

### VITAMIN A AND CHILD SURVIVAL

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Vitamin A was first discovered by McCollum as a fat soluble factor necessary for growth and prevention of xerophthalmia in rats(1). It is widely known to be associated with xerophthalmia and night blindness in human beings. More recent studies have shown that infections predispose to Vitamin A deficiency and *vice-versa* and thus suggest a more direct relationship between Vitamin A and childhood mortality. The present communication intends to examine this aspect of Vitamin A.

Vitamin A is a fat soluble unsaturated isoprenoid alcohol also called retinol. In human diet it is derived as retinol or as provitamin A carotenoids.  $\beta$ -carotene has the highest vitamin A activity among the carotenoids. While preformed retinol is derived from animal sources, liver being particularly rich, provitamin A carotenoids are derived from many plants specially dark green leafy vegetables. Its activity is

expressed in terms of international units (IU).

#### Vitamin A Deficiency

It is estimated that some 5 million children, in Asian countries, suffer from xerophthalmia, of which almost a quarter go blind(2). The only function of Vitamin A fully defined biochemically is its role in vision. Since Vitamin A is the part of retinol pigments, its deficiency leads to visual disturbances especially during dim light. This is called night blindness. Other features of Vitamin A deficiency are nyctalopia, photophobia, xerophthalmia, conjunctivitis and keratomalacia leading to blindness(3). The World Health Organization has recommended a revised classification(4) of various clinical signs of xerophthalmia in 1982. This classification is basically meant for prevalence surveys of Vitamin A status and generally reflect increasing severity of xerophthalmia.

#### Vitamin A and Infections

There are clinical reports of high mortality in association with keratomalacia in the literature of 18-20th century. This was presumed to be because of associated severe emaciation, systemic infections and compound deficiencies(2).

#### Experimental Studies

Experimental data suggest a stabilized effect of Vitamin A on lysosomal membranes(5) and augmentation of immune response(6-8). Cohen demonstrated non-specific resistance to infection in Vitamin A treated mouse as compared to untreated (control group). Gram +ve and -ve bacteria and *Candida albicans* were used as infecting organisms in this study(9). Mortal-

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ity was significantly less in vitamin A treated group. Nauss *et al.*(1) in their study showed a depression in cellular immunity (demonstrated by response of splenic lymphocytes to mitogenic stimulation) in rats fed on Vitamin A deficient diet, which returned to control levels within 3 days of Vitamin A supplementation. In another study from the National Institute of Nutrition, Hyderabad(11) effect of Vitamin A supplementation on macrophage function, obtained from activated peripheral blood monocytes of preschool children with marginal Vitamin A deficiency, were studied. Whereas cytotoxic functions remained unchanged there was a marked potentiation of interleukin I response in this study. Another study from same place(12) demonstrated a significant reduction in T-cell number in children with Vitamin A deficiency whereas neutrophil function, antibody response and salivary SIgA were comparable in two groups. Chandra(13) demonstrated increased bacterial binding to respiratory epithelial cells in Vitamin A deficiency state which may be another risk factor for higher incidence of respiratory infection in these children. All these experimental data point towards a role of Vitamin A in boosting the defence mechanisms against infection and thus an impact on child survival. All these studies had sound methodology hence results are convincing.

### Clinical Studies

The results of clinical studies are not so unequivocal. Studies from Indonesia(14) and Thailand(15) found increased susceptibility to diarrhea and respiratory tract infections in children with Vitamin A deficiency. Pinnock *et al.*(16) demonstrated compromised Vitamin A status in children who were prone to frequent respiratory

tract infections. Other studies(17-19), including one from India(17) did not find mild xerophthalmia as a risk factor for diarrhea. No clear explanation can be offered for such discrepancy in results. Moreover, all these studies have been criticized because of similar reasons; *viz.*, failure to adjust for confounding variables, *e.g.*, socio-economic status, nutritional factors and anomalies in alterations in mortality in relation to disease(20). Vitamin A deficiency was found to be a risk factor for persistent diarrhea by workers from Bangladesh(21). Another study from the same country(22) found a strong association between Vitamin A deficiency and diarrhea. However, it was not clear, whether Vitamin A deficiency predisposed to diarrhea and other infections or whether diarrhea and other infections precipitate acute Vitamin A deficiency in marginally nourished children. Findings of this study favoured the later hypothesis. Increased risk of xerophthalmia during diarrhea(23,24) and respiratory disease(23) was demonstrated in other studies as well. These studies provide strong evidence for the hypothesis that suggest diarrhea as a risk factor for Vitamin A deficiency. However, failure to control for potential confounders, *e.g.*, socio-economic status was a drawback in this longitudinal study. On the other hand cross-sectional studies fail to rule out the reverse hypothesis, *i.e.*, Vitamin A deficiency as a risk factor for diarrhea and also have the same problem of failure to exclude confounding variables. Reduced absorption of Vitamin A from intestines during episodes of diarrhea(25,26), respiratory infections(26), other infections especially measles(27,28) and malnutrition(29) has been shown by various studies and is considered the primary cause for compromised Vitamin A status following these infections.

## Intervention Studies

Based on above observation, it can be assumed that Vitamin A supplementation shall reduce childhood mortality in areas where Vitamin A deficiency is common. An intervention study in Indonesia by Aceh Study Group(30) showed a 34% reduction in mortality in villages which received Vitamin A supplementation as compared to control villages. However, many questions were raised regarding flaws in methodology and analysis of data(31-33). Later another communication from the same group(34) showed that results are still better when the data were analysed on the basis of non-recipients and recipient children rather than on the basis of 'intent to treat'. An Indian study also suggested a reduction in mortality after a weekly small dose supplementation of Vitamin A(35). This study, however, is not comparable to the study of Aceh study group as the later used single dose Vitamin A therapy. Weekly administration of Vitamin A resulted in frequent contact with health workers which in itself has been more important in reducing mortality than administration of vitamin A. This was demonstrated in another, well-controlled Indian study(36) in which there was no reduction in mortality in control group which received neither vitamin A nor placebo. However, there was reduction in mortality in both placebo and Vitamin A treated group. An African study showed reduced mortality in children with measles who were administered Vitamin A at admission(37). It was a well controlled study and showed results consistent with the previous African experiences.

Vitamin A deficiency is a common problem in developing countries. It is known to affect the defence mechanisms of

the body. The clinical studies have shown controversial results in relation to its role in causation of diarrhea and respiratory infections and intervention studies which are well controlled, have failed to show reduction in childhood mortality by more massive dose of Vitamin A supplementation. The National Institution of Nutrition had advised on a programme for prevention and control of night blindness through prophylactic massive Vitamin A dose as an interim measure in order to buy time to identify and promote long term measures for its control(38). Fortunately, the efforts to promote Vitamin A as 'instant remedy' for reducing childhood mortality have not materialised. It is high time when we should direct our research and practice towards eliminating this 'artificial means' of preventing and/or controlling Vitamin A deficiency rather than promoting it(38). This can largely be achieved by promoting consumption of easily available and cheap Vitamin A or  $\beta$ -carotene rich foods. This will go a long way in preventing Vitamin A related morbidity and thus is likely to improve child survival, not only in India, but in whole Third World. However, Vitamin A supplementation is certainly indicated in children who have symptoms and signs of Vitamin A deficiency, severely malnourished children who present with diarrhea, respiratory tract infection and measles and possibly those who have repeated episodes of these infections.

The guidelines for treatment and prevention of Vitamin A deficiency drawn up by the WHO/UNICEF/IVACG Task Force(39) in 1988 are shown in *Table I*. They are based on best available scientific data at the present time and should be followed till a better schedule based on further research and cumulating knowledge comes in picture.

**TABLE I—Xerophthalmia Treatment Schedule for Children Over 1 Year and Under 6 Years Old***Children over 1 year and under 6 years old*

Immediately on diagnosis	200, 000 IU Vitamin A orally*
The following day	200, 000 IU Vitamin A orally
4 weeks later	200, 000 IU Vitamin A orally

*Children under 1 year old and children of any age who weigh less than 8 kg*

Treat with half the doses as indicated for children 1-6 years old

*Children aged 6 years or over, adolescents and adults  
(except women of reproductive age)*

Treat with the same dosage as those for children 1-5 years old

*Women of reproductive age, pregnant or not*

For night blindness or Bitot's spot, treat with a daily dose of 10,000 IU of Vitamin A orally (1 sugar-coated tablet) for 2 weeks.

\*Note: If there is persistent vomiting or profuse diarrhea, an intramuscular injection of 100,000 IU of water miscible Vitamin A (but not an oil-based preparation) may be substituted for the first dose. The use of sterile syringe and needle is, of course, essential.

Source: WHO/UNICEF/IVACG Task Force from 1986-88 findings.

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