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A limit on the energy transfer rate from the human fat store in hypophagia

Seymour S. Alpert*

Department of Physics and Astronomy, University of New Mexico, Albuquerque, NM 87131-1156, USA

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Abstract

A limit on the maximum energy transfer rate from the human fat store in hypophagia is deduced from experimental data of underfed subjects maintaining moderate activity levels and is found to have a value of (290 ± 25) kJ/kg d. A dietary restriction which exceeds the limited capability of the fat store to compensate for the energy deficiency results in an immediate decrease in the fat free mass (FFM). In cases of a less severe dietary deficiency, the FFM will not be depleted. The transition between these two dietary regions is developed and a criterion to distinguish the regions is defined. An exact mathematical solution for the decrease of the FFM is derived for the case where the fat mass (FM) is in its limited energy transfer mode. The solution shows a steady-state term which is in agreement with conventional ideas, a term indicating a slow decrease of much of the FFM moderated by the limited energy transferred from the fat store, and a final term showing an unprotected rapid decrease of the remaining part of the FFM. The average resting metabolic rate of subjects undergoing hypophagia is shown to decrease linearly as a function of the FFM with a slope of (249 ± 25) kJ/kg d. This value disagrees with the results of other observers who have measured metabolic rates of diverse groups. The disagreement is explained in terms of individual metabolic properties as opposed to those of the larger population.

Keywords: Weight loss; Energy transfer; Metabolism

1. Introduction

The popular assumption made in cases of hypophagia is that energy deficits are balanced by appropriate decreases in the fat mass (FM)[1] resulting in the initial constancy of the fat free mass (FFM). It is sometimes assumed that this situation will persist until the total exhaustion of the FM at which point the FFM will then begin to decrease. As reasonable as this paradigm may appear, it will be demonstrated that it is not valid in the case of semi-starvation where the FFM decreases from the start of the dietary regimen. It is deduced from the experimental data that, in the case of severe dietary restriction, the FM can only provide a limited rate of energy transfer to the FFM forcing the energy deficit to be made up by a decrease in the FFM. The ability of the FM to provide whatever energy is required by the FFM is possibly restricted by the rate limited biochemical reactions of the energy transfer processes. If, however, the dietary restriction is not severe, it is possible that "protein sparing" can occur at least until the FM is depleted to the level where its limited energy transfer capability becomes challenged. Both cases of "protein sparing" and "non-protein sparing" are discussed in this paper and the transition from the former condition to the latter is considered.

In order to demonstrate the immediate decrease of the FFM during severe dietary restriction, we make use of

*Corresponding author. Tel.: +1 505 277 2616 (department secretary), +1 505 265 0296 (home); fax: +1 505 277 1520 (dept office).
E-mail address: sialpert1@juno.com (S.S. Alpert).

[1]In this paper, mass and weight are considered to be identical concepts measured in units of kilograms (kg).

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Nomenclature

ECW	extra cellular water, kg
FM	fat mass, kg
FFM	fat free mass, kg
RMR	resting metabolic rate, MJ/d
TBM	total body mass, kg
Q_{fd}	rate of ingested food energy, MJ/d
a	RMR multiplier of FFM, kJ/kg d ($=(249\pm25)$ kJ/kg d)
b	RMR offset term, kJ/d
f	fat mass, kg (mnemonic, $f\approx$fat)
f_0	initial FM, kg
f_{min}	minimum FM capable of sparing FFM, kg
ℓ	fat free mass, kg (mnemonic, $\ell\approx$lean)
ℓ_{ss}	steady-state FFM, kg
t	time, d, week
Δ	energy deficiency term, MJ/d (defined in Eq. (4))
α	energy density of FM change, MJ/kg ($=(39.2\pm1.7)$ MJ/kg)
β	energy density of FFM change, MJ/kg ($=(8.56\pm1.67)$ MJ/kg)
δ	activity coefficient, kJ/kg d
ε	food utilization factor
σ'	maximum energy transfer factor, kJ/kg d ($=(290\pm25)$ kJ/kg d)
σ	realizable energy transfer factor, kJ/kg d (decreased from maximum by activity coefficient)

data obtained in a humanitarian experiment done during wartime at the University of Minnesota by Keys et al. (1950). This experiment will be referred to as the Minnesota experiment (ME). In the ME, 32 young male volunteers of military status were semi-starved in order to evaluate optimal rehabilitation methods for use in treatment of the food deprived population of parts of wartime Europe. The data of the ME are used in this paper because of the long period of controlled semi-starvation (24 weeks), the multiple measurements of the FM, and the militarily mandated and enforced dietary compliance. Fortunately for this study, the average dietary restriction employed in the ME, (6.56 ± 0.31) MJ/d, was nearly ideal for demonstrating the limit on the energy transfer rate from the FM.

In the ME, the FM was measured at three different times during the 24-week semi-starvation period by densitometric means and corrections were applied to take account of excess fluids and minerals. The corrected data were presented in tabular form without indication of experimental uncertainties. This author has taken the uncorrected data of the FM and has proportionally applied these stated errors directly to the reduced data which is presented in Fig. 1. The error bars in Fig. 1 are indicative of the standard error of the mean and should be considered to be minimal since they do not include the unknown uncertainties introduced by the correction process. A least squares fit was done on the experimental points resulting in the expression

$$f = 9.51\exp[-(t/135)], \tag{1}$$

where f is the FM in kg and t is the elapsed time in d. Eq. (1) is shown in Fig. 1 by the solid curve. The correlation coefficient for the fitting process was 0.9991. Also shown in Fig. 1 is the popular, non-dynamic concept (dashed line) that a constant energy deficit results in a fixed rate of decrease of the FM. The dotted–dashed curve in Fig. 1 indicates a dynamic decrease of the FM based on the assumption that there is no limitation on the ability of the FM to transfer whatever energy is needed to the FFM. The equation for this curve will be derived in a later section of this paper and shows that the FM will be exhausted after 98 d of semi-starvation.

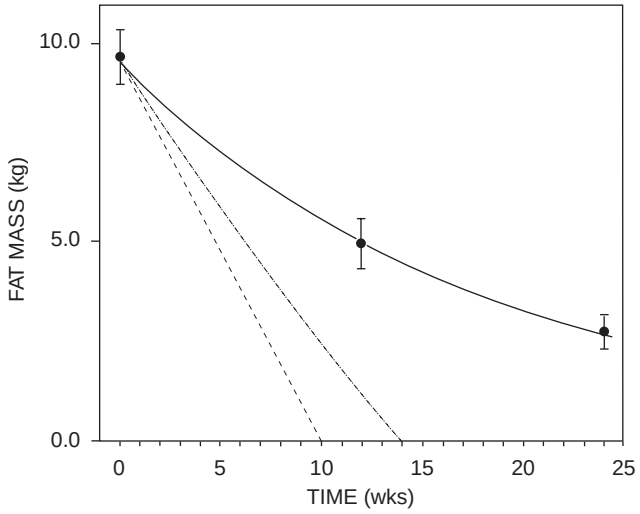

Fig. 1. The FM (kg) vs. time (weeks). The solid curve is an exponential least squares fit of the three averaged experimental data points. The straight dashed line represents the popular non-dynamic fat loss concept while the dotted–dashed curve is that for the dynamic concept of unlimited sparing of the FFM.

Point-by-point subtraction of the FM given by Eq. (1) from the experimental values of the total body mass (TBM) yields the results shown in Fig. 2 for the FFM during the semi-starvation period and for a few weeks prior to the beginning of the food energy restriction. There are three observations to be made from the data presented in Fig. 2. Firstly, there is an immediate decrease of the FFM. Secondly, the FFM reaches a constant value during the last 6 weeks of

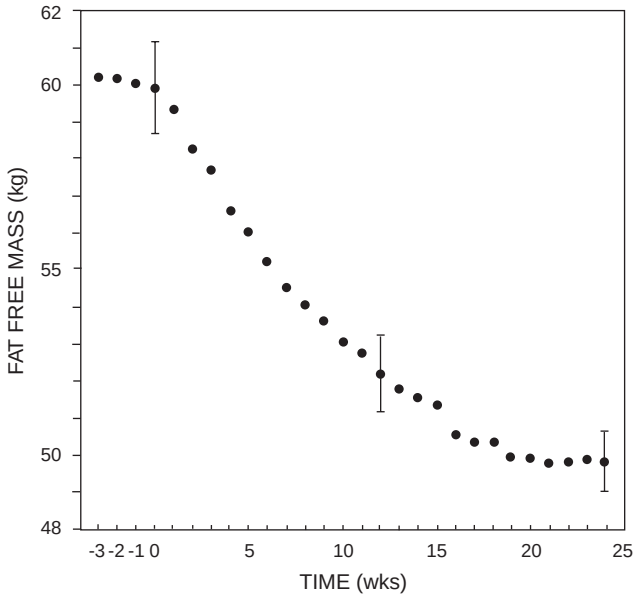

Fig. 2. The FFM (kg) vs. time (weeks). Data points are those of Keys et al. (1950).

semi-starvation. This constancy results from energy equilibrium between the slightly increased food energy input rate and both the decreased resting metabolic rate (RMR) and the lessened energy expended on activity. And lastly, it should be noted that the scatter of experimental points from a hypothetical smooth curve is well within the experimental error.

The two-reservoir energy model employed by Alpert (1979) will be used to develop a theory which explains the main features of the experimental data shown in Figs. 1 and 2. The model considers the body to be made up of only the FM and the FFM and that energy is stored in both of these reservoirs. In fact, the body has three separate energy stores: the sugar, glycogen, which is found in muscles and in the liver and is associated with muscular activity; protein which is found in many organ systems and is viewed as being living tissue; and the FM. We include glycogen and protein into the FFM along with many other inactive components such as bone mineral and extra cellular water (ECW). The word, inactive, in the preceding sentence is meant to refer to any body constituent which is not directly involved in oxygen consumption. The fact that glycogen and protein are both included in the FFM means that we will not be able to separate the energy properties of these two energy stores. The main reason for including glycogen and protein into a single entity, the FFM, results from the ability of densitometric experiments only to distinguish and measure the FM and the FFM.

The FM consists of glyceryl esters and fatty acids and should not be confused with adipose tissue of which it is a major component. In the sense used in the model, the FM is considered to be an external load only physiologically active in the transfer of energy to the FFM. It is the FFM which interacts with oxygen.

Since the FFM consists of protein, glycogen, and many other components, we discontinue use of the term "protein sparing" and replace it with a more appropriate term, FFM sparing.

2. Theoretical considerations

The conservation of energy principle is set forth here as

$$\text{rate of energy storage} = \text{rate of energy input} - \text{rate of energy output}. \quad (2)$$

In terms of the two-reservoir model, this is written as

$$\alpha\, \mathrm{d}f/\mathrm{d}t + \beta\, \mathrm{d}\ell/\mathrm{d}t = \varepsilon Q_{fd} - \mathrm{RMR}(\ell) - \delta(f+\ell), \quad (3)$$

where f is the FM and ℓ is the FFM. The symbol α is the energy density of change of the FM, is well known and is constant; β is the energy density of change of the FFM and is not well known and may not be of a constant nature. The quantity, β, represents catabolism of protein, the change in glycogen, changes in the ECW, and perhaps unknown energy costs of biochemical reactions which may be irreversible. Assuming the near constancy of β is a limitation on the accuracy of the two-reservoir model, but such an assumption allows us ultimately to derive an exact solution for the TBM in semi-starvation which agrees well with experimental data and which provides some interesting and worthwhile insights into weight loss phenomena.

The quantity, Q_{fd}, represents the average daily rate of ingested food energy and is given in units of MJ/d while the dimensionless multiplier, ε, is identified as the food utilization factor and takes into account energy lost to the thermic effect of food and also to detritus. The product, εQ_{fd}, is the food energy that is available for metabolism and activity. Thermal energy lost in nutrient digestion, transportation, and deposition is not available for metabolism and activity. These thermal losses are given for different food types by Ganong (1975) while detritus losses are given by Miles et al. (1986). The ingested food is assumed to contain all necessary food types, nutrients, minerals and is nutritionally complete.

The symbol RMR (ℓ) represents the resting metabolic rate, and in keeping with the two-reservoir model, is only a function of the FFM. If the RMR can be so described, it represents a significant mathematical simplification. We will later see that we will be able to deduce the RMR to be a linear function of the FFM.

The last term on the right-hand side of Eq. (3) indicates the rate of energy expenditure in activity and consists of the product of the TBM or (FM + FFM)

with a factor δ which is named the activity coefficient and has units of kJ/kg d. Several research efforts (van der Walt and Wyndham, 1973; Givoni and Goldman, 1971; Goldman and Iampietro, 1962) show that the rate of energy use in activity is proportional to the TBM or to the TBM with a load. This is especially valid in locomotion and may also be true when locomotion is not involved (Durnin and Passmore, 1967). The activity term combines physical work with the larger heat energy released by the thermic effect of exercise. The determination of the value of the activity coefficient is difficult and requires accurate long-term time accounting of different activities and their energy costs. An example of this calculation is given by this author in a previous paper (Alpert, 1979).

Eq. (3) is a dynamic equation. By this it is meant that temporal changes in the FM and FFM evolve as the conditions of equality change. The theory developed in this paper uses Eq. (3) as its fundamental equation and is restricted to adults engaged in normal daily activities decreasing their dietary input energy rate by the ingestion of lesser amounts of nourishing, mixed food types. In the case of an incomplete diet, which is lacking in one or more essential nutritional elements, Eq. (3) is still presumably valid, but the food utilization factor, ε, would likely fall to a smaller value which is not directly calculable, and the lost food energy would appear in thermal losses or detritus. In the case of complete fasting, Eq. (3) is incomplete and must be appropriately modified. This can be understood in terms of the protein component of the FFM which normally has a turnover rate by which the protein is constantly being synthesized and broken down. In the case of complete fasting, protein cannot be synthesized since the essential materials are absent and must necessarily decrease even though the FM may be able to provide all of the necessary deficit energy.

Eq. (3) is expected to be valid in hyperphagia and has been used by Alpert (1990) to develop a theory of weight gain; some results of this study are reviewed in the final section of this paper. Childhood and adolescent growth could be studied using Eq. (3); it may be that, β, the energy density of the change of FFM, is age related. The case of muscular hypertrophy caused by strenuous exercise training raises the interesting speculation that β may itself be a function of δ, the activity coefficient. Mathematically, this would be considered to be a nonlinear effect. Eq. (3) does not require that the rates of change of the FM and FFM be of the same sign. It is the general goal of body builders, some of whom succeed, to have $df/dt<0$ and $d\ell/dt>0$.

The main difficulty in the application of Eq. (3) is that the FM and FFM are two dependent variables and the time, t, is a single independent variable. Thus, in general, another relation between the FM and the FFM is required. If, however, it is assumed that the FFM is constant, then Eq. (3) becomes solvable for the FM. This is the situation of FFM sparing. In this case, since the FFM is taken to be constant, then $d\ell/dt = 0$, and we can rewrite Eq. (3) as

$$\alpha\, df/dt + \delta f = \varepsilon Q_{fd} - \mathrm{RMR}(\ell) - \delta\ell. \tag{4}$$

If the food energy input rate and the activity coefficient are constant, we can solve Eq. (4) for the time dependence of the FM. In hypophagia, the right-hand side of Eq. (4) will be negative. We indicate the right-hand side of Eq. (4) by the symbol, Δ, which we will call the energy deficiency term. The solution for Eq. (4) is given by

$$f = (f_0 + |\Delta|/\delta)\exp(-\delta t/\alpha) - |\Delta|/\delta, \tag{5}$$

where f_0 is the initial fat mass. In Eq. (5), we have introduced Δ as an absolute quantity in order to avoid confusion relating to its negative value. Since the FM cannot become negative, Eq. (5) ceases to be valid when $f = 0$. For the ME, we use as typical values $\varepsilon = 0.85$, $Q_{fd} = 6.56\,\mathrm{MJ/d}$, $\delta = 41.9\,\mathrm{kJ/kg\,d}$, $\mathrm{RMR} = 6.67\,\mathrm{MJ/d}$, $\ell = 59.88\,\mathrm{kg}$, $\alpha = 39.2\,\mathrm{MJ/kg}$, and $f_0 = 9.51\,\mathrm{kg}$. Solving Eq. (5) for t when $f = 0$, yields $t = 98\,\mathrm{d}$ as shown in Fig. 1 by the dotted–dashed line intercepting the axis.

Eq. (5) shows the FM time dependence when the FFM is constant. We now develop the formalism for the case where the FM is transferring energy at it maximum rate to the FFM, and both the FM and FFM are changing. We devote a section later in this paper to the transition between FFM sparing and non-FFM sparing and cite supportive experimental evidence.

The exponential nature of the FM dependence on time (Fig. 1) in semi-starvation requires that the time derivative of the FM be proportional to the FM. Since the product of the energy density of fat and the time derivative of the FM gives the rate of energy being provided by the FM in hypophagia, we write this as

$$\alpha\, df/dt = -\sigma' f, \tag{6}$$

where we have introduced the symbol, σ', which we call the maximum energy transfer factor. The units of σ' are kJ/kg d. The minus sign is introduced into Eq. (6) because, in the case of hypophagia, we expect that $df/dt<0$ and this allows σ' to be a positive quantity. The maximum energy transfer factor times the FM represents the limit of the total energy rate that can be extracted from the FM.

In order to facilitate the mathematical separation of dependent variables, we write

$$\sigma' = \sigma + \delta, \tag{7}$$

where σ is identified as the realizable energy transfer factor. Eq. (6) becomes

$$\alpha\, df/dt = -(\sigma + \delta) f. \tag{8}$$

The value of the realizable energy transfer factor is decreased from the maximum value by the activity

coefficient. The introduction of the maximum and realizable energy transfer factors is the fundamental issue of this paper.

The exponential nature of Fig. 1 demonstrates the existence of the maximum transfer factor as an average property for the 32 young male subjects of the ME. We do not know the individual variability of the maximum transfer factor or whether or not it can be applied to other populations under different conditions. We will speculate from other data sources that the limited transfer properties of the FM is credible and at least consistent with the results of other researchers.

There is one more point to be considered before we are able to find an exact solution for the FFM in the case of semi-starvation; we must know or determine the functional form of the RMR(ℓ). Alpert (1979), Webb (1981), Webb and Sangal (1991), Owen (1988), Ravussin et al. (1982), and Leibel et al. (1995), have all shown that the RMR correlates well with the FFM. We will fit the data of the ME to a linear hypothesis and experimentally justify it in the next section of this paper. We take

$$\mathrm{RMR}(\ell) = a\ell - b. \tag{9}$$

The minus sign is included in Eq. (9) in anticipation of b being a positive quantity. We will later show that the quantity, b, is a measure of the non-oxygen consuming part of the FFM.

The simple expression for the RMR given in Eq. (9) represents a significant departure from expressions developed in the past. Brody (1945), Kleiber (1975), and Heusner (1985) present the long and interesting history of some of the many mathematical formulations of the metabolic function. The fact that we are able to use a simple linear expression for the RMR as a function of the FFM greatly simplifies the mathematical solution achieved in this paper.

We now combine Eqs. (8) and (9) with Eq. (3) to get

$$\beta\, \mathrm{d}\ell/\mathrm{d}t = \varepsilon Q_{fd} - (a+\delta)\ell + b + \sigma f. \tag{10}$$

The solution of Eq. (8) is

$$f = f_0 \exp[-(\sigma+\delta)t/\alpha], \tag{11}$$

where f_0 is the initial FM. Combining Eqs. (10) and (11) with rearrangement of terms yields

$$\beta\, \mathrm{d}\ell/\mathrm{d}t + (a+\delta)\ell = \varepsilon Q_{fd} + b + \sigma f_0 \exp[-(\sigma+\delta)t/\alpha]. \tag{12}$$

Using standard mathematical techniques, differential equation (12) can be solved giving

$$\ell = \frac{\varepsilon Q_{fd} + b}{a+\delta} + \frac{\sigma f_0 \exp[-(\sigma+\delta)t/\alpha]}{(a+\delta) - \beta(\sigma+\delta)/\alpha} + K\exp[-(a+\delta)t/\beta]. \tag{13}$$

The significance of the three terms in the exact mathematical expression (13) is discussed here. The first term is the steady-state solution which will eventually occur after the two other terms exponentially decay away. The steady-state value of the FFM depends directly on the input food energy and also on the constant, b, which we have already indicated is a measure of the inactive component of the FFM and will soon justify. The steady-state term also depends inversely on the multiplying factor, a, appearing in Eq. (9) which is the mass specific indicator of the intensity of the RMR and also on the activity coefficient. The component terms of the steady-state solution for the FFM agree with common sense ideas and experience. Note that the steady-state term is completely independent of the energy density factors, α and β, and is therefore free of any uncertainties associated with these quantities.

The second term of Eq. (13) has in its numerator the exact expression for the rate of energy transfer from the FM while in the denominator, there are terms relating to interaction between both energy reservoirs. The significance of the second term is that it explicitly shows that the FFM decrease temporally tracks the energy transfer to it from the FM. Thus, although we have shown that there is no initial FFM sparing in semi-starvation, there is ongoing preservation or shielding of the FFM. The expected time constant for the shielding is the same as the time constant for the decay of the FM.

The last term in Eq. (13) is an unexpected one and results from the solution of the homogeneous equation associated with Eq. (12). The constant K is determined from initial conditions and is given in units of kg. The interpretation of this term is that it represents a part of the FFM that is not shielded by the decrease of the FM. We will soon determine the response time of this term to be about 4 weeks which is much shorter than the 135-d response time of the second term. It is noted that K, a mass, cannot be negative and that large positive values of K signify a deleterious condition for the organism since the significant loss of the FFM will be rapid. This suggests that the most desirable situation exists when $K = 0$. We will find $K = 2.72$ kg for the ME.

An insight concerning the importance of activity in semi-starvation is demonstrated in the exact mathematical solution, Eq. (13). It is seen there that the activity coefficient, δ, does not appear in isolation in any of the terms of the relation. It always appears in summation with either the RMR multiplier, a, or with the realizable energy transfer factor, σ. We will give values for these parameters in the next section, but the ordinary activity coefficient is about 15–20% of these parameters. Since δ is ordinarily a small term by comparison, any further modest change in activity will not be significant in altering the FFM. In this sense, we can say that the effects of modest changes in activity are lessened or that the FFM is "buffered" against such moderate alterations. This is not true in the case of large changes in activity.

3. Experimental considerations

Before we can test the validity of the theory presented in the previous section, we must first determine the experimental values of the many parameters which we have introduced.

The value of the maximum energy transfer factor is derived from the solution of Eq. (6) which is given by

$$f = f_0 exp(-\sigma' t/\alpha). \tag{14}$$

Since we know the response time of this equation to be 135 d and we know the energy density of fat, we can calculate the value of σ' to be 290 kJ/kg d. An uncertainty can be assigned by consideration of the least squares fit of Fig. 1. We determine that the response time of the exponential decay is uncertain to ± 10 d by adding and subtracting the residuals of the least squares fit to the experimental points and examining the resulting faster and slower decay forms. We suggest an uncertainty in α as ± 1.7 MJ/kg by observation of different values reported in the literature. In this manner, we conclude that the total uncertainty in the value of σ' is ± 25 kJ/kg d. To determine the realizable energy transfer factor, σ, we use Eq. (7) which indicates that we must subtract the value of the activity coefficient from the maximum energy transfer factor. The activity coefficient is seldom known in ordinary situations, but in the case of the ME where physical duties were closely monitored, Alpert (1979) was able to calculate that the initial activity coefficient was (50.2 ± 7.5) kJ/kg d resulting in a value of the realizable energy transfer factor of (240 ± 26) kJ/kg d.

Earlier in this paper, we introduced the RMR as a linear function of the FFM in the form of Eq. (9). We now justify this expression and evaluate the constants a and b. In the ME, the oxygen consumption rate was tabulated at three distinct times; however, graphical data without stated uncertainty values were given at four other times. In order to increase our data base, we include all seven data points in Fig. 3 and do a linear regression fit. This process gives

$$\mathrm{RMR}(\ell) = 249\ell - 8410, \tag{15}$$

where the RMR is in units of kJ/d and ℓ is in kg.

Considering the degree of fit of Fig. 3, we arrive at $a = (249 \pm 25)$ kJ/kg d and $b = (8410 \pm 1300)$ kJ/d. The correlation coefficient for the linear regression fit is 0.9939. In the derivation of Eq. (15) from the data of the ME, we used the factor, 20.3 kJ/l,[2] for converting consumed oxygen into energy units.

[2]This value is the median for fasting, 19.7 kJ/l (Kleiber, 1975), and the postabsorptive state, (21.0 ± 0.2) kJ/l (McLean and Tobin, 1987), and is meant to be more representative of the RMR than the basal metabolic rate (BMR). The choice of this value introduces an increase in the RMR over the BMR of 3.2%.

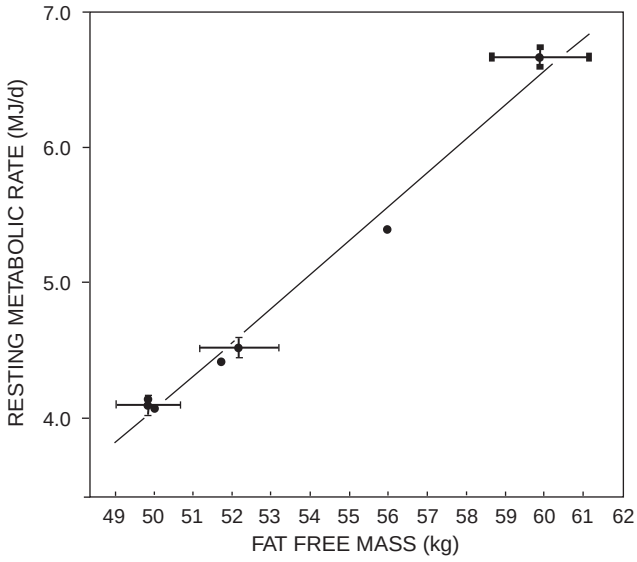

Fig. 3. The RMR (MJ/d) vs. the FFM (kg). The solid straight line is the least squares fit of all data points.

An interesting deduction can be made from Eq. (15); that is, the RMR(ℓ) is of zero value at a FFM of 33.78 kg which we interpret to be the mass of the inactive component of the FFM. By subtraction we find that the oxygen interactive component has an initial value of 26.10 kg which is 38% of the initial TBM. Roza and Schizgal (1984) using exchangeable potassium techniques on two well-fed groups of mixed subjects measured the body cell mass to be 35% and 31% of the respective TBMs and identify this as being the oxygen interactive component of the body. Our results agree qualitatively with those of Roza and Schizgal (1984) whose diverse experimental subjects had larger FMs than the subjects of the ME.

Webb and Abrams (1983), using deuterium methods, measured total body water for their subjects to be $72.3 \pm 2.0\%$. This should not all be considered as inactive matter, however, since some of the aqueous material must be intimately involved in oxygen consuming processes within the cellular structure.

In Fig. 3, experimental uncertainties are indicated where we were able to assign them. The four points taken from graphical data carry with them no assigned uncertainties, but it is reasonable to assume that all points are comparable in this regard. The cluster of points, especially the three at the lowest value of the FFM, indicates that the levels of uncertainty have been appropriately assigned.

Although Fig. 3 shows a good correlation of the RMR with the FFM, it does not agree with the results published by other researchers studying diverse populations. A suggestion for rationalizing this discrepancy is given in the appendix following the text of this paper.

The determination of the energy density of change of the FFM, β, presents some difficulty. We have drawn a smooth curve through the data of Fig. 2 in order to evaluate the slope, $d\ell/dt$, and then used the differential equation (12) to calculate β during six equally spaced points of time during the first 10 weeks of semi-starvation. We arrive at the value, $\beta = (8.56 \pm 1.67)\,\mathrm{MJ/kg}$. Using this value, we determine the response time of the last term of Eq. (13) to be 28.6 d.

The method of calculation of the food utilization factor, ε, is shown by Alpert (1979). This dimensionless factor takes into account energy losses both to the thermic effect of food and also to detritus and is evaluated to be $\varepsilon = 0.85$.

In the ME, the 24-week period of semi-starvation can be divided into three dietary segments. In the first 10 weeks, the subjects were fed a diet of $(6.84 \pm 0.09)\,\mathrm{MJ/d}$, during the next 6 weeks $(6.24 \pm 0.21)\,\mathrm{MJ/d}$, and during the last 6 weeks $(6.53 \pm 0.20)\,\mathrm{MJ/d}$. The initial value of the activity coefficient was taken as $(50.2 \pm 7.5)\,\mathrm{kJ/kg\,d}$.

We have calculated the TBM vs. time curve using the sum of Eqs. (1) and (13) and have displayed the results in Fig. 4 as a smooth curve along with the experimental data points. The lower part of the curve is broken into two segments at the point of transition between dietary regions. The lower branch uses the initial value of δ and corresponds reasonably well with the experimental data. In the upper branch, we have guessed at a value of $\delta = 41.9\,\mathrm{kJ/kg\,d}$ in order to show the reader the effects of likely decreased activity.

The theoretical curve shown in Fig. 4 is terminated at the 18th week because we have already seen that the FFM is in energy equilibrium for the last 6 weeks when the dietary energy rate was slightly increased. In this period, the FFM had an equilibrium value of $(49.86 \pm 0.06)\,\mathrm{kg}$. From Eq. (13), we see that the steady-state term, ℓ_{ss}, is given by

$$\ell_{ss} = \frac{\varepsilon Q_{fd} + b}{a + \delta}. \tag{16}$$

We know the value of every term in Eq. (16) except for the activity coefficient, δ. Solving for this quantity gives a value of $31.0\,\mathrm{kJ/kg\,d}$. While this value, in itself, is not very important, it shows a positive consistency with the other values of the activity coefficient and also with the observation that activity was decreasing during the semi-starvation period as qualitatively expressed by the authors of the ME.

4. The transition between FFM sparing and non-FFM sparing

The ME provides data which indicates that there is a limited ability of the FM to transfer energy to the FFM in the case of semi-starvation. A related question is, are there other less severe dieting regimens where the FM is capable of transferring energy at an adequate rate so as to spare the FFM? An experiment by Webb and Abrams (1983) provides an affirmative answer to this question. The experimental subjects of this work were 9 men and women grouped in the 20s and 40s all of whom, with one exception, were overweight. The total daily energy expenditure was determined and then the dietary input rate was decreased by 4.19 MJ/d for a period of 42 d. Some of the subjects lived at home while others resided in the laboratory. The FM was determined by underwater weighing. For these subjects the initial TBM and FM were, respectively, (81.90 ± 5.2) and $(24.8 \pm 6.57)\,\mathrm{kg}$ while the corresponding values for the subjects of the ME were (69.39 ± 1.03) and $(9.51 \pm 0.73)\,\mathrm{kg}$. The decrease of food energy rate was 5.38 MJ/d in the ME. The major differences between the work of Webb and Abrams (1983) and the ME were that the subjects of the former had larger FMs than those of the latter, their dietary restriction was not quite so severe, and the experimental period was of much shorter duration.

A result of the Webb and Abrams experiment was the observed linear loss of weight over the 42-d dietary period of which 4.4 kg was identified as change in the FM and 1.3 kg as change in the FFM. Webb and

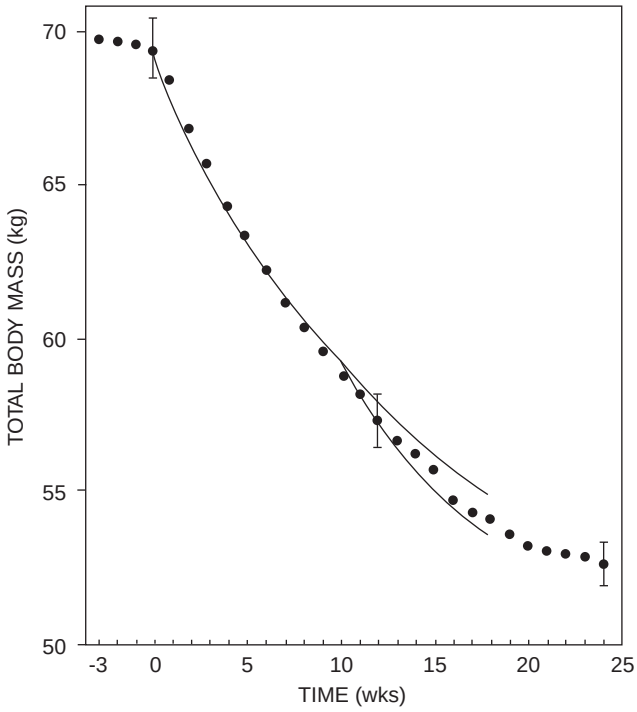

Fig. 4. The TBM (kg) vs. time (weeks). The smooth curve represents the theory presented in this paper while the discrete data points are those of Keys et al. (1950). The theoretical curve bifurcates after 10 weeks because we have chosen to use two different activity coefficients in our calculation. The lower branch corresponds to the same activity level used in the first 10 weeks while the upper branch is represents a lesser activity level.

Abrams suggest that the change in the FFM was totally water since nitrogen balance was always positive during the dietary period. Since the decrease in the FFM was small and apparently without change in the protein mass, it is probably safe to conclude that there is little or no energy associated with the FFM change. If this is the case, FFM sparing has occurred and the FM dependence on time is initially given by Eq. (5).

A problem in the application of Eq. (5) is that we do not know the appropriate activity coefficient for the subjects of the Webb and Abrams work. These authors acknowledge that there was no way of knowing the energy expended on activity. We will estimate the value of the activity coefficient to be half way between the maximum and minimum values of the ME. This gives a value of $\delta = 40.6\,\mathrm{kJ/kg\,d}$. In the exponential factor of Eq. (5), the decay time is given by $\alpha/\delta = 966\,\mathrm{d}$. Since the dietary period of the Webb and Abrams work was only 42 d, we are justified in using a Taylor series expansion for the exponential factor keeping only the first two terms. In this approximation, we can rewrite Eq. (5) as

$$f = f_0 - (f_0\delta/\alpha + |\Delta|/\alpha)t. \tag{17}$$

Eq. (17) displays the observed linear loss of the FM with time. We calculate from this equation the linear loss rate to be 0.114 kg/d. Since this value is partly a result of estimation, we do not expect much accuracy; however, the rate of FM loss measured by Webb and Abrams was $(0.105 \pm 0.010)\,\mathrm{kg/d}$. In Eq. (17), the first term in the factor which multiplies the time variable is generally less than the second term. If the first term is neglected, the rate of loss of the FM becomes $-|\Delta|/\alpha$ which corresponds to the popular calculation of fat or weight loss. The minimum FM, f_{min}, which can provide all of the dietary energy deficit is given by

$$\sigma f_{min} = |\Delta|, \tag{18}$$

where $|\Delta|$ is the absolute value of the energy deficiency term defined in association with Eq. (4). If we apply the value of the maximum energy transfer factor found in the ME to the experiment of Webb and Abrams (1983) to get a realizable transfer factor of $\sigma = 249\,\mathrm{kJ/kg\,d}$, we can calculate $f_{min} = 13.9\,\mathrm{kg}$. In this calculation, we must remember that the changes in food energy input rates must be multiplied by the energy utilization factor. We can take the value of f_{min} and enter it into Eq. (5) and solve for the elapsed time necessary for Eq. (18) to hold in the Webb and Abrams work. Using $f_0 = 24.8\,\mathrm{kg}$, we calculate $t = 101\,\mathrm{d}$. We expect FFM sparing to exist until this time has elapsed.

In the general situation after the FFM sparing period is over and the dietary restriction continues, we anticipate that non-FFM sparing would then occur. Eq. (18) sets the criterion for the transition between Eqs. (5) and (11). Considering Eq. (18) to be applied to the differential equation (4) slightly before and after the transition occurs allows us to see that the slope of the FM vs. time curve is continuous at the transition. Since the value of the FM is also continuous, there will be no sudden or observable event occurring at the time of transition; however, we anticipate a sudden change in the FFM at this time.

We demonstrate a likely scenario for the FM in the case of the ME where we have assumed a less severe dietary input rate of 9.43 MJ/d which is 80% of the calculated total energy expenditure of the subjects of the ME just prior to the proposed energy restriction. In this case, we calculate the energy deficiency term to be $|\Delta| = 1.527\,\mathrm{MJ/d}$ and using Eq. (18), we find that $f_{min} = 6.36\,\mathrm{kg}$ since $\sigma = 240\,\mathrm{kJ/kg\,d}$. Using Eq. (5), we find that f_{min} is reached in 64 d and that thereafter the FM falls off as an exponential curve with a time constant of 135 d. This scenario is displayed in Fig. 5 where a dot marks the FM value at the point of transition and the dashed curve is a reminder that non-FFM sparing is occurring. The initial linear decrease of the FM has been observed by Webb and Abrams (1983).

Another way of thinking about the two regions of Fig. 5 is that before the transition occurs, the time rate of change of the FM is dependent on the input food energy rate, the activity, and the FFM both directly and indirectly through the RMR(ℓ). After the transition, the FM can no longer meet all of the energy demands put upon it, and it produces energy at its maximal rate, the total amount being limited by its mass.

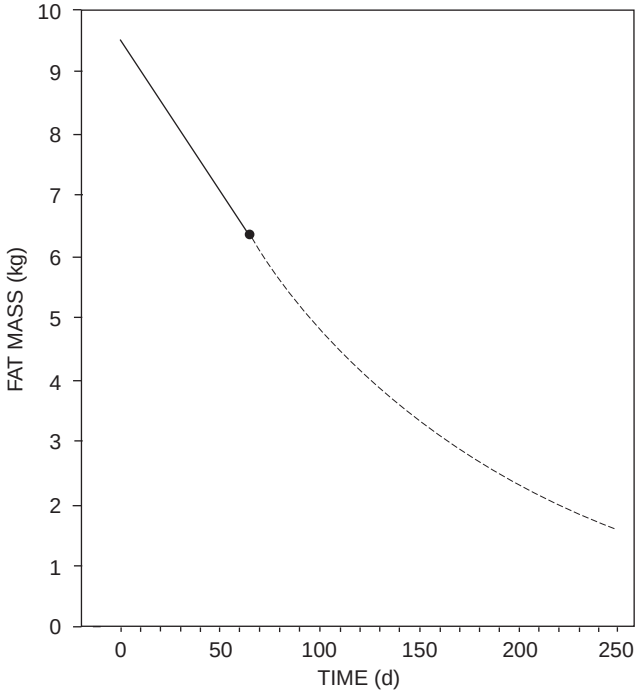

Fig. 5. The FM (kg) vs. time (d). The solid line represents the FM loss as the FFM is being spared while the dashed curve is the exponential decay of the FM when the FFM is not being spared. The dot shows the point of transition.

The scenario displayed in Fig. 5 may be a realistic situation in cases of severe long-term dietary restriction imposed on obese patients in controlled environments. Doré et al. (1982) put 19 seriously obese metabolic ward females with an average TBM of (104.5 ± 2.1) kg onto a diet of 3.35 MJ/d for a period of one year during which the TBM fell to (73.7 ± 2.4) kg and the resting oxygen consumption fell from (290.0 ± 7.5) to (234.0 ± 6.0) ml O_2/min. Using potassium studies, Doré et al. (1982) state that there was an average 8.1 kg loss of lean tissue during the 1 year dietary period and that 22.7 kg of fat was also lost. From these data, we are able to determine the quantity, a, in Eq. (9) and find its value to be (202 ± 57) kJ/kg d. This is to be compared with the value we found in the ME which was (249 ± 25) kJ/kg d. The uncertainty assigned in the Doré et al. measurement is our calculation based on the statistical data reported by these authors. The observed agreement of the multiplier, a, within the uncertainties, is unusual because two different methods of measurement were used and two different populations were studied. In both cases, however, there is a marked difference with the results of other researchers who have studied well-fed populations and determined the increase in RMR with FFM. This disagreement will be discussed in detail in the appendix to this paper.

The loss of both FFM and FM in the Doré et al. (1982) experiment is qualitatively consistent with the ideas presented in this paper. We presume that in the initial phase of the experiment, only FM was lost but as the restricted dietary period progressed, the FM fell to a value given by Eq. (18) where it could no longer make up all of the required energy deficit at which time, the FFM began to decrease along the lines given by Eq. (13).

Another interesting experiment attempting to correct cases of severe obesity was performed by Leibel and Hirsch (1984). Twenty-six obese (152.5 ± 8.4) kg hospital patients were put onto a restricted diet of 2.51 MJ/d for an average period of 202 d. The TBM of the 12 men and 14 women decreased to (100.2 ± 5.7) kg, and their mean total energy expenditure fell from an initial value of (15.28 ± 0.75) MJ/d to a final value of (9.09 ± 0.50) MJ/d. Leibel and Hirsch (1984) point out that the decrease in the total energy expenditure is too large to be explained by activity considerations. Additionally, these authors make the unexpected observation that the average total energy expenditure of their reduced subjects is less than that of the controls who have a smaller average TBM by about 40 kg.

The results of Leibel and Hirsch (1984) are in agreement with the principles discussed in this paper. If we guess at a small activity coefficient of 21 kJ/kg d and subtract out the estimated energy of activity from the total energy expenditure at the beginning and end of the experiment, we find a difference of 5.09 MJ/d which we assume to be the change in the RMR. If we take the RMR multiplying factor, $a = 249$ kJ/kg d, and divide this into the RMR difference, we conclude that about 20.5 kg of FFM has been lost. The corresponding decrease in the FM is found by subtraction to be 31.8 kg.

The seeming paradox of the heavier reduced subjects of the Leibel and Hirsch (1984) work having a smaller total energy expenditure than their much lighter controls can also be resolved. The paradox arises from the common view that the metabolic rate is a monotonic increasing function of the TBM or the TBM raised to an exponential power. This general view, however, applies to a well-fed population of subjects and may apply differently to any single individual member of the population. We suggest that the subjects of the Leibel and Hirsch work follow a decrease of their RMR by a rule similar to Eq. (15) and that their average RMR does not follow that of the larger population. This point has been made earlier in this paper and will be developed in detail in the appendix. We will calculate from an analog model of the Leibel and Hirsch experiment that the reduced subjects have less oxygen interactive tissue than do their smaller controls.

The experiments of Doré et al. (1982) and Leibel and Hirsch (1984) were designed to study and correct cases of severe obesity. The unstated and totally reasonable assumption in these experiments may have been that the very large FMs of the experimental subjects would be able to provide all of the long-term energy deficiencies resulting from the highly restricted energy input rates. The main point of this paper is that the FM is limited in its ability to provide energy to the FFM. This means that if a constant dietary restriction is maintained for too long of a period, the FFM will eventually not be spared and will decrease.

We propose a different strategy be used in the treatment of obesity. Initially, a severe dietary restriction would be applied and as the FM decreased, the condition of Eq. (18) would be approached. If this condition can be anticipated, the dietary restriction would be partially relaxed causing the absolute value of the energy deficiency term, $|\Delta|$, to lessen allowing the minimal FM to decrease with continued sparing of the FFM. This process could be repeated as often as necessary. The initial severe dietary restriction would be progressively relaxed until the final value of the FM was achieved. Such a program might be acceptable to the dietary subjects.

5. Conclusions and speculations

The main thesis of this paper is that the FM is able to transfer energy to the FFM up to a maximum rate of (290 ± 25) kJ/kg d. In realistic energy deficit situations, the actual transfer rate is decreased by activity

considerations. The value of the maximum transfer rate is derived from data for young, active male subjects studied by Keys et al. (1950). The applicability of these results have not been directly verified in other populations and conditions.

Experimental studies to determine the value and distribution of the energy transfer factor need not be so difficult and time consuming as the original work by Keys et al. (1950). Further studies would require that both the TBM and FM be frequently measured during a dietary period which would be designed to spare the FFM initially. At the transition between FFM sparing and non-FFM sparing, there will be no obvious change in the FM, but there should be an observable change in the FFM which will go from a constant value to decreasing values. If this behavior can be clearly observed, Eq. (18) can be used to calculate the value of the realizable energy transfer factor.

The ME employed a severe dietary restriction which immediately put the subjects into a non-FFM sparing situation. In a sense, this was fortunate because it allowed for a direct interpretation of the limiting energy transfer phenomenon. If the situation had allowed for both FFM sparing and non-FFM sparing as shown in Fig. 5, the interpretation might have been less obvious.

If the concept of a limiting energy transfer rate for fat is valid, the important question arises as to whether or not such a transfer rate can be increased in order to allow for greater loss of the FM. The macroscopic linear energy theory employed in this paper gives little insight into the mechanisms of this possibility. Very likely such an intervention would be a pharmacological one based on a clear understanding of the relevant microscopic biochemical interactions. Our model does not consider nonlinear processes which might become important in unusual situations but which could still be tested by Eq. (18). An unexpected feature of the maximum energy transfer factor is that it is quite modest in its magnitude. Alpert (1982) has demonstrated that the low value of σ' or σ is near optimal for increasing the duration of the change in the FFM. This optimization allows for a prolongation of the FFM by a factor of two when compared to the hypothetical case of an unlimited transfer rate.

Another optimization consideration is presented in the exact solution for the FFM displayed in Eq. (13). In this equation the final term represents a fast decay (28.6 d) of an unshielded or unprotected part of the FFM. In the case of the ME, the initial magnitude of this term is 2.72 kg or 22% of the total expected loss of the FFM. In an optimal situation, this term should be zero since it represents a rapid reduction of the FFM. Even though we consider the FFM to be a single energy entity, we in no way imply that the FFM is a uniform structure. Possibly the shielded part of the FFM deals with vital organ systems while the unprotected part has less survival significance. If we mathematically force the last term of Eq. (13) to be zero and keep all other variables constant, we calculate that the maximum energy transfer rate from the FM has a value of 358 kJ/kg d. This is to be compared with the observed value of 290 kJ/kg d.

As indicated in Eq. (3), the only non-invasive means an individual has to control the size of the energy stores are by modifying the rate of ingested food energy and/or the level of physical activity. For individuals living in modern industrial societies, the level of activity is mainly determined by occupation and life style and is not easily changed. Professional athletes and dedicated body builders, however, have been able to control their energy stores by extreme activity.

A result discussed in this paper is that a severely restricted dietary regimen ultimately will lead to significant loss not only of the FM but also of the FFM. Avoiding the loss of FFM when the FM is challenged up to its limited energy transfer capability requires that the severe dietary restriction must be terminated or relaxed before this situation occurs. The previous section of this paper quantitatively suggests how this may be done. The common adage that "if a little bit is good, more is better" does not apply to severe dietary restrictions.

Although the main dietary condition discussed in this paper is that of hypophagia, some of the same considerations apply to overeating (Alpert, 1990). Eq. (3), which is a statement of the conservation of energy, should be valid in both dietary regions. A basic difference is that in hyperphagia, energy is added or accreted to either or both the FM and the FFM. The main problem of an accretion model is that it is not clear how the body determines the division of excess energy between the two energy stores. An interesting feature of the accretion model can be derived from Eq. (3) by assuming that either the FM or FFM is held constant and the growth of the other isolated energy reservoir is determined. It can be shown by this means that an increase in the FM is several times less costly in energy terms than is an equal increase of the FFM. The main reason that it takes much more energy to grow the FFM is that the ingested food must also supply adequate energy for the increase in the RMR. The significant difference in energy costs for FM and FFM growth empirically suggests why some people remain lean and others get fat on overeating. Sims et al. (1968) performed a long-term overeating experiment on Vermont state prisoners and showed by means of a bar graph for eight subjects that weight gain division between the FM and FFM was quite diverse.

We expect that overeating response times for the FM to be long and the FFM to be short since their isolated exponential growth expressions formally use the same quantities already introduced in the

undereating situation. Ravussin et al. (1985) has found considerable FFM growth on overeating in only 5 days (Alpert, 1990).

Finally, we conclude that in semi-starvation, the FFM is buffered against modest changes in activity and also is mostly shielded by energy transferred from the FM which must be of adequate size in order to provide complete shielding. In the case of hyperphagia, we infer that the FM is easily enlarged. It appears that the human body is well adapted to a feast-famine evolutionary environment. The problem now developing in most of the world is that the feast-famine algorithm is no longer operational. The outstanding question is how do we deal with the historically recent situation of ever present plentitude?

Acknowledgments

This work is dedicated to the memory of Peter Franken (1928–1999), late Professor of Optical Sciences and Physics at the University of Arizona. Professor Franken was highly gifted with a wide range of curiosities and interests. The author appreciates his kind and critical comments of past years.

I wish to thank Professor Eric Ravussin of the Pennington Biomedical Research Center (PRBC) for inviting me to address the CALERIE Steering Committee meeting, June 10–12, 2003, in Baton Rouge, LA. The meeting was sponsored by the Duke Clinical Research Institute and hosted by the PRBC and the Louisiana State University. Some of the topics developed in this paper were initially presented at the meeting.

Two referees reviewed this paper and provided worthwhile and thought-provoking critical comments. The author further wishes to thank both Hisako Moriyama and Sandra Ortiz for their respective help with the graphics and text.

And lastly, I wish to inform the reader that I formerly held an adjunct position at the Noll Laboratory for Human Performance Research at the Pennsylvania State University which was then under the directorship of Professor Elsworth R. Buskirk.

6. Appendix

The purpose of this appendix is to justify the validity the relation displayed in Eq. (15) which shows the slope of the dependence of the RMR on the FFM to be $(249 \pm 25)\,\mathrm{kJ/kg\,d}$. This agrees with the results of Doré et al. (1982) but does not agree with the results of other researchers (Webb, 1981; Webb and Sangal, 1991; Ravussin et al., 1982; Owen, 1988; Leibel et al., 1995). Since Owen (1988) displays his results in a manner similar to ours, we quote his linear regression equation as

$$\mathrm{RMR}(\ell) = 98.8\ell + 779, \tag{19}$$

where the RMR is given in kJ/d and ℓ is in kg. Owen and the other researchers referenced above have measured the RMR as a function of the FFM for a diverse population of generally well-fed subjects.

We have displayed our results with those of Owen in Fig. 6 were Owen's linear regression line is shown as a straight solid line and ours as a dashed line with an arrow head indicating the decrease of the RMR as the FFM decreased. Initially, the average RMR of the subjects of the ME was measured to be 6.67 MJ/d for a FFM of 59.88 kg; this point is shown in Fig. 6 as a round dot carrying appropriate error bars and lies on the Owen regression line. As the semi-starvation regimen set in, however, the disagreement of the ME results with those of Owen increased more and more.

To help dispel confusion over the disagreement between Eqs. (15) and (19), let us ignore the statistical spread of experimental points. Consider the 32 subjects of the ME to lie initially somewhere on the Owen regression line and then be put onto the dietary restriction. Each of the 32 subjects would presumably follow a line similar to their average decrease as shown by the dashed line. The Owen line is a compendium of information about his well-fed experimental subjects. There is no requirement that the semi-starved subjects must follow the Owen regression line. If the Owen subjects were themselves put onto a semi-starvation diet, their regression line would not slide tangentially upon

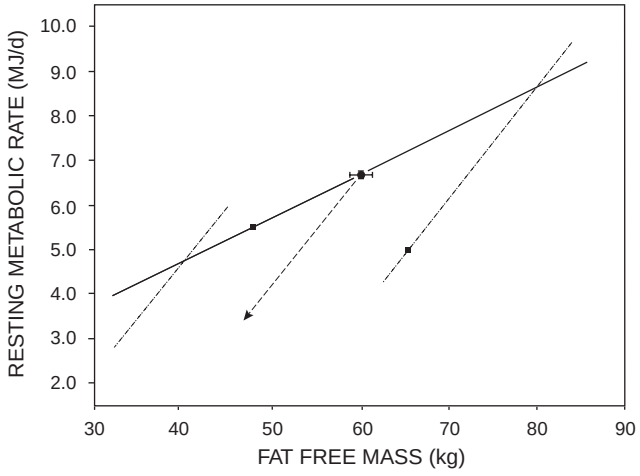

Fig. 6. The RMR (MJ/d) vs. FFM (kg). The round dot with error bars represents the average RMR and FFM for the subjects of the Keys et al. (1950) experiment prior to dietary restriction. The solid line is the regression fit of the data of Owen (1988) while the dashed line is that of this paper. The arrow head indicates the decrease of the RMR as the FFM decreases. The dotted–dashed lines are hypothetically assumed for a large and small person to demonstrate the difference in body composition. The square point on the right dotted–dashed line shows that a person with larger FFM can have a lesser RMR than a person of less FFM as shown by the square dot on the Owen regression line.

itself but would most likely be displaced downwards along the direction of the dashed arrowed line.

Leibel et al. (1995) studied the RMR vs. FFM dependence of several obese and non-obese subjects who lost 10% or 20% of their initial TBM. The resulting distribution of experimental points after weight loss appears to fall below the initial regression line.

Indicated in Fig. 6 are two additional curves shown as dotted–dashed lines with the same slope as given in Eq. (15). The line to the left intersects with Owen's linear regression line at a FFM of 40 kg while that at the right intersects at a FFM of 80 kg. Since both of these lines intersect with Owen's line and we know their slope, we can derive equations for these two lines in the form of Eq. (9) and then deduce the division of the FFM into active and inactive components. For the small person with a FFM of 40 kg, we calculate an inactive component of 21.00 kg and an active component of 19.00 kg for a ratio of inactive to active segments of 1.105 while for the larger person with a FFM of 80 kg, we calculate an inactive component of 45.13 kg and an active component of 34.87 kg for a ratio of inactive to active segments of 1.294. We see that the larger person has a larger ratio of inactive to active components than does the smaller person. In Fig. 6, we have extended the hypothetical dotted–dashed lines to regions above the Owen's regression line reasonably speculating that increases of the FFM for individuals would follow such a line. Perhaps this type of variation is the main cause of the point scatter found in the work of Owen and others.

Leibel and Hirsch (1984) found that their experimental subjects, when reduced in weight from 152.5 to 100.2 kg, had a final lower total energy expenditure than did their normal controls who were about 40 kg lighter. Leibel and Hirsch did not measure the FFM but instead used the TBM. For this reason, we cannot numerically evaluate their experimental results, but we can achieve an analogous understanding by using the RMR vs. FFM graph of Fig 6. Let us assume that a subject with an initial FFM of 80.00 kg undergoes a dietary restriction similar to that of the ME and follows the rightmost dotted–dashed line downward until the subject reaches the indicated square dot where his RMR is 5.0 MJ/d and his FFM is 65.21 kg. If we consider a control subject on the Owen regression line indicated by the square dot to the left, we find that the control has a RMR of 5.5 MJ/d and a FFM of 47.78 kg. We have created an analog to the situation observed by Leibel and Hirsch (1984). The subject of greater FFM has the smaller RMR. We can, however, determine the amount of the oxygen interactive component for both subject and control. Using methods discussed earlier in this paper and also in this section, we can determine that the control has an active component of 22.09 kg. The semi-starved subject has lost 14.79 kg of active tissue according to the slope given in Eq. (15) and has a final active component of 20.08 kg. The smaller control has the greater mass of active tissue and thus consumes oxygen at a higher rate.

The idea expressed in this paper that individual variations of RMR values result from the relative sizes of active and inactive components of the FFM partially shifts the concept of the scaling properties of the RMR from being solely a biochemical problem to the idea that structural geometric rules are also significant. Another way to consider this is to note that in Eq. (9), the RMR is related to the constants, a and b. The latter constant is a geometrically determined offset term while the former constant represents the magnitude of oxygen consumption by the active component of the FFM and is determined by biological and biochemical factors.

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