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METABOLIC ADAPTATION TO LOW INTAKES OF ENERGY AND PROTEIN

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CONTENTS

INTRODUCTION

Adaptation to low intakes of energy and protein is a very wide subject; the treatment of it here is inevitably superficial because of the limitations of space and of my own knowledge. The plan adopted has been to cover as many aspects as possible in short sections, which make no claim to be complete reviews of the

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literature, but which may stimulate further inquiries. I do not define adaptation nor distinguish it formally from related concepts such as homeostasis, regulation, or acclimatization (see 154). However, to bring the subject into perspective a brief discussion of terminology and general characteristics may be useful.

Some General Characteristics of Adaptation

1. Terminology: the word "normal" is used here, as in clinical and nutritional biochemistry, to describe the range of a given variable in a group of healthy people. It is therefore essentially a statistical concept, although "normal" in this sense does not necessarily coincide with Gaussian. "Acceptable" is a functional term and it must be a main objective of any study of adaptation to determine the acceptable range of the characteristic under consideration, according to whatever criteria are chosen. A "successful" adaptation is one that maintains the characteristic within the acceptable range. These are not offered as definitions but merely as descriptions of the commonsense usage adopted in this review.

2. Adaptations that are important for nutrition are of three kinds: biological/genetic; physiological/metabolic; behavioral/social. Here we are concerned with adaptations of the second kind, but the three cannot be completely separated. For example, peoples whose way of life is based on herds of animals and who drink a great deal of milk retain intestinal lactase activity into adulthood. This may be regarded as a metabolic adaptation, but the capacity to achieve it is genetically determined, perhaps by a single gene (80).

3. An adapted state is a stable state that is maintained as long as the stimulus that evokes it is maintained, often throughout life.

4. In classical physiology, adaptation and homeostasis are discussed in relation to particular variables, such as body temperature in hot or cold climates, oxygen transport at high altitudes, body fluid volumes, osmolarity, pH, etc. Unfortunately, in nutrition it is seldom possible to focus in this way on a single variable. Usually the criterion is vaguely described as the maintenance of an acceptable level of function. In principle, any discussion of an adaptive process should begin by defining "adaptation of what in response to what?".

5. One function may be maintained at the expense of another, so that, as has been said: "every adaptation has its cost." To put it in another way, the success or failure of an adaptation depends on the criteria adopted. It is seldom useful to discuss whether an adaptation is "successful" unless the criteria have been agreed, and here we enter the realm of subjective value judgments. A key question, for example, is whether or not maintenance of a constant body weight or of a normal rate of growth is a necessary and appropriate criterion.

In conclusion, it is almost impossible to discuss adaptation without making value judgments and without using indefinable concepts such as "normal," "healthy," "satisfactory," etc. D'Arcy Thompson said "sooner or later nature does everything that is physically possible" (146). Our problem is that what is physically possible may not be good enough.

Variability

The concept of adaptation implies that there is an acceptable state maintained by adaptive processes. This immediately raises the question of the variability between individuals and the range of normal variation.

In relation to energy metabolism the variation between people takes two forms, which are perhaps two sides of the same coin: the large differences in recorded food intake between similar people engaged in similar activities (big and small eaters), and the fact that some people get fat and others remain slim on apparently similar intakes. Both kinds of difference are relevant to the question of adaptation, since one asks: how do they manage to be so economical of energy? The classical story is of an almost two-fold range between the highest and lowest intakes of a group of similar people (163). Harries et al (60) summarized results of studies published up to 1962, and their results in turn are summarized in Table 1. It might be supposed that the low intakes so often recorded in Third World countries (e.g. 100, 108) represent a subgroup of "survivors" from the lower end of the range of intakes in the West. In that case the coefficient of variation (CV) should be lower, but I know of no evidence for this. A large range of variation in recorded intakes seems to be universal.

Cross-sectional surveys of intakes exaggerate the differences between individuals because they ignore the variability within the individual. The pioneering work of Sukhatme & Margen (143) drew attention to the importance of intraindividual variation. Their analysis of earlier data on cadets whose intake and expenditure were measured for three weeks (32) showed that the CV of intakes in the same subject from day to day was of the order of 20% and was greater than that between subjects. They also showed a significant variation

Table 1 Estimates of variability of energy intake and expenditure in subjects studied over 5 days or more[a]

	No. of studies	Total no. of subjects	Mean[d] CV (%)
Adult males			
intake[b]	26	1458	14.8
expenditure[c]	14	218	10.8
Adult females			
intake[b]	28	2247	18.3
expenditure[c]	6	99	10.8

[a]Summarized from Harries et al (60).

[b]Intakes were measured in each subject over 7 days or more except in 5 of the 54 studies.

[c]Expenditures were measured in each subject over 7 days or more except in 3 of the 20 studies.

[d]For each study, the mean is given of the CVs of the daily intake/expenditure of each individual. This column represents the overall mean of these mean CVs, without weighting for numbers.

Table 2 Within-subject ranges of energy intake and expenditure[a]

Subject	Days of study	Sex	BMI	Mean intake (kcal/d)	Range[b]	Mean expenditure (kcal/d)	Range[b]	Expenditu Intake
4	7	M	29.9	3602	1.81	3405	1.35	0.95
7	7	M	17.8	2417	1.19	2212	1.20	0.92
JB	7	M	25.4	3022	1.20	2900	1.13	0.96
RM	14	M	16.3	2432	1.74	2674	1.46	1.10
29	7	F	21.2	2419	1.07	2458	1.08	1.02
34	14	F	23.0	1595	1.77	1660	1.36	1.04
					Mean: 1.46		1.26	1.00

[a]Data of Booyens & McCance (10).
[b]Ratio of maximum/minimum intake or expenditure. Standard deviations are not given in this paper.

within subjects of the mean intake from week to week. In a study in Canada (7), in which intakes were estimated by dietary recall for one day on six occasions throughout the year, intra- and interindividual variation made roughly equal contributions to the total variance, each with coefficients of variation of 25–30%.

As is apparent from Table 1, the variability of energy expenditure (EE) seems in general to be less than that of intake. From the data of Booyens & McCance (10) the CV of lying, sitting, and standing rates of expenditure per m^2 surface area in 22 male subjects was 16% for all three rates. Their results for six subjects who were studied for 7–14 days are shown in Table 2. It shows that the within-subject variation of expenditure was less than that of intake, even though the expenditure was measured by the tedious and relatively inaccurate diary method. Analysis of a very large body of data (126) shows that the CV of BMR, adjusted for age, sex, and body weight, is 7–10%.

More precise methods give lower values for the variability of total EE. Calorimetric measurements of EE on nonobese subjects performing standardized activities over 24 h have given values of 6–7% for between-subject CV and 1.5–2.5% for within-subject CV (see 25, 44, 45). Admittedly, the conditions are far removed from those of real life. The method of measuring total EE over 10 days or more with doubly labelled water should greatly extend our knowledge. In a recent comparison (109) of measurements of EE by 24-h calorimetry and by the isotope method over 2–3 weeks, there was a significant rank order correlation between the two sets of results in 11 subjects. The interindividual CV of the isotope results was 24%, that of the calorimeter measurements 11.5%[1]. This difference may reflect the extent to which a measurement over 1 day is unrepresentative of a 2–3-week period.

[1]Values calculated from (109) as metabolic rates per kg body weight. When more than one set of measurements were made on a subject, only the first was used for estimating the CV. Two subjects were pregnant and two were obese. The data from one grossly obese woman were omitted.

There is less information about the variability of protein metabolism. It has been estimated from short-term balances that the average amount of protein needed for zero balance in groups of similar young men has a CV of 12.5% (37). Sukhatme & Margen's analysis of longer-term studies of nitrogen output on a fixed intake showed autocorrelated variations in time (142), although this effect has not been confirmed in other long-term studies (111). There is evidence of substantial interindividual differences in protein turnover (J. C. Waterlow, unpublished results). As with energy expenditure, intraindividual variation exists but appears to be less. In repeated measurements of nitrogen flux made on the same subjects over periods of up to four years, the intraindividual CV was only 4% (38). Data presented by Bier et al (8) on repeated measurements of amino acid flux in the same subjects show an average range of variation within the individual of about 10%.

Payne & Dugdale (104) proposed a model according to which the "*P* ratio," defined as the ratio of protein stored to total energy stored during weight gain, and conversely the ratio of protein lost to energy lost during weight loss, is characteristic and fixed for each person. This model attempts to link individual variability in protein and energy metabolism (62).

The important contribution of Sukhatme's thinking is that human beings should not be regarded as existing in a fixed and constant state. Nevertheless, even when allowance is made for the confounding effect of this variability, real differences between individuals remain, and there is increasing interest in the extent to which they are genetically determined. The genetic component in height has been analyzed in detail (117), and there have been a number of studies of the heritability of obesity (e.g. 12). A particularly interesting experiment, because it involves metabolic measurements, is that of Griffiths & Payne (57) showing that preschool children, not themselves overweight, who had an obese parent had lower food intakes, basal metabolic rates, and 24-h food intakes than the children of nonobese parents. More general discussions of genetic factors in nutrition are to be found in (149) and (167).

The large range of variation both between and within individuals provides an opportunity for the study of adaptive mechanisms of which more advantage could perhaps be taken.

Changes in Body Weight and Size

Changes in body weight are an important part of long-term adaptation—perhaps the most important part (74). This review concentrates on adults, in spite of the fact that children are more sensitive to deficient intakes of energy and protein, precisely because in children the most obvious response to deficiency of any nutrient is a retardation of growth that tends to overshadow other adjustments.

"Low" intakes mean intakes that are low in relation to supposed requirements. Both for energy and protein, requirements vary with body weight. It is

self-evident that a big person, unless obese, needs more food than a small one. The process of estimating requirements depends on the concept of balance—of determining the intake needed to balance the output or expenditure. It is implicit in measurements of energy or nitrogen balance that constant body weight should be maintained, and there are good practical reasons for this. For example, over a 10-day experimental period one can determine a negative nitrogen balance of −1 g of nitrogen per day with reasonable confidence. This loss corresponds to a decrease of about 300 g of lean body mass, a quantity too small to be measured with accuracy by methods currently available.

This experimental approach, which involves determining requirements at a particular body weight, does not necessarily imply that the body weight has to be fixed and constant. At any given height there is a range of body weight consistent with health. There is no reason, therefore, why a reduction in body weight should not be accepted as part of the process of adaptation to low intakes, provided that weight remains within acceptable limits. To adjust for height it is convenient to use the body mass index: BMI = Wt(kg)/Ht(m)^2. It has been proposed that the acceptable limits of BMI may be taken as 19–25 (11). The upper limit, with which we are not concerned here, has been reasonably well defined by studies on the excess morbidity and mortality of people who are overweight. The lower limit is much less clear. The evidence that morbidity risk increases if the BMI falls below about 19 may well be an artefact of conditions in Western societies (116). According to the analysis of Keys et al (77), death is likely to occur when 40% of body weight has been lost. This would correspond to a BMI of 13 in a person whose initial BMI was 22, and if Keys' analysis is correct, may be regarded as the absolute lower limit.

The more important question is to define a lower limit compatible with acceptable functional capacity. In many Third World countries the average BMI [calculated from average weight and average height (35)] is 18–19. If the coefficient of variation is taken as 10%, this would give a range (mean ± 2 SD) of BMI in these populations of about 15–23. Shetty (128) reported that poor Indian laborers were able to work and performed well in physiological fitness tests with a BMI of 15–16 and an estimated body fat content of 6%. Young women with anorexia nervosa may have a BMI as low as 14 (42, 120, 141), and such patients are often symptom-free and physically hyperactive. It may be suggested as a rule of thumb that a BMI of 15 be regarded as the absolute lower limit of what is acceptable. However, circumstances are clearly important. Shetty's laborers, after a lifetime of exposure to low intakes, were apparently functioning reasonably well at a BMI of 16 (and the same may be said of subject RM in Table 2), whereas Keys' volunteers, after 24 weeks of semistarvation, at a similar level of BMI were physically inactive and psychologically disturbed. In anorexia nervosa, the peculiar psychological motivation is presumably important.

The discussion so far has been in terms of BMI or weight for height. A further question is the significance in relation to adaptation of differences in height. In the Third World very large numbers of children are severely stunted in height, compared with international reference standards (76). The evidence summarized by Martorell (89) indicates that in schoolchildren in these countries there is a substantial difference in height between rich and poor, regardless of ethnic group, just as there used to be in industrialized countries such as the United Kingdom (18). It seems that height deficits in older children and adults are probably established in the first years of life. Satyanarayana et al (123) studied the growth of children who, at the age of five, were divided into groups described as well- or malnourished on the basis of height for age, the average difference in height between the extremes being 16.5 cm. This difference in height remained at the age of 17. It was remarkable, however, that the increment between 5 and 17 years was the same in both groups and equal to that found in American children. Thus the potential for growth was retained but it was not enough to overcome the original deficit.

Do these differences matter? Is it "smart to be small," or a handicap? There are some (e.g. 127, 140) who regard stunting in children as an adaptation: they need less food and are therefore more likely to survive. This, however, is not a sufficient criterion, since to survive without an acceptable level of functional capacity would not be a successful adaptation. Margen (88) has an interesting discussion on this subject. It is outside the scope of this review to examine the evidence on physical, mental, and immunological function in stunted children. However, in reply to those who maintain that stunting is a satisfactory adaptation one might invoke the UN Declaration of Human Rights, that everyone has a right to develop their full genetic potential (see also 56). This controversy illustrates the extent to which subjective value judgements may enter into a discussion of adaptation.

ADAPTATION TO LOW ENERGY INTAKES

Introduction

Several years ago I and others asked the rhetorical question "How much food does a man require?" (31). That letter pointed out the gross inadequacy of our knowledge on this subject. Since then much has been done, including the development in several countries of whole-body calorimeters capable of accurate measurements of energy expenditure over periods of 24 h or more. Nevertheless, as often happens, better methods have revealed further problems. For example, it has been estimated from calorimeter studies that the energy expenditure of subjects engaging in minimum physical activities is 1.4 × basal metabolic rate (BMR) (37). However, measurements of energy expenditure

by the labelled-water method of British housewives in their homes, carrying out their normal activities, was 1.38 × BMR (109). Have we been consistently overestimating energy expenditure and needs in ordinary life (e.g. 30)? In the face of such uncertainties, it is very difficult to discuss adaptation to low intakes, if we cannot define a baseline in people who have not needed to adapt.

In the following sections I examine the possibilities for adaptation in the two main components of energy expenditure—basal metabolic rate and physical activity. Nothing will be said about growth because in children the cost of weight gain depends largely on the composition of the tissue deposited. Although the gap between observed intakes and estimated requirements is particularly large in pregnant and lactating women (108), not enough is known about the energy costs of human lactation or of the development of the fetus and adnexa for a worthwhile discussion of adaptation in these processes. All that can be said is that undernourished women tend to produce smaller babies and less milk.

There are four strategies for adaptation, which are probably usually combined:

1. Achieving and maintaining a low body weight, as discussed above.

2. A reduction in voluntary and conscious activity, whether occupational or discretionary (37). This type of adaptation may be regarded by definition as undesirable. Very little is known about the extent to which it actually occurs when people are faced with a restricted intake, for example in the hungry season in some countries. However, this is a subject for anthropological rather than metabolic inquiry.

3. Unconscious economy of activity. It has often been suggested that big eaters are able to remain thin because they are more "tense," habitually making unnecessary movements, etc, and anecdotal impressions have been recorded of the smoothness and economy of effort with which people seem to move in tropical countries. Certainly there are easy and difficult ways of doing the same task and much depends on training, habit, custom, and experience. These points are mentioned because they have to be borne in mind when one looks at physiological studies of the energy cost of work.

4. True metabolic adaptations. In order to establish the existence of such adaptive changes, energy expenditure must be related to body weight or, if possible, to lean body mass (LBM).

Basal Metabolic Rate

The BMR is defined as the rate of energy expenditure in a subject who is fasting, and completely relaxed in a thermoneutral environment. The resting metabolic rate (RMR), in the post-absorptive state and physically at rest, is usually the best approximation that can be achieved in practice. The terms are used interchangeably here.

For most people in most occupations total energy expenditure (EE) is unlikely to be greater than twice the BMR (37). This is one reason why the BMR is so important in relation to adaptation. A second reason is that BMR or RMR is easier to measure than other components of EE.

In the following discussion the observed BMR is often compared with the expected BMR, calculated from body weight by equations recently published by Schofield et al (126) on the basis of an analysis of the world literature. These equations are simply descriptive of data from healthy populations. They do not claim to have the physiological significance of allometric equations (63).

The relationship of BMR, expressed as kcal per person per day, to body weight is not linear. In healthy people the BMR/kg rises as body weight falls and except at extremes this effect is independent of height (37). For example, from the Schofield equations a young adult male will have an expected BMR of 1750 kcal/d or 25 kcal/kg/d, whereas at 55 kg his expected BMR is 1520 kcal/d or 27.6 kcal/kg/d. However, on the basis of $Wt^{0.67}$ the two rates are the same (102 and 104 kcal/$wt^{0.67}$ respectively). This identity suggests at first sight that there can be no difference in body composition between the two subjects (63). Nevertheless, differences almost certainly do exist. The 55-kg man is likely to have a lower proportion of body fat and, at least in more extreme cases, to have a different make-up of his LBM (see below).

The available evidence for a metabolic adaptation in BMR is of three kinds, described in the next three subsections.

THE EFFECT OF WEIGHT LOSS There have been many studies, summarized by Apfelbaum et al (3) and by James (71), of the effect on BMR of restricted food intake and consequent weight loss. The results are rather variable. In general there is a rapid initial fall in BMR in response to severe and indeed artificial reduction of energy intake, as in the treatment of obese patients, followed by a slower fall that goes hand in hand with loss of weight. It is the second aspect that is of more interest in relation to long-term adaptation. Two examples may be given, one old, one new.

In the classical semistarvation experiment of Keys et al (77) the average weight of the subjects fell from 68 kg (BMI 21.4) initially to 52 kg (BMI 16.3) after 24 weeks of semistarvation. The BMR per kg fell during this time by 16%, most of this fall occurring in the first two weeks, whereas on the basis of body weight alone it would have been expected from the Schofield equations to rise by 12%. This, therefore, represents a very substantial reduction.

The second example comes from a study by Forbes and coworkers (42) of subjects with anorexia. They started with an average BMI of only 14.2; their BMR was 77% of expected and rose with treatment to 93, while the BMI was still only 16. However, in another series of anorexic patients with an even lower initial BMI, there was no reduction in resting metabolic rate per kg compared with standard values, for which the source is not given (141).

In severely malnourished children the BMR per kg weight or LBM has been found to be low (14, 93), but rapidly rises with treatment to levels that may be greater than normal. In these children (48, 157) and in rats (160) tissues such as muscle and skin, with a low metabolic rate, are preferentially lost, while the visceral tissues and brain, with a high metabolic rate, tend to be preserved. It is probable, therefore, that the person with a low body weight has, from a physiological point of view, a reduced metabolic rate per unit LBM, which is cancelled out by the effect of smaller body size per se. Admittedly this is an academic point, since from the nutritional point of view what matters is the overall expenditure, regardless of how it is made up.

COMPARISONS OF BIG AND SMALL EATERS Rose & Williams (118) investigated the hypothesis that if, with similar levels of physical activity, some people eat far more than others, they must differ in their efficiency of energy utilization. They studied two small groups of normal young men, one of which had a recorded energy intake nearly twice that of the other, but they found no difference in the BMR. Edmundson (33) made a similar comparison between two groups of Javanese workers with the same average weights and heights (BMI 20). One group had an energy intake 55% greater than the other. In the big eaters the average BMR/kg/d was 36.5 ± 6.5 kcal; in the small eaters it was 18.4 ± 2.7—a result totally different from that of Rose & Williams. The expected BMR in young men of the same body weight (52.5 kg) is 28.2 ± 2.9 kcal/kg/d, so that in one group the BMR was 30% greater than the expected level and in the other it was 35% less. This finding clearly needs to be substantiated.

STUDIES ON SUBJECTS WHO ARE PRESUMABLY HABITUATED TO LOW ENERGY INTAKES Schofield et al (126), in their review of the world literature on BMR, cite some 30 papers giving measurements on non-Europeans in developing countries, of which 20 come from India. They conclude that in Indians the BMR is significantly lower, by about 9%, than the expected rate, based on weight and height, of Europeans or North Americans. Many possible causes for this difference have been discussed in the literature—climate, ethnic group, diet—without any clear conclusions. Studies on Europeans in the tropics suggest that climate has only a small effect on BMR (119), and the more recent UN reports (36, 37) have removed the recommendation of previous committees that estimated energy requirements should be adjusted for environmental temperature.

A recent study by Shetty (128) throws some light on the relative importance of ethnic group and diet. Table 3 summarizes Shetty's results in poor Indian laborers, whose estimated daily energy intake was extremely low. The resting metabolic rate (RMR) of the laborers per kg was significantly lower than that of the Indian controls, particularly when related to lean body mass. It was some

Table 3 Metabolic rates in Indian laborers and control subjects

	Indian laborers[a]	Indian controls[a]	US volunteers[b]	
			Initial	At 24 wk
Number	14	14	32	32
Intake (kcal/d)	1540	2260	3490	1570
Body wt (kg)	45.8	61.4	69.4	52.6
BMI	16.6	20.7[d]	21.4	16.3
Body fat (%)	6.1	14.3[d]	13	5.2
RMR (kcal/kg)	25.1	26.5[d]	23.1	19.3
RMR (kcal/kg LBM)	26.7	31.0[d]	26.8	20.3
Expected BMR (kcal/kg)[c]	30.1	26.4	25.2	28.4
Observed/expected BMR (%)	83	100	92	68

[a]Data summarized from Shetty (128).
[b]From Keys et al (77).
[c]Expected BMR from Schofield et al (126).
[d]Difference between labourers and controls significant at $P = 0.01$ or less.

17% lower than the expected value for Caucasians at the same body weight. It is interesting to compare Shetty's laborers with Keys' subjects after 24 weeks of semistarvation. The BMI is the same in the two groups; the BMR per kg of Keys' volunteers was 68% of that expected on the basis of body weight. Thus the reduction was much greater in the Americans exposed to a low intake for a relatively short period than in the Indians, who were habituated to it. In this case adaptation seems to have achieved a successful compromise since the Indians were active and fit, but this could not be said of Keys' subjects.

Data from Third World countries other than India are scanty and are summarized in Table 4.

Finally, we have comparisons between different ethnic groups living in the same environment. Mahadeva et al (87) found no difference in the energy costs of walking and stepping between Europeans and Asians in Edinburgh. Geissler & Aldouri (51) compared European, Asian, and African students, matched for

Table 4 Resting metabolic rates in different ethnic groups

Subjects	Sex	No.	Food intake	BMI	RMR (kcal/kg/d)	BMR (% of expected)	Ref.
Chinese in Taiwan	M	50	normal	19.6	25.75 ± 2.7	93	66
Chinese in US	M	6	normal	19.4	25.95 ± 3.9	95	66
Jamaican	M	5	low	19.6	24.5 ± 2.9	88	4
Jamaican	F	5	low		25.8 ± 4.2	102	4
Javanese	M	5	high	19.8	36.5 ± 6.5	129	33
Javanese	M	6	low	20.2	18.35 ± 2.7	65	33
New Guineans	M	15	normal	24.6	25.4 ± 2.5	96	65
Japanese	M	10	normal	22.2	28.65 ± 4.7	112	65

weight and height, well nourished (average BMI 23.5), and presumably on an adequate diet. The lying metabolic rate was 17% lower in the Africans and Asians than in the Europeans. In a similar study in France, Dieng et al (29) found no difference in lying metabolic rate between Vietnamese refugees and French subjects. In both these studies the non-Europeans had been living in Europe for several months, so they may have lost any previous adaptation. These divergent results are difficult to interpret; perhaps the reason is that the lying metabolic rate was not precisely standardized.

In conclusion, the evidence is consistent with the hypothesis that there may be a significant reduction in BMR, of the order of 10%, in people on habitually low intakes. It is not clear how far and in what way this reduction is related to a fall in body weight. There is no evidence that ethnic differences are important, or that the low BMR is maintained when body weights and food intakes are within the normal range.

Diet-Induced Thermogenesis

In recent years there has been a great deal of interest in diet-induced thermogenesis (DIT), particularly in relation to obesity (47, 72, 119, 129, 165). "Big eaters" appear to have a larger thermic response than others (94). There is some disagreement about the extent to which DIT may be reduced in obesity. James & Trayhurn (75) found an inverse relation between the body fat content and the thermic response to feeding fat, but not to protein or carbohydrate, whereas Garrow & Hawes (49) showed that the response depended on the energy content of the meal and not its composition. Garrow (47) concluded that a failure of thermogenesis is unlikely to play an important role in causing or maintaining obesity.

There is not much information about the effect on DIT of habitually low energy intakes. Diet restriction has been said to produce a reduction in DIT (3), but this effect has not always been found (71). In severely malnourished children, who have a low BMR (14, 93), there was no DIT in response to food, but it reappeared when appetite was restored, food intake increased, and the children began to gain weight. In these studies the magnitude of the thermic response was linearly related to the rate of weight gain (13). In anorectic patients undergoing treatment the thermic response to a glucose meal was unusually high (16%), as in the recovering children (141).

When these children begin to gain weight they show a large increase in the rate of whole-body protein synthesis (54). It therefore seemed reasonable to conclude that DIT is not a catabolic response, as used to be thought, but represents the energy cost of protein synthesis and the conversion of carbohydrate to fat (5). This interpretation is confirmed by the finding that when the rate of protein turnover was measured in normal adults over 24 h, during the day (when they were eating) the rate of protein synthesis was high and during the

night (when they were fasting) it fell (23). One might, therefore, expect a reduction in DIT in conditions where protein turnover is depressed, as discussed below in the section on protein turnover.

DIT is usually about 10% of the energy value of a meal, so that over a whole day's intake it would amount to about 200 kcal. Thus a 50% fall in DIT, which, according to James (71) is the most that could be expected, would save some 100 kcal. This amount, though small, would still be a significant economy.

Efficiency of Physical Work

Work efficiency may be considered at several levels—biochemical, physiological, and "real life." At the biochemical level, the mechanical efficiency of muscular contraction is the product of the coupling efficiency (work done per unit ATP hydrolyzed) and the efficiency of energy transduction to ATP by oxidation of substrate. This aspect is not considered here.

MECHANICAL EFFICIENCY I use this term to describe the ratio between mechanical work done and the energy expended in doing it. The simplest and most usual method of measuring efficiency so defined is on a bicycle ergometer with an electric brake so that the mechanical work done can be adjusted and known precisely, while oxygen consumption and respiratory exchange ratio are measured to determine the amount of energy used. The great advantage of the bicycle ergometer is that it does not involve lifting the body, so that efficiency should be independent of weight. However, even with this simple system there are problems. To determine the energy cost of the work itself it is necessary to subtract the energy expenditure when no work is being done. Often this has been taken as equal to the BMR, but it is more accurate to use as the baseline the expenditure at zero load, since this takes account of the energy cost of moving the legs (162). Another method is to determine efficiency as the slope of the line relating increase in work to increase in oxygen consumption.

In studies in which careful attention was paid to the question of baseline (43), the mechanical efficiency in healthy men was found to be 26–30%. In these experiments the relation between work load on the ergometer and $\dot{V}O_2$ was linear, indicating constant efficiency, over the range 200–800 kp·m/min. However, the authors point out that the literature on the relation between work load and efficiency is very contradictory, there being reports of increasing, decreasing, or unchanged efficiency with increasing load. This may be because inadequate attention was paid to the baseline, or because of failure to reach a steady state. Another factor is the speed of work. In the experiments of Gaesser & Brooks (43), efficiency at constant load fell off with increasing speed of pedalling. On the other hand, Bunc et al (15) reported that in subjects running on a treadmill, there was a linear relationship between speed and $\dot{V}O_2$ within the range 20–80% of $\dot{V}O_2$ max. The question of speed may be more important in relation to "real life" work (see below).

In spite of the carefully controlled conditions of the studies quoted, there is considerable variability between subjects. In the study by Whipp & Wasserman (162) the increase in $\dot{V}O_2$ for a fixed load showed a three-fold range in eight presumably normal men. In that of Gaesser & Brooks (43) the coefficients of variation were of the order of 8%, giving a range of 1.4 from +2 SD to −2 SD.

Measuring the amount of mechanical work done in other activities, even simple ones such as running or stepping up and down, is extremely complicated (68, 78, 110). In their study on athletes, Bunc et al (15) obtained the results shown in Table 5. It is interesting that in spite of the large differences in calculated mechanical efficiency, the energy cost of moving 1 kg over 1 m, which might be regarded as an example of "real-life" efficiency (see below) was very much the same in the different kinds of athletes and was only some 10% higher in untrained subjects. This fits in with the statement (6) that, contrary to the common misconception, training (as opposed to adaptation) does not produce any change in the metabolic efficiency of the muscles.

Perhaps a solution of this apparent paradox lies in a different pattern of muscle fiber types in subjects adapted to different speeds of work. Komi et al (78) performed muscle biopsies on subjects who subsequently ran a marathon. There was a positive correlation between the proportion of slow-twitch fibers and $\dot{V}O_2$ at the anerobic threshold—a measure of maximum working capacity. Slow-twitch fibers are said to be more efficient than fast-twitch ones, in terms of mechanical force development per unit ATP used (see 161a). The studies of Russell and coworkers (83, 120) showed that in malnourished patients there was an increase in the ratio of slow to fast fibers, mainly due to a reduction in the number of fast fibers, the slow being better preserved. The same effect has been found in hypothyroidism (164). One might venture the hypothesis that a possible mechanism of adaptation is a relative preservation of slow-twitch fibers or, perhaps more generally, the achievement of an optimum pattern for a

Table 5 Work output and mechanical efficiency of different types of athletes[a]

Subjects	BMI	Cost of work[b] (kJ/kg/m)	Mechanical[c] efficiency (%)
Middle-distance runners	20.5	3.57	34.1
Endurance runners	20.1	3.63	32.4
Marathon runners	20.9	3.67	31.1
Football players	23.6	3.88	24.8
Pentathletes	23.6	3.95	22.6
Untrained subjects	—	4.0	19–20

[a]Data from Bunc et al (15).
[b]Energy cost of running on treadmill at 5% slope.
[c]Calculated according to Ito et al (68).

person's particular lifestyle. Bassey & Fentem (6) are cautious about the possibility of transformation of one fiber type to another, but they are discussing training rather than adaptation.

Attention has been drawn in this section to some technical points and to apparently contradictory results to emphasize the difficulty of establishing real differences between groups in the mechanical efficiency of muscular work.

PHYSIOLOGICAL EFFICIENCY What we are really interested in with respect to adaptation is the actual energy expenditure needed for a particular task or activity. In this context "efficiency" is often taken as the ratio (energy expended during work − energy expended at rest)/total energy expended while working. No attempt is made to estimate the actual mechanical work done. This might be called the "apparent efficiency." Very often, however, in comparisons between individuals and groups it is the gross rather than the net cost that is of greater real interest. It has been proposed (37) that the energy costs of activities and occupations should be expressed as multiples of the BMR since most common activities involve moving the body. It has been shown that for walking and running in normal subjects the cost per kg appears to be independent of body weight (55, 85, 165). Gross expenditure per kg is therefore probably the most useful parameter for comparisons between individuals or groups when one is looking at adaptive changes in working efficiency. In such comparisons it is clearly essential that activities should be standardized. When this condition has been strictly adhered to, no important differences between ethnic groups have emerged (29, 51, 87). However, in these cases, as mentioned above, the Asian and African subjects had been living in Europe for some time and might have lost any adaptation that they had acquired.

A study that has attracted much interest was made by Edmundson of working efficiency in Javanese farmers, comparing big and small eaters. In one experiment (33) the 24-h food intake and total energy expenditure were measured and an index of "relative efficiency" calculated as intake/output. This ratio varied from 0.6 in big eaters to 1.6 in small eaters. However, if these discrepancies between intake and output were real and habitual, there must in the long term have been changes in body weight, which were not recorded although the study lasted a year. In a second experiment (34) Edmundson measured the energy cost of work on a bicycle ergometer, and with work at 100 W found a significantly lower gross energy cost in small than in big eaters, although their weights and heights were the same. Norgan (99) has commented: "The net mechanical efficiencies are typical of values found in Europeans, except in the high intake group at high work loads (100 W), when the value of net efficiency was at the lower limit of the expected range (22 ± 4%). Thus a significant difference in work metabolism appears to arise from a low efficiency in the high intake group rather than from a high efficiency in those with a low intake." Spurr et al (135)

reported no difference in gross efficiency of walking on a treadmill between marginally malnourished and normal boys.

The problem remains that activities usually cannot be standardized. How can one suppose that the mechanical work of digging, for example, is the same everywhere? For this reason Norgan et al in their classical study in New Guinea (100) cautiously refrained from comparing the energy costs of different activities with the standard values obtained in well-fed countries (103). When such comparisons have been made, e.g. in the Philippines (27) and in pregnant women in the Gambia (81), they have not shown any differences. Parizkova concluded: "The gross or net efficiency of *standardized* tasks [italics mine] appears not to increase with low food intakes" (102).

EFFICIENCY IN REAL LIFE One also has to consider that people differ in their patterns of activity and the ways in which they live and carry out their work. It has often been suggested that some people remain thin in spite of a large food intake because they are more tense and fidgety. Garrow & Webster (50) attempted to assess the cost of such minor thermogenic stimuli and concluded that on a 24-h basis they might increase energy expenditure by some 12%. Avoiding unnecessary movements may be an important form of adaptation. Lawrence et al (81), in their studies on pregnant women in the Gambia, observed that "most activities were performed with considerable economy of effort, i.e. there were few superfluous movements." Booyens & McCance (10) say of their subject RM, who had an exceptionally low expenditure in running and cycling: "RM is both a cyclist and a long-distance walker of great experience and has a highly developed sense of rhythm, and all unnecessary movements were probably eliminated from both occupations twenty five year ago."

The speed at which people work may also be important. If there is a given task to be done, is it more economical to perform it slowly or quickly? Ashworth (4) measured the energy cost of moving a certain number of bricks from point A to point B. The greater the number of bricks carried in one load, and hence the fewer the journeys, the less the expenditure for the total task. When the subjects carried the number of bricks that was natural to them, their expenditure fell in the middle of the range. In a study of this kind the result will depend on the relative cost of carrying the load and of walking the distance. Evidently in this experiment walking accounted for the greater part of the cost.

It is generally considered (103) that in walking a fixed distance the total energy cost is the same regardless of the speed, within certain limits. In the study of big and small eaters referred to earlier (118), the natural pace of the big eaters was faster than that of the small eaters, but their energy expenditure over a given distance was the same. However, there is divergent evidence in both directions. The data of Goldman & Iampetro (55) indicate that with varying loads and grades the cost of walking 5 miles would on average be about 10%

lower at 2.5 than at 3.5 mph. Imms, who has given a very full discussion of this subject (67), has put the most economical rate even lower, at 1.8 km per h. On the other hand extrapolation from the results of McDonald (85) suggests that, over a range of body weights, in order to cover a given distance, walking at 100 m/min would be 15–20% more efficient than walking at 40 m/min.

The influence of load may be important. Data quoted by Passmore & Durnin (103) show that, in walking with a load of 40 lb, energy expenditure increased more than linearly with speed. Thus at 3 km/h the expenditure was 4 kcal/min and at 6 km/h it was nearly 11 kcal/min.

Here again, therefore, although the observations are relatively straightforward, there seem to be many contradictions. Perhaps the most practically useful conclusion is that of Bassey & Fentem (6) that short alternating periods of work and rest allow the same amount of work to be done in a given time with a much lower heart rate and lactate level than if the work and rest periods are longer.

This observation raises the question of work capacity, which is not strictly relevant to that of work efficiency. Many studies have been made (for a summary, see 134) of maximum working capacity ($\dot{V}O_2$ max—an index of cardiorespiratory fitness) in adults and children in developing countries. In general, when poorer, so-called undernourished, people are compared with more privileged groups, their absolute $\dot{V}O_2$ max is lower, but indices of physical fitness, when corrected for body weight, may be equal (28, 136) or even higher (39). Only with very severe deficits in body weight has there been found a lower working capacity per kg (122). It has been argued that if a given task involves a certain absolute energy cost, a person with a lower $\dot{V}O_2$ max will be at a disadvantage, at least in endurance, since he will be working at a higher proportion of his maximum capacity. However, this argument loses much of its force if it is accepted that in most tasks, though admittedly not in all, the rate of energy expenditure is proportional to the body weight. Only when $\dot{V}O_2$ max per kg is low will there be a real handicap.

Conclusion

The most important adaptation to a low energy intake is to have a low body weight. Beyond that, in the present state of knowledge it seems probable that any adaptation that occurs is the sum of several separate but small sources of economy. Of these the most important is a reduction in BMR, which is unlikely to be greater than 10%. There is no rigorous evidence of an increased efficiency of muscular work. However, there may perhaps be significant savings from a more economical pattern of work and lifestyle. In particular, for many tasks it may be more economical of energy to work slowly rather than quickly. This subject needs further study.

Possible biochemical mechanisms for economizing energy will be discussed in a future publication.

ADAPTATION TO LOW PROTEIN INTAKES

The ability to achieve nitrogen balance over a wide range of intakes is probably the most clear-cut example of nutritional adaptation. This is the first line of defense against an inadequate intake and its objective, in teleological terms, is to maintain the constancy of the body's protein mass. Once the capacity to economize N is exhausted, the second line of defense is a reduction in lean body mass. All committees that have been concerned with the subject have assumed that the protein requirement is directly related to body weight, or more precisely to lean body mass, so that in adults in the absence of growth, a single figure can be given for the protein requirement per kg. In fact there is no evidence either for or against this assumption; it is entirely possible that the nitrogen requirement follows the same rules as the oxygen requirement, as indicated by the BMR, and that the requirement per kg increases with decreasing body weight. Such a relationship would make biological sense, but it would reduce the extent to which adaptation could be achieved by a fall in lean body mass.

In children, if the intake of protein or indeed of any other nutrient is inadequate, there is a fall-off in the rate of growth in weight, so that in them the second line of defense is to sacrifice growth. It has been suggested (53, 155) that growth in height may be particularly sensitive to protein supply and that stunting in height is perhaps a manifestation of protein deficiency. Pregnancy and lactation are often regarded as coming under the heading of growth, since new protein is deposited or secreted. Here, however, the priorities seem to be different, since these kinds of growth can be achieved, at least to some extent, at the expense of the mother's own tissues.

This section is concerned with the metabolic adaptation that constitutes the first line of defense, in which the central concept is that of nitrogen balance and the conservation of body nitrogen.

Nitrogen Balance

At any given body weight the minimum N intake needed to secure balance, that is, the lower limit of adaptation, is determined by two factors: the obligatory N loss and the efficiency with which food protein is used to cover that loss.

OBLIGATORY LOSSES Numerous short-term balance studies, summarized by Bodwell et al (9) and in the most recent FAO/WHO/UNU report (37), have shown that in young North American men the average obligatory N loss in round figures is 60 mg/kg/d, of which 35–40 mg are excreted in urine, 15–20 mg in feces, and about 5 mg from the skin. The fecal component depends largely on the quality of the diet, being greater in diets high in fiber, such as those of Third World countries. Nitrogen is lost from the skin mainly as urea, and therefore this loss may be expected to be somewhat less on low-protein diets, when blood urea concentrations are low. However, skin loss is only a

small part of the total. Any possibility for economy lies in reduction of the urinary N loss. Even on minimal protein intakes, about 50% of urinary N is in urea. The amount of ammonia excreted is determined by the need to maintain acid-base balance and tends to be lower on diets containing vegetable rather than animal protein, because they produce smaller amounts of acid. As Folin pointed out 80 years ago (40), the excretion of the other N-containing metabolites (such as uric acid, creatine, and free amino acids) appears to be remarkably constant regardless of the level of protein intake, and there is no evidence of any physiological mechanism for regulating this source of N loss.

A number of studies confirm that there is little scope for economizing N by reducing obligatory loss. Nicol & Phillips (97) showed that in Nigerian farmers the obligatory urinary N loss was very similar to that of North American men. In collaborative studies organized by the United Nations University (113) the obligatory losses in different population groups were very constant, although there is an indication that they may be slightly lower in oriental people (66).

EFFICIENCY OF UTILIZATION The efficiency of utilization is the slope of the line relating N balance to intake. In adults who are not growing and in whom one cannot expect a positive balance, the slope has to be determined at submaintenance levels of intake. The requirement is the intake at zero balance—that is, the intake needed to make good the obligatory losses. Although individuals may have the same obligatory losses, they may differ in the amounts needed to cover them. The UNU studies concluded that there was no difference between the average protein requirement of different ethnic groups; the mean requirement was 0.6 g protein/kg/d. As long ago as 1956 Phanselkar & Patwardhan (105) stated that the N requirement of Indians was strictly comparable to that of Americans habituated to a high intake. However, there is not complete agreement; more recent studies in India (1, 7a) on men and women on vegetarian diets led to somewhat lower estimates of average protein requirements. The very detailed investigations of Nicol & Phillips (98) suggested that Nigerian farmers utilized protein more efficiently than American men did.

The balance studies mentioned so far were all short-term and it may be objected that they did not allow enough time for adaptation. This problem is discussed in some detail in the 1985 report on energy and protein requirements (37) and by Rand et al (112). The report points out that after the first few days on a protein intake close to maintenance "because of day to day variation in urinary N excretion it is difficult to make accurate measurements of the subsequent slope or to prove that it is significantly different from zero." It concludes from the evidence available at that time (1981)—and there does not seem to be any new information since then—that when subjects are fed a fixed low-protein diet over long periods, some do and some do not show a slow drift toward a lower rate of urinary N excretion. Data from a long-term study on men fed 0.64 g protein/kg/day showed that urinary N continued to fall for at least 90 days

(168). The rate of decline after the first two weeks was about 0.01 g N/kg/d, which would be statistically undetectable in short-term studies. Even after 100 days the cumulative loss (about 1 g of N) would be too small to be determined by any existing method of measuring total body nitrogen. To get a general answer to the question of long-term adaptation, it would be necessary to study a large number of individuals for a very long time on a fixed protein intake slightly below that needed for maintenance. This is clearly not a practical proposition with human subjects.

As in the case of energy, convincing evidence about long-term adaptation to habitually low intakes can probably only be obtained by observations in the field. For example, a typical Kaul woman in New Guinea, as described by Norgan et al (100), would weigh 50 kg and have a protein intake of 24 g/d, of which only 3.5 g would be animal protein. If such an intake is habitual, and if this woman is in balance, as she must be to survive, her daily N output would be 77 mg/kg/d $(24 \times 1000)/(6.25 \times 50)$. If her obligatory losses were 60 mg/kg/d, this would give an efficiency of utilization of dietary protein of better than 80%, in spite of its being of low quality. Of course, it may be and indeed has been argued that such people are depleted. The classical experiments of Allison et al (2) showed that dogs depleted of N utilized dietary N much more efficiently than did control dogs. Children in Jamaica recovering from malnutrition utilized almost 100% of milk N when it was fed at a low level (21). However, the New Guinea woman or the Nigerian farmer, unlike Allison's dogs or the Jamaican infants, were in a steady state. Therefore in this context it is difficult to distinguish depletion from adaptation.

Twenty or 30 years ago such subjects, although in balance, would have been described as having depleted protein stores. The transition from a high to a low protein intake involves a net loss of so-called labile protein, which is proportionately greater in the rat than in man. In the rat the total loss amounts to 3–5% of total body N, initially from liver and viscera, later mainly from muscle and skin (160). In man the loss that occurs before a new steady state is reached is only about 1% of total body N. In malnourished infants, whose stores should be depleted, the loss on moving from a high to a low intake was no less than in well-nourished children (20). We do not know from what tissues this protein comes, but it seems likely that the loss is too small to be of any significance. The important point is that the concept of some kind of labile protein as a "store" is no longer valid. The losses or gains that occur when the dietary protein intake is changed are simply a by-product of the metabolic changes involved in shifting from one steady state to another.

Utilization of Urea

In a person on a normal diet about 30% of the urea produced in the liver passes into the colon and is split to ammonia by bacterial urease (150). Part of this ammonia is recycled to urea and part of it is taken up into nonessential amino

acids. Picou & Phillips (106) and Jackson et al (70) have examined the question whether on a low protein intake increased utilization of urea N might contribute to nitrogen economy. They found that on a low intake there was an increase in the proportion of urea produced that was utilized for amino acid synthesis, but no increase in the absolute amount taken up. Walser (150) has objected to the word "utilized" in this connection, since the shuttling of N between urea and amino acids essentially constitutes a futile cycle. This view is correct to the extent that the exchange of N between urea and amino acids does nothing to replace the carbon skeletons of the essential amino acids lost by oxidation. The only natural situation in which the recycling of urea could be useful is if the diet contains a relative excess of the essential amino acids, the limiting factor being nonessential N (132). This situation is unlikely to arise in real life in people on low protein intakes. Studies with ^{15}N-labelled urea, showing that ^{15}N may be incorporated in plasma proteins (144), demonstrate uptake into amino acids and transamination of NH_3 derived from urea, but they provide no evidence of biosynthesis of the essential carbon skeletons.

It is a question for the future whether it may be possible to alter the colonic microflora to include strains of bacteria that synthesize essential amino acid, and whether they would be absorbed.

Energy Intake

Energy balance has a profound effect on nitrogen balance. Within a certain range of intakes each extra kilocalorie reduces urinary N loss by about 1.5 mg. These original observations of Munro (95) and of Calloway & Spector (17) have since been confirmed many times (37). The N-sparing effect of increased availability of energy is well shown in the obese (41).

This effect of energy intake on N retention or loss would militate in two ways against the capacity to adapt to low protein intakes. The very people whose diet is marginally low in protein are those whose total food intake is most likely to be inadequate. These people will also have small stores of body fat, as is now very well recognized. Thus the full capacity to adapt to a low protein intake can only be achieved if energy intakes are adequate.

Protein Turnover

One of the first questions that arose when interest in protein turnover was renewed in the 1960s concerned the relationship between N excretion and N flux. Is a constant fraction of the amino-N flux irreversibly oxidized to urea? Putting it in a different way: are alterations in N excretion determined by changes in the rates of protein synthesis and breakdown? The alternative hypothesis is that rates of protein turnover and of N excretion vary independently. Our earlier results suggested that the second hypothesis was correct (153). In studies on young children, changes in protein intake produced very little change in protein turnover. On a generous protein intake of 6 g/kg/d,

25% of the amino-N flux was excreted as urea, whereas on an intake of 1.2 g/kg/d the flux remained unchanged and only 4% of it was excreted (107). The body is therefore very efficient, reutilizing for protein synthesis almost, but not quite, all the amino acids entering the free amino acid pool. This leaves little scope for adaptive improvements in economy.

Later work has to some extent modified the view that the rate of protein turnover is independent of the intake. The early studies were done with protein intakes at or above the maintenance level. More recent work (summarized in 156) suggests that at submaintenance intakes rates of turnover are reduced. At the same intake the turnover rate is lower in children with kwashiorkor, who may be regarded as depleted, than in normal children (54). These malnourished children are also unable to increase their turnover rates in response to an infection and they excrete less nitrogen than infected children who are normally nourished (148). This finding recalls the old observation, that undernourished patients have a smaller "catabolic" response to trauma (24). It is difficult to decide whether this represents a protective mechanism to preserve body tissues or a failure to meet a challenge. The severely malnourished child has, at least in the acute stage, a reduced capacity to produce humoral antibodies and impaired cell-mediated immunity (22, 147). The evidence for impairment of these defense mechanisms is much weaker in moderate malnutrition (147), so that the point at which adaptation breaks down is not clearly defined.

Muscle plays an important part in the response of whole-body protein turnover to low protein intakes. Experiments in the rat have shown that there is a fall in both protein synthesis and breakdown, so that balance is achieved at a lower rate of turnover (46). The reduction in synthesis results from a fall in the cellular concentration of ribosomal RNA (RNA/DNA ratio), with little change in the efficiency of synthesis per unit RNA (92). In man it has been shown from measurements on biopsies that the diurnal changes in whole-body protein turnover in response to fasting and feeding (23) are accompanied by parallel changes in the rate of muscle protein synthesis (115). Malnourished children have a reduced rate of methylhistidine excretion (96), which suggests a fall in the rate of myofibrillar protein turnover (166). More detailed reviews of the effects of diet on protein turnover in individual tissues are to be found in (156) and (159).

Plasma albumin provides perhaps the clearest example of adaptive changes in protein turnover. The elegant study of James & Hay (73) in well- and malnourished children showed that when the protein intake was reduced there was an immediate fall in the rate of albumin synthesis, followed after a short lag by a fall in the rate of breakdown and a shift of albumin from the extravascular to the intravascular compartment. The result of these processes was to maintain the intravascular circulating albumin mass. Similarly, Hoffenberg et al. (64) in experiments on adults showed that lowering the dietary protein intake caused a

fall of 36% in albumin turnover with a reduction of only 7% in plasma albumin concentration. Therefore, if it were possible to measure it routinely, the rate of albumin turnover would be a much more sensitive index of response to low protein intake than the classical measurement of albumin concentration. It has been claimed that the levels of other plasma proteins, particularly those with short half-lives such as transferrin and thyroxin-binding prealbumin, provide more sensitive "tests" of protein deficiency (for review, see 52, 130), but I know of no information about the effects of low protein intakes on their turnover rates. By contrast, the turnover rates of circulating immunoglobulins are not reduced in malnutrition.

From all this evidence it is well established that when amino acid supplies are limited the rate of protein turnover falls in many tissues and in the body as a whole. Because protein turnover is relatively less reduced in liver and visceral tissues (86) than in muscle, the fall in the body as a whole is modest. It is not possible to discuss here the mechanisms by which these effects are produced: how far they depend on changes in pattern of the many hormones that are known to influence protein synthesis and breakdown; or how far they are mediated by changes in free amino acid concentrations (159). However, in view of the important effects of thyroid hormones on the components of energy expenditure, it should be pointed out that these hormones also play a role in the regulation of protein turnover, at least in muscle. In the rat a linear relation has been found between the plasma concentrations of free T3 and the rate of muscle protein degradation, through control of the activity of lysosomal proteinases (90). The catabolic effects of T3 are reduced by protein depletion (16, 19). T3 also influences the rate of protein synthesis, apparently by regulation of ribosome production (91). It is only when the hormone is present in relatively large amounts that its catabolic effects predominate.

In conclusion, what advantage is it for protein turnover rates to be low? We have two nitrogen cycles, input/output and synthesis/breakdown, connecting through the free amino acid pool (155). If one is out of balance, the other must be also since alterations in the size of the free pool are small in relation to the flux (158). However, in the context of long-term adaptation both must be in overall balance, within which there are short-term fluctuations. There is no obvious direct connection between the two cycles when they are in balance, but there seem to be three indirect ways in which a reduction in the rate of protein turnover could make a positive contribution to adaptation. First, there is a small saving in energy. If the cost of protein turnover accounts for 15% of the BMR, a reduction of 30% in its rate would save some 70 kcal. The other two bonuses both arise from the diurnal rhythm of protein turnover that has already been mentioned. As Millward has suggested (90), if there is less net protein synthesis in response to the ingestion of food, there will be a smaller requirement for essential amino acids, so that survival will be possible on a dietary protein

mixture of lower biological value. Secondly, if the increase in protein breakdown that occurs in the post-absorptive state is damped down, there will be a reduced influx of amino acids into the free pool and therefore fewer opportunities for them to be lost by oxidation. This aspect is considered in the next section. Whether or not any costs are attached to the lower rates of protein turnover is completely unknown.

The Biochemical Basis of Nitrogen Economy

The foundation stone of our knowledge on this subject is the work of Schimke (124), who showed that in rats on a low-protein diet there was a reduction in the activity of the urea cycle enzymes, measured in liver homogenates in vitro. He later proved that in the case of arginase there was a fall in the actual amount of the enzyme and not merely a masking of its activity (125). Following this lead, Das & Waterlow (26) showed that after an increase or decrease in protein intake the time-course of changes in the four urea cycle enzymes followed quite closely that of the change in urinary N output. However, the correspondence is not exact. The rate-limiting enzyme in the urea cycle is probably argininosuccinate synthetase (ASS). Saheki and coworkers (121) found that when the protein intake was altered the change in ASS activity lagged behind that of urea formation, which suggests that other factors exert more immediate effects, such as the concentrations of ornithine and of *N*-acetyl glutamate, (145) although doubt has been cast on the role of the latter (84). These in turn depend on the supply of amino acids, particularly of glutamate (139) and of arginine. These metabolic relationships provide for rapid regulation of urea output in response to amino acid input (150). For long-term adaptation, changes in the amounts of the enzymes would at first sight seem to be more significant. Thus Saheki et al (121) found that the amount of the rate-limiting ASS, measured immunologically, was almost an order of magnitude lower in rats on 5% compared with 70% protein (0.69 versus 5.9 units/g).

However, this is not the end of the story. The real adaptive changes must be further up the line, controlling the input of amino-N to the urea cycle. The activity of many enzymes of amino acid metabolism is modified by the level of dietary protein intake. This is a subject that was much more intensively studied 10–20 years ago (e.g. 58, 133, 161) than it is now. The activities of some enzymes that have very short half-lives (151), such as tyrosine aminotransferase and tryptophan pyrrolase in the liver, show rapid and profound changes in response to a single meal (151). The activities of glutamic dehydrogenase and of aminotransferases in the liver change pari passu with those of the urea cycle enzymes (26). It seems still unknown how this coordinated control is achieved of enzymes some of which are cytosolic, others mitochondrial.

If urea production falls, there is a potentially toxic accumulation of ammonia unless it is removed by recycling to amino acids and uptake into protein.

Following this line of thought, we showed both in rats (137) and in children (138) that a reduction in urea cycle activity was accompanied by increased activity of what were then called the amino acid synthetases, now the amino-acyl-tRNA-transferases. Protein synthesis cannot occur unless all the essential amino acids are available in appropriate amounts. Therefore the real limiting factor is the rate of oxidation of the carbon skeletons of the essential amino acids.

A case could be made for the hypothesis that the key amino acids in this respect are the branched-chain amino acids (BCAs). Although the BCAs together contribute about 20% of the amino acid residues of most proteins, their concentrations in the amino acid pool are relatively low and particularly sensitive to the level of amino acid supply. The first step in their catabolism is transamination, mainly in muscle, followed by irreversible decarboxylation of the keto acids by the BCA dehydrogenase complex. In experiments some years ago, when it was still thought that the BCAs were oxidized exclusively in muscle, some evidence was obtained of a decrease in their rate of oxidation in rats on a low-protein diet (131), which suggested that enzymes in muscle could be induced or repressed, like those in liver.

It is now recognized that the BCA dehydrogenase complex is widely distributed in tissues (59), and that its activity in liver is probably more important than in muscle. There are several ways by which that activity is controlled. As Krebs (79) pointed out, the K_m of the enzyme is close to the concentration of the substrate in the free pool, so that the activity is concentration dependent. The enzyme complex exists in an inactive phosphorylated form, which is activated by dephosphorylation (61). Finally, there is an activator protein that reactivates the enzyme without dephosphorylation (114). Both mechanisms contribute to a reduction in dehydrogenase activity when dietary protein is restricted. According to Randle (114), on low-protein diets the activity of the activator protein falls by 90%.

Most of the work in this area of metabolism relates to short-term responses. It remains a challenge to define the control mechanisms that are most important for long-term adaptation. It is clear that the body has a highly efficient capacity for responding rapidly to large variations in amino acid supply—to economize when they are in short supply and to dispose of them when in excess. This flexibility is necessary since there is no store of protein, like that of fat, to buffer the system during periods of shortage or glut of food. There is no evident disadvantage in operating at the lowest possible level of amino acid intake and oxidation, because the maintenance of protein turnover, even at a somewhat reduced rate, ensures that amino acids are always available for exchange between tissues, according to where they are most needed. Nevertheless, there are limits to the adaptive capacity; although Walser (150) states that "the stimulus to ureagenesis virtually ceases at a low value of circulating amino acid

concentration," in our experience (152) even depleted children on very low protein intakes continue to excrete small amounts of urea.

Conclusion

The body's mechanisms for reducing nitrogen loss on low intakes of protein are reasonably well defined. What is not yet clear is the extent to which long-term adaptation may lower the limit. This subject is exceedingly difficult to study experimentally in man without imposing totally artificial conditions. In epidemiological studies we come up against the problem that in most situations it is energy rather than protein that is likely to be limiting. However, more work might be rewarding on subjects whose dietary staple is starchy roots with a very low and unbalanced protein content. For example, the persistently negative nitrogen balances that yet appear to be compatible with health, described by Oomen (101) in sweet-potato eaters in New Guinea, have never been satisfactorily explained.

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