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The role of zinc and vitamin A deficiency in diarrhoeal syndromes in developing countries

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NUTRITION–INFECTION INTERACTIONS

Of all the infections which cause death among children aged 0–5 years in developing countries, diarrhoea is among the most important (Fig. 1). It may account for 10–20% of deaths and is often the single commonest cause of death during the first few years of life (UNICEF, 1991). The importance of protein–energy malnutrition (PEM) as a risk factor for mortality has been described for many years (Scrimshaw *et al.* 1968). Studies have shown that children who are undernourished (low weight-for-age, low height-for-age or low weight-for-height, or have a low mid-upper arm circumference) are all at risk of increased prevalence of diarrhoea (Tomkins & Watson, 1989). It appears that the attack rate is not particularly influenced by underlying malnutrition, whereas the duration of illness certainly is. Mortality rates in diarrhoea are often three–fourfold higher among severely malnourished children (less than 60% weight-for-age) than among moderate or mildly malnourished children (Vella *et al.* 1991). While this information has been useful

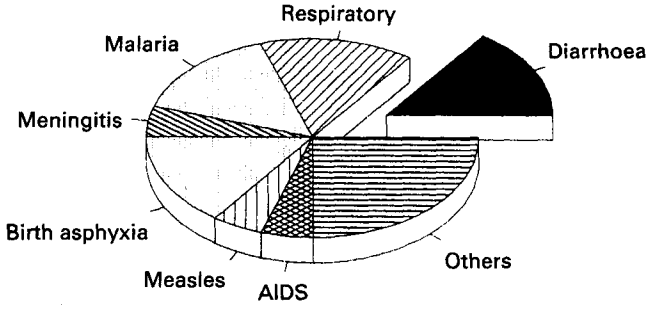

Fig. 1. Common causes of death in children 0–5 years in less-developed countries.

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in regard to screening of high-risk individuals, it has not been particularly useful in preventing death from diarrhoea because of the considerable problem in preventing or treating PEM in the short term. It is also fair to say that the striking relationship between PEM and diarrhoea has somewhat eclipsed the relationship between micronutrients and diarrhoea.

MICRONUTRIENT DEFICIENCIES IN DIARRHOEA

A range of micronutrient deficiencies during diarrhoeal disease has been described over the last decade. Some of the micronutrients identified are Cu, Fe, Mg, Se, Zn, vitamins A, B_{12} and D and folate. As with the PEM–diarrhoea relationship it is often far from clear whether nutritional deficiencies are the cause of diarrhoea or whether they contribute to its epidemiology. A number of research methodologies have been used in order to assess the role of individual micronutrients in diarrhoea. These include cross-sectional studies using case–control methodology and longitudinal studies examining the prevalence of diarrhoea during a defined period 4–12 weeks after an initial assessment of micronutrient status. Intervention studies have been performed, including both prophylaxis and treatment approaches. In addition, a series of studies have been performed in which the biological mechanisms associated with micronutrient deficiency have been investigated in order to link the micronutrient deficiency with diarrhoea in a biologically plausible manner. The present review will draw on a range of pieces of evidence to assess whether micronutrient deficiencies are involved in the pathogenesis of diarrhoeal syndromes.

CLINICAL SYNDROMES OF DIARRHOEA

It is helpful to distinguish between diarrhoeas of different types. Acute watery diarrhoea, often dehydrating, is caused by two major mechanisms. In the first, the mucosa is stimulated to secrete additional quantities of fluid and electrolytes as a result of the presence of an enterotoxin produced by the particular infectious bacteria. *Vibrio cholerae* and enterotoxigenic *Esherischia coli* are both very important organisms causing diarrhoea in children. Both organisms produce an enterotoxin which binds to the enterocyte and then enters the enterocyte stimulating an increase in production of cyclic AMP. This stimulates secretion of water and Na into the lumen. Alternatively the mucosa may be severely damaged as, for example, by infection with rotavirus, in which case the number of absorptive cells is so reduced that they are unable to re-absorb the secretions of the normal small intestine. The net result is that severe fluid losses, again often leading to dehydration, may occur. Most acute episodes of watery diarrhoea last for 3–5 d only. As long as hydration and adequate dietary intake is maintained, mortality or growth faltering may be minimal (Editorial, 1991). However, if duration of the diarrhoea exceeds this time and lasts for more than 14 d, the term persistent diarrhoea syndrome (PDS) is used. This is particularly likely to occur if invasive organisms cause the diarrhoea and is also likely to occur if the child is sufficiently malnourished to prevent the repair of the intestinal mucosa (Tomkins, 1981). Between 5 and 10% of acute diarrhoeal episodes go on to PDS. The proportion is greater if the child is malnourished.

Dysenteric syndromes, caused by certain types of *E. coli* (entero-invasive *E. coli*) and shigella for instance, are an increasingly important cause of morbidity and mortality.

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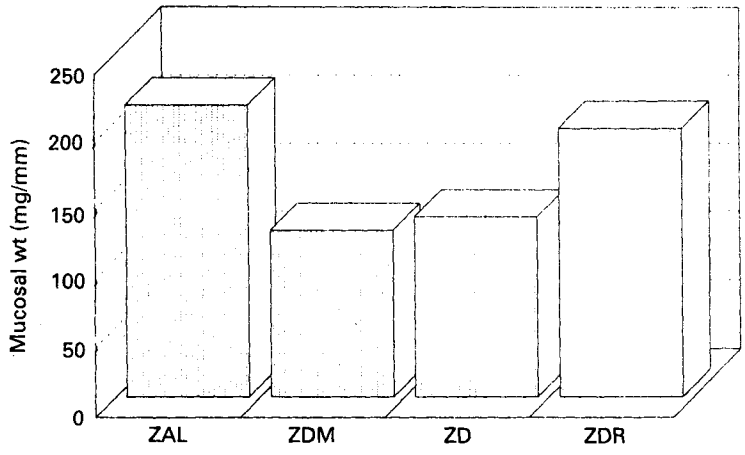

Fig. 2. Jejunal weight (mg/mm intestine) in experimental zinc deficiency. ZAL, Zn-replete diet fed *ad lib.*; ZDM, Zn-replete diet fed at the same level as Zn-deficient diet; ZD, Zn-deficient diet; ZDR, Zn-deficient diet refed for 48 h.

Whereas oral rehydration, so frequently popularized by UNICEF and World Health Organization, has profound effects on mortality from acute diarrhoea, it has relatively little impact in dysentery. A further problem is that organisms are increasingly resistant to the commonly available antibiotics. Thus, effective treatment of dysentery is particularly difficult. In addition the underlying nutritional status may have profound effects on the duration and severity of dysenteric syndromes (Becker *et al.* 1991). The importance of Zn in relation to intestinal disorders was first established during studies of the classical Zn deficiency syndrome acrodermatitis enteropathica (Kelly *et al.* 1976). In this condition the provision of Zn supplements resulted in a striking reduction in the diarrhoea and an improvement in mucosal function.

EXPERIMENTAL Zn DEFICIENCY

More recently studies of the impact of experimental Zn deficiency on intestinal structure and function have been performed (Roy & Tomkins, 1989). During experimental Zn deficiency, a characteristic cyclical change in body weight occurs and the animals develop a watery diarrhoea and become somewhat anorexic. For this reason there has been much discussion on the design of an appropriate control group. Food intake-matched groups are most commonly used and in the present review most of the results refer to comparisons between experimental Zn deficiency and animals receiving a Zn-replete diet but in the same quantity that their deficient counterparts were receiving.

Microscopic appearances of the small intestine are quite characteristic; there is atrophy of the jejunal mucosa and a range of changes of ultra-structure visible on light microscopy. Atrophy of the jejunal mucosa may be quantified by measurements of mucosal weight (expressed as mg/mm intestine) or mucosal mass as assessed by DNA per mg/mm intestine (Fig. 2). All these can be explained by the necessity for Zn during DNA synthesis; a reduction in the number of jejunal mucosal cells might be expected during Zn deficiency.

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Experimental studies have also shown an increased secretion in response to a standard stimulation such as cholera toxin (Roy *et al.* 1986). When an *in vivo* system of perfusion of the intestine in an anaesthetized animal is used, it is possible to measure a net absorption of fluid, Na and water. In the replete animal, there is a net absorption which is reversed if cholera enterotoxin is added to the perfusate. In Zn deficiency there is a significantly increased secretion in response to the same dose of enterotoxin. Several possible mechanisms could account for these findings. First, there may be such a reduction in the numbers of absorptive cells in Zn deficiency that the intestine does not adequately re-absorb the secreted fluid and electrolytes. Second, there may be more fundamental changes in the individual enterocytes. The latter possibility receives support from some of the ultrastructural abnormalities recorded in Zn deficiency but has not been studied in detail.

It is interesting that the addition of Zn to the experimental deficient animals is associated with a rapid improvement in weight gain and cessation of diarrhoea. There is even a significant increase in the weight of the intestinal mucosa within 48 h of the start of Zn supplementation (Fig. 2). Presumably, sufficient Zn was available to stimulate intestinal repair. The importance of Zn deficiency in relation to the immune system has been well described in experimental studies (Cunningham-Rundles *et al.* 1979). A recent study showing that Zn deficiency impairs the rate of clearance after an experimental intestinal parasitic infection suggests that Zn deficiency may be important in contributing to persistent diarrhoea because of delayed excretion of the pathogen which caused it in the first place (Fenwick *et al.* 1990). Thus, there seemed enough evidence that Zn could be an important factor in the severity and outcome of both acute and persistent diarrhoea, from the animal literature, that clinical studies were justified.

CLINICAL STUDIES IN Zn DEFICIENCY

The International Centre for Diarrhoeal Disease Research in Bangladesh is a major centre for the management of acute and persistent diarrhoea. A recent study has examined the impact of Zn supplementation in children with acute and persistent diarrhoea (Roy *et al.* 1992).

Table 1 shows the nutritional indices of children with diarrhoea which was severe enough to merit admission to hospital for inpatient management. In both acute diarrhoea and persistent diarrhoea it can be seen that a high proportion of the children were undernourished with respect to their anthropometric indices. In addition they had low levels of serum Zn and vitamin A. We recognize the extreme difficulty in assessing Zn status in human populations at the present time, and somewhat arbitrarily chose the cut-off values for serum concentrations of less than 14 μmol/l for Zn and 0·35 μmol/l for vitamin A to indicate deficiency.

Microbiological studies of the organisms responsible for the diarrhoea in each of the study groups are shown in Tables 2 and 3, demonstrating a wide range of both secretory and invasive organisms. In an initial study, children with acute diarrhoea and persistent diarrhoea were randomized to receive zinc acetate syrup for 2 weeks (5 mg elemental Zn/kg body weight per d) or placebo.

Among children with acute diarrhoea, Zn supplementation resulted in a decrease in intestinal fluid loss of 22%. This was significantly different from the placebo group in children of short stature or who had a low serum Zn at presentation (Fig. 3). A more

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Table 1. *Anthropometric and biochemical indices of children with acute persistent diarrhoea in Bangladesh who received zinc acetate (5 mg Zn/kg per d) or a placebo*

(Mean values with their standard errors)

	Acute diarrhoea				Persistent diarrhoea			
	Placebo		Zn supplement		Placebo		Zn supplement	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
n . . .	54		57		90		90	
Wt-for-age (% median)	67	6	67	7	72	12	70	11
Height-for-age (% median)	92	3	91	3	94	4	94	5
Wt-for-height (% median)	81	7	82	6	82	10	83	8
MUAC (mm)	115	10	113	10	116	10	116	10
Age (months)	11	4	11	4	8	3	8	3
Period of diarrhoea (d)	2·7	0·7	2·8	1·0	21	10	24	11
Serum Zn (μmol/l)	12·3	4	11·5	3	13·2	5	13·4	5
Serum vitamin A (μmol/l)	0·26	0·14	0·26	0·13	0·37	0·22	0·40	0·21

MUCA, mid-upper arm circumference.

Table 2. *Pathogens in stools from children with acute diarrhoea in Bangladesh who received zinc acetate (5 mg Zn/kg per d) or a placebo*

Treatment group . . .	Placebo (*n* 54)	Zn supplement (*n* 57)
Pathogens		
Rotavirus	13	21
Campylobacter spp.	8	6
Aeromonas spp.	4	3
Shigella spp.	1	4
Enterotoxigenic *Escherichia coli* (ST)	7	2
Enteropathogenic *E. coli*	3	2
Vibrio cholerae	3	4
No pathogens	20	24

striking effect was obtained among children with persistent diarrhoea syndrome. There was a significant reduction in the duration of diarrhoea (assessed by survival analysis; Roy *et al.* 1991) and this was particularly significant in those who were underweight (less than 70% weight-for-age; Fig. 4), short (less than 95% height-for-age) or thin (less than 80% weight-for-height). The implication is that Zn deficiency is more likely to occur among undernourished children.

Mucosal function was investigated more precisely by measurement of urinary lactulose and mannitol after an oral loading dose. Mannitol absorption tends to reflect the absorptive surface area whereas lactulose absorption tends to reflect damage to the intercellular space. If there is a loss of integrity of the tight junction, increased quantities of lactulose are absorbed.

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Table 3. *Pathogens in stools from children with persistent diarrhoea in Bangladesh who received zinc acetate (5 mg Zn/kg per d) or a placebo*

Treatment group . . .	Placebo		Zn supplement		Total *n*	Percentage of total
	n	Percentage	*n*	Percentage		
(a) Incidence of enteropathogens isolated in patients with persistent diarrhoea syndrome						
Enterpathogenic						
Escherichia coli	22	23·2	27	28·4	49	25·8
E. coli ST	22	23·2	17	17·9	39	20·5
E. coli LT	2	2·1	8	8·4	10	5·3
Rotavirus	10	10·5	10	10·5	20	10·5
Campylobacter jejuni	13	13·7	9	9·5	22	11·6
Shigella spp.	5	5·3	2	2·1	7	3·7
No pathogen	38	40·0	43	45·0	81	42·6
(b) No. of patients with one or more enteropathogens						
Occurrence:						
None	38	40	43	45		
One	37	39	33	35		
Two	18	19	16	17		
More than two	2	2	3	3		

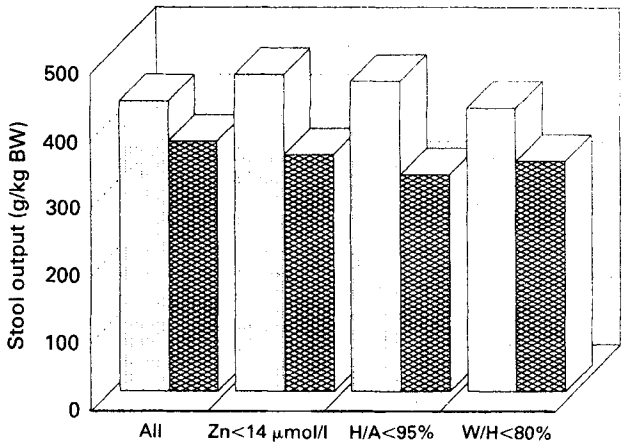

Fig. 3. Stool output (g/kg body weight (BW)) in children with acute diarrhoea in Bangladesh who received zinc acetate (5 mg Zn/kg per d; ■) or placebo (□). H/A, height-for-age; W/H, weight-for-age.

Fig. 5 shows that the addition of Zn resulted in a significant reduction in lactulose absorption towards normal levels.

When the children were followed at home-visits to make weekly assessments of their health and growth, it was discovered that children who received a 2-week course of zinc acetate had significantly lower prevalence of diarrhoea and respiratory symptoms. Although it was not possible to perform measurements of immune function in these children, it seems quite possible that the Zn supplement had improved resistance to subsequent infection, at least in the short term.

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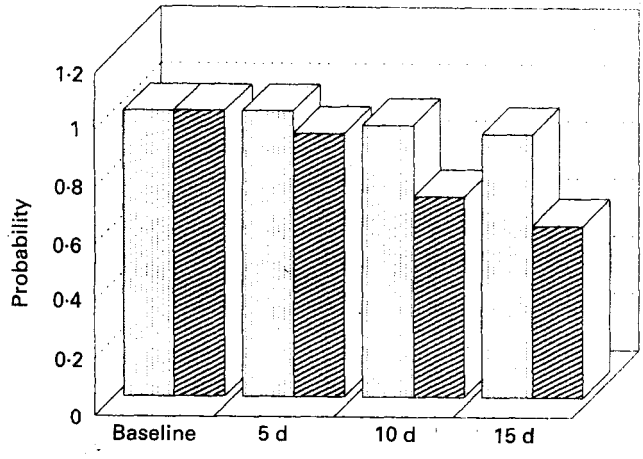

Fig. 4. Duration of symptoms among children with persistent diarrhoea in Bangladesh who were less than 70% weight-for-age and who received zinc acetate (5 mg Zn/kg per d; ▨) or placebo (□) (analysed by survival analysis).

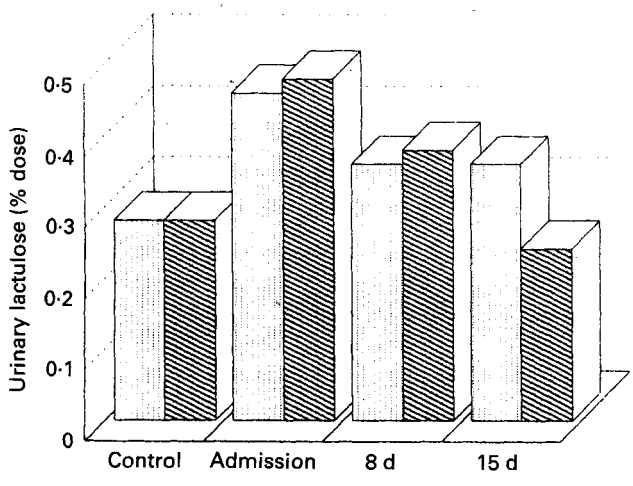

Fig. 5. Intestinal permeability (lactulose excretion) in acute diarrhoea in children in Bangladesh who received zinc acetate (5 mg Zn/kg per d; ▨) or placebo (□).

In summary, it appears that Zn supplementation is associated with improvements in intestinal function among children with acute and persistent diarrhoea. However, these effects are most striking among those who are moderately or severely malnourished. Previous work in the Caribbean (Golden & Golden, 1989) has demonstrated a high prevalence of Zn deficiency among severely malnourished children. Moreover, the importance of Zn deficiency in growth has been identified. It seems likely that moderately or severely malnourished children in Bangladesh also have Zn deficiency which is sufficiently marked to enable a significant response to Zn supplementation during acute and persistent diarrhoea. It seems rather important to study the effect of Zn

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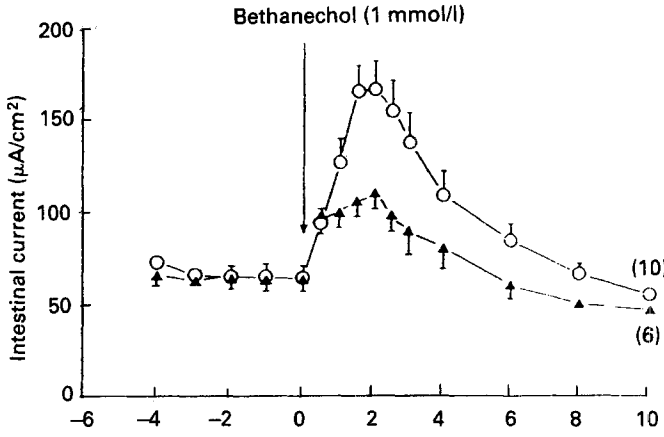

Fig. 6. Time-course of the response of the intestinal current to serosal addition of bethanechol in vitamin A-deficient (○) and control (▲; vitamin-deficient rats supplemented with 4·5 mg vitamin A/kg diet) rats. Values are means with their standard errors represented by vertical bars; no. of rats in parentheses. (From Nzegwu & Levin, 1991.)

on the gut in greater detail. For instance, although there are very high levels of Zn lost in the intestinal fluid of children with diarrhoea in South America (Casatillo-Duran *et al.* 1988), the optimum dose of Zn has yet to be defined.

EXPERIMENTAL VITAMIN A DEFICIENCY

The effect of experimental vitamin A deficiency on gut mucosa has been described in several studies recently. In contrast to the situation with Zn deficiency, changes in mucosal morphology in vitamin A deficiency are relatively mild (Ahmed *et al.* 1990), although there are significant differences in the mucosal morphology of a vitamin A-deficient animal when infected with experimental rotavirus infection. Recent measurements of electrogenic activity in the small and large intestine of the rat during vitamin A deficiency, have shown some complex results. In the small intestine there are changes in short-circuit current activity in response to bethanecol in vitamin A deficiency (Fig. 6; Nzegwu & Levin, 1991). Similar appearances occur in the proximal large intestine but in the distal large intestine there is a completely opposite result, i.e. a decrease in short-circuit current after stimulation with bethanecol (Fig. 7; Nzegwu & Levin, 1992). There are no reported results of the intestinal response to cholera toxin such as I described in the section on Zn deficiency.

COMMUNITY STUDIES OF VITAMIN A SUPPLEMENTATION

Considerable interest and debate has surrounded the observations from a number of field studies that vitamin A supplementation among children in areas where vitamin A is recognized to be a public health problem has been associated with a reduction in mortality, by 20–30%. The studies describing these findings are summarized in Table 4. It should be noted, however, that the degree by which mortality is reduced varies between the studies and in some studies vitamin A supplementation does not reduce

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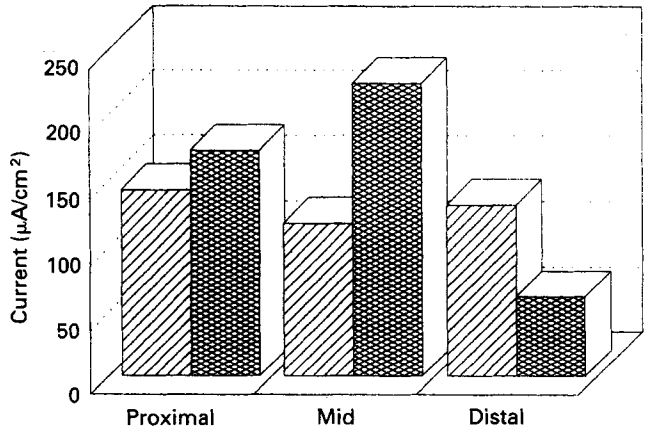

Fig. 7. Short-circuit current at different sites in the intestine in vitamin A-deficient (▩) and control (▨) rats.

Table 4. *Summary of studies (Nutrition Bureau for Research and Development, 1992) showing the effect of vitamin A supplementation on childhood mortality*

(Values are expressed as relative risk of death in supplemented *v.* unsupplemented groups)

Country	Age (months)	Effect (relative risk)
Sarlahi, Nepal	6–72	0·7
Madurai, India	4–59	0·46
Aceh, Indonesia	12–71	0·7
Jumla, Nepal	1–59	0·74
Java, Indonesia	12–70	0·55
Navrongo, India	6–60	0·80
Hyderabad, India	12–59	NS
Omdurman, Sudan	6–60	NS

NS, not significant.

mortality at all. In seeking an explanation for why vitamin A should have such striking effects, it is valuable to examine the impact of vitamin A in different populations according to the prevalence of diarrhoea.

In the studies in Indonesia and Nepal a high proportion of the deaths were attributable to diarrhoea. In the study in Madurai, South India, which showed no impact of vitamin A supplementation, there was a rather low infant and child mortality rate and, in particular, diarrhoea deaths seemed to be rather rare. The reason why vitamin A supplementation reduces mortality in most populations but not others is still obscure, but it would seem that differences in disease prevalence rates, availability of medical care, severity of disease, and underlying anthropometric indices are all important.

VITAMIN A DEFICIENCY AND DIARRHOEA

The relationship between vitamin A deficiency and prevalence of diarrhoea is largely unexplored (Table 5). A study in north-east Thailand showed a decrease in prevalence of

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Table 5. *Summary of studies (Nutrition Bureau for Research and Development, 1992) showing the effect of vitamin A supplementation on diarrhoea in children*

Country	Effect	Comment
Hyderabad, India	Nil	Low prevalence
Madurai, India	Significant	Major cause of diarrhoea
Thailand	Significant	High prevalence
Ghana	Significant	Severe episodes decreased

reporting of diarrhoea symptoms among the supplemented group. During a supplementation study in Ghana in which twenty-one symptoms are included in weekly interviews, it was noted that vitamin A supplementation had minimal impact on the incidence of infection. However, the number of children with severe dehydrating diarrhoea is significantly reduced and the number of children admitted to hospital with severe infections was reduced by 38% (Arthur *et al.* 1992).

Overall, therefore, it appears that vitamin A deficiency makes relatively little impact on attack rate for diarrhoea but it does influence the outcome of an episode. The amount of intestinal fluid loss is less and mortality rates are lower. In order to assess why vitamin A deficiency affects the outcome of infection, studies of immunoglobulins in tears and blood were performed. IgA levels in blood are elevated in vitamin A deficiency but the levels in tears were decreased, perhaps reflecting a decrease in transport of secretory immunoglobulins across the ocular mucosa (Filteau *et al.* 1992). If this impaired transport is also present in the respiratory and gastrointestinal epithelium there might be a significant reduction in the host immune response to severe infection. This might affect duration as well as the intensity of invasion by a diarrhoea pathogen.

The public health implications of these studies are considerable. There are few technical interventions with as great an effect as the supplementation with vitamin A. However, even three times per year may be too much for a regular interaction between health worker and child in the community. There has been considerable debate about the appropriate strategies for improving vitamin A status. Options range from fortification of commonly eaten food items such as sugar or monosodiumglutamate to administration of regular amounts of vitamin A precursors such as carotenoids or supplementation with high-dose vitamin A capsules.

Interactions between Zn and vitamin A deficiency

There are obvious interactions between Zn and vitamin A deficiency. For instance, Zn deficiency decreases the rate of production of retinol-binding protein. It may also hinder absorption of vitamin A. In the Bangladesh studies referred to in the present review we do not have to implicate the interaction between the two because the dietary sources of Zn and vitamin A are both poor in the children's diet. However, there are many possibilities for interaction with other agents in the serum. An intriguing possibility has been put forward following the recent demonstration that aldosterone and vitamin A interact at the level of the enterocyte (Nzegwu & Levin, 1992). Aldosterone regulates the passage of Na, K and water across membranes and the changes in short-circuit current that were demonstrated in vitamin A-deficient animals may involve changes in activity of aldosterone on the enterocyte.

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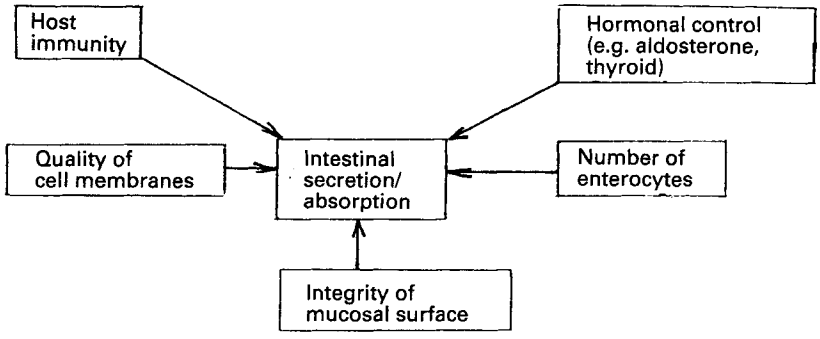

Fig. 8. Mechanisms by which micronutrient deficiency may influence intestinal secretion and absorption.

An even more complex and interesting situation occurs in the prevalence of vitamin A and I deficiency. Thyroxine and aldosterone interact closely. If there is deficiency of thyroxine, aldosterone has less effect. It seems possible, therefore, that if Zn and vitamin A deficiency exist in an area where there is also I deficiency, diarrhoeal episodes may be made worse because of the hypothyroidism on the Na-absorbing effect of aldosterone. Such an environmental situation occurs in Bangladesh. It may occur elsewhere.

Studies on the interaction between infection and micronutrients were performed first about 20 years ago. However, at that time they were mostly concerned with observations of changes in levels of plasma micronutrients following the induction of induced fever or during acute episodes of specific infections. There were no attempts to see how modification of micronutrient levels could be used during infection. The recent studies investigating such possibilities raise exciting areas of research and practical management for the future. Fig. 8 summarizes some of the means by which micronutrient deficiencies affect the gut.

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