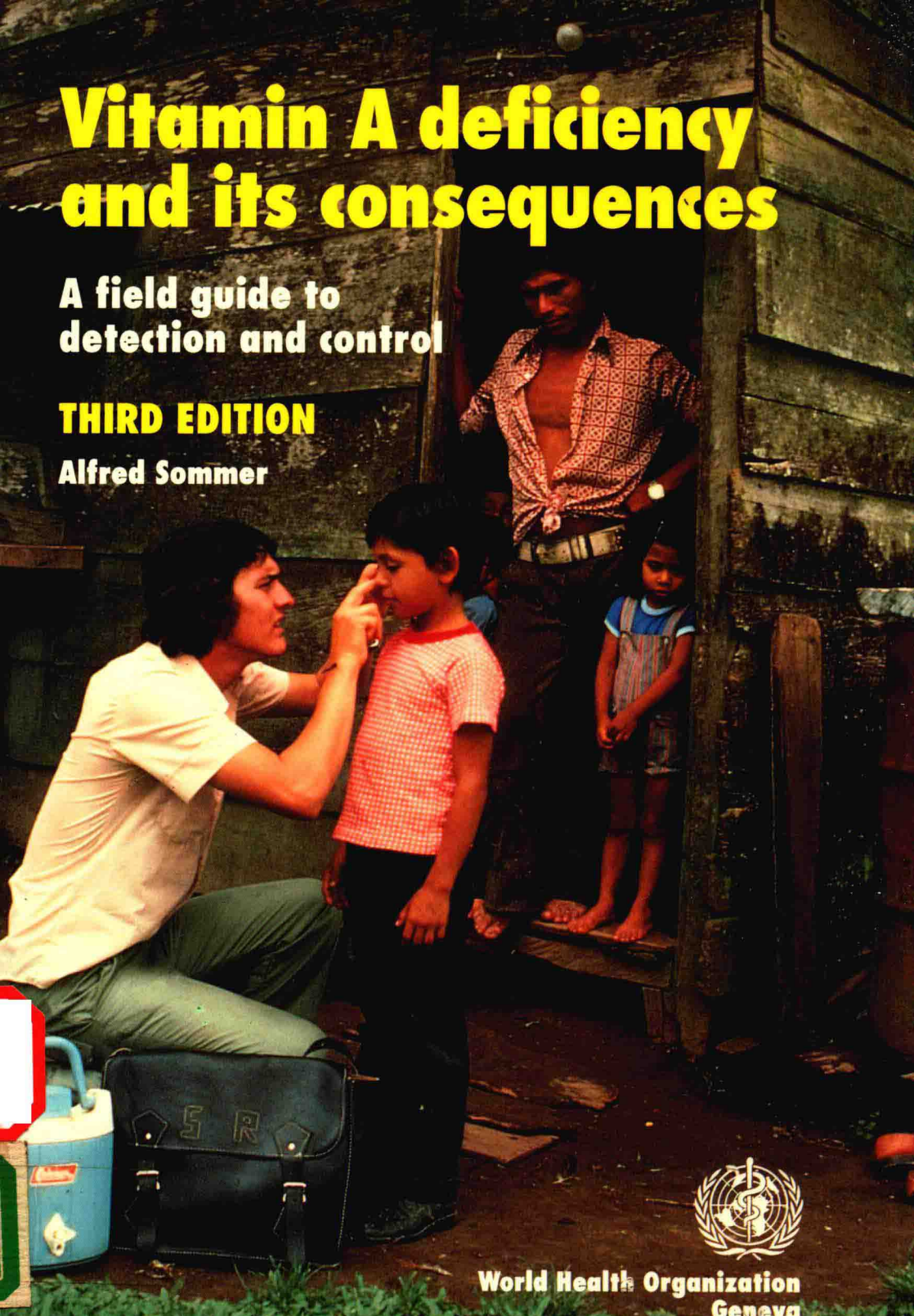
Vitamin A deficiency and its consequences

A field guide to detection and control

THIRD EDITION

Alfred Sommer



World Health Organization
Geneva

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Third edition

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PREFACE

The first edition of this manual was published in 1978 under the title *Field guide to the detection and control of xerophthalmia*, to meet the need for a practical guide for use by clinicians, nurses, and public health officials concerned with preventing xerophthalmia. This was in accord with a resolution of the Twenty-fifth World Health Assembly (1972), which urged an intensification of activities to prevent needless loss of sight from one of the three most important causes of preventable blindness.

A second edition of the manual was published in 1982 to reflect advances in understanding of the clinical manifestations, pathogenesis, epidemiology, and treatment of xerophthalmia (*1*); it included revisions to the clinical classification of the disease, prevalence criteria for establishing a public health problem, and treatment recommendations (*2*).

Since 1982, new information has increasingly pointed to the importance of vitamin A in the broader realm of child health and survival (*3–7*). This was recognized by the Thirty-seventh (1984) and Forty-fifth (1992) World Health Assemblies, which directed the World Health Organization to intensify its efforts to control the impact of vitamin A deficiency on child health, blindness, and survival. With extension and further refinement of this knowledge, growing commitment by governments to control and eliminate the problem — embodied notably in the World Declaration on the Survival, Protection and Development of Children (*8*) and the World Declaration and Plan of Action for Nutrition (*9*) — and programmatic momentum and leadership provided by WHO and UNICEF (*10*, *11*), it has again become necessary to revise and expand the scope of the original manual.

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CONTENTS

INTRODUCTION

Ocular manifestations of vitamin A deficiency, particularly night blindness, have been recognized since antiquity. Animal research and clinical observations early in the twentieth century indicated that vitamin A was important for numerous bodily functions: animals and humans deficient in vitamin A grew poorly, suffered more persistent or severe infections, and subsequently developed characteristic ocular manifestations termed "xerophthalmia" or "dry eye". Vitamin A-deficient animals died prematurely of overwhelming sepsis, usually before developing xerophthalmia.

Interest soon focused on the readily apparent, and devastating, ocular manifestations of vitamin A deficiency. By the early 1940s, these had been eliminated from wealthier countries through a variety of dietary interventions. Surveys subsequently revealed that vitamin A deficiency and xerophthalmia were largely limited to developing countries, especially in Africa, Asia, and the Western Pacific, with isolated foci in the Caribbean, Central and South America, and the Eastern Mediterranean (*1*, *2*). The World Health Organization now classifies countries according to evidence of subclinical as well as clinical deficiency in all or part of the territory. Accordingly, there are 39 countries in which vitamin A deficiency is a clinically significant public health problem, and 11 countries where, subclinically, it is sufficiently prevalent and severe as to constitute a serious public health problem; 27 countries where this is the case in at least some regions; and 18 other countries where there is likely to be a problem but where data are lacking and careful monitoring is called for. At least 5–10 million children develop xerophthalmia every year, of whom between a quarter and half a million go blind (*12*, *13*).

Modern concepts of xerophthalmia 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" (*14*). One hundred years elapsed before investigators realized that these changes were caused by lack of a specific nutrient (*15–17*), "fat soluble A", present in the lipid fraction of milk, eggs, butter, and cod-liver oil, and — as provitamin A carotenoids — in dark-green leafy vegetables and certain coloured fruits. Block noted that vitamin-A-deficient children were far more likely to develop urinary tract infections, and that vitamin A treatment cured the condition (*18*), and Mellanby dubbed vitamin A the "anti-infection vitamin" (*19*). Histopathological observations soon demonstrated the importance of vitamin A for maintenance of normal epithelial integrity (*20*), thus providing one possible explanation for its role in

resistance to infection. More recently, it has been suggested that vitamin A also affects immune competence (*21*).

Recent data indicate that mortality rates are increased among children with mild vitamin A deficiency (*22*) and that, in many areas, improvement in vitamin A status can reduce the risk of mortality from childhood infections by as much as 19–54% (*7*, *23–29*). The reduction in mortality that results from improvements in vitamin A status exceeds what would be expected solely from reducing the numbers of deaths associated with xerophthalmia: vitamin A deficiency appears to increase the risk of death even before xerophthalmia is clinically apparent. Vitamin A therapy reduces the severity of complications and the mortality rates associated with measles (*5*, *30–32*), and improvement in community vitamin A status reduces the subsequent risk of measles mortality (*26*, *28*, *29*). Thus, WHO and UNICEF recommend vitamin A supplementation as part of the case management of measles in populations among whom vitamin A deficiency is known to be a problem or measles case-fatality rates exceed 1% (*33*).

It is estimated that at least one million child deaths would be prevented each year if vitamin A nutriture were improved (*34*). The impact of improved vitamin A status on preschool mortality varies from one population to another and depends on a wide variety of factors. These include severity and prevalence of pre-existing vitamin A deficiency; concomitant nutritional and related disorders; and the type, intensity, and frequency of prevailing infections and related factors (*7*, *24*, *35*, *36*).

VITAMIN A METABOLISM

Vitamin A, or retinol, is a fat-soluble substance found in liver (particularly fish liver) and in egg yolk and dairy products. Carotenoids — potential provitamin A precursors that can be converted to retinol in the wall of the gut — are present in green leafy vegetables, red palm oil, yellow fruits, and the like. 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 retinyl palmitate, 0.6 μg of β-carotene, and 1.2 μg of other provitamin A carotenoids. Not only are carotenoids biologically less active than retinol, but their dietary sources are also less efficiently processed and absorbed from the gut. Thus, approximately six times as much provitamin A β-carotene (by mass) as retinol must be ingested for there to be a similar 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 retinyl palmitate. When needed, it is released into the bloodstream as retinol in combination with retinol-binding protein (RBP), a specific carrier protein elaborated by the liver; this 1:1 complex is referred to as holo-RBP. In the serum, the RBP–retinol complex combines with transthyretin, a large protein also synthesized in the liver. The retinol is then removed from the serum and utilized by target cells, such as retinal photoreceptors and epithelial linings throughout the body, whose metabolism it influences. Specific receptors exist on the cell surface and nucleus for the vitamin A complex or its active metabolites, particularly retinoic acid. Vitamin A affects the expression of several hundred different genes, and that number is rising as scientific understanding grows. Alterations in gene expression presumably explain resultant changes in cellular differentiation, immunity, and many other vitamin-A-dependent functions. A simplified schematic outline of these main metabolic pathways is shown in Fig. 1.

Liver stores form an important buffer against variations in the intake of vitamin A and provitamin A carotenoids. When intake surpasses requirements, which range from 180 to 450 μg/day of retinol or its equivalent, depending on age, sex and physiological status, the excess is stored and liver reserves increase. When vitamin A intake

[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 international units (IU).

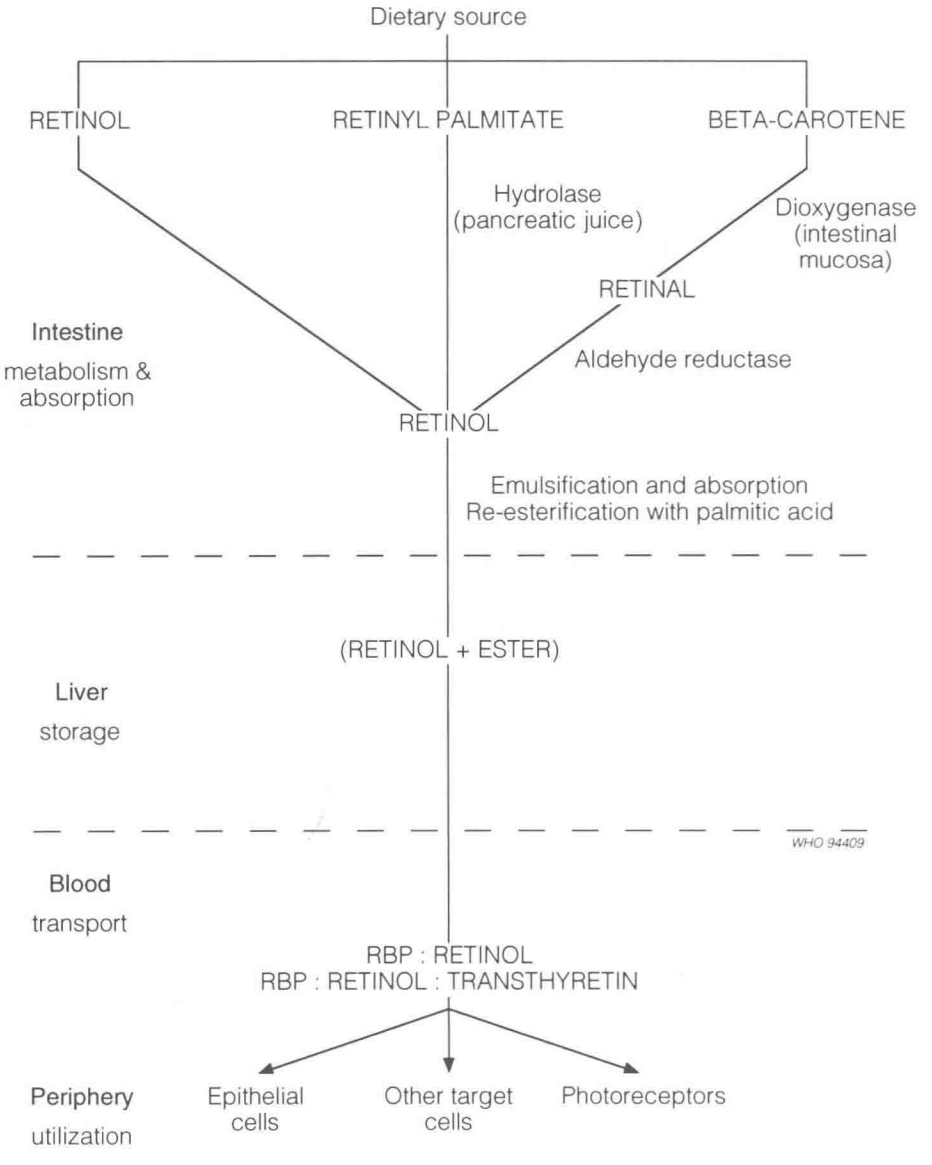

Fig. 1 Schema of vitamin A metabolism

is less than this amount, liver stores are drained to maintain serum retinol at a normal level (well above 0.7 μmol/litre or 200 μg/litre). If intake remains low for prolonged periods, liver stores become depleted, serum retinol levels drop, and cellular function is impaired, resulting in abnormal differentiation (e.g. xerophthalmia) and other physiological consequences and clinical manifestations of deficiency (e.g. anaemia, impaired resistance to infection). The duration of

inadequate intake required for this to occur depends on 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 as a result of a change in diet or because of impaired absorption (as in gastroenteritis), or a sudden increase in metabolic demand (febrile state — notably measles — or growth spurt) will cause rapid depletion of limited reserves. This can precipitate blinding xerophthalmia (even in a child whose eyes had previously appeared entirely normal) or overwhelming sepsis and death. When liver retinol stores are very high, however, an individual may go for months without vitamin A and not suffer serious consequences.

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

VITAMIN A STATUS

Normal vitamin A status implies that an individual is free of physiological or pathological consequences of vitamin A deficiency and has sufficient liver stores to provide protection against the increased metabolic demands in disease, reduced absorption as a result of diarrhoea or parasitic infection, or significant variations in dietary intake.

A normal, well nourished child in a developed country will commonly have adequate liver stores of vitamin A to maintain serum retinol levels of 1.0 to 1.4 μmol/litre or more. Lesser stores may fail to maintain normal serum levels or physiological function (*37*). Liver stores can be measured directly on liver specimens obtained at surgery or autopsy, but opportunities for such measurements are uncommon and not representative of the child population as a whole. A new test, that of relative dose-response (RDR), provides an indirect estimate of the adequacy of liver stores by measuring the degree to which the liver releases holo-RBP in response to a small priming dose of vitamin A (*38*).

As liver stores decline, serum vitamin A levels will eventually fall as well. Under carefully controlled conditions of depletion, physiological consequences of vitamin A deficiency, such as impaired dark adaptation or abnormal conjunctival epithelial differentiation (determined by impression cytology), generally begin to occur at levels below 1.0 μmol/litre, and especially below

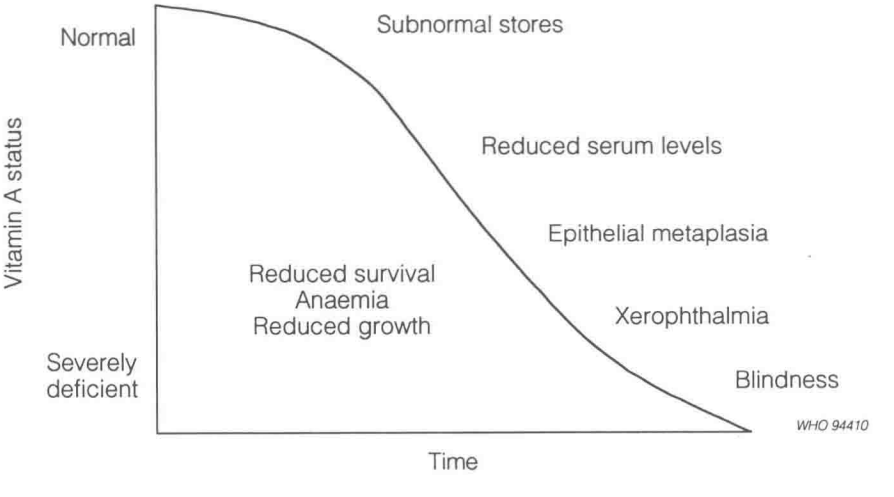

Fig. 2 Manifestations of vitamin A deficiency

0.7 μmol/litre (200 μg/litre) (*39*). Frank xerophthalmia may be manifest at levels below approximately 0.7 μmol/litre, but becomes far more frequent and severe at levels below 0.35 μmol/litre (*1*). The risks of interference with iron utilization and of death probably begin to increase even before the appearance of xerophthalmia, but become progressively greater as vitamin A status declines further (*36*, *40*; see Fig. 2).

Xerophthalmia remains the most specific and readily recognized clinical manifestation of vitamin A deficiency, and has served as *the* definitive criterion for assessing vitamin A status. However, it is now recognized that other serious consequences, including increased mortality, result from milder degrees of vitamin A deficiency, before xerophthalmia is apparent or prevalent in the population. It is thus important, even in the absence of obvious xerophthalmia, that vitamin A deficiency be carefully investigated as a potential public health problem in any area of high child morbidity and mortality.

XEROPHTHALMIA: CLINICAL CLASSIFICATION AND DIAGNOSIS

Vitamin A deficiency is a systemic disease that affects cells and organs throughout the body; the resultant changes in epithelial architecture are termed "keratinizing mataplasis". Keratinizing metaplasia of the respiratory and urinary tracts and related changes in intestinal epithelia probably occur relatively early in the disease, even before the appearance of clinically detectable changes in the eyes. However, since these non-ocular changes are largely hidden from view, they do not provide a ready basis for specific clinical diagnosis. Among vitamin-A-deficient populations, therefore, children with measles, respiratory disease, diarrhoea, or significant protein–energy malnutrition should be suspected of being deficient and treated accordingly.

Uncomplicated, gradual depletion of vitamin A stores results in xerophthalmia of increasing severity, manifest as night blindness, conjunctival xerosis and Bitot's spot, corneal xerosis, and corneal ulceration/keratomalacia (Plates 1 and 2) (*1*). All these conditions usually respond rapidly to vitamin A therapy, and the milder manifestations generally clear up without significant sequelae. The loss of deep corneal tissue from ulceration/keratomalacia, however, results in scarring and residual opacification. Sudden decompensation of marginal vitamin A status, as occurs in measles, can result in corneal ulceration that precedes the appearance of milder signs of xerophthalmia (*1*, *41*).

The major signs and symptoms of xerophthalmia are classified in Table 1 and illustrated in Plates 1 and 2.

Table 1. Classification of xerophthalmia[a]

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

[a] Source: reference *2*.

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 therefore 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 photic stress resulting from being in bright light, such as flying a kite on a sunny day. Affected children no longer move about the house or neighbourhood 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 typical of vitamin A deficiency. Other causes of the condition are relatively rare and almost never present in this age group. Some societies or cultures, particularly those in which vitamin A deficiency is endemic, use specific terms to describe the condition, such as "chicken eyes" (chickens lack rods and are thus night-blind).

The presence of night blindness is not always recognized, especially among children who have not yet begun to crawl or toddle. When mothers or other care-givers do complain that they have observed the condition, however, they are almost always correct (*1*, *42–44*), which 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

The epithelium of the conjunctiva in vitamin A deficiency is transformed from the normal columnar to the stratified squamous type, with a resultant loss of goblet cells, formation of a granular cell layer (Plate 3), and keratinization of the surface (Plate 4). This is the histopathological picture of conjunctival xerosis.

Clinically, these changes are expressed as marked dryness or unwettability; the affected area appears roughened, with fine droplets or bubbles on the surface, rather than smooth and glistening. The changes are best detected in oblique illumination; they are often subtle and may be obscured by heavy tearing. As the

tears drain off, however, the affected areas emerge like "sandbanks at receding tide".[1]

The abnormalities are often overlooked or, in apparent overcompensation, over-diagnosed. Thus they are not, by themselves, an accurate basis for establishing the prevalence of clinical xerophthalmia, and conjunctival xerosis cannot be regarded as an acceptable criterion for determining whether vitamin A deficiency is a significant public health problem.

Conjunctival xerosis first appears in the temporal quadrant, as an isolated oval or triangular patch adjacent to the limbus in the interpalpebral fissure (Plates 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. The overlying material is easily wiped off, and the amount present often varies from day to day. With more severe deficiency, similar, though less prominent, lesions form in the nasal quadrant. Bitot's spots are readily recognized and serve as a useful clinical criterion for assessing the vitamin A status of the population (Plates 7–13).

Bitot's spots should not be confused with pinguecula or pterygium, which are more often nasal than temporal and limited largely to adults. Pinguecula is an elevated, fatty, yellowish lesion; pterygium is fleshy and actually invades the cornea.

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 (Plates 14–16). 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 an earlier 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 spots begin to resolve within 2–5 days. Most will disappear within 2 weeks, although a significant proportion of temporal lesions may persist, in shrunken form, for months.

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[1] McLaren DS, Ooman HA, Escapini H. Ocular manifestations of vitamin A deficiency in man. *Bulletin of the World Health Organization*, 1966, **34**: 357–361.