THE NATURE OF HEREDITARY DEEP POLYMORPHOUS DYSTROPHY OF THE CORNEA: ITS ASSOCIATION WITH IRIS AND ANTERIOR CHAMBER DYGENESIS*

BY *Merrill Grayson,* MD

INTRODUCTION

IN 1969 AN OPPORTUNITY AROSE TO STUDY THE CHANGES IN THE ANTERIOR AND posterior limiting membranes of the cornea and their association with mesodermal dysgenesis of the iris and anterior chamber angle. This study represents an investigation of the nature of the changes (including ultrastructure) found in the posterior limiting membrane of the cornea. These changes were seen in several patients presenting the clinical picture of deep polymorphous dystrophy and anterior segment mesodermal dysgenesis. The material includes three affected generations of a family; two of the brothers requiring penetrating corneal transplants. The corneal buttons of the two brothers provide the specimans allowing the changes in the posterior and anterior corneal limiting membrane areas to be studied.

The paper is subdivided into the following categories:

1. Historical Review
2. Description of Cases
3. Material and Methods
   - A. Genetic aspects of affected family
   - B. Clinical laboratory findings
   - C. Histopathologic studies
     - a. Light microscopy of the corneal material
     - b. Transmission electron microscopy of the corneal material
     - c. Scanning electron microscopy of the corneal material
4. Discussion and Conclusions
5. Summary

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HISTORICAL REVIEW

In the early part of the twentieth century deep posterior polymorphous dystrophy of the cornea was described as a specific and solitary corneal entity. Subsequent investigations showed that the condition occurred not only as a solitary corneal finding, but was seen with alterations in the anterior membrane area of the cornea, in the iris, and in the anterior chamber angle. The historical review affords a presentation of the development of the study of deep posterior polymorphous dystrophy of the cornea and its association with anterior mesodermal changes of the iris and chamber angle. It also affords a view of the development of the nature of the pathology from the collected investigations of a number of different observers.

Many investigators have contributed to the volume of information concerning deep posterior polymorphous corneal dystrophy. Koeppe[11] in 1916 has been credited with the first description of the entity now termed deep posterior polymorphous dystrophy of the cornea. He studied six patients who exhibited lesions which he described as congenital pits on the posterior surface of the cornea and called the condition "keratitis bullosa interna." One of his patients had glaucoma; however, there was no indication as to whether anterior segment or angle anomalies were present. Clarification as to the clinical appearance of the specific deep corneal lesions was emphasized by Treibenstein[19] who reported three cases of deep posterior polymorphous dystrophy of the cornea when he pointed out the difference between it and cornea guttata.

In 1932 Freudenthal[8] described cases of deep posterior polymorphous dystrophy of the cornea in both a father and his son. The lesions in the endothelium were associated with deep stromal turbidity and since no pathology studies were performed the key to the nature of the stromal and endothelial lesions was not determined. After Freudenthal[8] described this family several investigators reported on their findings. Schlichting,[15] Cuntz-Schüssler,[21] Berliner,[20] and Forni,[7] described examples with similar clinical pictures. Schlichting[15] reported studying a father and his daughter with deep corneal lesions. He described these as deep corneal concavities and vesicles. Theodore[18] described three generations of a family presenting deep posterior polymorphous dystrophy of the cornea and felt that there were two forms; one congenital and the other senile. McGee and Falls[13] were the first investigators who determined that deep posterior corneal polymorphous dystrophy was genetically transmitted as an autosomal dominant trait with good penetrance. In addition, they concluded that recessive inheritance could not be excluded

in all cases. They observed that the anterior layers of the cornea were never involved nor was there any cornea guttata present. They thought that the disease was non-progressive. The typical findings of the posterior corneal lesions were seen by them and were described as vesicles, nodules, and opacities of varying sizes.

In the early literature, a number of authors stated that the vesicular appearing lesions seen in deep posterior polymorphous corneal dystrophy may have been caused by herpes simplex virus involvement of the endothelium and suggested the name "linear vesicular disease" since the lesions were lined up in a uniform fashion. Herpes simplex or herpes of the posterior cornea was suggested by Schnyder[25,26] in 1924. Knuesel,[10] Freudenthal,[8] Staz,[27] Stocker,[28] Bucci,[6] Kiffney[29] and Collier[30] all stressed and described the "vesicular" nature of the lesions. Kiffney[29] in 1965 suggested that the name "linear endothelial vesiculosis" be given to the condition which resembles the classical deep posterior polymorphous dystrophy of the cornea, and which is indeed one and the same thing.

Snell and Irwin[16] presented a family in which three generations showed the characteristic small bleb-like structures on Descemet's membrane which protruded into the anterior chamber. They noted that some of these lesions were surrounded by a white-gray halo while other lesions appeared to be flat thickenings of Descemet's membrane.. These authors thought that the lesions possibly progressed from an initial bullous stage to the stage of flat opacification just described. In addition, they noted that in the latter stage the deep stroma anterior to Descemet's membrane was affected and suggested the term "hereditary deep dystrophy of the cornea" for this entity.

The occurrence of deep posterior polymorphous dystrophy with pathology present in the anterior membrane area of the cornea was pointed out by Franceschetti and Montressor.[23] In 1960 they described a case of band-shaped keratopathy combined with deep posterior polymorphous dystrophy of the cornea in an 11-year-old girl. There was no systemic disease or other local eye disease to account for the band keratopathy and they considered the latter to be of genetic origin.

Magruder,[24] in 1961, suggested the possibility of a systemic disease as a factor in causing the corneal pathology in a patient with a positive Sulkowitz urine test for calcium. He entertained the diagnosis of hypophosphatasia as a possible cause of the corneal disease. Although his patient did not exhibit the clinical criteria for hypophosphatasia, the laboratory findings did suggest a metabolic disorder. He performed a lens extraction on this patient with no adverse effects on the cornea. Magruder[24] was the first investigator who suggested that the problem may have some sys-

temic association. This question was again raised by Hogan and Bietti.[33]

Anomalies of the iris together with the occurrence of deep polymorphous dystrophy have been reported by Bergman,[5] Soukup,[17] and Rubenstein and Silverman.[34] Bergman,[5] in 1964, reported a case of deep polymorphous corneal dystrophy associated with heterochromia of the eyebrows and lashes as well as a variation of iris color in a 12-year-old girl.

Soukup[17] described deep polymorphous corneal dystrophy complicated by anterior synechias and iris rarefication in two sisters. The deep posterior vesicles were visible in chains and irregular groups mainly located in the marginal areas of the cornea. The polymorphous opacity was dense and formed a prominent network. Local corneal edema and opacity of the endothelium were present and were considered to be primary changes by the author while the nodules, vesicles, and pits were thought to be secondary. The author reported that there was an improvement in the corneal condition after the patients were given corticosteroid drugs, but no further clarification of this was given.

Morgan and Patterson[31] were the first investigators to report on light microscopy of deep posterior polymorphous dystrophy of the cornea. Their patient exhibited a superficial post-herpetic corneal scar together with grayish corneal opacities at the level of Descemet's membrane with the lesions projecting into the anterior chamber. These were PAS-positive and each contained empty vacuoles. Descemet's membrane between the excrescences was normal in some areas, but thickened in other areas. The endothelium was thinned with flattening of the cell nuclei over the excrescences. The authors concluded that the lesions were similar to the Hassall-Henle wart and that the vacuoles in the fusiform swelling were due to an uneven laying down of material for Descemet's membrane formation by the endothelial cells. In 1965, Feeney and Garron[32] noted small fissures in Hassall-Henle warts when these structures were studied with the electron microscope and as noted these fissures resembled the findings described by Morgan and Patterson.[31]

The gross clinical appearance of the lesions described by Morgan and Patterson[31] appeared similar to those described by Hogan and Bietti[33] but the histological findings were very dissimilar. Both groups of investigators described their entities as deep polymorphous dystrophy of the cornea but the etiologies were not the same. Hogan and Bietti[33] noted calcium crystals in the deep stromal lesions but no calcium crystals were found in the examples described by Morgan and Patterson.[31]

Hanselmayer[9] described splits in Descemet's membrane in his studies of the histopathology of posterior deep corneal polymorphous dystrophy to account for the clinical picture, but he did not carry out any transmis-

sion electron-microscopic studies of the posterior membrane for ultrastructural tissue evaluation.

Rubenstein and Silverman[34] presented a comprehensive investigation of a congenital hereditary mesodermal dysgenesis in association with deep posterior polymorphous corneal dystrophy. These authors described a family in which a 12-year-old female was noted to have isolated vesicular lesions in the region of the endothelium. The child's mother had a Krukenberg spindle and iris atrophy, but no glaucoma. In another of their patients, endothelial vesicles were present in the right eye (a 22-year-old white male with glaucoma). They also described a family of a 30-year-old Negro mother, a 14-year-old son, and an 11-year-old daughter each of whom exhibited irregular endothelial vesicles surrounded by opacification. The mother had open angle glaucoma. The authors suggested the term "hereditary mesodermal dystrophy" be used since the presence of glaucoma associated with changes in the endothelium and Descemet's membrane suggest a more generalized mesodermal defect. Glaucoma associated with deep posterior polymorphous dystrophy was also reported by Pietruschka.[14]

Hogan and Bietti[33] described the clinical appearance of deep polymorphous corneal dystrophy characterized by flat polymorphous opacities and translucent vesicular lesions in the region of Descemet's membrane in the corneas of a 47-year-old white male. The problem was first noted when the patient was 31 years old. The authors state that the endothelium appeared to be absent in the patient's right eye which had the poorer vision. Corneal edema and deep stromal opacification were seen slightly below the pupillary area. There was increasing visual defect because of the corneal edema. The deep corneal polymorphous changes were described as small round areas which were bullous in nature. They characterized the lesions as having snail-trail-like patterns with irregularly sinuous margins deep in the cornea. Descemet's membrane showed concavities which were generally rough and sparkly when viewed with the slitlamp beam. These were all described as deep posterior polymorphous dystrophy. In their studies, there was no evidence of hereditary transmission of the disease. Three brothers and a cousin who were examined were found to have no eye disease.

Boruchoff and Kuwabara[35] described the electron-microscopic picture of deep posterior polymorphous dystrophy in a 35-year-old white male who developed painful bullous keratopathy. They found that the electron-microscopic studies revealed that the endothelial layer of the cornea was made up of cells which they characterized as being epithelial in nature.

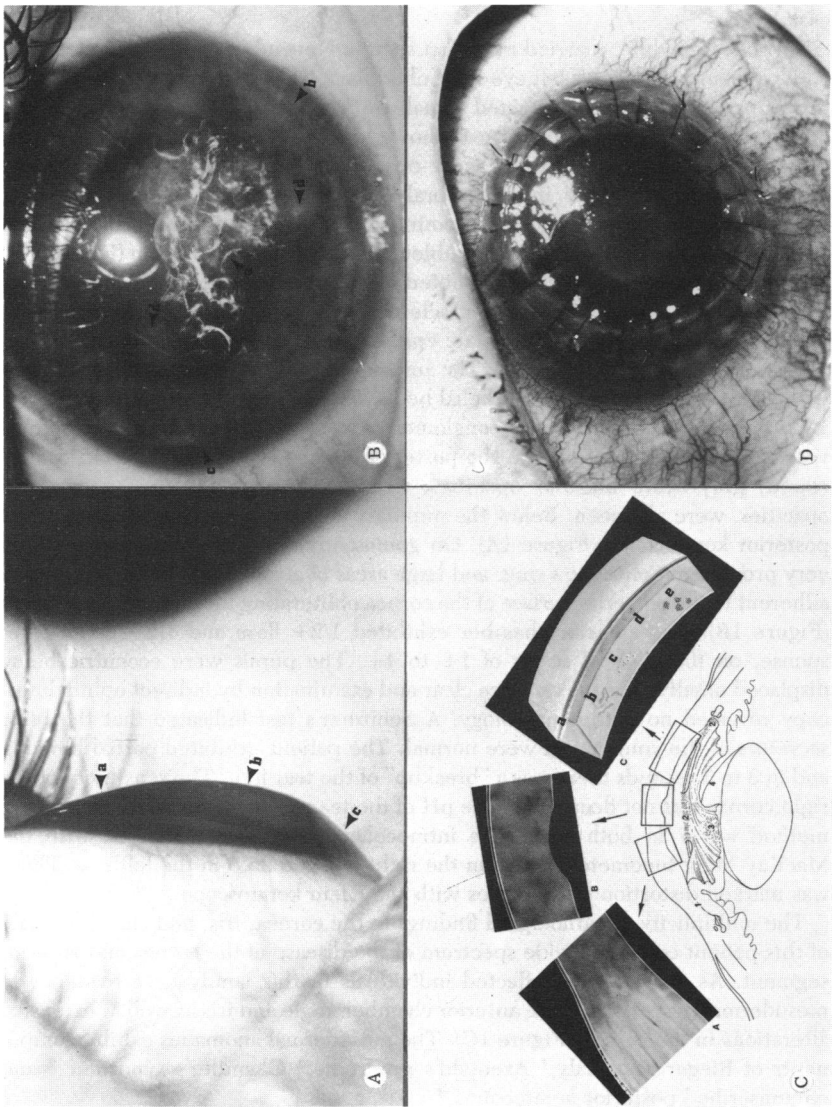
CASE REPORTS

CASE 1

A 28-year-old, white, married male first seen in November of 1969 stated that he had had poor vision in his left eye since childhood. There was no history of serious illness or injury. The uncorrected visual acuity was 20/60 in the right eye and 20/200 in the left eye. Both corneas showed a flattening of the anterior surface (Figure 1A). Semi-circular white-gray opacities were irregularly arranged and scattered throughout the interpalpebral area of the corneas. These irregular opacities were seen in Bowman's membrane and did not resemble the classical type of band keratopathy. They resembled strokes of an artist's brush (Figure 1B). More typical band keratopathy was noted towards the 9 and 3 o'clock positions of the peripheral cornea and areas of sclerocornea were seen superiorly and inferiorly (Figure 1A). Diffuse punctate epithelial lesions and epithelial fingerprint lines were noted in both corneas. The surrounding cornea was translucent rather than transparent, because of epithelial bedewing and stromal edema. The posterior surface of the cornea showed conglomerate areas of cornea guttata. Lesions of a vesicular nature were noted on the posterior surface of the cornea. Flat, oval or round, gray-white macular opacities, as well as large, sinuous geographic opacities, were also seen. Below the pupillary area was an area of circumscribed posterior keratoconus (Figure 1A). On gonioscopy, iris processes extended to a very prominent Schwalbe's ring, and large areas of atrophic iris were noted to be adherent to the posterior surface of the cornea obliterating the angle in these areas (Figure 1B). The anterior chamber exhibited 1/2+ flare and 1/2+ cellular response, on the basis of scales of 1+ to 4+. The pupils were eccentric being displaced nasally. The lenses were clear and examination by indirect ophthalmoscopy revealed no fundus pathology. A Schirmer's test indicated that the basic secretors of the conjunctiva were normal. The patient exhibited partial blinking and in 3 to 5 seconds there was a "breakup" of the tear film. The sensitivity of the right cornea was not decreased. The pH of the tears as determined by paper strip method was 7 in both eyes. The intraocular pressure as measured with the MacKay-Marg tonometer was 26 in the right eye and 26.5 in the left eye. There was marked distortion of the mires with the Klein keratoscope.

The multiplicity of pathological findings in the cornea, iris, and chamber angle of this patient covered a wide spectrum of the disease of the cornea and anterior segment. As can be seen, affected individuals in this family have evidence of mesodermal dysgenesis of the anterior chamber angle and iris as well as extensive alterations in the cornea (Figure 1C). The mesodermal anomalies exhibit components of Rieger's anomaly,[1] Axenfeld's syndrome,[1] Chandler's syndrome,[2] and circumscribed posterior keratoconus.[3]

An 8.1 mm penetrating corneal transplant was performed under general anesthesia on the left eye on October 26, 1971, using cryopreserved material which had been stored for twenty-eight days. The donor material was cryopreserved according to the method of Capella and Kaufman.[47] Twenty-two 10-0 interrupted nylon sutures were inserted (Figure 1D). During the first several postoperative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days striae in the deep stroma of the graft together with a mild haze pervaded the graft. This appeared to be characteristic of cryopreserved corneal material. After several days, the graft began to clear and the striae disappeared as detergescence of the donor material occurred.

The postoperative course was uneventful until December 13, 1971, at which time the intraocular pressure in the eye which had been operated upon rose to 58-62 mm Hg as recorded with the MacKay-Marg tonometer. As a result, the inferior suture line exhibited an ominous bulge. This was in the area where the posterior keratoconus had been seen with the slitlamp. Apparently the already compromised angle was further insulted by the inflammatory response induced by the surgical procedure. On January 14, 1972, the tension was still 40 mm Hg despite efforts to decrease the inflammation with 0.01% dexamethasone 3 times a day, and despite efforts to decrease the intraocular pressure with acetozolamide sequels (500 mg twice daily). The increased intraocular pressure apparently was not caused by the steroids since the pressure remained the same when they were withdrawn. In view of the unsuccessful medical efforts to decrease the intraocular pressure, cyclocryotherapy was performed. Eleven equally spaced applications of the cryoprobe at −60°C for 60 seconds were made 3 to 4 mm from the limbus. The intraocular pressure was controlled (18 to 20 mm Hg) and the inferior bulge was seen to flatten out considerably. By March, 1972, all of the 22 sutures had been removed.

A period of irritability of the eye occurred in April of 1972. Examination revealed a thinning of the sclera at the 12 o'clock position, 2 or 3 mm from the limbus. This disturbing finding could not be thoroughly explained, although, the cyclocryotherapy applications may have contributed to it. However, the area filled in and at the present time there is no apparent danger from this complication. The intraocular pressure is being maintained at 18 mm Hg as recorded with the applanation tonometer. The only medication being used is a dexamethasone drop 0.01% once a day. The graft remains clear, but the acuity is 20/100 due to the presence of a posterior subcapsular lenticular opacity.

FIGURE 1 *(opposite)*

A. Flattening of the superior portion of the cornea (a), area of circumscribed posterior keratoconus (b) and visible sclerocornea (c) are noted. B. Semi-circular, brush stroke-like opacities extend across the interpalpebral portion of the cornea (a). A prominent ring of Schwalbe (b) extends over a great area; the iris is atrophic and extends to the posterior surface of the cornea (c); area of deep opacity of the cornea wherein posterior deep polymorphous changes are noted in abundance and cornea guttata are seen with the biomicroscope (d). C. Diagrammatic representation of the biomicroscopic findings: (1) iridocorneal adhesions obliterating trabeculum, (2) abnormal iris processes, (3) patchy iris atrophy involving iris stroma, (4) displacement of the pupil. Sectional enlargements (A) epithelial and stromal edema, (B) area of circumscribed posterior keratoconus, (C) Section en bloc showing (a) calcific deposition in Bowman's membrane layer, (b) "sinuous" opacities (c) vesicular, (d) flat gray-white macular lesions, and (e) aggregations of guttata. D. An 8.0 mm penetrating keratoplasty with twenty-two 10-0 nylon sutures was performed using cryopreserved corneal donor material.

CASE 2

The brother of Case 1 was 33 years of age when first seen in 1969. He stated that the vision in his left eye had been "less than normal" since childhood and gradually became worse during adolescence and adult life. The visual acuity in the right eye was 20/25+3 and vision in the left eye was 20/200. Two years later the vision in the left eye had diminished to hand motion at five feet. The right cornea exhibited an area of typical band shaped keratopathy and a very prominent ring of Schwalbe (Figure 2A). Numerous iris processes were noted to be adherent to this ring. Synechia and an atrophic iris were also present. Epithelial bedewing and stromal edema were seen. The posterior corneal surface showed pigmentation together with some white-gray areas of haze and small bleb-like lesions surrounded by gray-white haloes. No cellular structure could be discerned on specular reflection but a diffuse endothelial translucency was noted. In this eye the circular conglomerate areas of cornea guttata and corneal edema were quite striking. The prominent ring of Schwalbe, iris atrophy, corectopia, and abnormal iris processes were seen. The anterior leaf of the left iris was adherent to the peripheral posterior surface of the cornea in several areas.

The pH of the tears was 7.0 and a Schirmer's test showed 20 mm wetting of the filter paper in 5 minutes in both eyes. The corneal sensitivity was decreased in the left eye but normal in the right. Indirect ophthalmoscopy did not show any fundus abnormalities. The MacKay-Marg readings in both eyes were 18 mm Hg.

The patient had experienced occasional convulsive episodes since he was 16 years old and was receiving 100 mg of metharbital four times a day. Brain scans, electroencephalogram, and roentgenograms of the skull did not reveal the cause of this problem.

The patient received a penetrating corneal transplant of the left eye under general anesthesia on October 26, 1971. An 8 mm cryopreserved donor button which had been preserved for 30 days was used. The cryopreservation technique was described by Capella and Kaufman.[47] A continuous suture of 10-0 nylon was employed (Figure 2B). There were no differences in graft healing using the continuous suture as compared with interrupted sutures which were used in his brother. The postoperative course was uneventful in this case. Medications used were 0.5% dexamethasone ointment once daily, Polysporin ophthalmic ointment once daily and 0.5% scopalamine hydrobromide ophthalmic drops twice each day. All medications were discontinued on February 18, 1972. The running suture was left in place until March 7, 1972, at which time it was removed. The visual acuity on May 12, 1972, with $-3.50 + 4.00 \times 90°$ was 20/25+2 in the eye that was operated upon.

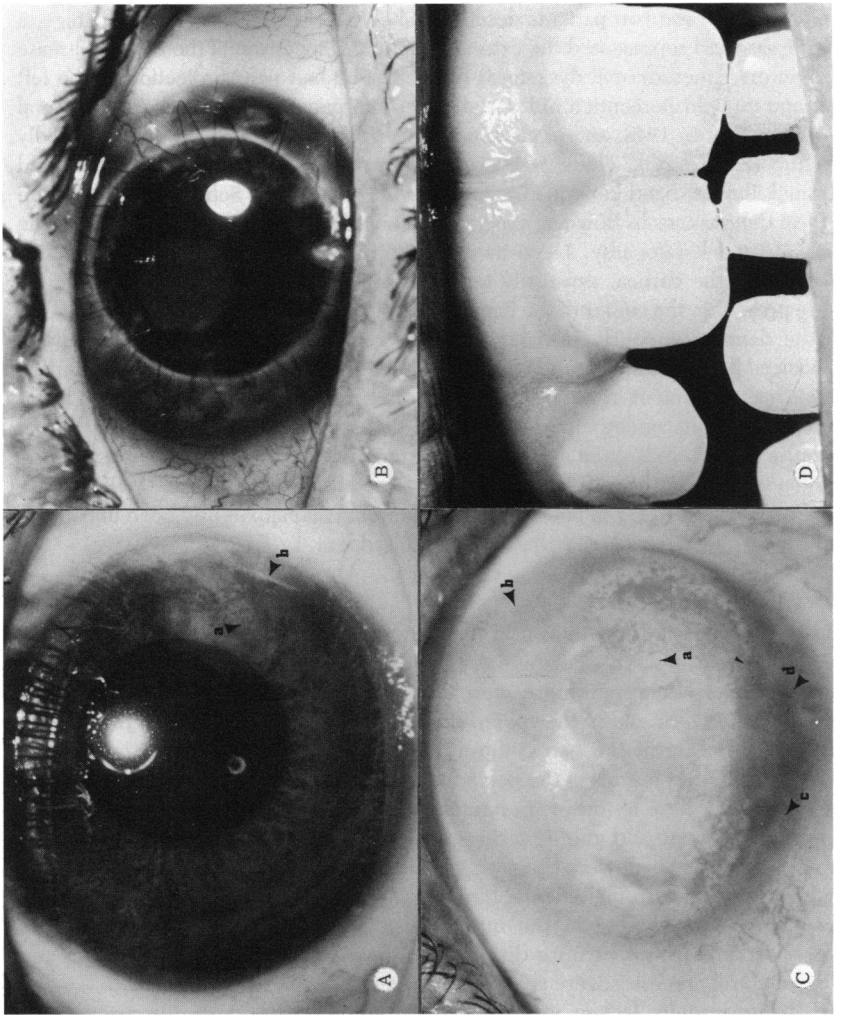


FIGURE 2

A. Typical band keratopathy (a) and a very prominent ring of Schwalbe (b) are noted. B. An 8.0 mm penetrating corneal transplant using continuous 10-0 nylon suture was employed on case number two. C. Extensive corneal disease is seen with band keratopathy (a), edema and opacification of the cornea (b), iris atrophy and iridocorneal adhesions (c), and Schwalbe's ring (d). D. Microdontia was a systemic manifestation of this disease in the younger sibling.

CASE 3

The mother of the two patients described above showed a very advanced stage of the disease and represented the extreme end of the spectrum of the corneal disease and anterior mesodermal dysgenesis (Table1). She had poor projection in the left eye and no light perception in the right eye. The patient gave a history of bilateral corneal ulcers in 1948, and of glaucoma in 1949. Both her corneas were markedly opaque (Figure 2C). There was extensive corneal thickening from edema and stromal fibrosis, band keratopathy, and a prominent ring of Schwalbe. There were typical dehiscences in Bowman's membrane noted in the peripheral portions of the area of band keratopathy. Deposits of calcium were also seen in the conjunctiva adjacent to the cornea, especially temporally. Small, yellow, oil-droplet deposits were present in the center of the band keratopathy. These had the same appearance as the deposits variously referred to as spheroid degeneration[49] or keratinoid.[48] Advanced bullous keratopathy was present in the right cornea. Superficial vascularization was prominent in the periphery of both corneas. In the areas where it could be discerned the endothelium exhibited a diffuse relucency. Areas of patchy iris atrophy with strands of anterior iris leaf extending to the posterior surface of the cornea were seen through less opaque portions of the cornea. The MacKay-Marg reading was 44 mm Hg in both eyes. The glaucoma had apparently been uncontrolled for many years and contributed to her blindness.

CASES 4 AND 5

These patients are the children of the first patient (Case 1). When first seen in 1969 the children were 1-year and 4-years of age and at that time the signs of this congenital hereditary problem were definitely manifest. These children represented the other end of the spectrum of this disease since it was in the earliest stages. The older of the two children exhibited vesicle-like lesions on the endothelium. Other lesions of the posterior membrane were gray, sinuous, macular opacities, and these lesions were randomly distributed. A large annular section of geographic-shaped and guttate lesions were noted centrally and inferiorly. These areas were overshadowed by a yellowish shagreen. There was no epithelial bedewing and no stromal edema; however, typical band-shaped keratopathy was noted to be developing in the interpalpebral fissure. There was evidence of posterior keratoconus or mire distortions; however, posterior embryotoxon and abnormal iris processes were seen in both eyes. The left cornea had bleb-like and gray-white macular lesions in annular distribution on the posterior corneal surface. Again, central and inferior guttate lesions were seen. There was no band-shaped keratopathy in this eye; but there were areas of iris atrophy, and extensive posterior embryotoxon with iris synechiae.

CASE 6

The 3-year-old sibling of the above two patients had bleb-like macular, and early geographic lesions on the posterior membranes of both corneas. Posterior embryotoxon, abnormal iris processes, and anterior synechiae were noted to a mild degree. Microdontia was a systemic abnormality found in this child (Figure 2D).

TABLE 1. DISEASE SPECTRUM NOTED IN DEEP POSTERIOR POLYMORPHOUS DYSTROPHY AND ANTERIOR SEGMENT MESODERMAL DYSGENESIS

Type A	Type B	Type C	Type D	Type E (Hogan & Bietti)	Congenital Hereditary Edema
1. Non-progressive	1. Non-progressive	1. Progressive	1. Iris processes and broad synechiae	1. No anterior segment anomaly	1. Corneal edema
2. Vesicular lesions projecting into the anterior chamber from the posterior corneal surface	2. Vesicular lesions on the posterior surface of the cornea project into the anterior chamber	2. Iris processes in chamber angle	2. Iris atrophy	2. Calcium deposition deep in stroma	2. Descemet membrane alterations with electron-microscope which resemble those changes seen in types C and D
3. No anterior segment disease	3. Iris processes in angle of anterior chamber	3. Posterior embryotoxon	3. Corectopia	3. Posterior membrane lesions which are "sinuous" & elevated	
		4. No glaucoma	4. Glaucoma		
		5. Posterior membrane changes exhibit blister-like droplets, flat macular-like and sinuous opacities	5. Band-keratopathy		
		6. Corneal edema	6. Corneal edema		
		7. Cornea guttata	7. Posterior embryotoxon		
			8. Posterior keratoconus		
			9. Cornea guttata		
			10. Progressive posterior membrane changes, i.e., sinuous lesions, blister-like and macular-like lesions in Descemet's area		
			11. Sclerocornea		

MATERIALS AND METHODS

GENETICS

Genetic screening of all available members of this family revealed that the present syndrome of anterior mesodermal dysgenesis and posterior limiting membrane disease of the cornea was transmitted as an autosomal dominant trait (Figure 3A). Three generations of the family were examined. The mother of the two patients from whom the corneal specimens were obtained; her brother, who was blind in adult life from a condition presumed to be similar to the problem described here; and two grandchildren were all affected.

The 28-year-old son has the problem in a more advanced stage than his 31-year-old brother. Two sons of the former, ages six and three, exhibit evidences of the disease. This was also noted when they were first seen at ages one and four. However, no findings have been noted in the children of the 31-year-old patient. The grandmother exhibits the most advanced stage of this progressive problem and the appearance of the corneas of the grandchildren affords us a clue as to how the disease manifests itself in the early stages. A continuous chronicle of the progressive corneal disease, therefore, is clear when the spectrum of disease is studied in grandchildren, their father, and their grandmother.

Recently, Tabbara[46] found that an isochromosome six has been noted in a patient with Rieger's syndrome. An investigation for an isochromosome six in our patients who exhibited the findings of Rieger's anomaly did not reveal this chromosomal alteration (Figure 3B).

CLINICAL LABORATORY FINDINGS

Clinical laboratory investigation was performed in order to help rule out any metabolic problem which could accompany the eye disease and account for some of the anterior and posterior corneal findings. The possibility of disturbances in calcium metabolism was suggested by Hogan and Bietti[33] when they reported cases of clinically appearing polymorphous dystrophy of the cornea due to deposits of calcium in the deep stroma of the cornea. Magruder[24] found calcium in the urine of one of his patients with this dystrophy. In the former instance, there was no report of investigation of the calcium, phosphorous, or magnesium levels in the serum.

Serum calcium, phosphorous, and magnesium levels were normal in all our patients. Low levels of magnesium may be associated with increased serum calcium and decreased serum phosphorous. The cations of the cellular fluids; especially, the calcium and magnesium, activate many

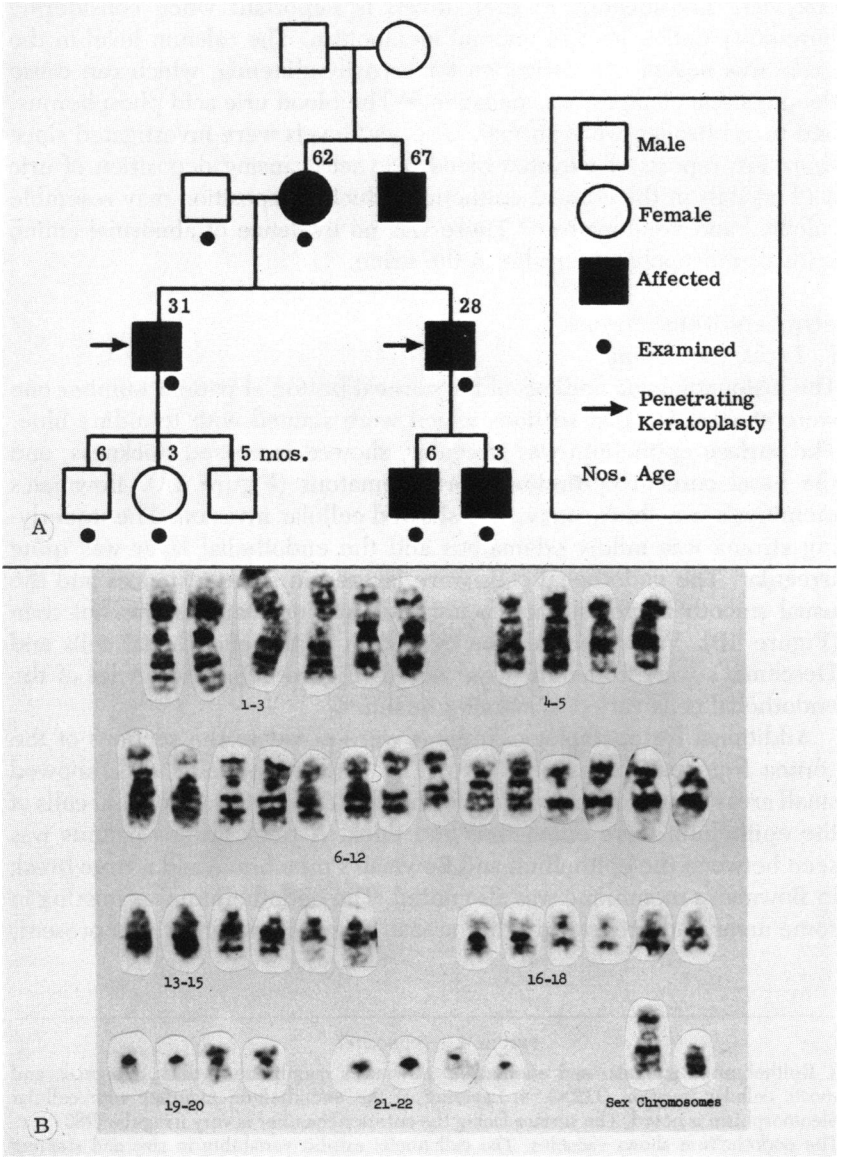


FIGURE 3

A. Pedigree of a family with deep posterior polymorphous corneal dystrophy, corneal edema, corneal guttata, anterior segment dysgenesis, calcific band-shaped keratopathy, sclerocornea, posterior circumscribed keratoconus and microdontia. The method of transmission is autosomal dominant. B. Normal karyotype and normal banding with trypsin digestion method. This karyotype is of case 1.

enzymes. Investigation of their levels is important when considering hereditary deficiencies of mineral metabolism. The calcium level in the urine was normal. Investigation for cryoglobulinemia, which can cause deep corneal changes, was negative.[44] The blood uric acid phosphorous, and urea nitrogen were normal. Uric acid levels were investigated since there are reports of elevated blood uric acid causing deposition of uric acid crystals in the corneal epithelium. Such a deposition may resemble calcific band keratopathy.[45] There was no evidence of abnormal amino acids or mucopolysaccharides in the urine.

HISTOPATHOLOGIC STUDIES

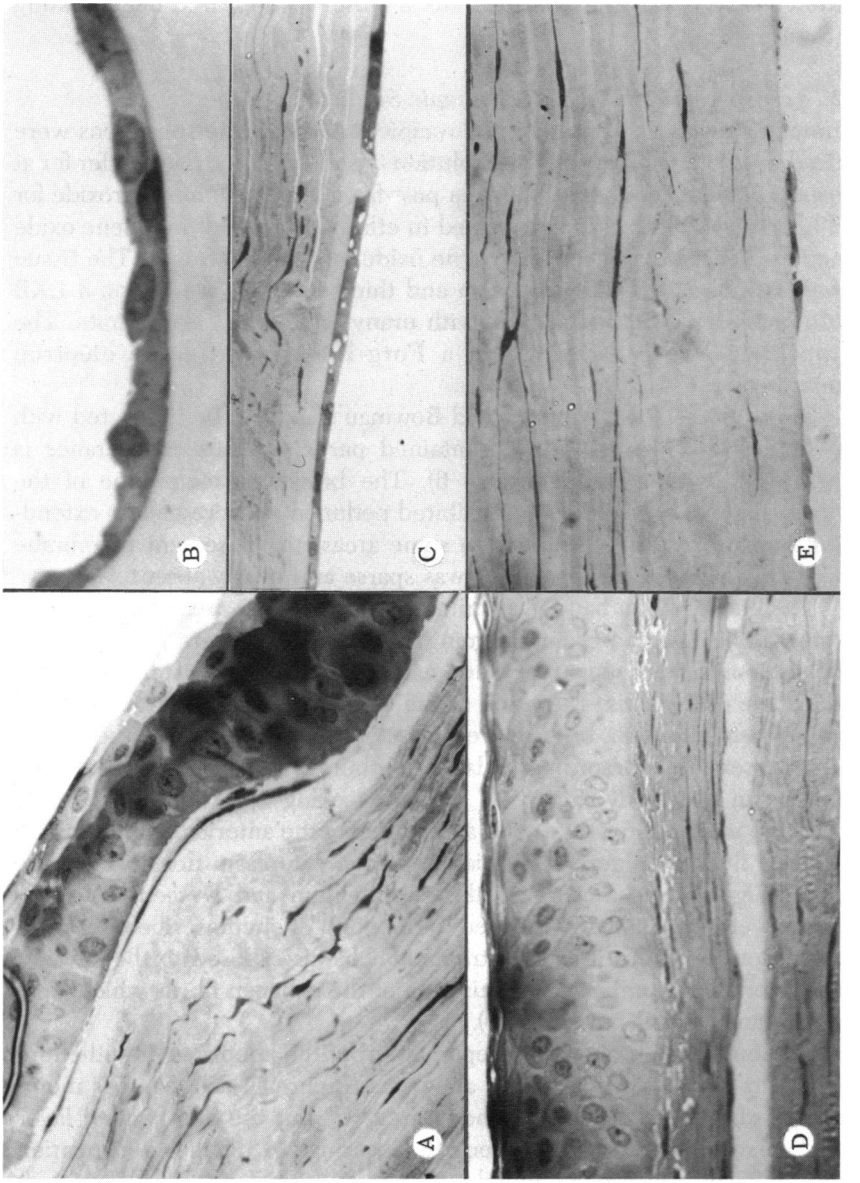
1. Light Microscopy

The histopathologic findings of the corneal button of patient number one were studied in epon sections which were stained with toluidine blue. The surface epithelium was irregular, showed increased thickness, and the basal corneal epithelium was edematous (Figure 4A). Bowman's membrane was thick, wavy, and showed cellular invasion. The underlying stroma was mildly edematous and the endothelial layer was quite irregular. The endothelial cells were layered in some instances and the usual smooth mirror surface facing the anterior chamber was not seen (Figure 4B). Vacuolation of the cytoplasm of the endothelial cells and Descemet's wart formation were noted (Figure 4C). The nuclei of the endothelial cells varied in staining qualities.

Additional histopathologic findings were noted in the sections of the cornea from patient number two. The surface epithelial cells showed small areas of erosion and vesicle formation (Figure 4D). The basal cells of the epithelium were edematous and thick. A thick fibrous pannus was seen between the epithelium and Bowman's membrane and a large break in Bowman's membrane was also noted. The endothelium was missing in some areas and present in other areas. However; where it was present,

FIGURE 4 *(opposite)*

A. Epithelium is irregular and edematous. Bowman's membrane is thick, irregular, and shows cellular invasion (112×). B. Layering of the endothelium together with cellular pleomorphism is noted. The surface facing the anterior chamber is very irregular (280×). C. The endothelium shows vacuoles. The cell nuclei exhibit variability in size and staining quality. A flat, buried Descemet's wart is noted on extreme left. A large dome shaped "wart" is also noted to the left (112×). D. Edema of the epithelium with small areas of surface erosion and vesicle formation can be seen. A pannus between the epithelium and an irregular Bowman's membrane is visible as is a break in Bowman's membrane (112×). E. Areas where the endothelium is completely absent can be noted. Endothelial cells in various stages of degeneration are seen (160×).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the cell layer was thin and the cells themselves appeared degenerating (Figure 4E).

2. Transmission Electron Microscopic Studies

Immediately after trephining the recipient corneas, the specimens were fixed in cold 2% glutaraldehyde solution in sodium cacodylate buffer for at least 24 hours. The tissue was then post-fixed in 2% osmium tetroxide for 2 hours. The tissue was dehydrated in ethyl alcohol and propylene oxide and treated with an epon propylene oxide mixture overnight. The tissue was flat-imbedded in epoxy resin and thin sections were cut on a LKB ultramicrotome III and stained with uranylacetate and lead citrate. The specimens were examined in a Forg-Flo 4° centigrade electron microscope.

Study of the specimens showed Bowman's layer to be infiltrated with lymphocytes (Figure 5), and contained particles whose appearance is consistent with calcium (Figure 6). The basement membrane of the epithelium was irregular and exhibited peduncular excrescences extending into the basal epithelium. In some areas, the basement membrane was thick while in other areas it was sparse and nearly absent.

The endothelium had fewer mitochondria per unit area of section and some mitochondria were undergoing degeneration (Figure 7). Myriads of desmosomes were apparent and masses of intracytoplasmic filaments filled the cell bodies. Elevation of the cell apices is not characteristic of corneal endothelium, but is more characteristic of basal cell epithelium.[52] The presence of extraordinarily large numbers of microvilli was a constant finding in this study (Figures 7, 8) and stacking up of endothelial cells with the irregularity of the cells' surface facing the anterior chamber was a notable finding (Figure 8). Variation of cell cytoplasm density was also seen (Figure 9). Areas where the endothelium and Descemet's membrane were missing corresponded to the point of circumscribed posterior keratoconus. In this area the stroma which was exposed to the anterior chamber showed great disorganization of the collagen fibrils which were coarse and irregular (Figure 10).

Descemet's membrane was separated from the abnormal endothelium by layers which were distinctly abnormal (Figure 11). Descemet's membrane exhibited the normal banded area,[38,39] but the non-banded layer was narrow and less homogenous than normal. A distinct demarcation line between Descemet's membrane and abnormal membrane existed. The abnormal membrane was stratified into a number of layers of basement membrane which rested in a milieu of abnormal collagen fibrils.

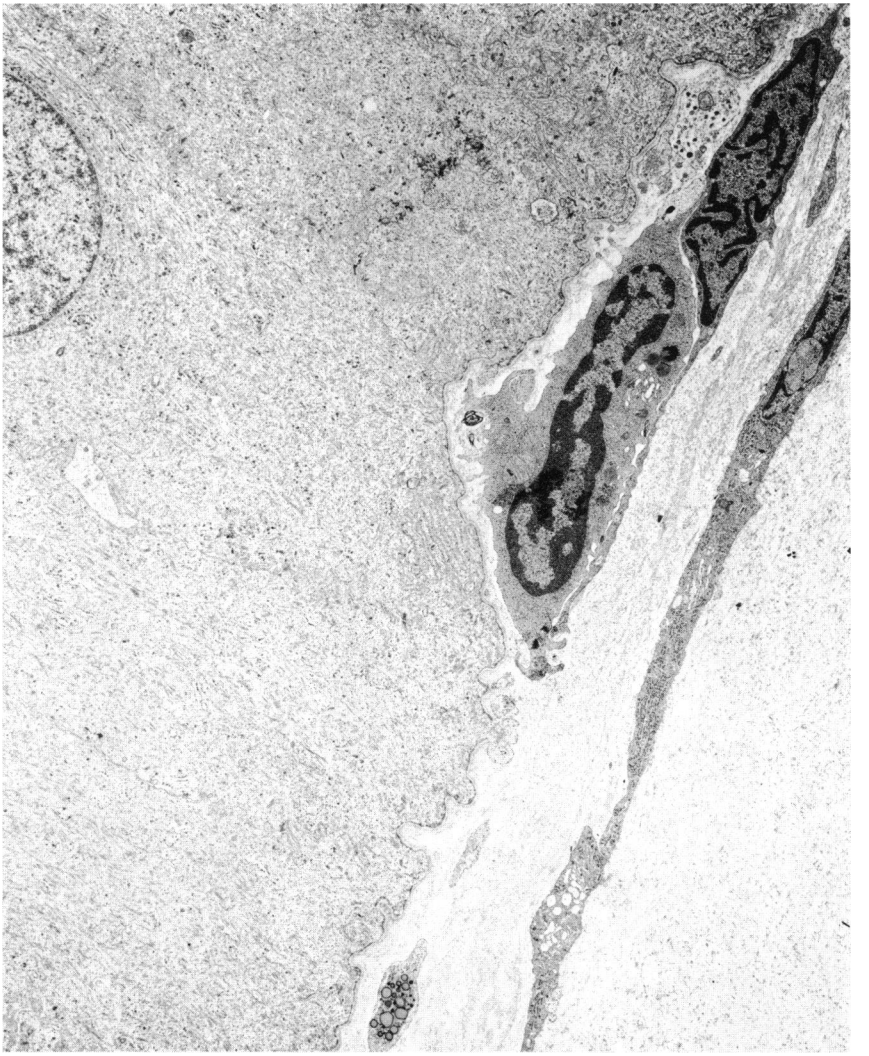


FIGURE 5
An invasion of Bowman's layer with lymphocytes is seen (4437×).

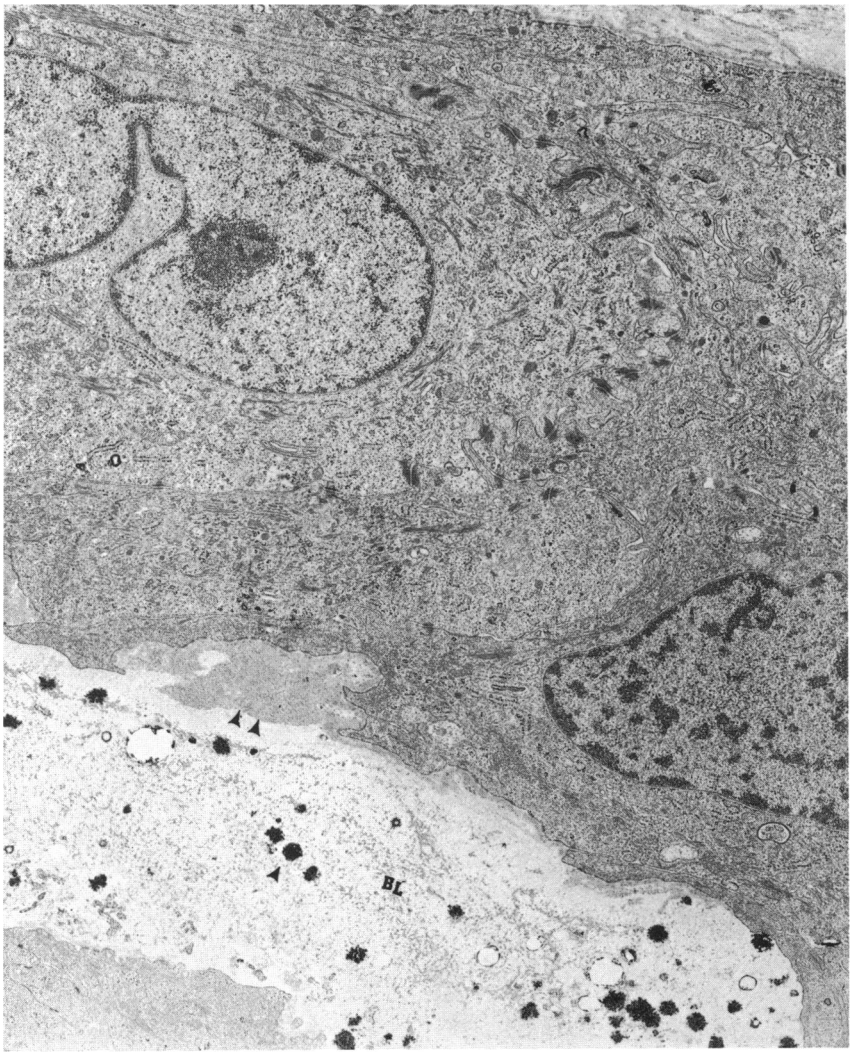


FIGURE 6

Irregular thickening of the basement membrane (double arrow) of the epithelium is present. Calcium deposits (single arrow) are noted in Bowman's layer (B.L.). Note the normal presence of many desomosomes and cytoplasmic filaments in the epithelial cells (8,714.5×).

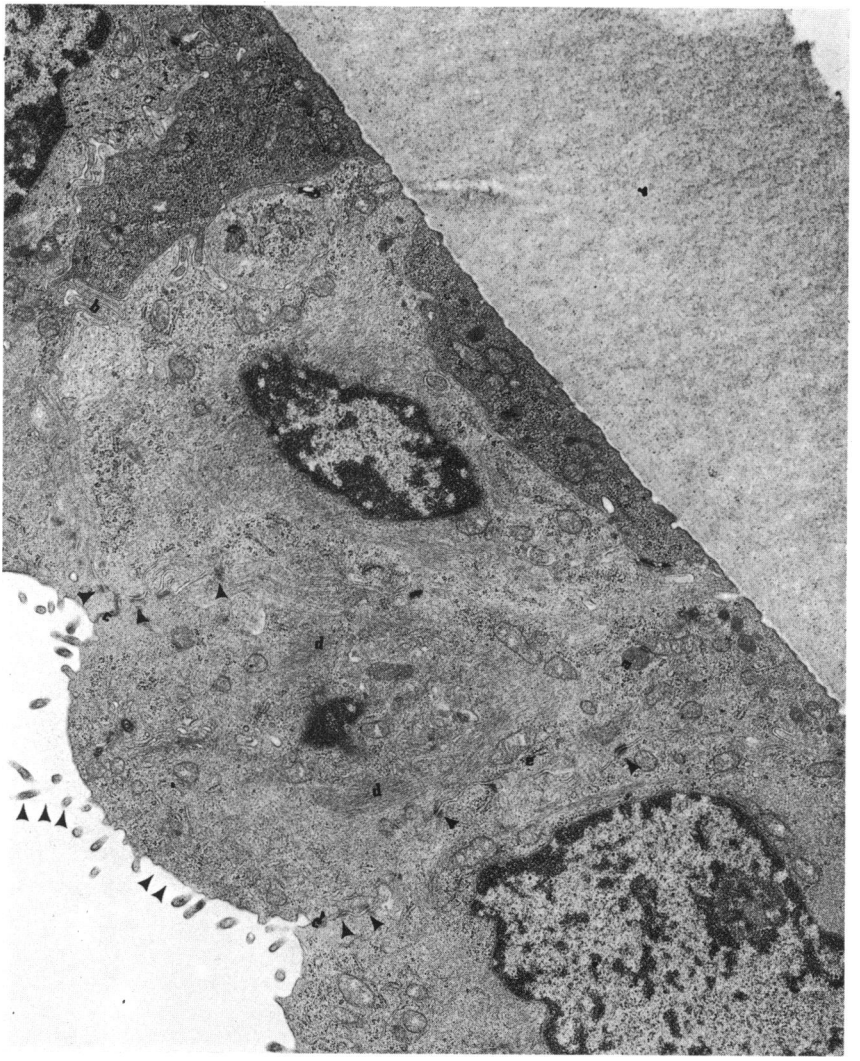


FIGURE 7

Mitochondria are few and those present are degenerating (a). The elevation of the cell apices is characteristic of the basal cell of epithelium (double arrow). Desmosomes (single arrows) are abundant and microvilli are numerous (triple arrow). Extensive interdigitation between cells (b) and zonulae occludentes are noted (c). Intracytoplasmic filaments are extensive (d). Elongated endoplasmic reticulum is seen (e). No terminal web area is noted (8,714.5×).

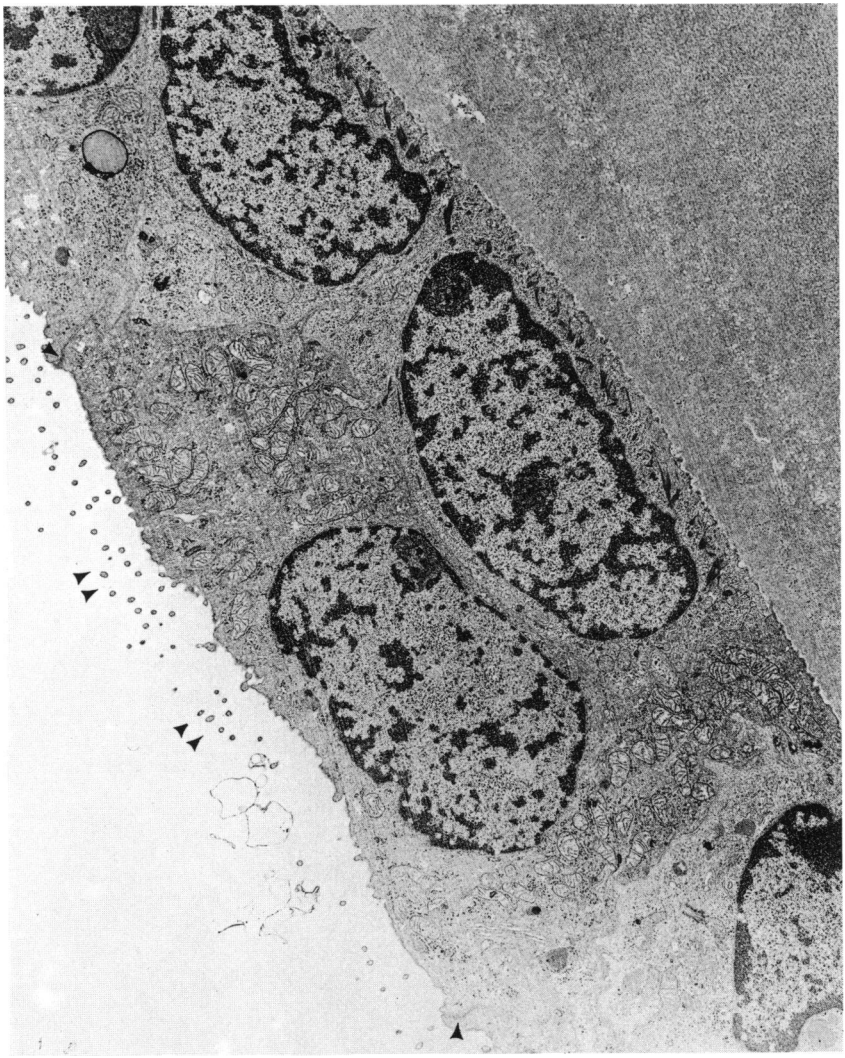


FIGURE 8
Stacking up of endothelial cells and many microvilli (double arrow) are notable. Zonulae occludentes is seen showing long dense attachments between cells on the anterior chamber surface (single arrow) (6,394.5×).

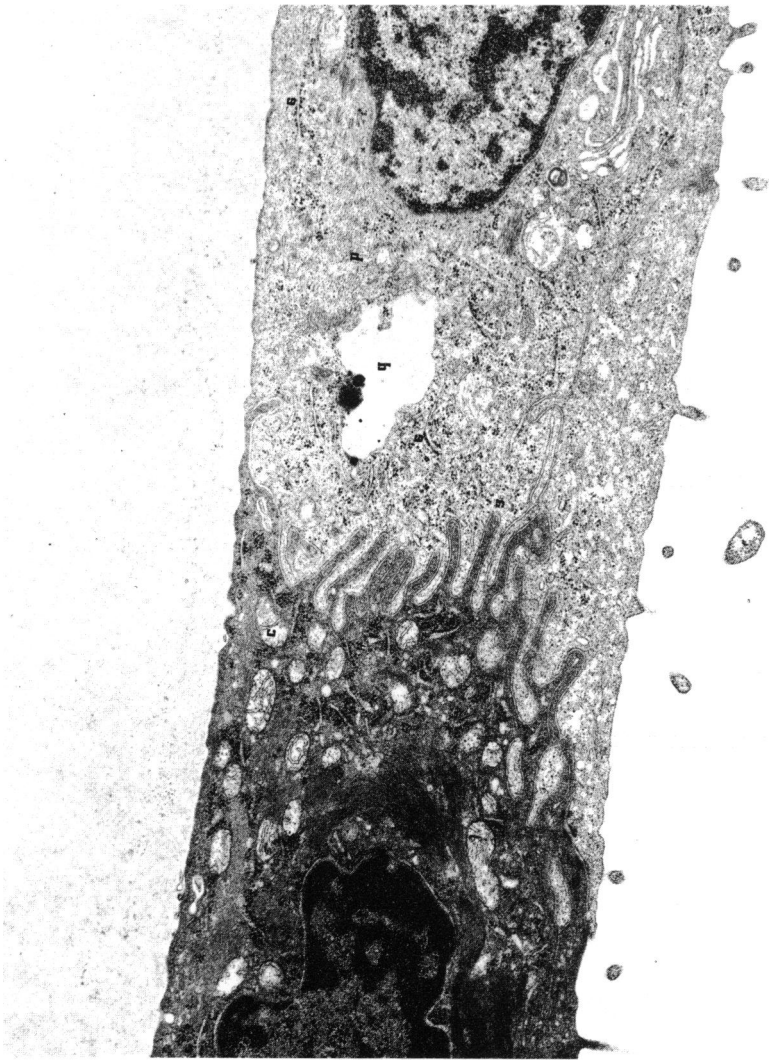


FIGURE 9
Interdigitation of cell walls is seen in normal endothelium (a). Intracytoplasmic filaments (b), degenerating mitochondria (c) and vacuolization of cytoplasm (d) and varying cellular density are noted. Abundant elongated endoplasmic reticulum is seen (e), (12,093×).

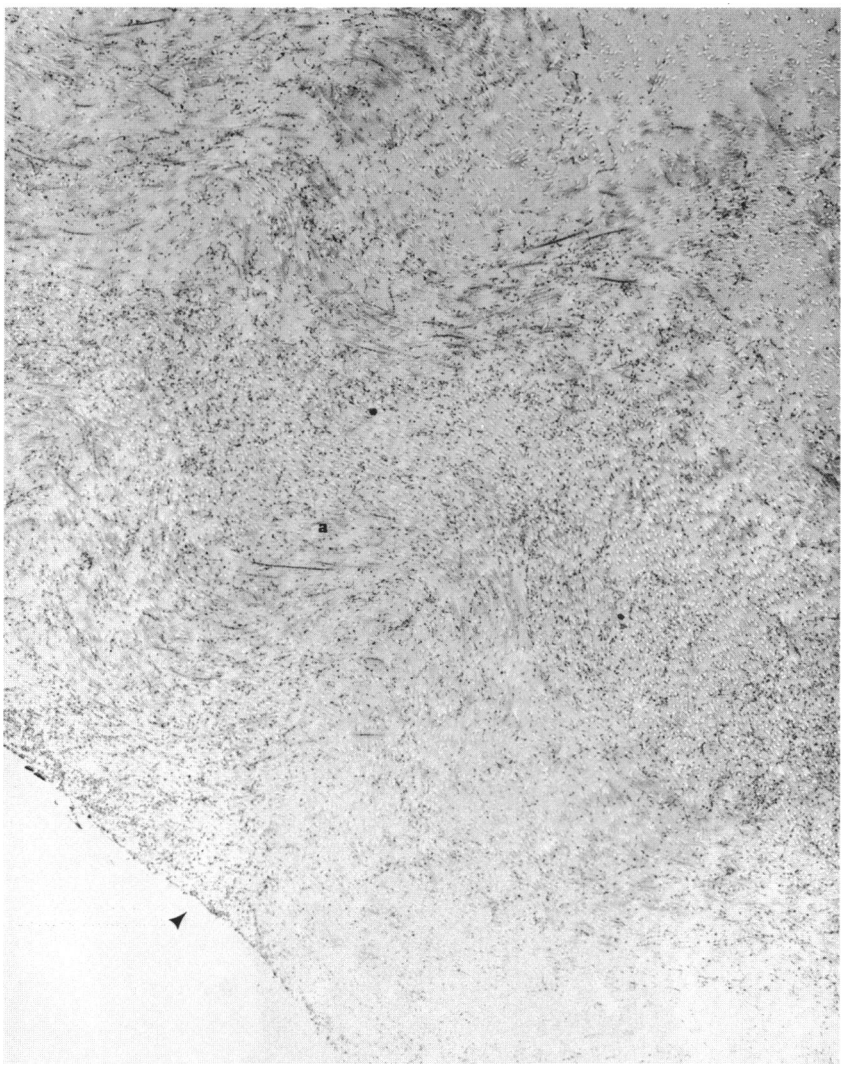


FIGURE 10
No Descemet's membrane or posterior cell layer is seen. The stoma directly borders on the anterior chamber (single arrow). Marked disorganization of the collagen fibers of the stroma resembles that seen in anterior keratoconus (8,714.5×).

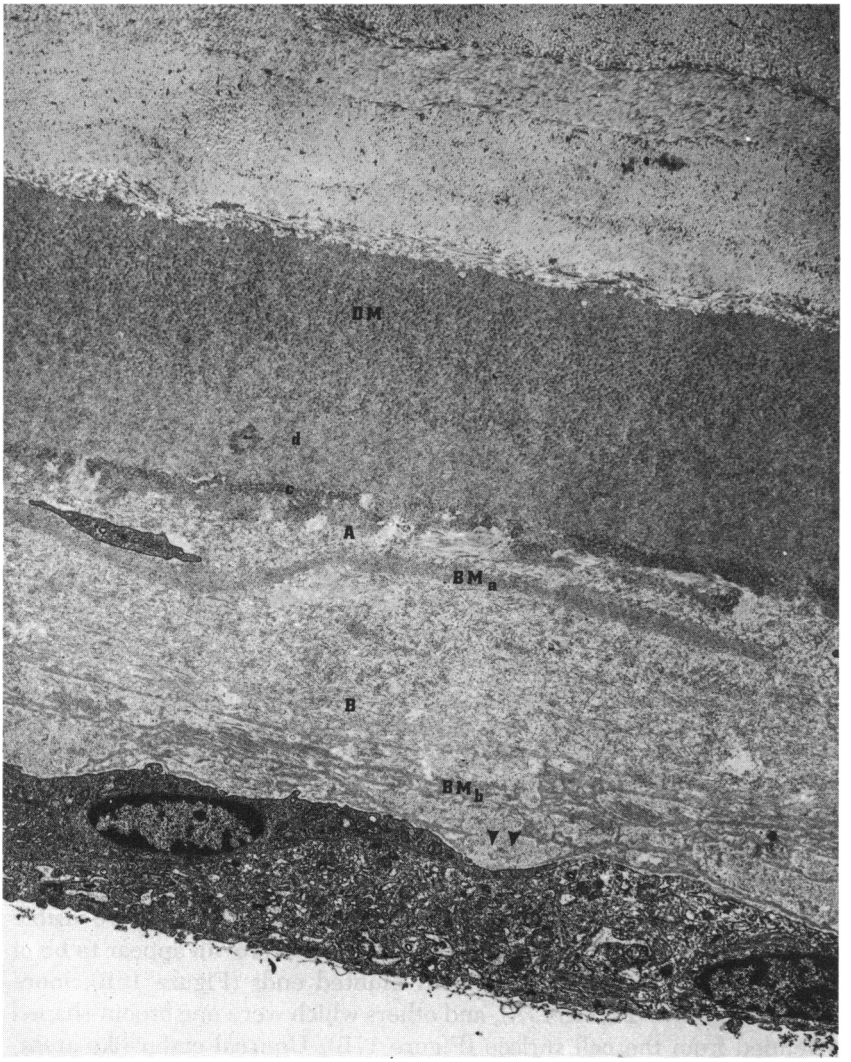


FIGURE 11

Abnormal membrane has been laid down in layers A and B. The abnormal membrane consists of collagen fibers and laminated areas of basement membrane (BM_a and BM_b). A demarcation line (c) is visible. BM_a separates collagen fiber layers A and B. The double arrows indicate areas where indentations are made into the posterior cellular layer, possible representing early guttate lesions. Descemet's membrane shows a narrow non-banded zone (6,394.5×).

Descemet's membrane was separated from basement membrane layer (BM_a) by a layer of collagen fibers; some of the latter consisted of long spaced spindle fibers. Basement layer (BM_b) was separated from BM_a by a wide area of collagen fibrils which were dispersed in a disorganized array. There were small diameter collagen fibers in cross and longitudinal section and long spacing spindle fibers (Figures 11, 12). The latter fibers are also seen in Hassall-Henle bodies[38] in new regenerative Descemet's membrane[37] and pathologic Descemet's membrane.[32,53] Extensions of the collagen layer into the posterior cellular area suggests the formation of early guttate lesions (Figure 11). It has been stated that newly formed basement membrane exhibits similarities to Descemet's membrane.[54]

The presence of dying cells on the posterior membrane is noted in (Figure 13) and this finding is rather significant in that it indicates a progressive degenerative process which reflects the progressive picture of the corneal pathology seen in successive generations of this family.

3. Scanning Electron-Microscopy

The tissue was prepared for scanning electron microscopy according to the technique of Cleveland and Schneider.[55]

The features of scanning electron-microscopy of the normal endothelium are seen in Figure 14 and its features are described under the discussion section of this paper.

Scanning electron-microscopy of the endothelium of the diseased cornea from our patients demonstrated a straightness of all cell borders (Figure 15A). The zigzag cell borders that are noted in normal endothelium were not seen. The cell borders of the diseased cells appeared to be made up of concentrations and aggregations of microvilli (Figures 15A, 15B). The unusual abundance of microvilli was a very striking finding and one which certainly is not seen on the normal endothelial surface. Long serpiginous folds which represent microplicae were visible (Figure 16A), but no border bars present. The microvilli appear to be of three types: long slender ones with blunted ends (Figure 16B), more filamentous ones (Figure 17A), and others which were mushroom-shaped extended from the cell surface (Figure 17B). Unusual crater-like areas, some large and some small, were scattered throughout the surface of the endothelial cell (Figure 18A). The rim of the larger craters showed a heaping up of tissue and an increased density. Collapse of cells, bunching up of the nuclei, and multi-nucleated cells were also features of the diseased endothelium (Figure 18B).

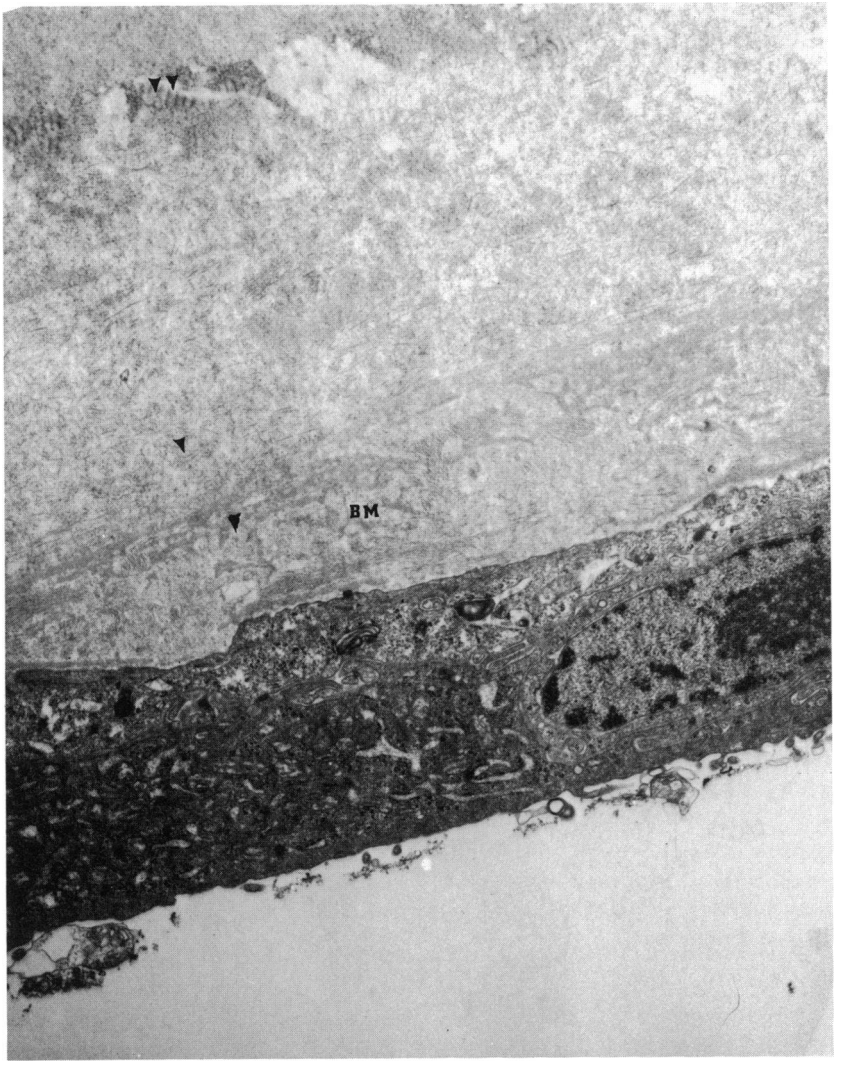


FIGURE 12
The abnormal basement membrane shows small-diameter collagen fibers in cross and longitudinal section (single arrow). Long spaced spindle fibers are also noted (double arrow). Basement membrane is present in multi-layers (B.M.), (12,093×).

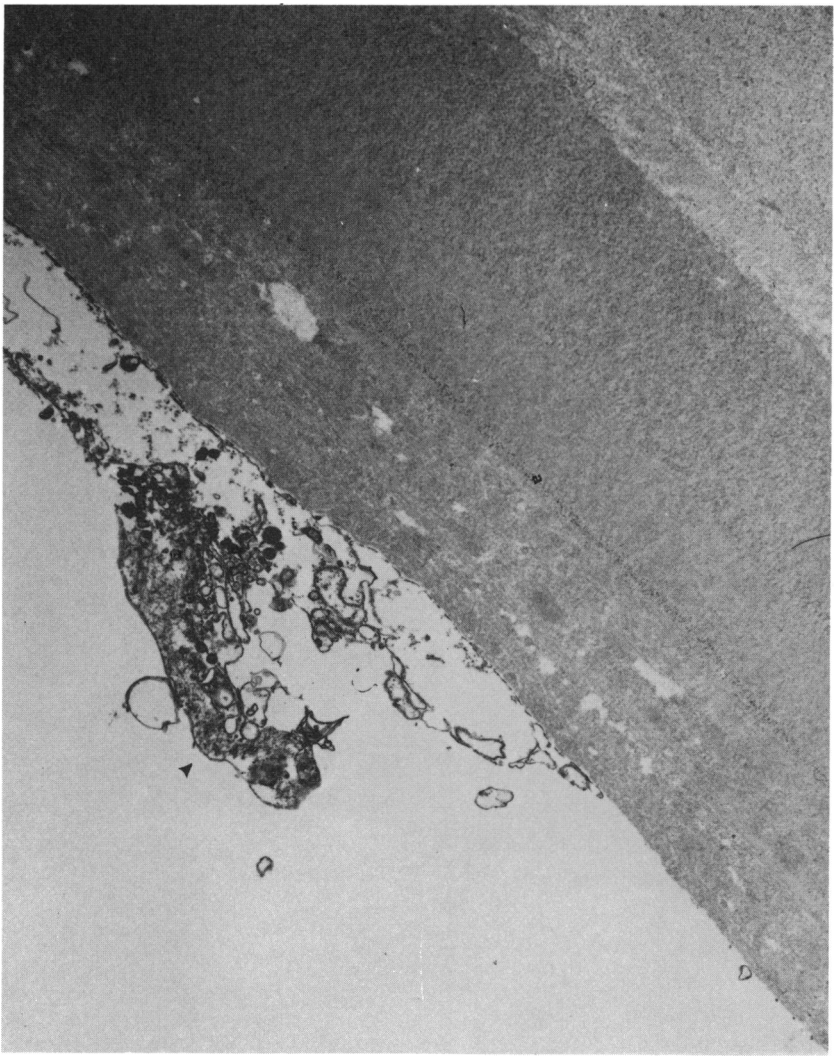


FIGURE 13
The presence of dying endothelial cells is noted (single arrow).

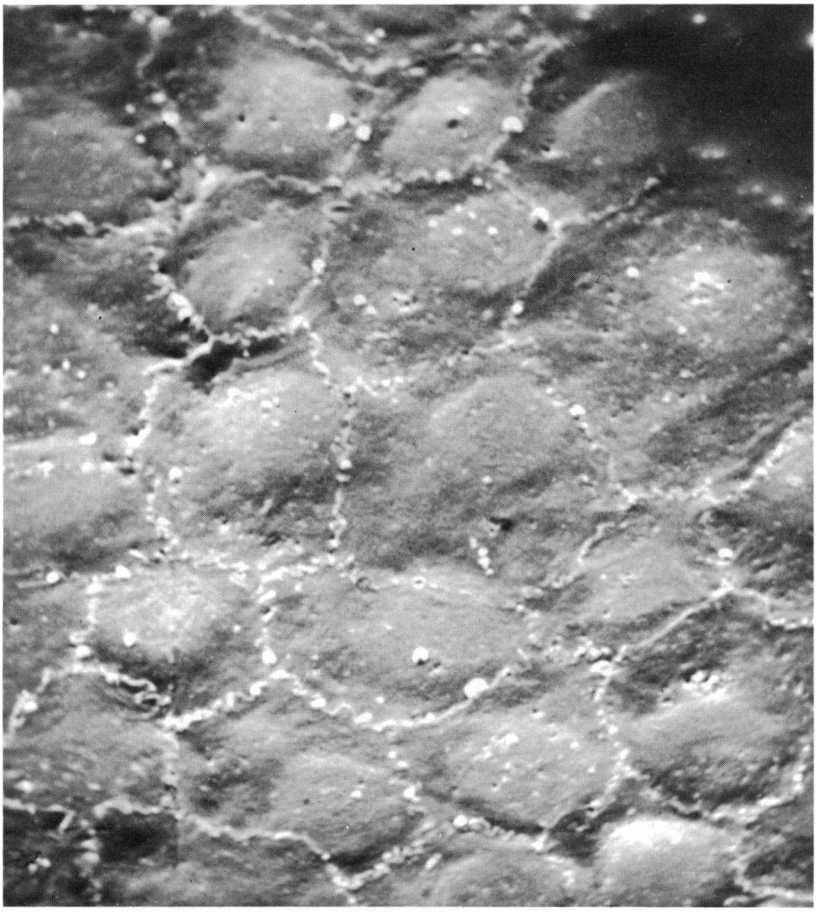
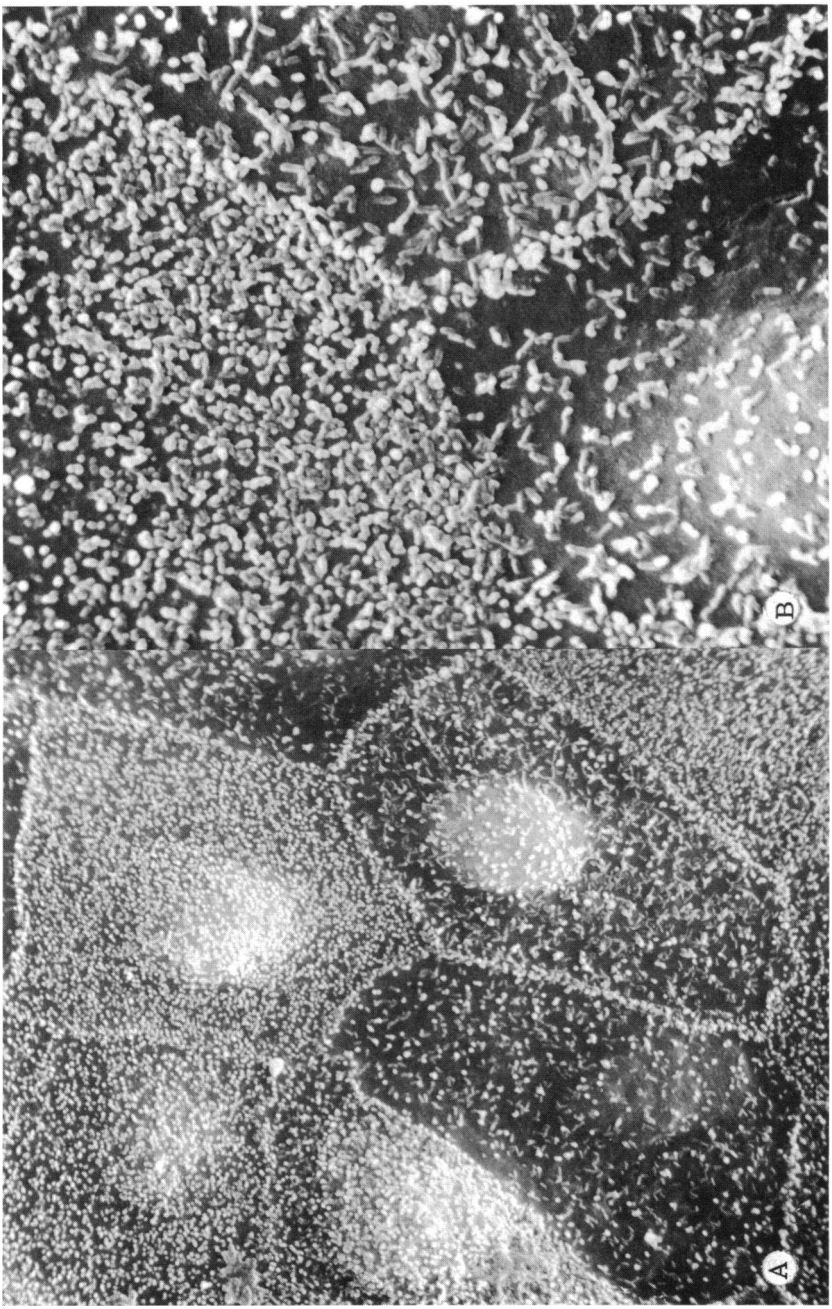


FIGURE 14
Scanning electron photomicrograph of normal endothelium shows orderly arrangement of hexagonal cells, few microvilli and zig-zag cell border outlines. Small pinocytotic openings and occasional cilia are noted (1,116×).

FIGURE 15 *(overleaf)*
A. Scanning electron microscopic photographs of the diseased endothelium of the cornea shows profusion of microvilli and prominent nuclei. The cells are separated by orderly arrangements of microvilli (1,580×). B. The endothelial cell border appears to be made up of concentrations of microvilli (3,950×).


B
A

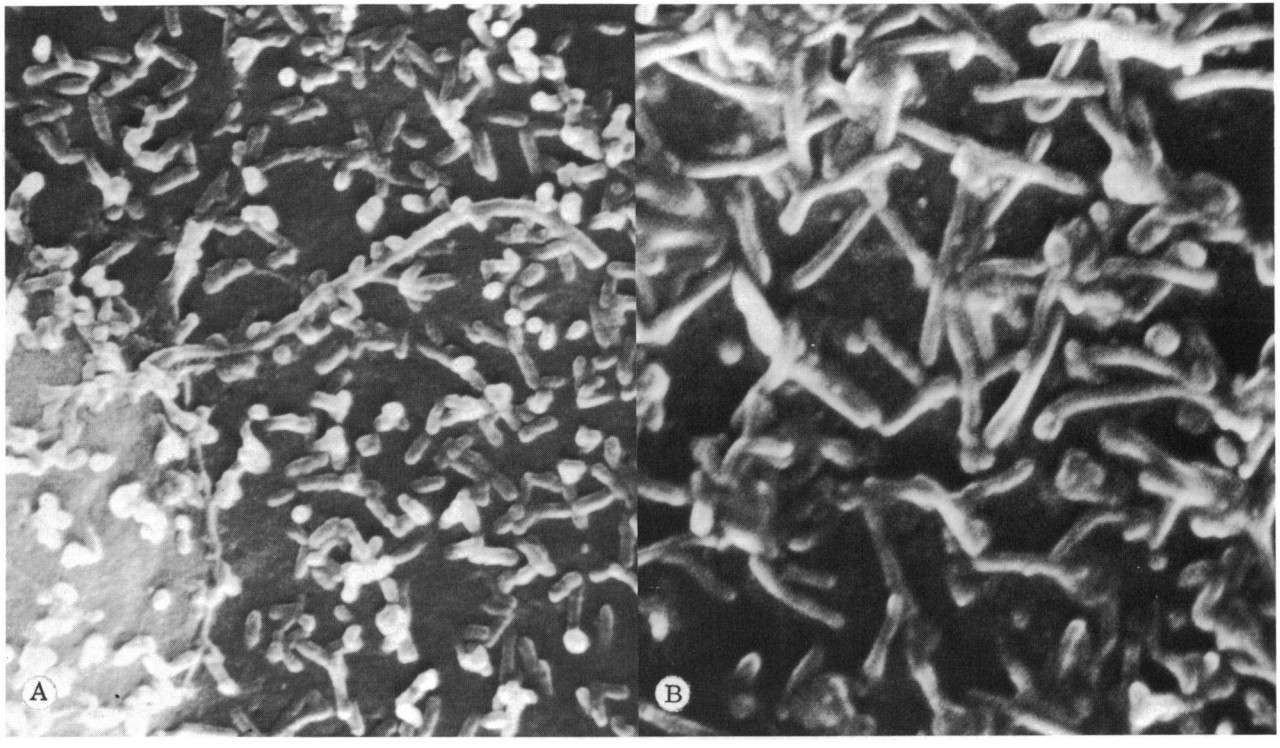


FIGURE 16

A. Long, serpiginous microplicae can be seen traversing the endothelial cell surface (7,900×). B. Scanning electron microscopy reveals the presence of long, slender microvilli with blunted ends (7,900×).

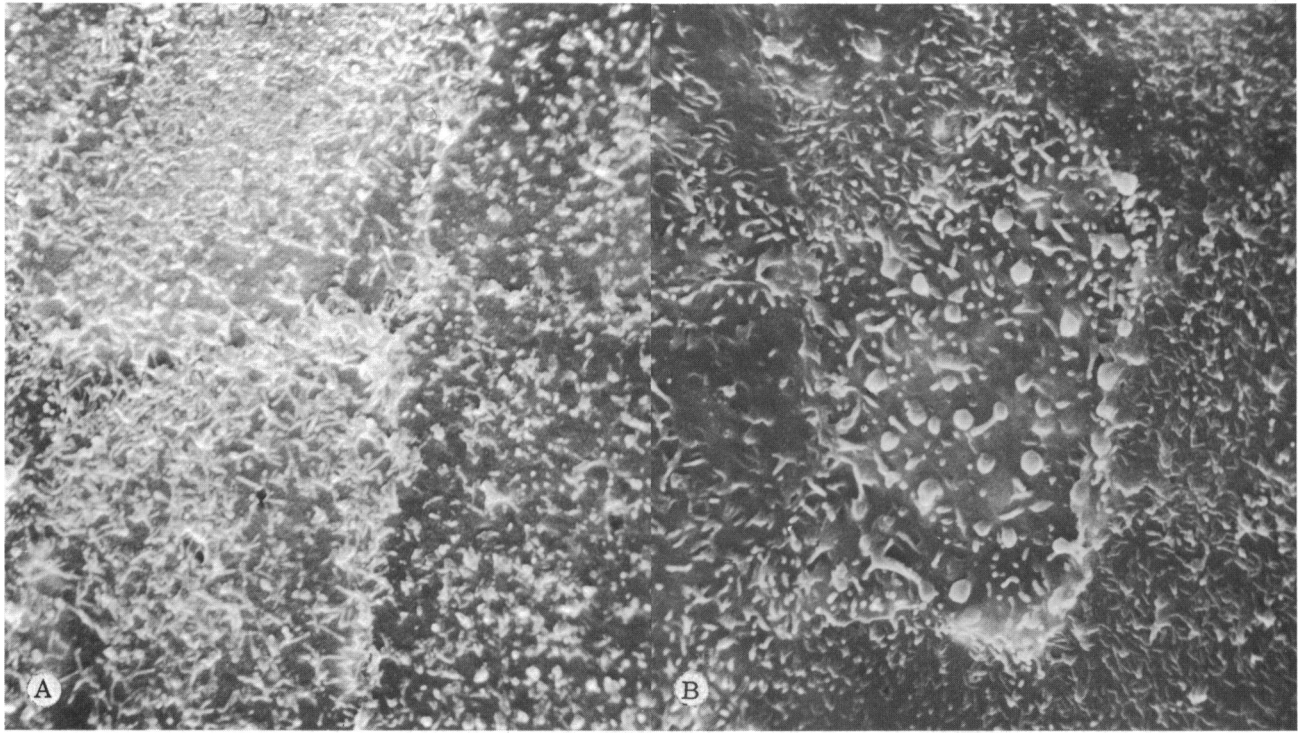


FIGURE 17

A. Filamentous microvilli are noted to be in profusion in several areas (2,370×). B. Mushroom-shaped microvilli are prominent on the surface of some endothelial cells (5,135×).

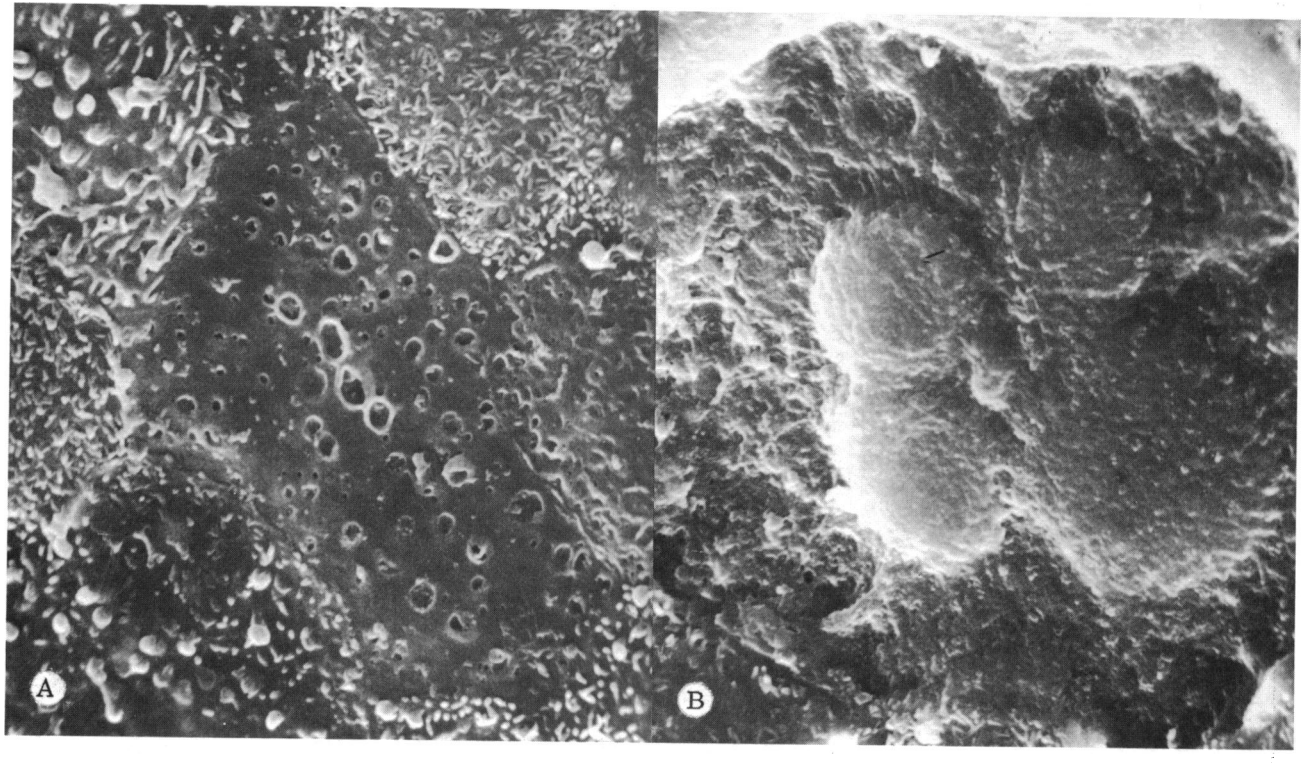


FIGURE 18

A. Large craters and pits are noted on the endothelial surface (5,135×). B. Scanning photos of collapsed and multi-nucleated cells (5,135×).

DISCUSSION

Figure 1C diagrammatically exhibits the spectrum of corneal change of deep polymorphous dystrophy. The bleb-like lesions are characteristic of the clinical appearance of this condition.[5-19] Macular or flat, gray-white opacities (Figure 1A) are frequently noted. Larger gray-white geographic opacities which are sinuous in outline are also seen (Figure 1C). In addition to these changes, corneal guttate lesions were organized in clusters although guttate changes are not included in the classical description of deep posterior polymorphous dystrophy. There was involvement of the epithelium and Bowman's layer in addition to the pathology of the posterior cellular membrane. This is not noted in the ordinary case of deep posterior polymorphous dystrophy.

The question as to whether or not deep posterior polymorphous dystrophy is progressive and how much the visual acuity is affected, depends on the presence and extent of the disease of the posterior and anterior corneal membrane areas, the degree of mesodermal dysgenesis, and the status of the intraocular pressure when these changes accompany the corneal dystrophy.

The transmission electron-microscopic appearance of the normal endothelial cell exhibits pinocytotic vesicles on the anterior and posterior borders. About 20-30 microvilli per cell can be noted extending into the anterior chamber.[50] The cells are joined together by zonula occludens and macula occludens but no true desmosomes are seen.[52,51] Zonulae occludentes join the cells near the anterior chamber[51] and maculae occludentes are seen along the anterior two-thirds of the lateral cell membrane.[51] Interdigitation of cell borders is prominent and there is a rich array of organelles.[50] Mitochondria are abundant.[50] Smooth and rough endoplasmic reticulum and a well developed Golgi apparatus are noted.[50] Ciliary processes are occasionally seen projecting into the anterior chamber.[50] Intracytoplasmic filaments are not normally seen.[38,39] A terminal web layer is visible.[50]

Svedbergh and Bill[56] in 1972 studied normal human corneal endothelium with scanning electron-microscopy and divided the cornea into four separate zones. The central zone was designated as Zone I and the area just adjacent to it as Zone II. Zones III and IV are not considered here since they are beyond the area of the cornea concerned in an 8.0 mm trephine section. Svedbergh and Bill[56] noted that in Zone I the posterior cells were hexagonal and only occasionally pentagonal. The nuclei were flat and bulged on the cell surface. Cell borders zigzagged and at various intervals along their borders "stick-like" structures crossed at right an-

gles. These structure are referred to as border bars.[55] The presence of centrally located ciliary proscesses[56] which extended into the anterior chamber was noted and they were abundant in Zone II. The ciliary proscesses had basal cuffs and club-like tips. Microvilli were observed in limited quantities. A few small pits which faced the anterior chamber represented pinocytotic vesicles.[57] Wolf[58] described depressed circular pit-like islets on the endothelial surface of the cornea but their significance was not clarified.

The scanning electron-microscopic study of the normal endothelium of a 19-year-old male is demonstrated in Figure 15A. Orderly well demarcated zigzag cell borders, occasional microvilli, blunt end ciliary proscesses, and pinocytotic opening on the cell surface are clearly seen. No border bars described by Svedbergh and Bill[56] are seen.

The scanning electron-microscopic picture of the normal epithelial surface demonstrates a regular, sharp arrangement of hexagonal cells with precise straight borders.[59] The nuclei are prominent, circular in contour and lie in the middle of the cell. The cell borders show a marked prominence due to densely arranged microvilli and microplicae. The abundance of microvilli and presence of prominent nuclei are characteristic epithelial features on scanning electron-microscopy.

On studying the scanning electron-microscopic alterations of the endothelium seen in our specimen one notes, in addition to the myriads of microvilli, several different types of microvilli. Long, slender, blunt-ended villi (Figure 17A) and filamentous villi (Figure 17B) are seen. Mushroom shaped microvilli (Figure 18A) are also seen. The cell borders are straight and appear to be made up of rows of microvilli. Large crater-like pits and smaller pits are seen on the endothelial cell surface. These craters give the cell surface the appearance of a slice of Swiss cheese. The holes exhibit elevated and well demarcated rims (Figure 18B). The finding of these villi and holes have not been previously stressed in deep polymorphous dystrophy. It should be noted that epithelial cells show many microvilli on their surfaces; however, metaplasia of the cells of the posterior membrane can also account for these peculiar findings.

Polack[60] when studying the scanning electron-microscopy of corneal graft rejection, noted a rejection line characterized by areas of epithelial disorganization, pits, craters, and deposition of debris on the epithelial surface. When referring to the endothelium he described craters and pits on its surface. Polack[60] also demonstrated cell shrinkage and multilayering of the cells in the areas of destruction due to corneal graft rejection, in addition to the pits and craters on the endothelium. Similar alterations in

our cases of deep polymorphous dystrophy are seen. The multilayering of cells may account for the biomicroscopic appearance of deep polymorphous dystrophy. It appears, therefore, that the extensive alterations in the posterior cell membrane seen in the corneal specimens of our patients can resemble damage to these cells due to diverse causes. In Polack's case it was a graft rejection phenomenon and in our cases it was a genetically derived stimulus.

Some endothelial cells were multinucleated and others showed collapse of the cell bodies. Multinucleated endothelial cells, also seen in Fuchs' corneal dystrophy, were described by Kaufman, Capella, and Robbins.[61] The multinucleated cells exhibited collapse of the cell bodies. This finding could very well account for the translucency and irregularity of the endothelial surface seen in our patients when studied with the biomicroscope.

There have been reports in the literature that refer to the endothelium of the cornea as mesothelium,[62,63,64] and state that the customary use of the term "endothelium" in ophthalmology is inaccurate and misleading. True endothelium in essence, it is stated, lines blood-filled or lymphatic channels.[52] The endothelial cells form tubes, and do not form sheets of cells as are seen on the posterior surface of the cornea. Endothelial cells have minute windows and the shape of the cell is irregular and extremely thin in areas away from the nucleus. The endothelial layer of the cornea does not line a vascular channel; the cells do not have minute fenestrae and are extremely regular in size; therefore, it can be said that no true endothelial cells are present in the cornea. The cells on the back surface of the cornea resemble the cells that line body cavities such as the pleura and peritoneum.[64] These cells are derived from paraxial mesoderm, and are mesothelium or mesenchymal epithelium in nature.[51,64] Verhoeff[65] was presented with the question of the nature of the endothelium and he stated that the reason "endothelium" is enclosed in quotation marks in his discussion is because it is not truly endothelium. It has been stated that mesothelia frequently are considered to possess the ability to readily undergo metaplasia to fibroblasts; a property that is not widely attributed to true endothelia.[52] If such is the case, then the concept becomes acceptable that this layer of cells can produce either pathologic or normal connective tissue membranes. On this basis, the peculiar changes observed in Fuchs' endothelial dystrophy, congenital hereditary edema, deep polymorphous corneal dystrophy, retrocorneal membrane formation in unsuccessful grafts following immune graft reactions, alkali burns, and cryoprobe application to the rabbit cornea can be more readily explained. The cells of the posterior cell membrane surface, seen in the

electron-microscopic studies in our cases, indeed have characteristics of fibroblasts and in all probability are fibroblasts or fibroblast-like cells.

These fibroblast-like cells show a paucity of mitochondria while the normal endothelial cells are quite active metabolically and possess an abundant amount of mitochondria. The normal endothelium does not possess intra-cytoplasmic filaments except in small amounts;[66] however, they can be seen in regenerating endothelium.[67] Terminal bars may be present in the corneal endothelium of man, but typical desmosomes as described by Farquhar and Palade[51] are not found. Lowry[68] has shown that the endothelial cells can proliferate in tissue culture and in doing so they undergo morphological differentiation which is more advanced than that found in normal conditions. Structures such as true desmosomes and epithelial filaments which are seen in situ in corneal endothelium are characteristic of highly differentiated epithelia in other anatomic sites.[51] There is an adaptive change to changes in the environment and an ability to develop more advanced structures. This in *vitro* change can be compared to the morphological changes seen in the endothelium of the cases presented and in other pathological conditions where desmosomes and many intracytoplasmic filaments are found.[67]

These points are emphasized because it is conceivable that the changes in the posterior membrane area in hereditary corneal edema,[36,37] posterior polymorphous dystrophy,[38] graft rejection, and retrocorneal membrane formation[40,60] are due to alterations in the mesothelial cells which have been adversely affected so as to alter their morphology and function and result in the changes described. The presence of abundant microvilli and intracytoplasmic filaments, and the sparsity or organelles indicate a change in the nature and function of the posterior cells. Thus the basic factor and common denominator in all these conditions is the change in the character of the posterior cellular layer of the cornea. There are similar pathological posterior corneal alterations in other disease entities. The severity of the corneal disease and the characteristics of the accessory Descemet's membrane or basement membrane will depend on the nature of the exciting agent or agents, the degree of severity of the insult, and the length of time of exposure to the insult.

Iwamoto and DeVoe[66] demonstrated by electron-microscopic studies of the posterior corneal cell that there were two types of cells in Fuchs' combined dystrophy. The type I cell had cytoplasmic filaments, increased rough endoplasmic reticulum, and cytoplasmic filaments simulating fibroblasts. The type II cell had elongated endoplasmic reticulum and lysosome within a less dense cytoplasm and it was probably a degenerate form of type I. They concluded that the endothelial cell morphology and

function became similar to fibroblasts and that they started producing collagen fibrils and basement membrane-like material. In our studies, cells similar to Iwamoto's and DeVoe's cell type I were found.

In this study, transmission electron-microscopic investigation of hereditary deep polymorphous corneal dystrophy with associated anterior mesodermal dysgenesis showed the posterior cells to contain an abundance of intracytoplasmic filaments, sparsity of an organelle system, and myriads of microvilli and microplicae. The scanning electron-microscopic study revealed severe changes on the posterior surface of the cornea. Ordinarily this surface exhibits few microvilli and hexagonal cells with cell borders made up of wavy junctions (Figure 15A). However, in this study the surface was covered with an abundance of microvilli and microplicae (Figure 15B). These features contributed to the lacklustre appearance of the surface that was noted biomicroscopically in our cases.

Electron-microscopic study of the corneal button in Hogan's and Bietti's[33] case of deep corneal polymorphous disease revealed that the endothelium was either absent or if present it appeared to show degenerative changes. The nuclei were pyknotic, reduced in size, and the cytoplasm appeared unusually dense. Descemet's membrane showed diffuse thickening to 13 μ and Descemet wart formation typical of cornea guttata in many areas. Nodules in the deep stroma contained long eliptical crystals. These were dispersed diffusely throughout the nodule or arranged in rosette-like fashion. The crystals were most numerous at the center of the nodules with fewer crystals toward the periphery. Alizarin red and von Kossa stains were positive for calcium. The corneal stroma exhibited some edema with separation of the layers but there was very little alteration of the collagen fibers. The stromal fibroblasts showed various stages of degeneration but Bowman's membrane and the epithelial basement membrane showed very little change.

The important point to be emphasized by Hogan and Bietti, in addition to finding calcium apatite crystals deep in the cornea resulting in the clinical picture described as deep polymorphous dystrophy, is that this condition may be associated with a systemic metabolic disease. This point was further discussed by Magruder.[24] He speculated that his case, although it did not manifest hypophosphatasia clinically, suggested that an imbalance of calcium metabolism was at fault. Systemic findings such as heterochromia of the eyebrows and lashes,[5] loss of hearing, and vitiligo[10] have been reported by other authors. In our cases, the systemic finding of microdontia was confined to the son of the first patient (Case 1). Although one of the patients had a history of convulsions (Case 2), no apparent connection with the corneal problem could be proven.

The case of deep posterior polymorphous dystrophy reported by Boruchoff and Kuwabara[35] showed extensive areas of broad iris synechia covering the trabeculum; however, the intraocular pressure was normal. A penetrating corneal graft was performed because of the painful bullous keratopathy. Examination of the corneal button showed that Descemet's membrane consisted of a thin layer of strongly PAS-positive membrane anteriorly and a thick layer of lamellated substance posteriorly. The endothelium was irregular in thickness. No guttate changes were found in Descemet's membrane and no abnormal substance was found in the stroma. Electron-microscopic study of the corneal plug revealed the presence of some microvilli and desmosomes. Micro-organelles were sparse, but endoplasmic reticulum and Golgi apparatus were present. They found an abundance of keratofibrils in the cytoplasm. An abnormal membrane was formed between the posterior cell layer and the original Descemet's membrane. The anterior portion of Descemet's membrane was thin, uniform in thickness, and consisted of coarse granular substances. This portion of the membrane was identical to that of the anterior portion of a normal adult Descemet's membrane. The abnormal membrane consisted of irregular layers of fine fibrils, short collagen fibers, and basal lamina substance. The authors stated that they did not see any fibroblastic elements in the posterior cell layer and concluded that the abnormal cells at the posterior surface of the cornea were epithelial cells. This was the first time that the presence of epithelium was suggested to account for the changes in the posterior cellular layer of the cornea in deep posterior polymorphous dystrophy. The anterior segment changes involved broad anterior iris synechiae. In their case, however, the intraocular pressure was normal. Posterior keratoconus was not noted, systemic involvement was not noted, and band keratopathy was not present. Their case represents one belonging to the broad spectrum of changes seen in deep polymorphous dystrophy of the cornea and would be included in type C of Table I.

The 3 year-old son of one of the propositi demonstrated band-shaped keratopathy. This was the youngest patient in this family exhibiting this finding. Calcific keratopathy in an advanced stage was present in the grandmother and in a moderate stage of development in her two sons. Snell and Irwin[16] reported one case of band keratopathy associated with deep posterior polymorphous dystrophy of the cornea. The keratopathy seen in our patients exhibited a spectrum of this finding with the least involvement found in the grandsons, intermediate changes in the sons, and advanced changes in their mother. This is a definite dominant finding in this family.

Table I attempts to clarify the associated findings accompanying deep posterior polymorphous dystrophy. At one end of the spectrum of disease there are no mesodermal defects associated with the dystrophy (type A) while on the other end of the spectrum (types C and D) one finds anterior segment anomalies in varying degrees of severity. The spectrum of findings in our family includes severe anterior mesodermal chamber angle changes, and it should be noted that the major alterations seen in Axenfeld's syndrome,[1] Rieger's anomaly,[1] and Chandler's syndrome[2] are to be seen in type D.

Axenfeld's syndrome[1] is characterized by the findings of posterior embryotoxon, abnormally prominent iris processes, and increased intraocular pressure. Rieger's anomaly[1] is exemplified by the presence of posterior embryotoxon, iris atrophy, corectopia, pseudo-polycoria, abnormally prominent iris processes, congenital anterior synechiae, and glaucoma. Findings of corneal epithelial edema, peripheral irido-corneal attachments, patchy iris atrophy, slightly distorted pupil, glaucoma and cornea guttata are illustrative of Chandler's syndrome.[2] Additional findings seen in our patients were posterior keratoconus, sclerocornea, and band keratopathy. The clinical appearance of deep posterior polymorphous change with calcium deposition in the deep corneal tissues with or without systemic metabolic disease is listed under type E (Table I). Hereditary corneal edema has been included in a separate but important area of Table 1 since there are significant electron-microscopic similarities of the posterior membrane area between this condition and deep polymorphous corneal disease.

Kanai et al[36] described five cases of hereditary corneal edema in the members of one family. Light microscopy revealed intercellular edema of epithelial cells, absence of Bowman's membrane, and disorganized stromal lamellae. Electron microscopy showed extensive changes in the stroma, Descemet's membrane, and endothelium; altered keratocytes, irregularity of the stromal lamellae, and stromal swelling. Descemet's membrane was irregular, undulating, and thin. Between this membrane and the posterior layer there were numerous non-uniform collagen fibers and keratocytes. The endothelium was replaced by cells which were two to three layers in thickness. These cells showed unusual characteristics such as the presence of some microvilli, desmosomes, and cytoplasmic tonofilaments. The posterior cell layers contained some mitochondria, Golgi complex, and rough endoplasmic reticulum. In some instances the cells resembled fibroblasts although the authors thought that there was less rough endoplasmic reticulum than what is usually seen in fibroblasts.

Kanai and Kaufman,[37] in further electron-microscopic studies of

hereditary corneal edema, showed that a number of the endothelial cells were absent and were replaced by a single layer of fibroblastic-like cells. These cells had fewer rough endoplasmic reticulum than that ordinarily seen in typical fibroblasts. Each cell exhibited many microvilli on the face of the anterior chamber and contained an oval shaped nucleus, few mitochondria, distended endoplasmic reticulum, and intracytoplasmic filaments throughout their cytoplasm. Two Descemet's membranes separated by numerous multiformed collagen fibers were described. The second Descemet's membrane had two different banded materials. The first Descemet's membrane lacked the normal non-banded material and demonstrated banded material as described by Jakus.[38,39] The second Descemet's membrane also lacked the true non-banded material. It was felt that the abnormal endothelium apparently produced this abnormal basement membrane substance and the abnormal collagen fibers. Abnormal basement membrane substance and collagen fibers are noted in Figures 22 and 23. The electron-microscopic changes noted in the posterior membrane area of our cases and in hereditary corneal edema appear to show basic similarities.

Kanai, Mustakallio, and Kaufman[40] reported cases of unsuccessful grafts in hereditary corneal edema which on electron-microscopic study revealed the endothelium to be layered with a few organelles of varying cytoplasmic density, endoplasmic reticulum, and intramitochondrial inclusion bodies. In another one of their cases they noted intraendothelial invasions of leukocytes, monocytes, fibroblasts, cells with moderate amounts of mitochondria, some endoplasmic reticulum, flocculent filaments, and Golgi complexes. Some microvilli were seen. In some mitochondria, a moderate amount of rough endoplasmic reticulum and dense granules were noted. There were layers of basement membrane-like material in the retrocorneal membrane. It can be seen from these electron-microscopic studies that the posterior layer cells exhibit findings in common with the conditions described by these authors and with our cases of deep posterior polymorphous dystrophy.

Michels, Kenyon, and Maumenee[41] produced a retrocorneal membrane by injuring the endothelium of the rabbit with transcorneal freezing and anterior segment inflammation. Descemet's membrane was said to be intact and therefore excluding the stromal fibroblast from retrocorneal activity. It was once thought to be of host origin.[42] The retrocorneal membrane contained cellular and extracellular products of small diameter collagen fibers interspersed with fine filaments and basement membrane-like substance. Here again, the findings of fine filaments and basement membrane substance were similar to those found in our

cases of deep posterior polymorphous dystrophy of the cornea.

Maruyama[43] demonstrated fibroblast-like cells in retrocorneal membrane which formed as a result of alkali injury to the cornea.

Changes in the endothelium and in Descemet's membrane may occur from a number of different causes. I believe that the alterations in the posterior membrane area noted in my cases are due to a faulty cleavage mechanism of the anterior chamber.[4] The insult sustained by the endothelium from faulty chamber formation may be enough to result in the metaplastic alteration previously described. The similarity of the altered cells to fibroblasts is convincing and the speculation that these cells are epithelial is less likely.

SUMMARY

This paper presents a study of three generations of a family with changes in the anterior segment of the eye, deep posterior polymorphous changes of the cornea, iris atrophy, iris synechiae, abnormal iris processes, corectopia, prominent ring of Schwalbe, open angle glaucoma, circumscribed posterior keratoconus, corneal edema, cornea guttata, scleral cornea, and band-keratopathy. In addition, microdontia was found in one patient. Clinical genetic, biochemical, light microscopy, transmission electron-microscopy and scanning electron-microscopy methods were used to investigate these cases. Current evidence seems to implicate a hereditary mal-formative problem occurring on the posterior surface of the cornea bordering the anterior chamber and chamber angle. Some investigators have speculated that cells found on the posterior surfaces were deposited there during embryologic development or shortly thereafter.[35] However, the more likely explanation is that a true metaplasia of endothelium into fibroblast-like cells has occurred. Similar appearing cells on the posterior corneal layer have been noted in other situations such as an immunological insult, trauma, inflammations, and hereditary corneal diseases. Although an isochromosome six was seen in Rieger's anomaly, none was found in these cases which presented all the features of this syndrome.

The association of deep posterior polymorphous dystrophy with dysgenesis of the anterior segment, band-keratopathy, posterior circumscribed, sclerocornea and glaucoma can cause marked decrease in vision. It is a progressive disease and can be associated with systemic findings. Fortunately, despite the alterations in the anterior segment anatomy, penetrating keratoplasty can be performed successfully in some of these patients.

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REFERENCES

1. Alkemade PPH: *Dysgenesis Mesodermalis of the Iris and the Cornea.* Springfield, Illinois. Charles C. Thomas Publisher, 1969.
2. Chandler PA, Grant WM: *Lectures on Glaucoma.* Philadelphia, Lea & Febiger Publisher, 1965.
3. Haney WP, Falls HF: The occurrence of congenital keratoconus posticus circumscriptus (in two siblings presenting a previously unrecognized syndrom). *Am J Ophthalmol* 52:52, 1961.
4. Reese AB, Ellsworth RM: *Anterior Cleavage Syndrome* (Chicago) 75:307, 1963.
5. Bergman GD: Posterior polymorphous degeneration of the cornea. *Am J Ophthalmol* 58:125, 1964.
6. Bucci MG: Su un caso di distrofia poliforma grovanile dell'endotelio corneale. *Boll Ocul* 39:384, 1960.
7. Forni S:Dégénérescence polymorphe familiale de la membrane limitante posterieure de la cornée. *Arch Ophthalmol* 11:162, 1951.
8. Fruedenthal E: Ueber zwei Fälle von familiärer endotheldystrophie der Hornhaut bei Vorhandensein allegemein degenerativer Veränderungen. *Augenheilkd* 78:244, 1932.
9. Hanselmayer H: Zur histopathologie der hinteren polymorphen Hornhautdystropie nach Schlichting. I Lichtmikroskopische befunde in beziehung zum klinischen bild. *Albrecht von Graefes Arch Klin Ophthalmol* 345, 1972.
10. Kneusel O: Ueber narben und Bläschenartige gebilde auf der Hornhautrückfläche. *Klin Monatsbl Augenheilkd* 75:318, 1925.
11. Koeppe L: Klinische Beobachtungen mit der lampe und dem Hornhautmikroskop. *Albrecht von Graefes Arch Klin Ophthalmol* 91:363, 1916.
12. Kwedar EW: Hereditary non-progressive deep corneal dystrophy. *Arch Ophthalmol* 65:127, 1961.
13. McGee HB, Falls HG: Hereditary polymorphous deep degeneration of the cornea. *Arch Ophthalmol* 50:462, 1953.
14. Pietruschka G: Uber eine familiäre endotheldystrophie der Hornhaut (in kombination mit glaukon, vitiligo und otosklerose). *Klin Monatsbl Augenkeilkd* 136:794, 1960.
15. Schlichting H: Blasen und dellenförmige endotheldystrophie der Hornhaut. *Klin Monatsbl Augenheilkd* 107:425, 1941.
16. Snell AC, Irwin ES: Hereditary deep dystrophy of the cornea. *Am J Ophthalmol* 45:636, 1958.
17. Soukup F: Polymorfní zadní degenerace. *Rohovky Cesk Oftalmol* 20:181, 1964.
18. Theodore FH: Congenital type of endothelial dystrophy. *Arch Opthalmol* 21:626, 1939.
19. Treibenstein O: Veränderung an der Hornhauthinterfläche. *Klin Monatsbl Augenheilkd* 74:777, 1925.
20. Berliner ML: *Biomicroscopy of the Eye: Slit Lamp Microscopy of the Living Eye.* Hoeber, New York, 1949, p. 322.
21. Cuntz-Schüssler E: Über zwei Sippen mit eigenartiger erblicher Hornhaut dystrophie. *Klin Monatsbl Augenheilkd* 112:70, 1947.

22. Franceschetti A. Klein D, Forni S, Babel J: Clinical and social aspects of heredity in ophthalmology. *XVI Concilium Ophthalmol* 1:157, 1950.
23. Franceschetti A, Montressor D: Band keratopathy. *Boll Ocul* 39:785, 1960.
24. Magruder GB: Lens extraction in hereditary deep corneal dystrophy. *Am J Ophthalmol* 52:677, 1961.
25. Schnyder WF: Mitteilungen über zwei weitere Fälle von blasigen Veränderungen der Hornhautrückfläche (herpes corneae posterior). *Klin Monatsbl Augenheilkd* 75:466, 1925.
26. Schnyder WF: Herpetiforme erkrankung der Hornhautrückfläche (herpes corneae posterior). *Klin Monatsbl Augenheilkd* 73:385, 1924.
27. Staz L: An unusual condition of the posterior surface of the cornea (posterior herpes of the cornea). *Br J Ophthalmol* 23:622, 1939.
28. Stocker FW: The endothelium of the cornea and its clinical implications. *Trans Am Ophthalmol Soc* 51:669, 1953.
29. Kiffney GT, JR.: Linear endothelial vesicle or herpes corneae posterior. *Am J Ophthalmol* 59:466, 1965.
30. Collier M: La dystrophie vesiculiforme groupée en ilots et en bandes de l'endothelium cornéae. *Bull Soc Fr Ophtalmol* 80:95, 1967.
31. Morgan G, Patterson A: Pathology of posterior polymorphous degeneration of the cornea. *Br J Ophthalmol* 51:433, 1967.
32. Feeney ML, Garron KK: Descemet's Membrane in the Human Peripheral Cornea. A study by light and electron microscopy. G.K. Smelser (ed). *The Structure of the Human Eye.* Academic Press, New York, 1961.
33. Hogan MJ, Bietti G: Hereditary deep dystrophy of the cornea (polymorphous). *Am J Ophthalmol* 68:777, 1969.
34. Rubenstein RA, Silverman JJ: Hereditary deep dystrophy of the cornea associated with glaucoma and ruptures in Descemet's membrane. *Arch Ophthalmol* 79:123, 1968.
35. Boruchoff A, Kuwabara T: Electron microscopy of posterior polymorphous degeneration. *Am J Ophthalmol* 72:879, 1971.
36. Kanai A, Waltman S, Polack FM, Kaufman HE: Electron-microscopic study of hereditary corneal edema. *Invest Ophthalmol* 10:89, 1971.
37. Kanai A, Kaufman HE: Further electron-microscopic study of hereditary edema. *Invest Ophthalmol* 10:545, 1971.
38. Jakus MA: The Fine Structure of the Human Cornea. G.K. Smelser (ed). *The Structure of the Eye.* Academic Press, Inc., New York, p. 343, 1961.
39. Jakus MA: Further observations of the fine structure of the cornea. *Invest Ophthalmol* 1:102, 1962.
40. Kanai A, Mustakallio AH, Kaufman HE: Electron-microscopic studies of corneal endothelium. The abnormal endothelium associated with retrocorneal membrane. *Ann Ophthalmol* 4:564, 1972.
41. Michels RG, Kenyon KR, Maumenee AE: Retrocorneal fibrous membrane. *Invest Ophthalmol* 11:822, 1972.
42. Sherrard ES, Rycroft PV: Retrocorneal membranes. I. Their origin and structure. *Br J Ophthalmol* 51:379, 1967.
43. Maruyama T, Haruyama S, Kitano S: Studies on the burn of the cornea. II. Autoradiographs observation. *Acta Soc Ophthalmol Jap* 72:935, 1968.
44. Oglesby RB: Corneal opacities in a patient with cryoglobulinemia and reticulohistiocytosis. *Arch Ophthalmol* 63:63, 1961.
45. Slansky HH, Kuwabara T: Intranuclear urate crystals in the corneal epithelium. *Arch Ophthalmol* 60:338, 1968.
46. Tabbara K: Unpublished data.
47. Capella JA, Kaufman HE, Robbins JE: Preservation of viable corneal tissue. *Arch Ophthalmol* 74:669, 1965.
48. Garner A: Keratinoid corneal degeneration. *Br J Ophthalmol* 54:769, 1970.

49. Fraunfelder FT, Hanna C, Parker JM: Spheroid degeneration of the cornea and conjunctiva. *Am J Ophthalmol* 74:821, 1972.
50. Hogan H, Alvarado J, Weddell J: *Histology of the Human Eye.* Philadelphia, London & Toronto, W. R. Saunders, 1971, p. 102.
51. Farquhar MG, Palade GE: Junctional complexes in various epithelia. *J Cell Biol* 17:375, 1963.
52. Fine FS, Yanoff M: *Ocular Histology. A Text and Atlas.* Hoeber Medical Division, Harper and Row, New York, 1972, p. 150.
53. McTigue JW: The human cornea. A light and electronmicroscopic study in various dystrophies. *Trans Am Ophthalmol Soc* 65:591, 1967.
54. Wulle KG, Leiche W: Electronmicroscopic observations of the early development of the human corneal endothelium and Descemet's membrane. *Ophthalmologica* 157:451, 1969.
55. Cleveland PH, Schneider CW: A simple method of preserving ocular tissue for scanning electronmicroscopy. *Vision Res* 9:1401, 1969.
56. Svedbergh B, Bill A: Scanning electron-microscopic studies of the corneal endothelium in man and monkeys. *Acta Ophthalmol (Kbh)* 50:321, 1972.
57. Donn A, Kaye GI, Mallett NM, Pappas GD: Pinocytosis in the rabbit corneal endothelium. *Arch Ophthalmol* 66:835, 1961.
58. Wolf I: Pit-like islets of the corneal endothelium. *Doc Ophthalmol* 25:196, 1969.
59. Blümcke S, Morgenroth K Jr.: The stereo ultrastructure of the external and internal surface of the cornea. *J Ultrastruct Res* 18:502, 1967.
60. Polack F: Scanning electron microscopy of corneal graft rejection: Epithelial rejection, endothelial rejection and formation of posterior membranes. *Invest Ophthalmol* 11:1, 1972.
61. Kaufman HE, Capella JA, Robbins JE: The corneal endothelium. *Am J Ophthalmol* 61:835, 1966.
62. Donn A: Cornea and sclera. *Arch Ophthalmol* 75:261, 1966.
63. Ham AW, Leeson TS: *Histology,* 4th ed. Philadelphia, Lippincott, 1961, p. 216.
64. Smith P, Copenhaver W: *Bailey's Textbook of Histology,* 2nd ed. Baltimore, Williams and Wilkins, 1944.
65. Verhoeff F: quoted by Lloyd R: Less evident cause of lowered activity in senility. *Am J Ophthalmol* 27:232, 1944.
66. Iwamoto T, DeVoe AG: Electron-microscopic studies in Fuchs' combined dystrophy. I. Posterior portion of the cornea. *Invest Ophthalmol* 10:9, 1971.
67. Inomato H, Smelser GK: Fine structural alterations of corneal endothelium during experimental uveitis. *Invest Ophthalmol* 9:27, 1970.
68. Lowry GM: Corneal endothelium in vitro: Characterization by vitrostructure and histochemistry. *Invest Ophthalmol* 5:355, 1966.