Review – hypothesis article

The control of partitioning between protein and fat during human starvation: its internal determinants and biological significance

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Human subjects vary in the extent to which their body’s protein and fat compartments are mobilized for fuel during starvation. Although an inverse association between the initial adiposity and the contribution of protein as fuel during starvation has been known for nearly a century, interest in the quantitative importance and functional significance of the initial percentage fat as a determinant of biological variation in energy-partitioning between protein and fat (and hence in determining the partitioning characteristic of the individual) is relatively recent. The present paper addresses these issues by revisiting the classic Minnesota experiment of semi-starvation and refeeding from a standpoint of system physiology. In a quantitative analysis of the relationship between the initial body composition (ratio FAT0 : fat-free mass (FFM0)) and the composition of weight loss (ratio \( \Delta \text{FAT} : \Delta \text{FFM} \)) in the thirty-two men in the Minnesota study, the arguments are put forward that the fraction of FFM lost when the fat stores reach total depletion is independent of the initial percentage fat, and that this fraction represents the ‘dispensible’ component of the protein compartment that is compatible with life (i.e. the protein energy-reserve, \( r_p \)). The concepts are developed that (1) the initial percentage body fat (which reflects the initial ratio FAT0 : FFM0) provides a ‘memory of partitioning’ which dictates the control of partitioning between protein and fat in such a way that both the protein energy-reserve (\( r_p \)) and the fat energy-reserve (\( r_f \)) reach complete depletion simultaneously, a strategy that would ensure maximum length of survival during long-term food scarcity, and that (2) variability in the relative sizes of these two energy reserves (i.e. in \( r_f : r_p \)) could, in addition to the initial percentage fat, also contribute to human variability in energy-partitioning. The basic assumptions underlying this re-analysis of the Minnesota data, and the concepts that are derived from it, have been integrated in the simple mathematical model for predicting the partitioning characteristic of the individual. This model is used to explain how variability in the fraction of the protein compartment that could function as an energy reserve (\( r_p \)) can be as important as the initial percentage fat in determining inter-individual variability in protein-sparing during the early phase of starvation, in fuel partitioning during prolonged starvation, or in the maximum percentage weight loss during starvation. The elucidation of factors underlying variability in the size of the protein energy-reserve may have important implications for our understanding of the pathophysiology of starvation and age-associated susceptibility to muscle wasting, and in the clinical management of cachexia and obesity.

Cachexia: Obesity: Malnutrition: Energy metabolism: Body composition

Life is sustained by chemical energy derived from the combustion of substrates whose continuous supply is ensured through the mobilization of the body’s fuel reserves whenever the external fuels supply from foods cannot meet the demands. Whereas on a day-to-day basis a small amplitude of negative energy balance can be buffered by the glycogen stores, the fuel needs during more prolonged food deprivation are derived from the catabolism of the body’s protein and fat. The relative proportion of energy withdrawn from these two compartments, referred to as energy-partitioning, and

Abbreviations: FFM, fat-free mass; Pc, partitioning characteristic; \( \text{P}_{\text{SDP}} \), fraction of energy mobilized as protein during total food deprivation; \( r_f \), fat-reserve fraction; \( r_p \), protein-reserve fraction.

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numerically defined as the fraction of energy mobilized as protein during food deprivation ($P_{\text{ratio}}$), is well known to be a variable. It is dependent on external factors (e.g. the degree of starvation, composition of the restricted diet, intensity of physical activity, resistance training); but also implicated in the variability in $P_{\text{ratio}}$ are internal factors which have been postulated to confer biological variability, and which hence determine the partitioning characteristic (Pc) of the individual. According to Payne & Dugdale (1977), the existence of such an internal (autoregulatory) control of energy-partitioning between protein and fat, which they stipulate is highly variable between individuals, but constant within the same individual, is central to the regulation of body weight and body composition. A conceptual representation of Pc during starvation, and its distinction from $P_{\text{ratio}}$, is presented in Fig. 1. The present paper addresses the subject of partitioning between protein and fat strictly in the context of body composition regulation in response to starvation in the adult human subject, and from a standpoint of normal physiology, such that concepts and their integrations are based primarily on the response of healthy individuals to starvation.

**Testing the notion of inter- and intra-individual variability in $P_{\text{ratio}}$**

By re-analysing data on prolonged fasting (total starvation) conducted earlier this century in normal-weight men, Henry et al. (1988) were able to demonstrate that the partitioning between protein and fat is indeed an individual characteristic on the basis that the $P_{\text{ratio}}$ remained relatively constant within the individual during the course of the fast, but varied considerably among individuals. For the calculation of $P_{\text{ratio}}$, advantage was taken of the fact that during fasting, since no food was eaten and physical activity was minimal, the amount of protein mobilized could be calculated from 24 h urinary N losses, and the total 24 h energy loss taken to be equal to the BMR. The data in Fig. 2 are from the fasting subject studied by Benedict (1915), and they illustrate the marked contrast between the constancy of the $P_{\text{ratio}}$ and the continuous variation of both N loss and BMR which have decreased by more than 25% at the end of the fast. The $P_{\text{ratio}}$ value of 0.187 indicates that on the third day and thereafter, approximately 19% of the energy loss from this subject’s body tissues was derived from protein catabolism. Using the same approach for calculating the $P_{\text{ratio}}$ in nine other healthy normal-weight individuals subjected to prolonged fasting, Henry et al. (1988) found that the results paralleled those obtained from Benedict’s (1915) data in that the $P_{\text{ratio}}$, after a few days following the onset of fasting, remained relatively constant during the course of the fast within a given individual, but was variable from one individual to another. These studies therefore clearly demonstrate inter-individual variability, but intra-individual constancy, in the pattern of lean and fat tissue mobilization, albeit during prolonged fasting in normal-weight men.

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**Fig. 1.** Inside the black box of body energy-partitioning during starvation. Schematic diagram encapsulating the concept of an individual’s partitioning characteristic (Pc) between the two main energy compartments of the body (protein and fat), and the distinction between Pc and the fraction of energy mobilized as protein ($P_{\text{ratio}}$) during the course of starvation. In a given adult individual, the Pc is assumed to be a constant, independent of time, whereas the $P_{\text{ratio}}$ reflects the integrated outcome of the Pc and other internal perturbations (e.g. protein sparing during early starvation) or external perturbations (e.g. extremes of physical activity, dietary composition); the curved arrows from within or from outside the black box represent the internal (I) and external (E) perturbations respectively. The two body compartments (protein and fat) are strictly energetic compartments, and refer to the protein-energy compartment (including protein in adipose tissues) and the fat-energy compartment (including lipids in lean tissues such as intramuscular lipids, and membrane lipids). Each of these two compartments is divided into an indispensible component (represented by the filled fraction of the compartment box) and a dispensible component which is conceptualized as the fraction of the compartment that can be lost without irreversible or lethal consequences. Note: (a) In their paper, Payne & Dugdale (1977) refer to the Pc of the individual as $P_{\text{ratio}}$. This has led to a debate regarding the validity of assuming intra-individual constancy of $P_{\text{ratio}}$ since the $P_{\text{ratio}}$ (defined as the fraction of energy mobilized as protein) of a given individual can clearly vary during starvation (Dulloo, 1998; Henry et al. 1998; Millward & Wijesinghe, 1998). However, Payne & Dugdale (1977) were describing a computer simulation of energy-partitioning (presumably in the absence of external or internal perturbations on the control of partitioning) and in that context their reference to $P_{\text{ratio}}$ could be equated with Pc depicted in this diagram. (b) In the present state of knowledge, however, it is not known whether the Pc of the individual is entirely genetically determined, whether it is entirely the result of previous exposure to external factors, or whether the phenotypic expression of the Pc is a combination of genetic predisposition and previous exposure to external factors. (c) The representation of the body compartments in this diagram (strictly in energetic terms as mentioned earlier) also differs from the Payne–Dugdale model for changes in energy balance and body weight, in which the body is divided into four ‘mass’ rather than ‘energy’ compartments as follows: tissue fat store (e.g. adipose storage), structural fat tissue (e.g. in cell wall and cytoplasm), the fast lean tissue (e.g. visceral organs) and slow lean tissue (e.g. skeletal muscle).
and hence support the hypothesis of Payne & Dugdale (1977) that the control of partitioning is an individual characteristic.

To gain further insights into the biological significance of these concepts in body composition regulation during food deprivation and refeeding, we (Dulloo et al. 1996) recently tested the concepts of inter-individual variability and intra-individual constancy of energy-partitioning by re-visiting the classic Minnesota experiment (Keys et al. 1950), a unique longitudinal study of semi-starvation and refeeding which has a reputation for being meticulous in detail, and conducted under tightly controlled conditions of diet and lifestyle. From the individual data on changes in body fat and fat-free mass (FFM) in the thirty-two men in the Minnesota study, we calculated the fraction of body energy either lost as protein during semi-starvation or deposited as protein during refeeding, i.e. an integrated $P_{\text{ratio}}$, using the equation:

$$P_{\text{ratio}} = \frac{1}{1 + \alpha \times \frac{\Delta \text{FAT}}{\Delta \text{FFM}}}$$  \hspace{1cm} (1)

where $\Delta \text{FAT}$: $\Delta$FFM is the ratio of changes in fat mass and FFM, and where $\alpha = 9.05$, the ratio of energy equivalents for fat mass (38.9 MJ/kg) and FFM (4.3 MJ/kg); the proportion of protein in FFM is taken as 23% (Forbes et al. 1953, 1956) and the energy density for endogenous protein is taken as 18.6 MJ/kg (Livesey & Elia, 1988).

Within this population of thirty-two young Caucasian men, the $P_{\text{ratio}}$ values were found to be highly variable during both semi-starvation and refeeding. Although the $P_{\text{ratio}}$ during refeeding was found to be lower than the $P_{\text{ratio}}$ during semi-starvation, they were nonetheless strongly correlated. By applying both statistical and numerical approaches to these data on $P_{\text{ratio}}$ assessed during two phases of weight change (loss and recovery), we were able to show that the lower $P_{\text{ratio}}$ during refeeding is not due to a shift in the individual’s $P_{\text{c}}$, but can be attributed to other mechanisms operating via the suppression of thermogenesis in response to severe fat depletion, with the energy thus conserved being directed specifically towards accelerating fat (and not protein) recovery (Dulloo et al. 1996). While this finding that the $P_{\text{c}}$ of the Minnesota men during semi-starvation was conserved during refeeding also supports the Payne & Dugdale (1977) hypothesis that the partitioning between protein and fat is a characteristic of the individual, it also argues against their stipulation that the $P_{\text{ratio}}$ during refeeding must be equal to the $P_{\text{ratio}}$ during starvation (Dulloo, 1998). Based on our reanalysis of the Minnesota experiment, it is clear that the notion of intra-individual constancy in fuel partitioning is valid only if, as shown schematically in Fig. 1, a distinction is made between: (a) the control of partitioning between protein and fat, which refers to a control system that underlies the $P_{\text{c}}$ of the individual, and (b) the $P_{\text{ratio}}$, which, defined as the fraction of energy mobilized or deposited as protein, refers to the integrated outcome of several control systems (the control of partitioning being only one) that operate to regulate body composition. Taken together, these findings from these classic human studies of prolonged fasting and semi-starvation–refeeding, therefore lend support to the notions of inter-individual variability and intra-individual constancy within the context of an autoregulatory control of energy-partitioning between protein and fat.

**Initial adiposity as a determinant of inter-individual variability in $P_{\text{ratio}}$**

From a historical perspective, it has long been known that the $P_{\text{ratio}}$ during starvation is influenced by the pre-starvation level of adiposity. As Elia (1991) reminded us in his elaborate review on the effect of starvation on protein–energy interrelationships, an inverse association between the contribution of protein as fuel during starvation and the initial degree of fatness was observed from inter-species studies nearly a century ago, notably by Voit (1901). However, interest in the nature and functional importance of this relationship in human subjects is relatively recent. First, on the basis of a meta-analysis of data on the composition of weight loss in lean and obese patients on low-energy diets, Forbes (1987) reported an inverse curvilinear relationship between the proportion of weight loss as FFM and the initial fat content. A number of other workers have added more data points to the original set analysed by Forbes, and they have confirmed the curvilinear form of this relationship, whether the proportion of weight loss as FFM is plotted against total body fat (Prentice et al. 1991) or against the BMI (Ferro-Luzzi et al. 1994). Second, in their re-analysis of human studies of prolonged fasting, Henry et al. (1988) reported that the fasting $P_{\text{ratio}}$ declines in an approximately linear manner with increasing adiposity. However, in his critical review on this topic, Elia (1991) pointed out that the greatest changes in fasting $P_{\text{ratio}}$ occur when the variations in BMI (or in estimated initial percentage fat) are at the lower end of the scale, and argued that the relationship is indeed curvilinear on the basis of these experimental data, as well as from

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**Fig. 2.** Diagram showing the relative constancy of the fraction of energy mobilized from protein ($P_{\text{ratio}}$) during the course of fasting in the subject (Mr Levanzin) studied by Benedict (1915). Between day 4 and day 31 of the fast the mean and standard deviation of the $P_{\text{ratio}}$ in this subject was 0.187 and 0.013. Data are reproduced from Henry et al. (1988); see p. 340.
theoretical considerations. Third, in an attempt to identify statistically the predictors of inter-individual variability in energy-partitioning among the men in the Minnesota experiment, we correlated the $P_{\text{ratio}}$ of the Minnesota men during semi-starvation against all available data on their physical characteristics during the baseline (pre-starvation) period, including height, sitting height, coinetic index (sitting height/height), body weight, BMI, fat, FFM, percentage fat, abdominal circumference, arm circumference and age. Several of these variables were correlated with the $P_{\text{ratio}}$ but in a stepwise regression analysis the initial percentage fat was the only predictor of the $P_{\text{ratio}}$ that remained, while other predictors (including the next best correlate, total fat) dropped out (Dulloo et al. 1996). As shown in Fig. 3, the relationship between the initial percentage fat ($FAT_0$) and the $P_{\text{ratio}}$ during semi-starvation is an inverse exponential, with an $r^2$ value of 0.71, suggesting that about 70% of the variation of $P_{\text{ratio}}$ could be explained by the variation in percentage fat before food deprivation in this population sample.

**Limitations of meta-analyses for studying ‘biological’ variability in $P_{\text{ratio}}$**

In a previous attempt to find out whether the strength of the relationship between initial adiposity and the $P_{\text{ratio}}$ would improve further if we included data from individuals with higher percentage fat in the regression analysis, we pooled the Minnesota data based on normal-weight Caucasian subjects with those derived from obese Caucasian subjects who also underwent prolonged semi-starvation (Passmore et al. 1958; Strong et al. 1958) or total starvation (Henry et al. 1988), and for whom we estimated pre-starvation percentage fat values on the basis of weight, height and age using the algorithm of Heitmann (1990). The correlation coefficient for such a meta-analysis was reported to be an ‘improvement’ over that based entirely on the Minnesota data ($r^2$ 0.84 v. $r^2$ 0.7) (Dulloo et al. 1996; Dulloo 1997). However, we were made to realize, retrospectively, by statistician colleagues, that since the distribution of data constituted two distinct clusters, with the Minnesota data in the range 6–25% fat and the obese data in the range 35–55% fat, the gap in data distribution (between 25 and 35% fat) introduces a statistical error which will tend to increase the correlation coefficient (Armitage & Berry, 1987). In other words, the ‘improvement’ in the regression coefficient in our meta-analysis may be interpreted as a statistical artifact. Furthermore, in meta-analyses of data from studies of partial and/or total starvation reported so far (Forbes, 1987; Henry et al. 1988; Elia, 1991; Prentice et al. 1991; Ferro-Luzzi et al. 1994; Dulloo et al. 1996) the importance of initial adiposity per se as a determinant of biological variability in $P_{\text{ratio}}$ is confounded by several variables inherent in such meta-analyses, such as sex, age, ethnicity, diet composition, degree and duration of starvation, exercise levels, types of obesity (variable abnormalities in metabolic and endocrine profiles), and by large errors in the estimation of percentage body fat from equations based on weight and height, or in the use of different methodologies in the measurement of body fat.

**Validity of the Minnesota data for studying ‘biological’ variability in $P_{\text{ratio}}$**

By contrast, the analysis of the Minnesota experiment in its own right, by virtue of its design vis-à-vis selection criteria of subjects (on the basis of physical, clinical, biochemical and psychological tests), more controlled conditions of diet and lifestyle before and during the experiment, and with body fat being measured (by hydrodensitometry) rather than estimated, bypasses many of these previously-mentioned limitations. For example, the thirty-two individuals (all Caucasians, men, and of similar age) were subjected simultaneously under the same environmental (laboratory) conditions, and measurements of body composition were made using the same methodology. They were subjected to the same semi-starvation diet, and lost approximately 25% of initial body weight over same time period (i.e. same starvation stress). Their day-to-day pattern of physical activity was controlled for the most part of the study, and no one among the Minnesota men was subjected to the type of intense physical activity or resistance training that would provide any major anabolic drive on muscle mass. Furthermore, the subjects were semi-starved (and not fasted) and consumed a balanced restricted diet with the carbohydrate level either adequate or nearly adequate vis-à-vis the obligatory glucose requirements of the brain and other vital tissues, such that the protein-sparing associated with the brain’s shift in fuel utilization partially towards ketone bodies was likely to be minimal and of short duration. It may still be argued that this analysis of the Minnesota data is limited by lack of individuals with higher percentage fat, and hence by a wider range of adiposity for the purpose of regression analysis. However, this ‘limitation’ needs to be weighed against the fact that the inclusion of overtly obese individuals in such an analysis would also have increased the risk for blurring our understanding of normal physiology of body composition regulation with pathophysiological conditions associated with more marked obesity, such as insulin resistance, and other disturbances in metabolic–endocrine profiles. Since in the present paper, the autoregulatory control of energy partitioning is examined first and foremost from a standpoint of normal physiology, we take the view that the population sample of healthy men in the Minnesota experiment, with a normal distribution of percentage body fat ranging from the very lean (6% fat) to the mildly obese (25% fat) provides a sufficiently large (4-fold) variability in initial adiposity for this purpose, particularly when it is within this range of 6–25% body fat that much of the steep part of the exponential curve between initial adiposity and the $P_{\text{ratio}}$ lies (Fig. 3). Bearing in mind the well-controlled and similar experimental conditions of diet and lifestyle to which the thirty-two men in the Minnesota study were exposed, it is likely that the large inter-individual variability in $P_{\text{ratio}}$ observed during the semi-starvation phase of the Minnesota experiment reflects essentially ‘biological’ variability in $P_{\text{ratio}}$. In this context, the reanalysis of its data underlines the critical importance of initial percentage fat as an internal determinant of human variability in fuel partitioning during starvation.
Fundamental questions

There are, however, two fundamental questions that arise from the relationship between initial percentage fat and $P_{\text{ratio}}$ shown in Fig. 3.

(i) In the context of the present paper whereby the partitioning between protein and fat is viewed to be under an autoregulatory control system of central importance in regulating body composition, and the well-known association between the initial percentage fat and the duration of starvation (hence the length of survival) (Elia, 1991), the challenge resides in providing a mechanistic explanation for the way the initial percentage fat, via the control of energy partitioning between protein and fat, confers maximal survival autonomy during food scarcity. In other words, what could be the biological significance (in terms of survival value) of this strong relationship between initial percentage fat and the $P_{\text{ratio}}$ shown in Fig. 3?

(ii) It is also clear from Fig. 3 that the initial percentage fat does not explain all the variance in $P_{\text{ratio}}$. For a given initial percentage fat value, there is still a 2-fold variability in the $P_{\text{ratio}}$, and the residual variance after adjustment for variability in the initial percentage fat ($sd = 0.044$) is still about half of the total variance in $P_{\text{ratio}}$ ($sd = 0.082$). In other words, the initial percentage fat explains only about half of the total variance in $P_{\text{ratio}}$

Fig. 3. Exponential relationship between the fraction of energy lost as protein during semi-starvation ($P_{\text{ratio}}$) and the initial percentage body fat ($\text{FAT}_0$) in the Minnesota experiment ($n = 32$) (Keys et al. 1950). The data for initial body fat (range 6–25 %) follow a normal distribution, with an almost 3-fold variability between the 10th percentile value (7.4 %) and the 90th percentile value (20.5 %), and with the 50th percentile (median) value being 13.7 %. For the regression ($n = 32$, $r^2 = 0.6$, $P < 0.001$), the 95 % CI are within the inner dotted lines, whereas the predictive intervals are within the outer broken lines. Only one data point (C) lies well outside the prediction lines, and it has been omitted in subsequent analyses; its omission in the regression analysis improves the $r^2$ from 0.6 to 0.7 ($P < 0.001$). The data for $P_{\text{ratio}}$ have been calculated using equation 1 (see p. 341) from the Minnesota experiment data on body fat and fat-free mass, corrected for excess hydration and for the relative bone mass at the end of semi-starvation on the basis of formula derived on a sub-group of the Minnesota men ($n = 17$) in whom extracellular fluid space was determined by the thiocyanate dilution technique (Keys et al. 1950). The exponential fit was performed using the computer software Peakfit Version 2.0 (Jandel Scientific Software, San Rafael, CA, USA).

Quantitative analysis of the relationship between initial percentage fat and $P_{\text{ratio}}$

The basic concepts and assumptions underlying this analysis (as discussed in detail earlier) are that (i) the Pc of the individual is a constant, independent of time during starvation, and that (ii) in the Minnesota experiment, the integrated $P_{\text{ratio}}$ during semi-starvation is a proxy of the Pc of the individual, given that the design of this unique study was such that internal or external perturbations on the fat and/or protein compartments were likely to be absent or of negligible quantitative importance when integrated over the 24-week study period.

Relationship between initial body composition and the composition of weight loss

Specifically, we have explored how the $P_{\text{ratio}}$ and the initial percentage fat of the Minnesota men (in Fig. 3) are related quantitatively by expressing both the independent and the dependent variables in the same form, i.e. in terms of fat and FFM, corrected for excess hydration and relative bone mass (Keys et al. 1950). Using equations 2 and 3, the $P_{\text{ratio}}$ is converted into a ratio of the loss in body fat to that in FFM, i.e.
as $\Delta\text{FAT} : \Delta\text{FFM}$, while the initial percentage fat is converted into a ratio of initial fat to that of FFM, i.e. as $\text{FAT}_0 : \text{FFM}_0$.

$$\frac{\Delta\text{FAT}}{\Delta\text{FFM}} = \frac{1}{\alpha} \times \left( \frac{1}{\text{P}_{\text{ratio}}} - 1 \right),$$

$$\frac{\text{FAT}_0}{\text{FFM}_0} = \frac{\%\text{FAT}_0}{(100 - \%\text{FAT}_0)},$$

where $\%\text{FAT}_0$ is the initial percentage body fat, and $W_0$ is the initial body weight.

A plot of the composition of weight loss ($\Delta\text{FAT} : \Delta\text{FFM}$) against the initial body composition ($\text{FAT}_0 : \text{FFM}_0$) is presented in Fig. 4, and shows that (i) all the data points lie above the line of identity and (ii) the relationship between $\Delta\text{FAT} : \Delta\text{FFM}$ and $\text{FAT}_0 : \text{FFM}_0$ is linear. The 95 % confidence and predictive intervals of this relationship are shown in Fig. 4, and the statistics for the regression model are provided in the legend to this figure.

**Interpreting the relationship in Fig. 4**

If it is accepted that the energy density of the FFM lost (after correction for excess hydration and for the relative bone mass) is close to the energy density of the initial FFM, then the following statements can be made:

(i) the fact that the data points do not lie on the line of
identity suggests that the composition of the weight lost ($\Delta$FAT : $\Delta$FFM$_0$) is not equal to the initial body composition (FAT$_0$ : FFM$_0$):

(ii) the position of the data points well above the line of orientation illustrates the fact that the proportion of fat to protein mobilized ($\Delta$FAT : $\Delta$FFM) during food deprivation is greater than the proportion of fat to protein present in the body before food deprivation (FAT$_0$ : FFM$_0$);

(iii) the linearity of this relationship underlies the fact that the ratio of these two proportions (the slope), being a constant, is independent of the initial degree of adiposity of the individuals in this population sample.

Based on the assumptions (discussed earlier) that for each of the Minnesota men, the ratio $\Delta$FAT : $\Delta$FFM calculated over the 24 weeks of semi-starvation represents the outcome of a control system underlying his Pc, and that the latter remains a constant over time during food deprivation, then by extrapolation, these derivations from Fig. 4 would imply that:

(i) since as indicated in the first two derivations above, i.e. $\Delta$FAT : $\Delta$FFM > FAT$_0$ : FFM$_0$, the body composition of a given individual changes continuously towards a leaner composition during the course of starvation. In other words, if the body composition at a given time (t) during starvation is FAT$_t$ : FFM$_t$, then as weight is being lost with time, the ratio FAT$_t$ : FFM$_t$ decreases relative to the initial ratio FAT$_0$ : FFM$_0$, and consequently, the fat compartment is virtually depleted well before that of the protein (FFM) compartment. Such a contention is supported by autopsy findings indicating that in human subjects who died of ‘uncomplicated’ starvation, the fat depots are virtually absent whereas the loss in fresh organs (i.e. lean tissue mass) is less than 50 % (Meyers, 1917; Keys et al. 1950; Elia, 1991), and

(ii) the fraction of protein compartment lost when the fat compartment is virtually depleted may be independent of the initial body composition (FAT$_0$ : FFM$_0$) or initial percentage body fat, a contention that can be shown mathematically in two steps as outlined here.

Step I. Since the value of the intercept in the relationship between $\Delta$FAT : $\Delta$FFM against FAT$_0$ : FFM$_0$ in Fig. 4 is not significantly different from 0 (see legend for statistics), the regression line is assumed to pass through zero. Although the statistical analysis supports a null hypothesis about the intercept, i.e. the intercept is not significantly different from zero, this does not, however, demonstrate that the intercept is zero. Consequently, one could entertain the possibility for this set of data (and other data sets) that the intercept may not be zero. If the alternative assumption (that the intercept is not zero) is put forward, then equation 5 will have to be rewritten as follows:

$$\frac{\Delta$FFM$_{zeroFAT}}{FFM_0} = \frac{1}{m}$$ (5)

where $a$ is the value for the intercept.

If for the present set of data, the value of $a$ is taken as 0.078 (SD 0.055) ($P = 0.16$, NS) and the slope $m$ as 2.29 (as indicated in the legend to Fig. 4), and if the FFM$_0$ : FAT$_0$ value for human adults is taken as ranging from 3 (30 % body fat) to 12 (5 % body fat), then this version of equation 5 indicates that values for the ratio $\Delta$FFM$_{zeroFAT}$ : FFM$_0$ would correspondingly range over about 30 %. If the value of the intercept is taken to be that for the upper confidence limit of the estimation (i.e. 0.18), then the corresponding range of $\Delta$FFM$_{zeroFAT}$ : FFM$_0$ would be 40 %.

On the other hand, if (as also indicated in the legend to Fig. 4) the two possible outliers are omitted in the analysis, in which case the value of $a$ is −0.033 (SD 0.034) ($P = 0.33$, NS), with an upper confidence limit of 0.035 and the slope $m$ is 3.15, then for the same range of FFM$_0$ : FAT$_0$ values for human adults (i.e. 3–12), the corresponding range for $\Delta$FFM$_{zeroFAT}$ : FFM$_0$ values would vary between 8 and 10 %. Thus, on the basis of the values of the intercept of this data set, when the body fat is virtually depleted, the fraction of FFM lost could vary by as much as 30–40 % depending on the initial body composition, or by as little as 8–10 %. In the present state of knowledge, one cannot safely accept nor reject any one of the possibilities that the actual value for the intercept is zero, 0.078 or −0.033 in this set of data, let alone to make the much wider assessment for all other data sets (i.e. in a general model). However, the principle of parsimony in modelling, coupled with statistical analysis indicating that the intercept is not significantly different from zero, guides us to choose the assumption (or to hypothesize) that the intercept is zero in the construction of our model. If future evidence suggests otherwise, then the model will have to be adapted to take into account the new parameters, whose biological significance would then need to be studied.
Concepts underlying optimal utilization of two energy reserves

On the basis of these new findings from the Minnesota data, coupled with autopsy findings that the fat depots are virtually absent in human subjects who have died of uncomplicated starvation (Meyers, 1917; Keys et al. 1950; Elia, 1991), we describe here the process of 'concept building' that provides possible explanations concerning the biological significance of (a) the relationship between initial percentage fat and the $R_p$ ratio in Fig. 3, and (b) the residual variability in this relationship.

Concept I

By virtue of its independence from the initial body composition, this value $1/m$, the fraction of FFM lost when fat mass is virtually depleted (in equation 5), could thus represent a critical threshold in the amount of protein that can be mobilized without irreversible or lethal consequences, and hence considered to represent the fraction of the total protein compartment that is 'dispensable'. In this context, it represents the fraction of the total protein compartment that functions as an energy reserve. This 'protein-reserve' fraction ($r_p$) can be described as:

$$r_p = \frac{\Delta \text{FFM}_R}{\text{FFM}_0},$$

where $\Delta \text{FFM}_R$ is the protein-reserve component of the total protein compartment $\text{FFM}_0$.

By analogy, there is a component in the fat compartment that is indispensible for life (e.g. membrane phospholipids, brain and nerve lipids). The fraction of the fat compartment that is 'dispensable' (essentially stored triacylglycerols) is hence considered as the fraction of the total fat compartment that functions as an energy reserve. This 'fat-reserve' ($r_f$) fraction can be described as follows:

$$r_f = \frac{\Delta \text{FAT}_R}{\text{FAT}_0},$$

where $\Delta \text{FAT}_R$ is the fat-reserve component of the total fat compartment $\text{FAT}_0$.

From a historical perspective, the concept of 'dispensable' and 'indispensable' components of FFM and/or fat compartments is not new, and their origins can be traced to the era soon after Voit's experiments on starving animals (Keys et al. 1950). In more recent decades, they have frequently been used in one form or another in the construction of models of starvation, notably by Payne & Dugdale (1977), Le Maho et al. (1988) and Elia (1991). However, the mathematical articulation of these concepts, as described earlier, is new. Although the body's fat and protein-energy compartments in these equations are denoted by fat mass and FFM by necessity of the data available, it needs to be emphasized that conceptually, the protein-energy compartment comprises protein in all tissues (including adipose tissues), and the fat-energy compartment comprises lipids in all tissues (including inter-muscular triacylglycerol stores, and membrane lipids).

Inter-individual variability in $r_p$, in $r_f$ or in both these two reserve fractions could explain the residual variance in the relationship between $R_p$ and initial percentage fat. Similar concepts can also be traced from the work of Le Maho et al. (1988) and Elia (1991).

A mathematical model of energy-partitioning during starvation

By integrating these concepts of dual energy reserves emptying simultaneously during starvation (i.e. the protein-reserve compartment, $\Delta \text{FFM}_R$, reaching total depletion at the same time as the fat-reserve compartment, $\Delta \text{FAT}_R$) into the
calculations of the $P_{ratio}$ i.e. by replacing $\Delta$FFM and $\Delta$FAT in equation 1 by $\Delta$FFM$_R$ ($=r_p \times$FFM$_0$) from equation 6 and by $\Delta$FAT$_R$ ($=r_f \times$FAT$_0$) from equation 7 respectively, we obtain a general equation that defines the theoretical Pc of an individual as follows:

$$Pc = \frac{1}{1 + \frac{r_f \times \%FAT_0}{r_p \times \%FAT_0}}.$$  \hspace{2cm} (8)

Using equation 3, equation 8 becomes:

$$Pc = \frac{1}{1 + \frac{r_f \times \%FAT_0}{r_p \times (100 - \%FAT_0)}}.$$  \hspace{2cm} (9)

or

$$Pc = \frac{100 - \%FAT_0}{100 - \left(1 - \frac{r_f \times \%FAT_0}{r_p \times \%FAT_0}\right)}.$$  \hspace{2cm} (10)

where $r_f : r_p$ is the ratio of the fat and FFM energy-reserve fractions.

This model can be used to study inter-individual variability in Pc, by varying the initial percentage body fat and the ratio $r_f : r_p$, i.e. the three factors which together confer the Pc of the individual. This is illustrated in Fig. 5, where the value of $\alpha \times r_f : r_p$ has been varied between 15 and 40 (corresponding to $r_f : r_p$ values between 1-66 and 4-42). It is also shown in Fig. 6 that the model, with an $\alpha \times r_f : r_p$ value of 25-4 (corresponding to an $r_f : r_p$ value of 2-8), produces a best fit which is superimposable to the exponential curve previously obtained for the relationship between $P_{ratio}$ and initial percentage fat among the Minnesota men in Fig. 3. As a whole, this model provides a tool which can be used to study inter-individual variability in fuel partitioning in response to starvation. It can in fact be used to examine the relative importance of each of these variables in determining the Pc of the individual in the Minnesota experiment. This first application of the model, together with several others, is described now.

Applications of the model

I. Relative importance of $r_p$ and $r_f$ as determinants of variability in partitioning characteristic

This mathematical model of partitioning thus embodies not only the concept that the Pc of the individual during starvation is determined by the pre-starvation ratio fat: protein compartments ($\%FAT_0$), but also the new concepts of a dual energy-reserve ($r_f : r_p$) emptying simultaneously. However, it can be shown in steps 1–4 here that variability in the fat reserve fraction ($r_f$) is essentially also a function of $\%FAT_0$, such that inter-individual variability in Pc is determined only by variability in $\%FAT_0$ and in $r_p$, i.e. in the initial percentage fat and in the protein-reserve fraction.

Step 1. It can be assumed that the ‘indispensable’ fat component is practically independent of body size and body composition in the adult human being, since it is constituted (a) from the brain whose size (and hence lipid content) is independent of body size in the adult man, and (b) from structural lipids in nerves and cell membranes whose

![Fig. 5. Model prediction for the partitioning characteristic (Pc) as a function of initial percentage body fat (%FAT$_0$), with variable values for the ratio fat-reserve fraction:protein reserve fraction $(r_f : r_p)$ using equation 10 (see above). The theoretical Pc (solid curves) are superimposed over the data for fraction of energy mobilized as protein ($P_{ratio}$) of the Minnesota men (Keys et al. 1950), and share the same Y-axis. Note that the $P_{ratio}$ data of the Minnesota men are found within theoretical Pc curves generated from $\alpha \times r_f : r_p$ values between 15 and 40, with $\alpha = 9.05$ (this corresponds to $r_f : r_p$ values in the range of 1.66–4.42).](https://www.cambridge.org/core/terms.https://doi.org/10.1017/S0007114599001580)
Variation with body size is likely to be quantitatively small. Consequently, the absolute amount of fat that is indispensable (non-reserve fat) can be considered to be a constant in such a population sample.

**Step 2.** Based on autopsy studies reporting that in men who died of starvation, the fat depots are virtually absent (Meyers, 1917; Keys et al., 1950), and that the remaining non-reserve fat is approximately 1 kg (Elia, 1991), the fat-reserve ($\Delta$FAT) and fat reserve fraction ($r_f$) in the Minnesota men can therefore be described as:

$$\Delta\text{FAT}_R = \text{FAT}_0 - 1,$$

$$r_f = \frac{\text{FAT}_0 - 1}{\text{FAT}_0}. \quad (11)$$

**Step 3.** Equation 11 shows that $r_f$ is a function of $\text{FAT}_0$, but given the very strong correlation between $\%\text{FAT}_0$ and $\text{FAT}_0$ (in the Minnesota men, $r \times 0.98$), $r_f$ is thus a function of $\%\text{FAT}_0$.

**Step 4.** Since the variability in $r_f$ is essentially reflected in the variability in $\%\text{FAT}_0$, it follows that the Pc has only two determinants: $\%\text{FAT}_0$ and $r_p$, namely:

$$P_c = f \left( \frac{1}{\%\text{FAT}_0}, r_p \right). \quad (12)$$

Thus the model, via equations 10 and 12, helps to explain the plausibility of the importance for $r_p$ in the residual variance in the relationship between $P_{\text{ratio}}$ and initial percentage fat (Fig. 3). It predicts that individuals with the highest $P_{\text{ratio}}$ values are those with low initial percentage fat and high $r_p$ (i.e., lean individuals with a large protein-reserve fraction), whereas individuals with the lowest $P_{\text{ratio}}$ values are those with high initial percentage fat and low $r_p$ (i.e., obese individuals with a small protein-reserve fraction). Furthermore, the model suggests that the contribution of $r_p$ to the variability in $P_c$ is equally as important as that of the initial percentage fat. For example, if either $\%\text{FAT}_0$ or $r_p$ is increased by 2-fold in equation 10, the same variation in $P_c$ is obtained.

Since $r_f$ values of the Minnesota men can now be estimated using equation 11, their $r_p$ values can be calculated from the ratio $r_f:r_p$, which in turn can be determined by applying the model (equation 10) to the data on $P_{\text{ratio}}$ and initial percentage fat. This is shown here.

**Step 1:**

$$r_f = 1 - \frac{1}{\%\text{FAT}_0}.$$
Step 2:  
\[ P_{\text{ratio}} = \frac{1}{1 + \alpha \times \frac{\Delta \text{FAT}}{\Delta \text{FFM}}} \]  

Step 3:  
\[ r_p = \alpha \times r_t \times \frac{\% \text{FAT}_0}{(100 - \% \text{FAT}_0)} \left( \frac{1}{P_{\text{ratio}}} - 1 \right) \]  

The frequency distributions of values obtained for \( r_t : r_p \) as well as for \( r_p \) and \( r_t \) are presented as histograms in Fig. 7, and each is compared with a normal distribution. Despite the apparent skewness of \( r_p \) and perhaps \( r_t \) also, application of statistical test reveals that all three parameters \( (r_t : r_p, r_p, r_t) \) could conform to a normal distribution (details of statistical test in the legend). The range of \( r_p \) for data points with 2SD of the mean is found to be between 0.13 and 0.53, and the \( r_p \) values corresponding to the 10th to 90th percentiles are 0.24 and 0.45 respectively. This large (at least 2-fold) variability in \( r_p \) contrasts with the much smaller variability (\(<25\%\) in \( r_t \), and even if the absolute amount of non-reserve fat was made to vary by 50\%, the variability in \( r_p \) would still be several-fold larger than in \( r_t \).  

II. Limits of the partitioning characteristic in a population of normal-weight individuals  

The range of \( r_t : r_p \) for data points with 2SD of the mean of the normal distribution curve is found to be between 1.6 and 4.0 (Fig. 7), suggesting that there is a 2.5-fold variability in \( r_t : r_p \) for the range covering 95\% of this population sample based on individuals of normal body weight. The curves of \( P_c \) predicted by the model for this range of \( r_t : r_p \) (variability essentially in \( r_p \)) are shown in Fig. 8, and could be considered to cover variability in \( P_{\text{ratio}} \) as a function of initial percentage fat for normal-weight men in general. At a given percentage fat in the zone of individuals with normal body weight and percentage fat, there is a 2-fold variability in \( P_c \).  

III. Extrapolation of the limits of the partitioning characteristic to a population of obese individuals  

By extrapolation of these curves (which are based on the values for \( r_t : r_p \) derived from a sample population of normal body weight) to greater values for percentage body fat (Fig. 8), it is found that the range of theoretical \( P_c \) predicted...
by the model for the obese covers the actual P ratio values determined in obese individuals in the zone of relative stability of their P ratio, i.e. as discussed later, several weeks after the start of semi-starvation (Passmore et al. 1958; Strong et al. 1958) or total starvation (Ashley & Whyte, 1961; Gilder et al. 1967a, b; Owen et al. 1967). It is of interest to note from these predictive curves that individuals with initial percentage fat > 35 fall on a relatively flat part of the exponential curve, such that in such obese individuals, variability in P ratio is independent of initial percentage body fat, and hence simply due to variability in r_p.

IV. Partitioning characteristic and human variability in protein sparing

The concepts underlying the model of energy-partitioning have implications concerning human variability in the protein-sparing effect during the early phase of starvation, a phenomenon well described since the turn of the century by Benedict (1915), and whose biochemical and hormonal basis was laid down by Cahill and his collaborators in the late 1960’s (Cahill, 1970). Since the fundamental assumption in this mathematical model is that the Pc of a given individual is stable over time during starvation, this would imply that in obese individuals, the partitioning mechanisms underlying their low Pc would be unable to provide sufficient protein as a substrate for gluconeogenesis and hence to meet their obligatory glucose requirements during the early phase of fasting as the glycogen stores become depleted. As the model predicts in Fig. 9, individuals with body fat > 30% would show a marked energy deficit between the brain’s energy requirements (horizontal shaded zone) and the amount of energy derived from protein, entirely on the basis of the Pc (referred to as Δprotein-Pc), with the deficit being greater with lower values for r_p. Consequently, other mechanisms that

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**Fig. 9.** Model prediction of the amount of energy that can be derived from protein mobilization entirely on the basis of the theoretical partitioning characteristic (Pc) of the individual (Δprotein-Pc) plotted as a function of the initial percentage body fat (%FAT_0). The calculations are based on data of BMR and percentage body fat of the Minnesota men (Keys et al. 1950) during the control (prestarvation) period, and the Δprotein-Pc is calculated as follows. Step 1: using equation 10 of the model, a minimum Pc and a maximum Pc of each of the Minnesota men can be calculated from his initial percentage fat, and with the values of fat-reserve fraction : protein-reserve fraction (r_f : r_p) between the limits shown in Fig. 8, i.e. with a minimum r_f : r_p value of 1.6 and a maximum r_f : r_p value of 4.0, i.e. 2SD below and above the mean r_f : r_p value obtained from Fig. 7. Step 2: since Pc is the fraction of energy mobilized from protein, and since during total starvation (zero energy intake) the total energy mobilized under sedentary conditions is close to the BMR before starvation (BMR_0), the amount of energy mobilized from protein due to Pc (referred to as Δprotein-Pc) for each of the Minnesota men can be described as: Δprotein-Pc (kJ/d) = Pc × BMR_0. Step 3: these values for Δprotein-Pc, obtained with a minimum Pc and a maximum Pc are plotted against the initial percentage fat (with an exponential fit across the data), and compared with the energy requirements for glucose-requiring tissues or organs in the absence of any adaptation in fuel requirements. This is taken as 100 g glucose/d (Sokoloff, 1960) which, taking into account the fact that some glucose is provided by glycerol (released as a result of lipolysis in adipose tissue), would correspond to the mobilization of 150 g protein/d (Frayn, 1996), i.e. approx. 2500 kJ/d. Since this threshold of about 2500 kJ/d would be lower if the overall energy requirements of the glucose-requiring tissues falls in response to starvation (unproven but not impossible), an arbitrary lower limit (about 1500 kJ/d) has also been placed in the Fig.
Fig. 10. Temporal changes in the fraction of energy mobilized as protein ($P_{\text{ratio}}$) and in body composition during the course of prolonged fasting, contrasting the relatively stable $P_{\text{ratio}}$ in lean individuals with the fall in the $P_{\text{ratio}}$ in the obese patients (over several weeks) before reaching relative stability. For lean individuals, the results are derived from data provided by Benedict (1915) and by Takahira (1925) who made sequential measurements of body weight, urinary nitrogen loss and BMR in individuals fasted for periods ranging between 12 and 31 d. Since no food was eaten and physical activity was minimal, the ratio urinary nitrogen losses : BMR is taken as a proxy for the fraction of energy lost as protein, i.e. the $P_{\text{ratio}}$, and is calculated according to the following equation:

$$P_{\text{ratio}} = \frac{\text{urinary N loss (g) \times 6.25 \times 18.6}}{\text{BMR}}$$

where 6.25 is the conversion factor for nitrogen to protein, and 18.6 is the metabolizable energy equivalent for protein (Livesey & Elia, 1988). Similar calculations of fasting $P_{\text{ratio}}$, from the data of Benedict (1915) and Takahira (1925), and the assumptions inherent in these calculations have previously been discussed by Henry (1984), Henry et al. (1988), Elia & Parkinson (1989), and Elia (1991). The data on changes in fat-free mass (FFM) are determined from the changes in protein losses (calculated from nitrogen losses), while those for body fat were calculated from the difference between body weight and FFM at various time-points during the progress of the fast. The data for one subject (no. 2) who developed fever in the Takahira (1925) fasting study were omitted in our analysis. For the obese individuals, the sequential changes in $P_{\text{ratio}}$ and in body composition are determined from the work of Gilder et al. (1967a,b) which reported sequential changes in body fat and FFM during fasting in obese patients. The $P_{\text{ratio}}$ is calculated according to equation 1 (see p. 341). Only patients who fasted continuously for more than 1 month are shown, and by this criterion, one patient (no. 2) whose period of continuous fasting never exceeded 2 weeks was omitted in our analysis. The broken (horizontal) lines correspond to the duration of preadaptation periods on a low-energy diet before the fast. Indeed, the design of this study (Gilder et al. 1967a,b) was such that the obese patients were put on a low-energy diet for periods varying between 0 and 4 weeks before the fast. It is observed that the longer this pre-fast period of adaptation (i.e. the longer the period for the brain to adapt to utilization of ketone bodies as fuel), the shorter the delay for their $P_{\text{ratio}}$ to reach relative stability and hence the shorter the period of specific protein-sparing after the onset of the fast.
specifically mobilize protein would be required to supplement the deficit in protein requirements for gluconeogenesis (Marliss et al. 1971; Marliss, 1978), and their importance would diminish as ketone bodies became part of the fuel substrate for the brain, i.e. when the brain became less dependent on glucose for its fuel needs, and hence leading to a specific sparing of protein. At the other extreme, the model predicts that lean individuals (body fat <12%), by virtue of their high Pc, have sufficient capacity to meet their brain’s glucose requirements entirely via the protein derived from the partitioning mechanism underlying their high Pc (Fig. 9). In other words, lean individuals (particularly those with high rp values) need not bring into action to any great extent the additional mechanisms that specifically mobilize protein for gluconeogenic needs, and they are hence unlikely to show any major protein-sparing effect.

These predictions can be shown to hold true, thanks to a handful of studies of prolonged fasting conducted in lean (Benedict, 1915; Takahira, 1925) and obese individuals (Gilder et al. 1967a,b) from which the data can be used to

\[ \Delta \text{WR} = \Delta \text{FFMR} + \Delta \text{FATR}, \]

where \( \Delta \text{FFMR} \) and \( \Delta \text{FATR} \) are the changes in the protein-reserve and fat-reserve compartments, respectively. Step 2: using equations 6 and 7, \( \Delta \text{FFMR} \) and \( \Delta \text{FATR} \) can be substituted so that \( \Delta \text{WR} \) can be rewritten as:

\[ \Delta \text{WR} = r_p \times \text{FFM}_0 + r_f \times \text{FAT}_0, \]

where \( r_p \) is the protein-reserve fraction, \( \text{FFM}_0 \) is the initial fat-free mass, \( r_f \) is the fat-reserve fraction and \( \text{FAT}_0 \) is the initial body fat. Step 3: using equations 3a and 3b, \( \text{FFM}_0 \) and \( \text{FAT}_0 \) in the equation above can be substituted to yield:

\[ \frac{\Delta \text{WR} (\%)}{\text{W}_0} = r_p \times (100 - \% \text{FAT}_0) + r_f \times \% \text{FAT}_0. \]

The middle line (—) is calculated with the mean value for \( r_p \) 0.33 and that for \( r_f \) 0.88, the upper line (---) with a maximum value for \( r_p \) (0.53) and for \( r_f \) (0.93), and the lower line (---) with a minimum value for \( r_p \) (0.13) and for \( r_f \) (0.83). The mean, minimum and maximum values for \( r_p \) and \( r_f \) are obtained from the mean ±2SD values shown in the histograms in Fig. 7. The star symbols (*) help to illustrate the importance of \( r_p \) in determining the percentage weight loss; in particular that the maximum percentage weight loss in a typical lean individual with a high \( r_p \) can be similar to that of an obese individual with a low \( r_p \).
calculate the temporal changes in $P_{ratio}$ during the course of the fast (Gilder et al. 1967a,b; Henry et al. 1988; Elia, 1991). As shown in Fig. 10, the $P_{ratio}$ of the lean individuals reaches relative stability within only 4–7 d after the onset of the fast, whereas the $P_{ratio}$ in obese individuals, although initially at the level found in the lean, decreases slowly to reach relative stability only several weeks later. Their slow reduction in $P_{ratio}$ and much longer delay in reaching the zone of relative stability of their $P_{ratio}$ is clearly due to a specific sparing of protein since, as shown in Fig. 10, it results from a reduction in the rate of lean tissue loss whereas the rate of fat loss is practically unchanged. In other words, the decrease in $P_{ratio}$ (protein-sparing effect) in the obese during the first few weeks of fasting is not due to a shift in the $Pc$ of the individual, but to the subsequent ‘downregulation’ of mechanisms that initially brought about the specific increase in protein mobilization (in excess of that determined by their low $Pc$) during the time-period necessary for ketone bodies to become part of the fuel substrate for the brain. In the lean, by contrast, the rapid entry into the zone of stability of their $P_{ratio}$ and hence the lack of specific protein-sparing effect during the course of starvation, implies that they meet their brain’s glucose requirements almost entirely via their high $Pc$. Coupled with the findings that $\Delta$FAT : $\Delta$FFM is greater than FAM $\Delta$FFM $\Delta$ during starvation (Fig. 4), the rapid entry into the zone of stability of the $P_{ratio}$ and hence the lack of specific protein-sparing effect during the course of starvation in the lean also implies that (a) the effectiveness of protein sparing is set at the beginning of the starvation (Le Maho et al. 1988), and that (b) the well-known reduction in the rate of urinary N loss that continues to occur during the progress of starvation is not due to a specific sparing of the body’s protein, but due to a general reduction in metabolic rate (Henry et al. 1988).

From this analysis showing differential temporal changes in $P_{ratio}$ in lean and obese individuals undergoing prolonged fasting, it can be concluded that it is the $Pc$ of the individual that determines the extent to which additional mechanisms specific for protein mobilization are recruited, the extent to which ketone bodies become fuel substrate for the brain, and hence the extent of the protein-sparing effect. Although the model predictions in Fig. 9 suggest that lean individuals with body fat $<12\%$ are likely to meet their brain energy requirements entirely on the basis of their $Pc$ irrespective of their $r_p$ and obese individuals with body fat $>30\%$ would be clearly deficit vis-à-vis brain energy requirements irrespective of their $r_p$, they also suggest that it is in individuals with body fat of intermediate values (12–30\%) that variability in $r_p$ is of critical importance in determining the brain’s energy requirements entirely on the basis of the $Pc$ of the individual, and hence the extent of subsequent protein-sparing.

V. Partitioning characteristic and variability in maximum percentage weight loss from starvation

The model can also be used to appreciate the quantitative importance of variations in the two determinants of $Pc$ (initial percentage fat and $r_p$) in determining the maximum percentage weight loss from starvation. According to the model prediction shown in the plot in Fig. 11, the percentage weight loss in a typical lean individual with a high $r_p$ can be similar to that of an obese person with a low $r_p$. The predictions of the model are not only in line with human data (Mitchell & Truswell, 1987; Elia, 1991) indicating that the mean values for maximum weight loss are 35–40\% for lean and 50–55\% for obese individuals, but they are also consistent with the large variability in maximum percentage weight loss for a given initial percentage fat on the basis of variability in $r_p$. Among those who could be classified under an initial ‘lean’ body weight are the thirty Irish hunger strikers who after 70 d total starvation (and sadly ten deaths) had a mean weight loss of 40\%, with individual values ranging between 30 and 50\% (Allison, 1992). Furthermore, losses of body weight exceeding 50\% in terminal cases of hunger-disease were observed by Jewish physicians of the Warsaw ghetto (Fliederbaum, 1979), and patients with anorexia nervosa losing up to 60\% of body weight have also been reported (Berkman et al. 1947). Among the obese, on the other hand, several cases of massive successful weight reduction beyond 60\% weight loss and up to 75\% have been reported during fasting in grossly obese patients (Bortz et al. 1967; McFarlan, 1991), and documented by Elia (1991).

Concluding remarks and perspectives

The focus in the present paper that the $Pc$ of the individual during starvation is determined not only by the pre-starvation ratio fat:protein compartments (FAT $\Delta$FFM), but also by the ratio of the two energy-reserve fractions ($r_f : r_p$), coupled with our previous demonstration from the Minnesota data that the $Pc$ of the individual during starvation is conserved during refeeding (Dulloo et al. 1996), suggests that the initial percentage fat and the $r_f : r_p$ together provide a ‘memory of partitioning’ which defines the $Pc$ of the individual, and determines not only the pattern of protein and fat mobilization during energy deficit, but also the way energy deposited during refeeding is partitioned in the protein and fat compartments. From the standpoint of system physiology, the ‘memory of partitioning’ dictates an autoregulatory control system that underlies the partitioning between protein and fat during weight loss and weight recovery, and its functional significance would be two-fold:

(a) during starvation: to meet the fuel needs of the individual in such a way that the energy-reserve component in both the protein and fat compartments would reach complete depletion simultaneously, a strategy that would ensure maximum duration of survival during long-term food scarcity, and

(b) during refeeding: to restore the two energy-reserve fractions in the protein and fat compartment in the same proportion as before starvation, and hence to re-establish the individual’s pre-starvation capacity for survival during long-term food scarcity.

In addition to the autoregulatory control of partitioning per se, other control systems operating via the control of food intake and thermogenesis with feedback loops from the fat and/or lean tissue compartment have also been proposed in a conceptual model of autoregulation of body...
composition based on re-analysis of data from the Minnesota experiment (Dulloo, 1997; Dulloo et al. 1997; Dulloo & Jacquet, 1998), and they are conceptualized to be dictated by ‘memories’ of the fat and/or FFM compartment. As shown in Fig. 12, they are however viewed as ‘attenuators’ of energy imbalance and/or ‘accelerators’ of tissue recovery that are superimposed over a more ‘basal’ control of energy-partitioning which is dictated by the ‘memory’ of partitioning.

On the basis of the findings here that variability in Pc among the Minnesota men is primarily determined only by the variability in the initial percentage fat and in $r_p$, (see first application of the model), it follows that the ‘memory of partitioning’ during starvation–refeeding is determined essentially by the ratio fat:protein tissue compartment before starvation (reflected in the initial percentage fat) and by the size of the energy-reserve fraction of the protein compartment ($r_p$). Future studies would need to elucidate the metabolic basis of this ‘memory of partitioning’ and to explore whether inter-individual variability in $r_p$ resides in the ratio visceral mass:skeletal mass, in the fibre and/or biochemical composition of the skeletal muscle mass or in variability in skeletal muscle metabolism. The elucidation of the factors underlying variations in $r_p$ would have important clinical implications vis-à-vis the pathophysiology of starvation since $r_p$ is likely to be a critical global variable underlying differential susceptibilities to various functional impairments in response to protein–energy malnutrition or to therapeutic weight reduction, as well as to variability in the recovery of bodily functions during refeeding after cachexia. Furthermore, alterations in $r_p$ might also be implicated in the loss of lean tissue mass that occurs during the ‘normal’ ageing process and in the greater susceptibility of the elderly to functional impairment during weight loss. Finally, the mathematical model described in the present paper (equation 10) could be useful for calculating the $r_p$ from a knowledge of the initial percentage fat, Pc and $r_f$ of the individual. Since the initial

Fig. 12. A conceptual model for autoregulation of body composition during weight recovery from starvation (adapted from Dulloo, 1997). Pc, partitioning characteristic of the individual; $r_p$, fraction of the protein compartment which can function as an energy reserve; FFM, fat-free mass; $\Delta$, change. The components of this model are derived from a series of papers (including the present one) based on re-analysis of data from the Minnesota experiment (Keys et al. 1950), and centre on distinct autoregulatory control systems outlined here. (1) The control of energy partitioning between protein and fat confers to the individual his or her Pc during starvation and subsequent weight recovery (Dulloo et al. 1996). It is dictated by a memory of the initial body composition, i.e. by the initial ratio fat:FFM (i.e. initial percentage fat) and by $r_p$. (2) Thermogenesis, which is suppressed during weight loss, remains suppressed during weight recovery by a magnitude which was proportional to the state of depletion of the fat stores, but unrelated to state of FFM depletion (Dulloo et al. 1996; Dulloo & Jacquet, 1998). This has led to the concept for the existence of a memory of the largest fat stores reached in a given individual, i.e. a ‘fat-stores memory’ which governs the suppression of thermogenesis as a function of the replenishment of the fat stores. The functional importance of the economy in thermogenesis during weight recovery is therefore to accelerate specifically the replenishment of the fat stores, thereby contributing to the disproportionate rate of fat relative to lean tissue recovery. This control of ‘fat-specific’ thermogenesis functions as a specific accelerator of body fat during weight recovery. It is distinct from the control of ‘non-specific’ thermogenesis which functions as an attenuator of energy imbalance, and is dictated by the food energy flux rather than by fat depletion–repletion. (3) Hunger–appetite drive leads to hyperphagia during weight recovery, and the magnitude of this hyperphagic response is determined by the extent to which body fat and FFM are depleted, with the degree of fat depletion being the stronger determinant (Dulloo et al. 1997). The hyperphagic response therefore seems to be dictated not only by a memory of the initial fat stores but also by a memory of the initial FFM (hence lean tissue) compartment. The functional importance of this increase in the hunger–appetite sensation, with consequential hyperphagia, is to accelerate the restoration of both lean and fat compartments, as defined by the Pc of the individual.
percentage fat and body weight can be measured, and \( r_f \) can be estimated (using equation 11), the future challenge in elucidating the physiological basis of human variability in fuel partitioning resides in devising appropriate methodological approaches (less drastic than prolonged starvation) to measure the PC of the individual.

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