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VITAMIN A DEFICIENCY AND XEROPHTHALMIA

Report of a Joint WHO/USAID Meeting

WORLD HEALTH ORGANIZATION

GENEVA

1976

" Never, whilst memory lasts, can one obliterate the mental pictures of those pitiful little bundles of marasmic, apathetic humanity, lying in the arms of gaunt women, on whose faces and forms famine had laid its devastating hands. Their faint, feeble, fretful wails ring still in one's ears to-day, summoning up visions of wasted stick-like limbs, of distended abdomens, of dry, inelastic, scurfy, scaly skins, of hair scanty, brittle and dry, and of sightless desiccated eyes... "

R. H. Elliot

Tropical ophthalmology, London, Oxford Medical Publications, 1920, chapter 6, p. 78

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VITAMIN A DEFICIENCY AND XEROPHTHALMIA

Report of a Joint WHO/USAID Meeting

A Meeting on Vitamin A Deficiency and Xerophthalmia was convened jointly by WHO and USAID in Jakarta from 25 to 29 November 1974 at the invitation of the Government of the Republic of Indonesia. The purpose of the meeting was to discuss priorities for research and action programmes. The following questions were considered:

(1) What should be the objective of an action programme—control of vitamin A deficiency or prevention of blindness?

(2) What should be the criteria for instituting a regional or national programme of action?

(3) How can vitamin A programmes be evaluated and monitored?

(4) What research is needed?

In attempting to answer these questions the Meeting reviewed modern concepts of vitamin A nutrition and made a number of recommendations concerning assessment of vitamin A status and the feasibility of various preventive measures. In addition, a protocol was developed for treatment of emergency cases of xerophthalmia.

1. INTRODUCTION

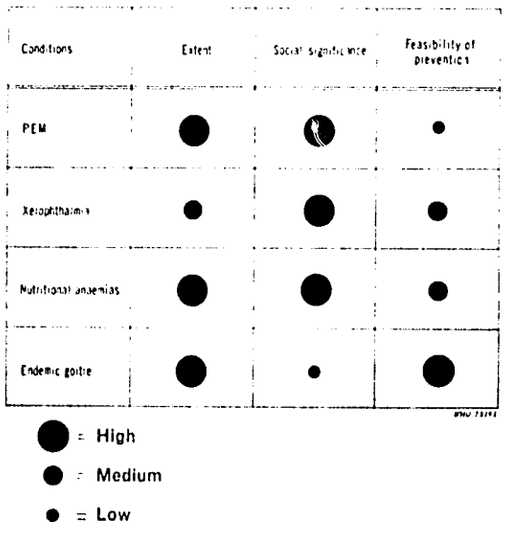
Vitamin A is a necessary nutrient for man and animals. In the absence of an adequate dietary intake of vitamin A, or of its carotenoid precursors, for a significant period, a number of abnormalities appear in experimental animals. These include loss of appetite, loss of weight, increased keratinization of epithelial tissues, a reduced frequency of mucus-secreting cells, and negative nitrogen balance. As the deficiency becomes progressively more severe stomach emptying becomes defective, nervous disorders of balance and motor skills appear, and night blindness, eye lesions, and then blindness occur. Resistance to infection is much reduced and the reproductive process is disrupted. Death ultimately ensues.

In man, and particularly in children, vitamin A deficiency most commonly and prominently affects the eyes, both externally by dis-

rupting the epithelia of the cornea and conjunctiva, and internally by lowering the sensitivity of the retina to light. The former condition is known as *xerophthalmia*, and the latter as *night blindness*. In severe vitamin A deficiency blindness can result from ulceration of the cornea, keratomalacia, and corneal opacity. Vitamin A deficiency, usually accompanied by protein-energy malnutrition (PEM), is also closely linked with an increased frequency of infection and with defective immunological defence mechanisms. Although all of the reported effects of vitamin A deficiency in experimental animals have not been confirmed in man, the deficiency does seem to follow the same general pattern in all species studied and ultimately it affects adversely essentially all tissues of the body.

Unfortunately, vitamin A deficiency is not a rare condition in the world, even though scientific knowledge and technological skills could now markedly reduce its prevalence at a relatively modest cost. Because of the possible tragic sequelae of the deficiency, the general involvement of the vitamin in the proper functioning of many physiological systems, and the availability of suitable knowledge and methods for attacking the problem, WHO has given high priority in its action programmes to the elimination of vitamin A deficiency (Fig. 1).

FIG. 1. PRIORITIES AMONG NUTRITIONAL CONDITIONS [a]



[a] See WHO Chronicle, 26: 160 (1972)

1.1 Definitions

Vitamin A malnutrition can be of two kinds—overnutrition, as exemplified by acute or chronic hypervitaminosis A, and undernutrition, which is termed hypovitaminosis A or vitamin A deficiency. Whereas hypervitaminosis A, which is almost invariably caused by the inappropriate ingestion of large pharmacological doses of vitamin A, is relatively rare, vitamin A deficiency is fairly common, particularly among poor children in developing countries. The nutritional wellbeing of an individual with respect to vitamin A can be expressed in terms of his *vitamin A status*, which can vary from *excessive* (hypervitaminosis) through *acceptable* and *marginal* to *poor* (hypovitaminosis) (see Table 1).

TABLE 1. VITAMIN A STATUS OF INDIVIDUALS

Category	Clinical signs	Biochemical, dietary, and biophysical indicators
Poor	Xerophthalmia including night blindness; common association with PEM and infection	Low plasma vitamin A levels; very low liver stores of vitamin A; impaired dark adaptation; very low dietary intake of carotene and vitamin A
Marginal	None	Inadequate liver reserves of vitamin A; low to normal plasma vitamin A; low dietary intake of carotene and vitamin A
Acceptable	None	Normal plasma and liver concentrations of vitamin A; adequate dietary intake of carotene and vitamin A
Excessive	Headache, vomiting, restlessness, bulging of fontanelle in infants	Abnormally high plasma vitamin A levels; ingestion of excessively large doses of vitamin A, either acutely or chronically

Each category has signs or criteria by which it is characterized. Particular attention is given in this report to marginal and poor vitamin A status.

An *acceptable* vitamin A status is defined in terms of a *protection period*. This is the period of time during which an individual might function normally on a vitamin-A-deficient diet without showing any signs of vitamin A deficiency. Since liver reserves normally represent 90% or more of total body reserves of vitamin A, the liver concentration of vitamin A generally correlates with various periods of protection for various age groups.

Marginal status is defined by the following conditions: (1) inadequate liver reserves to provide a minimally acceptable protection period, and (2) the absence of clinical signs of vitamin A deficiency.

Poor status is a state of deficiency characterized by a series of clinical, biochemical, and biophysical signs of increasing severity. Biochemical signs of *poor* status primarily include markedly depressed concentrations of vitamin A in the plasma and liver. The only biophysical sign of vitamin A deficiency that has hitherto been employed is impaired dark adaptation.

Xerophthalmia literally means "dry eye" and in this restricted sense is a term used exclusively by ophthalmologists to describe the changes in the eye that occur when the secretions of the paraocular glands or of the goblet cells of the conjunctiva dry up, leading to discontinuity of the fluid films usually present over the surface of the conjunctiva and cornea. This desiccation may result from a variety of clinical conditions, but the xerosis or dryness consequent upon vitamin A deficiency is by far the most common and important cause. In a broader sense, and in a public health context, the term xerophthalmia was chosen to apply to the syndrome of severe vitamin A deficiency (*1*).

The importance of xerophthalmia is stressed in this report, not only because of its extensive use in the past for describing poor vitamin A status but also because of its direct relation to the most tragic sequel of hypovitaminosis A—namely, blindness.

1.2 Significance

In its relationship to the health of a population a disease may be considered from four main points of view and its significance thereby assessed. These points are: (1) severity, (2) duration of morbidity, (3) mortality, and (4) prevalence. On all four counts vitamin A deficiency may be considered to have great public health significance and to merit very high priority.

1.2.1 *Severity*

Blindness, either partial or complete and usually irreversible, is the frequent outcome of xerophthalmia. The seriousness of this condition to the individual, to his parents and other close relatives, and to the community at large is self-evident. The social and economic consequences require careful consideration by all those responsible for the welfare of the handicapped. In many developing countries xerophthalmia is the most common single cause of blindness in infants and preschool-age children.

1.2.2 *Duration of morbidity*

Blindness due to xerophthalmia almost invariably occurs in early childhood, resulting in the disability of individuals and placing a heavy burden on society.

Available data suggest that about 25% of the survivors of severe xerophthalmia (X3A + 3B ; see p. 17) remain totally blind, about 50–60% are partially blind, and only 15–25% escape with unimpaired sight. These figures can be considerably improved by adequate treatment.

Estimates of the total annual number of cases of blindness resulting from xerophthalmia are almost impossible to make because of the paucity of reliable data. A figure of about 20 000 was originally suggested by McLaren (*2*) and this was raised to 100 000 several years later on the basis of further evidence. However, this estimate needs to be confirmed.

1.2.3 *Mortality*

Vitamin A deficiency is associated with high mortality ; although it is rarely the sole cause of death in man, it is an important contributory cause when present.

Most of the deaths associated with xerophthalmia occur in infants and children in the second year of life. In Denmark during the First World War the fatality rate was 24% (*3*) ; several reports from Indonesia quote rates of about 35%. McLaren et al. (*4*) reported a xerophthalmia fatality rate of 60% in Jordan, but in the same hospital in children who had equally severe PEM but no eye lesions the rate was only 15%. In a short-term follow-up study in Jordan of children with severe PEM but no eye lesions McLaren et al. (*5*) found a significantly lower plasma vitamin A level in those who died than in the survivors. In Surabaya, Indonesia, a follow-up study of discharged severe xerophthalmia patients at home showed that about 40% had died within a few years (*6*). Infections and general malnutrition may have contributed to this high fatality rate.

1.2.4 *Prevalence*

Vitamin A deficiency is widely prevalent in the densely populated countries of southern and eastern Asia and also in parts of Africa, the Middle East, and Latin America.

Experimental work in animals has shown that congenital malformations, low birth weight, retardation of physical and mental development,

and increased susceptibility to infections can all be attributed to vitamin A deficiency (*7*). Such clear-cut relationships have not been established in man.

2. VITAMIN A (RETINOL) [a]

In 1913 E. V. McCollum isolated a fat-soluble factor necessary for growth and the prevention of xerophthalmia in rats and he achieved full separation of vitamins A and D in 1922. β-carotene was shown by Steenbock in 1919–20 to have vitamin A activity. The standard work on vitamin A (*7*) provides details of the various discoveries in this field. The literature has been reviewed more recently by Olson (*8*), Wasserman & Corradino (*9*), De Luca & Suttie (*10*), and Underwood (*11*).

2.1 Chemistry

Retinol is a fat-soluble unsaturated isoprenoid alcohol ($C_{20}H_{30}O$) with five conjugated all-*trans* double bonds. The integrity of the basic carbon skeleton appears to be essential for specific biological activity. The position and number of conjugated double bonds in the basic carbon skeleton cannot be altered without considerable loss of biopotency. *Cis* isomers are less active than all-*trans* isomers. Derivatives with functional groups other than an alcohol group appear to depend for their activity in most cases on the ease with which they are converted to the parent compound. Affinity for retinol binding protein appears to be another measure of functional activity.

2.2 Units

Vitamin A in the human diet is derived from preformed vitamin A (retinol) and from provitamin A carotenoids. Of the latter, β-carotene

[a] In keeping with the usual practice, the term " vitamin A " is used here to refer to all substances of related chemical structure, excluding carotenoids and other compounds with significantly more than 20 carbon atoms, that have the same biological activity as retinol. Specific members of the group are referred to by their accepted chemical names—namely, retinol for vitamin A alcohol, retinal for vitamin A aldehyde, and retinoic acid for vitamin A acid. The term " provitamin A " is used to refer to all carotenoids and related compounds such as the β-apo-carotenals that are converted into vitamin A and consequently show the same biological activity. Specific members of the group are referred to by their accepted chemical names, e.g., α-carotene, β-carotene, etc.

has the highest vitamin A activity and is the most plentiful in human foods. Provitamin A carotenoids are active only after being converted into retinol during, or subsequent to, absorption through the intestinal wall. Because of the considerably poorer utilization of dietary provitamins as compared with retinol, the expression of the total vitamin A activity of a diet has to be qualified by indicating the percentages of the activity coming from retinol and from provitamins. Vitamin A activity in foods is expressed in international units (IU), 1 IU being equivalent to 0.3 μg of retinol, 0.344 μg retinyl acetate, 0.55 μg of retinyl palmitate, 0.6 μg of β-carotene, or 1.2 μg of provitamin A carotenoids other than β-carotene.

2.3 Dietary sources

Dietary sources of vitamin A are of two kinds : preformed vitamin A from animal sources, liver being a particularly rich source, and provitamin carotenoids from many plants (*12*). Major sources are α-, β-, and γ- carotenes and several related compounds. Dark green leafy vegetables and red palm oil are good sources of the α- and β-carotenes.

2.4 Requirements

Human vitamin A requirements have been considered by an FAO/WHO Expert Group (*13*) and were more recently reviewed by Rodriguez & Irwin (*14*). The recommended daily intakes in terms of retinol vary from 65 μg (195 IU) per kg of body weight in children aged 4 months to 12 μg (36 IU) per kg in adults. Adjustments have to be made in these amounts when, as is invariably the case, some retinol is obtained from precursors of plant origin. The report of the FAO/WHO Expert Group includes a method for calculating the vitamin A value of a diet based on the assumption that the utilization of β-carotene present in plant material is almost one-sixth that of retinol and the utilization of other provitamins is almost half that of β-carotene. Thus 1 μg of β-carotene in plant material is equivalent in biological value to only 0.167 μg of retinol.

2.5 Metabolism and function

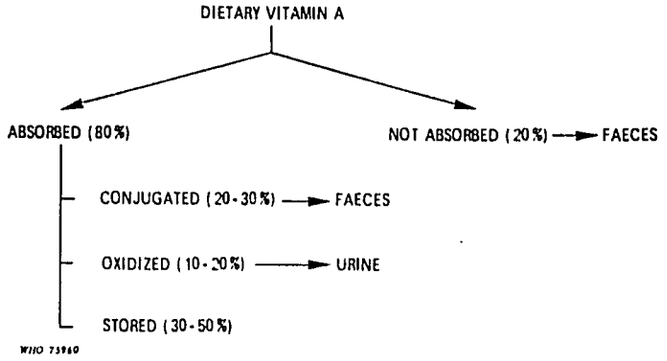
The metabolism and function of vitamin A in vertebrates have been frequently reviewed. Salient points are as follows : vitamin A is present in food mainly as the palmitate ester. In the upper small intestine the ester is largely hydrolysed to the free alcohol by a hydrolase in the pan-

creatic juice in the presence of bile salts. Together with the products of fat digestion, retinol is emulsified by bile salts and phospholipids and ultimately converted into a micellar form suitable for absorption. Under normal conditions over 90% of ingested vitamin A is absorbed, and the efficiency of absorption decreases only slowly as the dose increases. Being less polar than vitamin A, β-carotene is solubilized less well by surface-active agents, including the bile salts, and the chemical nature of the bile salt strongly affects micellization. However, under normal conditions β-carotene is reasonably well absorbed (about 70%) although the efficiency of absorption falls rapidly as the dose increases. Any condition that upsets intestinal function, such as reduced secretion of pancreatic juice or bile or impaired epithelial cell activity, will adversely affect the absorption of vitamin A and carotenoids but even when there is fairly drastic disruption of intestinal function some vitamin A is absorbed.

β-carotene is converted into retinaldehyde at a fairly slow rate by a soluble enzyme, termed " β-carotene dioxygenase ", in the intestinal mucosa (*15*, *16*). In protein deficiency the activity of this enzyme is significantly reduced Within epithelial cells of the gut, retinaldehyde is largely reduced to retinol (*17*), which is re-esterified mainly with palmitic acid and incorporated into chylomicra. The latter are transported via the lymph into the blood stream and are ultimately taken up mainly by the liver and stored for the most part as palmitate in fat-containing cells known as lipocytes—not in reticulo-endothelial Kupffer cells as was previously supposed (*18*). Both uptake and storage are efficient and relatively unaffected by the size of the dose of vitamin A. Rather surprisingly, little is known about the biochemical events involved in storage and mobilization of retinol. Retinyl ester released from the chylomicra may be hydrolysed and then re-esterified in the endoplasmic reticulum by an energy-independent process or it may be directly incorporated into low-density lipoprotein of liver cells. The vitamin-A-containing lipoprotein has not been well characterized, and the physiological signals for incorporation into, or release from, this low density lipoprotein have not been defined.

Of a dose of vitamin A given orally in oil or in an aqueous dispersion, or given intramuscularly in an aqueous dispersion, 30–50% is usually stored in the liver, although a larger or smaller proportion may be stored under special circumstances (Fig. 2). Two major reactions compete for the remainder : (1) conjugation of retinol and of retinoic acid with glucuronic acid in the liver followed by excretion of the conjugate in the bile and then into the faeces, and (2) metabolism of retinol and

FIG. 2. UTILIZATION OF DIETARY VITAMIN A



retinoic acid mainly in the liver and kidney, followed by excretion of the degradation products in the urine. Within a week after dosing, most of the retinol that is not stored is eliminated via these two routes. In several species of vertebrate retinyl ester stored in the liver is released by a first order process with a half-life of roughly 50 days in young growing animals and a much longer half-life in adult animals. The rate of utilization of vitamin A is much more rapid in vitamin-E-deprived animals than in normal animals or in vitamin-E-deprived animals treated with vitamin E (*19*). Since other chemical antioxidants did not replace vitamin E in maintaining liver stores of vitamin A, this effect is not solely due to the protection of vitamin A from oxidation (*20*).

During its mobilization from the liver, retinyl ester is hydrolysed to retinol, which then associates, probably in the Golgi apparatus, with a specific protein termed " retinol binding protein " (RBP). RBP is synthesized in the liver, and is released into the plasma only as a retinol RBP complex (*21*). In vitamin A deficiency release of RBP is inhibited and the concentration of apo-RBP in the liver rises, while plasma retinol and RBP levels both fall.

Alternatively, RBP synthesis is depressed in protein deficiency and consequently the steady state levels of RBP and of retinol in the plasma is reduced (*22*). Retinol (about 40–60 μg/100 ml) and RBP (about 40–60 μg/ml) are normally found in approximately equimolar concentrations in plasma. In the plasma the RBP–retinol complex is largely associated with an acidic protein called " tryptophan-rich prealbumin " (TRPA). The free RBP–retinol complex, having a half-life of about 3–5 hours, turns over very rapidly in the plasma ; combination with TRPA increases its half-life to 11–16 hours. RBP is degraded mainly in

the kidney. Under normal conditions the plasma concentration of vitamin A is largely controlled by the finely balanced interaction of RBP synthesis, release, and degradation.

RBP carries retinol from the liver to various organs. Interestingly, the biological activity of a series of methylated derivatives of retinol correlates well with their ability to saturate RBP but not with any other physiological parameter (Table 2). The functional form of vitamin A,

TABLE 2. RELATION OF BIOLOGICAL ACTIVITY OF RETINOL TO THE SATURATION OF RBP [a]

Compound	Dosage for		Bioactivity in growth (%)
	Saturation (μg)	Half saturation (μg)	
Retinol	10	3	100
Methyl retinol	100	30	16
Methyl retinone	150	45	5
Dimethyl retinol	1 000	300	0.3

[a] Tosukhowong & Olson, J. A., unpublished observations.

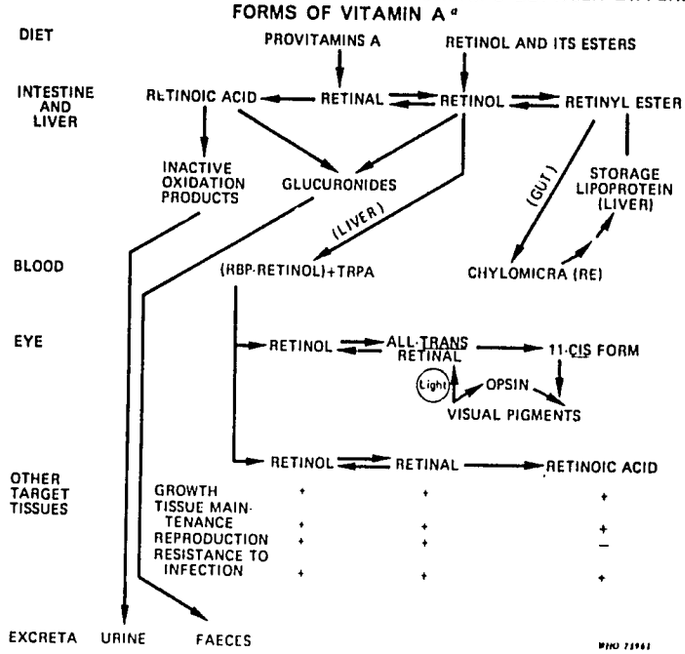
other than retinol, is still unknown. Fig. 3 is a simplified diagram of the relationships between the different forms of vitamin A found in the body.

Both acute and chronic forms of hypervitaminosis A occur (*7*). The mechanisms of the two forms appear to be different, for while an acute fatal form in previously healthy animals was associated by McLaren et al. (*23*) with high circulating levels of retinol, much of which was probably in the free form, the levels of the alcohol were in the normal range in animals with subacute and chronic hypervitaminosis A, although ester values were very high (D.S. McLaren, unpublished observations).

Free retinol, but not the retinol–RBP complex (*24*) is membrane-active and causes the rapid release of bound hydrolases from lysosomal particles, leaving the vitamin A-treated lysosomes intact (*25*).

Only one function of vitamin A has been well defined biochemically—namely, its interaction with various opsins of the retina to form visual pigments. On exposure to light, the 11-*cis* form of retinaldehyde is isomerized to the all-*trans* form, which in turn triggers off a series of chromophoric changes in the complex. Concomitantly, ion transport and membrane potentials are affected. The latter may well give rise to nerve impulses that are sensed in the brain as vision. In plants caro-

FIG. 3. METABOLIC AND FUNCTIONAL RELATIONSHIPS BETWEEN DIFFERENT FORMS OF VITAMIN A [a]



[a] RBP, plasma retinol binding protein; RE, retinyl ester; TRPA, tryptophan-rich prealbumin.

tenoids are closely associated with light-sensing and photosynthesizing organelles.

Retinoic acid, a metabolite of vitamin A, supports normal growth and tissue maintenance, but in animals receiving it as the only form of the vitamin retinal function is lost (*26*) and sterility occurs (*27*).

Vitamin A seems to control in some cases the differentiation of epithelial tissues, particularly of the skin, trachea, salivary glands, goblet cells of the gut, and the testes. Differentiation is an extremely complex and ill-understood process, and the role of vitamin A in it is even more obscure ; it is therefore difficult to make any generalizations at present. Since mucus production in some tissues tends to decrease and since squamous cells tend to proliferate in vitamin A deficient subjects, epithelial keratinization has been closely associated with vitamin A deficiency. On the other hand, in well controlled cases of rapidly induced vitamin A deficiency some animals die from the deficiency without any significant histological changes in sensitive tissues (*28*). Although reduced mucus secretion and increased keratinization may

not be primary effects of vitamin A deficiency they may still play an important role in the pathogenesis of xerophthalmia. In severe vitamin A deficiency the ducts of mucus secreting glands tend to be obstructed, resulting in a lower mucus concentration in the tears. Since mucus serves as a wetting agent under normal conditions and thereby preserves a tear film over the cornea, tear fluid that is deficient in mucus allows dry spots to form. This leads to epithelial cell injury as well as to reduced resistance to bacterial invasion.

The interrelationship of vitamin A deficiency and infection has long been known. Recent experiments have shown that under highly controlled conditions of rapidly induced vitamin A deficiency germ-free rats survive much longer than control rats. In experimental animals such effects can be specifically attributed to vitamin A deficiency, but the situation is much more complex in man. Experimental work suggests a probable role for vitamin A in the immune processes of the body. Retinol appears to be the only naturally occurring enhancer of the humoral immune response yet discovered (*30*) and has been shown to suppress induced tolerance (*31*). Vitamin A deficient chickens developed marked depletion of lymphocyte and plasma cell populations (*32*).

An early and universal sign of vitamin A deficiency in experimental animals is loss of appetite (*33*). Appetite is not restored by hypothalamic surgery, which normally produces hyperphagic animals, or by other procedures. Although the mechanism by which vitamin A controls appetite is not defined, changes in plasma amino acid patterns occur in vitamin A deficiency. These are similar to the changes that reduce food intake in rats with amino acid imbalance (*34*). In a practical sense, reduced food intake and increased susceptibility to infection act synergistically in impairing the nutritional state of the individual.

3. METHODS OF ASSESSMENT OF VITAMIN A STATUS

Methods available at present for assessing vitamin A status are (1) clinical, (2) biochemical, and (3) dietary. It is evident, however, that the results obtained from such studies have relevance for action programmes only if they are considered together with data relating to the causative factors in the particular environment concerned. Factors of a general nature, such as poverty, ignorance, poor living conditions, and large family size may be helpful in identifying children who are " at risk " in situations where xerophthalmia is known to occur with some frequency (*35*, *36*).

3.1 Clinical assessment

Vitamin A deficiency in experimental animals affects the whole body, producing retardation of growth and development and affecting many structures, in particular tissues of ectodermal origin, the epithelial surfaces of certain organs, and parts of the nervous system and its extensions such as the retina. However, most of these changes have not yet been demonstrated in man, are not specific in nature, and cannot be used for purposes of clinical assessment. Mention should be made here of the skin change known as " perifollicular hyperkeratosis " (also called " hyperfollicular keratosis ", " phrynoderma ", or " toad skin "). In the 1930s this lesion was associated with vitamin A deficiency in reports from Ceylon, China, and East Africa. Later studies in India showed a response to linoleic acid. In vitamin A deprivation studies in human adults in the United Kingdom (Sheffield) (*37*) and the USA (*38*) the heaping up of keratinized material around hair follicles was observed. This lesion is not specific to vitamin A or fatty acid deficiency, being a common feature of general inanition. Perifollicular hyperkeratosis is rarely seen in very young children, the vulnerable age group for xerophthalmia. Nevertheless, this sign is almost invariably included in the list of those to be looked for in a general-purpose nutritional survey, and is frequently mentioned when vitamin A status is being assessed. Methods of examination have been described by Jelliffe (*39*). Caution should be observed in assessing the significance of the occurrence of perifollicular hyperkeratosis.

3.1.1 *Classification of xerophthalmia*

For many years there has been a need for a classification of xerophthalmia to permit clearer reporting of the various eye changes generally agreed to be characteristic of the condition. The first classification scheme to gain some degree of general acceptance was that proposed by ten Doesschate (*6*), which was based on a scheme commonly used in Indonesia. This classification was subsequently expanded to include also night blindness and corneal sequelae. The classification proposed here for general use is a further modification of these earlier proposals.

Explanatory notes on the classification :

(1) These signs are descriptive rather than diagnostic ; all signs seen at the time of examination are recorded.

(2) In general, a progression of severity is reflected in the classification of primary signs.

(3) The classification can be used in both field surveys and the routine recording of findings in patients in hospitals and clinics.

(4) When tabulating the frequency of these signs each child should be included only once, under his or her most severe sign.

(5) Only those Bitot's spots accompanied by conjunctival xerosis, usually in the 0–5 years age group, are indicative of vitamin A deficiency. This xerosis may be hidden by the overlying foam of the Bitot's spot and revealed only when this is rubbed away.

(6) Secondary signs often occur in association with or result from vitamin A deficiency and should be noted separately.

Classification	*Signs—primary*
X1A	Conjunctival xerosis
X1B	Bitot's spot with conjunctival xerosis
X2	Corneal xerosis
X3A	Corneal ulceration with xerosis
X3B	Keratomalacia
	Signs—secondary
XN	Night blindness
XF	Xerophthalmia fundus
XS	Corneal scars

3.1.2 *Description of the eye lesions*

X1A Conjunctival xerosis (Plate 1A). The changes characteristic of vitamin A deficiency are usually confined to the bulbar conjunctiva but occasionally in long-standing cases the conjunctiva of the lower lid and adjacent lower fornix may be rough and wrinkled. The changes may be generalized throughout the exposed parts of the bulbar conjunctiva or localized to one or more small areas of it. Whatever their extent, the nature of the changes is the same; the characteristics are detailed below. A single characteristic, or even several characteristics together, does not constitute proof of the presence of conjunctival xerosis due to vitamin A deficiency but the presence of most or all of them is highly suggestive of such a diagnosis. This is confirmed by a return to a normal appearance under adequate therapy. Overdiagnosis of conjunctival xerosis, based on the presence of a few and minimal changes only, is a real and common error. Consequently, strict adherence to the principles stated here is most important in accurate diagnosis.

(*a*) Dryness—the literal meaning of " xerosis ". Dryness is judged by lack of the normal lustre or brilliance of the bulbar conjunctiva. The appearance has been likened to that of wax or dry paint.

(*b*) " Unwettability ". This occurs regardless of the presence or absence of tears. Patches of xerosis emerge from their surroundings " like sandbanks at receding tide " when the child stops crying. This probably results from the disruption of the continuity of the preconjunctival film by the xerotic process in the epithelium. Goblet cells play an important part in the formation of conjunctival mucus, and this mucus forms the inner layer of the normal tear film and maintains " wettability ". Goblet cells reappear after treatment (*40*).

(*c*) Loss of transparency. The ability of the conjunctiva to transmit light is impaired, leading to decreased visibility of the conjunctival vessels. The translucent conjunctiva, which normally looks clear (" like an aquarium ") and is crossed by blood vessels, appears milky owing to the presence of fine droplets. Soon, the vascular pattern, apart from the large arterioles, becomes obscured.

(*d*) Thickening. There is a tendency to generalized thickening and stiffness of the conjunctiva.

(*e*) Wrinkling. There are small, more or less vertical, folds in the conjunctiva. These are best demonstrated by rucking up the lose temporal conjunctiva against the outer canthus on maximal lateral movement of the eyeball.

(*f*) Pigmentation. In dark-skinned races there is a fine, diffuse, smoky pigmentation, which should not to be confused with the patchy and coarser pigmentation that is frequently observed in healthy subjects of these races. In prolonged xerosis, the lower fornix first becomes yellowish then light grey, and finally dark brown owing to the presence of chromatophores in the basal cell layer of the epithelium. This characteristic " gutter " pigmentation responds slowly, over a period of weeks or months, to treatment.

The changes are most marked in the exposed interpalpebral fissure. This exemplifies the important role played by the external environment (e.g., dust, smoke, eye infection, and ultraviolet light). These same external factors are probably important also in influencing the corneal changes.

(*g*) Accumulation of debris. In some cases of advanced xerosis debris accumulates on the surface of the bulbar conjunctiva and may

spread on to the adjacent part of the cornea. This material is creamy white, glistening, and non-foamy and it easily becomes detached to lie in the canthi, the lower fornix, or the borders of the eyelids. This is a quite unusual appearance, Bitot's spot being much more common; the material of Bitot's spot adheres more tenaciously to the eye.

It should be stressed that when conjunctival xerosis is the only change suspected to be present in the eye, and all else is judged to be normal, it is impossible by clinical assessment alone to make a firm decision as to whether the eye is normal or abnormal. This has been shown repeatedly by the inability of trained observers to agree on their diagnosis and single observers to be consistent in this respect. It is for this reason that conjunctival xerosis X1A is not recommended as a criterion for community diagnosis (p. 30). Nevertheless, in many studies a high incidence of conjunctival "thickening" or "wrinkling" or "pigmentation" has been used either alone or with biochemical or dietary data to support the contention that a xerophthalmia problem was present.

X1B Bitot's spot (Plate 1B). A Bitot's spot usually has the form of a small plaque with a silvery grey hue and a foamy surface; it is quite superficial and is raised above the general level of the conjuntiva. The spot is more or less readily removed by manipulation of the lids or direct wiping, when a xerotic conjunctival bed with a rough surface is revealed. A Bitot's spot is invariably situated on the bulbar conjunctiva; it is frequently bilateral and temporal and less commonly nasal, and is usually confined to the interpalpebral fissure close to the limbus. The characteristic location of the spot close to the protruding limbus would seem to be explained by the protection of the material there by the restricted wiping movements of the lids. The shape of the spot varies considerably; it is often irregularly circular or oval with the long axis horizontal. The classical triangular form with the base to the limbus is less common. Exceptionally, the following variations may be found. Bitot's spot material may be scattered widely over the conjunctiva, sometimes arranged in vertical corrugations. Not all Bitot's spots are foamy; some have a cheese-like or grease-like surface; some accumulations are quite exuberant rather than flat like a plaque. The significance of these differences in appearance is not known. The spots may be black in children whose eyelids are smeared mascara. If an unusual part of the conjunctiva is permanently exposed, as in strabismus, coloboma of the eyelid, or ectropion, a Bitot's spot may develop in relation to such an area, illustrating the etiological importance of exposure.

Bitot's spot may or may not be associated with generalized conjunctival xerosis (Plate 2A). When an association exists the subjects are usually young children who may also suffer from night blindness. The spots, together with the accompanying generalized xerosis, usually respond to vitamin A therapy. In some parts of the world Bitot's spots are encountered in the absence of generalized xerosis or evidence of retinal dysfunction, usually in older children and adults. These are often minimal lesions ; evidence of vitamin A deficiency may be lacking and patients may not respond to vitamin A therapy (*41*). It is very important to make a distinction between the two types of Bitot's spot. This is done not on a morphological basis, for there is no certain difference, but by taking into account the various factors, ocular and other, that indicate whether or not the spots are due to vitamin A deficiency. It is because the Bitot's spots associated with vitamin A deficiency are almost invariably accompanied by conjunctival xerosis and almost invariably found only in young (preschool) children that these characteristics have been chosen to designate those spots that alone should be included in classification X1B.

It should be stressed that serious eye lesions due to vitamin A deficiency may develop and progress to keratomalacia and blindness without Bitot's spots ever occurring. Bitot's spots are not therefore a stage in the progression of a disease process. They are, rather, a sign or lesion that may occur, and that is known to be associated with vitamin A deficiency.

X2 Corneal xerosis (Plate 2B). This usually follows upon conjunctival xerosis. The corneal surface has a rough, fine " pebbly " appearance and lacks lustre. The breaking up time (BUT) of the tear film is shortened (to less than the normal 10 seconds between the last blink and the occurrence of gaps in the precorneal film). Slit-lamp examination at this stage may reveal an increase of fine pigment in the paralimbal portions of the cornea, although it must be remembered that pigment in this area is common in healthy individuals in dark-skinned races. There may also be a loss of continuity of the surface epithelium and diminished tactile sensitivity. Later, cellular infiltration of the corneal stroma contributes to the intensity of the haziness of the cornea, which frequently has a bluish, milky appearance that is usually most marked in the lower central part. In some cases a cellular exudate is found in the lower part of the anterior chamber. This is called " hypopyon ".

X3A Corneal ulceration with xerosis (Plate 3A). This is the earliest change in which an irreversible element occurs ; there is bound to be

some residual defect, and vision will be affected. " Ulceration " is not an ideal term but it is the best available. Ulceration of the cornea may result, of course, from many causes. It is only the ulceration that accompanies corneal xerosis X2 that is referred to here. It involves loss of substance of a part or of the whole of the corneal thickness. Minimal denudation of the epithelial surface (erosion) without transgression of Bowman's membrane leaves no permanent damage and is not included here. There are only mild signs of reaction or inflammation unless there is accompanying secondary infection ; when the ulcer progresses to advanced stromal loss it may result in descemetocele and complete perforation with iris prolapse.

These lesions are most common in the lower half of the cornea.

X3B Keratomalacia (Plate 3B). This consists of a characteristic softening (colliquative necrosis) of the entire thickness of a part, or more often the whole, of the cornea, invariably leading to deformation or destruction of the eyeball. The process is a rapid one, the corneal structure melting into a cloudy gelatinous mass that may be dead white or dirty yellow in colour. Extrusion of the lens and loss of vitreous may occur. In untreated cases endophthalmitis not infrequently supervenes. Particularly in very young children, keratomalacia may rapidly develop in the absence of the characteristic changes, described earlier, in the conjunctiva. A striking feature of the condition is that it is initially accompanied by very little reaction of the surrounding structures.

From descriptions of the ways in which keratomalacia develops it is clear that considerable stretches of the corneal surface are immediately affected. Sometimes the central origin is stressed ; sometimes the origin is peripheral, crescentic, or quadrant-like. The term " perforation " is often used in keratomalacia. This is an understatement : after malacia, the cornea, or the majority of it, no longer exists. There is apparently no demarcation, as in local destruction, but infection and eventually panophthalmitis are always close at hand.

From time to time there have been suggestions that keratomalacia is not just the final stage of ocular vitamin A deficiency but that for this stage to be reached an additional factor (or factors) is necessary. The two main factors invoked have been protein deficiency and local infection. PEM of both the kwashiorkor and the marasmic types commonly, if not invariably, accompany blinding due to vitamin A deficiency. The general nutritional state of the child degenerates *pari passu* with the ocular manifestations. This should not, however, be taken as evidence that the one is causing the other. In controlled animal

experiments vitamin A deficiency alone can produce keratomalacia although germ-free animals show less severe eye lesions. The two eyes are frequently affected to different degrees, suggesting that local factors probably play a role in keratomalacia.

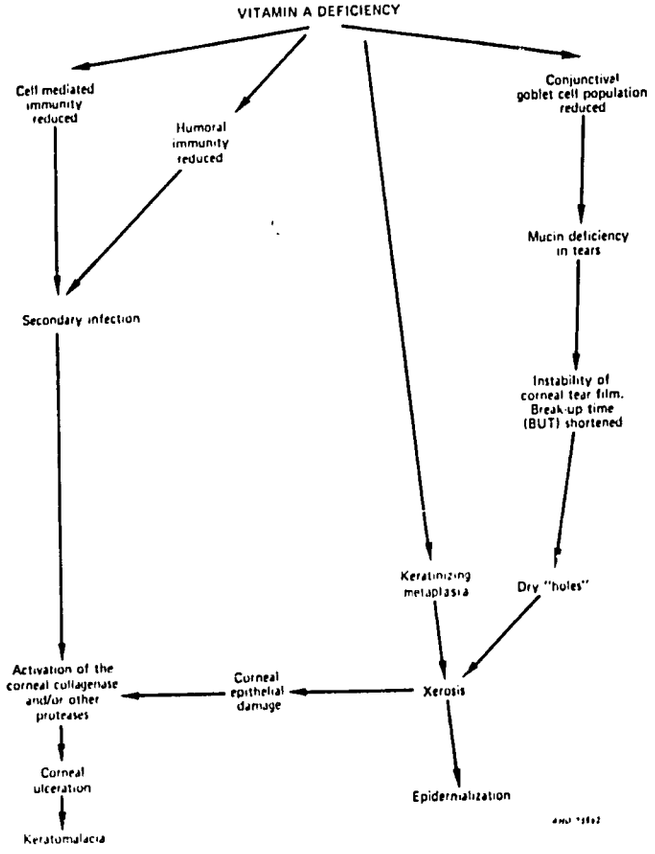
Recent work offers a possible explanation for the changes seen in keratomalacia and also some possibility for improved treatment. Lack of mucus in the tear film owing to vitamin A deficiency will predispose to instability of the film resulting in dryness of the cornea (pp. 16 and 19). This dryness will lead to epithelial damage and corneal ulceration. It has been shown that corneal collagenases can be activated by a variety of corneal diseases associated with corneal ulceration (*42*). Disruption of the integrity of this anatomical barrier may activate the collagenases of the corneal epithelium and stroma and/or invite secondary infection, which would produce corneal damage by direct invasion as well as by activation of the corneal collagenases (Fig. 4).

Signs that may be associated with vitamin A deficiency include those listed as secondary signs in the classification (p. 18) and noted as being of possible additional value. They either lack specificity, are difficult to test for in the vulnerable population group, or have not been widely described.

XN Night blindness. Diminution in the supply of vitamin A to the rod cells of the retina results in impairment of the function of dark adaptation. This may be detected by rod scotometry, dark adaptometry, and electroretinography long before the subject complains of night blindness. Unfortunately, none of these methods is applicable in the susceptible age group, i.e., preschool children, because a cooperative and responsive subject is essential. Also, the methods are not suitable for field studies because expensive and delicate equipment is required. The development of a simple but sensitive objective biophysical test of rod function applicable to all population groups susceptible to vitamin A deficiency would be a distinct advance in measuring the extent of the problem. The presence of night blindness should always suggest the possibility of vitamin A deficiency, but it may also, though rarely, result from non-nutritional causes such as congenital night blindness and retinitis pigmentosa.

In an attempt to detect impaired dark adaptation in young children Friderichsen & Edmund (*43*) measured what they called the " minimum reflexible ", i.e., the reflex irritability of the eye to light. Some adaptation of this procedure might be useful in measuring night blindness in young children.

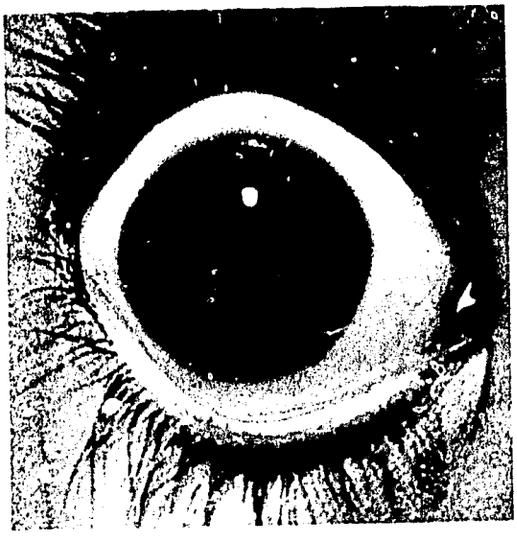
FIG. 4. A POSTULATED MECHANISM FOR THE PATHOGENESIS OF KERATOMALACIA IN VITAMIN A DEFICIENCY [a]



[a] Based on Brown, S. I. et al. (86).

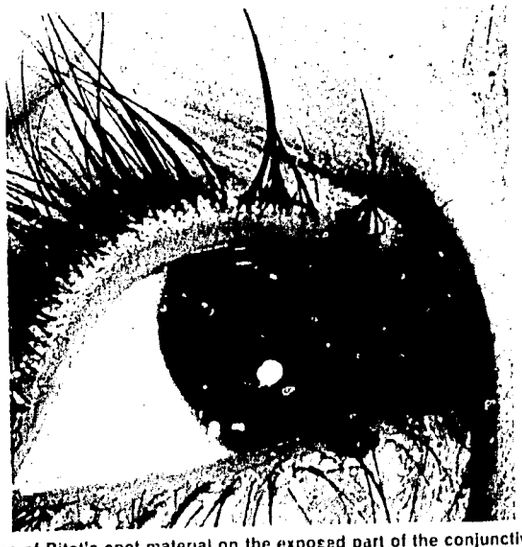
XF Xerophthalmia fundus. This appearance of the fundus (Plate 4A) is usually associated with night blindness, often in school-age children or young adults and it appears to be indicative of a chronic deficiency state (*44*). As the fundus photograph shows, there are usually multiple lesions, sometimes glaring white, scattered profusely along the course of the vessels. When the spots are few in number they tend to have a yellowish appearance and the retina is reddish-brown in colour. The spots may fuse together and are usually seen around the periphery of the fundus, the macula remaining free of spots. Spots are never seen on

A. X1A CONJUNCTIVAL XEROSIS[a]



[a]Conjunctival xerosis in a 4-year-old child (Case No. 18121). Wrinkling and dryness can be seen in the lower part of the bulbar conjunctiva. Note especially that xerosis is not a conspicuous change, it is difficult to observe and to reproduce photographically. Plasma vitamin A: 9 μg/100 ml; liver vitamin A: 10 μg/g. Reproduced by courtesy of Dr D. S. McLaren.

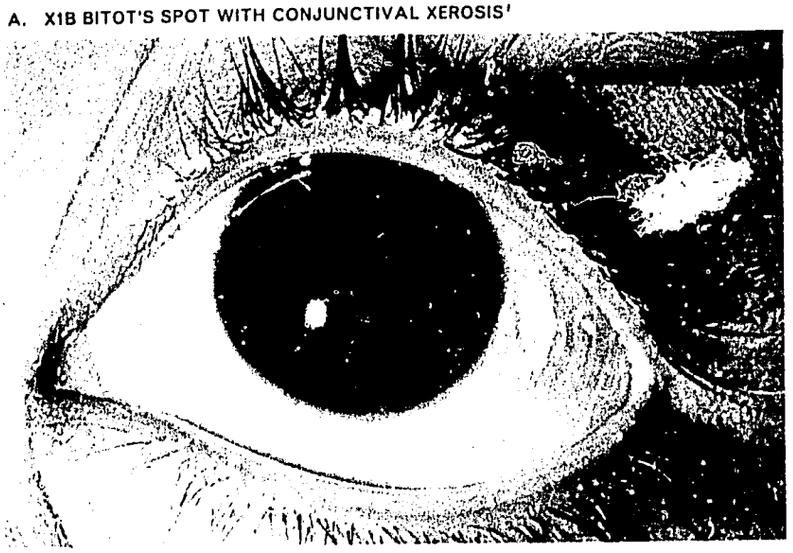
B. X1B BITOT'S SPOT[a]



[a]Numerous flakes of Bitot's spot material on the exposed part of the conjunctiva in a child aged 2 years (Case No. 15127). Plasma vitamin A: 8 μg/100 ml. It is important to be able to identify the less pronounced type of lesion shown here. For more classical examples see McLaren et al (1) Reproduced by courtesy of Dr D. S. McLaren.

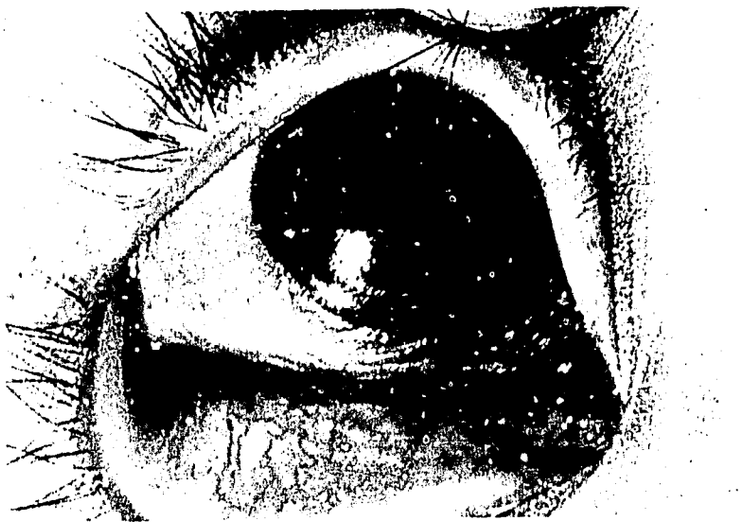
PLATE 2

A. X1B BITOT'S SPOT WITH CONJUNCTIVAL XEROSIS[1]



[a]Early Bitot's spot, the foam covering a patch of mild conjunctival xerosis. Five-year-old Indonesian boy with a 6-month history of night blindness. Reproduced by courtesy of Dr A. Sommer.

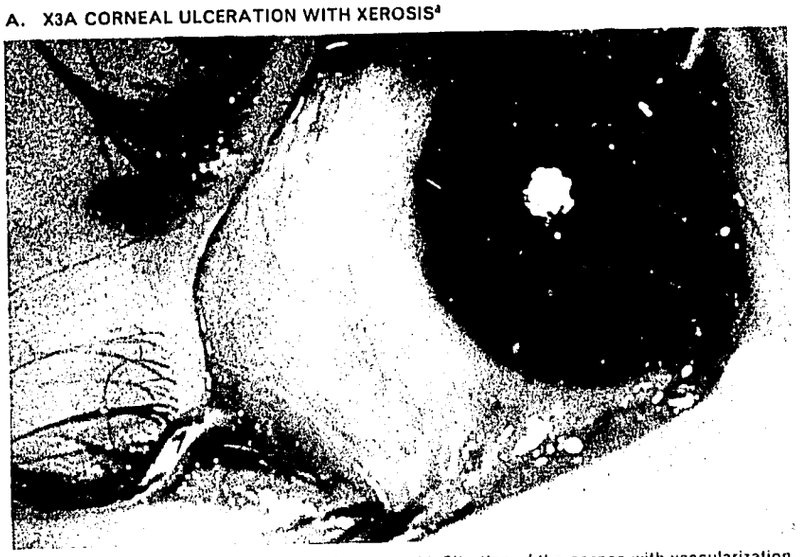
B. X2 CONJUNCTIVAL AND CORNEAL XEROSIS[1]



[a]Conjunctival and early corneal xerosis in a 2-year-old Indonesian boy. Both the conjunctiva and cornea have a coarse, dry, granular appearance in place of their normally smooth, shiny lustre. Reproduced by courtesy of Dr A. Sommer.

PLATE 3

A. X3A CORNEAL ULCERATION WITH XEROSIS[a]



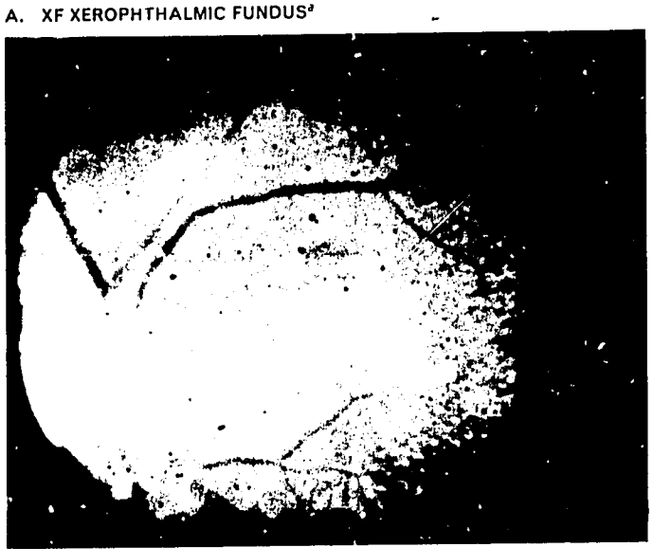
[a]Marked conjunctival thickening and wrinkling and infiltration of the cornea with vascularization. Early ulceration is present. Child aged 2 years 3 months (Case No. 15437). Plasma vitamin A: 3 μg/100 ml; liver vitamin A: 0.0 μg/g. For a more pronounced example of X3A, see McLaren et al (*1*). Reproduced by courtesy of Dr D. S. McLaren.

B. X3B KERATOMALACIA[a]

[a]Child aged 14 months with colliquative necrosis affecting the greater part of the cornea (Case No. 17937). The relative sparing of the superior aspect is typical. Plasma vitamin A: 4 μg/100 ml; liver vitamin A: 3 μg/g. Reproduced by courtesy of Dr D. S. McLaren.

PLATE 9

A. XF XEROPHTHALMIC FUNDUS[a]



[a]Fundus photograph showing typical seed-like, raised, whitish lesions scattered rather uniformly over the part of the fundus at the level of the optic disc. Reproduced by courtesy of Dr Teng-Khoen-Hing.

B. XS CORNEAL SCARS[a]

[a]Corneal scars (leucomata) of uncertain nature; their bilateral symmetry in a young malnourished child in an inferior position on the cornea is very suggestive of previous xerophthalmia. Reproduced by courtesy of Dr D. S. McLaren.

top of a vessel, but a vessel may run over them. Both eyes are always affected, but not necessarily to the same degree.

XS Corneal scars (Plate 4B). This is a better term than sequelae because the latter presupposes that corneal scars are definitely known to follow upon xerophthalmia, whereas this is rarely the case. There are many possible causes of corneal scars, but when the clinical picture is compatible with healed corneal ulcer and/or keratomalacia and onset between the ages of 2 months and 5 years seems probable, when there is association with severe generalized malnutrition with or without an acute decompensating event (diarrhoea, tuberculosis, urinary infections, etc.) and when there is no known trauma, prolonged purulent discharge, or severe trachoma, the scars are likely to be the result of vitamin A deficiency. Only these cases should be classified XS.

Corneal scars result from the healing of the irreversible corneal changes mentioned above. Vision is least seriously affected by nebulae and small leucomata situated away from the pupillary area, usually in the lower central part of the cornea. If the iris has prolapsed there will be leucoma adherens with distortion of the pupil. Large, often heavily vascularized and pigmented, total or subtotal leucomata cause loss of vision, fortunately often affecting only one eye with minimal changes in the other.

Keratomalacia, on healing, results in an anterior staphyloma composed of the scarred remnant of the cornea and incorporated elements of the uvea bulging forwards under the influence of the intraocular pressure. If the damaged cornea ruptures rather than bulges then the contents are extruded, and a shrunken globe—phthisis bulbi—is the result.

Other signs. Bitot's spots in adults or older children, which are not included in the xerophthalmia classification, may be sequelae to earlier xerophthalmia, although there is no proof of this. The periorbital skin and that of the lids is sometimes abnormally keratinized, dry, and rough. The pores of the Meibomian glands in the lid margins may be enlarged and protruding. The eyelashes are often long, stiff, and irregular, but this is a common occurrence in PEM without xerophthalmia.

3.2 Biochemical assessment

The process of vitamin A depletion of the body has been studied extensively in both animals and man under carefully controlled experimental conditions. Evidence of deficiency appears more rapidly in

young subjects, in whom initial stores are smaller and requirements relatively greater than in the adult.

Biochemical changes precede the clinical changes, and it is in the hope of achieving early detection of vitamin A deficiency that this approach has been pursued. Since the exact involvement of vitamin A in any specific metabolic function has not been defined, enzymatic tests, which are commonly used for some of the group B vitamins, cannot be employed. Hence, the two most commonly used tests are measurements of vitamin A in the plasma and liver.

3.2.1 *Methods of vitamin A determination*

At present, several methods are in use but none can be described as both simple and sensitive and all are subject to interference from other substances in the blood and liver. In all these methods the initial steps are basically the same. Plasma or serum is separated from a blood sample and the vitamin after being released from carrier protein, usually by treatment with ethanol, is extracted into a fat solvent such as petroleum ether. Similarly, liver samples are usually homogenized, saponified in the presence of ethanol, and then extracted with petroleum ether or other nonpolar solvent. The vitamin A content of the extract is measured by one of three methods : (1) ultraviolet absorption spectrophotometry ; (2) fluorimetry ; (3) colorimetry. Other methods (e.g., infrared and NMR spectrometry) have been described but have not found general acceptance.

Review of the commonly used methods shows clearly that each has its own problems in application and each has inherent errors. Reports of surveys of serum vitamin A levels in different populations show widely different values. This is certainly due in part to a real variation in status, but to what extent the variation is due to the different methods of determination has never been investigated. It has been shown (*45*) that a high carotenoid level can give rise to a falsely low reading for vitamin A when the vitamin is determined colorimetrically with trifluoroacetic acid, and probably also antimony trichloride, as the chromagen. Storage of samples in the presence of air for periods of more than about 2 weeks may result in the formation of an unknown compound that reacts with Lewis acids (such as antimony trichloride and trifluoroacetic acid) (*46*). Liver samples may be stored frozen for long periods without loss of vitamin A activity (*47*). The presence of phytofluene in the blood, which is likely where large quantities of tomatoes are eaten, will almost certainly produce high fluorescence readings.

In recent years it has become apparent that there is a close correlation between plasma levels of vitamin A and of retinol binding protein (RBP). In vitamin A deficiency plasma levels of holo-RBP (i.e., RBP plus retinol) fall and RBP accumulates in the liver, indicating the intimate relationship of RBP with retinol in plasma. Several methods are now available for determination of RBP (*22 82*); one method is fluorimetric, two others employ immunoassay. The immunoassay techniques are relatively simple and reproducibility is about 10%.

3.2.2 *Plasma vitamin A levels*

For circulating nutrients like vitamin A the plasma may be regarded as an extension of the body pool. For many nutrients that are not stored in the body an equilibrium exists for the nutrient between the tissues of the body and the plasma. In such cases the plasma level closely reflects the level in the body as a whole. This is *not* true for vitamin A, which is stored in high concentrations—almost entirely in the liver. Consequently, the plasma concentration reflects the body status only under two very different circumstances.

The first of these circumstances is when the liver stores have been largely depleted. Plasma vitamin A is then in equilibrium with that in the rest of the body, and for a very short period in the depletion process it is a sensitive indicator of deficiency.

The second instance is when the liver has become saturated with vitamin A and is unable to store any more. Then the ingestion of additional vitamin A will raise the plasma level of the vitamin and this will be a sensitive index of increasing hypervitaminosis.

In 1963 the United States Interdepartmental Committee on Nutrition for National Defense (ICNND)[a] recommended the following interpretation of plasma levels.

Level	*µg of vitamin A/100 ml*
high	over 50
normal	20–50
low	10–20
deficient	below 10

With respect to these categories, the "deficiency" state, i.e., less than 10 µg/100 ml, tends to be universally associated with both low liver reserves of vitamin A and an increased prevalence of clinical signs of

[a] Later renamed "Interdepartmental Commitee on Nutrition for National Development".

deficiency. On the other hand, the so-called "low" category (10–20 μg/100 ml) must be interpreted with caution since low plasma values may be associated with inadequate protein intake, parasitic infestation, liver diseases, and other conditions. In a recent study (*48*) normal liver reserves of vitamin A were found in a group of people with plasma levels in this category.

Plasma carotenoid levels indicate the recent previous intake, and after carotene load determinations of plasma carotene made at intervals they can be used as a test for malabsorption. Fractionation has shown that in a variety of normal diets two-thirds or more of carotenoids may be non-provitamin.

3.2.3 *Liver vitamin A*

A prerequisite for vitamin A determination in tissue is that it should be quantitatively freed from cells before extraction into organic solvents. Liver tissue, because it frequently has a high fat content, is often difficult to disrupt. Digestion with alkali at elevated temperature or, if much fat is present, actual saponification may be necessary before extraction of the vitamin from liver. In such cases addition of pyrogallol may help to reduce oxidation but values obtained for vitamin A may be low on account of destruction and incomplete extraction of the vitamin. On the other hand, when liver samples are ground with anhydrous sodium sulfate before extraction the values obtained are higher than, or equal to, those from studies in which homogenization and saponification are used.

Post-mortem vitamin A in liver has been measured following death from a wide variety of diseases and sudden accidents. From accident data for young children the lowest value found was 15 μg/g of fresh liver (*49*). A study in hospitalized children in Jordan showed that almost all children with severe PEM (marasmus or kwashiorkor) but without eye lesions had much lower liver vitamin A levels than normal. Among children of a low socioeconomic class hospitalized for non-nutritional conditions about 25% also had liver stores below 15 μg/g and may be considered to have been "at risk" with regard to xerophthalmia (49).

The liver stores that will protect a child for a given period can be estimated by making certain assumptions (*48*)—namely, that the body weight/liver weight ratio = 0.03, that 20% of an oral dose of vitamin A is stored in the liver, that the half-life for liver depletion is 50 days, that the daily vitamin A requirement of a 15-kg child is 400 μg of retinol, and that the final depletion rate is linear at 80 μg of vitamin A per day.

From these calculations, the relation of the protection period (i.e., the time during which a child could grow and function normally on a vitamin-A-free diet) to liver stores can be reduced (Table 3). A suitable, though arbitrary, protection period might well be 100 days, which corresponds to 20 μg of vitamin A per g of liver in a child or 10 μg/g in an adult. The occurrence of fatty liver, which is common in malnourished children, should be taken into account in making the calculation of total body stores by suitably increasing the liver weight to body weight ratio.

TABLE 3. HYPOTHETICAL LIVER STORAGE AND PROTECTION PERIODS FOR A HEALTHY 15-kg CHILD [a]

Liver vitamin A (μg/g)	Protection period (days)
100	220
40	156
20	106
10	56

[a] From Suthutvoravoot & Olson (*48*).

In Table 3 the calculated protection period for a given liver concentration of vitamin A is a rough estimate of protection and not a precise indicator. The protection period will be affected by the child's rate of growth, stress of various kinds, the integrity of the plasma transport system, and liver disease. Nevertheless, the calculated protection period is in keeping with the presumed protection given by specific massive doses of vitamin A and with the time of appearance of clinical signs of vitamin A deficiency in malnourished infants. Xerophthalmia is closely associated with very low liver reserves, as shown in Table 4.

TABLE 4. RELATION OF LIVER STORES TO EYE SIGNS OF VITAMIN A DEFICIENCY IN MALNOURISHED CHILDREN [a]

Diagnosis	Xerophthalmia	No. of cases	Mean liver vitamin A (μg/g)
Kwashiorkor	absent	22	17.5
Kwashiorkor	present	17	6.7
Marasmus	absent	32	14.6
Marasmus	present	10	6.6

[a] From McLaren (*49*).

3.3 Dietary assessment

The techniques available for the measurement of dietary intake of vitamin A are recognized to be imprecise ; many factors are difficult to control, making the results obtainable by even the most conscientious workers approximations only. The *Manual on household food consumption surveys* published by FAO (*50*) discusses the subject in detail. The recommended daily intakes proposed in the report of a Joint FAO/WHO Expert Group on Requirements of Vitamin A, Thiamine, Riboflavine and Niacin (*13*) should be followed in making the assessment (see also Passmore et al. (*51*)). Household food consumption, however, cannot be relied upon to provide an indication of the intake of individual members of the household, and this is especially true for the young child. It is difficult to calculate the amount of provitamin carotenoids in a given tissue from food composition tables, mainly because the concentration of carotenoid is determined by the ripening process, is very dependent on the species of plant (fruit or vegetable) concerned, and is very sensitive to the methods of storage and preparation employed. Dietary information is therefore most useful when the intake of foods containing vitamin A and carotenoids is extremely limited.

3.4 Criteria for community diagnosis of xerophthalmia and vitamin A deficiency

Uniform recording and reporting of the occurrence of xerophthalmia in different parts of the world, using the xerophthalmia classification proposed here, should greatly assist health planners in their work. For this purpose, a further extension of the xerophthalmia classification (p. 17) may be of value. Application of the classification alone for the purpose of arriving at a conclusion as to whether or not a xerophthalmia problem of public health magnitude exists in a community has several shortcomings. Certain of the indicators lend themselves more readily than others to field use. X1A, conjunctival xerosis, is especially liable to misinterpretation. In the absence of other indicators a decision about the presence or absence of conjunctival xerosis is highly subjective. The classification alone provides no indication as to how serious the situation may be in comparison with past experience and conditions elsewhere. Some criteria, admittedly arbitrary, that, when fulfilled, suggest a problem of public health magnitude might be useful. The classification is based on only one method of examination for assessing vitamin A status—i.e., clinical. Incorporation of biochemical assessment is desirable to provide additional information of an independent

nature for community diagnosis of xerophthalmia and vitamin A deficiency. The following point prevalence rates are suggested as criteria:

Clinical

X1B in more than 2.0% of the population at risk
X2 + X3A + X3B in more than 0.01% of the population at risk
XS in more than 0.1% of the population at risk

Biochemical

Plasma vitamin A level of less than 10 μg/100 ml in more than 5.0% of the population at risk

Explanatory notes on the criteria:

(1) The proposed tests should be carried out by competent personnel according to the guidelines described in this report.

(2) The criteria should be applied to a population considered to be "at risk" on general grounds, normally infants and preschool children of a low socioeconomic class. The sample must be representative of the population.

(3) The levels set are tentative and offered as suggested guidelines only; they should not be interpreted rigidly.

(4) In a vulnerable population the presence of one or more of the three clinical criteria should be considered as evidence of a xerophthalmia problem. The biochemical criterion is only indicative of significant vitamin A deficiency and may be used alone if the objective is to improve vitamin A status. The value of the corroborative evidence of more than one indicator has to be stressed.

(5) In a few research centres it may be possible to collect autopsy liver samples for vitamin A determinations in children from vulnerable groups suffering accidental death (*48*). Suggested criteria for vitamin A deficiency are liver vitamin A levels of less than 5 μg/g in 5% or more children or less than 20 μg/g in 20% or more.

(6) Much valuable information can be obtained from qualitative observations, often very inexpensively, that is useful in defining geographical areas where vitamin A deficiency may exist as well as in elucidating some of the social and economic reasons for the deficiency. However, such information alone should not be used

as a basis for establishing vitamin A control programmes, but only for preliminary assessment. Some of these observations are :

(*a*) Existence of night blindness based on interviews.

(*b*) Food intake patterns for the infant, including calculated vitamin A and carotene intakes.

(*c*) Review of hospital records.

(*d*) Questionnaires or interviews with health personnel, paediatricians, and ophthalmologists.

(*e*) Knowledge about weaning practices, particularly when weaning commonly occurs before 6 months of age.

(*f*) The prevalence of PEM.

4. ECOLOGY OF XEROPHTHALMIA

The genesis of xerophthalmia, like that of any other disease, can best be understood by consideration of host–environment–agent interrelationships.

4.1 Host factors

4.1.1 *Age*

Age is unquestionably predominant among all of the host factors. Young children constitute the most vulnerable age group ; the most severe eye lesions occur and the highest associated mortality rate is observed in this group (Table 5). Reasons for the susceptibility of the young child are evident. Vitamin A requirements are closely related to the rate of growth ; infectious diseases take a particularly high toll in early life ; and other nutritional disorders, especially PEM, reach their peak incidence at about the same time and aggravate the deficiency of vitamin A. Most important is the vulnerability of the young child in relation to its diet. Breast or animal milk, although not a rich source of vitamin A or its precursors, is adequate for the nursing infant unless it is produced by mothers who are themselves undernourished. The supplementary food of the infant and young child may consist of very little more than the staple food, which is almost invariably a poor source of carotene. Rice, for example, is totally devoid of carotene.

TABLE 5. THE AGE SPECTRUM OF VITAMIN A DEFICIENCY [a]

Stage	Pathogenic factors	Manifestations
Pregnancy	Basic diet low in vitamin A (mostly carotene); increased requirements; food taboos; strain of repeated pregnancies	Low plasma vitamin A; low liver stores; Bitot's spots (occasional); xerophthalmia (rare); night blindness
Fetus		Low liver stores; xerophthalmia (rare); ? abortion; ? congenital malformations
1st year of life	Breast milk: low concentration and diminished volume; artificial feeding; maternal neglect; infections	Lowering of plasma vitamin A; depletion of liver stores; xerophthalmia and keratomalacia (relatively common); xerosis conjunctivae and Bitot's spots (rare)
2-5 years	Supplementation with foods low in vitamin A; deposed child situation; infections	Peak incidence of xerophthalmia and keratomalacia; xerosis conjunctivae and Bitot's spots (not uncommon); fundus changes
School age	Diet low in vitamin A (mostly carotene), fat, and protein; infections	Xerosis conjunctivae and Bitot's spots predominate; night blindness; fundus changes
Adult	Factors as above plus special privation (famine, prison); liver disease; malabsorption	Night blindness predominates; Bitot's spots (occasional); keratomalacia (rare)

[a] From McLaren (*2*).

4.1.2 *Sex*

There is evidence that males are more susceptible to xerophthalmia; this is true for all stages of ocular lesions, all ages, many countries, and many periods. It is also true for plasma levels and liver stores. Oomen (*52*) in his analysis of 6300 cases of xerophthalmia found that a male preponderance of 58% in the first 2 or 3 years of life rose steadily to between 80% and 90% by the age of 10 years. The reasons for this constant sex difference are not entirely clear. It has been suggested that preference is shown for male children who are therefore taken more readily than girls to hospital, that for reasons of prestige a boy would receive fewer sources of carotene in his food, and that girls might have better access to the family cooking pot.

Recent work on plasma RBP levels shows that they are higher in adult males than in females (47.2 + 1.6 μg/ml against 41.6 + 1.6 μg/ml) and that there is an increase in RBP level from infancy to old age. The known high correlation between RBP and plasma retinol is consistent

with, and could at least in part explain, the above-mentioned observations.

4.1.3 *Secondary or endogenous vitamin A deficiency*

A disease that interferes with digestion, absorption (or, in the case of carotene, conversion), transport, storage, or metabolism, or leads to increased elimination or requirements may precipitate a nutritional deficiency. Prominent among those known to precipitate vitamin A deficiency, and occasionally severe enough to cause keratomalacia, are the various causes of fat malabsorption (coeliac disease, cystic fibrosis, sprue, lymphoma, etc.), interference with transport (α- and β-lipoproteinaemias), storage (cirrhosis, hepatitis). metabolic defects (diabetes mellitus, enzyme deficiency), and increased requirements (thyrotoxicosis, pyrexia, etc.).

4.1.4 *Race*

Although there are obvious differences in the prevalence of xerophthalmia in different racial groups living under similar climatic conditions there is no evidence that these differences cannot be explained by various ecological factors.

4.1.5 *Vitamin A deficiency itself*

Finally, it is clear that a vicious circle of pathology is set in motion so that the vitamin deficiency induces changes that in turn impair absorption or some other process so that the deficiency is increased, inducing more damage, and so on.

4.2 Agent factors : the diet

4.2.1 *Rice*

In many parts of the world rice forms the staple, and sometimes practically the only, food. Rice alone, however, does not constitute a complete diet and is, as already mentioned, devoid of carotene. The dangers of complete dependency on rice are thus considerable, especially in young children who are fed large amounts of rice by uneducated parents. Thus it is common to find " poverty in the midst of plenty " and destruction of eyes by xerophthalmia in environments where large quantities of green leaves containing carotene are available. Carotene is of supreme importance in developing countries where foods from

animal sources are either too expensive or are simply neglected. One example may be given of the importance of carotene in the diet in such circumstances. Xerophthalmia was found in all parts of Indonesia except the island of Flores, where, although the children were generally undernourished, there was no xerophthalmia. The staple food in Flores was yellow maize, elsewhere it was rice or cassava.

4.2.2 *Breast and artificial feeding*

Breast feeding usually provides considerable protection against the development of xerophthalmia unless the mother herself has a very low vitamin A status and her milk is deficient in the vitamin. Thus the relatively low vitamin A content of normal milk is adequately protective (*13*). The tendency towards early weaning or artificial feeding from birth, frequently accompanied by attacks of gastroenteritis, is now well recognized as being nutritionally disastrous for the young of underprivileged communities in all parts of the world. In those places where the child is fed a diet that lacks carotene as well as energy sources and protein, xerophthalmia may be expected to complicate marasmus and kwashiorkor. Here, the staple food may not be rice but, for example, cassava with sugar and water, as in north-eastern Brazil.

The important protective effect of breast feeding may perhaps be illustrated by experience gained over many years in Uganda where some of the classical discoveries on kwashiorkor have been made. Until recent years breast feeding was prolonged and although the staple diet consists mainly of *matoke*, i.e., steamed plantain, which is very poor in carotene, keratomalacia has been rare.

4.2.3 *Skimmed milk*

Skimmed milk is another infant food that, without fortification, is devoid of vitamin A and a potential or actual agent of blindness unless supplemented with vitamin A. Methods of fortification with vitamins A and D have been perfected and are extensively practised, but epidemics of xerophthalmia have occurred in association with food donation programmes in which unfortified preparations were used and it was assumed, wrongly, that the children would receive vitamin A in the form of capsules provided together with the milk.

4.2.4 *Other dietary factors*

Fat. Some tropical diets are low in fact, and there is good evidence to show that an adequate intake is necessary for the proper utilization of carotene (*13*).

Vitamin E. Vitamins A and E are intimately related in several aspects of their metabolism. Animals deficient in vitamin E absorb vitamin A poorly ; this poor absorption can be corrected by dosing with vitamin E. Vitamin A is not stored well in the vitamin-E-deficient animal, probably because vitamin E normally has an anti-oxidative, or other protective, effect. In man the two vitamin deficiency states frequently coexist, although in the case of vitamin E, not at the clinical level. Studies in human subjects having no evidence of tocopherol deficiency failed to show any increase in absorption of vitamin A following doses of tocopherol, and acute hypervitaminosis A toxicity symptoms were not reduced (*53*). Nevertheless, it has seemed desirable to include 10–40 IU of vitamin E in capsules containing 200 000 IU of vitamin A for mass dosing (p. 53) since there may be a beneficial effect and the procedure is harmless and corrects any tocopherol deficiency.

Protein and energy. Xerophthalmia complicates PEM rather than the converse. The highest observed complication rate in hospital cases is about 75%, reported two decades or so go ago in Indonesia by Oomen (*54*). The rate ranges down to almost zero in Chile (Santiago), Lebanon (Beirut) Uganda (Kampala), etc. Outside the rice-dependent areas the usual rate does not exceed 5–10% ; within rice-dependent areas the rate is likely to be 20–40% (*55*).

Malabsorption, interference with the synthesis of RBP, and possibly other derangements of vitamin A metabolism and function accompany severe PEM. Xerophthalmia occurs more frequently in kwashiorkor than in marasmus, and plasma vitamin A levels are lower in the former (*49*). Tests for vitamin A absorption have shown impaired absorption in both marasmus and kwashiorkor, but more severe in kwashiorkor. However, in one recent study employing labelled vitamin A no impairment of absorption was found in cases of PEM (*56*). The same group of investigators (*57*) reported impairment in infections. The almost universal association of infections with malnutrition suggests that vitamin A absorption may be impaired in the acute phase of PEM. Liver levels of vitamin A tend to be equally low in kwashiorkor and marasmus (Table 4). RBP levels are very low in kwashiorkor but normal in marasmus (*83*).

4.3 Environmental factors

4.3.1 *Season*

The annual periodicity in the fluctuation in dietary intakes of vitamin A and carotene, of plasma levels of vitamin A, and of the occurrence of xerophthalmia are all well documented for various parts of the world over many years (*7*, *58*). Xerophthalmia is associated with, among other things, particular seasons in which precipitating factors occur. Seasonal dry periods create shortages of fruit and vegetables while extended droughts may exacerbate signs of vitamin A deficiency, particularly in adults.

The pattern of xerophthalmia in young children differs from this in that not only vitamin A deficiency but many other nutritional factors also are operative. Where xerophthalmia endemicity is extremely high, as in parts of Indonesia, the disease tends to occur all the year round but more frequently in some seasons than in others. Where the incidence rate drops and the vitamin deficiency only becomes overt when most of the risk factors operate simultaneously, as in Jordan, xerophthalmia appears highly seasonal.

4.3.2 *Rural and urban environments*

In areas of high xerophthalmia endemicity, such as parts of Indonesia, the available evidence suggests that children in the lower socioeconomic classes are everywhere equally at risk. It is difficult to generalize about the effects of urban and rural environments on vitamin A deficiency but the present rapid rate of migration of the poor from a rural environment to urban slums should be evaluated to determine whether it is likely to reduce or increase the problem. An attempt is made in Table 6 to indicate some possible differences and similarities in the two kinds of environment in this respect.

4.3.3 *Infections and infestations*

Any serious illness, whether acute or chronic, depresses the appetite, increases vitamin A requirements, and has other effects on general metabolism that may lower the vitamin A status ; in an already depleted individual symptoms may be precipitated. The usual synergistic effect between a wide range of infections and mainutrition (usually of the PEM type) is well known, and xerophthalmia usually accompanies such a situation. It is not surprising, therefore, that there are numerous

TABLE 6. CONTRASTING RURAL AND URBAN ENVIRONMENTS IN RELATION TO XEROPHTHALMIA

Factor	Rural environment	Urban environment
Health services		better
Carotene sources	more	
Infectious diseases	equally common but different	
	? more parasitic infections	? more gastroenteritis
	measles equally common	
Breast feeding	more frequent and for a longer time	
PEM	kwashiorkor	marasmus
Rice-dependent diet	little variety of foods	greater variety of foods available
Money-consuming distractions	few	more numerous

accounts in the literature of a close association between xerophthalmia and respiratory tract infections including especially tuberculosis and pertussis, the "gastroenteritis" complex of diseases, dysentery, and parasitic infestations, especially ascariasis. Few detailed studies have been carried out on this subject but impaired absorption of labelled vitamin A has recently been reported in children with diarrhoea, respiratory tract infections, and ascariasis (*59*). The association of measles with xerophthalmia is however known to be of major importance. Where protein and energy intakes are deficient the systemic manifestations and complications of the disease are severe and mortality rates high, the prolonged excretion of giant cells suggests that there is marked impairment of the cell-mediated immune response (*60*).

Where xerophthalmia occurs regularly in the absence of measles the presence of this disease will act as yet another, though important, risk factor in the precipitation of the frank disease. It is becoming increasingly evident that situations often exist where vitamin A intake is not much more than marginal but in the absence of a strong risk factor a threat to sight does not arise. Under these circumstances measles can trigger off a disaster. The revealing role of measles may be expected especially in some of the areas of the world not dependent on rice, and reports from several countries in Africa are most informative in this respect.

Above all, measles must be implicated in the ocular lesions associated with vitamin A deficiency when the two are found together

because measles is invariably an eye disease to some extent. Thygeson (*61*) found in the USA that in measles multiple corneal infiltrates of considerable duration, visible only on slit lamp examination, were an invariable occurrence and, were probably responsible for the photophobia, which is a constant feature of the disease. In an intensive study in Kenya in 1974 J. J. M. Sauter [a] examined 45 well nourished and 234 malnourished children aged 0–6 years with measles keratoconjunctivitis. In both groups he noticed marked conjunctivitis and frequently also extensive keratitis. The tear film breaking-up time was very short in all cases owing to insufficient mucus production. Most malnourished children showed a poor inflammatory response and often a superficial keratinization of the conjunctival epithelium, which contained scarcely any goblet cells.

5. PREVALENCE

5.1 Nature of the information available

A global survey of xerophthalmia was made by Oomen et al. in 1962–63 (*55*). Data were compiled mainly from hospital records, impressions of physicians, and observations made by visiting consultants on the severe blinding lesions. Such impressions cannot be considered to provide evidence of true prevalence, but may indicate frequency of occurrence in a general way. Since that study was made other reports of a limited nature have given more up-to-date information on some of the countries originally visited by Oomen et al. It is now known also that xerophthalmia occurs on a significant scale in some places from which previously no information was available.

For a number of countries data have been obtained on dietary intake, plasma vitamin A levels, and, the occurrence of eye signs (*62*, *63*, *64*). In general, there are no marked discrepancies in the results obtained by the different methods. Most of the studies were not based on a random and representative selection of subjects; consequently, they give only an idea of frequency of occurrence and not prevalence. Very few prevalence studies have been made. Probably the first was that carried out in Jordan in 1963–65, which was associated with clinical studies, the introduction of a notification system for xerophthalmia throughout the country, and the first pilot trial of a massive dosing

[a] Unpublished observations.

programme (*62*). More recently well controlled field studies of xerophthalmia have been conducted in El Salvador, Indonesia, and the Philippines, and a further study began in Haiti in 1975.

5.2 Present world prevalence of xerophthalmia and vitamin A deficiency

With respect to vitamin A deficiency the world may be divided into three regions :

(1) technologically developed countries where there is no xerophthalmia problem but some hypovitaminosis A may exist ;

(2) some rice-dependent developing countries of Asia where there is a problem of public health magnitude ;

(3) the rest of the world including Africa, Latin America, and the Middle East where the problem is not extensive but is intermittently intensive and highly sensitive to changing social and economic conditions.

5.2.1 *Asia*

Xerophthalmia has virtually disappeared from Hong Kong and Singapore ; there is evidence that it is now less highly endemic in much of Indonesia than it was 20 years ago ; and reports from China indicate that xerophthalmia, like other nutritional deficiency diseases, no longer occurs in that country. Reliable information is needed about the situation in the Indochina peninsula. In Japan, only a few aged blind remain as a relic of a past, long forgotten, endemic.

Various nutrition surveys in several islands of the Philippines have shown low intakes of vitamin A, low serum vitamin A levels in children and adults, and some clinical evidence of xerophthalmia. A recent investigation of 1715 children in 12 different locations in Cebu has shown that 17% had serum vitamin A levels below 10 μg/100 ml and 57% had levels below 20 μg/100 ml (*84*, *85*). Altogether, 67% of the children had wrinkling of the conjunctiva and many had some conjunctival thickening and xerosis conjunctivae. Twelve children had xerosis of the cornea or other more serious clinical manifestations of vitamin A deficiency. A statistically significant relationship was found between low serum vitamin A levels and low intakes of both vitamin A and protein.

Xerophthalmia exists in Thailand but it is not a problem of major public health importance. The United States Interdepartmental Com-

mittee on Nutrition for National Defense survey of 1962 reported few serious eye lesions in a general randomized sample of over 5000 persons of all ages, although 0.2% of the sample showed Bitot's spots. The mean plasma level of vitamin A in the civilian population was only 23.7 μg/100 ml. Subsequent studies have indicated the presence of a vitamin A problem among children but its prevalence is decreasing. Over 50% of the patients with severe PEM studied at the malnutrition research centre in Chiang Mai in 1973 had xerophthalmia, including 10% who had keratomalacia.

Reports from Sri Lanka suggest that keratomalacia is reappearing in the clinics and wards of the large centres of population after having virtually disappeared some time ago. There is no evidence to indicate that the situation in India has improved generally. The economically poorer of the rice-eating states in southern India are still the most severely affected by xerophthalmia. Reports of the Indian Ministry of Health based on recent surveys indicate that in the poorer sections of the population the prevalence of vitamin A deficiency is about 3–8% in preschool children and 10–15% in schoolchildren. The magnitude of the problem at the central hospital clinical level is suggested by Table 7. What these data mean in terms of actual prevalence, it is impossible to say.

A report from the Government Erskine Hospital, Madurai, Tamil Nadu, India, indicates that 1014 cases of keratomalacia were treated in 1970. The results shown in Table 8 were obtained in those patients admitted either to a ward or to the rehabilitation unit. The better results obtained in the latter and the advantage of treating cases of corneal xerosis are obvious.

Individual reports from Bangladesh refer to a massive problem of xerophthalmia in that country; large numbers of cases of keratomalacia are reported from Dacca and other large urban centres. Initial examination of 21 300 children for a prevention programme showed 1% of night blindness, 31.89% of conjunctival xerosis, and 0.18% of corneal scars (Table 9). These figures would have met one of the clinical criteria for community diagnosis of xerophthalmia.

Pakistan, like northern India, has relatively few cases of xerophthalmia compared with neighbouring rice-eating countries. It is reported that cases of xerophthalmia are seen frequently in hospitals in both Afghanistan and Nepal.

TABLE 7. NUMBERS OF CASES OF KERATOMALACIA SEEN AT VARIOUS HOSPITALS IN INDIA, 1968–72[a]

Place	Total number of outpatients					Total number of cases of keratomalacia				
	1968	1969	1970	1971	1972	1968	1969	1970	1971	1972
Government Hospital, Trivandrum, Kerala	36 482	37 473	39 273	39 277	—	11	12	12	8	—
Minot Ophthalmic Hospital, Bangalore, Mysore	107 279	100 544	114 795	117 838	—	1 704	762	1 468	1 521	—
Government Erskine Hospital, Madurai, Tamil Nadu	39 416	39 026	40 217	48 305	47 512	216	245	313	220	142
						Active keratomalacia				
Sarojini Devi Hospital, Hyderabad, Andhra Pradesh	67 341	60 008	73 289	75 258	—	160	167	192	204	—
						Burnt-out keratomalacia				
						150	281	302	371	—
						310	448	494	575	—

[a] The total number of cases of keratomalacia seen at these four hospitals in 1968–71 inclusive was 8 319. From *Xerophthalmia Club Bulletin*, No. 3, May 1973.

TABLE 8. RESULTS OF TREATMENT OF KERATOMALACIA PATIENTS AT THE GOVERNMENT ERSKINE HOSPITAL, MADURAI, TAMIL NADU, IN 1970

	Total	Sight saved	Partial sight	Permanently blind	Died
Ward:					
Keratomalacia	153	4	31	118	Surviving children only included in the statistics
Rehabilitation unit:					
Keratomalacia	124	41	35	37	11
Corneal xerosis	150	104	33	13	0

TABLE 9. XEROPHTHALMIA IN CHILDREN AGED 0–6 YEARS IN BANGLADESH, 1974 [a]

Xerophthalmia classification	Before administration of vitamin A		After administration of vitamin A	
	No. of cases	%	No. of cases	%
X1A	6778	31.89	3615	15.11
X1B	140	0.66	123	0.51
X2	84	0.39	21	0.09
X3	13	0.06	14	0.06
XN	213	1.0	178	0.74
XS	39	0.18	33	0.14

[a] From Mahboober Rahman, unpublished data.

5.2.2 *The Middle East*

In the past decade living conditions generally have improved almost everywhere in the Middle East although the nomadic and semi-nomadic peoples remain relatively unaffected by the new wealth as yet. While PEM is still common among the poorer sections of the population in all Middle-Eastern countries, marasmus is by far the predominant form. Xerophthalmia has declined throughout the region; in the Gezira area of Sudan, for example, hundreds of cases were reported in 1962 but few are now seen. Cases of xerophthalmia are seen occasionally in Iraq, Jordan, and Syria—all previously highly endemic areas. In the prevalence study in Jordan conducted in 1963–65 (*62*) 532 randomly selected families including 1180 children below 6 years of age were examined. The rates per 10 000 were as follows: Bitot's spots, 60; healed corneal lesions 17; xerosis of conjunctiva, 650. In

1974 examination of about 5000 preschool children in refugee camps in Gaza and Jordan revealed none with advanced eye lesions and 5 with Bitot's spots.

5.2.3 *Latin America and the Caribbean*

Most of the South American countries do not report a major xerophthalmia problem despite quite low intakes and blood levels of vitamin A. The north-eastern part of Brazil has long been considered to be an exception, especially in the sugar cane area. Numerous cases of xerophthalmia have been reported by hospitals in this area (*65*).

Vitamin A status in the Central American countries has been extensively surveyed by the Institute of Nutrition of Central America and Panama (INCAP). In 1965–67 very low vitamin A levels were found, particularly in the rural areas, and these findings were supported by a high prevalence of low serum vitamin A values. However, clinical signs indicative or suggestive of the deficiency were not encountered on a significant scale. In April 1973, a biannual mass distribution of vitamin A capsules began in El Salvador in conjunction with a country-wide vaccination campaign and a study was carried out from September 1973 to December 1974 consisting of a nationwide prevalence survey of vitamin-A-related pathological occular signs among preschool children and a retrospective chart review of hospitalized keratomalacia patients (*66, 67*). The prevalence survey, which covered 9508 children, did not reveal any cases of active corneal involvement, but 5 children with Bitot's spots, and 3 with healed corneal lesions thought to have been due to vitamin A deficiency were found. On this basis it was estimated that in the whole country (total population, 5.5 million) there are about 43 new surviving cases of X3A + 3B per year, about 1 in 3 of which is likely to progress to blindness.

In Haiti, preliminary reports of a recent survey [a] suggest a significant xerophthalmia problem, with roughly 400 surviving patients suffering corneal involvement each year, a quarter of whom are relatively blind.

5.2.4 *Africa*

Traditionally, Africa south of the Sahara has not been considered to have a serious a xerophthalmia problem. Red palm oil is assumed to protect those who consume it in the western part of the continent. The drier northern parts of countries such as Nigeria and Ghana are,

[a] SOMMER, A., unpublished data.

however, very susceptible to vitamin A deficiency. The arid and semi-arid areas of the Sahel are probably always seasonally short of vitamin A sources, but little information is available. Recent data from Upper Volta show that there is considerable seasonal night blindness and some xerophthalmia.[a] Ocular lesions of measles, which are often associated with vitamin A deficiency are not infrequently encountered. Examination of 1313 children aged 0–6 years showed that 3 had X3A and 2 had X3B. X1A was reported to be common but there were few cases of X1B.

In the past 10 years reports of xerophthalmia have come from parts of Africa where previously it was not known to be common. These places include Johannesburg, South Africa (but not notably other parts of that country) (*68*), Southern Rhodesia (*69*), and the Luapula Valley of Zambia (*70*) where there is an association with measles though the role of vitamin A deficiency was not previously recognized. Other recent reports of xerophthalmia have come from East Africa (*71*), Malawi (*72*), Nigeria (*73*), and Rwanda (*74*).

5.3 Methods of assessing the prevalence of xerophthalmia

5.3.1 *Point prevalence surveys*

Regional or countrywide probability surveys are the only unbiased means of determining the prevalence and estimating the impact of vitamin A deficiency (Annex 1). The following points are basic to the design and execution of a successful survey.

(1) During the preparation of a survey, background information on the likely seasonality, geographic distribution, and prevalence of cases of xerophthalmia should be compiled from hospital records. Surveys should coincide with the period of peak prevalence.

(2) Clinical criteria should be easily recognized, relatively specific markers of vitamin A deficiency. Bitot's spots with conjunctival xerosis (X1B), corneal xerosis (X2), active corneal destruction (X3A + 3B), and corneal scars thought to be due to vitamin A deficiency (XS) are suggested for this purpose.

(3) Sample size should be determined on the basis of expected prevalence and desired confidence limits.

[a] RAOULT, A., unpublished data.

(4) Bias is minimized by visiting every house in the selected cluster and listing all eligible children, whether present or not.

(5) Sample clusters must be representative of the population to be described. Stratified multistage probability samples are most commonly used.

(6) Both data recording forms and teams should be tested in the field before any sampling sites are visited, and the ophthalmologists' diagnoses should be rigorously and repeatedly standardized against one another.

(7) Continued analysis of the data will identify problems and inconsistencies requiring attention.

5.3.2 *Hospital record reviews*

A thorough review of hospital records over several years for admissions of patients with pathological ocular signs of vitamin A deficiency can be carried out only in those hospitals that have an excellent record retrieval system. These are infrequent in developing countries. A classical study of 11 000 case histories of xerophthalmia was made in Indonesia about 20 years ago by Oomen (*52*).

6. TREATMENT OF XEROPHTHALMIA

" The physician who finds himself with the responsibility of treating cases of xerophthalmia will probably be subjected to a wide range of emotional feelings. On the one hand he will feel gratified with the dramatic response made by even quite advanced cases of xerosis corneae, and frequently even when there is residual scarring a useful degree of vision will have been preserved. Nevertheless, there will be occasions, and these will be disconcertingly numerous, where the disease is especially common, when one glance at the screwed up soggy eyelids and the underlying disorganized globes will be sufficient to tell him that all is already lost " (*2*).

Recognition of the need for treatment implies that clinical signs are present that are attributable to vitamin A deficiency. There is only one prompt and adequate treatment for xerophthalmia—adequate, that is, to reverse all the changes that will respond and to restore liver reserves against future needs. Under these circumstances there is no

justification for grading the vitamin A dose according to the apparent severity of the condition, especially as it may frequently not be possible to follow up the patient properly to ensure a full course of treatment. Delay for even one day at stages X2 or X3A, when changes may still be reversible, may make all the difference between sight and blindness for the patient. The following protocol is recommended.

Recommended preparations of vitamin A

Formulation	*Route*	*Dosage*
Water miscible	Intramuscular	100 000 IU
Oil solution (in combination with vitamin E)	Oral	100 000 IU
		200 000 IU

Treatment schedule for xerophthalmia

Immediately on diagnosis	100 000 IU ; water-miscible preparation, intramuscular
Second day	100 000 IU ; oil solution, oral
Prior to discharge (patients under 1 year of age)	100 000 IU ; oil solution, oral
(patients over 1 year of age)	200 000 IU ; oil solution, oral

Explanatory notes :

(1) Retinyl palmitate is the preferred active form of vitamin A in water-misicible formulations for intramuscular injection.

(2) Upon diagnosis, an oil solution of vitamin A (100 000 IU) should be substituted only if an intramuscular preparation is not available. Hospitals in areas where xerophthalmia is endemic should keep water-miscible intramuscular preparations of vitamin A on hand at all times.

(3) Oral water-miscible preparations of vitamin A may be substituted for oil solutions ; vitamin A acetate may be used in place of retinyl palmitate in oil solutions for oral use.

(4) Oil solutions of vitamin A should never be injected intramuscularly because the vitamin is liberated extremely slowly, if at all, from the injection site (*20*).

(5) Any failure of response to treatment should suggest a need to revise the diagnosis, provided that the dose of vitamin A was adequate, an intramuscular injection of an oil solution has not been given, and there is no gross interference with RBP synthesis, which may occur in kwashiorkor.

(6) Conversely, when an eye condition suspected of being due to infection fails to respond to appropriate antibiotics underlying xerophthalmia should also be suspected if the social circumstances of the patient indicate this possibility.

(7) Injection of a water-miscible preparation of vitamin A is especially important in patients with intractable vomiting and diarrhoea, when the oral route may be abandoned and parenteral dosing continued.

(8) The specific therapy has two aims: to halt active lesions and thereafter to replenish body stores.

(9) Underlying conditions must receive vigorous treatment. These conditions include PEM and other nutritional disorders, " gastroenteritis ", dehydration and electrolyte imbalance, infections (especially measles), and parasitic infestations.

(10) In some cases the ocular condition may appear to worsen temporarily as keratinized epithelium is sloughed off.

(11) The frequently differing degree of involvement of the two eyes often permits at least one useful eye to be saved.

(12) An especially dangerous, and not infrequent, situation is the omission of vitamin A therapy in the treatment of cases of PEM without obvious eye lesions. Xerophthalmia may be precipitated when growth is stimulated and vitamin A requirements are consequently increased (*75*).

7. PREVENTION

7.1 Control programmes

Inadequate vitamin A status varies from a *marginal* condition of inadequate body reserves of vitamin A *without* clinical signs to a severely depleted state mainly characterized by severe eye signs and the high probability of blindness (see p. 7). A vitamin A control programme can therefore be directed towards improving the vitamin status of a population, eliminating blindness causally related to vitamin A deficiency, or to an intermediate objective. Some guidelines for programmes with different objectives are given below.

The objective selected by government decision-makers at a given time in a given country will obviously depend on many factors, including the severity of the problem, the availability of human and financial resources, the socioeconomic situation, the technological and other means available for attacking the problem, and political considerations. However, *the objective must be clearly defined* because the methods used, the nature of the data collected, and the strategy employed will all depend on the goals set. *Quantification* of the objective is equally important ; that is, determination of prevalence data prior to instituting a programme and definition of minimally acceptable prevalence levels for a population or population group after the programme has been instituted.

7.1.1 *Objective : to control blindness causally related to vitamin A deficiency*

If the main objective is to reduce the prevalence of blindness due to vitamin A deficiency, the main criteria used for evaluating the need for a programme and the effectiveness of preventive measures will be (1) prevalence of blindness and corneal scars related to vitamin A deficiency (XS) and (2) occurrence of severe xerophthalmia (X2, X3A, and X3B) during the "high" season for vitamin A deficiency. Biochemical indicators are less useful although the existence of a significant proportion of *extremely low* vitamin A values for plasma and liver, i.e., less than 10 µg per 100 ml of plasma and less than 5 µg per g of liver, should give cause for concern. Milder clinical signs of vitamin A deficiency (X1A and 1B) are not particularly useful in this regard though a *high* incidence of these lesions indicates an increased probability of finding the more severe signs.

7.1.2 *Objective : to improve the vitamin A status of target groups*

If the objective is more broadly based, the criteria mainly used for evaluating need and effectiveness are (1) plasma and liver concentrations of vitamin A, (2) dietary intake data, and (3) frequency of the milder, more prevalent, clinical signs, particularly X1B.

In countries where childhood blindness related to vitamin A deficiency is not a major problem, the relative infrequency or absence of the more severe clinical signs (X2, X3A, and X3B) does not reduce the usefulness of the study. In countries where nutritional blindness is a matter of social concern, the prevalence of severe clinical signs and

childhood blindness and scars, as described in section 7.1.1, should also be carefully assessed.

Programmes designed to cover the majority of a population, although quite cheap, may be difficult to implement and may require long preparation. They will usually be developed as part of a comprehensive nutrition policy. Vitamin A fortification of foods and nutrition education are two such programmes.

7.1.3 *Periodic massive dose programmes*

About 30-50% of a 200 000 IU dose of vitamin A is stored by the body, and the protection period for a growing child has been calculated to be about 100 days. Man is usually susceptible to the blinding effects of vitamin A deficiency only during early childhood. On the basis of these observations periodic massive dose programmes have appeared to be a feasible control measure.

The first pilot trial was carried out in *Jordan* in 1965-66[a] in 180 healthy infants aged 35-180 days (xerophthalmia in infants was highly prevalent in Jordan at that time); 300 000 IU of vitamin A were administered orally without ill effects. Further trials elsewhere showed that oral dosing with 200 000 IU of retinyl palmitate in oil once every 6 months was probably the optimum regime for reducing the incidence of ocular lesions in a community and caused no serious acute hypervitaminosis symptoms (*76*). A single massive dose given to mothers has been shown in some instances to raise significantly for a number of weeks the vitamin A level of the milk (*77*). This method may be especially applicable in areas where xerophthalmia is common in infancy.

In *India* the National Vitamin A Prophylaxis Programme for the Prevention of Blindness in Children was initiated in 1970 after pilot studies at the National Institute of Nutrition in Hyderabad. The programme initially covered 19 districts in 7 states in the southern and eastern parts of the country. By 1974 it covered 97 districts in 14 states. During that period the number of preschool children to be covered rose from 2.4 to 4.25 million while the number treated rose from 1 million to about 3 million. These children receive 200 000 IU of vitamin A in oil orally every 6 months. In the next 5-year plan it is intended to increase the annual coverage to 12 million children. Problems encountered include lack of personnel, inadequate coordination, and poor record-

[a] PATWARDHAN, V. N., unpublished data.

keeping. Table 10 shows the difficulty experienced in achieving a high success rate for follow-up dosage. Supposing that the rate of attendance was 85% of all children between 1 and 5 years at the first distribution session, one can calculate from this table that the attendance rate

TABLE 10. PERCENTAGE DISTRIBUTION OF VITAMIN A DOSES TO CHILDREN IN INDIA, BY AGE GROUP AND DISTRIBUTION SESSION [a]

Age group	1st session	2nd session	3rd session	4th session	All sessions
1–2	15.9	8.7	3.8	1.1	29.5
2–3	17.6	10.9	5.4	1.2	35.2
3–4	11.4	6.8	2.9	0.9	22.0
4–5	6.4	2.3	0.6	0.6	9.8
Over 5	2.2	0.8	0.4	0.1	3.5
All age groups	53.5	29.6	13.0	3.9	100.0

[a] From Swaminathan, M.C., unpublished data.

decreased to 47% at the second, 20.6% at the third and 6.2% at the fourth session. Table 11 demonstrates the effectiveness of a second dose in reducing the prevalence of mild deficiency signs.

A government-sponsored periodic massive dose programme commenced on a national scale in *Bangladesh* in January 1973, the objective being to reach all children aged 0–6 years in the country (estimated at 15 million) with a 200 000 IU vitamin A capsule. The Bangladesh malaria eradication programme was given the responsibility of distributing the capsules. In a country devastated by " natural " and economic disasters implementation and evaluation of such a programme are clearly immensely difficult. It is estimated that about 65% of the child population of the country has been reached by the current programme activities. The refugee and " normal " slum-dwelling children remain unprotected. From the data available it can be calculated that over 90% of the eye lesions associated with vitamin A deficiency were due to conjunctival xerosis. The incidence of these lesions and of corneal xerosis, which is equally difficult to diagnose, was reported to have dropped markedly after the first distribution of vitamin A capsules but the incidence of the more definite lesions of Bitot's spot and keratomalacia was unchanged.

A periodic massive dose programme was launched in *Indonesia* in 1973 as a 2-year pilot project. Capsules containing 200 000 IU of

TABLE 11. PERCENTAGE PREVALENCE OF DEFICIENCY SIGNS BEFORE AND AFTER ADMINISTRATION OF VITAMIN A TO CHILDREN IN INDIA [a]

Age group (years)	Before vitamin A was administered				After 2 doses of vitamin A			
	No. of children	Conjunctival xerosis (%)	Bitot's spots (%)	Total (%)	No. of children	Conjunctival xerosis (%)	Bitot's spots (%)	Total (%)
<3	947	2.6	1.3	3.9	567	0.7	0.2	0.9
3–5	633	6.5	6.2	12.7	573	3.8	1.2	5.0
Total <5	1 580	4.2	3.2	7.4	1 140	2.3	0.7	3.0

[a] From Swaminathan, M. C., unpublished data.

vitamin A and 40 IU of tocopheryl acetate in oil were administered biannually by mouth. The target population was 100 000 children between the ages of 12 and 48 months in certain localities in three provinces of Java (representing about 1 in 70 of the children in that age group in Java). About 10–30% of the target population was left untreated. Field workers were assigned about 50 children per day. Reported difficulties included lacks of cooperation, migration of people, and frequent reports that the capsules had caused vomiting and diarrhoea. Actual refusals were less than 1 in 200. About 85% of the children who received the first capsule also received the second.

At the same time a study was carried out of the effectiveness of a massive dose of vitamin A under field conditions. The sample consisted of all children aged 1–5 years in 7 urban kampongs and 5 rural villages in central Java. A double-blind prospective experimental/placebo study was designed and the same capsules containing 200 000 IU of vitamin A and 40 IU of tocopheryl acetate in oil were used. Children with active xerophthalmia were treated and observed, and removed from the study group. Dosing was repeated after 6 months with re-examination. Xerophthalmia prevalence rates were lower than expected : 4.5% in urban and 5.2% in rural children. Six months after the first distribution of capsules there was significantly less night blindness, conjunctival xerosis, and Bitot's spot in the experimental group. Keratomalacia and corneal xerosis were not found. A small study employing 300 000 IU of an oral water-emulsion formulation of vitamin A with 100 IU of vitamin E gave good results after 1 year. Deworming produced no additional advantage.

A 3-year pilot project began recently in Cebu in the *Philippines*. Three different strategies for the control of vitamin A deficiency and xerophthalmia are being evaluated in each of four different communities or *barrios*, half of which are urban and half rural. One of the strategies is administration of 200 000 IU of vitamin A plus vitamin E every 6 months to all young children. Baseline dietary, clinical, and biochemical data have been collected, and examinations will be repeated. The other two interventions are (1) public health and horticultural activities, and (2) fortification of monosodium glutamate with vitamin A. The cost and effectiveness of these three types of control programme will be determined after 2 years' intervention.

The point prevalence survey in *El Salvador* has already been referred to. In April and May and again in November and December 1973 the Government of El Salvador distributed vitamin A capsules to every child between the ages of 1 and 5 years attending a distribution centre

during a well publicized mass measles vaccination campaign. Each capsule contained 200 000 IU of vitamin A and 40 IU of vitamin E. A thorough hospital record review of active vitamin-A-related corneal destruction was used as a means of evaluating the programme. The main conclusions were as follows.

(1) Almost half of the hospitalized patients with active corneal destruction would have been ineligible to participate in the periodical massive dose programme on account of their age: a third were under 1 year of age and 12% were 6 years of age or older. Since not more than 80% of the target population was reached the maximum potential effectiveness of the programme was 40%.

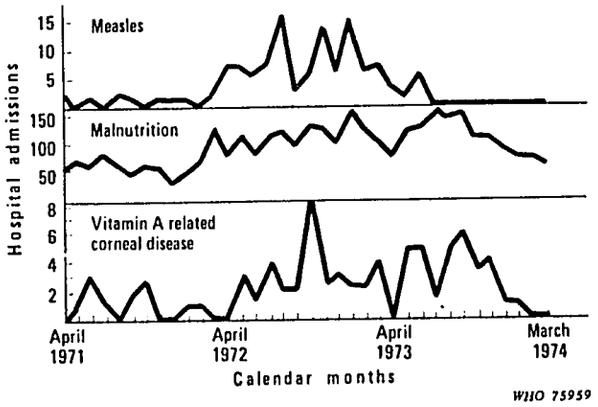
(2) The programme failed to influence the occurrence of xerophthalmia even when patients ineligible to receive the vitamin dose were excluded.

(3) Three-fourths of all patients were hospitalized between May and October: the programme was therefore well timed.

(4) A recent history of measles was more common in patients with xerophthalmia than in those admitted for malnourishment in general.

(5) The dramatic reduction in measles following vaccination appeared to have no effect on active corneal disease (see Fig. 5).

FIG. 5. ADMISSIONS TO BENJAMIN BLOOM CHILDREN'S HOSPITAL, SAN SALVADOR, EL SALVADOR, APRIL 1971 – MARCH 1974 [a]



[a] From Sommer et al. (67).

The carefully planned and executed studies in El Salvador raise certain questions that cannot be answered fully. Prevalence of xerophthalmia appears to be much lower than expected, but if rough extrapolations are made for India and elsewhere a similar order of prevalence is found in the vulnerable groups generally. Government of India estimates for the whole country show 13 000 cases of keratomalacia per year; the calculated prevalence of corneal scars is then about 2.4 per 10 000 children. The figure for El Salvador is 3.0 per 10 000 and for Indonesia the same if 50% of patients survive. These rates are all very close. They also demonstrate how difficult it is to cover members of populations most at risk. Even where the target population is appropriate, as in Indonesia, between 10% and 30% are not dosed initially and the drop out rate for the second dose is likely to be at least a further 20%. When dosing is left to the regular health services the drop out rate will be much greater, as figures from India show.

The Meeting concluded that more operational research and experience are needed before any final opinion can be formed regarding the effectiveness of this approach to the problem.

Cost. The cost of a periodic massive dose programme includes the cost of the vitamin A itself, which is relatively cheap, and the cost of the delivery system, which will vary greatly from country to country. In planning and conducting a periodic massive-dose programme for the prevention of vitamin A deficiency, special attention should be given to the following points.

(1) Personnel: whenever possible, existing health personnel should be employed. Any new personnel should form a part of an integrated health team rather than be established as a separate vitamin A task force. Auxiliary personnel would be largely responsible for operational aspects of the programme except supervisory activities.

(2) Training: medical and auxiliary personnel attached to the vitamin A project should be instructed in the significance of the programme, procedures for administering of vitamin A, and risk of overdosing.

(3) Community awareness: communities should be informed in advance about the programme and the benefits to be expected in order to ensure their cooperation. The mass communications media should be utilized to promote community involvement.

(4) Evaluation: evaluation is an essential component of the programme. Both the *operation* and the *biological effectiveness* of the programme

must be evaluated. Operational evaluation should provide continuing information on all administrative aspects of the programme such as supply and distribution of the vitamin, conditions of storage and handling, mobilization of personnel, and extent of coverage. A feedback mechanism should form an integral part of the evaluation system to ensure that necessary changes can be introduced without delay. Continuous evaluation is essential to ensure that the technical aspects of the programme are maintained in an optimum state. For an evaluation of the biological effectiveness of the programme a clear definition of the criteria to be employed is essential. A proper baseline study should be conducted before treatment commences. It is also important to include registration of other possible beneficial effects such as improved growth and of untoward side-effects. The effectiveness of the programme should also be assessed through its impact on the incidence of keratomalacia in a community.

7.1.4 *Fortification*

Fortification of foods with various nutrients has been practised extensively for a long time, and the principles of fortification have been established (*78*). A suitable food vehicle for vitamin A fortification should have the following characteristics : (1) the food should be widely or universally consumed by the population of the target area ; (2) there should be little variation in *per capita* daily consumption of the food ; (3) the food should show no appreciable changes in its organoleptic characteristics after addition of vitamin A ; and (4) it should be economically feasible to fortify the food on an industrial scale.

Where possible, the natural or traditional role of specific food vehicles as sources of vitamin A should be taken into consideration ; however, this is not essential. Similarly, if the missing nutrients can be related metabolically to other nutrients in a food vehicle, this will be an additional reason for selecting that vehicle. Administered vitamin A should, if possible, be given together with adequate protein to ensure proper and maximum utilization of the vitamin. Protein foods are therefore desirable vehicles for fortification. However, the ideal vehicles for added vitamin A are those foods that the target population will purchase and consume regularly on the basis of preference, habit, and economics.

Vitamin A is usually incorporated into food as retinyl ester (palmitate or acetate). Since vitamin A is subject to oxidation, which is accelerated by heat, light, and certain catalysts, application techniques

have been developed by which the tendency to oxidation is inhibited or delayed by physical or chemical means. Thus, a range of vitamin A preparations are available on the market, each with its own specifications and uses in food fortification (*79*).

Vitamin fortification of food involves the addition of a liquid or dry preparation to the food product during the batch or continuous process of manufacture. The vitamin compound mixed with a carrier to be added to food, particularly in a dry form, is referred to as a " premix ". The food manufacturer must decide whether to prepare the premix in his own plant or purchase a commercial product. In making this decision, a food manufacturer needs to consider the total cost of both approaches. Addition of a premix to food requires a suitable device for metering the flow of premix into the food product and adequate blending or mixing to ensure the uniformity of the fortified product.

Milk products. When fat is removed from milk, the fat-soluble vitamins, including vitamin A, are also removed. The rationale and practice of returning vitamin A and other fat-soluble vitamins to fluid skimmed (nonfat) milk have been documented. Adequate vitamin A stability is attained when fluid nonfat milk is properly fortified. Vitamin A has also been successfully added to evaporated milk and sweetened condensed milk.

In the fortification of dried skimmed milk with vitamins A, D, or E, there are three possible approaches : (1) the vitamin preparation can be dissolved in a triglyceride base such as coconut oil and homogenized into condensed milk prior to the spraying process ; (2) if a triglyceride-emulsifier base is used, blending into condensed milk can be accomplished without homogenizing ; or (3) the unfortified nonfat dried milk can be dry mixed with a dry, stabilized, water-dispersible preparation containing vitamins A and D in a controlled dry atmosphere. All three methods achieve a final fortified product with a stable vitamin potency when the food is properly packaged and stored.

All milk products originating in the USA supplied to assistance programmes have been fortified with vitamin A since 1968.

Cereal products. In recent years the development of stable, dry forms of vitamin A in various particle sizes has greatly broadened the range of foods amenable to vitamin A fortification, and it is now possible to fortify a number of products such as wheat flour that could not be fortified with liquid vitamin A preparations. It has been established also that other nutrients in a flour premix, such as the water-

soluble vitamins, iron, and lysine, do not affect the stability of vitamin A. Moreover, neither bromates nor the usual bleaching agents significantly reduce the stability of vitamin A in nutrified flour. Thus, wheat flour and also maize meal are excellent vehicles for vitamin A fortification since both these cereal products are widely consumed around the world. Retention of vitamin A in baked tortillas, muffins, chapaties, and breads is good to excellent.

Much of the wheat flour produced in the USA and in certain other countries is routinely fortified with niacin, thiamin, riboflavin, and iron. In addition, wheat flour procured by the US Department of Agriculture for shipment overseas for distribution in aid programmes is fortified with vitamin A and calcium. Where wheat flour is consumed by large segments of the population, and where vitamin A deficiency is a serious public health problem, consideration should be given to fortification of flour.

Rice without the husk is the staple food of well over half the world's population. Individuals on a predominantly all-rice diet are in need of additional nutrients such as vitamin A. Several methods have been developed for the preparation of rice premixes, and enrichment and stability data have been collected. Dry vitamin A palmitate may be added in a coating operation that produces a white rice premix with good stability characteristics.

A new premix method has been developed that is not based on the use of rice grains but on the manufacture of simulated grain kernels from a cereal dough. This has the advantage that many micronutrient substances such as vitamin A and amino acids can readily be incorporated into the simulated kernel premix. The rice kernel premix is added to normal white rice of an appropriate rate (1 : 200, for example) to provide the proper nutrient level in the fortified rice. During cooking the nutrients are released from the premix kernels and evenly distributed throughout the product. Fortified rice has been cooked by recommended and acceptable methods with little or no loss of vitamin A content.

Sugar. A project was initiated in Guatemala in 1969 to test and implement the fortification of a suitable vehicle with vitamin A. White table sugar was chosen because it is universally consumed by the population, the daily *per capita* consumption varies little, supplementation results in no appreciable change in the organoleptic properties of the vehicle, and the cost and nature of the vehicle make the supplementation process economically feasible on an industrial scale. Dry vitamin A

palmitate in a water-miscible form was used. Tests of physical stability, biological effectiveness, flavour, and acceptability have all proved favourable.

Tea products. A survey of food habits in the states of Gujarat and Maharashtra in western India revealed that 87% of the villagers in Gujarat, including 84% of those in the lowest income families, give tea to their children. It appears, therefore, that tea comes close to being an ideal vehicle for conveying vitamin A to millions of Indians in all age groups whose diet is seriously deficient in this vitamin.

Tea can be fortified by dry mixing the product with fine, powdered, dry vitamin A palmitate. Tea leaves are fortified with emulsions of vitamin A palmitate. These emulsions are made by homogenenizing vitamin A in thick solutions of acacia gum or dextrin, which are diluted in sucrose solutions and then sprayed on to the tea leaves and dried for satisfactory stability. Vitamin A applied in both forms showed excellent retention after the fortified tea was boiled for 1 hour. Trials on a commercial scale in a tea factory in southern India have demonstrated the feasibility of fortifying large quantities of tea during processing in individual factories or in blending plants.

Monosodium glutamate (MSG). In Cebu in the Philippines a pilot study is being conducted to evaluate the effectiveness of fortification of MSG with vitamin A. This is the first time that MSG has been used in a fortification programme. A preliminary detailed dietary investigation indicated that it was the most suitable, and probably the only suitable, dietary item for fortification. It is consumed regularly by over 95% of the families, variation in amounts consumed is not great, nearly all the MSG in the Philippines is made by one manufacturer, and the substance lends itself to vitamin A fortification without the product suffering any marked changes in colour, texture, or taste. Tests have shown that it is well accepted. At present 4 communities, 2 urban and 2 rural, are receiving fortified MSG. The product is normally sold in small packets containing 2.4 g, and each packet is enriched with 15 000 IU of vitamin A. The average family of 7 persons uses 2 packets per day.

7.2 Prevention

Xerophthalmia and vitamin A deficiency can be prevented by using the control methods mentioned earlier—namely, periodic massive dose programmes aimed at children at risk or fortification of a suitable

food that is consumed regularly in populations whose intake of the vitamin is likely to be inadequate.

Other means of prevention are also possible, depending on a variety of services and the conditions in the country or community that contribute to the underlying etiology of xerophthalmia. Three main " services "—health, food production (or agricultural), and educational—may contribute substantially to the prevention of xerophthalmia. All three should be operating in many countries and their activities should be coordinated towards similar objectives.

7.2.1 *Health services*

The health services need to be in a position to detect the presence of xerophthalmia and vitamin A deficiency in the population and to estimate their prevalence. They should be able to investigate the epidemiology of xerophthalmia in different ecological zones and devise a strategy for prevention. Staff trained in the diagnosis, treatment, and prevention of xerophthalmia should therefore be available.

One of the problems is that xerophthalmia is usually most frequent in the poorest and most deprived sections of the community. These families have least access to, and make the least use of, existing health services. Therefore, a health service that consists of numerous field units and encourages the use of mobile auxiliary personnel may have a better chance of dealing with the problem than a service based on a few urban hospitals and a staff mainly of physicians. The auxiliary or other health workers will need a knowledge of the diagnosis, treatment, and prevention of xerophthalmia. They should also be given a picture of the " at risk " individual. This will be based on epidemiological studies, which should, as a minimum, determine prevalence in terms of area, age, sex, and severity, and relate the findings to other conditions such as disease, season, and certain major socioeconomic factors. This epidemiological diagnosis may have to be undertaken by a nutrition institute or similar institution. Ensuring the constant availability in all health units of an adequate supply of vitamin A capsules (containing 100 000 IU and 200 000 IU of vitamin in oil) is a management problem.

In areas where xerophthalmia is a problem and where a periodic massive dose programme is not in operation all maternal and child health clinics and other health posts that treat children might with benefit give capsules containing 200 000 IU of vitamin A to all children attending for examination or treatment, every precaution being taken

to try to ensure that doses are not given at too frequent intervals. Pregnant and lactating mothers might similarly be routinely dosed with vitamin A (*80*). The control of diseases such as measles, gastroenteritis, and PEM, which are related to xerophthalmia, should be undertaken.

7.2.2 *Horticulture and related production activities*

In most, if not all, areas of the world where xerophthalmia is prevalent vegetable, rather than animal, products are the main available source of dietary vitamin A (i.e., carotene). The richest sources of carotene (other than red palm oil) are certain vegetables (especially carrots and the green leafy vegetables) and fruits. Some staple foodstuffs such as yellow corn also provide some carotene. Carotenoid vitamin A precursors known to occur in human foods have been reviewed by Bauernfeind (*12*).

Increased consumption of many of the carotene-rich foods will also ensure the increased consumption of other essential nutrients. For example, 100 g of *Amaranthus* leaves provide 3.6 g protein and useful amounts of ascorbic acid, iron, and other nutrients. Many horticultural crops are, however, available only seasonally, which may affect the prevalence and seasonal occurrence of vitamin A deficiency.

In many developing countries there are relatively few trained horticulturists, and knowledge is limited concerning the best varieties of fruits and vegetables for particular area, optimum means of production under local conditions, and control of the pests and diseases that attack the crops. In addition there are problems of transport, marketing, storage, and preservation.

Horticulturists may tend to encourage the production of vegetables and fruits that give high yields or realize good market prices but may ignore the nutritive value of the product. Many of the dark green leafy vegetables eaten traditionally in tropical countries have a much higher carotene content than do pale green leafy vegetables such as cabbage or temperate vegetables like turnips, radishes, and parsnips. Similarly, certain tropical fruits, notably mangos and papayas (pawpaws), provide useful amounts of carotene whereas citrus fruits and non-tropical fruits in general contain very little.

Few horticultural programmes have been launched as part of an effort to control xerophthalmia or vitamin A deficiency. In Cebu in the Philippines, however, one of three interventions being evaluated consists of a horticultural programme. Trials have been undertaken there to determine relative yields of certain vegetables both in terms of total

weight and weight of carotene produced per unit of area ; new varieties of tomatoes with a higher carotene content have been planted and seeds and seedlings distributed ; and a variety of extension methods have been used to encourage vegetable gardening and fruit growing, even in small urban plots. Elsewhere in the Philippines a remarkably successful campaign is under way to use all available space in towns, as well as back yards in the country, for vegetable production.

7.2.3 *Educational programmes*

The effectiveness of nutrition education programmes aimed at improving the consumption of vitamin-A-rich foods has never been adequately evaluated. Nevertheless, the importance of education directed especially to families at risk has to be recognized. This education must include aspects of production, storage, and utilization of food products, and in some cases may also include methods of preservation. Families need to be made aware of the special nutritional needs of young children, and this education must be based on an understanding of the local social and cultural conditions.

The need to make the best use of the media of mass communication must be recognized, but appropriate educational materials should also be available for professional personnel (physicians, nutritionists, etc.), intermediate level personnel (community development staff, teachers etc.), and members of the public (mothers, schoolchildren, etc.). This material may need to be specially prepared, or adapted, to meet the needs of each region or area.

8. RECOMMENDATIONS FOR RESEARCH

Research on vitamin A in the past has been extensive but concentrated mainly on fundamental aspects and animal studies. In man, much effort has been devoted to hospital-based studies of the gross and irremediable changes of keratomalacia but knowledge of possible earlier changes in the eye and lesions elsewhere in the body caused by vitamin A deficiency is extremely scanty. Information on the prevalence and epidemiological characteristics of xerophthalmia in different parts of the world is patchy and many data that are a decade or more old are still quoted, in a rapidly changing world situation, as if they were current.

Only in the last few years have certain programmes for the control of vitamin A deficiency been started, and it is vital that such programmes should be initiated only after adequate baseline data have been obtained from recent, well-executed surveys. Evaluation should be an inherent part of programme design. The Meeting made a number of recommendations for research ; these can be classified under four main headings : (1) clinical and biochemical studies ; (2) epidemiological investigations ; (3) evaluation of action programmes ; and (4) contributions made by horticulture and food technology.

8.1 Clinical and biochemical studies

(1) *Assessment of vitamin A status and diagnosis of xerophthalmia.* Although clinical signs, low plasma levels, and low dietary intakes are useful indicators of vitamin A deficiency, no simple methods exist for specifically diagnosing vitamin A deficiency or evaluating total body stores of vitamin A. It is recommended that further studies should be carried out on the biochemical, clinical, and pathological evaluation of vitamin A deficiency and on the assessment of total body stores of vitamin A. Pathological and ophthalmological studies should be directed towards producing a definitive clinicopathological description of Bitot's spots and conjunctival xerosis and elucidating the exact nature of corneal xerosis and keratomalacia. More specifically, studies should be conducted *inter alia* on the following aspects of vitamin A deficiency :

(*a*) Development of an improved method of assessing night blindness in small children in community studies ;

(*b*) Objective assessment of xerosis conjunctiva, possible cause of isolated wrinkling of the conjunctiva, and usefulness of staining techniques for the diagnosis of conjunctival and corneal lesions due to vitamin A deficiency ;

(*c*) Morphology of destructive corneal lesions and their relationship to vitamin A intake ;

(*d*) Additional information on xerophthalmia fundus and its occurrence outside Indonesia ;

(*e*) Standardization of methods for determination of plasma vitamin A ;

(*f*) Development of a simple method for determination of RBP in plasma ;

(*g*) New approaches to biochemical assessment of vitamin A status by determination of metabolites, labelling of body pool, or possibly enzyme assay;

(*h*) Collection of additional data on vitamin A status from analysis of post mortem liver samples;

(*i*) Improvement of methodology for dietary surveys aimed specifically at obtaining information on vitamin A and carotene consumption (is there a method based on infrequent consumption of foods containing vitamin A and carotene that could be used for rapid identification of high risk children ?).

(2) *Interrelationship between infectious and parasitic diseases and xerophthalmia.* Additional information should be collected on the influence of measles on xerophthalmia and keratomalacia. More information is also required on the effect of infectious and parasitic diseases on the absorption and utilization of vitamin A as well as on conversion of carotene to vitamin A.

(3) *Immediate and long-term effects of vitamin A deficiency.* Studies required include:

(*a*) Effects of prolonged marginal vitamin A deficiency on growth and development (including mental), immune response, birth weight, and congenital malformations;

(*b*) Follow-up of children recovered from clinical vitamin A deficiency relating to survival and ocular morbidity.

8.2 Epidemiological investigations

(1) Investigation is required in each geographical area where xerophthalmia is suspected to be a serious problem of the prevalence of the disease and its relation to mortality and morbidity, specifically to blindness.

(2) Causative factors relevant to prevention and amenable to change should be determined in areas where xerophthalmia is prevalent.

(3) Seasonal variations of xerophthalmia should be investigated to determine whether they are associated with food availability, seasonal diarrhoea, exposure to sunlight, etc.

(4) The importance of protein–energy malnutrition should be studied as an etiological factor in xerophthalmia.

(5) The high risk environment for keratomalacia and the vulnerable individual in whom the disease occurs should be characterized, including a determination of the sociological and cultural parameters that could influence the type of intervention programme required.

(6) Factors that result in intrafamily maldistribution of available foods rich in vitamin A and carotene should be elucidated.

8.3 Evaluation of action programmes

(1) Better use should be made of hospital statistics for this purpose.

(2) The cost/benefit component should be included in such evaluations.

(3) The minimum effective dose of vitamin A and the maximum interval between the doses in periodic massive dose programmes should be determined.

The administration of 200 000 IU of vitamin A once every 6 months to preschool children has been shown to reduce the incidence of mild ocular signs of vitamin A deficiency by about 70–75% and also to maintain blood levels of the vitamin above the presupplementation levels for periods ranging from 4 to 13 months. It is desirable to undertake additional control studies on a pilot scale to determine the effect of different forms of vitamin A, different dosages, various routes administration, various methods of dispersion (Annex 2), and periodicity of dosing on the degree of protection provided. A control group should be included along with the experimental group in these studies.

The size of the dose is at present limited by the occurrence occasional, transient, untoward side-effects. It is recommended that studies should be undertaken to identify either less toxic forms of vitamin A or ways, such as the possible addition of vitamin E, in which the toxicity can be controlled. Investigations may also undertaken to devise methods of improving the overall absorption, storage, and utilization of a massive dose of vitamin A. The possibility of preventing vitamin A deficiencies during the first year of life by improving the vitamin A status of lactating mothers should also be further investigated.

8.4 Contributions made by horticulture and food technology

(1) Ways should be found of improving and regulating the production and marketing of fruit and vegetables to reduce losses and increase year-round availability at reasonable and stable prices.

(2) Varieties of fruits and vegetables should be bred for improved nutritive values ; production of indigenous varieties should be stimulated and improved.

(3) Ways should be sought to strengthen the association between agricultural production and nutritional needs of populations at risk.

(4) Suitable vehicles for fortification programmes in high risk communities should be identified.

(5) Data should be collected on current production and consumption practices regarding carotene-containing foods to determine the use of non-cultivated sources of vitamin A and carotene and these foods should be analysed to determine the nutrients present. Home gardens should be improved and extended even in urban areas.

SUMMARY

In man, and especially in infants and preschool children, vitamin A deficiency most commonly affects the eyes—internally by impairing dark adaptation and leading finally to night blindness, externally by producing destructive lesions of the cornea that often result in blindness. Vitamin A deficiency is usually accompanied by protein-energy malnutrition (PEM) and is frequently precipitated by infections, particularly gastroenteritis and measles.

In spite of improvements in standards of living in many parts of the world during the last few decades, vitamin A deficiency is still a significant health problem in much of South and South-East Asia, in parts of Africa and South America, and in some areas of the Middle East. Vitamin A deficiency has recently reappeared in some areas where it had been controlled and has been shown to exist in areas where it was not previously reported.

For many years a number of clinical, biochemical, and dietary indicators have been used for detecting vitamin A deficiency. Rough guidelines for prevalence were set, and some preventive programmes launched, on the basis of such indications. Unfortunately, earlier efforts often suffered from isolation, unstandardized methods and treatment, and the use of methods and techniques whose value, in retrospect, proved to be uncertain.

In recent years knowledge about the metabolism of vitamin A has greatly increased, clinical procedures and classification systems have

been improved, the unit cost of vitamin A has fallen to a reasonable level, and techniques for handling vitamin A have been greatly refined and extended. These developments are important and far-reaching, and it is now possible to define modern concepts and propose guidelines for improving the state of vitamin A nutrition throughout the world.

Definitions

An individual's wellbeing with respect to vitamin A can be defined in terms of *vitamin A status*, which might vary from *poor* through *marginal* to *acceptable*, and even to *excessive* (see accompanying table).

Vitamin A status	Clinical signs	Plasma vitamin A level	Liver vitamin A level	Dietary vitamin A intake
Poor	Xerophthalmia, night blindness, association with PEM and infections	Low	Very low	Very low
Marginal	None known	Low to normal	Low	Low
Acceptable	None	Normal	Adequate	Adequate
Excessive	Headache, vomiting, anorexia	Abnormally high	High	Excessively large doses of vitamin A

An *acceptable* status is defined in terms of a protection period, that the time during which an individual might function normally on a amin-A-deficient diet. Hypothetical protection periods can be roughly calculated on the basis of concentrations of vitamin A in the liver, where 90% or more of total body reserves of vitamin A are stored.

A *marginal* status is defined as the state in which liver reserves are inadequate to protect an individual for a minimally acceptable period, but in which clinical signs are not apparent.

A *poor* status is a state of deficiency, characterized by a group of biochemical indicators and clinical signs of increasing severity. In this state vitamin A levels in the plasma and liver are markedly reduced and the dietary intake of vitamin A and carotenoid vitamin precursors is very limited.

Predominant among clinical signs is xerophthalmia. Because of its importance as a clinical sign and its direct association with blindness, the term " xerophthalmia " has also been used more broadly to encompass the whole syndrome of severe vitamin A deficiency.

Assessment of the problem

Classification of ocular signs of xerophthalmia

The diagnosis of xerophthalmia depends upon the proper identification of classical ocular signs. In order to facilitate the reporting and comparison of data from different countries a uniform classification of ocular lesions is proposed. Primary signs are indicative of clinically active vitamin A deficiency and are relatively easily detected in the hospital and field. Secondary signs are either difficult to assess, less specific, or unrelated to active disease.

Classification	*Signs—primary*
X1A	Conjunctival xerosis
X1B	Bitot's spot with conjunctival xerosis
X2	Corneal xerosis
X3A	Corneal ulceration with xerosis
X3B	Keratomalacia
	Signs—secondary
XN	Night blindness
XF	Xerophthalmia fundus
XS	Corneal scars

Explanatory notes on the classification :

(1) These signs are descriptive rather than diagnostic ; all signs seen at the time of examination are recorded.

(2) In general, a progression of severity is reflected in the classification of primary signs.

(3) The classification can be used both in field surveys and in the routine recording of findings in patients in hospitals and clinics.

(4) When tabulating the frequency of these signs each child should be included only once, under his or her most severe sign.

(5) Only those Bitot's spots accompanied by conjunctival xerosis, usually in the 0–5 years age group, are indicative of vitamin A deficiency. This xerosis may be hidden by the overlying foam of the Bitot's spots and revealed only when this is rubbed away.

(6) Secondary signs often occur in association with or result from vitamin A deficiency and should be noted separately. However,

their importance should not be underestimated because they may constitute major criteria in the assessment of the prevalence of xerophthalmia.

Assessment

The first step in any vitamin A programme should be proper assessment of vitamin A status, including clinical xerophthalmia, in the target population. Study of clinic and hospital statistics and the impressions of experienced physicians, and a knowledge of the general nutritional status and dietary habits of the population suggest whether or not a significant problem is likely to exist. However, only a carefully conducted prevalence survey can reveal the magnitude, severity, and geographical distribution of the problem and serve as an adequate basis for assessing the effectiveness of any intervention programme. Some criteria, admittedly arbitrary, are suggested as a means of determining whether there in a significant public health problem. These criteria should not be interpreted rigidly. The final determination of significance rests with the national health officials concerned and will vary with local conditions, particularly the available resources and competing priorities.

Proposed criteria for determining whether a significant public health problem of xerophthalmia and vitamin A deficiency exists

The following criteria are suggested for community diagnosis of xerophthalmia and vitamin A deficiency.

Clinical

1. X1B in more than 2.0% of the population at risk
2. X2 + X3A + X3B in more than 0.01% of the population at risk
3. XS (attributable to vitamin A deficiency) in more than 0.1% of the population at risk

Biochemical

4. Plasma vitamin A level of less than 10 μg/100 ml in more than 5.0% of the population at risk

Explanatory notes on the criteria :

(1) The proposed tests should be designed and carried out by qualified personnel.

(2) These criteria apply only to children aged 0–5 years, i.e., the population " at risk ".

(3) The sample of children studied should be representative of the target population. The results apply to this population, and to this population only.

(4) The presence of one or more of the clinical criteria should be considered as evidence of a significant xerophthalmia problem.

(5) The biochemical criterion is strong corroborative evidence in association with any of the clinical criteria. Biochemical data alone are indicative only of significant vitamin A deficiency not of xerophthalmia.

When the objective is control and prevention of xerophthalmia and its sequelae, these parameters must be measured. When the objective is to improve the general vitamin A status of the population, in the absence of significant xerophthalmia measurement of the milder clinical signs (X1B) and/or biochemical status is sufficient.

Treatment

The massive dose technique is particularly useful when a child is hospitalized with xerophthalmia. The following protocol is recommended.

Recommended preparations of vitamin A

Formulation	*Route*	*Dosage*
Water miscible	Intramuscular	100 000 IU
Oil solution (in combination with vitamin E)	Oral	100 000 IU
		200 000 IU

Treatment schedule

Immediately on diagnosis	100 000 IU ; water-miscible preparation, intramuscular
Second day	100 000 IU ; oil solution, oral
Prior to discharge (patients under 1 year of age)	100 000 IU ; oil solution, oral
(patients over 1 year of age)	200 000 IU ; oil solution, oral

Explanatory notes :

(1) Retinyl palmitate is the preferred active form of vitamin A in water-miscible formulations for intramuscular injection.

(2) Upon diagnosis, an oil solution of vitamin A (100 000 IU) should be substituted only if an intramuscular preparation is not available. Hospitals in areas where xerophthalmia is endemic should keep water-miscible intramuscular preparations of vitamin A on hand at all times.

(3) Oral water-miscible preparations of vitamin A may be substituted for oil solutions; vitamin A acetate may be used in place of retinyl palmitate in oil solutions for oral use.

(4) Oil solutions of vitamin A should *never* be injected intramuscularly because they are relatively ineffective, the vitamin being liberated extremely slowly, if at all, from the injection site.

Control, prevention, and evaluation

Where xerophthalmia is a serious problem consideration should be given to the possibility of introducing a control programme that is likely to make a major impact at an early stage and at the same time initiating other activities that may, in the long run, prevent the disease. Certain countries that have the necessary resources and motivation may, however, decide to introduce a comprehensive control programme in order to improve vitamin A intakes, even in the absence of a xerophthalmia problem.

In either case the objective of the programme should be clearly defined at the outset and the activities suited to the needs of the population and the existing situation. The objective of a programme to control xerophthalmia will usually be to eliminate in the target population vitamin A deficiency of the degree that leads to destructive eye lesions. On the other hand, the objective of a programme to control vitamin A deficiency should be to ensure that the vitamin A status of the large majority of the target population reaches an acceptable level in a given period of time.

Control and prevention

Among the available strategies to prevent and control vitamin A deficiency and xerophthalmia are the following.

Periodic massive dose programmes. In these programmes the generally recommended method is to provide 100 000 IU of vitamin A to children under 1 year of age and 200 000 IU of vitamin A with vitamin E to

children 1–6 years of age every 6 months. A delivery system has to be devised that will as far as possible ensure that children at the greatest risk receive these doses. Such children are often the most difficult to reach ; they come from the poorest families, are the least likely to utilize existing health and other services, and tend to live in places that are highly inaccessible. Massive dose programmes are suitable only for areas where there is a xerophthalmia problem.

Fortification of foods. Fortification of foods with appropriate amounts of vitamin A has the advantage of reaching all those who consume the fortified food and requires neither the active participation of the population nor an elaborate and costly delivery system. The problem, however, is to select a food vehicle for fortification that is widely consumed, especially by children at risk, shows little variation in *per capita* consumption, passes through a manufacturing process where fortification is feasible, and is suitable organoleptically for fortification. In addition, the fortified food product should be stable. At present in various parts of the world where vitamin A deficiency and xerophthalmia are considered to be serious problems dried milk and cereal grain products, sugar, tea, and monosodium glutamate are fortified with vitamin A. A well developed technology now exists for adding vitamin A to many types of food.

Public health measures. Health services need to be in a position to detect the presence of vitamin A deficiency and xerophthalmia in the community to estimate the prevalence of the conditions ; to provide some indication of their epidemiology ; and to have the staff and facilities to ensure early treatment of patients and carry out preventive measures in the community. All health units, even in the most remote locations, should at all times maintain stocks of vitamin A for treatment and " prophylaxis ". In high-risk areas where massive dose programmes or food fortification measures are not in operation, regular routine dosing with vitamin A of all young children and pregnant and lactating women attending hospitals, maternal and child health clinics, and other health units should be considered. The control of diseases, such as measles, diarrhoea, and PEM, known to be related to xerophthalmia should be undertaken.

Horticultural and food production activities. Efforts to increase production and consumption of foods containing carotenoid precursors of vitamin A should be a feature of most programmes designed to reduce vitamin A deficiency.

Nutrition education. Use of educational methods, including the mass media of communication (radio, television, etc.), should be an integral part of all vitamin A programmes.

Recommendations for prevention

The long-term solution to the problem of vitamin A deficiency must lie in improvement of dietary intakes of vitamin A and provitamin A by young children—the vulnerable age group. If the consumption of green leafy vegetables and suitable fresh fruits by this group could be substantially increased, there is every reason to believe that the problem would be solved. It is certainly true to say that in those countries and communities where the vitamin A intake is not low xerophthalmia does not exist, even if PEM and other contributory diseases are prevalent. The etiology of both PEM and xerophthalmia is complex, but while PEM usually does not respond to single preventive measures xerophthalmia will disappear it the intake of carotenoid vitamin A precursors is raised. Xerophthalmia can also be prevented by programmes such as periodic massive dosing or fortification of an appropriate food, if one is available.

Evaluation

It is important to evaluate all programmes for prevention or control of xerophthalmia. Evaluation should cover the operation of the programme as well as its effectiveness in reducing the prevalence of xerophthalmia or vitamin A deficiency. In some circumstances it might be valuable to evaluate also the relative effectiveness of alternative strategies of control. For successful evaluation adequate baseline data must be collected prior to the initiation of the programme.

The criteria to be employed for measuring the effectiveness of the programme are those discussed in the section on assessment of the problem (p. 69) and might include clinical, biochemical, and dietary data. Wherever possible cost-effectiveness studies should be undertaken; this is particularly important if the relative effectiveness of alternative control measures is being evaluated.

Research

Research should be related to (1) methods for assessing vitamin A status; (2) epidemiology and prevalence of xerophthalmia; and (3) action programmes.

Methods for assessing vitamin A status

Clinical :

(1) development of better descriptions and means of assessment of eye changes related to vitamin A deficiency ;

(2) continuing evaluation of the application of the xerophthalmia classification (see p. 68).

Biochemical. Standardization of methods for estimating vitamin A in plasma and liver suitable for use under field conditions.

Dietary. Improvement of methods for determining the vitamin A value of diets consumed particularly by young children.

Epidemiology and prevalence

Action is needed in the following areas :

(1) improvement of the characterization of the child " at risk " to vitamin A deficiency and xerophthalmia in relation to sociocultural and ecological conditions ;

(2) evaluation of the criteria for determining whether vitamin A deficiency is a significant public health problem ;

(3) compilation of data on global and local prevalence of xerophthalmia and vitamin A deficiency and the establishment of a regular monitoring system ;

(4) surveillance of health status, particularly in relation to the vitamin A status of vulnerable groups through points 1 and 3 above.

Action programmes

(1) Required activities are : investigation of alternative interventions, e.g., periodic massive dose programmes, food fortification, promotion of dietary use of dark green leafy vegetables and other rich sources of vitamin A, and nutrition education aimed at mothers of young children.

(2) Evaluation of action programmes.

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Annex 1

XEROPHTHALMIA SURVEY FORM

This clinical field survey form is designed for use by an ophthalmologist, and is sufficiently detailed to arrive at reasonably definitive estimates of the prevalence of xerophthalmia. The investigator may wish to make the form more elaborate for research purposes, or more condensed for screening programmes staffed by auxiliary personnel. The form should be expanded to include other anterior segment abnormalities (cataracts, trachomatous lesions, etc.) when necessary.

Use of the form

As a preliminary a nurse or auxiliary worker should visit every house in the sample area, compile identifying data on every eligible child (i.e., those within the selected age group), whether present or not, and collect all available eligible children at a central point for ancillary studies (height, weight, serum vitamin A levels, etc.) and examination by the ophthalmologist.

The ophthalmologist, or his assistant, should mark with a ring every appropriate finding. A "summation" technique has been employed to maintain discrete recording of each sign while economizing on punch-card columns. This summation should be carried out by a clerk at the survey office rather than during the field work.

In assessing visual acuity (30 and 31 on the form) the ophthalmologist estimates whether the potential visual acuity (clarity of the media) of the anterior segment of the eye is better than 20/200 (6/60) or not. If it is worse than 20/200 he reports what the structural abnormality is and his estimate of the probable cause.

Circles are drawn to represent the cornea. The location and size of corneal lesions should be indicated on these circles. The location and size of the leucoma or leucomas should be indicated (42, 43). In all cases of corneal destruction (40–45) the following history should be obtained from a responsible adult (46, 47):

(1) age of onset (congenital against early childhood, etc.);

(2) a clear history of whether or not there is trauma;

(3) measles (rash) preceding onset by 0–2 weeks;

(4) grossly purulent discharge as evidence of infection ;

(5) severe malnutrition ;

(6) systemic disease.

The most likely cause of the corneal abnormality, in the light of available clinical and historical data, is indicated (48, 49).

OCULAR EXAMINATION RECORD FORM

Examining ophthalmologist

Name .....

Signature .....

ESTIMATE OF POTENTIAL VISUAL ACUITY

(30) right eye .....

(31) left eye .....

1 Better than 20/200
2 Equal to or worse than 20/200
3 Uncertain

If equal to or worse than 20/200

structural abnormality is .....

.....

probable cause of the abnormality is

.....

CONJUNCTIVA

Infection

Right eye		*Left eye*	
1	Conjunctivitis	1	Conjunctivitis
2	Purulent	2	Purulent
9	Uncertain	9	Uncertain

(32) ..... Sum of 1, 2, or 9 (right eye)

(33) ..... Sum of 1, 2, or 9 (left eye)

Consistency

1	Dry (xerosis)	1	Dry (xerosis)
2	Wrinkling, thickening	2	Wrinkling, thickening
4	Diffuse pigmentation	4	Diffuse pigmentation
9	Uncertain	9	Uncertain

CONJUNCTIVA (continued)

(34) ..... Sum of 1, 2, 4, or 9 (right eye)

(35) ..... Sum of 1, 2, 4, or 9 (left eye)

Accretions

Right eye

1 Bitot's spot
2 Foam on cornea or conjunctiva
9 Uncertain

Left eye

1 Bitot's spot
2 Foam on cornea or conjunctiva
9 Uncertain

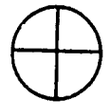
(36) ..... Sum of 1, 2, or 9 (right eye)

(37) ..... Sum of 1, 2, or 9 (left eye)

CORNEA

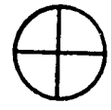
Right eye

1 Dryness (xerosis)
2 Epithelial erosion
4 Ulcer
9 Uncertain



Left eye

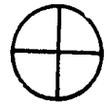
1 Dryness (xerosis)
2 Epithelial erosion
4 Ulcer
9 Uncertain



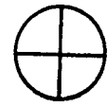
(38) ..... Sum of 1, 2, 4, or 9 (right eye)

(39) ..... Sum of 1, 2, 4, or 9 (left eye)

1 Keratomalacia
2 Descemetocele
4 Perforation
9 Uncertain



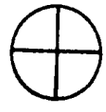
1 Keratomalacia
2 Descemetocele
4 Perforation
9 Uncertain



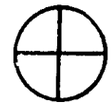
(40) ..... Sum of 1, 2, 4, or 9 (right eye)

(41) ..... Sum of 1, 2, 4, or 9 (left eye)

1 Leucoma
2 Adherent leucoma
9 Uncertain



1 Leucoma
2 Adherent leucoma
9 Uncertain

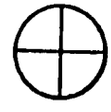


(42) ..... Sum of 1, 2, or 9 (right eye)

(43) ..... Sum of 1, 2, or 9 (left eye)

1 Staphyloma
2 Phthisis bulbi
9 Uncertain

1 Staphyloma
2 Phthisis bulbi
9 Uncertain



(44) ..... Sum of 1, 2, or 9 (right eye)

(45) ..... Sum of 1, 2, or 9 (left eye)

If any of 40–45 is positive, was there a history available?

Right eye	*Left eye*
1 Yes	1 Yes
2 No	2 No
4 Unclear	4 Unclear

(46) ..... Sum of 1, 2, or 4 (right eye)

(47) ..... Sum of 1, 2, or 4 (left eye)

Diagnosis based on clinical examination and history is:

Right eye	*Left eye*
1 Trauma	1 Trauma
2 Measles	2 Measles
3 Other infection	3 Other infection
4 Congenital	4 Congenital
5 Keratomalacia	5 Keratomalacia
6 Other	6 Other
7 Uncertain	7 Uncertain

(48) ..... Right eye

(49) ..... Left eye

History of onset of lesion:

(1) Age of onset
(2) Trauma
(3) Measles
(4) Purulent discharge
(5) Severe malnutrition
(6) Systemic disease (e.g., respiratory infection, gastroenteritis)

Annex 2

ADVANTAGES AND DISADVANTAGES OF VARIOUS DOSAGE FORMS OF VITAMIN A WITH OR WITHOUT THE ADDITION OF VITAMIN E [a]

Product	Advantages	Disadvantages
1. Opaque glass container of oil solution with calibrated dropper or spoon	Most economical; good stability in closed containers; drops easily placed on tongue; an acceptable flavour can be added	Not a unit dose—dose has to be measured; possible containination of container through frequent removal and return of dropper; possibility of breaking container or spilling the contents
2. 1-piece soft gelatin capsule with a nipple containing oil solution	Excellent stability in sealed capsule; is presented as a unit dose; can be swallowed whole or, by cutting off the nipple, the contents can be squeezed on to the tongue; small size for high vitamin potency	In humid atmospheric conditions, unprotected capsules absorb moisture, stick together, and are subject to microbial contamination; containers with good seals and reseals required
3. Bulk opaque container of water-emulsifiable concentrate	See advantages under (1); preparation will emulsify in the digestive tract, speeding up absorption	See disadvantages under (1)
4. 1-piece soft gelatin capsule with a nipple containing water-emulsifiable concentrate	See advantages under (2); preparation will emulsify in the digestive tract, speeding up absorption	See disadvantages under (2)
5. Plastic or metal container of dry vitamin beadlets with volume measuring device	Good stability in sealed containers; is a warm-water-miscible physical form, hence reconstitutable; can be formulated with flavours	Not a unit dose—dose has to be measured; personnel required to prepare and administer the beverage; unprotected beadlets absorb moisture in humid atmospheric conditions, accelerating deterioration
6. 2-piece hard shell capsule containing dry vitamin beadlets (with or without sweetener and flavours)	Good stability in sealed capsules; is presented as a unit dose; can be swallowed, whole or, when opened, the contents can be consumed alone or added to food	For children too young to swallow capsules contents would have to be given in other ways, requiring staff time; the capsule is fairly large because the beadlets are bulky
7. Chewable tablet made with dry vitamin A beadlets (with sweetener and flavours)	Fairly good stability; is presented as a unit dose; is quickly chewed and/or swallowed	Child without teeth would have difficulty in consuming these tablets, which may, however, be crushed; problem of flavour acceptability by young infants; tablet size is fairly large owing to volume of excipients
8. Sterile unit containers for aqueous emulsion or dispersion	Good stability in sealed unit; is presented as a unit dose; water-dispersible form is rapidly absorbed	Requires special containers and processing in manufacture; fairly large unit size; problems may arise during shipment and field handling
9. Glass ampoule containing the vitamin in aqueous base composition for intramuscular administration in advanced stages of xerophthalmia	Good stability in sealed ampoules; is presented as a unit dose; is water-dispersible; bypasses digestive tract and hence no risk of loss through emesis	Most expensive form; requires use of sterile syringe; administration requires some skill; ampoules are subject to breakage; not generally used in the field

[a] BAUERNFEIND, J. C., unpublished observations.

Annex 3

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