THE VICIOUS CYCLE OF MALNUTRITION-INFECTION WITH SPECIAL REFERENCE TO DIARRHEA, MEASLES AND TUBERCULOSIS

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Throughout history, a close association is observed between famine and pestilence. Situations of acute or chronic food deprivation, arising out of natural disasters or man made calamities are found to be associated with outbreaks and increased number of deaths due to infectious diseases. Besides such information, scientific data collected from epidemiological, clinical and laboratory studies support the synergistic interactions between malnutrition and infection. In other words, conditions of food inadequacy increase the susceptibility to infections while episodes of infection, in turn, precipitate nutritional deficiencies. These mutually adverse interactions between malnutrition and infection constitute a vicious cycle in the underprivileged communities where malnutrition is widespread among young children and the environment is conducive for the spread of infectious diseases *(Fig. 1)*.

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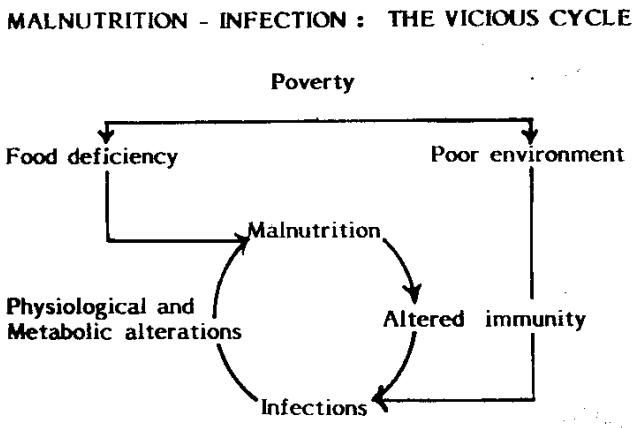

Fig. 1. The vicious cycle of malnutrition and infection.

The mechanisms involved in the interactions between malnutrition and three major childhood infections, *viz.*, diarrheal diseases, measles and tuberculosis with their public health relevance are briefly reviewed in this article.

Diarrheal Disease

Effect of diarrhea on nutritional status

Diarrhea is one of the commonest infectious diseases observed among young children in developing countries contributing to nearly 40% of deaths among preschool children. Precipitation of severe nutritional deficiencies like kwashiorkor and keratomalacia by preceding recurrent episodes of diarrhea is a common clinical observation. Several workers have emphasized the outstanding epidemiological relationship between diarrhea and severe PEM(1,2). Weanling diarrhea constitutes the best example to demonstrate the effect of recurrent diarrheal episodes on the evolution of malnutrition in children(3). Growth performance of children in devel-

oping countries is often adversely affected by recurrent diarrheal episodes(4,5).

It is now well understood that the effects of diarrhea on nutritional status are brought about by several mechanisms.

Decrease in food intake: As with many other infections, loss of appetite is profound in gastro-intestinal infections causing gross reduction in food intake. In addition to the effect of infection *per se*, the inherent disturbances in water and electrolyte imbalance that occur during diarrheal illness, aggravate the anorexia and may also lead to vomiting. Dietary restriction during the illness imposed by mothers worsens the problem.

Feeding habits of infants and children are grossly altered during any illness and particularly so in diarrheal illness. In a recent study carried out in the rural areas near Hyderabad, a detailed account of the feeding habits of children and change in these practices during diarrheal illness were recorded. Fortunately, majority of mothers continued to breast feed their babies even during diarrhea. However, food restriction was severe in children who were partially or totally weaned. Supplements were stopped and the diets contained weak tea and sago as substitutes for regular diets. Thus the diets during illness were poor in quality as well as quantity imposing a calorie deficit of more than 30%(6). Similar observations on change in feeding practices of children during diarrheal illness are reported from Bangla Desh also(7). Hoyle *et al.* reported in children from the same country that anorexia during diarrhea mainly affected consumption of supplementary foods while breast milk intake remained unchanged(8). These studies, while stressing the importance of diet during diarrhea, highlight the need to continue breast feeding. Absorption of breast milk nutrients is better, despite the presence of diarrhea and thus provides the required nutrition to the child. In addition, breast milk offers resistance to infection by providing the immune factors in the form of cells, immunoglobulins, lactoferrin, *etc.*(9,10). In the older child the calorie gap can be bridged by encouraging the child to eat soft and easily digestible diets at frequent intervals thus ensuring adequate nutrient intake. Early and efficient correction of electrolyte imbalance contributes to quicker restoration of appetite. Weight gain of children managed with oral rehydration therapy was higher than that of children in whom the early electrolyte imbalance was not corrected(11).

Increased nutrient losses: Nutrient losses due to malabsorption from the gut, vomiting and due to excessive metabolic losses are common to any childhood infection and are particularly prominent in diarrheal illness.

Scrimshaw *et al.*(12) observed decreased retention of nitrogen by children having common infections like tonsillitis, sinusitis, asthmatic bronchitis, *etc.* Several investigators demonstrated striking increase in urinary losses of nitrogen in typhoid fever(13). Similar observations are reported in tuberculosis as well(14). Parasitic infestations of the gut also have similar metabolic effects. Venkatachalam and Patwardhan noticed a significant decrease in fecal nitrogen following deworming of children having heavy ascarial infestation(15).

The adverse effects of acute diarrhea on intestinal absorption of several macro and micronutrients is clearly demonstrated. Children with diarrhea have malabsorption of carbohydrates, fats, nitrogen, aminoacids and protein thus leading to energy and protein deficits(16).

There is enough evidence to suggest defects in absorption of both water soluble and fat soluble vitamins in diarrhea. Lindenbaum reported malabsorption of B_{12} in patients with diarrhea(17). Infants with diarrhea had folate malabsorption(18). Reddy and Sivakumar observed malabsorption of vitamin A in children with infection(19). The absorptive defects of nutrients are reflected in their lowered serum concentration. Children with systemic or local gut infections have lower levels of retinaol in circulation(20).

Effect of diarrheal illnesses on the absorption of trace minerals is not extensively studied in humans. Back *et al.* observed excessive loss of magnesium during acute enteritis(21). However, definite impairment of absorption of this mineral has not been documented. Disturbances in trace mineral balance, with respect to zinc are recently demonstrated in infants suffering from acute diarrhea, suggesting fecal losses of this mineral during the illness(22).

Thus, malabsorption of several nutrients is documented during diarrhea which, if not replenished appropriately has the potential risk of precipitating nutritional deficiencies. It has been clearly demonstrated that despite the malabsorption, feeding of energy dense diets during diarrheal illness had beneficial effects on weight gain(23). These observations indicate the importance of early and adequate feeding during diarrhea.

Effect of Malnutrition on Diarrheal Morbidity

Several investigators from developing countries have examined the effects of various degrees of malnutrition on the attack rate, duration and severity of diarrhea while a few reported the effects on risk of mortality. The results from different parts of the globe have been different on any of these parameters studied.

Bevan(24) observed increased frequency as well as duration of diarrhea in malnourished infants in Bahrain. Similar observations were made by Gordon *et al.*(25) from malnourished Gautemalan children. Stetler *et al.*(26) from El Selvador found a close association between poor nutritional status and diarrheal incidence among children. Ghai and Jaiswal(27) made similar observations of increased frequency of diarrhea in undernourished than in wellnourished North Indian children.

Though all these studies demonstrate an association between malnutrition and diarrheal morbidity, the causal relationship between the two could not be established because among people belonging to poor socio-economic status living in poor environmental conditions, both malnutrition and diarrheal diseases are coexistent and interact adversely with each other. Contrary to these reports, Chen *et al.*(28) from Bangla Desh followed by Mathur *et al.*(29) from Central India reported no association between malnutrition and either frequency or duration of diarrhea.

However, distinguishing acute from chronic malnutrition using weight/height index, Tomkins(30) observed that acute malnutrition was significantly associated with more prolonged diarrhea among Nigerian children. Black *et al.* also showed that children in Bangladesh with low weight/height had prolonged episodes of diarrhea but the attack rates were not different. A case control study reported by Bhandari *et al.*(32) has shown that weight/age <70% increases the risk of persistent diarrhea which is a higher risk for the contribution of diarrhea-malnutrition vicious cycle. Mathur *et al.*(29) also found that severity of malnutrition had a significant

effect on severity of diarrhea as judged by degree of dehydration. They observed that the number of severe episodes of dehydration among several malnourished children was twice that seen in the better nourished.

Earlier, Kielman *et al.*(33) from Punjab and Chen *et al.*(28) from Bangladesh found higher risk of mortality due to diarrhea among children with severe malnutrition. The differences in the observations made by different investigators could be due to several factors. Differences in socio-economic status and environmental hygiene of the population studied, differences in the methods of assessment of the degree as well as duration of malnutrition appear to be important confounding variables.

The prevalence of diarrhea in a community depends to a great extent on the environmental and personal hygiene while the severity of the episode could be to some extent modulated by the appropriateness and adequacy of the immune response raised by the host in order to combat the microbial invasion. Low gastric acidity and altered gastrointestinal flora are well established changes in malnourished children. Lowered mucosal immunity could increase the mucosal susceptibility to infections(34).

Therefore, the heavy contamination in the environment along with the lack of satisfactory personal hygiene in the poor communities of the developing world could lead to high prevalence of diarrheal disease irrespective of the nutritional status. However, the compromised immune status of an undernourished child promotes the chances of prolongation of the diarrheal episodes and also could lead to increased severity.

A review of these studies thus stresses the need for improving environmental and personal hygiene *vis-a-vis* nutritional rehabilitation to make a significant impact in decreasing the morbidity and mortality due to diarrhea among poor children.

Measles

This is one of the acute viral exanthematous infections that affects more than 95% of the susceptible children before the age of 5 years. This infection in developing countries is believed to contribute to high morbidity and significant mortality among preschool children.

Effect of Measles on Nutritional Status

Several investigators have reported the unusual nutritional stress imposed by measles in undernourished children. Clinical observations reveal a close association between measles and severe PEM. It was observed that nearly 25% of the children admitted to hospital for severe PEM had an episode of measles in the preceding 3-6 months time(35). In a prospective study carried out in the urban slums of Hyderabad city, the effects of measles on nutritional status of children under 5 years of age were assessed. Measles caused significant loss of body weight ranging from 2-12% of the initial body weight during the acute episode in all the children. This was complicated by retarded growth in the post measles period for nearly 6 months. These changes in weight reflected on the profile of nutritional status in the community. Percentage of normal children decreased while the number of undernourished and severely malnourished children in the community increased following the measles season. Nearly 4% of the children who had measles developed clinical signs of kwashiorkor/maramus within 3-6 months following measles illness(35).

Growth changes were noticed in all the children who suffered from measles. How-

ever, the severe consequences were observed in children who were already undernourished at the time of measles. All the children who manifested clinical signs of severe PEM in the post measles period were undernourished before contracting measles. The effects of measles were noticed on metabolic parameters too. Serum albumin and retinol levels were significantly lower in children during measles compared to their own premeasles values. The fall was more profound in already malnourished children compared to the well nourished ones. These observations demonstrate the adverse nutritional effects of measles in all the children, clearly pointing out that more severe consequences were precipitated to a greater extent in already malnourished children. Thus, nutritional status of the child before measles appears to determine the severity of nutritional deficiencies and growth failure that is likely to occur in the postmeasles period.

The mechanisms by which measles influences nutritional status are more complicated than the general mechanisms observed with other infections. Like in any other febrile illnesses, measles contributes to severe reduction in food intake, vomiting and increased metabolic losses. In addition, excessive loss of nitrogen due to protein losing enteropathy is demonstrated in measles due to the viral enteritis(36). Induction of prolonged immunosuppression is peculiar to measles. A decrease in the circulating T cell number and impaired proliferation of T lymphocytes was demonstrated in children during the episode of measles which remained low for nearly 6 months following the acute illness. The degree of morbidity observed was similar in children belonging to different nutritional grades pointing out the importance of other factors associated with poverty in precipitating recurrent morbidity(37). The adverse effects of such repeated infections on an already malnourished child need not be over emphasized.

Measles and Blindness

Measles associated blindness has been recognized as a significant problem in several developing countries and is believed to be due to vitamin A deficiency caused by measles. The information obtained is from studies which have often been retrospective. Therefore, the exact relationship between measles and blindness cannot be established from these studies. Bhaskaram *et al.* in their recent prospective study delineated the causal role of measles *per se* from that due to vitamin A deficiency in the causation of measles related blindness(20).

Measles related blindness may be broadly classified as two different entities: (*a*) Blindness occurring during measles; and (*b*) Postmeasles blindness. The pathogenetic mechanisms of these two types of blinding eye lesions associated with measles are different, thus requiring preventive approaches.

The lesions occurring during measles are mainly due to proliferation of measles virus in the eye causing keratitis and local immunosuppression. A decrease in the immune factor content of tears predisposes the eye for secondary microbial invasion. This latter factor triggers ulceration of the cornea whose structural integrity is already compromised by viral keratitis and associated nutritional deficiencies(20) (*Fig. 2*).

Therefore, the blinding eye lesions due to measles can primarily be prevented by effectively implementing measles vaccination programme. However, if a child comes with measles and the eye is already at risk, the eye can be protected by instillation of antibiotic drops.

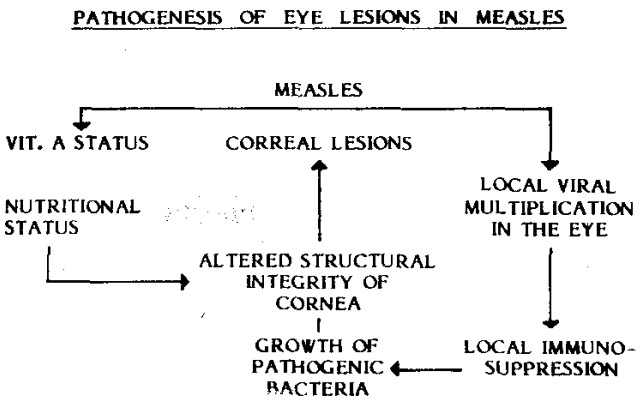

Fig. 2. Pathogenesis of corneal lesions in measles.

Post measles blindness is often associated with post measles protein energy malnutrition and is thus mainly of nutritional origin. While prevention of measles is a major factor, improvement of vitamin A status by giving vitamin A supplements constitutes an immediate and short term approach to prevent blindness due to post measles nutritional keratomalacia.

Effect of Nutrition and Measles

Measles is reported to be particularly severe among children in West Africa with mortality rates in endemic areas ranging from 25-30%(38). This severity of the disease has been attributed to the severe immunosuppression caused by the associated malnutrition. Measles in Asian countries is often less severe, though the severity of malnutrition in the developing countries in Asia is no less than it is in Africa. Studies reported in literature attribute malnutrition to be responsible for severe measles. However, these studies are either hospital based or semi-longitudinal studies in the community(39). In these studies, the pre-measles nutritional status of the child is often based on presumption. The study designs are not suitable to delineate the effects of nutritional status and other factors that are closely related to malnutrition on the course of the disease. Bhaskaram *et al.* in their prospective study on urban slum dwelling preschool children reported that the incidence, course and severity of measles were similar between well nourished and malnourished children thus clearly suggesting that nutrition *per se* does not influence the above features of the disease(40). However, factors associated with poverty and thus with malnutrition, like overcrowding, poor sanitation, lack of health care facilities, *etc.* could be responsible for the apparent severity and frequency of measles among children in poor communities when compared with the children from better social class.

It is believed that the malnourished child suffers from severe measles as it is subjected to the dual immuno-suppressive effects of measles and nutritional deficiencies. However, specific immune responses which are essential for recovery from measles *per se* were adequate in malnourished children and comparable with those developed in the well nourished children with measles. Thus, even a malnourished child appears to have an adequate potential to recover from measles(40). Therefore, the higher mortality observed in malnourished children could be due to social and environmental factors other than due to malnutrition *per se.*

Vaccination is the important tool in preventing measles and its associated complications. Often, tuberculosis and malnutrition are considered as contraindications for measles vaccination. The general and specific immune responses to vaccine and also the effect of nutritional status on the degree of immune response were examined. Unlike the virus of natural infection, the attenuated virus of the vaccine has no immunosuppressive effect and thus is likely

to activate latent tubercular lesions. Nutritional status did not alter the degree of cellular or humoral responses, thus indicating the efficacy and safety of the vaccine in undernourished communities(41).

Tuberculosis

Tuberculosis is another communicable disease that is closely associated with malnutrition and is widely prevalent in our country. Recent estimates indicate that over 1 million cases of tuberculosis with at least 10,000 deaths are reported(42). These figures, if anything, could only be underestimates as the notification of cases and causes of death are not satisfactory in our country. With such a high incidence of active diseases in adults, it is no surprise that the incidence of childhood tuberculosis is high.

The role of nutrition in the causation and in the management of tuberculosis have been doubted. Although it has been clearly shown that diet has no additional role in the management of tuberculosis(43), the absence of its effect on the pathogenesis of the disease has not been proved so far, scientifically.

From ancient times, the association between conditions of food deprivation and increased incidence of deaths due to tuberculosis has been highlighted. Besides this information, epidemiological and experimental data support this association(44,45). In their recent studies, Bhaskaram and coworkers have established the contributory role played by malnutrition in the evolution of tuberculosis in children. A significant association between malnutrition and tuberculosis was observed in both adults and children(46,47). Further, it was observed that there was a significant association between severe malnutrition and severe forms of tuberculosis suggesting a role for malnutrition in the development of severe forms of tuberculosis like meningitis, abdominal and skeletal tuberculosis. Immunological studies revealed that immune suppression was maximum in malnourished children with severe forms of the disease. The depression in T cell responses were more in these children compared to better nourished children with similar severity of the infection. These observations suggest the synergistic interactions between malnutrition and tuberculosis and also indicate the contributory role played by malnutrition in leading to immunosuppression, thus triggering the spread of disease to severe forms(46).

Macrophage (MO) dysfunction was observed in malnourished patients with tuberculosis and similar dysfunction was noted even in the contacts who were equally malnourished suggesting the effect of malnutrition in contributing to MO dysfunction in these subjects. These observations are important as they suggest the potential for establishment of disease in contacts and spread of disease in patients(47). Thus malnutrition appears to have an important contributory role in the evolution of tuberculosis.

Conclusions

These studies suggest that besides the effects of malnutrition *per se* on infection and vice versa, the influence of the other associated conditions with poverty like overcrowding, unsatisfactory environment is significant in the causation and severity of infectious diseases. These observations imply that improvement in nutrition and health status of individuals in the community can be achieved by an integrated approach of control and prevention of infections along with improvement in nutritional status by supplementary feeding.

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