

## Review article

# Control of energy balance in relation to energy intake and energy expenditure in animals and man: an ecological perspective

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In this paper, we consider the control of energy balance in animals and man. We argue that patterns of mammalian feeding have evolved to control energy balance in uncertain environments. It is, therefore, expected that, under sedentary conditions in which the diet is rich in nutrients and abundantly available, animals and man will overeat. This suggests that no physiological defects are needed to induce overweight and ultimately obesity in man. Several considerations arise from these observations. The time period over which energy balance is controlled is far longer than allowed by most experiments. Physiological models of energy balance control often treat excess energy intake as a defect of regulation; ecological models view the same behaviour as part of normal energy balance control in environments where resources are uncertain. We apply these considerations to common patterns of human and animal feeding. We believe that the ecological perspective gives a more accurate explanation for the functionality of excess fat and the need to defend nutrient balance and avoid gross imbalances, as well as explaining hyperphagia in the face of plenty. By emphasising the common features of energy balance control in different mammalian species, the importance of changes in behaviour to accommodate changes in the environment becomes apparent. This also opens up possibilities for the control of body weight and the treatment of obesity in man.

### Energy balance: Feeding behaviour: Man: Animal models: Body weight: Ecology

The control of energy balance (EB) in man attracts much attention in nutrition research because a considerable proportion of the human population in the developed world is now seen as being overweight (e.g. Stubbs & O'Reilly, 2000). There is much emphasis on the level of energy intake (EI) as a major factor determining the levels of lipid reserves that are achieved (e.g. Mela & Rogers, 1998). The focus in such studies varies widely. Some studies concentrate almost exclusively on psychological and sociological mechanisms and emphasise the role of cortical control over decisions with regard to feeding behaviour (e.g. Spitzer & Rodin, 1981). Other studies are mainly interested in the physiological mechanisms that may be involved in the control of food intake (e.g. Schwartz *et al.* 2000). Many such programmes study laboratory animals in an attempt to elucidate factors relevant to the control of food intake in humans. Studies that originate from the desire to improve the understanding of food intake control in humans frequently emphasise short-term mechanisms and limit attention to a time window that is much shorter than the time-span that is relevant for growth, survival and reproduction (Collier & Johnson, 1990).

Control of food intake in animals is also a major subject of research in ecology and animal science (e.g. Stephens & Krebs, 1986; van der Heide *et al.* 1999). Interest in food

intake regulation in ecology arises from the realisation that the level of food intake has important effects on survival and reproduction in wild animals (e.g. Stephens & Krebs, 1986). In such studies, the question of why animals control their intake in relation to their physiological requirements, in the context of different environments, receives much more attention. Such teleonomic frameworks abound in ecological studies of animal feeding behaviour, and the advantage of such an approach is also recognised in animal science (e.g. Tolkamp & Ketelaars, 1992; Emmans & Kyriazakis, 1995). Such frameworks are usually based on the assumption that current physiological processes and behavioural programmes have evolved because these directed animals to behave in a manner most conducive to their long-term fitness. Fitness, in an evolutionary sense, is defined as lifetime reproductive success and therefore depends on both survival and reproduction.

There are considerable differences in the approaches, assumptions and theoretical models used in the study of food intake by ecologists and evolutionary biologists on the one hand and by biomedical scientists, physiologists and molecular biologists on the other. The former are primarily concerned with the ecological forces that shape the feeding behaviour of animals in the wild; the latter are primarily concerned with understanding human feeding behaviour, with particular reference to obesity

in modern society. Various animal species are often artificially bred and used as models for various aspects of feeding physiology (York & Hansen, 1997). Is the use of these somewhat artificial species as models for human physiology justified? The view that man is not a mouse has often been aired in discussions of these models, but to what extent does man differ from the mouse? To what extent are humans and animals different in the design specifications of their feeding behaviour and the physiology that underlies it? Are there sufficient similarities to justify the use of animal models in human appetite and EB research? It is important to identify both similarities and differences. For example, the demonstration of functional brown fat in rodents (Rothwell & Stock, 1979, 1983) has led to a wide-scale search for similar thermogenic mechanisms in humans, to little avail (Bouillaud, 1999). The recognition of these differences has led to the general conclusions that non-shivering thermogenesis is not an important pathway affecting EB in humans. Similarities are valuable points of cross-species reference. The phenomenon of glucoprivic and lipoprivic feeding in humans (Thompson & Campbell, 1977, 1978; W. Langhams, personal communication) and rodents (Friedman *et al.* 1986, 1990) has formed the backbone of a new integrative model of how nutrient metabolism influences central feeding mechanisms.

At first glance, the prospect is pessimistic since the evolutionary paradigms used to explain the feeding behaviour of animals appear inappropriate to the study of human feeding behaviour. Teleonomic frameworks abound in studies of animal feeding behaviour, but they are less favoured in human studies. Why is this? Typically, why do such frameworks appear to 'fail' in their explanation of human eating behaviour?

It is important to recognise that investigators are not looking for the same things. Indeed, the investigators' expectations of animal and human goals are often antithetical. In many human studies of feeding behaviour, the main outcome of interest does not relate to the design and behaviour of a species in a given environment; instead, it relates to issues pertaining to longevity, health, reducing health-care budgets and limiting excess body weight. These are proximal, applied solutions rather than ultimate (teleological) explanations. In foraging theory, many models assume that animals are intake rate-maximisers (e.g. Stephens & Krebs, 1986). The study of human obesity has often focused on finding defects in a physiological system believed to defend against insufficient and excess EI (Blundell & Stubbs, 1997). Ecologists thus assume animals will maximise their intake unless constrained by various factors; human physiologists assume that humans will regulate EB unless that regulation is disturbed by some physiological defect or bypassed by some nutritional attributes of the diet. Ecologists have developed theoretical models that account for the factors that limit or constrain intake rate-maximisation (e.g. Belovsky, 1978; Poppi *et al.* 1994). Obesity researchers have developed models that account for the way in which EB is 'normally' maintained by physiological feedback loops and how such loops may be compromised (e.g. Kennedy, 1953; Mayer, 1955; Mellinkoff, 1956; Flatt, 1987).

Thus, the assumptions of the investigator about the behavioural goals of the subject and the theoretical models constructed to account for them differ between ecological and physiological investigations of feeding. These differences are largely properties of the investigator and not of the subject. Will it ever be possible to account for the forces that shape

feeding behaviour from mice to men and from molecules to whole animals in their natural habitat? Is it possible to describe human feeding behaviour, not just in terms of biological signalling systems, but in terms of the costs and benefits of feeding?

Few may want to consider the same paradigms of survival and reproductive success as the most important basis for the study of the control of EB in humans. In significant parts of the present world, limits at the lower end of food intake may sometimes still affect survival and reproduction, for example during famine and war. Few would, however, maintain that, in the developed world, food intake by humans is geared exclusively to the energetic demands of survival and reproduction. The fact that over half of the adult population in some countries are considered overweight, with its negative fitness consequences (Stubbs & O'Reilly, 2000), also seems to contradict the idea that EI will be well adapted to fitness. At first sight at least, this seems to indicate that approaches used in the study of animal feeding behaviour in ecology and in animal science may not be consonant with those used in human studies. We have, however, reasons to believe that we can increase our understanding of the control of EB by considering the concepts that have been developed in ecology and by analysing observations made in ecological and animal science. The present paper describes the common ground and shows how animal studies may contribute to progress in the study of the control of food intake and fatness in humans.

### The basis for a common approach

In many respects, the evolutionary histories of human ecology and foraging strategies are not essentially different from those of many other animal species (Foley, 1987; Harrison *et al.* 1988). That means that a framework of functional explanations, as used in ecological studies, might well provide us with a useful insight into the role of food intake and fat deposition in our evolutionary history. Such a framework tries to answer questions related to the 'why' of observed behaviours: why did such behaviour evolve, and how did it contribute to survival and reproduction? An attempt to construct such a framework may, at the very least, result in a powerful heuristic tool. It is evident that such a framework will be based upon the idea that the goals of human foraging strategies (food intake) will have affected long-term survival and reproduction. To be able to make a link between such a framework and short-term feeding behaviour, we need to understand the timescale that is most relevant to survival and reproduction.

Animal studies may also provide insight into the physiological mechanisms relevant to the human obesity problem as humans share many controlling mechanisms with other animals (Stubbs, 1999). One example is the way in which tissues and organs are supplied with the oxygen that is crucial to energy metabolism. Breathing and the transport of oxygenated blood to cells are both largely controlled by the primitive brain in both humans and animals. Humans can, within limits, bring breathing under cortical control but rely most of the time on 'the animal within' for an accurate control of oxygen supply. Short-term oxygen supply is so crucial to survival that it is largely under autonomic control. The time needed

for energy supply to become crucial is much longer than that for oxygen, but it is certain that survival and reproduction in the long term are to a large extent affected by the energy available to both humans and animals. It therefore seems logical to assume that at least some part of the controls of both EI and EB will also reside in the primitive brain that we share with other animals. This view can be emphasised by extending our consideration beyond adults. The drive to eat (but not necessarily food intake) of small children will be almost totally controlled by the animal within, and the possible effects of cortical control will only gradually become more important during maturation. This must mean that we share many of the mechanisms affecting EI and EB with animals, including, for that matter, the mechanisms of learning (Stubbs *et al.* 1998a). If so, we can hope to learn from studies of animal feeding behaviour. This is, of course, the reason for so much food intake research on rodents.

However, a potentially useful source of insights that is largely neglected by human nutritionists is studies with farm animals. High levels of EI resulting in the deposition of extensive fat reserves are not an exclusively human phenomenon but occur, under certain conditions, in farm animals as well (see later). An analysis of these conditions may help to identify some important factors and the mechanisms with which these are associated. Here, the two major factors that influence food intake and lipid deposition in animals – food quality and physical effort (in humans, often termed nutrient density and physical activity, respectively) – will be emphasised and compared with the human experience. Such a comparison might elucidate how high levels of food intake and an excessive deposition of lipid can be both a direct result of the adaptation of genotypes to their natural environment (i.e. in terms of a functional explanation of behaviour) and a direct threat to present fitness.

### Lipid deposits and long-term feeding strategies: in search of a functional explanation

Lipid deposition in mature organisms is the result of average EI exceeding average energy expenditure (EE) over a period of time. Humans share with many animal species the capacity to store large amounts of energy in the form of lipid deposits. For animals under natural conditions, this ability can be considered to be part of a very useful feeding strategy. Most species during most of their evolutionary history did not have continuous access to unrestricted amounts of high-quality foods. Most species have to spend a considerable part of their time, and devote considerable effort to, searching for and collecting food, with a frequently uncertain result. Excellent-quality food items would generally have been available only as a small part of the daily diet or only during limited periods in the year, or might only be obtained after considerable effort. Many species are confronted with a seasonal variation in food supply and benefit from the availability of good-quality foods only during a relatively narrow window of opportunity, such as the rainy season or the summer. It is evident that many species rely on this window of opportunity as an essential part of their long-term feeding strategy. They can thus overcome the limited quantity or quality of foods in the harsh period, such as the winter or the dry season, and can provide energy during a reproductive cycle. Therefore, many animal

species have evolved with foraging programmes that result in the formation of lipid reserves when good-quality food is readily available. Human adipose tissue contains around 33.1 MJ/kg (Forbes *et al.* 1982) and so represents a highly efficient form of energy storage.

For tens of thousands of generations, the foraging history of mankind was not essentially different from that of many animal species (Foley, 1987; Harrison *et al.* 1988; Mela & Rogers, 1998). The seasonal variation in food supply and EE, resulting in cycles of positive and negative EB, continues to this day for humans in large parts of the world (e.g. Schultink *et al.* 1993; Kigutha *et al.* 1995). Indeed, in subsistence communities, it is not uncommon for body weight to fluctuate by 10% or more with the changing seasons. For much of mankind's history, disruptions of food supply were routinely caused by seasonality and occasionally by droughts, flooding, failed harvests and war (see Keys *et al.* 1950, for a history of documented human famine). It has, therefore, been suggested that the same functional explanation that has been advanced to explain animal feeding behaviour could be applicable to humans. The alternation between periods of feast and those of famine could have resulted in physiological programmes that led to the deposition of reserves in adipose tissue when good-quality food was readily available, in humans as well as animals (Mela & Rogers, 1998). Indeed, it is difficult to imagine why a species would have the capacity to deposit large quantities of lipid unless this had once been a useful part of its strategy for survival and reproduction.

For larger mammals and humans alike, seasonality in food supply meant that during periods of up to several months' duration, average EI will have exceeded average EE, with a positive EB and lipid deposition as a result. Such good seasons then alternated with seasons during which the quantity or quality of readily available foods was such that these reserves were mobilised. This must mean that what happened, in terms of EB, in the short term can only be understood as part of a long-term strategy. We will, therefore, first discuss the relevant timescale for the understanding of EI and EB.

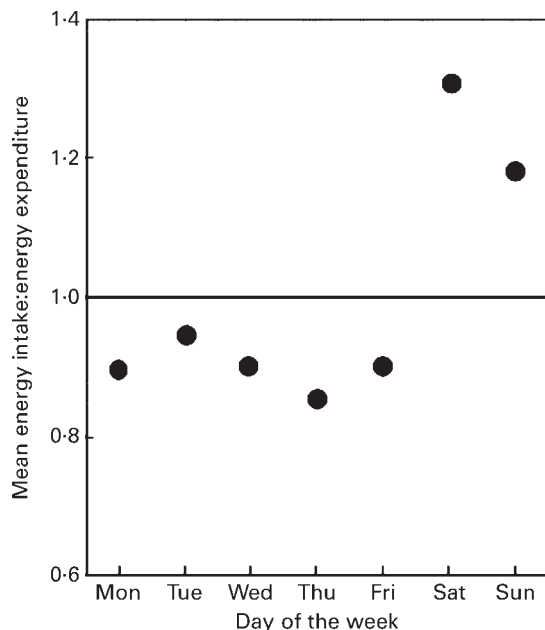
### The relevant timescale

For decades, the literature concerned with the food intake of mature animals and humans has been dominated by the concept of homeostasis (e.g. Brobeck, 1946; Mayer, 1955; Le Magnen, 1985; Mela & Rogers, 1998). This concept is frequently based on the assumption that there is some long-term set-point for body reserves and that, once this has been achieved, it will be defended. This means that short-term food intake behaviour would be aimed at exactly matching EI to EE in order to maintain the *status quo*, the constancy of the internal environment. Intake models are then of a relatively simple, short-term, depletion–repletion type (e.g. Kennedy, 1953; Mayer, 1955; Mellinkoff, 1956; Flatt, 1987). Indeed, many studies in human nutrition have depended on a short-term experimental model. In such models, the effects of some dietary manipulation (the preload) on subsequent intake during a single meal or the remainder of the day may be measured (see discussions by Spitzer & Rodin, 1981; Mela & Rogers, 1998; Stubbs *et al.* 1998b). However, concentrating only on short-term effects without considering

the longer-term timescale may fail to reveal the way in which food intake and EB are actually controlled.

Even in small animals such as the rat, short-term studies of feeding behaviour on a meal-to-meal basis may well be too short to inform us about control of EB. Although short-term observations of laboratory animals under some conditions may seem to agree with the concept of homeostasis, the general validity of the concept has been questioned (Collier & Johnson, 1997). These authors observed that rats that had to perform more work on some than on other days before they gained access to food still maintained their average weight in the long term, although they underconsumed on some days and overconsumed on others. They concluded that the relevant time window of feeding in rats was at least several days (Collier & Johnson, 1990, 1997).

Similar observations have long been available for humans. As an example, we summarise an elegant study of a single subject published more than three decades ago (Fig. 1). This study shows that, although no conscious effort to that effect was made, food intake was regulated in an entirely satisfactory manner in the longer term. On a weekly basis, EI almost exactly matched EE. However, imbalances in EI and EE existed for time spells of up to 5 d. Such behaviour is not consistent with the idea of short-term homeostasis and short-term depletion–repletion models of food intake. Recently, more extensive data show that feeding in humans follows a weekly cycle (De Castro, 1997). Longer-term cyclicality in human feeding also may occur over the course of a year (Tarasuk & Beaton, 1991, 1992; Kigutha *et al.* 1995). This must mean that EI only rarely matches EE exactly in the short term, yet Collier & Johnson (1990) have pointed out that most studies in laboratory animals, as well as in human subjects, have focused on investigating the very short-term mechanisms of food intake regulation. Such short-term experiments can certainly be valuable for studying



**Fig. 1.** The mean ratio of energy intake:energy expenditure in relation to day of the week recorded during a period of 80 d in which the pattern of eating was determined by choice and custom alone (after data recorded by Taggart, 1962).

these mechanisms but this focus on short-term mechanisms while ignoring questions about function has limited attention to a time window that is much narrower than the time-span that is apparently relevant for the actual control of food intake and EB. In other words, many investigators may be looking for evidence of regulation over a period during which no such regulation is likely to occur. The development of a framework of functional explanations that take into account these observed medium-term (weekly) and long-term (annually) trends would, at the very least, be a powerful heuristic tool in the search for explanations at the mechanistic level.

#### *When a positive energy balance becomes unadaptive*

From an ecological perspective, an EI exceeding EE at some point in time has benefits and can be considered adaptive. Fig. 1 shows that an individual who in the medium term has periods of time when EI is greater than EE need not end up with a high level of lipid depots. What makes such behaviour unadaptive is when this occurs over prolonged periods of time without being alternated with periods of energy mobilisation. Under such conditions, massive amounts of reserves may be built up to such an extent that they limit the health, well-being and even evolutionary fitness of the individual – such as life expectancy (e.g. Masoro, 2000). Under natural conditions, massive lipid reserves are rarely seen in most species. There are, however, many examples of excessive lipid deposition in laboratory, domesticated or semi-domesticated animals. An analysis of the conditions in which this occurs may reveal which underlying mechanisms could also play a role in development of human obesity.

**Excessive lipid deposits.** It is not immediately clear when lipid deposits become excessive. There are large differences in the year-round average lipid deposits as a proportion of mature body weight that can be observed in animals in their natural environment. What can be considered normal for some species, such as seals and whales, would be considered excessive for most land mammals. Similarly, there are large differences in the capacity to deposit lipid reserves within a species, between strains, for example between diet-induced obese-resistant and obese-susceptible rats (Levine & Keesey, 1998). In livestock, changes in animal fatness as a result of selective breeding show that there is a genetic basis for these differences (Emmans & Kyriazakis, 2000; Knap & Jorgensen, 2000). The increase in obesity of humans has, however, been so rapid during the last few decades that this must be caused mainly by environmental, rather than genetic, change. In the present paper, we will, therefore, concentrate on the conditions that seem to have a large effect on the level of lipid deposits for a given animal.

It is surprisingly difficult to establish what is, for a given mature animal, a normal or an excessive level of fatness. Taylor (1985), for example, defined mature size for ruminant livestock as the live weight of a skeletally mature animal with a normal level of lipid deposits and arbitrarily assumed that this would be equal to around 20% of its empty body weight. It is, however, evident that most if not all mature ruminants with unlimited access to good-quality food would continue to deposit lipid beyond such a point. Lipid contents of more than 50% of empty body weight have frequently been recorded in ruminants (Searle *et al.* 1972; Blaxter *et al.*

1982; Ogink, 1993). This does not, however, answer the question of where the transition between normal and excessive lies for a given animal.

It is, however, evident that, for a given organism, a high EI resulting in extensive lipid deposits can be associated with negative consequences in terms of Darwinian fitness. Such negative fitness effects can be manifested, for example, in reproductive problems (e.g. calving difficulties in cattle; McClure, 1994) or in metabolic disorders (e.g. resulting from the fatty liver syndrome; Higgins & Anderson, 1983). Other fitness effects show in an increased incidence of tumours and lesions, and a reduced vitality and lifespan, as demonstrated in many studies with rodents (e.g. Berg & Simms, 1960, 1961; Masoro, 2000). Similarly, high levels of fatness as measured by the BMI in humans are associated with a range of negative consequences that can be considered to exert a negative impact on Darwinian fitness (Royal College of Physicians, 1983; Garrow, 1988). When lipid reserves have reached such levels that these clearly have a negative impact on fitness, these levels can properly be seen as excessive.

In humans, obesity is generally defined as an accretion of adipose tissue to an extent that it causes functional deficits or compromises health, well-being and quality of life. A crude measure of obesity is often the BMI: weight (kg) divided by the square of height (m).

*Excessive lipid deposits in rodents:* Mela & Rogers (1998) provided a typical example of excessive levels of lipid deposition in laboratory animals. Food intakes and body weights were measured in three groups of mature female rats. One group had access to a standard low-fat laboratory diet (.....), and these animals consumed about 170 kJ/d and gained about 50 g during a 60 d period (Fig. 2). Rats with access to the standard diet and at the same time to fat, bread, peanuts and chocolate (cafeteria feeding)(—) consumed about 275 kJ/d and gained about 150 g during the same period. About 75% of the additional weight gained in this group was estimated to consist of body fat so that about 95% of the additional energy retention was in the form of lipid. At the end of this period, EI had decreased and body weight appeared to stabilise around a new (higher) point. A third group (---), with access to the standard diet plus fat, consumed slightly less energy and gained slightly less weight compared with the group on cafeteria feeding (Fig. 2). After 60 d, all animals were given access to the standard diet only. The groups that had gained additional weight initially consumed less than was needed to maintain that weight and lost reserves. Their weight curve approached that of the control group within the observation period (Fig. 2).

As shown in Fig. 2(A), it is evident that animals responded with different EI to differences in the quality and/or variety (see later) of the food that was available. This strongly suggests that there must be food quality parameters with a large effect on EI and hence on EB. Fig. 2(A) also shows that EI gradually approaches EE with no further increases in weight. The equilibrium weight is strongly affected by the foods available. This suggests that, for a given food quality, there is an increasing effect of weight, or perhaps the level of lipid reserves, on the level of EI and hence on the amount of energy that is converted into body lipid. This effect is also well documented in humans (Forbes *et al.* 1982; Elia *et al.* 1999).

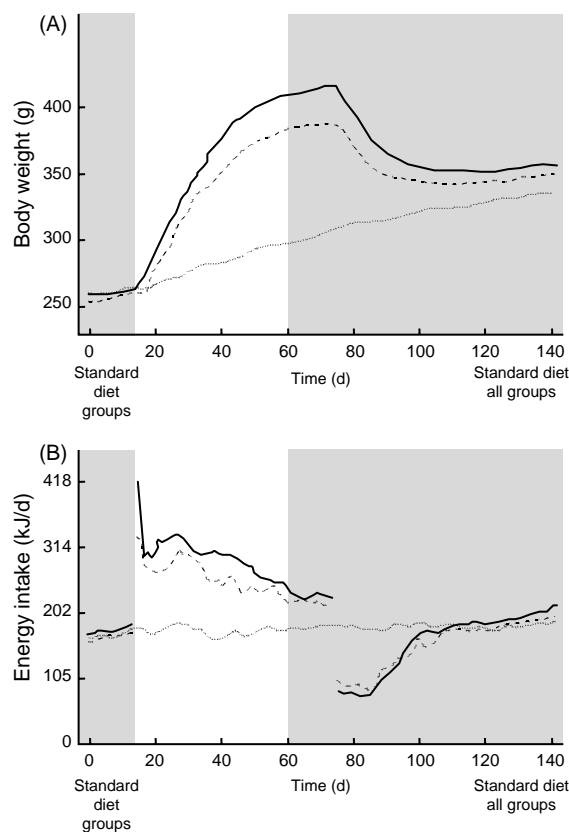
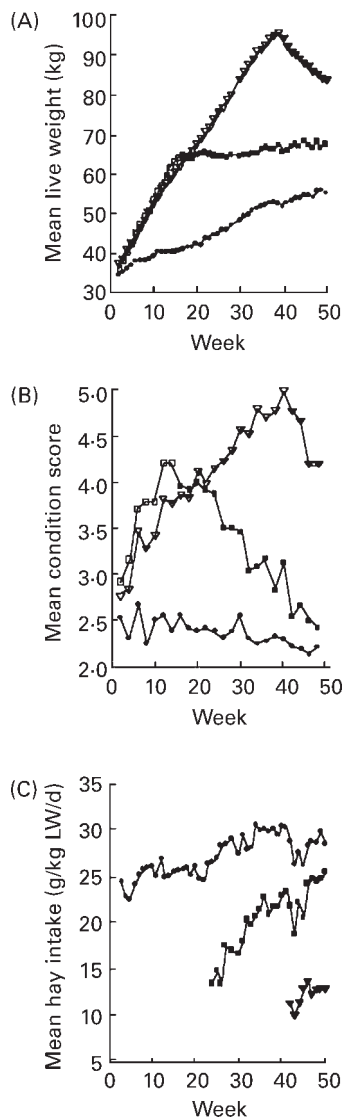


Fig. 2. Body weight and energy intake of adult female lister-hooded rats before, during and after being fed a cafeteria diet (—), high-fat diet, (---) and a control group fed a standard laboratory diet (.....) throughout (seven per group). Increased body fat content accounted for 75% of the excess weight gained during cafeteria feeding (adapted from Mela & Rogers, 1998).

Fig. 2(B) shows that weight, or perhaps the level of lipid reserves, has a considerable effect on EI and the resulting EB for animals with access to a given food. Apparently, the feedback from the high lipid stores in animals with previous access to high-quality foods caused animals to consume less than required for maintenance, which resulted in a mobilisation of body energy and hence weight loss (see later). For rodents, more examples of similar behaviour are available (Naim *et al.* 1985; Naim & Kare, 1991; Levine & Keesey, 1998). A similar phenomenon is apparent in humans when fed monotonous diets. This is a perennial problem for those concerned with the formulation of military operational rations (Baker-Fulco, 1995).

*Excessive lipid deposits in farm animals:* Similar behaviour has also been observed in farm animals, notably ruminants such as goats (BJ Tolcamp, unpublished results) and sheep. Ewes with access to the natural ruminant food of grass hay grew slowly to weights of between 50 and 60 kg during the experiment (Fig. 3). Another group of ewes received a good-quality pelleted food until they weighed around 60 kg and were then switched to the same grass hay diet. During the following 35-week experimental period, they consumed sufficient hay only to maintain this weight. A third group was given access to high-quality pelleted food and continued to grow fast until they reached a weight around 95 kg. They were then switched to the same grass hay that the animals in the first group had received throughout the experiment.



**Fig. 3.** Mean live weight (LW; A), condition score (B) and intake of hay per kg LW (C) of three groups of ewe lambs. Animals received grass hay from the start (●), from about 65 kg LW (■) or from about 95 kg LW (▼). The latter two groups received a pelleted high-concentrate diet (□, ▽) before they were switched to a grass hay diet (■, ▼).

The animals started losing weight quickly because they did not consume sufficient hay to maintain their weight. The graph suggests that the weights of ewes in all three groups gradually converged to around 70 kg, although the experimental period was too short to confirm this with certainty (Fig. 3). The first group had modest lipid reserves throughout the experiment. This was estimated from their condition scores, which were between 2 and 2.5 on a scoring system with a scale ranging from 1 (very thin) to 5 (excessively fat; Lowman *et al.* 1976). For reproducing animals, condition scores of between 2 and 2.5 are generally considered to be desirable (Lowman *et al.* 1976). In contrast, the third group continued to gain condition until the score reached the top of the scale (i.e. excessively fat) at weights around 95 kg. After switching to the grass hay diet, the condition scores of the very fat animals rapidly dropped, indicating a loss of lipid reserves.

Although the foods used in the experiments with ruminants differed considerably from those given to the rats depicted in Fig. 2, the behaviour of both species was very similar. Therefore, animals as different as rats and sheep are apparently prepared to deposit and defend larger or smaller lipid deposits depending on food quality. This suggests that, in ruminants as well, food quality parameters on the one hand, and level of lipid reserves on the other, interact to determine EI and, as a consequence, EB and the level of lipid reserves that is maintained in the long term. Therefore, the nature of the relevant food quality parameters that affect EI and EB merit a more detailed analysis.

### Relevant food quality parameters

Animal studies have suggested two mechanisms based on food quality parameters that may be related to a long-term positive EB, resulting in large lipid deposits. These relate to nutrient imbalances and to variation in the efficiency of energy utilisation. It should, however, be noted that, in the animal literature, various nutrient imbalances lead to a decrease in intake. The nutrient imbalances to which we refer here are imbalances in the protein:energy ratio of the diet in relation to that required for optimal growth and function.

### Nutrient imbalances

The first type of observation has led to the hypothesis of nutrient imbalance as an explanation for energy overconsumption. Although obesity is generally discussed in relation to EI, this hypothesis is based on the realisation that organisms do not live by energy alone. An adequate intake of energy has, of course, been shown to be an important motive for animal foraging behaviour (e.g. Collier & Johnson, 2000), but animals also rely on their food to supply them with amino acids and other essential nutrients. When animals are confronted with a food or foods in which the ratio of one or more nutrients to energy is lower than the ratio desired by the animal, energy overconsumption may result.

Table 1 shows the result of an experiment (Ferguson & Gous, 1997) in which pigs had access to single foods with different protein contents. On high-protein foods, animals typically grew protein at a high rate while they deposited relatively little lipid. However, as the protein content of the food dropped, daily EI, lipid retention and the ratio of lipid:protein in the gain all increased. Such data sets have been interpreted by animal scientists (e.g. Kyriazakis *et al.* 1991) as reflecting an attempt by the animal to consume sufficient protein to allow a potential rate of protein deposition to be attained. To obtain such an amount of protein, animals have to try to consume more food energy when the protein content drops. This results in intakes of excessive amounts of energy that are subsequently stored as lipid. In other words, animals have to try to consume more energy, and hence deposit more lipid, if they have access to an unbalanced food. Some studies show that animals that have been made fat in this way revert to a more normal body composition once they are given access to more than one food and are allowed to select their own diet (Kyriazakis & Emmans, 1991; Kyriazakis *et al.* 1991).

**Table 1.** Effects of varying protein concentration in the food on daily intake of metabolisable energy (ME), weight gain, deposition of protein and lipid and the ratio of lipid:protein retention in pigs. Animals were growing from 12 to 30 kg at an ambient temperature of 26°C (i.e. in the thermoneutral zone)

Crude protein (g/kg food)	Daily ME intake (MJ/d)	Daily weight gain (g/d)	Daily protein deposition (g/d)	Daily lipid deposition (g/d)	Lipid:protein deposition ratio (g/g)
230	15.4	720	118	78	0.66
201	15.7	722	116	94	0.81
178	17.8	716	114	122	1.07
151	20.3	724	105	158	1.50
125	20.3	670	94	164	1.75
93	19.4	573	64	193	3.00

Data from Ferguson & Gous (1997).

Data sets showing the effects of protein:energy ratio on food intake and the rate of lipid deposition are widely available for chicks and pigs (e.g. Burnham *et al.* 1992; Ferguson & Gous, 1997; Ferguson *et al.* 2000*a,b*). The same mechanism is perhaps also responsible for excessive lipid deposition when diets are fed that are imbalanced in terms of other nutrients, such as vitamin A (Ogunmodede, 1981). An evaluation of how general this phenomenon occurs is, however, hampered by several interpretational problems (Kyriazakis, 1994).

The nutrient imbalance hypothesis as a possible explanation for the occurrence of excessive lipid deposition is attractive for a number of reasons. First, it may provide a functional explanation for the observed behaviour. Growth as protein deposition is very relevant for the animal so it must be one of its main goals. A higher EI from protein-deficient foods will help the animal to achieve this goal, and the deposition of excess lipid is then a mere by-product of such behaviour. Second, it widens the scope from an emphasis on energy alone to the role of nutrients in an explicit and testable way. Finally, if the proposed mechanism plays an important role, it would offer possibilities to manipulate dietary composition to avoid excessive lipid deposition.

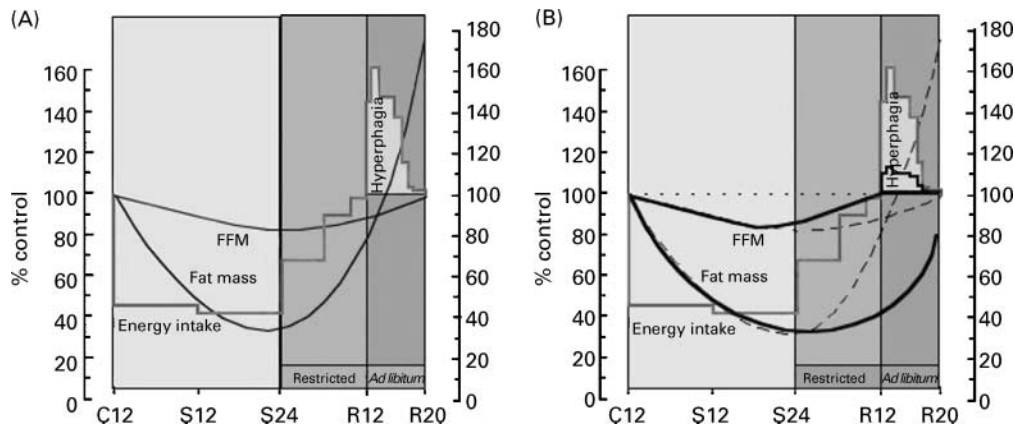
The evidence that nutrient imbalances (especially in the ratio of protein:energy) influence excessive lipid deposition in young, fast-growing animals is convincing. It is, however, questionable how generally this mechanism is involved in the deposition of excessive amounts of lipid in mature, non-reproducing animals. Requirements for nutrients in relation to energy are generally quite low in such animals. This does not imply that nutrient imbalances never result in excessive lipid deposition in mature organisms. However, we do not know of any animal studies in which the accumulation of large lipid reserves during maturity was prevented by the correction of a nutrient imbalance in an otherwise high-quality food. It seems certain that, for most mature individuals in developed societies, a possible imbalance is unlikely to be related to protein required *per se* since human diets that lead to obesity may be high in fat but are generally more than adequate in protein content.

It has been noted in surveys that high levels of soft drink consumption can displace both protein and micronutrients from the diet and are associated with a high EI (Gibson, 1997; Lee *et al.* 1998; Cavadini *et al.* 2000; Troiano *et al.* 2000; Ludwig *et al.* 2001). However, there is currently no clear evidence that the low intake of essential nutrients associated with high levels of soft drink intake actually drives an increase in EI in humans. The afore-mentioned

arguments may help to explain the apparent tendency for energy-rich soft drinks to promote overconsumption. They do not, however, explain the higher EI from sugar drinks *v.* solid sugar (DiMaggio & Mattes, 2000). In addition, there are many examples of nutrient imbalances that lead not to an increased intake but rather to lower weight gains or weight loss. Indeed, for most mineral and vitamin deficiencies in animal feed, the consequences for the animals are listed as anorexia and poor performance (e.g. Agricultural Research Council, 1980).

It is possible that nutrient imbalances may relate to the tendency to regain weight subsequent to therapeutic weight loss. One seminal study has enabled the relationship between tissue loss and subsequent feeding behaviour to be determined (Keys *et al.* 1950; Dulloo *et al.* 1996). The results were quite remarkable and have recently been revisited by Dulloo *et al.* (1996). During the Minnesota study, a group of lean men were chronically underfed for 24 weeks, consuming approximately 40% of their normal EI throughout this period. During this time, they lost in the region of 70% of their fat mass and 18–20% of their lean body mass. For the next 12 weeks, they were incrementally re-fed in a mandatory manner. By the end of this period, they were still in a deficit of approximately 25% for fat mass and 12–15% for lean body mass. During the final 8 weeks, subjects had access *ad libitum* to a range of foods. During this period, EI initially increased to 160% of requirements and gradually subsided to pre-weight loss levels. By this time, however, fat mass had reached 170% of pre-weight loss values, while lean body mass had returned to pre-weight loss levels (Keys *et al.* 1950). These relationships are depicted in Fig. 4. Thus, the cessation of post-weight loss hyperphagia coincided with a massive overshoot of fat mass and repletion of lean body mass. There are very few data sets of this quality available, which highlights the importance of conducting more detailed longitudinal studies with this degree of precision and accuracy.

During undernutrition, lean body mass becomes depleted (Pellet & Young, 1992; Elia *et al.* 1999). The Keys *et al.* (1950) data suggest that when food is available *ad libitum*, subjects do not stop eating when fat mass is replete but when lean body mass is replete. There is thus reason to hypothesise that the regulation of lean tissue (which helps to maintain normal physiological function), through oxidation of excess and repletion of deficits in protein intake, may exert some negative feedback effect on longer-term EI (see Stubbs & Elia, 2001). This hypothesis remains, however, to be tested.



**Fig. 4.** Relationship between energy intake, and tissue change during 6 months' severe undernutrition, 3 months' rehabilitation and 2 months' feeding *ad libitum* in twelve of the subjects who took part in the Minnesota study (A). Of particular note is the fact that *ad libitum* energy intake returned to pre-underfeeding levels at approximately the time lean tissue returned to baseline values. By this time, fat mass had overshoot baseline and reached approximately 170% of the original level. Based on a number of detailed considerations, Stubbs & Elia (2001) have suggested that, in previously undernourished subjects (e.g. after crash-dieting), a high-protein diet may lead to a more rapid repletion of lean tissue. If the repletion of lean tissue is also important in driving post-weight loss hyperphagia, the high-protein diet may lead to a stabilisation of body weight at a lower level of fat mass than if the subjects fed on a low-protein diet subsequent to their rapid weight loss. This hypothetical scenario is depicted in (B), and the hypothesis is currently under test. (Adapted from Dulloo *et al.* 1997.) FFM, free fat mass.

#### *Variation in the efficiency of energy utilisation: a role for oxidative metabolism?*

Metabolisable energy (ME) that is absorbed from the gut can be used for maintenance, growth, physical activity, deposition of lipid reserves, reproduction and other functions. Part of the consumed ME may be retained within the body (as protein and lipid) or in offspring, milk or eggs. All ME that is not retained is lost as heat, this heat resulting mainly from substrate oxidation. There are considerable differences in the efficiency with which ME is utilised between foods and in the contribution of different macronutrients to oxidative metabolism, especially in conditions of a positive EB. Before we return to this issue, however, the negative consequences of increased oxidative metabolism need to be addressed.

It is now generally accepted that oxidative metabolism causes oxidative damage as a result of the release of so-called reactive oxygen species or oxygen free radicals (Beckman & Ames, 1998; Miquel, 1998; Ashok & Ali, 1999; Finkel & Holbrook, 2000). Reactive oxygen species are thought to damage essential cell structures such as mitochondria, nuclear DNA and cell membranes. Such damage can lead to the occurrence of lesions and tumours, and is implicated in numerous diseases (Miquel, 2001; Wilson *et al.* 2001; Droge, 2002; Hensley & Floyd, 2002; Moskovitz *et al.* 2002). In addition, damage caused by reactive oxygen species is thought to accumulate and result in a gradual loss of vitality, ageing, senescence and, ultimately, death (Beckman & Ames, 1998; Miquel, 1998, 2001; Ashok & Ali, 1999; Finkel & Holbrook, 2000). It should be emphasised that many of these effects occur long before senescence, i.e. during the reproductive stage in the life history (e.g. Berg & Simms, 1961; Orr & Sohal, 1994). An increase in oxidative metabolism can thus be considered as a cost associated with food consumption. Studies with animals as well as with human subjects suggest that the relative contribution of foods or of specific macronutrients to oxidative metabolism may affect satiety and voluntary EI.

*Energetic efficiency and food intake in ruminant animals: a cost-benefit analysis.* Because of its economic importance, the efficiency with which farm animals convert food energy into animal product has been extensively studied (e.g. Agricultural Research Council, 1980; Blaxter, 1989; National Research Council, 2000, 2001). For example, ruminants may convert ME obtained with their food into retained energy (as lipid and protein in the body) with efficiencies ranging from less than 20% for poor-quality foods to more than 50% for good-quality foods (Agricultural Research Council, 1980; Blaxter, 1989; National Research Council, 2000). This means that, in order to gain 20 kJ net energy, an animal would have to consume only 40 kJ ME from a good-quality food but 100 kJ ME from a poor-quality food. These amounts of food energy will then add 20 and 80 kJ, respectively, to the heat production of the animal via oxidative metabolism. Under conditions of heat stress, higher levels of animal production can be achieved with good-quality than with poor-quality foods because of the higher heat loads associated with the latter foods (e.g. West, 1999). There are, however, also large differences in intake level between animals that are offered high- or low-quality foods in a thermoneutral environment. Indeed, it may be calculated that the observed levels of heat production under such conditions are frequently higher for animals receiving high-quality food than for animals receiving low-quality food (Agricultural Research Council, 1980). This means that the observed variation in ME intake under such conditions cannot be attributed to a constraint associated with heat loss. Nevertheless, voluntary intake levels of a wide range of typical ruminant foods are strongly correlated with how efficiently animals can convert the consumed ME into net energy (Tolkamp & Ketelaars, 1992; Weston, 1996).

Tolkamp & Ketelaars (1992) proposed a hypothesis of food intake control based on the efficiency of oxygen utilisation. The hypothesis assumes that there are both benefits and costs associated with an increase in ME intake. The benefits associated with an increased intake of a given food are



obvious and generally acknowledged (e.g. Stephens & Krebs, 1986). In a non-reproducing animal, it may prevent the mobilisation of body reserves and even add to these reserves. In a reproducing animal, it may result in more offspring or increase the growth rate and the chances of survival of the offspring. It is, however, not very common to ascribe direct costs to an increase in intake of a given food. Tolkamp & Ketelaars (1992), however, drew attention to the large differences between food qualities in their contribution to oxidative metabolism. Higher levels of oxygen consumption as a result of higher food intake would then result in earlier loss of vitality and a reduced lifespan (e.g. Sohal & Weindruch, 1996; Finkel & Holbrook, 2000; Masoro, 2000; Ramsey *et al.* 2000). This would mean that the benefits of the consumption of 20 kJ net energy in the example mentioned earlier would be associated with costs in terms of oxygen consumption equivalent to 80 kJ for a poor-quality, and only 20 kJ for an excellent-quality, food. The hypothesis assumes that animals will be prepared to consume more benefits (net energy) when the costs (in terms of oxygen consumption) are low, for example as a result of increased food quality. A quantitative model was developed that assumed that mature non-reproducing animals would try to maximise the amount of benefit (i.e. the net energy consumed) per unit of incurred costs (i.e. oxygen consumed). The hypothesis has been tested against available data obtained with mature non-reproducing sheep, and the predictions of the hypothesis match the observations well (Tolkamp & Ketelaars, 1992; Ketelaars & Tolkamp, 1996).

The proposed model is based on a curvilinear relationship between the intake of ME and the yield of net energy as it is assumed in current feed evaluation systems (e.g. Agricultural and Food Research Council, 1993). This assumption has, however, been disputed (Emmans & Kyriazakis, 1995). In addition, the evidence for the view that efficiency of energy utilisation declines when animals approach their plateau weight was not strong (Tolkamp & Ketelaars, 1992; Emmans & Kyriazakis, 1995; Ketelaars & Tolkamp, 1996; see also later). Finally, the model needs to be tested with other classes of livestock, such as young and growing or lactating animals (National Research Council, 2001). This is not straightforward because the costs and benefits of feeding are more difficult to define for such animals, as will be discussed later.

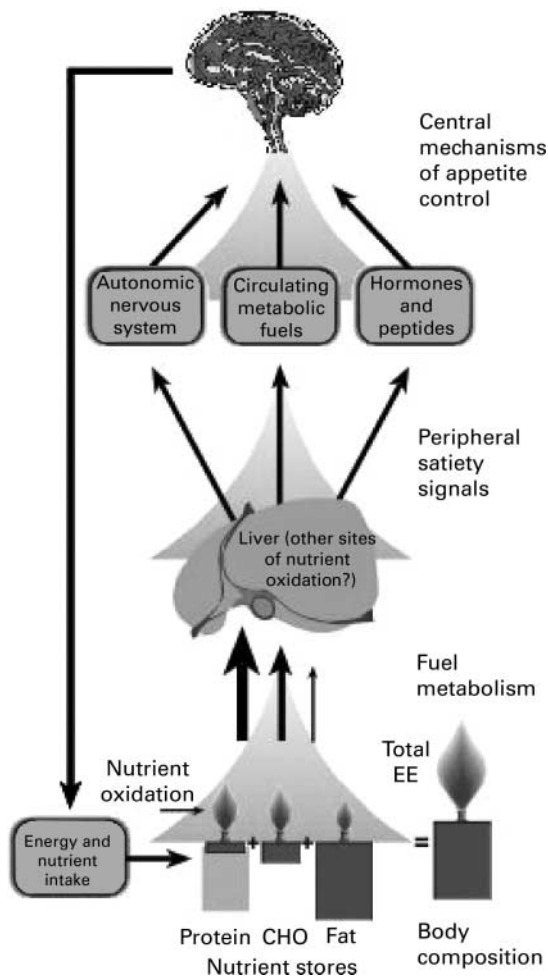
*Energetic efficiency and food intake in monogastric animals.* In mature monogastrics, the energetic efficiency with which fats, carbohydrates and proteins are converted into body reserves (mainly lipid) decreases in that order (Stubbs, 1995, 1998). The effects of these macronutrient groups on EI decrease in the same order (Stubbs, 1995, 1998). Differential effects of energy-yielding nutrients on satiety and EI can also be correlated with a variation in energetic efficiency within these broad macronutrient groups. For example, several studies show the effects of different types of fat. Fat structure varies in terms of: (1) chain length; (2) degree of saturation; (3) degree of esterification; (4), by combining (1), (2) and (3), through the development of novel structured lipids.

Data are scarce and fragmentary in this area, but some provisional patterns are beginning to emerge. The substitution of long-chain triacylglycerol with medium-chain triacylglycerol limits the high levels of EI that usually occur when animals or humans ingest high-fat, energy-dense diets (Stubbs &

Harbron, 1996). However, very large doses of medium-chain triacylglycerol are required in order to achieve these effects. Medium-chain triacylglycerol may suppress appetite relative to long-chain triacylglycerol as they are more readily absorbed and oxidised. There is considerable evidence that SCFA inhibit appetite in monogastrics. In particular, the large negative effect on the voluntary EI of birds after the incorporation of SCFA (which are utilised with a low efficiency in birds; Hume *et al.* 1993) is remarkable (e.g. Pinchasov & Jensen, 1989; Pinchasov & Elmaliyah, 1995; Savory *et al.* 1996; Savory & Lariviere, 2000). There are, therefore, frequent observations of correlations between the energetic efficiency of nutrient utilisation and satiety in monogastric animals.

*Energetic efficiency and food intake in humans.* Interestingly, studies in human subjects also suggest an effect of macronutrient composition on satiety and voluntary EI (e.g. Stubbs & O'Reilly, 2000). Fig. 5 shows that the contribution of the major macronutrients protein, carbohydrate and fat to oxidative metabolism decreases in that order. When combining the data on the effects of macronutrients on satiety, it is apparent that the hierarchy in the satiating efficiency of the macronutrients protein, carbohydrate and fat is present at several levels of feedback (Stubbs, 1998). It is apparent when macronutrients are ingested in the diet and also when macronutrients are infused parenterally. The latter means of delivery indicates a post-absorptive effect. Other work has examined the relationship between changes in nutrient balance and *ad libitum* feeding behaviour in subjects resident in a whole-body calorimeter for 7 consecutive days. Increases in protein balance on 1d predicted a lower EI than did increases in carbohydrate balance. Increases in fat balance exerted no apparent negative feedback on subsequent intake (Stubbs *et al.* 1995a,b). Further analysis has suggested that it is the tendency to regulate nutrient balance by oxidative disposal (see earlier) that underlies this hierarchy in the satiating efficiency of the dietary macronutrients. The constraints under which nutrient balance is regulated determines which fuels are oxidised and which are stored. Nutrients whose balance is tightly regulated by obligatory oxidative disposal appear to be more satiating in the fed state than those least readily oxidised and preferentially stored (Stubbs, 1998).

As with animals (see earlier), the differential effects of energy yielding nutrients on satiety and EI can also be correlated with a variation in energetic efficiency within these broad macronutrient groups. There is some preliminary evidence that ketone bodies (specifically  $\beta$ -hydroxybutyrate) are appetite suppressants when given orally (Rich *et al.* 1988), and this may enhance compliance when subjects attempt to lose weight using very low-energy diets. There is currently little evidence that the degree of fatty acid esterification influences appetite and EI (Johnstone *et al.* 1998a,b). It has been suggested that PUFA are protective against obesity since they are more readily mobilised and oxidised, and may influence the gene expression of appetite-controlling peptides (Storlien *et al.* 2001). Recent work in human subjects suggests that saturated fats are less satiating than mono- or polyunsaturates (French *et al.* 2000; Phinney *et al.* 1998). An intriguing study in human subjects has recently reported that supplementation with very high levels of  $\gamma$ -linolenate (at 5 g/d compared with 5 g/d olive oil) significantly reduced weight gain over 12 months after extensive weight reduction



**Fig. 5.** Schematic diagram illustrating the putative connection between dietary composition, fuel metabolism, peripheral satiety signals and central control of feeding. Dietary composition affects satiety. Protein is more satiating than carbohydrate (CHO) which is more satiating than fat. Diet composition also affects post-ingestive fuel metabolism since increases in protein and carbohydrate, but not fat, balance are tightly modulated by autoregulatory increases in their oxidative disposal. It is known that nutrient oxidation in the peripheral tissues appears to be associated with satiety. The hierarchical regulation of macronutrient balance by oxidative disposal may partially underlie the hierarchy in the satiating efficiency of the macronutrients. Indeed, high levels of protein and carbohydrate (but not fat) oxidation are indicative of the fed state. High rates of fat oxidation are usually synonymous with energy deficits. It has also been suggested that changes in the peripheral fuel metabolism may act as and trigger additional peripheral satiety signals, which are relayed to feeding centres of the brain believed to be concerned with the control of macronutrient balance. EE, energy expenditure.

using very low-energy diets (Phinney *et al.* 2000). Thus, the types of fat that are most readily metabolised (inefficiently retained) appear to be more satiating than those that are more readily stored (efficiently retained). These observations in human subjects are, therefore, consistent with the hypothesis that satiety and EI are linked to the way in which energy is partitioned between EE and energy retention.

On the basis of the afore-mentioned evidence, Friedman (1991, 1995, 1997, 1998) and others (Langhans & Scharrer, 1992) have suggested that a link exists between oxidative metabolism in the fed state, short-term satiety and longer-term EI. The mechanism is likely to be common to humans and animals. The logic is as follows. As regards dietary

composition, nutrient processing and peripheral signals related to feeding, there is now sufficient evidence to provisionally link changes in dietary composition to changes in the signalling systems concerned with the control of macronutrient balance. This notion is schematically illustrated in Fig. 5 and summarised as follows:

1. Changes in energy and nutrient intake can influence peripheral fuel selection (Acheson *et al.* 1982, 1988; Flatt, 1987; Abbot *et al.* 1988; Hellerstein *et al.* 1991; Jequier, 1992; Stubbs, 1998).
2. Peripheral changes in fuel selection are determined by a hierarchy in the immediacy with which the balance of recently ingested macronutrients is autoregulated by increases in their own oxidative disposal (protein > carbohydrate > fat; Flatt, 1987; Jequier, 1992; Pellet & Young, 1992; Elia *et al.* 1999).
3. This hierarchy appears to parallel a hierarchy in the satiating efficiency of the macronutrients (Stubbs, 1998). Thus, while the ingestion of each of protein, carbohydrate and fat contributes to satiety, it does so to differing degrees.
4. These two hierarchies may be causatively 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 (Friedman *et al.* 1991, 1995, 1997, 1998; Langhans & Scharrer, 1992; Ritter & Calingasan, 1994). In particular, Ritter & Calingasan (1994) have provided important evidence suggesting that neural pathways monitor fat oxidation in the periphery and carbohydrate oxidation (perhaps more precisely) in both the periphery and the central nervous system. Less is currently known about protein oxidation, except that at the level of nutrient metabolism, protein is the most satiating macronutrient (Stubbs, 1999).
5. Langhans & Scharrer (1992) note that the midbrain centres that are concerned with monitoring peripheral fuel utilisation are connected via extensive neural relays to certain areas of the forebrain. These areas (the hypothalamus and especially the paraventricular nucleus) are the sites of action of peptide systems concerned with the control of protein, carbohydrate and fat balance (Langhans & Scharrer, 1992).

An integrative model is thus beginning to emerge that may account for the manner in which the central nervous system is capable of monitoring physiological signals concerned with overall macronutrient intake and fuel flux (Friedman *et al.* 1991, 1995, 1997, 1998; Langhans & Scharrer, 1992; Ritter & Calingasan, 1994; Stubbs, 1999). This model accounts for the manner in which feeding behaviour responds to changes in peripheral physiology. The central nervous system appears to be capable of monitoring overall fuel flux rather than responding to negative feedback from any single nutrient. In essence, feeding responses are coupled to physiological changes rather than being directly determined by them. Such a flexible and adaptive system for the control of feeding behaviour is likely to have bestowed a far greater survival advantage on an opportunistic foraging species such as humans (or, for that matter, rodents) than a system in which behaviour is an inevitable outcome of rigid physiological signals.

*Is diet-induced thermogenesis a major source of interindividual variation in the efficiency of energy utilisation?* We have not used the term 'diet-induced thermogenesis' to a great extent in the present paper, although we mentioned the term 'heat increment of feeding'. In our view, diet-induced thermogenesis corresponds to heat increment of feeding and to what we have discussed in terms of an increase in oxidative metabolism in relation to food intake.

Stock (1999) published a classic paper in which he argued that the scope for energy-dissipating mechanisms in animals and humans has been overlooked. Based on estimates of the energy cost of weight gain in various overfeeding studies, Stock concluded that there is far greater scope for interindividual differences in energy-dissipating mechanisms than had previously been appreciated. We do not believe that, in humans, the magnitude of interindividual differences in diet-induced thermogenesis, as mediated by energy-dissipating mechanisms, is as great as suggested by Stock. This is not the place for a detailed critique of his classic paper; sufficient to say that, in the human studies, diet-induced thermogenesis was estimated as the energy cost of weight gain above a theoretical maximum energy cost of 45 MJ/kg, assuming that all of the weight gain were fat, deposited by *de novo* lipogenesis. However, in most of the human studies concerned, overfeeding was defined (by the investigators) as an EI in excess of estimated requirements. The estimate of energy requirements is usually made as a standardised multiple of BMR (e.g.  $1.6 \times \text{BMR}$ ), not accounting for interindividual differences in baseline physical activity. Thus, if subject A has an energy requirement of  $1.6 \times \text{BMR}$  and is overfed by 50%, he will receive  $1.6 + 0.8 = 2.4 \times \text{BMR}$ . If subject B has an energy requirement of  $2.2 \times \text{BMR}$ , he will also receive  $2.4 \times \text{BMR}$  but only be overfed by approximately 10%. In Stock's estimates, any difference in activity translates into an estimate of diet-induced thermogenesis. This is not a failing on Stock's part but a general failure of most human overfeeding studies actually to characterise the habitual energy requirements of subjects. These studies assume that all subjects have a similar sedentary EE when expressed as a multiple of BMR.

Some more careful studies, such as the work of Leibel *et al.* (1995), have characterised in exhaustive detail the energy costs associated with over- and underfeeding by 10–20% of original body weight. They examined the effects of altering body weight on EE and its components (resting and non-resting EE, and the thermic effect of feeding) in eighteen obese and twenty-three never-obese subjects. The subjects were studied at their usual body weight after losing 10–20% or gaining 10% usual body weight by underfeeding or overfeeding, respectively. Maintenance of a body weight at a level 10% or more below the usual body weight was associated with a mean reduction in total EE of 25 (SD 12.6) kJ/kg fat-free mass per d in the subjects who had never been obese ( $P < 0.001$ ) and 34 (SD 21) kJ/kg fat-free mass per d in the obese subjects ( $P < 0.001$ ). This is equivalent to approximately 1.25 MJ/d and 2.4 MJ/d, assuming a fat-free mass of 50 and 70 kg in the lean and obese subjects, respectively. Resting EE and non-resting EE each decreased 13–17 kJ/kg fat-free mass per d in both groups of subjects (in the region of 0.65 and 1.2 MJ/d). Maintenance of body weight at a level 10% above the usual weight was associated with an increase in total EE of 38 (SD 29) kJ/kg fat-free mass per d (around

1.9 MJ/d) in the subjects who had never been obese ( $P < 0.001$ ) and 33.6 (SD 17) kJ/kg fat-free mass per d (around 2.4 MJ/d) in the obese subjects ( $P < 0.001$ ). The thermic effect of feeding and non-resting EE increased by approximately 4–8 and 34–38 kJ/kg fat-free mass per d, respectively, after weight gain. The greatest change in EE clearly occurred through non-resting EE. The authors concluded that the 'maintenance of a reduced or elevated body weight is associated with compensatory changes in EE, which oppose the maintenance of a body weight that is different from the usual weight'.

We have also scrutinised a good deal of the rodent literature concerning susceptibility and resistance to obesity in rodent models. There are several forms of this. Studies are characterised by their tendency to infer rather than directly measure diet-induced thermogenesis. Thus, activity of uncoupling protein, energy cost of weight gain, various enzymes and metabolites are measured, but very few studies actually measure what James (1992) has called the one unambiguously measurable outcome – an increased heat output from the body. It is thus more difficult than we initially imagined to directly quantify diet-induced thermogenesis relative to other components of EE (shivering, physical activity, non-exercise activity thermogenesis, BMR, total daily EE) in these experiments. These measures have been made but often in different studies. Few studies have simultaneously and independently measured all of these components of EE. It is, therefore, extremely difficult to make quantitative statements about diet-induced thermogenesis in a way that allows a clear comparison between animals and humans. The purpose of the present paper is to look for common ground. We have found the least common ground between humans and rodent or farm animals in the area of adaptive diet-induced thermogenesis.

*Oxidative metabolism and equilibrium lipid reserves.* We reviewed evidence obtained with animals and human subjects, which suggests that the efficiency with which the energy of the (macronutrients in) food is utilised affects EI and EB. High-quality foods appear to result in a higher EI and EB than poor-quality foods. Figs. 2 and 3 suggest that a feedback mechanism must exist between the internal levels of lipid reserves and EI relative to EE. This is shown by the gradual decrease in energy retention when animals approach the asymptotic weight that is typical for a given food type in Fig. 2. The same is suggested by the immediate loss of weight that occurred when fat animals were switched from a high- to a medium-quality food, as shown in both Figs. 2 and 3. Tolkamp & Ketelaars (1992) speculated that a decrease in EI relative to the maintenance requirements of animals that approach their equilibrium weight could be related to a gradual decrease in energetic efficiency. At the time, there was little evidence for such a claim, and no relevant mechanisms were known (Tolkamp & Ketelaars, 1992; Emmans & Kyriazakis, 1995; Ketelaars & Tolkamp, 1996).

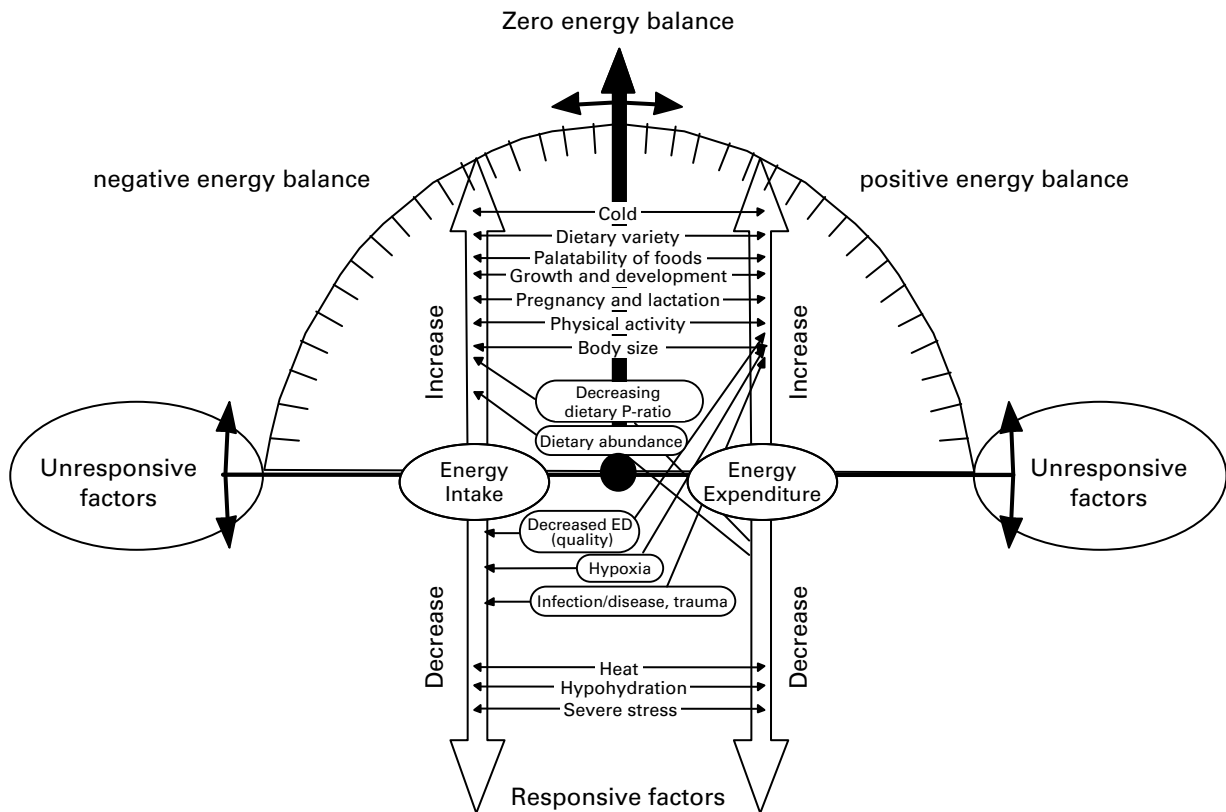
Considerable advances have, however, recently been made in identifying the mechanisms that could provide such a feedback between lipid reserves and voluntary EE and EB. In particular, the hormone leptin, which is produced by adipocytes (Reidy & Weber, 2000; Hynes & Jones, 2001), deserves attention in this respect. Plasma leptin levels affect many physiological processes (Hwa *et al.* 1997; Weigle, 1997; Lord *et al.* 1998; Woodside *et al.* 1998; Chilliard *et al.* 1999; Considine,

1999; Trayhurn *et al.* 1999; Reidy & Weber, 2000; Brann *et al.* 2002; Smith *et al.* 2002). In the context of the present paper, the effects of leptin on voluntary EI and oxidative metabolism seem especially relevant.

It is well documented that increased leptin levels increase oxidative metabolism (Friedman & Halaas, 1998; Houseknecht *et al.* 1998; Considine, 1999; Trayhurn *et al.* 1999; Wang *et al.* 1999; Hynes & Jones, 2001; Shimokawa & Higami, 2001) and oxidative stress (Bouloumie *et al.* 1999; Garcia *et al.* 1999; Yamagishi *et al.* 2001). At the same time, it has a negative impact on energy retention and lipid reserves (Houseknecht *et al.* 1998; Wang *et al.* 1999; Reidy & Weber, 2000). Some of the physiological effects of an increase in leptin concentration can be completely abolished when the effect of leptin on oxidative metabolism is blocked (Schneider *et al.* 1998; Schneider & Zhou, 1999). It has been suggested that part of the physiological effect of leptin is mediated via its effect on oxidative metabolism (Schneider *et al.* 1998). There is evidence that peripheral oxidative metabolism is monitored (e.g. Langhans & Scharrer, 1992; Horn *et al.* 1999) and that reactive oxygen species have a direct signalling role in the process (Finkel & Holbrook, 2000). Note that leptin is (by its absence) also a powerful signal for energy depletion (see Schwartz *et al.* 2000).

These findings offer a possible mechanism for the theoretically difficult observation that animals do not continue to deposit lipid but attain an equilibrium weight that depends on food quality (Figs. 2 and 3). When animals are offered a

food that is converted very efficiently into body reserves, animals deposit considerable amounts of lipid. As the lipid reserves increase, the leptin signal becomes increasingly stronger and has a negative effect on energetic efficiency. The gradual decrease in energetic efficiency causes a gradual decrease in EI in relation to EE, to the point at which these are equal. The animal then stops depositing lipid. In contrast, consider a lean animal offered a food that is converted into body reserves with a low energetic efficiency. Such an animal will have an EI that allows much lower daily gains of lipid. Nevertheless, in this animal as well, an increase in lipid reserves causes an increase in circulating leptin levels, which depresses energetic efficiency even further. In such an animal, energetic efficiency reaches a point at which EI equals EE at much lower leptin signals, that is, lipid reserves. Finally, consider an animal that has received high-quality food for a long time and is very fat when it is switched to a lower-quality food. In such an animal, the high leptin levels depress the energetic efficiency with which the animal can utilise the low-quality food to such an extent that optimum EI is lower than EE. As a result, animals are not prepared to eat enough to defend their fat reserves (Figs. 2 and 3) and start mobilising lipid. As these reserves are gradually depleted, the strength of the leptin signal decreases and the energetic efficiency with which the animal utilises its food gradually increases. This continues up to the point at which EI is equal to EE and the animal reaches an equilibrium weight that is specific for that food quality.



**Fig. 6.** Schematic diagram indicating the impact of a range of common environmental influences on energy intake, energy expenditure and energy balance in animals and man. It can be seen that some factors increase both intake and expenditure, whereas some decrease both. Other factors have opposite effects on intake and expenditure. The balance between these influences will determine the overall energy balance.

The data depicted in Figs. 2 and 3 are consistent with such a mechanism. If this is the case, the cues that animals receive from the food (i.e. how much it contributes to oxidative metabolism) could well be integrated directly with the cue it receives from its lipid reserves via the effect of leptin on oxidative metabolism. Fig. 6 is a schematic diagram indicating the impact of a range of common environmental influences on EI, EE or EB in animals and man. It can be seen that some factors increase both intake and expenditure, and some decrease both. Other factors have opposite effects on intake and expenditure. The balance between these influences will determine the overall EB for a given individual in a specific environment.

### Effects of energy expenditure as a result of physical activity on energy intake and energy balance

We have drawn attention to various studies with farm and laboratory animals and with human subjects that suggest a link between voluntary EI with food and the contribution of that food to oxidative metabolism (i.e. EE). In these studies with rodents, with farm animals under controlled conditions and with human subjects, access to food was continuous and easy. No effort, apart from that associated with ingestion, digestion and metabolising food energy, was required to obtain net energy and nutrients from the food sources.

This contrasts sharply with the conditions under which animals and humans obtained food during their evolutionary history. Just how much physical effort must have been required before animals (and humans) obtained access to food in the evolutionary past can be observed from the foraging behaviour of animals living in the wild today. Predators chasing prey and animals travelling between patches that supply food frequently expend considerable energy in the process. It is evident that such physical effort to obtain food decreases the proportion of food ME that is available as net energy and will increase the proportion of ME that is respired. If oxidative metabolism is a cost to the animal, it may be expected that the amount of physical effort that animals have to make to obtain a given quantity of ME will also affect their level of voluntary EI. We will, therefore, very briefly draw attention to studies in ecology, with laboratory animals and with human subjects that may shed some light on the effects of EE on EI and EB.

#### *Animals in the wild*

Several studies of the foraging behaviour of animals in the wild have shown behaviour that is consistent with an efficiency-maximisation hypothesis (e.g. Montgomerie *et al.* 1984; Schmid-Hempel *et al.* 1985; McLaughlin & Montgomerie, 1990; Welham & Ydenberg, 1993; Rasheed & Harder, 1997; Biesmeijer & Toth, 1998). In these studies, animals behaved as if they were attempting to maximise the benefits obtained (energy or protein or food) per unit of energy expended (i.e. substrate oxidised) through physical and physiological activities associated with the foraging process (Tolkamp *et al.* 2002). This is essentially the same efficiency-maximisation model as that proposed for sheep by Tolkamp & Ketelaars (1992).

Maximisation of efficiency in feeding behaviour is as yet poorly understood in ecology (e.g. Ydenberg *et al.* 1994) because such behaviour only makes sense if resources are

allocated from a limited budget (as discussed by Stephens & Krebs, 1986). However, energy availability in these studies was not restricted, that is, there was no limited energy budget. Several studies show, however, that a higher intensity of foraging (i.e. a higher level of EE per d) reduces foraging lifespan (Schmid-Hempel *et al.* 1986; Rasheed & Harder, 1997; Biesmeijer & Toth, 1998). This could well be related to the negative effects of reactive oxygen species on vitality and lifespan. The limited budget then does not relate to the available energy but to the limited capacity of the organism to metabolise (i.e. oxidise) energy. The same model could then apply to the foraging animals observed in the studies mentioned earlier in which oxygen consumption appears as a cost of food intake (Tolkamp *et al.* 2002). This cost may be caused by either inefficiency in the utilisation of the ME that is obtained with food (sometimes referred to as heat increment of feeding or diet-induced thermogenesis) or by the physical activity undertaken during searching for and obtaining food (as discussed by Tolkamp *et al.* 2002).

#### *Animals under controlled conditions*

In most studies of animals in the laboratory, there is free access to food. For the purpose of the present review, studies of the effects of varying levels of required effort to obtain food on voluntary EI are of special interest. Collier & Johnson (1997) measured the food intake of rats that had to work harder (pushing levers) on some days than on others. This variation in required effort had a marked effect on daily intake, the lowest intakes being recorded during days with the highest required effort.

The same authors studied the effects of varying amount of effort required on the food intake and dietary composition of rats with access to a normal laboratory chow and sucrose solution (Collier & Johnson, 2000). It is well known that rodents in such situations frequently consume considerable amounts of carbohydrate solution and increase their daily EI. A common explanation for such observations relates to the palatability or taste of the carbohydrate solution (Collier & Johnson, 2000). However, when the amount of effort that rats had to do to obtain access to either the chow or the carbohydrate solution was varied, rat feeding behaviour changed in a predictable way. The authors observed that, for these rats, the effort to obtain food had a substantial effect on their feeding behaviour. When minimal effort was required, overconsumption was likely. They concluded that the efficiency with which energy was obtained appeared to be more important than dietary composition, and they ranked the taste of the foods as the factor that affected feeding behaviour least (Collier & Johnson, 2000). This work is important because it suggests that the effort required to obtain food has a profound effect on feeding behaviour. This is especially pertinent to the modern consumer who regularly forages in supermarkets where literally thousands of products are available with minimal foraging effort.

#### *Human subjects*

The results of studies that investigate the effects of physical activity (often exercise) in human subjects on EI and EB are very diverse and not always easy to interpret (King, 1998).

The commonly held belief that, in humans, exercise causes a compensation in EI to match the exercise-induced expenditure is, certainly in the short term, not supported by the results of most studies. King *et al.*'s review (1997) of the effects of exercise regimes on EI shows that, of short-to-medium-term intervention studies (often no longer than 2–5 d), 19% report an increase in EI after exercise, 65% show no change and 16% show a decrease. It is evident that high levels of physical activity cannot be continued for very long periods of time unless compensation does occur at some point (King, 1998). Studies of the effects of long-term exercise on EI and EB have shown that individuals with high exercise levels can sustain negative EB (between 2 and 7 MJ/d) for periods of up to around 50 d (Stroud *et al.* 1993; Milon *et al.* 1996). Longer-term studies that measure body composition suggest that some fat mass is lost but that lean body mass tends to be preserved in response to exercise regimens, depending on the absolute level of EB (Ballor & Poehlman, 1994; Sum *et al.* 1994). Even when, at some stage, such individuals on high levels of exercise again match EI with EE, it seems likely that this will occur at a reduced level of lipid deposits. This suggests that humans and animals alike are not prepared to defend large lipid reserves at high levels of physical activity.

Other studies have, however, suggested that there is an interaction between food quality and whether or not exercise results in a decrease in EB. Stubbs *et al.* (1995*a,b*), for example, found that when identical diets were provided *ad libitum* to individuals who were forced into low activity levels, they consumed a similar level of energy to individuals with higher activity levels in a free-living situation. However, individuals who reward themselves after exercise by selecting foods that are more energy dense (especially higher in fat content) can completely reverse a negative EB created by exercise (Tremblay *et al.* 1994; King & Blundell, 1995; King *et al.* 1996). And life is actually even more complex than this!

One study has given us an initial, albeit imperfect, assessment of the rate and extent of compensation of EI and EE in response to perturbations of EB due to altered diet and exercise (Stubbs *et al.* 2004). The study examined the effect of no exercise (control) and a high exercise level (approximately 4 MJ/d), as well as two dietary manipulations – high fat (50% energy, 700 kJ/100 g) and low fat (20% energy, 300 kJ/100 g) – on compensatory changes in EI and EE over 7 d periods. Nine lean men were each studied four times, in a 2 × 2 design. EI was directly quantified by weight of food consumed. EE was assessed by heart rate monitoring, and body weight was measured daily. Mean daily EE was 17.6 and 11.5 MJ/d ( $P < 0.001$ ) on the pooled high-exercise and no-exercise treatments, respectively.

EI was higher on the high-fat diets (13.4 MJ/d pooled) compared with the low-fat diets (9.0 MJ/d). Regression analysis showed that these energy imbalances induced significant compensatory changes in EB over time of around 0.3–0.4 MJ/d ( $P < 0.05$ ). Compensation was due to changes in both EI and EE in the direction opposite to the perturbation in EB. These changes were significant, small but persistent, amounting to approximately 0.2 and 0.35 MJ/d for EI and EE, respectively. It is of special note that subjects, while feeding on the low-fat diet, which had a low energy density (low food quality), appeared to balance the stress of consuming far greater amounts of this food against the stress of exercise. They

thus maintained a marked negative EB on the low-fat diet, high-exercise treatment. This is presumably because the cost of attempting to double food intake (using a diet of fixed composition and energy density) while undergoing a strenuous exercise regimen would have exceeded the cost of mobilising lipid reserves.

Although these estimates may be provisional and imperfect, they do suggest that: (1) cross-talk between changes in EI and EE does exist; (2) this cross-talk is stronger in relation to energy deficits than surfeits; (3) it takes weeks for significant compensatory changes in EB to occur in relation to a sustained perturbation of EB; (4) the human subjects in this experiment appeared to eat to a level determined by a balance of costs. Here the costs were those of mandatory exercise *v.* the cost of doubling food intake to achieve EB. In real life, several of these influences are likely to be superimposed on each other, making the determinants of both EI and EE multifactorial. Interactions between the two will be similarly complex in both their nature and their overall impact on EB.

Observations such as discussed earlier suggest the following picture. Animals and humans with an increase in EE as a result of physical activity do not completely compensate the expenditure by an increase in EI when they have access to the same food, and as a result they maintain a weight with lower fat stores. However, if following exercise (with its stimulating effect on EE) foods (e.g. high-fat, energy-dense foods) are selected that can mitigate the lower efficiency as a result of exercise, then lipid stores are defended. This suggests that a decrease in energetic efficiency associated with exercise can be abolished by increases in the (post-ingestive) efficiency of energy utilisation. If this is the case, this also points to an effect of EE *per se* on food intake and EB.

## General discussion

Under natural conditions, there will generally be variation in the quantity and quality of foods available, and there will be variation in the effort that is required to obtain foods. For many species, such variation is associated with periods of positive EB when high-quality foods can be obtained for relatively little effort. These periods are alternated with periods during which high-quality food is scarce or considerable effort is required to obtain it, and body reserves are mobilised. Deposition of lipid reserves can then be considered to be part of a longer-term feeding strategy. The fact that man also has a large capacity for lipid deposition suggests that, in our evolutionary past as well, (temporary) lipid reserves played a significant role in survival and reproduction.

For such a long-term feeding strategy to work, there must be shorter-term mechanisms that control EI to levels that may be lower than, equal to or higher than actual EE depending on the cues the animal receives from its environment and from its actual internal state. In order to understand actual feeding behaviour, the controlling mechanisms and the cues that animals use need to be known. In the present paper, we have highlighted research with animals and human subjects suggesting that a variation in EE (or rather oxidative metabolism) may be such a cue because this variation is associated with variation in satiety and voluntary EI levels. If the release of reactive oxygen species that are associated with oxidative metabolism leads to cellular damage, disease, loss of vitality and reduced lifespan, this may

have affected the evolution of the mechanisms that control EI. Such mechanisms would allow the animal to accumulate reserves when the costs, in terms of oxidative damage, were low because good-quality food could be obtained at little effort. This would subsequently allow the animal to avoid the high costs, again in terms of oxidative damage, that would be associated with maintaining EB in other periods, when considerable effort would be required to obtain food or when food quality was low. From an ecological perspective, we would expect that animals are adapted, in the sense that such mechanisms contributed to survival and reproduction in the natural environment.

If, however, an organism is taken from its natural environment and placed in an alien environment, the very same mechanisms that contributed to survival and reproduction in the natural environment may be totally unadapted to the new environment. This can be expected if the change in environment occurs at a rate that is much faster than genetic change. In the developed world, the incidence of obesity and related health problems has increased tremendously during the past few decades (World Health Organization, 1999; James *et al.* 2001). Indeed, a recent report (World Health Organization, 1999) predicted that cases of health problems as a result of high EI and obesity will soon outnumber cases of health problems associated with undernutrition. This period is much too short for significant changes in the human genetic make-up, which shows that obesity-related problems are mainly the result of changes in the environment coupled to individual differences in susceptibility to overconsumption.

We have emphasised two aspects of this change in environmental conditions, that is, the quality of available foods (nutrient and energy density) and the physical effort required to obtain food. Similar changes in environment can lead to excessive lipid deposits in animals, such as mature farm animals, laboratory animals and pets (Bauer, 1998; Burkholder & Bauer, 1998), as well as in humans. This occurs when very little physical effort is required (i.e. have to consume very little oxygen) to obtain high-quality foods (i.e. foods that contribute relatively little to oxidative metabolism). This may well be a direct result of the mechanisms controlling EI levels under conditions of feast in their natural environment. The change in environment has, however, abolished the periods of famine. The result is that animals continuously receive cues that lead to the deposition of energy until these are mitigated by the feedback from the lipid reserves. Such large reserves not only serve little function in such an environment, but are also associated with very negative fitness consequences. However, this then cannot be considered to be a result of a malfunctioning in the control of EI. Instead, it is the unsuitable environment that leads to the negative consequences of EI control mechanisms that function well.

We have reviewed the evidence that the contribution of foods and specific macronutrients to oxidative metabolism has effects on satiety and voluntary EI levels in a number of species, including humans. However, for proper tests of the hypothesis that voluntary EI is related to EE, quantitative predictive models are required. Before such models can be constructed, many remaining questions need to be answered.

One important question relates to the effects of oxidative metabolism on long-term fitness. There is now overwhelming evidence obtained with species ranging from nematodes (such as *Caenorhabditis elegans*; e.g. Finkel & Holbrook, 2000),

fruitflies (*Drosophila melanogaster*; e.g. Orr & Sohal, 1994), rodents (e.g. Masoro, 2000) even to primates (e.g. Kim *et al.* 1997) showing that high intensities of oxidative metabolism lead to reduced vitality, an increase in disease and a reduced lifespan. There is much interest in the positive health effects of energetic restriction in primate models (e.g. Cefalu *et al.* 1999; Lane, 2000; Roth *et al.* 2000; Lane *et al.* 2001) and in the role of antioxidants (e.g. Finkel & Holbrook, 2000). However, before a quantitative fitness function of food intake can be constructed, much more must be known about the quantitative relationships between oxygen consumption and its negative consequences. Such questions can be investigated best with animal models.

Many questions are still unanswered about the effects of food composition on oxidative metabolism as measured in respiration chambers. More research in this area could lead not only to an increase in our understanding of the mechanisms involved, but also to the design of diets that are both satiating and do not lead to large levels of lipid reserves. Such work can be done with human subjects (e.g. Dulloo *et al.* 2000) as well as animals. For long-term studies, animal models may be the most appropriate as human subjects cannot be expected to agree to be confined for extended periods of time.

The literature on the effects of effort (or exercise) on EI and EB is rather confusing, especially since the short- and long-term effects may be different. This is because the effects of a short and intensive burst of activity in an untrained individual will exert quite a different effect on oxidative stress compared with the same activity in a trained person. There is evidence that subjects defend water balance at the start of an exercise regimen and that this takes priority over EB. As energy deficits due to exercise accrue, the possible feedback from depleted tissues is also likely to increase. It thus only really makes sense to consider the effects of exercise on oxidative metabolism, EI and EB in human subjects over a time window appropriate to the mechanisms or issue under study.

There are also important questions about the nature of the relationships that are best suited for quantitative modelling. Quantitative models based on the principle of maximisation of benefits per unit of oxygen consumed have resulted in quite accurate predictions of locomotory and foraging behaviour in some species (Tolkamp *et al.* 2002). In all of the studies that we reviewed, costs were estimated or measured from oxygen consumption (or EE), and benefits could be expressed in a single currency (such as food or energy or protein obtained). At present, it is not clear how this approach can be extended to other types of animals, for example reproducing female animals. For such animals, the benefits of food intake not only relate to the protein and lipid reserves of the dam, but may also include the growth of fetuses and the production of milk, or the production of eggs. Similarly, for young growing animals, the benefits relate both to growth (i.e. protein retention) and the deposition of (lipid) reserves. In the long term, benefits should of course be expressed in terms of fitness. More animal research is, however, needed before such diverse benefits of feeding can be combined into a single currency in short-term optimisation models. Perhaps even the benefit/cost maximisation model may be too simple, and more appropriate models may need to be developed.

In this paper, we have reviewed studies with animals and have drawn parallels with results from studies in human subjects with the assumption that human feeding behaviour is affected by

the mechanisms of the animal within. This is not at all intended to suggest that 'the animal within' is the only relevant factor affecting human feeding behaviour. EI can be brought entirely under cortical control (Keys *et al.* 1950; Garrow, 1988), and there are many examples of how effective such a control can be. On the other hand, most studies on the effect of dieting show that the loss of lipid stores by cortical control is very easily reversed when this control is subsequently relaxed (Keys *et al.* 1950; Garrow, 1988). This suggests that human feeding behaviour is also strongly affected by the urges originating from the mechanisms of the animal within.

Finally, we would like to make a plea for more cooperation between scientists from different disciplines, such as ecology, animal science and human nutrition. Problems of food intake and EB can be studied at very different levels. Some researchers (e.g. ecologists) may be mainly interested in the question of why organisms evolved with the behavioural programmes that control intake. The consideration of such questions can have, at the very least, a great heuristic value for research in human nutrition. Others (e.g. physiologists) may study in great detail the 'how' (i.e. the immediate mechanisms) of the control of food intake. Both types of question are relevant if we are to achieve a better understanding of the control of EB. Because of the economic importance of efficient feed conversion in animal agriculture, the effects of food composition on voluntary intake and energetic efficiency have been studied in great detail in animal science. Such detailed data may help in understanding the processes that are relevant for determining human EB. In our experience, cooperation between scientists of different disciplines can be exciting as well as very fruitful.

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