Abstract
Energy is a concept of universal importance. In applying it to body weight regulation, the focus has been on energy balance and how this balance is affected by intakes and expenditures. However, energy is an abstract concept without biological equivalent and applying it to explain body weight regulation has led to various misconceptions and created intellectual obstacles in understanding the obesity problem. When nutrient and substrate interactions are considered, instead, a number of important issues pertaining to body weight regulation and to the obesity epidemic can be much more pertinently addressed.

Keywords: Obesity, body weight regulation, energy balance, nutrient balance, energy expenditure, basal metabolic rate, food intake, carbohydrate balance, dietary fat, exercise

Introduction
During the past few decades, the preponderance of obesity has steadily increased around the world while, at the same time, the adverse effects of obesity on health have been documented in greater detail. One now recognizes an obesity pandemic and sees it as a major public health problem. As one would expect, the issue is visited abundantly in print and in the media, and considerable research efforts, ranging from epidemiological to physiological and molecular aspects continue to be focused on the causes of obesity and in attempting to find appropriate treatments. A central issue in this quest is to understand the physiology of body weight regulation and its interactions with the environment.

Biologists have long been intrigued by the mystery of body weight regulation, which leads to the stability of body weights in adult life. Weight stability requires that average energy intakes match average energy expenditures. However, this can happen while body weights are low, appropriate or excessive, and for a wide range of energy turnovers. The tendency to maintain energy balance does not explain why adults regain weight lost during dieting or food deprivation, or spontaneously lose the weight gained during periods of deliberate overeating when food intake is again voluntary. Ultimately, the problem of body weight regulation and obesity boils down to understanding two phenomena: 1) What are the mechanisms which operate to correct the imbalances created by the common, large short-term variations in energy intake and expenditure, whether they result in exact energy balances or in slow rates of gain or loss of fat over time? and 2) Why should weight maintenance and the state of energy balance be reached for such widely differing levels of adiposity? While many potential explanations may be advanced to account for this diversity, they can only be satisfactory if they are consistent with the large day-to-day variations in intake and expenditure.
expenditure and with the mechanisms that bring about the corrective responses necessary to compensate or attenuate large short-term energy imbalances (Figure 1).

The aim of this article is to describe how considerations based on nutrient balance, rather than energy balance, provide a rationale for body weight regulation, and how this rationale explains why changes in the environment can lead to weight maintenance at higher levels of adiposity.

The energy balance concept
The energy balance equation is often invoked to frame issues relating to body weight regulation and obesity. The equation states that

\[ \text{Energy Balance} = \text{Energy Intake} - \text{Energy Expenditure} \]

A positive energy balance obviously has to occur to permit growth. If body weight is to remain constant later in life, an even energy balance has to be achieved and sustained. Accumulation of body fat takes place whenever overall energy intake exceeds energy expenditure, i.e. when the energy balance is positive. Positive energy balances can be attributed to excessive intakes and/or to insufficient rates of energy expenditure. Enormous research efforts have been made to understand the phenomena affecting energy intake on one hand, and energy expenditure on the other. Unfortunately, such research is often undertaken and interpreted without realizing that the real issue is the adjustment of intake to expenditure, or the failure to do so.

About energy intake
Experimental animals can be maintained on chemically defined diets, where their intake can be accurately assessed under ad libitum feeding conditions. Thus, there is an abundance of data on food intake in animals. Most relevant perhaps to the problem of human obesity are the studies describing how much experimental animals overeat when given free access to ‘cafeteria diets’ providing a variety of palatable foods. Such experiments revealed that in many cases such overeating elicits substantial increases in energy expenditure, though these are not sufficient to prevent weight gain.

While humans are readily willing to consume prescribed amounts of food of known contents, it is nearly impossible to determine nutrient and energy intake accurately under free-living conditions with the variety of foods available. Furthermore, self-recording of food consumption rarely reaches a satisfactory level of accuracy as substantial under-reporting is likely. It is evident, however, that under ad libitum conditions, the size of the meals and the total amounts of foods consumed vary considerably, causing large variations in daily energy intakes. In one of the most carefully conducted and comprehensive studies, intra-individual coefficients of variation (CV) were found to average ±23% in adults. Similar variability was reported more recently even among dieticians and data obtained in children also reveal comparably large variations.

There are many reasons for this variability, including food diversity, variable energy densities, as well as the presence of other diners (i.e. ‘social facilitation’), which also influences the consumption of alcoholic and energy containing beverages. Physical activities are often not regularly scheduled and also elicit various food intake responses. Not surprisingly, individual weekly patterns in intake can be observed.

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Figure 1. The two main issues about body weight regulation and obesity.
The ultimate limiting factor in studying human energy intakes is that individuals tend to change eating habits when they realize that what, and how much, they eat is to be observed or recorded. As pointed out by Garrow\(^{23}\), a kind of ‘uncertainty principle’ complicates the study of human eating behavior. One can either know exactly how much an individual eats under artificial conditions, or one can study food consumption under natural conditions, but then one cannot assess intakes accurately.

Three important insights derive from these considerations:

(a) Large variations in nutrient intakes are well tolerated. In the course of biological evolution, there was no great advantage or need for the development of a food intake regulatory system that would tightly control daily food intake, when metabolic fuel reserves are relatively large in comparison to daily energy turnover.

(b) Understanding the physiological regulation of food intake, i.e. hunger, appetite and satiety, must be expected to be rather challenging, as the signals which they may convey are readily overridden by seemingly random effects. The physiological mechanisms involved in controlling food intake should therefore be expected to explain only a minor part of the observed variability in daily food intake.

(c) The issue is further confused by the near impossibility to appropriately assess deliberate, voluntary and/or psychological influences on food selection and portion control, a complication that does not come into play in animal studies.

Nevertheless, it would be erroneous to conclude that the physiological regulation of food intake does not have considerable significance. One only needs to consider the remarkable accuracy with which energy intake tends to adjust itself to energy expenditure over the long-term\(^{24}\), as weight gains of 1 to 2 kg per year, common during many years of adult life, reflect imbalances of only 1 to 2% between total energy intake and expenditure! Furthermore, there is no epidemiological correlation between stature and adiposity\(^{25,26}\), in spite of the greater energy needs associated with increased stature. This reveals that food intake regulation spontaneously compensates for the fact that many meals of the same composition are served to subjects of differing stature. This procedure is known as ‘metabolic chambers’, allowing indirect calorimetry experiments to be conducted over several consecutive 24 h periods. If nutrient intakes are accurately known, indirect calorimetry data can serve to establish nutrient balances, which provide much more insight into metabolism than merely the overall energy balance. Such experiments have yielded a wealth of information, but only under tightly controlled and confined conditions\(^{29}\).

**About energy expenditure**

Energy is constantly needed to drive the various functions that sustain the body’s functions. In the body, the energy needed to drive these processes is provided primarily by adenosine triphosphate (ATP). When the terminal phosphate of this coenzyme is hydrolyzed, an unusually high amount of energy is liberated. The hydrolysis of these ‘high-energy bonds’ is catalyzed by enzymes, which couple it to specific chemical reactions and processes, thereby driving them to proceed. ATP is constantly regenerated from adenosine diphosphate (ADP) and phosphate (Pi) through the process of oxidative phosphorylation, which is linked to the oxidation of various metabolites generated during the degradation of glucose, fatty acids and proteins. The biological oxidation of the carbohydrates (CHO), fats and proteins absorbed from the foods consumed, provide 4.1, 9.1 or 4.7 kcal/g\(^{-1}\), respectively. Because intestinal absorption is not complete, one generally uses value of 4, 9, and 4 kcal/g (known as the ‘Atwater factors’) to compute the energy provided by foods. Adults at rest spend about 1 kcal/min, generally somewhat more in men than in women, as influenced by their body size. This is comparable to the heat produced by a 75W bulb or a burning candle. The rate of energy expenditure changes during the day, most dramatically during physical activity.

Energy expenditure can be measured very accurately. Heat release can be directly measured in a calorimeter, though this is such a technically complex operation that it is only rarely carried out. The common approach is to measure \(\text{O}_2\) consumption, \(\text{CO}_2\) production and N excretion in the urine\(^{28}\). This can be done in man by having a subjects’ head in a ventilated hood and analyzing the air drawn from it, to determine the amounts of \(\text{O}_2\) removed from the air and the amounts of \(\text{CO}_2\) added to it, and by collecting the urine to determine the amount of N excreted. Since CHO and fat contain no N and the N content of proteins is generally close to 16%, the excretion of 1 g of N implies the oxidation of 6.25 g of protein. The contributions made by CHO and by fat to the fuel mix oxidized can be assessed based on the observed ratio of \(\text{CO}_2\) produced to \(\text{O}_2\), known as the ‘respiratory quotient’ or ‘RQ’. It varies between the values of 1.0 when CHO is the predominant fuel, and 0.7, when oxidation of fat provides most of the body’s energy. This explains how it is possible to determine not only the amounts of protein, but also the quantities of CHO and fats oxidized over a period of time and to compute total energy expenditure\(^{27}\). This procedure is known as ‘indirect calorimetry’.

Several research centers have built ‘metabolic chambers’, allowing indirect calorimetry experiments to be conducted over several consecutive 24 h periods. If nutrient intakes are accurately known, indirect calorimetry data can serve to establish nutrient balances, which provide much more insight into metabolism than merely the overall energy balance. Such experiments have yielded a wealth of information, but only under tightly controlled and confined conditions\(^{29}\).
Misconceptions in body weight regulation

An elegant procedure was later developed to measure energy turnover under free-living conditions. In this approach, subjects ingest a dose of doubly-labeled water *i.e.* enriched with deuterium (D), a stable (non-radioactive) heavy isotope of hydrogen, and with $^{18}$O, a stable heavy isotope of O$_2$. During the subsequent days, D leaves the body with water, while $^{18}$O is lost in water and in CO$_2$. The rates of elimination are determined by mass spectrometry and the difference in their rates is used to calculate the amount of CO$_2$ produced. An average RQ is estimated based on macronutrient consumption and weight changes, to obtain a measure of O$_2$ consumption and ultimately a value for the overall energy expenditure during the period of observation, usually 10 days to 2 weeks. The remarkable advantage of this doubly-labeled water, or DW-method, is that it is applicable to free-living subjects, yielding realistic assessments of energy turnover under normal conditions. One of the most significant results of such studies has been the unambiguous demonstration that energy expenditure is increased by obesity. A set of DW studies performed in some 1000 adults was available to estimate energy turnover and energy needs to establish Daily Reference Intakes (DRI).

Since humans willing to participate in metabolic studies are cooperating with the experimental demands, energy expenditure under different conditions can be studied much more effectively in man than in animals. Resting energy expenditure is often measured after an overnight fast, when it is generally considered that metabolic rates are at their lowest. Hence, the name 'basal metabolic rates'. These are usually normalized for body size, using either body weight, body surface area, or height and weight. Food consumption raises energy expenditure above the resting rate, a phenomenon known as the 'thermic effect of food' (TEF). TEF is in the order of 10% of the caloric intake on a mixed diet. It is due mainly to the ATP expended for the absorption, transport, storage and processing of the nutrients consumed. During periods of food deprivation a decline in energy expenditure takes place, whereas increases in energy expenditure are induced during periods of excessive food intake. These changes may be greater than explicable by the difference in the TEF and the changes attributable to weight losses or gains. They are referred to as 'adaptive thermogenesis'. The sum of the latter plus TEF is considered to be 'diet induced thermogenesis' (DIT). These changes can only slightly attenuate, but not reverse the impact of changes in energy intake on the energy balance.

Much greater increases in energy expenditure are elicited by exercise. The increments caused by different forms of physical activity have been accurately determined. They are described in various tables, being generally expressed as the ratio of expenditure while performing a given activity, divided by the same person's energy expenditure at rest. For most activities the energy cost is proportional to body weight, notable exceptions being bicycling and swimming, because these are not a weight-bearing activity. When considered over 24 h, the ratio of total over resting energy expenditure provides a measure of the physical activity level (PAL).

Knowledge of human energy expenditure is now so complete, that models and equations could be developed from which weight changes can be accurately anticipated when nutrient intakes are known and physical activity predictable. In addition, data on body weight changes over time can be used to evaluate energy intakes in a population, as well as individual compliance with restricted diet programs. Furthermore, food wastage could be assessed by comparison with information on food production.

Misconceptions in the interpretation of the energy balance concept

The energy balance is a concept constantly referred to in discussing the obesity problem. However, energy is an abstract concept without biological equivalent and applying it to explain body weight regulation has led to several widespread misconceptions, as considered below:

1. The energy balance equation is taken to imply that obesity is due to a 'positive energy balance'. This view ignores the fact that obese individuals, like lean subjects, tend to reach a state of approximate energy balance, with similar short-term fluctuations in the energy balance. *Thus one confuses past and present.*

2. The energy balance equation suggests that energy intake and energy expenditure occupy equivalent roles in determining energy balance. However, factors influencing energy intakes affect the energy balance far more powerfully than factors determining resting energy expenditure and DIT. *This important fact is not recognized by simple consideration of the energy balance equation.*

3. To understand weight stability one needs to understand the phenomena regulating the energy balance. The body’s regulatory functions may strive to maintain CHO, protein and/or fat balances, but not energy balance. The body ignores that 1 g of fat contains more than twice the energy present in 1 g of CHO, an element of information needed to study the energy balance. One may be in awe at the body’s ability to maintain approximate energy balances over extended periods of an individual’s life, but this is a consequence of the organism’s ability to maintain substrate balances. *Attempts to understand body weight regulation as the result of a regulatory process directed at the energy balance itself are therefore doomed to be frustrated.*

4. The goal of food intake regulation is maintenance of the energy balance. The powerful drive to regain weight lost by dietary restriction, as well as the spontaneous drive to lose weight gained after a period of deliberate overeating clearly demonstrate that this is a misconception.
5. Obesity is due to a positive energy balance, either because energy intake is excessive and/or energy expenditure is too low. It is therefore useful to study both intake and expenditure. Considering the challenges faced in studying the regulation of food intake in man on one hand, and the relative ease with which the phenomena influencing energy expenditure can be determined, on the other, much more effort has been devoted to study the latter. The justification for this one-sided approach is the belief that increases in energy expenditure will necessarily act to reduce weight gains and adiposity, whereas decreased energy expenditure will necessarily promote weight gain. However, this notion hinges on the critical, but widely overlooked and erroneous assumption that energy intakes remain clamped at a particular level, even when energy expenditure changes.

6. Low rates of energy expenditure are due to a higher 'metabolic efficiency', which may account for greater than normal energy retention, sometimes referred to as the 'thrifty gene hypothesis'. Although metabolic efficiency can be defined in many different ways, this concept is often tossed around without a proper definition, leading to various misinterpretations. It is amazing that the notion that obesity could in any manner reflect a higher efficiency was not dispelled long ago, since overall energy expenditure is raised in obesity, due to the increase in lean body mass (LBM) associated with weight gain and the greater costs associated with moving a heavier body. Even during period of weight stability, large daily variations in food consumption cause energy balance to be positive on some days and negative on others, so that metabolic efficiency would oscillate between positive and negative values! Thus, the energy efficiency concept can only cause utter confusion.

7. Basal as well as resting metabolic rates (BMR, RMR) are low in obese subjects explaining excessive fat accumulation. Basal and resting energy expenditure are higher in obese than in lean subjects, because of their greater fat-free mass (FFM). It is only when expressed per kg body weight, or per kg FFM, that metabolic rates appear to be lower in obese than in lean subjects, simply because there is a positive intercept in the correlations between energy expenditure and body weight or FFM.

Several facts argue against the deeply entrenched notion that low RMRs contribute to the development of obesity.

a) Stature, which is positively correlated with resting and with total energy expenditures, has no impact on adiposity.

b) There is no correlation between % body fat and deviations from the average RMRs normalized for weight and height (Figure 2).

It is generally considered that causes cannot safely be inferred from correlations, especially from cross-sectional correlations. In the case considered here, however, the crucial fact is the lack of correlation. This is a much simpler to interpret, as this evidence directly and simply demonstrates that other factors overwhelm the possible effect of such deviations in determining the degree of adiposity associated with the steady-state of weight maintenance.

8. Adaptive thermogenesis or the lack thereof influence adiposity. Adaptive thermogenesis describes changes in resting energy expenditure which have the effect of reducing weight gains during periods of over-consumption, or weight losses during starvation or dieting, relative to the weight changes expected, if changes in energy expenditure were solely due to changes in body size and in the thermic effect of food. While adaptive thermogenesis has been found to be substantial in some animal models, it is modest in man, to the point that it has been difficult to establish it unambiguously. The fact that differences in resting energy expenditure have no statistically recognizable impact on adiposity (c.f. Figure 2) would have to be considered to imply that differences in adaptive thermogenesis, which occur only occasionally, do NOT play a significant role in preventing or promoting the preponderance of obesity.

9. Futile cycles, brown adipose tissue and uncoupling proteins (UCP) can reduce adiposity by raising energy expenditure. In man, the impact of exercise on metabolism and adiposity is be more specifically addressed later, when the impact of exercise on metabolism and adiposity is considered.

10. Exercise causes a negative energy balance. Initiating a regular program of physical activities generally leads to a period of negative energy balance and to a reduction in adiposity. However, it is also true that physically active individuals reach a steady-state in which their average energy expenditure is even and body weight remains stable. The reason for this difference is not understandable by consideration of the energy balance alone.

Two ways of looking at the gap between energy intake and expenditure

Everything considered, one has to remain amazed by the fact that over the long run energy intake generally adjusts itself to within 1–2% of energy expenditure. For energy turnovers in the range of 2000 to 3000 kcal per day, this corresponds to an average 'daily energy gap between intake and expenditure' of only 20 to 60 kcal.
This has led to the notion that the obesity epidemic could be controlled, if only overweight individuals could reduce their intake by some 100 kcal/day, thereby reversing their weight gaining trend\(^4\). However, if some specific items in an individual’s diet could be singled out to be reduced or excluded, one would have to expect a compensatory change in intake, as individuals are generally quite unaware of what and how much they eat. The very fact that average intake tends to adjust itself closely to expenditure, which suggested that a small correction would have a significant impact, also indicates that in the absence of precise, calorie-counting habits, intakes will probably continue to remain at their usual level.

A more sober manner to consider the gap between intakes and expenditures is to see it as the difference between habitual intake and the intake that would be appropriate to maintain a normal body weight\(^4\). This shows that decreases in intake of several hundred kcal/day \(^5\) (i.e. some 25 kcal/day per kg to be lost) are required to close the ‘energy gap between current and desirable energy intakes’. Even when such limitations are implemented and sustained, a very long time has to elapse before normal weights are approached\(^3\).

**Conditions for body weight stability: ‘settling point’ versus ‘set-point’**

Although less obvious than the fact that energy intake must be equal to energy expenditure, weight stability also requires that the substrate mixture oxidized be equivalent, on average, to the composition of the nutrient mix consumed. When ‘substrate balance’ is not achieved, changes in body composition occur, which in time are bound to elicit adjustments in food intake\(^6\).

When adequate amounts of food providing sufficient protein (i.e. DRI for protein in adults is 0.8 g/kg body weight/day\(^3\)) are consumed, amino acid oxidation spontaneously adjusts itself to protein intake, allowing for some protein build up during periods of growth. Protein intake can be computed by using food composition data, or by analysis of their N content (1 g N corresponds to 6.25 g of protein). N losses in the stools (1–1.5 g N/day) and cutaneous N losses (0.5 g N/day) are relatively constant. N is mainly lost in the urine, primarily in the form of urea produced by the liver to eliminate the ammonium ions produced from the N released by amino acid degradation. Measuring N loss in 24 h urine collections makes it possible to monitor a person’s ‘N balance’. As recognized long ago, the N balance tends to maintain itself spontaneously implying that, except during periods of growth, the body’s protein content is constant. Amino acids consumed in excess of those needed for growth and to replace the proteins lost to turnover are oxidized and contribute to ATP resynthesis.

The ratio of CO\(_2\) produced to O\(_2\) consumed during the biological oxidation of a representative sample of the diet consumed is defined as the ‘Food Quotient’, or ‘FQ’\(^3\). Stable body compositions will only be sustained if the average RQ matches the average FQ of the diet. The composition of the fuel mix oxidized and hence the average RQ are influenced by the size of the body’s substrate reserves. For the steady-state of weight maintenance to become established, the particular body composition must be reached which, for a given individual living under a particular set of circumstances, complements the other regulatory interactions in causing the average RQ to match the average FQ\(^4\). This links the energy balance to a particular body composition and provides an explanation for the stabilization of body weights at a particular ‘settling point’\(^5\). Because such a stabilization cannot be expected when one considers merely energy intake and expenditure, the phenomenon of weight maintenance has often been seen as begging for some explanation. To provide it, the
levels, maintenance of appropriate glycogen stores presents a considerable metabolic challenge. Evolution was therefore compelled to develop appropriate regulatory features to adjust glucose oxidation to CHO availability, through adjustments of the activity of key enzymes and by hormonal signals, notably those conveyed by insulin and glucagon. Thanks to these, large variations in CHO intake can be accommodated without noticeable stress. Other phenomena cause the oxidation of amino acids to adjust themselves to protein intake. On the other hand, the body’s large fat stores are hardly affected by daily gains or losses and adjustment of fat oxidation to fat intake has received much lower priority in metabolic regulation. Indeed, consumption of fat has little or no effect on fat oxidation, which declines even following fatty meals. While numerous mechanisms operate to prevent large deviations from CHO and protein balances, no such functions are at work to limit daily fat imbalances. Not surprisingly, deviations from fat balance tend to be much greater than deviations from CHO and protein (or N) balances. It follows that energy balance cannot be expected to be more accurately maintained than fat balance. The roles which CHO and fat play in the body’s fuel economy and in body weight regulation are therefore markedly different, another fact that is not taken into consideration when only the energy exchanges are considered.

Fat oxidation and fat accumulation

The rate of fat oxidation varies greatly during the day, influenced mainly by CHO intake and physical activity. The amount of fat oxidized in a 24 h period does in effect not correlate with variations in daily fat intake, but is primarily determined by the difference between total energy expenditure and the energy provided by the amounts of CHO plus protein consumed. CHO intake can contribute to increased adiposity primarily by sparing fat from oxidation, rather than by being converted into saturated fatty acids (FA) by de novo lipogenesis. Indeed, the fatty acid composition of human adipose tissue triglycerides reflects the FA composition in the diet. Deliberate, extensive overconsumption of CHO during several days is required to induce rapid rate of lipogenesis, demonstrating that the usual limitation of pyruvate oxidation to acetyl-CoA can be overcome.

Over the long-term, however, gains in the adipose tissue mass will lead to higher free FA (FFA) levels and induce some degree of insulin resistance. This has the overall effect of raising the rate of fat oxidation relative to the rate of CHO oxidation. Thanks to this long-term, ‘chronic’ influence, body composition will drift toward the degree of adiposity for which the average rate of fat oxidation becomes commensurate with fat intake.

Pyruvate oxidation: the site of the crucial metabolic interaction between carbohydrate and fat

Lactate and pyruvate are constantly reconverted into glucose by gluconeogenesis in the liver. The reaction...
which determines the actual rate of CHO oxidation is the conversion of pyruvate to acetyl-CoA catalyzed by pyruvate dehydrogenase (PDH), which is irreversible. Ninety percent of the energy in glucose is liberated when pyruvate and acetyl-CoA are oxidized. PDH is a very large enzyme, formed by several subunits needed to carry out this complex chemical reaction. The activity of PDH is modulated in several ways. It can be inhibited by phosphorylation of its subunits, as well as by acetyl-CoA produced by oxidation of FAs. This has the effect of sparing CHO from oxidation, when CHO intake is limited and during starvation. However, as most of the dietary energy is often provided by CHO, it is important that CHO can become the primary fuel for ATP resynthesis, notably after meals. This is made possible by increasing PDH activity by dephosphorylation at the regulatory sites, a reaction carried out by an insulin-activated protein phosphatase. Evolution has perfected this interplay, as in addition, insulin inhibits FFA mobilization from adipose tissue, thereby limiting the production of acetyl-CoA and its inhibitory effect on PDH.

As time elapses after the absorption of food, blood glucose and insulin levels decline, allowing for greater fat mobilization. This leads to a gradual shift to greater use of FAs, with acetyl-CoA restraining pyruvate oxidation and sparing CHO. Pyruvate oxidation appears as the most significant reaction in determining how the relative contributions made by CHO and fat to energy generation change and complement each other over time, an interplay classically described by Randle as the ‘glucose-fatty acid cycle’.

Effects of exercise on the energy balance and on adiposity

Regular physical activity effectively reduces the likelihood of developing obesity and the recommendation to increase exercise to control body weight is constantly emphasized. However, as mentioned earlier, it has been difficult to find a consistent explanation to account for the fact that exercise causes a negative energy balance in some situations, but not in others. The issue is complicated by the fact that physical exertion causes major perturbations in metabolism, as it initiates rapid breakdown of glycogen, as well as rapid fat mobilization to provide the substrates needed to sustain ATP regeneration. Furthermore, exercise affects metabolism beyond the period of physical activity itself, by causing the so-called ‘excess post-exercise oxygen consumption’ (EPOC), as well as changes in substrate utilization and appetite.

The epidemiological data clearly show that regular practice of physical activities leads to a steady-state of weight maintenance at lower levels of adiposity. In effect, exercise reduces the expansion of the adipose tissue mass needed to raise fat oxidation to the rate commensurate with the diet’s fat content and to bring about an average RQ equal to the diet’s FQ. This is well illustrated in children whose spontaneously high physical activities used to limit childhood obesity, until increased inactivity caused the rise in its prevalence. It can be inferred that physical activities enhance fat oxidation relative to CHO oxidation. This is the case even though glucose often makes a major contribution to the fuel mix oxidized at the onset of exercise, as this is evidently compensated later by an increase in fat oxidation. Contributing to this is the fact that exercise has the effect of lengthening the meal-to-meal interval, when one considers it in terms of calories burned rather than in terms of hours elapsed. In addition, physical training increases the body’s ability to use more FAs and less glucose.

The introduction of physical activities into the daily routine enhances fat oxidation to a greater extent than CHO oxidation. Thus the additional amount of food needed to maintain CHO balance is less than the exercise-induced increase in energy expenditure, resulting in weight loss. On the other hand, once a steady-state accommodating the impact of habitual physical activity on fuel metabolism has been reached, eating to maintain glycogen levels again provides fat and calories in amounts appropriate to maintain energy balance. With these considerations in mind, one can readily understand why exercise sometimes induces negative energy balance and sometimes not.

Increases in energy expenditure elicited by uncoupling protein and drugs

Given that long-term CHO balance will be maintained under all circumstances, increases in energy expenditure brought about by activation of UCPs or by drugs should only be expected to bring about a reduction in adiposity, if such increases are largely covered by increments in fat oxidation, setting up an effect similar to that elicited by physical activity. Failure to alter the RQ may explain the limited impact on obesity of increases in energy expenditure elicited by drugs and by factors likely to enhance the activity of UCP. It seems possible that body size may be a factor in the impact of these agonists, as enhanced fat oxidation may be more promptly elicited in small laboratory animals whose fuel reserves are limited. Speculations about the potential significance of UCP and of futile cycles in man should therefore be made cautiously.

Food intake regulation and carbohydrate balance

Maintenance of appropriate glycogen levels under conditions of ad libitum food intake would be facilitated if, in addition to adjustment of glucose oxidation to CHO intake, food intake were to be regulated in a manner helping to sustain the balance between the use of glucose and the influx of dietary CHO. Making such considerations at a time when the existence of specific glucose receptors in the brain had just been revealed, Mayer developed the concept of ‘glucostatic’ regulation of food intake, in which it is presumed that monitoring of blood glucose levels by the brain generates signals for the regulation of food intake by the central nervous system. Indeed, it is now known that transient small declines in blood glucose levels tend to elicit eating. If no food is consumed, blood glucose will
Nevertheless tend to rebound, thanks to the actions of glucagon and catecholamines, so-called 'counter-regulatory hormones'. Blood glucose levels vary greatly during the day, and there is much overlap between the values that prevail under different nutritional and metabolic conditions. Subsequently, it was therefore considered that changes in liver glycogen levels or in liver substrate oxidation rates would be more suitable or more likely to provide appropriate feedback signals to the brain, as such inputs can be based on some integrated parameter of substrate and CHO utilization and availability. Little is known about the mechanisms and signals, which may be involved, though there is a possibility that they could be transmitted to the central nervous system via the autonomous nervous system.

In addition, one should probably entertain the notion that the rate of change, instead of, or in addition to the size of the body’s glycogen stores, could provide signals affecting hunger, much as glucagon is secreted before hypoglycemia sets in. Hunger is said to become less acute after a few days of total starvation and it is relatively well tolerated on protein-sparing diets. It appears as if the usual drive to eat to replenish glycogen levels may be attenuated, once the organism has adapted to low, but stable glycogen and blood glucose levels. This may be a reason why restriction on CHO consumption can sometimes be more successfully sustained to lose weight than unspecified restraint on eating.

**Experimental evidence about the role of carbohydrate balance in food regulation**

In one of the few studies suitable to examine this issue, Stubbs et al. used continuous indirect calorimetry in a respiratory chamber to establish 24 h substrate balances during seven consecutive days in young men serving themselves ad libitum from platters providing various foods. Importantly, the menus offered had been previously tested and selected for not inducing excessive intake when offered in this manner. A negative correlation between 24 h CHO imbalances and subsequent energy balances, and hence food intakes were observed.

To the disappointment of the investigators, this effect accounted for only 5 to 10% of the variance in the next day’s energy intakes. However, one needs to consider that most factors influencing food consumption and variations in the daily energy balance occur pretty much at random, once a particular lifestyle has become established. Even modest, but systematic regulatory effects can then exert a significant long-term ‘steering effect’.

Role of carbohydrate balance in food intake regulation versus habitual glycogen levels

Regulation of food intake in a manner helping to maintain CHO balance provides means to achieve body weight stability, but only when the situation has been reached for which the composition of the fuel mix oxidized matches, on average, the nutrient distribution in the diet. However, in relation to body weights and health, the mechanisms involved in stabilizing body weights are less important than the factors determining the body fat content for which weight maintenance tends to occur.

Glycogen levels are spontaneously maintained at levels sufficient to prevent hypoglycemia and to carry out habitual physical tasks. They also spontaneously remain far below the level at which rapid conversion of CHO into fat is induced in adults consuming mixed diets. Glycogen levels in adults can be estimated to vary between a lower limit of some 150 to 200 g and an upper limit of 500 to 600 g. Glycogen levels are known to be higher on high-CHO than on low-CHO diets and are therefore not likely to vary over the entire range when conditions are stable, but to oscillate within a narrower range. Since neither the lower nor the upper limits are specifically determined, the range within which glycogen levels are habitually maintained can differ among individuals and be affected by circumstances as well.

**Recent increases in the preponderance of obesity**

The progressive increase in the prevalence of obesity during the past few decades has occurred, even though neither the population gene pool, nor the parameters commonly blamed for causing the progressive increase in obesity in affluent societies (e.g. higher dietary fat content, increased buying power, decreased physical activity), have changed substantially. However, food diversity and their appetizing qualities, their energy density and portion size, as well as advertising to promote foods and beverages have continued to increase. In various ways, these factors encourage food consumption, with the result that higher glycogen levels are reached after meals. Furthermore, depletion of glycogen levels between meals is counteracted by the ubiquitous availability and promotion of appetizing snacks and caloric drinks. It will be readily appreciated that together these environmental changes are bound to raise the range within which glycogen levels are habitually maintained.

When this range rises, daily fat oxidation can be expected to decrease, promoting fat accumulation. Although actual measurements of glycogen levels in human populations are not yet available from which one could gauge the influence of glycogen levels in reducing fat oxidation, this effect can be recognized in experiments performed in respiratory chambers, where changes in glycogen content can be established. It is very important to become aware of this effect and thereby of the role, which increased ‘habitual glycogen levels’ will play in promoting obesity.

**Assessment of the impact of habitual glycogen levels by a computer model**

A number of computer models have been developed to address body weight regulation issues. Because of the
lack of reliable data on energy intake, they have primarily been based on energy expenditure considerations at preset nutrient intakes, with only one model attempting to include food intake regulation\(^9\). In this model, an attempt was made to assess the scope of the impact of habitual glycogen levels in human metabolism. The two-compartment model, i.e. glycogen and fat, was set to create daily patterns of rest, meals and exercise. Meal size was determined by the amount of CHO needed to restore glycogen levels to some specified amounts and by the dietary CHO-to-fat ratio. An ‘insulin-function’ promoting CHO oxidation when CHO availability is high had to be included in tuning the model to reproduce the post-prandial changes in CHO and fat oxidation observed in experiments with human volunteers\(^9\).

The model reflects the impact of exercise in leading to lower steady-state adiposity. This is due mainly to the lengthening of the meal-to-meal interval, as it manifests itself in terms of calories expended, rather than time elapsed. Consumption of snacks reduces CHO and energy intake at subsequent meals, but the compensation is not sufficient to prevent an increase in adiposity, because snacks inhibit fat oxidation between meals, when it should be allowed to rise. On the other hand, slowing down intestinal absorption to mimic consumption of low glycemic index CHO leads to a reduction in steady-state adiposity. Finally, the model’s responses indicate that an increase by 25 g in the range within which glycogen levels are habitually maintained would require an increase in body fat content of some 5% to restore fat oxidation to the previous level. This would correspond to a weight gain of some 7 kg and to an increase of about 4 kg/m\(^2\) in the body mass index (BMI = Weight(kg)/Height(m)\(^2\))\(^9\). The model’s behavior illustrates that changes in glycogen levels too small to be documented by current means, can readily explain recent gains in adiposity. It appears therefore that the impact of environment factors on body weight is translated to a metabolic effect through their effect on glycogen levels.

**Why don’t people eat even more?**

In man, restraint on food intake can be due to conscious efforts, to a degree susceptible to cultural influences\(^3\) and to the prevailing level of adiposity among family\(^4\), friends and in the public\(^5\). Unfortunately, such efforts fail all too frequently to prevent excess weight gain. In a large segment of the population, control over overall energy intake seems to be largely dependent on physiological mechanisms. These have been shaped by evolution to facilitate the build up of fat reserves during periods of plenty, but not to prevent excessive weight gain when abundant food is available. In fact, it is commonly thought that food intake regulation is more powerful in preventing energy deficits than weight gain\(^9\), which tends to bring about weight gain by a ‘ratchet effect’\(^9\). A number of signals influencing food intake originate in the gastro-intestinal tract and others are elicited by circulating substrate and hormone levels. For the most part, however, these decay overnight and do not carry over much information from one day to the next\(^9\). Thus they are part of the phenomena which keep food consumption within the range described by intra-individual coefficients of variations, found to average \(±23\%)\(^2\). Other mechanisms must therefore be at work in modulating food intake from one day to the next.

When one considers the pleasure associated with eating and drinking, the loose regulation of daily energy intake, the great tolerance for excessive intakes, the frequency of social events promoting overeating and the constant availability of appetizing and energy-dense foods, it is nothing but astonishing that body weights should remain relatively stable! Even among individuals who appear to combine dietary and lifestyle habits expected to promote the development of obesity, weight gain over the years is much slower than one might expect.

Evidently, people eat substantially less on most days than the amounts that they readily consume on high-intake days, but why?\(^3\). The fact is that we know much about factors promoting food intake, but very little about the phenomena limiting food intake, other than those preventing overloads of the digestive system on a given day\(^5\). The existence and power of regulatory effects serving to correct for recently incurred energy gains or deficits is not only made evident by the commonly experienced weight stability, but also by the weight loss, which spontaneously takes place after periods of deliberate overfeeding\(^6,7\). Further evidence can be seen in the fact that there is no correlation between adiposity and stature\(^8,43\), even though resting and total energy expenditure are positively correlated with stature\(^8\) and many meals of standard size are served to short and tall people.

It appears that signals limiting food intake, related somehow to body composition, reach a balance in opposing hunger and appetite. However, when the incentives to eat are heightened, more food will be consumed before intake is stemmed. This is currently the case in much of the world. The effect of the environmental forces encouraging consumption can therefore be seen as shifting a steady-state, still maintained thanks to the usual regulatory corrective effects. This entails quite a different way of thinking about the effects of appetizing foods on caloric intake.

The impact of appetite reducing drugs can be seen as affecting the balance between the signals tending to limit food intake and the incentives to overeat, but only as long as the drugs are taken. One could also imagine that the role of leptin in body weight regulation\(^41,104\) is in altering the body’s regulatory responsiveness and thereby the body composition for which a steady-state tends to become established, rather than by eliciting corrective changes in food intake from day to day\(^10\).

We know that the interactions between food intake and metabolism effectively serve to maintain glycogen levels sufficient to prevent hypoglycemic events, while keeping them well below the levels at which appreciable de novo lipogenesis would provide an escape for

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Dietary fat versus dietary carbohydrate as a cause of weight gain

In view of the considerations made above, it is not surprising that a high incidence of obesity is typically encountered in sedentary populations consuming diets providing substantial amounts of fat\textsuperscript{2,86,106–108}. As shown recently for free-living and unrestricted eating conditions, energy intakes are positively correlated with the fat content of the foods consumed on a particular day\textsuperscript{13}. In most animal models high fat diets similarly promote fat accumulation. This evidence appears to be contradicted by the often remarkably good weight losing results achieved on regimen severely restricting CHO, but not fat intake, such as the Atkins-type diets.

While limiting fat intake generally leads to some weight loss\textsuperscript{109}, numerous testimonials report that sharply reducing dietary CHO facilitates losing weight\textsuperscript{83}. These conflicting impressions, often promoted with much publicity, have caused great confusion. The point has been reached where some investigators and much of the public consider dietary CHO to be the major culprit in causing the current obesity pandemic\textsuperscript{83}, whereas other experts, as well as most dieters, many food manufacturers and much of the public see dietary fat as the major risk factor for gaining excess weight\textsuperscript{107,108}. When such opposite opinions are held, it is probable that neither one is correct.

An often neglected, but important distinction in this regard is whether one deals with situations where intake is unrestricted or set by specific diet plans, aiming for relatively rapid weight loss, or rather long-term weight control. The seemingly contradictory views considered above can be accommodated simply by allowing for the fact that severe restriction on the consumption of any major macronutrient, and notably CHO, substantially reduces the selection of desirable foods from which to partake. This will reduce the incentives to overeat\textsuperscript{15,16}, even without having to engage in formal ‘calorie-counting’! Thus the answer to the question asked above is that the major force driving the obesity pandemic is the unrestricted and ubiquitous availability of a mixed diet, offering numerous appetizing foods, often in large portions, in which sugar, and to an even greater extent fat, contribute to raise the energy density\textsuperscript{18,110}.

Environmental versus circumstantial effects on adiposity

The relative impacts of inherited and non-inherited factors on body composition are commonly judged by the contribution that they make to the variance around the mean of BMI data. However, this does not appropriately recognize the impact of factors causing shifts in the means. Figure 3 shows the BMI distributions documented by the NHANES surveys in 1976–1980 and 2005–2006\textsuperscript{111}. In each case, the variability about the mean is brought about by inherited and non-inherited individual differences; the latter reflect the influence of the conditions affecting individual lives, such as life-style, socio-economic status, etc. They may be considered to reflect the ‘circumstantial factors’ acting to reduce or to enhance adiposity. This is in contrast to the ‘environmental factors’ which cause a shift in the mean, a unidirectional effect bound to have a more powerful influence on the proportion of individuals whose BMI will exceed certain limits. Consider for instance that the mean BMI (±SD) of Nigerian men was reported to be 21.0 ± 4.2 kg/m\textsuperscript{2}, whereas it was 27.0 ± 5.4 kg/m\textsuperscript{2} when living in Chicago\textsuperscript{112}. The data summarized by Costa and Steckel\textsuperscript{113} show the average BMI of adult men in the USA as rising from 22.5 kg/m\textsuperscript{2} in 1894 to 23.6 kg/m\textsuperscript{2} in 1944, 25 kg/m\textsuperscript{2} in 1991; in the 2002/06 NHANES the mean reached 27.5 kg/m\textsuperscript{2} (32).

To deal rationally with obesity epidemic, one needs to take into account that environmental, circumstantial, and genetic factors contribute in different ways to adiposity. In most situations, only the circumstantial factors should be thought to be controllable by individuals. Figure 3 shows how much more would have to depend under current conditions on individual resolve and circumstances to maintain BMIs qualified as normal (≤25 kg/m\textsuperscript{2}), or as overweight, but not obese (25–30 kg/m\textsuperscript{2}). This should reduce the expectations about the results likely to be achievable by advice to individuals. Strategies for weight...
control directed at families and group settings may be more effective, inasmuch as they may alter the circumstances shaping individual living conditions, thereby reducing the environmental incentives to overeat. The development (one may want to say ‘imprinting’) of physical activity habits and involvement in active games and sports among children and adolescents\textsuperscript{73,114} also offers the potential for immersing participating individuals into a more favorable set of circumstances, if such habits could become an enjoyable routine in a population.

Impact of inherited traits on body weight regulation

One can readily appreciate that inherited personality traits\textsuperscript{115,116}, learned and cultural behavioral traits\textsuperscript{94,95,117} and income levels will influence food selection\textsuperscript{118}, the ability to control eating behavior, the tendency to engage in physical activities, and thereby steady-state adiposity. At the level of metabolism, there is no reason to think that the way in which the organism is poised to regulate the relative use of CHO and fat as fuels should not be affected by inherited metabolic and hormonal differences\textsuperscript{119,120}. For instance, the persons maintaining relatively high RQs under standardized conditions were found to gain the most weight during subsequent years, as a greater expansion of the fat mass was needed for them to achieve an appropriate fat-to-CHO oxidation ratio under free-living conditions\textsuperscript{121,122}. This effect is likely to be magnified when dietary CHO is accompanied by substantial amounts of fat\textsuperscript{93}. Any inherited or permanently acquired effect\textsuperscript{123} affecting the mechanisms regulating the sparing effect of fat on glucose oxidation and vice versa, and in particular the regulation of PDH activity, can be expected to exert a powerful leverage on body weight regulation\textsuperscript{93}. On the other hand, one should not expect genetic effects causing RMRs to be higher or lower than average to significantly influence adiposity\textsuperscript{43}.

The problem of extreme obesity

In most people, increases in FFA levels brought about by incremental adiposity ultimately tend to reduce CHO oxidation and thereby exert a restraining effect on spontaneous food intake\textsuperscript{8}. One has to wonder why this feedback effect does not seem to operate in the usual manner to prevent extreme obesity, although fat stores can always be mobilized and used effectively when food intake is restricted. Several questions come to mind: (a) Could studies of 24 h RQ patterns and average daily RQ identify unusual trends in fuel metabolism in extreme obesity? And if so, (b) Do FFA levels reach the concentration range prevailing in normal and overweight individuals between meals? And how does the RQ response change when adherence to a prescribed diet plan can be assured? (c) Could the increased insulin levels required for blood glucose regulation in the presence of insulin resistance and/or in extreme obesity be so high as to overcome the inhibitory effect of FA-derived acetyl-CoA in the regulation of PDH activity? If so, (d) Does pyruvate oxidation allow de novo lipogenesis to proceed when it should not? (e) Is there any evidence of altered PDH sensitivity to the normal regulatory phenomena?

Raising the public awareness of the progression of obesity

In its simplicity, the BMI is well suited to establish epidemiological data and in classifying individuals as overweight, if their BMI is between 25 and 30 kg/m\textsuperscript{2}, or obese if it exceeds 30 kg/m\textsuperscript{2}. BMI is a very abstract criterion and it seems a shame that one should not aim to make individuals more realistically aware of their particular weight status. Clearly this is essential when one needs to enroll the public in individually addressing their particular weight problem. The concept of ideal body weight (IBW), the weight associated with the longest life expectancy as judged from life insurance experience, is readily understood. Learning how one’s body weight compares to, or deviates from IBW is therefore much more useful than being assigned a BMI value. Does your %IBW place you into the overweight range (i.e. 20–40% above IBW) and where in this range? Or how alarmed should you be by a %IBW exceeding the threshold of obesity, set at 40% above IBW? The %IBW criterion used to be common, but was replaced by assigning BMI values, which does not require the somewhat cumbersome need to consult IBW tables. Now that hand-held computers are widely available, this obstacle to the use of %IBW could be readily solved by an appropriate ‘App’. In creating this software, it would be desirable to incorporate recent data on changes in IBW related to age and perhaps to describe by how much life expectancy would, on average, be expected to change\textsuperscript{124-127}.

Implications

a) Relying on the abstract concept of energy in addressing the obesity issues fails to make evident that changes in energy intake affect the energy balance much more powerfully than differences in expenditure. It has also promoted false perceptions. In particular, the unjustified, but widely accepted notion that obesity is due to unusually low metabolic rates, has created much confusion. It has encouraged the fruitless search for evidence proving that low metabolic rates cause obesity and spawned unlikely expectations about the potential benefits of increasing metabolic rates by drugs or by stimulation of UCP activity.

b) The excessive focus on the energy balance has obscured the fact that the really important difference between lean and obese individuals is the degree of adiposity at which, on average, their energy intake tends to adjust itself to their energy expenditure. This varies widely between individuals, in a manner influenced by genetic, as well as by environmental and circumstantial factors. In effect, obesity is brought about by a failure of the interactions between body composition, metabolism and food intake regulation to restrain eating when the body’s energy stores are more than adequate for health.
c) Replacing the emphasis on energy balance by recognizing the importance of nutrient balance adds a previously overlooked consideration, with which the relative stability of body weights, as well as the impact of the environment on adiposity can be better understood.

d) As long recognized, the abundance of food combined with a sedentary life-style is the main factor driving the growing obesity pandemic \(^ {128}\). When the differences between CHO and fat metabolism are taken into account, the powerful metabolic leverage of a diet rich in fat in shifting the steady-state conditions for weight maintenance becomes more obvious. One can understand nevertheless that some key features of the physiological regulation of food regulation remain operative and one might search for better ways of taking advantage of this regulatory phenomenon.

e) The fact that high dietary fat content and a sedentary lifestyle have a synergistic effect on the prevalence of obesity should be duly recognized \(^ {107}\). This view is supported by the evidence that selecting a low fat diet and maintaining a substantial level of physical activity are precisely the behaviors needed to maintain long-term success in major weight reduction \(^ {129}\).

f) One should not be distracted from this conclusion by arguments blaming dietary CHO, rather than fat for the increase in obesity \(^ {83}\), as these are based on situations, where CHO restriction greatly limits food choices and the enticement to eat. It remains, however, that food restriction is often better tolerated when one significantly limits CHO consumption (82–84). This can be advantageously used in facilitating weight reduction.

g) The public should be made to better understand that consumption of snacks and caloric drinks \(^ {90,130}\) should not be expected to elicit sufficient compensatory decreases in intake during subsequent meals, because they inhibit fat oxidation during the periods of the day where it should occur at the highest rates. It is, indeed, failure to burn as much fat as one eats that leads to obesity.

h) Some important issues beg to be better understood \(^ {103}\). It is plausible that replete glycogen stores will tend to limit further food intake, but the mechanisms affecting food intake from one day to the next, other than self-imposed restraint, are still poorly understood. To make progress in understanding food intake and body weight regulation in man, one needs at the onset to take into account the large variability in daily intakes.

## Conclusions

The common perception that food intake regulation is very inaccurate in controlling daily energy intakes deserves to be complemented by greater awareness of its powerful contribution in maintaining energy balance over the long-term. This physiological behavior should be considered in explaining or designing strategies for long-term weight control.

The currently prevailing ‘obesogenic’ environment \(^ {47}\) will continue to drive the obesity pandemic, while inactivity habits \(^ {112}\) are likely to be further promoted by the pervasive use of computer and electronic gadgets. Furthermore, one has to be concerned about the erosion of the motivation to restrain eating in societies where excessive body weights predominate \(^ {96}\). In attempting to control the obesity pandemic, one should appreciate that in complementing the influence of hereditary factors on body weights, the leverage of circumstantial variables affecting individuals is limited, compared to the impact of environmental factors (Figure 3). Thus the Centers for Disease Control (CDC) and many other organizations are advocating changes in the food supply and lifestyle, as well as limits on advertising that could alter the environment. Unfortunately, such changes seem unlikely to happen in the bulk of the public, so that the obesity problem is likely to get worse \(^ {131}\). Furthermore, several common misconceptions shared by experts and the public in the stand in the way of a better understanding of the causes of obesity and of stemming its progression.

Finally, the considerations made here point to a singularly significant area of metabolism, namely on how the various regulatory responses balance out \textit{in vivo} in controlling PDH activity and how they are affected by environmental pressures. It is also in this sector of metabolic regulation that inherited differences and perhaps drugs at some hoped for time, may have the most likely impact on body weight regulation and obesity.

## Declaration of interest

The authors state that there are no conflicts of interest regarding the publication of this article.

## References


20. de Castro JM, Brewer EM. The amount eaten in meals by humans is a power function of the number of people present. Physiol Behav 1992;51:121–125.


46. Swinburn BA, Sacks G, Ravussin E. Increased food energy supply is more than sufficient to explain the US epidemic of obesity. Am J Clin Nutr 2009;90:1453–1456.


81. Wadden TA, Foster GD, Letizia KA. One year behavioral treatment
80. Tian Q, Nagase H, York DA, Bray GA. Vagal-central nervous
79. Friedman MI. Body fat and the metabolic control of food intake. 
75. Warren A, Howden EJ, Williams AD, Fell JW, Johnson NA. Post-
72. Dietz WH, Gortmaker SL. Do we fatten our children at the television 
69. Barwell ND, Malkova D, Leggate M, Gill JM. Individual 
66. Blair SN, LaMonte MJ, Nichaman MZ. The evolution of physical 
65. Wadden TA, Vogt RA, Andersen RE, Bartlett SJ, Foster GD, Wilk J, 
62. Randle PJ, Hales CN, Garland PB, Newsholme EA. The glucose 
50. Stillman MC, Hyson RL, Arthington KD, White CK. Dietary 
49. Zijlstra N, de Wijk RA, Mars M, Stafleu A, de Graaf C. Effect of bite 
48. Levy DT, Mabry ML, Wang YC, Gortmaker C, Huang TTK, Marsh T, 
47. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
46. Acheson KJ, Schutz Y, Bessard T, Ravussin E, Flatt JP, JŽquier E, 
45. Johnson SL, Birch LL. Parents’ and childrens' adiposity and eating 
44. Zijlstra N, de Wijk RA, Mars M, Stafleu A, de Graaf C. Effect of bite 
43. Kennedy E, Goldberg J. What are American children eating? 
42. Levy DT, Mabry ML, Wang YC, Gortmaker C, Huang TTK, Marsh T, 
41. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
40. Bray GA, Nielsen BJ, Popkin BM. Consumption of high-fructose 
39. Blair SN, LaMonte MJ, Nichaman MZ. The evolution of physical 
38. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
37. Windhauser MM, Volaufova J, Bray GA. Concurrent physical 
36. Blundell JE, Halford JCG. Regulation of nutrient supply: the brain 
35. Christakis NA, Fowler JH. The spread of obesity in a large social 
34. Zijlstra N, de Wijk RA, Mars M, Stafleu A, de Graaf C. Effect of bite 
32. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
31. Smith SR, de Jonge L, Zachwieja JI, Heli R, Nguyen T, Rood JC, 
28. Barbosa-Canedo V, Pons J, Aranda J, Pujol M, Pujol J, Alcântara M, 
27. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
25. Johnson SL, Birch LL. Parents’ and childrens’ adiposity and eating 
24. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
23. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
22. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
21. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
20. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
19. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
18. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
17. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
16. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
15. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
14. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
13. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
12. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
11. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
10. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
9. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
8. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
7. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
6. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
5. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
4. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
3. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
2. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp- 
1. Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp-


