

Effects of Vitamin A Deficiency on the Ocular Surface

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Abstract: Vitamin A deficiency remains an important cause of ocular morbidity among patients with chronic liver disease and lipid malabsorption, and is a major cause of blindness in developing countries. Early ocular surface changes include keratinization of the conjunctiva and development of superficial punctate keratopathy. More severe deficiency results in corneal keratinization, ulceration, and necrosis. Vitamin A is necessary for normal differentiation of nonsquamous epithelium; keratinization is a direct consequence of its deficiency. Exposure exacerbates the process and surface phenomena, especially localized drying from loss of mucus-secreting goblet cells, reduced aqueous tear production, and irregularities of the keratinized surface may all contribute to stromal melting, which can occur in the absence of inflammatory infiltration or bacterial invasion. Surface abnormalities respond rapidly to systemic vitamin A. Significantly, corneal changes disappear long before the reappearance of goblet cells. Inflammation sometimes masks or reverses the xerotic process. [Key words: keratomalacia, ocular surface, vitamin A deficiency, xerophthalmia.] *Ophthalmology* 90:592-600, 1983

Vitamin A deficiency is one of the most common causes of ocular surface abnormalities and blindness. It is a frequent, and often unrecognized problem among patients with chronic liver disease,¹ cystic fibrosis,² regional enteritis,³ and other causes of malabsorption and dietary deprivation.⁴ At least five million African and Asian children develop clinically significant vitamin A deficiency every year of whom a quarter million go blind.⁵ In the vast majority of cases surface abnormalities precede destructive alterations in the corneal stroma.

Vitamin A is a fat soluble substance found in animal tissue, principally liver, and dairy products, or formed in the small intestines from the splitting of carotenoids of plant origin. It is stored in the liver as retinol palmitate and subsequently released and transported to target cells as retinol in a one:one molar association with retinol-binding protein.⁶ Cellular receptors bind this holo-RBP complex, allowing the retinol to enter the cell.^{6,7} Other forms of vitamin A, such as retinoic acid, circulate in small amounts, have specific cellular receptors, and support many of the same physiologic functions.^{6,8,9}

Vitamin A is required for normal differentiation of mucus-secreting epithelia.¹⁰ In vitamin A deficiency mucosal epithelium of a wide variety of organs undergoes keratinizing metaplasia.^{11,12} The eye is but the most obvious and dramatic example.

Gradual deterioration of vitamin A status results in xerophthalmia of increasing severity (Table 1).¹³⁻¹⁵ The earliest clinical manifestation is impaired dark adaptation and nightblindness.¹⁶⁻¹⁸ Subsequently an oval or triangular patch of temporal conjunctiva develops a dry, nonwettable, xerotic appearance. When covered by a

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Carried out under Cooperative Agreement AID/DSAN-CA-0267-931-0045 between the Office of Nutrition, USAID, and ICEPO.

Presented at the Eighty-seventh Annual Meeting of the American Academy of Ophthalmology, San Francisco, California, October 30-November 5, 1982.

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Table 1. Classification of Active Xerophthalmia

×N	Night blindness
×1A	Conjunctival xerosis
×1B	Bitot's spot
×2	Corneal xerosis
×3A	Corneal ulceration/keratomalacia < 1/3 corneal surface
×3B	Corneal ulceration/keratomalacia ≥ 1/3 corneal surface

From World Health Organization.¹⁵

superficial foamy substance it is termed a Bitot's spot (Figs 1, 2).^{19,20} Histopathologic examination of the lesion reveals typical keratinizing metaplasia: loss of surface infolding and microvilli (Fig 7); absence of goblet cells; and formation of prominent keratin and granular cell layers (Figs 3, 4).²¹ The superficial foamy substance is composed of desquamated keratin and saprophytic diptheroids (Fig 8).^{21,22} Even though clinical changes appear limited to the temporal quadrant histopathologic abnormalities are generalized, goblet cells being absent throughout the conjunctiva.^{21,23}

With more severe deficiency the nasal, inferior, and lastly superior quadrants become xerotic and the changes more pronounced. The conjunctiva appears thickened and corrugated, resembling skin, and frank corneal abnormalities are usually obvious (Fig 5).

The earliest change noted in the human cornea is a fine punctate keratopathy located in the inferonasal quadrant (Fig 9) (24). This is already present in 60% of individuals with night blindness who have yet to develop clinically apparent conjunctival disease (Fig 10). In the vitamin A deficient rabbit a lusterless epithelial graying, due to edema of the epithelial cells, is said to precede the development of punctate erosions.²⁵ Punctate erosions have also been noted in the vitamin A deficient guinea pig.²³

In both man and rabbit, more severe deficiency is associated with increasingly dense punctate keratopathy

Table 2. Tear Production in Otherwise Well-nourished* Cases of Xerophthalmia and Controls

	Eyes examined (n)	Eyes with <15 mm wetting	
		(n)	(Percent)
Corneal Controls†	86	8	9.3
Conjunctival xerosis (×1)	38	9	23.7
Corneal xerophthalmia (×2/×3)	62	17	27.4

* All had serum albumin ≥ 3.5 g/dl, and weight for heat ≥ 80% of standard.

† Includes multiple controls for the same abnormal case.

Test for linear trend, $P < 0.01$.

From Sommer et al.²⁸

Table 3. Tear Production and Transferrin Levels in Cases of Corneal Xerosis

Wetting (mm)	Serum Transferrin (mg%) (Percent of Eyes in Column)		
	<50	50-100	>100
0-4	44.4	16.7	22.0
5-9	27.8	16.7	10.0
10-14	5.6	33.3	4.0
15-19	11.1	—	12.0
20-24	—	—	8.0
≥25	11.1	33.3	44.0
Total (n)	18	12	50

Chi square = 23.6, df = 10, $p < 0.01$.

From Sommer et al.²⁸

which spreads upwards to cover the corneal surface (Fig 6).²⁴⁻²⁶ Corneal involvement is then obvious on hand-light examination, as a dry, hazy appearance secondary to punctate keratopathy, polycystic microbullae, keratinization, and stroma edema (Fig 11).^{25,26} The cornea becomes frankly keratinized with a peau d'orange appearance and may even develop Bitot's spot-like foamy accretions (Figs 5, 12).²⁶

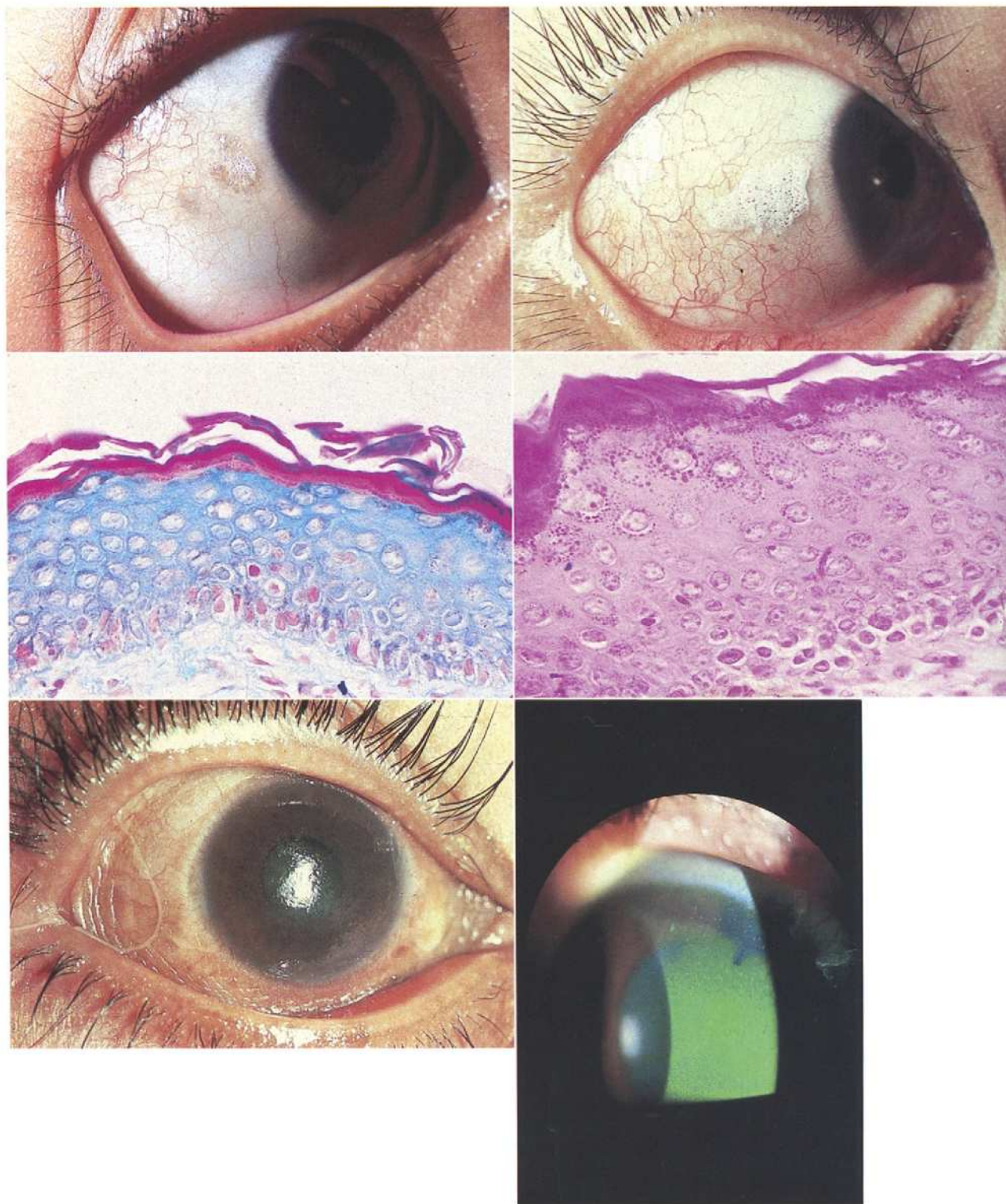
These surface abnormalities are primarily a direct consequence of impaired vitamin A metabolism on cellular differentiation.¹³ Within two to four days of systemic vitamin A therapy punctate keratopathy and conjunctival and corneal xerosis begin to resolve, disappearing entirely within one to two weeks.^{20,24,26} Keratin and granular cell layers have usually disappeared, and microvillous projections reappeared, within four to seven days.²¹ Local variations in exposure, mechanical stress, and tear film dynamics may explain the localization of early changes but are unlikely to play a significant role in their pathogenesis.

It has been suggested that changes in tear production and loss of mucus-secreting goblet cells may be important.²⁷ Aqueous tear production falls in human xerophthalmia in relation to both vitamin A and protein status and the level of hydration (Fig 18, Tables 2, 3).²⁸ But

Table 4. Presence of Conjunctival Goblet Cells In Xerophthalmia Following Systemic Vitamin A

Weeks After Treatment	Temporal Quadrant	Inferonasal Quadrant
1	0/4	0/2
2	0/4	2/4
3-4	1/2	1/2
5-8	4/4	4/4
9-12	1/4	5/5

From Sommer et al.²⁹



Figs 1 and 2. Top left and top right, typical Bitot's spots ($\times 1B$) that eventually responded to vitamin A therapy. (Fig 2 from Sommer.¹³) **Fig 3.** Center left, light microscopy of conjunctival biopsy from eye shown in Figure 5. Note heavily keratinized surface (Danes stain, $\times 185$). (From Sommer.¹⁴) **Fig 4.** Center right, light microscopy of another section from same specimen in Figure above demonstrates prominent granular cell layer (hematoxylin-eosin, $\times 250$). (From Sommer.¹⁴) **Fig 5.** Bottom left, advanced conjunctival ($\times 1A$) and corneal ($\times 2$) xerosis in 25-year-old Indonesian women. The inferior conjunctiva has a skin-like quality. (From Sommer.¹³) **Fig 6.** Bottom right, extensive punctate keratopathy, densest inferiorly in a patient with corneal xerosis. (From Sommer et al.²⁶)

Table 5. Conjunctival Inflammation Among Cases of Monocular Conjunctival Xerosis

Inflammation Present	
Both eyes	4
Only xerotic eye	1
Only nonxerotic eye	15
Total patients	20

* $P < 0.01$.

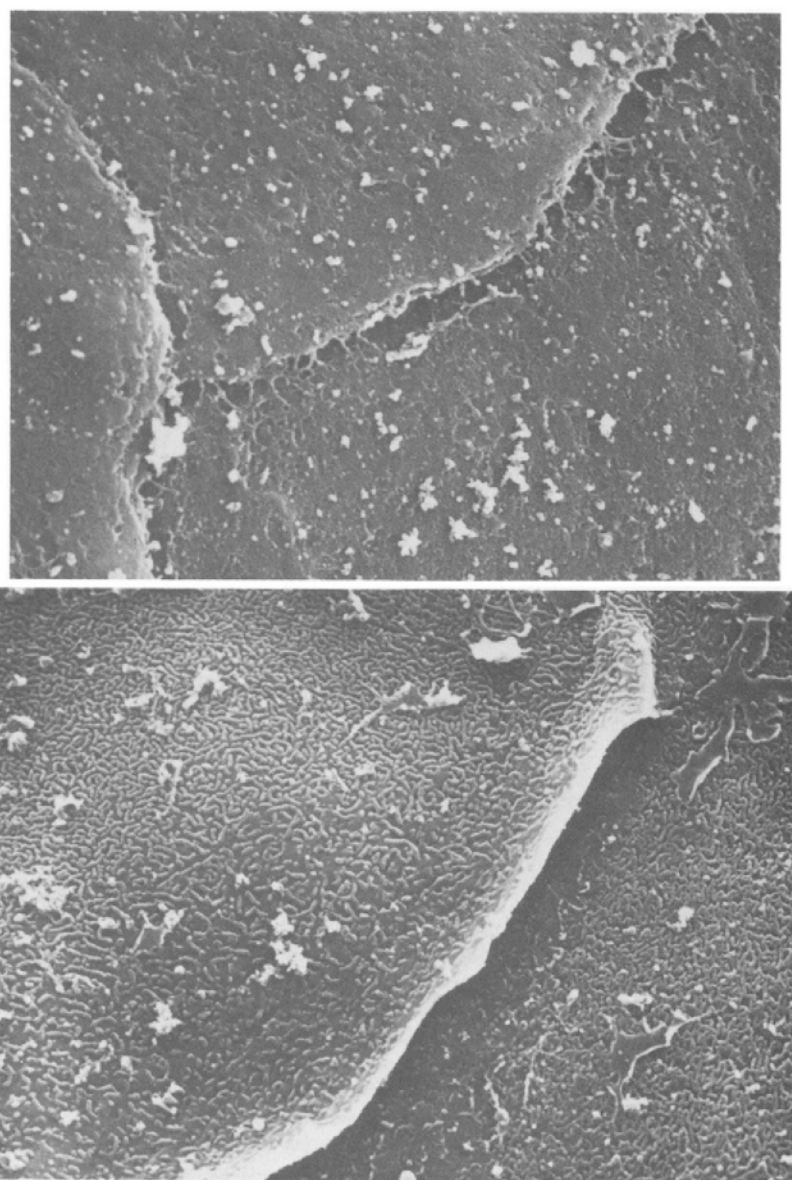
Modified from Sommer et al.³²

by Schirmer's test many xerophthalmic individuals have normal tear production,²⁸ and the rate of tear production is unchanged in the xerotic rabbit.²⁵ The bladder,

constantly bathed in an aqueous medium, develops marked keratinization.¹¹ Mucus production is undoubtedly affected as well, and mucus deficiency could conceivably result in localized corneal drying.²⁷ But corneal changes disappear long before goblet cells begin to reappear (Table 4).^{21,29} Unless alternative sources of mucus^{30,31} respond more rapidly to vitamin A status than do goblet cells, it is difficult to imagine how mucus deficiency could play an important role.

Two recently recognized facets of conjunctival xerosis should be mentioned. Chronic vitamin A deficiency can result in persistent metaplasia, no longer responsive to restitution of normal vitamin A status.^{20,21} These non-responsive lesions are usually limited to the temporal quadrant, with an abrupt transition between histologically normal and abnormal conjunctiva (Fig 19).²¹ This

Fig 7. Scanning electron microscopy of biopsy specimen of temporal conjunctiva from 6-year-old girl who presented with bilateral Bitot's spots. *Top*, pretreatment specimen from right eye demonstrates absence of surface microvilli ($\times 5,500$). *Bottom*, 14 days following vitamin A therapy specimen from left eye demonstrates presence of normal-appearing microvilli and microplicae ($\times 5,000$). (From Sommer et al.²¹)



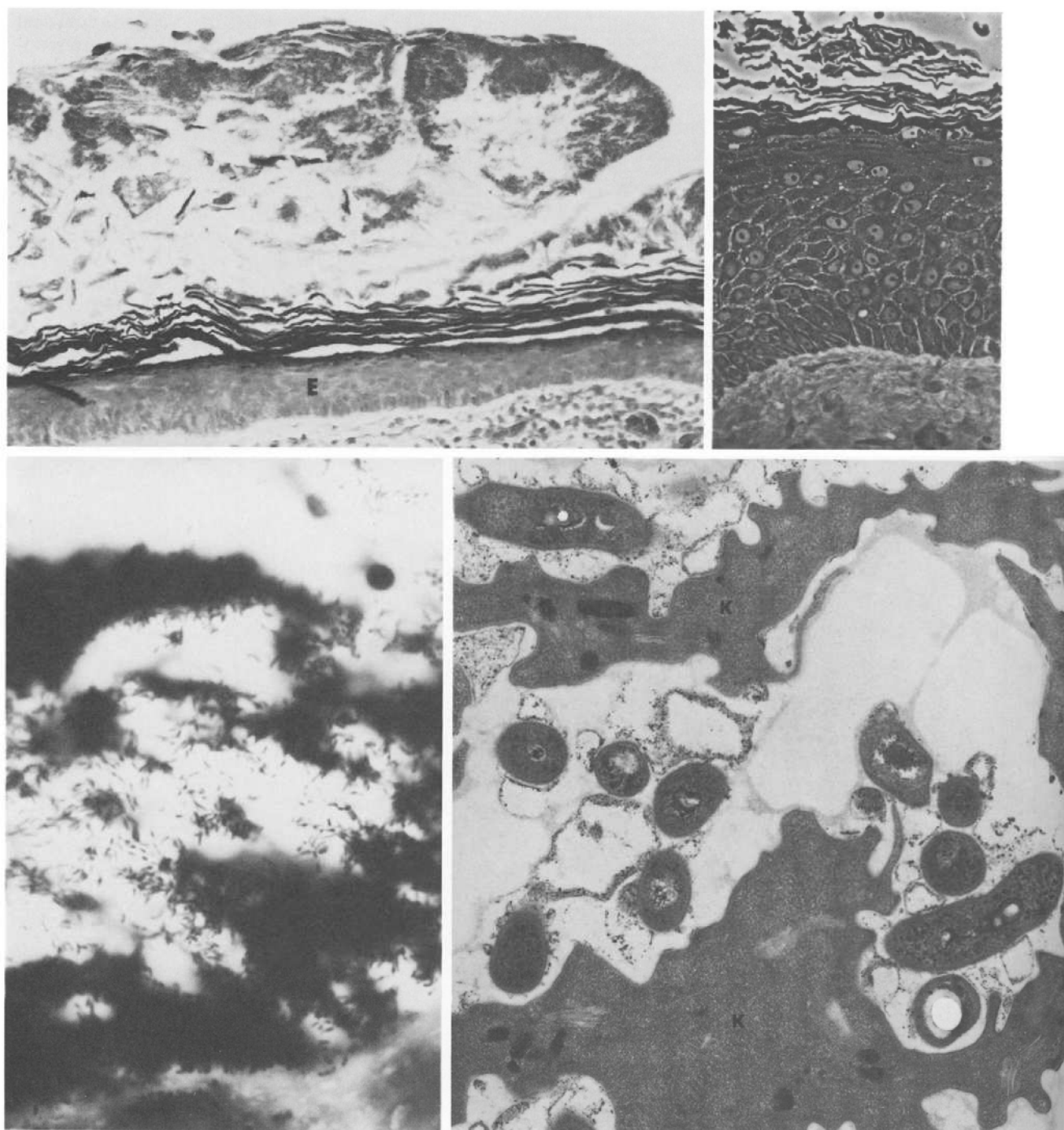


Fig 8. Biopsy specimen of prominent Bitot's spot from 20-year-old man that was nonresponsive to vitamin A. *Top left*, light microscopy shows large plaque of material overlying keratinized surface (Danes stain, original magnification $\times 125$). *Top right*, phase-contrast microscopy shows extensive surface keratinization (paraphenylenediamine, original magnification $\times 750$). *Bottom left*, higher magnification light microscopy reveals plaque composed of massive accumulation of gram-positive bacilli (Brown and Hobbs stain, original magnification $\times 1300$). *Bottom right*, transmission electron microscopy resolves bacterial profiles interspersed among keratinized squames (original magnification $\times 24,000$). (From Sommer et al.²¹)

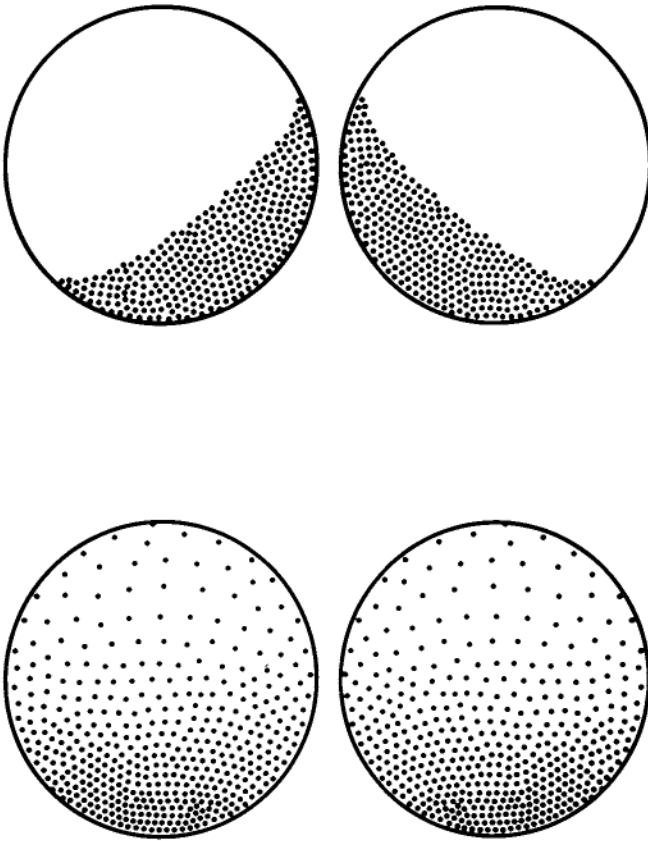


Fig 9. Xerophthalmic punctate keratopathy begins in the inferonasal quadrant. With more severe vitamin A deficiency the lesions become more numerous and spread superiorly. (From Sommer et al²⁴).

explains at least some cases of vitamin A-refractory Bitot's spots. The second is the apparent disappearance of conjunctival xerosis in inflamed eyes (Table 5).³² Further investigations into the mechanisms responsible for these phenomena would undoubtedly advance our understanding of the biochemical and physiologic control of xerosis.

We are even more ignorant of the pathogenetic mechanisms responsible for corneal ulceration and necrosis. Xerophthalmic ulcers have a classical appearance. Most are small, round to ovoid punched-out craters or full-thickness perforations, that look as if a trephine had been applied to the eye (Fig 13). They are most often peripheral, located in the inferior and nasal quadrants, and respond rapidly to vitamin A.^{13,26,33} Of even greater concern is localized and generalized keratomalacia: full-thickness corneal necrosis that commonly presents as swollen, edematous, opaque cornea (Fig 14).^{13,26} Still viable stroma responds rapidly to systemically administered vitamin A, smaller lesions often healing with surprising restoration of central clarity (Fig 15).^{13,26} In larger lesions much of the necrotic stroma sloughs, leaving a descemetocoele to slowly scar over (Fig 16). One to 2 mm of peripheral cornea are almost invariably spared.

Punched-out ulcers can proceed to typical necrosis. But whether this is the common course of events or merely incidental is unknown.¹³

The role of epithelial loss, inflammatory infiltration, and bacterial infection, mechanisms traditionally invoked to explain stromal necrosis, are uncertain. There is no doubt epithelial defects occur. Thick, keratinized epithelial layers have been seen to slough carrying deeper epithelial plugs with them.^{13,26} Microcystic epithelial and subepithelial bullae have also been noted to break through the surface.^{13,26} Stroma is then potentially exposed to epithelial-generated collagenase activity and the risk of bacterial infection.^{34,35} Yet in both humans and animals, stromal necrosis has been observed below intact, keratinized epithelium^{13,26,36-38} in the absence of bacterial invasion (Fig 17).³⁶ Certainly the xerotic eye is host to increased numbers of bacteria¹³; in the animal model, xerophthalmic eyes are more susceptible to bacterial invasion^{39,40}; pathogenic bacteria can be cultured from a large proportion of ulcerated xerophthalmic corneas⁴¹; and bacterial invasion is evident on histopathologic examination of advanced necrosis in humans.³⁶ But positive cultures are no more frequent from ulcerated than nonulcerated corneas of malnourished children,^{13,42} and the addition of antibiotics to the basic nutritional regimen does not significantly alter the rate of corneal healing.¹³

The role of inflammatory cells is also unclear. Inflammatory infiltration and release of collagenases and pro-

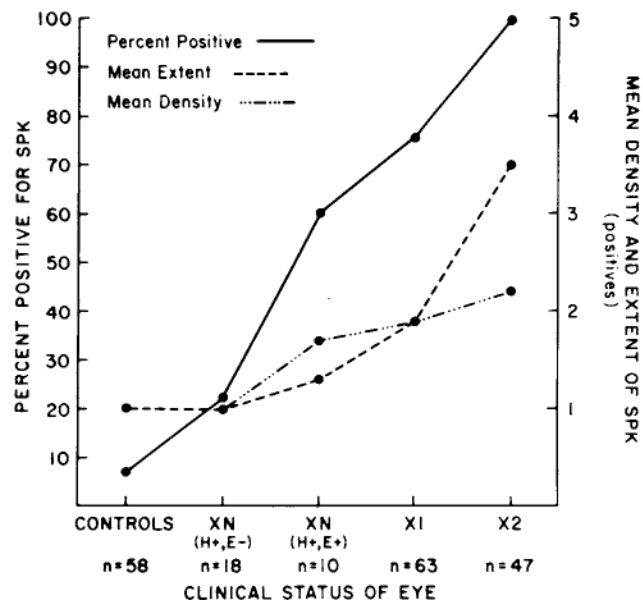


Fig 10. The prevalence, extent, and density of fluorescein-staining punctate keratopathy increase with the severity of vitamin A deficiency and xerophthalmia ($P < 0.01$ for linear trend). Extent: 1 (inferonasal), 2 (inferior half), 3 (inferior three-fourths), and 4 (entire) corneal surface. Density: 1 (mild), 2 (moderate) and 3 (heavy). H+, E-, = positive history but negative examination for XN. (Drawn from Sommer et al.²⁴)

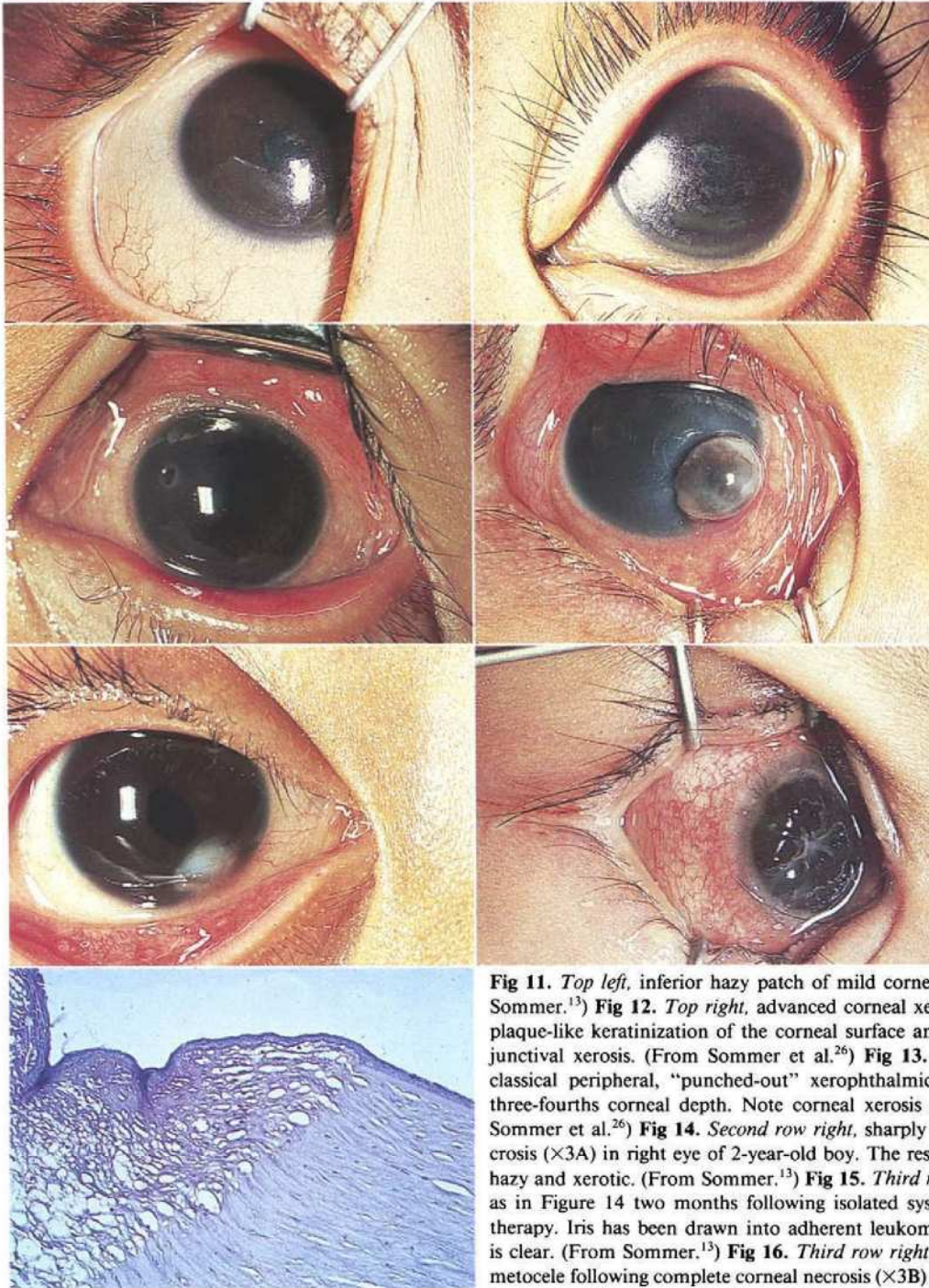


Fig 11. Top left, inferior hazy patch of mild corneal xerosis. (From Sommer.¹³) **Fig 12.** Top right, advanced corneal xerosis with heavy, plaque-like keratinization of the corneal surface and advanced conjunctival xerosis. (From Sommer et al.²⁶) **Fig 13.** Second row left, classical peripheral, "punched-out" xerophthalmic ulcer ($\times 3A$) of three-fourths corneal depth. Note corneal xerosis inferiorly. (From Sommer et al.²⁶) **Fig 14.** Second row right, sharply focal corneal necrosis ($\times 3A$) in right eye of 2-year-old boy. The rest of the cornea is hazy and xerotic. (From Sommer.¹³) **Fig 15.** Third row left, same eye as in Figure 14 two months following isolated systemic vitamin A therapy. Iris has been drawn into adherent leukoma but visual axis is clear. (From Sommer.¹³) **Fig 16.** Third row right, extensive descemetocele following complete corneal necrosis ($\times 3B$) in 4-year-old girl. Note typical preservation of peripheral-most corneal zone. (From

Sommer et al.²⁶) **Fig 17.** Bottom left, light microscopy of xerophthalmic ulceration in a 1-year-old boy. Note sharp delineation between normal and necrotic stroma, paucity of bacteria or inflammatory infiltrate, and presence of intact, keratinized epithelium (hematoxylin-eosin, $\times 100$). (From Sommer et al.³⁶)

teases is a prominent component of keratomalacia in rats,^{43,44} and corneal abrasion of vitamin A deficient but not control rats commonly results in keratomalacia-like ulceration.⁴⁰ However, this is not necessarily the situa-

tion in spontaneously occurring human disease where early xerophthalmic ulceration and necrosis can occur in the absence of clinical^{26,38,45} and histologic^{4,36} evidence of an inflammatory infiltrate (Fig 17).

Fig 18. Schirmer tests (with topical anesthesia) indicate decreased tearing is more prevalent among cases of corneal xerophthalmia than among their healthy age, sex, neighborhood matched controls ($P < 0.001$). (Drawn from Sommer et al.²⁸)

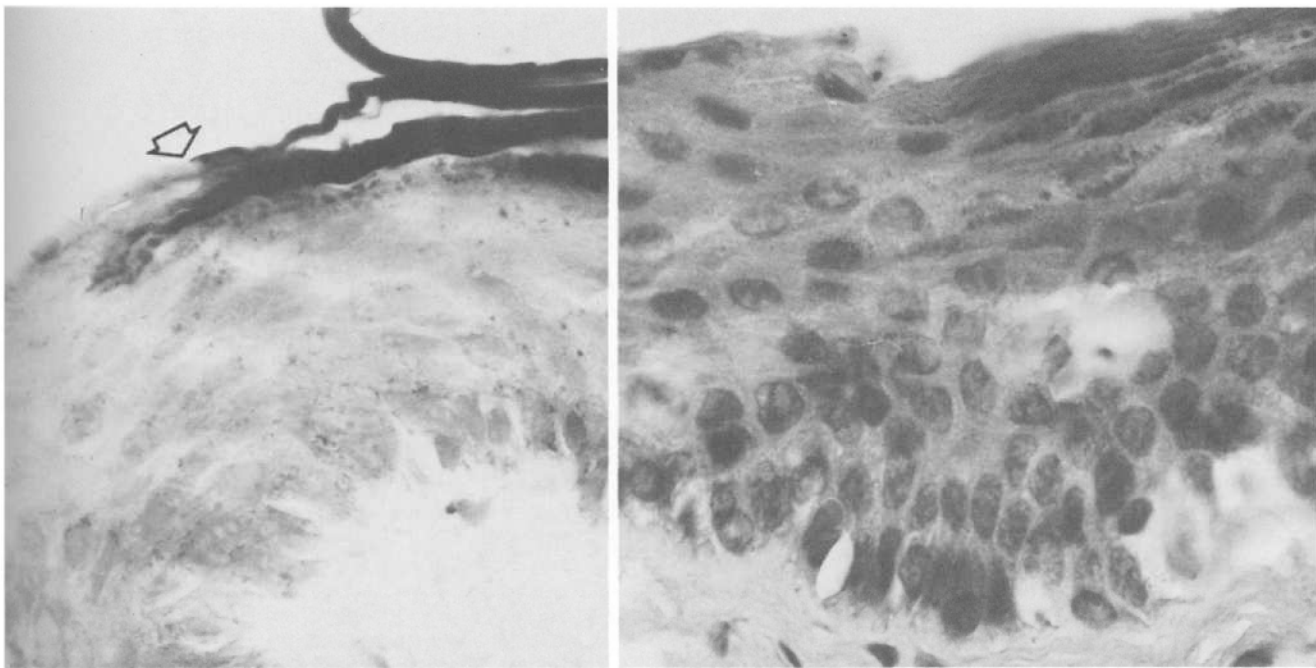
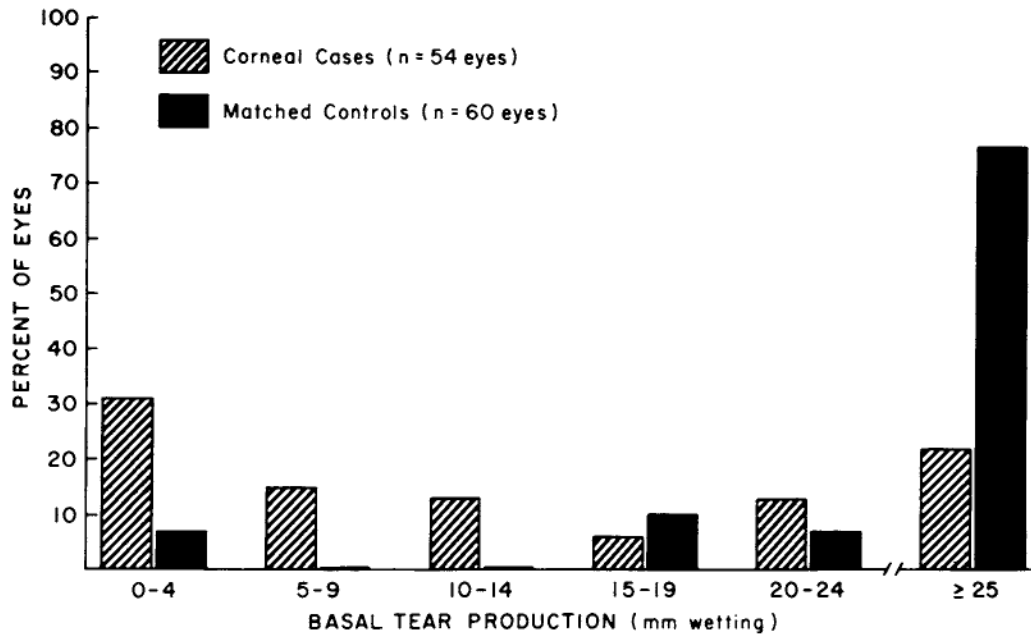


Fig 19. Temporal conjunctival biopsy specimen from 13-year-old girl with Bitot's spots that failed to respond to systemic vitamin A. *Top left*, abrupt transition (arrow) between abnormally heavily keratinized surface (right) and more normal adjacent conjunctiva (left) (Danes stain, $\times 825$). *Top right*, another section demonstrates abrupt transition between normal epithelium (left) and abnormal epithelium (right) with prominent keratin, granular cell layer, and irregular maturational sequence (PAS, $\times 825$). (From Sommer et al.²¹)

In summary, surface changes in xerophthalmic eyes are reasonably well documented and understood. Their contribution to corneal destruction however remains unclear. Evidence suggests unique, still poorly elucidated vitamin A-dependent biochemical processes in the stroma may also be important.^{13,46}

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