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Thermogenesis above maintenance in humans

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The responses to overfeeding in humans have been the subject of considerable interest and controversy. About 20 years ago Miller *et al.* (1967) revitalized the idea of an energy-dissipating mechanism operating during overfeeding to maintain energy homeostasis. The effect had been proposed by Neumann (1902) at the turn of the century to explain an apparent ability to maintain his weight on widely different energy intakes. Miller *et al.* (1967) suggested this occurred after meals and was potentiated by work. Such a mechanism would have implications in understanding the origins of obesity and the question of adaptations to varying planes of nutrition, undernutrition as well as overnutrition. At that time (1967), measurements of individual 24 h energy expenditure were of unknown accuracy. Developments in instrumentation and the construction of calorimeter rooms marked a new period of more precise measurements and the application of more accurate techniques in general. From this has come evidence of differing responses to overfeeding in humans and small rodents, such that there is doubt as to the relevance of mechanisms of facultative regulatory thermogenesis in small mammals (Rothwell & Stock, 1979) to humans. Facultative thermogenesis in response to overfeeding results from no net synthesis or mechanical work being performed. It has the effect of reducing the efficiency of energy utilization (kJ gain/excess kJ) and so regulating the energy stores in the body. Obligatory thermogenesis in respect to overfeeding results from the thermic effect of the extra food, its ingestion, digestion, absorption and processing. In the present paper, an overview is presented of recent studies of human overfeeding and the mechanisms behind the responses.

MAINTENANCE

Maintenance, in the context of nutritional energetics, refers to constant body energy content over a period of at least 24 h. It is also used as a shorthand notation for maintenance energy intake or requirement, the energy intake required for constant body energy content. It is a term that appears widely in the animal and comparative nutrition literature and is used in a consistent manner, being a landmark in the continuum, minimal, basal, fasting, maintenance, habitual, up to maximal energy expenditure. Like many of these landmarks, it depends on the conditions of the measurement. The major determinants of maintenance are: (1) the body size and composition, (2) the degree of physical activity, (3) the thermic effects of feeding, (4) thermoregulatory heat production, (5) the genotype. In animals, physical activity and thermoregulatory heat production are usually kept to a minimum during the measurement of maintenance. The interspecies mean is about 440 kJ/kg live weight $(W)^{0.75}$ per d compared to the basal metabolism of 290 kJ/kg $W^{0.75}$ per d so that, as a rule of thumb, the energy cost of maintenance has been taken as 1·5 times basal metabolic rate (BMR).

Constant body energy content can be achieved on a range of energy intakes with consequent effects on body size, energy stores and physical activity. In human nutrition

maintenance is an uncommon term, and is used inconsistently to refer to both the minimum level compatible with survival and habitual energy intakes. In overfeeding studies, maintenance may refer to the initial levels of the subjects in a metabolic unit or continuing with their everyday lives. Estimates of maintenance requirements of men and women from calorimeter studies agree well with the animal values, 432 (SD 33) kJ/kg $W^{0.75}$ per d (Van Es *et al.* 1984). Dauncey (1981) reported lower values, 373 (SD 20) kJ/kg $W^{0.75}$ per d, the difference probably being a result of the higher calorimeter temperature, 28 and 21° and shorter exercise periods, 30 and 75 min/d respectively. The maintenance requirement of many individuals in today's sedentary society may fall below 1·5 times BMR and even 1·4 times BMR (Prentice *et al.* 1985) at least in the short term. It is not known if these can be regarded as compatible with long-term good health. Maintenance is clearly a function of the conditions of the measurement. The responses to energy intakes above maintenance will depend on these conditions and the pre-existing maintenance state, the energy stores and the genotype.

RESPONSES TO SUPRA-MAINTENANCE ENERGY INTAKES

Supra-maintenance intakes (overfeeding) bring about increases in body-weight and energy stores and rises in 24 h energy expenditure and its components, basal and resting metabolism and the thermic effect of food. The magnitude of the responses depends on: (1) the level and duration of overfeeding, (2) the source of energy; fat, carbohydrate or mixed, (3) the fate of the excess energy, whether stored as triglyceride or glycogen, (4) the current maintenance level, (5) the genotype. The responses are adaptive in that they may allow the attainment of a new state of maintenance after several months or years but at a higher level of energy stores.

Weight gain is not a thermic response but it influences 24 h energy expenditure. The composition of the static difference between lean and obese individuals is 25% fat-free mass (FFM) and 75% fat (FM) (Webster *et al.* 1984). However, Forbes *et al.* (1986) found a higher FFM component, 40–45% depending on the method of calculation, in the weight gained by overfeeding. Weight gain and lean body mass (LBM) gain were significantly correlated with excess energy intakes in forty-eight individuals (r 0·77 and 0·49 respectively, $P<0·01$). They were linearly related, with intercept terms near zero, suggesting no evidence for varying efficiency of utilization in response to overfeeding over the range 80–300 MJ. This could not be expected to persist indefinitely as the increasing weight would decrease the energy available for gain. There was, however, considerable inter-individual differences in the responses to a given excess energy intake.

Forbes (1987) has also shown how the composition of weight gain in overfeeding is affected by the initial level of energy stores, that is the current maintenance state. Individuals with 10 kg body fat gain weight of 50% LBM, on average, those with 30 kg, gain weight with 25% LBM on average. As the energy cost of gain (kJ/g) depends on the composition of the gain, the efficiency of energy utilization (kJ stored/excess kJ) may vary in individuals with different body compositions. This illustrates how different responses may occur at different maintenance states but it does not represent regulatory thermogenesis.

The thermic responses to overfeeding mixed diets in six studies arranged in order of increasing duration are shown in Table 1. The results indicate that 24 h energy expenditure and resting metabolic rate (RMR), measured 12–14 h after the last meal, are

Table 1. *Thermic responses to overfeeding mixed diets*
(Mean values with their standard errors)

Study	Duration (d)	*n*	Sex	24 h energy expenditure (% increase) Mean	SE	Resting metabolism (% increase) Mean	SE	Excess energy (% expended) Mean	SE
Dauncey (1980)	1	8	♂, ♀	10***	2	12***	3	13	3
Ravussin *et al.* (1985)†	9	5	♂	15*	—	8*	(0–18)‡	—	—
Apfelbaum *et al.* (1971)	15	8	♀	11	—	13**	—	15	—
Welle *et al.* (1986)	20	5	♂, ♀	—	—	7	(1–18)‡	—	—
Forbes *et al.* (1986)	21	15	♂, ♀	—	—	9	2	—	—
Norgan & Durnin (1980)	42	6	♂	11	—	12	3	15	—

† Increases are for day 9 of overfeeding.
‡ Range.
Mean percentage increase was significant: * $P<0{\cdot}05$, ** $P<0{\cdot}01$, *** $P<0{\cdot}001$.

Table 2. *Thermic responses to overfeeding high-fat and high-carbohydrate diets*

Study	Duration (d)	*n*	Sex	24 h energy expenditure (% increase) Mean	SE	Resting metabolism (% increase) Mean	SE	Excess energy (% expended) Mean	SE
High-fat diet									
Dallosso & James (1984*a*)	7	8	♂	6**	(2–10)†	4***	—	10	(4–18)†
Zed & James (1986)	6	8	♀	8	1	10	2	14	1
High-carbohydrate diet									
Schutz *et al.* (1985)	7	3	♂	(12, 40)‡	—	—	—	27	—
Bisdee & James (1984)	14	8	♂	10	1	10	2	18	1

† Range.
‡ Averages on day 1 and day 7 of overfeeding.
Mean percentage increase was significant: ** $P<0{\cdot}01$, *** $P<0{\cdot}001$.

raised by some 7–15%. The effect begins within 24 h but appears unaffected by the duration or amount of overfeeding. This is true too for the proportion of the excess energy expended by this stimulated metabolism.

The responses to high fat or carbohydrate overfeeding are shown in Table 2. With high-fat supplements, rises in metabolic rate are smaller and less is expended. For a given excess, energy gains are higher for fat overfeeding than with mixed diets. With high-carbohydrate diets, increases in 24 h energy expenditure up to 40% were measured by Schutz *et al.* (1985). Here, increasing amounts of a very-high-carbohydrate supplement, predominantly sucrose, were fed and weight was gained at 0·7 kg/d. Over the whole of the overfeeding period, the average excess energy intake was 7·5 MJ/d and the raised metabolism was equivalent to 27% of the excess. The responses in the study of Bisdee & James (1984) with intakes of 1·5 times maintenance from supplements of starch and sucrose are more comparable to those with mixed diets.

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Sims (1986) has summarized the results of all recent studies of overfeeding. What these typical studies show is that increases in metabolic rate are of the order of 5–15% depending on the type of overfeeding and occur rapidly, within 1 d. The percentage of the excess energy intakes expended in this stimulated metabolism is about 10–15. The most notable feature in the responses is the variability within each study. Its origins are difficult to identify. There are few measurements of repeated overfeeding and it is not known how real the differences are. However, over half the studies have values from calorimeters which have a high precision and reliability. Forbes *et al.* (1986) could find no effect of initial body-weight, fat content, sex, duration of overfeeding, type of food, maintenance intake or smoking behaviour on g gain/excess energy. Type II errors, accepting the null hypothesis when it is false, are a danger in all these overfeeding studies with their small sample sizes. Earlier, Dallosso & James (1984*a*) found that in men the proportions of the excess energy expended was inversely related to initial fatness. This may be related to the higher proportion of fat in the gain of fatter individuals described previously. Genotype may also have an effect. Bouchard (1987) has described the role of genetic factors in body composition and energy metabolism. Estimates of heritability based on intra-class correlation suggest significant effects on body composition, energy intake, physical activity, energy expenditure and adipose tissue metabolism. In a study of six monozygotic twins overfed 22 d, resting metabolic rates increased 7% with considerable, but non-significant, within-pair resemblance (r 0·43, $F = 2·51$, not significant). The magnitude of the change in the thermic effect of a meal showed significant within-pair resemblances (r 0·70, $F = 5·5$, $P<0·05$; Poehlman *et al.* 1986).

The rises in metabolism and consequent losses of excess energy result from the increased body size, the thermic effect of the extra food, including the costs of net storage, and any facultative, regulatory thermogenesis. The latter component cannot be measured directly and is usually demonstrated by rises in metabolism unexplained by the other two factors, or by pharmacological intervention. The increases in metabolic rate exceed those of body-weight except in the 42 d study of Norgan & Durnin (1980) and the time-course of the responses suggest that weight gain is not the major effector. However, the thermic effect of the extra food is related to the degree of overfeeding of mixed diets (Ravussin *et al.* 1985; Welle *et al.* 1986).

The expected rise depends on the costs of storage and the composition of the gain. The theoretical costs (Flatt, 1978) for fat deposition are 3% of the excess when fat is the substrate and 23% with carbohydrate. For glycogen deposition it is 7% and protein 25%. The true costs are difficult to measure and it cannot be stated categorically that what is being measured does not have a regulatory component but in growing, simple-stomached animals they are about 25% of the excess for fat and 55% for protein deposition (Webster, 1988). In humans, with their limited capacity for lipogenesis from carbohydrate, the cost of fat deposition may be lower. Recent values from low-birth-weight infants are 15 and 42% (Roberts & Young, 1988). For weight gain of 40% LBM and 60% fat described by Forbes *et al.* (1986), it would be expected that 20% of the excess would be expended in storage. Most of the losses in Tables 1 and 2 are below this value so that, even without taking into account the effect of higher body-weight on energy expenditure, there may be no need to invoke a facultative, regulatory, component. However, the estimates are tenuous and other evidence, including responses to single carbohydrate loads, have been interpreted as evidence of facultative thermogenesis.

FACULTATIVE REGULATORY THERMOGENESIS IN HUMANS

Several mechanisms for facultative regulatory thermogenesis have been proposed including uncoupled oxidative phosphorylation, and increases in protein turnover, sodium pumping and futile cycling, under the actions of the sympathetic nervous system (SNS), catecholamines, the thyroid hormones and insulin. There has been considerable support in recent years for uncoupling in brown adipose tissue (BAT) mediated by the SNS and catecholamines, at least in small animals. This follows the suggestion of Rothwell & Stock (1979) that cold and diet had similar effects on metabolism and on BAT in particular. Although evidence is accumulating of the presence of BAT in adults and of the 32K uncoupling protein, the contribution to noradrenaline stimulated thermogenesis appears low (Cunningham *et al.* 1985). The importance of BAT and the evidence for SNS stimulation of BAT or thermogenesis in other organs in response to overfeeding in humans is unresolved (Sims, 1986). Ingestion of protein, fat and carbohydrate at maintenance results in significant thermic responses, but raised plasma noradrenaline concentration is observed only after carbohydrate (Welle *et al.* 1981), and Astrup *et al.* (1985) have proposed skeletal muscle as the site of a facultative component of glucose-induced thermogenesis.

With overfeeding mixed diets, neither Ravussin *et al.* (1985) nor Welle *et al.* (1986) found support for the involvement of the SNS or thyroid hormones. Responsiveness to infused noradrenaline was not enhanced and β-blockade with propranolol had the same effect before and after overfeeding. SNS involvement in the greater rises in 24 h energy expenditure with carbohydrate overfeeding was found by Schutz *et al.* (1985) but not by Welle & Campbell (1983). Using the euglycaemic glucose clamp procedure, Acheson *et al.* (1983) found that the later part of the thermic effect of glucose was β-blockable, i.e. an SNS-mediated facultative component. However, these are acute unphysiological conditions.

Plasma levels of the thyroid hormone triiodothyronine (T_3) are altered by energy balance in the same direction as metabolic rate. Increases with overfeeding are found with carbohydrate and mixed-diet overfeeding but not with fat. Induced mild T_3-toxicosis raised RMR by 6% but had no effect on the thermic effect of food or the efficiency of exercise (Acheson *et al.* 1984). The roles of the thyroid hormones and the sodium pump in thermogenesis are described in the preceding papers of Dauncey (1990) and Kelly & McBride (1990). These and other possible mechanisms have been reviewed by Sims (1986).

The original proposal for facultative thermogenesis in overfeeding was a work-potentiated increase (Miller *et al.* 1967). Garrow (1978) found little evidence for this effect in his review of the literature and this has been confirmed by Dallosso & James (1984*b*), Welle (1984), and Welle *et al.* (1986). Segal & Gutin (1983) reported a potentiation in women but the effects during work were small (50 kJ). In men, the potentiation was 60 kJ/3 h (Segal *et al.* 1987). In the overfeeding twin study of Bouchard and colleagues (Tremblay *et al.* 1987), no significant increase in mean exercise oxygen consumption was observed with overfeeding but there was again a large variation and moderate to high within-pair resemblances in responses (r 0·51–0·78, $F = 3{\cdot}0$–$8{\cdot}2$, P not significant – $<0{\cdot}05$), i.e. a genotype–overfeeding interaction. High but non-significant intra-class correlation coefficients (0·4–0·7) between changes in exercise O_2 consumption with overfeeding and plasma catecholamines and, negatively, body-fat gain were described as consistent with the concept of a role for the sympathoadrenal system in the regulation of adaptive thermogenesis and the predisposition to store fat.

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THERMOGENESIS BELOW AND AT MAINTENANCE

If a facultative regulatory mechanism is effective, it may be evident below and at maintenance and there are many observations that have been interpreted in this way. Seventy years ago, Benedict *et al.* (1919) showed that metabolic rate fell faster than weight in experimental undernutrition and recovered faster too. The magnitude of the effect was related to the increase with overfeeding, 10%, which suggested a common or similar mechanism, but being suppressed instead of activated. More recently, Jung *et al.* (1979) reported a difference in the thermic response to noradrenaline in the obese and the previously obese compared with controls. Although the evidence in man is equivocal, it has been interpreted as consistent with a suppression of sympathetic activity with energy restriction (Landsberg & Young, 1983). However, Mansell & MacDonald (1988) underfed six women for 7 d and found similar changes in metabolic rate and plasma noradrenaline following a test meal in the maintenance and underfed states, suggesting no SNS suppression. Similarly, intravenous infusion of nutrients produced effects unaltered by β-adrenergic blockade (Vernet *et al.* 1987).

What of the chronic energy deficiency of the Third World? Gambian women show a remarkable adaptation in the first two trimesters of pregnancy of reducing their BMR. However, similar decreases have been reported in some women in this country (Prentice *et al.* 1989). In both countries, the change in BMR is positively related to initial fatness, i.e. the pre-existing maintenance condition. Similar effects might be expected in lactating women, lactation being equally energy demanding, but there is no evidence for falls in BMR. The thermic effect of food and responses to noradrenaline are lower and insulin sensitivity is increased (Illingworth *et al.* 1987). The effect is equivalent to 200 kJ/d. In rodents, the mechanism appears to be reduced BAT thermogenesis.

Further examples of the responses to food and overfeeding varying with maintenance state are the negative relationships between fatness and thermic effect of food (Robson *et al.* 1977), work-potentiated thermic effect of food (Segal *et al.* 1984) and the proportion of the excess energy expended (Dallosso & James, 1984*a*).

The question of small and large eaters on apparently similar activity patterns has been raised many times over the last 50 years. Do the big eaters exhibit regulatory thermogenesis? Apparently not. The big eaters are invariably heavier than the small eaters. When matched for size as in the recent study of McNeill *et al.* (1988*a*) there were no significant differences in 24 h energy expenditure and BMR measured under controlled conditions. This casts doubt on the representativeness of the intake values, particularly when these are barely sufficient to meet requirements for BMR. Related to this is the suggestion that maintenance requirements are raised in the obese, particularly the experimentally obese, and reduced in the post-obese who have maintained weight for several months. In the Vermont prison studies, it was reported that maintenance requirements of the overfed had increased 50% even though weight gain was only 25%. However, energy expenditure was not measured and, again, there are doubts about the intake values. In the obese, increases in 24 h energy expenditure are explained largely by increased FFM (Ravussin *et al.* 1981) and interest has been in thermogenic defects, such as a blunted response to food, an effect that could contribute to weight gain. One suggestion is that this blunted response is related to insulin resistance and impaired glucose tolerance and reduced rates of glucose disposal and storage. When glucose uptake is held constant by varying insulin infusion, the effect of glucose is the same in lean and obese subjects (Ravussin *et al.* 1983).

In the post-obese, there is no consistency in the findings. Basal or resting metabolism has been reported as being normal (McNeil *et al.* 1990), lowered (Geissler *et al.* 1987) and raised (Tremblay *et al.* 1989). The thermic effect of food too has been reported recently as being unchanged compared with controls. There is less information on 24 h energy expenditure and the possibility of reduced activity but there is no evidence that the post-obese of average size can live on low energy intakes. Suggestions that those who regularly lose then regain weight, weight cyclers or yoyo dieters, may have energetic abnormalities has not yet been substantiated. In animals, increased efficiency (g gained/excess kJ) has been reported. One mechanism might be a reduced RMR but this was not observed by Van Dale & Saris (1989) or Goldberg *et al.* (1990), as reported at the present meeting. The latter study of seven women with 6% weight loss in three 2-week cycles found no decreases in absolute BMR or per kg FFM and no excessive loss of lean tissue.

Energy intake is intermittent. Short- or long-term storage is required along with a mechanism to partition nutrients between metabolism and storage, and mobilization of stores. If there were a propensity to use more or less efficient pathways this could have implications for weight gain. However, fuel mixtures over 24 h are closely related to diet composition (Hurni *et al.* 1982) and fasting respiratory quotient is unrelated to body composition (McNeil *et al.* 1988*b*).

CONCLUSIONS

There is little evidence for significant facultative regulatory increases in energy expenditure with supra-maintenance intakes in normal weight adults, certainly not sufficient to dispose of intakes of 1·5 times maintenance. Large obligatory increases occur with high-carbohydrate loads and there may be a facultative component. These are rather unphysiological conditions and extrapolation to other conditions may be unjustified. Involvement of the sympathetic nervous system is controversial and the maximum stimulation of resting energy expenditure for any period of time by pharmacological doses of noradrenaline may only be about 20%. However, a 1 or 0·1% rise in efficiency might be enough to lead to obesity, in the absence of compensatory changes in energy intake. In considering the origins of obesity, Jequier & Schutz (1985) have calculated that if there exists a defect in the thermogenic response to food of about one-third, by the time 10 kg weight had been gained, the raised energy expenditure from the increased weight would balance the energy saving. Therefore, in obesity, defective thermogenesis alone is unlikely to be the only cause and defective appetite control may be implicated, too.

Facultative thermogenesis in overfeeding diets of mixed energy sources appears a rather elusive phenomenon. Stock & Rothwell (1987) have said in relation to the animal work that an elusive phenomenon may still be an important one and that, if in the past, elusive phenomena in science had been ignored, our knowledge and understanding would be much less than it is today. The individual variability in the responses to overfeeding requires more detailed study.

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