

## **The part played by variation of energy expenditure in the regulation of energy balance**

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Energy balance is the difference between the amounts of energy gained and lost by an organism over any period. Since energy is conserved, non-zero energy balance is necessarily associated with an equal change in the energy content of the body; since this is in chemical form, there must be a change in the weight of some body constituent, and so in general in body-weight. Energy balance must therefore approximate to zero over adult life. This would not come about by chance. The necessary control might be exerted on energy intake, expenditure, or both. Even though it may not be subjectively obvious to humans, there is much evidence that 'voluntary' energy intake is regulated in the long term to match energy expenditure with impressive precision (Hervey, 1975). Energy expenditure, however, must to a considerable extent at least be determined inflexibly by physiological requirements and the demands of the outside world for activity and thermoregulation.

There is no doubt that imposed changes in energy intake are followed by changes in energy expenditure. Although precise information is surprisingly scarce, general experience of feeding humans and animals less energy than they would eat voluntarily seems to show that they still maintain steady, though lower, body-weights. Such measurements of energy expenditure in chronically underfed animals and humans as have been reported confirm that it is reduced (Keys *et al.* 1950). The mechanism of this is unknown, but it seems to take time and to have the characteristics of a regulatory response.

Perhaps understandably in an 'affluent society', the effect of increased energy intake upon expenditure has attracted more interest. When more energy is absorbed, energy expenditure must be expected to increase. Feeding has long been known to be followed by increased heat output, which presumably reflects costs of digestion, absorption and metabolism; this is probably best called Heat Increment of Feeding (Webster, 1981), a descriptive term that does not prejudice the mechanism. It must be expected to increase with energy intake. Further, since no process can be perfectly efficient, whatever is done with energy absorbed in excess of requirements must cost some energy. In particular, storing excess energy will entail expenditure in synthesizing fat or building tissue.

In the context of regulation of energy balance, the important questions are: is there a component of energy expenditure accessible to physiological control and used as an effector; and if so, what contribution does it make? To find answers, the regulatory component (or components) must be distinguished from other, inevitable changes in expenditure, such as those due to the heat increment of feeding and the cost of fat synthesis.

The questions are important for human obesity. If a facultative mechanism exists that increases energy expenditure in response to excess intake, obesity could reflect some fault in it, and search for this would be of high priority. On the other hand, if the only increases in energy expenditure after overfeeding are inevitable costs of handling the extra intake, their only significance is that they somewhat mitigate the effects of imperfectly controlled intake. Reliable answers must be based on accurate studies of the relationships between energy intake and expenditure, and require some understanding of the behaviour of control mechanisms.

The relationships have been studied by direct measurement by agricultural scientists. An earlier concept of a single exponential relationship between energy intake and retention—which implies a relationship for energy expenditure—was replaced by the concept of two near-linear ones holding good below and above the intake for zero retention (Blaxter & Wainman, 1961; Blaxter, 1962). Most of the existing calorimetry information refers to agricultural animals, whose energy intakes were normal or low, and the experiments were short compared with the time likely to be needed for regulation of energy balance in large animals.

#### *The 'Luxuskonsumption' theory*

A concept of some antiquity and recently much advocated depends on the following argument. Estimates of energy intake and of change in energy stores, however arrived at, often seem inconsistent. In particular, body-weight does not increase when estimates of energy intake suggest that it should. Since conservation of energy is unquestionable, this must, so the argument runs, show that the body has a mechanism for dissipating excess ingested energy. In essence the argument goes 'Look at all the food X eats and yet he remains slim, whereas Y who eats less is overweight; X must burn it off'. This was surely first noted in the cattle in Pharaoh's dream (*Genesis* Ch. 41). It is, however, possible to explain such apparently paradoxical associations between fat content and food intake in a quite different way, as 'load errors' of a control mechanism for body fat (Hervey, 1975).

The 'Luxuskonsumption' concept was put forward by Neuman (1902), who argued from the relative constancy of his own weight from year to year despite changes in energy intake; he invoked a mechanism for dissipating excess energy, to which he gave this well-chosen name. Grafe & Graham (1911) and Grafe (1931) reported apparent confirmation. Gulick (1922) made similar observations, again on himself as subject; interestingly, he drew attention to the practical impossibility of overeating voluntarily to more than a limited extent.

Grafe's claims for luxuskonsumption were challenged by Wiley & Newburgh (1931). Among other points, they noted that where Grafe had reported measurements showing a rise in 'basal' metabolic rate in a dog and in a human subject after increased feeding, in their 'control' state the subjects were in fact undernourished; the fact that underfeeding was associated with reduction in energy expenditure had, they pointed out, been known since 1897. Newburgh (1944) also described another experimental pitfall; changes in diet are followed by

changes in body water content which can obscure the changes in non-aqueous weight related to energy balance for as long as three weeks in man.

Sims' experiments on overfeeding human volunteer subjects in the Vermont State Prison (Sims *et al.* 1968; Sims *et al.* 1973) have been widely but uncritically quoted. The subjects experienced anorexia and nausea and not all of them completed the overfeeding schedule. The earlier studies (which were not designed to measure energy balance) appeared to show large discrepancies between intake and weight gain. Even so, Sims *et al.* (1973) concluded: 'whether there may be additional adaptive increase in thermogenesis in response to ingestion of excess calories remains unresolved.' In a subsequent paper Goldman *et al.* (1975) again emphasized the difficulty subjects experienced in maintaining excessive food intake and admitted to doubts as to whether all the excess food had been consumed, even though the subjects were now in a hospital metabolic ward and were offered a smaller excess. Goldman *et al.* (1975) did their best to obtain full energy balances, and found that when the excess food was principally fat, all the excess energy intake was accounted for by the estimated storage of fat (Table 10 of their paper). When the excess was carbohydrate, the authors tentatively concluded that it had produced 'thermogenesis'. They did not, however, include the cost of synthesizing fat from carbohydrate in their balances; since 70–80% of the excess intake was accounted for by storage and the discrepancy in energy balance largely disappeared soon after overfeeding was stopped, it may only have reflected the cost of synthesis.

The history of luxusconsumption has been reviewed by Miller & Mumford (1973) and more extensively by Garrow (1978). Although Garrow's review describes a divergence among investigators' conclusions as to the existence or non-existence of luxusconsumption (or 'thermogenesis'; a synonymous but in our view less useful term, since any process whatever produces heat), it would appear that those who have measured energy expenditure and obtained complete energy balances have generally reported negatively. Passmore *et al.* (1955*a,b*), Passmore *et al.* (1963) and Strong *et al.* (1967) reported a series of experiments in which normal, lean and fat subjects were overfed for up to 14 d and balances of body constituents were estimated as accurately as possible. No evidence of luxusconsumption was found. Norgan & Durnin (1980) overfed six young men for six weeks and came to the same conclusion. Glick *et al.* (1977) also failed to find evidence of thermogenesis. Garrow suggests that luxusconsumption in humans may become evident only when excess energy intake has exceeded some 22 mcal (92 MJ). This might, however, reflect the cumulative properties of errors in inferred energy balances, and reports, unchecked by balances, that subjects were able to sustain large excess energy intakes for long periods must be open to some doubts on the score of plausibility.

Luxusconsumption has also been reported in animals. Miller & Payne (1962) reported measurements on two groups of three rats and on two young pigs. The pigs received energy intakes that varied by a factor of no less than five and yet showed the same weight gains. This paper, which has proved something of a

challenge to nutritionists, was criticized by Blaxter (1975). There are several general considerations to be borne in mind in interpreting experiments of this type. The most obvious is the cost of storing energy as fat. The published data on this are less than could be desired, but it clearly cannot be zero if storage occurs. Secondly, growth is expensive of energy; young animals whose rate of growth can vary—and this applies to some extent to adult rats—have a potential 'sink' for surplus energy. Thirdly, if a diet provides adequate energy but inadequate protein, lean tissue will be lost and fat gained; this can occur with little change in total body-weight, which then conceals a large difference in body energy content. Fourthly, the undoubted reduction in energy expenditure when intake is below the level for zero retention means that, if 'control' animals are on a restricted food intake, 'experimental' groups on a higher intake will show apparently increased metabolism. It is possible to find grounds for arguing that any or all of these factors affected Miller & Payne's experiments.

Rothwell & Stock (1979c, 1981) championed the following propositions: the energy expenditure of experimental animals can be reliably estimated by difference between estimates of energy intake and of change in stored energy; such estimates show large increases in the energy expenditure of overfed animals; the increases in expenditure cannot be accounted for by factors such as costs of assimilation and synthesis, but reflect activity of a specific energy-dissipating mechanism; and this mechanism is provided by brown adipose tissue. It is therefore under the control of noradrenergic sympathetic nerves and ultimately the hypothalamus.

Earlier, however, Rothwell & Stock (1979a,b), using sample measurements of oxygen consumption as well as estimates of energy intake and storage, had reported that resting oxygen consumptions of control and cafeteria-fed groups of rats were the same (though increased after withdrawal of cafeteria foods). They (Rothwell & Stock, 1979c, 1981) attributed the contrasting results to strain and intrastain differences among rats.

We have criticized the evidence offered by Rothwell & Stock (1979c) (Hervey & Tobin, 1981). Prediction of expenditure, the quantity of interest, by difference between estimates of intake and of storage is subject to serious errors, which increase with the time considered. Our experience of measuring energy intake by bomb calorimetry of the food supplied and scattered, and of excreta, confirms the view of Paul & Southgate (1978) that the energy obtained from food cannot be predicted accurately from manufacturers' data and food tables. Although 'cafeteria' feeding is an effective way of inducing rats to overeat, unconsumed portions of the sticky, greasy, energy-dense foods are particularly difficult to recover quantitatively and this leads to overestimation of energy intake, which cannot be distinguished from evidence for 'thermogenesis'. Underestimation of the energy obtained from the control diet would have the same effect. We wonder whether it is significant that Rothwell & Stock (1979a) reported that they had used a diet with a determined metabolizable energy density of 17.3 kJ/g, whereas, in experiments which showed 'thermogenesis' (1979c, 1980) the maker's estimate of the metabolizable energy density of the (different) control diet used was 10.7 kJ/g.

It is not sufficiently appreciated that as a balance period progresses the error in estimating energy intake, whatever it may be, cumulates with time (a point also relevant to possible mechanisms of physiological regulation).

Measurement of the composition and energy content of living bodies is also inevitably difficult. There are internal difficulties in this area in Rothwell & Stock's (1979c) data (their Table 1). Our experience would suggest that the proportion of fat in the weight gained by the control group (40%) was high for actively growing rats. Also the ratios of the reported body energy gains to body-weight gains by control and cafeteria-fed groups were almost the same at 17.4 and 17.0 kJ/g respectively. Virtually all the additional weight gained by the cafeteria-fed group was fat. It is thus unlikely that the ratios would have been the same for the two groups; and the fat component alone of the gain by the cafeteria-fed group would contain sufficient energy to raise the ratio to approximately 19 kJ/g. We consider some doubt must arise as to the reliability of the estimates of body energy changes. Our own values for these ratios, obtained from regressions in a replication of Stock & Rothwell's experiment, were 11.5 and 19.8 kJ/g for control and cafeteria-fed rats respectively.

#### *Measurement of energy expenditure*

To the best of our knowledge, claims that substantial, physiologically facultative increase in energy expenditure (i.e. 'luxuskonsumption' or 'thermogenesis') occurs in response to increased intake have all rested upon estimates of energy expenditure obtained by difference, and not by continuous measurement. Short-term sample measurements of energy expenditure are not satisfactory for predicting long-term energy balance; where they have been reported, however, they have not suggested increases of the order of those postulated from discrepancies between estimates of intake and storage.

It is surprising that the question has not been more studied by direct measurement in small animals. The rat, as an omnivore and a good regulator of energy balance, should be a fair model for human energy balance. Matched individuals in statistically adequate numbers can be used, and entire bodies analysed accurately to measure stored energy. In 1975 we obtained support from the Medical Research Council to construct a multi-channel, continuous-running indirect calorimeter for rats, to investigate the part played by variation of energy expenditure in the regulation of energy balance (Armitage *et al.* 1979).

The calorimeter uses the 'flow-over' principle. The cages are ventilated from atmosphere and measurements made of the mass of air flowing through and the concentration differences across the cages for oxygen and carbon dioxide. The method depends upon gas analysers capable of measuring accurately concentration differences in the range 0.5–1%. It is probably the best current method of indirect calorimetry. The use of mass flowmeters, which work by a thermal dilution principle, avoids most of the problems associated with temperature and pressure changes. The calorimeter has five cages, four containing rats and one empty, all ventilated continuously and switched to the measuring line in turn for 10 min in

each hour. In the remaining 10 min the analysers are calibrated against air and a 'span gas' previously analysed with Haldane's apparatus (a precision gas blender, now under study, may supersede the span gas as calibration standard).

The empty cage is used in alternate hours as a blank and a recovery standard: a mixture of CO<sub>2</sub>-N<sub>2</sub> (21:79, v/v) is introduced into it through another mass flowmeter, so simulating the respiratory exchanges of a group of rats. Measurements are interrupted for 1 h daily to allow rats to be weighed and food to be changed etc. The system is controlled and readings from all instruments collected and processed by a minicomputer. Carcasses were analysed to determine gut contents, water, fat-free solids and fat with an accuracy better than 0.1 g for each constituent (Hervey & Hervey, 1967). Energy contents of carcass fat and fat-free solids and of diets and excreta are determined by adiabatic bomb calorimetry.

The rats used for most experiments were first generation hybrids between sibling-mated strains ultimately derived from Wistar albino and Lister hooded strains. Measurements were generally made on groups of four, matched for rate of weight gain as well as for weight and age. Sufficient matched groups were set up to allow carcass data to be obtained at intermediate stages of experiments as necessary. We are currently studying how the carcass energy content of the surviving groups can be predicted most accurately from analyses of parallel groups.

We have pursued four experimental approaches to the role of energy expenditure in regulation of energy balance.

#### *Energy expenditure when intake is externally fixed by tube-feeding*

Feeding rats entirely by stomach-tube by-passes physiological control of food intake and creates a situation in which regulation of energy balance by control of expenditure should be most easily demonstrable. Five experiments have been carried out, each lasting 2 to 3 months and using six-month-old female hybrid rats in matched groups of four. In each experiment, voluntary metabolizable energy (ME) intake was measured first with the animals eating *ad lib.*: in the first experiment a commercial pelleted diet and in later experiments a powdered experimental diet. Subsequently, the experimental diet was given by stomach-tube in suspension in 4.5-10 ml water three (occasionally four) times daily. Carbohydrate, protein and fat provided 48, 22 and 30% of the dietary energy respectively. In the first two experiments, replicate groups were given different levels of energy intake in the range 1.0-2.0 × voluntary ME intake in succession. In the last three experiments, all four groups were first fed approximately 1.0 × voluntary intake; each was then fed at one level in the range 1.0-2.0 × voluntary intake for the rest of the experiment. Over all balance periods the discrepancy between measured ME intake and the sum of measured energy expenditure and change in carcass energy was in the range +5 to +10 kJ/d, i.e. about +5% of resting energy turnover. The mean recovery of the 'simulated rat' gas mixture (measured later over 127 d) was 100.5% (SE ± 0.4%).

When underfed, the rats lost weight for the first 2–3 d; their weight then became stable. Their energy expenditure became stable at the same time, at a reduced level. Readjustments to new steady levels of weight and energy expenditure followed within 2–3 d of subsequent changes in energy intake. The new levels of energy expenditure were below control level in almost the same proportion as the ME intake (Fig. 3). This evidently reflects the long known but little explored ability of animals to maintain steady body-weights on energy intakes less than they would take voluntarily. The reduction in energy expenditure can reasonably be regarded as regulatory, since it succeeded in re-establishing energy balance and stabilizing weight. The range of decrease in energy intake over which compensation is possible remains to be determined.

When overfed, the rats gained weight; this continued as long as overfeeding was continued. Fig. 1 shows the course of an experiment. The gain of weight was nearly linear, with only a slight falling off with time. The rate of gain was approximately proportional to the amount by which ME intake exceeded the voluntary level. As Fig. 1 shows, energy expenditure increased at first, but in 2–5 d it became steady apart from apparently unrelated fluctuations. The amount of the increase in energy expenditure was also proportional to excess intake.

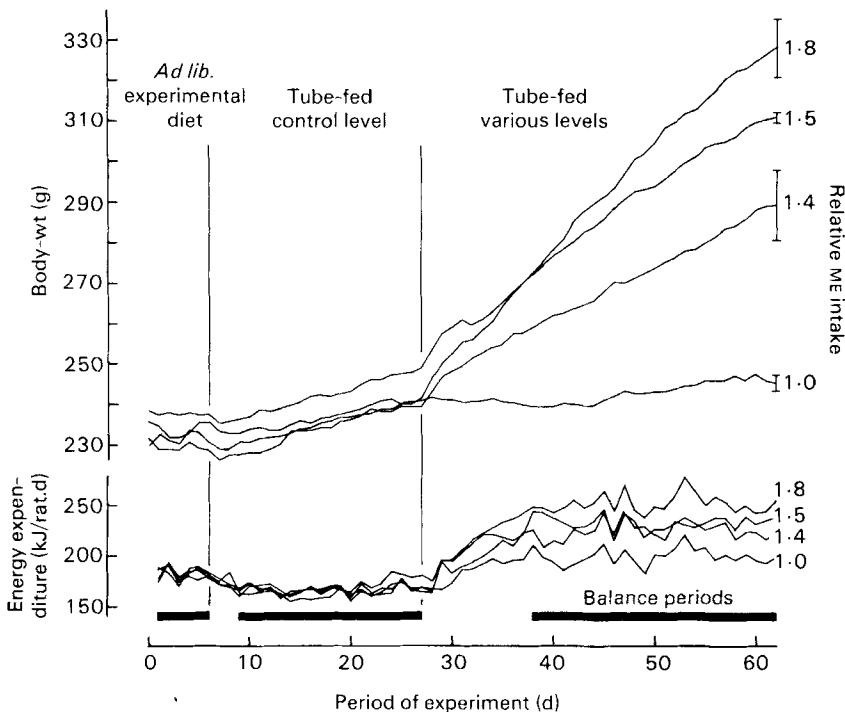


Fig. 1. Body-weight and energy expenditure changes during an overfeeding experiment. During the final phase the four groups of four rats were tube-fed approximately 1.0, 1.4, 1.5 and 1.8  $\times$  *ad lib.* intakes of energy.

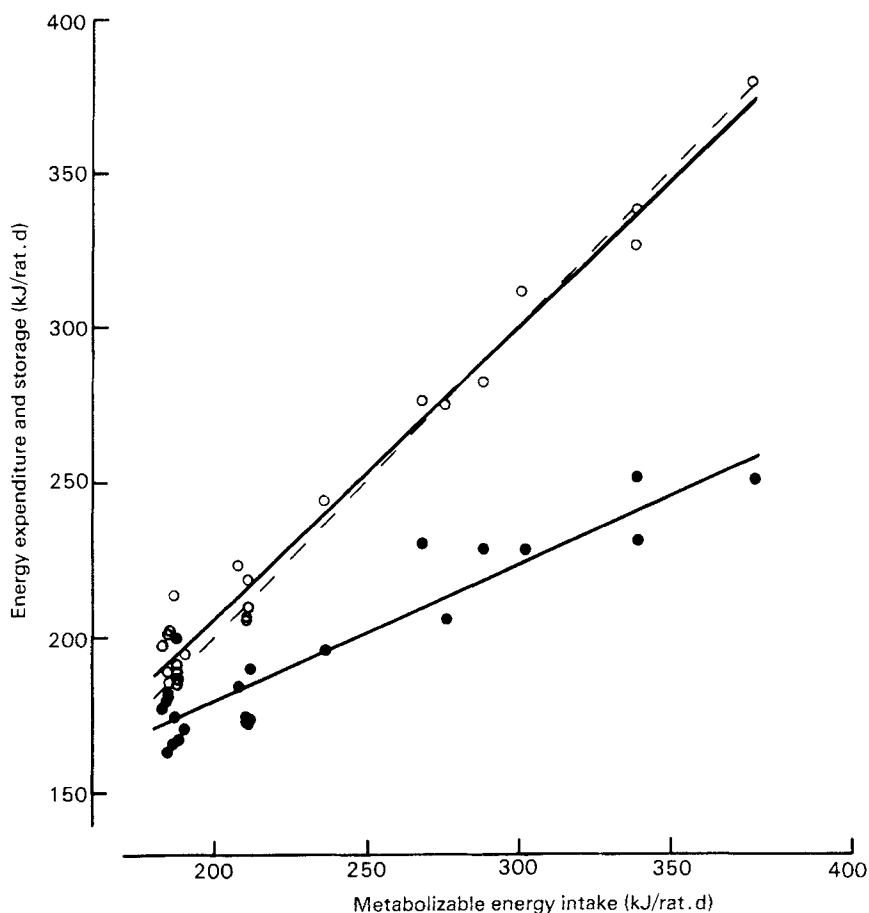


Fig. 2. Regressions (lower line) of energy expenditure ( $b=0.44 (\pm 0.08)$ ) and (upper line) of the sum of energy expenditure and change in carcass energy content ( $b=0.94 (\pm 0.06)$ ), on ME intake in the three overfeeding experiments. Each point is the mean of 4–27 successive 24-h totals over a period during which energy expenditure and weight gain were reasonably steady (the horizontal bars in Fig. 1).

ME intakes (which were not precisely known in advance since they depended on energy lost in excreta) and energy expenditures were averaged over periods for which expenditure was steady apart from the fluctuations (bars in Fig. 1). Change in carcass energy was estimated over these periods. Fig. 2 shows the results from the three overfeeding experiments as regressions of expenditure, and of expenditure plus storage, on intake. The statistical data indicate the precision of the experiments. Within this degree of precision the sum of expenditure and storage matched intake. The regression of expenditure on intake shows that, of every 100 kJ excess ME intake, 44 kJ ( $\pm 8$  with 95% confidence) were added to expenditure, and the remaining 56 kJ were stored. Storage was almost all as fat.

The energy cost of synthesizing this amount of fat is believed to be around 20 kJ (Blaxter, 1975; van Es, 1977; Pullar & Webster, 1977). Our own measurements of



the heat increment of feeding in this experimental situation give a value of about 8 kJ/100 kJ ME intake. When energy expenditure during the course of overfeeding was regressed on body-weight the relationship was just significant: expenditure increased by 0.1 kJ ( $\pm 0.1$ )/g weight gained. This effect presumably reflected the energy cost of maintaining and moving a heavier body, and caused the slight falling off of weight gain with time. Its contribution to energy balance would depend on the weight gained, the limits being 0–20 kJ for 100 kJ excess intake.

Fig. 4(a) shows diagrammatically the way in which we suggest each 100 kJ excess intake was disposed of. Although energy expenditure undoubtedly increased during overfeeding by stomach-tube, all of the increase, within the limits of experimental precision, can be ascribed to inevitable consequences of acquiring and storing the excess intake. This clearly means that the effect of the excess intake on energy stores was less than it would have been if the costs did not exist; but in our view the increased expenditure cannot be described as regulatory. The additional costs were an approximately constant proportion of excess intake; they were not related to the disturbance of energy balance; they did not appear to be under physiological control; and they did not achieve energy balance nor stabilize body-weight. Inspection of the records in Fig. 1 illustrates both the continuing weight gain and the lack of relationship between the disturbance of weight in a particular group at a particular time, and their energy expenditure. If a control mechanism were acting we should expect its response to be proportional to the error in the regulated quantity, and the regulated quantity to become stable at a new level. Thus, for example, when weight is disturbed by cafeteria feeding, physiological regulation of energy intake is still operative, and weight eventually becomes steady again at a new level.

Fig. 3 illustrates the relationship between ME intake and energy expenditure over the whole range studied in the five experiments. To achieve better comparability, both quantities have been expressed relative to the levels during *ad lib.* feeding (this accounts for the small change in calculated slope). We suggest that the graph expresses a true two-part relationship, the two parts coming about through different mechanisms. The lower part, whose physiological mechanism is unknown, has the properties of a regulatory response. The upper part reflects obligatory costs of assimilating and storing excess energy, and is not regulatory of energy balance or weight.

The finding of a two-part relationship parallels the earlier results for ruminants (Blaxter & Wainman, 1961; Blaxter, 1962). Although these were not presented in terms of energy expenditure as such, the data in Blaxter & Wainman's paper enable graphs similar to Fig. 3 to be plotted for sheep and for steers. The part of each graph above maintenance intake is similar, with a slope of approximately 0.5 kJ/kJ excess ME intake for sheep and 0.6 kJ/kJ for steers, both on a grass diet. Below maintenance intake energy expenditure did not change much and the animals were in negative energy balance. We believe the difference in the lower part of the relationship may reflect a long time constant of regulatory reduction in energy expenditure in large animals (Keys *et al.* 1950).

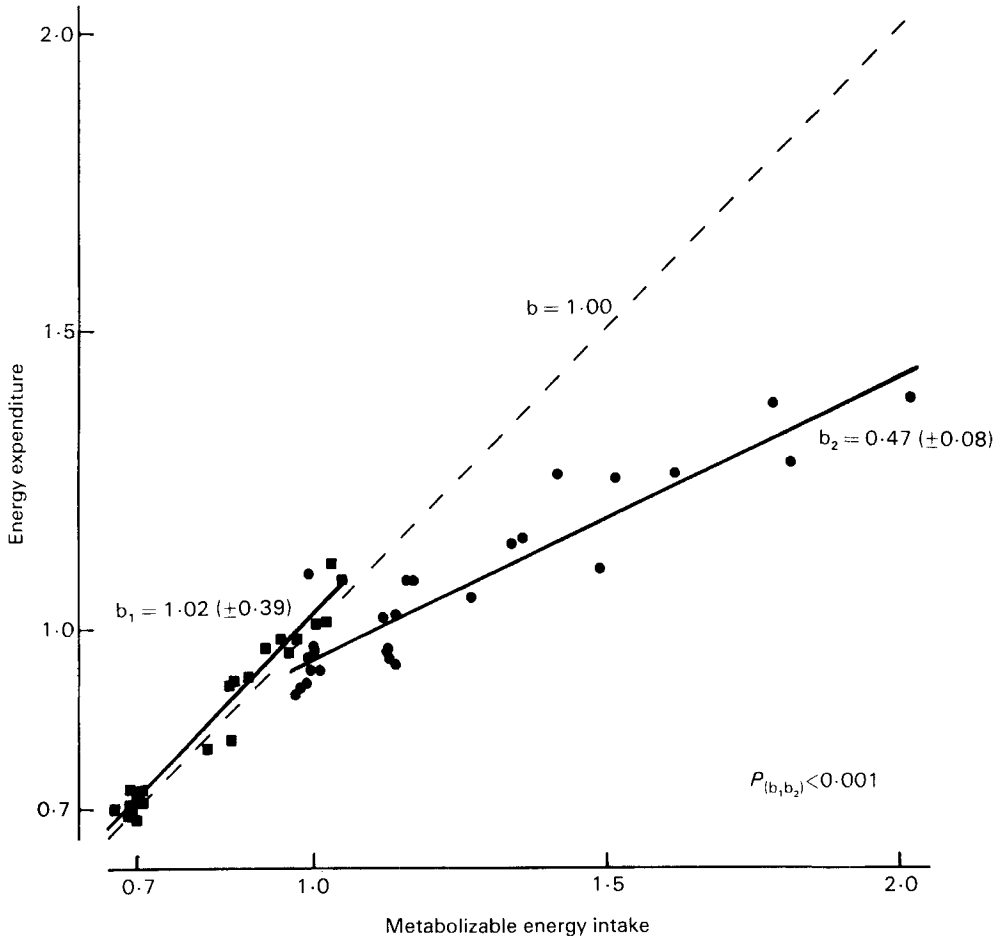


Fig. 3. Regressions of energy expenditure on ME intake, for the two underfeeding and the three overfeeding experiments, with intake and expenditure expressed relative to the levels during voluntary feeding. (■) underfeeding, (●) overfeeding experiments. Periods 4–27 d.

#### *Energy expenditure when intake is voluntarily increased by cafeteria feeding*

Rats substantially increase their voluntary intake of energy if their usual pelleted diet is supplemented by a variety of palatable foods ('cafeteria feeding'). This provides a convenient way of experimentally increasing energy intake, and may be considered to model the human situation in an 'affluent society'. We have measured energy expenditure continuously during cafeteria feeding in four experiments, the first (Tobin *et al.* 1981) a pilot experiment.

We next performed two experiments each with twenty matched groups of female hybrid rats, aged 6 months at the start in the first experiment and 6 weeks in the second. In the first experiment expenditure was measured in four groups, two on normal diet and two on the cafeteria diet, throughout the nine-week experiment. In the second, in order to allow for changes in carcass composition due

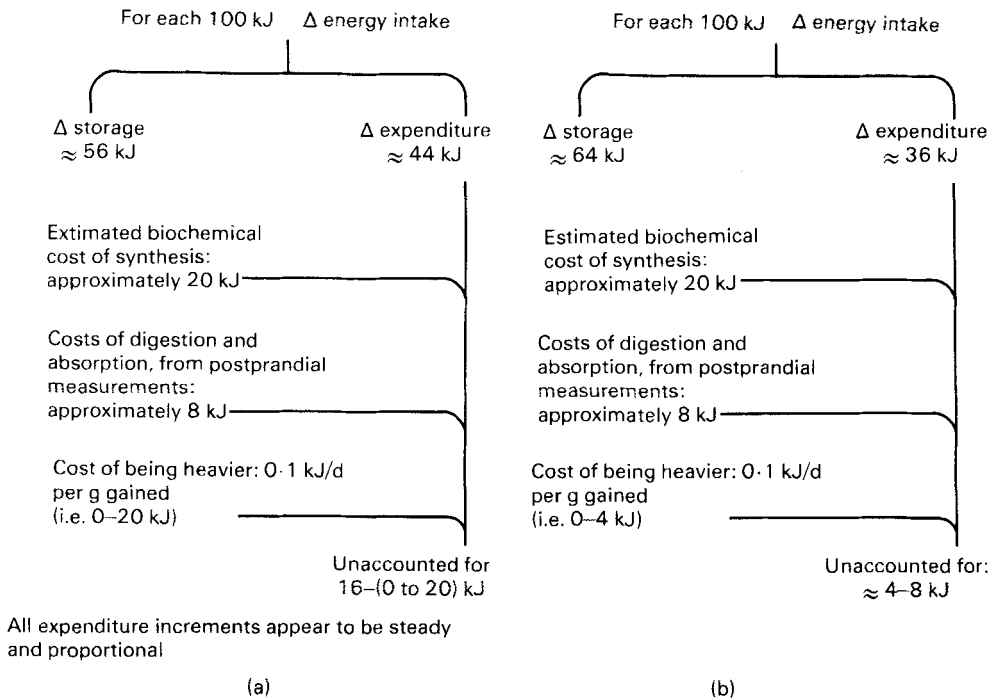


Fig. 4. Suggested disposal of excess ME intake: (a) given by tube-feeding; and (b) ingested voluntarily by adult rats in response to 'cafeteria' feeding.

to growth, successive sets of four groups were moved into the calorimeter for two-week periods and then killed and analysed; the experiment lasted eleven weeks. Bacon grill, cheddars, cheese puffs, chocolate and shortbread (selected out of a wider range as the foods the rats ate most readily) were supplied in varied combinations of four to the 'cafeteria' groups. Methods were otherwise as above.

Energy intake over the whole period of cafeteria feeding increased by 66 kJ/rat per d (33%) in the adult rats and by 40 kJ/rat per d (24%) in the young rats. The excess intake produced by cafeteria feeding varied among groups of young rats over single weeks from 9–76 kJ/rat per d. Energy expenditure over the whole period increased by about 24 kJ/rat per d (13%) in cafeteria-fed adult rats compared with rats fed standard pellets only, and in young rats by 9 kJ/rat per d (8%). The increase occurred over the first few days of cafeteria feeding, after which expenditure became more or less stable. Excluding the first week, the increase in expenditure in the adults was 23 kJ/rat per d, against an increase in intake by 51 kJ/rat per d; i.e. 45% of the increase in ME intake was added to expenditure. In the young rats expenditure increased by 12 kJ/rat per d while intake increased by 36 kJ/rat per d; 33% of the increase was added to expenditure. Storage of energy averaged over the whole period amounted to 42 kJ/rat per d in adult rats and 14 kJ/rat per d in young rats. Fig. 4(b) shows diagrammatically the suggested breakdown of the disposal of excess ME intake over the whole period in

the cafeteria-fed adult rats. The known costs associated with the increased energy intake leave little margin for Luxuskonsumption.

The systematic error in the total balance of energy (cf. p. 142) was considerably increased during cafeteria feeding, to 13 and 17 kJ/rat per d in the two experiments. We believe this was due to increased losses of energy in unrecovered food and the more numerous weighings. Although these errors are only a few per cent of daily intake they are a larger proportion of excess intake, and they are integrated over the duration of the experiment when compared with carcass changes. If we had used manufacturers' data or food tables to predict ME intake the errors must have been greater and, in the absence of measurements of energy expenditure, could well have created the illusion that expenditure changed by much more than it actually did.

We think it unlikely that strain differences among rats are of major importance, since in a fourth experiment, using the same strain and source of rats and the same pelleted diet and cafeteria feeding schedule as Rothwell & Stock (1979c), we obtained results indistinguishable from those described above for adult hybrid rats. It may be argued that luxuskonsumption may only be evident at levels of excess intake higher than we observed. Bearing in mind the errors of measurement, we believe some doubt must arise as to whether much greater intakes have actually been achieved. If they have, it would be difficult to interpret the significance for energy balance regulation of a response only evident at extreme intakes—which would have the consequence that moderate excess intake would lead to weight gain whereas extreme excess intake would not—and elicited by cafeteria feeding, but not by tube-feeding at any level of intake.

#### *Energy expenditure in congenitally obese Zucker rats*

In the Zucker strain of rat congenital obesity occurs as a Mendelian recessive character in the *fa/fa* (or 'fatty') genotype. The abnormality presumably depends upon a single protein, but its nature has not been identified. Since the obese rats have been reported to be more sensitive to cold than normal rats the suggestion has been made that they may have a defect in their ability to increase metabolism in the cold and that the mechanism at fault is also that responsible for luxuskonsumption; so that defective luxuskonsumption might explain the obesity (Trayhurn *et al.* 1976).

We have measured the energy expenditure of 5-month-old female non-obese and obese Zucker rats in the calorimeter with the cage temperatures held for 4–11 d at each of eleven temperatures from 5–30°. They were fed normal pelleted diet *ad lib*. Rectal temperatures were measured daily with a thermistor probe. The obese rats maintained normal rectal temperatures in environments down to 4°; they did not appear to shiver or to be adversely affected.

Fig. 5 shows the daily energy expenditures of non-obese and obese rats plotted against cage temperature. Each point is the mean of the daily readings from two cages of three rats each, starting 1 d after changing cage temperature. Both genotypes showed a similar, steeply sloping, slightly curvilinear relationship

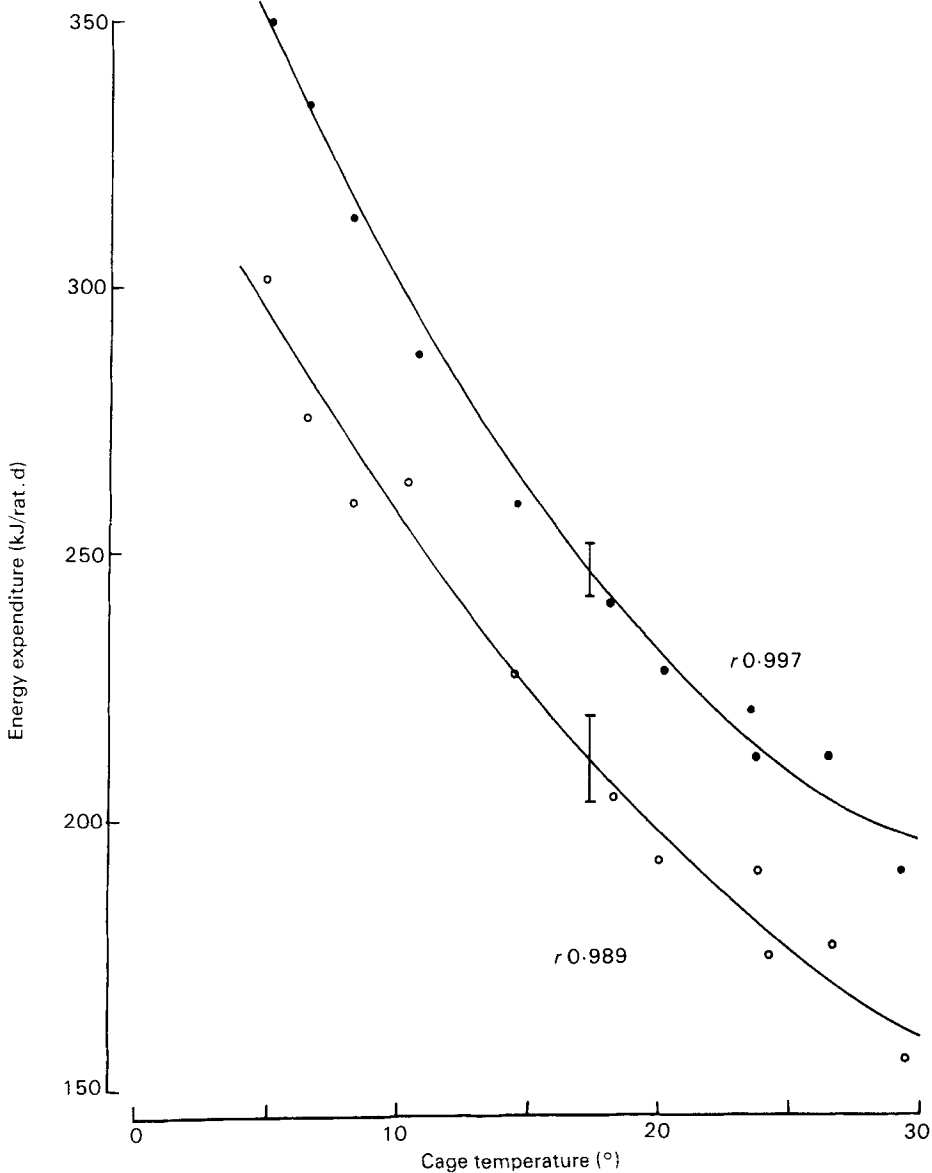


Fig. 5. Second-order regression of energy expenditure of 5-month-old female obese (●) and non-obese (○) Zucker rats on ambient temperature. Means of two groups of three, over 3–10 d, excluding the first day after a change of temperature. Vertical bars give the standard deviations for the prediction of  $Y$  from  $X$  at the means.

between ambient temperature and 24 h metabolism. At all temperatures the obese rats had greater energy expenditures on a 'per rat' basis than non-obese rats, by about 40 kJ/rat per d.

In rodents, in contrast to humans, variation of energy expenditure is the major effector of thermoregulation, and the relationship shown in Fig. 5 is what would be

expected for any rodent. There is no defect in this response in obese Zucker rats. Their defect in energy balance regulation, whatever it may be, thus does nothing to establish the existence of *luxuskonsumption* by way of a deficiency syndrome.

*The effects of propranolol on energy expenditure*

Proposals that excess ingested energy can be dissipated by a regulatory increase in expenditure have been linked with the suggestion that the effector for the mechanism is brown adipose tissue (Himms-Hagen, 1979; Rothwell & Stock, 1979c, 1980; Himms-Hagen *et al.* 1981; James & Trayhurn, 1981). This is known to be a thermoregulatory effector in new-born animals and awakening hibernants, under the control of a  $\beta$ -noradrenergic sympathetic pathway (Hull & Segall, 1965). The ability of the  $\beta$ -blocking drug propranolol (5 mg/kg intravenously) to block the response to cold in new-born rabbits provided part of the evidence for this (Heim & Hull, 1966). Propranolol should, therefore, provide a test for activity of brown adipose tissue in the context of overfeeding.

Two groups of rats were tube-fed at approximately 1.1 and 1.6 times voluntary intake. After 2 months the group maintained on the higher intake, receiving 104 kJ/rat per d more ME than the group on slightly elevated intake, were gaining 2.6 g/d more weight, and were dissipating 39 kJ/rat per d more energy—a similar response to that seen in previous tube-feeding experiments. Energy expenditure was then measured continuously in one group at a time. At 17.30 hours the rats in the lower-intake group received a tube 'meal' of 61 kJ (their normal meal), or no meal; the higher-intake group received a meal of 61 kJ, or 95 kJ (their normal meal), or no meal. Propranolol, 15 mg/kg body-weight, was given by stomach-tube 1 h before the meal, or omitted. The room lights were switched off at 19.30 hours. Each of the ten combinations of previous level of intake, size of meal and presence or absence of drug was replicated six times. Measurements of heart rate confirmed that the dose of propranolol took effect almost immediately, and mean heart rate was still reduced from approximately 420 to 300 beats/min 10 h after administration.

Fig. 6 shows the course of energy expenditure for rats maintained at 1.1 times voluntary energy intake and given their normal meal of 61 kJ with and without propranolol; and for rats maintained at 1.6 times voluntary intake and given their normal meal of 95 kJ, or no meal, with and without propranolol. All groups showed a steady raised level of energy expenditure over the period 1–4 h after the meal. Table 1 gives the mean energy expenditures for all ten treatment combinations over this period (with standard errors for the six replicate runs). Analysis of variance showed that the effect of the level of energy intake over the previous 2 months was highly significant; so also was the effect of a meal. Within the higher maintenance group, to which both sizes of meal were given, the regression of postprandial energy expenditure on meal size was significant. Propranolol had no discernible effect upon the increase in energy expenditure; neither that associated with the previously maintained level of energy intake nor that following absorption of a meal. Thus there was no evidence that either the increased daily energy

expenditure of overfed rats, or the increase following ingestion of a meal, are mediated by noradrenergic pathways.

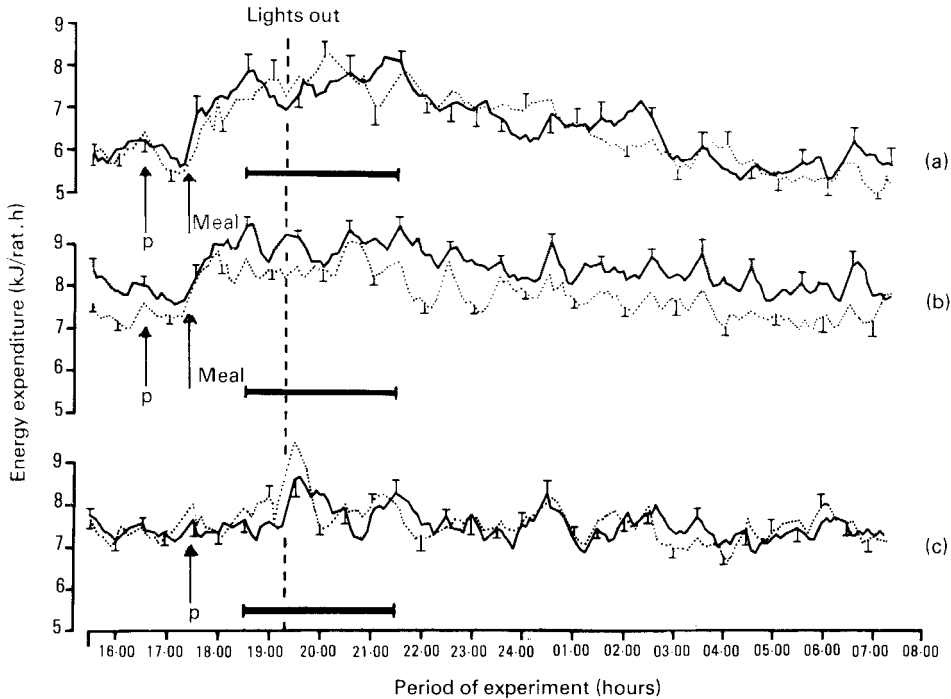


Fig. 6. Energy expenditure from 3 h before to 12 h after the normal meal-time: (a) in rats maintained by tube-feeding at approximately 1.1 × voluntary ME intake and given their usual meal of 61 kJ; (b) in rats maintained at 1.6 × voluntary ME intake and given their usual meal of 95 kJ; (c) in rats maintained at 1.6 × voluntary ME intake, with the meal omitted; in each case with (—) and without (· · · · ·) propranolol (15 mg/kg body-weight) given by tube 1 h before the meal. Points are means with their standard errors for six replicate days given by vertical bars.

Table 1. Energy expenditure (kJ/h) from 1 h to 4 h after a tube-feed

(Values are means of six runs with their standard errors for groups of four adult PVG/C × WAG/C rats)

Maintenance level	Meal	No drug		Propranolol*	
		Mean	SE	Mean	SE
1.1 × <i>ad lib.</i> (61 kJ/meal)	None	7.2	0.7	6.9	0.5
	× 1.1	7.7	0.7	7.7	0.7
1.6 × <i>ad lib.</i> (95 kJ/meal)	None	8.2	0.2	7.8	0.5
	× 1.1	8.4	0.3	8.4	0.2
	× 1.6	8.6	0.3	9.1	0.3

\*15 mg/kg body-weight orally 1 h before meal.

ANOVA shows effects of: maintenance level,  $P < 0.001$ ; meal size,  $P < 0.001$ ; propranolol, not significant.

An interesting point that emerged from the experiment (Fig. 6 and Table 1) is that the rise in energy expenditure after a meal was smaller in the rats maintained on the higher energy intake, absolutely and relatively, and even when the meal was larger. If it were not known that the groups were genetically and (initially) physically uniform, the finding of a difference such as this might have been thought to reflect some constitutional difference in capacity for 'thermogenesis', which might in turn be thought a possible cause of the obesity. Somewhat similar experiments with human subjects have been claimed to suggest this (Shetty *et al.* 1981). In the rats, however, the difference was clearly a consequence, not a cause.

#### *Concluding remarks*

In conclusion, we believe that comprehensive measurements of energy expenditure are necessary to support a case that a regulatory increase in expenditure occurs in response to excess energy intake, that is, that 'luxuskonsumption' exists. To the best of our knowledge no measurements of energy expenditure have been reported, from humans or animals, that show clear evidence of luxuskonsumption. We suggest, therefore, that the matter still rests as it did exactly fifty years ago, when Wiley & Newburgh (1931) published their paper entitled "The doubtful nature of "Luxuskonsumption"".

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#### REFERENCES

- Armitage, G., Hervey, G. R. & Tobin, G. (1979). *J. Physiol., Lond.* **290**, 15P.
- Blaxter, K. L. (1962). *The Energy Metabolism of Ruminants*. London: Hutchinson.
- Blaxter, K. L. (1975). In *Obesity in Perspective* p. 127 [G. A. Bray, editor]. DHEW Pub. No. (NIH) 75-708.
- Blaxter, K. L. & Wainman, F. W. (1961). *J. agric. Sci., Camb.* **57**, 419.
- Garrow, J. S. (1978). *Energy Balance and Obesity in Man*. 2nd ed. Amsterdam: Elsevier/North Holland.
- Glick, Z., Shvartz, E., Magazarik, A. & Modan, M. (1977). *Am. J. clin. Nutr.* **30**, 1026.
- Goldman, R. F., Haisman, M. F., Bynum, G., Horton, E. S. & Sims, E. A. H. (1975). In *Obesity in Perspective* p. 165 [G. A. Bray, editor]. DHEW Pub. No. (NIH) 75-708.
- Grafe, E. (1931). *Metabolic Diseases and their Treatment*. New York: Lea & Febiger.
- Grafe, E. & Graham, D. (1911). *Hoppe-Seyler's physiol. Chem.* **73**, 1.
- Gulick, A. (1922). *Am. J. Physiol.* **60**, 371.
- Heim, T. & Hull, D. (1966). *J. Physiol., Lond.* **187**, 271.
- Hervey, E. & Hervey, G. R. (1967). *J. Endocr.* **37**, 361.
- Hervey, G. R. (1975). In *Neural Integration of Physiological Mechanisms and Behaviour*, p. 109 [G. J. Mogenson and F. R. Calaresu, editors]. Toronto: University of Toronto Press.
- Hervey, G. R. & Tobin, G. (1981). *Nature, Lond.* **289**, 699.
- Himms-Hagen, J. (1979). *Can. med. Assoc. J.* **121**, 1361.
- Himms-Hagen, J., Triandafillou, J. & Gwilliam, C. (1981). *Am. J. Physiol.* **241**, E116.
- Hull, D. & Segall, M. M. (1965). *J. Physiol., Lond.* **181**, 449.
- James, W. P. T. & Trayhurn, P. (1981). *Br. med. Bull.* **37**, 43.
- Keys, A., Brozek, J., Herschel, A., Mickelsen, O. & Taylor, H. L. (1950). *The Biology of Human Starvation*, Vol. I. Ch. 17. Minneapolis: University of Minnesota Press.
- Miller, D. S. & Mumford, P. M. (1973). In *Régulation de l'Équilibre Énergetique chez l'Homme*, p. 196 [M. Apfelbaum, editor]. Paris: Masson.
- Miller, D. S. & Payne, P. R. (1962). *J. Nutr.* **78**, 255.



- Neuman, R. O. (1902). *Arch. Hyg. Bakt.* **45**, 1.
- Newburgh, L. H. (1944). *Physiol. Rev.* **24**, 18.
- Norgan, N. G. & Durnin, J. V. G. A. (1980). *Am. J. clin. Nutr.* **33**, 978.
- Passmore, R., Meiklejohn, A. P., Dewar, A. D. & Thow, R. K. (1955a). *Br. J. Nutr.* **9**, 20.
- Passmore, R., Meiklejohn, A. P., Dewar, A. D. & Thow, R. K. (1955b). *Br. J. Nutr.* **9**, 27.
- Passmore, R., Strong, J. A., Swindells, Y. E. & El Din, N. (1963). *Br. J. Nutr.* **17**, 373.
- Paul, A. A. & Southgate, D. A. T. (1978). *McCance and Widdowson's The Composition of Foods*, p. 31. London: H.M. Stationery Office.
- Pullar, J. D. & Webster, A. J. F. (1977). *Br. J. Nutr.* **37**, 355.
- Rothwell, N. J. & Stock, M. J. (1979a). *J. comp. physiol. Psychol.* **93**, 1024.
- Rothwell, N. J. & Stock, M. J. (1979b). In *Animal Models of Obesity*, p. 141 [M. F. W. Festing, editor]. London: Manchester.
- Rothwell, N. J. & Stock, M. J. (1979c). *Nature, Lond.* **281**, 31.
- Rothwell, N. J. & Stock, M. J. (1980). *Can. J. Physiol. Pharmacol.* **58**, 842.
- Rothwell, N. J. & Stock, M. J. (1981). *Nature, Lond.* **289**, 699.
- Shetty, P. S., Jung, R. T., James, W. P. T., Barrand, M. A. & Callingham, B. A. (1981). *Clin. Sci.* **60**, 519.
- Sims, E. A. H., Danforth, E., Horton, E. S., Bray, G. A., Glennon, J. A. & Salans, L. B. (1973). *Recent Prog. Horm. Res.* **29**, 457.
- Sims, E. A. H., Goldman, R. F., Gluck, C. M., Horton, E. S., Kelleher, P. C. & Rowe, D. W. (1968). *Trans. Ass. Am. Physns* **81**, 153.
- Strong, J. A., Shirling, D. & Passmore, R. (1967). *Br. J. Nutr.* **21**, 909.
- Tobin, G., Armitage, G. & Hervey, G. R. (1981). *Int. J. Obesity* **5**, 379.
- Trayhurn, P., Thurlby, P. L. & James, W. P. T. (1976). *Proc. Nutr. Soc.* **35**, 133A.
- van Es, A. J. H. (1977). *Nutr. Metab.* **21**, 88.
- Webster, A. J. F. (1981). *Proc. Nutr. Soc.* **40**, 121.
- Wiley, F. H. & Newburgh, L. H. (1931). *J. clin. Invest.* **10**, 733.