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REGULATION OF ENERGY BALANCE

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INTRODUCTION

Two major components are involved in the regulation of energy balance: nutrient intake and energy expenditure. The interaction of these determines body energy stores so that the basic equation can be considered to be $\Delta E = E_{in} - E_{out}$. A chapter on the regulation of energy balance by Rothwell & Stock appeared in the first volume of the *Annual Review of Nutrition* (68). In that review, recent work on the experimental aspects of this area of metabolism and the evidence in animal models for dietary-induced thermogenesis (DIT) were presented. In order to provide a complementary view, our chapter focuses on the importance of thermogenesis in humans and the interactions of intake and output in energy balance. Current research on DIT in animals is concerned mainly with the contribution made by brown adipose tissue. This is the subject of another chapter in this volume (34) and is not presented here.

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COMPONENTS OF THERMOGENESIS

The identification of possible defects in the regulation of energy balance continues to be of interest to both clinicians and investigators. Obesity is a problem of energy imbalance. Inappropriately high intakes or low expenditures produce energy surfeits, increased fat storage, and gain in body weight. The relationships appear to be relatively straightforward. However, understanding the regulation and integration of the terms in the balance equation, E_{in} and E_{out}, is complex. While E_{in} is always the metabolizable energy of the foods consumed, E_{out} consists of two components: $E_{out} = E_{excr} + E_{ther}$, where E_{excr} is the metabolizable energy lost from the body, usually in urine and stool, and E_{ther} is heat production (thermogenesis).

More attention has focused on E_{ther} than the others because of evidence in humans (84) that excess caloric intake does not always increase energy stores to the degree expected. Thermogenesis is the sum of four moities: resting metabolic rate (RMR)—a by-product of cellular and body maintenance; the thermic effect of food (TEF); the thermic effect of physical exercise (TEE)—exercise-induced heat production; and the phenomenon of adaptive thermogenesis (AT)—heat produced in response to an alteration in metabolic efficiency associated with changes in environmental conditions. Of the four, only AT cannot be measured directly and is detected by changes in the other components. Metabolic adaptations, seen as variations in RMR and TEF, and changes in physical activity, seen as TEE, are the two principal mechanisms involved in changes of energy expenditure.

The relative contribution of each to total energy expenditure can be safely estimated in the weight-stable individual (Figure 1) (35). The RMR in an average 70-kg male amounts to approximately 1500 kcal/day or 60–75% of the total daily expenditure. It is the energy expended for maintenance of normal body functions and homeostasis, plus a small component related to sympathetic nervous system (SNS) activity. The RMR is measured when an individual is at rest in a thermoneutral environment at least 8–12 hours after the last meal or any significant physical activity. The basal metabolic rate, as originally defined by Boothby & Sandiford (8), is measured in the morning upon awakening after 12 to 18 hours of rest. It may be somewhat lower than the RMR, but the difference is small and the RMR is now the more commonly used measurement.

Factors traditionally accepted as determinants of RMR are listed in Table 1. Differences in RMR due to age, sex, or body size are largely corrected if the data are related to fat-free mass (FFM), although the difference between some individuals can still be as much as 30% (28, 97a). The decrease in RMR associated with age generally reflects a loss of lean tissue. In addition, changes in cellular metabolism may possibly occur. The lower RMRs of women over men are due mainly to their smaller size, although when energy output is

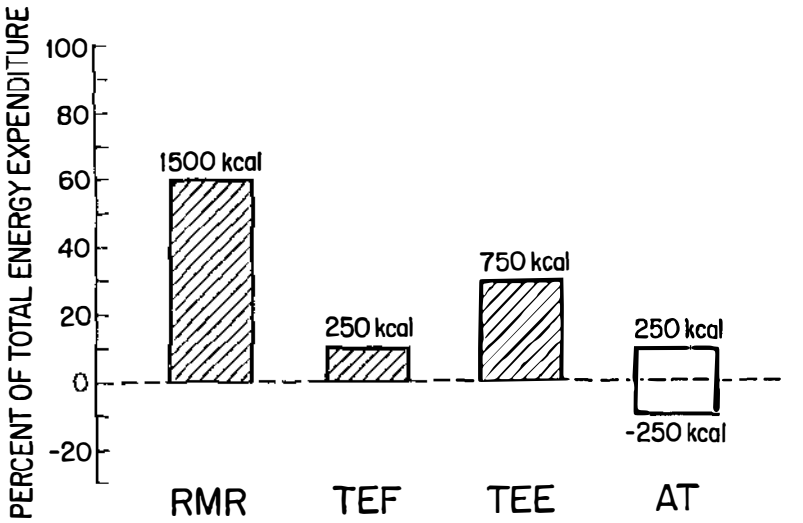

Figure 1 Components of energy expenditure during weight maintenance and the potential modifying effect of adaptive thermogenesis. Approximate percentage of total calories expended by a 70-kg man consuming 2500 kcal/day (from 35).

expressed per unit of fat-free mass, some investigators have found slightly higher metabolic rates in women (37). Early work (30, 73) suggested, and recent data (87) confirm, that the RMRs of women change with the menstrual cycle. A fall occurs before ovulation and a sharp rise (approximately 5%) occurs after ovulation, associated with changes in body temperature. Ambient temperature also affects RMR. Deviations from thermoneutrality cause changes in metabolic rate (5, 14). Hormones, such as insulin, the thyroid hormones, and norepinephrine, the latter reflecting activity of the sympathetic nervous system, are known to influence RMR. The role played by diet is still not clearly understood. The increases in resting metabolic rate after overeating (28) or decreases after undereating (37) involve not only the long-term energy cost of digestion and metabolism of food ["substrate traffic" as described by Flatt (26)] but adaptive responses as well.

Table 1 Factors that influence resting metabolic rate

Invariable	Variable
Age	Preceding diet
Sex	Body composition and weight
Genes	Temperature
	Hormones and drugs
	Stress

Another component of E_{ther} is the thermic effect of food (TEF) itself. This refers to the increase in energy expenditure above the RMR that can be measured for several hours after a meal. It was formerly thought that protein alone elicited the thermic response to food (specific dynamic action) (72). It is now known that carbohydrate and fat are also thermogenic. The TEF can be accounted for largely by the energy required for the digestion, absorption, transport, metabolism, and storage of ingested food. However, other factors such as activation of the sympathetic nervous system by carbohydrates or other dietary components can contribute significantly to the thermic response. The energy content (10, 33) and composition of the meal itself (56, 60, 98), as well as the nutritional state (90) and antecedent diet of the individual (3) have been studied for their effect on the magnitude of the TEF. While significant changes in TEF have been seen, these factors may play a greater role in determining resting metabolism. Although the TEF can vary between individuals, on average it accounts for a daily energy expenditure of approximately 10% of caloric intake.

The TEE is the energy expenditure required for muscular activity. Its contribution to total daily energy expenditure will vary greatly depending on the intensity of the work performed and duration of activity. In a moderately active, 70-kg man requiring an energy intake of 2500 kcal/day to maintain energy balance, the TEE accounts for approximately 750 kcal/day or 30% of total energy requirements. Of all the components of E_{ther}, that due to physical activity is the most variable. The rate of energy expenditure can be as high as 10 to 15 times the RMR. In humans the metabolic efficiency of performing physical work is approximately 30% and total energy expenditure is closely correlated to the amount of work done. No differences in the efficiency of exercise have been found between individuals when the energy cost of moving the increased body weight of heavier subjects is taken into account (10, 32). Alterations of the nutritional state, which may have major effects on the RMR, seem to have no significant effect on the TEE. However, interest has been renewed recently in the interaction of physical exercise and food intake on metabolic rate with the possible potentiation of the TEF by exercise (54, 81).

The last component of E_{ther}, AT, is least understood when applied to humans. It appears to account for no more than about $\pm$ 10–15% of total daily expenditure but could be a major determinant of long-term weight changes. AT is seen primarily as a change in RMR that is caused by adaptation to environmental stresses such as changes in ambient temperature, food intake, emotional stress, or other factors. During periods of undernutrition, such as starvation, there is a progressive decline in the RMR, which is, at least initially, greater than that which can be accounted for by the loss of body mass. During overnutrition, there is a 10–15% increase in RMR above that seen during energy balance. The mechanisms involved in these changes are related in part

by the SNS, catecholamines (47), thyroid hormones, and insulin (20). Biochemical changes are likely to be involved and include the activation or suppression of futile metabolic cycles, changes in the efficiency of oxidative phosphorylation, changes in rates of protein synthesis and degradation, and activity of the sodium-potassium pump.

METHODS FOR MEASURING ENERGY EXPENDITURE

There are many methods available for measuring energy expenditure in humans under resting and active conditions. Each has its advantages and disadvantages with regard to accuracy, complexity, versatility, availability, and cost. Direct calorimetry (38) is considered the "gold standard" for measuring energy expenditure over long periods of time, but it is a technique that measures heat loss and not production. Because heat storage also occurs in the body, the total heat loss will not be equivalent to heat production for periods less than 24 hours. For this reason, the method is inappropriate for short-term measurements. Heat storage can be measured by thermometry (15, 89), but its accuracy is much less than that needed for energy balance studies. The measurements are also very difficult to do in a free-living subject. A mobile "spacesuit" direct calorimeter was designed by Webb et al (97) in an attempt to avoid some of these limitations. Results with this mobile direct calorimeter compare favorably to those obtained by indirect calorimetry.

The most widely used techniques are those that employ indirect calorimetry. Heat production (metabolic rate) is determined from oxygen consumption and carbon dioxide production. When the urinary excretion of nitrogen is also known, information on the type and "net" rate of fuel oxidation within the body can be calculated (27, 52). A steady state of CO_2 production and respiratory exchange must be reached and subjects should have normal acid-base balance. When these conditions are met, the accuracy is generally within 2–5% for energy expenditure.

There are several methods to study oxygen consumption and CO_2 production, either at rest or during exercise (28). At one end of the spectrum there is the respiration chamber (38), which can be used in studies of energy expenditure over periods of several hours to days in subjects who have room to sleep, eat, and exercise. At the other end are portable respirometers, which collect expired air via a tight fitting face mask or mouthpiece and are suitable only for intermittent determinations of gas exchange (36, 58). Ventilated hood systems have increased in popularity recently and are very satisfactory for making relatively long-term (several hours) measurements (44). Instead of a mask or mouthpiece, the subject is fitted with a transparent hood with a snugly fitting collar. Fresh air is drawn into the hood via an intake port and expired air is drawn out of the hood by a motorized fan. The flow rate is measured by a

pneumotachograph and aliquots of the outflowing air are analyzed for oxygen and CO_2 content. Such systems are as accurate as stationary respirometers and make possible continuous measurements of energy expenditure.

Other noncalorimetric methods for estimating metabolic rate are available, but the errors inherent in them are too great to permit sufficiently accurate measurements (75). These include techniques based on physiological measurements (e.g. heart rate, pulmonary ventilation volume), human observation and recording methods (e.g. time and motion studies, activity diaries), and kinematic recordings such as radar and mechanical activity meters.

Recently, double isotopically labeled water ($^2H_2$ and ^{18}O) was used to measure energy expenditure for long periods (5–10 days) in free-living subjects. While this method is expensive and requires access to a specialized mass spectrometer for analyses of samples, it does permit normal day-to-day activities. The accuracy of this method in adults is approximately 6% when compared to direct or indirect calorimetry techniques (45, 74).

There are several ways in which energy expenditure data can be expressed. Commonly used terms in energy balance studies are kcal/time, Mj/time, or watts. A controversy exists over which parameter to use as the denominator. Data may be expressed per individual, per unit of body weight, per unit of body weight to an exponential power, per unit fat-free mass, or to some derivative of height and weight (35). Selecting the appropriate factor may depend on the purpose of the study in which it is a part. If the interest is in comparing metabolic rate determinations, data should be expressed according to body composition, namely, per kg fat-free mass, which is the best indicator of the respiring cell mass. This normalizes the data and allows comparisons between individuals of different size and composition, as well as in the same individual before and after a weight change. If the study is in energy balance, expressing the data per individual is most appropriate.

FACTORS AFFECTING METABOLIC RATE AND ENERGY BALANCE

As mentioned earlier, marked variations in resting metabolism can occur between two individuals of similar weight, age, sex, and habitus (28). The source of this interindividual variation is not easily identified. Recent attention has focused on the role of genetic factors, with strongest support found in animal models.

It is known that mice with single-gene mutations differ in metabolic efficiency. Studies by Coleman (16) show that genetically obese (ob/ob) mice have a decreased RMR and gain extra body weight and fat while being fed half the energy given to lean controls. The conversion of food energy into thermic energy appears to be normal when induced by temperature changes. In con-

trast, efficiency of its conversion into stored energy is abnormally high and may be attributed in part to the hyperinsulinemia associated with the obesity (17).

In humans, the Pima Indians of Arizona have both an abnormally high incidence of obesity and diabetes and a relative genetic homogeneity. Measurements of RMR in lean and obese, diabetic and nondiabetic Pima volunteers revealed an inheritable component. The offspring of diabetic parents have higher RMRs than those of nondiabetic parents. While the implications of this observation are not easily understood, the evidence supports a genetic factor in the regulation of RMR.

The role played by genetic background in determining the response to food (TEF) is also of current interest. However, evidence supporting a defect in this type of energy expenditure in obese persons is equivocal (7, 42, 79, 82–84, 99). Possibly, the conflicting results are due to heterogeneity of the obese subjects studied and/or to the difference in methodologies used. It is increasingly recognized that obesity consists of a number of different subtypes; some of which have strong genetic influences (85).

Recently, Bessard et al (7) studied the thermic response to a mixed meal in lean and obese women. Using an open circuit ventilated hood system, volunteers were observed continuously for five hours after the ingestion of the test meal. The obese subjects had significantly lower thermic responses than their lean controls. In these subjects, only 7.6 ± 0.4% of the ingested calories were utilized for heat production compared to 9.5 ± 0.4% for the lean group.

In order to allow for a delayed response in the obese group that might cancel this difference, the thermic response induced by three meals over 14 hours in another group of obese and lean women was studied using a respiration chamber (40). The total response was greater in both groups but that of the obese was still lower than that of the lean (8.7 ± 0.5% vs 14.8 ± 1.1%) (see Figure 2). To determine whether or not this reduced thermic response to meal ingestion persists after weight reduction and might therefore precede weight gain, subsequent studies in "reduced-obese" individuals were conducted (76). Volunteers were the same women who had been studied in the previous five-hour tests. Those who participated had completed an 11-week protein-supplemented modified fast (40) in which a mean of 12 kg of weight was lost. The thermic response to the meal was still found to be reduced, which suggests that this low response is not a consequence of obesity.

The factors responsible for the reduced thermic response in obese persons are not clear. They may have their basis in endocrine as well as metabolic changes. Jung et al (41) reported that obese women with a family history of obesity exhibit a reduced thermic response to norepinephrine (NE) infusion when compared to nonobese controls. They noted that the defect was similar to that described in genetically obese rodents (94). In contrast, Danforth (20) found a

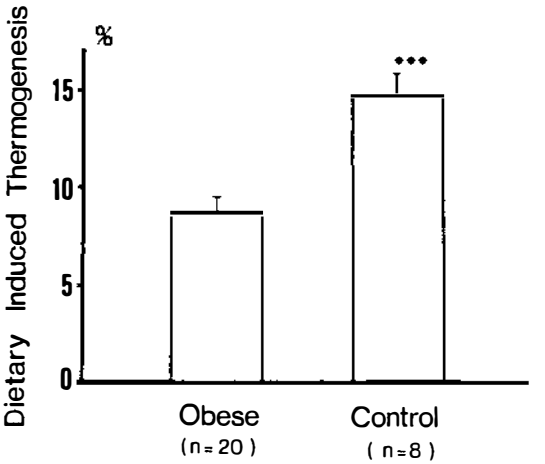

Figure 2 Dietary-induced thermogenesis due to three meals measured over 14 hours in obese and lean women in a respiration chamber, expressed as percentage of energy content of the meals: *** $P < 0.001$ (from 40).

normal thermogenic response to graded doses of NE in obese Pima Indians when compared to the response in lean Caucasians.

Glucose-induced thermogenesis (GIT) was measured by Jequier & Schutz (40) in three groups of obese patients, all of whom had family histories of obesity. Subjects were classified according to their glucose tolerances, with obese diabetics giving the lowest thermic response. The results suggest that insulin is required in nondiabetic individuals for a full response after glucose ingestion. If true, the insulin resistance of obese, nondiabetic individuals should be expected to attenuate any glucose-induced thermic responses. Support for this comes from work of Golay et al (29) showing an inverse relationship between insulin resistance and thermogenic response in nondiabetic and diabetic subjects given a 100-g oral glucose load. Ravussin et al (64) reported similar findings using the euglycemic-hyperinsulemic clamp technique.

While the insulin resistance associated with obesity may contribute to the reduced TEF seen in overweight individuals, it is unclear whether or not this precedes the obesity itself. Since the decreased thermogenic response to glucose administration can be partially restored by weight loss (64, 79), some consider the defect to be a consequence rather than a cause. Others, as mentioned earlier, have not seen a normalization (7, 51) and believe it contributes to the development of obesity.

Jequier (39) hypothesized that a certain weight gain must occur in an individual with this defect in order to compensate for it. Observations from subjects studied in the respiration chamber indicate that a linear relationship

between excess body weight and total energy expenditure exists. The slope of the regression line is about 16 kcal/kg body weight per day, which means that for each kilogram of excess body weight the overall energy expenditure is increased by 16 kcal per day. Conceivably, excessive body weight accompanied by increased expenditure will compensate for the low TEF in subjects with a reduced response. Given this assumption, to expend the same number of daily calories (e.g. 2500 kcal per day), an obese individual with a 9% DIT would have to weigh 9.4 kg more than a lean individual with a 15% DIT. It seems unlikely that massive obesity (greater than 15 kg of excess body weight) can be explained solely on this basis. In these patients, increased energy intake must also occur.

Jequier's hypothesis is made on the presupposition that changes in intake or physical activity do not also play a compensatory role. This cannot be readily assumed since intake and expenditure are known to interact with each other. Diet-induced thermogenesis is an involuntary expenditure produced by intake. Physical activity, in contrast, may or may not be regulated by the nutritional status. While decreased activity is associated with severe undernutrition, the influence of overfeeding on physical activity is unknown (37). Physical activity, usually a voluntary expenditure, could be utilized to compensate for an abnormally low DIT. Intake and expenditure are both determinants of energy balance and it must be the long-term coupling of the two that maintains energy equilibrium and stable body weight. To be well-matched, changes in physical activity should result in proper shifts in energy intake. It has been postulated that exercise plays a role in energy balance by both expending energy and regulating food intake.

While epidemiological data suggest a positive relation between inactivity and obesity, experimental evidence in humans supporting a regulatory mechanism are equivocal (88, 92). Part of the problem is the difficulty of measuring voluntary intake behavior both in a laboratory and in the field (61). The former may be abnormal, the latter inaccurate. Most studies that address this question were done by adding an exercise regimen onto an otherwise sedentary existence in free-living subjects. However, no direct, quantitative measurement of food intake was made. For most, body weight was used to back extrapolate this information. We are aware of only two studies in obese individuals (101, 102) and four in normal-weight individuals (25, 58, 96, 103) in which accurate energy balance techniques and ad libitum feeding were included.

In the studies of Woo et al (101, 103) weight-stable lean and obese women were subjected to a paradigm that allowed for voluntary food intake but prescribed physical activity. Three different activity levels, one sedentary and two with treadmill walking, were imposed. Food intake was covertly monitored throughout these 62-day studies. While the intakes of both groups matched their sedentary levels of activity, when exercise was included this

coupling of intake and expenditure was sustained only in the lean women. Regardless of whether exercise was added to or subtracted from daily activity, the obese subjects did not adjust their intakes to their expenditures (see Figure 3). Physical activity produced a negative energy imbalance for these women because it did not signal an increase in intake. The results of these studies are in agreement with many of those done with out-patients (92) and confirm an uncoupling of the intake of energy from the expenditure of energy as physical activity in obese women. The difference in the intake responses of lean and obese women to exercise may be related to the excess energy stores of the latter. If so, compensatory intake behavior may not occur until these are depleted. To date, studies in reduced-obese persons have not been done.

In a group of obese subjects exercised for 57 days while consuming about 2200 kcal/day (102) and in a group exercised while on a protein-sparing modified fast (59), a decrease in RMR accompanied the exercise-induced energy deficits. This argues against the putative, beneficial effect of exercise on resting metabolism during hypocaloric dieting. The idea that exercise is able to maintain RMRs during weight reduction in obesity originated in results from metabolic studies on the effect of exercise in the hours after the bout and also in the seemingly synergistic effects of diet and exercise together (9, 10, 22, 54, 91, 107). Data from recent studies (23, 33, 50, 81) suggest that factors such as aerobic fitness and the timing and size of a meal are determinants of the metabolic response to exercise and may account for differences between lean and obese subjects.

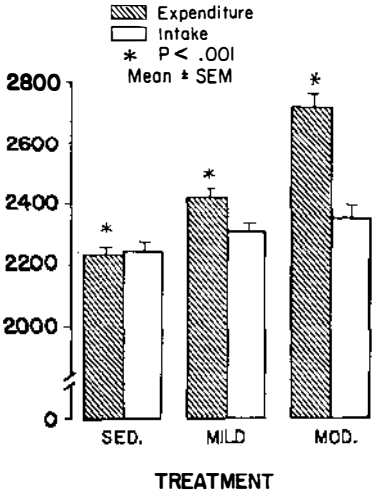

Figure 3 Effects of exercise treatments on mean daily energy expenditure and intake (in kcal per day) in six obese women (from 103).

NUTRIENT FACTORS IN DIET-INDUCED THERMOGENESIS

It is well-accepted that protein, fat, and carbohydrate all exert thermogenic effects. The mechanisms involved are currently under investigation and a basic model has been proposed. Drs. Landsberg & Young (48) hypothesize that since the SNS plays a critical role in the regulation of adaptive thermogenesis in response to cold exposure, and since changes in dietary intake can alter SNS activity, then the sympathetic nervous system should be involved in mediating some of the changes in energy expenditure that accompany changes in intake. Factors to be considered are (*a*) the nutrient or food of interest; (*b*) the substrate derived from it, and (*c*) the signal triggered by it, which coordinates dietary intake and sympathetic outflow. Criteria for this signal include that it be altered by intake, evoke corresponding alterations in sympathetic activity, and be recognized by a mechanism in the central nervous system which, in turn, initiates an appropriate change in the response of the SNS.

Experiments by Young & Landsberg (104, 105) have established that fasting suppresses and sucrose feeding stimulates sympathetic activity. The results from these early experiments suggested that glucose, or glucose and insulin, might serve as the signal(s) for carbohydrate-induced thermogenesis. Both change significantly during fasting and sucrose feeding. Using animal models of experimental hypoglycemia (46, 106), these investigators showed that the SNS, but not the adrenal medulla, is suppressed by diminished plasma glucose concentrations. Subsequent studies with 2-deoxyglucose (62) pointed to the intracellular utilization of glucose, rather than the blood glucose concentration per se, as a major determinant of changes in sympathetic activity in response to carbohydrate intake. Recently, corroborative evidence in humans has been obtained with insulin and glucose studies (2, 24, 53, 71, 80, 100).

The glucose clamp techniques, which depend upon priming and continuous infusions of glucose or glucose plus insulin, permit the attainment of steady-state hyperglycemia or steady-state hyperinsulinemia with maintenance of normal plasma glucose concentrations. Rowe et al (71) assessed plasma NE concentrations during such procedures and demonstrated a dose-related increase in plasma NE in response to insulin infusion.

While insulin and insulin-mediated glucose metabolism are important determinants of carbohydrate-induced thermogenesis, the thyroid hormones also make a contribution. Rothwell et al (69) studied the hormonal and metabolic responses of rats during fasting, followed by carbohydrate refeeding. Under these circumstances, thyroid hormones seem to play a significant role. Fasting causes a decrease in triiodothyronine (T_3), but this drop is not entirely responsible for the fall in RMR that also occurs. Restoring T_3 to normal levels does not

increase the RMR of fasting rats (12). In contrast, a transient T_3 increase occurs when fasted rats are refed a small amount of carbohydrate and this is followed by a rise in RMR. Both increases in T_3 and RMR can be blocked by propranolol, a beta-adrenergic antagonist. Taking these observations together, Rothwell et al (70) hypothesize that insulin, acting via an insulin-sensitive region in the CNS, stimulates the SNS and this in turn increases plasma T_3. Both the increase in T_3 and the nutrient supply are essential for the rise in RMR with refeeding. Therefore, the fasting animal with its low T_3 level must have its T_3 restored before the metabolic rate can increase in response to nutrient intake. Fat refeeding would be without effect on RMR in fasted animals because it does not increase T_3.

The effect of overfeeding or fasting followed by refeeding on thyroid hormones in humans has been studied. Both serum concentrations and production of T_3 are increased with overfeeding (19), and return toward normal after fasting when carbohydrate or a mixed diet is refed (13, 18, 43, 95). As in animals, the absence of such an effect when fat is refed (6) and the importance of the carbohydrate content of the diet in producing these changes (19) have been seen. The relationship between diet-induced alterations in thyroid hormone metabolism and thermogenesis has been studied directly during overfeeding but not refeeding.

Acheson & Burger (1) observed that in isocalorically fed subjects when T_3 was reduced by administration of an inhibitor of monodeiodination, metabolic rate did not change. Subsequent studies (4) found that mild increases in plasma T_3 concentrations, induced by replacement amounts of L-thryoxine plus L-triiodothyronine administration so as to mimic overfeeding-induced changes in thyroid hormone metabolism, increased RMR without changing the energy costs of exercise or the TEF. Whether or not increased T_3 production is a prerequisite for the increased RMR of overfeeding is not known. These studies remain to be done.

The changes in energy metabolism following a period of carbohydrate overfeeding may be the result of energy-requiring processes different from and/or supplementary to those involved in energy production from an individual meal. Investigations into the contribution of the SNS to carbohydrate-induced thermogenesis indicate that the longer-term increases in RMR that occur in overfeeding experiments are achieved in part by differences in the metabolic fate of the ingested carbohydrate. Schutz et al (77) studied volunteers for seven days in a respiratory chamber. Each day, progressively greater amounts of carbohydrate were eaten while protein and fat were maintained at their initial levels. Rapid weight gain and an increase in energy expenditure that accounted for one third of the increase in energy intake were observed. The respiratory quotient (RQ) rose to 1.12 from 0.76. Since an RQ above 1.0 is associated with net lipogenesis, these results were taken to indicate that a

portion of the glucose in these overfed subjects was converted into lipid rather than oxidized or converted to glycogen. Since lipogenesis from glucose is relatively inefficient, part of the increase in energy expenditure induced by the carbohydrate overfeeding must be attributable to this metabolic change as well as to activation of the SNS.

The signals mediating the thermic effect of dietary fat are less well known. Adding fat to a basal diet can increase the SNS activity in rats (78). Since this effect is prevented by cholestyramine treatment, intestinal absorption of fat must be required. The nutrient-SNS signals generated by fat consumption are hypothesized to be the free fatty acids (FFA) themselves or the intestinal hormones they stimulate. Recent work by Bukowiecki et al (11) suggests that products of lipolysis, especially palmitic acid, may mediate the cellular response to NE. Palmitic acid is able to mimic 80–85% of the effect of NE in isolated brown adipocytes. The increase in BAT respiration is attenuated by the addition of albumin, which binds FFAs but not by propranolol. NE is known to stimulate hormone-sensitive lipases in BAT and increase lipolysis. The FFAs so formed are available in the cell as substrates for beta-oxidation and as messengers for altering mitochondrial function. Whether the FFAs in the blood play a similar role is unknown. In humans, FFAs rise during underfeeding when RMR is depressed and also during exercise when metabolism is stimulated. Therefore, it may be that fat stimulates the SNS via several signals (such as glucagon or cholecystokinin) of which FFAs are but one.

Little work has been done to determine which signal(s) mediate protein-induced thermogenesis. Attention in this area has focused instead on the ability of protein to produce a larger thermic response than carbohydrate or fat. Recent work by Nair et al (56) indicate a more prolonged increase in the metabolic rate of lean and obese subjects after a protein meal than after glucose ingestion (see Figure 4). Since dietary protein but not glucose can stimulate protein synthesis,

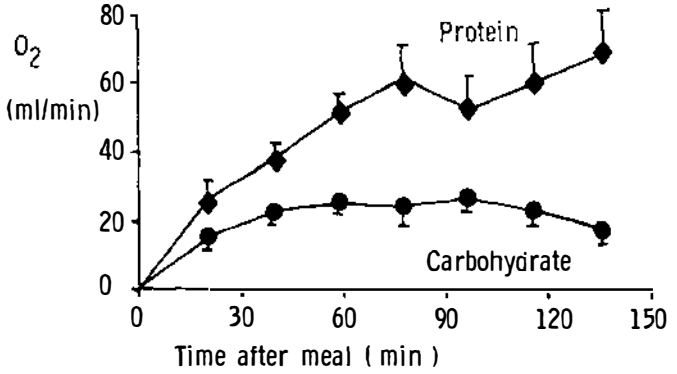

Figure 4 Thermic response to 300 kcal of protein or glucose in normal subjects (from 56).

the prolonged thermic effect is believed to reflect the energy cost of the synthesis of tissue protein.

Rennie et al (65), using the ^{13}C-leucine continuous infusion technique to measure in vivo protein synthesis, showed that in the fed state, skeletal muscle contributes more than half the total protein turnover, and that in the fasting state a fall in muscle synthesis can account for most of the change in whole body turnover. Conceivably, this change in protein synthesis rate should have considerable implications for energy expenditure. Direct evidence of the contribution of protein synthesis to metabolic rate was provided in recent studies by Nair et al (55, 56a). Using the continuous infusion technique in fasting, insulin-deprived, type I diabetic subjects given insulin to alter their catabolic states, they demonstrated that the metabolic rate follows the trend in protein synthesis.

Other factors associated with food intake that have been investigated for the role they might play in dietary-induced changes in expenditure are preabsorptive (see Figure 5). LeBlanc (49) observed different thermic responses between young men given a mixed meal orally versus a meal by an intragastric tube. Food bypassing the oral cavity was less thermogenic than that tasted and chewed. The potentiating effect of stomach distension on TEF is also of interest. Recent studies in humans are in agreement with earlier work in rats (66), but provide only very preliminary data.

REGULATORY MECHANISMS OF DIT

Identifying the regulatory steps in DIT requires both a whole-body and cellular approach. Much of the work done in this area comes from animal research, with the effects of cold and diet in rodent models being studied at both levels (68). Attention in the last five years has focused on BAT as the effector of both cold- and diet-induced thermogenesis. BAT is postulated to be an "energy buffer" in the regulation of energy balance in rodents. This is the subject of another chapter in this volume and the reader is referred to it (34).

The importance of BAT in humans is unclear, largely because the amount existing in the adult is so small and its contribution is difficult to assess (67). Attempts have been made to extrapolate the information obtained from studies of BAT in rodents to humans. Most experiments have been based on two premises drawn from the observations in animals: (*a*) that thermogenesis is associated with BAT activity, this being mediated by beta-adrenergic receptors; and (*b*) that overfeeding and cold increase NE-stimulated sympathetic activity, which, in turn, increases BAT activity. The evidence that SNS stimulation of BAT or activation of thermogenesis in other target organs is involved in the regulation of DIT in humans, however, is controversial.

An increase in plasma NE concentrations has been shown only after inges-

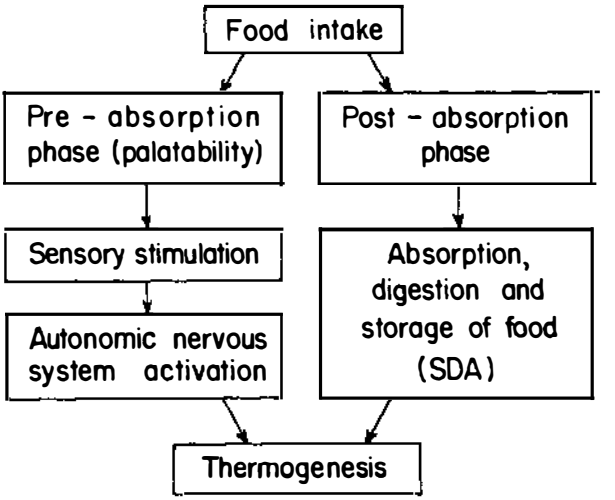

Figure 5 Suggested mechanisms of enhanced thermogenesis following the ingestion of food (from 49).

tion of glucose and not protein or fat (98), but ingestion of all three foodstuffs is accompanied by significant thermic responses. As mentioned earlier (71), NE levels appear to rise more in response to hyperinsulinemia than to hyperglycemia. Several investigators have attempted to study the role of beta-adrenergically-mediated SNS activity in glucose-induced thermogenesis by using beta-adrenergic antagonists. Acheson et al (2) measured energy expenditure in normal volunteers during steady-state administration of glucose and insulin (clamp technique) before and after administration of propranolol. After beta-adrenergic blockade, energy expenditure decreased while glucose uptake did not change. This suggests the presence of a beta-adrenergically mediated sympathetic component in this type of DIT.

In contrast, studies by Welle & Campbell (100) in lean volunteers overfed carbohydrate or a mixed diet found no changes in the thermic response to infused NE, no effect of beta-adrenergic blockade on the RMRs of the overfed subjects, and no inhibition by propranolol on the pre- or postprandial TEF compared with weight-maintaining diets. A slight increase in RMR with overfeeding was observed. Obviously, their conclusion that there is no evidence of SNS involvement in the regulation of DIT in humans is difficult to reconcile with those in animal models and that of Acheson et al (2). It is possible that the level of overfeeding achieved was insufficient to elicit changes in NE sensitivity that were detectable by the techniques used. A lack of uniformity in test conditions between laboratories is a problem in this area. Seaton et al (80) have also studied the effects on oxygen consumption of a 100-g oral glucose load in subjects given a beta-adrenergic (propranolol) or an

alpha-adrenergic (phentolamine) antagonist. The former did not alter the normal thermic response to glucose with saline; the latter increased the response but also was able to elicit a response in the absence of any glucose load. Phentolamine was thought to exert its thermic effect by increasing plasma NE concentrations.

These results are puzzling given the known beta-receptor-mediated effects of NE. In agreement with Acheson et al (2), DeFronzo et al (24) also demonstrated sympathetic mediation of DIT. Using euglycemic clamps, they observed that phentolamine administered to normal volunteers did not alter the insulin-induced thermic response to glucose-insulin infusions, whereas propranolol decreased the incremental energy expenditure and insulin-mediated glucose metabolism. The conflict with the data of Welle & Campbell (100) is not easily resolved and may be due in part to the difference in the types of hyperinsulinemia induced. The clamp technique establishes and maintains a continuously high insulin concentration, whereas an oral glucose load elicits a transient hormonal rise. Minaker et al (53) used both clamps and oral glucose testing in two groups of volunteers. The sustained hyperinsulinemia of the former elicited a large NE response in the young but not in the older subjects. The transient increase in plasma insulin following oral glucose elicited opposite NE responses in the two groups of subjects.

Conclusions from these studies about the relative alpha- or beta-adrenergic receptor contributions to thermogenesis in humans are limited by the nonphysiologic nature of the euglycemic-hyperinsulinemic clamps and the pharmacologic dosages used with adrenergic blocking agents. It is not clear that phentolamine crosses the blood-brain barrier; propranolol does not. If the hypothalamus is involved in the DIT of humans, as it is in rodents, this alone might explain the lack of effect of propranolol. The response to chronic treatment or to bolus injections has not yet been studied and it is unclear which of these methods is the appropriate physiological model.

While information on the specific receptors involved in DIT is incomplete, it is generally accepted that the catecholamines themselves make a significant contribution (57). Several investigators (21, 43, 64, 86) have used catecholamine infusions to elicit thermic responses in studies of the metabolic differences between lean and obese individuals.

Sjostrom et al (86) infused both epinephrine (E) and NE in lean and obese volunteers. Their results indicate that E is more potent than NE in stimulating metabolic rate. The obese subjects had normal to high responsiveness to both catecholamines but, after weight reduction, E sensitivity was reduced. They postulated that an increased sympathetic responsiveness at a higher weight could protect against further weight gain. However, a decrease with weight loss would increase efficiency and facilitate weight gain.

Other investigators have used NE but not E infusions during under- and

overfeeding. Katzeff & Daniels (43) and Daniels et al (21) studied the thermic response to NE infusions in lean and obese Caucasians and Pima Indians during weight maintenance and overfeeding. Surprisingly, overfeeding did not alter the thermogenic sensitivity to NE in any of the groups. In agreement with the epinephrine work, an apparent higher responsiveness to infused NE was observed in obese Pima Indians. However, this may be attributed to a lower metabolic clearance rate in this group resulting in higher NE concentrations at a given dose (based on fat-free mass). When thermic responses were plotted against the plasma NE concentrations, the NE sensitivity of this group was similar to that of the others. Because basal NE values are normal in this group, it was hypothesized that the low metabolic clearance rate is indicative of a depressed SNS activity. In contrast to Sjostrom et al (86), underfeeding in both obese Caucasians and Pima Indians did not reduce NE sensitivity.

While the obese Pima Indians with their relative genetic homogeneity are the most likely to demonstrate a genetic defect for obesity, the effect of their insulin insensitivity, indicated by high basal plasma insulin concentrations, on any metabolic aberrations also cannot be discounted. Recently, it has been estimated that 50 to 70% of the thermic response associated with glucose infusions in normal-weight individuals can be accounted for by the cost of glucose storage alone (63, 93).

Obese and non-insulin-dependent diabetic subjects are insulin resistant and demonstrate a reduced glucose uptake during insulin/glucose infusions. This can be attributed to both altered glucose storage and oxidation. Ravussin et al (64) studied the thermic effect of infused glucose and insulin in normal-weight (I), obese (II), obese-glucose intolerant and non-insulin-dependent diabetics before (IIIa) and after (IIIb) weight loss of 10.8 ± 0.4 kg (see Figure 6). During the hyperinsulinemia of the clamp procedure, total glucose disposal from combined endogenous production and glucose infusion was measured. Glucose disposal was greatest in the normal-weight group and lowest in the glucose-intolerant groups. The increased energy expenditure seen was correlated with glucose storage. No apparent thermic effect of the infusions was observed in Group III until after therapy.

Since the restoration correlated with both changes in glucose storage and suppression of endogenous glucose production, it was postulated that the thermic effect of glucose is the net result of (*a*) the increase in energy expenditure due to the energy cost of glucose storage; (*b*) the decrease in expenditure due to the suppression of endogenous glucose production (hepatic gluconeogenesis), an energy-requiring process (64); and (*c*) an "unaccounted" increase, possibly SNS-mediated. In insulin-resistant subjects, increased gluconeogenesis in combination with other mechanisms such as activation of the SNS, recycling of glucose as three-carbon compounds (Cori cycle), increased protein turnover, and increased Na-K ATPase activity, all of which might be

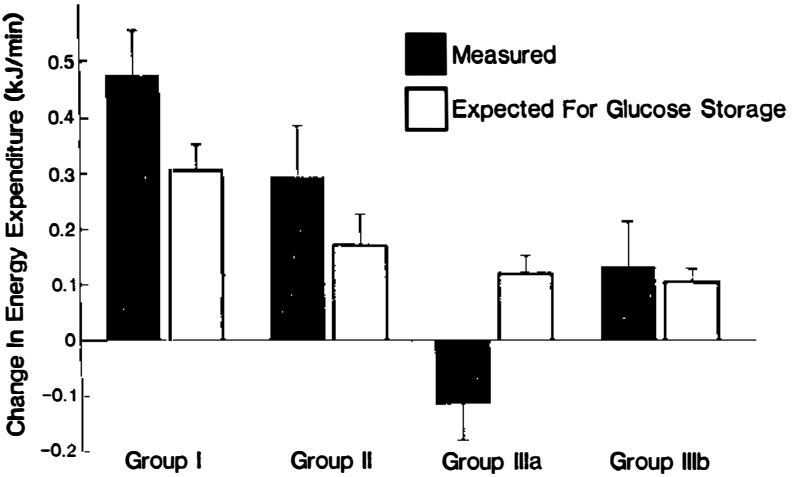

Figure 6 Change in energy expenditure during a euglycemic-hyperinsulinemic clamp procedure in normal volunteers (Group I), obese subjects with normal glucose tolerance (Group II), and obese subjects with abnormal glucose tolerance before (Group IIIa) and after (Group IIIb) weight loss (from 64).

blunted, could contribute to the decreased thermic effect of infused insulin/glucose. An inverse relation between the degree of insulin resistance and the thermic effect of hyperinsulinemia-euglycemia, as well as the effect on energy metabolism of differential fuel utilization are supported by this study.

As noted earlier, Schutz et al (77) observed an increase in energy expenditure during carbohydrate overfeeding that could also be accounted for in large part by alterations in glucose oxidation and storage. Thermogenesis must of necessity reflect net rates of carbohydrate, protein, and lipid oxidation in the whole organism. Factors such as insulin resistance (64), the antecedent diet (3), and physical activity influence the metabolic processing of carbohydrate, fat, and protein. Possibly then, some of the differences observed between lean, obese, and diabetic individuals may be attributed to differences in these factors.

SIGNIFICANCE

An understanding of the mechanisms involved in regulating energy production requires knowledge of the metabolism and regulation of specific nutrients of the nutrients, as well as overall nutritional state and hormonal milieu. It appears likely to be the integrated effect of all of these factors in the whole organism that controls the sympathetic response and thermic effect of a stimulus.

Because of these interrelationships, E_{ther} may be influenced by both expenditure and intake. Obviously, an equilibrium state is achieved when energy intake is equal to energy expended. Could a subnormal capacity to generate heat

(which could lead to an increase in body weight and fat stores) be due to alterations in intake or independent of them? Can thermogenic defects be offset by adjustments in intake? These are questions basic to the research in this area.

The significance of alterations in the metabolism of obese compared to lean persons depends upon their causative and/or contributory roles. Identifying defects that precede and predispose the individual toward weight gain could help in the prevention of this disorder. Knowledge of the metabolic changes accompanying obesity would be useful in treatment. It is difficult to distinguish between these roles, in part, because human obesity is heterogeneous and only some forms are the result of metabolic abnormalities. Careful definition of populations being studied and perturbations used is therefore most important.

Recent research indicates that a complex network of nutrient and hormonal factors act to regulate diet-induced thermogenesis in humans. These have yet to be well defined. Present understanding of these factors permits us to assign them a significant role in determining the long-term balance state of an individual. However, while such factors would appear to be involved in and useful for fine adjustments, it seems unlikely they can serve a single, pivotal role in the body weight regulatory system.

Literature Cited

1. Acheson, K. J., Burger, A. G. 1980. A study of the relationship between thermogenesis and thyroid hormones. *J. Clin. Endocrinol. Metab.* 51:84–89
2. Acheson, K., Jequier, E., Wahren, J. 1983. Influence of beta-adrenergic blockade on glucose-induced thermogenesis in man. *J. Clin. Invest.* 72:981–86
3. Acheson, K., Schutz, Y., Bessard, T., Ravussin, E., Jequier, E., Flatt, J.-P. 1984. Nutritional influences on lipogenesis and thermogenesis after a carbohydrate meal. *Am. J. Physiol.* 246:E62–E70
4. Acheson, K., Jequier, E., Burger, A., Danforth, E. Jr. 1984. Thyroid hormones and thermogenesis, the metabolic cost of food and exercise. *Metabolism* 33:262–65
5. Andrews, F., Jackson, F. 1978. Increasing fatness inversely related to increase in metabolic rate but directly related to decrease in deep body temperature in young men and women during cold exposure. *Ir. J. Med. Sci.* 147:329–30
6. Azziz, F. 1978. Effect of dietary composition of fasting-induced changes in serum thyroid hormones and thyrotropin. *Metab. Clin. Exp.* 27:935–42
7. Bessard, T., Schutz, Y., Jequier, E. 1983. Energy expenditure and postprandial thermogenesis in obese women before and after weight loss. *Am. J. Clin. Nutr.* 38:680–93
8. Boothby, W. M., Sandiford, I. 1929. Normal values for standard metabolism. *Am. J. Physiol.* 90:290–91
9. Bradfield, R. B., Curtis, D. E., Margen, S. 1968. Effect of activity on caloric response of obese women. *Am. J. Clin. Nutr.* 21:1208–10
10. Bray, G. A., Whipp, B. J., Koyal, S. N. 1974. The acute effects of food intake on energy expenditure during cycle ergometry. *Am. J. Clin. Nutr.* 27:254–59
11. Bukowiecki, L. J., Follea, N., Lupien, J., Paradis, A. 1981. Metabolic relationships between lipolysis and respiration in rat brown adipocytes. The role of long chain fatty acids as regulators of mitochondrial respiration and feedback inhibitors of lipolysis. *J. Biol. Chem.* 256:12840–48
12. Burger, A. G., Berger, M., Wimpfheimer, K., Danforth, E. 1980. Interrelationships between energy metabolism during starvation in the rat. *Acta Endocrinol.* 93:322–31
13. Burman, K. D., Dimond, R. C., Harvey, G. S., O'Brian, J. T., Georges, L. P., et al. 1979. Glucose modulation alterations in serum iodothyronine concentration induced by fasting. *Metab. Clin. Exp.* 28:291–99
14. Buskirk, E. R., Thompson, R. H., Whe-

don, G. D. 1963. Metabolic response to cold air in men and women in relation to total body fat content. *J. Appl. Physiol.* 18:603–12
15. Chappius, P., Pittet, P., Jequier, E. 1976. Heat storage regulation in exercise during thermal transients. *J. Appl. Physiol.* 40:384–92
16. Coleman, D. L. 1982. Thermogenesis in diabetes-obesity syndromes. *Diabetologia* 22:205–11
17. Coleman, D. L. 1985. Increased metabolic efficiency in obese mutant mice. *Int. J. Obesity.* In press
18. Croxson, M. S., Hall, T. D., Kletzky, O. A., Jaramillo, J. E., Nicoloff, J. T., et al. 1977. Decreased serum thyrotropin induced by fasting. *J. Clin. Endocrinol. Metab.* 45:560–68
19. Danforth, E., Horton, E. S., O'Connell, M., Sims, E. A. H., Burger, A. G. 1979. Dietary-induced alterations in thyroid hormone metabolism during overnutrition. *J. Clin. Invest.* 64:1336–47
20. Danforth, E. 1983. The role of thyroid hormones and insulin in the regulation of energy metabolism. *Am. J. Clin. Nutr.* 38:1006–17
21. Daniels, R. J., Katzeff, H. L., Ravussin, E., Garrow, J. S., Danforth, E., et al. 1982. Obesity in the Pima Indians: Is there a thrifty gene? *Clin. Res.* 30: 244A
22. Dauncey, M. J. 1980. Metabolic effects of altering the 24 hour energy intake in man, using direct and indirect calorimetry. *Br. J. Nutr.* 43:257–69
23. Davis, J. R., Tagliaferro, A. R., Kertzer, R., Gerardo, T., Nichols, J., Wheeler, J. 1983. Variations in dietary-induced thermogenesis and body fatness with aerobic capacity. *Eur. J. Physiol.* 50:319–29
24. DeFronzo, R. A., Simonson, D., Ferrannini, E. 1982. Hepatic and peripheral insulin resistance, a common feature of type 2 (non-insulin dependent) and type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 23:313–19
25. Durrant, M. L., Royston, J. P., Wloch, R. T. 1982. Effect of exercise on energy intake and eating patterns in lean and obese human. *Physiol. Behav.* 29:449–54
26. Flatt, J.-P. 1978. The biochemistry of energy expenditure. In *Recent Advances in Obesity Research,* ed. G. A. Bray, 2:211–28. London: Newman
27. Frayn, K. N. 1983. Calculation of substrate oxidation rates in vivo from gaseous exchange. *J. Appl. Physiol.* 55:628–34
28. Garrow, J. S. 1978. *Energy Balance and Obesity in Man.* New York: North Holland/Elsevier. 243 pp. 2nd ed.
29. Golay, A., Schutz, Y., Meyer, H. U., Thiebaud, D., Curchod, B., et al. 1982. Glucose-induced thermogenesis in nondiabetic and diabetic obese subjects. *Diabetes* 31:1023–28
30. Hafkesbring, R., Collett, M. E. 1923. Day to day variations in basal metabolism of women. *Am. J. Physiol.* 70:73
31. Deleted in proof
32. Hanson, J. S. 1973. Exercise response following production of experimental obesity. *J. Appl. Physiol.* 35:587–91
33. Hill, J. O., Heymsfield, S. B., McMannus, C., DiGirolamo, M. 1984. Meal size and thermic response to food in male subjects as a function of maximum aerobic capacity. *Metabolism* 33:743–49
34. Himms-Hagen, J. 1985. Brown adipose tissue metabolism and thermogenesis. *Ann. Rev. Nutr.* 5:69–94
35. Horton, E. S. 1983. Introduction: An overview of the assessment and regulation of energy balance in human. *Am. J. Clin. Nutr.* 38:972–77
36. Humphrey, S. J. E., Wolff, H. S. 1977. The oxylog. *J. Physiol.* 267:12P
37. James, W. P. T. 1983. Energy requirements and obesity. *Lancet* 2:386–89
38. Jequier, E. 1981. Long-term measurement of energy expenditure in man: direct or indirect calorimetry? In *Recent Advances in Obesity Research,* ed. G. A. Bray, 3:130–35. London: Libbey
39. Jequier, E. 1983. Does a thermogenic defect play a role in the pathogenesis of human obesity? *Clin. Physiol.* 3:1–7
40. Jequier, E., Schutz, Y. 1985. New evidence for a thermogenic defect in human obesity. *Int. J. Obesity.* In press
41. Jung, R. T., Shetty, P. S., James, W. P. T. 1979. Reduced thermogenesis in obesity. *Nature* 279:322–23
42. Kaplan, M. L., Leveille, G. A. 1976. Calorigenic response in obese and nonobese women. *Am. J. Clin. Nutr.* 29:1108–13
43. Katzeff, H. L., Daniels, R. J. 1985. Sympathetic nervous system activity in human obesity. *Int. J. Obesity* In press
44. Kinney, J. M. 1980. The application of indirect calorimetry to clinical studies. In *Assessment of Energy Metabolism in Health and Disease,* pp. 42–48. Columbus, Ohio: Ross Laboratories
45. Klein, P. D., James, W. P., Wong, W. W., Irving, C. S., et al. 1984. Calorimetric validation of the doubly-labelled water method for determination of energy expenditure in man. *Hum. Nutr. Clin. Nutr.* 38:95–106
46. Landsberg, L., Greff, L., Gunn, S., Young, J. B. 1980. Adrenergic mechanisms in the metabolic adaptation to fasting and feeding: effects of phorizin on

diet-induced changes in sympathoadrenal activity in the rat. *Metabolism* 29:1128–37

47. Landsberg, L., Young, J. B. 1983. The role of the sympathetic nervous system and catecholamines in the regulation of energy metabolism. *Am. J. Clin. Nutr.* 38:1018–24
48. Landsberg, L., Young, J. B. 1985. Insulin-mediated glucose metabolism in the relationship between dietary intake and sympathetic nervous system activity. *Int. J. Obesity*. In press
49. LeBlanc, J. 1985. Thermogenesis in relation to feeding and exercise training. *Int. J. Obesity*. In press
50. LeBlanc, J., Mercier, P., Samson, P. 1984. Diet-induced thermogenesis with relation to training state in female subjects. *Can. J. Physiol. Pharmacol.* 62:334–37
51. Leibel, R. L., Hirsch, J. 1984. Diminished energy requirements in reduced obese patients. *Metabolism* 33:164–70
52. Lusk, G. 1924. Analysis of the oxidation of mixtures of carbohydrates and fat. *J. Biol.* 59:41–42
53. Minaker, K. L., Rowe, J. W., Young, J. B., Sparrow, D., Pallotta, J. A., Landsberg, L. 1982. Effect of age on insulin stimulation of sympathetic nervous system activity in man. *Metabolism* 31:1181–84
54. Miller, D. S., Mumford, P., Stock, M. J. 1967. Gluttony: 2. Thermogenesis in overeating man. *Am. J. Clin. Nutr.* 20:1223–29
55. Nair, K. S., Garrow, J. S., Ford, C., Mahler, R. F., Halliday, D. 1983. Effect of poor diabetic control and obesity on whole body protein metabolism in man. *Diabetologia* 25:400–3
56. Nair, K. S., Halliday, D., Garrow, J. S. 1983. Thermic response to isoenergetic protein, carbohydrate or fat meals in lean and obese subjects. *Clin. Sci.* 65:307–12

56a. Nair, K. S., Halliday, D., Garrow, J. S. 1984. Increased energy expenditure in poorly controlled Type 1 (insulin-dependent) diabetic patients. *Diabetologia* 27:13–16

57. O'Dea, K., Esler, M., Leonard, P., Stockigt, J. R., Nestel, P. 1982. Noradrenaline turnover during under and overeating in normal weight subjects. *Metabolism* 31:896–99
58. Passmore, R., Thomson, J. G., Warnock, G. H. 1952. A balance sheet of the estimation of energy intake and energy expenditure as measured by indirect calorimetry using the Kofranyi-Michaelis calorimeter. *Br. J. Nutr.* 6:253–64
59. Phinney, S. D., LaGrange, B. M., O'Connell, M., Danforth, E. Jr. 1984. Effects of aerobic exercise on energy expenditure and nitrogen balance during a very low calorie diet. *Clin. Res.* 32: 235A
60. Pittet, P., Gygax, P. H., Jequier, E. 1974. Thermic effect of glucose and amino acids in man studied by direct and indirect calorimetry. *Br. J. Nutr.* 31:343–49
61. Pudel, V. E. 1977. Human feeding in the laboratory. See Ref. 26, pp. 66–74
62. Rappaport, E. B., Young, J. B., Landsberg, L. 1982. Effects of 2-deoxy-D-glucose on the cardiac sympathetic nerves and the adrenal medulla in the rat: further evidence for a dissociation of sympathetic nervous system and adrenal medullary responses. *Endocrinology* 110:650–56
63. Ravussin, E., Bogardus, C. 1982. Thermogenic response to insulin and glucose infusion. A model to evaluate the different components of the thermic effect of carbohydrate. *Life Sci.* 31:2011–18
64. Ravussin, E., Bogardus, C., Schwartz, R. S., Robbins, D. C., Wolfe, R. R., et al. 1983. Thermic effect of infused glucose and insulin in man: decreased response with increased insulin resistance in obesity and non-insulin-dependent diabetes mellitus. *J. Clin. Invest.* 72:893–902
65. Rennie, M. J., Edwards, R. H. T., Halliday, D., Matthews, D. E., Wolman, S. L., Millward, D. J. 1982. Muscle protein synthesis measured by stable isotope techniques in man: the effect of feeding and fasting. *Clin. Sci.* 63:519–23
66. Rothwell, N. J., Stock, M. J. 1978. A paradox in the control of energy intake in the rat. *Nature* 273:146–48
67. Rothwell, N. J., Stock, M. J. 1979. A role for brown adipose tissue in diet-induced thermogenesis. *Nature* 281:31–35
68. Rothwell, N. J., Stock, M. J. 1981. Regulation of energy balance. *Ann. Rev. Nutr.* 1:235–56
69. Rothwell, N. J., Saville, M. E., Stock, M. J. 1982. Sympathetic and thyroid influences on metabolic rate in fed, fasted and refed rats. *Am. J. Physiol.* 243: R339–46
70. Rothwell, N. J., Saville, M. E., Stock, M. J. 1985. Hormonal and metabolic responses to fasting and refeeding. *Int. J. Obesity*. In press
71. Rowe, J. W., Young, J. B., Minaker, K. L., Stevens, A. L., Pallotta, J., Landsberg, L. 1981. Effect of insulin and glucose infusions on sympathetic nervous

system activity in normal man. *Diabetes* 30:219–25
72. Rubner, M. 1902. *Die Gesetze des Energieverbrauchs bei der Ernahrung*. Leipzig: Deutiche
73. Sandiford, I., Wheeler, T., Boothby, W. M. 1931. Metabolic studies during pregnancy and menstruation. *Am. J. Physiol.* 96:191
74. Schoeller, D. A., Webb, P. 1984. Five-day comparison of the doubly labelled water method with respiratory gas exchange. *Am. J. Clin. Nutr.* 40:153–58
75. Schutz, Y. 1981. Use of non-calorimetric techniques to assess energy expenditure in man. See Ref. 38, pp. 153–58
76. Schutz, Y., Golay, A., Felber, J. P., Jequier, E. 1984. Decreased glucose-induced thermogenesis after weight loss in obese subjects: a predisposing factor for relapse of obesity? *Am. J. Clin. Nutr.* 39:380–87
77. Schutz, Y., Acheson, K. J., Jequier, E. 1985. Twenty-four hour energy expenditure and thermogenesis, response to progressive carbohydrate overfeeding in man. *Int. J. Obesity*. In press
78. Schwartz, J. H., Young, J. B., Landsberg, L. 1983. Effect of dietary fat on SNS activity in the rat. *J. Clin. Invest.* 72:361–70
79. Schwartz, R. S., Halter, J. B., Bierman, E. 1983. Reduced thermic effect of feeding in obesity: Role of norepinephrine. *Metabolism* 32:114–17
80. Seaton, T., Welle, S., Lilavivat, U., Campbell, R. G. 1984. The effect of adrenergic blockade on glucose-induced thermogenesis. *Metabolism* 33:415–19
81. Segal, K. R., Gutin, B. 1983. Thermic effects of food and exercise in lean and obese women. *Metabolism* 32:581–89
82. Sharief, N. N., Macdonald, I. 1982. Differences in dietary-induced thermogenesis with various carbohydrates in normal and overweight men. *Am. J. Clin. Nutr.* 35:267–72
83. Shetty, P. S., Jung, R. T., James, W. P. T., Barrand, M. D., Callingham, B. A. 1981. Postprandial thermogenesis in obesity. *Clin. Sci.* 60:519–25
84. Sims, E. A. H., Danforth, E., Horton, E. S., Bray, G. A., Glennon, J. A., Salans, L. B. 1973. Endocrine and metabolic effects of experimental obesity in man. *Rec. Prog. Horm. Res.* 29:457–96
85. Sims, E. A. H. 1982. Characterization of the syndromes of obesity. In *Diabetes Mellitus and Obesity*, ed. B. N. Brodoff, S. J. Bleicher, pp. 219–26. Baltimore, Md: Williams & Wilkins
86. Sjostrom, L., Schutz, Y., Gudinchet, F., Hegnell, L., Pittet, P. G., Jequier, E. 1983. Epinephrine sensitivity with respect to metabolic rate and other variables in women. *Am. J. Physiol.* 245:E431–42
87. Solomon, S. J., Kurzer, M. S., Calloway, D. H. 1982. Menstrual cycle and basal metabolic rate in women. *Am. J. Clin. Nutr.* 36:611–16
88. Stern, J. S. 1984. Is obesity a disease of inactivity? *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* 62:131–39
89. Stolwijk, J. A., Hardy, J. D. 1966. Partitional calorimetric studies of responses of man to thermal transients. *J. Appl. Physiol.* 21:967–77
90. Stordy, B. J., Marks, V., Kalvey, R. S., Crisp, A. H. 1977. Weight gain, thermic effect of glucose and resting metabolic rate during recovery from anorexia nervosa. *Am. J. Clin. Nutr.* 30:138–46
91. Swindells, Y. E. 1972. The influence of activity and size of meals on caloric response in women. *Br. J. Nutr.* 27:65–73
92. Thompson, J. K., Gregory, J. J., Lahey, B. B., Cureton, K. J. 1982. Exercise and obesity: etiology, physiology and intervention. *Psychol. Bull.* 91:55–79
93. Thiebaud, D., Schutz, Y., Acheson, K. J., Jacot, E., DeFronzo, R. A., et al. 1983. Energy cost of glucose storage in man during glucose-insulin infusions. *Am. J. Physiol.* 244:E216–21
94. Thurlby, P. L., Trayhurn, P. 1979. The role of thermoregulatory thermogenesis in the development of obesity in genetically obese (ob/ob) mice pair-fed with lean siblings. *Br. J. Nutr.* 42:377–85
95. Vagenakis, A. G., Burger, A. G., Portnay, G. I., Rudolph, M., et al. 1975. Diversion of peripheral thyroxine metabolism from activating to inactivating pathways during complete fasting. *J. Clin. Endocrinol. Metab.* 41:191–94
96. Wamold, I., Lenner, R. A. 1979. Evaluation of a heart rate method to determine the daily energy expenditure in disease: A study in juvenile diabetes. *Am. J. Clin. Nutr.* 30:304–15
97. Webb, P., Annis, J. F., Troutman, S. J. 1980. Energy balance in man measured by direct and indirect calorimetry. *Am. J. Clin. Nutr.* 33:1287–98
97a. Webb, P. 1981. Energy expenditure and fat-free mass in men and women. *Am. J. Clin. Nutr.* 34:1816–26
98. Welle, S., Lilavivat, U., Campbell, R. G. 1981. Thermic effect of feeding in man. Increasing plasma norepinephrine levels following glucose but not protein or fat consumption. *Metab. Clin. Exp.* 30:953–58
99. Welle, S. L., Campbell, R. G. 1983.

Normal thermic effect of glucose in obese women. *Am. J. Clin. Nutr.* 37:87–92
100. Welle, S. L., Campbell, R. G. 1983. Stimulation of thermogenesis by carbohydrate overfeeding. Evidence against sympathetic nervous system mediation. *J. Clin. Invest.* 71:916–25
101. Woo, R., Garrow, J. S., Pi-Sunyer, F. X. 1982. Effect of exercise on spontaneous calorie intake in obesity. *Am. J. Clin. Nutr.* 36:470–77
102. Woo, R., Garrow, J. S., Pi-Sunyer, F. X. 1982. Voluntary food intake during prolonged exercise in obese women. *Am. J. Clin. Nutr.* 36:478–84
103. Woo, R., Pi-Sunyer, F. X. 1985. Effect of increasing physical activity on voluntary intake in lean women. *Metabolism* 34(5):In press
104. Young, J. B., Landsberg, L. 1977. Suppression of SNS during fasting. *Science* 196:1473–75
105. Young, J. B., Landsberg, L. 1977. Stimulation of the sympathetic nervous system during sucrose feeding. *Nature* 269:615–17
106. Young, J. B., Landsberg, L. 1979. Sympathoadrenal activity in fasting pregnant rats: dissociation of adrenal medullary and SNS responses. *J. Clin. Invest.* 64:109–16
107. Zahorska-Markiewica, B. 1980. Thermic efffect of food and exercise in obesity. *Eur. J. Appl. Physiol.* 44:231–35