MORTALITY ASSOCIATED WITH MILD, UNTREATED XEROPHTHALMIA*

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INTRODUCTION

XEROPHTHALMIA IS THE LEADING CAUSE OF CHILDHOOD BLINDNESS IN MANY "DEveloping" countries.[1,2] An estimated 5 million Asian children develop xerophthalmia every year. One-tenth of these have severe corneal involvement, half of whom become blind.[3] Despite these appalling statistics, few countries allocate significant health resources to the prevention of vitamin A deficiency and xerophthalmia. In areas where childhood mortality itself is an enormous problem, health planners have little interest in "merely" preventing blindness.

Mortality rates are very high among patients with xerophthalmia in which the cornea is involved. In-hospital mortality rates average 15% to 25%.[4-10] However, most children never receive treatment. Discrepancies between the incidence of new cases of active corneal xerophthalmia, and the prevalence of corneal scars in community surveys, suggest that the true untreated mortality rate may reach 85%.[11] The proportion of childhood deaths associated with corneal xerophthalmia is small, and their excess mortality is commonly ascribed to the severity of concurrent illnesses that are responsible for high childhood mortality in general (eg, protein-energy malnutrition, diarrhea, respiratory infections, and childhood exanthems).

In contrast to xerophthalmic corneal involvement, mild xerophthalmia (night blindness and Bitot's spots) occurs in a substantial proportion of otherwise healthy, well-nourished children. If mild xerophthalmia were also associated with excessive mortality, mild xerophthalmia would account for a significant proportion of all childhood deaths, would not be

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easily explained by other associated factors, and would provide a strong argument for intensifying xerophthalmia control programs.

Vitamin A has many important systemic effects in addition to its role in ocular health: it is required for normal differentiation of a wide variety of epithelial structures[12,13]; growth[14-16]; and quite possibly, immune competence and resistance to infection.[17] It is therefore conceivable that even mild vitamin A deficiency could profoundly affect health and mortality, especially under the adverse environmental conditions that are common in developing countries.

Assessing the effect of mild, untreated vitamin A deficiency and xerophthalmia in its native habitat is not easy. Such assessment requires frequent and careful reexamination of very large numbers of preschool-age children under often-difficult field conditions, precise registration and follow-up of the study population, and management of enormous volumes of data. It is not surprising that such information is as yet unavailable.

This thesis addresses the question of differential mortality rates in mild xerophthalmia, utilizing a unique data set available from a prospective longitudinal study carried out in an endemic focus of xerophthalmia in West Java, Indonesia.

BACKGROUND

Xerophthalmia is an ancient disease; the Ebers Papyrus from Egypt describes night blindness, and its treatment with liver extracts.[18] During the 19th and early 20th centuries, reports of conjunctival and corneal xerosis, and corneal ulceration and keratomalacia in malnourished persons appeared frequently in the medical literature, concomitant with increasing industrialization and the growth of the dairy export trade, with their effects on socioeconomic status and dietary habits.[9,16,19-24] Since then, enlightened government policies have all but eliminated the disease from wealthier industrialized societies. Unfortunately, xerophthalmia remains a chronic problem in poorer developing countries, especially those of Asia, where preschool-age children account for the vast majority of cases.[1,2,25-33]

XEROPHTHALMIA CLASSIFICATION

Gradual, progressive deterioration of vitamin A status results in xerophthalmia of increasing severity. These signs were recently reclassified as shown in Table I.[2,11] The earliest manifestation is night blindness. After dusk, affected children are unable to locate their food or toys, or navigate

TABLE I: XEROPHTHALMIA CLASSIFICATION[2]

XN	Night blindness
X1A	Conjunctival xerosis
X1B	Bitot's spots
X2	Corneal xerosis
X3A	Corneal ulceration/ keratomalacia involving less than one-third of corneal surface
X3B	Corneal ulceration/ keratomalacia involving one-third or more of corneal surface
XF	Xerophthalmic fundus
XS	Corneal scars

about their village or house. Specific terms for the condition commonly exist in cultures in which the disease is endemic.

More severe deficiency of vitamin A results in squamous metaplasia of the conjunctiva (Fig 1A), which becomes keratinized and overgrown with saprophytic bacteria.[23,34-38] This results in localized or generalized xerosis or Bitot's spots. These alterations are most severe, and hence first recognized, in the interpalpebral area temporal to the limbus (Fig 1B).

Corneal involvement occurs relatively early in the disease as fine punctate epithelial erosions in the inferonasal quadrant (Fig 2A).[39] With more advanced disease the corneal surface becomes dry and xerotic (Fig 2B), and may become covered with a thick keratinized layer.

Xerophthalmic corneal ulceration has a distinctive appearance as round to ovoid, sharp margined, almost "punched-out" stromal defects (Fig 3A

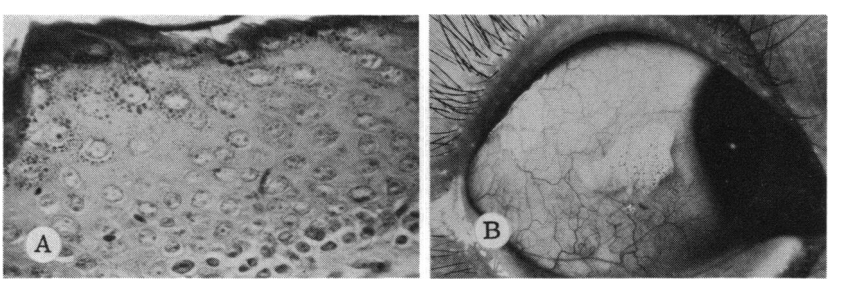

FIGURE 1

Conjunctival xerosis. A: Conjunctival biopsy from temporal quadrant of 25-year-old woman with advanced conjunctival and corneal xerosis depicted in Fig 2B. Surface keratinization, prominent granular cells, and mild acanthosis are present (hematoxylin-eosin, × 625). B: Classical foamy Bitot's spot in 29-year-old man that responded to vitamin A therapy. (Fig A reproduced with permission from ref 37, Fig B from ref 11.)

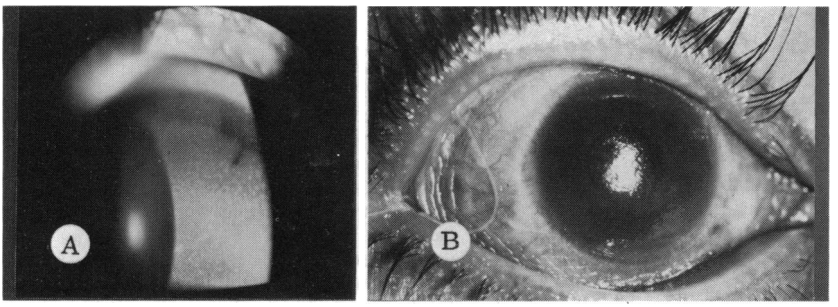

FIGURE 2
Corneal xerosis. A: Extensive vitamin-A-responsive punctate keratopathy, most marked inferiorly, in 10-month-old boy. B: Advanced conjunctival and corneal xerosis in 25-year-old woman that responded rapidly to vitamin A therapy. Changes are most marked inferiorly, where conjunctiva has almost a skin-like appearance and cornea is hazy from keratinization and edema. Cornea has a dry, pebbly, ground-glass appearance. (Fig B reproduced with permission from ref 37.)

and B).[40] There is little if any swelling of the surrounding cornea or evidence of inflammatory infiltration.

Keratomalacia represents full-thickness, localized or generalized corneal necrosis (Fig 4A and B), sometimes beginning below an intact epithelium (Fig 4C).[41] Typically, the peripheral 1 to 2 mm of corneal tissue is spared.

Except for generalized keratomalacia, in which all stroma has been lost, xerophthalmic changes respond rapidly to systemic administration of vitamin A (Fig 4D).[42]

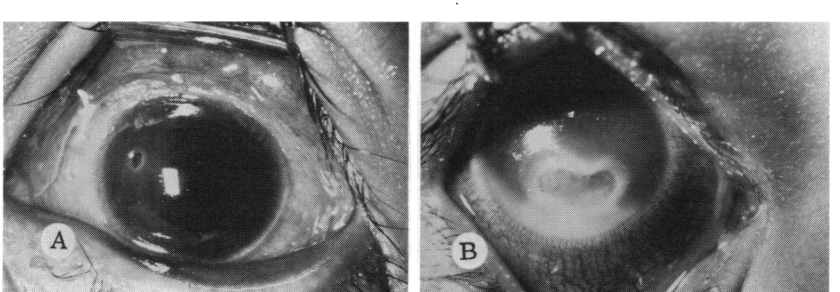

FIGURE 3
Xerophthalmic corneal ulcers. A: Classical "punched-out" circular ulcer of three-fourths corneal depth in 4-year-old boy. Corneal xerosis is apparent inferiorly. B: Oval, fluorescein-staining corneal ulcer in 2-year-old xerophthalmic girl. A 20% hypopyon is present inferiorly. (Fig A reproduced with permission from ref 40.)

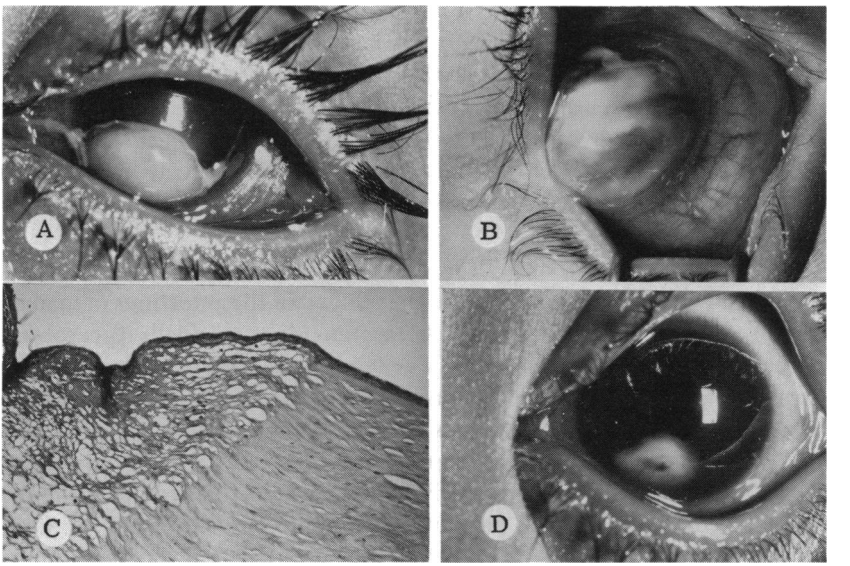

FIGURE 4

Keratomalacia. A: Typical, localized corneal necrosis in an otherwise healthy 2-year-old boy. Conjunctival xerosis is present. All abnormalities responded rapidly to vitamin A (Fig 4D). B: Limbus-to-limbus corneal necrosis in 10-month-old boy. Cornea of other eye was heavily keratinized. C: Sharp-margined corneal necrosis below an intact epithelium in 1-year-old boy who died 3 days after initiation of therapy. Cornea was obtained at autopsy. Clinically, lesion was a three-fourths-depth corneal ulcer. Note relative paucity of inflammatory cells. Cornea of other eye was completely necrotic. D: Healed localized keratomalacia, 1 month after a single oral dose of vitamin A. Note clear pupillary zone. (Pretreatment appearance is shown in Fig 4A.) (Figs A, B, and D reproduced with permission from ref 40 and C from ref 41.)

SYSTEMIC MANIFESTATIONS OF VITAMIN A DEFICIENCY

Xerophthalmia is but the most obvious and dramatic manifestation of vitamin A deficiency. In addition to its role in the visual cycle,[43,44] vitamin A is necessary for proper differentiation of mucosal epithelium.[13,45] In vitamin A deficiency, surface epithelium of the respiratory and urinary tracts and other organs undergoes keratinizing metaplasia.[12,13] The chronic dry cough, increased susceptibility to respiratory infections, and pyuria observed in severely deficient children have been ascribed partly to these epithelial changes.[8,12]

Other systemic changes thought to result from vitamin A deficiency are less well understood. The most prevalent is its effect on growth.[11] Indeed, the existence of "fat-soluble A" was first suspected because vitamin deprived, weanling rats failed to grow as rapidly as their litter-

mates.[14,15,46] Bloch,[16] who first demonstrated that human xerophthalmia is due to the specific deficiency of fat-soluble A, termed the disease "dystrophia alipogenetica," growth failure secondary to a deficiency in a critical factor present in the lipid fraction of dairy products. Vitamin A has since been imbued with additional attributes, most significantly an ability to enhance resistance to systemic infection.[17] This effect, however, has yet to be demonstrated conclusively in man.

VITAMIN A METABOLISM

Vitamin A is a fat-soluble substance produced in the intestines of man and other animals from pro-vitamin A carotenoids, principally β-carotenes, that are found in dark green leafy vegetables, carrots, and some colored fruits, like papaya and mango. Once absorbed, vitamin A is carried to the liver where its storage provides a "buffer" against vagaries in dietary intake.[47] When needed, it is released as retinol in a 1:1 molar association with retinol-binding protein (RBP).[48,49] This holo-RBP complex binds to specific cellular receptors, permitting retinol to enter the cell.[50,51] Other forms of vitamin A, specifically retinoic acid, circulate in smaller amounts and may bind to cellular receptors of their own.[52]

Because of the nature of the RBP transport system, adequate protein and vitamin A are necessary to maintain serum vitamin A levels at a normal level. In vitamin A deficiency, first liver vitamin A levels, and then serum levels, fall while RBP accumulates in the liver.[53-55] In protein deficiency, RBP synthesis is reduced, and both liver and serum levels of RBP fall. While serum holo-RBP (physiologically active vitamin A) levels decline, liver vitamin A stores rise.[54]

Except for malnourished children "in extremis,"[56] isolated protein deficiency does not cause xerophthalmia. However, protein deficiency exacerbates the effects of vitamin A deficiency, which explains why both deficiencies are usually present in children with severe, destructive, xerophthalmic corneal disease.[57,58]

VITAMIN A DEFICIENCY

Xerophthalmia and other manifestations of vitamin A deficiency arise when the delivery of vitamin A to target tissues is inadequate to meet metabolic demands. The single most important cause of such deficiency is inadequate dietary intake. Recommended daily allowances (RDA) of vitamin A for children range from 250 μg to 400 μg, depending upon age.[59] Many children in developing countries never receive these amounts. Whereas most children in industrialized nations receive much of their requirements as the pre-formed vitamin from meat (primarily liver) and

dairy products, after they are weaned, Asian children obtain what little vitamin A they receive from fruits and vegetables as less well absorbed pro-vitamin A carotenoids. Even an RDA-equivalent vegetable diet may be inadequate for their needs, because RDA represent extrapolations from a limited number of observations on otherwise healthy, western adult volunteers.[60,61] Asian and African children, however, are subject to worm infestations, recurrent diarrhea, and protein-energy malnutrition, all of which interfere with vitamin A absorption[62-64]; febrile illnesses, especially childhood exanthems, which increase metabolic demands and depress protein synthesis[65-67]; and frequent respiratory infections, which increase urinary losses of vitamin A.[68] Given the multiplicity of adverse influences they encounter, it is not surprising that vitamin A deficiency and xerophthalmia are commonest among preschool-age children.

The more severe and chronic are the factors contributing to vitamin A deficiency in an individual, and the more these factors coincide, the more severe the resultant disease. In numerous clinical and epidemiologic studies, xerophthalmic corneal involvement was strongly associated with the presence of kwashiorkor (nutritional edema and severely depressed serum albumin levels),[27,57,69,70] wasting (as percentage standard weight for height or age),[57,71,72] diarrhea,[16,71] respiratory infections,[11,16,35,71,73] and a severely ill or debilitated general health status.[11,16,20,27,74]

In contrast, mild xerophthalmia (night blindness and Bitot's spots) commonly results from isolated dietary deficiency and is less closely and only variably associated with the contributory conditions listed above.[8,11,29,30,75] When compared with non-xerophthalmic age-matched and sex-matched control subjects living in the same village, Indonesian children with Bitot's spots were most likely to be stunted (mean height for age) and to consume a diet poorer in preformed and pro-vitamin A.[11] They were *not* at greater risk of active protein-energy malnutrition or measles, and were only slightly more likely to have a history of recent diarrhea or of shedding worms.

XEROPHTHALMIA AND MORTALITY

Corneal xerophthalmia is associated with extremely high mortality rates, although exactly how high is not precisely known. Most studies are based on hospitalized children, and are therefore biased by selection criteria, treatment, and short periods of follow-up. In 1868, Hirschberg[22] reported a mortality rate of 100% in European children with keratomalacia. Cases of keratomalacia in early 20th century Europe experienced a mortality of 50% to 80%.[76,77] In the turn-of-the-century xerophthalmia epidemic that struck Denmark, mortality rates ranged from 39% among children 1 to 3

months of age to 11% among those 1 year and older.[9] Scragg and Rubridge[56] reported, in the 1950s, that the mortality rate among Bantu children with kwashiorkor and rapidly developing corneal perforations was an astounding 95%. In recent studies in Indonesia, mortality among severely malnourished children admitted to a special treatment ward for all degrees of corneal involvement reached 17% by the end of the first month of follow-up.[11]

In general, children in the above-cited studies were all severely malnourished. Since severe malnutrition itself carries a high mortality rate, the degree to which xerophthalmia and vitamin A deficiency contributed to the observed mortality is uncertain.

Long-term field studies of children with severe malnutrition suggest an annual mortality rate for those below 5 years of age of 7% to 12%. Sommer and Loewenstein[78] recorded a 3-month mortality rate in their most malnourished group of 3.2% and a 12-month mortality rate of 11.9%; Kielmann and McCord[79] recorded a 12-month mortality rate of 7.9%; and Chen and co-workers[80] recorded a 12-month mortality rate of 7%. Ten percent of non-xerophthalmic children admitted to a nutritional rehabilitation center in India died.[81] Eleven percent of children hospitalized for malnutrition in El Salvador died.[5] Many years ago, 30% to 35% of severely malnourished children admitted to the central hospital in Jakarta, Indonesia, died, whether or not they had accompanying xerophthalmia.[6] Overall hospital mortality for severely malnourished African children was reported to be 25%.[7]

A number of investigators have suggested that the presence of vitamin A deficiency and xerophthalmia increases mortality beyond that attributable to protein-energy malnutrition alone. McLaren et al[82] reported that mortality among Jordanian children hospitalized with both protein-energy malnutrition and xerophthalmia was 56% to 64%, four times the rate for children of the same age and nutritional status admitted with protein-energy malnutrition alone. Pereira and co-workers[10] reported an in-hospital mortality among Indian children with concomitant keratomalacia and kwashiorkor of 28%, which was twice the rate among children with kwashiorkor alone. An important but unanswered question, however, is whether the children without keratomalacia were indeed as severely malnourished as those with keratomalacia. The broad categories by which children were matched for nutritional status do not preclude the possibility that significant gradations of malnutrition existed within these categories.

Brown and co-workers[8] found that hospitalized Bengali children with both xerophthalmia and protein-energy malnutrition had a slightly higher

mortality rate than those with protein-energy malnutrition alone. But they also discovered that children with xerophthalmia tended to be more severely malnourished than those with normal eyes. In El Salvador,[5] mortality among severely malnourished hospitalized girls with xerophthalmia was greater than among malnourished girls without xerophthalmia; but among boys mortality was independent of the presence or absence of xerophthalmia. This difference was attributed to a greater delay in the admission of malnourished girls.

One of the major limitations in the above studies was the method of case selection: all children had been admitted to a malnutrition ward because they suffered, first and foremost, from severe protein-energy malnutrition. In the Indonesian studies,[11] case ascertainment took place at an eye hospital, not at a general hospital, and children were enrolled in the study on the basis of having corneal xerophthalmia independent of the presence or absence of severe malnutrition. Twenty percent of the children had normal weight for height (greater than 90% of "Western" standards[83]) and an additional 33% had only mild malnutrition (80% to 89% of the weight for height standards). Pedal edema (indicating kwashiorkor) was present in less than one-third of the patients, and 30% had entirely normal serum albumin levels (at least 3.5 g/dl).

The most important determinant of mortality during the first month of follow-up was general nutritional status. Among the most severely malnourished group (with pedal edema, serum albumin equal or less than 2.5 g/dl, or weight for height of less than 70% of Western standards) the mortality rate was, as already mentioned, 17%, vs 1% for those better nourished, even though the severely malnourished children received vigorous therapy.[11]

Few data exist on the long-term mortality rates among children with corneal xerophthalmia. Menon and Vijayaraghavan[84] reported that 20% of xerophthalmic Indian children died within 3 to 4 months of leaving the hospital, the rates being highest for those with keratomalacia. Venkataswamy and co-workers[81] reported that 20% of xerophthalmic children died after discharge from a nutrition rehabilitation unit during a follow-up of 2 to 17 months. ten Doesschate[71] reported that 43% of children who were blinded by xerophthalmia in Surabaya died within 1 to 6 years of follow-up, the same mortality rate as for those blinded from other causes. The mortality rate during long-term (14 months) follow-up of children with corneal xerophthalmia enrolled in the Indonesian studies averaged 13%, ranging from 26% for those originally admitted with severe malnutrition, to 4% for those whose original nutritional status was better.[11]

The major limitation in each of the above studies is that all of the

children had received treatment for both their xerophthalmia and their general malnutrition. They therefore reveal little about the natural history of the disease, which is particularly crucial since the vast majority of xerophthalmic children reside in remote rural villages with limited access to health care facilities. Epidemiologic studies conducted in Indonesia provided the first rough estimates of the true mortality suffered by non-hospitalized children with corneal xerophthalmia, uninfluenced by therapeutic intervention. Adjusted for the national prevalence of active xerophthalmia, data generated in a longitudinal study in West Java[3] suggested a minimal incidence of cornea-destructive xerophthalmia among preschool-age Indonesian children of 1.5 per 1000 per year. As a result, the prevalence of xerophthalmic corneal scars in preschool children should have averaged 4.5 per 1000, if those with active corneal destruction experienced the same overall mortality as the rest of their age group.[11,85] Instead, the prevalence of xerophthalmic scarring actually observed nationwide was only 1.3 per 1000, suggesting that the survival rate among children with active cornea-destructive xerophthalmia was less than a third that of preschool children as a whole.[11]

For obvious ethical reasons, there have been no direct studies of the natural history, including mortality, of children with untreated corneal xerophthalmia, nor for that matter have there been, until now, long-term mortality studies on large numbers of free-living children with untreated mild xerophthalmia (night blindness or Bitot's spots). The opportunity to conduct such a study was recently provided in Indonesia, where a large proportion of preschool children develop mild xerophthalmia sometime during the first 6 years of life; and where government officials wished to determine the rate at which the disease occurs and spontaneously disappears, and to identify risk factors associated with its occurrence.

Children enrolled in the study were closely followed for the development of corneal xerophthalmia. The small proportion of children in which this occurred were quickly hospitalized and treated, with none dying, and only one child developing monocular blindness. In addition, any child who was found to have a severe, life-threatening infection or protein-energy malnutrition during any of the seven examinations received symptomatic therapy and was referred to an appropriate local government health facility whether or not he or she had evidence of night blindness or Bitot's spots.

It was not suspected, nor did any existing literature suggest, that otherwise healthy children with night blindness or Bitot's spots would experience increased mortality. The presence of the survey team and treatment and referral of severely ill children undoubtedly reduced mor-

tality in all the groups. Nonetheless, the data demonstrate that otherwise healthy children with night blindness and/or Bitot's spots experienced much higher mortality than children without clinical evidence of vitamin A deficiency.

METHODS

A prospective longitudinal study of 4600 children who were less than 6 years of age at entry was carried out in six rural villages of Purwakarta District, West Java, Indonesia, which is a 2-hour drive northward from Jakarta, the capital city. The site was selected for its known high rate of xerophthalmia.

Previous reports have documented the high rate of mild xerophthalmia and its spontaneous regression in this population.[11] The annual incidence of Bitot's spots and night blindness in the preschool-age children averaged 9%. Spontaneous cure rates, with 3 months between each examination, ranged from 43% to 59%. In some of the children who developed mild xerophthalmia, the condition had already been present and had spontaneously disappeared at an earlier round. Adjusting for these multiple episodes, it was estimated that over one-third of all children in the area develop at least one episode of mild xerophthalmia during their first 6 years of life.

Previous reports have also demonstrated that these cases of night blindness and Bitot's spots represent episodes of active vitamin A deficiency. All but 1 of 37 children with Bitot's spots studied in Bandung, West Java, responded to vitamin A therapy.[86] Eighty-five percent of children with Bitot's spots or a history of night blindness during their first examination in the longitudinal study had low (< 20 μg/dl) serum vitamin A levels.[87] Mean serum vitamin A levels were directly related to the presence and severity of mild xerophthalmia, the levels being 13.9 μg/dl, 13.4 μg/dl, and 12.1 μg/dl, respectively, for children with a positive history of night blindness, Bitot's spots with a negative history of night blindness, and the concurrence of both conditions. In contrast, the mean serum vitamin A level among their matched controls, children who were of the same age and sex who were living in the same neighborhood, was 17.6 μg/dl; and for those living in the same village but in a more distant neighborhood, 20.0 μg/dl. The relatively low serum vitamin A level in this population as a whole explains their high risk of clinical xerophthalmia.

A positive history of night blindness, called "koto kuen" or "buta ayam" ("chicken blindness") in the local language, was highly specific for the condition. In addition to the fact positive cases had low serum vitamin A

levels, 97% were found, by objective assessment, to be night blind.[87] The mean serum vitamin A level of the 3% alleged to be night blind but who had a negative test for night blindness was 13.7 μg/dl, exactly the same as for those who tested positive, suggesting that the mother's assessment of the child's condition was a better index of the presence of night blindness than was the clinical examination. The sensitivity of a history of night blindness was not directly tested. Some children who were thought to be normal on the basis of a negative history might well have been night blind, although probably not to the same degree as those with a positive history.

Members of Indonesia's Central Bureau of Statistics completely surveyed, mapped, and censused the six study villages. All families containing at least one child below 7 years of age were enrolled in the study. Records were kept on all eligible children.

A special team, consisting of an ophthalmologist, pediatrician, nutritionist, two nurses, and six field workers revisited and attempted to examine all eligible children seven times over an 18-month period, with 3 months between each examination. No new families were enrolled in the study during the 18 months, although children of eligible age who joined families already enrolled (either through birth or in-migration lasting more than 6 months) were added to the study population. Children who died or migrated out of the six study villages were, of course, omitted from the examination. Children who died or were members of families who permanently left the area were dropped from the study; children who left for at least 2 months, without their families, were dropped for that round but were reentered upon their return.

Obviously, not all children who were eligible for examination were always present to have it. Children and family members were sometimes absent because they were visiting relatives or friends outside the village; were living in the fields (a special problem during harvest season); or were attending the weekly market some distance away. Frank refusal to cooperate was extremely low, however, averaging less than 1%. Despite the temporary absence of some children and/or adults, enumeration of deaths was essentially complete. Due to the close-knit nature of Sundanese society, strict tenets of Islam, and active oversight by the villeage headman, all deaths that occur within the village are known and recorded.

At each examination, field workers visited every enrolled household and recorded interval medical histories and any changes in socioeconomic status or composition of the family. Children were then brought to a central examination point, where their weight and height were recorded by the nurses and nutritionist; their general health status was assessed by

the pediatrician; and their eyes were examined by the ophthalmologist using a handlight and magnifying loupe. Standard diagnostic criteria for xerophthalmia were employed.[85] Any children with xerophthalmic corneal disease were immediately given a vitamin A capsule and transported to Bandung for hospitalization, study, and treatment. Children without corneal xerophthalmia but with life-threatening infections (respiratory disease, severe diarrhea) or severe malnutrition were given symptomatic therapy and referred to the local government health facility. Children with night blindness or Bitot's spots were managed in the same way as all the other children, and received no therapy unless they fell into one of the above-mentioned categories.

Because of local taboos, children under 3 months of age were generally not examined, which accounts for the under-representation of this age group.

All data collection forms were checked at least twice for accuracy and completeness before being forwarded for card punching. Data analysis was carried out in batch on an IBM 370 computer utilizing the SPS data management system.

As the population was obviously aging during the course of the study, each child's age was updated, by computer, for each round.

RESULTS

As shown in Table II, an average of 4597 children were enrolled in the study during each round. Complete interview data were collected on an average of 4090 (89%), the remainder of the families being away from

TABLE II: PATIENT PARTICIPATION RATES DURING FIELD VISITS

SURVEY ROUND	CHILDREN ENROLLED	INTERVIEWS COMPLETED		CHILDREN ELIGIBLE FOR EXAMINATION*	CHILDREN EXAMINED†	
		NO.	%		NO.	%
1	4682	4359	93	4308	3963	92
2	4378	3938	90	3896	3367	86
3	4641	4037	87	3970	3262	82
4	4645	3807	82	3749	3082	82
5	4597	4088	89	4047	3569	88
6	4599	4202	91	4145	3923	95
7	4617	4199	92	4181	3987	95
Mean	4597	4090	89	4042	3593	89

*Excludes children who died or left the village permanently (for more than 6 months) or temporarily (for more than 2 months but less than 6 months).

†The number of children examined during the first round is substantially larger than the number followed during the first interval because several subdistricts were dropped during the second round.

home at the time of the visit. An average of 4042 children were alive and eligible for examination, of whom 3593 (89%), were actually examined.

Because of the high incidence and spontaneous cure rate of xerophthalmia in this population, a large degree of precision would have been lost if mortality rates were simply related to ocular status during the first clinical round. Instead, the ocular status of each child was reclassified at each of the rounds. Mortality was then determined for each interval between the seven examinations, based upon the children's ocular status at the examination immediately preceding that interval. Overall ocular-status-specific mortality rates were computed by summing the interval mortalities over the 18 months of observation. For example, during the first 3-month interval (between clinical rounds one and two), mortality was partitioned between children found to have night blindness, Bitot's spots, the two together, or neither of these conditions during round one. As children who were not examined during round one could not be assigned an ocular status, they are not included in the calculation of mortality rates during the first interval. During the second interval, ocular-status-specific mortality rates were computed according to the children's ocular status during the second examination.

Because of out-migration, not all children examined at an interval-initiating round were necessarily eligible for inclusion in the mortality rate calculations of that interval. A total of 20,885 examinations were conducted, however, on children who were eligible (an average of 3481 per interval). The age distribution of these children at each of their interval-initiating examinations is shown in Table III. As already discussed, local

TABLE III: AGE OF CHILDREN AT EACH INTERVAL-INITIATING EXAMINATION

AGE*	NO. OF EXAMINATIONS†	% DISTRIBUTION
0 to 5 months	97	0.5
6 to 11 months	1301	6.2
1 year	3678	17.6
2 years	3705	17.7
3 years	3585	17.2
4 years	3651	17.5
5 years	2758	13.2
6 years	1750	8.4
7 to 8 years	360	1.7
Total	20,885	100

*Age at interval-initiating round.
†Number of examinations performed during the six interval-initiating rounds.

taboos against examination of very young children, their greater likelihood of accompanying their mothers on errands outside the village, and our decision not to enroll newborn infants except within families already enrolled in the study resulted in under-representation of this age group. Similarly, although enrollment was limited to children below 7 years of age, some children reached 7 or even 8 years of age during the course of the study. These too were under-represented, due to attendance at school or work in the fields.

Age-specific prevalence of night blindness, Bitot's spots, and the two conditions together for the 20,885 examinations used in computing interval mortality rates are shown in Table IV. The prevalence of mild xerophthalmia rose dramatically during the third year of life, plateauing at a relatively constant 7% by the age of 3.

In contrast, the age-specific mortality rate "per child interval" was highest during the first 3 years of life, declining to less than 3 per 1000 for those who were 4 years and older (Table V). This difference in the peak distribution of xerophthalmia and the peak distribution of mortality eliminates a potentially important source of bias. Had the two distributions coincided, xerophthalmia might appear to adversely affect survivorship merely because xerophthalmia and mortality were highest in the same age group. As it is, excess mortality associated with xerophthalmia will, if anything, be underestimated.

For comparison with more traditional expressions of mortality, age-specific mortality rates "per child" rather than "per child-interval" is also shown in Table V. As the average number of children followed throughout the six intervals (3481 $\pm$ 306) is obviously one-sixth the number of "child-intervals," these "per child" rates are merely six times the mortality rates when expressed per "child-interval." Also shown for comparison are annualized age-specific mortality rates. Since the six intervals spanned 18 months, these annualized rates are merely the "per child" mortality rates divided by 1.5.

A total of 132 deaths occurred among children included in the 20,885 interval examinations. Twenty-four, or 18.2%, were xerophthalmic at the examination that initiated the interval in which they died (Table VI). The largest number of deaths associated with mild xerophthalmia occurred during the third through fifth years of life, reflecting those ages when the risk of xerophthalmia and the risk of dying overlapped the most.

Remaining analyses deal with the association between mild xerophthalmia (night blindness, Bitot's spots, or the two conditions concurrently) and mortality.

Age-specific mortality rates for normal children and children with mild

TABLE IV: AGE-SPECIFIC XEROPHTHALMIA RATES PER CHILD-EXAMINATION

AGE*	NO. OF EXAMINATIONS	CLINICAL STATUS (NO.)†				CLINICAL STATUS (%)†			
		NORMAL	NB	BS	NB+BS	NORMAL	NB	BS	NB+BS
0 to 5 months	97	97	0	0	0	100.0	. . .	. . .	. . .
6 to 11 months	1301	1301	0	0	0	100.0	. . .	. . .	. . .
1 year	3678	3658	8	11	1	99.5	0.2	0.3	0.0
2 years	3705	3566	61	40	38	96.2	1.6	1.1	1.0
3 years	3585	3324	133	53	75	92.7	3.7	1.5	2.1
4 years	3651	3359	180	65	47	92.0	4.9	1.8	1.3
5 years	2758	2580	86	55	37	93.5	3.1	2.0	1.3
6 years	1750	1629	68	38	15	93.1	3.9	2.2	0.9
7 to 8 years	360	340	11	7	2	94.4	3.1	1.9	0.6
Total	20,885	19,854	547	269	215	95.1	2.6	1.3	1.0

*Age at interval-initiating examination.
†Ocular status at interval-initiating examination.
NB = night blindness; BS = Bitot's spots. The term "normal" in all the tables means "non-xerophthalmic."

TABLE V: AGE-SPECIFIC MORTALITY RATES

AGE*	PER 1000 CHILD-INTERVALS†	PER 1000 CHILDREN	ANNUAL RATE PER 1000 CHILDREN
0 to 5 months	. . .	. . .	. . .
6 to 11 months	8.46	50.8	33.9
1 year	8.70	52.2	34.8
2 years	12.15	72.9	48.6
3 years	6.69	40.1	26.7
4 years	3.01	18.1	12.1
5 years	0.73	4.4	2.9
6 years	2.86	17.2	11.5
7 to 8 years	2.78	16.7	11.1

*Age at interval-initiating examination.
†The interval between two successive examinations, with a total of six intervals in the 18-month study.

xerophthalmia are shown in Table VII. Overall, the mortality rate among xerophthalmic children was four times the rate among children with normal eyes.

There were either few deaths or few instances of xerophthalmia in children 0 to 11 months, 5 years, or 7 to 8 years of age. For the remaining age groups, xerophthalmic children died at 4 to 12 times the rate of their non-xerophthalmic peers.

The risk of dying increased with the severity of xerophthalmia (Table VIII). Children with night blindness were at almost three times the risk; children with Bitot's spots almost seven times the risk; and children with both night blindness and Bitot's spots, almost nine times the risk of dying as children with normal eyes ($P < 0.05$).

TABLE VI: NUMBER AND PROPORTION OF DEATHS ACCORDING TO OCULAR STATUS

AGE	NO. OF DEATHS			% OF DEATHS	
	NORMAL	XEROPHTHALMIC	TOTAL	NORMAL	XEROPHTHALMIC
0 to 5 months	0	0	0	. . .	. . .
6 to 11 months	11	0	11	. . .	. . .
1 year	30	2	32	94	6
2 years	36	9	45	80	20
3 years	18	6	24	75	25
4 years	6	5	11	54	46
5 years	2	0	2	100	. . .
6 years	3	2	5	60	40
7 to 8 years	1	0	1	100	. . .
Uncertain	1	0	1	100	. . .
Total	108	24	132	81.8	18.2

TABLE VII: AGE-SPECIFIC MORTALITY ACCORDING TO OCULAR STATUS AT INTERVAL-INITIATING EXAMINATION

AGE	NO. OF EXAMINATIONS		NO. OF DEATHS		MORTALITY (PER 1000)*		MORTALITY (REL RISK)†
	NORMAL	XEROPHTHALMIA	NORMAL	XEROPHTHALMIA	NORMAL	XEROPHTHALMIA	NORMAL:XEROPH
0 to 5 months	97	0	0	0	. . .	. . .	. . .
6 to 11 months	1301	0	11	0	8.5	. . .	. . .
1 year	3658	20	30	2	8.2	100.0	1:12
2 years	3566	139	36	9	10.1	64.7	1:6
3 years	3324	261	18	6	5.4	23.0	1:4
4 years	3359	292	6	5	1.8	17.1	1:10
5 years	2580	178	2	0	0.8	. . .	. . .
6 years	1629	121	3	2	1.8	16.5	1:9
7 to 8 years	340	20	1	0	3.0	. . .	. . .
Total	19,854	1031	107	24	5.3	23.3	1:4

*Mortality per 1000 child-intervals.

†Relative risk calculated by dividing mortality rate in xerophthalmic children by mortality rate in children without xerophthalmia.

TABLE VIII: MORTALITY RATES IN RELATION TO OCULAR STATUS

OCULAR STATUS	NO. OF CHILD-INTERVALS*	NO. OF DEATHS	MORTALITY (PER 1000)†	MORTALITY (REL RISK)‡
Normal	19,889	108	5.4	1.0
Night blind	547	8	14.6	2.7
Bitot's spot	269	6	35.5	6.6
NB + BS	215	10	46.5	8.6
Total	20,920	132	6.3	1.2

*Includes 35 children whose exact age was unknown.
†Mortality per 1000 child-intervals.
‡Relative risk calculated by dividing mortality rate in xerophthalmic children by mortality rate in children without xerophthalmia.

Although the large-scale country-wide prevalence survey revealed little association between mild xerophthalmia and specific major risk factors for death (low weight for height, pedal edema, and respiratory infections),[11] the same was not entirely true for this special study population. Respiratory infections were more prevalent in children with xerophthalmia, and the prevalence increased with the severity of the xerophthalmia (Table IX). The increased risk of respiratory infection, however, is not nearly as great as the increase in mortality associated with xerophthalmia.

To rule out the possibility that differences in the prevalence of respiratory infection accounted for a significant degree of the association between mortality and xerophthalmia, Table X presents differential mortality rates stratified by whether or not respiratory infection was present. Even among children without respiratory infection, mortality rose linearly with the severity of xerophthalmia ($P < 0.05$). Mortality rates among children with respiratory infection were, as expected, greater than among children of comparable ocular status without respiratory infection. Despite the small number of xerophthalmic children who had respiratory infections, mortality in children with respiratory disease showed the same increase with the degree of xerophthalmia.

TABLE IX: PREVALENCE OF RESPIRATORY INFECTION IN RELATION TO OCULAR STATUS

OCULAR STATUS	NO. OF EXAMINATIONS	NO. WITH URI*	RATE OF URI	REL RISK OF URI†
Normal	19,889	1568	7.9	1.0
Night blind	547	61	11.2	1.4
Bitot's spot	269	34	12.6	1.6
NB + BS	215	32	14.9	1.9

*Number of children with respiratory infection at interval-initiating examination. Includes 35 children whose exact age was unknown.
†Relative risk calculated by dividing rate of respiratory infection in xerophthalmic children by rate in normal children.

TABLE X: MORTALITY RATES IN CHILDREN WITH AND WITHOUT RESPIRATORY INFECTION AT INTERVAL-INITIATING EXAMINATION

RESPIRATORY INFECTION	OCULAR STATUS	NO. OF CHILD-INTERVALS*	NO. OF DEATHS	MORTALITY (PER 1000)†
Absent	Normal	18,321	93	5.1
	Night blind	486	6	12.4
	Bitot's spot	235	6	25.5
	NB + BS	183	7	38.3
Present	Normal	1568	15	9.6
	Night blind	61	2	32.8
	Bitot's spot	34	0	. . .
	NB + BS	32	3	93.8

*Includes 35 children whose exact age was unknown.
†Mortality per 1000 child-intervals (see text).

To rule out the potential biasing effects of differences in age distribution of deaths and of xerophthalmia, Table XI presents age-specific mortality rates in children without respiratory infection for those age groups at greatest risk of these two conditions (2 to 4 years). The same nearly linear relationship between mortality and severity of xerophthalmia was present in all three age groups ($P < 0.05$).

Although kwashiorkor (judged by pedal edema) was more common among xerophthalmic children, only a tiny proportion (< 0.2%) of children had kwashiorkor. Among the vast majority of children free of kwashiorkor, mortality was linearly related to their degree of xerophthalmia. In children with night blindness, Bitot's spots, and the two conditions concurrently, the risk of dying was, respectively, 2.1, 4.3, and 8.3 times that of children without xerophthalmia.

TABLE XI: AGE-SPECIFIC MORTALITY RATES IN CHILDREN WITHOUT RESPIRATORY INFECTION AT INTERVAL-INITIATING EXAMINATION

AGE	OCULAR STATUS	NO. EXAMINED*	NO. DIED	MORTALITY (PER 1000)†
2 years	Normal	3105	30	9.7
	Night blind	54	2	37.0
	Bitot's spot	33	3	99.0
	NB + BS	26	3	115.4
3 years	Normal	3033	15	5.0
	Night blind	118	2	17.0
	Bitot's spot	45	1	22.2
	NB + BS	62	2	32.3
4 years	Normal	3165	4	1.3
	Night blind	152	1	6.6
	Bitot's spot	55	1	18.2
	NB + BS	43	1	23.3

*Number of examinations at interval-initiating rounds.
†Mortality rate expressed per 1000 child-intervals.

TABLE XII: PROPORTION OF CHILDREN WITH VARYING CATEGORIES OF "WEIGHT FOR HEIGHT"*

OCULAR STATUS	TOTAL	WEIGHT FOR HEIGHT					
		LESS THAN 90%		90% TO 99%		100% OR GREATER	
		NO.	%	NO.	%	NO.	%
Normal	19,826	6079	31	9107	46	4640	23
Xerophthalmia	891	273	31	466	52	152	17

*Percentage of standard weight for height of "Western" children.[83] Total numbers of children were slightly reduced by omission of small numbers of "outliers," subjects whose weight for height fell completely outside of normal standards.

The prevalence of wasting (as percentage standard weight for height) was almost identical in children with and without xerophthalmia (Table XII). Differences in acute nutritional status would therefore not be expected to account for the association between mild xerophthalmia and mortality. This is demonstrated in Table XIII. Children who were wasted (< 90% of expected weight for height[83]) were at significantly higher risk of dying than were more normally nourished children (90% to 99% of expected weight for height) ($P < 0.01$). Within each of these two major nutritional categories, mortality was related to the degree of accompanying xerophthalmia ($P < 0.05$). The numbers of children who were severely malnourished (< 80% of standard weight for height) was too small to be analyzed separately.

The influence of diarrhea, a commonly cited cause of death among young children in the tropics, was not studied. Its presence is difficult to ascertain during a brief examination, and results of the much larger nationwide prevalence survey revealed that the association between diarrhea and xerophthalmia was variable and weak.[11] Although differences in

TABLE XIII: MORTALITY RATES IN CHILDREN ACCORDING TO THEIR DEGREE OF WASTING

WEIGHT FOR HEIGHT*	OCULAR STATUS	NO. EXAMINED†	NO. DIED	MORTALITY (PER 1000)‡
Less than 90%	Normal	6079	58	9.5
	Night blind	111	2	18.0
	Bitot's spot	94	5	53.2
	NB + BS	68	8	117.7
90% to 99%	Normal	9107	38	4.2
	Night blind	283	4	14.1
	Bitot's spot	107	1	9.3
	NB + BS	76	2	26.3

*Expressed as percentage of standard weight for height.[83]
†Number of examinations at interval-initiating round.
‡Mortality rate expressed per 1000 child-intervals.

diarrheal experience may have influenced the results, they clearly would not have explained the very large differences in mortality between children with and without xerophthalmia, or the nearly linear relationship between mortality and severity of mild xerophthalmia among these otherwise healthy, well-nourished children.

Only a miniscule proportion of children had measles or chickenpox at examination, and at the same rate in xerophthalmic and non-xerophthalmic subjects.

DISCUSSION

The high mortality that accompanies severe corneal xerophthalmia is well recognized. The present study demonstrates, for the first time, that otherwise healthy free-living children with mild xerophthalmia are at significantly greater risk of dying than children without xerophthalmia.

On the average, children with mild xerophthalmia died at four times the rate of non-xerophthalmic children. If anything, this is an underestimate, for the following reasons:

1. As already discussed, the incidence and spontaneous cure rate of xerophthalmia in the study population was extremely high. Although children were reexamined, and their ocular status was reclassified at the start of each 3-month interval, previous analyses on a small subsample of this population suggested that their ocular status varied considerably within this time period.[11] Had they been reexamined at shorter intervals, and their ocular status been known just prior to death, it is likely the association between xerophthalmia and mortality would have been even greater.
2. Presumably the increased mortality experienced by xerophthalmic children was not so much a function of their ocular status as it was of their underlying vitamin A nutriture. As indicated by serum vitamin A levels obtained during the first clinical round, the vitamin A status of the entire study population was marginal at best.[87] Since mortality was directly related to the severity of even mild xerophthalmia, it is reasonable to suspect that mortality among children with subclinical vitamin A deficiency is also excessive. Hence, the mortality rate observed in the "normals"—the children without ocular involvement—might have been lower had their vitamin A nutriture been truly

adequate. In such case, the relative mortality among xerophthalmic children would have been even more excessive.

3. The very presence of the survey team, and the provision of symptomatic therapy and referral of all severely ill and malnourished children, undoubtedly reduced the observed mortality, quite probably to a greater extent in those who were xerophthalmic.

Despite the conservative nature of the estimates of xerophthalmia-associated mortality established by this study, they indicate that even mild xerophthalmia has a considerable impact on overall mortality in preschool-age children in developing countries.

Among 1 to 6 year olds, the age group studied in which xerophthalmia was most prevalent, the annual mortality rate among children without xerophthalmia was 20.8 per 1000. Among those with xerophthalmia, it was 94.8 per 1000, an excess annual mortality of 74 per 1000.

The average prevalence of mild xerophthalmia in this age group was 5.5%. Because of the increased mortality among mildly xerophthalmic children, the overall annual mortality rate for all the 1 to 6 year olds was 24.6 per 1000, of which 3.8 per 1000 (24.6 minus 20.8) or 16% was directly attributable to the presence of mild but clinically demonstrable vitamin A deficiency. Where the prevalence of xerophthalmia is higher, its contribution to overall mortality will be greater.

It is unlikely that the excess mortality associated with mild xerophthalmia is directly attributable to the presence of night blindness or Bitot's spots—although the former may reduce, to some extent, the child's ability to compete at the cooking-pot with his better-sighted peers. More likely, this excess mortality is a result of the systemic effects of impaired vitamin A metabolism, particularly those effects that are related to resistance to infection.

Vitamin A deficiency results in keratinization of the respiratory, gastrointestinal, and genitourinary tracts (among others), thus decreasing local resistance and increasing the risk of bacterial colonization and infection.[8,12,13,16,35,88-91] Whether it is these "mechanical" changes, interference with normal immune responses,[17,92-94] or not yet determined additional factors that lead to systemic infection and death is unknown.

The presence of excessive mortality in children with mild xerophthalmia and vitamin A deficiency also suggests that the prevalence of severe ocular sequelae, especially corneal scars, is a poor means by which to estimate the extent of even severe vitamin A deficiency in a community.[85] Not only are children with severe xerophthalmic corneal disease likely to

die, but those with milder ocular disease will often not survive long enough to develop corneal involvement.

Public health officials can no longer think of night blindness and Bitot's spots as mere "nuisances" of limited importance. They appear to be important premonitory signs of increased mortality. This finding has several important implications:

1. The existence of even mild xerophthalmia in a community justifies initiation of vigorous intervention measures, not only to prevent rare cases of blindness, but also to significantly reduce childhood mortality by improving vitamin A nutriture.
2. Night blindness and Bitot's spots should be accorded the same respect as low "weight for height" when screening children to ascertain those in need of serious medical and nutritional attention.
3. Prevalence criteria currently used for determining the existence of a serious vitamin A problem need to be reevaluated.
4. The mechanisms responsible for excessive mortality in children with mild vitamin A deficiency and xerophthalmia urgently need elucidation.

The existence of vitamin A was originally suspected from its systemic growth-promoting effects. With the recognition of xerophthalmia, concern dramatically shifted to the ocular consequences of vitamin A deficiency, and responsibility for management of the disease was passed to the ophthalmic community. It is now necessary for nutritionists, pediatricians, public health workers, and government officials to be re-alerted to the serious systemic consequences of this condition.

SUMMARY

The high mortality rate among children with severe corneal xerophthalmia is well recognized. The present study investigates, for the first time, mortality among the very much larger number of otherwise healthy free-living children with mild xerophthalmia (night blindness and Bitot's spots).

An average of 3481 children (under 6 years of age) living in six Indonesian villages were reexamined by an opthalmologist, pediatrician, and nutritionist every 3 months for 18 months. The overall prevalence of mild xerophthalmia was 4.9%. During the 18 months of observation, 132 chil-

dren died. Of these, 24 had mild xerophthalmia and 108 had normal eyes at the 3-monthly examination preceding their death.

Mortality rates were calculated for each 3-month interval by classifying all children by their ocular status at the start of the interval, and then dividing the number of deaths within the interval by the number of children of the same ocular status followed up for that interval. Mortality rates for the six 3-month intervals were then added together, and the results expressed as deaths per 1000 "child-intervals" of follow-up.

Overall mortality rates for children with mild xerophthalmia and for children with normal eyes were 23.3 and 5.3, respectively, a ratio of 4 to 1. Excess mortality among the mildly xerophthalmic children increased with the severity of their xerophthalmia. Mortality rates for children with night blindness, with Bitot's spots, and with the two conditions concurrently were 2.7, 6.6, and 8.6 times the mortality rate of non-xerophthalmic children. This direct, almost linear relation between mortality and the severity of mild xerophthalmia was still present after standardizing for age and for the presence or absence of respiratory infection and protein-energy malnutrition.

In the population studied, 16% of all deaths in children 1 to 6 years of age were directly related to vitamin A deficiency identified by the presence of mild xerophthalmia.

These results suggest: that the existence of mild vitamin A deficiency in a community justifies initiation of vigorous intervention measures to reduce mortality, as much as to prevent the rarer cases of blindness; that night blindness and Bitot's spots should be accorded the same respect as is low "weight for height" in identifying those children in urgent need of medical attention; that ocular criteria used for determining the existence and severity of a vitamin A problem be reevaluated; and that the ophthalmic community, which has long been responsible for managing xerophthalmia, must now re-alert nutritionists, pediatricians, and public health workers to the serious systemic consequences accompanying even mild forms of the disease.

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