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Nutrition, Infection, and Growth Part II: Effects of Malnutrition on Infection and General Conclusions

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This article critically reviews evidence about the effects of malnutrition on infection. Unequivocal evidence shows that the cellular immune response is reduced in severe malnutrition. There is also evidence suggesting a diminished cellular immune response in moderate malnutrition, particularly in wasted children. Studies about the incidence, duration, and severity of illnesses in moderately malnourished children indicate that malnutrition increases the duration of infections (especially diarrhea), although probably not their incidence. General conclusions are presented. (CLIN NUTR 1988;7:163-7.)

There are three major areas of evidence related to the effect of malnutrition on infection. The first is information on the effect of nutrition on immunologic response; the second is that provided by clinical and field studies of the incidence or duration of the most frequent infections in groups of children with different levels of nutritional status; and the third is evidence derived from studies of food supplementation.

NUTRITION AND IMMUNOLOGIC RESPONSE

There is currently ample evidence to show conclusively that severe malnutrition affects an individual's immunologic response.[1-3] However, not all components of the immunologic system are equally affected. Of all components, the cellular immunologic response is the one most markedly altered. The ways some components of the cellular system are routinely affected are as follows: atrophy of the lymphatic tissue, especially the thymus (the organ involved in T lymphocyte maturation), reduced number and proportion of T lymphocytes (responsible for cellular immunity), depressed transformation of active lymphocytes to lymphoblasts (the functional cells responsible for cellular immunologic response), reduction in the delayed hypersensitivity reaction (a test widely used to measure in vivo cellular immunologic response), and a larger percentage of children with lymphopenia than in well-nourished groups of children.

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In most studies it is not very clear if the cellular immune deficiency is due to malnutrition, infection, or an interaction between the two.

Some deficiencies in cellular immune response function in malnourished children disappear as a result of nutritional rehabilitation,[4] a fact that strengthens the hypothesis that malnutrition affects immune function. Unfortunately, there are few studies that adequately control for the effect of infection. It is known that infection causes depression of some indicators of the cellular immune response. It is also known that infection is associated with malnutrition; therefore, in most studies it is not very clear if the cellular immune deficiency is due to malnutrition, infection, or an interaction between the two. However, some studies that have controlled for the effect of infection suggest that severe malnutrition affects depression of cellular immunologic response independently of infection.[5]

Other components of the immunologic system are affected by severe malnutrition, although to a lesser degree; among these are the complement system[6,7] and bactericidal activity.[8]

The humoral response is less altered in severe malnutrition, although a decrease in the antibody response to tetanus toxin and to *Salmonella tiphi* has been found.[9] Finally, there are decreased levels of secretory IgA in saliva and tears, the respiratory tract, and the mucosa of the jejunum.[10]

Severe malnutrition affects only a small percentage of preschool children in Third World countries. However, moderate malnutrition, diagnosed by anthropometric measurements, affects a high percentage of children in those countries — a fact that lends importance to its study.

There are about a dozen studies of the effect of moderate malnutrition on different components of the immunologic system in children. Most of these studies have found that the cellular immune response is depressed. Among the cellular response components that are affected are the transformation of active lymphocytes to lymphoblasts,[7,11] the proportion of T lymphocytes in the peripheral blood,[12-14] and, in most cases,

Table I. Simple regression equations of cellular immune response indicators on anthropometric indices at time of immunologic tests

Diameter of induration*	=	0.49 + 0.088 % weight-for-age	
		SE = 0.048	
R^2 = 0.03		t = 1.83†	
Diameter of induration*	=	−6.89 + 0.150 % weight-for-height	
		SE = 0.050	
R^2 = 0.07		t = 3.00‡	
Diameter of induration*	=	14.70 − 0.077 % height-for-age	
		SE = 0.099	
R^2 = 0.00		t = 0.77	
% of T lymphocytes§	=	−83.01 + 1.506 % weight-for-age	
		SE = 0.334	
R^2 = 0.43		t = 4.51‡	
% of T lymphocytes§	=	−83.26 + 1.251 % weight-for-height	
		SE = 0.265	
R^2 = 0.47		t = 4.72‡	
% of T lymphocytes§	=	45.63 − 0.057 % height-for-age	
		SE = 0.824	
R^2 = 0.00		t = 0.07	

From Rivera JA [Thesis]. Cornell University, 1985.[17]

* Largest diameter of induration on intradermal injection of 5U of tuberculin 5 weeks after administration of BCG.

† $p<0.1$.

‡ $p<0.05$ (t test).

§ Percentage of T lymphocytes in peripheral blood.

delayed type sensitivity tests.[7, 11, 13-16] Some of the studies used the tuberculin test in children previously vaccinated with bacille Calmette-Guérin (BCG). Levels were found to be depressed in the studies in which BCG was injected intradermally within a short period (4 to 6 weeks) after the child's contact with specific antigens. It is very possible that in this short period, the response to the test is not influenced by such factors as differential exposure to the antigen, which would make it invalid. Furthermore, it is probable that the effect of malnutrition consists of increasing the period necessary between the initial contact with the antigen and the immunologic response. Another factor that appears to influence the results of delayed hypersensitivity is the dose applied via intradermal injection. Differences between malnourished and healthy children are more frequently found when low dosages are used. This suggests that the intensity of the response may be decreased in moderate malnutrition.

Unfortunately, most studies of moderate malnutrition have not controlled for the effect of infection, either. The ones that have controlled for the effects of infection and other factors such as socioeconomic level found that the association between the transformation of lymphocytes to lymphoblasts and nutritional status was no longer significant,[16] but that the association between nutritional status and both the percentage of T lymphocytes and delayed hypersensitivity continued to be significant.[17] This suggests that moderate malnutrition affects some components of the cellular immune response independently of infection.

Some other components of the immunologic system, such as the complement system, phagocyte function,[12] and the levels of secretory IgA in tears were found to be depressed in children with moderate malnutrition.[18]

Only one of the studies of humoral response found reduced serum IgA levels in children with moderate malnutrition.[16]

Finally, the cellular immune response (measured by the percentage of T lymphocytes and delayed hypersensitivity) was found to be associated with indicators of wasting (percent weight-for-height and arm circumference) and not with indicators of stunting (percent height-for-age) (Table I).[13, 17]

In summary, the evidence showing that the cellular immune response is reduced in severe malnutrition is unequivocal. There are also strong indications of a diminished cellular immune response in moderate malnutrition, although some results are contradictory. It appears that the decrease in cellular response is principally related to wasting and not to stunting. However, as McMurray et al.[11] have stated, the functional significance of these findings is not known; they add that no one has measured the minimum cellular response activity to prevent illness. Until this problem is resolved, the study of the effect of malnutrition on immunologic response does not provide enough information to understand the effect that malnutrition ultimately has on the incidence, duration, and severity of infections, which is what we need to understand.

The evidence showing that the cellular immune response is reduced in severe malnutrition is unequivocal.

FREQUENCY AND DURATION OF ILLNESSES IN CHILDREN WITH MODERATE MALNUTRITION

There are two types of information available that can help elucidate the effect of moderate malnutrition on the incidence and duration of illnesses. The first is that provided by studies of the case fatality rates of various common childhood infections. The second type of information is derived from studies of frequency and duration of infections in children classified according to nutritional status.

Case Fatality Rates

Measles is almost always innocuous in children from well-to-do societies. For example, the case fatality rate was about 0.1% in the United States at the end of the 1960s.[19] On the other hand, case fatality rates of 3.7% to 15% have been reported for various Third World countries.[20-23] There may be many explanations for this phenomenon. In de-

veloped countries, measles strikes children at older ages when they first go to school, whereas measles occurs much earlier in developing countries. This is significant because death due to measles is inversely associated with age, being greatest for very young children. Furthermore, in Third World countries measles is frequently complicated by other secondary infections that increase the risk of death. Finally, it has been suggested that poor nutritional status in children from developing countries increases case fatality rates.

It has been observed that the presence of kwashiorkor notably increases the fatality rates for measles,[19] and that measles complications are more frequent in malnourished children.[26, 27] On the other hand, some studies have not found an association between death due to measles and nutritional status.[28]

High fatality rates for some other diseases, such as chickenpox[27] and diarrhea,[29] have also been reported for malnourished children.

Nutritional Status and the Incidence and Duration of Infections

Hospital studies of children infected with *Vibrio cholerae* in Bangladesh found that the duration of diarrhea was greater in malnourished than in well-nourished children. Nutritional status was determined by percent weight-for-age[29, 30] and percent weight-for-height[31] calculations.

Most of the evidence on nutritional status and subsequent incidence and duration of infections is found in epidemiologic field studies.

Delgado et al.[32] studied indigenous Guatemalan children and found that indicators of both acute malnutrition (percent weight-for-height ≤75) and chronic malnutrition (percent height-for-age ≤90) were good predictors of the incidence and duration of simple diarrhea, as well as diarrhea with blood or mucus. Morbidity was monitored for 3 months subsequent to the anthropometric assessment.

James[33] carried out a 1-year study relating the association of the incidence and duration of diarrhea and upper respiratory tract infections to the weight-for-age value at the beginning of the study period. The incidence of diarrhea was greater in malnourished children (<75% weight-for-age) than in children with a higher weight-for-age value, but this relationship was observed only in children 3 years of age or older. There were no significant associations found with the incidence of respiratory infections. However, the duration of both diarrheal episodes and respiratory infections was greater in malnourished children, especially in children older than 1 year. The number of diarrheal episodes accompanied by high fever and blood was significantly higher in malnourished children, as was the number of cases of complication by respiratory infections. Finally, the rates of hospitalization and death for the malnourished children were higher than those for the well-nourished ones.

In a similar study by Tomkins[34] in Nigeria, in which the observation period was 3 months and in which not only weight-for-age but also weight-for-height and height-for-age values were calculated, it was found that the incidence of diarrhea was related only to wasting (weight-for-height). However, the percentage of time that the child was ill with diarrhea was significantly related to all three indicators. The highest association was with weight-for-height, an indicator of wasting.

Trowbridge et al.[35] found that the percent weight-for-age value, as well as those for height-for-age and weight-for-height, were all associated with the percentage of time that children suffered from diarrhea during the year after the anthropometric assessment.

In Bangladesh, Chen et al.[36] studied the predictive value of various anthropometric indicators of nutritional status on the incidence of diarrhea (during 1 year after anthropometric studies were performed) and on hospitalization for diarrhea (during 2 years after anthropometric evaluation). No significant association was found between any of the anthropometric indicators and the incidence of diarrhea or hospitalization. It should be pointed out that the duration and severity of the episodes were not taken into account.

Black et al.[37] studied the association between various anthropometric indicators and the incidence and duration of diarrhea for periods of 2 months after anthropometric assessment in children 2 to 48 months of age in Bangladesh. They found that the incidence of diarrhea in children <2 years old was independent of level of nutritional status; on the other hand, the duration of diarrhea increased as nutritional status worsened. In children >2 years old, there was no difference in either the incidence or the duration of diarrhea in comparisons of malnourished and healthy children. Similar results were obtained when the incidence and duration of diarrhea specifically due to *Escherichia coli* and *Shigella* was investigated. When the children were classified according to level of stunting (percent height-for-age) or level of wasting (percent weight-for-height), it was found that wasted children had a longer duration of diarrhea than stunted children.

The weight-for-height value, which is a measure of current nutritional status, seems to be a better predictor of future infection than height-for-age, a measure of long-term nutritional status.

It is important to point out that these studies are not conclusive, because higher prevalences of diarrhea in malnourished children can be explained by their greater exposure to pathogenic microorganisms, which are more common in low socioeconomic levels, where sanitary conditions are deficient. But there is no reason to expect differences in the duration of diarrhea as a result of greater exposure to pathogenic organisms. There may be, however, other factors distorting this association that have not yet been taken into account.

Another potential problem is that the period of observation during which infections were monitored varied in the different studies. It is probable that the effect of malnutrition on the risk of infection decreases over time; if so, the studies for periods of 1 and 2 years would be inappropriate. Also, the studies have uniformly ignored changes in nutritional status subsequent to the initial anthropometric assessment, even when the period of follow-up has been as long as 2 years.

Finally, although there are discrep-

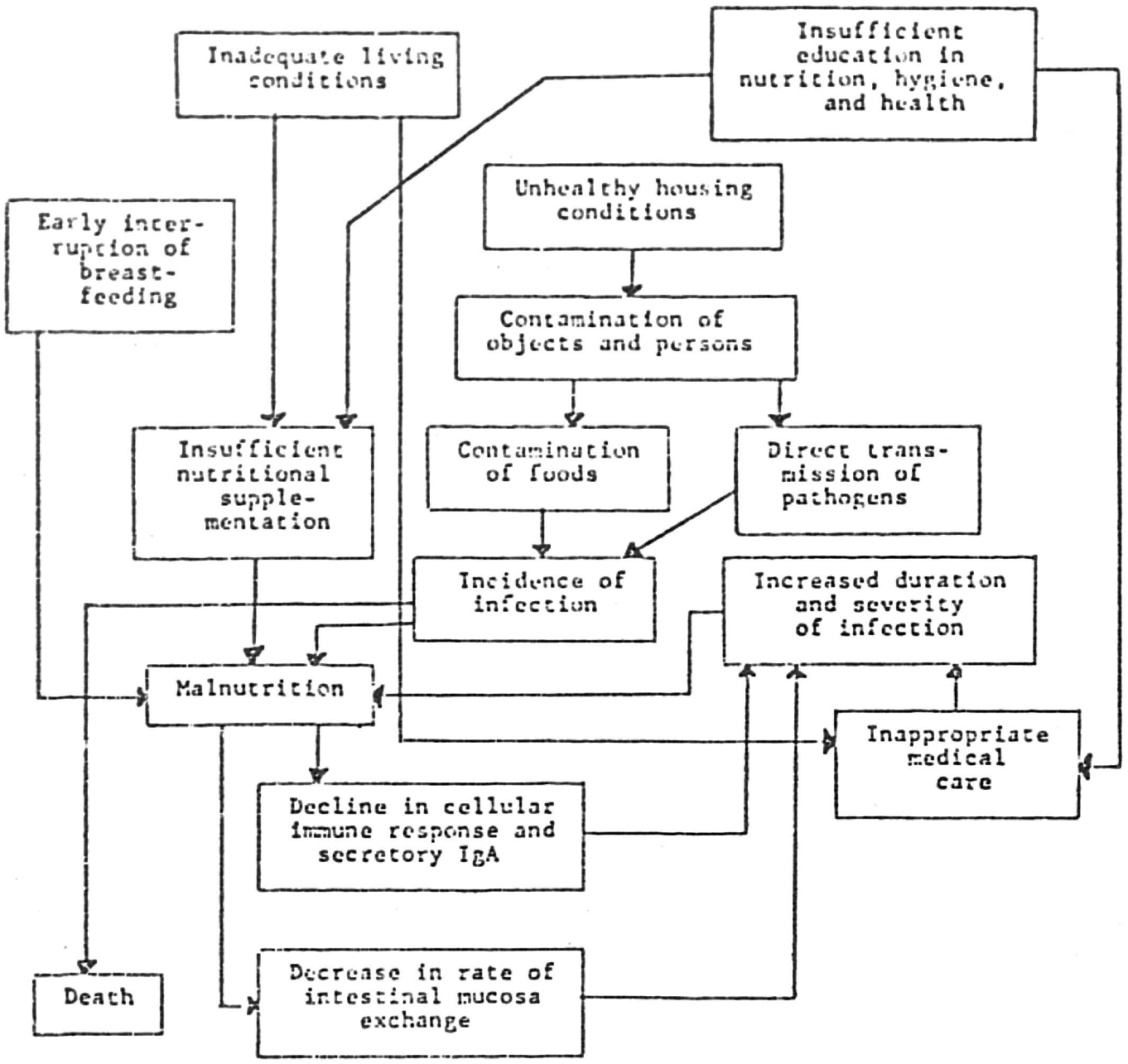

Fig. 1. Possible interactions between malnutrition and infection.

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NUTRITION INTERVENTION STUDIES

The last important line of evidence useful in determining if nutritional status affects infection is provided by nutrition intervention studies.

Most such studies have had a positive effect on nutritional status and have been associated with decreased infant and preschool mortality rates. However, results about the effects on the incidence and duration of infections have been contradictory.

Wray[38] observed a reduction in the incidence of infections in children who received supplements in Colombia. Chavez and Martinez[39] also found a reduction in the incidence of infections in children who received supplements, but the principal effect was in the duration of infections in children ≥6 months old in Mexico.

Scrimshaw et al.[40] found lower measles fatality rates in Guatemalan children who received supplementary foods as compared with a control group. This suggests that the severity of infections is greater in malnourished children. However, Kielman et al.[41] in India and Barba et al.[42] in the Philippines found no differences in the duration of infections between groups that did and did not receive supplements.

Thus, the studies of the effect of nutritional supplementation on infection have yielded contradictory results.

Taking all of the studies together, there can be no doubt that there is strong evidence for the notion that malnutrition increases the duration of infections (especially diarrhea), although probably not their incidence. The duration of infections is probably related to severity, which would explain the high fatality rates for some common childhood diseases among malnourished children.

The longer duration of diarrhea may be due to defects in the immune response of malnourished children, in particular to inadequate levels of secretory IgA in the digestive tract and probably to deficiencies in cellular immune response. There are, however, other possibilities. It is known that epithelial cell exchange in the intestine decreases in severe malnutrition. The recuperation of intestinal mucosa during infection is probably slower in malnourished children, and this may increase susceptibility to infection or recovery time. Another hypothesis is that malnourished children probably have a higher frequency of lactose intolerance. This condition has been associated with prolonged diarrhea after acute episodes.

CONCLUSIONS

The main ideas are summarized in Fig. 1, which shows the possible interactions between malnutrition and infection and identifies key factors that influence malnutrition and infection.

The principal conclusions are as follows:

1. In studies carried out in poor children from developing countries, associations between infection and growth retardation have been consistently reported.
2. There is abundant clinical evidence documenting reduced growth rates and, in some cases, the appearance of clinical signs of malnutrition, after episodes of infections, particularly diarrheal diseases and measles. Furthermore, there is epidemiologic evidence of a relationship between growth deceleration and episodes of diarrheal diseases. Finally, it is known that various infections cause decreased food intake and nutrient absorption, as well as metabolic changes that increase nutritional requirements. This is consistent with clinical and epidemiologic evidence. The data, as a whole, indicate that some diseases, especially diarrhea, cause a deterioration in nutritional status.
3. Severe and moderate malnutrition have been found to be associated with decreased cellular im-

mune responses, reductions in secretory IgA levels, and defects in some components of the complement system. However, the functional significance of these immunologic alterations is not known.

4. There is evidence that fatality rates are greater for some infections in malnourished children as compared with well-nourished ones; however, the evidence is not conclusive.
5. Various studies have reported results about the incidence or duration of infections subsequent to the diagnosis and classification of nutritional status, based on anthropometric measurements. The studies of incidence have yielded contradictory results. Some suggest that moderate malnutrition does not predispose children to a higher incidence of infections. On the other hand, studies of the duration of infections have been more consistent in indicating that malnourished children seem to have infections of longer durations. Among other causes, this may be due to a depression of the immunologic system or to a deficiency in recuperation of the intestinal mucosa during diarrheal infections.

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