Chapter 15. Vitamin A deficiency

Vitamin A was discovered in 1913 when experiments showed that if the only fat present in diets of young animals was lard, their growth was retarded, and when butter was substituted the animals grew and thrived. A substance in butter but not in lard was found also in egg yolk and cod-liver oil. It was named vitamin A. It was later established that many products of vegetable origin had nutritional properties similar to those presented by vitamin A in foods of animal origin; they were found to contain a yellow pigment, carotene, which is converted to vitamin A in the body. Preformed vitamin A or retinol is a fat-soluble vitamin found only in animal products. Carotenes or carotenoids can act as a provitamin. There are many carotenoids in plants, but the most important for human nutrition is beta-carotene, which can be converted to vitamin A by enzymatic action in the intestinal wall. Breastmilk is an important source of vitamin A for infants.

Dietary deficiency of vitamin A most commonly and importantly affects the eyes, and it can lead to blindness. Xerophthalmia, meaning drying of the eyes (from the Greek word xéros, meaning dry), is the term now used to cover the eye manifestations resulting from vitamin A deficiency. Vitamin A deficiency also has a role in a variety of clinical conditions not related to the eyes, and it may contribute to higher child mortality rates, especially in children who develop measles. It has been demonstrated that laboratory animals on diets deficient in vitamin A have increased rates and severity of infections. Vitamin A deficiency also adversely affects epithelial surfaces apart from the eye and is associated with an increased incidence of certain cancers, including cancer of the colon. The serious eye manifestations of vitamin A deficiency leading to corneal destruction and blindness are mainly seen in young children. This condition is sometimes called keratomalacia.

Until recently vitamin A deficiency was a relatively neglected condition, probably for the following four reasons:

- Public health and nutrition efforts were concentrated on the control of protein-energy malnutrition (PEM), with which vitamin A deficiency is associated, and which is the most important form of malnutrition in non-industrialized countries.

- Where xerophthalmia is prevalent there were few eye specialists or health workers who could correctly diagnose the condition.

- The condition occurs in the very young child behind closed eyelids, or it does not appear to the parents to warrant medical attention until too late, when the cornea is irreversibly damaged.

- Because the fatality rates from advanced xerophthalmia are high, relatively few blind children survive in the community, which reduces the social significance and visibility of the problem.

However, recently the World Summit for Children (1991) and the International Conference on Nutrition (1992) called for the virtual elimination of vitamin A deficiency and its consequences, including blindness, by the year 2000. Much more emphasis is now being placed on the control of vitamin A deficiency.

Causes

An inadequate intake of carotene or preformed vitamin A, poor absorption of the vitamin or an increased metabolic demand can all lead to vitamin A deficiency. Of these three, dietary deficiency is by far the most common cause of xerophthalmia.

Good sources of retinol, or preformed vitamin A, are liver, fish-liver oils, egg yolks and dairy products. In most non-industrialized countries, however, the majority of poor people get most, often 80 percent or more, of their vitamin A from carotene in foods of vegetable origin. The yellow colour of carotene may be masked by
chlorophyll in many dark green leafy vegetables. Carotenes are present in good quantities in a wide variety of green and yellow vegetables and fruits, in yellow maize and in yellow root crops, e.g. sweet potatoes. A rich source is red palm oil, which is eaten extensively in West Africa and widely grown but infrequently consumed in many other areas, e.g. Malaysia. In many tropical diets important sources are dark green leafy vegetables [e.g. amaranth, cassava and drumstick (Moringa oleifera) leaves], mangoes, papayas, tomatoes and sometimes local yellow pumpkins, squash and yellow maize. The wet tropics often abound in both cultivated and wild food sources of carotene, but the poor often consume too little of these foods, and young children often dislike green vegetables. In some seasons the main sources of vitamin A may be less available or more expensive.

The biological activity of vitamin A is now usually expressed as retinol equivalents (RE) rather than in international units (IU). One RE is equal to 1 µg of retinol or 6 µg of beta-carotene. The World Health Organization (WHO) has recommended an intake of 300 RE daily for infants and 750 RE for adults.

Vitamin A, either preformed (retinol) or converted from carotene, is stored in the liver. Retinol is transported from the liver to other sites in the body by retinol binding protein (RBP), a specific carrier protein. Protein deficiency may influence vitamin A status by reducing the synthesis of RBP.

Low intake of vitamin A and carotene over an extended period is the most common cause of xerophthalmia. The condition may be influenced by other factors, however, e.g. intestinal parasitic infections, gastro-enteritis or malabsorption. Measles often precipitates xerophthalmia because it leads to lowered food intake (in which anorexia and stomatitis may be factors) and to increased metabolic demands for vitamin A. The virus may also affect the eye, aggravating lesions caused by vitamin A deficiency. PEM is also important as a cause or accompaniment of xerophthalmia. Data from Indonesia and elsewhere suggest that serious corneal involvement in xerophthalmia seldom occurs except in children who have moderate or severe PEM.

**Epidemiology**

Vitamin A deficiency is the most common cause of blindness in children in many endemic areas. Xerophthalmia occurs almost entirely in children living in poverty. It is extremely rare to find cases in more affluent families, even in areas where xerophthalmia is prevalent. It is a disease related to low socio-economic status, low levels of female literacy, land shortages, inequity, poor availability of curative and preventive primary health care, high rates of infectious and parasitic diseases (often related to poor sanitation and water supplies) and grossly inadequate family food security. As with PEM, three essentials for prevention of vitamin A deficiency are adequate food security, care and health.

It is always frustrating and extremely sad to see a child with advanced xerophthalmia that includes a perforated cornea when a few days earlier the sight of the child could easily have been saved. A few days and a few cents could have prevented a whole lifetime of blindness. The parents are often poor and uneducated. They love their children, but they may be resigned about the illness because they have inadequate access to good health care, and they may be fatalistic or suspicious of Western medicine. Therefore a small eye problem may not lead the parents to seek early health care even if it is easily available.

In recent decades xerophthalmia has been especially prevalent in children of poor rice-eating families in South and Southeast Asia (e.g. Bangladesh, India, Indonesia and the Philippines). There is a high incidence in some African countries (e.g. Burkina Faso, Ethiopia, Malawi, Mozambique and Zambia), whereas other countries, especially in West Africa, seem to have a lower prevalence in part because of the consumption of red palm oil, which is high in carotene. In the Western Hemisphere, Haiti and northeastern Brazil are areas where xerophthalmia is highly prevalent. It occurs also in many poorer areas of Central and South America. Vitamin A deficiency used to be a problem in the Near East, but few recent data on its prevalence there are available. In poor developing countries where vitamin A deficiency is endemic, it is also prevalent among lactating mothers. In Europe and North America, and in affluent people everywhere, vitamin A deficiency may occur in
alcoholics, in those with malabsorption or anorexia nervosa and in persons who for any reason consume diets low in carotene or vitamin A.

Prevalence rates of five different signs have been recommended as criteria for judging whether xerophthalmia is a significant public health problem in a given population (Table 27). It is suggested that if the prevalence of any one sign (i.e. the percentage of children examined having the sign) in children aged six months to six years in a vulnerable population is above the cut-off, then xerophthalmia should be considered a public health problem in that population.

**TABLE 27 Prevalence criteria for determining public health significance of vitamin A deficiency**

<table>
<thead>
<tr>
<th>Sign</th>
<th>Prevalence above (%)</th>
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<tbody>
<tr>
<td>Night blindness</td>
<td>1</td>
</tr>
<tr>
<td>Bitot's spots</td>
<td>0.5</td>
</tr>
<tr>
<td>Corneal xerosis/corneal ulceration/keratomalacia</td>
<td>0.01</td>
</tr>
<tr>
<td>Corneal scar</td>
<td>0.05</td>
</tr>
<tr>
<td>Plasma vitamin A &lt;10 µg/dl</td>
<td>5</td>
</tr>
</tbody>
</table>

*Source: WHO, 1982.*

It is believed that worldwide between 500 000 and 1 million children each year develop active xerophthalmia with some corneal involvement. Of these, perhaps half will become blind or have serious visual impairment, and a large proportion will die. In addition, many millions of children are vitamin A deficient or at risk but do not have xerophthalmic eye manifestations. Deficiency is manifested by low liver stores of retinol and low serum vitamin A levels.

**Clinical manifestations**

Clinical signs of xerophthalmia are illustrated in Figure 9. WHO and others have accepted a classification of the disease according to these signs (Table 28). The classification is now widely used in surveys.

Night blindness (XN) is often the first evidence of vitamin A deficiency; the individual has a reduced ability to see in dim light. In many countries where xerophthalmia is endemic, there are local terms for night blindness. Parents may notice that their young child is clumsy in the dark or fails to recognize people in a poorly lit room. Night blindness occurs because vitamin A deficiency reduces the rhodopsin in the rods of the retina.

*FIGURE 9 Clinical signs of xerophthalmia*
TABLE 28

Classification of xerophthalmia

<table>
<thead>
<tr>
<th>Ocular signs</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night blindness</td>
<td>XN</td>
</tr>
<tr>
<td>Conjunctival xerosis</td>
<td>X1A</td>
</tr>
<tr>
<td>Bitot's spots</td>
<td>X1B</td>
</tr>
<tr>
<td>Corneal xerosis</td>
<td>X2</td>
</tr>
<tr>
<td>Corneal ulceration/keratomalacia &lt;1/3 corneal surface</td>
<td>X3A</td>
</tr>
<tr>
<td>Corneal ulceration/keratomalacia _1/3 corneal surface</td>
<td>X3B</td>
</tr>
<tr>
<td>Corneal scar</td>
<td>XS</td>
</tr>
<tr>
<td>Xerophthalmia fundus</td>
<td>XF</td>
</tr>
</tbody>
</table>

The next sign is drying of the conjunctiva, which is known as conjunctival xerosis (X1A). Patches of xerosis give the appearance of sandbanks at receding tide. The conjunctiva loses its shiny lustre and often becomes thickened, wrinkled and sometimes pigmented.

Sometimes accompanying the conjunctival xerosis are Bitot's spots (X1B), which are usually triangular-shaped, raised whitish plaques that occur in both eyes. When examined closely they look like a fine foam with many
tiny bubbles. This foamy, sticky material can be wiped away. Bitot's spots in the absence of xerosis may have a cause other than vitamin A deficiency.

The next stage is corneal xerosis (X2), drying of the corneal surface, which first appears hazy and then granular on simple eye examination. The drying is followed by a softening of the cornea, often with ulceration and areas of necrosis.

Corneal ulcers are usually circular and punched out in appearance. They may initially be small (X3A), but they may extend centrally to involve much of the cornea (X3B). Ulceration may lead to perforation of the cornea, prolapse of the iris, loss of ocular contents and perhaps destruction of the eye, a condition termed keratomalacia. Although the lesions usually occur in both eyes, the corneal ulceration may be more advanced in one eye. With these severe manifestations the child is also usually seriously ill, sometimes with a high fever.

If treatment is instituted when a corneal ulcer is still small, it will heal, forming a corneal scar (XS). The size of the scar and the limits it imposes on future vision will depend on how large or advanced the corneal ulceration was and its location.

Xerophthalmia of the fundus (XF) is sometimes seen early in the disease under examination with an ophthalmoscope. The retina has white dots around the periphery of the fundus. They disappear following treatment.

The ocular signs of xerophthalmia allow diagnosis on clinical grounds, especially when the condition is moderately advanced. Corneal xerosis and ulceration are easily detected and cannot be mistaken easily for trachoma, which usually begins on the conjunctival surface of the upper lid. A history of night blindness in areas where vitamin A deficiency occurs provides strong evidence of the deficiency. The diagnosis is often missed because the sick child presents with serious PEM (kwashiorkor or nutritional marasmus), measles, tuberculosis, dehydration or some other condition that occupies the attention of the medical attendant. A failure to look into the eyes of a sick child is a common, sad and inexcusable reason for missing xerophthalmia and preventing blindness. The eyes of sick children must always be examined. The only requirement is good natural light or a simple torch or flashlight.

Non-ocular effects of vitamin A deficiency have been described better in experimental animals than in humans. In young animals growth retardation is marked. It is likely that vitamin A deficiency in children has similar consequences, but the association has not been clearly shown. Although vitamin A deficiency depresses immune response, recent detailed studies in Ghana, India, Indonesia, Nepal, the Sudan and the United Republic of Tanzania did not show lower prevalence of most common infections in children receiving regular doses of vitamin A. The prevalence and severity of diarrhea and respiratory infections were not significantly reduced by vitamin A supplementation. In contrast, there is much evidence that providing vitamin A to children with measles is highly beneficial. Research in several countries showed that providing vitamin A supplements reduced young child mortality by 20 to 40 percent, but a few other studies showed no impact on mortality rates. In areas where supplements reduced mortality significantly, rates of PEM were usually high, measles immunization rates were low and primary health care was poor.

**Laboratory tests**

Since vitamin A is stored in the liver, a diet deficient in vitamin A results eventually in low hepatic stores. Thus the best way to judge vitamin A nutritional status is to obtain an estimate of the level of vitamin A in the liver. This level can be measured easily only at autopsy.

Determination of serum vitamin A levels is useful for community surveys. Serum retinol levels often fall from normal levels of 30 to 50 µg per 100 ml of plasma to low or deficient levels below 20 µg per 100 ml of plasma.
Children with xerophthalmia will usually have levels below 10 µg per 100 ml. Ocular manifestations of xerophthalmia seldom occur before serum vitamin A levels are deficient.

Techniques known as the relative dose response and the modified dose response are now favoured but are more complex. They give a better picture of liver vitamin A stores than does the simple measure of serum vitamin A levels. RBP levels may also be low. Conjunctival impression cytology, in which conjunctival cells are stained and examined microscopically, holds promise for early detection of vitamin A deficiency.

**Treatment**

Effective treatment depends on early diagnosis, immediate dosing with vitamin A and proper treatment of other illnesses such as PEM, tuberculosis, infections and dehydration. Severe cases with corneal involvement should be treated as emergencies. Sometimes hours, and certainly days, may make the difference between reasonable vision and total blindness.

Treatment for children one year of age or over should consist of 110 mg of retinyl palmitate or 66 mg of retinyl acetate (200 000 IU of vitamin A) orally or preferably 33 mg (100 000 IU) of water-miscible vitamin A (retinyl palmitate) by intramuscular injection. Vitamin A in oil should not be used for injection. The oral dose should be repeated on the second day and again on discharge from hospital or seven to 30 days after the first dose. These doses should be halved for infants.

When there is corneal involvement it is desirable to apply an antibiotic ointment such as topical bacitracin to both eyes six times per day. Appropriate systemic antibiotics should also be administered.

Night blindness and conjunctival xerosis are completely reversible and respond quickly to treatment using oral doses of vitamin A on an out-patient basis. Corneal ulceration is arrested by treatment and will heal within a week or two but will leave scars. The case fatality rate is often high because of accompanying PEM and infections.

**Prevention**

In the long term, sustainable control will be achieved by increasing the production and consumption of foods rich in vitamin A and carotene by at-risk populations. Other methods include medicinal supplements, often consisting of high doses of vitamin A every four to six months; fortification of foods; and nutrition education. Control methods are discussed in detail in Chapter 39.