Protein–energy malnutrition: the nature and extent of the problem

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ABSTRACT—The paper begins by describing how the names 'protein malnutrition' and 'protein-energy malnutrition' (PEM) developed from the local name 'Kwashiorkor'. The central feature of severe PEM is oedema; the classical theory suggests that the cause is a deficiency of protein, but other factors are also involved. In the community mild–moderate PEM is defined by deficits in growth. A distinction has to be made between low weight for height (wasting) and low height for age (stunting). Stunting in particular affects some 50% of children worldwide. Its causes and consequences are briefly discussed.

In adults, severe PEM has essentially the same features as in children and includes the condition 'famine oedema' or 'hunger oedema'; there are again controversies about its cause. In the community, chronic malnutrition is assessed by the body mass index (BMI) (Wt/Ht^2). Grades of deficiency have been defined and examples are given of functional consequences of a low BMI.

Secondary malnutrition differs from primary PEM because of the role played by cytokines and other concomitants of illness or injury. The importance is emphasized of chronicity or duration in determining the clinical picture.

Introduction

My experience has been almost entirely with protein–energy malnutrition (PEM) in the developing world, particularly in children (1). I think that most of the members of ESPEN are more concerned with malnutrition secondary to disease, as we see it in hospital in Europe. A connecting link is that our studies on PEM gave rise to the work on protein turnover, which was the subject of the Arve Wretlind lecture I gave to this Society in 1982 (2).

Protein–energy malnutrition in children

Clinical characteristics

The term protein–energy malnutrition (PEM) was first introduced in relation to children and it is worth pausing to look at the history of this name. Richard Asher (3) has remarked that a disease does not exist until it has a name. In the early 1930s, Dr Cicely Williams, the first professional paediatrician to be appointed to the British Colonial Medical Service, working in the then Gold Coast, produced two papers in which she introduced the name 'kwashiorkor' (4, 5). The characteristics of the condition, which carried a high mortality, are shown in Table 1.

There had been many previous descriptions from other parts of Africa and from Latin America of what seems to be essentially the same syndrome. The earliest that I have found, courtesy of Dr Sylvestre Frenk of Mexico, is from Mexico more than 100 years ago. There were almost as many names as there were reports; why, then, is 'kwashiorkor', one name among many, still so widely used? I think the reason is simply that the earlier papers were

Table 1

A. Height gains between 5 and 20 years in Hyderabad and Guatemala

	Height at 5 years (% of reference)	Gain, 5–20 years (cm)
*Hyderabad, affluent	95	63.1
*Hyderabad, poor	81	68.5
†Guatemala, affluent	94	68.9
†Guatemala, poor	86	63.8
USA	100	66.4

*From ref. 38
†From ref. 39

B. Height gains between 10 and 18 years in Kenya

	Male		Female	
	Well nourished cms	Malnourished cms	Well nourished cms	Malnourished cms
Age 10	143	130	144	124
18	164	165	157	157
Gain	21	35	13	34

From ref. 40

mostly published in local journals, in French or Spanish, whereas Williams' papers were written in English and appeared in internationally read journals. This in no sense detracts from her contribution, because her clinical description is first-class, but it is a point that is perhaps important for the history of medicine.

In the Ga language 'kwashiorkor' means 'the disease of the displaced child' but to anyone other than a Ghanaian it is a meaningless collection of syllables. That is what I call a 'code' name. Williams did not explicitly make the transition from a code name to a causal name – protein malnutrition – but she came very near to it. She pointed out that the disease occurred in children when they were

displaced from the breast by the birth of a new baby and put onto starchy paps low in protein, and she showed that it could be cured by milk.

After World War II, missions were sent out by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) to Africa, Central America and Brazil to investigate the frequency and cause of kwashiorkor. The Brazil report emphasized the difference from marasmus, or semistarvation, which had been known under various names for centuries, and made the point that intermediate cases were also seen. The conclusion of these reports was that kwashiorkor is a result of protein deficiency. This view was generally accepted, and so we moved from a code name to a causal name – 'protein malnutrition'. When it was realized how wide-spread the condition was, the United Nations (UN) set up the Protein Advisory Group to stimulate the production of weaning foods high in protein.

Then in the 1970s doubts began to creep in. Dietary surveys suggested that almost all diets in different countries met the protein requirements of young children as estimated by FAO/WHO in 1973 (6), whereas the energy intakes were well below the estimated requirements. McLaren, working in Beirut, in an article provocatively entitled 'The great protein fiasco', pointed out that marasmus was far commoner than kwashiorkor and vigorously attacked the UN policy (7). Gopalan in India claimed that children developed marasmus or kwashiorkor on diets that were quantitatively and qualitatively the same (8). So the term 'protein–energy malnutrition' came into being to cover the whole spectrum of clinical syndromes: at one end marasmus, reflecting an overall deficiency of energy, at the other end kwashiorkor, resulting, perhaps, from a relative deficiency of protein.

'Kwashiorkor' continues to this day to be used by clinicians to describe cases with oedema, fatty liver, skin lesions and so on, because they are clinically different from marasmics who do not show these signs. Thus the blanket name 'protein–energy malnutrition' is of more use for public health than for clinical medicine.

The question then arose: what characteristics must be present for the diagnosis of kwashiorkor to be made? An international working party concluded that the essential features are a significant degree of weight deficit and the presence of oedema (8). Kwashiorkor could be redefined as oedematous malnutrition, and there was general agreement at the time that oedema was the result of a relative deficiency of protein. This, then, would be an example of a general rule in nutrition: that specific clinical features arise only when a diet is unbalanced and deficient in particular nutrients – i.e. is qualitatively rather than quantitatively inadequate, although, of course, the two types of inadequacy are often combined.

Aetiology

There is still controversy about the cause of oedema in malnutrition. I myself believe in what may be called the 'classical' theory (1, 9), according to which an inadequate supply of protein leads to reduced albumin synthesis. There is plenty of evidence for this, both in man (e.g. 10) and from animal experiments; the consequent hypoalbuminaemia is, according to Starling's law, the main cause of oedema, although potassium deficiency, which is common in these children, also plays a part. Fatty liver is statistically associated with oedema in PEM. These livers are more fatty – up to 50% of wet weight – than any that have been described in experimental animals or in other pathological conditions in man. The hypothesis, not yet proven, is that they result from a failure of transport of fat out of the liver, and this in turn is caused by a reduction in synthesis of apolipoprotein, parallel to that of albumin. There is also epidemiological evidence in support of the classical theory: oedematous malnutrition occurs particularly in populations where the staple is low in protein, such as cassava, or contains protein of poor quality, such as maize.

The opposing theory points out that there is not absolute consistency between oedema and hypoalbuminaemia, and proposes that oedema results from damage by free radicals to capillary walls and cell membranes. One effect of this would be increased capillary leakiness. Certainly infections, which are common in PEM, can cause increased leakage (11), but in the only direct measurements of capillary leakiness that have been made in kwashiorkor, no increase was found (12). It is proposed that the fatty liver also is a result of free radical damage. However, according to classical pathology, the toxic fatty liver is quite different histologically from the fatty infiltration of kwashiorkor; in toxic states there is very little increase in fat content, but only in what used to be called fat phanerosis (appearance). My own belief is a compromise (1). I do not think that free radicals are direct causes of cardinal features such as oedema and fatty liver; rather, on the background of a diet inadequate in protein and micronutrients, including free radical scavengers, free radicals may damage cell membranes in a way that is perhaps irreparable. This may be occurring particularly in the intermediate condition of marasmic kwashiorkor where, in addition to oedema, there is severe wasting, which according to most accounts has the highest mortality.

The practical result of the free radical theory, as propounded by my colleagues and successors in Jamaica, Alan Jackson and Michael Golden, was that more attention was paid to infection, particularly small bowel overgrowth, and to trace element and micronutrient deficiency. They showed, for example, that in PEM there is a decrease in red cell glutathione (13), which is an anti-oxidant, and an increase in plasma ferritin (14), which is a pro-oxidant. Ferritin levels in fact correlated closely with mortality. The result of all this work was a substantial decrease in mortality in the Jamaica unit, although sadly this has not yet happened in hospitals elsewhere, where the mortality rate still ranges from 20 to 40% (1).

Prevalence

It is impossible to give figures for the incidence or pre-

valence of severe PEM, as defined by the Wellcome classi-fication (8). It does seem, however, to be becoming less common. In Calcutta, for example, where there used to be large numbers of cases, kwashiorkor is now scarcely seen (Bhattachariyya, personal communication). One sign of a high prevalence is when PEM occurs not only in young children but in older children and even adults. Such cases used to occur in the past and have been described also in India, Uganda, Zaire, Guatemala and elsewhere, but now I think they are seldom seen except under famine conditions.

PEM in children in the community

The severe forms of PEM described above are the tip of the iceberg. For every such case there are many more less severe, without typical clinical signs. In children mild–moderate malnutrition is defined in terms of growth failure. In the developing world the main causes of inadequate growth are deficient food and infections, usually combined.

For public health purposes, a child is defined as 'mal-nourished' if it is more than 2 SD below the median weight for its age of an international growth reference. Since 1978 the WHO has given international status to the American data set called the NCHS (National Child Health Statistics) reference, which was mostly collected in the 1930s. A new international base may well be introduced in due course, since extensive data on well-nourished children are now available from many European countries. However, this is not particularly important. The main value of the reference is to make possible comparisons between different popula-tions or descriptions of the situation at different times, and for these purposes it does not matter what reference is used, so long as it remains the same. It should be clear, of course, that the reference is not necessarily an optimum, although derived from apparently healthy children.

The nature of the reference is not the only problem. It is obvious that a cut-off point of –2 SD in a continuous distrib-ution is an arbitrary dividing line between well-nourished and malnourished, but at least it has a logical statistical basis.

We now recognize that there are two types of growth deficit in children, thinness and shortness. Thinness is defined by weight for height, and a degree of thinness below –2 SD may be regarded as verging on the pathological and called 'wasted'. Shortness is defined by height for age, and below –2 SD is called 'stunted'. These two kinds of deficit represent separate biological processes. Though they may often be found together in the same child, they are in fact statistically independent. It is therefore an important advance that the WHO, in collecting statistics worldwide on the prevalence of childhood malnutrition, has provided separate columns for wasting and stunting (e.g. 15).

The peak prevalence of wasting is in the second year of life, coinciding with the introduction of weaning foods and a high incidence of diarrhoeal disease (16) (Fig. 1A). The cause of wasting therefore seems quite straight-forward: inadequate food aggravated by infections. Once the infectious episode is over, if the food is available,

A   Patterns of Wasting by Age

% wasted (% below-2SD.weight-for-height)

AFRICA
SOUTH ASIA
REST OF ASIA
AMERICAS
GLOBAL

B   Patterns of Stunting by Age

% Stunted (% below - 2SD height-for-age)
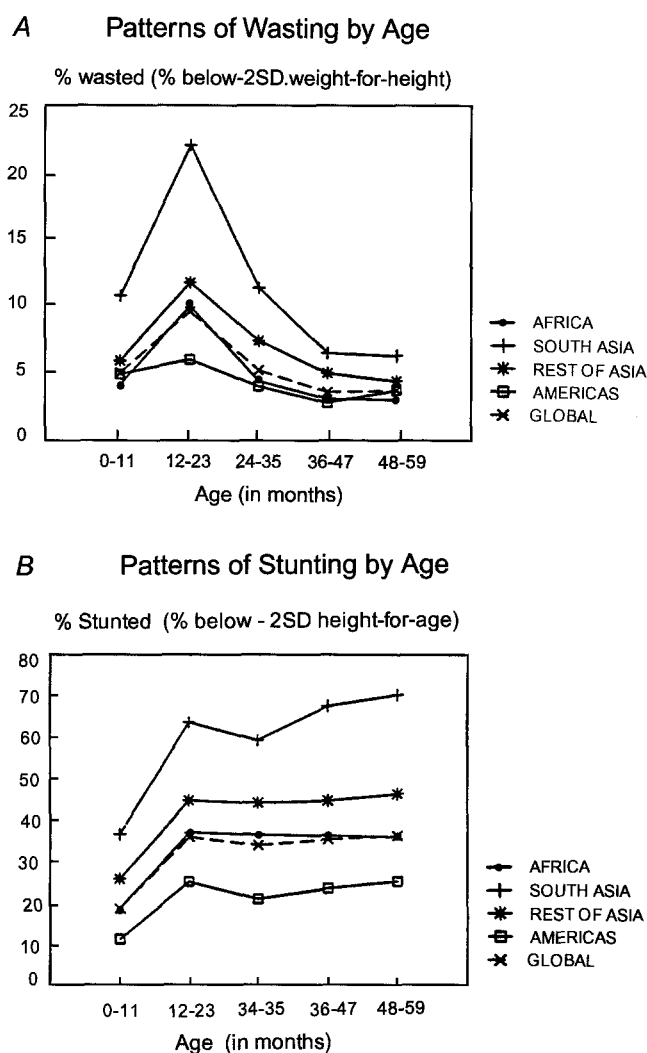
AFRICA
SOUTH ASIA
REST OF ASIA
AMERICAS
GLOBAL

Fig. 1 A Prevalence and age distribution of wasting in different regions of the world. From Carlson & Wardlaw (16). B Prevalence and age distribution of stunting in different regions of the world. From Carlson & Wardlaw (16).

weight is regained. The extra food required for catch-up is not very large, and has to be somewhat richer in protein than in energy (17).

The role of infections is very important. Pelletier (18) has recently made a meta-analysis which suggests that by potentiating infections, malnutrition accounts for over 50% of child deaths, most of whom are only mildly or moderately malnourished. He argues convincingly that the effects of malnutrition and infection are not additive but multiplicative. In his analysis no distinction was made between wasting and stunting.

Stunting has a different natural history. Typically, slow-ing in linear growth begins within 3 months of birth, and continues for 2 or 3 years (Fig. 2) (19). The prevalence of stunting is shown in Figure 1B (16); in South Asia it affects more than 50% of children. The rate of growth is restored more or less to normal by the age of 5 (Fig. 2). By that age the deficit in height compared with that of a normal child may be as much as 15 cm and be maintained into adulthood. Between 5 and 18 years the rate of growth
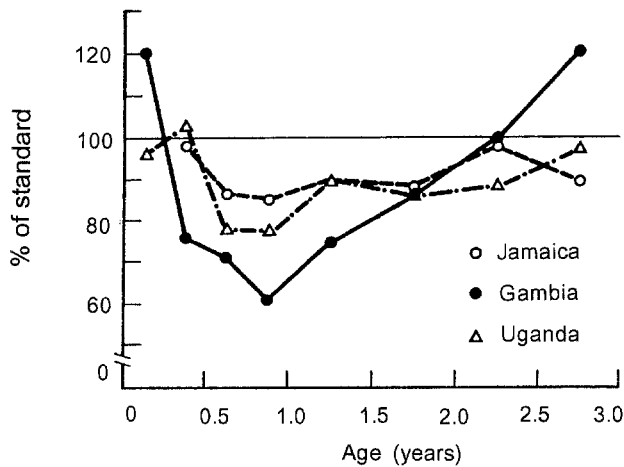
Fig. 2 Height velocity in relation to age in longitudinal studies of children under 5 in Jamaica, Gambia and Uganda. The horizontal line represents 100% of the normal rate of height gain. From Waterlow & Rutishauser (19).

is normal, but there is no catch-up. That is the pattern found in India and Guatemala (Table 1A). Consequently, some workers have suggested that the child is irreversibly programmed in its early years, or perhaps even before birth, to end up as a small adult. I am sure that this is not correct. Kenya, for example, shows a different pattern (Table 1B), with virtually complete catch-up, and there is plenty of evidence from studies on children who were brought from developing to developed countries, that catch-up is physiologically possible, at least up to the time of puberty.

It has frequently been suggested that the differences in height between different populations of children are genetic. There are, of course, individual, genetically determined, variations in height, but comparison of children from well-to-do families in different populations shows a remarkable degree of constancy. By and large, at the population level, genetic differences seem to be much less important than environmental ones.

The question is sometimes asked: why should it matter if these children are small and remain small as adults? They can still function perfectly well. However, recent work in Jamaica (20) has shown very clearly that retardation of mental development in young children is correlated with stunting but not with wasting. Even if a child is able to catch-up perfectly well from physical retardation, the effects on mental development may well be more longlasting.

The final question is the cause of stunting: it is not enough to regard it simply as an effect of a deprived environment – lack of food, frequent infections, inadequate social stimulation. Nor is it enough to regard it as a scar left behind by early malnutrition. There is good evidence, going back to Boyd Orr's work in the 1930s, that supplements of milk can improve linear growth (e.g. 21). But what it is in milk that produces this effect we still do not know – whether it is protein, a particular amino acid, e.g. methionine, a trace element such as zinc or some other micronutrient. It is very difficult to carry out controlled trials with individual nutrients over the long periods that would be

necessary. Broadly speaking, however, I think we can regard wasting as the result of an inadequate quantity of food, stunting the result of inadequate quality. Since, if you lump together children of 0–5 years, stunting is about 5 times as common as wasting, the question of the prevalence of PEM in the community depends entirely on whether or not stunting is regarded as a form of malnutrition.

PEM in adults

Clinical factors

Trowell, co-author of the first book on kwashiorkor, that appeared in 1954 (23), described a condition in adults which had most of the clinical and pathological features of kwashiorkor in children, particularly oedema, and which he said 'appears to be largely due to protein deficiency'. He cited no fewer than 34 previous reports, mainly from different parts of Africa. Trowell made a distinction between adult kwashiorkor and hunger oedema or famine oedema, because the latter cases are more severely wasted. I doubt, however, whether the distinction is valid; perhaps it arose because in hunger oedema changes in skin and mucosae suggestive of a multi-deficiency state are not as common as in kwashiorkor.

The question of plasma albumin concentration is clearly important and relevant. McCance (24), in his superb historical review of hunger oedema, with references going back to Hesiod (8th century BC), is unable to help us because, with a few exceptions, it is only in the last 50 years that plasma albumin has been measured. McCance did not find hypoalbuminaemia in the oedematous subjects in his studies in Germany, immediately after World War II, nor did Sinclair (25) in Holland. On the other hand, Gounelle (26) in occupied France laid much stress on hypoalbuminaemia in oedematous patients, although, like those working on PEM in children, he admitted that there was not always a strict concordance between oedema and the level of serum albumin.

The picture from the developing world seems more consistent. In Trowell's adult cases in Uganda the mean plasma albumin level was 2.1 g/dl. In the two Indian famines of 1942 and 1966 even lower concentrations were found in oedematous cases – as low as 1–1.5 g/dl (27). In the group of severely malnourished labourers in Colombia described by Barac-Nieto et al (28) the mean albumin level was 2.1 g/dl and, although oedema is not mentioned, there was an increase in extra-cellular water per kg body weight. Barac-Nieto et al's paper is of particular interest because it emphasizes the decreased muscle mass of these subjects and the consequent great reduction in working capacity. In refugees in Somalia oedema, which was common, carried a bad prognosis, and many of those who were oedematous said that they had been living mainly on cassava, which is very low in protein (Collins, personal communication).

To summarize, I firmly believe, in spite of the arguments of Michael Golden, that in malnourished people oedema is evidence of a diet deficient in protein, probably over

a fairly long period. However, the correlation with hypo-albuminaemia is not precise, because there are other features that determine whether or not oedema will develop, such as potassium deficiency, sodium intake and cardio-vascular function. The arguments are developed in more detail elsewhere (1).

PEM in adults in the community

The emphasis here has been on energy rather than protein, and in recent years the term 'chronic energy deficiency' (CED) has become popular. For the definition of CED it seemed sensible to follow, but in the opposite direction, Garrow's system for the classification of overweight and obesity. This is based on the Quetelet index or body mass index (BMI) (Wt/Ht^2), which is a measure of body weight that is largely independent of height. It is thus analogous to weight for height in children.

The 'normal' range of BMI was originally established from Norwegian mortality data; mortality increased above a BMI of 25 (overweight) and below a BMI of 21, giving a U-shaped curve. However, it seems now accepted that the rise at the lower level is an artefact of the particular population, thin people tending to have various risk factors, such as excessive smoking (29).

I was asked to chair a small working group on the definition and classification of CED (30). In our original proposals we took as a reference population a large sample of British soldiers, both men and women, because they are known, from periodic medical examinations, to be both healthy and fit. This gave a range of BMI that could be accepted as normal, with a lower limit of 18.5. Below that, grades of CED were defined in a rather arbitrary way. As shown in Table 2 grade III, below 16, would represent severe deficiency with some loss of function. Women with anorexia nervosa, whose average BMI is about 14, although typically very active physically, are excessively prone to infections. From the scanty literature available we took a BMI of 12 as the lower limit compatible with life.

So far no serious modifications have been proposed to this very crude classification. Henry (31) summarized BMIs in 10 subjects who died from starvation. The mean in 6 men was 13.1 and in 4 women 11.0, suggesting that women are more resistant. Collins (personal communication) studied 537 patients admitted to a refugee camp in Somalia, of whom 23% died. The mean BMI of survivors on admission was 13.2 and the minimum 9.6. Henry's data (31) also show a good deal of variation between individuals.

Table 2   Classification of chronic energy deficiency (CED) in adults according to grade of body mass index (BMI)

BMI	Grade of CED
18.5 – 25	normal
18.4 – 17.0	I
16.9 – 16.0	II
< 16.0	III

From James et al (30).

Table 3   BMR in undernourished Indian labourers

	Normal	Thin, normal height	Undernourished
Weight, kg	67.5	51.7	43.6*
Height, m	1.75	1.76	1.62*
BMI, kg/m^2	22.1	16.7	16.6
Fat, kg	13.7	7.1	4.8*
Muscle mass, kg	31.7	22.2	18.9*
Non-muscle mass, kg	22.2	22.4	18.9
BMR, kJ/kg LBM	119	121	131*

* = significantly different from thin group from Soares et al (33).

Table 4   Birth weight by categories of pre-pregnant body mass index (BMI) in Indonesia: mean, standard deviation and % low birth weight (LBW)

Pre-pregnant BMI	n	Birthweight		% LBW
		Mean	SD	
< 16.0	27	2731	338	22
16.0–	93	2852	339	10
17.0–	266	2941	380	8
18.5–	561	3014	349	5
≥ 22.5	46	3157	440	6
All	993	2978	368	6.6

Statistical significance		
BMI < 17 vs > 17	$P < 0.0001$	$P < 0.003$
BMI 17–18.4 vs ≥ 18.5	$P = 0.01$	NS
BMI < 18.5 vs 18.5	$P = 0.01$	$P = 0.003$

LBW < 2500 g.
NS = not significant.
From Kusin et al (35).

Since the classification of CED was originally published, much effort has been put into finding out the extent of functional impairment, if any, associated with lesser degrees of CED (32). A recent review gives examples of the distribution of the grades of BMI in various countries. Thus, in surveys in India, 72% of people had a BMI below 18.5, compared with 9% in the UK. One of the most interesting things that has come out of the studies of Shetty and his co-workers in India (33) is that in poor labourers, with a BMI a little above 16, much of the deficit in body weight compared with controls represents loss of muscle; the visceral mass per kg body weight was virtually unchanged (Table 3). Because of this change in the make-up of the body, the BMI per kg LBM may be higher than normal. The same observation was in fact made many years ago in children with severe PEM (34).

Other functional relationships are being actively explored. For example, Table 4 (35) shows a relation between mother's BMR and birthweight in Indonesia, and similar data have been recorded from India. Figure 3 shows an inverse relation between BMI and number of days off work by men in Bangladesh (36). This could be interpreted in various ways; an obvious possibility is that men with low BMI are more prone to infection. I have not seen any systematic studies of immunological status in relation to BMI but these are bound to come. I think one could say that at the present time the study of the correlates of low BMI is a growth industry, at least in developing countries.
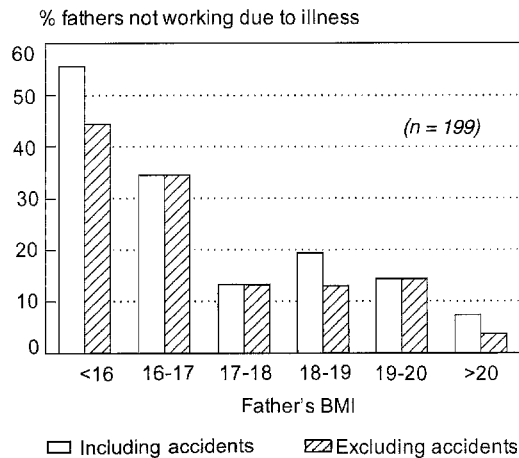
% fathers not working due to illness

Fig. 3 BMI and loss of work due to illness in previous month in fathers of under-five children. From Pryer (36).

Table 5 Effects of infection and malnutrition on protein turnover in Nigerian children

	Acute infection not under-nourished	Acute infection under-nourished	Chronic infection under-nourished	No infection very under-nourished
Wt for age, % of standard	79	63.5	59	53
Plasma albumin, g/L	38	38	19	17
Temperature °C	39.3	37.4	37.6	36.3
Protein synthesis g/9h	3.9	4.0	2.35	1.33
Protein breakdown g/9h	5.2	4.4	2.27	1.18
Protein balance g/9h	−1.30	−0.37	+0.08	+0.15

From Tomkins et al (37).

PEM in hospital patients

There is much literature on the value of biochemical and immunological tests in predicting the response to surgery and the rate of recovery, with some putting more stress on them, others regarding them as unclear.

I think it is fair to say that, in spite of the pioneer work of a few surgeons interested in metabolism, such as Francis Moore, John Kinney and Douglas Wilmore, general interest in the problems of secondary malnutrition only began to develop some years after the detailed studies of severe PEM in children which multiplied in various countries after World War II. To some extent there was an element of rediscovery of features that had been well described in the children. However, it would obviously be wrong to suppose that there are no qualitative differences between primary and secondary PEM. How is the picture modified by features such as the outpouring of cytokines and the increased synthesis of acute phase proteins? This is a field of active research. The only study that I have had any part in was on children in Nigeria (37), where those with kwashiorkor had very low rates of protein turnover and degradation, and were able to maintain nitrogen balance, whereas those who also had an infection had higher rates of degradation and were in negative N balance (Table 5). But what effect this had on the ultimate prognosis I do not know. I suspect, but cannot prove, that it is better to maintain one's protein turnover rate at the expense of a temporary small loss of lean body mass.

Another factor of importance is the duration of the insult. I have always been struck by the amazing difference between two groups with the same low BMI of about 16: one group is Shetty's Indian labourers who, although they may have had a relatively low total work capacity, were functioning in a fairly normal way; the other group is Keys' volunteers in the Minnesota experiment. At the end of 24 weeks of semi-starvation their BMI had fallen to about the same level as that of the Indians but they were in a state of total physical and psychological collapse. One can only suppose that in the Indian labourers there were life-long mechanisms of adaptation which are unlikely to be developed in relatively short-term secondary malnutrition.

References

1. Waterlow J C. Protein–Energy Malnutrition. London: Edward Arnold, 1992: 93.
2. Waterlow J C. Protein turnover and nutrition: the beginnings of a new development. Clin Nutr 1982; 1: 43–61.
3. Asher R. Talking Sense. Sir Francis Avery Jones, ed. London: Churchill Livingstone, 1986.
4. Williams C D. A nutritional disease of childhood associated with a maize diet. Arch Dis Childh 1933; 8: 423–433.
5. Williams C D. Kwashiorkor: a nutritional disease of children associated with a maize diet. Lancet 1935; ii: 1151–1152.
6. World Health Organization. Energy and protein requirements. Wld Hlth Org Tech Rep Ser No. 522. Geneva, 1973.
7. McLaren D S. The protein fiasco. Lancet 1975; ii: 93–96.
8. Wellcome Trust Working Party. Classification of infantile malnutrition. Lancet 1970; ii: 302–303.
9. Waterlow J C. Kwashiorkor revisited: the pathogenesis of oedema in kwashiorkor and its significance. Trans Roy Soc Trop Med Hygeine 1984; 78: 436–441.
10. James W P T, Hay A M. Albumin metabolism: effect of the nutritional state and the dietary protein intake. J Clin Invest 1968; 47: 1958–1972.
11. Fleck A, Raines G, et al. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. Lancet 1985; i: 781–783.
12. Richardson D, Iputo J. Effects of kwashiorkor malnutrition on measured capillary filtration rate in forearm. Am J Physiol 1992; 262: H496–H502.
13. Golden M H N, Ramdath D. Free radicals in the pathogenesis of kwashiorkor. Proc Nutr Soc 1987; 46: 53–68.
14. Ramdath D D, Golden M H N. Non-haematological aspects of iron nutrition. Nutr Res Rev 1989; 2: 29–50.
15. de Onís M, Monteiro C, Akré J, Clugston G. The world-wide magnitude of protein-energy malnutrition: an overview from the WHO Global Database on Child Growth. Bull Wld Hlth Org 1993; 71: 703–712.
16. Carlson B A, Wardlaw T. A global, regional and country assessment of childhood malnutrition. Staff working paper no. 7. New York, UNICEF, 1990.
17. Dewey K G, Beaton G, Fjeld C, Lönnerdal B, Reeds P. Protein requirements of infants and children. Eur J Clin Nutr 1996; 50, Suppl 1: S139–S143.
18. Pelletier D L. Potentiating effects of malnutrition on child mortality: epidemiologic evidence and policy implications. Food Nutr Bull 1995; 16: 206–213.

19. Waterlow J C, Rutishauser I H E. Malnutrition in man. In: Cravioto J, Hambraeus L, Vahlqvist B, eds. Early Malnutrition and Mental Development. Swedish Nutrition Foundation Symposia no. XII. Stockholm: Almqvist and Wiksell, 1974: 13–26.

20. Grantham-McGregor S M. The effect of malnutrition on mental development. In: Waterlow J C, ed. Protein-Energy Malnutrition. London: Edward Arnold, 1992: 344–360.

21. Malcolm L A. Growth retardation in a New Guinea boarding school and its response to supplementary feeding. Br J Nutrt 1970; 24: 297–305.

22. Roediger W E W. New views on the pathogenesis of kwashiorkor: methionine and other amino acids. J Pediatr Gastroent Nutrf 1995; 21: 130–136.

23. Trowell H C, Davies J N P, Dean R F A. Kwashiorkor. Part IV. Protein malnutrition in adults. London: Academic Press, 1954, reprinted 1982.

24. McCance R A. The history, significance and aetiology of hunger oedema. In: Studies of Undernutrition, Wuppertal, 1946–9. Med Res Coun Spec Rep Ser. no. 275. London: HMS0, 1951.

25. Sinclair H M. Nutritional oedema. Proc Roy Soc Med 1948; 41: 541–544.

26. Gounelle H. Carence protéique. Gazette Médicale de la France, 1962; 69: 3–47.

27. Bose J P, De U N, Mukerjee P. A preliminary study of the biochemical changes in starvation cases. Ind J Med Res 1946; 34: 143–150.

28. Barac-Nieto M, Spurr G B, Maksud M G, Lotero H. Aerobic work capacity in chronically undernourished adult males. J Appl Physiol: Resp Environ Exercise Physiol 1978; 44: 209–215.

29. World Health Organization. Physical status: the use and interpretation of anthropometry. Wld Hlth Org Tech Rep Ser no. 854. Geneva, 1995.

30. James W P T, Ferro-Luzzi A, Waterlow J C. Definition of chronic energy deficiency in adults. Eur J Clin Nutr 1988; 42: 969–981.

31. Henry C J K. Body mass index and the limits of human survival. Eur J Clin Nutr 1990; 44: 329–335.

32. James W P T, Ralph A, eds. The functional significance of low body mass index. Eur J Clin Nutr 1994; 48 (Suppl. 3).

33. Soares M J, Piers L S, Shetty P S, Robinson S, Jackson A A, Waterlow J C. Basal metabolic rate, body composition and whole body protein turnover in Indian men with differing nutritional status. Clin Sci 1991; 81: 419–425.

34. Montgomery R D. Changes in the basal metabolic rate of the malnourished infant and their relation to body composition. J Clin Invest 1962; 41: 1563–1663.

35. Kusin J A, Kardjati S, Renqvist U H. Maternal body mass index: the functional significance during reproduction. Eur J Clin Nutr 1994; 48 Suppl. 3): S56–S67.

36. Pryer J A. Body mass index and work-disabling morbidity: results from a Bangladeshi case-study. Eur J Clin Nutr 1993; 47: 653–657.

37. Tomkins A M, Garlick P J, Schofield W N, Waterlow J C. The combined effects of infection and malnutrition on protein metabolism in children. Clin Sci 1983; 65: 313–324.

38. Satyanaryana K, Prasanna Krishna T, Narasinga Rao B S. Effect of early childhood malnutrition and child labour on growth and adult nutritional status of rural Indian boys around Hyderabad. Eur J Clin Nutr 1986; 40C; 131–139.

39. Martorell R, Rivera J, Kaplowitz H. Consequences of stunting in early childhood for adult body size in rural Guatemala. Annales Nestles 1990; 48: 85–92.

40. Kulin H E, Bwibo N, Mutie D, Santner S J. The effect of chronic childhood malnutrition on pubertal growth and development. Am J Clin Nutr 1982; 36: 527–536.