB in greater detail. At this time considerable attention was being given to focus on the components of the EB equation, macronutrients. Pioneering work was being undertaken in a number of laboratories, especially at Lausanne in Switzerland, in understanding how the balances of individual macronutrients are regulated and the implications this may have for body-weight control. These studies led to the development of the nutrient balance concept.

The nutrient balance concept

While it was becoming increasingly apparent that the ability to adaptively alter EE in relation to EI is limited in human subjects, studies of macronutrient metabolism using indirect calorimetry were beginning to demonstrate the importance of considering the manner and efficiency with which individual macronutrients are handled by the body. Macronutrients in foods summate to determine total EI. EE can be divided into the energy expended in the oxidation of each of the macronutrients. Body energy stores are also composed of proteins (structural, functional and labile amino acid pool), glycogen (stored in liver and muscles) and fat (adipose tissue). The studies conducted throughout the 1980s were critical in describing the constraints and circumstances under which macronutrient balance is maintained, fuel selection determined and body weight and composition influenced by changes in dietary macronutrient intake (Acheson et al. 1980, 1988; Acheson & Jequier, 1982; Schutz et al. 1985, 1989; Abbot et al. 1988; Flatt et al. 1988; Jequier, 1992; Suter et al. 1992).

The profile of metabolic fuels being utilized by the body changes with the composition of the diet and the level of EI. Furthermore, there appears to be a hierarchy in the immediacy with which the stores of the macronutrients (alcohol, protein, carbohydrate and fat) are regulated by increases in their own oxidative disposal. This hierarchy is determined by the following constraints.

(1) A large body of literature now suggests that the major determinants of EE are metabolic body size and level of physical activity (see p. 342). Beyond these determinants of total EE there is very little scope to up- or down-regulate metabolic turnover in relation to changes in EI (see p. 342). There is, therefore, a ceiling on total EE for a given level of physical activity, which limits the rate at which recently ingested energy can be disposed of by oxidation. Energy ingested in excess of total EE is therefore stored. However, within these thermodynamic constraints, all nutrients are not equal, when considering the tendency to oxidize or store them.

(2) There is a hierarchy in the extent to which the macronutrients can be stored and this has implications for their metabolic fate, once ingested. Alcohol is a toxic drug which cannot be stored. The storage capacity for protein and carbohydrate is limited and converting these nutrients to a more readily stored form is energetically expensive. The storage capacity for fat is potentially very large. In some very obese subjects body fat can exceed 40% of total body weight.

(3) It appears that under Western dietary conditions at least, the net interconvertibility of protein, carbohydrate and fat is fairly limited, although this is clearly not the case under extreme conditions such as massive carbohydrate overfeeding (Acheson & Jequier, 1982; Hellerstein et al. 1991).

These three constraints determine the manner in which the major metabolic fuels, protein, carbohydrate and fat, are handled by the human body, once they are ingested. A positive balance of protein will lead to rapid metabolism of a high proportion of the amount ingested, the percentage depending on the body’s requirements for specific amino acids. Similarly as carbohydrate intake increases, more of it is disposed of by oxidation. Because there is a ‘ceiling’ on adaptive changes in EE, an increased oxidation of protein and carbohydrate will lead to a decreased oxidation of fat. Conversely intake of fat (long-chain triacylglycerol) does not promote fat oxidation and leads to fat storage (Flatt et al. 1988; Schutz et al. 1989). Indeed the contribution of fat oxidation to total EE appears to be primarily determined by the amount of protein and carbohydrate being oxidized. Alcohol cannot be stored and is disposed of by obligatory oxidation, ultimately at the expense of fat oxidation, so this too promotes fat storage (Suter et al. 1992). From a metabolic viewpoint, the human body is analogous to an engine which runs continually (EE) but has a specific order in which it burns up certain fuels (the macronutrients) since it can store an excess intake of some fuels less readily (alcohol < protein < carbohydrate) than others (long-chain triacylglycerols). Thus, there is a hierarchy in the immediacy with which recently ingested macronutrients are metabolized which is inversely related to the hierarchy in the body’s capacity to store them. The constraints under which macronutrient balances are regulated are depicted in Fig. 1. Because physiological studies show that excess energy taken in as either alcohol or fat ultimately promotes fat storage, it has been suggested that consuming a high proportion of EI as fat and alcohol predisposes individuals to dietary obesity. However, excess energy ingested in the form of any macronutrient will ultimately promote fat storage. It is therefore erroneous to suggest that because excess carbohydrate intake does not promote de novo lipogenesis it does not promote fat storage. The process of autoregulating carbohydrate stores will suppress fat oxidation and promote storage of recently ingested fat.
How are the physiological mechanisms involved in the regulation of nutrient balance likely to affect body weight? If the total level of EE is not greatly influenced by the nutrient composition of the diet (except under extreme conditions of overfeeding), then any diet-induced changes in nutrient balance can only significantly influence EB if fat, protein, carbohydrate and alcohol have different effects on appetite regulation, or different satiating efficiencies. (The relative satiating efficiency of a macronutrient (per unit time) would be the extent to which each MJ of positive nutrient balance suppresses subsequent EI compared with other macronutrients.) This is best illustrated by a hypothetical example. If EI is regulated, regardless of diet composition, on the basis of feedback changes in EB, then an excess EI as fat would lead to a positive fat (and hence energy) balance. But the energy-based control of feeding would suppress subsequent intake, leading to the mobilization and oxidation of the recently stored fat load thus restoring EB. The same argument can be made for each of the macronutrients. It is possible, however, that some particular aspect of nutrient balance may exert a primary influence on appetite control and EI (Stubbs et al. 1995b). Several times during the last half century theoretical models have been developed which propose that aspects of carbohydrate metabolism or storage play a major deterministic role in appetite and EI control.

Carbohydrate-based models of feeding

Carbohydrates have always had a special place in the minds of theorists concerned with the role of diet composition in producing physiological signals which may influence feeding behaviour. Mayer (1955) initially suggested that EB regulation occurred predominantly through short-term ‘glucostatic’ responses that could be corrected by longer-term ‘lipostatic’ regulation, should short-term regulation be sufficiently perturbed. Russek (1963) postulated the presence of glucose receptors in the liver and formulated the hepatostatic theory of EB regulation. Flatt (1987) extended these models, and evolved the glycogenostatic model of appetite regulation, which is based on the logic relating to nutrient balance discussed earlier. These models are depicted in Fig. 2.

Dietary carbohydrates have also been viewed as being central to nutrient selection models through their putative effects on the synthesis of the neurotransmitter, serotonin (5-hydroxytryptamine). It was hypothesized that dietary-induced biochemical oscillations in the ratio plasma tryptophan : plasma levels of the large neutral amino acids directly influenced tryptophan transport and its availability for serotonin synthesis and, therefore, for serotoninergic activity. This activity, in turn, was thought to influence, directly, a behavioural oscillation between the selection of protein and carbohydrate (Femstrom & Wurtman, 1972). One of the model’s original proposers, Femstrom (1987) has reviewed this model and he, with others, has concluded that the system does not operate as a mechanism for diet selection, although the importance of the serotonin system as a central mechanism influencing feeding behaviour remains undiminished (Blundell, 1990). The detailed reasoning for these conclusions can be found in Femstrom (1987) and associated discussion papers.

Most recently, the work of J. P. Flatt has been instrumental in generating a testable theoretical model which appeared to
explain the influence of diet composition on body weight in epidemiological and diet-survey-based studies. Flatt argues that the body's storage capacity for carbohydrate is limited and approximately equal to that oxidized per day. The storage capacity for fat is considerably larger than the daily flux. Flatt suggested, therefore, that the major factor influencing food intake is the smaller carbohydrate store; since carbohydrate stores fluctuate to a proportionately greater extent, it is a more likely candidate to monitor nutrient flux. Fat stores are suggested to have a much weaker influence on food intake since they are only perturbed by a very small fraction of the total, on a day-to-day basis.

In order to remain in EB for periods longer than a few days, the fuel mix oxidized, reflected by the RQ, must equal the fuel mix in the diet, represented by the food quotient. In other words the RQ of the substrates being oxidized must be equal to the food quotient ingested, and all macronutrients will be in balance. Flatt argues that people eat to maintain a certain range of glycogen stores (balance), on a day-to-day basis regardless of the fat content of the diet. Thus as carbohydrate is displaced by fat as a proportion of dietary energy, the greater the voluntary EI. Flatt predicts that this set of circumstances will persist until the percentage of body fat is so great that the contribution of fat to the substrate mix will again equal the dietary composition, due to an increase in the circulating non-esterified fatty acids, brought about by expansion of the adipose tissue mass. Under these conditions, he argues that a new steady state will be achieved. Flatt's model therefore unites the rationale of Mayer with fundamental tenets of energy metabolism research, and with sound observations of the interactions between fat and carbohydrate and their relative storage capacities. Flatt effectively generated a synthesis which theoretically explained how diet composition determines macronutrient flux and in turn body composition. In addition, experiments were conducted in mice fed ad libitum to examine whether carbohydrate balance predicted changes in EI in a manner consistent with the main prediction of his model. The experiments showed that there was a negative correlation between changes in carbohydrate stores and the subsequent day's ad libitum EI (r = 0.2; P < 0.025). In other words the mice ate less when replete with glycogen and vice versa (Flatt, 1987). The association between fat balance on one day and EB on the subsequent day was positive, stronger and more significant (r = 0.35; P < 0.001). There was no apparent feedback from EB on one day on to EI on the subsequent day. These data were consistent with the concept of glycogen stores exerting negative feedback on EI on a day-to-day basis. Furthermore, this evidence of negative feedback arising from carbohydrate stores in mice appeared to be supported by indirect evidence in human subjects which repeatedly demonstrated that (1) the greater the percentage of EI derived from fat the greater the risk of having a higher BMI and (2) when human subjects feed ad libitum on energy-dense high-fat diets they consume more energy and gain weight relative to less energy dense, lower-fat diets. Mayer, Russek and Flatt's models of carbohydrate control predict broadly similar effects on feeding behaviour: (1) carbohydrate stores or metabolism exert a negative feedback on EI; (2) that, because of this feedback, diets high in fat but low in carbohydrate will promote excess EI; (3) that manipulating carbohydrate status, i.e. oxidation or carbohydrate stores, will reciprocally influence EI; and (4) excess ad libitum EI on high-carbohydrate diets should be very difficult to achieve without a conscious effort, due to the strength of putative negative feedback arising from carbohydrate status. The key question in relation to these models is

Fig. 2. The glucostatic and glycogenostatic models of energy intake regulation in which changes in peripheral glucose utilization (glucostatic) or carbohydrate (CHO) stores (glycogenostatic) are proposed to exert negative feedback on subsequent energy intake. EE, energy expenditure.
models of feeding but do not test those predictions directly. This is because carbohydrate balance was not measured in any of those studies. In our own studies, we were able to use indirect calorimetry to continually monitor nutrient balance (and nutrient oxidation) patterns as predictors of subsequent feeding behaviour while subjects were given access to diets of different composition. Six men were each studied three times in experiments conducted over 1 week per treatment (randomized, within-subject design). During this time subjects were continually resident in a whole-body indirect calorimeter (Stubbs et al. 1995a). On each 7 d study period the men consumed, ad libitum, covertly manipulated low-, medium- or high-fat diets. The energy density of the diets increased with the percentage of fat in them. As the fat content of the diet increased, the total weight of food eaten stayed the same, so EI increased, leading to a progressively positive EB. The relationship between the changes in actual, cumulative nutrient balance over time and the subsequent day’s EI was examined to assess possible feedback from macronutrient balances on EI and so assess whether carbohydrate stores exerted negative feedback on EI. The previous day’s cumulative balance of carbohydrate and protein was negatively related to the subsequent day’s EI (and balance), but there was no apparent suppression of intake in relation to the previous day’s cumulative fat balance. The effect of a positive protein balance was greater than that for carbohydrate storage. The effect for carbohydrate alone accounted for only 5.5% of the variance in subsequent EI. The model accounting for all three of the macronutrients accounted for 27.8% of the variance in subsequent EI. This suggests that models relating nutrient balance to feeding behaviour should consider the combined effects of the macronutrients as they appear to have a greater predictive power than single nutrient-based models. The oxidation of all of the macronutrients predicted a reduction in the subsequent day’s EB, but this effect was again hierarchical, with protein oxidation exerting a stronger predicted fall in intake than carbohydrate which, in turn, exerted a marginally stronger effect than fat (Stubbs et al. 1995a). Thus the previous day’s cumulative stores and the oxidation of protein and carbohydrate were negatively related to subsequent EI. Importantly, while fat oxidation seemed to predict, to a modest extent, the subsequent day’s EI, alterations in fat stores did not show any effect on the subsequent day’s EI. These data suggest (1) that at the level of nutrient balance, macronutrients appear to exert hierarchical effects in their potentially suppressive effects on subsequent EI and (2) that it is the component of obligatory oxidative disposal which underlies the potentially suppressive effects that protein and carbohydrate, but not fat balance, exert on subsequent EI. This is discussed further, later.

Is excess energy intake on high-fat diets due to a drive to maintain carbohydrate balance?

Carbohydrate-based models of feeding predict that excess EI occurs on high-fat diets, not because they are energy-dense, but because the negative feedback from carbohydrate oxidation or stores is diminished and subjects are actively increasing EI to optimize carbohydrate status. It is apparent that
excess EI on high-fat, energy-dense diets is a passive process since subjects eat similar amounts of food and fail to decrease intake in response to the increased energy density of the diet (Duncan et al. 1987; Lissner et al. 1987; Tremblay et al. 1989, 1991; Cotton et al. 1993; Lawton et al. 1997). At very high energy densities food intake will decrease but not enough to prevent excess EI (Tremblay et al. 1992). Two studies have actually examined the effects of allowing subjects to consume, ad libitum, high-fat and low-fat isenergetically-dense diets. One study was conducted in women (dietary energy density was 4-2 kJ/g) (van Stratum et al. 1978) and one in men (energy density was 4-8 kJ/g) (Stubbs et al. 1996). In both studies subjects ate near-identical amounts of food and hence energy, regardless of diet composition. There was no evidence of excess EI or weight gain as the carbohydrate content of the diet diminished (and the fat content increased) in either study. Thus despite large differences in carbohydrate intake (and hence carbohydrate status) there were no differences in EI. These data cast doubt on the notion that increases in carbohydrate balance of 4.99 MJ between the high- and low-carbohydrate diets, by the morning of the fifth day there was no detectable difference in muscle glycogen stores using a randomized crossover design in eight men (Snitker et al. 1997). Subsequent ad libitum food intake was measured with an automated food-selection system for 2 d in a whole-body indirect calorimeter. Despite a 46 (SE 21) % difference in muscle glycogen between the two treatments, ad libitum 2 d food intakes (energy, weight, or macronutrients) were similar between treatments (high glycogen: 23-80 (SE 4-67) MJ/d; low glycogen: 21-20 (SE 6-73) MJ/d). However, EI on the second day of ad libitum feeding was negatively correlated with carbohydrate balance on the first day, although this effect only explained 9 % of the variance in EI on day 2.

There are, of course, some limitations to these studies. They do not address the issue of food or nutrient selection since subjects were only able to increase or decrease the amount but not the composition of foods they chose to eat. These studies also uncouple learned behavioural responses from the physiological signals produced by large dietary manipulations. Taken together, these studies do suggest that in the short-to-medium term changes in carbohydrate stores per se do not exert powerful unconditioned negative feedback on EI.

The effect of manipulating whole-body carbohydrate status on subsequent energy intake

Carbohydrate-based models of feeding also predict that manipulation of carbohydrate status (oxidation or stores) will reciprocally influence EI. Three studies have examined this issue in detail. In the first of these studies the effect of altering carbohydrate balance on day-to-day food intake was examined (Stubbs et al. 1993). Nine men were each studied twice during which time they were housed in an indirect calorimeter for 48 h. Carbohydrate stores were depleted over the first 24 h to create a difference of 2.45 (SE 0-67) MJ, compared with a control (medium-fat) diet, while controlling EB. Ad libitum food intake was assessed over the subsequent 24 h. The carbohydrate 'depletion' was achieved using a very-high-fat (85 % of energy), low-carbohydrate (3 % of energy) diet. This extreme dietary manipulation did not affect the subsequent day’s ad libitum EI, compared with the control. Instead carbohydrate balance was re-established by directing more dietary carbohydrate towards storage, and maintaining high rates of fat oxidation throughout the ad libitum day. Thus, plasticity in fuel utilization, not appetite, was the primary mechanism for re-establishing nutrient balance.

A subsequent follow-up study extended this investigation in six men who were each studied three times in 5 d experiments (Shetty et al. 1994). They received either a high-carbohydrate diet, providing 79 % of EI as carbohydrate, a medium-carbohydrate diet comprising 48 % of EI as carbohydrate or a low-carbohydrate diet which provided only 9 % of EI as carbohydrate, over 48 h, after 2 d on a maintenance diet. The impact of these manipulations on food intake throughout the fifth day was examined. EB proved to be similar on each treatment and, despite a difference in carbohydrate balance of 4-99 MJ between the high- and low-carbohydrate diets, by the morning of the fifth day there was no significant effect on EI during that day. Again, carbohydrate balance was re-established by an autoregulatory change in carbohydrate oxidation rather than by altered food intake. In a third study in another laboratory, exercise and dietary manipulations were used to produce either high or low glycogen stores using a randomized crossover design in eight men (Snitker et al. 1997). Is it difficult to consume excess energy on high-carbohydrate diets?

The Guru Walla model (Pasquet & Apfelbaum, 1994) has demonstrated that under culturally prescribed conditions at least it is possible to overeat and gain weight when consuming a high-carbohydrate diet. Carbohydrate-based models of feeding predict that excess EI on high-carbohydrate diets is unlikely to occur because of the strength of negative feedback arising from carbohydrate ingestion. We tested this prediction in six normal-weight men who were each studied twice during 14 d (Stubbs et al. 1997a). During this time they had ad libitum access to one of two covertly-manipulated diets. The fat, carbohydrate and protein in each diet, expressed in terms of energy, were in the proportions of 22 : 65 : 13 on the low-energy-density diet which was set at a density of 348 kJ/100 g. The high-energy-density diet (617 kJ/100 g) had similar macronutrient proportions. Subjects could change the amount but not the composition of the foods they chose. EI were 8-56 and 14-56 MJ/d, leading to weight loss or gain on the low- and high-energy-density diets respectively. Intake was not influenced by perceived pleasantness of the diets. However, subjects felt significantly more hungry on the low-energy-density diet than on the high-energy-density diet, as judged by a linear hunger scale (30-4 mm v. 25-7 mm (F (1, 160) 30-28; P < 0.001)). In a previous study where subjects consumed excess energy on high-fat, high-energy-density diets there was no detectable difference in subjective hunger between dietary treatments. These data suggest that excess EI are possible on high-carbohydrate, high-energy-density diets in ad libitum feeding subjects, where conditions preclude diet selection. We interpret the difference in hunger between the diets as being due to an increase in hunger to above-normal levels, only when carbohydrate depletion and a negative EB coincided.
It is known that changes (particularly decrements) in both carbohydrate and fat metabolism do influence feeding behaviour in rodents and also human beings. Thus, a small (6–12%) drop in plasma glucose has been reported as a predictor of meal initiation in rodents and human subjects (Campfield & Smith, 1990; Langhans & Scharrer, 1992; Smith et al. 1992; Raben, 1995; Stubbs, 1995). In rodents a small infusion of glucose which blocks this drop also delays feeding by up to 3 h. Pharmacological inhibition of glucose and fat oxidation also increases feeding in rats (Friedman & Tordoff, 1986). Postprandial carbohydrate oxidation correlates negatively with hunger in man (Raben, 1995). Parenteral infusions of amino acids, glucose or lipid in rats led to compensatory decreases in oral EI. However, the degree of energy compensation was only complete when amino acids were infused, whereas about 70% compensation occurred with glucose and less than 50% when fat was infused (Walls & Koopmans, 1992). Similar effects have been found in one study in human subjects (Gil et al. 1991).

There is also new evidence which suggests that the central nervous system monitors carbohydrate and fat oxidation separately but that these signals are integrated in a way which allows the animals to take account of overall fuel status, at least in relation to glucoprivic and lipoprivic rodent-based feeding models (Ritter & Calingasan, 1994). Thus, while there is evidence that decrements in fat and carbohydrate intake and oxidation are well detected and compensated for (Friedman & Tordoff, 1986; Langhans & Scharrer, 1992), the evidence suggests that increments in fat and carbohydrate intake induce less compensation than decrements in intake.

It would appear from the preceding discussion that (1) the predictions of carbohydrate-based models of feeding behaviour are not supported by the experiments that have been devised to test them. The effects of carbohydrate status per se appear to explain, at best, only a small proportion of the variance in EI; (2) models that take account of all of the dietary macronutrients appear to predict changes in EI to a greater extent than nutrient specific models; (3) models based on the flux of metabolic fuels should account for the effect of both increases and decreases in nutrient flux on EI; (4) macronutrients appear to exert differential effects on appetite and EI, and (5) the effects that macronutrients exert on appetite and EI need to be considered under ecological conditions (where fat contributes disproportionately to the energy density of the diet) and under conditions where the confounding factor of energy density is controlled out of experimental comparisons. Therefore, it is important to consider carefully the effects of macronutrients on the EI of real people living their normal lives in their familiar environment and also in more artificial but carefully controlled laboratory studies.

Comparing the effects of macronutrients on appetite control and energy intake

Evidence from dietary surveys

A number of studies suggest that fatter people appear to consume a higher proportion of their EI from fat rather than from carbohydrate (for a review see Lissner & Heitmann, 1995). However there are potential problems associated with mis-reporting of dietary intakes and it is possible that mis-reporting may be specific to certain nutrients. Nevertheless, more recent data which exclude implausible dietary records (i.e. intakes below 1-2 x BMR) have recently been analysed. These data still suggest that the higher the percentage of EI derived from dietary fat the greater the risk of having a BMI in excess of 25 kg/m² (Mcdiarmid et al. 1996).

The most consistent finding in relation to dietary macronutrients is that protein appears to be the most satiating macronutrient. Studies by DeCastro (1987) and DeCastro & Elmore (1988) have shown that in free-living subjects, self-recording their food intakes by using food diaries for 7 d at a time, protein was the most effective at suppressing energy intake, independent of its contribution to total energy. In a recent study by Bingham et al. (1994) the food and energy intakes of 160 postmenopausal women living at home in the Cambridge area were measured on four consecutive days in each of the four seasons. This approach produced 16 d of weighed intakes per subject kept over 1 year. The proportion of EI from protein correlated negatively with total EI (r = -0.45), carbohydrate did not correlate at all with total EI (r = 0.0) and, fat correlated positively with total EI (r = 0.18).

Taken with the work of DeCastro (1987) and DeCastro & Elmore (1988) these studies all suggest that under naturalistic conditions (where dietary fat contributes 2-2-3 times the energy per gram as protein or carbohydrate), joule for joule, fat appears to be less satiating than carbohydrate or protein. Protein appears to be, consistently, the macronutrient whose intake (joule for joule) suppresses subsequent EI to the greatest extent. It should be noted that protein intakes are markedly constant when comparing one study population with another. This may be partly due to the large effect protein has on satiety and learned feeding patterns.

Work by DeCastro & Orozco (1991) suggests that in moderate drinkers at least, the energy derived from alcohol is not regulated, but is added to the energy derived from other macronutrients contained in foods. This is not entirely surprising since alcohol has pharmacological (depressant) effects which are not likely to suppress EI.

Evidence from experimental interventions

Energy derived from alcohol appears to completely by-pass the appetite control (DeCastro & Orozco, 1991). This is not surprising since alcohol is also a physiological depressant and this effect may override or cancel any satiating potential from its energy content. A recent meta-analysis by Mattes (1996) suggests that alcohol produces counter-compensatory increases in EI. In recent years it has been repeatedly demonstrated that increasing the fat content and energy density of experimental diets or modified foods induces subjects to eat a similar amount of food and hence higher levels of EI as the fat content and dietary energy density rise. This effect is more pronounced in studies where subjects are given ad libitum access to systematically manipulated diets than under conditions where subjects have ad libitum access to a range of familiar food items (e.g. Foltin et al. 1990, 1992). In longer-term studies these changes are paralleled by changes in body weight (Lissner et al. 1987; Kendall et al. 1991; Stubbs et al. 1995a,b). Weight losses are typically modest when subjects feed ad libitum on low-fat, low-energy-
There are a number of individually rather subtle effects that dietary fat exerts on appetite, in comparison with carbohydrate, which are independent of the contribution of dietary fat to overall energy density. These effects may be additive, synergistic or cancel each other out under real-life conditions. At the present time there are insufficient data to derive a model which articulates the cumulative and aggregate signiﬁcance of these effects in human subjects. Nevertheless the results of these studies suggest that dietary fat exerts subtle but signiﬁcant effects on EI and appetite control that are independent of its contribution to dietary energy density. There is also evidence that the type of fat and carbohydrate may also exert relatively subtle differences on appetite and EI. However more detailed, longer-term studies are required before conclusive statements can be made about the importance of types of protein, carbohydrate and fat on appetite and EI.

Comparing the effects of macronutrients on appetite and energy intake at the same level of energy density

There are a number of examples which show that fat exerts detectable, albeit relatively modest, effects on appetite and EI which are independent of its contribution to dietary energy density. Carbohydrate appears to exert a more acute effect on satiety than fat (Cotton et al., 1994), and three other studies have found this relatively subtle effect to be independent of energy density (Rolls et al., 1994; Johnstone et al., 1996; Stubbs et al. 1997a). In one of these studies, the low satiating efficiency of fat in the short term appeared to be related to its low osmotic load, as indicated by the subjective thirst of the subjects (Stubbs et al., 1997b). Pronounced differences in the satiating efficiency of intravenously infused fat and carbohydrate have been recorded by Gil et al. (1991).

In one study isoenergetic, isoenergetically-dense, weight-reducing diets (4·18 MJ/d) were given to six women, who were also given snacks of a constant composition to ingest if they felt the need to eat more. Only on the high-fat treatment were snackBar EI signiﬁcantly, albeit marginally, higher than the high-protein or high-carbohydrate treatments (Johnstone et al., 1996).

Fat also exerts sensory inﬂuences on the diet by adding moisture and mouth-feel to food as well as acting as a vehicle for a large number of fat-soluble volatile substances. These effects may also be independent of energy density. Furthermore, there is evidence that the oro-sensory qualities of dietary fat and sugars may interact to inﬂuence the sensory stimulation to eat. Drewnowski (1997) has shown that sugar–fat mixtures appear to exert a synergistic effect on sensory pleasure response of human subjects, relative to fats or sugars alone. A comparison of the effects of high-carbohydrate-sweet, high-carbohydrate-savoury, high-fat-sweet and high-fat-savoury snacks on short-term intake has recently been made. Ingestion of high-fat-sweet snacks exerted a far greater effect on EI, which was independent of energy density, since EI was about twice that on any other treatment despite the fact that the energy density of the high-fat-savoury snacks was higher (Green & Blundell, 1996).

In sum, when the satiating effects of macronutrients on appetite and EI are compared at the same level of energy density, protein is consistently (at doses above 1·2–1·4 MJ) more satiating than either fat or carbohydrate. However, there are a number of individually rather subtle effects that dietary fat exerts on appetite, in comparison with carbohydrate, which are independent of the contribution of dietary fat to overall energy density. These effects may be additive, synergistic or cancel each other out under real-life conditions. At the present time there are insufficient data to derive a model which articulates the cumulative and aggregate signiﬁcance of these effects in human subjects. Nevertheless the results of these studies suggest that dietary fat exerts subtle but signiﬁcant effects on EI and appetite control that are independent of its contribution to dietary energy density. There is also evidence that the type of fat and carbohydrate may also exert relatively subtle differences on appetite and EI. However more detailed, longer-term studies are required before conclusive statements can be made about the importance of types of protein, carbohydrate and fat on appetite and EI.

A model to explain the hierarchical, postsorptive effects of macronutrients on satiety

At this point it is necessary to reconsider the statistical analysis we conducted between changes in nutrient balance and subsequent EI, on a day-to-day basis over the 7 d subjects were resident in the calorimeter, each on three separate occasions, feeding ad libitum on low-, medium- or high-fat diets (Stubbs et al. 1995b). This analysis should be considered in relation to the evidence and arguments concerning the effect of diet composition on appetite and EI outlined earlier. The multiple regression analysis we conducted suggested that cumulative stores (balance) and the absolute 24 h oxidation of protein and carbohydrate were negatively related to
subsequent EI. However while 24 h fat oxidation was negatively related to the subsequent day's EI, alterations in cumulative fat stores did not show a relationship to the subsequent day’s EI. These data appear to demonstrate that the hierarchy in the satiating efficiency of the dietary macronutrients is causatively related to the parallel hierarchy in the immediacy with which the balance of those macronutrients is regulated. In other words it may be the regulation of nutrient balance by obligatory oxidative disposal which underlies the potentially suppressive effects that a positive protein and carbohydrate, but not fat balance, exert on subsequent EI (Fig. 3). The macronutrients whose balance is most tightly regulated exert suppressive effects on subsequent EI, while fat (whose balance is not tightly regulated) does not exert such an effect. Thus, it may well be that the constraints under which macronutrient metabolism and balance are regulated may create the conditions which determine the hierarchy in the satiating efficiency of the dietary macronutrients (Stubbs, 1995). These interpretations of the relative metabolic contribution of different macronutrients to changes in subsequent intake do not make statements about the importance of nutrient metabolism and postabsorptive events relative to other influences on intake. The quantitative role of metabolic v. non-metabolic or nutritional v. non-nutritional influences on intake is at present unquantified.

Evidence that changes in nutrient metabolism influence feeding behaviour

If autoregulatory increases in the oxidative disposal of recently ingested protein and carbohydrate (but not fat) are involved in suppressing subsequent EI, it follows that fat may, in part, be less satiating because it is less readily oxidized. A form of fat which is not readily stored but is readily oxidized, should show some tendency to suppress subsequent EI. We have recently tested this in six men who were each studied three times in experiments in which they had 14 d ad libitum access to covertly manipulated energy-dense (640 kJ/lOO g), high-fat diets (61 % fat, 10 % protein and 29 % carbohydrate by energy). Medium-chain triacylglycerol (MCT) was substituted for long-chain triacylglycerol (LCT) in ratios of 1 : 2, 1 : 1 and 2 : 1, corresponding to low-, medium- and high-MCT diets. On the high-MCT diet both food intake and EI were suppressed, by 9 % relative to the other two diets (Stubbs & Harbron, 1996), which was sufficient to prevent the weight gain seen on the other two diets. This study supported the notion that a readily oxidized form of fat (MCT) was more effective at suppressing EI than the less readily oxidized LCT. This study illustrates another important point. When all cognitive cues are minimized, and only one factor is manipulated (here the MCT : LCT ratio in isoenergetic diets), then it appears that relatively large changes in the composition of the diet, and the signal produced by its ingestion, are required to influence appetite. The same observation has already been made for protein. Similarly, Langhans & Scharer (1992) observed in rodents that ‘... a synergism of various stimuli controlling food intake seems to be an important principle in the control of eating that could explain the frequent finding that unphysiological high doses of putative satiety agents are necessary to affect eating behaviour’. These observations attest to the redundancy of appetite control mechanisms.

**Negative feedback**

![Negative feedback diagram](https://doi.org/10.1079/PNS19980052)

**Fig. 3.** The ‘hierarchical oxidation hypothesis’ whereby the regulation of nutrient balance by obligatory oxidative disposal of protein and carbohydrate (CHO) but not fat correlates with satiety. EE, energy expenditure.
If relatively large changes in the oxidation of metabolic fuels are important in influencing feeding behaviour the converse should be true, i.e. inhibition of nutrient oxidation should stimulate feeding. Friedman & Tordoff (1986) have shown that glucose and fat oxidation interact to influence food intake. In a remarkable study, rats were given graded doses of 2-deoxyglucose (2DG) which inhibits glucose oxidation by competitive inhibition of phosphohexose isomerase (EC 5.3.1.9) activity. There was a dose-dependent increase in food intake as glucose oxidation was inhibited; a glucoprivic feeding response. Using the inhibitor of LCT oxidation, methyl palmoxirate (which inhibits mitochondrial uptake of long-chain acyl CoA), they showed a similar dose-dependent increase in lipoprivic feeding. However when both inhibitors were given simultaneously there was a massive synergistic increase in food intake, suggesting that when the metabolism of only one fuel is inhibited the rats may default to another available metabolic fuel. When no alternative fuels are available endogenously the rat attempts to obtain them exogenously, by feeding. 2DG has also been found to increase hunger and food intake in human subjects when given at doses of 50 mg/kg body weight (Thompson & Campbell, 1977; Welle et al. 1980). A further study by Friedman et al. (1990) in rats, suggested that it is indeed the oxidation of metabolic fuels that is somehow linked to satiety. Methyl palmoxirate inhibits the carnitine palmitoyl transferase (EC 2.3.1.21) transporter that shuttles the long-chain fatty acids across the inner mitochondrial membrane, inside which they are oxidized. Inhibition of this shuttle stimulates food intake. When rats were given methyl palmoxirate while feeding on a diet rich in MCT, there was no increase in food intake. MCT is not dependent on the carnitine palmitoyl transferase transporter to move across the inner mitochondrial membrane to its site of oxidation, suggesting that it takes into account the availability of both carbohydrates and fatty acids (Ritter et al., 1994). This is important since the physiological and behavioural responses of the appetite regulatory system need to be able to take account of prevailing changes in the environmental supply of the metabolic fuels (macronutrients) and the manner in which they are physiologically utilized.

New, integrative models of peripheral signals affecting feeding behaviour

Recent neuroanatomical work also suggests that both fat and carbohydrate oxidation are separately monitored by the central nervous system and that these signals are integrated within the brain to monitor overall fuel status (Ritter & Calingasan, 1994). Ritter & Calingasan (1994) have used the antimetabolic drugs mercaptoacetate (which causes lipopri

viva by blocking mitochondrial acyl-CoA-dehydrogenases and so reduces β-oxidation of fatty acids), and 2-DG as tools to produce lipoprivic and glucoprivic signals. Using surgical and chemical lesions together with neurochemical approaches they have provided important evidence that the response to lipoprivic signals is likely to be dependent on vagal sensory neurones. In other words, they have provided evidence that fatty acid oxidation is monitored in the periphery and these signals are relayed to specific areas of the brain, which they have identified through a combination of lesion and behavioural studies, together with work using markers of neuronal activity in specific regions of the brain. These areas of the brain are also activated by 2DG-induced glucoprivic feeding. However glucoprivic feeding appears to be partially mediated by receptor populations that are different from those mediating lipoprivic feeding, since glucoprivic feeding is not dependent on vagal sensory neurones (i.e. not influenced by vagotomy or capsaicin treatment, which damages vagal sensory neurones) and can be stimulated by activation of metabolic receptors actually within the brain, which exist in addition to those monitoring lipoprivic feeding. This is supported by work using another antimetabolite 2,5-anhydro-D-mannitol which, unlike 2DG, does not cross the blood–brain barrier and so only inhibits glucose oxidation in the periphery. 2DG inhibits glucose oxidation in both the brain and the periphery. The glucoprivic feeding response to 2,5-anhydro-D-mannitol is also characterized by activation of the same immunoneurochemical markers (Fos-like activity) in the same region of the brain that responds to lipoprivic feeding, the area postrema and nucleus of the solitary tract (the AP/NTS). This area receives central vagal sensory terminals. Lesioning of AP/NTS which destroys the sensory but not the motor nucleus abolishes mercaptoacetate- but not 2DG-induced feeding. Total subdiaphragmatic vagotomy abolishes the feeding response to low (but not high) doses of 2,5-anhydro-D-mannitol. It has been suggested from these lines of evidence that fatty acid oxidation is monitored in the periphery, while glucose oxidation is monitored both in the centre and in the periphery. These observations may help explain why carbohydrate status appears to be more accurately monitored than changes in fat balance. The authors observe that simultaneous activation of these distinct systems appears to produce an integrated feeding response that takes into account the availability of both carbohydrates and fatty acids (Ritter & Calingasan, 1994). This is important since the physiological and behavioural responses of the appetite regulatory system need to be able to take account of both changing metabolic requirements and fluctuations in the environmental supply of metabolic fuels. To date, no putative signalling system that has been suggested for glycogen stores or adipose tissue, appears, on its own, to explain much of the variance in feeding behaviour. There is, however, a growing literature which suggests that: (1) changes in diet composition can influence peripheral fuel selection, (2) peripheral changes in fuel selection are determined by physiological and thermodynamic constraints which determine a hierarchy in the immediacy with which the balances of recently ingested macronutrients are autoregulated by increases in their own oxidative disposal. (3) This hierarchy appears to parallel a hierarchy in the satiating efficiency of the macronutrients. (4) These two hierarchies may be causally related since a growing body of literature suggests that nutrient oxidation in the periphery is monitored by the central nervous system as a component of satiety. In particular

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Ritter & Calingasan (1994) have provided important evidence which suggests that neural pathways monitor fat oxidation in the periphery and carbohydrate oxidation (perhaps more precisely) in both the periphery and the central nervous system. (5) Langhans (1996) notes that the mid-brain centres that are concerned with monitoring peripheral fuel utilization, are connected via extensive neural relays to the areas of the fore-brain (especially the lateral hypothalamus and the paraventricular nucleus) that are concerned with the control of protein, carbohydrate and fat balance. Thus, an integrative model is beginning to emerge which may account for the manner in which the central nervous system is capable of monitoring physiological signals concerned with overall macronutrient balance and fuel flux, and which accounts for the manner in which feeding behaviour responds to changes in peripheral physiology. In essence, feeding responses are coupled to physiological changes rather than being directly determined by them. The evolution of a flexible and adaptive system concerned with the control of feeding behaviour is likely to have bestowed a far greater survival advantage on an opportunistically foraging species such as man (or for that matter rodents) than a system in which behavioural outcomes are an inevitable and rigid outcome of physiological signalling.

Appetite control appears to be governed by a redundant system in which feeding behaviour is the outcome of a large number of minor effectors which influence behaviour rather than a minority of major effects which switch feeding on or off. This statement is consistent with what we know of the anatomy of this system, the way it functions and the combined literature which has explored the influence of a wide range of physiological, pharmacological and environmental factors on appetite control, feeding behaviour and EB. The models that are developed to help understand and predict feeding behaviour need to be aware of the redundancy of appetite control and the complexity of mammalian behavioural responses. Such models would also serve to simplify such a complex system, so that the key aspects of appetite control can be targeted for maximal therapeutic and health-related effect. This necessitates the whole-body approach as a reference against which specific and detailed mechanisms must necessarily be evaluated. It follows from these considerations that future trends in human appetite research should perhaps target key areas that are theoretically most likely to alter directionally the amount of food eaten (and hence EI) and the type of nutrients selected.

**Future trends in human appetite and energy balance research**

It is perhaps important that future trends in human appetite and EB research are characterized by a number of features most likely to improve our understanding of the mechanisms which influence the amount and type of foods we eat (quantitative and qualitative feeding respectively). There is a growing concern amongst some workers that there should be more studies focusing on longer-term interventions. This concern has arisen from the somewhat spectacular changes in EI that can be produced by dietary or other manipulations in the short term, which do not appear to continue into the longer term in real life. It may well be that the appetite control system accommodates many short-term changes and re-establishes EB over longer periods. It is equally important to compare protocols conducted under the controlled but artificial conditions of the laboratory with studies conducted under more naturalistic conditions. In this way it should be possible to understand better the quantitative importance of laboratory-derived data for the feeding behaviour and EB control of real people living their normal lives in their natural environment. It is worth remembering that the experimental environment can affect experimental outcomes and the interpretations that arise from them. Furthermore the degree of food selection and the familiarity of those foods to the subject determines the degree of constraint that the dietary aspects of the experimental design place on the subject’s behavioural response. At the present time a number of phenomena discussed in this paper are demonstrable in the laboratory and in real life (e.g. the effect of increasing the fat content and energy density of the diet on EI and EB). A number of others have not been so widely researched and it would be premature to derive conclusions pertinent to policy formulation at the present time.

Future discoveries of putative physiological signals believed to be important mechanisms of appetite and EB control should also be examined across a range of conditions. In particular, the importance of any putative signalling system should be assessed in relation to what is already known about the behaviour of the appetite control system at the level of the whole body. Ultimately the quantitative importance of a putative signalling system needs to be examined in relation to whole-body feeding behaviour.

It does not need to be emphasized that future research programmes aimed at understanding the major factors influencing quantitative and qualitative feeding should necessarily be of a multidisciplinary nature. This is because EB does not change in human beings without a change in behaviour. The study of human appetite and EB is therefore the study of the relationship between physiology and behaviour. Mechanisms operate at a number of levels ranging from associative-conditioning at the whole body level to molecular signals important in recognizing a change in the supply of energy and macronutrients.

All of these requirements of appetite and EB research would at first glance appear to be beyond the grasp of most research groups (it is ironic that there are few, if any, centres dedicated to human ingestive behaviour in Europe). However, research is becoming increasingly collaborative and interactive in nature. It is through such interactions that multidisciplinary programmes can be developed which organize research protocols as clusters of related studies, structured around key issues pertinent to appetite and EB in man. In other words key issues could be explored through multiple protocols that rotate theoretical models in a number of ways which are capable of testing their robustness. Such targeted and interactive programmes may accelerate the rate at which integrative models of appetite control can be fully explored and developed. In this way the fruits of appetite research, in terms of contribution to fundamental knowledge, policy development and benefits through commercial exploitation and clinical application, may be harvested more rapidly and in greater abundance than ever before.


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