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Nutritional Factors in Corneal Xerophthalmia and Keratomalacia

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• Six measures of nutritional status were studied in 162 consecutive cases of presumed nutritional keratopathy ranging from mild xerosis through full-thickness necrosis (keratomalacia) and in a variety of control subjects. The severity of corneal involvement was related to the severity of wasting, prevalence of edema, and serum levels of albumin, transferrin, and vitamin A. Even the most severe corneal alterations were compatible with normal indices of protein and anthropometric status, but not with normal serum vitamin A levels. Analysis suggests that interaction between vitamin A and protein status determines cellular adequacy of vitamin A metabolism, which virtually collapses in keratomalacia. Serum levels of holoretinol-binding protein were severely and uniformly depressed in all degrees of corneal involvement.

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Nutritionally related corneal disease has long been recognized[1,2] and still accounts for at least 250,000 new cases of blindness every year.[3] Vitamin A deficiency is clearly the basis of punctate keratopathy[4] and corneal xerosis.[5-9] The relative importance of vitamin A and protein deficiencies in the etiology of severe ulceration and "keratomalacia" remains less certain.

See also p 404.

Reports of corneal destruction are almost entirely limited to malnourished persons[1,2,10,11] in whom serum protein levels have been severely depressed.[12,13] Yap,[14] Kuming,[15] and Emiru[16] believed protein deficiency is the basis of keratomalacia. However, most authors studied only a limited spectrum of corneal disease, relied on fragmented nutritional data collected retrospectively, and observed highly biased groups of subjects seen initially for severe protein-energy malnutrition. Interpretation and comparisons are further hampered by variations in diagnostic criteria. We present nutritional and biochemical data on the 162 consecutive cases of gross corneal involvement described and classified in the accompanying report (p 404). Results indicate that severity of corneal involvement is directly related to adequacy of vitamin A metabolism.

SUBJECTS AND METHODS

As already described (p 404),[3] 162 consecutive patients with corneal xerophthalmia or keratomalacia seen at the Cicendo (Indonesia) Eye Hospital between June 1977 and September 1978 underwent detailed ophthalmic, pediatric, and bacteriologic examinations and were classified, by severity of corneal involvement, into eight files grouped into three categories (Table 1). They ranged in age from 1 month through 12 years (median, 3 years); 53% were male.

Three milliliters of venous blood was collected from each patient and spun, and the supernatant was stored at −20 °C. The vitamin A level was determined by the method of Neeld and Pearson,[17] usually within one week and never more than two weeks after collection. The holoretinol-binding protein (HRBP) level was determined by the method of Glover et al,[18] usually within two months and never more than eight months after collection. Transferrin levels were determined by the technique of Mancini et al.[19] All laboratory investigations were conducted in a coded, masked fashion. Owing to equipment failure, vitamin A determinations could not be run on blood specimens collected between

Table 1.—Clinical Classification of Corneal Cases*

Class	File	Clinical Description	No. of Cases
X2	1	Mild xerosis: haziness and loss of luster	24
	2	Moderate xerosis: surface has dry, "peau d'orange" appearance	24
	3	Severe xerosis: presence of keratinized plaques	5
X3A	4	Small ulcer: sharply demarcated, 1-3 mm in diameter, superficial or deep	45
	5	Large ulcer: usually full thickness, may be variant of file 4 or 6 lesion	5
X3B	6	Localized stromal necrosis	34
	7	Complete corneal necrosis: unilateral	13
	8	Complete corneal necrosis: bilateral	12

*Classified by most severe lesion in worst eye (p 404).

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Table 2.—Severity of Corneal Disease Among All Abnormal Cases and Those With Matched Control Cases

	% Distribution by File	
File	All Abnormal Cases (n = 162)	Those With Matched Control Cases (n = 33)
1	14.8	15.2
2	14.8	15.2
3	3.1	3.0
4	27.8	33.3
5	3.1	0.0
6	21.0	12.1
7	8.0	18.2
8	7.4	3.0
1-3	32.7	33.3
4-5	30.9	33.3
6-8	36.4	33.3

Table 4.—Prevalence of Pedal Edema in Corneal Xerophthalmia

File*	No. of Cases	Edema Present, No.(%)
1-3	53	10(18.9)
4-5	50	15(30.0)
6	30	9(30.0)
7-8	24	12(50.0)
Total	157	46(29.3)

*Files 1 through 6 vs 7 and 8: $P < .05$.

July 16, 1977, and Jan 14, 1978, and on HRBP collected after May 15, 1978. Initial values of one or the other were available on more than 90% of cases. All were offered free hospitalization and received one of several high-dose vitamin A treatment schedules.[1,20]

A subsample of cases, representative of the various forms of corneal involvement, was selected for epidemiologic study. Twenty-five children living in the immediate vicinity of each of these patients were examined, and clinically nonxerophthalmic children were selected as control subjects matched for age and sex. Their parents were encouraged to return with them to the hospital for examination. Among 60 such matched control subjects, nine had clinical evidence of xerophthalmia when examined in the hospital. The remaining 51 belonged to 33 corneal cases, providing a maximum of 33 paired comparisons.[1] When more than one control subject was available for a patient, the average value for the multiple control determinations was used in the paired comparison. The severity of corneal involvement among all patients was similar to that in the subgroup with matched control subjects (Table 2).

Statistical tests included χ^2 analysis with Yates' correction, Fisher's exact test, Student's t test for paired and unpaired samples, the normal deviate (z) corrected for continuity, linear trend for proportions, and coefficient of correlation.[21,22]

RESULTS

General Nutritional Status

Weight for height, expressed as a percentage of standard,[23] is a convenient measure of body mass. Being self-correcting for past episodes of growth retardation (stunting), it provides data on present nutritional status (wasting). Table 3 indicates that severity of corneal involvement was directly related to the degree of wasting (< 80% of standard, $P < .02$ by linear trend); however, all corneal manifestations, including complete limbal-to-limbal necrosis (keratomalacia, files 7 and 8), are compatible with normal anthropometric status. Abnormal subjects had a weight for height 15% ± 2.5% below that of their matched control subjects (n = 32 pairs, $P < .001$).

Pitting edema (kwashiorkor) was present in 29% of all corneal cases, the prevalence increasing with the severity of corneal involvement and being particularly common among cases of total corneal necrosis (Table 4). Twenty-one percent of matched cases, but none of their control subjects, were edematous (n = 33 pairs, $P < .01$).

Stomatitis was present in 21% of cases, without any consistent variation by type or degree of corneal involvement. Cheilosis was present in only two cases.

Table 3.—Weight for Height of Corneal Xerophthalmia Cases

Clinical Severity (File)	No. of Cases	% Distribution by % of Standard*				
		≥90%	80%-89%	70%-79%	60%-69%	< 60%
1-3	53	32.1	30.2	30.2	3.8	3.8
4-5	49	20.4	38.8	32.7	8.2	0.0
6	32	12.5	34.4	50.0	0.0	3.1
7-8	25	8.0	28.0	24.0	24.0	16.0
Total	159	20.8	33.3	34.0	7.5	4.4

*Adapted from Jelliffe.[23] Degree of wasting correlated with severity of corneal involvement, $P < .02$ by linear trend.

Table 5.--Serum Albumin Levels in Corneal Xerophthalmia

File	No. of Cases	% Distribution by Serum Albumin Level					Mean*	SE
		≥ 3.5 g/dL	3.4-3.0 g/dL	2.9-2.5 g/dL	2.4-2.0 g/dL	< 2.0 g/dL		
1-3	53	35.8	34.0	24.5	3.8	1.9	3.20	.07
4-5	48	29.2	35.4	25.0	6.3	4.2	3.12	.08
6	33	27.3	27.3	36.4	6.0	3.0	3.07	.09
7-8	25	20.0	4.0	28.0	44.0	4.0	2.65	.15
Total	159	29.6	28.3	27.7	11.3	3.1	...	...

*Mean levels files 1 through 6 vs 7 and 8, $P < .01$

Table 6.—Serum Transferrin Levels in Corneal Xerophthalmia

File	No. of Cases	% Distribution by Transferrin Level					Mean*	SE
		≥ 200 mg/dL	199-150 mg/dL	149-100 mg/dL	99-50 mg/dL	< 50 mg/dL		
1-3	47	36.2	12.8	17.0	12.8	21.3	151.3	13.4
4-5	45	17.8	17.8	31.1	13.3	20.0	128.6	12.0
6	30	26.7	13.3	20.0	16.7	23.3	135.9	18.3
7-8	22	9.1	4.5	9.1	27.3	50.0	75.4	15.1
Total	144	24.3	13.2	20.8	16.0	25.7	...	...

*Mean levels files 1 through 6 vs 7 and 8, $P < .01$

Protein Status

Both serum albumin and transferrin are useful indices of basic protein status; however, albumin, with a half-life of 14 days,[24] responds less rapidly to alterations in diet.[25,26] Both are more stable than prealbumin, which has a half-life of only two to three days[27,28] and is sensitive to acute, moderate alterations of protein intake in even well-nourished persons.[25]

Serum albumin (Table 5) and transferrin (Table 6) levels in corneal cases varied widely. Mean levels were especially depressed in instances of total corneal necrosis, but even severe disease was compatible with normal levels.

The mean difference in albumin levels between corneal cases and matched control subjects, on paired analysis, was 0.84 ± 0.13 (SE) g/dL (n = 32, $P < .001$), and in transferrin levels was 181 ± 22 (SE) mg/dL (n = 24, $P < .001$).

Table 7.—Serum Vitamin A Levels in Corneal Xerophthalmia

File	No. of Cases	% Distribution by Serum Vitamin A Level: < 10 μg/dL	10-14 μg/dL	15-19 μg/dL	≥ 20 μg/dL	Mean*	SE
1-3	26	61.5	26.9	7.7	3.8†	8.2	0.94
4-5	32	68.8	28.1	3.1	0.0	7.2	0.70
6	25	92.0	4.0	4.0	0.0	5.4	0.72
7-8	15	80.0	20.0	0.0	0.0	5.2	1.01
Total	98	74.5	20.4	4.1	1.0	...	...

*$r = .964$, $P < .01$.
†Represents a single borderline case (21 μg/dL).

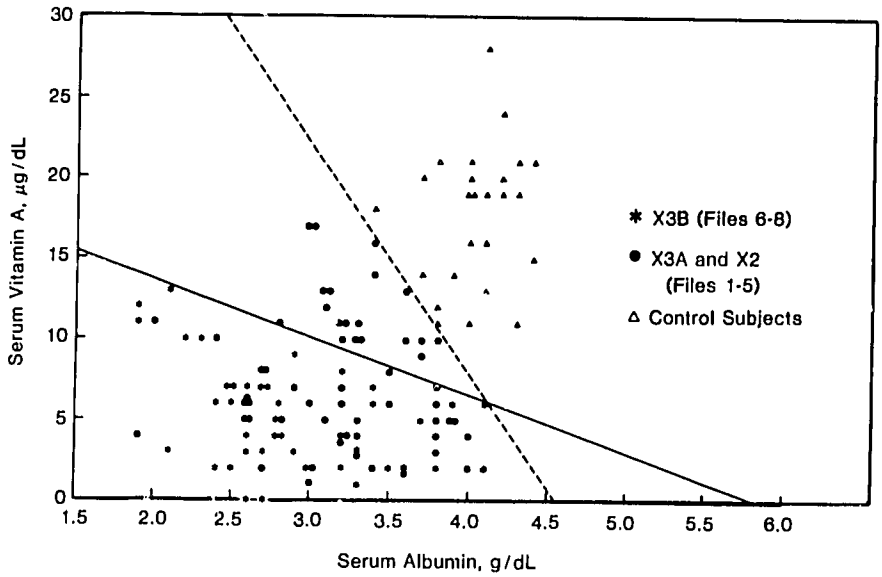

Fig 1.—Serum albumin and vitamin A levels of corneal cases and control cases. All cases of corneal necrosis (files 6 through 8) fall below solid line; all corneal cases fall below dotted line and all control cases fall above dotted line.

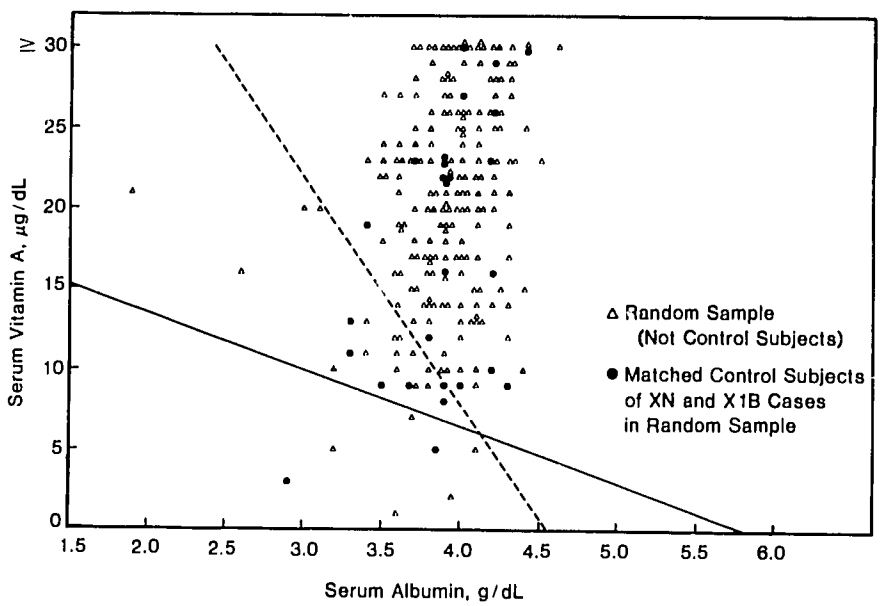

Fig 2.—Serum albumin and vitamin A levels of randomly sampled, clinically normal children in longitudinal field survey conducted in same province as hospital study.[30] Random sample includes children who were and were not matched control subjects of cases of night blindness (XN) and Bitot's spots (X1B) encountered in survey. Boundaries same as those in Fig 1.

Table 8.—Serum Holoretinol-Binding Protein (HRBP) in Corneal Xerophthalmia

File	No. of Cases	HRBP, μg/mL: Mean	SE
1-3	38	1.13	0.22
4-5	28	1.00	0.23
6	15	1.33	0.31
7-8	14	1.07	0.22

Vitamin A Status

In addition to equipment failure already mentioned, three subjects were excluded from analysis: two, both in file 8, were known to have received oral vitamin A before joining the study, and one, in file 7, with a completely necrotic left cornea and classic xerophthalmic ulcer in the right cornea, had a serum vitamin A level grossly out of range (32 μg/dL), being 6 SDs from the mean and higher than any value observed in cases of vitamin A-responsive Bitot's spots[29] or normal control subjects. We suspected that the child had recently received oral vitamin A or that there was laboratory error. Three patients known to have recently received oil-injectable vitamin A, which has little effect on serum vitamin A levels,[3] are included in the analysis: two had the highest vitamin A levels in file 7 (12 and 13 μg/dL, respectively), and one, in file 2, had the highest level of all (21 μg/dL).

Aside from these exceptions, serum vitamin A levels were depressed (< 20 μg/dL) in all cases (Table 7). Mean levels were directly related to the severity of corneal involvement ($r = .964$, $P < .01$).

Serum HRBP levels were severely depressed in all categories of corneal involvement (Table 8).

The mean differences in serum vitamin A and HRBP levels between corneal cases and matched control subjects were 10.2 ± 1.5 (SE) μg/dL (n = 16, $P < .001$) and 9.8 ± 1.6 (SE) μg/mL (n = 17, $P < .001$) respectively.

Vitamin A-Protein Interaction

Corneal cases and control subjects are plotted by serum vitamin A and albumin levels in Fig 1. The overlap between abnormal and control subjects when these factors are considered independently disappears when they are considered together. The single control subject falling within the X3B (files 6 through 8) boundary was a 3-month-old twin of an abnormal subject. Although his conjunctiva and cornea appeared normal, he could, conceivably, have been night-blind.

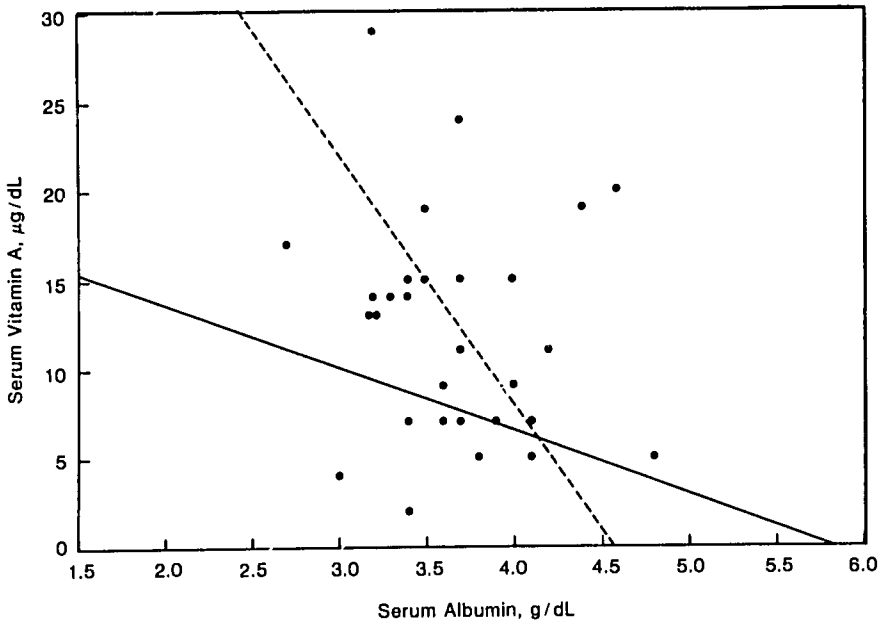

Fig 3.—Serum albumin and vitamin A levels of vitamin A-responsive cases of Bitot's spots studied in same hospital.[29] Boundaries same as those in Fig 1.

Table 9.—Albumin-Standardized Serum Vitamin A Levels

Albumin Category, g/dL	Clinical Classification*			
	Normal	X2 (Files 1-3)	X3A (File 4)	X3B (Files 6-8)
> 3.5-< 4.0				
No.	110	9	7	6
Albumin, mean	3.8	3.8	3.7	3.8
Vitamin A, mean	19.6	7.8	8.4	3.8
Vitamin A, SD	7.7	5.5	3.2	2.0
≥ 3.0-< 3.5				
No.	10	11	12	8
Albumin, mean	3.3	3.2	3.2	3.3
Vitamin A, mean	14.5	8.9	9.2	4.1
Vitamin A, SD	5.7	5.2	4.6	2.6
< 3.0				
No.	3	5	7	25
Albumin, mean	2.5	2.7	2.4	2.5
Vitamin A, mean	13.3	8.4	6.4	5.6
Vitamin A, SD	9.3	2.1	2.6	3.5

*Normal subjects: random sample of preschool Indonesian children.[3]

To test the stability of these corneal boundaries, a larger group of normal subjects (randomly sampled children in a field study from the same province[30]) is shown in Fig 2, and cases of vitamin A-responsive Bitot's spots (seen at the same hospital[29]) in Fig 3. The difference in the distribution of normal subjects, cases of X2/X3A (files 1 through 5), and cases of X3B (files 6 through 8) across the boundaries was statistically significant at every level of serum vitamin A ($P < .001$ by χ^2 or Fisher's exact test at vitamin A levels of < 10 μg/dL, 10 to 14 μg/dL, and 15 to 19 μg/dL). Even the differences in the distribution of cases of vitamin A-responsive Bitot's spots and cases of X3B were significant at vitamin A levels of less than 10 μg/dL ($P < .001$) and 10 to 14 μg/dL ($P < .004$).

The mean serum vitamin A values, by albumin level, for normal subjects (random sample of longitudinal field study) and the three classes of corneal disease (X2, X3A, and X3B) are given in Table 9. Because the exact clinical classification of cases in file 5 is uncertain (p 404), they are omitted from this tabulation. The differences in these albumin-standardized mean vitamin A levels between cases of X3A and X3B are significant for albumin levels of greater than 3.5, and less than 3.5 but greater than or equal to 3.0 g/dL ($P < .05$). At an albumin level below 3.0 g/dL, the difference is small and statistically insignificant. The only difference in vitamin A levels between cases of X2 and X3A, at an albumin of less than 3.0 g/dL, does not reach statistical significance.

The slope of the regression of vitamin A on albumin is positive for the normal random sample ($P < .05$), negative for cases of X3B ($P < .01$), and indefinite for mild corneal diseases (X2 and 3XA) (Table 10).

COMMENT

The relative importance of vitamin A and protein deficiency in the etiology of keratomalacia is controversial.[14-16,31,32] The present study suggests the basic underlying etiologic factor in all forms of nutritional keratopathy investigated was impaired vitamin A metabolism. Whereas both protein and vitamin A status affect the adequacy of vitamin A metabolism, the latter seems to be the more important determinant.

Severity of general malnutrition and protein deficiency and the prevalence of kwashiorkor were all correlated with the severity of corneal involvement; however, frank corneal lesions, including full-thickness necrosis (X3B, files 6 through 8), occurred in children in whom all of the previously mentioned values were entirely normal. In contrast, vitamin A levels were depressed in every case. The degree of depression was directly related to the severity of corneal involvement, although this relationship is less obvious when standardized for serum albumin level.

The overlap of vitamin A levels for normal subjects and cases of corneal disease of varying severity and the correlation between protein status and severity of corneal involvement require explanation. In part, these seem to represent independent events. Vitamin A variability is partially explainable by fluctuations in laboratory results, the variable proportion of serum "vitamin A" that is physiologically active,[20,33] and the inconstant relationship, except at low levels, between serum vitamin A levels and liver stores.[34-36] The relationship between protein status and severity of corneal involvement is partially explained by the fact children who consume more calories and protein are likely to consume more vitamin (and provitamin) A as well. This factor undoubtedly accounts for the correlation and positive slope of the regression of serum vitamin A on albumin observed in normal children (Tables 9 and 10).

Available data suggest that direct

Table 10.—Regression Analysis of Vitamin A on Albumin*

Clinical Status (File)	r	y Intercept	Slope/SE
Normal	+0.8849	1.498	+4.521/2.33
1-3	−0.5592	10.352	−0.610/2.14
4	+0.7983	2.430	+1.792/1.54
6-8	−0.9618	9.303	−1.499/0.39

*From Table 9. Linear regression (least squares) and correlation based on mean vitamin A and albumin levels for each of the three albumin categories, thus giving equal weighting to the relationship at each of the data points along the curves. Since none of the abnormal subjects had a serum albumin level of 4 g/dL or more, normal subjects with values this high were excluded from the analysis.

interaction between vitamin A and protein status occurs as well. Synthesis of retinol-binding protein and, therefore, the release of HRBP from the liver are depressed in protein deficiency.[36] Feeding severely protein-deficient children (who have adequate vitamin A stores) a high-protein diet raises serum vitamin A and retinol-binding protein levels,[26,37,38] but this does not entirely explain our observations, since HRBP levels in our patients were uniformly depressed in all degrees of corneal involvement. As Fig 1 and Tables 9 and 10 suggest, a more intimate balance between vitamin A and protein status may determine adequacy of vitamin A metabolism, perhaps at the level of target cells. This feature is most evident for severe disease (X3B, files 6 through 8), in which vitamin A metabolism has virtually collapsed. In all cases in which protein levels were normal or only moderately depressed, serum vitamin A levels were severely depressed. Conversely, severe depression of protein status was compatible with higher (though never normal) vitamin A levels. This relationship resulted in an inversion of the relationship between serum albumin and vitamin A levels observed in normal subjects, the correlation and slope of the regression being negative. In milder corneal disease, in which interference with vitamin A metabolism is less complete, the interaction is less obvious.

Although protein status seems to influence vitamin A metabolism in target cells, vitamin A availability seems to play a dominant role. None of our patients, except the single unexplained exclusion, had a normal serum vitamin A level, though many had normal levels of albumin and transferrin. None of the children in whom high-protein, low-vitamin diets reportedly raised serum vitamin A levels were clinically xerophthalmic,[26,38] and massive vitamin A therapy resulted in healing (if only transiently) of viable corneal tissue, even in the presence of severe protein deficiency and general malnutrition.[3,20,33]

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