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Energy cost of growth of premature infants

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The objective of this paper is to review approaches to the determination of the energy cost of growth in premature infants. Two approaches are compared: one based on the composition of weight gain, and one based on the determination of energy balance. Data are lacking on the composition of weight gained by the premature infant after birth, while the composition of fetal weight gain and its energy cost can be calculated from data on fetal body composition. These calculations show that energy storage amounts to less than 8.4 kJ/g weight gain below a body weight of 2 kg; the total energy cost of growth is less than 10.5 kJ/g. Estimates twice as high have been obtained from energy balance studies of growing premature infants and older infants. We conclude that the energy cost of growth in premature infants is still uncertain and requires further study.

The survival of the prematurely born infant is related to its ability to grow. However, premature birth poses a threat to the maintenance of energy intake, and as a consequence, to growth. It is therefore of obvious clinical interest to know how much energy is required by the premature infant in order to grow in the extra-uterine environment.

This question can best be put within the context of overall energy balance. In the absence of external work, the energy balance of the whole body may be stated as follows:
Gross Energy Intake = Energy Excretion + Energy Expenditure + Energy Storage
The energy is measured in units of kilojoules (kJ), which may be converted to kilocalories (kcal) by dividing by 4.18.

Gross, Digestible and Metabolizable Energy. The gross energy of a food is measured by determining the heat produced by its combustion in a bomb calorimeter. The gross energy of a food, determined by complete combustion in an atmosphere of compressed oxygen, is greater than the energy value of the food to the body for two reasons: (1) part of the food escapes absorption and is excreted in the stool, and (2) *in vivo* oxidation does not convert the nitrogen component of the food to oxide of nitrogen but leads to the formation of urea and other compounds which are excreted in the urine.

Digestible energy is defined as the gross energy of the diet minus the heat of combustion of the stool, and metabolizable energy is defined as digested energy minus the heat of combustion of the urine. Digestible energy represents the fuel value of the food after taking into account losses due to incomplete digestion, and metabolizable energy represents the fuel value of the absorbed components of the food after taking into account the energy losses due to incomplete oxidation.

The Fate of Metabolizable Energy: Expenditure and Storage. In the non-working subject, metabolizable energy is expended as heat or stored. The expenditure of energy is conventionally divided into two major components: basal energy expenditure, and expenditure above the basal rate (for example, that due to activity or elicited by thermal stress) [5].

Basal energy expenditure cannot be measured in the infant. Growth itself requires the expenditure of energy, so the basal rate of energy expenditure cannot be measured in the growing infant. Moreover, in the non-growing adult, basal energy expenditure is measured under defined conditions which require the subject to be at rest in a post-absorptive state. There is no physiologically equivalent circumstance in the growing infant, who is either "digesting one meal or actively anticipating the next" [7].

In growing infants, the closest approximation to the basal energy expenditure is the "minimal" rate of energy expenditure measured when the infant is in quiet sleep in a thermoneutral environment. The minimal energy expenditure thus determined includes an increment above basal due to food intake and growth.

The presence of food in the gastrointestinal tract leads to an increase in the level of energy expenditure [6] due to the physiological work of digestion, absorption and assimilation. This increased rate of energy expenditure over the basal state is referred to as the heat increment of feeding.

In the growing baby, a fraction of the energy expenditure is used to support the biosynthetic processes involved in net tissue synthesis. This is part of the energy cost of growth. The other, and larger, part of the energy cost of growth consists of the energy stored in growing tissues and organs (chiefly as fat and protein); this component of the energy cost of growth is represented by the "energy storage" term of the energy balance equation.

In this paper, we review two approaches that have been used to estimate the energy cost of growth in premature infants:

1. The body composition approach, and
2. The clinical physiology approach.

Energy Cost of Growth as Estimated from Body Composition

If the net accretion rates of fat and protein in growing infants were known, energy storage could be calculated from the gross energy values for fat and protein respectively. Data on the body composition of full term newborns and infants provide a basis for calculating the composition of weight gain of such subjects during infancy.

The "male reference infant" of Fomon [2] is assumed to weigh 3.5 kg at birth and to double his weight by four months of age. The composition of weight gain during that four-month interval is 11.4% protein, 40.8% fat, and 45.3% water. Assuming gross energy values of 23.8 kJ/g for protein and 38.9 kJ/g for fat [4], the energy stored per gram of weight gain is therefore 18.6 kJ/g. The total energy cost of growth is the sum of the energy value of the tissues laid down, plus the energy expended in the anabolism of these tissue components from the materials absorbed from the digestive tract. The energy costs of protein and fat formation differ because of the difference in the complexities of the metabolic processes leading to their formation from their respective precursors. Kielanowski estimated the overall cost of depositing one gram of protein and of fat as 31.4 and 48.5 kJ/g respectively [3]. If we apply these factors, derived from experiments in baby pigs, to the male reference infant, we obtain a figure of 23.4 kJ/g for the total energy cost of growth.

Changes in body composition following premature birth are not accurately known; therefore, the composition of weight gain in growing premature infants cannot be calculated because of the lack of suitable data. However, the body composition of the growing fetus has been studied in considerable detail [10, 11]. Ziegler et al [11] summarized existing data and constructed from these data a "reference fetus" whose body composition changes during the latter part of gestation as shown in Fig. 1. As can be seen, the increase in size is accomplished by an increase in each of the major body components. However, as shown in Fig. 2, the composition of weight gain changes throughout the last part of gestation. It is of particular relevance to the topic of this paper to note that fat comprises

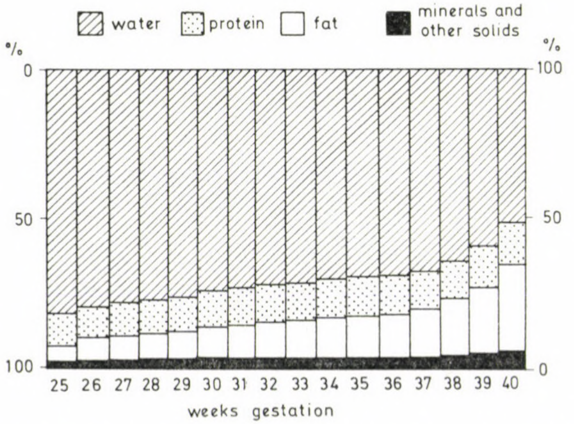

FIG. 1. Body composition of the human fetus at different gestational ages, from data of Ziegler et al [11]

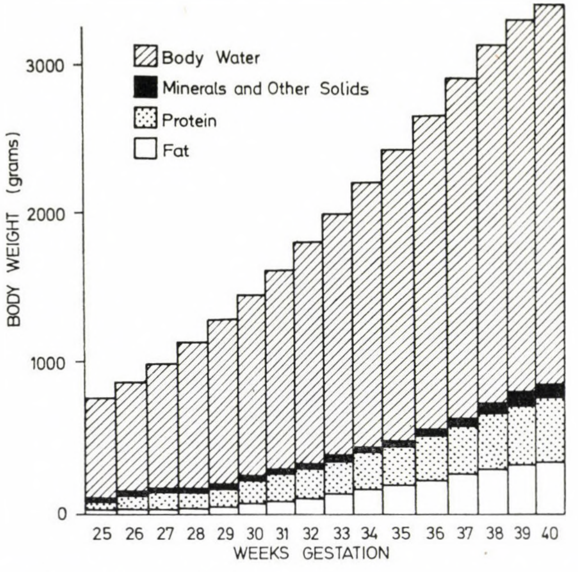

FIG. 2. Composition of weight gain in the reference fetus with gestational age, from data of Ziegler et al [11]

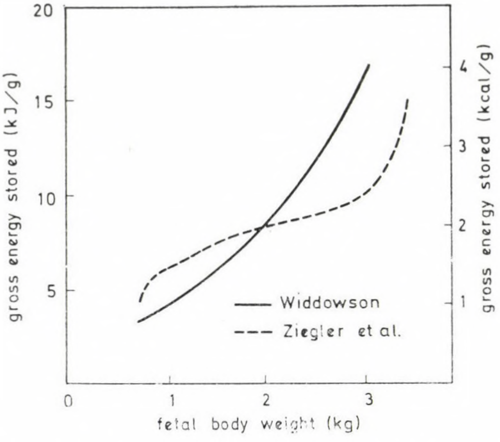

FIG. 3. Gross energy stored (kJ/g weight gain) as fetal weight increases. Calculations are based on the fetal body composition data of Ziegler et al [11] and Widdowson [10]. Assumed gross energy values (kJ/g) are 38.9 for fat, 23.8 for protein

a very small proportion of weight gain in the pre-term period, and that this proportion rises substantially as term approaches.

The energy equivalent of fetal weight gain can be calculated from such data on the rate of accretion of fat and protein. As shown in Fig. 3, the studies of both Ziegler et al [11] and Widdowson [10] predict that the energy stored per gram of fetal weight gain is not a constant figure, but increases with fetal weight. Although the two studies do not agree closely (particularly in the upper range of fetal weight), there is reasonably close correspondence in the projection that below a fetal weight of 2 kg, energy storage varies between 4.2–8.4 kJ/g. Applying the factors of Kielanowski [3], it can be calculated that the total energy cost of growth varies between 5.0 and 10.5 kJ/g in the fetal weight range below 2 kg.

It is a major assumption that the composition of the premature infant's weight gain in the extrauterine environment is the same as that which would have occurred in utero over the same weight interval had the fetus not been delivered prematurely. Without making this assumption, it can be shown that during fetal growth the available data on body composition predict that the energy storage and the total energy cost of growth are considerably lower than the similarly calculated values for growth in infancy after full term birth. Moreover, during fetal growth, compositional data predict a varying energy storage due to the changing composition of weight gain. Below a body weight of 2 kg, the total energy cost of growth is calculated as less than 10.5 kJ/g weight gain. This low value is determined primarily by the relatively small lipid content of weight gain in the very low weight range.

The question then arises: in growing premature infants, are values for energy storage and the total energy cost of growth similar to those calculated from the body composition of the growing fetus? To answer this question we required clinical studies of the energy balance of growing premature infants.

Energy Cost of Growth as Estimated by Clinical Physiological Studies

The energy cost of growth can be determined from measurement of the energy balance in growing subjects. For such measurements of the energy cost of growth to be precise the energy storage must be a relatively large fraction of the gross energy intake; therefore, the subjects should be growing rapidly. During the late fetal and early postnatal periods, a growth rate of 1.5% per day (15 g/kg day) is typical. Thus, energy storage is measurable with reasonable precision in growing premature infants by applying the energy balance principle. The study should extend over a period that is long enough to measure weight gain precisely (10–14 days). In order to determine the increment in energy expenditure associated with growth, the subjects should be growing at different rates (i.e. there should be both fast growing and slowly growing or non-growing subjects included for comparison).

There are two general methods whereby the energy cost of growth has been deduced from energy balance.

1. The total energy cost of weight gain has been determined from the relationship between metabolizable energy intake and weight gain. The

slope of the regression of metabolizable energy intake on weight gain describes the increment in metabolizable energy intake per gram of weight gain and has been taken to represent the total energy cost in weight gain. It should be noted that this slope is determined by the sum of the increments in both energy storage and in total daily energy expenditure expressed per gram weight gain. The increment in total daily energy expenditure per gram weight gain is approximately equal to the energy expended for growth, although there may be additional factors to consider (see below).

2. The total energy cost of growth has been calculated by determining separately the energy storage and the energy expended for growth, and adding the two.

Energy storage is calculated from the energy balance:

Energy storage = Gross energy intake — Energy excretion — Energy expenditure.

The major technical obstacle is the measurement of total daily energy expenditure. Energy storage can be related to weight gain in two ways: (*1*) by the ratio method, whereby energy storage is divided by weight gain to obtain the energy stored per gram of weight gain (the ratio method is theoretically valid if, at zero weight gain, energy storage is zero [9]); and (*2*) by the regression method, whereby energy storage is plotted as a function of rate of weight gain, so that the slope of the linear regression gives energy stored per gram of weight gain.

The increase in energy expenditure in association with weight gain has been determined by the regression of total daily energy expenditure on weight gain. The slope of this line has been taken to give the increment in energy expenditure per gram of weight gain. This can be held to represent the energy expended in the net synthesis of new tissue if one assumes that other factors affecting total daily energy expenditure are constant over the range of growth rates studied. However, this assumption would not be valid if, for example, activity were to vary systematically with growth rate. Thus, the slope of the regression of total daily energy expenditure on weight gain gives a measure of the empirical relation between the two: determinants of this relationship include energy expended for growth and possibly other types of energy expenditure which vary systematically with growth rate.

The energy cost of growth has been calculated by the above methods in studies reported by Brooke et al for premature infants [1], and by Spady et al for malnourished older infants during recovery [8]. Both reports will be cited in order to establish certain similarities and differences.

* The infants were fed Cow and Gate® V Formula. The gross energy of V Formula as determined by Brooke et al [1] by bomb calorimetry, was 344 kJ/dl. This is 32% more than the label declaration for metabolizable energy (261 kJ/dl). This large discrepancy is unexplained; it should be borne in mind when considering the absolute values reported for gross energy intake, metabolizable energy and energy storage.

Brooke et al. [1] studied growing premature infants, including several under 1500 g in birth weight. Metabolizable energy intake of these infants averaged 601 kJ/kg.day.* Total energy expenditure amounted to 370 kJ/kg.day. This left 230 kJ/kg.day for energy storage, which represented 38% of metabolizable energy intake.

Brooke et al plotted weight gain (y-axis) as a function of metabolizable energy and stored energy (x-axis). We have re-analysed these data in order to display the energy variables as a function of weight gain (i.e. kJ energy/g weight gain).

Figures 4 and 5 show the relationships between metabolizable energy intake and weight gain and between stored energy and weight gain for the premature infants studied by Brooke et al. At zero weight gain, the metabolizable energy intake was 349 kJ/kg.day. Each gram of weight gain was associated with an increment of 18.3 kJ in metabolizable energy intake. This is one estimate of the total energy cost of weight gain. Each gram of weight gain was associated with an energy storage of 15.6 kJ.

For each gram of weight gain, the data of Brooke et al show a larger

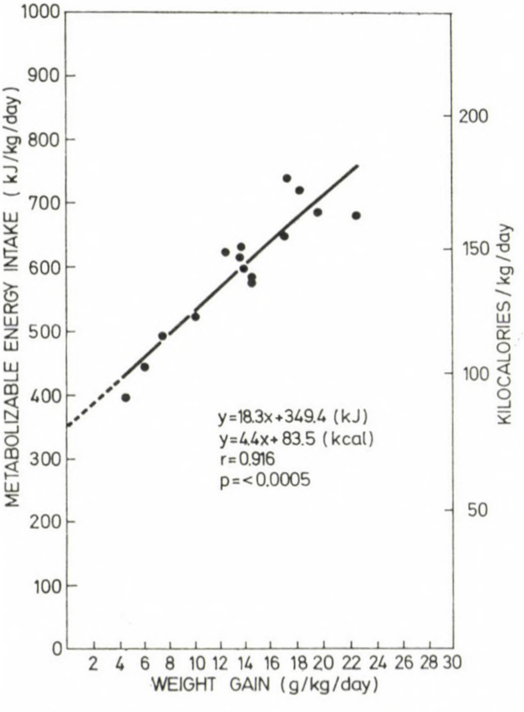

FIG. 4. Relation between metabolizable energy intake and weight gain in growing premature infants (data of Brooke et al, ref. 1). The intercept (349 kJ/kg day) defines the metabolizable energy intake at zero weight gain. The slope of the line (18.3 kJ/g) defines the total energy cost of weight gain

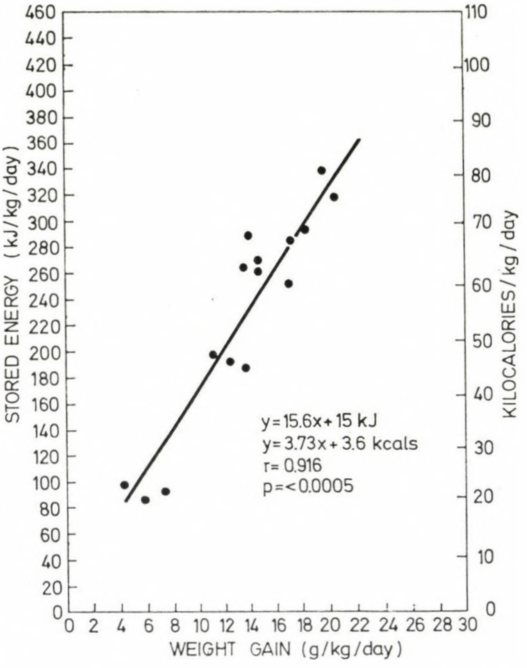

FIG. 5. Relation between energy storage and weight gain in growing premature infants (data of Brooke et al, ref. 1). The slope of line (15.6 kJ/g) defines the energy stored per gram weight gain. As predicted the energy stored at zero weight gain is not significantly different from zero

increment in metabolizable energy intake (18.3 kJ) than could be accounted for as energy storage (15.6 kJ). Therefore, as rate of weight gain increased, energy expenditure must have increased as well.

We have performed further analyses of the data published by Brooke et al to explore the source of the increased energy expenditure of rapidly-growing infants. As rate of weight gain increased, postprandial energy expenditure increased significantly (0.7 kJ/g) (Fig. 6) and resting energy expenditure increased significantly (4.0 kJ/g) (Fig. 7). These values, when added to the energy storage equivalent of weight gain (15.6 kJ/g), give an estimate of the total energy cost of weight gain (20.3 kJ/g) which is greater than the increment of metabolizable energy intake (18.3 kJ/g). This difference may be due to the decline in activity energy expended by the babies with increasing weight gain; however, this relation was not significant statistically. In summary, as metabolizable energy intake increased, total energy expenditure increased, due to increases in both resting and postprandial energy expenditure. These increases were partially offset by a fall in energy expended in activity.

The results obtained by re-analysis of the data of Brooke et al for

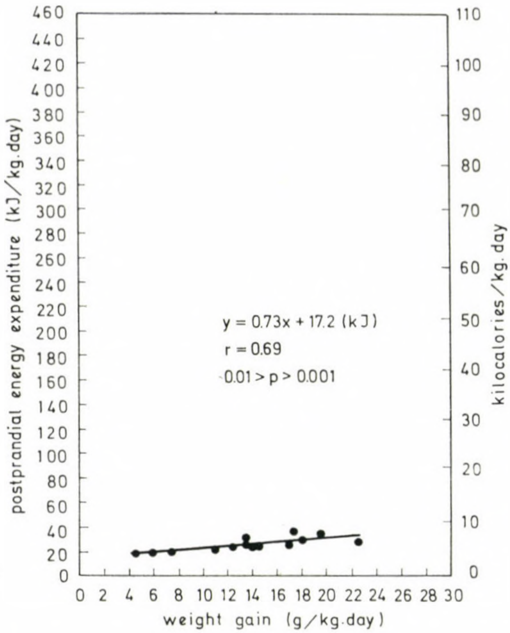

FIG. 6. Relation between postprandial energy expenditure and weight gain in growing premature infants (data of Brooke et al, ref. 1). Postprandial energy expenditure increases significantly (0.7 kJ/g) as rate of weight gain increases

growing premature babies may be contrasted with those obtained in an energy balance study of similar design in malnourished but recovering infants aged 8–18 months, reported earlier by Spady and co-workers [8] (Table I). The values for the two quite disparate groups are astonishingly similar.

By contrast, the values for the (total) energy cost of weight gain that we have calculated from the data of Brooke et al are considerably greater than those we have calculated on the basis of increments in fetal body composition in the low-weight range (Table II). In fact, the values obtained from the data of Brooke et al. closer to what would be predicted on the basis of body composition for the growing term infant during the first four months after birth. It is tempting to speculate that premature birth triggers a shift to a more "mature" composition of weight gain, comprising yet another example of precocious maturation. However, error could also account for the discrepancy. Three kinds of error must be mentioned in regard to the clinical study of energy balance.

First, the study of energy balance is beset by possibilities for error which all tend to over-estimate energy storage. This results because of systematic tendencies to over-estimate energy intake (e.g. because of milk remaining in the inside of tubes and

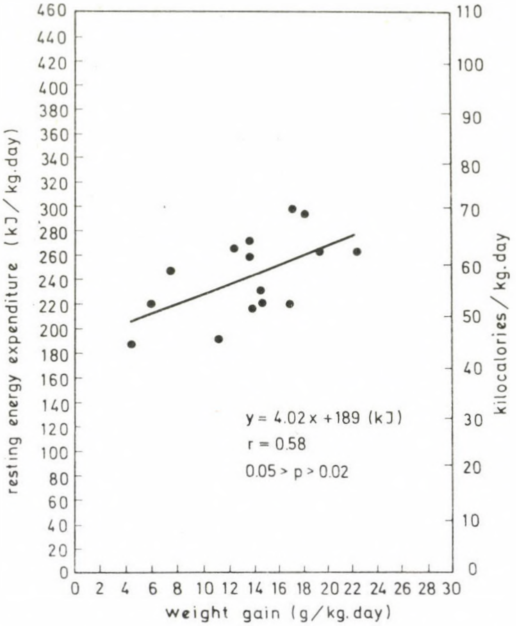

FIG. 7. Relation between resting energy expenditure and weight gain in growing premature infants (data of Brooke et al, ref. 1). Resting energy expenditure increases significantly (4.0 kJ/g) as rate of weight gain increases

syringes, undetected regurgitation) and to underestimate energy excretion (incomplete collection of stool or urine).

Second, there are numerous opportunities for experimental error in the study of energy balance which could affect the results in either direction. Examples include errors in the determination of gross energy intake (dilution error or non-homogeneity of milk feeding, error in bomb calorimetry)

TABLE I

Energy intake, energy storage, and weight gain in premature infants and 8–18 month infants

	Subjects	
	Premature infants (ref. 1)	8–18 month infants recovering from malnutrition (ref. 8)
Maintenance energy requirement, kJ/kg day	349	357
Metabolizable energy intake per gram weight gain, kJ/g	18.3	18.4
Energy storage per gram weight gain, kJ/g	15.6	16.7

TABLE II

Energy cost of weight gain (kJ/g)

	Basis of estimate		
	Body composition		Clinical experiment
	Term infant 0–4 month (ref. 2)	Premature infant (ref. 10, 11)	Premature infant (ref. 1)
Energy storage	18.6	4.2–8.4	15.6
Increment in energy expenditure	4.8	0.8–2.1	2.7–4.7
Total energy cost of weight gain	23.4	5.0–10.5	18.3–20.3

or errors in measurement of total daily energy expenditure. As regards the study of Brooke et al, we have noted previously the unexplained large discrepancy between the experimentally determined gross energy of the formula and the label declaration of (metabolizable) energy. A modest overestimation of gross energy intake would result in a relatively large overestimation of calculated energy storage.

Third, there are problems related to analysis. When an attempt is made to relate energy intake, expenditure or storage to weight gain, problems arise when other variables such as body weight, are related to both the independent and dependent variables. For example, there may be a positive correlation between metabolizable energy intake and both body weight gain, so that for babies of different weights regression analysis of metabolizable energy intake (kJ/day) against weight gain (g/day) could result in a positive relationship largely attributable to the relationship between metabolizable energy intake and body weight.

This problem is clearly recognized by both Brooke and Spady, who have sought to standardize for weight by expressing energy intake, energy expenditure, energy storage and weight gain in kilojoules/kilogram body weight or grams/kilogram body weight. The subsequent regression analysis of, say, metabolizable energy intake (kJ/kg.day) on weight gain (g/kg.d) produces a slope whose value is fallaciously expressed as kJ metabolizable energy intake/grams weight gain.

That the expression

$$\frac{\text{Mean kJ/kg}}{\text{Mean g/kg}} \quad \text{does not equal} \quad \frac{\text{Mean kJ}}{\text{Mean g}}$$

is demonstrated algebraically in the Appendix. The only conditions under which the two expressions are equivalent are obtained when either all babies are of the same weight or when the ratios of kilojoules metabolizable energy intake to grams weight gain are identical between each subject.

The appropriate way in which to examine such a relationship is to estimate a partial regression coefficient for each variable. Thus, for daily metabolizable energy intake

$$\text{Metabolizable Energy Intake (kJ)} = \text{Energy Expended (kJ)} + \text{Energy Stored (kJ)} \quad (1)$$

$$\text{if Energy Expenditure (kJ)} = a_1 + b_1 \text{ Body Weight (kg)} \quad (2)$$

$$\text{and Energy Storage (kJ)} = a_2 + b_2 \text{ Weight Gain (g)} \quad (3)$$

where a_1 and a_2 are constants and b_1 b_2 are the regression coefficients of the equation.

Then

$$\text{Metabolizable Energy Intake (kJ)} = a_1 + a_2 + b_1 \text{ Body Weight (kg)} + b_2 \text{ Weight Gain (g)} \quad (4)$$

Let

$$\text{constant } A = a_1 + a_2 \quad (5)$$

Then

$$\text{Metabolizable Energy Intake (kJ)} = A + b_1 \text{ Body Weight (kg)} + b_2 \text{ Weight Gain (g)} \quad (6)$$

The solution to this question is now available using multiple linear regression analysis. This will give a true estimate of the coefficient b_2, the slope of metabolizable energy intake on weight gain, in kilojoules per gram.

Unless the relationship between the dependent and independent variables is such that the line of best fit passes through the origin, quite different results may be anticipated from the two relationships:

$$y\,(\text{kJ/kg}) = A + bx\,(\text{g/kg})$$

and

$$y'\,(\text{kJ}) = A' + b_1 x'\,(\text{g}) + b_2 \text{ Wt (kg)}$$

Certainly the regression equation between metabolizable energy intake and weight gain has a substantial intercept quite different from the origin (Fig. 4) and we may expect the regression coefficients (kJ/kg on g/kg, versus kJ on g) to be quite different.

On the other hand where the line of best fit passes close to the origin (i.e. where A approximates zero) we may expect the regression coefficients to be similar for both calculations.

The multiple linear regression model allows to make estimates (by extrapolation) of metabolizable energy intake when weight gain is zero for infants of specified weight — thus, from equation 6 at zero weight gain

$$\text{Metabolizable Energy Intake (kJ)} = A + b_1 \text{ Wt (kg)}.$$

The multiple linear regression model allows for adjustment of these regression coefficients as further variables are identified and added.

We are unable to re-examine the data of Brooke or Spady by multiple linear regression, as daily weights were not published. Further work on energy balance with close attention to the three major sources of error described above will give closer estimates of the energy cost of growth. This information along with nitrogen balance will make it possible better to interpret the composition of weight gain in the low birthweight infant.

Appendix

Consider three subjects, of weight w_1, w_2 and w_3 kilograms respectively, whose daily weight gains are g_1, g_2 and g_3 grams per day and whose daily energy intakes are respectively e_1, e_2 and e_3 kJ/day.
Then energy intakes (kJ/kg.day) are

$$\frac{e_1}{w_1}, \frac{e_2}{w_2}, \frac{e_3}{w_3}$$

and weight gains (g/kg.day) are

$$\frac{g_1}{w_1}, \frac{g_2}{w_2}, \frac{g_3}{w_3}$$

so that mean energy intake in kJ/kg.day is

$$\left(\frac{e_1}{w_1} + \frac{e_2}{w_2} + \frac{e_3}{w_3}\right) \div 3$$

and mean weight gain in g/kg.day is

$$\left(\frac{g_1}{w_1} + \frac{g_2}{w_2} + \frac{g_3}{w_3}\right) \div 3$$

Therefore mean energy intake (kJ/kg.day) divided by mean weight gain (g/kg.day) is

$$\frac{\frac{e_1}{w_1} + \frac{e_2}{w_2} + \frac{e_3}{w_3}}{\frac{g_1}{w_1} + \frac{g_2}{w_2} + \frac{g_3}{w_3}} =$$

$$= \frac{e_1w_2w_3 + e_2w_1w_3 + e_3w_1w_2}{g_1w_2w_3 + g_2w_1w_3 + g_3w_1w_2}$$

Now mean daily energy intake (kJ) equals

$$\frac{e_1 + e_2 + e_3}{3}$$

and mean weight gain (grams) equals

$$\frac{g_1 + g_2 + g_3}{3}$$

so mean energy intake (kJ) divided by mean weight gain (g) is

$$\frac{e_1 + e_2 + e_3}{g_1 + g_2 + g_3}$$

Now

$$\frac{e_1w_2w_3 + e_2w_1w_3 + e_3w_1w_2}{g_1w_2w_3 + g_2w_1w_3 + g_ew_1w_w} \neq$$

$$\neq \frac{e_1 + e_2 + e_3}{g_1 + g_2 + g_3}$$

unless either $w_1 = w_2 = w_3$
and/or

$$\frac{e_1}{g_1} = \frac{e_2}{g_2} = \frac{e_3}{g_3}$$

It is a condition of the linear regression model that the line of best fit passes through the mean value for y and the mean value for x. As this point may differ according to the mode of expression of variables (kJ/kg or kJ, g/kg or g) then it follows that the linear regression model cannot be identical for both types of analysis, unless either of the two conditions above is present.

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