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HUMAN ENERGY METABOLISM: What Have We Learned from the Doubly Labeled Water Method?

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INTRODUCTION

Human accommodation and adaptation to changes in energy intake have been an area of controversy for decades. Although it is well established that human energy expenditure does change when intake is changed, the magnitude of change remains cloaked in controversy. Similarly, changes in energy expenditure that occur when energy requirements of pregnancy, lactation, and growth are added to maintenance needs remain controversial.

Two basic approaches have been used in the study of energy balance in humans. The first approach calculates energy expenditure using diary methods such as activity logs with factorial analysis or dietary intake records assuming energy balance. The second approach measures energy expenditure under laboratory conditions. These measurements include the postabsorptive resting metabolic rate (RMR); the thermic effect of meals (TEM) or postprandial metabolic rate; the energy costs of specific physical activities but not total energy expenditure in physical activity; and recently, a 24-h metabolic rate while the subject is housed in a room-sized respiration chamber.

Studies using the different methods lead to quantitatively different conclusions. Factorial or energy intake analyses have indicated that energy expenditure is quite variable, with alterations of up to 1000 kcal per day in order to defend against changes in body weight in the face of changes in intake or energy needs (4, 13, 22). In contrast, changes in the components of energy expenditure measured under laboratory conditions are more on the order of several hundred kcal per day (28, 35). Thus, whether energy needs are quite flexible or relatively fixed remains an area of fundamental controversy.

Only recently has a method to measure total energy expenditure in free-living subjects become available and made it possible to resolve the controversies that limit our understanding of weight regulation and energy balance in humans. The doubly labeled water method has enabled researchers to demonstrate that adaptive changes in energy expenditure of the human organism are relatively small and that most changes in energy expenditure are mediated through changes in body size and physical activity.

DOUBLY LABELED WATER

The doubly labeled water method, which was developed by Nathan Lifson (23), is a form of indirect calorimetry and is based on the differential elimination of deuterium and ^{18}O from body water subsequent to a loading dose of these stable isotopes. The isotopes are eliminated at different rates because deuterium is eliminated only as water while ^{18}O is eliminated as water and carbon dioxide. The elimination via carbon dioxide results from the rapid equilibration of oxygen between water and carbon dioxide. The difference between the two elimination rates is therefore a measure of carbon dioxide production, from which total daily energy expenditure (TDEE) is calculated according to the methods of indirect calorimetry.

The single greatest attribute of the doubly labeled water method is that it provides an integral measure of total carbon dioxide production over 4 to 21 days, yet only requires periodic sampling of urine or other physiologic fluids for the measurement of deuterium and ^{18}O remaining in body water. Because doubly labeled water obviates the need to collect respired gases, subjects need not be restricted by cumbersome monitors but instead can be studied in the free-living state.

Lifson validated the doubly labeled water method in small animals by comparing the method with measured carbon dioxide production (23). The doubly labeled water method was adapted by comparative zoologists who further validated the method in numerous small animal models (27). It was almost thirty years, however, before the method was first applied to humans (44). Small modifications have been made in the kinetic model to improve accuracy in humans (7, 32, 42). With these modifications the method is accurate to 1–2%, with a relative standard deviation of 3–9% depending on the dose of doubly labeled water and the length of the metabolic period (7, 32, 42). The method has been validated in infants and young adults, healthy individuals and patients with gastrointestinal disorders, subjects under metabolic ward conditions, and free-living individuals under laboratory and nonlaboratory conditions.

The doubly labeled water method, however, does have several limitations. One limitation is that it measures carbon dioxide production and not energy expenditure. Thus, knowledge of the macronutrient composition of the substrates being oxidized is needed to convert moles of carbon dioxide to heat production. In out-patients studies, substrate oxidation cannot be known exactly but can be estimated from dietary intake records. The method is therefore not totally independent of subject records, but the errors due to uncertainty in intake are typically less than 3% (3). A second limitation is that both stable isotopes are naturally occurring and isotope enrichment must be measured as the concentration in excess of background isotope abundances. Because these background abundances are not constant throughout nature, the method is subject to error if large uncontrolled changes in background occur during a study (37). These topics, as well as other general discussions of the method, have been extensively reviewed elsewhere and the reader is referred to those publications for details (7, 32, 42).

OBESITY

Energy Requirements

Although RMR expressed as kcal per day is usually greater in obese than in nonobese subjects, dietary intake records indicate that obese subjects generally consume no more energy than nonobese controls. As a result, it is often stated that excess energy intake does not play a role in the maintenance of obesity and that the obese state is characterized by a large reduction in physical activity or an increase in energy efficiency.

The doubly labeled water technique has been used by several investigators to test the hypothesis that the obese have low rates of energy expenditure. Prentice et al (33) compared the TDEE of nine obese women (88 ± 14 kg, and 156 ± 21% ideal body weight) with that of 13 nonobese women (58 ± 6 kg, 105 ± 11% ideal body weight) and found that the TDEE of the obese was 28% greater than that of the nonobese (2440 ± 330 versus 1890 ± 290 kcal per day). Recently, these results have been confirmed in adult women and extended to obese and nonobese adult men (26). Only four obese men were studied (109 ± 20 kg and 33 ± 6% fat), but they expended 27% more energy than the six nonobese controls (74 ± 8 kg and 18 ± 3% fat).

Figure 1 summarizes the results of the studies that have included nonobese and obese subjects living in industrialized countries. TDEE is well correlated with fat-free mass in both men and women ($r = 0.87$ and 0.68, respectively). Thus, the increase in TDEE observed among the obese is largely explained by

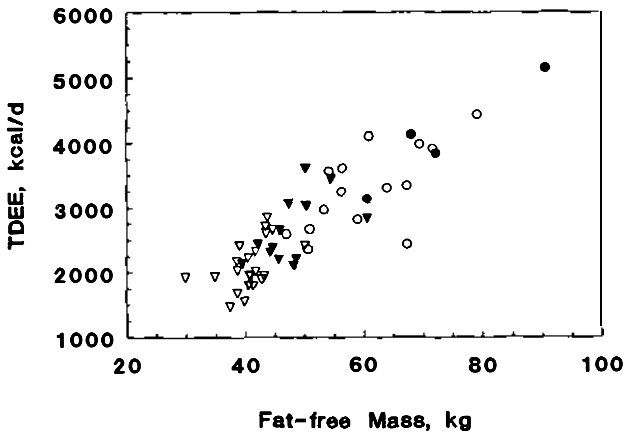

Figure 1 Energy expenditure measured by doubly labeled water in nonobese men (○), obese men (●), nonobese women (▽), and obese women (▼) living in industrialized countries increases with increasing FFM. The relationship does not differ among obese and nonobese subjects. Data adapted from (6, 26, 33, 42, 45).

increased fat-free mass in the obese subjects. It should be noted, however, that the relationship is not quite linear, but tends to flatten at greater fat-free mass (FFM).

Because of the burgeoning incidence of childhood obesity, a similar doubly labeled water study was performed in obese and nonobese adolescents (2). The study showed that obese boys expended 16% more energy than nonobese boys (3610 ± 640 versus 3110 ± 510) and obese girls expended 38% more energy than nonobese girls (3282 ± 558 versus 2880 ± 450 kcal per day). Again, TDEE was highly correlated with FFM (r = 0.85); however, the nonlinearity with increasing FFM was more pronounced than in adults.

Contrary to reported dietary intake, these doubly labeled water studies clearly demonstrate that, on average, obese subjects expend more energy than nonobese controls. Although there is considerable interindividual variation in TDEE, 60–80% of the variance can be explained by FFM. Thus, obese, who tend to have increased FFM, also have increased energy expenditure. The increase, however, is not completely proportional to body size, and some curvature in relationship between TDEE and FFM is evident. Thus the obese do not have low TDEE as suggested from dietary intake studies. The low dietary intakes reported by obese subjects must therefore be attributed to systematic underreporting (24, 43).

Physical Activity

Population surveys have repeatedly indicated that obese subjects spend less time in physical activities that are classified as moderate or heavy exercise (5–7 × RMR) (21, 41). A number of these population-based studies also show a significant negative correlation between physical activity and degree of obesity, but the correlations are typically quite low, accounting for only a few percent of the interindividual variability in body mass index (21, 41). Total daily energy expenditure is the sum of RMR, TEM, and energy expended in physical activity. Therefore, combining the doubly labeled water method with measurements of RMR and TEM permits calculation of energy expended in physical activity. Thus, the doubly labeled water method can be used to determine indirectly whether the obese are less physically active than nonobese controls. Unfortunately, few studies to date have included TDEE, RMR, and TEM; however, most have included TDEE and RMR. Therefore, one can calculate the nonbasal energy expenditure by difference. Because TEM is only 10% or less of TDEE, TEM comprises the minority of nonbasal energy expenditure and nonbasal expenditure can be used to approximate the energy expended in physical activity.

In absolute terms, obese individuals have recently been shown to expend slightly more energy in physical activity than do the nonobese. The difference between sleeping metabolic rate and TDEE was 270 kcal per day more in obese men than in nonobese controls (26). Obese females expended an almost identical 260 kcal per day more in nonbasal metabolism than did their nonobese controls (26). Very similar results were reported by Bandini et al (1) in an adolescent population.

A very different picture emerges when the nonbasal expenditure is normalized for body weight. In so doing, the values provide a measure of the activity levels of the individuals because energy expenditure for activities involving displacement of the body increases in proportion to body mass (20, 30). When expressed in this manner, the level of physical activity is inversely correlated with fatness expressed as percent body fat (Figures 2 and 3). Correlation coefficients are small ($r = 0.3$) and do not reach statistical significance in the small number of adults studied to date. In adolescents, however, correlation coefficients are 0.7 and 0.6 for males and females, respectively, and are statistically significant. Interestingly, no evidence indicates that the relationship differs between males and females, although scatter is considerable and it may not be possible to detect a gender difference with this small number of subjects.

The relationship between nonbasal energy expenditure and fatness suggests that physical activity may play a greater role in obesity than previous questionnaire-based studies have suggested. Note, however, that these relationships do not demonstrate causality. That obesity leads to reduced physical activity or that reduced physical activity leads to obesity are equally possible. Additional controlled studies that also incorporate a measure of TEM are needed to decide this issue.

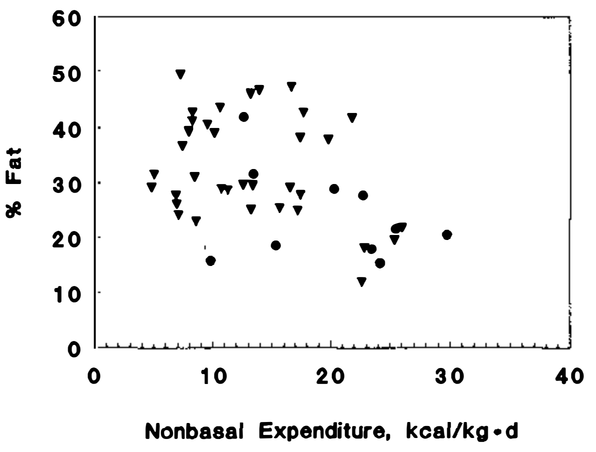

Figure 2 Physical activity as estimated by nonbasal energy expenditure (TDEE-RMR) per unit body weight is inversely correlated with body fatness in adult men (●) and women (▼). Data adapted from (6, 26, 33, 42).

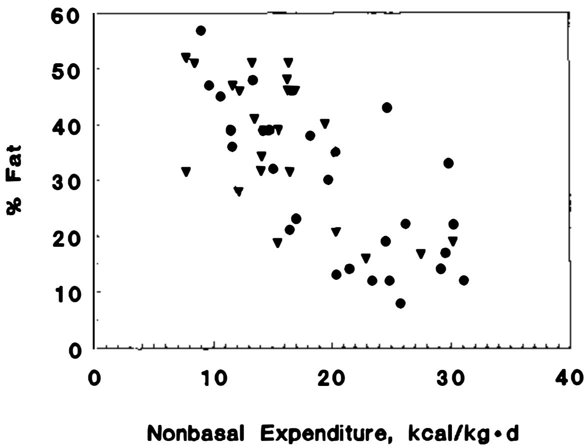

Figure 3 Physical activity as estimated by nonbasal energy expenditure (TDEE-RMR) per unit body weight is inversely correlated with body fatness in adolescent boys (●) and girls (▼). Data from (2).

Overfeeding

A third potential mechanism for the development of obesity that has been a source of controversy is the potential for some subjects to increase energy expenditure during a period of overfeeding and thus minimize weight gain and the ultimate development of obesity. Most previous overfeeding studies have identified a wide variation in the response to overfeeding, with some individuals gaining weight sufficient to account for the excess energy intake while others gain too little to account for all but a small fraction of the excess energy intake (4, 22). While this finding suggests that energy expenditure can increase dramatically during overfeeding, measures of RMR or TEM have demonstrated only small or modest changes.

The doubly labeled water method allows investigators to measure TDEE before and during excess energy intake to determine if expenditure increases during overfeeding. Roberts et al (40) overfed seven young men by 1000 kcal per day above energy intake necessary to maintain constant weight. The men were overfed for 20 days. As a group, these nonobese (14 ± 3% fat) men did not demonstrate a large increase in energy expenditure (3320 ± 490 versus 3420 ± 430 kcal per day in maintenance and overfeeding, respectively). Despite the small group changes in expenditure, individuals varied dramatically with regard to increase in energy stores as estimated by underwater weighing and nitrogen balance (860 ± 524 kcal per day). This variation, however, was due not to variable increases in energy expenditure but rather to variations in the excess energy intake. The study design called for the subjects to consume 1000 kcal per day more than their energy intake during a period of weight maintenance. Weight maintenance, however, is an insensitive measure of changes in body energy stores. When the energy required for maintenance was instead obtained from the energy expenditure measured by doubly labeled water, the mean was found to be nearly 1000 kcal per day, but the large individual variations were noted (1010 ± 728 kcal per day). Energy deposition correlated highly with excess intake calculated by the latter method ($r = 0.95$), indicating that the variability in energy storage was due to variability in overfeeding and not to differences in efficiency of storage.

A second overfeeding study in a group of obese and nonobese adult men has shown that TDEE increased by only 330 ± 480 kcal per day during six weeks of overfeeding by 1480 ± 450 kcal per day (11). The increase was almost completely explained by increased TEM owing to the larger meal size and increased RMR owing to increased FFM. Again, there was no evidence for any independent process that mediates weight gain when humans overeat.

Because growing adolescents may respond to overfeeding differently than adults, Bandini et al (2) investigated energy metabolism in nine obese or nonobese adolescents. These subjects were overfed by 1350 ± 350 kcal per day for 14 days. TDEE only increased 160 ± 280 kcal per day in response to overfeeding, and no difference between the obese and the nonobese was detected. Individually, changes ranged between a decrease and an increase of 560 kcal per day, or 40% of intake. It should be noted, however, that the random error of the doubly labeled water method accounts for half of the total variation. It is also of interest that the two individuals showing the greatest fraction of excess intake as an increase in TDEE were obese, not nonobese, subjects.

These three overfeeding studies provide no evidence for a general increase in energy expenditure beyond that due to increases in meal size, FFM, and body size. The remaining increases, which may be adaptive changes, thus are smaller than might be inferred from previous intake studies in which TDEE was not measured. The individual variability in TDEE during overfeeding is larger, but it must be remembered that much of the individual variation results from random measurement error owing to the 3–5% uncertainty of the doubly labeled water method. On an individual basis, this random error amounts to an individual uncertainty of 200 kcal per day for the estimate of change in energy expenditure during overfeeding, which accounts for more than half of the observed interindividual variability. The doubly labeled water studies, however, have provided data that may explain the source of the controversial results. Previous overfeeding studies have generally defined excess energy intake as being in excess of the energy intake needed to maintain constant weight for a 10–20 day period. Doubly labeled water studies have shown that this method tends to underestimate energy expenditure by 200 kcal per day, especially for the shorter maintenance periods, and that the individual uncertainties in maintenance intake are about 250 kcal per day (2, 36). Thus, the apparent excess energy intake tends to be an uncertain overestimate of the true excess. About half of the individual variation in weight gain during previous overfeeding studies can be accounted for by uncertainty in the assessment of excess energy intake based on weight maintenance.

UNDERNUTRITION

Chronic Energy Restriction

Similar to the controversy regarding changes in energy expenditure during overfeeding, a long-standing controversy exists regarding the extent of adaptation during chronic underfeeding. Individuals in developing countries are able to perform manual labor on reported energy intakes that are near to their calculated RMR, suggesting that they have dramatically reduced total daily energy expenditures (31). Doubly labeled water is well suited to measuring energy expenditure of subjects living in developing countries because it neither restricts their activity nor depends on the availability of complex equipment at the monitoring station.

Huss-Ashmore et al (18) measured the energy expenditures of a group of female university students in Swaziland. Energy expenditures were about 500 kcal per day lower than expected when compared as a function of fat-free mass with data collected on women in Western countries. Expressed as a function of RMR, TDEE only averaged about 1.3 × predicted RMR; however, RMR was not measured in these subjects so it is not possible to identify which component of total energy expenditure was reduced.

Both RMR and TDEE were measured in nonpregnant, nonlactating female agricultural workers in The Gambia (46), a particularly interesting population because previous reports of dietary intake in women in this local suggested that they consumed only 1300–1700 kcal per day (31). Doubly labeled water studies, however, showed TDEE in these subjects was 2070 ± 300 kcal per day, which is greater than previous reported intakes. This level of energy expenditure expressed as a function of FFM (Figure 4) or as a multiple of RMR is slightly elevated compared to women in developed countries (1.7 ± 0.2 versus 1.6 ± 0.2) and thus does not give any evidence of reduced energy needs. RMR was depressed by 5% relative to the level predicted from FFM (8), but this decrement is within the normal range.

Because TDEE of the Gambian women was greater than expected based on previous evaluation of dietary intake, a second study was initiated in which intake was assessed along with expenditure (46). These women were found to have even higher rates of TDEE (2910 ± 670 kcal per day); however, their reported dietary intakes were similar to previous reported values (1450 ± 470 kcal per day). Despite this apparent gross imbalance, the subjects were only

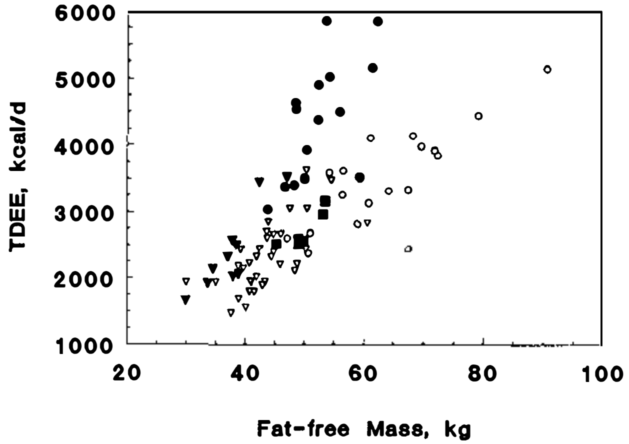

Figure 4 Total daily energy expenditure for individuals of the same FFM is elevated in Gambian female agricultural workers (▼) and male laborers (●), but not in Chilian laborers (■). Data from (12, 36, 46) and from men (○) and women (▽) living in industrialized countries (Figure 1) are included for reference.

losing weight at a rate of 29 ± 58 g per day, indicating that only about 200 kcal per day of the apparent energy deficit could be derived from body stores. Thus, it is highly likely that the energy intake was underestimated.

Energy Supplementation

An additional paradigm used in the investigation of alterations in energy expenditure is to provide energy supplements to subjects who are living in an energy-restricted environment. Thus it is possible not only to detect a reduction in expenditure relative to some control group but also to determine whether the reductions are obviated during supplementation. Riumallo et al (36) measured TDEE and RMR in five young, underweight men living in Santiago, Chile, before and during 12 weeks of energy supplementation. Despite the subjects' low average weight (56 ± 4 kg), BMI (19 ± 2), and body fat, TDEE was similar to that of individuals of the same FFM living in developed countries (Figure 4). RMR was only 95% of that predicted for FFM (8) and thus did not indicate a significant reduction in energy requirements. Nonbasal expenditure, on the other hand, was 22 kcal/kg per day, indicating a high level of physical activity. Consistent with the absence of any significant decreases in expenditure compared to western controls, energy supplementation did not result in any change in energy expenditure. Instead the supplement resulted in an increase in body fat.

Diaz et al (12) provided an energy supplement to male workers in The Gambia during the period of the year when dietary intake is insufficient to maintain weight. These subjects had high TDEE in the unsupplemented period (Figure 4). The RMR values, however, averaged only 87% of that predicted for FFM (8), This decreased RMR is in contrast to the findings of Riumallo et al (36) and is probably related to the fact that the unsupplemented period in the study of Diaz et al (12) was a period of insufficient intake and weight loss while that of Riumallo et al (36) was one of weight maintenance intake. This decrease in RMR was not apparent from TDEE because of the large nonbasal energy expenditure (49.5 kcal/kg per day). Energy supplementations did not result in a significant increase in TDEE but did partially normalize RMR, which increased 120 kcal per day. Work output, either as total loads or loads per hour, did not increase during supplementation. Thus, the study showed a decrease in energy requirements that was partially reversed by supplementation, but this decrease was only evident in RMR. In the absence of supplementation, the increased energy needs for manual labor were met from body energy stores as evidenced by a decrease in body weight and fat.

The studies from developing countries demonstrate little evidence of decreased energy expenditure relative to the subjects' FFM. Indeed, TDEE tends to be high except for those subjects engaged in sedentary activities. Only one study demonstrated any decrease in energy expenditure. Gambian men showed a 13% reduction in RMR, which conserved approximately 200 kcal per day. This decrease, however, was not detected in TDEE due to high levels of physical activity.

In contrast to the small to modest reductions in RMR normalized for body size, these subjects had FFMs averaging 1–5 kg and body weight averaging 5 to 20 kg less than Western controls, which permited energy savings of 200–500 kcal per day. Only in Gambian male laborers with severe energy deficits did decreases in RMR normalized for FFM become evident. Even then, energy savings were only half of those due to decreased FFM and weight. Thus, the major mechanism leading to decreased energy needs for the individual was not increased energy efficiency but rather a smaller body size.

PREGNANCY AND LACTATION

The National Research Council (NRC) at the National Academy of Science has estimated that 300 supplemental calories are needed daily during the second and third trimester to support the energy demands of full-term pregnancy and that a supplement of 500 kcal per day is needed to support lactation. (29). This recommendation is based primarily on estimates of placental, fetal, and maternal weight gain and weight gain composition, i.e. the energy contained within all tissue gained during pregnancy. The council's estimates of energy costs of lactation were based on the estimated quantity and energy density of milk produced. In making their recommendations for supplemental dietary energy, the council assumed that all the requirements for pregnancy would be met by increased dietary intake, whereas they assumed that body fat catabolism could provide 100 to 150 kcal per day during 6 months of lactation and that supplemental dietary energy would be needed to meet the remainder of the energy costs of lactation. If, however, there are compensatory mechanisms that reduce energy expenditure, the NRC recommendations would result in maternal overfeeding. Indeed, the NRC underscored the possibility that compensatory decreases in energy expenditure may occur during pregnancy but, at the time the recommendations were published, there were no well-controlled studies that tested this hypothesis.

To date, only 2 studies using the doubly labeled water method in a total of 16 women in the second and third trimesters of pregnancy have been reported (17, 46). Preliminary findings, however, provide no evidence of decreases in total energy expenditure. Indeed, one study showed a significant increase in total energy expenditure (46).

Total daily energy expenditure was slightly but not significantly higher in pregnant women (36 weeks gestation) living in Cambridge, UK, than in a subsample of the same women at 15 weeks postweaning (17). In Gambian women, Singh et al (46) reported that total daily energy expenditure was over 500 kcal per day higher in the pregnant group than in nonpregnant-nonlactating (NPNL) women. However, the NPNL women were characterized as being more lethargic than average and thus were not the optimal controls. At this time there is no evidence that total energy expenditure is reduced during the second and third trimesters of pregnancy.

Basal or resting metabolic rates were increased significantly (nearly 300 kcal per day) in pregnant women in both studies, (17, 46). When expressed as a function of fat-free mass (8), the Gambian women's RMR was 5% lower than predicted but did not differ between groups. Similarly, the increase in RMR during pregnancy in the Cambridge women could be explained by changes in body size and composition. Thus, there is no evidence that resting energy expenditure is reduced to compensate for the added energy costs of pregnancy. Indeed, data from both studies indicate increases in daily expenditures at rest, and in one study data show that expenditure is also increased per kilogram of fat-free mass.

The only evidence for energy sparing during pregnancy was that nonbasal energy expenditure, recalculated as the arithmetic difference between total and testing energy expenditure, was decreased in both pregnant groups (11 and 12 kcal/kg per day) compared to the control groups (16 and 18 kcal/kg per day) (17, 46), which suggests that activity may be reduced in the second and third trimesters of pregnancy.

Energy costs of lactation can theoretically be met by catabolism of maternal fat stores, increased dietary energy intake, and/or through adaptations that reduce energy expenditure either by reducing maternal maintenance requirements or by reducing energy expenditure for activity. While the NRC recommendations for supplemental energy intake during lactation are based on the assumption that women mobilize fat in early lactation (29), there is little experimental evidence in support of the hypothesis that the energy costs of lactation require the recommended level of dietary energy supplementation.

Goldberg et al (17) have made repeated measurements of energy expenditure in women during the last trimester of pregnancy and again at 4, 8, and 12 weeks of lactation, and 15 weeks post-weaning. Total daily energy expenditure tended to be less than post-weaning at all stages of lactation by nearly 200 kcal per day, but the difference was not statistically significant. Since there was no evidence of reductions in basal metabolic rate, these findings therefore suggest that the women expended less energy for activity. These findings further suggest that the energy costs of milk production are met in part by decreased activity (200 kcal per day), but a larger data base is needed to confirm this hypothesis.

GROWTH

Energy Requirements of Children

The most recent recommendations for energy intake for children published by the FAO/WHO/UNU (14) and the NRC/NAS (29) were based on reported dietary intake in well-nourished healthy children. Because accurate measurement of energy intake is extremely difficult under normal circumstances, the FAO advised that future estimates of energy requirements be based on measured energy expenditure, once such measurements became feasible. Doubly labeled water meets this criterion and energy expenditure has now been measured in more than 600 children (5, 9, 10, 15, 19, 25, 38, 39, 47). The large dataset, however, includes children who were healthy, postsurgical, malnourished, preterm, obese, or with chronic disease, and thus not all the data should be combined for analysis.

Energy requirements were recalculated from doubly labeled water studies as suggested by Prentice et al (34), but herein the data base is limited to children considered to be healthy at the time of study. The results are contrasted with current FAO energy recommendations in Figure 5. For this comparison, energy requirements were calculated as the sum of energy expenditure and energy stored. Energy stored was calculated from reference rates and reference composition of weight gain (16). The FAO recommendations for energy intake for children under 3 years of age are 112 to 125% greater than requirements estimated from energy expenditure and storage.

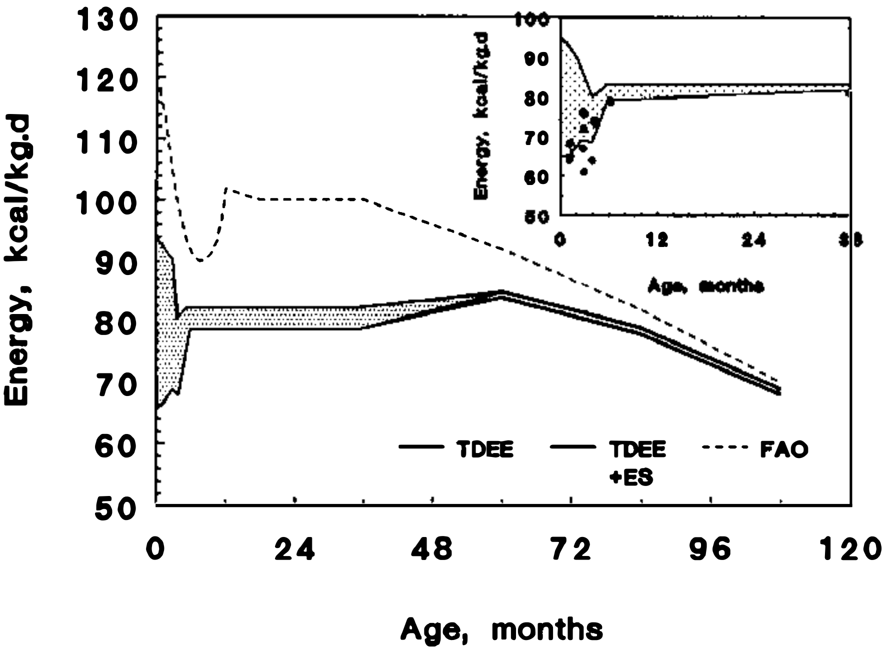

Figure 5 FAO/WHO/UNU estimates of energy requirements for infants and children are overestimates compared to requirements estimated by doubly labeled water and increases in body energy stores in healthy infants through 6 months of age. Data are group means (5, 10, 25, 39). The *lower solid line* is TDEE and the *shaded area* is ES.

Part of this discrepancy is due to the fact that the FAO recommendation is based on gross energy intake, whereas the calculated values in Figure 5 are based on metabolizable energy intake (34). Nevertheless, differences between the estimates on the order of 20% remain (34). By contrast, requirements published by the FAO and those derived in the present analysis for children at 5, 7, or 9 years of age are virtually identical; however, these findings should be interpreted cautiously because the data for the latter group comes from a single study (10).

Weight Gain

In some of the pediatric doubly labeled water studies, energy intake and rates of weight gain were also reported. The data, all from studies in young infants, permit an evaluation of the relative effects of increased energy intake on energy expenditure and weight gain. Figure 6 illustrates the relationship between energy intake and energy expenditure and weight gain in healthy infants up to 4 months old. A linear regression of energy expenditure on intake *(solid squares)* suggests that only a third of the increased intake is

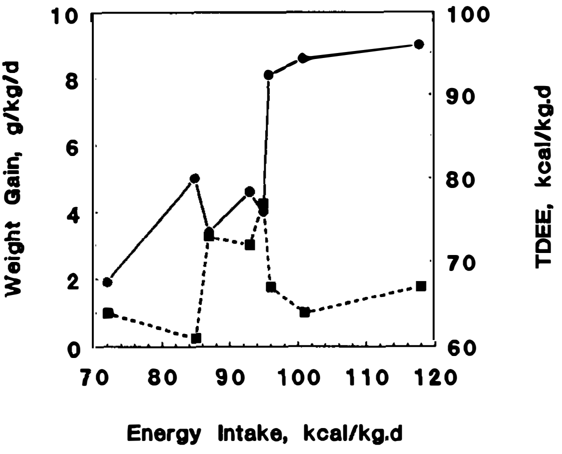

Figure 6 Increasing energy intake in healthy, full-term infants through four months of age partitions more to increased weight gain (—●—) than to increased energy expenditure (—■—). Data are group means (5, 25, 39).

expended. The greater fraction is accounted for by weight gain *(solid circles)*, particularly in infants under 4 months of age.

Underlying these trends is a significant interindividual variation in TDEE. Coefficients of variation in the various studies range from 10 to 30% (34): Although some of the variation is due to measurement error, there does appear to be an important physiological variation. Roberts et al (39) investigated whether TDEE in 3-month-old infants might have an effect on the risk of becoming overweight before the age of 12 months. Children who became overweight had lower energy expenditure than those who did not become overweight (61 ± 16 versus 78 ± 11 kcal/kg per day). In contrast to the above relationship between intake and weight gain, no difference in reported intake was detected. The study, however, involved only 18 infants; intake records were kept for only 24 h and thus are probably not representative.

The doubly labeled water method used in conjunction with accurate food intake records (5, 25, 39) also enables calculation of the energy density of tissue gained, which is an indicator of the fat and fat-free proportions of weight gained. The energy density of weight gained ranged from 3.6 to 5.7 kcal per gram, and an effect of increased energy intake on the energy density of weight gain is apparent. Among infants 4 and 5 weeks of age (5, 25), results were reported for three groups of infants. The mean energy intakes were 96, 101, or 118 kcal/kg per day, and the respective rates of weight gain were 8.1, 8.6, and 9 g/kg per day (p = ns). However, the energy density of the weight gained increased with increasing energy intake. From the lower to the higher caloric intakes, respectively, the energy densities of the weight gained were 3.6, 4.6, and 5.7 kcal per gram, indicating that more fat is deposited at higher caloric intakes. The relationship in 16-week-old infants (5) paralleled that of the 4- and 5-week-old infants (5, 25). In contrast, the effect of increased caloric intake among 11–12-month-old children was to increase energy expenditure rather than to increase the energy density of weight gain (25, 39). The more positive association between energy intake and energy expenditure in the 11–12-month-old group may reflect variation in levels of physical activity and gross motor skill development at these ages, but it may also reflect the limitations of the data base, as some of these studies were not designed to address the question of physical activity.

Breast versus Formula Feeding

Multiple studies have shown that breast-fed infants consume less energy and gain less weight than formula-fed infants. A very important finding from a doubly labeled water study by Butte et al (5) was that differences in energy intake altered the rate of weight gain but did not result in differences in the energy density of weight gained (4.2 versus 4.1 kcal/g for breast and formula-fed infants, respectively). Intriguingly, the doubly labeled water method demonstrated a decreased energy expenditure among four month-old breast-fed infants (64 ± 8 versus 73 ± 9 kcal/kg per day for formula-fed infants supplemented with solid foods). Similarly, low energy expenditures in breast-fed infants were reported by Lucas et al (25).

Among children with severely depleted protein and fat stores, the effect of increasing energy intake appears limited to increasing weight gain. A single study has been performed using the doubly labeled water method to compare the relatively high energy intakes used as an alternative therapy to rehabilitate undernourished children (15). Overall, about 20% of excess energy intake was expended. Increases in energy intake significantly increased rates of weight gain but did not result in excess fat deposition, estimated either on the basis of energy balance or on the basis of total body water.

The use of doubly labeled water in pediatric studies has provided the first measures of TDEE in healthy children living in their home environment. As such, these studies represent the best data for estimating energy requirements and indicate that previous FAO/WHO/UNU recommendations for energy should be reevaluated. These studies also provided intriguing evidence that TDEE of infants is influenced by the source of energy intake more so than adults, as breast-fed infants are found to expend less energy than bottle-fed infants. Otherwide, increasing energy intake has only a small effect on TDEE and a larger effect on weight and fat gain.

CONCLUSIONS

The doubly labeled water method has filled a gap in methods for the investigation of energy metabolism by enabling investigators to measure energy expenditure in free-living subjects. Application of the method during the last five years has contributed to several key findings regarding the effects of changes in energy intake or the added energy needs of pregnancy, lactation, and growth on energy expenditure. Obesity researchers have demonstrated that obese subjects generally expend more energy than lean controls and that the increase is in proportion to FFM. With regard to adaptive thermogenesis, the use of doubly labeled water has demonstrated that adaptive thermogenesis is modest and rarely balances more than a third of the change in energy intake. About two thirds of the changes in expenditure is mediated through alterations in body size and composition. Similarly, the energy costs of pregnancy, lactation, and growth have been shown to be generally additive to energy requirements, and little decrease in expenditure has been noted. The major exception is a reduction in physical activity during the second and third trimesters of pregnancy that compensates for a portion of the added energy needs. Finally, application of doubly labeled water has identified an effect of diet composition on energy expenditure in breast-fed infants whose expenditure has been found to be less than that of formula-fed infants.

Clearly more controlled studies with concurrent measures of energy intake, expenditure, and body composition are needed to better characterize human energy metabolism. Most studies to date have been designed to test hypotheses regarding large changes in energy expenditure. These studies have shown that changes in expenditure are mediated mostly through changes in body size and composition. Individual changes in voluntary physical activity and adaptive thermogenesis, however, have also been noted. Well-controlled studies incorporating repeated measures are needed to differentiate between measurement error and true individual adaptations or accommodations.

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