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# REGULATION OF ENERGY BALANCE

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## INTRODUCTION

The task of reviewing the literature on such a vast and controversial topic as the regulation of energy balance presents a daunting prospect. The lack of precedents in this series of Annual Reviews has not made this any easier, particularly as any study from Lavoisier onward could have a legitimate claim for inclusion. It obviously has been necessary to restrict the review to only a fraction of the published work in this area of metabolism, and an



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attempt has been made to concentrate on some of the more recent and radical ideas, and to emphasize the experimental rather than the clinical aspects.

Some of the major omissions from this review include ruminant and farm animal energy metabolism, control mechanisms in energy intake, exercise, human obesity, and adipocyte cellularity. For a more general account of the topic, Garrow's book (49, 50) provides one of the most readable descriptions of the regulation of energy balance in man. Readers requiring greater detail, particularly on some of the more contentious topics, should consult the proceedings of two conferences (9, 11) on obesity and await the imminent publication of another (6). The basic principles of energy metabolism are best described in two classics of animal energetics (14, 91) and the more recent monograph by Blaxter (7).



## CONCEPTS AND METHODS

An understanding of elementary thermodynamics and physiological accountancy indicates that energy balance is achieved when ingested food energy equals the energy expended in performing external work plus that lost in feces, in urine, and as heat. It is an elementary concept that should not require repetition, but there are many examples where workers have ignored or failed to grasp it. A common failure, which can afflict even eminent authorities, is to equate the gross energy of a food (i.e. its heat of combustion) with its metabolizable energy (heat of combustion less urinary and fecal energy losses). At the other extreme, but equally erroneous, is the assumption that the retention of 1 g of protein represents an increase in body energy content of 17 kJ (i.e. its metabolizable energy) when in fact bomb calorimetry will indicate an increase of 22 kJ (its gross energy). The complex and diverse pathways of intermediary metabolism occasionally cause confusion and have led some authors to contradict the law of constant heat sums by suggesting that the metabolizable energy of a nutrient can vary according to the pathway used to complete its catabolism.

The elementary nature of these examples should not detract from their importance, particularly as studies occasionally appear that seem to challenge the very foundations of the subject and the methods used. The latest example was reported by Webb (157), who used data from several energy balance studies to demonstrate the presence of an unmeasured and variable quantity ($Qx$) required to balance the results obtained from direct or indirect calorimetry. Included in the author's list of possible sources of $Qx$ are changes in entropy and energy states, but it seems that errors in the measurement of recognized components provide the most likely source. For example, Webb's analysis was restricted to human studies where changes

in body energy storage can only be inferred from indirect estimates of body composition and are therefore a potential source of large errors, particularly in short-term studies. It is also worth remembering that a balance calculated from intake and output is a small difference between two large numbers and will include the errors associated with these large numbers. The need to postulate a factor such as *Qx* has not appeared in animal nutrition, perhaps because changes in carcass energy can be determined accurately, but Webb's paper does serve as a forceful reminder of the methodological problems involved in measuring energy balance in man.

Some of these problems and many new developments in methods and apparatus for human studies have been reviewed by Garrow (50). Recent technical advances have made continuous and accurate indirect calorimetry in animal studies much easier (e.g. 3). However, many workers still prefer the carcass balance method for determining energy expenditure (i.e. energy expenditure = metabolizable energy intake − carcass energy gain), because many animals can be studied simultaneously and it provides an estimate of expenditure over the entire course of the experiment. Its disadvantage is that progressive or dynamic changes during the experiment are subsumed within the total expenditure. However, acute changes can be monitored by calorimetry and there are several simple designs for closed- or open-circuit systems available (32, 33, 146). Although of limited value in energy balance trials, in vivo methods for estimating body water (46, 128) allow progressive changes in body composition to be followed, and when used to match the initial composition of experimental groups, such a method greatly improves the accuracy of the carcass balance method. In spite of differences in opinion over carcass energy losses during hot-air oven drying (94, 99), it appears safer to prepare samples for bomb calorimetry by freeze-drying or drying at low temperatures in a vacuum oven.

With growing awareness of the similarities between diet- and cold-induced thermogenesis (130, 149, 151), environmental temperature has become an important factor in the interpretation of results, particularly as various strains of the same species may have a different thermoneutral temperature. Nevertheless, too strict a definition of thermoneutral temperature may be an unwarranted physiological abstraction, since Poole & Stephenson (122) have shown, at least for the rat, that behavioral responses can extend the thermoneutral range over 18–28°C.

Comparisons of energy utilization in animals on isoenergetic intakes require use of the pair-feeding technique, but this in itself introduces another variable—meal pattern. An elegant solution to the problem has been the introduction of "yoke-feeding" (e.g. 28), in which the ad libitum fed animal presses a lever to obtain food and this simultaneously delivers an identical amount of food to its pair-fed partner. With more animal studies

involving the presentation of varied human food items the determination of metabolizable energy intake has become even more laborious and tedious. One solution is to determine the heat of combustion of combined collections of spilt food, feces, and urine and subtract this from the gross energy of the total food supplied to the cage.

## REGULATION OF ENERGY BALANCE

The title of this section implies that body energy content is a regulated variable that might be compared to other functions such as body temperature and blood glucose. However, this concept would be questioned by many who argue that variations in body weight are considerably larger than those observed in other homeostatic functions. Nevertheless, it is important to realize that the limits for regulation of a physiological parameter are largely determined by the limits for survival, which are obviously much wider for body weight than for temperature, and the incidence of obesity in man does not invalidate the concept of energy balance regulation any more than diabetes questions our acceptance of glucose homeostasis. In fact, many reports have noted that the body weight of normal adult animals remains remarkably constant over long periods of time (e.g. 10, 84) in spite of large variations in energy intake and expenditure. Although many domesticated animals can become obese in later life, these have been selected for rapid weight gain, and the wild strains of these species tend to remain lean even when adequate food is available. However, constancy of a physiological parameter does not necessarily imply regulation. A more stringent criterion is that deviation from the normal value or range should elicit compensatory responses that tend to restore the parameter to its original level, and there is now considerable evidence to show that animals can recover from experimentally induced pertubations in body fat mass.



### *Fat Depletion*

FOOD RESTRICTION Underfeeding is one of the simplest methods of producing weight loss, but it is important to distinguish effects of fat depletion from more severe changes in lean body mass (i.e. growth). The results of most studies on adult animals suggest that both rats (68, 95, 101, 110) and man (88, 159) can completely recover from fat depletion.

LIPECTOMY There is considerable disagreement over the chronic effects of lipectomy in rats and mice, although several authors (e.g. 21, 96) suggest that experimentally and genetically obese mice are able to compensate for surgically removed fat, whereas lean animals apparently do not show full recovery (37, 92). Faust, Johnson & Hirsch (39) reported that lean mice

failed to recover from lipectomy, but recalculation of their data reveals that the body fat content of these animals was almost identical to that of controls 4 weeks after lipectomy. The same authors (40) later reported regeneration of adipose tissue following surgical removal of subcutaneous fat in weanling rats and complete recovery when these animals were allowed access to a high fat diet.

### *Excess Fat Deposition*

Most attempts to increase fat deposition have concentrated on inducing hyperphagia, but in this context it is necessary to consider only the reversible, nondestructive means of producing obesity, which therefore excludes techniques that involve permanent damage to the ventromedial hypothalamus.



HIGH FAT FEEDING Offering rats and mice a palatable high fat diet often results in hyperphagia and obesity (63, 93, 100, 120), though the success of this treatment depends on the strain and age of the animals (136) and few workers have studied recovery from the obese state. Schemmel & Michelsen (136) reported that obesity is not maintained when animals are returned to the conventional stock diet, and both Peckham et al (120) and Macdonald (100) report fat losses in animals after withdrawal of the high fat diet, but the extent of recovery in these animals is not known.

INSULIN INJECTIONS Chronic administration of insulin has been widely used to produce hypoglycemic hyperphagia and obesity in rats and mice (e.g. 61, 70, 101). Hoebel & Teitelbaum (70) found that rats became aphagic and rapidly returned to control weight when the injections were stopped, but no data on body composition were presented. Others (101) have found that the spontaneous weight loss after withdrawal of insulin injections in rats is accompanied by a reduction in epididymal fat pad weight and adipocyte diameter. Overall, these findings suggest that the rat is able to recover from increases in fat content induced by insulin, but some care must be exercised in the interpretation and extrapolation of these data as it is often difficult to distinguish between the responses to increased fat mass and the effects of insulin per se.

TUBE FEEDING Cohn & Joseph (23–25) force-fed rats by gastric intubation to produce a large increase in body fat mass. When tube feeding was terminated, these animals became hypophagic and rapidly lost weight until they had returned to the level of controls. These workers (23) also found an increased fat content in rats fed 100 or 80% of control intake by stomach tube, although body weight was unaltered, thus demonstrating the large

increase in metabolic efficiency that occurs when food is delivered to the rat in a small number of discrete "meals" (38). Rats tube-fed varying proportions of their normal daily food intake and allowed free access to the stock diet (127) reduced voluntary intake such that total daily energy intake was identical to that of controls, but all intubated animals showed excessive weight gains. This increase in body weight was largely (80%) due to an increase in body fat, all of which was lost when tube-feeding was ceased.

CAFETERIA FEEDING Attempts to influence the rat by flavoring and research in this field was hampered by the widely held view that food intake in the rat, unlike that of man, is relatively unaffected by factors such as palatability and variety. This assumption was seriously questioned by the work of Sclafani & Springer (138), who reported that rats offered a highly palatable diet composed of foods normally consumed by man rapidly became obese. When these animals were allowed access to the stock diet alone, all of the excess weight was lost. Rats fed a diet similar to that of Sclafani & Springer (the "cafeteria" diet) consume about 80% more energy than stock-fed controls and exhibit large increases in weight, which are entirely due to increases in fat content (129). When the cafeteria diet was removed and the animals were allowed only the stock diet, body weight and body fat returned to control levels. It is interesting that animals of the same strain and age as these, but from a different colony, become only moderately obese on the cafeteria diet (132) and weanling rats do not gain any excess weight in spite of a 50–60% increase in food intake (133). Conversely, older cafeteria rats (N. J. Rothwell, & M. J. Stock, unpublished data) (137) become obese rapidly but show relatively poor recovery of body weight when returned to the stock diet, suggesting that energy balance regulation becomes less effective as the rat ages. Rolls et al (124, 125) have produced obesity in rats by cafeteria feeding, but when they were returned to the stock diet body weight remained permanently elevated. The discrepancy between the results of Rolls' group and those discussed above may be due to genetic factors or to the fact that their animals were quite old by the end of the experiments.

Very few of the human overfeeding studies have involved detailed investigations during the recovery period, but Sims' group (141) and Norgan & Durnin (116) have reported, though no quantitative data were given, that when subjects were allowed to eat freely again they all lost weight without conscious effort.

Further evidence supporting the regulation of energy balance can be derived from the work on parabiosis, where animals are joined surgically by the skin and peritoneal surfaces. Several groups have demonstrated that

a lean animal parabiosed to an obese partner exhibits hypophagia and weight loss (26, 64, 119). King (89) has observed that a food-deprived rat consumed less food when cross-perfused with an obese partner and more food when perfused with a very lean animal, indicating that some humoral factor is involved in the regulation of body fat content.

## *Mechanisms of Energy Balance Regulation*

CONTROL OF FOOD INTAKE It has generally been assumed that energy intake is the major controlling factor in energy balance regulation and that a defective appetite control (i.e. hyperphagia) is the primary cause of obesity in man and experimental animals. Since a number of detailed reviews exist on the central and peripheral mechanisms of food intake control (e.g. 117, 155), it is not intended to discuss these mechanisms but instead to reconsider the importance of food intake in determining energy balance in the light of more recent data.

In 1947 Adolph (1) noted that the variation in caloric intake of young rats was relatively small and that intake remained constant over a range of dietary energy densities. This observation, which has subsequently been confirmed by a number of workers (e.g. 19, 79), provided the basis of the idea that animals regulate their intake precisely. Constancy of intake has also been observed in rats allowed to adjust voluntary intake while receiving varying proportions of their normal daily food intake by stomach tube (127). However, this seemingly precise control over total energy intake was inappropriate and totally unrelated to any component of energy balance, because these rats rapidly became obese. In fact, many studies into the control of food intake have been concerned with only short-term variations (24 h or less) and have often failed to relate these to body energy content or to the state of energy balance of the animal.

A closer study of the mechanisms of weight gain and loss of animals described in the previous section reveals that variations in food intake are not always the major cause of changes in body fat or weight. Several workers have reported greater fat deposition without any increase in intake in rats subjected to tube feeding (23, 127) or high fat diets (63, 93). It also seems that the greater energy retention of genetically obese rodents (22, 28, 149) and animals with electrolytic (54, 60) or chemical lesions in the ventromedial hypothalamus (34) is partly due to a reduced energy expenditure and still occurs when they are pair-fed with lean or untreated controls.

The recovery from experimentally induced pertubations in fat content can also be dissociated from changes in food intake. The weight loss of rats made obese by cafeteria feeding is accompanied by high rates of energy expenditure, and recovery of normal body weight can often occur without any reduction in food intake (129). Others (95) have found that the excess

food consumption of rats starved for 1–4 days was independent of the length of the fast or the weight lost, and normal body weight would be recovered even when intake was held at prefast levels. Oscai (118) has reported that after 30 days of food restriction, rats spontaneously returned to normal body weight within 18 weeks without any increase in food intake. He concluded that neither body weight nor adipocyte size determines voluntary food intake in the rat. However, the dissociation that can occur between food intake and body weight is perhaps best illustrated by a comparison of tube- and cafeteria-fed rats. The former show excessive fat deposition and body weight gain in spite of normal food intakes (23, 127), whereas young cafeteria-fed rats exhibit normal weight gain when consuming up to 80% more energy than stock-fed controls (130, 133).

In man it is possible to observe a two- to three-fold range of food intake in a population of subjects of the same age and weight (156, 158), and one can divide people, apparently similar in all other respects, into "large eaters" and "small eaters" (126). York et al (163) found that their group of small eaters had a higher body fat content than a group of large eaters and many workers have failed to show that the obese eat more than lean individuals (81, 103, 143). One group (87) has even found a negative correlation between food intake and body weight. The accuracy of many measurements of customary food intake, particularly in obese subjects, has been questioned (e.g. 111), but nevertheless it is difficult to support the contention that food intake is the primary determinant of body weight in man or experimental animals.

CONTROL OF OUTPUT When considering the role of output in the regulation of energy balance it is usual to divide expenditure into several components: basal metabolic rate, physical activity and thermogenesis induced by cold [nonshivering thermogenesis (NST)], or diet (DIT). For present purposes and simplicity, the term DIT refers to any change in expenditure induced by diet. However, these changes can be further divided into the short-term effects of a meal [specific dynamic action or thermic effect (TE)] and the long-term adaptive changes in expenditure originally referred to by Neumann (112) as "luxusconsumption." This distinction is based on the assumption that the mechanisms of the TE differ from those of luxusconsumption, and Flatt (42) suggests that the former represents the metabolic cost of transporting and converting the absorbed nutrients to their respective storage forms. However, it seems that the increase in metabolic rate (MR) following a meal varies considerably between individuals and is partly dependent on the nutritional state. Kaplan & Leveille (85) reported a lower TE in obese than in lean women, and York et al (163) found a much larger TE in large eaters than in small eaters of a similar body weight. In the rat,

a 3-day fast almost competely abolishes the TE, whereas in normal rats TE can be largely abolished by β-adrenergic blockade. (N. J. Rothwell, M. E. Saville, & M. J. Stock, unpublished data). In spite of the elaborate theoretical arguments proposed by Flatt (42), it is difficult to accept that an increase in MR of 20% in some subjects can be entirely explained in terms of conventional pathways when the same meal can result in only a 5% TE in another subject. Thus, it seems that a small but constant response to a meal is due to transport and assimilation of nutrients, but there is also a large increase in MR in some subjects, which may involve nonconservative mechanisms of energy utilization.

Since the work of Neumann (112), several reports have suggested that overfeeding is accompanied by a compensatory increase in MR (e.g. 57), but it was probably the work of Miller & Payne in 1962 (109) that stimulated the greatest interest and controversy in this field. They produced weight maintenance in two weanling pigs either by protein (PR) or energy restriction (ER), and over the 42 days of the experiment the PR pig consumed five times more energy than its ER partner. The authors concluded that most of the extra energy intake of the PR pig had been expended as heat, although no measurements of body composition or MR were made. Blaxter (8) has strongly criticized this experiment and suggests that the results could be explained largely by differences in meal frequency, even though the feeding pattern was identical for both pigs. Miller & Payne's experiments (109) have now been repeated (58) with more pigs and extensive measurements of energy balance, but with similar results. The energy expenditure of PR pigs was elevated by 100% and this increase could not be accounted for by differences in physical activity or the energy cost of fat deposition.

Similar effects of diet on energy expenditure have been reported for rats (98, 104, 109, 145, 153) and adult human subjects (107). Although the demonstration of DIT in animals has usually required feeding nutritionally unbalanced diets, striking changes have also been produced simply by stimulating food intake by using the cafeteria diet. Increases in food intake of up to 80% in young rats fed the cafeteria diet can result in little or no increase in body weight gain or the rate of fat deposition (130, 133, 144, 152), but it can produce large increases in total energy expenditure (130, 133). These results demonstrate that DIT can be of major importance in the regulation of energy balance in the rat, but the role of thermogenesis in man remains controversial.

Garrow (49, 50) has reviewed most of the human overfeeding experiments and points out that of the ten studies in which resting MR was measured, nine found this to be elevated but only five concluded that energy expenditure was increased by overfeeding. The remaining four investigations were probably too short and achieved insufficient increases in food

intake (less than 92 MJ), since most of the reported increases in MR were seen after nearly 2 weeks of overfeeding and with excess intakes greater than 96 MJ. Durnin & Norgan (36) claimed that they found no evidence for increased energy expenditure during a 6-week overfeeding study. However, as Garrow (51) points out, their subjects consumed an excess of 293 MJ and gained only 6 kg in weight, indicating that some of this excess energy was probably dissipated. In a more recent report Norgan & Durnin (116) state that a large portion of this excess energy might be accounted for by errors in the measurements, but even allowing for this, the authors still found an excess intake of 1.5–2.1 MJ/day, which they were forced to ascribe to further unknown errors.

It is possible that a large portion of the excess energy reported in some of the human overfeeding studies might be due to these unknown errors, which for some reason consistently overestimate intake and underestimate body energy content. It is difficult, however, to apply these arguments to some of the results from Sims' group (141). They persuaded lean volunteers to increase food intake for several months to produce an average increase in body weight of 20%. The energy cost of maintaining this greater weight was 11.3 $MJ/m^2$/day compared to a value of 7.5 before overfeeding and 5.4 in spontaneously obese subjects, indicating that overfeeding had resulted in a large increase in MR that was not accounted for by the weight gain alone.

In 1962 Hervey (65) claimed: "There is no doubt that over long periods of time animals take in and give out equal amounts of energy and it appears that as long as enough food is available the equality is a result of adjustment of intake to match output rather than vice versa." At the time this statement was made there was indeed little evidence to suggest that energy expenditure was involved in energy balance, although this is hardly surprising since few workers had actually attempted to study this aspect of metabolism. Since 1962, however, evidence has accumulated to indicate that expenditure is a major component in the regulation of energy balance and in some situations may be of greater importance than changes in food intake.

There have been numerous hypotheses relating body energy content or body fat to changes in food intake, any of which might apply equally to the control of expenditure. It is interesting that insulin, which has been involved in a number of theories of food intake control (e.g. 31, 102, 160, 161), may also be involved in thermogenesis since diabetic rats fail to exhibit DIT and NST (135). Furthermore, it now seems that the central mechanisms that affect intake and output are also closely linked and it has been suggested that the ventromedial hypothalamus (VMH), an area of the brain involved in feeding, may also affect thermogenesis (121). This finding could explain the increased metabolic efficiency and obesity of animals with VMH lesions and suggests that the extensive literature on VMH control of food intake

and body weight may have to be reassessed, taking into account this additional output function.

## MECHANISMS OF DIET-INDUCED THERMOGENESIS

Few biochemists and physiologists have studied the metabolic origins of DIT, largely because the quantitative significance of this form of heat production was not well-recognized, but also because a suitable animal model of DIT has not been available. There was an early suggestion (145) that DIT could result from processes similar to those involved in NST, but it was only recently that the close similarities between these two phenomena became obvious (130). The convergence of ideas from these two previously unconnected areas therefore allows the nutritionist to take advantage of the more detailed work on NST, and earlier reviews on mechanisms of cellular thermogenesis (e.g. 52, 66, 69) can now be gleaned for material relevant to energy balance regulation.

A simple consideration of biochemical energetics reveals that approximately 75% of substrate enthalpy is normally lost as heat during intermediary metabolism and oxidative phosphorylation, and most (90%) of this occurs during the oxidation of reduced mitochondrial substrate (123). Further increases in heat production (e.g. NST or DIT) must obviously occur at the expense of the remaining 25% of substrate enthalpy conserved in ATP. This could result from either a lower efficiency of ATP formation [e.g. proton conductance pathway in brown adipose tissue (BAT) (115)] or from increased hydrolysis of ATP [e.g. lipid (4) or protein (165) turnover, substrate cycles in intermediary metabolism (113), and increased cation transport (74)].

At some time or another, all of these thermogenic processes have been suggested as candidates for the source of DIT, but the associations recently established between NST and DIT have considerably reduced the field. The common features of these two forms of thermogenesis include increases in food intake, metabolic rate, thermogenic and lipolytic responses to noradrenaline (130) and noradrenaline turnover (164), inhibition by $\beta$-adrenoreceptor antagonists (130) and by hypoxia (15), and BAT hypertrophy and hyperplasia (130, 152). These similarities are consistent with the proposal (130, 131) that DIT, like NST, results from sympathetic activation of BAT thermogenesis.

Until recently, the contribution made by BAT to total metabolic rate was considered small even in NST. Following the elegant blood flow studies of Foster & Frydman (44, 45), this view is no longer tenable and it is now accepted that in the cold-adapted rat this small amount of tissue (usually

less than 1% of body weight) can receive up to a third of the cardiac output and extract most of the oxygen supplied to it. By using similar techniques to measure the in vivo oxygen uptake of BAT, it has recently been shown that BAT accounts for all of the increased thermogenic response to noradrenaline in hyperphagic cafeteria-fed rats (134). The corollary to this is the finding by Thurlby & Trayhurn (150) that the impaired thermogenic response seen in the obese (ob/ob) mouse is due to the low blood flow and oxygen extraction of BAT in this animal.

There are many biochemical similarities between BAT from cafeteria-fed and cold-adapted rats, such as increased mitochondrial mass and respiratory enzyme activity, higher in vitro rates of mitochondrial respiration, recoupling of mitochondrial respiration by purine nucleotides (e.g. GDP), and increased mitochondrial binding of GDP (16). Conversely, genetic obesity is associated with decreases in BAT respiratory capacity and reduced mitochondrial mass and GDP binding (55, 67). However, it is not yet possible to quantify the contribution these changes in BAT mitochondria make to NST or DIT, and therefore the possibility that other thermogenic pathways are involved cannot be excluded. Studies on the ouabain inhibition of hamster BAT respiration (72), for example, suggest that sodium-potassium transport may serve as a source of thermogenesis. Similarly, in rats exhibiting DIT, large increases in the $Na^+$ $K^+$-ATPase activity of BAT are seen and the in vitro stimulation of this enzyme by noradrenaline is considerably enhanced (N. J. Rothwell, M. J. Stock, & M. G. Wyllie, unpublished data). Horwitz (73) has recently reviewed this aspect of BAT thermogenesis, but it is by no means clear whether the $Na^+$ $K^+$-ATPase system makes an important thermogenic contribution, indirectly modulates mitochondrial respiration, or simply responds to the changes in membrane permeability caused by high rates of sympathetic stimulation.

The role of thyroid hormones in DIT is probably small, even though fasting (154) and hyperphagia (30) cause marked changes in the peripheral metabolism of thyroxine ($T_4$) to triiodothyronine ($T_3$) and "reverse" triiodothyronine ($rT_3$). Thyroid gland function in genetic obesity is essentially normal (13), although there are reports of a defect in thyroid hormone action. The genetically obese mouse is reported to possess fewer nuclear $T_3$ receptors and lower $Na^+K^+$-ATPase activity (56), which fails to respond to $T_3$ injections (162). Others (97) have confirmed the lower $Na^+K^+$-ATPase activity, but they found that it responds dramatically to $T_4$ treatment, the obese mice being two to three times more sensitive than the lean.

In some situations (29, 140) it is possible to dissociate the changes in circulating $T_3$ levels from changes in metabolic rate, and it may be that, like NST (47), DIT only requires the presence of thyroid hormones for their

permissive effects on catecholamine-induced thermogenesis. It has even been suggested that the thermogenesis resulting from sympathetic stimulation of BAT and thyroid thermogenesis are mutually exclusive (147). Whether or not increased sodium pumping is responsible for thyroid-mediated thermogenesis is still debatable since any causal relationship between the two has been disputed (20, 43, 66), although these criticisms of the original hypothesis have recently been countered (142).

The contribution made by protein turnover to total metabolism and its role in thermogenesis has yet to be defined. There have been suggestions that turnover is increased in the cold (165) and reduced in obesity (50, 139), whereas others (105) have demonstrated that the linear relationship between protein turnover and energy intake seen in lean mice is absent in ob/ob mice. However, this failure of turnover to respond to variations in energy intake results in a paradoxical situation where at low levels of energy intake obese mice have higher turnover rates than the lean. A major difficulty in accepting protein turnover as an important factor in thermogenesis is that raised levels of DIT commonly occur in situations where turnover is low—e.g. during consumption of low protein diets by man (107, 108), pig (58, 109), and rat (104, 145, 153).

Finally, there is the possibility that substrate cycles (e.g. in glycolysis) are involved in thermogenesis. Newsholme (113) has recently presented detailed theoretical arguments for DIT arising from such futile cycles and has proposed that obesity results from a low capacity for substrate cycling. Although the biochemical arguments are sophisticated, others (86) have warned of the difficulties in estimating the energy cost of these cycles and the dangers of extrapolating from in vitro to in vivo conditions. Furthermore, there is very little experimental evidence (direct or indirect) to suggest an involvement of this mechanism in DIT. The only relevant study is one in which the maximal activity of key enzymes and dehydrogenases in three substrate cycles were found to be greater in ob/ob mice than in lean mice (114). By Newsholme's own criteria this study contradicts his proposal, and attempts to resolve the dilemma by invoking modulation of these cycles by unknown and undefined endocrine factors are unconvincing.

## OBESITY

The study of obesity in man has posed numerous problems and these have been discussed in some detail in previous reviews (9, 11, 17, 49, 50, 75). However, if obesity is considered in terms of energy balance, it is obvious that this condition arises from a situation where energy intake exceeds energy output, although it is uncertain whether this imbalance is due to a high input or a low output. In a previous section it was concluded that there

is little evidence to show that obese subjects consume more food than do lean, but there is equally little data to suggest that the obese have a reduced energy expenditure. In fact, several studies have found elevated basal or resting metabolic rates in obese subjects (71, 76), although the TE of food (85) and the response to cold exposure (2, 18) are both reportedly reduced in the obese.

The observation of normal or elevated metabolic rates in obese subjects has supported the suggestion that excess body fat gain is primarily due to an increased food intake, but this extrapolation is not necessarily valid. Very often obese subjects are stable in body weight and probably in energy balance, and unfortunately there are very few data on intake and expenditure during the dynamic phase of weight gain. James & Trayhurn (78) have suggested that during this period expenditure is reduced and have tried to distinguish between cause and effect by studying post-obese subjects (82). Because of these, and other problems associated with the long-term measurements of energy balance in man, many workers have turned to the study of obese animals.



## *Animal Models of Obesity*

Three major types of obesity exist in laboratory rodents, hypothalamic, genetic, and diet induced, and because all have been reviewed elsewhere (11, 13, 41), this discussion is restricted to recent findings and their relevance to the regulation of energy balance.

DIETARY OBESITY Previously, dietary treatments have involved feeding synthetic diets high in fat or carbohydrate, both of which produce moderate hyperphagia and increased efficiency. It is interesting that the type of fat or carbohydrate used can have a marked effect on weight gain because long-chain triglycerides usually produce an increased body fat content whereas feeding medium-chain triglycerides may cause a reduction in body weight (12, 59) and sucrose feeding tends to cause greater weight gains than glucose (83). Recently, cafeteria or snack diets have been employed to study energy balance in the rat (see above). The variation in weight gain in response to cafeteria feeding with age and strain (132, 133, 137) has obvious analogies with the human population, and it is interesting that the final nutrient composition of the foods selected by cafeteria-fed adult rats is remarkably similar to that consumed by man in affluent societies (128).

HYPOTHALAMIC OBESITY It has long been known that electrolytic or chemical lesions in the VMH result in hyperphagia and excess weight gain, suggesting that this area may be involved in satiety (see 13, 48, 90, 155 for reviews). In weanling rats VMH lesions produce increases in body fat

without any changes in food intake or body weight (54), and even in the adult, VMH obesity is partly due to an increased metabolic efficiency (60). Therefore, it has been suggested that the VMH is involved in the control of energy output as well as food intake (34) and electrical stimulation of this area can result in sympathetic activation of BAT thermogenesis (121). Conversely, destruction of the VMH results in atrophy of BAT and a diminished in vitro response to noradrenaline (L. Girardier, personal communication). Many other features of the VMH syndrome, such as altered glucose and free fatty acid levels, could also be due to a reduced sympathetic tone, whereas the hyperinsulinemia of these animals may result from an increased vagal activity (48). Whether it is the ventromedial nucleus itself or, as Gold (53) suggests, the adjacent noradrenergic bundle that is responsible for these effects, it is obvious that this area of the hypothalamus is involved in many aspects of energy metabolism.



GENETIC OBESITY A number of genetically transmitted obesity syndromes have now been characterized in rodents (13, 27, 41) and the most common of these [the obese (ob/ob) mouse, the diabetic (db/db) mouse, and the fatty (fa/fa) rat] all exhibit hyperphagia, increased metabolic efficiency, hypothermia, impaired pituitary and reproductive function, hyperinsulinemia, and massive increases in body fat content. Thurlby & Trayhurn (149) have made detailed measurements of energy balance during pair feeding studies in ob/ob mice and demonstrated that in spite of a large increase in food intake the obesity of this mutant is mainly due to a reduced thermogenesis. This impairment in DIT and NST has been ascribed to a defect in BAT (67, 150) and could explain both the hypothermia and the obesity of the ob/ob mouse. The diabetic mouse (28) and the fatty rat (22) also become obese when pair-fed with their lean littermates, and Goodbody & Trayhurn (55) have reported a mitochondrial defect in the BAT of the db/db mouse similar to that of the ob/ob. It is difficult to distinguish the primary cause of obesity in these mutants, because many of the reported aberrations are a result rather than a cause of excess fat deposition. However, the diversity of the alterations seen in obese rodents strongly suggests a central or hypothalamic defect.

The relative contributions of genetic and environmental influences in human obesity are by no means clear, although a number of studies show strong familial trends in body weight (77, 91). Miller (106) has compared the importance of these factors in determining metabolic efficiency in genetically obese, laboratory, and wild rats fed either stock or high fat diets and concluded that genetic background has a greater effect on metabolic efficiency than does diet. In fact, both Miller (106) and Berg (5) have claimed that the stock-fed laboratory rat is obese compared to its wild counterpart

and a comparison of laboratory and wild rodents might yield further information on the moderate obesity frequently seen in man.

## SUMMARY AND FUTURE TRENDS

The past 10–15 years have produced a significant increase in knowledge and theories concerning the regulation of energy balance, but the precision of this regulation is still uncertain. However, the fact that investigators have had to resort to a variety of techniques and ploys (some of them bizarre) to produce marked pertubations in body weight is in itself an indication that the regulatory system can be very robust. Although control of food intake obviously plays a major role in this system, control of energy expenditure (i.e. DIT) also has to be considered as an important factor in the maintenance of energy balance.

In this review most of the evidence for DIT and its biochemical origins has been derived from studies on experimental animals. Many of the overfeeding studies carried out on man are consistent with the animal work, but because of differences in interpretation and some equivocal results, the role of DIT in human metabolism is still a contentious issue. This problem may not be fully resolved to everyone's satisfaction until complete, continuous, and very precise energy balance measurements are made on chronically overfed lean subjects. Before this expensive and arduous experiment is undertaken, evidence for thermogenesis in man will continue to depend on acute measurements of the metabolic response to various stimuli. An increasing number of studies (e.g. 35, 80) have demonstrated the existence of NST in man, and the possibility that this could originate from BAT is supported by histological (62, 148) and thermographic data (130). Conversely, reductions in cold tolerance (2, 18) and thermogenic responses to noradrenaline (82) with increasing adiposity are similar to the blunted responses seen in genetically obese animals, which suggests that human obesity may also involve an impairment in thermogenesis.

At the present time these ideas concerning the importance of DIT in man and its role in obesity remain somewhat speculative, but no doubt this area will now be the subject of further research. Similarly, the impact of early nutritional influences on subsequent energy balance regulation and resistance to obesity will receive more attention following the report (144) that hyperphagia in rats during early life results in a reduced body fat content and leanness in adulthood. The relative contributions and interactions between intake and output in energy balance need clarifying, and in terms of central organization, the mechanisms of appetite control should now be considered for their relevance to the control of thermogenesis. Finally, there is the possibility of treating obesity with thermogenic agents, and although

this approach has already attracted the pharmaceutical industry, the recent developments arising from academic research should help to identify those areas where pharmacological intervention could be most effective.

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