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THE EPIDEMIOLOGY OF VITAMIN A DEFICIENCY AND XEROPHTHALMIA

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INTRODUCTION

The clinical syndrome now known as xerophthalmia has been recognized since early Egyptian times (143). Even then, physicians recognized the therapeutic value of liver. The association of xerophthalmia with poor nutritional and low socioeconomic status was identified in the early 1800s (7, 8, 24, 28, 40). Thus, even before the discovery of vitamin A (60) and the elucidation of its biochemical mechanisms (33, 137), the ocular manifestations of vitamin A deficiency (and their cure) were known. Despite its long history and our understanding of some of the physiologic processes involved in tissue utilization of vitamin A, xerophthalmia remains a major public health problem in developing countries and is an area of active research.

CLINICAL FEATURES OF XEROPHTHALMIA

Retinal Involvement

NIGHTBLINDNESS Nightblindness, also known in the literature as hemeralopia and nyctalopia, is a result of impaired dark adaptation by the light-sensitive retina. Animal and human deprivation experiments have demonstrated that nightblindness is the earliest clinical manifestation of vitamin A deficiency (15, 27, 38, 41).

Because objective tests for nightblindness are difficult to perform in young children and a medical history is subjective, as recently as 1976 nightblindness was considered only a secondary sign of xerophthalmia and an unreliable criterion for assessing the burden of vitamin A deficiency in a community (138, 144). It is now accepted that in some populations a history of nightblindness in preschool children is an even more sensitive and specific marker of vitamin A deficiency than Bitot's spots (110, 145) and that it can serve as a primary criterion for the presence of clinically significant vitamin A deficiency.

In Indonesia, serum vitamin A levels among preschool children with histories of nightblindness and among those with Bitot's spots were similar and significantly lower than among controls matched by age, sex, and neighborhood (100, 110). A group of the children with histories of nightblindness was given an objective test for nightblindness. Ninety-seven percent showed definite impairment of scotopic vision, and in the 3% that tested negatively, serum vitamin A levels were similar to those in children whose scotopic vision was reduced. Twice as many children had a positive history of nightblindness as had Bitot's spots, which suggests that in this culture at least, nightblindness was a more sensitive marker of vitamin A deficiency than Bitot's spots. Local languages of numerous Asian and African countries contain specific terms for

nightblindness (46), and these are now being studied to determine whether they too are valuable indicators of vitamin A deficiency.

Nightblindness due to vitamin A deficiency responds promptly to supplementation with vitamin A (11, 38, 41, 100, 110).

XEROPHTHALMIC FUNDUS Since the early twentieth century, unusual fundus lesions have been observed occasionally in xerophthalmia patients (34, 131, 146). These lesions tend to regress during the course of vitamin A therapy (14, 100, 118, 128, 129) but can reoccur on rare occasions (100, 118).

Clinical observations include small, yellowish-white dots in the equatorial and peripheral regions of the retinas of both eyes (Figure 1) (14, 34, 100, 129, 131). Fluorescein angiography suggests that pigment has been lost from the retinal pigment epithelium in these areas (100, 118).

The presence and severity of the lesions appear to be related to the severity and chronicity of the vitamin A deficiency (29, 100). Xerophthalmic fundus is more prevalent in the older than younger children and is more prevalent, at every age, in cases with corneal xerosis than in those with conjunctival xerosis (100).

Conjunctival Involvement

Conjunctival xerosis and the white foamy conjunctival lesion known as Bitot's spots were first described during the mid-1800s (10, 40, 53). Conflicting

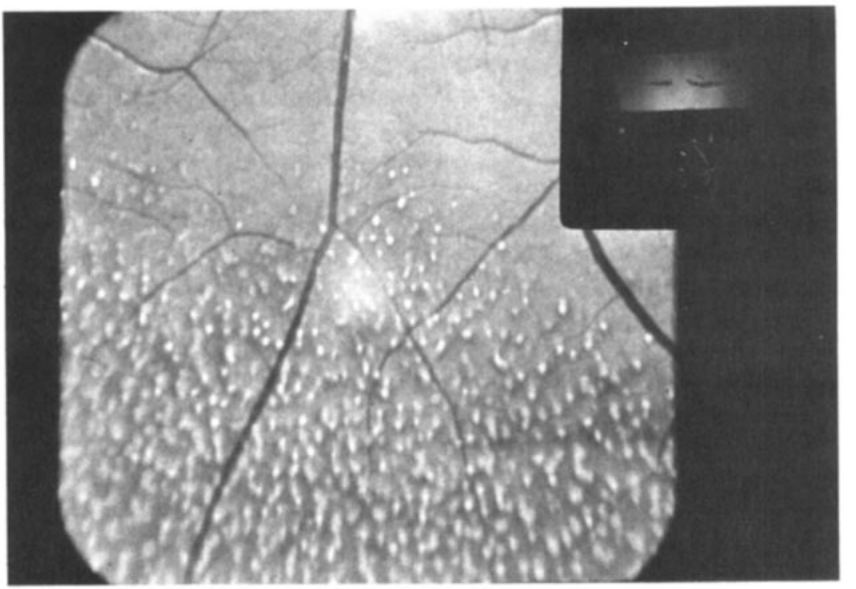


Figure 1 Xerophthalmic fundus (XF)

descriptions, particularly of their responses to vitamin A, led a number of investigators to question whether Bitot's spots were truly related to vitamin A deficiency (23, 66, 70, 73, 84, 87, 93, 94, 142). The recent Indonesian studies have helped to resolve this conflict and to provide a coherent description of conjunctival involvement in vitamin A deficiency (100).

In the vast majority of cases, especially in countries where vitamin A deficiency is prevalent, generalized squamous metaplasia of the conjunctiva induced by deficiency of vitamin A is responsible for these characteristic changes (100). They first occur in the temporal quadrant and appear as unwettable areas, sometimes with thickened and wrinkled conjunctival folds (Figure 2). Bitot's spots are composed of keratinized debris, often combined with saprophytic bacteria *(Xerosis bacilli)*, and appear as an adherent whitish foamy or cheesy deposit that can cover an area of xerotic conjunctiva (Figure 3) (10, 22, 59, 108, 118). As the vitamin A deficiency persists, xerotic changes appear in the nasal, inferior, and superior quadrants. In advanced stages of xerophthalmia, the conjunctiva appears almost leathery, and corneal involvement is the rule (13, 28, 100, 146).

The clinical appearance of vitamin A–responsive and –nonresponsive Bitot's spots is similar. The differences between them are primarily the extent and location of conjunctival involvement (100). Histologically, nonresponsive Bitot's spots tend to have more surface bacteria and more chronic inflammation, and all abnormalities are limited to the temporal quadrant (106, 108). By

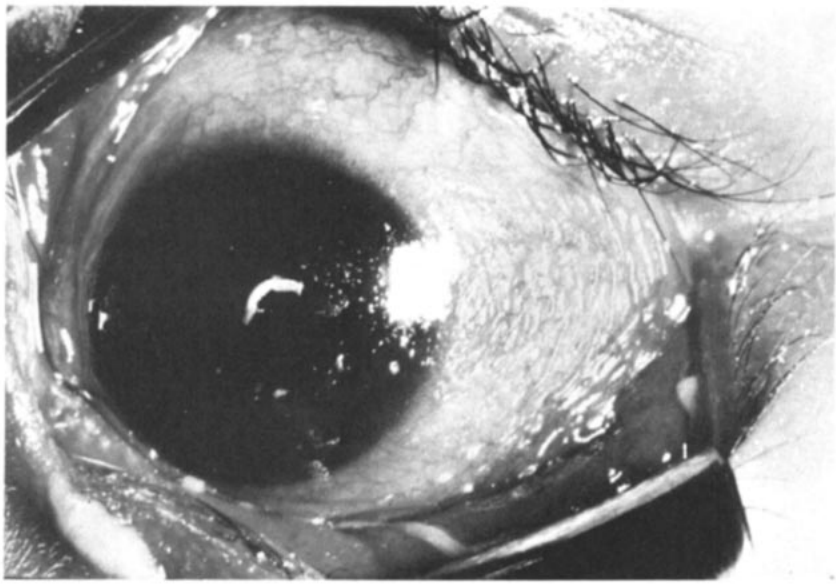


Figure 2 Temporal patch of wrinkled, xerotic conjunctiva (X1A)

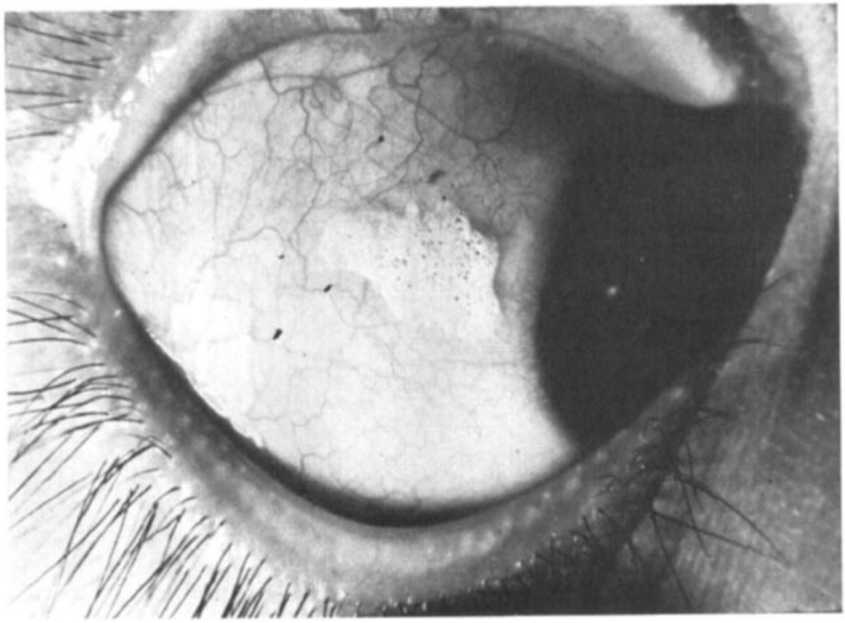


Figure 3 Bitot's spot (X1B)

contrast, even when a responsive lesion appears to be limited clinically to the temporal quadrant, histologic abnormalities are present throughout the bulbar conjunctiva. In addition, those with nonresponsive cases tend to be older and are less likely to have nightblindness, superficial punctate keratopathy, or other evidence of active vitamin A deficiency (106). While there are these differences between vitamin A–responsive and –nonresponsive Bitot's spots, the underlying etiology of the two lesions is most likely the same. A large proportion of nonresponsive Bitot's spots are the result of past vitamin A deficiency (100, 106, 108). For unknown reasons, the temporal keratinized metaplastic lesions can persist long after vitamin A levels have returned to normal (100). The two types of lesions (responsive, nonresponsive) can only be distinguished with certainty by their response to vitamin A.

Corneal Involvement

In the absence of prompt therapy, corneal involvement from vitamin A deficiency carries a high risk of blindness. The devastating effects of corneal ulceration and melting (keratomalacia) have been known since the early 1800s (17). In spite of the potentially dramatic consequences, the earliest sign of corneal involvement is a superficial punctate keratopathy first detectable only with fluorescein staining and slit-lamp biomicroscopy (105). It begins inferiorly and, as the vitamin A deficiency worsens, spreads across the entire cornea and deepens in intensity until corneal haziness is apparent with handlight

illumination (105). In Indonesia, 60% of subjects with confirmed nightblindness and 75% of those with vitamin A–responsive conjunctival xerosis have superficial punctate keratopathy, as compared to less than 10% of matched controls (100, 105). Resolution begins within one week of vitamin A therapy, and cure is complete within four weeks (105).

When the superficial punctate keratopathy becomes confluent, the cornea assumes a *peau d'orange* or ground glass appearance (Figure 4). The haziness produced by this involvement is enhanced by stromal edema and poor tear production and wetting (100, 104). In more severe cases, tree bark–like sections of keratinized epithelium or elevated xerotic plaques may be seen, most often in the interpalpebral zone (100).

Loss of corneal stromal integrity, as evidenced by either ulceration or necrosis, results in the blinding sequela of vitamin A deficiency. Unfortunately, this is frequently bilateral and can occur quite suddenly, often without preceding milder evidence of disease, when intense demands are made on already-depleted body stores of vitamin A (61, 100, 101).

The most common form of stromal loss is an ulcer that typically has a sharply defined, punched-out appearance (Figure 5). The depth of the ulcer may vary from a shallow, saucer-shaped lesion to full thickness perforation with subsequent prolapse of the iris and loss of intraocular contents. With adequate treatment, the ulcer may heal and scar, often leaving a leukoma that spares the pupillary zone and visual axis (100).

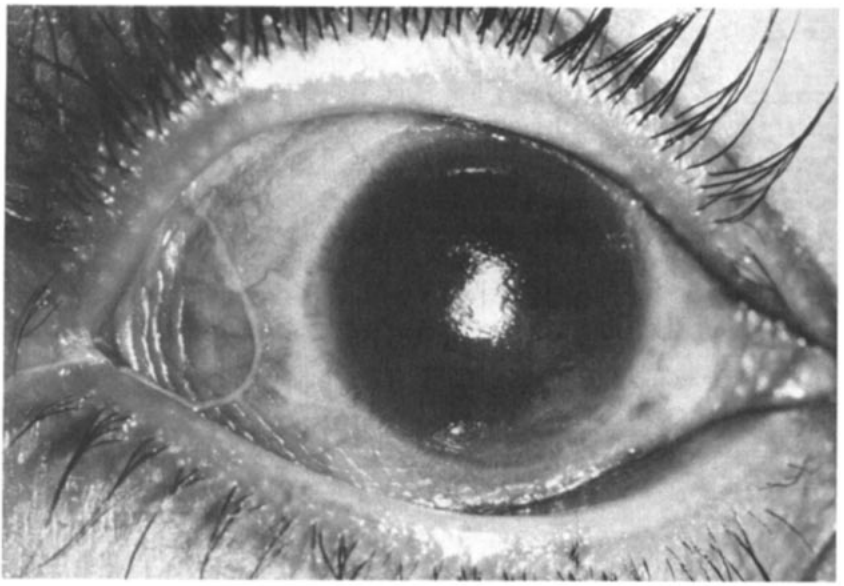
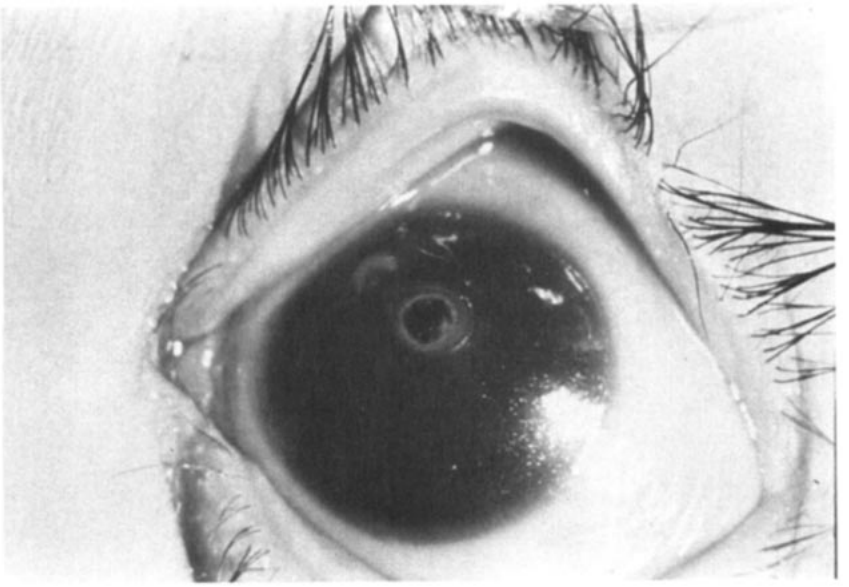


Figure 4 Thick, skin-like generalized conjunctival xerosis (X1) and keratinized, dry, cornea (X2)



Necrosis of the cornea, commonly referred to as keratomalacia, is the most severe form of xerophthalmia. It may involve only one area, most often the inferonasal quadrant, or the entire cornea (100). It is characterized by full-thickness corneal softening, which results in a white or yellow gelatinous mass that eventually sloughs (Figure 6), leaving a thin descemetocele. Depending upon their size and the speed with which therapy is initiated, these may heal as adherent leukomas (localized vascular scars to which underlying iris adheres) or as bulging anterior staphylomas, which usually result in a phthisical (soft, shrunken) eye. Cases of total corneal melting result in either a large delicate descemetocele or complete prolapse with loss of intraocular contents. In either case, phthisis bulbi usually results. Histopathologic studies suggest xerophthalmic melting may involve unique pathogenetic processes (109).

World Health Organization Clinical Classification

The World Health Organization (WHO), in collaboration with a number of other agencies involved in international health, published in 1976 and again in 1982 a classification scheme for xerophthalmia that has gained wide acceptance (144, 145). The WHO has also developed prevalence criteria for determining whether xerophthalmia is a serious public health problem in a particular population (Table 1) (145). The presence of any one of these parameters establishes a significant problem, although multiple criteria are usually met.

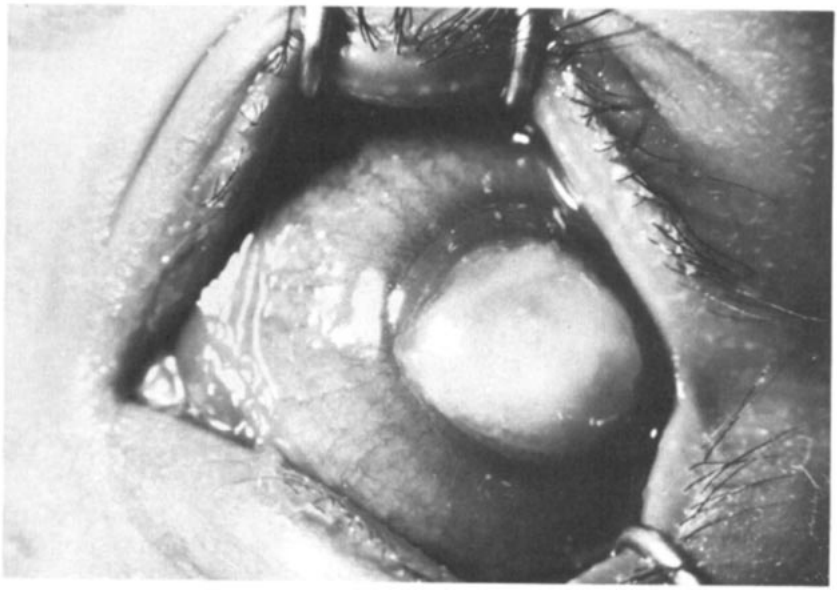


Figure 6 Full thickness corneal necrosis, "keratomalacia" (X3B)

MAGNITUDE OF THE PROBLEM

Xerophthalmia is one of the leading causes of childhood blindness. The burdens of childhood blindness and mortality associated with vitamin A deficiency are especially heavy in the underdeveloped countries of Asia, Africa, and Latin America (83).

Although there is an extensive literature on the magnitude and worldwide distribution of xerophthalmia, careful attention must be given to the methods of data collection and the criteria used to define the disease. Important lessons have been learned from reviews of hospital and clinic records, food production figures, and dietary practices. These are inherently biased, however, by the quantity and quality of the existing data and the method by which it was ascertained (100, 103, 111). On the other hand, properly designed and conducted population-based studies of prevalence and incidence of xerophthalmia can provide accurate, unbiased estimates of the magnitude and distribution of the disease and of the factors associated with it.

Prevalence and Incidence

DEVELOPED COUNTRIES Xerophthalmia is now extremely rare in North America, Europe, and Japan. Most cases presently seen in these countries result from malabsorption secondary to biliary disease, enteritis and colitis, sprue, cystic fibrosis, and cirrhosis (most often caused by chronic alcoholism)

Table 1 World Health Organization classification scheme for xerophthalmia[a]

Classification code	Clinical description	Prevalence levels among preschool children indicating significant public health problem
XN	Nightblindness	> 1%
X1A	Conjunctival xerosis	
X1B	Bitot's spots	> 0.5%
X2	Corneal xerosis	
X3A	Corneal ulceration/keratomalacia involving less than 1/3 of the corneal surface	> 0.01%
X3B	Corneal ulceration/keratomalacia involving 1/3 or more of the corneal surface	
XS	Corneal scar	> 0.05%
XF	Xerophthalmic fundus	
Biochemical Criterion:	Plasma vitamin A 0.35 μmol/liter (10 μg/dl) or less	> 5%

[a]Source: WHO (145).

(57, 79, 120, 133). Xerophthalmia also occurs in food faddists (14, 36, 133, 139).

ASIA The "rice bowl" countries of Asia are the traditional home of xerophthalmia and have yielded the most data and scientifically important research on vitamin A deficiency. A combination of poverty, ignorance, and population pressures have produced a situation in which the number of children affected is enormous and the number at serious risk of developing xerophthalmia is even larger.

There is considerable variation in the prevalence of xerophthalmia both between and within the countries of East and Southeast Asia. In India, rates for corneal disease (WHO classifications X2 and X3) reportedly range from undetectable to as high as 3.4%; for mild disease (XIB), they range from 1% to 15% in preschool children (68, 76, 89, 95, 122, 123). Results from the Nepal Blindness Survey show a geographic influence on the prevalence of xerophthalmia in Nepal. The nationwide rate of Bitot's spots in children under six years of age was 0.59%, with the highest rate, 1.18%, in the Terai region and the lowest rate, O%, in the valleys (12). In Bangladesh, a baseline survey prior to the start of a nationwide intervention program showed a prevalence of 0.45% for corneal disease and 0.66% for mild disease (30). The results from an ongoing evaluation of that intervention program suggest that the corneal disease rate has dropped to 0.085% (N. Cohen, personal communication, 1983). The rate in Sri Lanka is also high; the prevalence of Bitot's spots (X1B) is 1.1% and ranges up

to 2.3% in certain parts of the country (16). A number of surveys have been conducted in the Philippines to evaluate their monosodium glutamate (MSG) vitamin A fortification intervention program. The baseline survey on the island of Cebu revealed a prevalence of Bitot's spots of 1.7% and of corneal disease of 0.5% in children 1–16 years old. In addition, 17% of the study population is reported to have had serum vitamin A levels below 10 μg/dl, which is considered seriously deficient (99). Large numbers of severe corneal cases are seen in hospitals and clinics in the Manila area (132).

Xerophthalmia is well known in Indonesia, where a number of investigations have been conducted (63, 124, 127). The recent Nutritional Blindness Prevention Project conducted a nationwide prevalence survey and a longitudinal study in Central Java (100, 117). The average prevalence of Bitot's spots in the nationwide survey was 1% and of corneal disease, 0.064%. The longitudinal study is the only large study that has permitted estimation of incidence rates for xerophthalmia; approximately 4600 children were examined every three months for two years. These rates are most likely lower than the true incidence, because new cases that regressed or died between examinations were missed, and because the referral of ill and severely malnourished children to local health facilities resulted in the removal of children from the group at highest risk (100). Corneal disease incidence was estimated at 0.35–0.58% per year; noncorneal disease incidence was 9% per year with a spontaneous cure rate of approximately 50% (100).

Numerous cases have been reported over the years from localized areas of China (39), Vietnam (69), Kampuchea (82), and Thailand (130), but no comprehensive surveys have been undertaken in these countries.

MIDDLE EAST Jordan is the only Middle Eastern country in which the prevalence of xerophthalmia has been carefully studied. Children less than six years of age had a prevalence of nightblindness of 1.3%, of Bitot's spots of 0.6%, and of corneal disease of 0.169% (75).

AFRICA The extent of xerophthalmia in Africa is unclear. While numerous cases have been reported, especially among children suffering from protein-energy malnutrition (5, 6, 48, 51, 54, 72, 86, 88, 136), corneal blindness in children has most often been associated with measles (9, 21, 80). In recent years, several investigators have claimed that much of the corneal blindness said to be due to measles is in reality xerophthalmia (31, 93). This prompted the WHO and the United States Agency for International Development (USAID) to support a series of preliminary assessments in the region (145). While reliable data on prevalence remains unavailable, these assessments identified countries where xerophthalmia may pose a significant problem. Among East and Central African countries, Malawi, Tanzania, Zambia, and Kenya most likely have

endemic foci of the disease. In West Africa, the areas of highest risk are those in the Sahel region, north of where red palm oil (rich in β-carotene) is plentiful (145). Even within areas where red palm oil is consumed, pockets of endemic disease exist. Accurate epidemiologic surveys are currently being planned for Malawi and Tanzania.

CENTRAL AND SOUTH AMERICA A number of countries in Central and South America have reported prevalence rates indicative of endemic disease. In Haiti, the overall prevalence of corneal scars presumed secondary to vitamin A deficiency among children six years of age and younger was 0.25% (119). The rate in the north of the country was 6.8 times higher than in the south (0.81 versus 0.12%). Vitamin A deficiency was presumed to be the cause of all pediatric binocular blindness encountered during the survey.

A biannual vitamin A mass-distribution program was initiated in El Salvador in 1973 in response to results of serum surveys that indicated El Salvador had the highest prevalence of hypovitaminosis A in Central America (43, 114). A nationwide prevalence survey at the time when the mass distribution program was initiated found the prevalence of Bitot's spots to 0.53% and the prevalence of corneal scars to be 0.32% (114).

During the same period, Guatamala initiated and evaluated a program of fortifying sugar with vitamin A. The effects on clinical signs of xerophthalmia were not evaluated; the focus was on changes in per capita consumption and serum levels of vitamin A. The baseline survey indicated that 19% of children had serum retinol levels that were less than 20 μg/dl (3).

A recently reported xerophthalmia survey indicated a focus of endemicity in at least one area of Brazil (91). Among children 0–12 years old, the prevalence of nightblindness was 0.18%; of Bitot's spots 0.58%; of corneal xerosis, 0.002%; and of corneal scars 0.1%.

Worldwide Impact

It is difficult to construct precise estimates of the total number of children in the world who are affected by xerophthalmia. Nonetheless, estimates based on incidence rates from Indonesia and prevalence surveys in other countries provide a sense of the magnitude of the problem.

The incidence of active corneal disease (X2 and X3) among preschool Indonesian children was conservatively estimated at 0.27% per year (117). Assuming that the disease is just as common in India, Bangladesh, and the Philippines, approximately 500,000 preschool children will develop sight-threatening corneal disease every year (117); actually, all available evidence suggests that the disease is more common in India and Bangladesh. Moreover, this minimal estimate includes only four countries of Asia, ignores the fact that a significant proportion of cases occur in school-age children, and cannot

account for the cases with corneal disease who died before they could be counted (100). If one includes noncorneal disease, the number of children affected in these four Asian countries alone may reach five million each year (100).

Blindness Due to Xerophthalmia

In spite of the high rate of blindness from corneal xerophthalmia, most of the cases that are diagnosed and treated in time do very well (115). In Indonesia, of 147 active corneal cases who were treated, 89% had at least 6/6 (20/20) vision in one or both eyes. Only those with total, bilateral corneal melting failed to recover useful vision; twelve of 12 were bilaterally blind (100).

Unfortunately, it is likely that the vast majority of children who develop corneal involvement receive inadequate treatment or none at all. Some of these children die, some go blind, and some spontaneously recover, although the distribution between these various outcomes is unclear. The Indonesian data suggest that one half or more of active corneal cases at large are blinded in both eyes (100).

Mortality Due to Xerophthalmia

The close association of corneal xerophthalmia and severe protein-energy malnutrition precludes a simple separation of their independent effects on childhood mortality. Data from Indonesia suggest that over the short-term, mortality among children with corneal xerophthalmia is determined by general nutritional status (100). This impression is supported by data from India (135), Bangladesh (18), and El Salvador (107); while mortality rates for cases with severe xerophthalmia tended to be slightly higher than for other protein-energy malnourished children, and xerophthalmia cases also tended to be more severely malnourished. On the other hand, a study in Jordan reported a fourfold excess in mortality among children with xerophthalmia compared to children who did not have xerophthalmia but had equivalent protein-energy nutritional status (64). In a study of children with kwashiorkor from India, the overall prevalence of keratomalacia was 14%, but among those who died, it was 28% (78). These two studies concluded that vitamin A deficiency per se increased the risk of dying. It is impossible to determine from these two studies whether children with xerophthalmia were not in fact more malnourished, within the broad categories used, than their peers who did not have the disease. Regardless of whether vitamin A deficiency increased the risk of death among the severely xerophthalmic children, the risk is extraordinarily high and corneal disease should be considered a medical as well as an ophthalmic emergency.

The situation is less clouded for children with mild xerophthalmia (XN–X1B). Data from Indonesia indicate that the death rate for these children is substantially higher than for their peers of comparable anthropometric status

(116). Mortality increased linearly with the severity of xerophthalmia; there was a 2.7-fold excess mortality in children with nightblindness, a 6.6-fold excess in children with Bitot's spots, and an 8.6-fold excess in children with both nightblindness and Bitot's spots. This excess mortality could not be accounted for by concurrent respiratory tract infection, gastroenteritis, or childhood exanthems.

RISK FACTORS FOR XEROPHTHALMIA

Age

Xerophthalmia is primarily a disease of young, preschool-age children. Adult corneal cases are only occasionally reported (81, 118), although nightblindness is a well-recognized condition among pregnant women in India (26, 134).

In countries where xerophthalmia is endemic, the rates of active disease peak in children two to four years of age (16, 74, 99, 100 119), and in general, the younger the child, the more severe the disease (62, 100, 122). The age distribution is closely associated with the weaning process, and younger cases can often be attributed to the "deposed child situation" that results from the close birth of a sibling, as is seen with kwashiorkor (62).

Rates of active disease, especially corneal involvement, in school-age children are usually very low.

Sex

The impression exists that xerophthalmia is more prevalent in males than in females. At every age, the prevalence of Bitot's spots in Indonesia was higher among preschool-age boys than girls (100). Similar results have been reported elsewhere (16, 62, 88, 99, 124, 127).

Corneal xerophthalmia is much less closely associated with sex. In longitudinal and nationwide prevalence studies in Indonesia, no significant differences were found between corneal disease rates for boys and for girls (100). Others have found similar results (18, 127), although some male excess has been reported (61).

The origin of the excess risk of mild disease in males is not well understood. Indications are that this excess risk is culturally determined and not an intrinsic physiologic susceptibility.

Seasonality

The level of vitamin A intake can fluctuate with the seasonal availability of fruits and vegetables containing β-carotene. In Asia, the risk of xerophthalmia peaks during the hot, dry months, when dark green, leafy vegetables are scarce and the risk of diarrhea is highest (62, 71, 95, 100, 127). Other factors that may

affect the seasonality of the disease include religious fasting and feasting and the seasonality of precipitating systemic and parasitic infections.

Socioeconomic Status

Xerophthalmia is primarily confined to children from the lowest social classes (16, 74, 114). This general rule is not always clearly apparent, however, especially in the largely homogenous, peasant social class that accounts for the bulk of the population in developing countries. In South Asia, highly polished and nutritionally poor rice is the staple of choice; the poorest families are sometimes forced to feed their children vegetables that are unattractive to the children; this may lower the risk of xerophthalmia relative to that of a family that can afford to eat rice on a regular basis. In spite of this confounding factor, families in lower social classes in general have poor access to preformed vitamin A–rich foods and tend to have a poor understanding of the role that proper nutrition plays in the well-being of their children (147). In addition, mothers in poor families have lower vitamin A levels in their blood and breastmilk (35, 134), which increases the risk even to breastfed children.

In Indonesia, families with characteristics ascribed to lower socioeconomic status were at higher risk for xerophthalmia than comparable neighborhood and national control families (100).

Nutritional Status

It has been well recognized that xerophthalmia rarely occurs as an isolated deficiency (144) except in its mildest forms (100).

Weight for height is an excellent measure of current nutritional status because it inherently adjusts for height and does not require accurate birth dates. Low weight for height, or wasting malnutrition, is strongly associated with corneal xerophthalmia. In the Indonesian nationwide survey, 45% of corneal cases were at least moderately wasted (less than 80% of standard) and the proportion of cases who were wasted increased with increasing severity of corneal disease (100). The relative prevalence of corneal disease for those who showed moderate wasting malnutrition compared to those who did not was 19 to 1.

In spite of this strong association with corneal disease, wasting was not associated with mild xerophthalmia (100). This observation has also been reported in other studies in Asia and the Middle East (16, 74, 123).

Low height for age, or stunting malnutrition, is a measure of inhibited long-term growth and has been closely associated with protein-energy malnutrition. Xerophthalmia, in all forms, is also associated with stunting. Corneal cases were more stunted than their matched controls in the Indonesian data (100). However, the degree of stunting was inversely associated with the severity of corneal signs. This probably reflects the fact that the more severe

xerophthalmia occurred in younger children who had not yet had the opportunity to express the poor longitudinal growth that would eventually result in stunting (100). In the nationwide prevalence survey, corneal cases were the most severely stunted, followed by children with Bitot's spots (100). Similar associations of stunting with xerophthalmia and serum vitamin A levels have been reported (2, 16).

Relation to Protein Malnutrition

If the diet is poor in protein, it may also be poor in other nutrients including β-carotene or vitamin A. In addition, there is a direct interaction between protein and serum vitamin A status. Retinol-binding protein (RBP) is required for the release of vitamin A by the liver and for its transport in the blood and absorption at the target tissues (25). Even if the liver stores of vitamin A are adequate, if protein malnutrition has depressed RBP synthesis, serum vitamin A levels may be low (148). Arroyave (4) found high liver levels but low serum levels of vitamin A in children with kwashiorkor. Ingenbleek (42) demonstrated a significant rise in serum RBP when children with kwashiorkor were begun on a high protein diet. Sommer et al (112) found the holo-RBP response to massive-dose vitamin A therapy was directly related to the level of protein nutriture.

The close interaction of protein and vitamin A status is also linked to xerophthalmia. In Indonesia, serum albumin levels were strongly associated with all forms of xerophthalmia, and the severity of corneal disease was closely correlated with serum albumin and transferrin levels (100).

In spite of this close association between protein status, vitamin A levels, and severity of xerophthalmia, it is unlikely that protein malnutrition in the absence of vitamin A deficiency commonly results in xerophthalmia (100).

Dietary Intake

Dietary intake of foods containing β-carotene or vitamin A is the most critical factor determining the risk of xerophthalmia. This intake must provide adequate levels for daily physiologic demands and for development of liver stores necessary to compensate for periods when intake falls below minimum daily requirements. Accessability to sources that can supply these levels is age-related, especially during early childhood.

The adequacy of maternal intake and storage is important during the prenatal period of development. If maternal stores are marginal, the stress of pregnancy itself may precipitate clinical disease in the mother (26). When maternal serum levels are low, levels will also be low in the fetal blood, which may even result in xerophthalmia in the fetus (58, 100). In severe maternal deficiency, vitamin A supplementation can significantly raise vitamin A levels in cord blood (134),

but supplementation of pregnant women with massive doses may carry a teratogenic risk for the fetus (145).

During the neonatal period, breast milk is the primary source of vitamin A for children in areas where xerophthalmia is endemic. Because vitamin A levels in breast milk reflect maternal serum levels, even regular, ordinarily adequate levels of breast-feeding may result in xerophthalmia if the mother is vitamin A–deficient. In general, however, breast-fed children have been shown to be at significantly lower risk of xerophthalmia than bottle-fed children (62, 100, 126). Data from Indonesia show that the risk of Bitot's spots was eight times higher for those two-year-old children who were not breast-fed during the first year of life than for those who were (100, 126).

The weaning period is a time of great risk to children in developing countries. Feeding practices for this age group vary widely between cultures, but in many areas, especially in Asia, the weaning diet may consist of rice and little else. The additional vitamin A demands resulting from child growth combined with a sudden disruption in vitamin A intake caused by an abrupt change from breast milk to rice can precipitate acute deficiency and xerophthalmia. Even within a community, family feeding practices are important determinants of vitamin A intake. In Indonesia, xerophthalmic children were those who consistently consumed fewer fruits such as mango and papya, fewer dark green leafy vegetables, and fewer eggs than the sample of normal children (100, 126). These findings were confirmed by comparison of serum carotene levels (126).

Easy access to and rigorous consumption of foods containing β-carotene may be a major determinant in the geographic distribution of xerophthalmia. There appears to be little xerophthalmia, even among malnourished populations, in sub-Saharan Africa where red palm oil, an excellent source of β-carotene, is consumed ubiquitously (6, 19, 46, 52, 72).

Precipitating Conditions

In addition to protein-energy malnutrition, a variety of diseases are associated with xerophthalmia in developing countries. Infectious diseases form the bulk of this associated precipitating pathology. Xerophthalmia has been associated with diarrhea (84, 100, 127), respiratory tract infections (85, 100, 127), exanthems such as measles and chicken pox (92, 100, 127), worm infestation (74, 84, 100, 127), and a variety of other common infectious diseases (100). While most of these conditions are also associated with protein-energy malnutrition, some have specific effects on serum vitamin A levels.

Absorption of vitamin A or β-carotene is inhibited in children with diarrhea and worm infestations (55, 56, 67, 97). Respiratory infections seriously depress serum vitamin A levels (2, 49) by decreasing absorption (49, 96) and increasing excretion (50). In addition, fever, which is often associated with these infectious diseases, can produce a nonspecific depression of serum vitamin A (65).

The association between measles and xerophthalmia is not completely clear. In some countries, one fourth to one half of corneal xerophthalmia cases are associated with measles (6, 19, 64, 92, 100, 107). But the role, if any, that xerophthalmia plays in the development of post-measles blindness, especially in Africa, is particularly uncertain. The clinical picture of post-measles corneal destruction mimics xerophthalmia (5, 32, 54), and the course that it takes, usually including a general deterioration of nutritional status and ultimately corneal melting two to four weeks after the original onset of rash, strongly suggests a nutritional component (102). Several investigators have concluded that measles blindness is merely a reflection of underlying vitamin A deficiency (5, 31, 72). However, there have been no well-conducted, population-based, epidemiologic studies demonstrating that vitamin A deficiency accounts for most of the post-measles blindness in Africa, and recent reports suggest a role for secondary herpes simplex infection (90, 141).

PREVENTION

Three basic approaches have been taken with regard to prevention of xerophthalmia (140): enhancement of dietary intake of vitamin A, fortification of a commonly eaten food, and periodic administration of massive doses of vitamin A. Unfortunately, there is a paucity of carefully conducted studies to demonstrate the benefits of large-scale intervention activities.

Increasing the dietary consumption of foods rich in vitamin A or β-carotene is the preferred approach to reducing the risk of xerophthalmia in a population (45). It is generally held that a combination of horticultural, educational, and general economic development approaches are needed. In Indonesia however, careful assessment revealed that green, leafy vegetables rich in β-carotene were already consumed on a regular basis by families with and without xerophthalmia (126). The difference was whether or not the children consumed the greens, which provides a clear indication of the potential value of educational campaigns by themselves. There has been little in the way of formal, intensive intervention along these lines. A successful, rigorously documented and rigorously evaluated model is needed.

Vitamin A fortification of a widely consumed food can be an inexpensive and effective method of increasing vitamin A intake, raising serum levels, and reducing xerophthalmia (3, 98). The demonstration of fortification technology for margarine and dairy products prompted its expansion to other vehicles such as sugar and monosodium glutamate (3, 98). For a particular food to qualify as a potentially useful vehicle for fortification, it must be commonly consumed by the population at risk (primarily preschool-age children), fortifiable using available technology, manufactured or processed in a limited number of central locations, and either exclusively marketed or competitive with nonfortified brands. If these conditions can be met, fortification has the potential for good

short-term and medium-term effects on vitamin A deficiency in a population (140). Aside from having their use in reducing the prevalence of hypovitaminosis A in Guatemala, however, large-scale intevention programs and evaluations are lacking.

Periodic administration of massive doses of vitamin A, usually 200,000 IU of retinyl palmitate in oil with 40 IU of vitamin E every six months, has been the most popular approach to controlling xerophthalmia and has been adopted by a number of countries (145). The optimal program using this approach provides universal dosing to all preschool-age children and lactating mothers every six months. The object is to provide a large enough liver reserve to maintain the child in relative adequacy until the next dose. In spite of the poor performance of these programs in terms of serum vitamin A levels (1, 77), the evidence from controlled trials and clinical studies suggest a prophylactic efficiency of 90% or better for four to ten months (100, 122, 124).

Various capsule distribution programs are proceeding in several Asian, African, Latin American, and Carribean countries (140). One advantage of the massive dose is that the same preparation can be used to treat, as well as to prevent, xerophthalmia. The recommended oral treatment schedule, 200,000 IU a day for two days (145), is as biochemically and clinically effective as the more expensive use of parenteral preparations (113). The major effort and costs are in reaching the children. Universal distribution schemes are costly and may not reach more than 40–60% of the preschool population on a long-term basis (107, 121, 125). More efficient but less complete coverage is achieved by targeting distribution to children at highest risk encountered at various levels of the health care system, e.g. those with protein-energy malnutrition, measles, respiratory infection, and diarrhea (140). Whether this technique reaches sufficient children to make a practical difference remains to be determined. Preliminary data suggest that children with very severe protein-energy malnutrition handle massive doses poorly and may require more frequent doses (112).

Literature Cited

1. Araujo, R. L., Borges, E. L., Silva, J. D., Costa Val, V. P., Vieira, E. C. 1978. *Failure of massive oral doses of vitamin A to prevent hypovitaminosis A*. Paper presented at XI Int. Cong. of Nutr. Rio de Janeiro, Brazil
2. Arroyave, G., Calcano, M. 1979. Depression of serum levels of retinol and of retinol-binding protein (RBP) during infections. *Arch. Latinoamer. Nutr.* 29: 233–60
3. Arroyave, G., Mejia, L. A., Aguilar, J. R. 1981. The effect of vitamin A fortification of sugar on the serum vitamin A levels of preschool Guatemalan children: a longitudinal evaluation. *Am. J. Clin. Nutr.* 34:41–49
4. Arroyave, G., Wilson, D., Mendez, J., Behar, M., Scrimshaw, N. S. 1961. Serum and liver vitamin A and lipids in children with severe protein malnutrition. *Am. J. Clin. Nutr.* 9:180–85
5. Awdry, P. N., Cobb, B. 1964. Vitamin A deficiency and blindness in the Luapula Valley of Northern Rhodesia. *Exp. Eye Res.* 3:373
6. Awdry, P. N., Cobb, B., Adams, P. C. G. 1967. Blindness in the Luapula Valley. *Cent. Afr. J. Med.* 13:197–201
7. Baillie, H. 1816. Observations on hemer-

alopia or nightblindness. *Medico-Chirurgical J. Rev.* 2:179–82
8. Bampfield, R. W. 1814. A practical essay on hemeralopia or nightblindness. *Medico-Chirurgical Transactions* 5:32–66
9. Ben Ezra, D., Chirambo, M. C. 1977. Incidence and causes of blindness among the under 5 age group in Malawi. *Br. J. Ophthalmol.* 61:154–57
10. Bitot, C. 1863. Sur une lesion conjunctivale non encore decrite, coincidant avec l'hemeralopie. *Gazette Hebdomadaire de Medecine et de Chirurgie* 10:284–88
11. Blankhart, D. M. 1967. Individual intake of food in young children in relation to malnutrition and nightblindness. *Trop. Geogr. Med.* 19:144–53
12. Blindness Prevention and Control Programme 1982. The epidemiology of blindness in Nepal. Final report of the Nepal blindness survey. Volume 1 Executive Summary. Kathmandu, Nepal: Wld. Health Org. 52 pp.
13. Bloch, C. E. 1921. Clinical investigation of xerophthalmia and dystrophy in infants and young children (Xerophthalmia et dystrophia alipogenetica). *J. Hygiene (Cambridge)* 19:283–301
14. Bors, F., Fells, P. 1971. Reversal of the complications of self-induced vitamin A deficiency. *Brit. J. Ophthalmol.* 55:210–14
15. Brenner, S., Roberts, L. J. 1943. Effects of vitamin A depletion in young adults. *Arch. Intern. Med.* 71:474–82
16. Brink, E. W., Perera, W. D. A., Broske, S. P., Cash, R. A., Smith, J. L., Sauberlich, H. E., Bashor, M. M. 1979. Vitamin A status of children in Sri Lanka. *Am. J. Clin. Nutr.* 32:84–91
17. Brown, J. 1827 Case of ulcerated cornea from inanition. *Edinburgh J. Med. Sci. (Corres.)* 3:218
18. Brown, K. H., Gaffar, A., Alamgir, S. M. 1979. Xerophthalmia, protein-calorie malnutrition, and infections in children. *J. Pediatr.* 95:651–56
19. Budden, F. H. 1974. Blindness in Northern Nigeria. pp. 2–35. Consultant Report, Wld. Health Org. Prevention of Blindness Prog./75.1
20. Deleted in proof
21. Chirambo, M. C., Ben Ezra, D. 1976. Causes of blindness among students in blind school institutions in a developing country. *Br. J. Ophthalmol.* 60:665–68
22. Damiean-Gillet, M. 1958. Conjunctival lesions in avitaminosis A. A histopathological study. *Trop. Geogr. Med.* 10: 233–38
23. Darby, W. J., McGanity, W. J., McLaren, D. S., Paton, D., Alemu, A. Z., Medhen, A. M. G. 1960. Bitot's spots and vitamin A deficiency. *Publ. Health Rep.* 75:738:43
24. DeGouvea, H. 1883. Beitrage zur Kenntnis der Hemeralopie und Xerophthalmie aus Ernahrungsstorungen. *Graefe's Arch. Ophthalmol.* 29:167–200
25. DeLuca, L. M. 1978. Vitamin A. In *Handbook of Lipid Research,* Vol. 2, *The Fat Soluble Vitamins,* ed. H. F. Deluca, pp. 1–67. New York: Plenum
26. Dixit, D. T. 1966. Night-blindness in third trimester of pregnancy. *Ind. J. Med. Res.* 54:791–95
27. Dowling, J. E., Wald, G. 1958. Vitamin A deficiency and night blindness. *Proc. Natl. Acad. Sci. USA* 44:648–61
28. Elliott R. H. 1920. *Tropical Ophthalmology,* pp. 75–86. London: H. Frowde, Hodder & Stoughton
29. Fells, P., Bors, F. 1969. Ocular complications of self-induced vitamin A deficiency. *Trans. Ophthalmol. Soc. UK* 89:221–28
30. Franken, S. 1975. *Blindness prevention program in Bangladesh.* WHO Consultant Report, South-East Asia Region/ Ophthal., Rep. 4
31. Franken, S. 1974. Measles and xerophthalmia in East Africa. *Trop. Geogr. Med.* 26:39–44
32. Frederique, G., Howard, R., Boniuk, V. 1969. Corneal ulcers in rubeola. *Am. J. Ophthalmol.* 68:996–1003
33. Fridericia, L. S., Holm, E. 1925. Experimental contribution to the study of the relation between night blindness and malnutrition: Influence of deficiency of fat-soluble A-vitamin in the diet on the visual purple in the eyes of rats. *Am. J. Physiol.* 73:63–78
34. Fuchs, A. 1959. White spots of the fundus combined with night blindness and xerosis (Uyemura's Syndrome). *Am. J. Ophthalmol.* 48:101–03
35. Gebre-Medhin, M., Vahlquist, A., Hofvander, Y., Uppsall, L., Vahlquist, B. 1976. Breast milk composition in Ethiopian and Swedish mothers. 1. Vitamin A and β-carotene. *Am. J. Clin. Nutr.* 29: 441–51
36. Gombos, G. M., Hornblass, A., Vendeland, J. 1970. Ocular manifestations of vitamin A deficiency. *Ann. Ophthalmol.* 2:680–84
37. Herron, W. L., Riegel, B. W. 1974. Production rate and removal of rod outer segment material in vitamin A deficiency. *Invest. Ophthalmol. Vis. Sci.* 13:46–53
38. Holm, E. 1925. Demonstration of hemeralopia in rats nourished on food devoid of fat-soluble A vitamin. *Am. J. Physiol.* 73:79–84
39. Hsu, P. T. 1978. *Prevention and treat-*

ment of trachoma and blindness in Heilungkiang rural areas. Paper presented at WHO Meeting on Programs for the Prevention of Blindness, Asilosmar, Calif.
40. Hubbenet, M. 1860. Observations sur l'hemeralopie. *Ann. Oculist. (Paris)* 44:293
41. Hume, E. M., Krebs, H. A. 1949. *Vitamin A requirement of human adults: An experimental study of vitamin A deprivation in man, Vitamin A Subcommittee of the Accessory Food Factors Committee, Med. Res. Counc. Spec. Rep. Ser. No. 264.* pp. 7–145 London: Her Majesty's Stationery Off.
42. Ingenbleek, Y., Van den Schrieck, H., De Nayer, P., De Visscher, M. 1975. Albumin, transferrin and the thyroxine-binding prealbumin/retinol-binding protein (TBPA-RBP) complex in assessment of malnutrition. *Clin. Chim. Acta* 63:61–67
43. Institute of Nutrition of Central America and Panama and The Interdepartmental Committee on Nutrition for National Development 1972. *Nutritional Evaluation of the Population of Central America and Panama. Regional summary 1965–1967. Dept. Health Educ. Welf. Publ no. [HSM] 72–8120* Washington D.C.: Dept. Health Educ. Welf.
44. Deleted in proof
45. International Vitamin A Consultative Group. 1983. *Minutes of the 7th Ann. Meet. Nutr. Found., Dakar, Senegal*
46. International Vitamin A Consultative Group. 1981. *Rep. Ann. Meet., Nairobi, Kenya.* New York: IVACG Secretariat: Nutr. Found.
47. Jacobs, A. L., Leitner, Z. A., Moore, T., Sharman, I. M. 1954. Vitamin A in rheumatic fever. *J. Clin. Nutr.* 2:155–61
48. Kuming, B. S., Politzer, W. M. 1967. Xerophthalmia and protein malnutrition in Bantu children. *Br. J. Ophthalmol.* 51:649–65
49. Lala, V. R., Reddy, V. 1970. Absorption of β-carotene from green leafy vegetables in undernourished children. *Am. J. Clin. Nutr.* 23:110–13
50. Lawrie, N. R., Moore, T., Rajagopal, K. R. 1941. The excretion of vitamin A in urine. *Biochem. J.* 35:825–36
51. Lechat, M. F., Bouche, R., de Goyet, C., Boucquey, C. 1976. Epidemiologie de l'avitaminose A au Niger. *Ann. Soc. Belg. Med. Trop.* 56:333–42
52. LeFrancois, P., Chevassus-Agnes, S., Benefice, E., Dyck, J. L., Maire, B., Parent, G., Seymat, G., Ndiaye, A. M. 1980. Vitamin A status of populations in three West African countries *Internat. J. Vit. Nutr. Res.* 50:352–63
53. Mackenzie, W. 1830. *A Practical Treatise on Diseases of the Eye,* pp. 88–199. London: Longman
54. MacManus, E. P. 1968. Xerophthalmia in Matabeleland. *Cent. Afr. J. Med.* 14:166–70
55. Mahalanabis, D., Jalan, K. N., Maitra, T. K., Agarwal, S. K. 1976. Vitamin A absorption in ascariasis. *Am. J. Clin. Nutr.* 29:1372–75
56. Mahalanabis, D., Simpson, T. W., Chakraborty, M. L., Ganguli, C., Bhattacharjee, A. K., Mukherjee, K. L. 1979. Malabsorption of water miscible vitamin A in children with giardiasis and ascariasis. *Am. J. Clin. Nutr.* 32:313–18
57. Mandel, H. G., Cohn, V. H. 1980. Fat-soluble vitamins. In *The Pharmacological Basis of Therapeutics,* ed. A. G. Gilman, L. S. Goodman, A. Gilman, pp. 1583–92. New York: Macmillan. 6th ed.
58. Maxwell, J. P. 1932. Vitamin deficiency in the antenatal period, its effects on the mother and the infant. *J. Obstet. Gynaecol. Brit. Emp.* 39:764–76
59. Mayou, M. S. 1904. II. Disease of the conjunctiva. 1. The pathological anatomy of the plaques in epithelial xerosis. *Trans. Ophthalmol. Soc. UK* 24:9–16
60. McCollum, E. V., Davis, M. 1913. The necessity of certain lipids in the diet during growth. *J. Biol. Chem.* 15:167–75
61. McLaren, D. S. 1960. Nutrition and eye disease in East Africa: Experience in Lake and Central Provinces, Tanganyika. *J. Trop. Med. Hyg.* 63:101–22
62. McLaren, D. S. 1980. *Nutritional Ophthalmology.* London: Academic
63. McLaren, D. S., Oomen, H. A. P. C., Escapini, H. 1966. Ocular manifestations of vitamin A deficiency in man. *Bull. Wld. Health Org.* 34:357–61
64. McLaren, D. S., Shirajian, E., Tchalian, M., Khoury, G. 1965. Xerophthalmia in Jordan. *Am. J. Clin. Nutr.* 17:117–30
65. Mendez, J., Scrimshaw, N. S., Salvado, C., Lopez, S. M. 1959. Effects of artificially induced fever on serum proteins, vitamin levels and hematological values in human subjects. *J. Appl. Physiol.* 14: 768–70
66. Metivier, V. M. 1941. Bitot's spots in Trinidad. *Am. J. Ophthalmol.* 24:1029–34
67. Nalin, D. R., Russell, R., Greenberg, H., Levine, M. M., Garrett, M. 1980. Reduced vitamin A absorption after enteric infections. In *Current Chemotherapy and Infectious Disease, Proc. 11th*

Int. Cong. Chemother. 19th Intersci. Conf. Antimicrobiologic Agents Chemother., II. Boston, ed. J. D. Nelson, C. Grossi, pp. 947–48
68. National Institute of Nutrition. 1981. *Report for the Year 1980*. Hyderabad: Natl. Nutr. Monitoring Bureau, Indian Counc. Med. Res.
69. Nguyen Dinh Cat. 1958. La keratomalacie infantile au Viet Nam. *XVIII Cong. Ophthalmol., Belgium*, pp. 1127–35
70. Oomen, H. A. P. C. 1961. An outline of xerophthalmia. In *Review of Tropical Medicine* pp. 131–213. New York/London: Academic
71. Oomen, H. A. P. C., ten Doesschate, J. 1973. The periodicity of xerophthalmia in South and East Asia. *Ecol. Food Nutr.* 2:207–17
72. Oomen, J. M. V. 1971. Xerophthalmia in Northern Nigeria. *Trop. Geogr. Med.* 23:246–49
73. Paton, D., McLaren, D. S. 1960. Bitot's spots. *Am. J. Ophthalmol.* 50:568–74
74. Patwardhan, V. N. 1969. Hypovitaminosis A and epidemiology of xerophthalmia. *Am. J. Clin. Nutr.* 22:1106–18
75. Patwardhan, V. N., Kamel, W. W. 1967. *Studies on vitamin A deficiency in infants and young children in Jordan, Part II, Rep. to Wld. Health Org., Geneva*
76. Pereira, S. M. 1972. *Vitamin A deficiency in preschool children in North Arcot District*. Presented at 9th Meet. Nutr. Experts for Consultation on Prevention of Xerophthalmia, South-East Asia Reg. Off., Nutr. Unit, Wld. Health Org.
77. Pereira, S. M., Begum, A. 1971. Failure of a massive single oral dose of vitamin A to prevent deficiency. *Arch. Dis. Child.* 46:525
78. Pereira, S. M., Begum, A., Dumm, M. E. 1966. Vitamin A deficiency in kwashiorkor. *Am. J. Clin. Nutr.* 19:182–86
79. Petersen, R. A., Petersen, V. S., Robb, R. M. 1968. Vitamin A deficiency with xerophthalmia and night blindness in cystic fibrosis. *Am. J. Dis. Child.* 116:662–65
80. Phillips, C. M. 1961. Blindness in Africans in Northern Rhodesia. *Cent. Afr. J. Med.* 7:153–58
81. Pillat, A. 1929. Does keratomalacia exist in adults? *Arch. Ophthalmol.* 2:256–87
82. Pizzarello, L. 1979. *Visual Status of Children of Indochinese Refugees Currently Residing in Thailand, Final Rep. Helen Keller Int., New York*, pp. 1–20
83. Protein Advisory Group. 1976. Vitamin A enrichment of donated foods (with special reference to dry skim milk powder). *Protein Advisory Group Bull.* 6:4
84. Reddy, P. S. 1965. Bitot's spots and vitamin A deficiencies. *Trans. Ophthalmol. Soc. N. Zeal.* 17:90–93
85. Reddy, V. 1978. Vitamin A deficiency and blindness in Indian children. *Ind. J. Med. Res.* 68 (Suppl):26–37
86. Rodger, F. C. 1959. *Blindness in West Africa*. London: H. K. Lewis
87. Rodger, F. C., Saiduzzafar, H., Grover, A. D., Fazal, A. 1963. A reappraisal of the ocular lesion known as Bitot's spots. *Br. J. Nutr.* 17:475–85
88. Roels, O. A., Debeir, O., Trout, M. 1958. Vitamin A deficiency in Ruanda-Urundi. *Trop. Geogr. Med.* 10:77–92
89. Royal Commonwealth Society for the Blind (South Asia) 1982. Xerophthalmia prevalence surveys. *Xero. India*, pp. 10–11 Bombay: R. Commonwealth Soc.
90. Sandford-Smith, J. H., Whittle, H. C. 1979. Corneal ulceration following measles in Nigerian children. *Br. J. Ophthalmol.* 63:720–24
91. Santos, L. M. P., Dricot, J. M., Asciutti, L. S., Dricot-d'Ans, C. 1983. Xerophthalmia in the state of Paraiba, Northeast of Brazil: clinical findings. *Am. J. Clin. Nutr.* 38:139–44
92. Sauter, J. J. 1978. *Causes of Blindness Detected in 19 Schools for the Blind in Tanzania, Final report to the Ministries of Health and National Education, Dar es Salaam*
93. Sauter, J. J. M. 1976. *Xerophthalmia and Measles in Kenya*. Groningen: Drukkerij Van Denderen
94. Sinha, D. P., Bang, F. B. 1976. The effect of massive doses of vitamin A on the signs of vitamin A deficiency in preschool children. *Am. J. Clin. Nutr.* 29: 110–15
95. Sinha, D. P., Bang, F. B. 1973. Seasonal variation in signs of vitamin-A deficiency in rural West Bengal children. *Lancet* 2:228–31
96. Sivakumar, B., Reddy, V. 1972. Absorption of labelled vitamin A in children during infection. *Br. J. Nutr.* 27: 299–304
97. Sivakumar, B., Reddy, V. 1975. Absorption of vitamin A in children with ascariasis. *J. Trop. Med. Hyg.* 78:114–15
98. Solon, F. S., Fernandez, T. L., Latham, M. C., Popkin, B. M. 1979. An evaluation of strategies to control vitamin A deficiency in the Philippines. *Am. J. Clin. Nutr.* 32:1445–53
99. Solon, F. S., Popkin, B. M., Fernandez, T. L., Latham, M. C. 1978. Vitamin A deficiency in the Philippines: A study of

xerophthalmia in Cebu. *Am. J. Clin. Nutr.* 31:360–68
100. Sommer, A. 1982. *Nutritional Blindness: Xerophthalmia and Keratomalacia*. New York: Oxford Univ. Press. 282 pp.
101. Sommer, A. 1982. Conjunctival appearances in corneal xerophthalmia. *Arch. Ophthalmol.* 100:951–52
102. Sommer, A. 1984. Nutritional blindness. In *Clinical Ophthalmology*, ed. T. D. Duane. Philadelphia: Harper & Row. In press
103. Sommer, A. 1982. *Field Guide to the Detection and Control of Xerophthalmia*. Geneva: Wld. Health Org. 58 pp. 2nd ed.
104. Sommer, A., Emran, N. 1982. Tear production in vitamin A-responsive xerophthalmia. *Am. J. Ophthalmol.* 93:84–87
105. Sommer, A., Emran, N., Tamba, T. 1979. Vitamin A-responsive punctate keratopathy in xerophthalmia. *Am. J. Ophthalmol.* 87:330–33
106. Sommer, A., Emran, N., Tjakrasudjatma, S. 1980. Clinical characteristics of vitamin A responsive and nonresponsive Bitot's spots. *Am. J. Ophthalmol.* 90:160–71
107. Sommer, A., Faich, G., Quesada, J. 1975. Mass distribution of vitamin A and the prevention of keratomalacia. *Am. J. Ophthalmol.* 80:1073–80
108. Sommer, A., Green, W. R., Kenyon, K. R. 1981. Clinical-histopathologic correlations of vitamin A responsive and nonresponsive Bitot's spots. *Arch. Ophthalmol.* 99:2014–27
109. Sommer, A., Green, W. R., Kenyon, K. R. 1982. Clinical-histopathologic correlations in xerophthalmic ulceration and necrosis. *Arch. Ophthalmol.* 100:953–63
110. Sommer, A., Hussaini, G., Muhilal, H., Tarwotjo, I., Susanto, D., Saroso, J. S. 1980. History of nightblindness: a simple tool for xerophthalmia screening. *Am. J. Clin. Nutr.* 33:887–91
111. Sommer, A., McLaren, D. S., Olson, J. A. 1977. Assessment of vitamin A status. In *Guidelines for the Eradication of Vitamin A Deficiency and Xerophthalmia*. New York: Nutr. Found.
112. Sommer, A., Muhilal, H., Tarwotjo, I. 1982. Protein deficiency and treatment of xerophthalmia. *Arch. Ophthalmol.* 100: 785–87
113. Sommer, A., Muhilal, H., Tarwotjo, I., Djunaedi, E., Glover, J. 1980. Oral versus intramuscular vitamin A in the treatment of xerophthalmia. *Lancet* 1:557–59
114. Sommer, A., Quesada, J., Doty, M., Faich, G. 1975. Xerophthalmia and anterior-segment blindness among preschool-age children in El Salvador. *Am. J. Ophthalmol.* 80:1066–72
115. Sommer, A., Sugana, T. 1982. Corneal xerophthalmia and keratomalacia. *Arch. Ophthalmol.* 100:404–11
116. Sommer, A., Tarwotjo, I., Hussaini, G., Susanto, D. 1983. Increased mortality in children with mild vitamin A deficiency. *Lancet* 2:585–88
117. Sommer, A., Tarwotjo, I., Hussaini, G., Susanto, D., Soegiharto, T. 1981. Incidence, prevalance and scale of blinding malnutrition. *Lancet* 1:1407–8
118. Sommer, A., Tjakrasudjatma, S., Djunaedi, E., Green, W. R. 1978. Vitamin A–responsive panocular xerophthalmia in a healthy adult. *Arch. Ophthalmol.* 96:1630–34
119. Sommer, A., Toureau, S., Cornet, P., Midy, C., Pettis, S. T 1976. Xerophthalmia and anterior segment blindness. *Am. J. Ophthalmol.* 82:439–46
120. Sullivan, W. R., McCulley, J. P., Dohlman, C. H. 1973. Return of goblet cells after vitamin A therapy in xerosis of the conjunctiva. *Am. J. Ophthalmol.* 75: 720–25
121. Swaminathan, M. C. 1974. *A program for the prophylaxis against blindness in children caused by vitamin A deficiency in India: an appraisal*. Presented at Joint WHO/USAID Meet. on Vitamin A Deficiency and Xerophthalmia, Jakarta, Indonesia
122. Swaminathan, M. C., Susheela, T. P., Thimmayamma, B. V. S. 1970. Field prophylactic trial with a single annual oral massive dose of vitamin A. *Am. J. Clin. Nutr.* 23:119–22
123. Tandon, B. N., Ramachandran, K., Nath, L. M., Sood, N. N., Gahlot, D. K., Gupta, M. C., Wali, J. P., Sinha, S. N., Hasteer, P. C., Kutty, P. R. 1975. Vitamin A nutritional status of rural community of Khol block in Haryana, North India. *Am. J. Clin. Nutr.* 18:1436–42
124. Tarwotjo, I., Gunawan, S., Reedy, S., ten Doesschate, J., House, E., Pettiss, S. T. 1975. An evaluation of the vitamin A deficiency prevention pilot project in Indonesia, 1973–1975. New York: Found. for Overseas Blind, Inc.
125. Tarwotjo, I., House, E., Tjakrasujatma, R. S., Gunawan, S., Basuki, M., Santoso, S. 1975. Large scale distribution of massive dose vitamin A in Indonesia (A study of the operational aspects). *Bull. Penelitian Kesehatan. Health Studies in Indonesia* 3:27–31
126. Tarwotjo, I., Sommer, A., Soegiharto, T., Susanto, D., Muhilal, H. 1982. Dietary practices and xerophthalmia among Indonesian children. *Am. J. Clin. Nutr.* 35:574–81
127. ten Doesschate, J. 1968. *Causes of blindness in and around Surabaja, East Java,*

Indonesia pp. 159–241. PhD Thesis. Univ. of Indonesia, Jakarta. 331 pp.
128. Teng, K. H. 1965. Further contributions to the fundus xerophthalmicus. *Ophthalmologica* 150:219–38
129. Teng Khoen-Hing. 1959. Fundus Changes in Hypovitaminosis A. *Ophthalmologica (Basel)* 137:81–85
130. Thanangkul, O., Promkutkaew, C., Waniyapong, T., Damrongsak, D. 1974. *Comparison of the effects of a single high dose of vitamin A given to mother and infant upon plasma levels of vitamin A in the infant*. See Ref. 121
131. Uyemura, M. 1928. Ueber ein merkwurdige Augenhintergrundveranderung bei zwei Fallen von idiopathischer Hemeralopie. *Klin. Monatsbl. Augenheilkd.* 81:471–73
132. Valenton, M. J., Tan, R. V. 1975. Secondary ocular bacterial infection in hypovitaminosis A xerophthalmia. *Am. J. Ophthalmol.* 80:673–77
133. Vaughan, D. G. 1954. Xerophthalmia. *Arch. Ophthalmol.* 51:789–98
134. Venkatachalam, P. S., Belavady, B., Gopalan, C. 1962. Studies on vitamin A nutritional status of mothers and infants in poor communities of India. *J. Pediatr.* 61:262–68
135. Venkataswamy, G., Cobby, M., Pirie, A. 1979. Rehabilitation of xerophthalmic children. *Trop. Geogr. Med.* 31:149–54
136. Voorhoeve, H. W. A. 1966. Xerophthalmia in the presence of kwashiorkor in Nigeria. *Trop. Geogr. Med.* 18:15–19
137. Wald, G. 1955. The photoreceptor process in vision. *Am. J. Ophthalmol.* 40: 18–41
138. Walien, C. I. 1974. A study of the effect of vitamin A supplementation in Egyptian children. In *Vitamin A deficiency and Blindness Prevention*, p. 13. New York: Am. Found. Overseas Blind, Inc.
139. West, C. 1980. Corneal disease. In *Principles and Practice of Ophthalmology*, ed. G. A. Peyman, D. R. Sanders, M. F. Goldberg. Philadelphia: W. B. Saunders
140. West, K. P., Sommer, A. 1983. *Large Oral Doses of Vitamin A as an Intervention*. Rep. prepared under a cooperative agreement between The Johns Hopkins Univ. Int. Center for Epidemiol. Prevent. Ophthalmol. and USAID. 106 pp.
141. Whittle, H. C., Sandford-Smith, J., Kogbe, O. I., Dossetor, J., Duggan, M. 1979. Severe ulcerative herpes of mouth and eye following measles. *Trans. R. Soc. Trop. Med. Hyg.* 73:66–69
142. Williamson, A. D., Leong, P. C. 1949. Keratomalacia in Singapore and its relation to vitamin A in milk. *Med. J. Malaya*. 4:83–87
143. Wolf, G. 1978. A historical note on the mode of administration of vitamin A for the cure of night blindness. *Am. J. Clin. Nutr.* 31:290–92
144. World Health Organization. 1976. *Report of a joint WHO/USAID meeting. Vitamin A deficiency and xerophthalmia. Tech. Rep. Ser. No. 590*
145. World Health Organization. 1982. *Report of a joint WHO/UNICEF/USAID/HKI/IVACG meeting. Control of vitamin A deficiency. Tech. Rep. Ser. No. 672*
146. Wright, R. E. 1922. Keratomalacia in Southern India. *Br. J. Ophthalmol.* 6:164–75
147. Yap, K. T. 1957. A comparative study of the diets and results of some blood analyses, of children living in different environments in Jogjakarta (Central Java). *Br. J. Nutr.* 11:158–61
148. Zaklama, M. S., Gabr, M. K., Maraghy, S. E., Patwardhan, V. N. 1972. Liver vitamin A in protein-calorie malnutrition. *Am. J. Clin. Nutr.* 25:412–18