CONTROVERSIES IN MEDICINE

Two groups have been invited to present opposing views on energy expenditure and weight regulation

Luxuskonsumption, diet-induced thermogenesis and brown fat:
a critical review

G. R. HERVEY AND G. TOBIN
Department of Physiology, The University of Leeds, Leeds, U.K.

Introduction

That a steady body weight can be maintained over long periods of life is a remarkable fact. Human food intakes vary widely [1], and do not seem subjectively to be closely controlled; it is an old observation that they sometimes vary oppositely to what might be expected from body weight—it will be recalled that in Pharaoh's dream [2] the lean kine were the over-eaters. How, then, is constancy of weight achieved?

Apart from fluctuations in water content, body weight must ultimately be governed by conservation of energy. Any difference between the amounts of energy gained and lost by the body changes the body's energy content: since the latter is in chemical form, this implies weight change. In man the store of energy is such that energy imbalance over single days causes little disturbance. Over periods of years, however, simple calculation shows that even a tiny systematic error in the balance between energy intake and output would cause gross change in weight: for example, Evans' hypothetical subject who in 10 years gained 100 lb more than her twin through indulging daily in "a little deeper cut in the pat of butter" [3]. Measurements of intake and output in man show no relationship over single days, but an approach toward equality over days to weeks [4, 5]. Evidently some mechanism operates that achieves equality with increasing accuracy as time progresses [6].

The nature of the feedback signal and the central control involved in weight maintenance raise questions of great interest [6, 7]. The currently topical question, however, concerns the effector through which control is exerted. In principle this must be variation of energy intake, or energy expenditure, or both. Human subjective impressions notwithstanding, there is much evidence that energy intake from food is controlled to maintain balance. The classical demonstration, readily repeated, is that of E. F. Adolph [8, 9]. Rats in a constant environment 'eat for energy': when the concentration of energy in their diet is changed they accurately adjust the amount they eat. Adjustment takes 1–2 weeks in rats and probably more in man [10]; this may explain why it is not perceived subjectively.

If food intake is the effector of a negative feedback control system that regulates energy stored as fat, it is also possible to explain why food intake and body weight tend to be related paradoxically. If, for example, energy expenditure is low and food attractive and readily available (as is the case for man in 'Western' society), excess of intake over expenditure will cause fat to accumulate; as this happens, however, it is—by some means—sensed as a proportionately increasing inhibitory signal by the control system. When the signal eventually becomes strong enough to hold food intake down to match expenditure, a steady state is attained, in which high body fat accompanies low food intake. This
effect is directly demonstrable in one ‘natural experiment’ in which a population migrated from a poor rural to an affluent urban environment [6, 11].

In considering energy expenditure as a possible effector of energy balance regulation, a distinction must be made between the responses to upward and downward disturbances. When energy intake is restricted to less than would be eaten voluntarily, energy balance can only be re-established by reduction of expenditure. Body weight is found to fall initially and then become steady at a lower level. Although the extent of the ability to reduce expenditure has not been thoroughly studied, and the mechanism not at all, there is no controversy as to its existence [12]. Our own data from continuous calorimetry show that rats fed by tube 0.7 to 1.0 times their voluntary energy intake reduce their energy expenditure in the same proportion [13–16]. This response restores energy balance and stabilizes body weight, and we therefore regard it as regulatory. This is in contrast to what is seen when rats are overfed (see below). The conclusion that there is a two-part relationship between energy intake and expenditure with a transition at maintenance of body structure and composition, concerned with the response to excess intake. When rats are overfed (see below). The conclusion that there is a two-part relationship between energy intake and expenditure with a transition at expenditure during underfeeding as if they applied to overfeeding. It could also apply to some of the animal evidence, for example Miller & Payne’s much-quoted experiment on two groups of three rats, and two pigs [25], which indeed reported dramatic findings. The energy intakes of the two pigs, one of which was given a low-protein, high-energy diet, differed by a factor of five, yet they showed the same weight gains. Aside from the small scale of the experiments, however, several factors might account for the findings without invoking Luxuskonsumption.

Reduction of metabolic rate in ‘controls’ fed at less than voluntary intake has already been referred to. The energy cost of synthesis of stored fat must obviously be allowed for, and also the cost of digesting and absorbing the extra energy. An important point, made by Blaxter [26] and McCracken [27], is that, if storage of energy takes place as an alternative to growth, as occurs when young animals eat a diet that provides inadequate protein, the energy stored per unit weight of carcass changes drastically, and arguments based on body weight alone become

Luxuskonsumption or diet-induced thermogenesis

The first such evidence was a perception that body weight is maintained despite changes in intake. Both Neumann in 1902 [18] and Gulick in 1922 [19] argued from their own body weights. Gulick, interestingly, also pointed out how difficult it is to overeat voluntarily. The early workers gave the energy-dissipating mechanism they postulated the apt name ‘Luxuskonsumption’. It was again advocated, with some evidence from metabolic rate determinations, by Grafe [20, 21]. The evidence for Luxuskonsumption to 1973, and the quantitative properties it would have, were reviewed by Miller & Mumford [22].

In a foreshadowing of current controversy 50 years earlier, Wiley & Newburgh [23] disputed Grafe’s claims. Among other points, they suggested that ‘control’ metabolic rates were in fact obtained with the subjects undernourished, and that the already known effect of undernutrition on metabolic rate was all that had been demonstrated. The same error of interpretation is implicit in the quotation, by James & Trayhurn [24], of our own recent results for energy expenditure during underfeeding as if they applied to overfeeding. It could also apply to some of the animal evidence, for example Miller & Payne’s much-quoted experiment on two groups of three rats, and two pigs [25], which indeed reported dramatic findings. The energy intakes of the two pigs, one of which was given a low-protein, high-energy diet, differed by a factor of five, yet they showed the same weight gains. Aside from the small scale of the experiments, however, several factors might account for the findings without invoking Luxuskonsumption.
invalid. Finally, and this appears to be essentially true for all the reported claims of Luxuskonsumption, the argument in these experiments rested only on the demonstration of an apparent discrepancy between estimates of energy intake and storage; not on demonstration of increased energy expenditure by measurement of energy expenditure, and still less on demonstration that the timing and extent of such increase was consistent with a regulatory response of the sort envisaged.

The experiment with pigs has since been repeated by Gurr et al. [28]. The results were not entirely clear-cut: the over-eating pigs stored substantial amounts of fat; one of three experiments was thought to show substantial ‘thermogenesis’. (The terms ‘thermogenesis’ and ‘diet-induced thermogenesis’ are recent alternatives to ‘Luxuskonsumption’. The meaning is the same [29], or includes costs of digestion and absorption [22], or costs of synthesis also [30]. We prefer ‘Luxuskonsumption’ [16].) In two of the experiments indirect calorimetry, performed for 1 day in each 5-day balance period, showed lower energy expenditure than the difference between intake and storage; the authors, for reasons explained in their paper, preferred the higher values given by the difference method. The experiment has been repeated again by McCracken [31], who found no evidence of ‘diet-induced thermogenesis’ in young pigs on low-protein diet.

The evidence up to 1978 for and against Luxuskonsumption in man has been reviewed by Garrow [32]. It includes several experiments on overfeeding in man designed to test for Luxuskonsumption, for example the series by Passmore and co-workers [33–36], that of Glick et al. [37], and the 6-week-long, carefully conducted experiment of Norgan & Durnin [38]. All of these reported negatively. Garrow suggested that the conflicting conclusions might be reconciled if Luxuskonsumption occurred only when excess intake exceeded 22 Mcal (92 MJ). We believe it is an equally fair interpretation to suggest that Luxuskonsumption was not found in those investigations in which a serious attempt was made to measure energy expenditure over the over feeding period; and that, where the highest levels and the longest durations of overfeeding were reported, the estimates of energy intake are likely to be least reliable.

Among the largest reported intakes must be those of the subjects of the experiments of Sims and associates, which have been widely quoted as evidence for Luxuskonsumption [e.g. 24]. The earlier experiments [39, 40] conducted on prisoners who volunteered to overeat, were not designed to study energy balance (but rather effects of obesity on endocrine function). The results revealed large discrepancies between energy intakes and weight gains. Some subjects, however, had experienced anorexia and nausea, not all had completed the overfeeding schedule, and the recorded intakes must be considered open to some doubt. The authors concluded only that the question of ‘thermogenesis’ “remained unresolved”.

In a follow-up study [41], intended to obtain complete energy balances, this time carried out in a hospital metabolic ward and with smaller intakes, tolerance of the excess food was again a problem. Even in these more favourable circumstances doubts were admitted as to the actual intakes. The results showed that when the excess energy intake was principally from fat, within reasonable limits of precision all of it was stored. When the source was carbohydrate, the authors concluded tentatively that ‘thermogenesis’ might have occurred. The unaccounted-for expenditure, however, at 20–30 kJ/100 kJ excess intake, is consistent with current estimates of the cost of synthesis of fat from carbohydrate [26, 42, 43].

Recent interest in ‘thermogenesis’ derives largely from a paper in Nature by Rothwell & Stock in 1979 [29]. This advanced the hypothesis that brown adipose tissue is the site of ‘thermogenesis’ in response to overfeeding by ‘cafeteria’ diets—that is, diets supplemented with a choice of attractive foods. Although the experimental evidence was on a small scale (one experiment with six rats given a normal rat diet and six a cafeteria diet), it calls for discussion because it has been widely quoted as the standard reference for thermogenesis by brown adipose tissue, and because the effect described was impressive: the ‘cafeteria’ diet increased energy intake by 80% over the 3-week period, and ‘thermogenesis’ dissipated 90% of the extra intake. We have twice commented on it [16, 44]. Our criticisms centre on the derivation of energy expenditure over the period, the quantity of interest, from the difference between estimates of energy intake and of change in body energy content, rather than from measurement; and on the assumption that the demonstration of a discrepancy between intake and storage of energy would be adequate evidence for the existence of a regulatory mechanism for energy balance. It must be more accurate to measure a quantity than to infer it, in this case from values that are not themselves readily and directly measurable. If all three components of energy balance are measured it also becomes possible to check how
nearly the sum of expenditure and storage matches intake. If all three are not measured, evidence for (or against) 'thermogenesis' cannot be distinguished from experimental error.

To illustrate this, the 'PRD' control diet used in this experiment was reported to have had, by previous experimental determination, a metabolizable energy content of 10.75 kJ/g. This is unusually low for a rat diet, but it is the figure given by the manufacturer. We have found 12.07 kJ/g by standard calorimetric techniques, and in a recent paper Rothwell & Stock [45] give values of 12.07 and 12.00 kJ/g. This is not to say that the value of 10.75 was wrong, but in so far as there may be any uncertainty, the difference would account for a quarter of the missing energy assumed to have been dissipated by thermogenesis. 'Cafeteria' foods tend to be sticky, greasy and energy-rich, and in our experience uneaten residues cannot be recovered from the cages as completely as can standard rat diets, again augmenting missing energy. Many foods lose water while in the cage; if reliance is placed upon weighing and tables of initial composition, yet more 'energy' is lost. At best, tables of metabolizable energy can only make an approximate prediction of the energy particular animals will retain from their diet in a particular case [38, 47].

Measurement of carcass energy is also error-prone. This applies particularly to the start of any balance period, when it is necessary to know the energy content of live animals. We have commented [16] on what appear to us to be important inconsistencies in the relative amounts of fat and energy in the reported weight gains of Rothwell & Stock's [29] rats. The proportion of fat in the weight gained by the control group was, at 40%, surprisingly high for normal growing rats, but was still clearly less than the proportion of fat in the extra gain on cafeteria feeding, which was almost 100%. Yet the energy concentrations in the substance gained ('body energy gain' divided by 'body weight gain', both from Table 1 of [29]), were almost identical at 17.4 and 17.0 kJ/g in control and cafeteria groups respectively. If the proportions of fat in the weight gains had been those we have found in similarly treated rats from the same source, the energy concentrations would have been 11.5 and 19.8 kJ/g respectively, and the missing energy ascribed to 'thermogenesis' would have been less by about a third. Thus, we do not think Trayhurn & associates' statement [48] that the errors risked in estimating intake and storage only are "certainly too small to have more than a minor impact" is well-founded. Whether the errors are large or small remains unknown if they are not detected.

The outcome of our own studies has also led us to question Rothwell & Stock's results. We have recently summarized the findings so far [16]. When we set out to study systematically the part played by variation of energy expenditure in regulation of energy balance, it seemed to us that this could only be done by continuous measurement of energy expenditure, which we chose to do by way of oxygen consumption. The calorimeter [13] uses the 'flow-over' principle, i.e. gas exchanges are measured from the mass flow of air through the five cages and the concentration differences for oxygen and carbon dioxide across them. We have made every effort to achieve accuracy. The gas analysers are calibrated hourly, and the recovery of the whole system is regularly checked by introducing an N₂/CO₂ mixture via an independent mass flowmeter. Energy intake is measured by adiabatic bomb calorimetry of food, residues and excreta; carcass energy at the end of balance periods by analysis of whole carcasses followed by bomb calorimetry of constituents; and initial carcass energy from regression plots of the energy contents by analysis of substantial numbers of comparable rats. With all three measurements available it is possible to check that the values for energy intake, storage and expenditure are consistent. We find the sum of intake and storage exceeds expenditure by a margin of 5–10 kJ/day per rat, or about 5% of resting energy turnover. We think the discrepancy reflects the impossibility of reducing to zero errors that occur even with the utmost care; and which are mainly losses that lead to over-estimation of the animals' intake. The discrepancy increases during 'cafeteria' feeding [49].

The principle of the experimental approach has been to manipulate energy balance, and look for changes in expenditure that might be regulatory. We believe feeding animals entirely by stomach tube to be the most effective method of altering energy balance: it puts food intake entirely under the experimenter's control; the disturbance of energy balance can thus be varied over a wide range; and it seems reasonable to expect that, when a disturbance of energy balance has been produced and ability to respond by control of intake rendered inoperative, any capacity to regulate by control of expenditure would be most likely to be called into play. We have also employed 'cafeteria' feeding. Although this also disturbs energy balance, the extent of the disturbance varies and cannot be controlled by the experimenter, and after a time food intake falls.

Rats overfed by tube gain weight at an almost constant rate. This falls off only slightly with time, and weight gain seems ultimately to be
Thermogenesis in weight regulation

limited by some limitation to the body fat content compatible with life. Thus it does not appear that any regulation of energy balance, body fat or body weight is operating. Energy expenditure increases initially, and reaches a new steady level a few days after starting overfeeding. The increase in expenditure and the rate of weight gain are then both fairly accurately proportional to excess energy intake.

By recording energy expenditure from shortly before to many hours after a meal, we can separate a component of increased energy expenditure that immediately follows the meal, and a continuous component. The meal-related component corresponds to the Heat Increment of Feeding, i.e. the costs of digestion, absorption and immediate metabolism (the term [50] replaces the earlier, less apposite, 'Specific Dynamic Action'). It accounted for approx. 8 kJ/100 kJ excess intake under the conditions of the experiments. The major, continuous component is of the right magnitude to reflect the cost of synthesizing and depositing fat, in the range 20–30 kJ/100 kJ excess intake [26, 42, 43], and appears to be proportional to the rate of fat synthesis. If it reflected a regulatory mechanism for energy balance we should have expected it to be proportional to the extent of disturbance of body weight and fat. There is only a just significant component of increased energy expenditure proportional to body weight, which we would interpret as reflecting the cost of maintaining and moving a heavier body. Our conclusions as to the disposal of excess energy intake, from tube and 'cafeteria' feeding, are shown in Fig. 1. Within the limits of accuracy the sum of the costs discussed accounts for all the increased energy expenditure found during overfeeding. We find no measurable margin of expenditure, otherwise unaccounted for, that might be attributed to Luxuskonsumption.

In the tube-feeding experiments the increase in energy expenditure was 40–50% of the excess intake given. With 'cafeteria' feeding the increase in expenditure was a somewhat lower proportion, 20–40%, of the excess energy eaten; this may reflect the higher fat content of the cafeteria foods. There were no evident differences among the several strains and ages of rats tested [16, 46, 49, 51, 52]. Schemmel et al. [53] used a high-fat diet to increase voluntary energy intake over a 10-week period in seven strains of rats, and found that all deposited about 80% of the excess intake as body fat.

'Thermogenesis' is described as a more variable phenomenon. The first experiments reported by Rothwell & Stock [54, 55] (which included sample oxygen consumption measurements) showed no increase in energy expenditure during 'cafeteria' overfeeding (but did show transient 'thermogenesis' after stopping overfeeding—one wonders how evoked if this was a regulatory response). In the experiment reported in Nature [29] 'thermogenesis' dissipated nearly all of a large increase in energy intake. The difference was ascribed to intra-strain differences between colonies of rats [29, 56]. If thermogenesis has the significance for energy balance claimed for it [57], and if rat colonies really differ so greatly in their capacity for thermogenesis, it seems surprising that colonies lacking it did not show spontaneous obesity. It is also difficult to see why

![Fig. 1. Suggested disposal of excess ME (metabolizable energy, i.e. energy absorbed into the body and not excreted) intake: (a) given by tube-feeding; (b) ingested voluntarily by adult rats in response to 'cafeteria' feeding [16].](image-url)
thermogenesis should occur in response to cafeteria feeding, but not (54; M. J. Stock, contributions to discussions at meetings) when energy balance is disturbed as much or more by tube-feeding.

In more recent papers, four rat strains were reported to show energy intakes increased by 34-54% by cafeteria feeding, and expenditures 22-63% above control values [58]. Cafeteria-fed young and adult lean Zucker rats were both reported to show increases in energy intake by 70%, and increases in energy expenditure equivalent to 90% and 70% respectively of the increase in intake [45]. Younger rats from the same source that had originally showed marked thermogenesis [29] were reported to have increased their energy intake by 50%, while expenditure increased by 68% of the additional intake [59].

The most noteworthy feature of Rothwell & Stock's recent reports lies in the checks applied to the 'energy balance' method of measuring energy expenditure (i.e. the use of the difference between intake and storage). The paper [45] is largely concerned to show that predictions of metabolizable energy intake from food tables [47] or manufacturers' data for 27 'cafeteria' food items, ranging from chopped ham to cheese, agreed, apparently with zero mean discrepancy and individual differences of only 2%, with measurements by bomb calorimetry. This implies that such effects as loss of weight by evaporation while the food was in the cages, incomplete recovery of scattered food, and variations in retention of energy in the body can be reduced virtually to zero.

In [59] measurements of energy expenditure by the 'energy balance' method were compared with sample measurements by oxygen consumption. On days 9 and 13 the rats were in a calorimeter in turn for two 4-h periods; values for oxygen consumption for the 2 days were obtained from the mean of these periods. The average 24-h energy expenditure for the 15-day period was taken as the mean of these two values. The resulting mean energy expenditures were identical with those obtained by the 'energy balance' method for the controls, and differed by 3% for the overfed group.

Since over the 15 days the rats grew from 155 g to 260-280 g, it is surprising that averaging values of energy expenditure for 2 days towards the end gave a valid prediction of total expenditure over this period. That it did so seems to us incompatible with the authors' statement that the difference between the values for days 9 and 13 can be accounted for by a relationship of oxygen consumption to body weight (kg0.75). The extremely constant oxygen consumption of the control group throughout the day (Fig. 1 of [59]), irrespective of feeding or the transition from light to darkness, differs from Morrison's [60] experience and ours, and in this case different rats provided the data at different times. In several earlier papers Rothwell & Stock reported moderate increases in oxygen consumption (such as we should expect) from sample measurements, while they postulated that much larger increases in energy expenditure occurred over the whole period of 'cafeteria' feeding, on the basis of large increases in energy intake accompanied by little or no additional weight gain [29, 45, 61-64]. In an earlier comment on the discrepancy between sample calorimetry and the 'energy balance' method they imply that agreement is not to be expected [28]. It is not clear how the conditions and methods of making sample oxygen consumption measurements have altered in the recent experiment; it seems doubtful whether the agreement now can be considered to validate results obtained by the 'energy balance' method in earlier experiments in which measurements of oxygen consumption did not agree with the 'energy balance' method.

We are convinced that there is a need for further independent studies by thoroughly checked continuous calorimetry, to achieve a reliable consensus as to the amount of increased energy expenditure associated with overfeeding, and its relationships, in particular to rate of synthesis of fat and to disturbance of energy balance. It is necessary not only to settle the doubt as to the amount of the increase, but also to distinguish evidence for an 'adaptive' component from, for example, evidence that would only suggest that the costs of storing energy might be higher than had been supposed.

Little further evidence is available as yet. Andrews & Donne [65] confirmed an increase in energy expenditure after 'cafeteria' feeding, but their oxygen consumption method was not described, and they did not measure energy intake or storage. McCracken & Barr [27, 31, 66] have carried out more complete studies, not yet fully reported. They conclude that 'diet-induced thermogenesis' was not demonstrated.

Brown adipose tissue

Our principal ground for doubting that brown adipose tissue effects 'diet-induced thermogenesis' is the fact that a non-existent mechanism requires no effector. Since, however, the prop-
position that brown adipose tissue plays a role relevant to human obesity has been so widely and strongly advocated, for example by James & Trayhurn [24] and Himms-Hagen [67], it is necessary to discuss brown adipose tissue from this point of view.

Brown adipose cells differ from white fat cells in being smaller and in containing numerous small fat droplets and abundant mitochondria and cytochrome. Most occur in pads surrounding the thoracic viscera in the newborn of a number of species including the rat and man, in cold-adapted adults and in hibernants [68–70]. In response to cold brown adipose cells increase their heat production by a factor of up to five [71, 72]. They are controlled by noradrenergic sympathetic nerves [73, 74]. The discovery of the thermoregulatory function of brown fat in the 1960s was an exciting event, and there is no doubt as to the reality of this function.

The claim that brown fat is relevant to human obesity hinges on presuppositions or evidence that: Luxuskonsumption (or ‘diet-induced thermogenesis’) occurs; adult man possesses functional brown adipose tissue; this also effects non-shivering thermogenesis in response to cold; activity of brown adipose tissue increases in response to feeding; deficiency of brown adipose tissue function is demonstrable in obese patients, by diminished metabolic responses to feeding, cold and sympathomimetic stimulation; congenitally obese rodents show similar defects. We have explained our grounds for doubting the existence of Luxuskonsumption. We believe the other foundations of the theory are equally unsound.

Typical brown adipose cells become fewer with increasing age and most become indistinguishable from white adipose cells [70]. Persistence of the macroscopic pads of the newborn does not necessarily imply functioning cells, and histology is made difficult by the occurrence of cells of intermediate appearance, which may reflect the transition with age, or different levels of activity. The most comprehensive study in man is that of Hassi [75]. It shows an abrupt change at about 1 year of age from plentiful brown adipose cells in all subjects, to trace numbers in only a minority of subjects; accompanied by a change of brown cell type from multi-vacuolated to predominantly single-vacuolated. Heaton’s earlier anatomical study [76] is consistent with Hassi’s, although the resolution of age was only to “under 10 years”.

The only claimed observations of brown adipose tissue functioning in adult man, both using ephedrine as stimulus, have been Rothwell & Stock’s [29] infrared thermograms of the interscapular region, and W. P. T. James’ demonstration with needle thermocouples, in a ‘Horizon’ television programme, of temperature rise in the same region. Haemodynamic effects of ephedrine could have accounted for the changes [44]. As it happens, Heaton and Hassi found the interscapular region showed the most marked loss of adipose cells with maturation: three-quarters of the cells were brown at 28 weeks of gestation, whereas no brown cells were found in the age-range 14–24 years, and only sparse cells in about 10% of subjects over the whole range from 1 year upwards [75].

In the context of thermoregulation it has generally been considered that adult man has little or no capacity to increase heat production other than by shivering. Jessen’s recent work [77] has been quoted as demonstrating such capacity, but shivering was only excluded subjectively as cause of the substantial increases in oxygen consumption in the cold. He found a smaller rise in oxygen consumption in brain-damaged, curarized patients [78]. In these papers changes in oxygen consumption were reported as differences between maximum values in the experimental period and mean values in the control period, which leaves the amount or existence of real increase in the cold uncertain. Johnson et al. [79] had earlier found no increase in heat production in paralysed patients in response to cooling.

Davis [80] is often quoted as having demonstrated that non-shivering thermogenesis replaces shivering in cold-adapted man. Subjects adapted to cold in summer and in winter were thought to show similar increases in heat production on exposure to cold, but achieved them with less shivering (quantified by EMG recordings) when adaptation had been in winter. Brück et al. [81] regressed measurements of oxygen consumption on EMG activity as adaptation to cold progressed, and they concluded that there was no evidence that ‘non-shivering thermogenesis’ developed. If Davis’ data are regressed similarly the points for winter and summer are indistinguishable; 80% of the variation in heat production is explained statistically by the amount of shivering, and the intercept of the regression (i.e. heat production in the absence of shivering) is 50 kcal h⁻¹ m⁻² or 1 met, the standard figure for normal resting metabolism. Our interpretation is that in the winter months the subjects reduced their requirement for increased heat production, perhaps by increasing body insulation.

Noradrenaline provides a test for capacity to increase energy expenditure by activating brown
fat. It causes substantial increases in oxygen consumption in newborn rabbits [74] and cold-adapted adult rats [82]. Rats that are not cold-adapted show a progressive decrease in response with age, approaching zero in adulthood [71]. Early work in man showed no metabolic response to injected noradrenaline [83, 84]. Some later studies suggested that, in subjects previously acclimatized to cold, metabolic rate might increase to 10% above resting level [85-87]. This is a small effect compared with normal variation in resting metabolic rate, or with shivering or exercise, and might only reflect increased tension due to the injections [88]. A further group of workers have described elevation of metabolic rate by 10–30% of resting metabolism, related probably causally to mobilization of fatty acid from white fat, and occurring only in fasted subjects [89-91].

Arguments for a deficiency of thermogenesis in obese people have been put forward by James & associates [24, 92]. Shetty et al. [93] examined postprandial metabolic rates of obese patients, partly recovered ‘postobese’ subjects and control subjects after a liquid meal. The obese patients showed a smaller increase in metabolic rate relative to the pre-meal reading, but their absolute metabolic rates were higher. The ‘postobese’ subjects also showed a reduced rise in metabolic rate compared with the controls, and the argument for a constitutional difference in metabolic response hinged on this. However, the graph of their metabolic rate (Fig. 1 of the paper) was almost superimposed on the controls’ except for the single point giving the pre-meal value, and the difference therefore entirely depends on this point.

We [16] have observed that rats made obese by tube-feeding show the same pattern of postprandial energy expenditure as the patients of Shetty et al., i.e. a higher starting value and a smaller increase after a meal. In the rats, however, the difference clearly must have been a consequence of obesity and not a pre-existing constitutional cause for it, since they were uniform at the start and the obesity was produced by overfeeding.

Jung & James [92] claim that exposure to cold reveals defective thermogenesis in obese patients, evidenced by smaller increases in oxygen consumption and greater falls in body temperature. They quote Blaza & Garrow [94] incorrectly as evidence for lower heat production. The data in this abstract actually show no change in oxygen consumption in lean or obese subjects in the cool environment: it was reported that the obese showed lower heat loss. This may reflect greater thermal insulation. It is well established that subcutaneous fat confers insulation. In cold conditions this enables fatter people to defend their body temperature with less expenditure of energy; as a result body temperature undoubtedly falls more slowly in fatter subjects exposed to cold of any severity [95–104]. The opposite finding of Andrews & Jackson [105], which Jung & James quote as evidence for faster temperature fall in the obese, is not typical; it depended upon tympanic temperature measurements, which (in the absence of fuller information) could have reflected body surface rather than deep temperature changes.

Jung et al. [106] infused noradrenaline in fasting lean, partially recovered and obese subjects (in similar doses, since these were based upon ‘ideal’ weight; similar plasma concentrations were produced, but see [107]). Resting metabolic rate rose by about 20% in the lean subjects but only by about 10% in the obese and ‘postobese’. It is difficult to define comparable doses for subjects of widely differing weight; fasting lean and obese subjects are not in the same metabolic state, which may affect the action of noradrenaline [89]; the pre-infusion metabolic rates in the obese were higher than those the lean subjects achieved even under the influence of noradrenaline. It seems doubtful whether a constitutional defect in energy expenditure in the obese has been demonstrated.

The arguments that brown fat becomes active in overfed experimental animals have from the start been based on supposed parallels with changes on exposure to cold [61]. The most widely quoted evidence has been the finding that brown adipose tissue (or specifically the interscapular brown adipose tissue pad (IBAT) of the rat) increases in weight with ‘cafeteria’ feeding [29, 45, 56, 61, 108–110]. IBAT weight also increases in rats exposed to cold [69]. Much of the weight of the pads, however, is lipid (irrespective of cell type). Since cafeteria feeding (at least in our experience and in that of its originators, Sclafani & Springer [111] and Rolls & Rowe [112]) causes increased body fat content, the pads must be expected to increase in weight simply as part of this.

It should be possible to distinguish increase in IBAT weight due to storage from hypertrophy, by examining its relationship to body weight or total fat content. In rats exposure to cold causes the regression line for IBAT weight against body weight to move upward, with little change of slope [113]. We have found that IBAT weights fall on the same regression line against total body fat in: normally and ‘cafeteria’-fed young and
91% of the variation in IBAT weight [114]. The data comprised 231 rats ranging in body fat content from 10 g to 230 g; the dependence on total body fat explained 91% of the variation in IBAT weight [114]. Exposure to cold, however, did shift the regression line upward. McCracken & Barr have also reported that increased IBAT weight in 'cafeteria' feeding is proportional to increase in white adipose tissue [66]. The increase in IBAT weight with overfeeding, though real, appears to be virtually entirely attributable to fat storage, not to hypertrophy such as occurs with cold exposure.

A noradrenergically controlled mechanism can be blocked by a β-receptor-blocking drug such as propranolol; this was part of the original evidence for the thermoregulatory function of brown fat in the newborn [74]. Rothwell & Stock [29, 61] reported that in cafeteria-fed and cold-adapted rats propranolol (5 mg/kg subcutaneously) reduced resting oxygen consumption over 2-h periods at 29°C (as already noted, this was not elevated to the extent to which thermogenesis was claimed to be operating) toward control levels; control animals showed no change. Using continuous calorimetry, we [16] have found that propranolol (15 mg/kg orally) had no effect upon the increase in oxygen consumption that follows a tube-fed normal or over-sized meal; or upon the continuous increase in oxygen consumption associated with the continuous weight gain of rats being overfed by tube (at 1·6 × voluntary energy intake).

Vaughan Williams et al. [115] and Evemy et al. [116] found that prolonged administration of propranolol decreased growth rate in young rabbits by reducing food intake [116]. In man, Zwillich et al. [117] found that propranolol (80 mg orally) did not affect the rise in oxygen consumption that followed ingestion of 250 g of glucose. Propranolol is a widely used drug; if 'thermogenesis' by brown fat protects a population from obesity, it seems surprising that propranolol treatment has not been noticed to cause fat deposition.

Biochemical studies in cold-exposed and cafeteria-fed animals have also been adduced as evidence for brown adipose tissue function. According to the chemiosmotic theory of mitochondrial respiration, protons are expelled from the mitochondrial matrix and a proton concentration gradient is set up across the inner mitochondrial membrane. Re-entry of protons down this gradient is via ATPase, and thus generates ATP [118]. Nicholls has proposed that in brown adipose tissue there is a proton conductance pathway that allows protons to return without generating ATP; this is dependent on the presence of a protein of molecular weight 32 000; binding of purine nucleotides to this protein inhibits dissipation of heat by this path [119]. The concentration of the 32 000 mol. wt. protein and the number of purine binding sites (determined by the capacity to bind exogenous GDP) have been reported to correlate with the capacity of brown adipose tissue to respond to cold [120, 121].

Stock and his associates [108] reported a threefold increase in mitochondrial GDP-binding in cafeteria-fed rats, and a fivefold increase on exposure to cold; they interpreted this as evidence that an increase in proton conductance by the non-ATP-generating pathway provides the mechanism for diet-induced thermogenesis. Himms-Hagen et al. [110] confirmed the increase in GDP binding but did not find an increase in the 32 000 mol. wt. protein, although they had found this in cold-exposed rats. Trayhurn et al. [48], however, found that GDP binding increased equally in 'lean' (i.e. normal-weight) and congenitally obese mice after cafeteria feeding, although only the lean mice were thought to show 'thermogenesis'. The lack of thermogenesis in the obese mice was attributed to a secondary deficiency of cytochrome oxidase: obese mice had lower levels and these did not increase with cafeteria feeding. This, however, is inconsistent with Himms-Hagen & associates' results: they reported no difference in cytochrome oxidase activity in brown adipose tissue from lean and obese mice [122], and cold acclimatization led to increases in the same proportion in both genotypes [123].

The biochemical findings in brown fat in overfed animals thus do not so far give a consistent picture, or one identical with that seen in exposure to cold. It is not possible to review here the fascinating problem posed by the defects in congenitally obese rodents and their relevance to human obesity [124]. However, there is no clear evidence that brown fat is at fault in any of the obese mutants. We have failed to confirm a suggested failure of the obese Zucker rat to increase metabolism normally in the cold [16].

Human obesity is an intractable and distressing condition for patient and clinician. At first sight the 'brown fat thermogenesis' theory is supported by a wide range of evidence, and it is not surprising that a theory that claims to reveal a new mechanism of body weight regulation should arouse interest. There is an obvious appeal in explaining obesity other than in terms of over-
References


