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How dieting makes some fatter: from a perspective of human body composition autoregulation

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Dieting makes you fat – the title of a book published in 1983 – embodies the notion that dieting to control body weight predisposes the individual to acquire even more body fat. While this notion is controversial, its debate underscores the large gap that exists in our understanding of basic physiological laws that govern the regulation of human body composition. A striking example is the key role attributed to adipokines as feedback signals between adipose tissue depletion and compensatory increases in food intake. Yet, the relative importance of fat depletion *per se* as a determinant of post-dieting hyperphagia is unknown. On the other hand, the question of whether the depletion of lean tissues can provide feedback signals on the hunger–appetite drive is rarely invoked, despite evidence that food intake during growth is dominated by the impetus for lean tissue deposition, amidst proposals for the existence of protein–static mechanisms for the regulation of growth and maintenance of lean body mass. In fact, a feedback loop between fat depletion and food intake cannot explain why human subjects recovering from starvation continue to overeat well after body fat has been restored to pre-starvation values, thereby contributing to 'fat overshooting'. In addressing the plausibility and mechanistic basis by which dieting may predispose to increased fatness, this paper integrates the results derived from re-analysis of classic longitudinal studies of human starvation and refeeding. These suggest that feedback signals from both fat and lean tissues contribute to recovering body weight through effects on energy intake and thermogenesis, and that a faster rate of fat recovery relative to lean tissue recovery is a central outcome of body composition autoregulation that drives fat overshooting. A main implication of these findings is that the risk of becoming fatter in response to dieting is greater in lean than in obese individuals.

Obesity: Weight cycling: Weight fluctuation: Adaptive thermogenesis

The ancient prescription of Hippocrates (400 BC) that the obese should eat less and exercise more[1] continues nowadays to be a widespread approach for weight management despite its well-documented failures[2]. Weight regain is generally the rule, with long-term follow-up studies indicating that one-third to two-thirds of the weight lost is regained within 1 year and almost all is regained within 5 years[3]. Repeated cycles of weight loss and weight regain, referred to as weight cycling or yo–yo dieting are a frequent occurrence, with the potential for increased cardiovascular risks[4]. Despite these failures, national surveys in Europe and North America indicate that 30–50% women and 10–30% men are currently or have recently attempted dieting to lose weight[5–7]. With studies of the long-term outcomes of energy-restricting diets showing that at least one-third of dieters regain more weight than they lost[8], together with population groups as diverse as obese and lean, young and old, sedentary and athletes attempting to lose weight on some form of diet therapy[4,5], there is concern as to whether dieting may

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paradoxically be promoting exactly the opposite of what it is intended to achieve. To put it bluntly, does dieting make people fatter as proposed nearly three decades ago by Cannon and Einzig[9] in a book entitled *Dieting makes you fat*.

Prospective studies linking dieting to future weight gain

In an article published in 1994 in which a panel of experts for the National Task Force on the Prevention and Treatment of Obesity[10] addressed concerns about the effects of weight cycling and provided guidance on the risk-to-benefit ratio of attempts at weight loss, a main conclusion was that 'the (then) available evidence is not sufficiently compelling to override the potential benefits of moderate weight loss in significantly obese patients'. In the decade that followed, however, more than a dozen prospective studies[11–24], conducted over periods ranging from 1 to 15 years, have suggested that dieting to lose weight is associated with future weight gain and obesity, with many of them showing this association even after adjustment for potential confounders such as baseline BMI, age and several lifestyle and behavioural characteristics. Particularly informative are the 3-year follow-up studies of Stice *et al.*[15] showing that adolescents with baseline dieting had three times the risk of onset of obesity than the non-dieters, and the 6–15-year follow-up study of Korkelia *et al.*[16] reporting that initially normal-weight subjects who were attempting to lose weight had two times the risk of major weight gain (>10 kg) than non-dieters. In contrast, the history of weight-loss attempts in initially overweight men and women subjects in the latter cohort[16] was not consistently associated with increased risk of major weight gain, thereby raising the possibility that the long-term impact of dieting on proneness to fatness may be greater in the lean than in the obese, albeit in young and middle-aged population groups. Furthermore, the recent analysis of a large population-based cohort with a follow-up from adolescence to young adulthood, suggest a dose-dependent association between the number of lifetime intentional weight losses, gain in BMI and risk of overweight[24]. A single episode of weight loss was found to increase the risk of becoming overweight by the age of 25 years almost 3-fold in women and 2-fold in men. In addition, women who reported two or more weight-loss episodes had an even higher (5-fold increased) risk of becoming overweight at the age of 25 years compared with subjects with no intentional weight loss. Weight cycling has also been shown to be a predictor of subsequent weight gain and the risk of obesity in athletes[25]. In a national cohort of 1838 male elite athletes who had represented Finland in international sport competitions between 1920 and 1965, men who performed power sports (boxers, weight lifters and wrestlers), where weight cycling is common, gained 5·2 units of BMI from age 20 to 60 years. In contrast, men without an athletic background gained only 4·2 units of BMI, and athletes without weight cycling gained even less (3·3 units of BMI). These findings are therefore in support of the contention that dieters and weight cyclers may be more prone to future weight gain than non-dieters and non-cyclers.

Causality in the link between dieting and propensity to fatness

But whether dieting *per se* is a causative factor for subsequent weight gain and contributes to the current obesity epidemic is, however, debatable[26–28]. Hill[26] has argued that 'it is not that dieting makes you fat, but that being fat makes you (more likely to) diet', a contention that is supported by data from the Finnish Twin cohort study[16] showing that dieting aggregated in families, and hence suggesting a familial predisposition to gain weight. Indeed, twin studies have demonstrated that, like proneness for obesity, episodes of intentional weight loss have substantial genetic components[29], such that the possibility arises that subjects who are genetically most prone to obesity end up dieting the most and subsequently gain the most weight. In a recent study that directly addressed this question of whether weight gain associated with dieting is better related to genetic propensity to weight gain than to the weight-loss episodes themselves, Pietiläinen *et al.*[24] investigated the association between dieting and weight gain in 4129 individual twins whose weight and height were obtained from longitudinal surveys at 16, 17, 18 and 25 years and examined in relation to the number of lifetime intentional weight-loss episodes of >5 kg at 25 years. In monozygotic twin pairs discordant for intentional weight loss, co-twins with at least one weight-loss episode were found to be 0·4 BMI units heavier at 25 years than their non-dieting co-twins despite no differences in baseline BMI levels. Similarly, in dizygotic twin pairs, co-twins with intentional weight losses gained progressively more weight than non-dieting co-twins (BMI difference 1·7 units at 16 years and 2·2 units at 25 years). Overall, therefore, these findings not only confirm previous studies that dieters may be more prone to future weight gain and that dieters have a genetic propensity for obesity, but they also provide evidence that dieting *per se* may promote subsequent weight gain, independent of genetic factors, in an essentially normal-weight cohort (i.e. <10% overweight as adolescents). Support for this contention that dieting *per se* may drive excess weight gain in non-obese adults, can in fact be derived from classic studies of food deprivation and refeeding showing that more weight is recovered than is lost; a phenomenon referred to as post-starvation weight (or fat) overshooting[30].

Post-starvation fat overshooting

The phenomenon of post-starvation weight overshoot, first documented by Benedict[31,32] in studies of experimental starvation, was subsequently observed during follow-up studies of famine victims of World War II, in men volunteers subjected to experimental semi-starvation or in young army recruits recovering from an 8-week training that included food and sleep deprivation. As shown in Table 1 and elaborated later, data available on dynamic changes in body weight, food intake and/or body composition are informative about the consequences of large weight losses and subsequent weight regain resulting in weight overshooting.

Table 1 Post-starvation hyperphagic overcompensation and weight overshooting in human subjects (Table updated from Dulloo[30])

References	Type of energy deprivation	n	Energy intake after 100% weight recovery	Weight (fat) overshoot (kg)
Benedict[31]	Total fast	5	*	2·7
Benedict et al.[32]	Semi-starvation	11	*	3·1
Fleisch[33]	Food rationing	700	*	6·5†
Keys et al.[35]	Semi-starvation	12	*	3·3 (4·6)‡
Nindl et al.[36]	Army training	10	–	5·0 (4·0)§
Young et al.[37]	Army training	8	–	5·4
Friedl et al.[38]	Army training	10	*	2·4 (4·2)§

*Increased energy intake above levels prior to energy deprivation.
†Data calculated from graph published by Martin & Demole[34].
‡Body fat measured by hydrodensitometry.
§Body fat measured by dual-energy X-ray absorptiometry.

The Swiss food rationing experiment

In Switzerland, when food rationing was implemented in 1941, the physiologist Fleisch[33] was asked by the 'Federal Commission for Wartime Feeding' to monitor the health consequences of this intervention. In addition to the assessment of mortality and morbidity related to CVD, digestive and infectious diseases, the nutritional status was also monitored in 700 persons of different ages, social status and living areas, every 1–2 months between autumn 1941 and spring 1946. The data collected on food consumption and body weight, compiled and published about 30 years later by Martin and Demole[34] indicate that food intake and body weight dropped to the lowest level during the summer of 1945. At the end of that year, food rationing was abandoned and products were available again in larger quantities; food consumption and body weight rose rapidly. During the subsequent months when food availability improved further, the phenomena of energy overcompensation (hyperphagia) and weight overshooting became evident (Table 1).

The Minnesota experiment

Coincidentally, it was during the same time period that Keys et al.[35], motivated by the desire to obtain quantitative information upon which to base an efficacious relief programme directed at nutritional rehabilitation of the starvation victims of World War II, were conducting their study of experimental semi-starvation and refeeding in Minnesota. The thirty-two healthy volunteers who completed the study (many of whom were conscientious objectors of war), were in continuous residence at the University of Minnesota during the 12-week control baseline period, 24 weeks of semi-starvation and 12 weeks of restricted rehabilitation; furthermore, twelve of them also remained in the laboratory during the first 8 weeks after removal of dietary control, i.e. *ad libitum* refeeding. The total loss in body weight of about 25% of the original weight in each individual reproduced the conditions of severe semi-starvation, and is comparable with values found in severe famine. Following removal of dietary control at the end of week 12 of restricted rehabilitation, the food intake increased markedly above the pre-starvation level, and this hyperphagic response persisted for several weeks after body weight had reached the pre-starvation level, and contributed to weight overshooting mostly as fat.

The Army Ranger multi-stressor experiments

In more recent years, similar body weight and fat overshooting have also been reported in young men at the US Army Ranger School recovering from about 12% of weight lost following 8–9 weeks of training in a multi-stressor environment that includes energy deficit and sleep deprivation[36–38]. Nindl et al.[36] found that at week 5 in the post-training recovery phase, body weight had overshot by 5 kg, reflected primarily in large gains in fat mass, with all ten subjects showing higher fat mass than before weight lost. Similarly, in young male volunteers participating in another 8-week US Army Ranger course that involved four repeated cycles of restricted energy intake and refeeding, Friedl et al.[38] found that more weight was regained than lost at week 5 of recovery following training cessation, with fat overshooting representing an increase of 40% in body fat above pre-training levels. Data obtained in a parallel group of subjects revealed that hyperphagia peaked at about 4 weeks post-training, thereby suggesting that hyperphagia was likely persisting over the last week of refeeding during which body fat had already exceeded the baseline.

The search for control systems regulating body composition during weight recovery

The earlier observations raise the question of what drives hyperphagia well after body weight or body fat had been fully recovered. Is it an explanation based solely on long-lasting psycho-biological reaction to food deprivation? Preoccupations with food and food obsession have often been described long after episodes of food deprivation or dietary restraint[39]. However, what is particularly striking from a closer inspection of data on the real-time pattern of hyperphagia relative to changes in body composition in the men recovering weight in the Minnesota Experiment (Fig. 1) is that when their body fat had been completely recovered (i.e. 100% of control period), at which point the fat-free mass (FFM) was not yet fully recovered, the hyperphagia was still very much evident. It only disappeared as FFM recovery approached 100% of the control level. These observations about hyperphagic overcompensation and its relationship with changes in body composition suggest a link between lean tissue recovery relative to fat recovery, sustained hyperphagia and fat overshooting, and raise fundamental questions about how control systems operate to re-establish lean and fat tissues during weight recovery:

(i)   What is the relative importance of fat and lean tissue depletion as determinants of post-starvation hyperphagia?
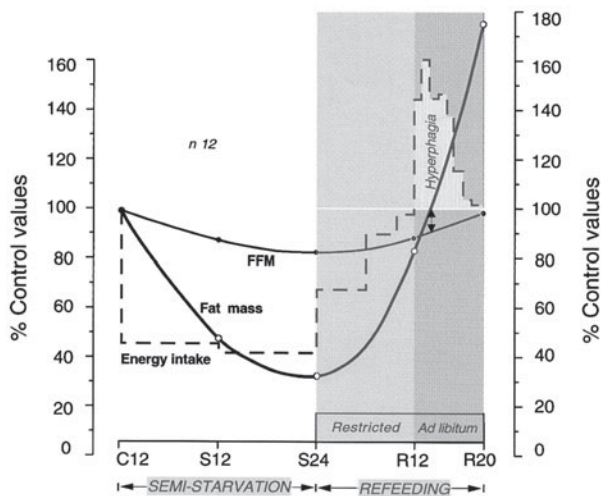
Fig. 1. Pattern of changes in energy intake, body fat and fat-free mass (FFM) during semi-starvation and refeeding in the twelve men who completed all phases of the Minnesota Experiment (including the *ad libitum* phase of refeeding). All values are expressed as percentages of corresponding values during the control (pre-starvation) period. C12: end of 12 weeks of control period; S12 and S24: end of 12 weeks and 24 weeks of semi-starvation respectively; R12 and R20: end of 12 weeks of restricted refeeding and 8 weeks of *ad libitum* refeeding, respectively. The double-headed arrow indicates that at the time-point when body fat had been fully recovered (i.e. 100% of control period value), FFM recovery is still far from complete, with hyperphagia persisting until completion of FFM recovery. Adapted from Dulloo *et al.*[41].

(ii) What drives the faster rate of fat recovery relative to lean tissue recovery even in the absence of hyperphagia as observed in the period of restricted refeeding in the Minnesota Experiment? Could this be explained by the adaptive reduction in energy expenditure (i.e. suppressed thermogenesis) that occurs during weight loss and which persists during weight recovery? What then is the relative importance of fat and lean tissue depletion as determinants of such adaptive suppression of thermogenesis during weight recovery?

(iii) What determines the large inter-individual variability in partitioning of energy into lean and fat tissues during weight recovery?

In addressing these questions, we revisited the Minnesota Experiment and applied more elaborate statistical and analytical tools in a re-analysis of the data on the dynamic changes in body composition, food intake and BMR in response to the 24 weeks of semi-starvation, 12 weeks of restricted refeeding and subsequent 8 weeks of *ad libitum* refeeding. The methodological approaches and results of this re-analysis have been reported in detail elsewhere[40–44], and are summarised below.

Energy partitioning between lean and fat tissues: an individual characteristic

The notion that the control of partitioning between the body's protein and fat compartments is an individual characteristic was first proposed by Payne and Dugdale[45]

and supported by data from studies of prolonged fasting showing that the fraction of energy mobilised from protein (termed the P-ratio) during weight loss is relatively constant in a given individual but varies considerably between individuals[46]. Using a quantitative index of energy partitioning defined as body energy mobilised from protein during weight loss (the semi-starvation P-ratio) or as the proportion of energy gained as protein during weight recovery (the refeeding P-ratio) in the first part of our Minnesota Experiment re-analysis[40], we showed that the highly variable P-ratio during refeeding is strongly correlated with the P-ratio during semi-starvation, particularly after controlling for inter-individual variability in the degree of fat recovery (Fig. 2(a)). This demonstration that the individual's P-ratio during semi-starvation is conserved during refeeding therefore provides direct evidence to the proposal of Payne and Dugdale[45] that the control of energy partitioning is an individual characteristic. Furthermore, in the search for predictors of the large inter-individual variability in energy partitioning[40], we found that the initial % body fat (i.e. % body fat prior to weight loss) to be the most important determinant of inter-individual variability in P-ratio (Fig. 2(b)), which suggests that the higher the initial adiposity, the lower the proportion of energy mobilised from body protein, and hence the greater the propensity to mobilise fat during weight loss and to subsequently deposit fat during weight recovery. In order to examine in more detail the relationship between initial adiposity and the partitioning characteristic (Pc) of individuals, we have pooled the Minnesota data on P-ratio in normal-weight Caucasians with those calculated for obese Caucasians undergoing prolonged fasting[46] or semi-starvation[47]. As can be seen in Fig. 2(b), >85% of the variance in the P-ratio could be explained by the % body fat prior to weight loss. The steep part of the exponential curve lies between 8 and 20% body fat, and a shift from the lower to the upper values in this range, generally considered to reflect a 'normal' range of adiposity for men living in affluent societies, results in 2·5–3-fold reduction in P-ratio. This extremely high sensitivity of the P-ratio with regard to the initial body composition emphasises the critical importance of even small differences in the initial % body fat in dictating the individual's energy-Pc and, hence, the pattern of lean and fat tissue deposition during weight loss and subsequent weight recovery.

Suppressed thermogenesis: feedback signals from fat tissue

It is well established from longitudinal studies of fasting and energy restriction that the reduction in BMR and total energy expenditure during weight loss is greater than can be accounted for by the loss of active tissues. This reduction in the energy cost of maintenance is adaptive in that it reduces the rate at which body's tissues are being depleted, and has been demonstrated both in normal-weight subjects[35,48–50] as well as in obese individuals[48–50]. In order to determine whether this adaptive reduction in thermogenesis during weight loss persists during weight recovery, and underlies the disproportionately greater rate of recovery of fat mass relative to FFM, the
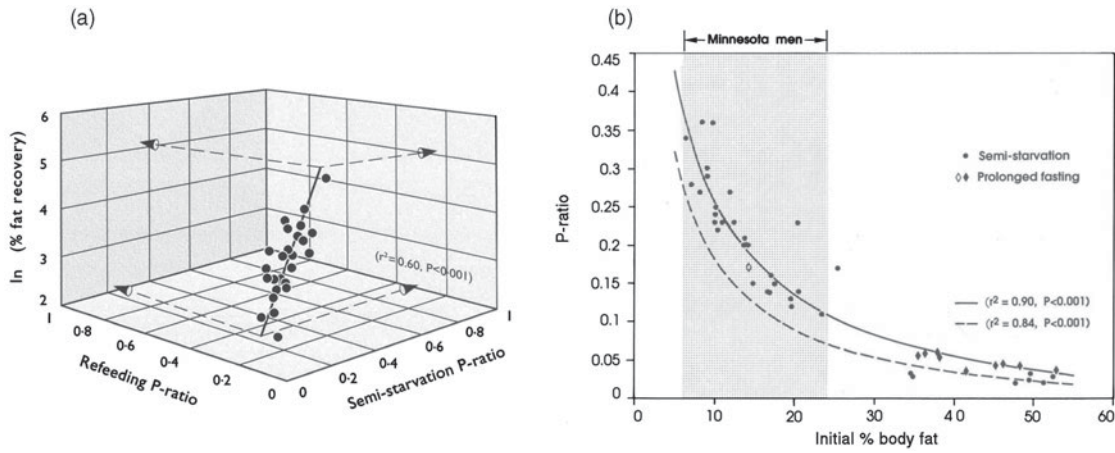
Fig. 2. (a) Three-dimensional plot showing inter-relationship between P-ratio during semi-starvation (i.e. proportion of energy mobilised from protein), P-ratio during refeeding (i.e. proportion of energy deposited as protein), and the natural logarithm of body fat recovery during refeeding; Adapted from Dulloo et al.[40] (b) Relationship between the proportions of energy mobilised from protein (P-ratio) during severe energy deficit and the initial (pre-starvation) percentage body fat. All data are from Caucasians and derived from studies of Keys et al.[35], Henry et al.[46] and Passmore et al.[47]. (●) Semi-starvation; (◇ ◆) prolonged fasting; (——, – –), based on Minnesota Experiment data of body composition either corrected or uncorrected for excess hydration and relative bone mass, respectively; (∷) the range of percentage body fat for normal-weight individuals. Adapted from Dulloo et al.[40].
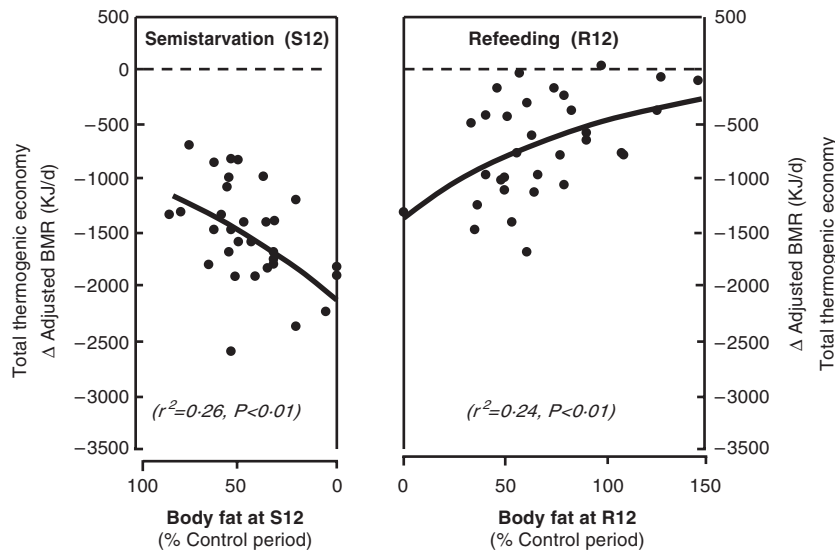

Fig. 3. Relation between suppressed thermogenesis, assessed as change in BMR adjusted for changes in fat-free mass (FFM) and fat mass, and the state of depletion of body fat stores, during weight loss (S12, week 12 of semi-starvation) and during weight recovery (R12, week 12 of restricted refeeding). Adapted from Dulloo and Jacquet[42].

dynamic changes in body composition and BMR of the thirty-two Minnesota men who completed the 24 weeks of semi-starvation and first 12 weeks of restricted refeeding were re-analysed. The data on changes of BMR after adjusting for changes in FFM and fat mass (i.e. an index of energy conservation through suppressed thermogenesis) revealed that (i) the suppression of thermogenesis which was evident during the phase of weight loss persisted during weight recovery and (ii) the extent to which thermogenesis was suppressed during the phases of weight loss and weight recovery was determined not only by the food energy deficit *per se* but also by the extent to which body fat was depleted[42]. This continuum in the relation between suppressed thermogenesis and fat depletion (and not with FFM depletion) during both phases of weight loss and weight recovery (Fig. 3) therefore reflects the operation of a control system with a negative feedback loop between a component of adaptive thermogenesis and the state of depletion of the fat stores, such that suppressed thermogenesis during weight recovery would accelerate body fat recovery. Quantitatively, this suppressed thermogenesis during weight recovery is calculated to
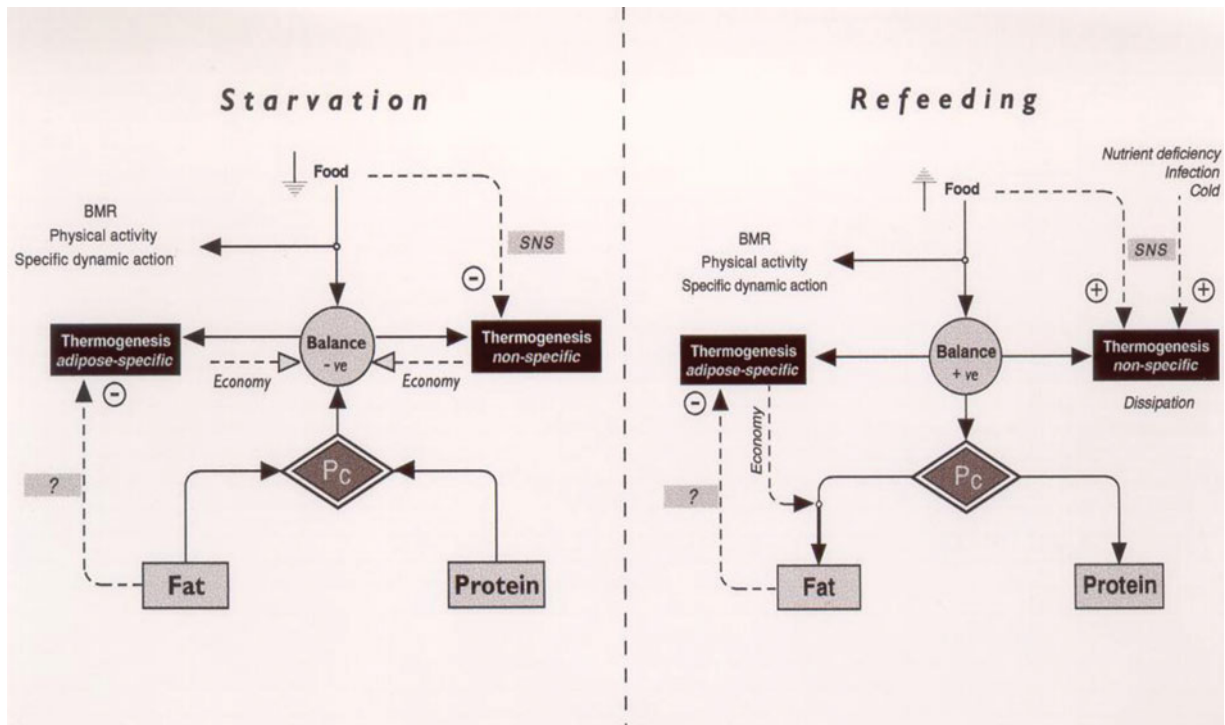
Fig. 4. (Colour online) Schematic representation of the regulation of body weight and body composition during a cycle of weight loss (starvation) and weight recovery (refeeding). In this diagram, the two distinct control systems underlying adaptive thermogenesis (the non-specific control and the adipose-specific control) are integrated with the more 'basal' control of partitioning between the body fat and protein compartments as determined by the partitioning characteristic (Pc) of the individual; see text for details; SNS: sympathetic nervous system; adapted from Dulloo and Jacquet[51].

represent an energy economy of 10–15% in BMR when integrated between 0 and 100% fat recovery[40,42].

Integrating the control of energy-partitioning and adaptive thermogenesis

An integration of these control systems in the regulation of body composition during a cycle of weight loss and weight recovery is discussed with the help of a schematic diagram presented in Fig. 4. This diagram embodies the findings that the control of body energy-partitioning between protein and fat is an individual characteristic, i.e. individuals vary in their Pc during weight loss and weight recovery, and takes into account the two distinct control systems for adaptive thermogenesis which can operate independently of each other: (i) one that is a direct function of food intake and energy balance (referred to as the non-specific control of thermogenesis, which is under the control of the sympathetic nervous system) and (ii) the other that is a direct function of the state of depletion of the fat stores (referred to as the adipose-specific control of thermogenesis)[51]. During starvation, the control of partitioning determines the relative proportion of protein and fat to be mobilised from the body as fuel (i.e. the individual's Pc), and the energy conserved due to suppressed thermogenesis is directed at reducing the energy imbalance, with the net result that there is a slowing down in the rate of protein and fat mobilisation in the same proportion as defined by the Pc of the individual. During starvation, therefore, the

functional role of both control systems underlying suppressed thermogenesis is to reduce the overall rate of fuel utilisation. During refeeding, the control of partitioning operates in such a way that protein and fat are deposited in the same relative proportion as determined by the Pc of the individual during starvation, and the increased availability of food leads to the rapid removal of suppression upon the non-specific (sympathetic nervous system-mediated) control of thermogenesis. In contrast, the suppression of the thermogenesis under adipose-specific control is only slowly relieved as a function of fat recovery, such that the energy that continues to be spared is directed specifically at the replenishment of the fat stores. The net effect, as demonstrated[40] using both statistical and numerical approaches in our re-analysis of data from the Minnesota Experiment, is that fat is deposited in excess of that determined by the Pc of the individual, thereby contributing to the disproportionate rate of fat relative to lean tissue recovery. Direct evidence in support for the existence of mechanisms that suppress thermogenesis and accelerate specifically fat mass (and not FFM) can be obtained from animal studies of refeeding after energetic restriction[51]. In human subjects, a role for suppressed thermogenesis driving catch-up fat can also be derived from patients recovering from malnutrition resulting from non-neoplastic gastrointestinal disease[52], as well as from men and women recovering weight (essentially fat) over 6 months after 2 years of sustained energy restriction in the biosphere 2 experiment[53].
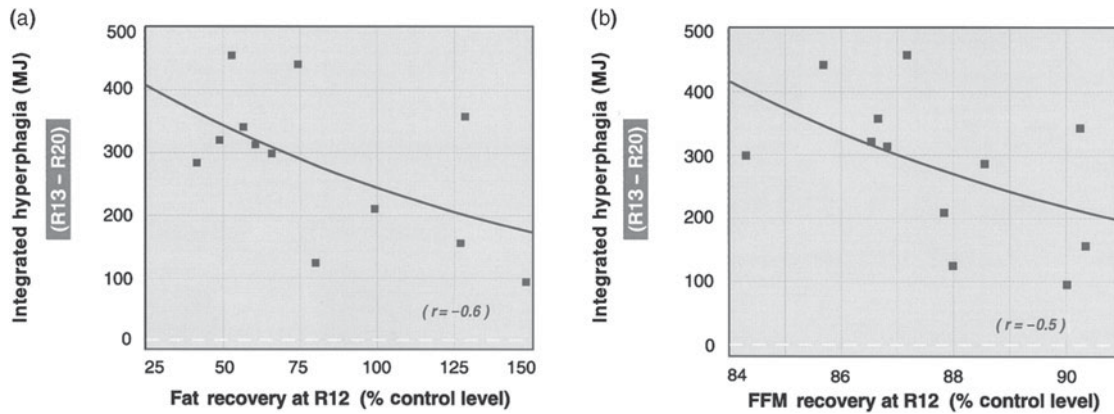
Fig. 5. Relationship between hyperphagic response during *ad libitum* refeeding and the degree of (a) fat recovery or (b) fat-free mass (FFM) recovery, both expressed as % control values. The correlation between hyperphagia and one of the two tissue compartments persists after adjusting (by partial correlation) for variability in the other compartment. Adapted from Dulloo *et al.*[41]. R12, R20 correspond to the end of 12 weeks of restricted refeeding and 8 weeks of *ad libitum* refeeding, respectively. R13 corresponds to the first week of *ad libitum* refeeding.

Compensatory hyperphagia: feedback signals from fat and lean tissues

To gain insights into the determinants of post-starvation hyperphagia in the Minnesota Experiment, the individual data on food intake, body fat and FFM of the twelve subjects who remained in the laboratory during the 8 weeks period of *ad libitum* refeeding (Fig. 1) were used to calculate the following variables[41]:

(i) A quantitative index of hyperphagia, i.e. the total hyperphagic response during the 8-week *ad libitum* refeeding period, calculated as the energy intake in excess of that during the pre-starvation (control) period;

(ii) A quantitative index of the degree of fat and FFM depletion just before *ad libitum* refeeding, calculated as the deviation in fat and FFM from their respective pre-starvation values; and

(iii) A quantitative index of the deficit in energy intake just before *ad libitum* refeeding, calculated as the difference between the energy intake during the period of restricted refeeding and that during the pre-starvation (control) period.

The results indicate that the hyperphagic response over the 8-week *ad libitum* period was inversely and independently correlated to both the degree of fat depletion and FFM depletion (Fig. 5). Furthermore, the results of stepwise-regression analysis indicated that of the three determinants of hyperphagia, it is the degree of fat depletion that is the strongest, with a significant contribution from lean tissue depletion as well as from the energy intake deficit prior to *ad libitum* refeeding; the three variables together explained nearly 80 % of variability in post-starvation hyperphagic response. A considerable component of the hyperphagic response to energy deprivation can therefore be regarded as the outcome of an autoregulatory control system that contributes to the restoration of body weight and body composition, with feedback loops between the state of depletion of both the fat and FFM compartments and

hunger–appetite centres in the central nervous system. These findings therefore suggest the existence not only of adipostatic mechanisms, e.g. via leptin system[54], but also of proteinostatic mechanisms in the control of food intake.

The existence of an appetite mechanism driven by the demands for protein generated by lean tissue growth is consistent with the animal and human literature that the nutrient requirements during growth or catch-up growth and the control of food intake are dominated by the impetus for lean tissue growth[55–57]. More recently, the notion that a signal(s) associated with lean mass exerts a determining effect over self-selected food consumption has also been proposed by Blundell *et al.*[58], who in a reassessment of data on food intake over a 12-week intervention period in adult human subjects found that it was FFM, but not fat mass or BMI, which predicted (as well as correlated with) meal size and daily energy intake. They postulated that this signal may interact with a separate class of signals generated by fat mass. In his proposal for 'protein–stat' mechanisms that regulate lean body mass, Millward[57] emphasised that its mode of operation would require an aminostatic component of appetite regulation in which food intake is adjusted to provide the amino acids and protein needs for lean tissue growth or maintenance. However, the evidence in support of the aminostatic theory is fragmentary, and the extent to which the protein requirements for lean tissue (re)growth and appetite control are mediated by plasma changes in amino acids is unknown. An alternative explanation may reside in the increasingly recognised role of the skeletal muscle as an endocrine organ. Recent applications of proteomic approaches to investigate factors secreted by skeletal muscle[59] have revealed that myocytes are capable of producing several hundred secreted proteins (i.e. myokines), the identity and function of most of which remain to be elucidated. The recognition that a multiplicity of adipokines and myokines are secreted by adipocytes and myocytes, respectively, opens new avenues for research towards their
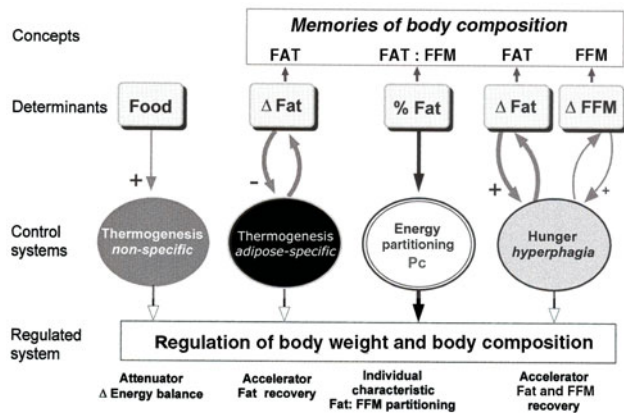
Fig. 6. Conceptual model for autoregulation of body composition during weight recovery. (I) The control of energy partitioning between lean and fat compartments confers to the individual his/her partitioning characteristic (Pc). The demonstrations that the initial adiposity explains most (about 90%) of the variability in Pc, and that the Pc of the individual during semi-starvation is conserved during refeeding[40], suggest that the initial body composition expressed as % body fat (which reflects the ratio of fat to fat-free mass (FFM)) provides the individual with a 'memory of partitioning' which dictates an autoregulatory control system that underlies partitioning between protein and fat during weight loss and subsequent weight recovery. (II) Thermogenesis, which is suppressed during weight loss, remains suppressed during weight recovery as a function of fat depletion, but unrelated to FFM depletion[42]. This leads to the concept for the existence of a 'fat-stores memory' which governs the suppression of thermogenesis as a function of the replenishment of the fat stores. Its functional importance is to accelerate specifically fat replenishment, thereby contributing to the disproportionate rate of fat relative to lean tissue recovery. This adipose-specific control of thermogenesis, which specifically accelerates fat recovery is distinct from the 'non-specific' control of thermogenesis which functions as an attenuator of energy imbalance, and is dictated by the food energy flux rather than by fat depletion. (III) Hunger–appetite drive leads to hyperphagia, the magnitude of which is determined by the extent to which body fat and FFM are depleted, with the degree of fat depletion being the stronger determinant[41]. This hyperphagic response therefore seems to be dictated not only by a memory of the initial fat stores but also by a memory of the initial FFM compartment. The functional importance of this increase in the hunger–appetite sensation, with consequential hyperphagia, is to accelerate the restoration of both lean and fat compartments, as defined by the Pc of the individual.

potential role in the control of food intake and adaptive thermogenesis.

Body composition autoregulation: a conceptual model

On the basis of the findings mentioned earlier, the control systems that operate through the control of energy-partitioning, adaptive thermogenesis and hunger–appetite can be incorporated into a conceptual model of autoregulation of body weight and body composition depicted in Fig. 6. In addition to the control of partitioning *per se*, other control systems operating via the control of food intake and thermogenesis with feedback loops from the lean and/or fat tissue compartments are conceptualised to be dictated by 'memories' of the FFM and/or fat compartment; these are,
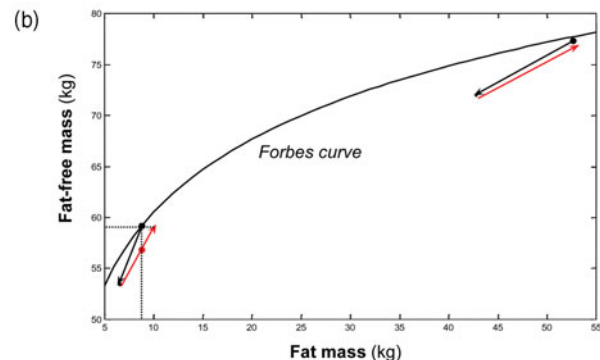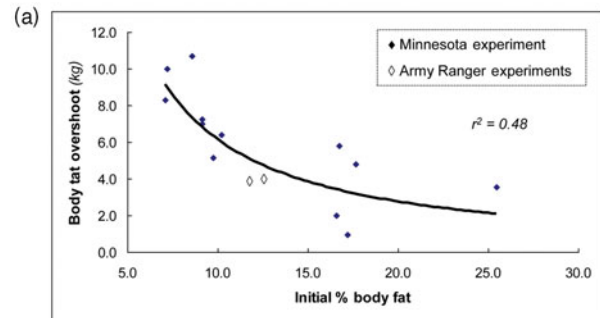

Fig. 7. (Colour online) (a) Relationship between the extent of fat overshooting and the initial (pre-starvation) percentage body fat. The exponential curve is drawn from data (◆) on the twelve men who participated in all phases of the Minnesota experiment. The symbols (◇) represent the mean value for men (*n* 10) participating in each of the Army Ranger training experiments for which body composition data are available[36,38]. (b) Mathematical model prediction of 12% weight loss on recovery of body composition and fat overshooting in a lean individual (body weight, 68 kg; % body fat, 13%) and an obese individual (body weight, 130 kg and % body fat, 45%); these data are superimposed on Forbes curvilinear relationship between FFM and fat mass[60] in lean and obese Caucasians. For the lean data, the dotted line indicates that by the time 100% fat mass is recovered; FFM recovery is incomplete, with fat overshooting.

however, viewed as attenuators of energy imbalance and/or accelerators of tissue recovery that are superimposed over a more 'basal' control of energy partitioning.

Implications for 'Dieting makes some fatter'

One important feature of this model (Fig. 6) is the sharp contrast between the determinants of the two accelerators: whereas the control system operating through increased hunger–appetite is dictated by the degree of depletion both in body fat and FFM, that operating through the adipose-specific suppression of thermogenesis is dictated specifically by the degree of depletion of body fat only (and not by FFM depletion). This differential relationship of hyperphagia and suppressed thermogenesis with regard to the two main energy-containing compartments suggests that there is an asymmetry in the way FFM and fat mass are recovered, with fat being recovered at a faster rate than FFM. Thus, the greater the severity of weight loss (and the degree of fat and FFM depletion), the more the suppression

of thermogenesis that enhances specifically fat deposition (and not FFM deposition) and hence the greater the disparity in the rate of fat *v*. FFM recovery. This would provide an explanation for the fact that when fat recovery in the Minnesota men reached 100% of pre-starvation values, the FFM recovery was still far from complete (Fig. 1). Since depleted FFM can also drive hyperphagia, a consequence of disparity between 100% fat recovery and incomplete FFM recovery is that the hyperphagia is prolonged until FFM is also fully recovered. However, since the completion of FFM recovery can only be achieved through the process of energy-partitioning, more body fat is also deposited, which hence underscores the phenomenon of fat overshooting.

From a perspective of body composition autoregulation therefore, the critical event that eventually leads to the prolongation of hyperphagia and fat overshooting resides in the suppression of thermogenesis which drives fat recovery at a rate that is greater than that determined by the Pc of the individual. As this adipose-specific suppression of thermogenesis (that drives fat acceleration) is a function of fat depletion, and the prolongation of hyperphagia (after 100% fat recovery) is a function of depleted FFM still to be recovered, the extent of fat overshooting would therefore depend on the extent to which both fat mass and FFM are depleted; this in turn depends on the Pc of the individual which is dictated primarily by the initial adiposity (Fig. 2(b)). To substantiate this contention, we show here, from the individual body composition data of the twelve men who completed the Minnesota Experiment, that the extent of fat overshooting decreases exponentially with increasing initial adiposity (Fig. 7(a)). Using a mathematical model (J Jacquet and AG Dulloo, unpublished results) that incorporates the relationships shown in Figs. 2 and 3, the differential body composition responses of an average lean dieter and an average obese dieter losing 12% of their respective body weight is illustrated in Fig. 7(b); their changes in fat mass and FFM being superimposed on Forbes curve that relates fat mass and FFM[60]. Should the lean dieter be subjected to multiple weight cycles, it can also be predicted that the amount of fat overshoot will nonetheless decrease with each successive cycle, since each cycle leads to increased adiposity. The cumulative fat overshoot over several cycles will nonetheless amount to substantial excess of body fat. These results predicting little or no fat overshooting in obese dieters in accord with studies in which obese individuals subjected to one cycle[61] or three successive cycles[62] of dieting failed to show altered body composition. They are also in line with data from lean individuals who during rehabilitation after losing about 12% of their weight due to food deprivation (Table 1) showed fat overshooting of about 4 kg[36–38]; these data are now superimposed on the curve shown in Fig. 7(a).

Conclusions

Our analysis of how dieting makes some fatter suggests that the lean dieters are at greater risk for fat overshooting than the obese dieters. This contention is in line with prospective studies indicating more consistent association with increased risks for major weight gain in initially normal-weight subjects than in initially overweight and obese subjects attempting to lose weight[16,24]. With the prevalence of dieting increasing among individuals in the normal-weight range (due to pressure for a slim image, body dissatisfaction or athletic performance) and accumulating evidence suggesting increased cardiometabolic risks associated with weight fluctuations in the non-obese population groups[4,63], the notion that dieting makes some fatter warrants greater experimental scrutiny and deserves greater public health concern than so far acknowledged.

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