

## Experimental demonstration of human weight homeostasis: implications for understanding obesity

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The existence of a set-point for homeostatic control of human body weight is uncertain. To investigate its existence, technically difficult determinations of energy expenditure must be performed: this has resulted in contradictory reports. The present study was performed with new methods in two stages (77 and 133 d respectively). Two healthy male subjects with rigorously controlled physical activity ingested three standardized diets of processed foods from the same manufacturer. Hypo-, iso- and hyperenergetic diets containing 6255 kJ (1494 kcal), 10 073 kJ (2406 kcal) and 13 791 kJ (3294 kcal) respectively were ingested during alternate periods; changes in body weight were measured. A new index of energy expenditure was calculated as the amount of weight lost in an 8 h overnight period (WL8H). A digital scale was used in stage 1 and a mechanical scale in stage 2. The change in body weight in response to the isoenergetic diet differed according to the circumstances. In basal conditions, it was associated with weight stability. After weight loss from energy restriction, the isoenergetic diet led to weight gain. After weight gain from overeating, it led to weight loss. Diets of higher energy content were associated with greater WL8H ( $F > 20$ ;  $P < 0.0001$  for both subjects). Measurement variability was lower using a mechanical scale. The present study demonstrates the existence of a homeostatic control of human weight and describes a new index of energy expenditure measured in weight units. It also demonstrates that strict dietary supervision for months is possible. Investigation of the human body weight set-point is vital in understanding obesity.

**Body weight: Body weight change: Weight loss: Weight gain: Obesity**

As faecal energy content and urine N are not normally affected by food ingestion (Leibel *et al.* 1995), excessive energy intake results in weight gain or extra energy expenditure (EE). Dissipation of unnecessary energy could protect against becoming overweight by setting the metabolism into an ‘unthrifty’ mode. Metabolism could then be switched back into a ‘thrifty’ mode in response to starvation. In fact, a homeostatic mechanism for weight control is known to exist in laboratory rats, whose control of set-point has been traced to the hypothalamus (Hallonquist & Brandes, 1984; Bernardis *et al.* 1986; Hunsinger & Wilson, 1986). On the other hand, the existence of a human body weight set-point is a matter of debate. Some authors consider its existence improbable (Payne & Dugdale, 1977; Amatruda *et al.* 1993; Garrow, 2000), while others seem convinced that it is real (Ravussin *et al.* 1985; Leibel *et al.* 1995). If such a set-point exists, it could be investigated by changing the energy content of the diet and measuring the corresponding body weight changes in subjects with controlled activity. There is, however, a huge variation in dietary energy intake among individuals; measuring its effects is considered non-viable because it requires that the subjects are kept under supervision for

several months. Instead, determinations of EE are performed as the only feasible approach, drawing inferences from these surrogate measurements (Garrow *et al.* 1980). If EE is found to be the same in obese and lean individuals, it is inferred that overweight subjects have a greater energy intake than lean subjects (Amatruda *et al.* 1993). The opposite has been concluded when overweight is associated with relatively low EE (Ravussin *et al.* 1985; Weigle, 1988; Leibel *et al.* 1995). Nevertheless, measurement of EE is difficult because it is comprised of three fractions: (1) RMR; (2) thermic effect of feeding; (3) activity-related EE. The difficulty in obtaining reproducible measurements has resulted in multiple contradictory reports. As an example of the chaotic situation, for variations in the thermic effect of feeding alone there are more than fifty published studies and many of the results negate others (for review, see Granata & Brandon, 2002). As current determinations of EE have become a methodological impasse in determining if there is a homeostatic control of the human body weight, the present study was designed with a different approach.

The present study was designed to determine if there is a homeostatic control of human body weight. The design

included: (1) experimental modification of energy ingested from observation of weight response; (2) inference from a new surrogate index of EE measured in weight units. The present study was performed in two healthy subjects with controlled activity. Three standardized diets of different energetic content were ingested in succession, body weight changes were measured and the surrogate index calculated. Table 1 shows the products that were used to prepare the diets, as well as their energy content (taken from the manufacturers' labels). Foods of the same brand were always used, from the same manufacturer (Tesco Stores Ltd, Cheshunt, Bucks., UK). For dessert, the same chocolate bar was used (Mars chocolate-nougat; Masterfoods, Slough, Berks., UK). Water or non-energy-containing soft drinks were allowed *ad libitum*. From the experience of the author, a diet of 10 073 kJ (2406 kcal)/d was considered isoenergetic (not normally resulting in body weight changes) for the present subjects and their living conditions. A second diet of 6255 kJ (1494 kcal)/d was considered hypoenergetic, and a third diet of 13 791 kJ (3294 kcal)/d was considered hyperenergetic.

With regard to the surrogate index for inference of the body weight set-point, a new method for measuring RMR was devised. This index consisted in the amount of weight lost in an 8 h overnight period (WL8H). Body weight was measured wearing shorts every day immediately after voiding urine at 23.00 and 07.00 hours. The urine passed during that overnight period was collected and measured with a burette. The difference in body weight (g) – urine volume (ml) for that period was taken as the WL8H. For the purposes of the present study, the weight of 1 ml urine was considered to be 1 g and that of the overnight insensible water losses to be constant. Thus,

$$\begin{aligned} \text{WL8H} &= \text{body weight (g) at 23.00 hours} \\ &\quad - \text{body weight (g) at 07.00 hours} \\ &\quad - \text{urine (g) passed between 23.00 and 07.00 hours.} \end{aligned}$$

### Subjects

The study was performed on two normal healthy subjects (A. E. M. (subject A)) and a volunteer (subject B). Both subjects lived in the same house, as students of the same graduate programme in London, UK, away from their native countries and families and in relative social

seclusion. Subject A was a married 47-year-old male of Spanish ethnicity, height 1.70 m and BMI 23.4 kg/m<sup>2</sup>. Subject B was a married 45-year-old male of Persian ethnicity, height 1.68 m and BMI 25.4 kg/m<sup>2</sup>.

### Stages and conditions of the study

The study was performed in two stages. Stage 1 (77 d) included only subject A (7 October – 24 December 2002). Stage 2 (133 d) was performed on both subjects (27 February – 10 July 2003). The subjects complied with the following conditions: (1) a fixed physical activity schedule according to their academic activities and not allowing social events; (2) an intake of standardized diets, not allowing any other food; (3) a timed intake of food and body weight measurements. For the fixed physical activity the subjects walked the same short distance every day to take underground trains to reach the facility at which their graduate programme took place, staying there from 08.00–09.00 to 17.00–19.00 hours, including Saturdays. On Sundays, the subjects went to the library or visited museums in the South Kensington area of London, spending the day there. There was no extended exposure to cold or hot weather; the temperature at home was maintained at 20–23°C, turning the central heating on at 06.00 hours and off at 23.00 hours. The schedule for meals was the following (with a tolerance of  $\pm 30$  min): breakfast at 07.30 hours, lunch at 12.30 hours and dinner at 19.00 hours, with no fluid or food after 22.00 hours.

### Measurements and food intake

During stage 1, body weight was measured using a digital scale with sensitivity to changes of 100 g (Salter 994; Tonbridge, Kent, UK). To validate a measurement, two equal readings, or two readings with a difference < 100 g, had to be observed consecutively. The mean of two determinations was recorded when the displays were not equal. The sequence of the dietary regimens was: (1) isoenergetic for 2 weeks; (2) hypoenergetic for 5 weeks; (3) isoenergetic for 4 weeks.

During stage 2, a new mechanical scale with sensitivity to changes of 50 g was used for weight determinations. The scale was certified for medical use in the UK and calibrated

**Table 1.** Composition of the three standardized diets

Food	Hypoenergetic*		Isoenergetic*		Hyperenergetic*	
	g	kJ	g	kJ	g	kJ
Whole milk	250†	670	500	1340	750	2010
Processed orange juice	250†	448	500	896	750	1344
Processed tomato juice	250†	230	250	230	250	230
Wholemeal bread	720	3559	792	3915	864	4271
Cooked chicken breast	100	448	200	896	250	1118
Tomato	200	209	200	209	200	209
Cheese	0	0	100	942	140	1319
Biscuit (cookie)	15	314	31	628	62	1256
Chocolate-nougat bar	20	377	54	1017	108	2034

\* Hypoenergetic 6255 kJ (1494 kcal); isoenergetic 10 073 kJ (2406 kcal); hyperenergetic 13 791 kJ (3294 kcal).

† ml.

to the International Standard ISO 9002 before leaving the factory (Weylux 424; H. Fereday & Sons Ltd, London, UK). This scale was kept at home and calibrated daily to zero before the weight determination at 23.00 hours. Oral temperature was determined at 07.00 hours using individual electronic thermometers controlled weekly against each other with equal determinations in water at 35–37°C. In addition to the regimens used in stage 1, a hyperenergetic diet was used in stage 2. The succession of diets for stage 2 was: (1) isoenergetic for 2 weeks; (2) hypoenergetic for 5 weeks; (3) isoenergetic for 3 weeks; (4) hyperenergetic for 5 weeks; (5) isoenergetic for 4 weeks.

#### Analysis of data

The body weight determinations at 07.00 hours were used to analyse trends. To standardize a starting point for both subjects, the mean of the body weights at 07.00 hours determined during the first 2 weeks was considered as the basal body weight. This basal body weight was subtracted from every determination, with the resulting value used to plot a graph. The relative variations of the WL8H determined with the digital and mechanical scale were estimated using the CV. For inference of the body weight set-point, the null hypothesis stated that the body does not change its metabolic rate, measured by the mean WL8H, in response to diets of different energy content. Student's *t* test (two-tailed) and ANOVA were used to compare the mean values. A *P* value < 0.05 was judged significant for rejecting the null hypothesis.

## Results

### Stage 1: subject A

During the initial 2 weeks, the isoenergetic diet was not associated with any sustained trend in body weight change (mean value 67.5 kg). The hypoenergetic regimen was associated with accelerated initial weight loss that tended to level off after 2 weeks, as illustrated in Fig. 1. This initial rapid loss was associated with diuresis during the first 3 d. By the end of the first week of hypoenergetic

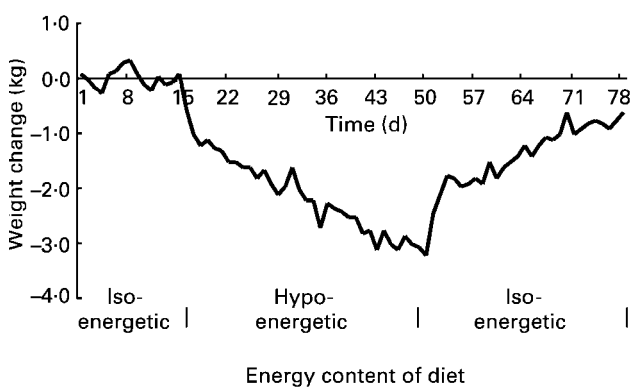
intake, the subject had lost 1.5 kg and by the end of the second week, 2.1 kg. After 5 weeks of hypoenergetic intake, 3.2 kg had been lost. Weight homeostasis could be observed graphically as the isoenergetic diet led to sustained weight gain when it was resumed after the hypoenergetic regimen, on day 50 of the study, as seen in Fig. 1. An initial rapid weight gain of 1.4 kg during the first week tended to level off and only a further 1.2 kg was recovered during the following 3 weeks. Although the curve of weight gain suggests a trend to bring the determinations to their original 'defended' level, a complete recuperation of the initial weight was not achieved by 24 December (day 77), when the subject stopped the study with a deficit of 0.6 kg.

The WL8H was determined seventy-five times (two results were missing due to improper urine collection). The means of the WL8H determined under the hypo- and isoenergetic regimens were significantly different (227.9 v. 268.1 g respectively; *P* = 0.0351). The CV of these determinations (digital scale) were 33.5 and 31.3 % respectively (see Table 2).

### Stage 2: subjects A and B

Stage 2 lasted 19 weeks for subject A and 18 weeks for subject B. The isoenergetic diet was not associated with any sustained trend in body weight change during the first 2 weeks (mean values 67.7 kg for subject A and 71.6 kg for subject B). Body weight changes associated with different diets had a pattern similar to that observed during stage 1, with fast initial loss or gain, tending to level off after the first 2 weeks. The shape of graphs for body weight changes was very similar for both subjects, although subject B lost more weight by the end of the hypoenergetic regimen, as seen in Fig. 2 for subject A and Fig. 3 for subject B (3.5 and 4.0 kg respectively). During this hypoenergetic period, subject B suffered three mild episodes of oral *Herpes simplex*. The existence of a homeostatic defence of the body weight could also be observed graphically in both subjects, as the body weight reaction to the isoenergetic diet was different according to the circumstances. In normal initial conditions, this diet was associated with body weight stability in both subjects. After 5 weeks of energy restriction and body weight loss, the isoenergetic diet led to sustained body weight gain. On the other hand, after 5 weeks of the hyperenergetic diet, the isoenergetic diet led to sustained body weight loss tending to level off. Subject B completed only 20 d of the last period, losing 1.2 kg with the isoenergetic diet, still 0.7 kg above the initial basal body weight (total 125 d). Subject A completed the final 4 weeks under the isoenergetic regimen, losing a total of 1.6 kg, still 0.7 kg above the initial basal weight (total 133 d).

The WL8H was determined 125 times for subject A and 118 times for subject B (eight missing determinations for subject A and seven for subject B, due to improper urine collection). Diets of higher energy content were also associated with a larger WL8H in stage 2. The existence of the body weight set-point was inferred statistically, as shown in Table 2. The mean values of the WL8H



**Fig. 1.** Stage 1: accumulated body weight changes in subject A eating two standardized diets: isoenergetic (10 073 kJ (2406 kcal)/d) and hypoenergetic (6255 kJ (1494 kcal)/d). For details of subject, diets and procedures, see Table 1 and p. 480.

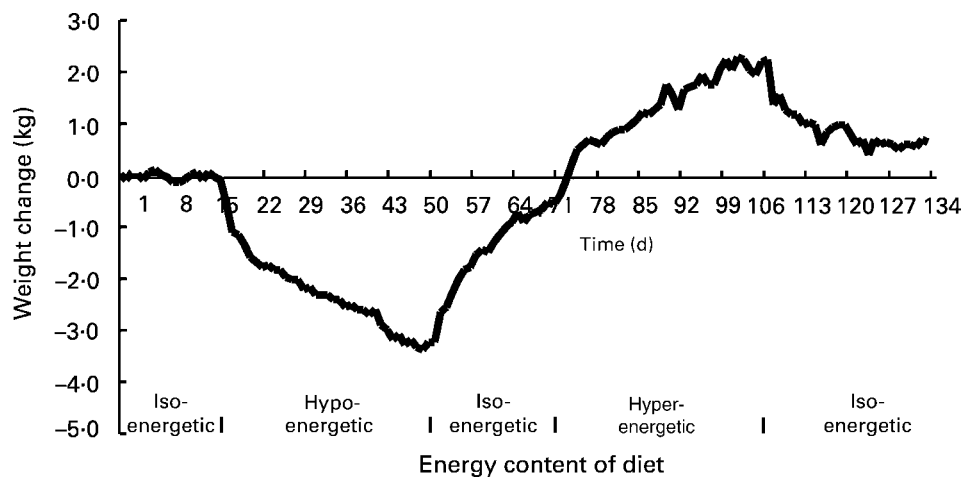
**Table 2.** Weight lost in 8 h overnight (WL8H) and body temperature at 07.00 hours in response to three diets of different energy content\* (Mean values and standard deviations)

Diet...	Hypoenergetic				Isoenergetic				Hyperenergetic				Statistical significance of effect	
	Mean	SD	<i>n</i>	CV (%)	Mean	SD	<i>n</i>	CV (%)	Mean	SD	<i>n</i>	CV (%)	<i>F</i>	<i>P</i>
Subject A, stage 1 WL8H (g)	227.9	76.4	34	33.5	268.1	84.0	41	31.3	NA				2.371†	0.0351
Subject A, stage 2 WL8H (g)	235.4	43.5	32	18.5	261.8	37.3	60	14.2	301.3	38.6	33	12.8	23.34	<0.0001
Temperature (°C)	35.95		35		35.93		63		35.99		35		2.22	0.1127
Subject B, stage 2 WL8H (g)	249.2	38.9	33	15.6	271.5	39.9	52	14.7	313.2	47.3	33	15.1	20.1	<0.0001
Temperature (°C)	36.35		35		36.40		55		36.51		35		11.33	<0.0001

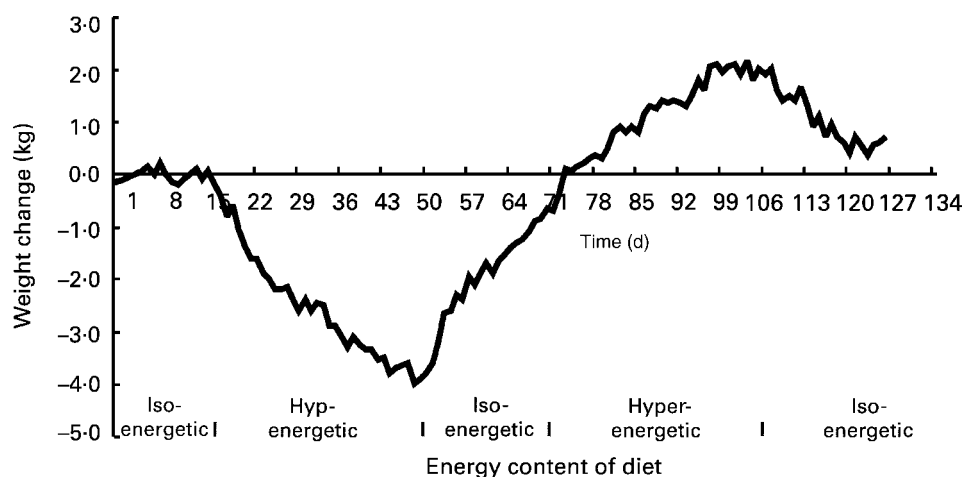
WL8H, weight loss over 8 h; NA, not applicable.

\* For details of subjects, diets and procedures, see Table 1 and p. 480.

† *t*.



**Fig. 2.** Stage 2: accumulated body weight changes in subject A eating three standardized diets: isoenergetic (10 073 kJ (2406 kcal)/d), hypoenergetic (6255 kJ (1494 kcal)/d) and hyperenergetic (13 791 kJ (3294 kcal)/d). For details of the subject, diets and procedures, see Table 1 and p. 480.



**Fig. 3.** Stage 2: accumulated body weight changes in subject B eating three standardized diets: isoenergetic (10 073 kJ (2406 kcal)/d), hypoenergetic (6255 kJ (1494 kcal)/d) and hyperenergetic (13 791 kJ (3294 kcal)/d). For details of the subject, diets and procedures, see Table 1 and p. 480.

determined for the different dieting periods were significantly different ( $F > 20$ ;  $P < 0.0001$  for both subjects). The absolute difference of these mean values was, however, greater for hyper- v. isoenergetic diets than for

hypo- v. isoenergetic diets (subject A 39.5 v. 26.4 g, subject B 41.7 v. 22.3 g). The mean value for temperature at 07.00 hours was approximately 0.5°C greater in subject B than in subject A, as shown in Table 2. In both subjects, the mean

temperatures tended to be greater under the hyperenergetic regimen, but the difference was significant only for subject B.

The variability of the WL8H determinations was substantially reduced by the use of a mechanical scale during stage 2, as demonstrated by smaller CV (range 12.8–18.5 %; Table 2).

## Discussion

The present study strongly supports the body weight set-point theory in several ways. First, the most notable evidence is the body weight reaction to experimental modifications of the amount of energy ingested. After energy restriction, body weight increased in both subjects with the isoenergetic diet; after overfeeding, the same regimen caused weight loss. Second, analysis of the surrogate index (WL8H) showed that RMR is reduced during starvation and increases under excessive feeding. Third, the body weight lost or gained is not commensurate with the amount of deficient or excessive energy taken. After 5 weeks of overeating 3718 kJ/d (total 130 130 kJ), the body weight gain for both subjects was about half the theoretical minimum 3.9 kg, as 1.0 kg stored weight may contain a maximum 33 077 kJ (7900 kcal) (Peters *et al.* 2000). On the other hand, after 2 weeks of energy restriction the weight loss tended to level off during the following weeks. Last, in normal conditions of isoenergetic diets, there were only small daily variations in weight. During the last week of stage 2 in subject A, the difference between days was very small (mean value 75 g). If we consider that this amount is about 0.1 % of the subject's weight, we can conclude that the precision is extraordinary enough to call the body weight set-point the 'ponderostat' (from Latin *ponder*, weight).

Energy homeostasis can be expressed in a simple equation: energy stored (weight) = energy ingested (food) – EE (broken into three components). If we know the values of two parts of the equation, the other can be calculated. Body weight and energy intake are the best choices, because choosing EE means that its fractions will have to be measured. Nevertheless, the equation is normally solved through determinations of EE, because food intake is considered immeasurable for the purpose of long studies. Measuring EE, however, is beset by methodological difficulties. Total daily EE can be measured after the administration of water labelled with isotopes, followed by the measurements of the clearance of the isotopes and calculations with equations (Seale *et al.* 1989; Amatruda *et al.* 1993; Levine *et al.* 1999). The RMR can be measured in immobile subjects by analysing a portion of expired gases and calculating the EE with equations (Rodriguez *et al.* 2002). The thermic effect of feeding is measured by comparison with the pre-feeding value (Leibel *et al.* 1995). Finally, the EE of activity is calculated as the difference between total EE and the sum of the other measured components. From these complexities, it is not surprising that the results from different studies are discordant.

Food standardization, activity control and weight measurement appear more reproducible. The WL8H was

designed as a straightforward index of RMR, feasible for multiple determinations and statistical analyses. As a proxy index, however, the WL8H is not necessarily equivalent to energetic determinations, since the energy content per g is different for fat, carbohydrate and protein. In a hypoenergetic period there is limited glycogen storage. Thus, EE from fat will result in a lower weight loss compared with EE from glycogen + fat. This assumption is supported by the relatively small difference in WL8H for the hypo- and isoenergetic diets in stage 2. Yet the fact that the isoenergetic diet can cause body weight gain or loss cannot be explained by changes in substrate metabolism. Future studies could combine measurements of WL8H with EE measurements to calculate the substrate balance. Although body temperature might be used as a proxy index of EE, results are less reproducible because they seem affected by volition, such as using a blanket.

The present study has limitations because of the strict supervision and great amount of work required, which makes it difficult to apply on a larger scale. The mean values for many WL8H determinations are required to compensate for variability resulting from the scale's sensitivity (50–100 g). To make the WL8H a useful marker with few determinations we need to use more accurate scales, with capacity to weigh within a precision of 1 g. Such scales are available for industrial use, but they would need adaptation to weigh subjects in recumbent position, as muscle activity from standing up would make readings invalid. There are other issues to consider with regard to the methodology used in the present study. First, use of the WL8H assumes that overnight insensible losses are constant, as expected for a temperate climate like that in London, but changes in temperature or humidity would be an issue in tropical areas. Second, strict control of activities is impossible. Yet, as the RMR is the main consumer of energy (Leibel *et al.* 1995; Garrow, 2000), it is improbable that minor deviations from sedentary activities explain the observed phenomena. Last, a study of two individuals is hardly representative of the population. The consistency of the observations, however, suggests that many individuals may have similar homeostatic mechanisms.

A body weight set-point would defend us against continuously changing body masses at the whim of our energy intakes. On the other hand, a 'ponderostat' cannot function like a thermostat, fixed to a permanent range, because we require adaptation for growing and development. This means that we defend an established set-point, but the system yields upon continuous demands. For instance, entering or leaving marriage influences the body weight and postpartum weight retention is a common problem in women (Ohlin & Rossner, 1996; Sobal *et al.* 2003). Then, it seems that the body weight set-point functions rather as a settling point with new levels set after continuous demands of the outer limits coming from hormonal influences or overfeeding. Obesity could be easily induced in genetically predisposed individuals, although even those at low risk may fall to the attack of an obesogenic environment (Egger & Swinburn, 1997).

In conclusion, the present study strongly suggests that human body weight is homeostatically controlled, at least in some subjects. In addition, it describes a simple and economical method for measuring EE in weight units. Finally, the present study demonstrates that strict dietary supervision for months is difficult, but not impossible. Investigation of a human body weight set-point is important in understanding obesity.

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