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THE SYMPTOMS AND SIGNS OF VITAMIN A DEFICIENCY AND THEIR
RELATIONSHIP TO APPLIED NUTRITION

A Report of the
International Vitamin A Consultative Group
(IVACG)

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INTRODUCTION

This series of monographs is concerned with various aspects of nutritional science that relate to the eradication of vitamin A deficiency and xerophthalmia. Fundamental to the control of any disease are the accurate description of its symptomatology and a clear understanding of the circumstances in which it occurs. Accounts of the ocular manifestations of vitamin A deficiency long antedate knowledge of the role of vitamin deficiencies in disease and all other aspects of this field. Increasingly sophisticated methods of clinical examination, knowledge gained from animal experimentation, biochemical techniques for determining concentration of vitamin A and related compounds in tissues, and the development of statistical sampling of population groups have all contributed to our present understanding of the nature and occurrence of this serious health hazard.

The purpose of this report is to review existing knowledge of the symptoms and signs of vitamin A deficiency and to draw attention to those areas where research efforts may be directed most profitably in order that yet more effective measures for control of the problem may be forthcoming in the future.

Background

Vitamin A is an essential nutrient for man and all mammalian species that have been tested. An adequate diet meets the vitamin A requirements of the body (the adult human Recommended Daily Allowance is 750 ug retinol equivalents) from the preformed vitamin in animal foods and/or from pro-vitamin carotenoid precursors in plant foods. In developing countries, where the total retinol intake is frequently below requirements, about 80 per cent is of vegetable origin. The usually more than adequate intake in technologically developed countries comes about equally from animal and vegetable sources. Under normal circumstances considerable amounts of the vitamin are stored in the liver and act as a reserve to be drawn upon in times of deficient intake.

The deficiency state has been extensively studied in experimental animals. Early signs include loss of appetite, growth failure and lowered resistance to infection. When liver stores are almost exhausted and the circulating concentration of vitamin A falls below the normal range, impairment of rod function is detectable. As depletion proceeds further epithelial keratinization of conjunctiva and cornea, lung, exocrine glands and gastro-intestinal and genito-urinary tracts occurs with a reduction in mucus secreting cells and accompanying xerosis. Late changes include impaired bone modelling with secondary effects on parts of the nervous system, liquefactive changes in the cornea leading to blindness, and sterility. Congenital malformations occur in the young of severely deficient mothers. Death with emaciation and secondary infections, especially of the lung and urinary tract ultimately ensues.

The process of deficiency is similar in man but less well understood and more complicated because of inability to control accompanying dietary

deficiencies and infections. The ocular manifestations are the best understood. They occur characteristically in the young child. Xerophthalmia is the term in general use for the ocular manifestations of vitamin A deficiency. When individual signs and symptoms are referred to in this report specific terms will be used. Extra-ocular manifestations in man have hitherto been largely neglected but are now beginning to attract attention (see below).

Public health significance

Blindness is one of the most serious disabilities an individual can suffer from and constitutes a great social and economic burden for the community. This is especially the case in xerophthalmia in which blindness almost always occurs in early childhood and in those who survive results in handicap for the rest of their lives. It is impossible to form an accurate estimate of the residual blindness from untreated xerophthalmia in a community. The poor prognosis of those who are fortunate enough to be treated in hospital suggests that very few indeed of those untreated in the community survive. Hospital data indicate that about 25 per cent of the survivors of severe xerophthalmia (X3A+B) remain totally blind, about 50-60 per cent are partially blind, and only 15-25 per cent have unimpaired vision (1). A follow-up study in Indonesia of children discharged after treatment for severe xerophthalmia showed that about 40 per cent had died within about 2 years (1).

Severe vitamin A deficiency is associated with a high mortality, usually more than 25 per cent in hospitalized cases (2). The rate may be as high as 60 per cent in children under 2 years of age (3). A comparison of the prevalence of active corneal destruction and corneal scars due to xerophthalmia in Indonesia, suggests that the mortality rate in the population at large may be as high as 50-80 per cent (4). Vitamin A deficiency is not the sole cause of death as Protein-Energy Malnutrition and infections are almost always present. That vitamin A deficiency itself predisposes to a poor prognosis is suggested by a reported 4-fold greater mortality in malnourished children with xerophthalmia than in those without (3) and among the latter a significantly lower plasma vitamin A in those who died than in those who survived (5).

Global occurrence and prevalence

The Protein-Calorie Group of the United Nations listed 73 countries and territories where it was considered that a vitamin A deficiency problem of public health significance occurred (6). The reliability of data varies from country to country, and the situation varies within a given country. The problem is greatest in India, Bangladesh, Indonesia and other countries in South and East Asia; and parts of the Middle East, Africa and Central and South America. In many of these countries xerophthalmia is the major cause of blindness in preschool children.

The world-wide prevalence of blindness from xerophthalmia is not known with any certainty. In the mid 1960s an annual rate of about 100,000 was suggested and this was widely quoted until recently (7). It was based on

Information collected during the global survey of xerophthalmia sponsored by WHO (8) together with an intensive investigation in Jordan including countrywide notification (9).

Recently a countrywide point-prevalence survey of xerophthalmia has been undertaken in Indonesia in conjunction with a 2 year prospective study of 5,000 rural preschool children (4). In the prevalence survey more than 27,000 rural and 9,000 urban preschool children were examined in more than 250 sample sites. In 11 out of 23 provinces the WHO criteria for a public health problem were exceeded. Table 1 shows the estimations made from the Indonesian data for Asia taking account of the population at risk and available information on severity of the problem.

Table 1 Estimations of annual incidence of xerophthalmia in Asia based on Indonesian data (4)

<u>Indonesia</u>	Annual incidence preschool	Population at risk	Cases per year
Corneal	4/1,000	12 million	48,000
Non-corneal	104/1,000	12 million	1,250,000
Total cases of corneal xerophthalmia annually	68-80,000 (about 250,000 go blind)		

Asia

Corneal xerophthalmia annually	500,000 (about 250,000 go blind)
Non-corneal	8-9 million

The estimated figure of 250,000 children going blind annually is for Asia alone and, as it does not take account of the many other but quite unknown number of cases occurring in other countries, may be taken as a quite conservative estimate.

Casual factors

These may relate to 1) the host, 2) the diet and 3) the environment.

The Host

Age

Young children constitute the most vulnerable group and the most serious eye lesions commonly occur in them. This is related to their relatively high vitamin A requirements for growth, increased needs due to the frequent occurrence of infections, and a low intake from milk of under-nourished mothers and failure to supplement carotene-poor staples with dark green leaves and other rich sources (see following).

Sex

The male is more susceptible to night blindness (10), Bitit's spots (11), and to corneal xerophthalmia (12,13). In the latter study of records of 6,000 cases of xerophthalmia the male preponderance was 58 per cent in the first 3 years of life and rose steadily to 80-90 per cent by the age of 10 years. Healthy men tend to have higher plasma concentrations of vitamin A than women (14), but there was no sex difference in liver values of accident victims in the United States (15). Plasma Retinol-binding protein (RBP) is also higher in men than in women (16), but there is no sex difference before puberty (17). These findings do not help to explain the greater susceptibility of the male to clinical deficiency and it is possible that the reasons are cultural rather than biologic.

Secondary deficiency

Sporadic cases may occur associated with diseases that interfere with the utilization of vitamin A by the body, such as those that impair absorption of fat or damage the liver (18).

The Diet

Apart from yellow sweet potatoes and plantains, all staple foods rich in starch such as cereals, roots, and tubers have very low carotene content. Even so the problem could be averted by the incorporation of locally available carotene-rich dark green leafy vegetables and some fruits, usually abundant where xerophthalmia is rife, in suitable form into the infant's diet. Availability and use of these may explain differences in incidence of xerophthalmia within the same country. For example in South Africa PEM is common among the urban poor and is frequently accompanied by xerophthalmia in Johannesburg (19) but not in Cape Town where squash and pumpkin are readily available and fed to young children (20). Sources of preformed vitamin A (milk, butter, eggs, liver) are usually expensive and beyond the means of communities in which xerophthalmia is endemic.

Normal breast milk contains about 50ug retinol/dl (colostum is 2-6 times richer) and the average intake of 840ml forms the basis for the recommended daily allowance of 420ug for infants (21). This intake is not achieved when the mother is undernourished, due to lowered concentration of vitamin A and reduced output of breast milk. The abandonment of breast feeding for artificial feeding in many communities undergoing rapid social change predisposes to gastro-enteritis and other infections and to the marasmic form of PEM.

Unfortified skimmed milk powder fed to undernourished children in supplemental feeding has precipitated many cases of xerophthalmia in the past. Nearly all the milk now so used is fortified with vitamin A.

PEM almost invariably accompanies xerophthalmia in the young child, although the incidence of xerophthalmia in PEM varies greatly in different areas. Malabsorption, depressed synthesis of retinol-binding protein (RBP) and perhaps other derangements of vitamin A metabolism may occur (see Monograph VI).

Dietary fat is necessary for the metabolism and absorption of carotenoids and vitamin A in the intestine. Most tropical dietaries, especially those of the preschool child, are very low in fat content. Other nutrients with which vitamin A is known to have important interactions are iron (see following), vitamin E, and zinc (see Monograph VI).

The Environment

Season

Availability of vegetables and fruit is often seasonal and vitamin A status varies accordingly. Extended drought may precipitate frank deficiency in a population. Where PEM is seasonal and tends to peak in relation to outbreaks of infectious disease, xerophthalmia follows the same pattern.

Infection and infestations

These tend to depress appetite, impair absorption and increase requirements for vitamin A. The 'gastro-enteritis' complex of disorders, respiratory infections including tuberculosis and pertussis, dysentery, giardiasis and ascariasis are frequently associated with xerophthalmia (22, 23 and Monograph VI).

In a recent study of PEM cases with and without xerophthalmia the incidence of various infections did not differ in the two groups, with the single exception that those with xerophthalmia had a much higher rate of bacteriuria (24). Measles appears to occupy a rather special position. Not only does it take a severe form in the undernourished child, with marked impairment of the cell-mediated immune response (25) but it affects the cornea even in the well-nourished child (26). Many cases of xerophthalmia reported from parts of Africa have been associated with measles (e.g. 27,28).

SIGNS AND SYMPTOMS OF VITAMIN A DEFICIENCY

These are considered below under three broad headings, 1) the anterior segment of the eye, 2) the posterior segment of the eye, and 3) non-ocular manifestations. The eye lesions have been the subject of numerous investigations over many years. Detailed descriptions and photographs of the various stages have appeared in several standard works (7, 18, 29, 30). A field guide on the subject has recently been published by WHO (31). The intention here is to summarize the available information and interpret it in the light of experience to date.

Xerophthalmia classification and criteria

Before proceeding further it would seem to be helpful to reiterate the decisions that were taken at the WHO/AID meeting held in 1974 and reported in the WHO Technical Report No. 590 (7) concerning the agreed classification of xerophthalmia and the suggested criteria for community diagnosis of xerophthalmia classification is as shown in Table 2.

Table 2 Xerophthalmia Classification

<u>Classification</u>	<u>Signs - primary</u>
XIA	Conjunctival xerosis
XIB	Bitot's spot with conjunctival xerosis

or more patches of dry, nonwettable conjunctiva, well described as "emerging like sandbanks at receding tide". Usually best seen on oblique illumination they almost always involve the interpalpebral area of the temporal quadrant, and often the nasal quadrant as well. In more advanced disease the entire bulbar conjunctiva may be affected. In exceptional cases advanced corneal changes may develop very rapidly without being accompanied by conjunctival xerosis. In some individuals typical xerosis may be accompanied by various degrees of conjunctival thickening, wrinkling, and pigmentation. These latter signs are however poorly reproducible, highly variable and nonspecific and should not be used in isolation, as they have sometimes been in the past, in making a diagnosis of conjunctival xerosis.

Frequently bubbly or cheesy material, consisting of keratinized, desquamated conjunctival epithelial cells, may occur some or all of the xerotic surface. Forming Bitot's spots (X1B). In cultures in which vitamin A deficiency is widespread, typical conjunctival xerosis/Bitot's spots in preschool-age children are likely to represent true active vitamin A deficiency, and will usually begin to respond to systemic vitamin A therapy within about one week, with complete resolution within 2-4 weeks, though in some instances it may take longer (35). Lesions with an identical appearance are sometimes found in individuals in whom the vitamin A status is normal. The subjects are usually older children or young adults and the lesions do not respond to vitamin A. At least some of these lesions are probably sequelae of old, corrected vitamin A deficiency, though some other factors, such as exposure, dryness, etc. may be important.

Although the only definite way of distinguishing the two types of lesions is by their response to therapy, other, more immediate clues exist. When Bitot's spots (not least classical xerosis) occur both nasally and temporally (i.e. on both sides of the cornea), or when night blindness is present, the lesions are almost certainly associated with active vitamin A deficiency (35). Unfortunately not all active cases have lesions on both sides of the cornea, or recognise that their dark adaptation is impaired and so the presence of these clues is far more helpful than their absence.

Vital staining of the conjunctiva and cornea with various dyes has long been used to reveal minimal superficial lesions. Rose bengal and lissamine green are considered to stain only degenerate and dead cells and mucus and their use has been proposed on experience in Kenya and Indonesia as a survey technique for the identification of early conjunctival xerosis due to vitamin A deficiency (36). Workers in India (37) recommended the test although a high proportion of false positives occurred and false negatives were not mentioned. Examination of a large number of children in Indonesia (38) showed many false positives and false negatives in relation to serum vitamin A levels. After treatment of some of the children with vitamin A the percentage of positive tests actually increased. Another study in Indonesia (39) found that vital staining was neither sufficiently specific (the eyes of approximately 10 per cent of otherwise normal children staining positive) nor sensitive (the eyes of 20-50 per cent of individuals with true vitamin A deficiency related-night blindness, conjunctival xerosis, and corneal destruction not staining at all). In addition, the test did not distinguish active vitamin A deficient xerosis from other lesions. Furthermore, when performed by inexperienced field workers it is often difficult to standardize (this may account for the reported discrep-

ancies), carries the risk of corneal abrasion and transmission of ocular infection, and impedes the survey's progress.

Long lashes and plugged meibomian glands have been reported to be common in xerophthalmic children. The changes in the lashes appear to be related to the generalized protein-energy malnutrition that commonly accompanies xerophthalmia and not to vitamin A deficiency per se. Plugged meibomian glands were rarely found among xerophthalmic children in the recent survey in Indonesia.

Cornea

The pre-corneal tear film is normally maintained complete for at least 10 seconds after a blink (40). In the vitamin A deficient eye a tear film forms but lack of mucus results in a more rapid break-up-time than normal.

Recent studies in Indonesia (41) indicate that the cornea is involved in the xerophthalmic process much earlier, and at higher serum vitamin A concentrations than previously recognized. Slit lamp examination of the fluorescein-stained cornea indicated that definite punctate epithelial keratopathy was already present in half the children with night blindness and normal conjunctiva and cornea by hand light examination, and in over 70 per cent of those with conjunctival xerosis but an apparently normal cornea. These lesions characteristically began in the infero-nasal quadrant.

With more severe vitamin A deficiency the punctate lesions become denser and spread upward and temporally, eventually involving the entire cornea. At this stage the cornea has a dry hazy appearance on hand light examination, termed corneal xerosis (X2). More severe involvement results in frank epithelial loss and stromal ulceration, either partial or full thickness (X3A). Perforating ulcers may become plugged with iris and heal as adherent leukomas. Large ulcers will cause loss of the anterior segment and occasionally intra-ocular contents as well. All these changes are due to vitamin A deficiency, and where some normal cornea still exists, will heal with vitamin A therapy (42).

Keratomalacia (X3B), full thickness limbus-to-limbus corneal melting usually occurs in the presence of combined deficiencies of protein and vitamin A. The exact cause of this change is not yet clear. Vitamin A administration will not save the eye, but may prevent similar changes, if not yet apparent, occurring in the other eye.

An hypopyon commonly accompanies xerophthalmic ulceration and melting, and does not necessarily imply local infection. Similarly, many eyes with vitamin A-related ulceration and melting lack typical conjunctival xerosis, the absence of which should in no way preclude a diagnosis of xerophthalmia. The invariably bilateral nature of the corneal involvement, even if of different severity, is a useful clue to the underlying cause.

Secondary infection is a frequent accompaniment of corneal xerophthalmia and may lead to neglect of the underlying nutritional deficiency. The role of local infection in the production of destructive corneal lesions is not clear. Pathogenic and commensal organisms have repeatedly been cultured, without proof that they are causally involved. Germ-free rats fail to develop keratomalacia

when deprived of vitamin A for long periods (43). Experimentally, corneal epithelial damage from alkali burns of the cornea (44) and vitamin A deficiency (45) leads, as does secondary infection, to activation of corneal collagenases and/or other proteases which can result in corneal liquefaction.

Since healing of ulceration and keratomalacia results in a leukoma, adherent leukoma, staphyloma or phthisis bulbi the prevalence of corneal scars and deranged globes among young children has proved useful in estimating the magnitude of blinding xerophthalmia in a community. However, not all corneal scars will have been due to xerophthalmia, and a careful history is important in attempting to arrive at the correct cause of those encountered. In general, bilateral corneal scarring with an onset after the first 2 months of life, especially in an area where xerophthalmia is known to occur, is likely to have been due to vitamin A deficiency. Unilateral scars, especially if mild, can be due to many causes including vitamin A deficiency and despite the history, the diagnosis will often remain in doubt. A history of severe generalized PEM, especially kwashiorkor, or diarrhoea or other severe systemic illness accompanying or immediately preceding onset of the ocular lesion is strong supportive evidence of underlying vitamin A deficiency as the cause.

The role of measles in the etiology of such lesions is presently uncertain. In many areas, especially Africa, measles is a common precipitating event in bilateral corneal destruction. This is usually related to exacerbation of some underlying nutritional deficiency. Whether this deficiency is vitamin A, protein, some other factor or a combination of 2 or more factors remains uncertain.

A large proportion of children with severe corneal destruction, especially that vast majority untouched by health services, will die while, or soon after, becoming blind. This mortality, estimated at between 30-80 per cent, drastically reduces the number of blind children remaining in the population. Had they survived the true prevalence of scars, and the magnitude of the problem estimated thereby, would likely be 3-5 times as great.

Research

The etiology and pathophysiologic processes that result in keratomalacia, and the association between, and mechanism responsible for, measles-related corneal destruction urgently require elucidation.

Posterior segment eye manifestations

Dark adaptation and night blindness

The one specific function known for vitamin A is its participation in the photochemical reactions in the outer segments of rods and cones that is an early event in the transforming of light into optic nerve impulses. When healthy, young adult volunteers were maintained on diets deficient in vitamin A, impairment of visual functions as revealed by measurements of dark adaptation and dark adapted cone thresholds, did not occur for nine months or more and until the serum concentration of vitamin A was approximately 10 ug/100ml (46,47,48). When these subjects were given vitamin A, visual function returned to normal and there was no evidence of permanent impairment.

In areas where vitamin A deficiency is endemic, those most likely to be affected are young children in whom objective testing is impracticable. Pregnant and lactating women not infrequently suffer from night blindness. In these populations, impaired scotopic vision is widely recognised in the community and the language of the region often has phrases to designate the condition (e.g. "night eyes" or "chicken eyes" (chickens have a predominantly cone retina).

A recent study in Indonesia (49) demonstrated that a history of night blindness was as closely correlated with vitamin A deficiency as was the presence of Bitot's spots, and that twice as many children had such a history as had Bitot's spots (Table 4). Less than one-third of the cases with a history of night blindness also had Bitot's spots, while over half of the cases with Bitot's spots had a concomittant history of night blindness (Table 5). A small proportion of children with a positive history for night blindness appeared to have normal scotopic vision by objective assessment. The serum vitamin A levels in these children were just as low as those in cases abnormal by this same criterion, suggesting the mothers' response was more reliable than the crude clinical test employed. The value of a history of night blindness as a screening tool will likely depend upon the care with which the question is presented and answers sought, and with the degree that night blindness is recognised by the community.

Table 4

NIGHTBLINDNESS AND BITOT'S SPOTS AS INDEPENDENT
SCREENING CRITERIA FOR XEROPHTHALMIA (FROM 49)

Clinical Status (1)	N	Mean Serum Vitamin A (ug/d10 (2)	S.E.	Proportion Total Cases Identified
XN	273	13.4	0.35	84%
XIB	132	12.6	0.46	41%
XN and/or XIB	325	13.4	0.31	100%

- (1) XN includes cases with and without conjunctival xerosis (XIA), Bitot's spots, or XIB. XIB includes cases with and without nightblindness.
- (2) Serum vitamin A values were not available on 3 of 273 cases of night blindness (XN), 2 of 132 cases of conjunctival xerosis with Bitot's spots (XIB) and 4 of 325 cases with either.

Table 5

SERUM VITAMIN A LEVELS BY CLINICAL STATUS (FROM 49)

Clinical Status (i)	N	Mean (ug/dl)	Deficient (0-9ug/dl)	Percent of Individuals	
				Low (10-19ug/dl)	Adequate (≥20ug/dl)
XN(+), XIB(-)	174	13.9	27	55	18
Controls	161	17.6			
XN(-), XIB(+)	51	13.4	31	57	12
Controls	45	17.1			
XN(+), XIB(+)	79	12.1	38	53	9
Controls	76	18.3			
R Random Sample	268	20.0	9	38	53

- (1) XN = night blindness; XIB = conjunctival xerosis with Bitot's spot;
 XN(+), XIB(+) = XN and XIB coexistent in the same child.

Direct measurement of dark adaptation and dark adapted cone thresholds is not practical in these young children but simple, less quantitative methods for impaired scotopic vision can be devised, such as playing games in which the subjects find objects or their mothers in a dimly lit room (50).

Color Vision

Over many years anecdotal accounts have suggested that vitamin A deficiency is accompanied by disturbances of color vision, yet when patients were tested with conventional methods such as Ishihara plates there was little evidence of abnormality (51). Several studies of adult patients with vitamin A deficiency have shown that the ability to distinguish colors of low saturation is impaired (52,53,54).

In a preliminary trial, children (age 4-7) were asked to pick out the differently colored objects in a series of pictures. Failure to find the correct object correlated with other evidence of vitamin A deficiency (55). These results suggest that a graded series of colored plates might be developed to find the threshold of hue discrimination and indicate vitamin A deficiency with good specificity and sensitivity.

Experience with a few cases indicates that genetically determined mild anomalies of red-green color vision do not interfere with hue discrimination in the yellow-orange regions of the spectrum (55).

Other tests

Other retinal functions can be measured and shown to be impaired at various stages of vitamin A depletion but most of these are unlikely to be useful in clinical situations because they are deranged late in the course of depletion or require elaborate apparatus and complex techniques for standardization of test conditions.

For example, the electroretinogram is grossly reduced in late stages of vitamin A depletion in younger children but not in older children. The more subtle alterations, found in the earlier stages, are difficult to reproduce consistently (56). Similar considerations apply to the elevation of dark adapted cone thresholds (46), fundus reflectometry (57), measurement of the visual fields of the dark adapted eye (46), and changes in the electro-oculogram (58). Form sense and visual acuity are not affected before other signs are obvious.

Xerophthalmia fundus

Lesions of the posterior segment in vitamin A deficiency have been reported rarely and only after the deficiency is prolonged. The lesions are described as white spots scattered over the fundus (59,60,61). In all subjects the white spots disappeared after repletion with vitamin A. In one case (62) fluorescein retinal angiography showed small window defects corresponding to the white lesions, indicating that these probably represent areas of depigmentation of the retinal pigment/epithelium. The post repletion angiogram showed persistence of some of the window defects.

Differential diagnosis

Each of the posterior segment manifestations of vitamin A deficiency can be mimicked by certain congenital or acquired retinal dystrophies and degenerations. For example, retinitis pigmentosa and other tapeto-retinal degenerations have profound disturbances of the electroretinogram which usually precede severe night blindness.

Various forms of genetically determined color blindness and early senile macular degeneration produce defects of color discrimination but not impairment of dark adaptation. Congenital stationary night blindness has as its only manifestation absence of the scotopic phase of dark adaptation. Leber's congenital amaurosis has severe impairment of visual acuity and absent electroretinogram. Fundus flavimaculatus and fundus punctata albescens mimic the white spots in the fundus. In endemic areas for vitamin A deficiency all of these lesions are rare.

In all of these diseases having night blindness, the condition develops slowly over many years or is present from birth. Sudden onset of night blindness in a child is almost pathognomonic of severe vitamin A deficiency.

Each of the confounding conditions will not be influenced by treatment with vitamin A and restoration of normal function following vitamin A therapy confirms the diagnosis of vitamin A deficiency.

Research

Development of game playing and other appropriate procedures for measuring dark adapted scotopic thresholds in children.

Conducting of night blindness surveys to determine their sensitivity and specificity for detecting clusters of vitamin A deficient subjects.

Development of game playing and other appropriate procedures for measuring thresholds of hue discrimination and determination of the best spectral and color difference ranges, for detection of early vitamin A deficiency.

Manifestations other than those affecting the eye

Growth and development

In experimental animals lack of adequate amounts of vitamin A results in complete cessation of growth in early deficiency. This results from a reduction of food intake due to anorexia (63). In children lack of growth is suspected to be associated with vitamin A deficiency. In both experimental animals and in children an insufficient intake of energy, protein or other essential nutrients may also result in cessation of growth. Infections and infestations also impair growth and their common occurrence, together with other deficiencies, in the child with inadequate vitamin A status, has hitherto precluded the demonstration of the effect.

Skin

The response of the integument to vitamin A deficiency is quite different in adults and in children. A common lesion accompanying vitamin A deficiency in adults is follicular hyperkeratosis and may be preceded or accompanied by acne (46,47). Both lesions are most prevalent in areas of skin containing many sebaceous glands and subject to exposure and local trauma. This lesion is uncommon in pre-school children.

Follicular hyperkeratosis is not specific to vitamin A deficiency and has also been attributed to starvation, low fat intake in general or essential fatty acid in particular, and vitamin B complex deficiency.

Sensation

Deficiency of vitamin A has been shown to cause metaplastic changes in the vestibular apparatus in the guinea pig (65) and may be responsible for the late sign called 'twisting' (63). Impairment of vestibular balance has been reported in children and adults and abnormalities of the electronystagmogram in adults (Hodges, personal communication).

Abnormalities of taste and smell have been found in animals made deficient in vitamin A (64). These perversions of sensory function, although probably of late onset, have been considered as possible contributors to the decreased food intake that occurs in association with deficiency of vitamin A.

Hematopoiesis and plasma volume

Vitamin A deficiency was first identified as a cause of anemia by Wolbach (66) and has since been both confirmed and refuted. In fact, some investigations described polycythemia as a manifestation of this deficiency (67). Additional studies in animals have shown that a rapid onset of deficiency of vitamin A can lead to severe anorexia, with diminished water intake following shortly afterwards (63), leading to reduction in the plasma volume (68). This, of course, may mask the presence of anemia. Preliminary studies have shown that vitamin A deficient children may have an aversion to water (55). The anemia of vitamin A deficiency is accompanied by hepoferremia which is not responsive to oral iron, despite a normal rate of iron absorption. There is an abnormal deposition of iron in the liver and spleen accompanied by low levels of iron in the circulation (68).

Resistance to infection

Lack of vitamin A has long been associated with an increased susceptibility to infections, especially of the respiratory tract and the digestive tract. Immune mechanisms become impaired, mechanical barriers disintegrate and a state of cachexia develops. Antibody synthesis is diminished (69) and cell-mediated immunity is impaired (70). Loss of epithelial cilia and of mucus secretions favors the penetration of micro-organisms into the respiratory and digestive tract tissues. General inanition is thought to favor the growth of pathogenic organisms and to impair the host defences against infection.

Reproduction

In experimental animals, deficiency of vitamin A has an adverse effect on reproduction. This is most apparent in females in whom severe deficiency prevents conception, moderate deficiency causes abortion or resorption of a litter, and milder deficiency may cause teratogenic effects. Few studies of male responses to deficiency are available but the effects are generally adverse (71).

Cerebro-spinal fluid pressure

In animals changes in the choroid plexus lead to impaired absorption of cerebro-spinal fluid and rise in intracranial pressure (72). In fetal rabbits this results in hydrocephalus (73).

Research

Additional information in the area of sensory perception offers the possibility that with a better understanding of the mechanisms involved, some of these tests could be used diagnostically to assess vitamin A status. Further investigation is warranted to determine whether or not vitamin A functions in the physiologic processes that make possible the perception of pain, thermal, deep pressure and other sensations.

The common occurrence of infectious diseases in association with vitamin A deficiency and their important contribution to a fatal outcome, point to the need for a better understanding of the role of vitamin A in immune mechanisms and of the possible value of vitamin A in the prevention and treatment of infectious diseases under these circumstances.

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