Field guide to the detection and control of xerophthalmia

Second edition

A. SOMMER

World Health Organization

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By means of direct technical cooperation with its Member States, and by stimulating such cooperation among them, WHO promotes the development of comprehensive health services, the prevention and control of diseases, the improvement of environmental conditions, the development of health manpower, the coordination and development of biomedical and health services research, and the planning and implementation of health programmes.

These broad fields of endeavour encompass a wide variety of activities, such as developing systems of primary health care that reach the whole population of Member countries; promoting the health of mothers and children; combating malnutrition; controlling malaria and other communicable diseases including tuberculosis and leprosy; having achieved the eradication of smallpox, promoting mass immunization campaigns against a number of other preventable diseases; improving mental health; providing safe water supplies; and training health personnel of all categories.

Progress towards better health throughout the world also demands international cooperation in such matters as establishing international standards for biological substances, pesticides and pharmaceuticals; formulating environmental health criteria; recommending international nonproprietary names for drugs; administering the International Health Regulations; revising the International Classification of Diseases, Injuries, and Causes of Death; and collecting and disseminating health statistical information.

Further information on many aspects of WHO's work is presented in the Organization's publications.

FIELD GUIDE TO THE DETECTION AND CONTROL OF XEROPHTHALMIA

Second Edition

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PREFACE

XEROPHTHALMIA remains the most important cause of childhood blindness in many developing countries. Recognizing the gravity of the situation, the Twenty-fifth World Health Assembly in 1972 urged an intensification of activities to prevent needless loss of sight, identifying xerophthalmia as one of the three most important causes of preventable blindness in the world today.

The first edition of this manual was published in 1978 to meet the need that had been expressed by various agencies and governments for a simple, practical guide for use by clinicians, nurses, and public health officials concerned with preventing this appalling disease. Recent advances in our understanding of the clinical manifestations, pathogenesis, epidemiology, and treatment of xerophthalmia[1] have led to revisions of the classification of the disease, of the prevalence criteria for determining when it constitutes a significant public health problem, and of recommended treatment schedules;[2] these, in turn, have made it necessary to revise the manual and publish this updated, second edition.

[1] SOMMER, A. *Nutritional blindness: xerophthalmia and keratomalacia*, New York, Oxford University Press, 1982.

[2] *Control of vitamin A deficiency and xerophthalmia. Report of a joint WHO/USAID/UNICEF/HKI/IVACG Meeting*, Geneva, World Health Organization, 1982 (WHO Technical Report Series, No. 672).

INTRODUCTION

XEROPHTHALMIA is the general term applied to all the ocular manifestations of impaired vitamin A metabolism, from night blindness through complete corneal destruction (keratomalacia). It is among the oldest recorded afflictions of mankind, having been recognized by both the ancient Egyptians and the Greeks. As recently as the late nineteenth and early twentieth centuries numerous cases still occurred among malnourished individuals in such widely scattered parts of the globe as Brazil, China, England, Japan, Denmark, and Russia.

Today blinding xerophthalmia is largely limited to developing countries, especially those in Africa, Asia, and the Western Pacific. Isolated foci also exist in the Caribbean, Latin America, and the Eastern Mediterranean.[1,2] Recent data indicate that at least 5 million children in Asia develop xerophthalmia every year, 250 000 of whom go blind.[3]

Modern concepts of the disease date from the early 1800s, when dogs that were "starved" on sugar and distilled water developed perforating corneal ulcers resembling those in "ill-nourished infants."[4] It took one hundred years before investigators realized that these changes were due to lack of a specific nutrient,[5-7] "fat-soluble A", present in the lipid fraction of milk, eggs, butter and cod-liver oil, or as provitamin A carotenoids in dark-green leafy vegetables and certain coloured fruits. Histophathological observations soon demonstrated the importance of vitamin A for the maintenance of normal epithelial integrity.[8]

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[1] SOMMER, A. *Nutritional blindness: xerophthalmia and keratomalacia,* New York, Oxford University Press, 1982.

[2] *Control of vitamin A deficiency and xerophthalmia. Report of a joint WHO/USAID/-UNICEF/HKI/IVACG meeting,* Geneva, World Health Organization, 1982 (WHO Technical Report Series, No. 672).

[3] SOMMER, A. et al. *Lancet,* **2**: 1407 (1981).

[4] MACKENZIE, W. *A practical treatise of diseases of the eye,* London, Longman, 1830.

[5] GOLDSCHMIDT, M. *Graefe's Arch. Ophthalmol.,* **90**: 354 (1915).

[6] McCOLLUM, E. V. & SIMMONDS, N. *Biol. Chem.,* **32**: 181 (1917).

[7] BLOCH, C. E. *J. Hyg.,* **19**: 283 (1921).

[8] WOLBACH, S. B. & HOWE, P. R. *J. exp. Med.,* **47**: 753 (1925); *Arch. Pathol. Lab. Med.,* **5**: 239 (1928).

VITAMIN A METABOLISM

VITAMIN A, or retinol, is a fat-soluble substance found in liver, particularly fish liver, and in poultry, meat, and dairy products. Carotenes—potential precursors present in green leafy vegetables, red palm oil, yellow fruits, and the like—can be converted to retinol in the wall of the gut. The relative biological values of these various substances were formerly expressed in international units (IU) of vitamin A activity,[1] 1 IU being equivalent to 0.3 μg of retinol, 0.55 μg of retinol palmitate, 0.6 μg of β-carotene, and 1.2 μg of other provitamin A carotenoids. Not only are carotenes biologically less active than retinol, but their dietary sources are less efficiently processed and absorbed from the gut. One must therefore ingest up to six times as much provitamin A β-carotene (by weight) as retinol for a similar degree of effect.

Some 50–90% of ingested retinol is absorbed in the small intestine and transported, in association with chylomicra, to the liver, where it is stored primarily as retinol palmitate. When needed, it is released into the bloodstream in combination with retinol-binding protein (RBP), a specific carrier protein elaborated by the liver. The retinol is then removed from the serum and utilized by epithelial cells throughout the body. The diagram overleaf gives a simplified schematic outline of these metabolic pathways.

The liver stores form an important buffer for variations in vitamin A and β-carotene intake. When vitamin A intake surpasses 300–1200 μg/day of retinol, or its equivalent, the excess is stored and liver reserves are increased. When vitamin A intake is less than this amount, liver stores are drained to maintain serum retinol (vitamin A) at a normal level (above 200 μg/l or 0.7 μmol/l). When intake remains low for prolonged periods of time the liver stores become depleted, serum retinol levels drop, epithelial function is impaired, and xerophthalmia appears. The duration of inadequate intake required for this to occur depends upon the amount of vitamin A (or precursor) ingested, the extent of pre-existing liver stores, and the rate at which vitamin A is being utilized by the body.

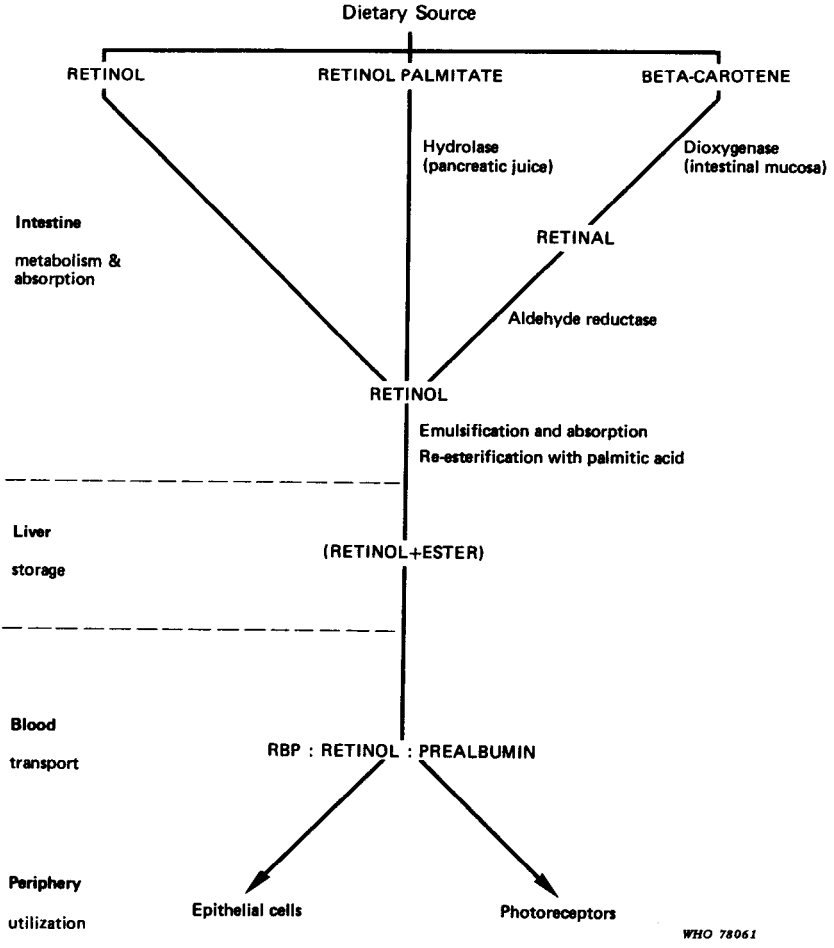
A child with borderline, marginal intake to begin with will have very limited stores. Any sudden drop in intake, either from a change in diet or interference with absorption (as in gastroenteritis) or a sudden

[1] The international units for vitamin A and provitamin A were discontinued in 1954 and 1956 respectively. However, since their use persists, particularly in the labelling of capsules and injectable preparations, all intakes and dosages mentioned in this book are expressed both in micrograms (μg) or milligrams (mg) and in the former international units.

increase in metabolic demand (febrile state or growth spurt), will quickly deplete the limited reserves and may precipitate frank corneal destruction, even in eyes that had previously appeared entirely normal. Where liver stores have been very high, however, an individual may go for months without vitamin A and not suffer serious consequences.

The availability of stored vitamin A will also depend upon the child's general nutritional status. Severely malnourished, protein-deficient children synthesize RBP at a much reduced rate. Serum retinol levels will therefore be subnormal, even if liver stores are high. Finally, a diseased liver cannot store as much vitamin, or make as much RBP, as a normal one.

SCHEMA OF VITAMIN A METABOLISM



CLINICAL CLASSIFICATION AND DIAGNOSIS

VITAMIN A deficiency is a systemic disease affecting epithelial structures in a variety of organs, the eye being the most obvious and dramatic example. Keratinizing metaplasia of the respiratory and intestinal epithelia is thought to be responsible for the pulmonary and gastrointestinal symptoms found in the most severely affected children. But the classic clinical expression is xerophthalmia, or "dry eye".

Uncomplicated, gradual depletion of vitamin A stores results in xerophthalmia of increasing severity: night blindness, conjunctival xerosis and Bitot's spot, corneal xerosis, and corneal ulceration/keratomalacia (Fig. 1 and 2).[1] All usually respond rapidly to vitamin A therapy, the milder manifestations usually clearing without significant sequelae. The loss of deep corneal tissue, however, from ulceration/-keratomalacia generally results in scarring and residual opacification.

The major signs and symptoms of xerophthalmia were recently reclassified (Table 1).[2] Experience has shown that, in the appropriate

Table 1. Classification of xerophthalmia (1982 revision)

XN	Night blindness
X1A	Conjunctival xerosis
X1B	Bitot's spot
X2	Corneal xerosis
X3A	Corneal ulceration/keratomalacia $< 1/3$ corneal surface
X3B	Corneal ulceration/keratomalacia $\geq 1/3$ corneal surface
XS	Corneal scar
XF	Xerophthalmic fundus

[1] SOMMER, A. *Nutritional blindness: xerophthalmia and keratomalacia*, New York, Oxford University Press, 1982.

[2] *Control of vitamin A deficiency and xerophthalmia. Report of a joint WHO/USAID/-UNICEF/HKI/IVACG Meeting*, Geneva, World Health Organization, 1982 (WHO Technical Report Series, No. 672).

setting, a history of night blindness and characteristic retinal specks are both highly specific for xerophthalmia, eliminating the need to distinguish between "primary" and "secondary" signs. All Bitot's spots are accompanied by underlying xerosis; hence the presence of xerosis does not distinguish new, active lesions from old, residual ones. And the extent of active corneal destruction (ulceration/keratomalacia) is a better index of visual prognosis than is its appearance, and therefore a better basis for subclassifying the severity of involvement.

XN. Night blindness

Retinol is essential for the elaboration of rhodopsin (visual purple) by the rods, the sensory receptors of the retina responsible for vision under low levels of illumination. Vitamin A deficiency can interfere with rhodopsin production, impair rod function, and result in night blindness.

Night blindness is generally the earliest manifestation of vitamin A deficiency. When mild, it may become apparent only after a photic stress, such as flying a kite on a sunny day. Affected children no longer move about the house or village after dusk, but prefer to sit in a secure corner, often unable to find their food or toys.

Night blindness of recent onset in a preschool child is practically pathognomonic of vitamin A deficiency. Other causes of night blindness are relatively rare and almost never present in this fashion. Among some societies or cultures, particularly those in which vitamin A deficiency is endemic, specific terms exist to describe the condition, such as "chicken eyes" (lacking rods, chickens are night-blind).

Mothers do not always recognize the presence of night blindness, especially among children who have not yet begun to crawl or toddle. When a mother does complain that it is present, however, she is almost certainly correct,[1,2] and this makes objective assessment unnecessary in most routine clinical situations.

Night blindness responds rapidly, usually within 24–48 hours, to vitamin A therapy.

X1A, X1B. Conjunctival xerosis and Bitot's spot

Alterations in epithelial architecture accompanying vitamin A deficiency are termed "keratinizing metaplasia". The epithelium of the conjunctiva is transformed from the normal columnar to the stratified

[1] SOMMER, A., et al. *Am. J. Clin. Nutr.*, **33**: 887 (1980).
[2] GUPTA, M. C. & TANDON, B. N. *Am. J. Clin. Nutr.*, **34**: 1985 (1981).

squamous type, with a resultant loss of goblet cells, formation of a granular cell layer (Fig. 3), and keratinization of the surface (Fig. 4). This is the histopathological picture of conjunctival xerosis.

Clinically, these changes are expressed as marked dryness or unwettability, the affected area appearing roughened, with fine droplets or bubbles on the surface, rather than smooth and glistening. These changes may be obscured if there is heavy tear-shedding. As the tears drain off, however, the affected area will emerge like "sandbanks at receding tide". Abnormalities are best detected with an oblique illumination.

Conjunctival xerosis first appears in the temporal quadrant, as an isolated oval or triangular patch adjacent to the limbus in the interpalpebral fissure (Fig. 5 and 6). It is almost always present in both eyes. In some individuals keratin and saprophytic bacilli accumulate on the xerotic surface, giving it a foamy or cheesy appearance. Such lesions are known as Bitot's spots (Fig. 7–13). The overlying material is easily wiped off, the amount present often varying from day to day. With more severe deficiency, similar, though less prominent lesions form in the nasal quadrant.

Bitot's spot should not be confused with pinguecula or pterygium, which are more often nasal than temporal and limited, for the most part, to adults. Pinguecula is an elevated, fatty, yellowish lesion. Pterygium is fleshy and actually invades the cornea (Fig. 14).

Generalized conjunctival xerosis, involving the inferior and/or superior quadrants, suggests advanced vitamin A deficiency. The entire conjunctiva appears dry, roughened, and corrugated, sometimes skin-like (Fig. 15 and 16). There may be prominent conjunctival thickening and folds. This is an advanced lesion, almost always accompanied by gross corneal involvement.

Isolated, usually temporal, patches of conjunctival xerosis or Bitot's spot are sometimes encountered in the absence of active vitamin A deficiency. The affected individuals are usually of school age or older and may have a history of previous bouts of night blindness or xerophthalmia. In most instances these patches represent persistent areas of squamous metaplasia induced during a prior episode of vitamin A deficiency. The only certain means of distinguishing active from inactive lesions is to observe their response to vitamin A therapy. Active conjunctival xerosis and Bitot's spot begin to resolve within 2–5 days. Most will disappear within 2 weeks, though a significant proportion of temporal lesions may persist, in shrunken form, for months.

X2. Corneal xerosis

Corneal changes begin early in vitamin A deficiency, long before they can be seen with the naked eye. Many children with night blindness (without clinically evident conjunctival xerosis) have characteristic superficial punctate lesions of the inferior-nasal aspects of their cornea that stain brightly with fluorescein (Fig. 17). Early in the disease they are visible only through a slit-lamp biomicroscope.

With more severe disease the punctate lesions become more numerous and spread upwards over the central cornea, and the corneal stroma becomes oedematous. Clinically, the cornea develops classical xerosis, a hazy, lustreless, dry appearance, first apparent near the inferior limbus (Fig. 15, 16, 18, 19, 20). Thick, keratinized plaques resembling Bitot's spot may form, on the corneal surface (Fig. 21). These are often densest in the interpalpebral zone. With treatment, these corneal plaques peel off, sometimes leaving a superficial erosion which quickly heals.

Corneal xerosis responds within 2–5 days to vitamin A therapy, the cornea regaining its normal appearance in 1–2 weeks.

X3A, X3B. Corneal ulceration/keratomalacia

Ulceration/keratomalacia indicates permanent destruction of part or all of the corneal stroma, resulting in permanent structural alteration.

Ulcers are classically round to oval "punched-out" defects, as if a trephine or cork-borer had been applied to the eye (Fig. 22, 23). The surrounding cornea is generally xerotic but otherwise clear, and typically lacks the grey, infiltrated appearance of ulcers of bacterial origin (Fig. 24). There may be more than one ulcer. Small ulcers are almost invariably confined to the periphery of the cornea, especially its inferior and nasal aspects. The ulceration may be shallow, but is commonly deep. Perforations become plugged with iris, thereby preserving the anterior chamber. With therapy, superficial ulcers often heal with surprisingly little scarring; deeper ulcers, especially perforations, form dense peripheral adherent leukomas (Fig. 26).

Localized keratomalacia is a rapidly progressive condition affecting the full thickness of the cornea. It first appears as an opaque, grey to yellow mound or outpouching of the corneal surface (Fig. 25). In more advanced disease the necrotic stroma sloughs, leaving a large ulcer or descemetocele. As with smaller ulcers, these are usually peripheral and heal as dense, white, adherent leukomas (Fig. 26).

Ulceration/keratomalacia involving less than one-third of the corneal surface (X3A) generally spares the central pupillary zone; prompt therapy ordinarily preserves useful vision. More widespread involvement (X3B), especially generalized liquefactive necrosis (Fig. 27–29), usually results in perforation, extrusion of intraocular contents, and loss of the globe. Prompt therapy may still save the other eye and the child's life.

It is not always possible to distinguish cases of ulceration/necrosis due to vitamin A deficiency from those due to bacterial or fungal infections. The most obvious reason is that vitamin-A-related lesions can become secondarily infected. In addition, however, once ulceration/keratomalacia occurs, the conjunctiva usually becomes inflamed (Fig. 18 and 28), and for reasons that are not well understood, inflammation commonly masks or reverses conjunctival xerosis. Examination of the other, unulcerated eye, may then reveal the true nature of the problem. But not always. When vitamin A status deteriorates precipitously—as happens with measles, severe gastroenteritis, or kwashiorkor in children previously in borderline vitamin A balance—corneal necrosis can precede the appearance of night blindness or conjunctival xerosis. In such instances it is safest to assume that both vitamin A deficiency and infection are present and the child should be treated accordingly.

XS. Scars

Healed sequelae of prior corneal disease related to vitamin A deficiency include opacities or scars of varying density (nebula, macula, leukoma) as in Fig. 26, weakening and outpouching of the remaining corneal layers (staphyloma as in Fig. 31, and descemetocele as in Fig. 30) and, where loss of intraocular contents had occurred, phthisis bulbi, a scarred shrunken globe. Such end-stage lesions are not specific for xerophthalmia and may arise from numerous other conditions, notably trauma and infection.

XF. Xerophthalmic fundus

The small white retinal lesions described in some cases of vitamin A deficiency are at present of investigational interest only (Fig. 32). They may be accompanied by constriction of the visual fields and will largely disappear within 2–4 months of vitamin A therapy.