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

J. C. WATERLOW
London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK (Correspondence and reprint requests to J.C. Waterlow, 15, Hillgate Street, London W8 7SP, UK)

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/Ht²). 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 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

<table>
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<th>Table 1</th>
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<tr>
<td>A. Height gains between 5 and 20 years in Hyderabad and Guatemala</td>
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<tr>
<td>Height at 5 years (%) of reference</td>
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<tr>
<td><strong>Hyderabad, affluent</strong></td>
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<tr>
<td><strong>Hyderabad, poor</strong></td>
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<tr>
<td><strong>Guatemala, affluent</strong></td>
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<tr>
<td><strong>Guatemala, poor</strong></td>
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<tr>
<td><strong>USA</strong></td>
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<td>From ref. 38</td>
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<td>From ref. 39</td>
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<th>B. Height gains between 10 and 18 years in Kenya</th>
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<tr>
<td>Male Well-nourished Male Malnourished Female Well-nourished Female Malnourished</td>
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<tr>
<td>Age 10</td>
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<td>18</td>
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<tr>
<td>Gain</td>
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<td>From ref. 40</td>
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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 widespread 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 marasms 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 hypoaalbuminaemia 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 hypoaalbuminaemia, 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 pronounced 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 classification (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 ‘malnourished’ 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 populations 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 distribution 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 (c.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 straightforward: inadequate food aggravated by infections. Once the infectious episode is over, if the food is available, 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, slowing 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...
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 long-lasting.

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) \((\text{Wt/}\text{Ht}^2)\), 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 communi-
cation) studied 537 patients admitted to a refugee camp
in Somalia, of whom 23% died. The mean BMI of sur-
vivors 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)

<table>
<thead>
<tr>
<th>BMI</th>
<th>Grade of CED</th>
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<tbody>
<tr>
<td>18.5–25</td>
<td>normal</td>
</tr>
<tr>
<td>18.4–17.0</td>
<td>I</td>
</tr>
<tr>
<td>16.9–16.0</td>
<td>II</td>
</tr>
<tr>
<td>&lt; 16.0</td>
<td>III</td>
</tr>
</tbody>
</table>

*From James et al (30).*

Since the classification of CED was originally published,
much effort has been put into finding out the extent of func-
tional impairment, if any, associated with lesser degrees
of CED (32). A recent review gives examples of the dis-
tribution 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 LB M 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.
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


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

<table>
<thead>
<tr>
<th></th>
<th>Acute infection not undernourished</th>
<th>Acute infection undernourished</th>
<th>Chronic infection undernourished</th>
<th>No infection very undernourished</th>
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</thead>
<tbody>
<tr>
<td>Wt for age, % of standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma albumin, g/L</td>
<td>38</td>
<td>38</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Temperature °C</td>
<td>39.3</td>
<td>37.4</td>
<td>37.6</td>
<td>36.3</td>
</tr>
<tr>
<td>Protein synthesis g/9h</td>
<td>3.9</td>
<td>4.0</td>
<td>2.35</td>
<td>1.33</td>
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<tr>
<td>Protein breakdown g/9h</td>
<td>5.2</td>
<td>4.4</td>
<td>2.27</td>
<td>1.18</td>
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<td>Protein balance g/9h</td>
<td>-1.30</td>
<td>-0.37</td>
<td>+0.08</td>
<td>+0.15</td>
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</table>

From Tomkins et al (37).