CALCIFIC BAND KERATOPATHY*

BY *G. Richard O'Connor*, MD†

CALCIFIC BAND KERATOPATHY, FIRST DESCRIBED BY DIXON IN 1848, HAS long been a mystery to those interested in its pathogenesis. Although it has been observed frequently in cases of juvenile uveitis, especially those associated with juvenile rheumatoid arthritis (Still's disease), it is clear that this condition occurs in many other inflammatory and metabolic diseases affecting a wide range of patients. It would, indeed, seem to represent a final common pathway for the expression of a calcifying tendency in a number of morbid conditions, regardless of their different etiologies.

The entity to be described in this paper is limited to the deposition of calcium salts, principally hydroxyl apatite, in the anterior layers of the cornea. Characteristically the deposition of calcium occurs in Bowman's layer, in the basement membrane of the corneal epithelium, and in the most superficial lamellae of the stroma, leaving the remainder of the cornea clear. In this sense calcific band keratopathy can be distinguished from calcareous degeneration of the cornea, which characteristically affects the deeper parts of the cornea as well as its anterior layers. Moreover calcareous degeneration of the cornea, seen in phthisis bulbi, in seriously injured eyes, and in such conditions as necrotic neoplasms, is often associated with bone formation elsewhere in the globe.

For reasons that are incompletely understood calcific band keratopathy occurs principally in the interpalpebral area of the cornea. A clear margin separates the calcific band from the limbus, and holes, thought to occur at sites where corneal nerves penetrate Bowman's layer, are seen scattered throughout the opacity. Fortunately the apical area of the cornea is generally the last to be affected. The chemical and pathologic bases for the appearance and location of the calcific deposits have

*Francis I. Proctor Foundation for Research in Ophthalmology and the Department of Ophthalmology, University of California, San Francisco.
†This work was supported in part by Program EY-00310 from the National Institutes of Health, Department of Health, Education and Welfare, Bethesda, Maryland.

never been firmly established, nor has the general predeliction for this disease to occur in juvenile uveitis been explained.

MATERIALS AND METHODS

In the attempt to find answers to some of these baffling questions, the case histories and physical findings of 36 patients with the probable diagnosis of uveitis associated with Still's disease were reviewed. These patients had been seen in connection with the Uveitis Survey conducted by the Francis I. Proctor Foundation of the University of California in San Francisco. Similar studies were performed on other patients, both children and adults, with other types of uveitis.

In addition, the histopathologic findings in 550 freshly enucleated eyes, sent to the Proctor Foundation in connection with a study on the causes of uveitis, were reviewed. Specimens thought to have any form of corneal calcification on initial examination were examined in detail. Additional sections were cut in some cases, and specific staining for calcium was performed by the von Kossa technique in many of these. Finally, histologic sections from 8 eyes with established sarcoidosis and sections from 18 eyes with calcific band keratopathy chosen at random from the slide files of the Eye Pathology Laboratory at the University of California were reviewed.

Electronphotomicrographs of normal corneal tissues were obtained from Dr Michael J. Hogan and his coworkers in the Electron Microscopy Unit of the Francis I. Proctor Foundation. Ultramicrophotographs of pathologic specimens were obtained through the courtesy of Professor Yves Pouliquen of the Hôtel Dieu in Paris. Electron microscopic photographs of experimentally induced calcific band keratopathy in rabbits were obtained from Dr Ben Fine of the Armed Forces Institute of Pathology, Washington, DC.

RESULTS

Of 36 patients with the presumptive diagnosis of Still's disease 35 showed evidence of calcific band keratopathy either grossly or on slit-lamp examination. Of these patients 31 were female and 4 were male. The age range was from 2 to 14 years, but the majority of patients were less than 7 years of age when first seen. The arthropathy preceded the onset of iridocyclitis in a little over half of the cases. The knee was the joint most often affected in those cases where the arthropathy could be documented.

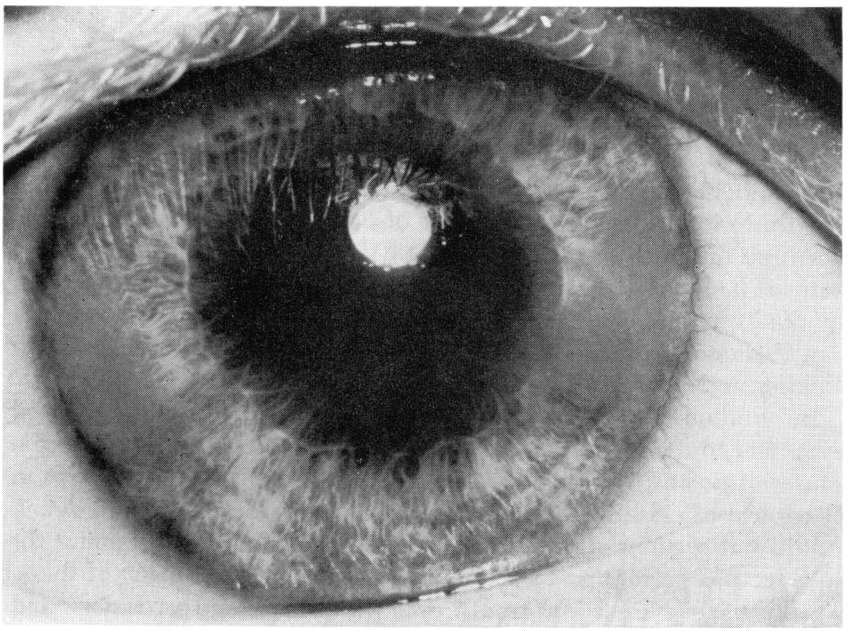

FIGURE 1
External appearance of calcific band keratopathy in a child with Still's disease.

The severity of band keratopathy could, in general, be related to the known duration of the ocular inflammation. However the true duration of the disease was often difficult to determine, because the patients had been assumed to have no eye disease until a school nurse detected a loss of visual acuity or until the patient's parents noted a color change in one of the two eyes. Thus florid inflammatory disease characterized by redness, pain, and photophobia could not be documented as the precursor of band keratopathy in most of these children. All of them, however, were assumed to have had iritis prior to the development of band keratopathy, and the presence of posterior synechiae as well as complicated cataracts provided additional evidence of this. Three of these children, interestingly, had no ocular complaints.

Although the keratopathy varied a great deal in its severity, the basic pattern (Figure 1) was quite similar in all cases. The deposition of calcium was limited to the interpalpebral area in all eyes. The opacity affected only Bowman's layer or the most superficial layers of the stroma. A clear area between the band and the limbus was present in all but two eyes. Only four of the eyes had calcific deposits at the apex

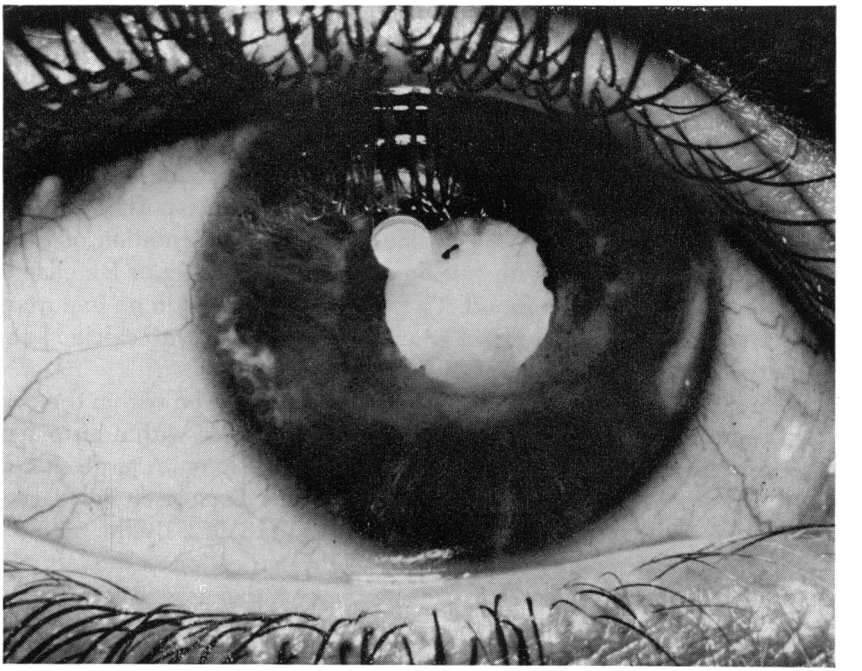

FIGURE 2
Band keratopathy in one eye of an 11-year-old girl with chronic cyclitis and complicated cataract.

of the cornea; however some patients had undergone treatment with chelating agents prior to the time that they were seen in our clinic.

The calcific band keratopathy observed in Still's disease could not be differentiated clinically from that seen in other varieties of juvenile uveitis, e.g., chronic cyclitis or sarcoidosis. Figure 2 shows the band opacity seen in a typical eye with chronic cyclitis with low-grade inflammation of the anterior uvea, a whitish membrane on the pars plana, and snow-ball opacities in the anterior vitrous. This patient, aged 11, later developed a complicated cataract.

Essentially the same pattern was observed in another patient of the same age and sex with sarcoidosis documented by biopsy. This patient had been plagued by attacks of recurrent granulomatous iridocyclitis for several years before the band keratopathy developed. Her serum calcium was not elevated in contradistinction to other known examples of sarcoidosis with hypercalcemia.

Although calcific band keratopathy is seen only rarely in patients with an adult onset of uveitis, at least three such patients have been seen by

us in the past five years. Figure 3 shows the typical facial features of a patient with lepromatous leprosy. This patient developed calcific band keratopathy in his left eye following many years of low-grade granulomatous iridocyclitis. While this patient also showed evidence of primary lepromatous inflammation of the cornea, his calcific band keratopathy appeared in an area remote from the inflammatory lesion. This patient died at the age of 56 of a myocardial infarction. At postmortem examination (Figure 4) typical calcification and fragmentation of Bowman's membrane along with calcific changes in the anterior lamellae of the corneal stroma were found. These findings differed in no important way from those recorded by other authors in patients with calcific band keratopathy associated with juvenile arthritis.

The same is true of two other adult patients observed within the past two years. One of these was a 54-year-old housewife with a history of recurrent uveitis of the left eye of 3 or 4 years' duration. A large chorioretinal lesion suggestive of toxoplasmosis had been seen by earlier observers, and her toxoplasma dye-test titer was 1:512. By the time the patient was first seen by us she had no light perception in the left eye; 2+ cells and flare were noted in the anterior chamber as well as extensive posterior synechiae and a hypermature lens. Calcific band keratopathy was evident on the slit-lamp examination at both the nasal and temporal margins of the cornea.

Another patient, 50 years of age, suffered from recurrent iritis in both eyes since 1942. Her disease began at age 20 with acute pain, swelling, and tenderness in both knees, followed in three weeks by acute bilateral iridocyclitis. The right eye showed very faint calcific band keratopathy with negligible cells and flare in the anterior chamber. The left eye showed marked band keratopathy, 1+ flare and cells, and a small peripheral iridectomy superiorly (Figure 5). Roentgenography showed a healed marginal erosion of the left second metacarpal head and changes of the spinous processes of the third and fourth cervical vertebrae which were judged to be characteristic of rheumatoid arthritis. This would seem to represent an example of iridocyclitis with rheumatoid arthritis of adult origin.

A review of the histopathological specimens made available through our study of freshly enucleated eyes revealed a wide range of pathologic changes. Although the original purpose of this study on freshly enucleated eyes had been to correlate clinical and histopathologic findings on uveitis patients with cultural studies performed on their fresh, minced uveal tissues, the specimens received by us actually represented a large number of diseases other than uveitis. The primary diagnoses ranged from sarcoid uveitis to old perforating injuries, from retinal detach-

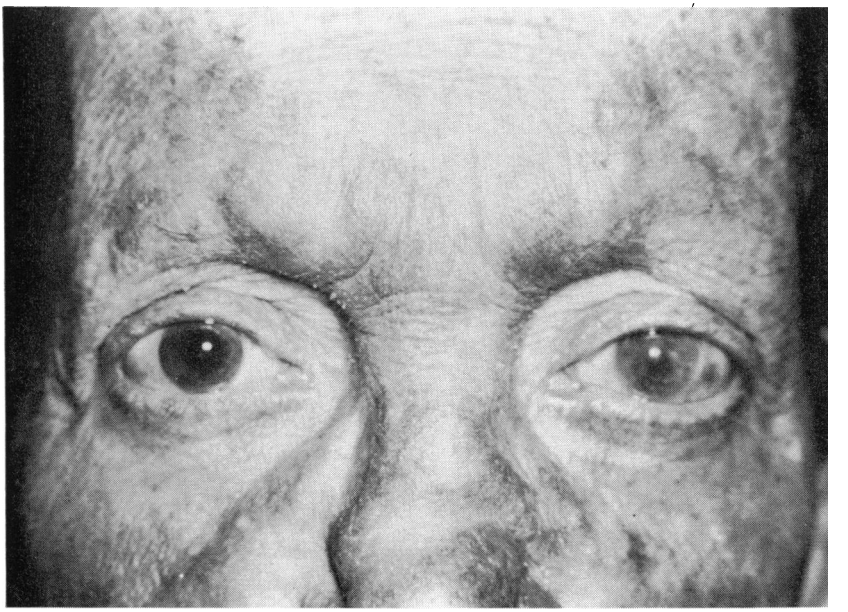

FIGURE 3

Lepromatous leprosy in a 54-year-old male with calcific keratopathy, chronic iridocyclitis, and lepromatous keratitis.

FIGURE 4

H&E stained section of the left cornea from the patient pictured in Figure 3. Arrow indicates heavily calcified Bowman's layer which is detached from the epithelium. × 25.

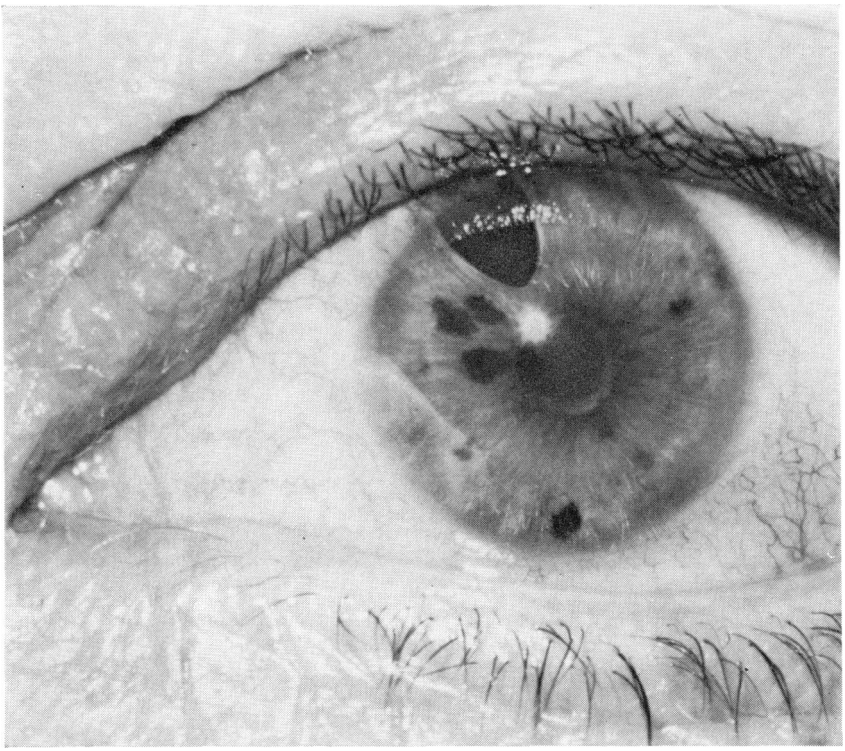

FIGURE 5
External appearance of calcific band keratopathy in a 50-year-old woman with rheumatoid arthritis of adult origin.

ments to absolute glaucoma, and from lens-induced uveitis to buphthalmos.

Many different stages of calcific band keratopathy were observed in these specimens as well as in those obtained from the general files of the Eye Pathology Laboratory. The earliest changes observable by light microscopy consisted of a basophilic staining of the basement membrane of the epithelium (Figure 6). This was followed by a similar change in the most anterior portion of Bowman's layer, as exemplified by this specimen from a patient with sarcoid uveitis (Figure 7). When such areas were stained by the von Kossa technique, two juxtaposed rows of black dots could often be observed, one in the basement membrane and one in Bowman's layer (Figure 8). As the lesion developed, Bowman's layer became calcified through its entire thickness (Figure 9). Perhaps because of its brittleness, Bowman's layer appeared to fragment into multiple tiny islands or plaques, and the corneal epithelium often be-

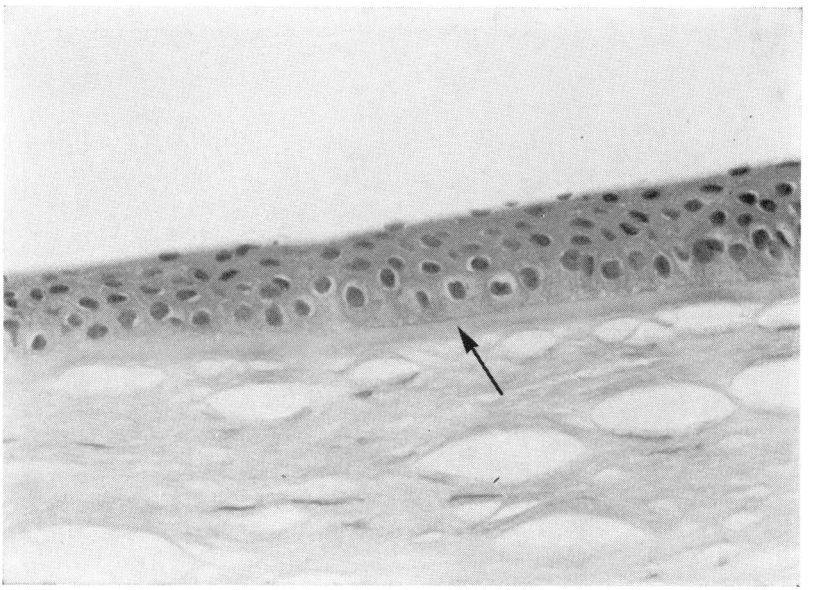

FIGURE 6

Interstitial keratitis with signs of early band keratopathy. Arrow indicates early basophilic change in basement membrane of epithelium. H&E, × 60.

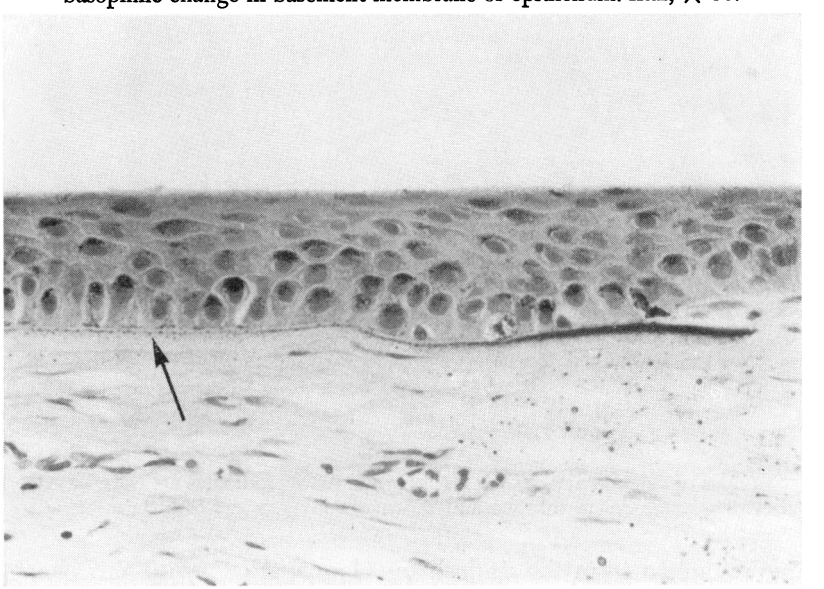

FIGURE 7

Early calcific deposits in the basement membrane and in the most anterior portion of Bowman's layer. von Kossa stain, × 60. Arrow indicates area of earliest changes.

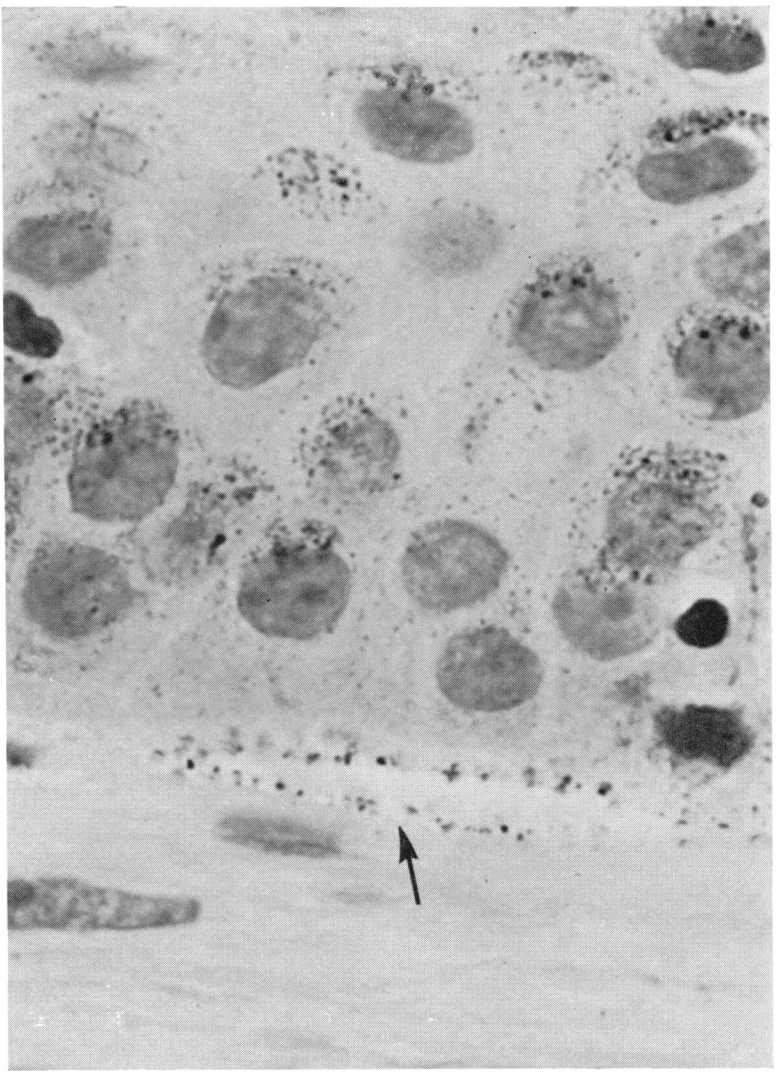

FIGURE 8

Granules of calcium arranged in double row. Arrow indicates area of cleavage between basement membrane and Bowman's layer. von Kossa stain, × 320.

came detached from the underlying plaque. Along with this change, masses of eosinophilic amorphous connective tissue insinuated themselves between the fragments of calcified Bowman's membrane and the overlying epithelium. To this extent, at least, the changes described

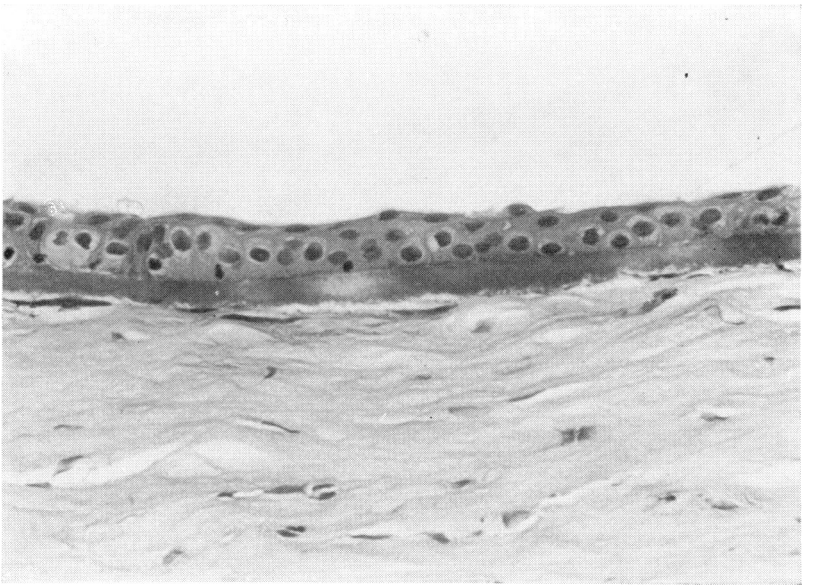

FIGURE 9
Calcification throughout the entire thickness of Bowman's layer. H&E, × 60.

appeared to be equally applicable to all examples of band keratopathy regardless of the primary diagnosis.

In those eyes where scarring of the cornea was a prominent feature a considerable thickness of connective tissue separated the epithelium from the underlying calcific plaque. In some eyes where penetrating injury had preceded the formation of a calcific band reduplication of the calcified Bowman's layer was observed along with ingrowths of corneal epithelium (Figure 10).

Calcification of the anterior lamellae of the stroma occurred in a patchy fashion beneath the calcified Bowman's layer. Often a few lamellae of normal stromal fibers could be seen between Bowman's layer and the calcified lamellae (Figure 11). Calcification of the anterior lamellae was easy to distinguish from the coarse clumps of calcium sometimes seen in the deep stroma of cases of calcareous degeneration (Figure 12). Areas where fibroblastic proliferation seemed to be occurring were also the sites of calcium deposition. This was of interest in the light of Obenberger's[1] recent work on experimental corneal calcification in animals treated with dihydrotachysterol. He found that, following the freezing of the corneas of rabbits so treated, calcification occurred only in those areas where cellular proliferation was taking place. This ob-

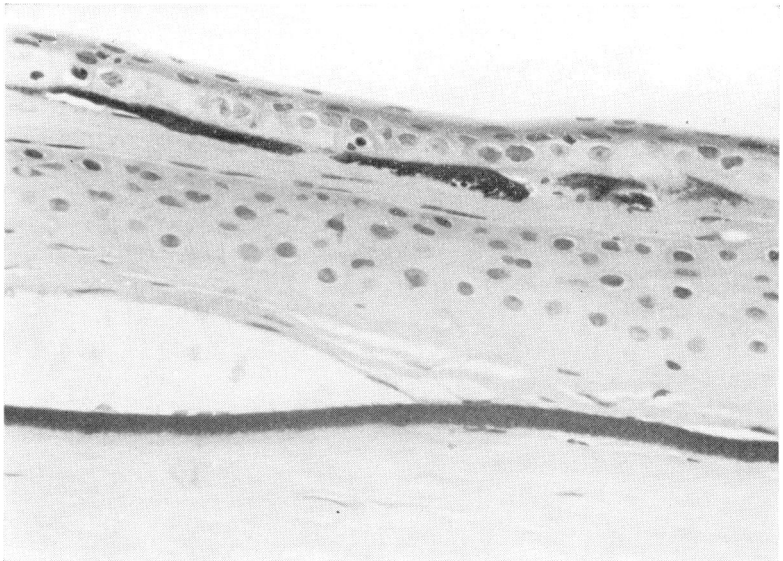

FIGURE 10
Reduplication of Bowman's layer. Multiple layers of epithelium. H&E, × 60.

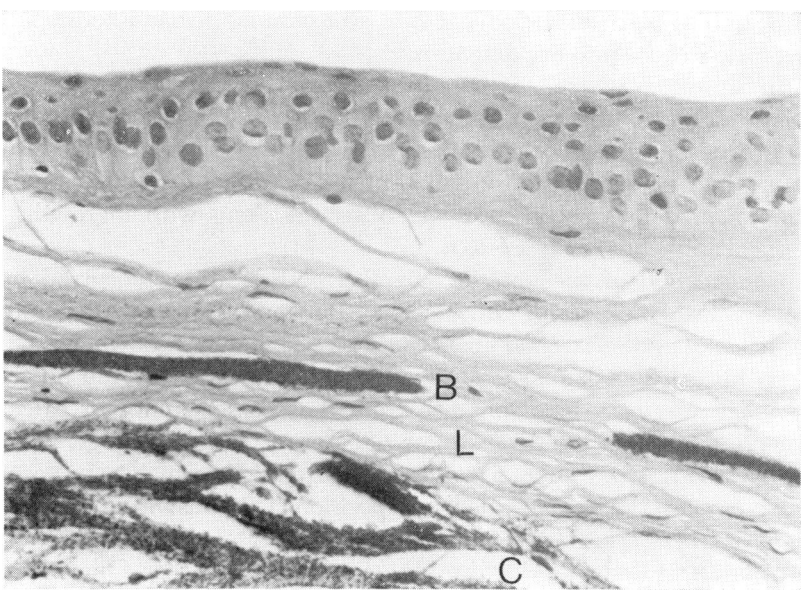

FIGURE 11
Normal lamellae between calcified Bowman's layer and deposits in the anterior stroma. B: Bowman's layer; L: Normal lamellae; C: calcified anterior stroma. H&E, × 60.

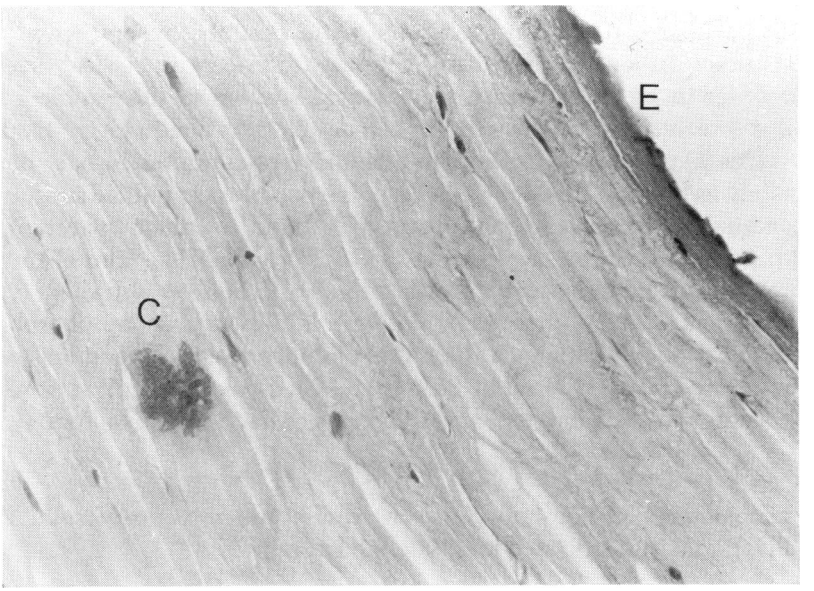

FIGURE 12
Calcarious degeneration of the cornea with coarse clumps of calcium in the deep stroma. C: calcium; E: damaged endothelium. H&E, × 60.

servation is particularly applicable to four eyes with chronic interstitial keratitis reviewed in this series. Calcification appeared to be occurring directly in relation to cellular activity.

Of the 550 freshly enucleated eyes reviewed, 27 showed microscopic evidence of corneal calcification. Of these, 19 manifested typical band keratopathy, and the remainder showed various forms of calcareous degeneration. In the group of 19 typical band keratopathies 9 patients had severe glaucoma. This was manifested in some of the specimens as stromal or epithelial edema, in others as cracks or reduplications of Descemet's membrane, and in still others as deep excavation of the optic nerve head. Since corneal edema has been thought to play some role in the pathogenesis of calcific band keratopathy, these facts seem worthy of mention.

DISCUSSION

It would appear that calcific band keratopathy is the end-product of a large number of inflammatory and degenerative processes and must be looked upon as a non-specific change. In the series under discussion in this paper no striking differences could be found in the calcific keratopathy due to one disease as opposed to another.

What are the factors that lead to the precipitation of calcium salts in this peculiar pattern characteristic of band keratopathy, and why does this precipitation occur with such regularity in certain corneal layers? In order to provide at least a theoretical solution to this problem we must look at the more general problem of calcification in target tissues.

Over 99 per cent of the body's calcium is present in the form of bone, mainly as hydroxyl apatite.[2] The latter is a complex crystalline substance containing calcium and phosphate in addition to minor quantities of other ions. Its empirical formula is $Ca_{10}(PO_4)_6(OH)_2$. The chemical laws applicable to hydroxyl apatite, whether in bone or elsewhere (e.g., the cornea) depend principally on the solubility of calcium phosphate under various conditions. At best, the solubility of this compound is very low (about 2 mg/100 ml at 25°C, pH 7.0). Looked at in a somewhat oversimplified fashion, its ionization can be described as follows:

$$Ca_3(PO_4)_2 \rightleftarrows 3Ca^{++} + 2PO_4^{\equiv}.$$

The ionization constant K of an equilibrium mixture of solid $Ca_3(PO_4)_2$ and its dissociated ions is derived as follows:

$$\frac{[Ca^{++}]^3 \cdot [PO_4^{\equiv}]^2}{[Ca_3(PO_4)_2]} = K.$$

Higher degrees of ionization are favored by conditions of low pH, whereas precipitation is favored by an increase in pH. The amount of ionized calcium is thus higher at acidic pH values than at alkaline pH levels. Because of the slightly alkaline pH of blood and the interstitial fluids, calcium and phosphate are already present at levels which nearly exceed the solubility product

$$[Ca^{++}]^3 \cdot [PO_4^{\equiv}]^2 = P.$$

This being the case, the blood and interstitial fluids are at all times in danger of supersaturation. Precipitation can therefore be easily triggered by minor local events such as a change in pH, sudden evaporation, an increase in the local concentration of one of the two principal ions, or the appearance of a crystal of calcium phosphate in an area where the saturation limits have almost been exceeded.

Looked at from this somewhat oversimplified, mechanistic point of view the formation of calcific band keratopathy in cases of hypercalcemia is relatively easy to understand. An excess of calcium would certainly favor the precipitation of this element, presumably as calcium phosphate. The literature is now replete with cases of calcific band keratopathy in primary hyperparathyroidism,[3] in nephrocalcinosis,[4] in

cases of vitamin D intoxication,[5] and in sarcoidosis.[6] Why are the anterior layers of the cornea a special target for such calcification, and why does it occur principally in the area of the interpalpebral fissure?

Attempting to answer this and other questions Doughman[7] and his colleagues created an experimental model for band keratopathy in the rabbit. Experimental immunogenic uveitis was induced by the intravitreal injection of ovalbumin. Alternately, polyethylene sulfonic acid was injected into the vitreous cavity of other animals. When vitamin D intoxication was superimposed on either of the above conditions by the intramuscular injection of calciferol, calcific band keratopathy resulted. Although hypercalcemia was never documented, the band keratopathy produced in these experiments resembled that of the commonly observed human disease in nearly all regards. Subepithelial and superficial stromal calcification occurred only in the area of the palpebral fissure. Surgical closure of the lids prevented the formation of calcific band keratopathy, whereas the maintenance of the animals in an environment of total darkness had no effect on the development of the lesion. Doughman concluded from this that ultraviolet radiation was not a factor in band keratopathy, but that evaporation of water from the interpalpebral region of the cornea brought about the deposition of calcium salts in this area.

While it is true that an increased concentration of salts resulting from the evaporation of water would favor the precipitation of calcium phosphate, it would seem that Doughman and his colleagues have neglected one other factor that might be of great importance; namely the diffusion of gases. At any freely exposed mucosal surface the loss of CO_2 affects the ionization of carbonic acid in such a way as to decrease the availability of free hydrogen ions and thus increase the pH. Viewed in a somewhat oversimplified manner, the law of mass action would favor a shift of the following equation to the left as additional quantities of CO_2 were released from the surface:

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^- \rightleftarrows H^+ + CO_3^{=}.$$

The combined buffering action of several different chemical systems within circulating blood would tend to minimize this pH change in areas that are highly vascularized. This may account for the clear zones at the margins of corneas affected by calcific band keratopathy, where the limbal circulation might be expected to have its greatest effect. The dissolution of calcified plaques by invading blood vessels was also observed by Obenberger *et al.*[1] in their experimental model of calcific band keratopathy.

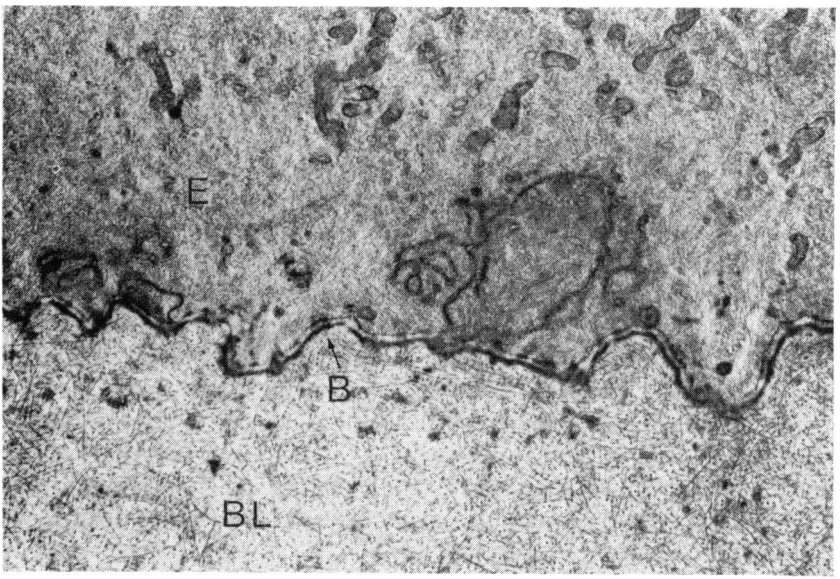

FIGURE 13

Basement membrane of normal corneal epithelium. E: epithelium; B: basement membrane; BL: Bowman's layer. Electron photomicrograph, × 24,500. From M.J. Hogan, et al., Histology of the Eye, Philadelphia, Saunders, 1971.

Although calcific band keratopathy is usually limited to the interpalpebral area, diffuse calcification of the entire cornea is occasionally seen. Such an example was described by Cogan[8] in 1957. This patient was shown to have sarcoidosis and eventually developed florid granulomatous uveitis in both eyes. The reason for the diffuse calcification of the subepithelial layers in this patient is not clear. It may be that the tendency to calcification was so great as to overshadow the relatively minor influences of evaporation and gaseous exchange.

The reasons for the anterior location of the calcific deposits in band keratopathy may also be related to pH. Kinoshita[9] has shown that anerobic glycolysis is the principal mode of metabolism in the deep corneal stroma. If lactic acid accumulation in the deep stroma produces a slightly lower pH there than in the superficial layers, the differences might be sufficient to render the deeper layers clear and the subepithelial layers opaque.

The structural peculiarities of certain subepithelial tissues may also make them especially susceptible to calcification. Are there crystalline structures in the subepithelial layers which might act as the nuclei for

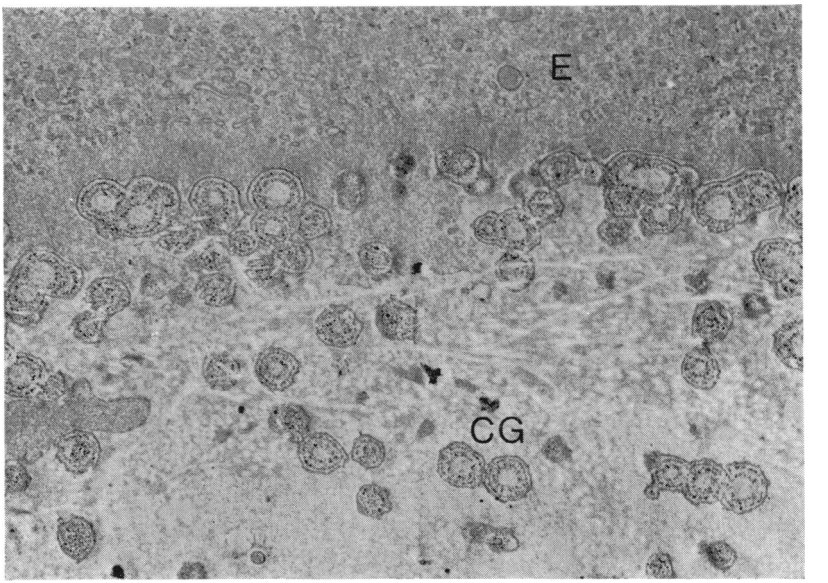

FIGURE 14

Granules of calcium in superficial stroma of rabbit cornea exposed to CO_2-laser radiation. E: epithelium; CG: calcium granules. Electron photomicrograph, × 16,800. From B.S. Fine, et al., Corneal calcification, Science, 162:129, 1961.

hydroxyl apatite deposition? Fanconi[2] states that "given a crystal nucleus of hydroxyl apatite, the body fluids are supersaturated enough to form a complete crystal spontaneously." In cartilage and osteoid, moreover, the nucleus for crystal seeding is provided by collagen, the only crystalline material of organic composition.[10] It is entirely possible that the basement membrane of the epithelium (Figure 13) with its peculiar irregular thickenings and hemidesmosomes may act as a lattice upon which crystal structures might be built. In rabbits exposed to CO_2-laser irradiation Fine[11] has produced calcific band keratopathy characterized by the extracellular accumulation of calcium granules in and around the basement membrane. These granules began as fine spherical nuclei which developed denser concentric rings about them (Figure 14). They eventually coalesced to form a solid plaque (Figure 15) in the basement membrane of the corneal epithelium.

Nearly the same kind of granule was noted by Pouliquen[12] in ultramicroscopic sections of human corneas with band keratopathy. The granules he demonstrated were of low electron density in the center with centrifugal rays or hair-like structures radiating out into the peri-

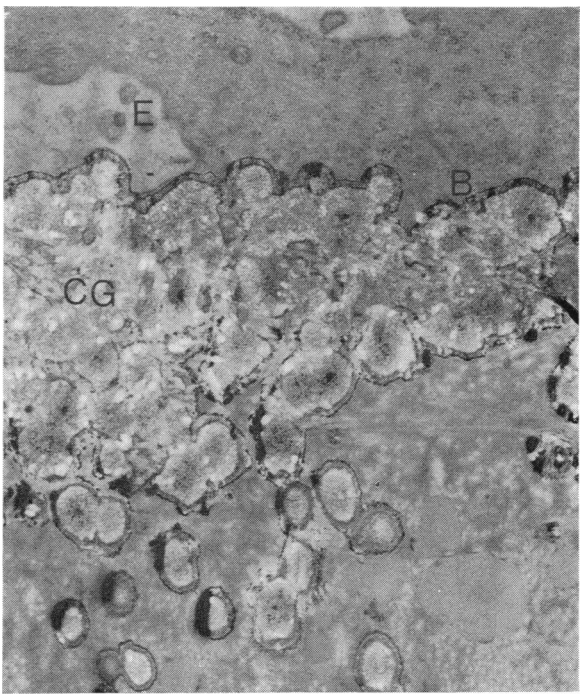

FIGURE 15

Coalescing granules of calcium in the superficial stroma of a rabbit cornea. E: epithelium; B: basement membrane; CG: coalescing granules. Electron photomicrograph, × 16,800. From B.S. Fine, et al., Corneal calcification, Science, 162:129, 1961.

phery of the granule (Figure 16). The granules coalesced to form a solid plaque in the area of the basement membrane.

Pouliquen also recognized another form of calcification occurring on fine collagen fibrils in the region of Bowman's layer. These fibrils were partially masked by dark transverse bars which were wider than the fibril itself, giving the structure the general aspect of a fish bone (Figure 17). Although Pouliquen inferred that the fibrils he observed were pathologic structures, being somewhat finer and more irregular than normal collagen fibrils, one wonders whether the very delicate, randomly arranged collagen fibrils that normally make up the meshwork of Bowman's layer might not, under certain conditions, act as a natural latticework for the deposition of hydroxyl apatite crystals. This fibril meshwork might also act as a filter of high resistance, entrapping or binding ions

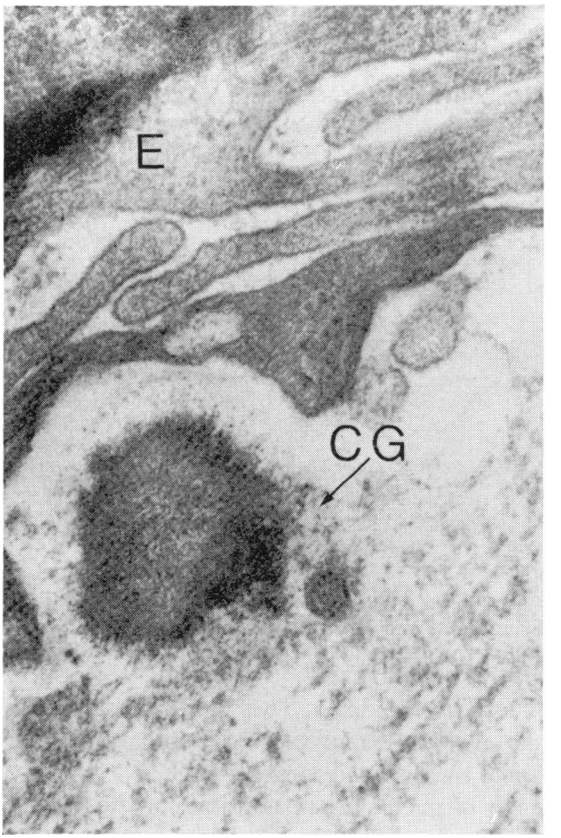

FIGURE 16

Calcium granule in Bowman's layer. Human interstitial keratopathy. CG: calcium granule; E: epithelium. From Y. Pouliquen, et al., Ultrastructure de la kératopathie en bandelette, Arch. Ophtal. (Paris), 27:149, 1967.

important to the ultimate formation of hydroxyl apatite crystals. Urry[13] has suggested that binding of calcium to neutral sites on protein fibers is the initial step in the calcification of target organs. This is then followed by ionic binding of counter-ions such as phosphate. High levels of sulfated mucopolysaccharides inhibit ionic binding and are thought to be an important element in preventing the calcification of normal structures. If the sulfated mucopolysaccharides of the cornea were somewhat altered by disease they might fail to exert this inhibiting influence. Obenberger *et al.*[14] noted a decrease in the acid mucopolysaccharide content of rabbit corneas subjected to endothelial trauma. This trauma

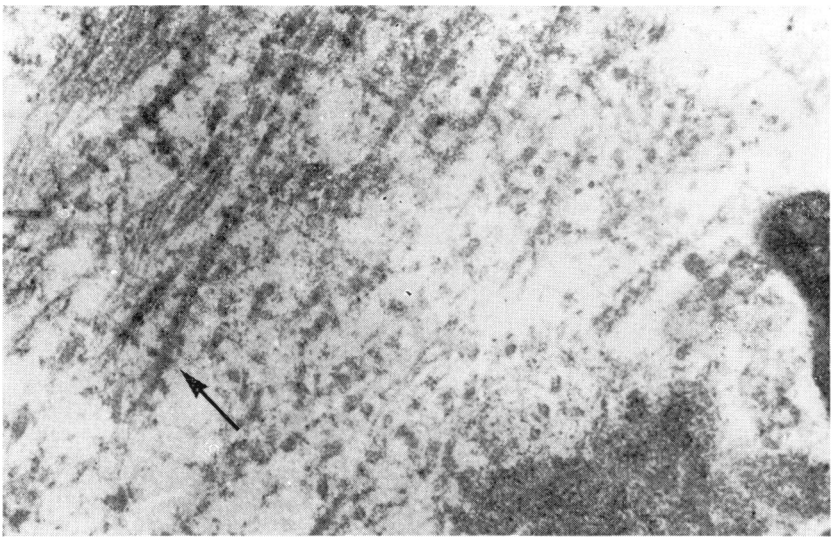

FIGURE 17
Deposition of calcium on collagen fibrils in the superficial stroma. Arrow indicates fish-bone configuration. From Y. Pouliquen, et al., Ultrastructure de la kératopathie en bandelette, Arch. Ophtal. (Paris), 27:149, 1967.

also resulted in corneal edema. They inferred that corneal edema and the associated loss of mucopolysaccharides might be responsible for the mineralization of the diseased corneas.

What features of uveitis are responsible for the deposition of calcium in the anterior layers of the cornea? Does damage to the endothelium, occasioned by the formation of keratic precipitates, cause calcific keratopathy? Is edema of the cornea essential for the deposition of hydroxyl apatite? Obenberger and Babicky[15] have shown that rabbits sensitized by injections of dihydrotachysterol developed calcific keratopathy after the endothelium had been damaged by toxic chemicals (potassium permanganate). Corneal calcification appeared only in corneas that developed pathologic hydration. Radioactive calcium chloride ($^{45}CaCl_2$), injected intravenously into these same animals, appeared in the cornea in maximal concentrations approximately thirty minutes after the injection; but the concentration of radioactive calcium varied insignificantly from the central to the peripheral parts of the cornea. These same animals developed a mild uveitis in connection with the perfusion of their anterior chambers with $KMnO_4$. With the subsequent breakdown of the blood-aqueous barrier and the formation of a plasmoid aqueous the entry of both diffusable and non-diffusable plasma calcium into the anterior chamber was facilitated.

From these experiments it would seem that the combination of uveitis and endothelial damage might well result in the movement of calcium into the cornea. The fact that the concentration of calcium was the same in all parts of the cornea, however, is difficult to reconcile with the usual appearance of calcific band keratopathy in the periphery of the cornea. If Obenberger's observations are correct, one would expect that the central portion of the cornea might be affected at the same time or even earlier than the periphery. Such is not the case in human disease. It would seem, rather, that calcium diffuses into the periphery of the cornea from the limbal circulation, and that local conditions in the cornea bring about mineral deposition in the characteristic band shape.

It is well known that epithelial edema often appears in areas corresponding exactly to the position of keratic precipitates on the endothelial side of the cornea. It seems logical to assume that keratic precipitates might produce a localized alteration of the endothelial pump mechanism that is normally responsible for keeping the cornea deturgesced. If fluid is allowed to flow across the cornea to the epithelium, it is entirely possible that certain normal corneal constituents lying in its path might be altered. If the acid mucopolysaccharide content of the cornea is reduced by pervaporative flow, as Barber[16] has suggested, mineralization of the cornea, normally inhibited by these substances, might freely occur.

In addition to the corneal edema produced by endothelial damage in eyes with uveitis, a more diffuse corneal edema generally results from glaucoma. It may be recalled that 9 out of 19 eyes with typical band keratopathy in our series had signs of severe glaucoma. Intrastromal and intraepithelial edema were visible in many of these. The same mechanisms of pervaporative flow, referred to above, could be called upon to explain the calcific keratopathy in these cases. Furthermore it is known that transient asymptomatic rises of pressure accompany many forms of uveitis. It is entirely possible that intermittent glaucoma with or without visible epithelial edema might result in calcific band keratopathy both in adults and in children.

Other factors in childhood, however, may provide the basis for the seemingly higher incidence of calcific band keratopathy in juvenile uveitis. The principal reservoir for calcium is mineralized bone. Fanconi[2] points out that the crystals of hydroxyl apatite in the bones of children are very small, and that these crystals grow larger with age. The younger the child, the smaller the hydroxyl apatite crystals and the larger the surface available for ionic exchange. In the adult only 5 grams out of the total 1,200 grams of calcium deposited in the bones are available on crystal surfaces for ionic exchange. It would seem, therefore, that the child has greater possibilities for mobilizing and depositing calcium in

a given focus than the adult. By the same token the child has a greater potential for reversing his calcific band keratopathy once the basic disturbance has been corrected, and Hatherley[17] has documented the spontaneous disappearance of band keratopathy in a child with Still's disease.

Lastly some mention should be made of *calciphylaxis*, a term coined by Selye[18] to account for the appearance of calcium deposition in many areas of the body. Calciphylaxis is a condition of induced systemic hypersensitivity in which tissues respond to appropriate challenging agents with a precipitous, though sometimes evanescent, local calcification. In the experiments of Doughman *et al.*[7] calciferol was the sensitizing agent, and experimentally induced uveitis represented the challenging agent. It seems likely that the increased ability of the child to mobilize calcium represents the condition of hypersensitivity, and uveitis or other forms of corneal trauma represent the challenging agent. The systemic sensitizer is not known in many cases. Thus the rabbits in which Fine[10] produced calcific band keratopathy by CO_2-laser treatments had no known systemic abnormality, yet the irritation of the cornea by the laser beam produced band keratopathy. The atypical band keratopathy noted by Kennedy[19] in a group of glaucomatous patients may represent a similar circumstance. In the latter group the application of irritating miotics may have represented the challenging agent, whatever the nature of the systemic sensitization might have been. These and other mysteries remain unsolved in our search for the cause of band keratopathy, yet we have come closer to a knowledge of the basic chemistry of corneal calcification.

SUMMARY

Histopathologic studies on a large number of eyes with calcific band keratopathy were performed. Calcific deposits in Bowman's layer, in the basement membrane of the epithelium, and in the superficial stromal lamellae were common to a large number of diseases regardless of their etiology. Various factors thought to be responsible for the deposition of calcium salts in the interpalpebral region of the anterior corneal layers are discussed. Among these, gaseous exchange at the surface of the exposed cornea with subsequent loss of CO_2 and a localized elevation of pH are thought to be significant. The influence of special anatomic factors in the basement membrane of the epithelium and in Bowman's layer are also discussed. The decreased content of acid mucopolysaccharides in edematous corneas is mentioned in connection with the

inhibiting effect that such substances are supposed to have upon the ionic binding of phosphates to calcium in tissue.

REFERENCES

1. Obenberger, J., D.E. Ocumpaugh, and M.G. Cubberly, Experimental corneal calcification in animals treated with dihydrotachysterol, Invest. Ophthal., 8:467, 1969.
2. Fanconi, G., Physiology and pathology of calcium metabolism, Advances Ped., 12:307, 1962.
3. Berkow, J.W., B.S. Fine, and L.E. Zimmerman, Unusual ocular calcification in hyperparathyroidism, Amer. J. Ophthal., 66:812, 1969.
4. Wagener, H.P., The ocular manifestations of hypercalcemia, Amer. J. Med. Sci., 231:218, 1956.
5. Cogan, D.G., F. Albright, and F.C. Bartter, Hypercalcemia and band keratopathy, Arch. Ophthal., 40:624, 1948.
6. Walsh, F.B., and J.E. Howard, Conjunctival and corneal lesions in hypercalcemia, J. Clin. Endocr., 7:644, 1947.
7. Doughman, D.J., G.A. Olson, S. Nolan, and R.G. Hajny, Experimental band keratopathy, Arch. Ophthal., 81:264, 1969.
8. Cogan, D.G., and P.H. Henneman, Diffuse calcification of the cornea in hypercalcemia, New Eng. J. Med., 257:451, 1957.
9. Kinoshita, J.H., Some aspects of carbohydrate metabolism of the cornea, Invest. Ophthal., 1:178, 1962.
10. Neumann, W.F., The Chemical Aspects of Bone Mineral, Chicago, Univ. of Chicago Press, 1958.
11. Fine, B.S., J.W. Berkow, and S. Fine, Corneal calcification, Science, 162:129, 1968.
12. Pouliquen, Y., C. Haye, J. Bisson, and G. Offret, Ultrastructure de la kératopathie en bandelette, Arch. Ophtal. (Paris), 27:149, 1967.
13. Urry, D.W., Neutral sites for calcium ion binding to elastin and collagen: A charge neutralization theory for calcification and its relationship to atherosclerosis, Proc. Nat. Acad. Sci., 68:810, 1971.
14. Obenberger, J., J. Čejková, and I. Brettschneider, Experimental corneal calcification: A study of acid mucopolysaccharides, Ophthal. Res., 1:175, 1970.
15. Obenberger, J., and A. Babbický, Experimental corneal calcification: A study of transport of ^{45}Ca into the aqueous and cornea, Ophthal. Res., 1:187, 1970.
16. Barber, C.W., Physiological chemistry of the eye, Arch. Ophthal., 87:72, 1972.
17. Hatherley, E., Uveitis and band-shaped keratitis in a case of Still's disease, Proc. Roy. Soc. Med., 44:978, 1951.
18. Selye, H., Calciphylaxis, Chicago, Univ. of Chicago Press, 1962.
19. Kennedy, R.E., Atypical band keratopathy in glaucomatous patients, Amer. J. Ophthal., 72:917, 1971.

DISCUSSION

DR FREDERICK W. STOCKER. The basic facts of the histology of band keratopathy were already known before the turn of the century. In the first slide (slides not included here), the artist's drawing from v. Michel shows a pannus-like connective tissue membrane between the epithelium and Bowman's membrane and calcium deposits in that membrane and in the anterior layers of the stroma. Bowman himself, in 1849, described the membrane as

the site of these deposits. Rheumatism, uveitis, glaucoma, and trauma were considered as underlying causes and increased permeability of the endothelium was supposed to play a part for the deposition of calcium beneath the epithelium, located mostly in the lid space because of increased evaporation of water in this area (F. Schieck, Kurzes Handbuch Der Ophthalmologie, Berlin, Springer, 1931).

Dr O'Connor beautifully presented some interesting details. When reading his review on underlying causes one must admit, however, that the discussion revolves around the same theories and not much progress in the basic understanding of band keratopathy has been made during the last hundred years.

The author rightly pointed out that corneal edema produced in front of keratic precipitates (KP) during uveitis as demonstrated in this slide by Irvine and Irvine (Amer. J. Ophthal., 36:1272, 1953) does not explain the usual beginning of band keratopathy near the limbus. On the other hand, it has been our experience that a toxic effect on the endothelium during uveitis may cause edema of the cornea even before the formation of keratic precipitates. One then could speculate that the periphery of the cornea, due to its proximity to the iris and ciliary body, might be particularly exposed to a toxic effect of the inflammatory process.

As to the role played by mucopolysaccharides, the next slide shows how the corneal lamellae in the normal cornea are enveloped by a fine layer of that substance, stained blue with colloidal iron. In the next slide the cornea from an eye stored in a moist chamber for two weeks is edematous and the mucopolysaccharides have faded out, particularly beneath the epithelium. This also occurs in Fuchs's dystrophy. If the dislocation of mucopolysaccharides were disposing to the deposition of calcium, one would expect to find such deposits in late states of Fuchs's dystrophy. In the next slide, demonstrating such an example, connective tissue has developed between epithelium and Bowman's membrane not unlike that in band keratopathy, but no calcium deposits are present. Hypercalcemia as reported by Cogan and others is present in some but not all patients with band keratopathy. Thus all the theories advanced so far are plagued by inconsistencies.

Hypersensitivity and auto-immune reactions seem probable underlying causes in band keratopathy.

I now should like to mention that Dr S.D. McPherson, Jr has made an interesting contribution to the pathology of band keratopathy. He found band keratopathy in five of the twelve eyes in which he had found amyloid (Proc. of Internat. Congr., Mexico, 1970; Amer. J. Ophthal., 62:1025, 1966). The next slides show amyloid stained with Congo red, along with calcium and fat, in a histologic section of an eye with band keratopathy. The fact that amyloid is stained beautifully after scraping off the epithelium in vivo has clinical significance. It is well known that if the opacification of the cornea is primarily due to calcium, chelation with EDTA may produce spectacular improvement, as seen in the next two slides. It is not always easy to tell how much calcium is present. If a lesion such as this [slide] shows strong staining with Congo red, the chances for successful chelation are not too good.

And finally another therapeutic hint for an eye affected with band keratopathy which is blind and unsightly: Here [slide] is the very unsightly appearance of the blind left eye of a young girl, and then the appearance with a cosmetic contact lens [slide].

It was a great pleasure to read this thought-provoking paper, and I should like to congratulate Dr O'Connor on his thorough and well presented study.

DR FREDERICK C. BLODI. It has been proven in several cases that the calcium deposits of systemic hypercalcemia are different from the degenerative type that you showed, Dr O'Connor, namely, that the primary deposition is in the epithelial cells themselves and not in the collagen nor in the basement membrane. Therefore I wonder whether you could unify your theory on the pathogenesis, taking into account this different deposition in systemic hypercalcemia.

DR O'CONNOR. I wish to thank both of the discussants for their comments. I think we must conclude that calcific band keratopathy represents a final common pathway for the expression of a calcifying tendency in a large number of diseases.

As Dr Stocker has rightly pointed out, every theory that has been brought forth thus far has some inconsistencies in it. If we consider endothelial damage to be the basis for the lesion in the majority of cases, an increased amount of calcium entering the cornea at the site of endothelial damage, we should expect the lesion to be inferior or central in location in the majority of cases.

What we actually observe, on the other hand, is calcification in the periphery of the cornea. This suggests that the major source of the calcium is the limbal circulation and that local factors, whatever they may be, result in the precipitation of calcium in this peculiar band form.

I think Dr Stocker's studies on amyloid are both interesting and thought-provoking. I did not examine the specimens given to me for the deposition of amyloid, but that may also provide a common denominator for the formation of calcium in some of the specimens studied.

Dr Blodi's statement that calcium tends to be deposited intracellularly in cases of hypercalcemia is one that has been confirmed by Fine and his colleagues. In these instances one may be able to differentiate cases representing hypercalcemia from cases which are primarily ascribable to local inflammatory or degenerative conditions.

There is no readily apparent explanation why the calcium deposits should be intracellular in hypercalcemia and extracellular in the degenerative or inflammatory conditions that I have described. It is known, however, that many intracellular structures can both bind and precipitate calcium. It is possible that hypercalcemia, which would tend to favor calcification under any circumstances, is most easily expressed by precipitation on intracellular organelles.

Again I thank the discussants for their thought-provoking comments.