Undernutrition, infection and immune function

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Abstract

Undernutrition and infection are the major causes of morbidity and mortality in the developing world. These two problems are interrelated. Undernutrition compromises barrier function, allowing easier access by pathogens, and compromises immune function, decreasing the ability of the host to eliminate pathogens once they enter the body. Thus, malnutrition predisposes to infections. Infections can alter nutritional status mediated by changes in dietary intake, absorption and nutrient requirements and losses of endogenous nutrients. Thus, the presence of infections can contribute to the malnourished state. The global burden of malnutrition and infectious disease is immense, especially amongst children. Childhood infections impair growth and development. There is a role for breast-feeding in protection against infections. Key nutrients required for an efficient immune response include vitamin A, Fe, Zn and Cu. There is some evidence that provision of the first three of these nutrients does improve immune function in undernourished children and can reduce the morbidity and mortality of some infectious diseases including measles, diarrhoeal disease and upper and lower respiratory tract infections. Not all studies, however, show benefit of single nutrient supplementation and this might be because the subjects studied have multiple nutrient deficiencies. The situation regarding Fe supplementation is particularly complex. In addition to immunization programmes and improvement of nutrient status, there are important roles for maternal education, improved hygiene and sanitation and increased supply of quality water in the eradication of infectious diseases.

Malnutrition: Undernutrition: Infection: Immunity: Micronutrients

Introductory comments

Along with undernutrition, infection is a primary cause of morbidity and mortality in the developing world. Complex interactions exist between these two threatening problems. Despite a greater awareness of the implications of nutrient deficiencies in diminishing the host's

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

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defence towards infection, the increased understanding of the actions of different kinds of infectious agents, and the use of chemotherapy and immunization, malnutrition, nutrient deficiencies and infectious diseases persist. Increased survival through childhood has led to significant extension of life expectancy in developing countries. Nevertheless, globally one child in three does not survive to adulthood. The aim of this present article is to define the global burden of infectious disease, to identify the extent of malnutrition and micronutrient deficiencies and their impact on childhood growth, to describe some of the interactions between malnutrition and infectious disease, and to review some of the attempts to reduce the rates of morbidity and mortality from infectious disease by using nutritional interventions; in addition, some key aspects of the impact of nutritional deficiencies on immune function will be described. Many of these topics are vast, with a large number of studies in animal models as well as in community and hospital settings. As such, this article does not aim to review exhaustively the entire subject. However, the key issues will be highlighted. The reader is referred to Scrimshaw *et al*. (1959, 1968), Chandra (1983*a*, 1991), Tomkins & Watson (1993) and Scrimshaw & SanGiovanni (1997) for earlier, elegant, reviews of this topic.

Malnutrition and infectious disease: the global burden

Malnutrition and infection play a major role in the causation of preventable deaths and disabilities that occur within the developing world, especially among children. Improvements in health over the last 50 years or so, including immunization programmes, have brought about marked improvements in morbidity and mortality. Nevertheless, the global burden of malnutrition and infectious disease is enormous: it is estimated that at least 2 million children per year die from diseases for which vaccines already exist (World Health Organization, 1998). Low birth weight is an indicator of fetal undernutrition and WHO estimates that 25 million low birth weight babies are born each year, constituting 17 % of all live births; 95 % of these low birth weight infants are born in the developing world (World Health Organization, 1998). Born with low birth weights and then subjected to sub-optimal breast-feeding practices, these infants are at particular risk of malnutrition and disease. Low birth weight is associated with neonatal and postnatal mortality, particularly in Bangladesh and India (World Health Organization, 1997*a*, 1998). Because much (50 %) of the transfer of some nutrients from mother to fetus occurs in the last 6–8 weeks of gestation, prematurity and low birth weight are often associated with nutrient deficiencies (e.g. of Zn, Cu, Fe and vitamin A) (Farrell *et al*. 1985; Powers, 1993). Low birth weight increases susceptibility to diarrhoea and pneumonia, and increases risk of death from diarrhoea, pneumonia and measles (for review see Ashworth, 2000).

Inadequate dietary intake and disease are immediate causes of malnutrition and they reinforce one another synergistically (Scrimshaw *et al*. 1968; Fig. 1). Malnutrition makes the individual more susceptible to infection and decreases immune defences against invading pathogens. In turn, certain pathogens influence nutritional status, mediated by changes in dietary intake, absorption, and nutrient requirements and losses of endogenous nutrients (Fig. 2). Malnutrition takes several forms that often appear in combination, such as protein–energy malnutrition and deficiencies in micronutrients such as vitamin A, Fe, Zn, and I. Growth of the individual is also impaired owing to the combination of poor nutrition, malabsorption and the host response to infection, which can involve anorexia and altered metabolism of nutrients. Infection also alters behaviour, which can affect feeding practices.

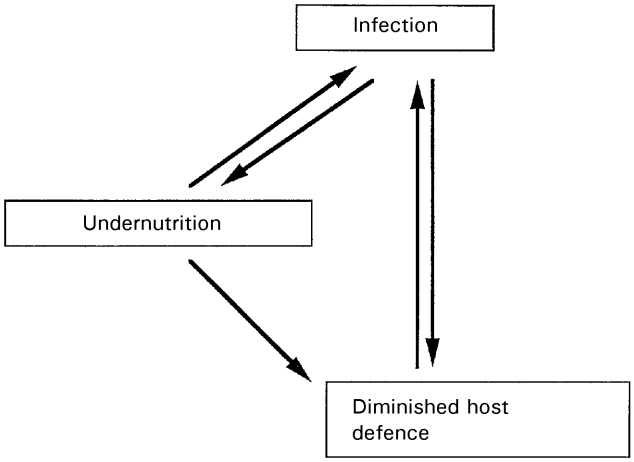

Fig. 1. Interrelationship between malnutrition and infection.

Malnutrition and infection can also occur in combination because of the environment which pertains. For example poverty, ignorance, poor hygiene, lack of water supplies, poor housing, poor health services, cultural practices, and discriminatory social structures often occur in combination and these create an environment of poor nutrition and exposure to infectious agents. Food and water can themselves be sources of infectious agents (Henry *et al.* 1990). A number of studies in different settings have now shown that improved sanitation and hygiene significantly reduce the incidence of diarrhoeal disease (Alam *et al.* 1989; Aziz *et al.*

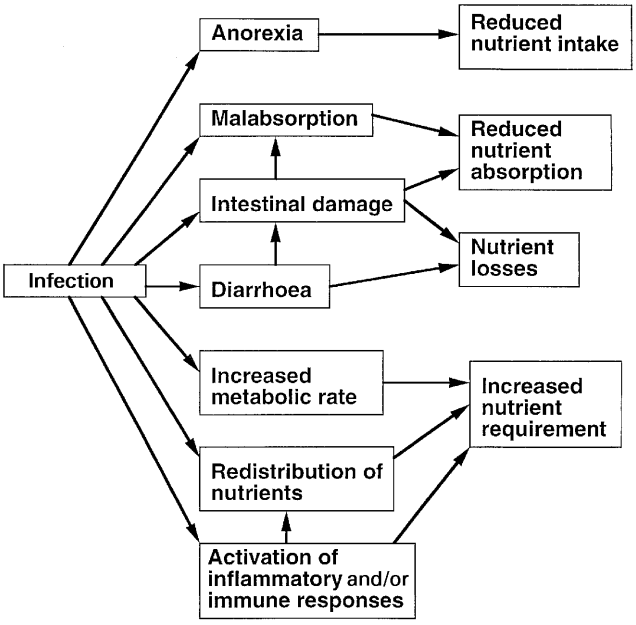

Fig. 2. Effects of infection on the host which can decrease nutrient status.

1990; Henry & Rahim, 1990; Ekanem *et al*. 1991; Haggerty *et al*. 1994; Alam, 1995; Gorter *et al*. 1998).

The disease burden of malnutrition is immense. Each year over 10 million children under 5 years of age die in developing countries, mainly from preventable causes; over 6 million of these deaths ($>50\%$) are directly or indirectly attributable to malnutrition (World Health Organization, 1998). In the developing world over 6 million children died in 1995 from one, or a combination of more than one of five, conditions: malaria, malnutrition, measles, acute respiratory infections, diarrhoea (Table 1). Over 30 % of neonatal deaths are directly due to infection (World Health Organization, 1998). The great majority of maternal deaths (99 %) occur in the developing world (40 % of these are in South-East Asia); many of these deaths are due to infectious diseases related to malnutrition (World Health Organization, 1998).

Parasite infections are the most common infections globally. Among the protozoans, *Plasmodium*, *Entamoeba* and *Giardia* spp. infect 300–500 million, 500 million and 200 million individuals respectively, worldwide (Molyneux, 1997). Among the nematodes, *Ascaris*, schistomes, Trichuris and hookworm infect 1000 million, 200 million, 900 million and 500 million individuals respectively, worldwide (Molyneux, 1997). These infections are most common and most severe in children. The peak of infection is in childhood but the infections and their effects persist into adulthood.

WHO predicts that, by the end of 1999, 13 million women will have been infected with human immunodeficiency virus (HIV) and 4 million will have died of acquired immune deficiency syndrome (AIDS). Each day 1600 children become infected with HIV, mainly through mother-to-child transmission. By the end of 1999 as many as 10 million children under 10 years of age may have been orphaned as a result of maternal AIDS in sub-Saharan Africa alone and the projected deaths from AIDS may increase child mortality rates by as much as 50 % in this region. Total numbers of individuals infected with HIV are estimated at 30 million in 1997, with 6 million new infections occurring per year. Of those infected with HIV (about 20 million) 60–65 % are in sub-Saharan Africa, with a further 6 million in South and South-East Asia and 1·3 million in South America.

One key change in the incidence of infectious disease in relatively recent times has been the re-emergence of tuberculosis (Bloom & Murray, 1992). This disease, which has been a target of immunization programmes for many years, has re-emerged in both developed and developing countries. High-risk populations include those where malnutrition is common; in

Table 1. Major causes of death among children under 5 years of age in the developing world in 1995*

Cause of death	Deaths (millions)	Deaths associated with malnutrition (%)
Lower respiratory tract infections	2·1	44
Diarrhoea	2·0	70
Prematurity	1·0	40
Measles	1·1	65
Birth asphyxia	0·9	35
Malaria	0·7	40
Congenital abnormalities	0·5	30
Pertussis	0·4	50
Neonatal tetanus	0·4	20
Birth trauma	0·4	30
Neonatal sepsis and meningitis	0·4	30
Malnutrition	0·3	100
Tuberculosis	0·1	60
All other causes	0·2	40

* Data from World Health Organization (1998).

Table 2. Global burden of disease and injury attributable to selected risk factors*

Risk factor	Total deaths (millions)	Total deaths (%)	DALY (millions)	Total DALY (%)
Malnutrition	5·9	11·7	219.6	15·9
Poor water, sanitation, hygiene	2·7	5·3	93·4	6·8
Unsafe sex	1·1	2·2	48·7	3·5
Tobacco	3·0	6·0	36·2	2·6
Alcohol	0·8	1·5	47·7	3·5

DALY, disability-adjusted life years.
* Data from Murray & Lopez (1996).

developing countries the elderly are particularly at risk (Rajagopalan & Yoshikawa, 1998) and this might be associated with their poorer nutrient status and the decline in immune function which accompanies ageing. Remarkably, tuberculosis is now the second most common cause of death in Indonesia (Gross & Schultink, 1997). HIV infection causes a decline in host immune defences and this most likely explains the increased rates of infection of HIV patients with tuberculosis; tuberculosis is a major contributor to the body wasting that accompanies HIV infection in 'Slim disease' (Lucas *et al*. 1994). Globally, there are about 8·8 million new cases of tuberculosis each year and it is estimated to cause 3 million deaths per year (World Health Organization, 1995).

The Global Burden of Disease Study (Lopez, 1997) has calculated the future potential years of life lost or lived with a disability (disability-adjusted life years). In 1990 about 1·3 billion disability-adjusted life years were lost as a result of new cases of disease or injury; almost 90 % of these occurred in developing countries. Of the major risk factors evaluated, malnutrition was by far the leading contributor to disability-adjusted life years worldwide, causing an estimated 16 % of the global burden of disease in 1990 (18 % in developing countries), with contributions to disease burden being particularly evident in sub-Saharan Africa (33 %) and India (22 %) (Lopez, 1997). Malnutrition is the major cause of death, accounting for 11·7 % of total deaths, followed by poor water and sanitation (Table 2) (Murray & Lopez, 1996). The ultimate cost of malnutrition cannot be accurately calculated. It includes visible costs (costs of drugs, hospitalization, transportation, food, treatment of non-nutritional diseases) which can be estimated but the undoubtedly larger invisible costs (including loss of family income and national productivity) cannot be readily quantified but must be immense.

The incidence of childhood malnutrition

It is estimated that 168 million children under 5 years of age (27 % of the world's children in this age group) are malnourished (as measured by weight-for-age); 76 % of these children live in Asia, 21 % in Africa and 3 % in Latin America (World Health Organization, 1998). As many as 206 million children are stunted (i.e. height-for-age more than 2 SD below the mean value of the reference population; this equates to a height-for-age which is <90 % of the mean value of the reference population). In South Asia as many as 17 % of children under 5 years of age are wasted (i.e. weight-for-height more than 2 SD below the mean value of the reference population; this equates to a weight-for-height which is <80 % of the mean value of the reference population) and 60 % are stunted; figures for the developing world as a whole are 9 % and 41 % respectively. Worldwide, 160 million children are underweight (weight-for-age more than 2 SD below the mean value of the reference population; this equates to a weight-for-age which is <80 % of the mean value of the reference population), with over half of these being in South

Table 3. Regional variation in childhood malnutrition*

Region	Low weight-for-height† (wasted; %)	Low height-for-age‡ (stunted; %)	Low weight-for-age§ (underweight; %)	Low birthweight ‖ (%)
South Asia	17·1	59·5	58·3	33
East and South-East Asia	5·2	33·3	23·6	11
Sub-Saharan Africa	7·0	38·8	30·2	16
Middle East and North Africa	8·8	32·4	25·3	10
Latin America and Caribbean	2·6	22·7	12·0	11
Developing countries	9·1	40·7	33·9	19

* Data are from United Nations (1994), United Nations International Children's Emergency Fund (1996), Food and Agriculture Organization (1996).
† Weight-for-height more than 2 SD below mean for reference population.
‡ Height-for-age more than 2 SD below mean for reference population.
§ Weight-for-age more than 2 SD below mean for reference population.
‖ Small for gestational age: <10th centile of expected weight for gestational age for reference population.

Asia. In Bangladesh 10 % of girls aged between 10 and 16 years and over 35 % of those who were 15 years of age were stunted (Ahmed *et al*. 1998). In an earlier study from this group, as height-for-age and weight-for-age among Bangladeshi children aged 5–12 years increased, so did serum concentrations of haemoglobin, protein, vitamin A and Zn (Ahmed *et al*. 1993*a*). Table 3 provides information on the regional variation in childhood malnutrition.

Malnutrition predisposes to infections

Good nutrient status is required if the host is to combat infections effectively. Effective protection against invasion of the host by micro-organisms requires an intact skin surface and intact linings of the naso-oesophageal, gastrointestinal and genito-urinary tracts, since these provide a barrier to invasion. This barrier also includes the ability of cells to produce mucous secretions and to maintain other physiological protective mechanisms (e.g. pH). Importantly, the cells in these linings are continually turning over, so that nutrients required for cell growth and replication must be available in order for the protection against infection to be maintained. These barriers to invasion by infectious agents must be effective at all times. The immune response to infection involves a vast increase in cell differentiation and replication, in the production of immunoglobulins and acute-phase proteins and in the production of peptide- and lipid-mediators (cytokines and eicosanoids respectively); clearly, this will require an appropriate supply of nutrients to optimize the response. Finally, a component of the host response to infection is the production of damaging reactive O species; protection of the host from this damage requires an appropriate status of antioxidant protective mechanisms which include

Table 4. Prevalence of vitamin A and iron deficiencies*

Region	Children <5 years of age with xerophthalmia in 1991		No. of women aged 15 to 49 years with low haemoglobin	
	No. (millions)	%	No. (millions)	%
Africa	1·3	1·4	59·4	44
Latin America	0·1	0·2	32·7	31
South-East Asia including India	10	4·2		
West Pacific including China	1·4	1·3		
Asia including India and China			335·1	45
Total	13.8	2·8	427	44

* Data from United Nations (1996).

antioxidant enzymes (all of which include metal ions such as Fe, Zn, Cu, Mn or Se as an active component), antioxidant vitamins (e.g. vitamin E, vitamin C) and small peptides (e.g. glutathione). Thus, in order to maintain protection against infective agents and to mount a successful response if infected, the host requires a supply of a range of nutrients. It is self-evident that the poorly nourished state is characterized by limited exogenous supply and endogenous reserve of nutrients. Thus, there is a vast body of evidence that many infections are increased in prevalence or severity by specific nutritional deficiencies (Scrimshaw *et al*. 1968). Table 4 indicates the extent of vitamin A and Fe deficiencies in the developing world.

Vitamin A

Vitamin A deficiency is associated with increased morbidity and mortality in children (Sommer *et al*. 1983, 1984; Milton *et al*. 1987) and may predispose to different types of respiratory infections (Solon *et al*. 1978; Tielsch *et al*. 1986; DeSole *et al*. 1987; Sommer *et al*. 1987; Bloem *et al*. 1990); these studies are population-, clinic- and hospital-based. Some population-based studies fail to detect this association (Brilliant *et al*. 1985; Stanton *et al*. 1986; Gujral *et al*. 1993). However, prospective community-based studies confirm that there is an increased risk of respiratory disease in children with vitamin A deficiency (Sommer *et al*. 1984; Milton *et al*. 1987; Vijayaraghavan *et al*. 1990; Dibley *et al*. 1996). Vitamin A deficiency renders young children vulnerable to diarrhoea and to severe measles and high mortality (Markowitz *et al*. 1989; Butler *et al*. 1993). Although vitamin A deficiency increases the risk of infectious disease, the interaction is bidirectional such that infections can lead to vitamin A deficiency: diarrhoea, respiratory infections, measles, chickenpox and HIV infection are all associated with the development of vitamin A deficiency (Campos *et al*. 1987; Sommer *et al*. 1987; Rahman *et al*. 1996; Semba, 1997). Vitamin A status was not improved despite supplementation in Bangladeshi children with acute respiratory infections (Rahman *et al*. 1996); the authors interpreted this to mean that the presence of disease prevented a return to adequate status.

Vitamin A deficiency is common in HIV patients (Semba, 1997), and low plasma or serum vitamin A levels are associated with accelerated HIV progression (Baum *et al*. 1995), increased mortality (Semba *et al*. 1993), higher rates of transmission of HIV from mother to baby (Semba *et al*. 1994; Greenberg *et al*. 1997), child growth failure (Semba *et al*. 1997) and increased HIV load in breast milk and the birth canal (Nduati *et al*. 1995; John *et al*. 1997; Mostad *et al*. 1997). Breast milk is an important route of transmission of HIV from mother to child; the incidence of postnatal transmission of HIV through breast-feeding ranges from 4 to 32 %. Replacement feeding is the most effective measure to decrease transmission of HIV via breast milk; alternative measures include halting breast-feeding and using animal milk, or heat-treating breast milk.

Iron

Fe deficiency is the most common nutritional deficiency worldwide, affecting 1 billion people, particularly women of reproductive age and young children (United Nations, 1996). Anaemia among these groups is high in many regions (e.g. 77 % of non-pregnant females aged 15–45 years in Bangladesh had haemoglobin levels below 100 g/l; Kolsteren *et al*. 1999). Fe deficiency is associated with gastrointestinal and respiratory infections (Berger *et al*. 1992). However, the influence of Fe status on infection is complicated by the fact that micro-organisms also require Fe (Payne & Finkelstein, 1978). Thus, low Fe status should protect against

the spread of infection and mechanisms have developed for withholding Fe from invading organisms: these include the higher affinity for Fe of lactoferrin than bacterial siderophores, and the sequestration of lactoferrin by macrophages once it has reached 40 % saturation with Fe (Birgens *et al*. 1983; Baynes *et al*. 1986). Lactoferrin is found in human breast milk and probably plays a role in defence of the infant (Bullen *et al*. 1972). Thus, there is competition for Fe between the host immune system, host stores and invading pathogens.

The situation regarding Fe status and malaria is also complicated by the fact that it is the erythrocyte which is parasitized. The malaria parasite is totally dependent upon the erythrocytes of the host to complete its life cycle. This might explain the observation that malaria is more common in Fe-replete than Fe-deficient individuals (Oppenheimer *et al*. 1986).

Zinc

Zn deficiency is probably more widespread than is currently appreciated and may be an important contributor to childhood morbidity. Low plasma Zn levels predict the subsequent development of lower respiratory tract infections and diarrhoea among Indian infants (Bahl *et al*. 1988). Indeed, diarrhoea is considered a symptom of Zn deficiency. Low serum Zn is associated with more rapid HIV disease progression in homosexual men (Graham *et al*. 1991; Baum *et al*. 1995).

Other nutrients

In animal studies, as the level of protein in the diet decreases so the level of malaria parasitaemia and mortality decrease (Edirisinghe *et al*. 1981). However, this is not borne out in human subjects, where protein–energy malnutrition did not protect against malaria (Snow *et al*. 1991); however, this latter study did note that children experiencing clinical attacks with high parasitaemias tended to have higher weight-for-age at the start of the transmission season than children whose malaria attacks were associated with lower parasitaemia. Malaria parasites in erythrocytes are susceptible to oxidative stress. In animal models, decreasing vitamin E in the diet or feeding fish oil decreases parasitaemia and increases survival (Fevang *et al*. 1995; Levander *et al*. 1995; Taylor *et al*. 1997). Riboflavin deficiency also appears to protect against malaria, possibly owing to induction of oxidative stress (Das *et al*. 1990). Se deficiency was noted to be common in HIV infection and was linked to increased mortality (Baum *et al*. 1997). Many HIV patients have decreased circulating concentrations of vitamins B_2, B_6, B_{12}, and C and niacin (see Semba & Tang, 1999).

Infections can cause malnutrition and can decrease growth in childhood

Infections can cause malnutrition

Infections can alter nutritional status, mediated by changes in dietary intake, absorption, and nutrient requirements and losses of endogenous nutrients. Coupled with one or more existing nutrient deficiencies, the effect of infection can be particularly detrimental.

Infection is characterized by anorexia. Clearly, a reduction in food intake (anorexia) will result in reduced intake of all macro- and micronutrients. This could lead to nutrient deficiencies even if the host was not already deficient and it could make existing borderline

deficiencies apparent. Guatemalan children with acute respiratory infections or diarrhoea consumed 8 and 18 % less dietary energy per day respectively, than children without these infections (Martorell *et al*. 1980). In Bangladeshi children less than 5 years old, dietary energy intake was reduced by more than 40 % during the acute stage of diarrhoea compared with that after recovery (Molla *et al*. 1983*b*). Energy intake among infants who were exclusively or partly breast-fed was less affected by illness, suggesting a protective effect of breast-feeding (Brown *et al*. 1990). Indeed, when energy intakes from breast milk and from other foods were examined separately, only the intakes from non-breast milk sources declined significantly (Brown *et al*. 1990). African children examined during the acute phase of measles consumed 75 % less dietary energy than they did after recovery (Duggan *et al*. 1986). Withdrawal of food from individuals with fever, diarrhoea or other symptoms of infection is a common practice that will exacerbate the effects of anorexia. However, it is difficult to separate the effects of anorexia and food withdrawal but the combination could be devastating to the individual.

Infection is characterized by nutrient malabsorption and loss. The range of infections associated with nutrient malabsorption is wide and includes bacteria, viruses, protozoa and intestinal helminths. Apparent protein absorption by children in Panama with diarrhoea was generally reduced by 10–30 % and sometimes by as much as 40 % (see Scrimshaw & San-Giovanni, 1997). In Bangladesh, absorption during diarrhoea caused by rotavirus averaged 43 % for N, 42 % for fat, 74 % for carbohydrate and 55 % for total energy (Molla *et al*. 1983*a*); absorption during diarrhoea caused by enteropathogenic *Escherichia coli* and *Shigella* spp. was slightly higher. Rates of absorption of macronutrients for healthy children would be expected to be >90 %. Infection blocks Fe absorption (Cartwright *et al*. 1946). Vitamin A malabsorption also occurs during infections: children with acute diarrhoea, *Ascaris* infection or respiratory infections absorbed only 30–70 % of ingested vitamin A (Sivakumar & Reddy, 1972, 1975). In contrast to these findings, Ahmed *et al*. (1993*b*) reported efficient (>95 %) absorption of a vitamin A dose among *Ascaris*-infected children in Bangladesh. Diarrhoea results in loss of Zn and Cu (Castillo-Duran *et al*. 1988). Measles infection increases nutrient losses in the faeces (Reddy *et al*. 1986; Markowitz *et al*. 1989; Butler *et al*. 1993). Diarrhoea and malabsorption of fat, carbohydrate, fat-soluble vitamins and vitamin B_{12} appear to be common to all stages of HIV infection (Miller *et al*. 1988, 1991; Harriman *et al*. 1989; Ehrenpreis *et al*. 1994; Castaldo *et al*. 1996; Koch *et al*. 1996).

Apart from malabsorption, nutrients may also be lost through the faeces as a result of damage to the intestinal wall. Measles and diarrhoea, especially due to *Shigella*, can lead to protein loss in the faeces. Nearly 65 % of patients with enterotoxigenic *E. coli* and 40 % of those with rotavirus diarrhoea had excessive losses of protein in their faeces (see Scrimshaw & SanGiovanni, 1997). In patients with shigellosis, 100–500 ml serum was lost in the faeces each day (see Scrimshaw & SanGiovanni, 1997). Intestinal helminths, especially hookworm infections, cause gastrointestinal loss of blood (and energy) and these are a major cause of Fe-deficiency anaemia in some regions. Each adult hookworm can cause a loss of up to 250 mg blood and 4·2 kJ energy per d (Briscoe, 1979). Less than one-half of Fe lost this way is reabsorbed. Total blood loss during helminth infection could be greater than 5 ml/d (Pawlowski *et al*. 1991). Severe infection with whipworm (*Trichuris* spp.) alters the large intestine mucosa leading to loss of erythrocytes and plasma; this infection is associated with decreased haemoglobin levels, reduced erythrocyte volume and reduced erythrocyte haemoglobin (Ramdath *et al*. 1995). Haemoglobin concentration is negatively associated with the number of *Trichuris* eggs appearing in the faeces, a measure of infestation (Ramdath *et al*. 1995). Infection with *Schistosoma haematobium*, which directly damages the wall of the bladder, can lead to blood loss in the urine and this can contribute to Fe deficiency. Protein and nutrients are also lost in

the urine as a result of infection; of importance is the loss of retinol-binding protein (the serum transport protein for vitamin A) which is lost increasingly in the urine as the severity of infections increases (Stephenson *et al.* 1994).

Infection is characterized by increased resting energy expenditure. Infection increases BMR: there is a 13 % increase for each 1° increase in body temperature. During a period of high fever, metabolism may increase by nearly one-third (DuBois, 1936), so increasing the requirement for energy-yielding nutrients and the cofactors which participate in their metabolism. This places a significant drain on body pools of nutrients particularly when coupled with anorexia, diarrhoea and other nutrient losses (e.g. in urine and sweat). The increase in resting energy expenditure has been well documented in HIV infection (Melchior *et al.* 1993). Asymptomatic HIV-infected individuals had a 16 % greater resting energy expenditure than uninfected individuals, while HIV-infected subjects who also had other opportunistic infections had a 57 % greater resting energy expenditure than controls. The increased energy expenditure often occurs in combination with anorexia and malabsorption, resulting in body wasting (for review see Macallan, 1998). Macallan *et al.* (1995) showed that the weight loss among British adults with HIV infection was largely a consequence of reduced energy intake, rather than increased energy expenditure.

Infection is characterized by altered metabolism and redistribution of nutrients. The acute-phase response is the name given to the metabolic response to infections (and often to immunization) and it includes the onset of fever and anorexia, the production of specific 'acute-phase reactants' and the activation and proliferation of immune cells. Such a catabolic response occurs with all infections even when they are subclinical (Beisel, 1972, 1975; Keusch & Farthing, 1986). This serves to cause redistribution of nutrients away from skeletal muscle and adipose tissue and towards the host immune response. This redistribution is mediated by production of pro-inflammatory cytokines by leucocytes and associated endocrine changes. These lead to mobilization of amino acids, primarily from skeletal muscle, which are used as gluconeogenic substrates in the liver with the N released being lost in the urine. Some of the amino acids are used by the liver for the synthesis of the so-called acute-phase proteins and by leucocytes and other cells for synthesis of immunoglobulins and cytokines. The average loss of protein over a range of infections has been estimated to be 0·6 g/kg per d (Powanda, 1977). Diseases associated with diarrhoea or dysentery produce a higher protein loss than this (0·9 g/kg per d), with severe infections such as typhoid fever inducing even greater loss (1·2 g/kg per d) (Powanda, 1977). Tuberculosis infection leads to loss of both lean and fat tissue by 15–20 % (Onwubalili, 1988). Kennedy *et al.* (1996) showed that anti-tuberculosis drugs caused weight gain in all subjects studied. The metabolic response to infection also results in increased oxidant stress (Grimble, 1999), which can potentially deplete reserves of cellular and plasma antioxidant vitamins (vitamin E, vitamin C, β-carotene; Grimble, 1999).

One metabolic consequence of infection is a decrease in serum Fe, Zn and vitamin A concentrations. There are contrasting views as to the role of this: one is that the nutrients are preferentially moved to tissue sites to promote host defence and the other is that they are cleared from the circulation in order to deprive pathogens of nutrients that they need. These alternatives are important in understanding the meaning and role of changes in plasma concentrations and in designing appropriate nutritional interventions. For example, it might be wrong to interpret low blood levels as defining a deficiency state. Correspondingly, it may be unwise or even impossible to restore 'normal' circulating levels of micronutrients during episodes of infection. Furthermore, an infection which causes diarrhoea and so results in vitamin A, Fe and Zn loss in the faeces, involves an interaction between redistribution of these nutrients within the body and loss of these nutrients from the body.

Childhood infections decrease growth

Mata *et al*. (1977) (see also Mata, 1992) very elegantly showed the relationship between nutrition, infection and growth in children. Fig. 3 shows the growth curve of an individual child: before weaning (about 6 months of age) the child is growing at the expected rate, despite the occurrence of infections. After weaning there is a high incidence of infections (particularly those due to diarrhoeal pathogens) and these episodes of infection are associated with weight loss. The high frequency of infections also limits the opportunity for catch-up growth between episodes of infection.

Diminished weight gain, an indicator of infection and/or malnutrition, has been associated with increased rates of diarrhoeal and respiratory diseases in a number of studies (e.g. Ballard & Neumann, 1995). As weight-for-age decreases so the duration and severity of diarrhoea increases (Martorell *et al*. 1975; Condon-Paolini *et al*. 1977; Rowland *et al*. 1977; Black *et al*. 1984; Zumrawi *et al*. 1987; Briend *et al*. 1989; Lutter *et al*. 1989; Moy *et al*. 1994; Morris *et al*. 1996).

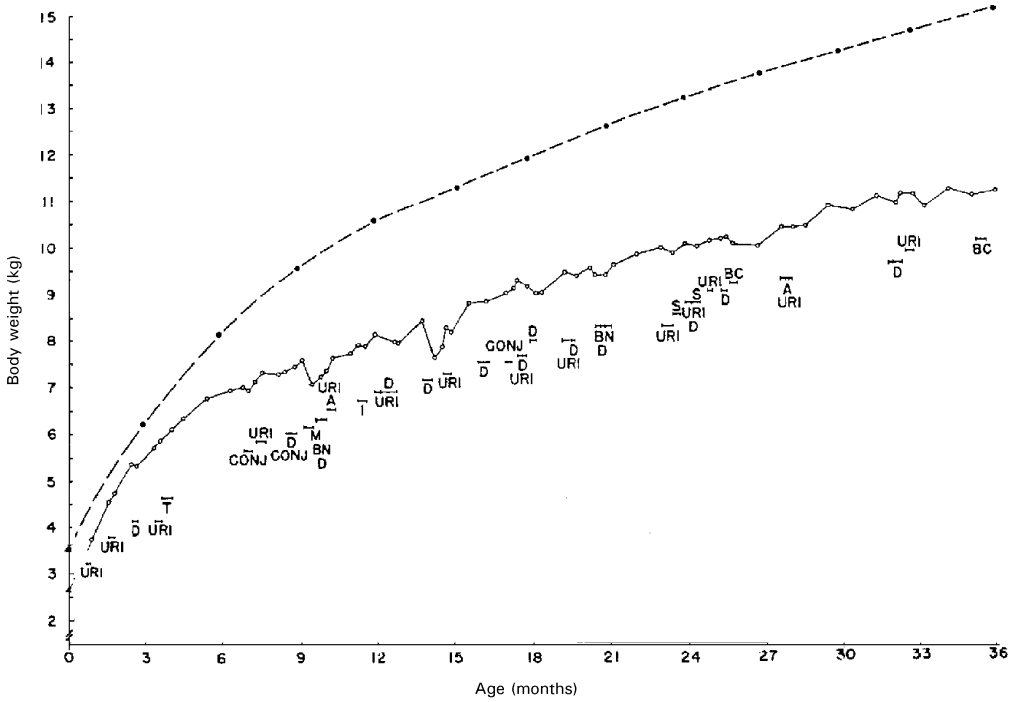

Fig. 3. Association between repeated episodes of infection and weight gain of a Guatemalan child during the first 3 years of life. (o–o) The weight of the child; (•- - - •), the median of the weight-for-age standard curve; A, abcess; BC, bronchitis; BN, bronchopneumonia; CONJ, conjunctivitis; D, diarrhoea; I, impetigo; M, measles; S, stomatitis; T, oral thrush; URI, upper respiratory tract infection. The length of the horizontal lines indicates the duration of individual episodes of infectious disease. Adequate growth was seen during the period of exclusive breast-feeding and subsequent weight loss was associated with periods of infection. Reproduced from Mata *et al.* (1977) with permission from the American Society for Clinical Nutrition.

The association between infections and linear growth is more difficult to document than the association with weight. This is because height does not decrease (weight does) and because longer time intervals are required to document linear growth than to document weight changes. However, such associations have been observed. A longitudinal study of Guatemalan children (<7 years of age) found that those with a high prevalence of diarrhoea had slower linear growth than those with a low prevalence (Martorell *et al*. 1975). In the Gambia, infants in the first year of life showed reduced increase in length (by about 1 mm/week) during diarrhoea compared with their own growth rate during diarrhoea-free periods (Rowland *et al*. 1977). A similar study in rural Bangladesh showed that a child without diarrhoea would gain on average 42 mm/year more than a child with the average prevalence of diarrhoea (13 % of days) (Black *et al*. 1984). However, not all diarrhoeal pathogens appear to have the same impact on growth; *Shigella* infection was associated with impaired linear growth whereas infection with *E. coli* or rotavirus was not (Black *et al*. 1984). In Brazil, hospitalization of children for either diarrhoea or pneumonia during a 2-year period was associated with diminished linear growth over that period of time, with the effect of diarrhoea being greater than that of pneumonia (Victora *et al*. 1990). Infection with *Ascaris* and other gut helminths is associated with impaired linear growth (Stephenson, 1987; Hlaing, 1993). Early infection with HIV is also associated with impaired linear growth: a 6-year longitudinal study of the growth of infants born to HIV-infected mothers showed that those infants who were infected perinatally with HIV had impaired linear growth by 15 months of age compared with infants who were not HIV infected and eventually had a height deficit of about 80 mm (Saavedra *et al*. 1995). Interestingly, this impairment of linear growth was apparent well before an impairment in weight gain (which was not decreased until 36 months of age; Saavedra *et al*. 1995), suggesting that HIV infection might have a specific effect on long-bone growth, perhaps by infection of osteoclasts by HIV.

The urinary lactulose : mannitol ratio, an indicator of gut permeability, increased as infant growth (height or weight) decreased, suggesting that impaired growth is associated with gut dysfunction (Lunn *et al*. 1991) which will, in turn, decrease nutrient availability.

Nutrition and immune function

There is now overwhelming evidence from both animal studies and studies with human subjects that particular nutrients are required for an optimal immune response and that deficiencies in one or more of these nutrients diminish immune function and provide a window of opportunity for infectious agents. It is logical that multiple nutrient deficiencies might have a more significant impact on immune function, and so on resistance to infection, than would a single nutrient deficiency.

A large number of studies in animals have demonstrated the adverse effects of protein deficiency on immunity and these effects have been confirmed in various human settings (e.g. Chandra, 1975, 1979, 1983*b*; Chandra *et al*. 1982, 1984). It is not surprising that protein deficiency diminishes immune responses and increases susceptibility to infection because immune defences are dependent upon cell replication and the production of proteins with biological activities (e.g. immunoglobulins, cytokines, acute-phase proteins). Practically all forms of immunity may be affected by protein–energy malnutrition, but non-specific defences and cell-mediated immunity are more severely affected than humoral (antibody) responses (Table 5) (for review see Kuvibidila *et al*. 1993); indeed, circulating concentrations of immunoglobulins are often unaffected by malnutrition (see Kuvibidila *et al*. 1993). That impaired immunity has a functional consequence was shown by a study in malnourished

Table 5. The effect of protein–energy malnutrition on immune function

Function and/or test	Response
Weight of thymus, spleen, tonsils	⇓
Leucocyte counts	⇔
T lymphocytes in blood	⇓
CD4 cells in blood	⇓
CD8 cells in blood	⇓
CD4 : CD8 in blood	⇓
Blood lymphocyte proliferation	⇓
TNF, IL-1 and IL-6 production	⇓
IL-2 and IFN-γ production	⇓
B lymphocytes in blood	⇔
Antibody response	⇔
Immunoglobulin A in tears, saliva	⇓
Thymulin levels in blood	⇓
Activity of leucocytes to kill bacteria	⇓
Delayed-type hypersensitivity response	⇓

⇓, Decreased; ⇔, not affected; TNF, tumour necrosis factor; IL, interleukin; IFN, interferon.

Bangladeshi children: those who showed the fewest skin reactions to common bacterial antigens (i.e. the weakest cell-mediated immune response) had a greater incidence of diarrhoeal disease (Koster *et al*. 1987; Baqui *et al*. 1993). In addition to reduced protein availability, deficiencies in specific amino acids may affect immune function.

Experimental animals made deficient in vitamin A have impaired immunity (Table 6) and increased susceptibility to infection (for review see Semba, 1998). Vitamin A-deficient mice were more susceptible to rotavirus infection (Ahmed *et al*. 1990), and had lower serum specific antibody levels after challenge with rotavirus and a decreased delayed-type hypersensitivity response (Ahmed *et al*. 1991). Vitamin A is also essential for maintaining epidermal and mucosal integrity, and vitamin A-deficient mice had histopathological changes in the gut mucosa consistent with a breakdown in gut barrier integrity and had a decreased number of goblet cells in the small intestine villi, suggestive of impaired mucus secretion (Ahmed *et al*. 1990).

Fe deficiency has multiple effects on immune function (Table 6) (for review see Sherman & Spear, 1993). There was a positive correlation between Fe status in malnourished Indian children and lymphocyte proliferation, phagocytic respiratory burst and bacterial killing by phagocytes (Chandra, 2000). Natural killer cell activity and interleukin 2 production are enhanced when Fe-deficient children are given Fe supplements (Chandra, 2000).

Zn deficiency in animals is associated with a wide range of immune impairments including thymic atrophy, depressed cell-mediated immunity and increased susceptibility to infections (Table 6) (for review see Fraker *et al*. 1993). In acrodermatitis enteropathica, which is char-

Table 6. The effect of nutrient deficiencies on immune function

	Effect on				
Nutrient deficiency	Thymus weight	No. of T lymphocytes	Lymphocyte proliferation	IL- 2 production	DTH
Vitamin A	⇓	⇓	⇓	⇓	⇓
Iron	⇓	⇓	⇓	⇓	⇓
Zinc	⇓	⇓	⇓	⇓	⇓
Selenium	⇓	⇓	⇓	⇓	⇓
Copper	⇓	⇓	⇓	⇓	⇓

⇓, Decreased; IL, interleukin; DTH, delayed-type hypersensitivity.

acterized by reduced intestinal Zn absorption, thymic atrophy, impaired lymphocyte development and reduced lymphocyte responsiveness are observed. Zn administration to such patients and others with Zn deficiency improves immune-cell function and the delayed-type hypersensitivity response (Shankar & Prasad, 1998). Malnourished Zn-deficient children given Zn (2 mg/kg body weight per d for 10 d) had increased thymus size as judged by radiography (Golden *et al*. 1977). Topical application of Zn to malnourished children improved the delayed-type hypersensitivity response in the area of skin on which the application was made (Golden *et al*. 1978). Zn administration to pre-term low body weight infants (1 mg/kg per d for 30 d) increased the number of circulating T lymphocytes and lymphocyte proliferation (Chandra, 1991). Providing 5 mg Zn/d to low birth weight, small-for-gestational-age infants for 6 months increased measures of cell-mediated immune function and decreased the incidence of gastrointestinal and upper respiratory tract infections (Lira *et al*. 1998); a Zn dose of 1 mg/d was without effect. Zn-sufficient mice had a lower helminth burden than those which were Zn or protein deficient (Shi *et al*. 1998). Excessive Zn intakes impair immune responses: for example, 150 mg Zn given twice daily for 6 weeks to young adult human subjects decreased lymphocyte and phagocyte function (Chandra, 1984).

Cu deficiency impairs immune function in experimental animals, and Cu deficiency in experimental animals is associated with increased morbidity and mortality to a *Salmonella typhimurium* challenge (for reviews see Prohaska & Failla, 1993; Failla & Hopkins, 1998). Children with Menke's syndrome, a rare congenital disease resulting in Cu deficiency, have increased bacterial infections, diarrhoea and pneumonia (Vyas and Chandra, 1983).

Deficiencies in many other micronutrients including Mg, Se, vitamin C, β-carotene, pyridoxine, folic acid, vitamin B_{12} and vitamin E reduce immune function in experimental animals and in human populations (for reviews see Bendich, 1993; Siegel, 1993; Stabel & Spears, 1993; Scrimshaw & SanGiovanni, 1997), and may play a role in increasing susceptibility to infections.

Improved nutrition, including breast-feeding of infants, can reduce infection rates and the impact of infection on growth

The thymus was twice as large, as determined by ultrasound, in 4-month-old Danish infants who had been exclusively breast-fed since birth than in those who had been exclusively formula-fed; thymus size in partially breast-fed infants was intermediate (Hasselbalch *et al*. 1996). This study suggests that breast milk contains immunostimulating factors which aid early development of the immune system and which will be most likely to help the infant combat infection. This idea is supported by the data of Mata *et al*. (1977) (Fig. 3) which suggest that breast-feeding might reduce the incidence of infections. If this is so, then it is probably due to a combination of factors including better nutrient supply (both quantity and quality) than that received post-weaning, and decreased exposure to infectious agents. Other studies support the notion that breast-feeding has a key role in the prevention of infectious disease. Infants in Peru were divided into five feeding categories (exclusively breast-fed, water + breast-feeding, milk + breast-feeding, solids + breast-feeding, no breast-feeding); the risk of diarrhoea, respiratory infections and mortality was lowest in the exclusively breast-fed group and highest in the group that were not breast-fed (Brown *et al*. 1989). In the absence of diarrhoea, linear growth of those infants fed exclusively by breast was 3-fold higher than those who were not breast-fed. The prevalence of diarrhoea did not affect growth of exclusively breast-fed Peruvian infants whereas it reduced the growth of those who were not breast-fed (Brown *et al*. 1991). A study in Scotland found that babies who were breast-fed for 13 or more weeks had significantly less gastrointestinal illness than those who were bottle-fed from birth (Howie *et al*. 1990); the

protective effect of breast-feeding was maintained beyond the breast-feeding period and resulted in a decreased rate of hospital admissions. Breast-feeding for less than 13 weeks was not protective (Howie *et al*. 1990). Golding *et al*. (1997*a*,*b*,*c*) have reviewed the impact of breast-feeding and conclude that during the first 4–6 months of life it protects against gastroenteritis and diarrhoea in both the developed and developing world and that it may be protective against lower, but probably not against upper, respiratory tract infections.

One other important aspect of the impact of the type of infant feeding to consider is the marked differences in the composition of human compared with cows' milk. Human milk is rich in immunoglobulins, in the antimicrobial proteins lactoferrin (which binds Fe, so preventing its uptake by bacteria) and lysozyme (which has direct antibacterial action), in vitamins A, D and E, in polyunsaturated fatty acids and in free amino acids; in contrast, cows' milk either lacks or contains only traces of these factors. Jackson & Golden (1978) speculate that the role of cows' milk is to aid development of the rumen in the calf; thus the composition of cows' milk should be one which will promote bacterial growth in the gastrointestinal tract. Clearly, this is undesirable in the human neonate and could have disastrous consequences, particularly when combined with exposure to micro-organisms.

Prisoners of war who received Red Cross food parcels had a lower incidence of tuberculosis (1·2 %) compared with those who did not receive food parcels (15 %) (Leyton, 1946). A recent trial in Vietnam showed that home-production of foods and nutrition education was associated with a decreased incidence of acute respiratory infections among children aged 1–6 years (11·2 % *v* 49·1 % in the control group; English *et al*. 1997). During a measles outbreak in India, infected children who had received and continued to receive a food supplement (1·30 MJ (310 kcal) plus 3 g protein per d) gained weight at the same rate as non-infected children whereas those who were infected but had not received the food supplement lost weight (Gopalan *et al*. 1973).

Can supplementation with specific nutrients influence the incidence and severity of infectious disease?

Deficiencies of vitamin A, Zn, Fe and other micronutrients are widespread in the developing world (see earlier). Such deficiencies impair the immune response (see earlier), which probably makes the host less resistant to infection. Thus, provision of these nutrients should improve immune function and so diminish the severity and duration of infectious diseases. Ultimately this effect could decrease mortality from these diseases.

Vitamin A

There have been a number of studies of vitamin A administration and morbidity and mortality in children; most, though not all, of these studies show large drops in mortality (Muhilal *et al*. 1975; Sommer *et al*. 1986; Rahmathullah *et al*. 1990). Indonesian infants given vitamin A (15 mg retinol equivalents) orally at birth had half the mortality rate of a control group during the first year of life (Humphrey *et al*. 1996). Several studies demonstrate a decline (by 18–76 %) in measles-related deaths in vitamin A-deficient children supplemented with vitamin A (Barclay *et al*. 1986; Hussey & Klein, 1990; Rahmathullah *et al*. 1990; Vijayaraghavan *et al*. 1990; West *et al*. 1991; Daulaire *et al*. 1992; Herrera *et al*. 1992; Ghana VAST Study Team, 1993). Hussey & Klein (1990) showed that South African children given vitamin A had fewer complications arising from measles, with a resulting shorter hospital stay and less-frequent

intensive care than the placebo group. Coutsoudis *et al*. (1991) showed that vitamin A administration to South African children with measles resulted in increased weight gain and a reduction in episodes of diarrhoea, upper respiratory tract infections and pneumonia. The severity of measles was also diminished after vitamin A supplementation in children in Kenya (Ogaro *et al*. 1993) and India (Sinha & Bang, 1976). A meta-analysis of nine vitamin A supplementation studies showed a 30 % decrease in measles-related mortality in children aged more than 6 months after vitamin A supplementation (Fawzi *et al*. 1993). Glasziou & Mackerras (1993) also conducted a meta- analysis of vitamin A supplementation trials and concluded that vitamin A reduces measles deaths by 55 %; they excluded one large study (Herrera *et al*. 1992) which was included by Fawzi *et al*. (1993) and which showed no significant impact of vitamin A on child mortality from measles. WHO recommends that, in areas where the measles fatality rate is greater than 1 %, children with measles should be supplemented with vitamin A (World Health Organization, 1997*b*).

A number of studies have shown that vitamin A supplementation decreases the severity but not the incidence of diarrhoea in children (Bloem *et al*. 1990; Ghana VAST Study Team, 1993; Lie *et al*. 1993; Barreto *et al*. 1994; Bhandari *et al*. 1994; Biswas *et al*. 1994; Sempertegui *et al*. 1999). However, some vitamin A supplementation studies do not report a reduction in either incidence or severity of diarrhoea (Rahmathullah *et al*. 1991; Ramakrishnan *et al*. 1995). It is possible that those studies which show no effect of vitamin A supplementation included children with deficiencies in other nutrients. In addition, it appears that age might influence the effectiveness of vitamin A: in a study of Indonesian children Dibley *et al*. (1996) found that, while overall there was no effect of vitamin A supplementation on the incidence of diarrhoea, vitamin A tended to increase incidence in children <30 months of age and to decrease incidence in older children.

A number of trials of vitamin A supplementation in respiratory tract infections have been performed. A meta-analysis of twelve large field trials (The Vitamin A and Pneumonia Working Group, 1995) failed to detect significant effects on incidence or mortality. Five of these trials had information on pneumonia incidence and prevalence and overall there was no effect; indeed, there was a trend towards a possible harmful effect of vitamin A supplementation in 6–11-month-old infants, but a beneficial effect in those 4–5 years old. One study showed a significant reduction in pneumonia incidence (Daulaire *et al*. 1992). Some smaller trials have shown a beneficial impact of vitamin A on respiratory morbidity (Bloem *et al*. 1990; Lie *et al*. 1993). Pneumonia mortality has been assessed in five trials of vitamin A supplementation: the impact varied but for most studies the effect of vitamin A was the same as the placebo (Rahmathullah *et al*. 1990; West *et al*. 1991; Daulaire *et al*. 1992; Ghana VAST Study Team, 1993). A number of randomized, placebo-controlled trials have failed to show any beneficial effects of vitamin A supplementation in infants and children with acute onset of lower respiratory tract infections (Kjolhede *et al*. 1995; Bresee *et al*. 1996; Dowell *et al*. 1996; Nacul *et al*. 1997); indeed, some of these studies show adverse effects of vitamin A (Bresee *et al*. 1996). This may relate to the nutritional status of the infants. A recent study (Sempertegui *et al*. 1999) reported that vitamin A (3 mg retinol equivalents per week for 40 weeks) decreased the incidence of lower respiratory tract infections in underweight children compared with placebo treatment, but increased the incidence in normal-weight children. Supplementation of Australian children with a history of respiratory infections caused a reduction in rate of lower respiratory disease of 25 % (Pinnock *et al*. 1986). Shenai *et al*. (1987) reported reduced incidence of bronchopulmonary dysplasia in vitamin A-deficient low birth weight infants given vitamin A.

Vitamin A supplementation resulted in a significant reduction in mortality and morbidity among HIV-infected children (Coutsoudis *et al*. 1995). In contrast, a single oral dose of

vitamin A did not alter HIV load in intravenous drug users in Baltimore (Semba *et al*. 1998). Semba *et al*. (1994) reported that mother-to-child transmission rates of HIV increased as the concentration of vitamin A in maternal plasma decreased, and suggested that maternal vitamin A deficiency contributed to mother-to-child transmission. Despite this, maternal vitamin A supplementation throughout the third trimester of pregnancy and at delivery did not alter the rate of mother-to-child HIV transmission up to 3 months of age of the infants (Coutsoudis *et al*. 1999). The effect of supplementation with vitamin A or multivitamins alone or in combination has been investigated in a placebo-controlled trial in pregnant women with HIV infection. Multivitamins decreased fetal death (miscarriage and stillbirth), lowered the incidence of low birth weight (by 40 %), lowered the rate of severe pre-term births (<34 weeks) and decreased the number of small-for-gestational-age infants; vitamin A was without effect (Fawzi *et al*. 1998). Likewise, multivitamins, but not vitamin A, increased CD4 and CD8 counts, the number of T lymphocytes and haemoglobin levels (Fawzi *et al*. 1998). In another study, a combination of drug and micronutrient (vitamins A, C, E and Se and Zn) therapy did not decrease diarrhoea or mortality over 1 month compared with drug plus placebo in AIDS patients in Zambia (Kelly *et al*. 1999).

Iron

The situation relating to Fe supplementation is complex: although an efficient immune response requires Fe, micro-organisms also require Fe for multiplication and it has been argued that the decline in circulating Fe concentrations which accompanies infection is an attempt by the host to 'starve' the infectious agent of Fe. Thus, providing Fe to an infected individual could make the infection worse. The complication of the competition between host and invader for available Fe is illustrated by the observation that Fe-deficient rats display the same level of protection against *Salmonella* as do Fe-replete rats (Baggs and Miller, 1973). Indeed if Fe-deficient individuals who have compromised resistance to infection are given large doses of Fe parenterally or orally, an exacerbation of infection and death can occur (McFarlane *et al*. 1970; Brock, 1993). Likewise, parenteral Fe administration to low birth weight babies increased the incidence of septicaemia (Barry & Reeve, 1974). Chilean children who received Fe-fortified milk (12 mg Fe/l) had a 20 % higher incidence of diarrhoea than those who received a control milk containing 1 mg Fe/l (Brunser *et al*. 1993). Likewise, Bangladeshi children aged 2–48 months who received supplemental Fe (15 mg/d for 15 months) in addition to vitamins A, D and C, had 26 % more days with diarrhoea than children who received the vitamins alone (Mitra *et al*. 1997); the detrimental effect of Fe was even greater among children <12 months of age. There were no differences in acute respiratory infections between the two groups (Mitra *et al*. 1997). In contrast to these studies, Heresi *et al*. (1995) reported no difference in incidence or severity of diarrhoeal or respiratory infections between infants receiving Fe-fortified and non-fortified milk.

In contrast to these observations, supplementation of poorly nourished individuals with low amounts of Fe (up to 100 mg/d for adults and proportionally less for children) can in some cases result in decreased frequency and severity of infectious disease. For example, compared with a placebo, Fe supplementation for 12 weeks decreased infectious morbidity in Indonesian school children (Chwang *et al*. 1988).

As indicated earlier, the situation regarding Fe status and malaria is particularly complicated because the malaria parasite infects erythrocytes. Since reduced Fe availability decreases the number of erythrocytes, low Fe status should protect against malaria (indeed, the incidence

of malaria in Fe-deficient individuals is less than in Fe-replete individuals; Oppenheimer *et al.* 1986) and giving Fe to malaria-infected individuals should make the disease worse. Indeed, it could be argued that lowering Fe status might improve malaria outcome: this is borne out by the observation that Fe chelation therapy enhanced the clearance of parasites and speeded up the effect of anti-malarials (Thuma *et al.* 1998). Earlier studies showed that levels of malaria infection and the severity of the disease were increased by Fe supplementation (Murray *et al.* 1978*a*,*b*). In contrast Fe supplementation did not affect the rate of malarial infection in Tanzanian infants (Menendez *et al.* 1997). However, the Fe supplementation, which would induce erythropoiesis so increasing the number of erythrocytes available to be parasitized, did increase parasitaemia (i.e. the number of erythrocytes infected and the level of parasites per erythrocyte) and so the lack of increase in the disease suggests increased host defence.

Zinc

There are now a number of studies showing that Zn supplementation decreases the incidence of childhood diarrhoea (Ninh *et al.* 1996; Sazawal *et al.* 1996, 1998; Rosado *et al.* 1997; Roy *et al.* 1997, 1999; Ruel *et al.* 1997) and respiratory illness (Ninh *et al.* 1996; Sazawal *et al.* 1998; Roy *et al.* 1999). However, some studies fail to show benefit of Zn supplementation in respiratory disease (Bates *et al.* 1993; Rosada *et al.* 1997; Ruel *et al.* 1997; Lira *et al.* 1998). A recent placebo-controlled study in Mexico compared Zn supplementation with Zn plus other nutrients (including Fe). Zn alone decreased the risk of developing diarrhoea whereas the Zn + other nutrients supplement increased the risk (Rosado *et al.* 1997). This may be due to the presence of Fe, which has been shown to increase diarrhoea in young infants if added to milk (see earlier). In a recent study (Roy *et al.* 1999) Zn supplementation (20 mg/d) to malnourished children reduced diarrhoea-induced growth faltering.

Zn supplementation (200 mg/d) for 30 d reduced infectious disease morbidity in adults with AIDS (Mocchegiani *et al.* 1995). In contrast, those AIDS patients who had the highest intakes of Zn showed the most rapid progression of the disease (Tang *et al.* 1993) and the poorest survival (Tang *et al.* 1996).

Concluding comments

Health is multidimensional and, by the very nature of things, humans must share an environment in which large numbers of other organisms exist, some of which cause disease. The risk of infection can be limited by ensuring that the environment is structured to reduce the exposure to potentially harmful organisms and by enhancing the resistance of individuals and groups of people. The creation of a clean and safe environment, improved housing and a reduction in overcrowding, safe sexual practices and immunization programmes all contribute to decreasing the risk of infection and cross-infection. Enhanced nutrient status increases the likelihood of success of each of these approaches, generally by maintaining the effectiveness of the non-specific barriers to infection (the skin, mucous membranes and bacteriostatic secretions), and ensuring a vigorous inflammatory and immune response. Protecting and maintaining the provision and availability of sufficient food of adequate quality is paramount and remains a central issue. Less apparent, but of equal significance, is the ability to ensure that unbalanced losses of nutrients from the body are minimized, most importantly by protecting against diarrhoeal

disease, especially during early life. Diarrhoeal disease obviously limits the body's ability to absorb adequate nutrients from the diet, but more perniciously depletes the body of nutrients which are critically important for inflammatory and immune defences. Maternal education, appropriate child-rearing practices, the development of personal hygiene, the availability of plentiful amounts of water together with adequate water quality, and the ability to dispose of solid waste effectively remain fundamental imperatives of sound policies for the protection of the health of the public. Together, they are crucial for the cycle of infection and poor nutrition to be broken. Sustained effort is required to maintain established changes in behaviour.

Potential exposure to infectious agents is always present and in many areas of the world where it coexists with malnutrition it is readily translated into disease. Malnutrition diminishes immune function and so prevents the host from mounting an adequate protective response to infectious agents. In turn, infections alter nutrient status and can create a deficiency state. Thus, malnutrition and infection often act synergistically to increase morbidity and mortality, particularly among infants and children. The impact of vaccination programmes has been immense, but the global burden of malnutrition and infection remains vast. Fully understanding the impact of nutrients upon immune function and host resistance to infection, including interactions among nutrients, and fully understanding the impact of different infectious agents upon nutrient status remain key challenges to the scientific community. Putting this increased understanding into practice to relieve the developing world of this burden must be seen as a priority for action in the early years of the 21st century.

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