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Metabolic response to starvation, injury and sepsis

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Starvation has often been described as producing a series of stereotyped metabolic changes, such as progressive diminution in resting and total energy expenditure, a progressive decrease in the proportion of endogenous energy derived from protein mobilisation and an increase in the proportion derived from fat and ketone bodies. However, many of the metabolic changes are neither progressive nor stereotyped. They are influenced by the age, sex and the initial body composition of the individual. Furthermore, protein oxidation and resting energy expenditure may temporarily increase before they begin to decrease,[1] and the contribution of protein oxidation to total energy expenditure in lean individuals undergoing prolonged starvation may actually increase. Similarly, the metabolic response to injury is influenced by the age, sex and nutrition status of the subject, as well as ambient temperature and interventions such as blood transfusions and use of analgaesics, sedatives and antibiotics. Whilst these are important factors, it is also necessary to understand the inter-relationships that exist between lean and fat tissues (and inter-relationship between individual organs) during starvation and injury and how these might be linked to survival.

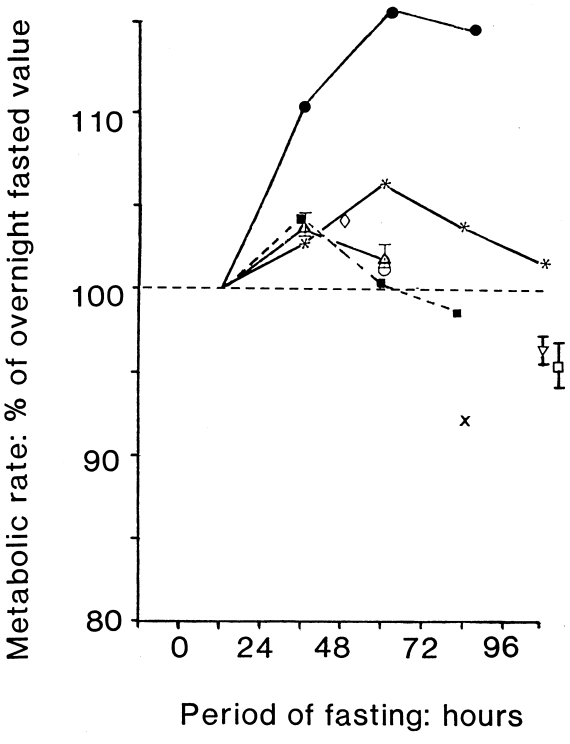

Figure 1.1 – Changes in resting energy expenditure in early starvation. The results are expressed as a percentage of overnight fasted value (100% at 12 hours). Each point represents results from a variable number of subjects ranging from one to 13. Based on Elia.[1]

Starvation

Short term starvation

Energy metabolism

Although prolonged starvation is associated with an absolute reduction in basal metabolic rate (BMR), which is partly due to loss of lean tissue, there is often a small absolute increase in BMR during the first 2 days of starvation (Fig. 1.1). This occurs despite a decrease in body weight and lean tissue mass (about 2%). Classic starvation studies such as that reported by Benedict[2] (included in Fig. 1.1 – square symbols) and Takahira[3] (not included in Fig. 1.1) are amongst those that reported a transient increase in BMR. The classic study of Cetti[4] is difficult to interpret because the first baseline measurement was made 1 h after breakfast, which means that dietary induced thermogenesis is likely to have influenced the results.

The temporary rise in BMR during early starvation could be due to: (a) an increase in the requirement of adenosine triphosphate (ATP) for a variety of metabolic processes, or (b) an increase in the energy equivalent of ATP as the body reduces the proportion of energy derived from glycogen decreases (17.52 kcal kJ/mole ATP gained) and that from fat (18.93 kcal/mole ATP gained) and ketone bodies increases.[5]

An increase in the requirement of ATP probably results from multiple metabolic processes: increased gluconeogenesis[6,7]; increased triglyceride-fatty acid cycling[8,9] which is thought to account for 1–2% of BMR in early starvation; increased protein-amino acid recycling (protein turnover) during the first 3 days of starvation;[10] and increased acetyl CoA-ketone body recycling. The last cycle occurs because ketone bodies are synthesised from acetyl CoA (AcCoA) in the liver, whilst other tissues such as muscle and brain, convert ketone bodies back to AcCoA before final oxidation. The overall cost is 1 ATP/cycle. On the basis of the rate of ketone body production and utilisation during early starvation[11] and the energy equivalent of ATP[5,12], it is estimated that this cycle alone contributes to 1–2% of BMR. After the first 1–3 days of starvation BMR decreases to values that are lower than those observed after an overnight fast.

The mechanisms are incompletely understood, but they are probably due to a combination of factors: losses of metabolically active tissues, altered proportions of tissues with different metabolic rates and changes in the metabolic rates of specific tissues.

Protein metabolism

A transient increase in nitrogen (N) excretion has frequently been observed in early starvation (Fig. 1.2).[1,2,14] Most of these studies did not take into account the change in the size of the urea pool, but the study of Elia *et al.*[14] reported a tendency for the blood urea concentration to rise, which would make the corrected N balance even more negative at this time. The N found in urine during early starvation does not entirely reflect increased protein oxidation, since there is a net contribution from the oxidation of free amino acids particularly glutamine (this also occurs in injury – see below). The free muscle glutamine pool (45 g of glutamine or 15 g of N; 20–25 mmol/L intracellular water) almost halves between 12 and 72 h of starvation.[15,16] Since during this period the total urine N excretion is about 28 g (9–13 g N/day), it can be estimated that the loss of muscle glutamine corresponds to about a quarter of the urine N excretion. There is a general tendency for other amino acids to be lost from the free pool of amino acids in muscle, but some may accumulate, e.g. the branched chain amino acids. However, these other changes are relatively small compared to the loss of glutamine, which has two N atoms per molecule, in comparison with most other amino acids which have only one N atom per molecule.

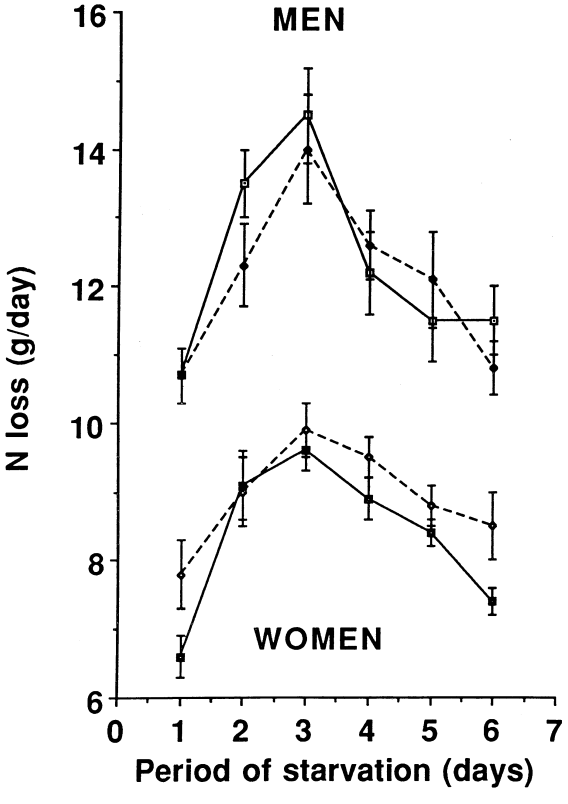

Figure 1.2 – Changes in urine N excretion in lean and obese subjects during early starvation. Solid line = lean subjects; dotted line = obese subjects; $n = 12$ for each point. See Elia[1] – based on Goschke *et al.*[13]

Prolonged starvation

In the 19th century a number of workers, notably Chossat[17] reported that a variety of animals died from starvation after they had lost 40–50% of their body weight. The concept of lethal weight loss was developed and extended to humans. Krieger[18] suggested that the lethal level of weight loss in adults was 40% for acute starvation and 50% for semi-starvation. However, there is substantial variation in the weight loss of subjects dying of starvation (even in the subjects studied by Krieger[18]) and therefore the above figures can only be regarded as approximate. Furthermore, successful massive weight loss amounting to 65–80% of initial body weight has been described in grossly obese individuals with an initial body weight in excess of 200 kg.[1] The associated survival time during starvation can be considerably prolonged in the obese (Table 1.1) because of their excess energy stores. Autopsy studies of humans dying of starvation or semi-starvation frequently show that body fat has virtually disappeared, implying that energy reserves are linked to survival. In contrast, there is a loss of only 25–50% of most other tissues and organs, and only a small proportion of the brain and skeleton. Examples of human (typical lean subject) and non-human species dying from 'total starvation' are shown in Table 1.2. In lean humans, there is a loss of about 40% body weight before death (e.g. 41% in the subject studied by Myers[19] and 38% in the Northern Ireland fasters – Table 1.1). From this information it is possible to construct a table of the available energy reserves in lean and obese subjects (Table 1.3). It is clear that the major energy reserve is fat, for good physiological reasons. First, the energy density of endogenous fat (~9.4 kcal/g) is more than 2-fold greater than that of protein (~4.44 kcal/g) and glycogen (~4.2 kcal/g).[5] Second, the loss

Table 1.1 – Effect of obesity on survival time during 'total' starvation in mice and humans.

	Survival time (days)	Author
Humans		
Lean		
(n = 9)	57–73	Northern Ireland fasters[1]
(n = 1) (prior gunshot wound)	43	Northern Ireland faster[1]
(n = 1)	63	Meyers, 1917[71]
Obese (successful fasts)		
(n = 1)	382	Stewart and Fleming, 1973[72]
(n = 1)	315	Barnard *et al.*, 1969[73]
(n = 1)	249	Runcie and Thomson, 1970[74] Thomson *et al.*, 1966[75] Collinson, 1967[76]
(n = 1)	231	Barnard *et al.*, 1969[73]
(n = 1)	210	Runcie and Thomson, 1970[74]
Several	100–200	Drenick *et al.*, 1967[77] Runcie and Thomson, 1970[74] Thomson *et al.*, 1969 Barnard *et al.*, 1969[73]
Mice (8 weeks old)		
Lean		
Winter	4	Cuendet *et al.*, 1975[92]
Summer	8	Cuendet *et al.*, 1975[92]
Obese (ob/ob)		
Summer	> 28	Cuendet *et al.*, 1975[92]

Based on Elia.[1]

Table 1.2 – Percentage loss of organs during starvation.

	Pigeons	Cats	Rats	Dogs[a]	Man
Skeleton	3	10.4	14	5	–
Muscle	42	57.9	31	42	40.7
Brain and cord	1	2.2	3	22	6.9 (brain)
Heart	45	34.0	3	16	40.4
Spleen	71	68.5	–	57	18.4
Liver	53	59.8	54	50	28.6
Pancreas	64	55.2	–	62	48.8
Kidneys	32	50.9	–	55	49.2
Lungs	32	50.9	–	29	28.6
Fat	–	–	97	–	–

[a] Loss of fresh fat-free organs, see Elia.[1]

of 1 g of protein and glycogen is associated with the loss of up to four times more water, which is the major component of lean tissue (73% of lean tissue is water). In the examples given in Table 1.3 the energy associated with the loss of 1 g fat is 10-fold greater than the loss of 1 g fat-free tissue. Calculations based on the composition of adipose tissue which consists mainly of fat (~80% in lean subjects and up to ~90% in obese subjects) also suggests that loss of 1 g of adipose tissue is associated with the mobilisation of severalfold more metabolisable energy (7.5–8.5 kcal/g) than 1 g of other tissues. Therefore, for obvious mechanical reasons, it is advantageous to store energy as fat when food energy is readily available, and utilise fat when food energy is not available.

Table 1.3 – Hypothetical values of body composition, fuel availability and survival time in a lean 70 kg man and an obese man twice ideal body weight.

	Lean subject	Obese subject
Initial[c]		
Body weight (kg)	70.0	140.0
Fat (kg)	9.0	61.5
Protein (kg)	12.2	15.7
Glycogen (kg)	0.3	0.4
Loss during starvation		
Weight (% of initial)	38.0	69.0
Weight (kg)	26.6	96.6
Fat (kg)[a]	8.0	61.5
Protein (kg)[b]	14.0	15.7
Glycogen (kg)	0.3	0.4
Available energy during starvation		
Fat (kcal)	75,200	568,700
Protein (kcal)	17,760	33,300
Glycogen (kcal)	1,260	1,680
Total	94,220	603,680
Mean daily total energy expenditure (kcal/day)[d]	1,500	2,250
Survival time (days)	63	268

[a] Fat accounts for 30% of the loss of body weight in the lean subject and 63% of the loss in the obese subject. Fat free tissue accounts for 70% of the weight loss in the lean subject and 37% in the obese subject.
[b] Assuming 1 g N = 6.25 g protein, there is a loss of 24.0 g N.kg loss of body weight in the lean subject, and 12.4 g N/kg in the obese subject.
[c] The composition of the body in the lean subject is based on reference man (Snyder *et al.*[21]), and the excess weight in the obese individual is assumed to be 75% fat and 25% fat-free tissue, which are typical values.
[d] These are only approximate values partly because resting energy expenditure decreases to a variable extent below that predicted for normal individuals of the same weight (~25% during long-term starvation in lean individuals – Elia[1]), and partly because physical activity frequently decreases to a variable extent. Both of these changes can be regarded as adaptations.

From the information presented on the changes in body composition during starvation (Table 1.3) it is possible to make four predictions:

1. Survival is considerably longer in obese individuals than lean individuals.
2. Although lean subjects have less initial body protein than obese subjects, it is predicted that they oxidise more protein during prolonged starvation. As shown in Table 1.3 the overall protein oxidation is 2-fold greater in the lean subjects than the obese subjects (58 vs 28 g protein/day; 9.4 vs 4.5 g N/day).
3. The percentage of total energy expenditure derived from protein oxidation (p%) is greater in lean individuals. Calculations based on the figures given in Table 1.3 suggest that p% is 3-fold greater in the lean than the obese (see Table 1.4).

Table 1.4 – Per cent of total available energy derived from fat, carbohydrate and protein during starvation in lean and obese subjects[a].

	Lean subject	Obese subject
Fat	79.8	94.2
Protein	18.9	5.5
Carbohydrate	1.3	0.3

[a] Calculated from data on Table 1.2.

4. Increased physical activity during prolonged starvation will not only reduce survival time, but it will increase daily N excretion (and leave p% unaltered).

Although there is insufficient information to adequately examine the last prediction, there is sufficient data to confirm the first three predictions.

There is abundant evidence to suggest that individuals with extra energy reserves survive longer during starvation (e.g. see Table 1.1 and Keys[20]). It is also noteworthy that women, who have more per cent body fat than men, survive famines longer than men. Young children survive the shortest but this is largely related to their high resting energy expenditure which may be up to 2-fold greater (kcal/kg/day) than that of adults.

The other predictions are based on the premise that fuels are utilised in proportions that would favour prolonged survival. If obese individuals continued to oxidise protein at the same rate as in early starvation, or at the same rate as lean individuals, their lean tissues would be depleted more quickly and they would die with considerable available energy reserves (fat stores). This is obviously not the optimal physiological strategy for prolonged survival. It would therefore be advantageous for obese individuals to reduce the rate of protein oxidation (and per cent of total energy expenditure derived from protein oxidation) to a greater extent than lean individuals.

Fat-free tissue contains about 30–35 g N/kg,[21] whereas fat contains no N. If fat-free mass was preferentially catabolised the ratio of N loss to weight loss (gN/kg) would be expected to be high, and if fat was preferentially lost, the ratio will be expected to be low. Although the ratio of N loss to weight loss provides only semi-quantitative information about protein–energy inter-relationships – Figure 1.3 shows that the cumulative N loss/cumulative weight loss is lower in the obese than in the lean. There is complete separation of the two sets of results after 2 weeks, and by 1 month there is a 2-fold difference between them. More direct information about the absolute rate of protein oxidation can be obtained from the rate of urine N excretion.

Figure 1.4A shows the cumulative N excretion in lean individuals undergoing starvation, and Figure 1.4B shows that the values for groups of obese individuals fall below the dotted line, which represents the typical curve for lean individuals (derived from Fig. 1.4A). Figure 1.5A shows the changes in daily N excretion, in the obese are 2-fold lower than in the lean, and Figure 1.5B shows the corresponding values for p% are 2 to 4-fold lower than in the obese after 3 weeks of starvation[22]. This is also shown in Figure 1.6 in relation to initial body mass index (BMI) and per cent

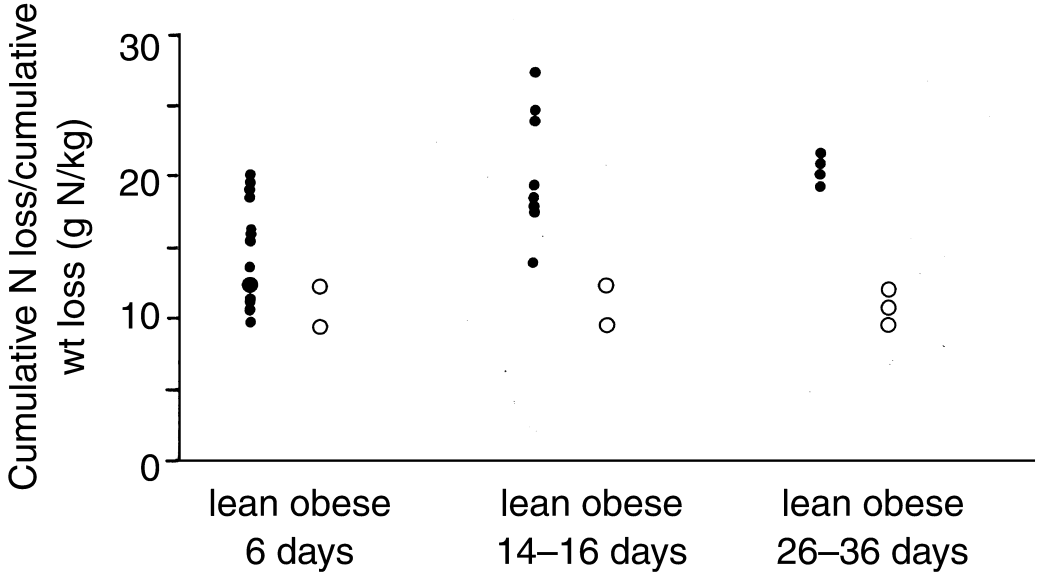

Figure 1.3 – The ratio of cumulative N loss to cumulative weight loss during starvation in lean (●) and obese (○) subjects. The small solid circles represent data from individual subjects, and the larger solid circles represent data from a group of subjects. Reproduced with permission from Elia.[1]

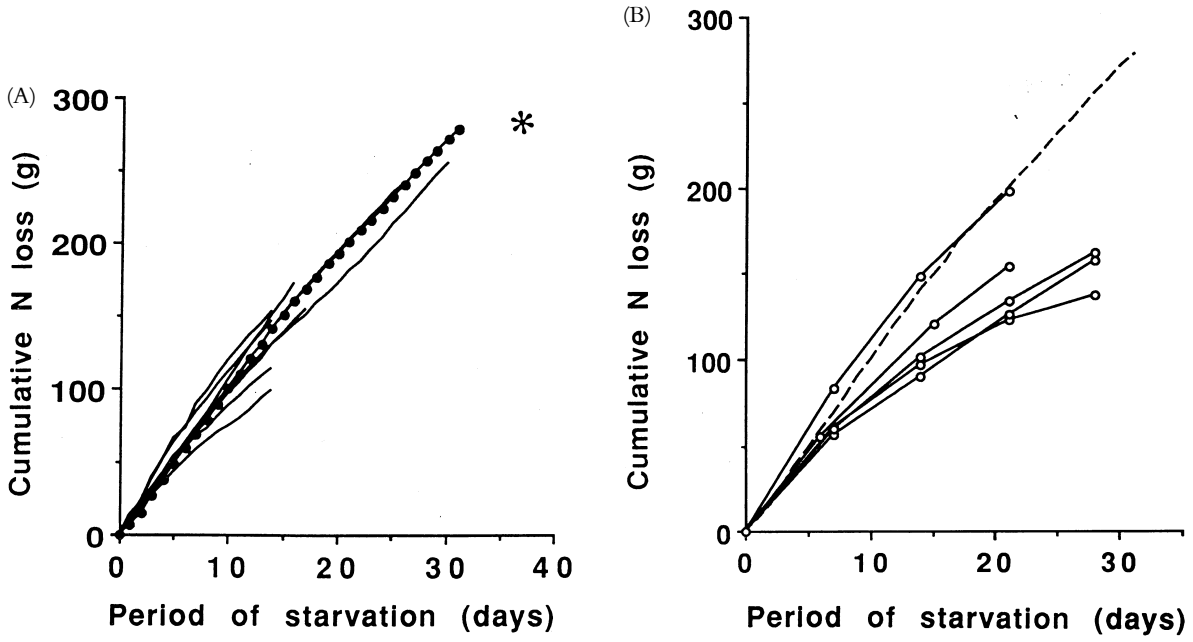

Figure 1.4 – (A) Cumulative N excretion in lean subjects undergoing total starvation. The large dots represent data from Benedict[2] and the other eight curves with small dots (some hidden behind the other curves) are derived from a variety of other starvation studies between 1905 and 1925. The asterisk represents the cumulative N loss of another subject. (B) Cumulative N loss in lean subjects (– – – – derived from A) and groups of obese subjects undergoing total starvation. Reproduced with permission from Elia.[1]

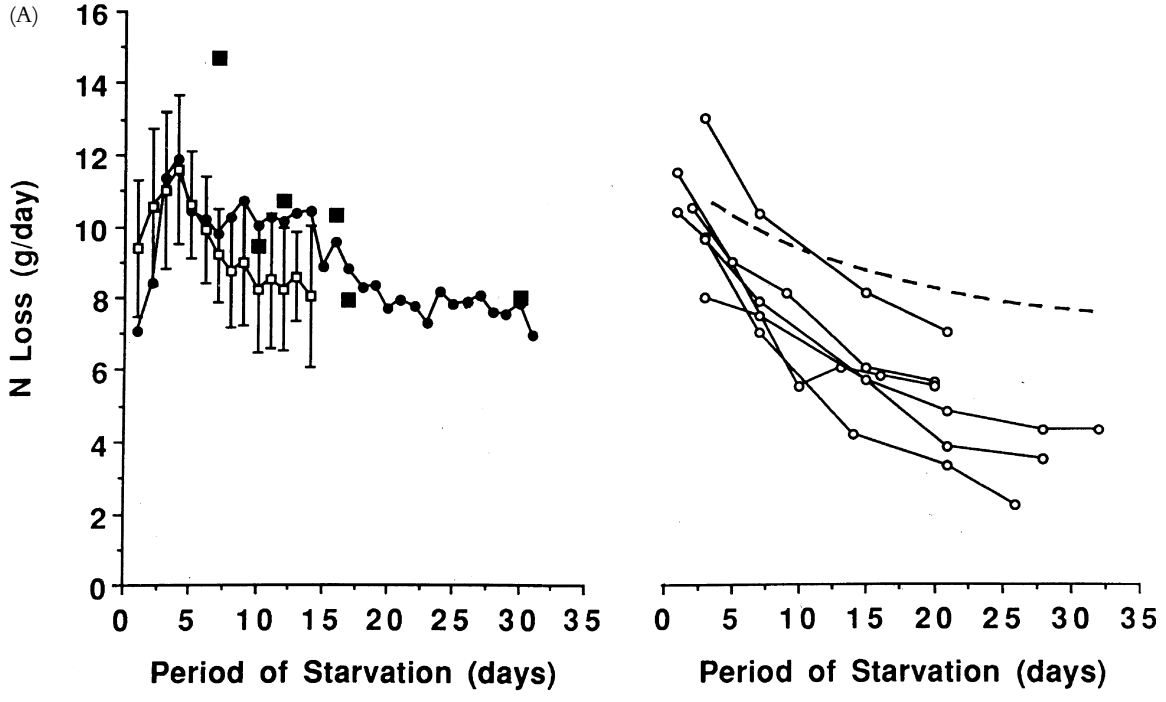

Figure 1.5 – (A) The daily N excretion during total starvation in lean subjects (left and dotted line on graph on the right) and groups of obese subjects (right).

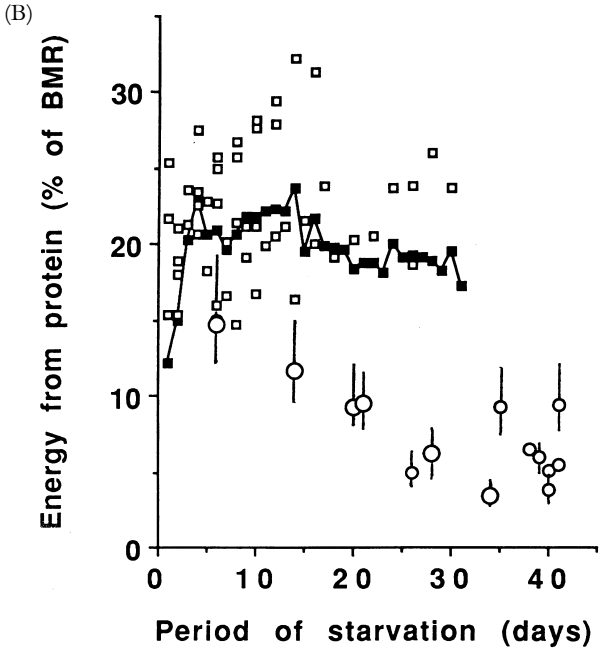

Figure 1.5 – (B) Effect of length of total starvation on the per cent contribution of protein oxidation to basal metabolic rate (BMR), in lean (solid squares – Benedict[2] and obese subjects (large circles represent results of groups of individuals and small circles represent results of individual subjects). Reproduced with permission from Elia.[1]

body fat in individuals undergoing total starvation for more than 16 days. If the energy derived from protein oxidation is expressed in relation to total energy expenditure instead of BMR, all the values will be lower than those shown in Fig. 1.6. Furthermore, although some variability will be introduced (by effect of physical activity) this is unlikely to blur the large differences that exist between lean and obese subjects.

The above concepts developed for humans are consistent with information available from other species. For example the pig, with its copious body fat, has a value for p% that is only 7% of BMR (after 3 days of starvation) compared to 15–30% in leaner species such as dog, rabbit and man clean man).[1] Similarly, birds such as geese that have considerable body fat reserves have a particularly low value for p% during starvation compared to leaner birds.[1] A pre-mortal rise in N excretion when stores of body fat are depleted has been reported in a variety of mammals and birds.

It is also relevant to human physiology that the differences in protein economy which occur during total

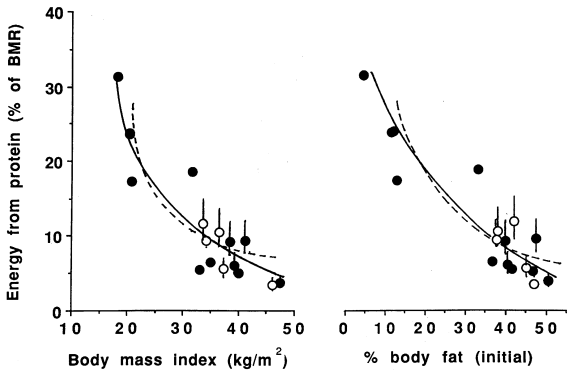

Figure 1.6 – The effect of initial BMI (left) and per cent body fat (right) on the contribution of protein oxidation to basal metabolic rate in subjects undergoing starvation (>16 days). Solid circles represent individual data (nine males, four females) and open circles group mean data. The dotted curve is a theoretical one based on calculations similar to those in Tables 1.3 and 1.4, assuming the ratio of total energy expenditure to BMR is 1.3. Reproduced with permission from Elia.[1]

starvation also occur during partial starvation.[1] Examples include the changes that occur during ingestion of low calorie or very low calorie diets for therapeutic weight reduction, and prolonged experimental semi-starvation in lean individuals. For example, in the study by Keys[20] normal subjects were semi-starved for 6 months until they lost 25% of their body weight. The leaner subjects lost a greater proportion of this weight as lean tissue[23] and had a higher value for p%. During recovery the reverse trends in body composition were obtained.

All these observations raise questions about the control mechanisms responsible for the protein–energy interrelationships. How does excess adipose tissue produce a reduction in protein oxidation? What are the nature of the signals? How is the 'memory' retained so that those who lose a high proportion of lean to fat tissue during starvation regain a high proportion of lean to fat tissue during refeeding?[23] Why do the differences become apparent during prolonged starvation and not early starvation (first few days)? These questions remain largely unanswered and deserve further investigation.

Intermediary metabolism during starvation

The glycogen pool in the liver is lost early during starvation (Fig. 1.7), although some persists in muscle for utilisation in 'stress' or 'emergency' situations. Since the glycogen reserves are small, the tissues of the body either have to depend on alternative fuels, or

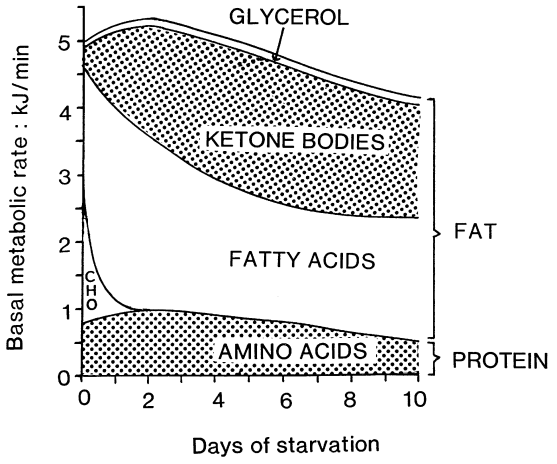

Figure 1.7 – Changes in BMR and fuel selection in a lean subject undergoing total starvation. Note the transient small increase in BMR, and the small and rapidly declining contribution of glucose (derived from glycogen) to BMR. Ketone bodies which are derived from fatty acids become a major fuel for the tissues of the body accounting for up to 40% of BMR. Reproduced with permission from Elia.[11]

they form glucose from glucogenic amino acids and the glycerol component of triglyceride (~8 g/1000 kcal during starvation). Both processes operate but the net conversion of 10 g N (62.5 g amino acids) to glucose (65% conversion) will only furnish about 40 g glucose (60 g glucose, if glycerol derived from the net oxidation of 2000 kcal triglyceride is included in the calculation)[22]. This is 4- to 5-fold less than the dietary intake of carbohydrate in a normal man in nutrient balance with an energy consumption of 2500 kcal/day, 45% of which is from carbohydrate. Lean tissues would quickly be lost if a high rate of net glucose oxidation persisted during starvation. Therefore, two important adaptations occur. First, glucose oxidation is inhibited. For example, the pyruvate dehydrogenase complex, which catalyses the first irreversible step in the oxidation of glucose carbon, is inhibited by a low insulin concentration, a rise in the AcCoA/CoA ratio (which occurs when fat oxidation predominates), and a rise in 3-hydroxybutyrate/acetoacetate ratio (which also occurs during starvation). Although it is possible for glucose to recycle through 3C fragments (glucose-lactate and glucose-alanine recycling; e.g. red blood cells, muscle, brain) this does not involve irreversible glucose oxidation. Secondly, tissues utilise energy from fatty acids, which are derived from triacylglycerol (TAG). However, the brain does not utilise fatty acids directly, partly because fatty acids do not readily penetrate the blood–brain barrier and partly because the brain has little enzymatic potential to oxidise them. After the first few days of total starvation, ketone bodies, which are formed from fatty acids in the liver, become an important energy source for the body (Fig. 1.7) and the dominant energy source for the brain. They are water-soluble, readily cross the blood–brain barrier and undergo oxidative metabolism. However, there are differences in ketone body metabolism between lean and obese subjects[22], and these are reflected in a number of ways: their circulating concentrations (Fig. 1.8); the ratio of 3-hydroxybutyrate (β-OHB) to acetoacetate (AcAc) (Fig. 1.9), which is an index of the mitochondrial redox state; the rates of ketone body production relative to their circulating concentration (Table 1.5); and their exchange across tissues. For example, arterio-venous exchange studies undertaken by Elia *et al*[24] suggest that the contribution of ketone bodies to oxidative metabolism in the resting forearm muscle of lean individuals is about 5% after an overnight fast, 10% after 36–40 h of starvation and 20% after 60–66 h of starvation. In contrast, after 3 days of starvation ketone bodies account for up to about half of the oxygen utilised by the forearm muscle of obese individuals. However, after 3 weeks of starvation the forearms of obese individuals take up β-OHB and release some of the carbon as AcAc, with the overall result that ketone bodies account for only 18% of the O_2 utilisation,[25] or only 10% according to other studies.[26] It appears that in lean individuals the release of AcAc from forearm tissues observed at 36–40 and 60–66 h of starvation[24] occurs much earlier than in the obese.

An important factor controlling the uptake and utilisation of substrates is their circulating concentration. For example, it is believed that the major reason for ketone body utilisation by the brain is the circulating concentration of ketone bodies. However, this does not explain why the progressive rise in the circulating ketone body concentrations that occurs between 3 days and 3 weeks of starvation in the obese is associated with a decrease in ketone body uptake by the forearm (whilst non-esterified fatty acids become a more important fuel). A change in the activity of key enzymes involved in ketone body metabolism may provide a possible explanation. Another difference between lean and obese subjects during short term starvation is that glucose tolerance has been reported to deteriorate more in lean subjects than in obese subjects. Lean subjects also show a much greater increase in leucine oxidation during short term starvation, and a greater proportion of urine N in the forms of urea[22].