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### SYMPOSIUM ON 'NUTRITION AND RESISTANCE TO INFECTION'

#### **Protein–energy malnutrition and risk of infection**

By ANDREW M. TOMKINS, *Department of Human Nutrition, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT*

It is now well established that there is a close relation between malnutrition and infection. On the one hand, infections precipitate malnutrition and, on the other, malnutrition aggravates the outcome of many infections. Previous comprehensive reviews (Scrimshaw *et al.* 1968; Chandra, 1983) have examined the two-way relation between infection and nutrition emphasizing the clinical, epidemiological and experimental studies of risks associated with malnutrition. More recently the unravelling of the intricacies of the host immune response has been followed by studies of individual components of the response which are affected by nutrition (Suskind, 1977). In the majority of these reports the authors have concentrated on the severely malnourished. This has been valuable in focusing attention on the high prevalence of infection, complications of infection and death among children with marasmus and kwashiorkor. However, the majority of the world is not severely malnourished and little attention has been given to the relative risks of infection in those with milder or moderate malnutrition. It is the purpose of this paper to examine what is known, and suggest what we still need to learn, about the risks of protein–energy malnutrition (PEM), concentrating mainly on young children in underdeveloped communities.

We have to start by defining PEM. Golden (1985) defined PEM in protein-related terms but the dietary background of an undernourished child in a disadvantaged environment is complex and a working definition of PEM can be given as 'a condition in which deficiencies of major body nutrients, resulting from a diet which is generally inadequate in energy and protein, are frequently accompanied by deficiencies of micronutrients'.

*Assessment of grades of PEM*

The next question is how to measure nutritional status. After about 20 years of comparisons of serum and urinary metabolites, anthropometric indices and sometimes combinations of several indicators in scoring systems, it seems that the most appropriate way for community-based studies is by the use of weight, height and possibly mid-arm circumference (MAC). There have been major discussions about the use of international standards for such measurements in view of the lighter weight and shorter stature of children in communities in whom severe malnutrition is endemic compared with the children in the more privileged communities in which these standards were developed. However, despite certain genetic factors within families or entire ethnic groups, the growth of the children of elite families in most developing countries is indistinguishable from international standards and there seems limited advantage in using local standards (Martorell, 1985).

Several classifications of PEM have been proposed. Weight/age or more accurately weight as a proportion of expected weight for a child of that age (W/A) has been used in the Gomez classification (Gomez *et al.* 1956). Those with W/A less than 60% are described as severely malnourished or grade 3. Any child with nutritional oedema would also be classified as grade 3. Those between 60 and 75% are classified as grade 2 (moderate malnutrition) and those between 75 and 90% are graded as grade 1 (mild malnutrition). The Wellcome classification divides children into those who are above 80% W/A, those who are between 60 and 80% and those who are less than 60%, thus giving a wider span for those who could be classified as moderately malnourished. More recently there has been a move towards a classification on more statistical grounds, using the Z score (or standard deviation score) (Waterlow *et al.* 1977). The Z score is (the observed weight for age - reference weight for age)/(SD of reference weight for age). Thus the nutritional status of individuals and populations can be referred to as 0, -1, -2, -3 Z scores of the reference population. In practice a Z score of -2.0 is equivalent to 80% W/A for children between 12 and 36 months.

A necessary consideration in assessing the significance of underweight is whether it matters in biological, social or economic terms. There has been much discussion on nutritional adaptation in populations who are habitually eating less than the reference populations. As many of these children who are underweight are also short (height as percentage of expected height for a child of that age; H/A) with respect to standards, they may have a normal body proportion as expressed as weight/height (W/H). Thus it has been emphasized that a child could be undernourished for a long time resulting in 'stunting' but with normal proportions (low H/A, normal W/H). Alternatively the child could be recently undernourished with a low W/H and normal H/A. The description of 'wasting' has been developed in the classification of Waterlow (1972) where children may be divided into those less than 70%, those between 70 and 80%, those between 80 and 90% and those more than 90%. Similarly, stunting can be classified as <80%, 80-90%, >90%. As

the proportion of children who are less than 80% is often rather low (less than one-tenth) and many children are between 80 and 90%, it is sometimes better to subdivide the moderately-thin group into 80–84 and 85–89%. This has been useful in monitoring thinness in feeding programmes for young children during the current famine in the Sahel. Despite the difficulties in obtaining accurate, reliable, reproducible measurements of MAC in clinical or field studies, this measurement has the attraction of being rapidly performed in large numbers of individuals. A comparison of W/H and MAC shows a reasonably satisfactory correlation and 'thinness', in terms of MAC, can be classified as  $<0.125$  m (severe),  $0.125-0.135$  m (mild/moderate),  $>0.135$  m (satisfactory). These classifications are not just for statisticians; they do provide an opportunity to examine the risk differentials for infection between those who could be called severely, moderately or mildly malnourished.

In all anthropometric studies of young children it has to be emphasized that the impact of age is very important. The differences in proportions of children within a population who are less than a certain standard varies considerably when analysed by 6-monthly age-groups. Fig. 1 shows findings from an urban Gambian community in which the proportion of children underweight at different ages varied considerably (Tomkins *et al.* 1986a). The overall prevalence of stunting appears to increase steadily between 12 and 36 months in many developing communities whereas the prevalence of wasting is maximal in the second year of life. These differences are important in interpreting the results of anthropometric studies which include results from young children of widely-differing ages (Martorell, 1985).

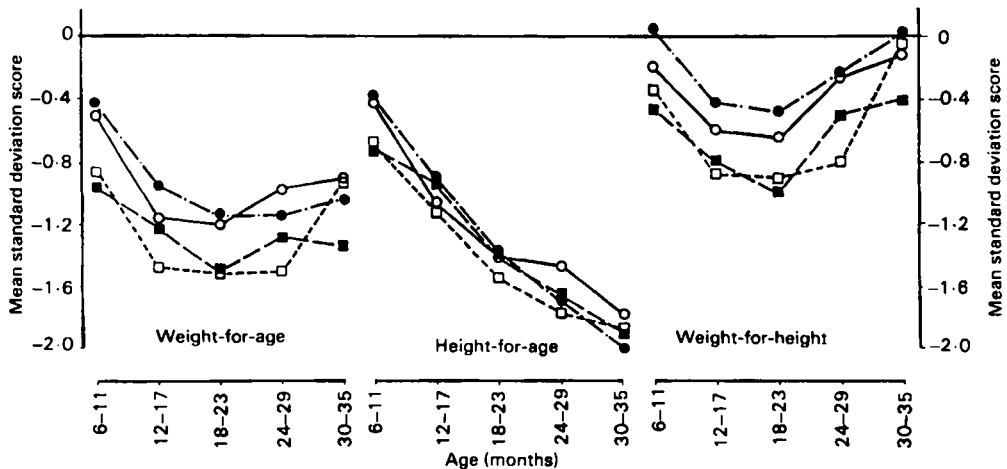


Fig. 1. Nutritional status of young children in urban Gambia according to 6-month age-groups. (○—○), May 1981; (□--□), Oct 1981; (●---●), Feb 1982; (■---■), Sept 1982 (Tomkins *et al.* 1986a).

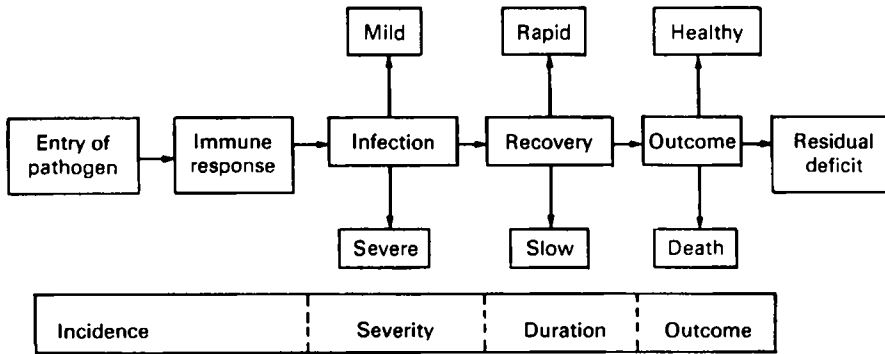


Fig. 2. A simplified model of the outcome of an infection and points at which this may be influenced by nutrition.

### *PEM and incidence of infection*

In any assessment of risk of infection in relation to nutritional status it is necessary to define how 'infection' is measured. Fig. 2 shows a simple model in which the pathogen (whether virus, bacteria or parasite) and the basic immune response are considered. The results of interactions between these two determine whether the pathogen will invade, replicate and produce infection. The next stage involves the severity of the infection which can be measured by various indices such as height of pyrexia, extent of spread of infection and quantities of body nutrients which are catabolized. This is then followed by recovery in which the duration of the illness and complications such as residual damage or death all affect what we may call outcome.

There are several stages at which nutrition may be important. The first is in determining the incidence, i.e. the number of new cases during a specified time divided by the population at risk. These rates are usually expressed as cases/thousand persons per year. Information on incidence requires some kind of morbidity recording such as health centre reports, hospital admission information or prospective studies within communities using domiciliary visits by trained field workers. All methods have their deficiencies, the hospital-based reports have the advantage of accurate disease diagnosis but are biased towards selection of the severest cases only. The community-based reports rely on observation and maternal reporting; less accurate than hospitals but they at least have the advantage of determining the prevalence in the community as a whole if appropriate sampling methods are used (Ross & Vaughan, 1984). Thus incidence rates for common childhood infections such as measles, diarrhoea and pneumonia can be assessed in the months following an anthropometric measurement.

Results of several population-based studies are now available. Studies of young children in Bangladesh (Black *et al.* 1984; Chen *et al.* 1981), Nigeria (Tomkins, 1981*b*) and Costa Rica (James, 1972) did not show a higher incidence of diarrhoea

among those who were underweight or stunted. A study in Guatemala (Delgado *et al.* 1983), however, did show a greater incidence of diarrhoea in the underweight, but the difference was minimal. Similarly the presence of wasting was not a significant risk factor for incidence of diarrhoea in Bangladesh (Black *et al.* 1984) or Indonesia (Sommer *et al.* 1984) but was in Nigeria (Tomkins, 1981*b*). (It was not examined in Costa Rica or Guatemala.) Why this difference? It has been suggested that the children who are wasted come from poorer environmental conditions. This was not apparent in the rural Nigerian study in which there were few differentials in housing, employment and other indicators of wealth. However, a retrospective analysis of why the children were wasted in the first place showed that a high proportion gave a history of measles, a major precipitating cause of malnutrition in northern Nigeria. The immune suppression following infection with measles virus persists for 3–4 months after infection (Whittle *et al.* 1973). Post-measles diarrhoea is well described in this population (Whittle *et al.* 1980) and this and potentially other 'carry-over' phenomena may be important in interpreting prospective field studies.

Clinical studies of children with severe malnutrition indicate a very high prevalence (and probably incidence) of diarrhoea but the general conclusion from the results from the studies reviewed previously is that diarrhoea is not experienced more frequently by those who are only moderately malnourished.

PEM and subsequent risk of respiratory infection has been examined with respect to W/A in Costa Rica (James, 1972) and with respect to W/H in Indonesia (Sommer *et al.* 1984). Neither study showed any influence of malnutrition on incidence. Similarly there was no relation between W/A, H/A, and W/H and prevalence of respiratory infection in urban Gambia (Tomkins *et al.* 1986*a*).

#### *PEM and host immune response*

A key element in determining whether an infection in the environment enters a host and replicates at a sufficiently-fast rate to cause an illness is the strength of the series of host immune responses. In the severely malnourished there is selective suppression of these immune mechanisms. Cell-mediated immunity (CMI) appears to be the most affected and atrophy of thymus and thymus-dependent lymphoid tissues (such as the tonsils and other lymph glands) together with impaired functional activity of lymphocytes (whether tested by *in vitro* or skin-sensitivity methods) are well described among children with kwashiorkor and marasmus (Smythe *et al.* 1971). Chandra (1983) has reviewed immunological changes in PEM. Of the humoral immune system, the IgA system is the most important to be affected by PEM. The secretory IgA levels are often low and consequently the mucosal response to pathogens such as rotavirus and *Escherichia coli* in the intestine and measles virus in the nasopharynx are impaired. Antibody affinity is decreased in experimental protein deficiency but there is no information on affinity in humans.

Similarly the complement system, especially C<sub>3</sub> and factor B, are affected by nutritional status. PEM affects the opsonic function of plasma and, together with

impaired chemotactic migration of neutrophils and impaired killing of intracellular bacteria, accounts for the reduced ability to handle invading pathogens.

The development of monoclonal antibodies has enabled the identification of the various subsets of lymphocytes. In severe PEM there is pronounced reduction of T<sub>4</sub> helper cells and a less severe reduction of T<sub>8</sub> cytotoxic suppressor cells. The whole process seems to revolve around changes in the configuration of antigens on the cell surface brought about by PEM. These cell surface glycoproteins may alter sufficiently to change certain immunoregulatory mechanisms. These changes in CMI probably explain why there is such a high prevalence of tuberculosis and fungal infection among children with severe PEM. Despite the growth in knowledge of these processes it is still not clear how much change occurs in mild and moderate PEM as distinct from severe PEM. However, there are interesting results for tuberculin conversion rates among infants of different nutritional status. Chandra (1981) showed a gradation of responses to BCG vaccination in malnourished infants and those who were small for gestational age. The latter infants also have impaired function of other components of CMI and their neutrophils have reduced bactericidal capacity. Indeed these abnormalities appear to persist for several months or years among those who do not achieve catch-up growth. By contrast pre-term babies who have low birth weight have relatively normal immune status.

The humoral immune response is surprisingly little affected by nutritional status. Reduced but adequate levels of antibodies are achieved following typhoid vaccination in severe malnutrition (Chandra, 1972). There was a slightly decreased seroconversion rate following measles immunization among marasmic compared with better-nourished children in Tanzania when antibodies were measured at 21 d (Wesley *et al.* 1979). However, when the levels were measured 3 weeks later, seroconversion had occurred in over 90% of both groups. There is supporting experimental evidence that PEM delays rather than impedes humoral immunity.

What about mild and moderate malnutrition? A study of Indian infants classified according to W/A showed that the specific antibody response to tetanus immunization and serum IgG and IgM levels were unaffected by nutritional status. However, tests of CMI showed that there was some gradient in the response between >80%, 65–79% and <65% (Kielmann *et al.* 1976). A separate study in India showed that only children with severe malnutrition had impaired antibody response to tetanus and diphtheria toxoid and even these differences were marginal, whereas there was a gradient in results for measurement of percentage of lymphocytes that were T cells (Reddy *et al.* 1976). There was, in addition, some evidence of lowered phagocytic activity of leucocytes in the moderately malnourished. Colombian children with moderate malnutrition had impaired response to BCG vaccination and decreased lymphocyte transformation tested *in vitro* in comparison with results obtained in mildly malnourished children (McMurray *et al.* 1981). Ziegler & Ziegler (1975) showed impaired delayed hypersensitivity responses in Nepalese children who were thin (W/H <80%). There are variable findings with respect to complement pathways and bactericidal

Table 1. *Factors affecting incidence of diarrhoea*

- (1) Prevalence of pathogen in environment
- (2) Social factors favouring spread of infection
- (3) Climate
- (4) Dose of pathogens ingested
- (5) Colonizing characteristics of pathogen
- (6) Gastric acidity
- (7) Intestinal immunity

activity of leucocytes but the CMI response was affected in moderate and possibly mild malnutrition as well as severe PEM.

There are frequent questions as to the impact of PEM on immunization programmes. In general it seems that immunizations producing antibodies will nearly always occur satisfactorily, albeit sometimes delayed, whatever the nutritional status, whereas immunization responses requiring cellular systems are likely to be affected even in moderate malnutrition. A further consideration is whether impaired immune response in PEM alters the outcome of a naturally acquired infection? It almost certainly does in severe PEM which is reviewed elsewhere (Scrimshaw *et al.* 1968) but it is difficult to judge the significance of mild-moderate PEM because there has been no study which has compared the cellular or humoral immune response in a group of individuals against the subsequent risk of developing infection. The field studies suggest that mild and moderate malnutrition has little to do with disease incidence. It seems more likely that the high attack rates for disease, such as pneumonia, diarrhoea and measles are more related to the environmental, social and behavioural problems that underprivileged populations face, than to nutrition. The factors which may influence the incidence of diarrhoea are given in Table 1.

Nevertheless, many malnourished children with infection appear to suffer particularly severe forms of illness with a high prevalence of complications. A mild respiratory infection develops into pneumonia; measles appears to develop in a very dangerous form with many complications; diarrhoea is associated with particularly severe fluid, electrolyte, nitrogen and mineral losses (Scrimshaw *et al.* 1968). Unfortunately, the impact of nutrition on severity of infection has received little attention in clinical studies and the whole subject has been overwhelmed by a vast amount of conflicting experimental findings, some of which suggest that nutritional deficiencies actually inhibit the replication of pathogens, decrease parasitaemia or bacteraemia and may even enhance survival (Ederisinghe *et al.* 1982). The relevance to human nutrition is not clear but children with severe PEM very rarely die of cerebral malaria and there is some evidence that nomadic populations in the Sahel developed severe clinical malaria after refeeding during the 1972 drought (Murray *et al.* 1978).

#### *PEM and severity of infection*

Of greater importance are the many situations in childhood infection where malnutrition appears to aggravate the condition. Measles is a serious condition in

the severely malnourished (Morley *et al.* 1963). Complications including pneumonia, septicaemia and diarrhoea are frequent, possibly due to the marked abnormality of the CMI response in severe malnutrition. Differences in nutritional status would also explain the high case fatality rates (CFR) in measles in underprivileged communities. Children in Europe or North America have CFR of around 0.1 deaths/100 cases, whereas in rural Nigeria and Gambia rates of 7 and 14% respectively have been recorded (Foster, 1984).

The frequent co-existence of high fatality rates and poor nutrition has been noted many times and is undoubtedly important in severe PEM. However, recent studies in Guinea-Bissau (Aaby *et al.* 1983) and comparative urban-rural studies in South Africa (Loening & Coovadia, 1983) have emphasized that very-high CFR for measles can occur in relatively well-nourished children in urban populations. Analysis of the patterns of infection rate and mortality with respect to housing conditions showed that the greatest problem occurred among children coming from the most crowded households. They were not necessarily poorer and had similar W/A to children from less crowded houses. The measles mortality was particularly high in those who came from households where there was more than one child with measles irrespective of nutritional status. The mechanisms involved have not been defined but this close association of measles mortality with crowding was noted in Scotland earlier this century (Morley, 1974).

One explanation could be that crowding increases the size of the infective dose as there is some evidence that the severity of viral infection relates to the size of inoculum. A particularly high measles mortality in the presence of satisfactory nutrition has been noted among young black children in an urban study in South Africa in whom severe measles was characterized by an extensive rash and a lymphocyte count of less than 2000/mm<sup>3</sup>. One suggestion is that a particularly severe viraemia causes profound immune suppression (Coovadia *et al.* 1978). It has been recognized by physicians for centuries that a spreading confluent rash is a bad prognostic sign and it has been postulated that the severity of measles is due to the inhalation of a particularly high dose of measles (readily available in a crowded household with more than one infected child) in association with a hot, dry environment to facilitate nasopharyngeal colonization (as occurs during the hot dry months which herald the onset of measles epidemics in Savanna Africa). An overwhelming viraemia then ensues, sufficient to depress the lymphocyte count and facilitate secondary invasion by bacteria and parasites.

The analysis of nutrition *v.* environment in the cause of high CFR for measles in developing countries becomes more complicated when age is taken into account. Nearly all studies emphasize that mortality is higher in the youngest children. Indeed CFR may be four times as high in the infant than the child aged more than 4 years. Most comparative studies have shown that measles tends to attack children in urban areas at a much younger age than their rural counterparts; perhaps as a result of the crowding and exposure that is more common in urban slums than scattered rural compounds (Loening & Coovadia, 1983). A further variable is the presence of other factors affecting immune response such as malaria.



The absence of malaria in mountainous areas of Kenya may help to explain the lower CFR there compared with areas which are endemic for malaria (Williams, 1985).

One of the problems in assessing the CFR from measles is that the death from post-measles complications may be more important than the uncomplicated viral infection itself. Studies in The Gambia showed a steadily increasing mortality rate among children during the 6 months following an attack of measles (Hull *et al.* 1983). Most of the deaths were from chronic diarrhoea or pneumonia. The impact of PEM on the chronic diarrhoea initiated by measles is likely to be particularly important.

Several studies have documented the striking weight loss that occurs during measles in young children, the most classical descriptions coming from West Africa (Anon., 1984). Studies in well-nourished Nigerian children have shown that rates of synthesis and breakdown of body protein are elevated during acute measles infection but rates of breakdown exceed rates of synthesis (Tomkins *et al.* 1983). This results in marked losses of N, creatinine and 3-methylhistidine in the urine. Similar rates of synthesis and breakdown were observed in moderately malnourished children with infection although their urinary losses of N, creatinine and 3-methylhistidine were less as were their leucocyte, temperature and pulse-rate responses. However, rates of body protein turnover, expressed on a body-weight basis, were markedly reduced in children with severe PEM and infection. Body temperatures were lower and leucocyte responses were minimal in this group. In fact their results were not much different from those obtained in a group of severely-malnourished children without acute infection. Thus although synthesis of some proteins such as the antibodies to measles virus after immunization appears to be possible (Wesley *et al.* 1979), there is evidence of a marked reduction in the metabolic response to infection in children with severe PEM. This is almost certainly the cause for the severity and delayed recovery in severe PEM and there is some evidence that the response is also blunted in moderate malnutrition (Anon., 1983).

In summary, severe PEM seems to be associated with a high prevalence of measles, presumably as a result of severely decreased host resistance. In moderate or mild PEM, however, there is little evidence of an important role for nutrition in the first stage of the illness; environmental, climatic and behavioural factors seem more important. Thereafter as complications of measles develop (usually bacterial and parasitological infections which become superimposed on tissues which are damaged by measles virus), the role of nutrition becomes more important, especially affecting recovery and duration of disease.

#### *Mechanisms of increased severity of infection in PEM*

The association between diarrhoea and malnutrition is a particular problem in the severely malnourished where intestinal lesions appear to be the result of a combination of villus damage by pathogens and delayed epithelial regeneration because of impaired mucosal nutrition. There is some evidence that faecal losses of

sodium and water during acute intestinal infection are greater in the malnourished than in the better nourished (Palmer *et al.* 1976). This may be because the intestinal mucosa in PEM is covered by relatively immature 'crypt' cells which are more secretory than the normal columnar villus tip cells. Thus a given dose of toxin such as that produced by *Vibrio cholera* or *E. coli* which binds to the membrane of the enterocytes, penetrates the cell and then increases the concentration of cyclic AMP, may well produce a greater net secretion in the gut of a malnourished child. A further problem is that lactase (EC 3.2.1.23) levels of the gut mucosa are likely to be very low in severe PEM. The malabsorption of dietary lactose during an enteric infection caused by an organism (e.g. rotavirus) which reduces the intestinal lactase level even further may contribute to the osmotic stimulus to water and electrolyte secretion. This may explain why severely malnourished children become dehydrated so quickly and would explain the greater faecal losses in malnourished compared with better nourished subjects with cholera (Palmer *et al.* 1976).

So far this review has concentrated where possible on PEM in as uncomplicated a form as possible. However, in real life PEM is often accompanied by micronutrient deficiencies including zinc and folate. Both these nutrients have profound effects on intestinal structure in experimental studies. Atrophy of intestinal mucosa as assessed morphologically, by measurement of DNA/mm intestine and gut enzymes occurs in experimental folate deficiency and there are striking changes in the specific activities of sucrase (EC 3.2.1.48) and Na,K-ATPase (EC 3.6.1.37) within enterocytes from different sites on the intestinal villus. The decrease in activity of the Na,K-ATPase enzyme, associated with the lateral basement membrane of the enterocyte, may be a major factor in the impaired transport of sodium and water that has been documented (Tomkins, 1979b).

Similar abnormalities of water and electrolyte transport have been demonstrated in experimental Zn deficiency in which gut atrophy also occurs. The secretory response to cholera toxin is markedly increased by the presence of Zn deficiency (Roy *et al.* 1986). The significance of these experimental findings to human infection is not defined but folate therapy has profound effects on cellular metabolism and function in tropical malabsorption syndromes. It seems that Zn may be as important in malnourished children with diarrhoea.

There is a mass of experimental findings suggesting that the severity of illness caused by gut parasites is affected by host nutrition, probably via its effect on the CMI response (Duncombe *et al.* 1979). Tissue invasion by *Strongyloides stercoralis* is described in children with severe PEM in the Caribbean. Similarly, nearly all such children have heavy loads of *Ascaris* and *Giardia lamblia*, at much higher levels than those found in better nourished children from the same compound or village area (Mata, 1978). In summary the impact of nutrition on severity of disease seems fairly well established in severe PEM where the host's immunological and physiological response to pathogens is quite abnormal. However, the impact of mild or moderate malnutrition on severity of infection is largely conjectural at the present time.

*PEM and duration of infection*

A third feature of any infection is its duration. The clinical features of any infection are influenced by the time that the organism remains within the host and the time which is necessary for tissue repair and improvement of symptoms. Moderate PEM, whether it is expressed as W/A, H/A or W/H, is an important determinant of duration of diarrhoea. The most comprehensive study, in Bangladesh, showed a graded increase in duration of diarrhoea due to *E. coli* infection for all the three anthropometric indices (Black *et al.* 1984). Diarrhoea lasted twice as long in wasted children than better nourished children in Nigeria (Tomkins, 1981a). It is unclear whether this represents sufficient effect on immune clearance mechanisms to delay excretion of a pathogen. Similarly it is not clear whether moderate malnutrition is sufficient to impair regeneration of gastrointestinal mucosa with recovery of absorption. Recent studies of the role of gut hormones in affecting intestinal transit and mucosal growth suggest that enteroglucagon among others may be important in the control of the intestinal response to mucosal damage. Extremely high levels have been recorded in malnourished children with diarrhoea (Tomkins *et al.* 1984). Whatever the true explanation the strength of evidence is that even moderate malnutrition prolongs symptoms. This is potentially of major importance because of the vicious circle that can develop in which illness-malnutrition causes further deterioration of nutritional status. The impact of diarrhoea on nutrient intake is a major feature in growth-faltering of young children. The longer the diarrhoea the longer the time-period before food intake is restored to 'normal' levels. Some of the factors affecting duration of diarrhoea are given in Table 2.

In considering the clinical or public health importance of an infection, a major factor is the outcome; whether the individual recovers completely, survives with some damage or prolonged symptoms, or dies. In previous years the mortality rates among children in nutrition centres with severe PEM were sometimes upwards of 30%. High-energy feeding made a marked difference in growth and some improvement in mortality but many children continued to die during the first 48 h of admission to a nutrition centre. Those centres which have recognized the importance of treating the infections with energy supplements during the first week have experienced a decrease in mortality. In these children it is obvious that severe PEM is a major risk factor for mortality. However, it is unclear how much the presence of mild or moderate malnutrition increases the risk of dying, especially from infective disease.

Table 2. *Factors affecting duration of diarrhoea*

- (1) Delayed clearance of enteropathogen
- (2) Persistent mucosal damage (e.g. food allergy)
- (3) Delayed mucosal recovery (e.g. folate, protein-energy malnutrition, zinc)
- (4) Carbohydrate intolerance

*PEM and mortality from infection*

Several longitudinal studies, similar to those on nutrition and morbidity, have now been performed. W/A and subsequent risk of dying during the following 12 months was examined in Narangwal, India (Kielmann & McCord, 1978). Among children aged 12–36 months there was a graded increase in the relative risk of dying when the better nourished (1.0), mildly malnourished (1.2 times), moderately (2.8 times) and severely malnourished (13.0 times) were compared. W/A predicted deaths more accurately in the first 6 months of the study than in the second 6 months. A similar study in Bangladesh (Sommer & Loewenstein, 1975), but using MAC/H (QUAC stick), showed that over the ensuing 18 months the relative risk of death showed a graded increase with deteriorating nutritional status: the difference in relative risk between mildly- and moderately-malnourished was greatest in the children who were 2 or 3 years old at the beginning of the study. The value of the QUAC stick in predicting death was greatest in the 3 months following measurement. Subsequent re-analysis showed that the predictive value of MAC in forecasting death could not be improved by the addition of height and the findings showed a graded increase in mortality with decreasing MAC (Trowbridge & Sommer, 1981).

A further study in Bangladesh (Chen *et al.* 1980) examined W/A, H/A and W/H as predictors of death and showed an increased risk of death by all three nutritional criteria during the following 23 months for the most malnourished but not for the mildly- or moderately-malnourished groups. It might be argued that the period of follow-up was so long that any association with moderate PEM was lost as other determinants of mortality became stronger during the 2 years after anthropometric measurements.

Mortality rates (measured over 18 months following anthropometry) among children aged 6–30 months in Papua New Guinea were nearly twice as high in those who were thin (less than 90% W/H) compared with the better nourished. Interestingly the mortality rates among the thin children who were short (less than 90% H/A) were nearly three times higher than those in thin children who were taller (Heywood, 1983).

In Zaire nutritional status and subsequent mortality were examined over 100 d only (Kasonjo Project Team, 1983), and there was no correlation between them. It is possible that the wider age-span of the study (6–59 months) obscured a relation for the 2- and 3-year-olds only. However, a striking 54% of the deaths were attributed to measles, much higher than the percentage in Bangladesh (17%). The Zaire study was performed in an urban area, as was the study of Aaby *et al.* (1983) in Guinea-Bissau who found no relation between CFR from measles and malnutrition. It would be interesting to analyse the relation between non-measles death and nutrition in Zaire. Nevertheless, the results stand and raise the important question of why malnourished children of similar age have a greater risk of death in some communities than in others.

It seems necessary to consider the determinants of mortality in greater detail.

Traditional ways of managing illness vary enormously between countries and even between different communities within the same country. It was the custom to withhold breast-milk and other nutrients and administer purgatives to children with diarrhoea in London (Ward, 1929). These practices are present in many other parts of the world and could have profound effects on survival. Quite detailed dietary restrictions and sacrificial oblations for measles are described in Ethiopia and there are many reports of culturally specific food avoidance (Barnabas, 1982). However, not all communities adopt these practices which are detrimental to nutritional status and survival. The greater mortality among girls in some communities is likely to be related in part to disease management (John *et al.* 1980; Abdullah & Wheeler, 1985). There is insufficient comparative information to make anything but a general statement on this important determinant and more information is required. However, it is the practice of many Asian communities to withhold or limit food during infection whereas many African communities do not, rather encouraging these anorectic children to eat. This may explain the differentials in CFR from certain illnesses, especially diarrhoea.

Few studies have made detailed examination of the socio-economic status of the households in which children died. Chen *et al.* (1980) found that the discriminating power of anthropometry was enhanced when housing floor space was incorporated into the analysis of risk factors for mortality. The weight and height of the mother, reasonably regarded as indicators of deprivation at the household level, increased the discriminating power of anthropometry of the child still further. Availability of time and resources for adequate child care, have not been systematically examined as co-risk factors for mortality but the 'hungry season' of many West African farming communities during which time food stores are lowest is also the time of

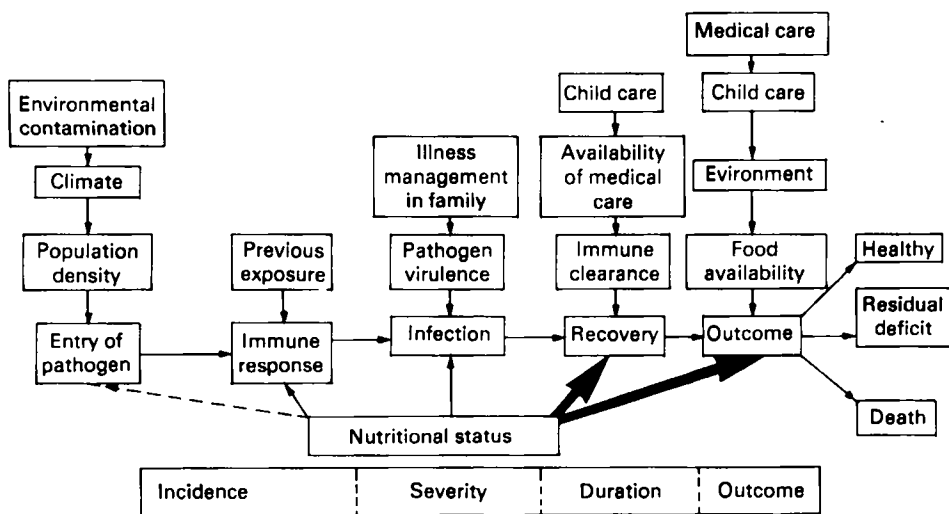


Fig. 3. A model which incorporates factors which co-operate with nutrition in increasing the complications and mortality from infectious disease.

the greatest separation of mothers from children because of the urgent need to spend hours labouring in the fields. Child care, however it is described or quantified, can only deteriorate in such conditions.

Mortality rates from infective disease can also be markedly affected by medical care. Oral rehydration, antibiotics, antimalarials and aspirin can all reduce mortality from diarrhoea, measles, malaria and pneumonia (Anon., 1984). Even in the devastating conditions of a refugee camp, prompt primary health care reduced the CFR for measles to 0.1% (Drew & Bauhaun, 1982), and in underprivileged Indian villages the mortality from measles in those able to obtain primary health care was less than one-third of that experienced by those who could not (John *et al.* 1980). The implication is that families with malnourished children are usually the underprivileged families with greatest difficulties in obtaining employment, food, potable water, decent housing or access to even the most basic medical care facilities. Thus the significance of PEM as a risk factor for infection is seen not just as a biological influence on immune response or physiological function during an infective process, but as a marker for those who are without sufficient resources to survive in the environment.

#### *Towards a more comprehensive analysis*

The purpose of any analytical framework of the relation between PEM and infection in poor communities is to provide a conceptual approach which enables the development of policies and activities for decreasing the incidence, severity, duration and fatality of infection. The framework in Fig. 3 is only a suggestion which needs developing and refinement. The published information on community-based research is insufficient to draw many conclusions about the utility of this approach but more studies on cultural, behavioural, educational and economic determinants of infection and its outcome might provide information which would be complementary to anthropometry in assessing the role of PEM as a risk factor.

Conclusions about the relation between PEM and infection must be made with great caution. In experimental laboratory conditions the relation is straightforward and the first model (Fig. 2) can be used for examining levels of PEM at which detectable changes occur. The situation in the real world is more complex and analyses must include the 'confounding variables'. Using multivariate analysis it is possible to rank the proximate determinants of nutritional status in community studies (Tomkins *et al.* 1986*b*) and to assess the relative power of the factors influencing metabolic response to infection (Tomkins *et al.* 1986*a*). However, such approaches have not so far been used in the analysis of the more complex relation between PEM and risk of infection.

Although relations between PEM and infection vary between continents, communities and even between households, the situation is not too complex to analyse: all the variables suggested in Fig. 3 are measurable. More importantly they are real factors, amenable to change, which can be addressed by social policies as well as by programmes aimed at increasing the availability of food and

improving health care. The practical implication of such an analysis is that future interventions and evaluation in communities with limited resources would be well advised to regard PEM as only one, albeit an important one, of a number of co-factors contributing to morbidity and mortality from infection.

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