Chronic Actinic Keratopathy—A Condition Associated with Conjunctival Elastosis (Pingueculae) and Typified by Characteristic Extracellular Concretions

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Morphologic observations on a peculiar type of corneal reaction with a predisposition for the superficial stroma of the interpalpebral portion of the cornea are reviewed. Histochemical evidence is provided which indicates that the corneal concretions, though not homogenous, are proteinaceous in nature and contain amino acids not normally detectable in the cornea. The corneal concretions were associated with conjunctival elastosis (pingueculae) in all 22 instances in which the eyes were sectioned in the horizontal plane. Identical concretions were identified within these associated pingueculae, as well as in a large percentage of other pingueculae and cutaneous lesions with actinic elastosis. The findings suggest that the abnormal material arises in the pericorneal conjunctival connective tissue from whence it diffuses into, and deposits in, the superficial corneal stroma. The data also raise the possibility that the concretions may be derived, at least in part, from altered elastic tissue. Morphologic and epidemiologic observations on the condition taken together strongly suggest that this unique reaction is a sequel to the cumulative effect of chronic actinic irradiation. Further observations on this keratopathy are needed to establish whether this unique response can be provoked by other noxious stimuli (Am J Pathol 67:327–348, 1972).

NUMEROUS CORNEAL DISEASES are recognized today, due largely to meticulous clinical observations that have accumulated since the birth of ophthalmology. Some are characterized by the occurrence of opacities with a predisposition for the horizontal meridian in the exposed interpalpebral portion of the superficial cornea. In the most

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What may be the same phenomenon has been described in the literature under a variety of terms including hyaline degeneration of the cornea, degeneratio hyaloidea granuliformis corneae, Bietti's nodular dystrophy, nodular hyaline band-shaped degeneration, degeneratio sphaerularis elaioides, "the blindness of Dahalach," tropical corneal dystrophy, type II white limbus girdle of Vogt, keratinoid corneal degeneration or keratopathy, Labrador keratopathy, nodular band-shaped dystrophy of tropical countries of arid soil, and degeneratio primaria oleoguttata centrale et superficiale.[1–10]

common variety, termed band keratopathy, the deposits are calcified granules, and the corneal lesions commonly accompany other ocular lesions, particularly uveitis, chronic glaucoma and phthisis bulbi. In another entity, bilateral, white, greyish or yellow noncalcific opacities accumulate in the same location. The latter condition is designated chronic actinic keratopathy in the present paper, for reasons which will become apparent later. Initially, the deposits concentrate in the peripheral cornea and form symmetric bilateral concentric arcs between the limbus and the cornea. With time the opacities often converge towards the center of the cornea, and form a nontransparent horizontal band across the entire cornea. The deposits accumulate with advancing age, often in the absence of other associated ocular disease, and as a rule without clinical features of inflammation. Though the latter condition has been observed in inhabitants of several countries, it is prevalent, particularly in its severe form, in certain geographic areas such as Labrador, Libya, Somali Republic and countries bordering the Red Sea.[2–5]

The present report reviews morphologic observations on the entity in patients that had spent all, or most, of their life in the south eastern United States. Evidence is provided which strongly suggests that this unique reaction may be a sequel to the accumulative effect of chronic actinic irradiation.

Materials and Methods

Corneal tissue from 35 patients with variable degrees of the keratopathy was studied. The material included 6 corneal buttons obtained from penetrating keratoplasty, 4 corneal biopsies, 13 surgically enucleated eyes and 12 eyes obtained at autopsy (Table 1). Representative corneal and other ocular tissue, from these cases was fixed in 10% buffered formaldehyde (pH 6.8) and embedded in paraffin for light microscopy. In one (Case 10), unfixed corneal tissue obtained at a superficial keratectomy was rapidly frozen to −20°C and sectioned with a cryostat. Control tissue included normal eyes procured at necropsy and enucleation for orbital neoplasms. All corneal tissue was sectioned at 7 μ perpendicular to the epithelial surface and stained by numerous techniques including: hematoxylin and eosin; nuclear fast red; connective tissue stains [Masson's trichrome (standard method with both solution A and B, as well as with each solution separately), Weigert's resorcin-fuchsin, Verhoeff's elastic tissue stain, Wilder's reticulum, Taenzer-Unna acid orcein and phosphotungstic acid hematoxylin]; glycosaminoglycans [periodic acid-Schiff (PAS), Mowry's modification of Hale's colloidal iron reaction, alcian blue]; proteins [diazotisation-coupling, Danielli's coupled tetrazolium (with and without prior blocking with dinitro fluorobenzene, performic acid, and benzyol chloride), performic acid-alcian blue, *p*-dimethylaminobenzaldehyde (DMAB)-nitrite, dihydroxy-dinaphthyl disulphide (DDD), thioglycollate-DDD, diazo-reaction, post-coupled benzylidene, Sakaguchi, ferric ferricyanide, ninhydrin-Schiff, Millon]; lipids [luxol fast blue, Oil red O, Sudan III, osmium tetroxide—naphthyl-

Table 1—Summary of Cases Studied

Case and tissue examined	Age	Sex	Race	Location	Severity	Associated pinguecula	Associated conditions
1. Corneal button	48	F	N	CC, PC	++++	?	Cataracts
2. Corneal button	54	M	C	CC, PC	++++	?	Postsympathetic ophthalmitis
3. Corneal button	61	F	N	CC, PC	+++	?	Neonatal keratitis
4. Corneal button	45	M	N	CC, PC	+++	?	Keratoconus
5. Corneal button	43	M	N	CC, PC	+++	?	Keratoconus
6. Corneal button	23	F	N	CC, PC	+++	?	Congenital corneal dystrophy
7. Corneal biopsy	30	F	N	CC, PC	++++	?	
8. Corneal biopsy	62	M	C	PC	++	+	
9. Corneal biopsy	51	M	C	PC	+	+	Basal cell carcinoma nose Carcinoma of conjunctiva
10. Corneal biopsy	47	M	N	CC, PC	++	?	Vascularized corneal leukoma
11. Globe	38	F	C	PC	+	+	
12. Globe	65	M	N	PC	+	+	
13. Globe*	32	M	N	CC	+++	?	Glaucoma
14. Globe	69	F	N	PC	+	+	Glaucoma, diabetic retinopathy
15. Globe	69	M	N	PC, SS	+	+	
16. Globe	52	M	N	PC	+	+	Acute leukemia
17. Globe	75	M	N	CC, PC	++++	+	Glaucoma (post-traumatic)
18. Globe*	56	M	N	CC	++++	?	Chronic buphthalmos
19. Globe	62	M	C	PC	+	+	Glaucoma (post-traumatic)
20. Globe	84	F	N	PC	+	+	
21. Globe	65	M	N	PC	+	+	
22. Globe*	46	M	C	CC	+++	?	
23. Globe	75	M	C	PC	+	+	
24. Globe	59	M	N	PC	+	+	
25. Globe	55	F	N	PC	+	+	Glaucoma, diabetic retinopathy
26. Globe	53	M	C	PC	+	+	Diabetic retinopathy
27. Globe	50	M	C	PC	+	+	Diabetic retinopathy
28. Globe	52	F	N	PC	+	+	
29. Globe	68	M	C	PC	+	+	Glaucoma
30. Globe	56	M	C	PC	+	+	
31. Globe	?	?	?	PC	+	+	
32. Globe	?	?	?	PC	+	+	

Table 1—(CONT.)

Case and tissue examined	Age	Sex	Race	Location	Severity	Associated pinguecula	Associated conditions
33. Globe	62	M	C	PC	++	+	
34. Globe	76	M	N	PC	+	+	Glaucoma (chronic open angle)
35. Globe	63	M	N	PC	+	+	

F = Female
M = Male
N = Negroid
C = Caucasoid
PC = Peripheral interpalpebral cornea
CC = Central interpalpebral cornea
SS = Superficial bulbar sclera
* = Eye sectioned vertically calottes not examined

amine (OTAN)], nucleic acids [Feulgen, methyl green pyronin]; amyloid [Congo red, thioflavin T]; phosphates [Von Kossa]; calcium [alizarin red]; ferric ions [Perl's Prussian blue]; pre-keratin and keratin [hematoxylin-phloxine-alcian blue-orange G, hematoxylin-Shorr S3 stain, performic acid-Schiff].[11-15] Unstained sections were examined for birefringence under a polarized light, with and without a first order interference filter. Unstained tissue sections, as well as those stained with the fluorescent dye thioflavin T were mounted in a nonfluorescent mounting medium (glycerine or Harleco Fluorescence Mountant, Hartman-Leddon Company, Philadelphia, Pennsylvania) and studied by fluorescence microscopy. Observations were made with bright and dark field illumination using both an ultraviolet and a blue violet light source and appropriate barrier filters to eliminate the excitation radiation.

The cornea from Case 24 was excised from the globe immediately following enucleation. It was sectioned into small pieces and fixed in cold 1% sodium cacodylate-buffered osmium tetroxide (pH 7.4) for 1 hour, dehydrated in graded alcohols, infiltrated with propylene oxide and embedded in Epon 812 for electron microscopy. Corneal biopsies from two other cases with clinically observed yellow deposits (Cases 9 and 10) were processed in an identical manner. A portion of the lesion from another patient (Case 2) that had previously been embedded in paraffin was excised from the paraffin block, deparafinized, fixed in cold 1% sodium cacodylate-buffered osmium tetroxide (pH 7.4), and processed for electron microscopy as well. Thick sections (2 mμ) were cut with the Sorvall Porter-Blum microtome, and stained with thionine-azure blue for orientation.[16] Companion thin sections were cut and mounted on 200-mesh copper grids and stained for 6 minutes with 4% magnesium uranyl acetate in distilled water, rinsed with distilled water (2 changes) and then stained for 4 minutes with lead citrate (pH 12) at room temperature.[17] Electron microscopic observations were made with a RCA EMU-3G microscope at 50 kV.

In view of evidence that basophilic degeneration of the cutis (solar elastosis, actinic elastosis), and pingueculae (focal conjunctival elastotic degeneration) are both causally related to chronic ultraviolet irradiation, tissue from 50 consecutive examples of cutaneous actinic elastosis and 50 pingueculae were examined for concretions with morphologic and tinctorial attributes similar to those of the keratopathy.

Observations

A. Cornea

Light microscopy. The superficial corneal stroma in all cases contained granules and concretions of variable size and shape in the horizontal meridian (Figures 1–6). In 22 instances in which the periphery of the interpalpebral portion of the cornea was available for examination, it was involved without exception, and in the mildest cases the deposits were limited to the marginal cornea. When the keratopathy was more extensive, the deposits were more numerous, as well as larger, and extended towards the central cornea sometimes forming a horizontal band across the entire cornea. In three instances the entire inferior half of the cornea was affected. Bowman's zone was frequently involved, but in some instances the abnormal material was extensively deep to it (Figure 7), and in corneas with a superficial subepithelial pannus, the deposits were often predominantly external to Bowman's zone.

In unstained preparations the smaller concretions (1 to 3 μ in diameter) were granular and generally of the same color as the surrounding cornea. The larger globules (10 to 60 μ in diameter), which were often restricted to the central cornea, frequently manifest a distinct yellow hue (Figure 3), and in at least three instances globules with this color were evident in the cornea with the slit lamp (Cases 7, 9, 10). When viewed by fluorescence microscopy the corneal deposits frequently manifest a pronounced autofluorescence in unstained tissue sections. The fluorescence was greenish-yellow (about 575 mμ) with blue violet exciting radiation, and blue (about 470 mμ) in ultraviolet light (Figure 4). Though the concretions varied in size, shape, and in certain staining characteristics there were sufficient morphologic gradations between them to suggest a common nature. The deposits consistently manifest a marked avidity for the red dyes in Masson's trichrome stain (acid fuchsin and Ponceau de xylidine). They also gave positive reactions with histochemical techniques that demonstrate protein, including those thought to demonstrate amino (ninhydrin—Schiff), guanidyl (Sakaguchi reaction), indole (*p*-dimethylaminobenzaldehyde (DMAB)—nitrite method), and sulfhydryl (Dihydroxy-dinaphthyl disulphide (DDD) reaction) groups (Table 2). The concretions, including the yellow ones, failed to stain in unfixed frozen tissue with a variety of methods used to demonstrate lipids. Several other staining attributes of the concretions varied from case to case, and sometimes even within the same cornea. In some cases the abnormal material was

Table 2—Characteristics of Corneal Deposits

Method	Present study	Other investigations
Unstained Preparations		
Color	Pale yellow or colorless	
Fluorescence microscopy	Most nonfluorescent, but often autofluorescent (especially large globules)	
Polarization microscopy	Not birefringent	
Tinctorial Reactions		
Proteins		
Reactive Groups		
Amino (eg, lysine, ornithine, peptide terminal)		
Ninhydrin-Schiff	Positive (except large globules)	
Guanidyl (eg, arginine)		
Sakaguchi reaction	Positive	Positive [6]
Danielli's coupled tetrazonium*	Positive	
Imidazole (eg, histidine)		
Diazo reaction	Negative	
Danielli's coupled tetrazonium*	Positive	
Phenyl (eg, tyrosine)		
Danielli's coupled tetrazonium*	Positive	Positive +++ [6]
Millon	Some positive, others negative	
Diazo reaction	Negative	
Diazotisation-coupling	Negative	Positive [6]
Indole (eg, tryptophan)		
Danielli's coupled tetrazonium*	Positive	
p-dimethylaminobenzaldehyde (DMAB)-nitrite	Positive	
postcoupled benzylidene	Positive (blue)	
Sulfhydryl (eg, cysteine)		
Dihydroxy-dinaphthyl disulfide (DDD)	Positive	Positive [6]
Danielli's coupled tetrazonium*	Positive	
Tetrazolium	Positive	
Ferric ferricyanide	Negative	
Disulfide (eg, cystine)		
Performic acid-Schiff	Negative	±or + [6]
Performic acid-alcian blue	Negative	Negative [6]
Thioglycollate-ferric ferricyanide	Negative	
Tetrazolium following reduction	Positive	
DDD following reduction (thioglycollate-DDD)	Positive	Positive [6]
Stains for Basophilic Compounds		
Phosphates		
Von Kossa	Negative	Negative [6]
Calcium		
Alizarin red	Negative	
Ferric Ions		
Perl's iron	Negative	

Table 2.—(CONT.)

Method	Present study	Other investigations
DNA		
Feulgen	Negative	Negative [6]
RNA		
Methyl green pyronin	Purple	Pink or Green/Pink [6]
Glycosaminoglycans		
Hale's colloidal iron-binding method	Few positive, most negative	
Periodic acid-Schiff	Usually negative	Negative [6]
Alcian blue (pH 2.5)	Negative	Negative [6]
Lipids		
Unsaturated Lipids		
Sudan black B	Negative	Negative [6]
Triglycerides		
Oil red O	Negative	Negative [6]
Sudan III	Negative	Positive [21], negative [8]
Phospholipids		
Luxol fast blue (copper phthalocyanine)	Usually negative, some globules positive	Negative [6]
Osmium tetroxide-naphthylamine (OTAN)		Positive (red-brown) [6]
Pre-keratin + Keratin		
Hematoxylin-phloxine-alcian blue-orange G	Positive (orange to red)	
Hematoxylin-Shorr S3	Positive	
Performic acid-Schiff	Negative	±or + [6]
Cationic Dyes		
Nuclear fast red	Positive	
Stains for Amyloid		
Congo red	Negative	Negative [6]
Thioflavin T	Negative	Negative [6]
Miscellaneous Stains		
Hematoxylin-eosin	Variable (hematoxophilic, eosinophilic, or not stain)	Basophilic, eosinophilic or either [6]
Connective Tissue Stains		
Masson's trichrome	Red or purple	Purple, red/purple [6]
Solution A: Ponceau Masson	Red	
Solution B: Masson	Red	
(Mallory's) phosphotungstic acid hematoxylin	Purple	
Wilder's reticulum stain (Wilder silver method)	Black, olive or negative	Negative or fine particulate [6]
Elastic Fiber Stains		
Taenzer-Unna acid orcein	Negative	
Verhoeff Van Gieson (Verhoeff's elastica stain)	Usually negative, some olive or black	
Weigert's Resorcin-Fuchsin (Weigert's elastica stain)	Yellow	
Gomori's aldehyde-fuchsin	Negative	

* Reaction diminished but not completely blocked by prior treatment with dinitrofluorobenzene, performic acid or benzoyl chloride.

predominantly, or entirely intensely, hematoxophilic; in some it was eosinophilic; in other corneas individual granules stained variably. The small basophilic granules often suggested calcification, but this impression was not borne out by histochemical methods for calcium which were invariably negative. Inconsistent tinctorial reactions were also noted with several stains (including elastic fiber stains, Wilder's reticulum stain, luxol fast blue, alcian blue, and Hale's colloidal iron-binding method and some histochemical methods for protein). Though most concretions did not stain with methods used for elastic fibers or Wilder's reticulum method, some concretions were intensely argyrophilic with these techniques (Figure 5). As a rule the abnormal accumulates lacked the histochemical attributes of glycosaminoglycans. However, in several instances they either stained positively with alcian blue and Hale's colloidal iron method, or were intimately surrounded by material possessing this property. The larger, and presumably older, concretions frequently reacted poorly with stains that usually discolored those with smaller dimensions.

In the mildest cases the overlying epithelium was as a rule ostensibly unremarkable, though some cases manifest variations in nuclear size, atypical epithelial cells, and slight deviations in epithelial differentiation. Occasionally the concretions encroached upon the overlying epithelium, and sometimes basal epithelial cells surrounded several of them (Figure 6). Even when numerous concretions were present the epithelium like that of the normal cornea was not keratinized.

Of the 25 globes that were examined, 22 were sectioned horizontally. The subepithelial connective tissue of the bulbar conjunctiva in the interpalpebral fissure adjacent to the corneal limbus in all of these eyes, with corneal concretions, possessed the morphologic characteristics of pingueculae (Figure 8). The conjunctival lesions, though commonly not appearing to the naked eye as elevated yellow patches, were characterized by typical connective tissue alterations. These included variable sized large convoluted fibers that resembled hypertrophic collagen fibers, but which possessed an affinity for a variety of dyes known to stain elastic tissue. These tortuous tangles were insensitive to elastase, and though usually limited to the subepithelial connective tissue of the bulbar conjunctiva, they were occasionally also evident in the superficial subconjunctival sclera, but not in the cornea. The tortuous fibers frequently intermingled with granules and globules possessing the identical morphologic, and tinctorial attributes to those previously described in the contiguous cornea.

Electron microscopy. When viewed in the transmission electron

microscope the concretions were invariably extracellular and electron dense (Figures 9 and 10). The concretions were surrounded by intact collagen fibers of the usual uniform diameter and periodic cross-striational pattern. Most of the overlying corneal epithelium, and adjacent stromal cells, were conspicuously unremarkable (Figures 11–13). As a rule they did not manifest any of the fine structural attributes of cells actively engaged in phagocytosis, or in the synthesis of macromolecules. Their cytoplasm was devoid of material with the morphologic attributes of keratohyalin granules, the extracellular concretions, or possible precursors of them. Some of the closely related cells exhibited features of cellular degeneration, such as intracytoplasmic autophagic vacuoles.

Pingueculae

Random tissue sections of 34 of the 50 consecutive pingueculae studied contained concretions indistinguishable from those described in the keratopathy (Figure 14). In 3 others equivocally similar granules were identified. In 2 of 24 investigated globes with pingueculae, identical concretions were evident in the conjunctival lesions, but not in the cornea.

Cutaneous solar elastosis

The essential morphology and staining characteristics of the 50 consecutive examples of basophilic degeneration of the cutis studied was as described by others.[18–21] In common with pingueculae, variable sized tortuous fibers were prominent in the altered dermis. These possessed an affinity for those dyes known to stain elastic fibers, but also manifest numerous additional tinctorial attributes that distinguished them from normal elastic or collagen fibers.[18] The fibers were frequently surrounded by material with the cytochemical attributes of glycosaminoglycans. Amorphous homogenous masses that closely resembled the corneal concretions existed in the involved areas of cutaneous elastosis in 42 of the lesions investigated. (Figure 15)

Discussion

Though insufficient tissue for chemical analyses preclude a precise identification of the corneal concretions, their tinctorial and cytochemical attributes provide an indication about certain characteristics. As Garner [6] recently pointed out in a study of what is probably the identical phenomenon, the cytochemical findings indicate that the abnormal material is probably predominantly proteinaceous with several reactive amino acid groups including tyrosine, tryptophan, arginine, and

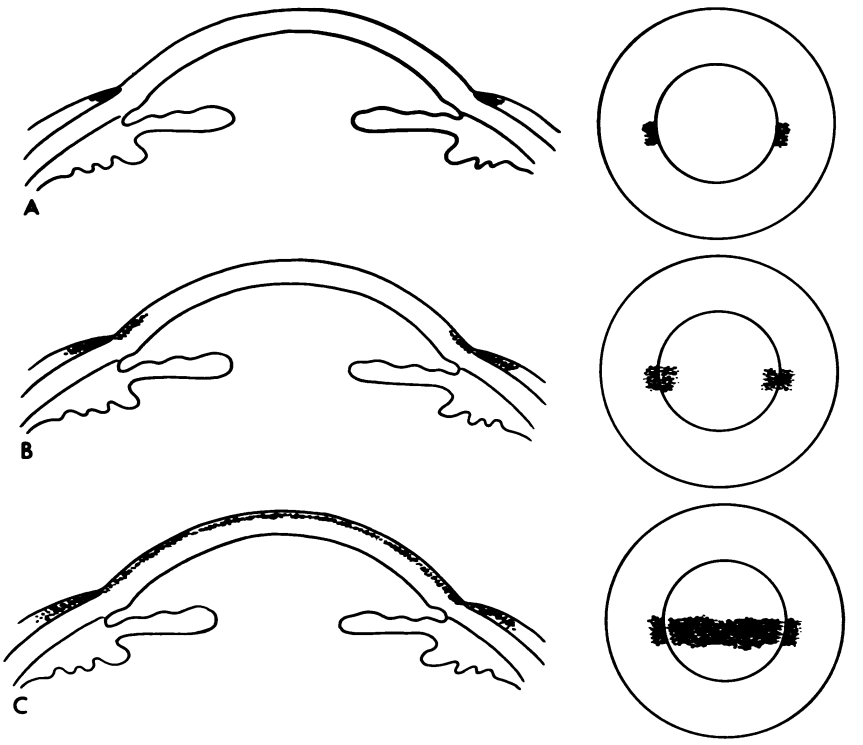
sulphur-containing amino acids. The resemblance of the larger yellow globules to oil droplets has led some clinical ophthalmologists to suspect that the corneal deposits are composed of lipid. This question has not been entirely resolved as the literature contains data on relatively few cases in which the material was analyzed for lipid. Using histochemistry conflicting views have been expressed about the lipid content. In one case unfixed material was reported to be sudanophilic,[22] while in others there was no evidence of lipid.[6,8] In the present investigation the concretions including the yellow ones were insoluble in organic solvents and did not possess an affinity for lipid stains, even when such techniques were performed on unfixed cryostat frozen tissue. Though the avidity of the material for osmic acid in preparation for electron microscopy may connote the presence of some lipid, lipid is clearly not a major component.

As Garner indicated the material is probably an insoluble protein composed in part of amino acids not normally detected in the corneal stroma. Proteins produced by epithelial cells and possessing many disulphide cross links, and a high content of basic amino acids have been designated keratin by some investigators.[23,24] Viewing the corneal deposits in the light of this all-embracing definition of keratin, Garner[6] was impressed not only by a composition suggestive of a keratin related protein, but by several observations that led him to suspect that the material might be a product of the corneal epithelium. In the corneal tissue which he studied by light microscopy, the deposits were in close proximity to the epithelium, and in some instances apparently within it. He also noted signs of epithelial disturbance in the form of excessive desquamative activity, individual cell keratinization, and epitheliolysis.

The present study confirms Garner's observation that the corneal concretions have many tinctorial attributes of keratin, but several additional observations cast doubt on his interpretation of the data. The concretions not only lack the birefringence characteristic of keratin, as produced in other locations in man, but were not associated with keratinizing cells. In most cases and particularly in the mildest, which are presumably also the earliest, the epithelium was ostensibly devoid of similar material. Corneal epithelial keratinization was not observed, even when the stromal deposits were abundant, and in some instances the deposits were a considerable distance from the overlying epithelium. Moreover, the cytoplasm of the overlying corneal epithelium of the cases studied by electron microscopy lacked keratohyalin granules, as well as material with the ultrastructural attributes of the extracellular concretions.

Certain observations raise the possibility that the concretions are not synthesized in the cornea, nor formed there by the degradation of formed components: morphologic evidence of concretion synthesis by either corneal epithelial or stromal cells was not detected; histochemical evidence indicates that the concretions contain a high content of amino acids not normally detectable in the cornea. It would seem more likely that the abnormal corneal deposits are derived from tissue other than the cornea. A likely site of their origin can be inferred from observations on eyes with variable quantities of them. In the mildest examples of the keratopathy, which presumably reflect an early stage in the genesis of the condition, the deposits are restricted to the superficial peripheral cornea in the interpalpebral fissure. This finding together with the observation of the co-existence of corneal lesions with conjunctival elastosis containing identical concretions, and the occasional detection of the concretions in pingueculae of eyes that do not have them in the adjacent cornea, strongly suggests that the abnormal material arises in the pericorneal conjunctival connective tissue. One is led to suspect that they progressively diffuse into the superficial cornea, and precipitate in it over a prolonged period of time, with the larger globules forming by the coalescence of minute granules (Text-figure 1). This perception is consistent with clinical observations on individuals with variable degrees of keratopathy. Frequently the earliest clinically detectable deposits involve only the medial and lateral portions of the cornea in the interpalpebral strip, with subsequent progression occurring by centripetal extension across the cornea. Parenthetically, it should be stressed that the peripheral cornea has not been examined microscopically in those few instances in which it appeared to be clear clinically, and one might suspect that the smaller deposits may be of insufficient dimension to be observed with the slit lamp.

Though relatively few corneal concretions stain positively with dyes that demonstrate elastic tissue, the co-existence of the corneal concretions with conjunctival elastosis poses the question of whether the concretions are derived from constituents of the elastotic material. The nature of the latter substance is not entirely settled, but it is thought to contain derivatives of both collagen and elastic tissue. It is of interest that these elastic fibers are not normally present in the cornea. Moreover, elastic fibers like the elastotic material, and some of the concretions exhibit a brilliant autofluorescence when viewed by fluorescence microscopy.[25,26] Ultrastructural observations of elastic fibers have revealed two components—a microfibril (110 Å in diameter) and an amorphous component (elastin).[27-29] Elastin is markedly insoluble, resistant to hydrolysis by mild acid and alkali, and demonstrates a selec-



TEXT-FIG 1—The inferred sequence of events in the genesis of the keratopathy is depicted schematically. It is postulated that the earliest concretions occur in the exposed interpalpebral portion of the pericorneal conjunctival connective tissue (*A*) and that these progressively diffuse into the adjacent cornea where they precipitate in the superficial cornea (*B*). In advanced cases they extend across the entire cornea (*C*).

tive susceptibility to elastase digestion, and consists of a unique combination of amino acids, including two special amino acids—desmosine and its isomer isodesmosine. Though it contains very little cystine, this amino acid is present in large quantities in the microfibrillary protein component.[29,30]

At present the cause of this unique corneal reaction remains speculative. It is axiomatic that all tissues, including the cornea possess limited responses to noxious stimuli and one would anticipate that this reaction could be provoked by several factors. Unlike several other corneal diseases in which abnormal materials accumulate in the cornea, there is almost no evidence to suggest that the primary defect resides in the DNA molecule, and that the lesions are the culmination of a genetically controlled chain of biochemical events. Ultraviolet light possessing wave lengths of less than 295 mμ are known to be almost entirely absorbed by the cornea, and in short term experiments, single

or multiple exposures to ultraviolet light have a detrimental effect on the cornea, particularly its epithelium.[31–33] Though the keratopathy discussed in the present report is clearly different from that produced by acute ultraviolet irradiation, several epidemiologic and morphologic observations strongly suggest that actinic irradiation over a prolonged period of time may be an important cause of it. At least 22 of the 35 cases had morphologically confirmed evidence of other probable sun induced lesions such as pingueculae, and cutaneous basal cell carcinomas of the face.[34,35] Five patients in the present series were exposed to abundant solar irradiation because of an outdoor occupation (Cases 7, 11, 12, 17, 19) and the remainder certainly had the opportunity to spend abundant leisure time outdoors in the sun-exposed southeastern United States. Though the geographic areas prone to the type of keratopathy discussed in the present article differ climatically, abundant sunshine is prevalent in them, and their inhabitants have in common the potentiality for excessive exposure to radiant energy from the sun. The male preponderance can be accounted for, at least in part, by outdoor occupations that expose individuals to excessive ultraviolet light, known to be reflected by sun, desert, and water. A causal relationship to the absorption of radiant energy from the sun would also account for the predisposition for the exposed portion of the eye in the interpalpebral fissure, and their usual bilaterality. Moreover, as the condition is not related to aging alone, its increased incidence with advancing years may reflect an increase in time of solar exposure.

Not only was the keratopathy associated with morphologic evidence of conjunctival elastosis (pingueculae) in the same eye, but concretions indistinguishable from those of the keratopathy existed in the associated pingueculae. Similar concretions were also identified in a high percentage of other pingueculae, and in the morphologically, and probably etiologically analogous actinic elastosis of the skin. In the absence of x-irradiation, there is abundant evidence that basophilic degeneration of the cutis (solar elastosis, actinic elastosis) is due to prolonged exposure to sunlight.[36,37] It is limited to parts of the body customarily exposed to solar irradiation, the degree of change is greatest in sites that receive the most intense and prolonged exposure to sunlight, and it is less evident in heavily pigmented skin. In addition these changes have been produced experimentally with ultraviolet light.[38]

As the corneal deposits are occasionally unilateral and may accompany other ocular diseases, it remains an open question whether this corneal reaction can be provoked by other stimuli. Nevertheless, almost all instances of the keratopathy included in the present study are con-

sistent with the hypothesis that they are secondary to exposure to ultraviolet light over a prolonged period of time. Associated lesions are variable and dissimilar, and many are probably coincidental. In some an impaired blink reflex protective mechanism may have exposed the eye to excessive ultraviolet light and dessication.

The possibility of the keratopathy being causally related to ultraviolet light poses the question of how actinic rays could produce the concretions. Does the irradiation result in an alteration of preexisting structural components of connective tissue, or on the other hand does it provoke a cellular synthesis of abnormal extracellular constituents? One of the primary effects of ultraviolet light on protein is the cleavage of disulfide bonds,[39] and one might wonder whether the apparent increase in histochemically detectable thiol groups might be due to an effect on noncorneal proteins such as those of elastic tissue.

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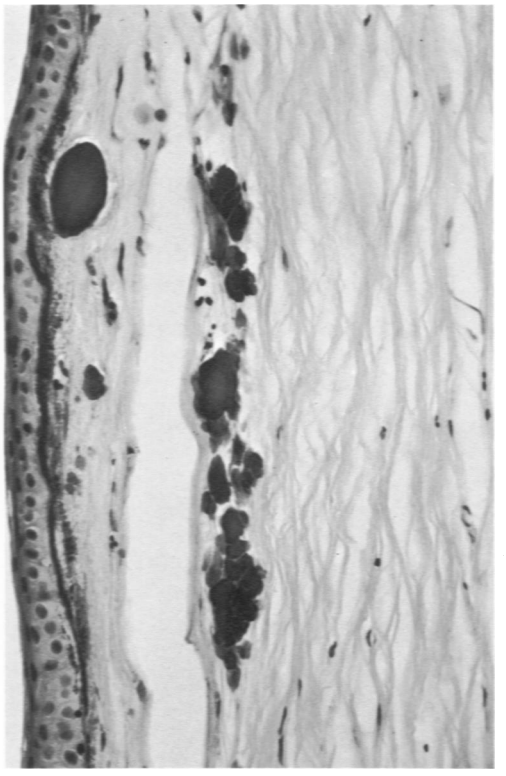
Legends for Figures

Fig 1—Numerous concretions of variable shape and size are shown in the superficial corneal stroma (H&E, × 228).

Fig 2—A more extensive accumulation of the abnormal material is evident in the anterior portion of this cornea from a patient who had an opaque cornea for many years (Masson's trichrome stain, × 190).

Fig 3—The larger deposits are sometimes evident in unstained sections of the cornea because of a distinct yellow hue (unstained preparations, × 112).

Fig 4—Yellow and colorless concretions frequently manifest autofluorescence when viewed in ultraviolet or blue violet light (unstained preparation, × 102).



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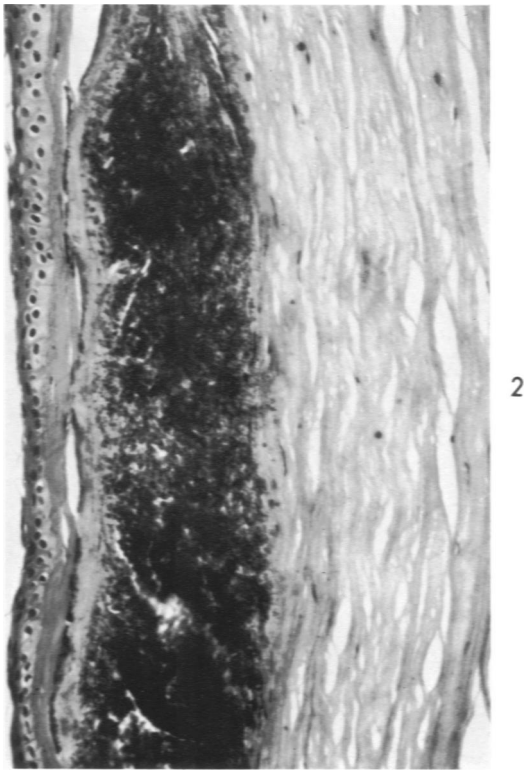

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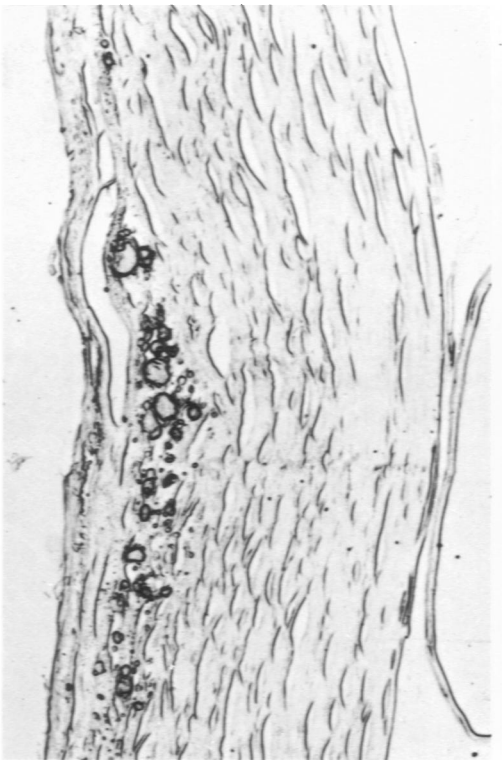

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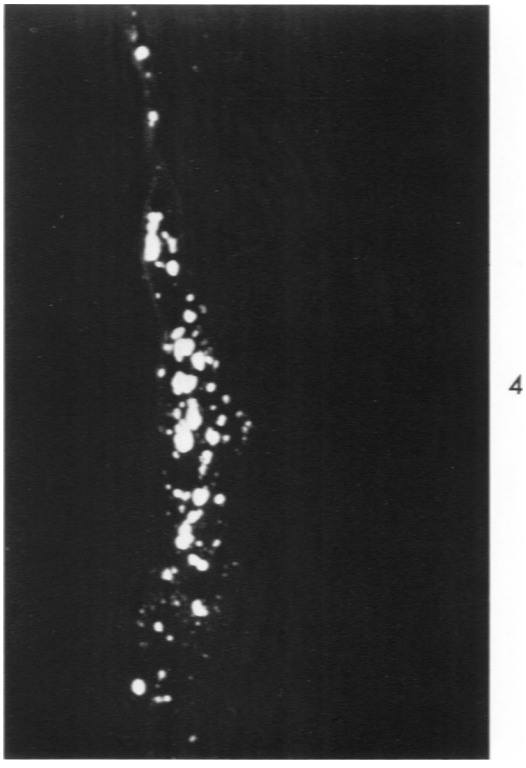

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Fig 5—Though most of the corneal deposits lack an affinity for stains used to demonstrate elastic tissue, some do, such as these (Verhoeff–Van Gieson stain, × 100).

Fig 6—The corneal deposits are frequently in close proximity to the corneal epithelium (Masson's trichrome stain, × 200).

Fig 7—In some instances the corneal concretions, though in the superficial cornea, are distinctly separated from the overlying epithelium (Masson's trichrome stain, × 300).

Fig 8—At the limbus corneae of eyes containing corneal concretions, tangles of argyrophilic fibers can be demonstrated in the horizontal plane using stains that demonstrate elastic fibers (Verhoeff-Van Gieson, × 152).

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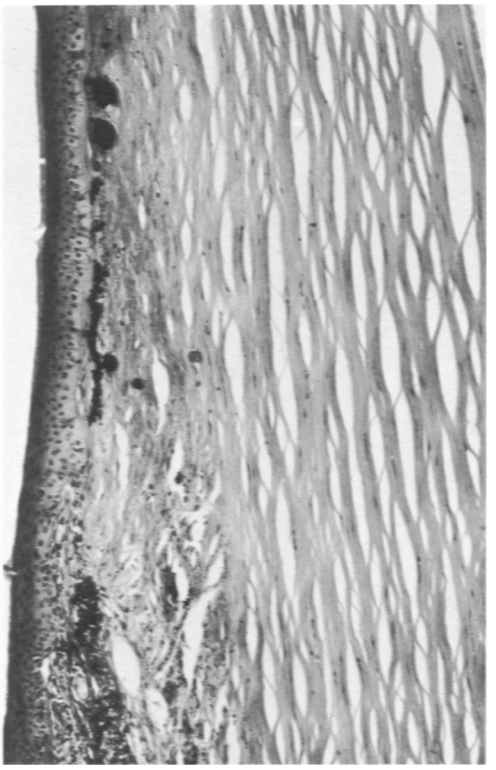

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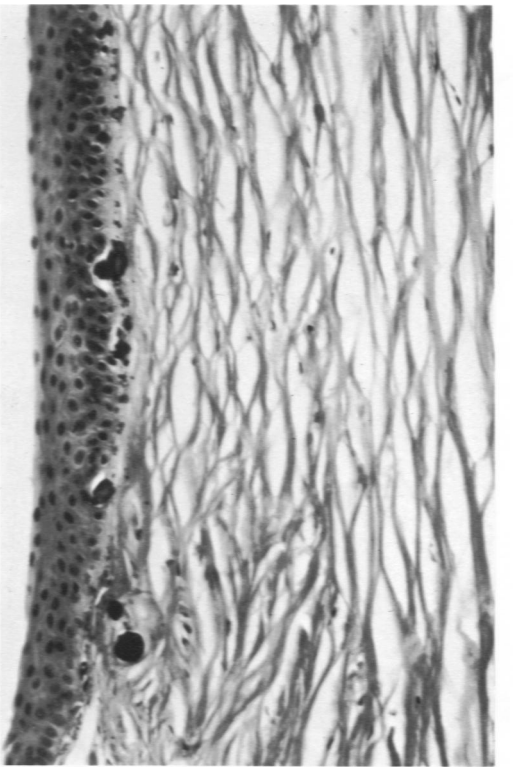

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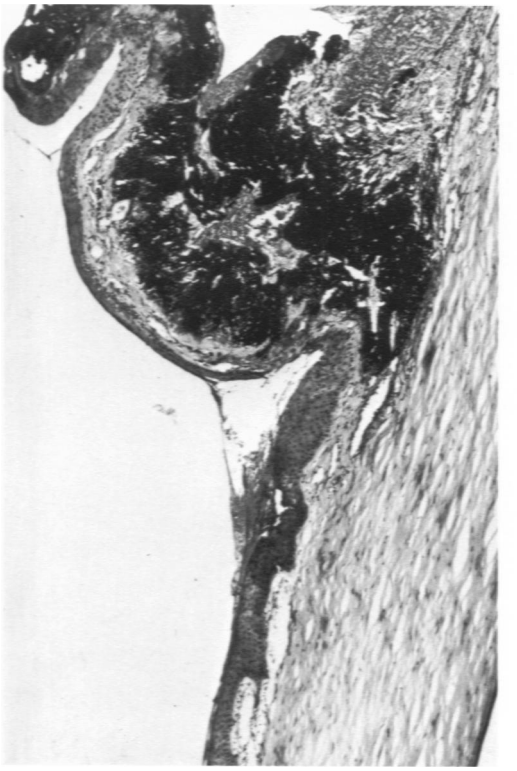

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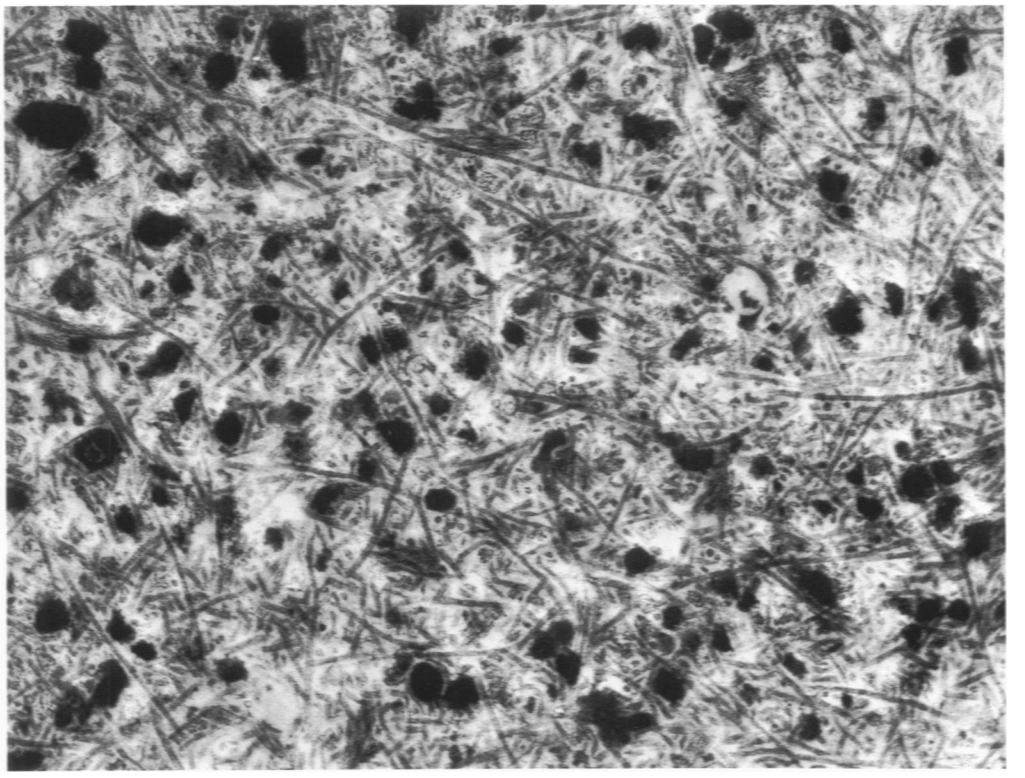

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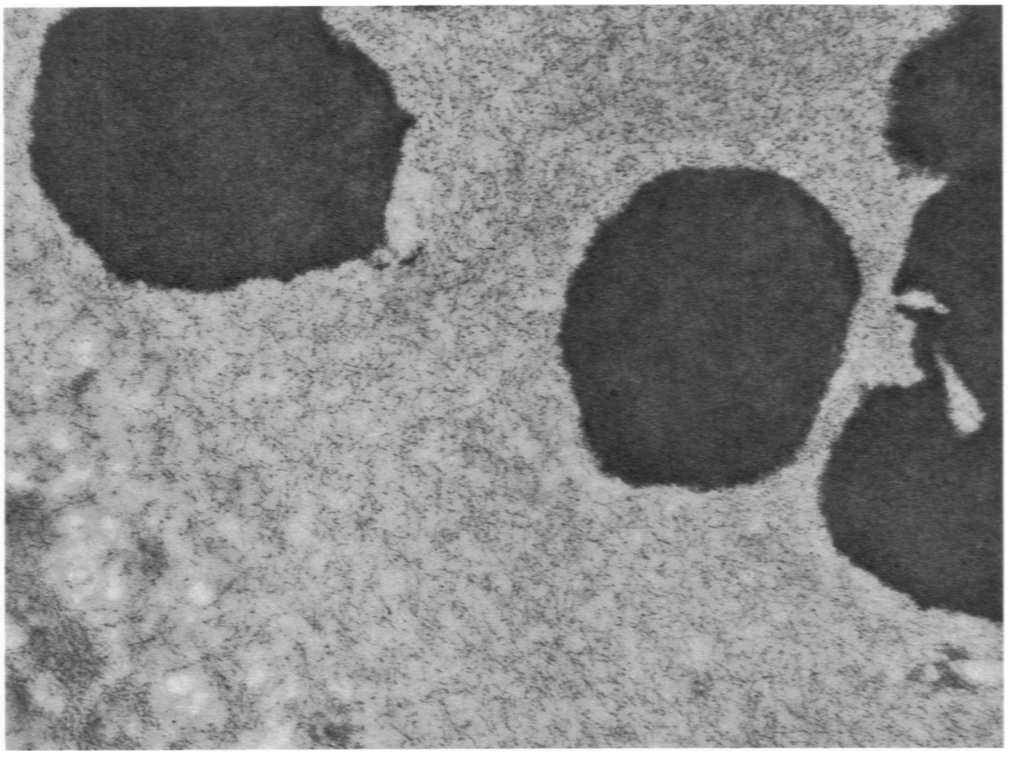
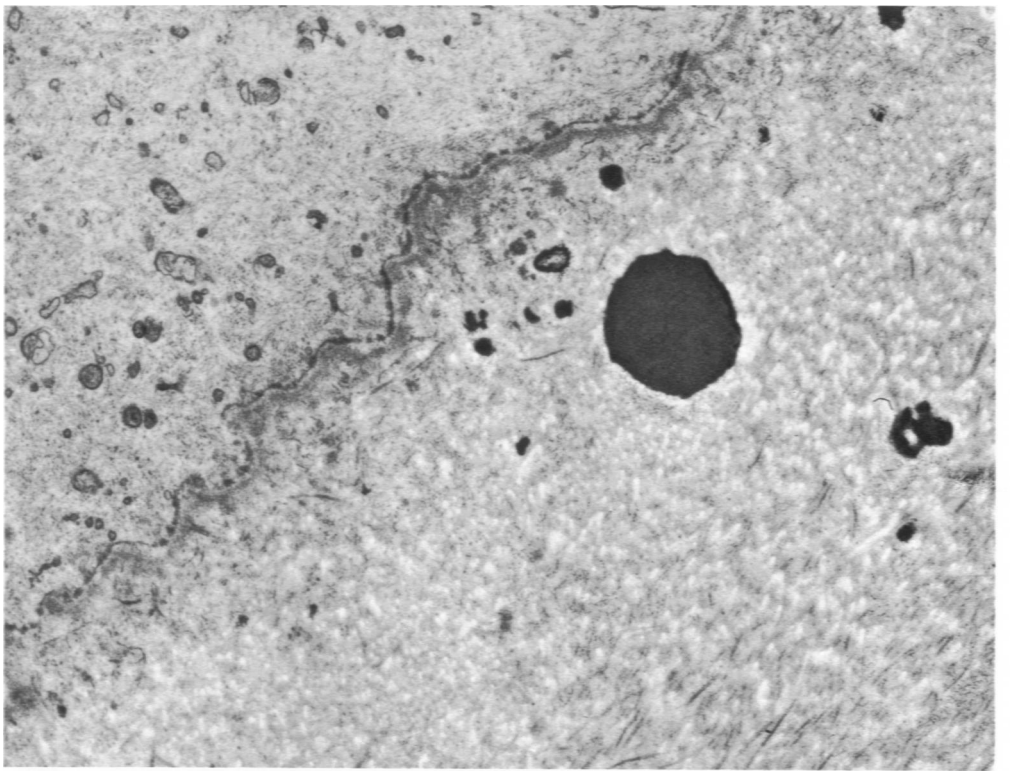


Fig 9—Numerous irregularly shaped electron-dense deposits are interspersed between the haphazardly arranged collagen fibers in Bowman's zone of this affected cornea (× 24,000).
Fig 10—The extracellular deposits are markedly electron dense and are often surrounded by delicate microfibrils (× 44,500).



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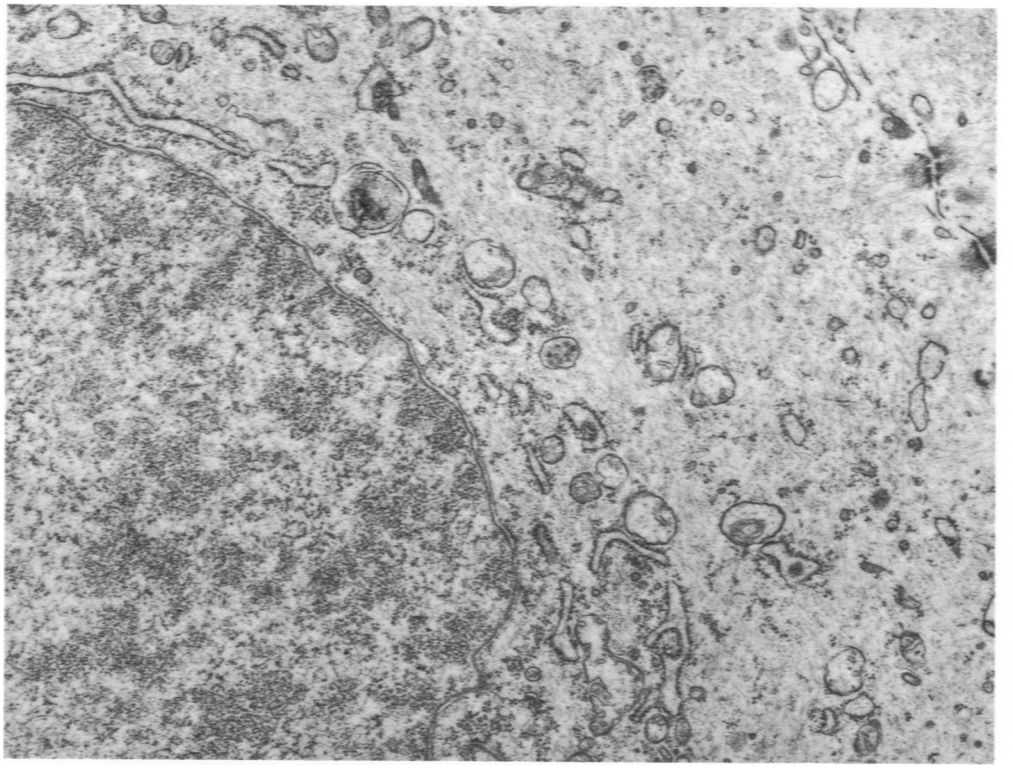

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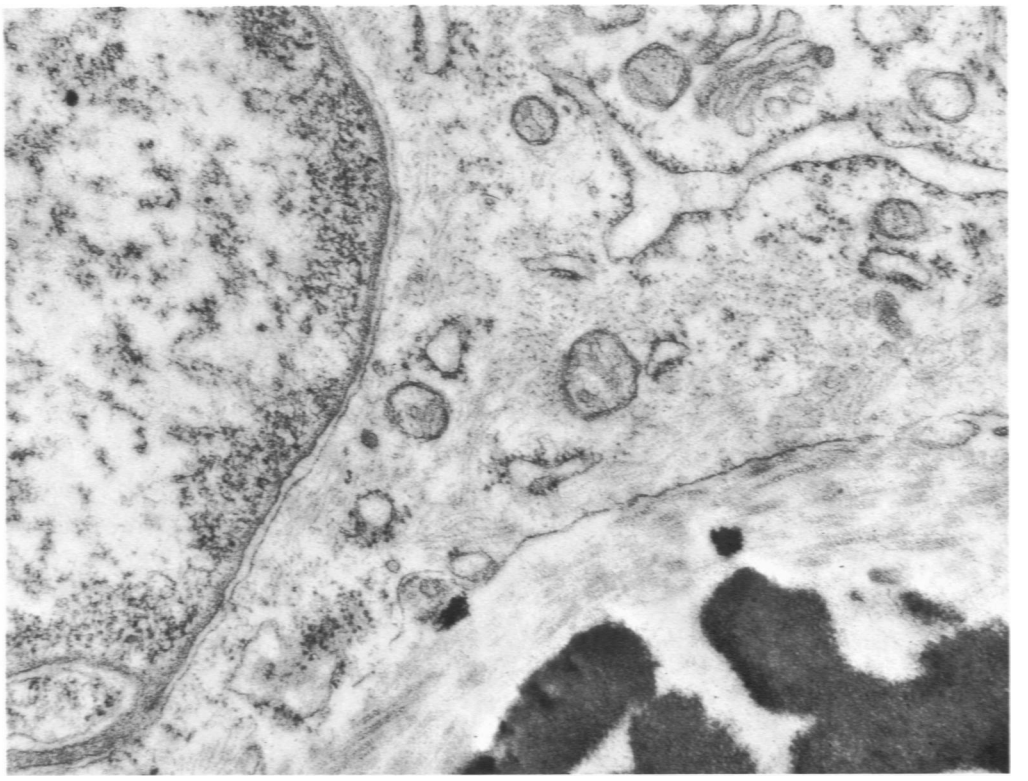
Fig 11—The corneal epithelium adjacent to the deposits lacks electron-dense material (× 17,000).
Fig 12—The overlying corneal epithelium is usually unremarkable. Significant negative features include the lack of intracellular electron-dense material resembling the concretions and the absence of morphologic evidence of synthetic activity. (× 16,500).

13



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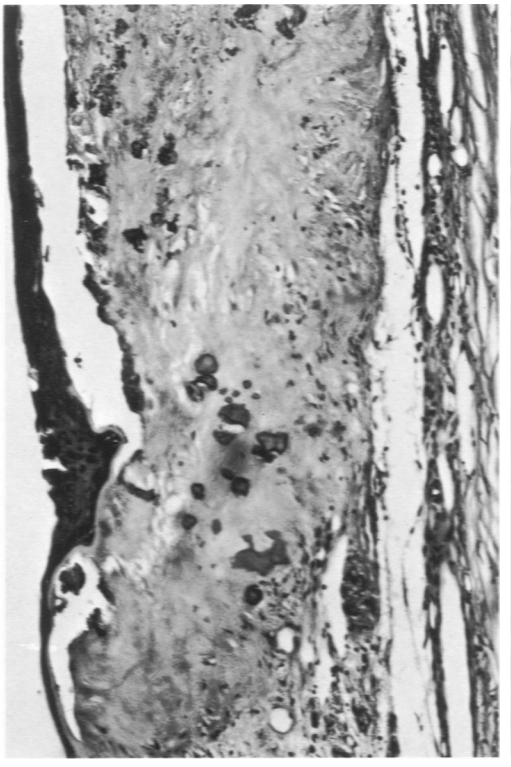

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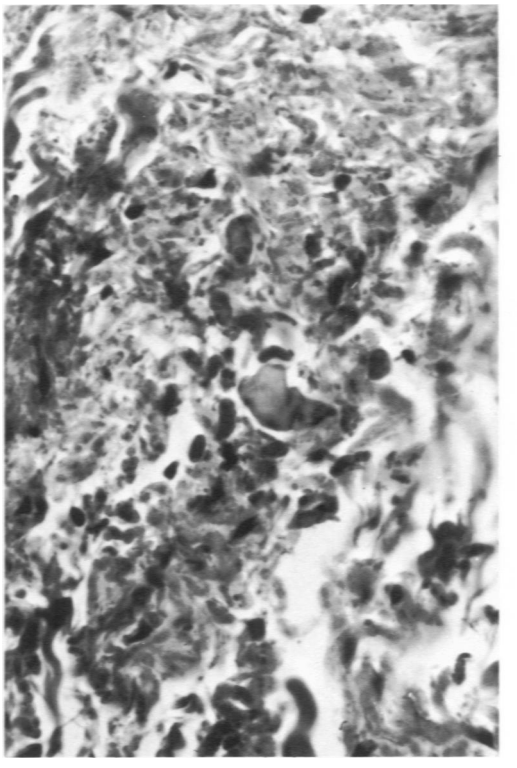

Fig 13—Like the corneal epithelium, shown in Fig 12, the corneal fibroblasts (keratocytes) usually show no significant abnormality, even when adjacent to extracellular concretions (× 43,000). **Fig 14**—Concretions, such as these, which closely resemble those of the cornea in morphology and staining characteristics were observed in the conjunctival elastosis of eyes with the keratopathy and in numerous other pingueculae (Masson's trichrome, × 100). **Fig 15**—Aside from the cornea and conjunctiva, similar concretions were identified in numerous examples of cutaneous actinic elastosis (Masson's trichrome, × 470).