CLINICAL PATHOLOGICAL REVIEW

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Clinicopathologic Features of Chandler's Syndrome

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Abstract. The clinicopathologic features of Chandler's syndrome are elucidated based on a study of nine patients. Keratoplasty, trabeculectomy and/or iris specimens were studied by light, electron and, in six cases, specular microscopy. The prominent pathologic features were abnormalities of the endothelially-derived cells lining the posterior corneal surface, the inner surface of the trabecular meshwork, and the anterior iris surface. In all four corneal buttons, the endothelium was diffusely attenuated and focally absent, and posterior collagen layers were present. Extension of the endothelial cell layer and Descemet's membrane deposition over the trabecular meshwork were observed in two trabeculectomy specimens, and similar proliferation onto the anterior surface of the iris was evident in four iris specimens. Other abnormalities of the endothelial cells included increased intracytoplasmic filaments. These pathologic alterations are consistent with the concept of Chandler's syndrome as representing one variant of the iridocorneal endothelial (ICE) syndrome. Interestingly, although both endothelial proliferative and degenerative responses can be observed in Chandler's syndrome, their occurrence within the same eye is apparently not simultaneous. (**Surv Ophthalmol 27**:327–344, 1983)

Key words. Chandler's syndrome • clinical specular microscopy • cornea • corneal endothelial cells • Descemet's membrane • electron microscopy • epithelial characteristics • glaucoma • iris • posterior collagenous layer • trabecular meshwork • ultrastructure

Chandler[4] described a group of patients with unilateral corneal edema, normal or slightly elevated intraocular pressure, broad iridocorneal adhesions, and mild iris stromal atrophy. Corneal endothelial abnormalities were noted by slit-lamp examination in some of the patients. More recently, similarities have been detected among patients with Chandler's syndrome and those with essential iris atrophy and the iris-nevus syndrome.[20] The designation "iridocorneal endothelial" (ICE) syndrome has been suggested to include all three disorders, since they share corneal endothelial dysfunction, broad iridocorneal adhesions, iris stromal atrophy, nevus-like formations, and glaucoma.[3,21,23]

In addition, in early stages of these three disorders, there is a diffuse corneal endothelial abnormality that is detectable with specular microscopy.[9] This supported the contention that the primary disorder in these three diseases is an abnormality of the corneal endothelium — with chamber angle,

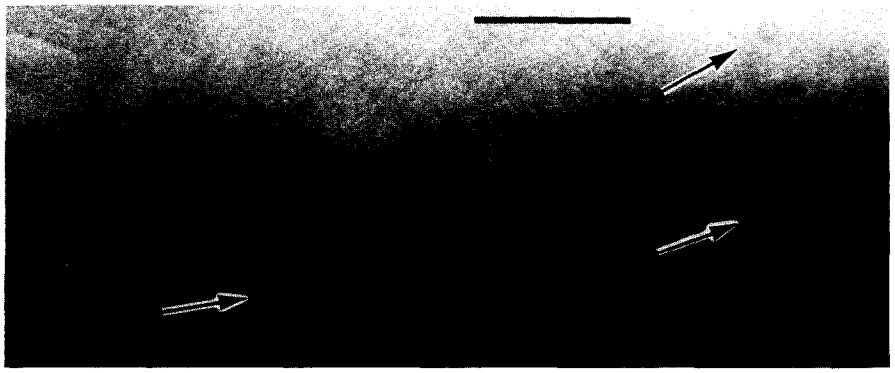

Fig. 1. Case 1. Small-field specular micrographs of right eye showing gross pleomorphism (mean cell size, 654 ± 438 square microns; n = 36) bizarre cell shapes, and intracellular "blackout" areas (arrows) (bar = 50 microns).

iris, and glaucomatous changes as a secondary phenomenon.[3]

In previous reports of Chandler's syndrome,[5,7,16–18] corneal endothelial cells were sparse in number, and often severely abnormal in appearance. To date, we are aware of only five corneal buttons from patients with Chandler's syndrome having been studied ultrastructurally.[8,16,17,23] Some ultrastructural and immunohistochemical features of epithelium have been observed in the corneal endothelium in Chandler's syndrome.[8,16,24] Among the three clinical entities, the presence of such cells with epithelial characteristics has been previously observed only in posterior polymorphous dystrophy of the cornea.[1,19]

To investigate further the characteristics of the endothelial cells in Chandler's syndrome, we examined corneal, trabecular meshwork, and iris specimens from nine cases by light and electron microscopy (Table 1). In each case, detailed clinical examinations had been performed, including specular microscopy in six cases.

The nine patients ranged in age from 26 to 57 years. All were Caucasian; five were females and four were males. The condition was sporadic in all nine patients. The clinical and pathologic characteristics are summarized in Table 1. Six of the nine patients were examined by wide-field and/or small-field specular microscopy.[2,11] A minimum of 36 photographs were taken of each cornea.

Trabeculectomy and peripheral iridectomy specimens were obtained from five patients. The specimens were fixed in a phosphate-buffered solution of 1% glutaraldehyde and 4% formaldehyde for at least three hours. They were then put into a 2.5% glutaraldehyde solution for two hours and later post-fixed with 2% phosphate-buffered osmium tetroxide. After standard dehydration, the specimens were embedded in epoxy resin. One-micron thick sections were stained with p-phenylenediamine for orientation and phase-contrast microscopy. Ultrathin sections were doubly stained with uranyl acetate and lead citrate and examined in a JEM 100-B transmission electron microscope.

Corneal buttons were obtained from four patients. The specimens were trisected, with one-third processed for light microscopy, one-third for transmission electron microscopy, and one-third for scanning electron microscopy. An iris specimen was also obtained from two patients who underwent keratoplasty.

Specimens for scanning electron microscopy were fixed as for transmission electron microscopy. After standard dehydration in a graduated series of acetones, the specimens were critical-point dried, coated with gold palladium, and then examined at 20 KV with the AMR-1000 A scanning electron microscope.

Case Reports

CASE 1.

A 37-year-old woman had had normal eye examinations from 1964 to 1976. In 1976 she was noted to have a distorted right pupil. In 1979 her vision was 20/40 in the right eye (OD) and 20/20 in the left (OS), with pressures of 39 mm Hg and 18 mm Hg respectively. There was diffuse endothelial stippling at slit-lamp examination of the right eye, with a normal endothelial mosaic on the left. Diffuse atrophy of the iris stroma OD was noted. This atrophy was more prominent in the superonasal quadrant where it was associated with a cellophane-like sheen on the anterior iris surface. There was a broad peripheral anterior synechia from the 12:00 to 2 o'clock position, and advanced glaucomatous cupping of the disc. The examination of the left eye was normal.

Clinical specular microscopy of the right eye revealed bizarre cells with gross pleomorphism and intracellular "blackout" areas with no remaining endothelial mosaic observed (Fig. 1). The endothelium of the left eye appeared somewhat pleomorphic but maintained a fairly regular hexagonal array.

In June 1979, because of uncontrolled glaucoma,

TABLE 1

Chandler's Syndrome: Clinical Features, Tissue Studied, and Histopathologic Features

Case	Age	Race/Sex	Clinical course	Specular microscopy	Tissue studied: Cornea	Tissue studied: Trabeculum	Tissue studied: Iris	Pathologic findings
1	37	W/F	Glaucoma Iris atrophy w/ PAS No corneal edema Trabeculectomy	Pleomorphic endothelial cells	−	+	+	No endothelium or Descemet's membrane proliferation
2	40	W/M	Corneal edema Glaucoma PAS Penetrating kerataoplasty	−	+	−	−	Posterior collagenous layer; attenuated and degenerated endothelial cells with intracytoplasmic filaments
3	45	W/M	Glaucoma PAS & iris atrophy No corneal edema Trabeculectomy	Pleomorphic cells	−	+	+	Endothelial and prolif. on trabecular meshwork and iris
4	47	W/M	Glaucoma PAS Cornea gauttata,*OU* Trabeculectomy	Enlarged, pleomorphic endothelial cells w/ areas of cell loss [guttae only in other eye]	−	+	+	Endothelial & basement membrane proliferation on trabecular meshwork & iris; intracytoplasmic filaments in endothelial cells
5	51	W/M	Glaucoma PAS Corneal edema Penetrating keratoplasty & cataract extraction	Enlarged, pleomorphic endothelial cells	+	−	+	Posterior collagenous layer; attenuated and degenerated endothelial cells w/ intracytoplasmic filaments & microvilli
6	47	W/F	Glaucoma Iris atrophy w/ PAS Penetrating keratoplasty & cataract extraction	—	+ +	−	+	Posterior collagenous layer; attenuated and degenerated endothelial cells w/ intracytoplasmic filaments & microvilli. No proliferation of cells or Descemet's membrane on iris
7	57	W/F	Glaucoma Cornea guttata PAS Trabeculectomy Corneal edema Penetrating keratoplasty & cataract extraction	−	+	−	+	Posterior collagenous layer; attenuated and degenerated endothelial cells. No proliferation of cells or Descemet's membrane on iris
8	76	W/F	Glaucoma Iris atrophy PAS	Pleomorphic endothelial cells	−	+	+	Endothelial & basement membrane proliferation on trabecular meshwork and iris
9	34	W/F	Glaucoma Iris atrophy Cornea guttata? Trabeculectomy	Pleomorphic endothelial cells	−	+	+	Endothelial & basement membrane proliferation on trabecular meshwork and iris

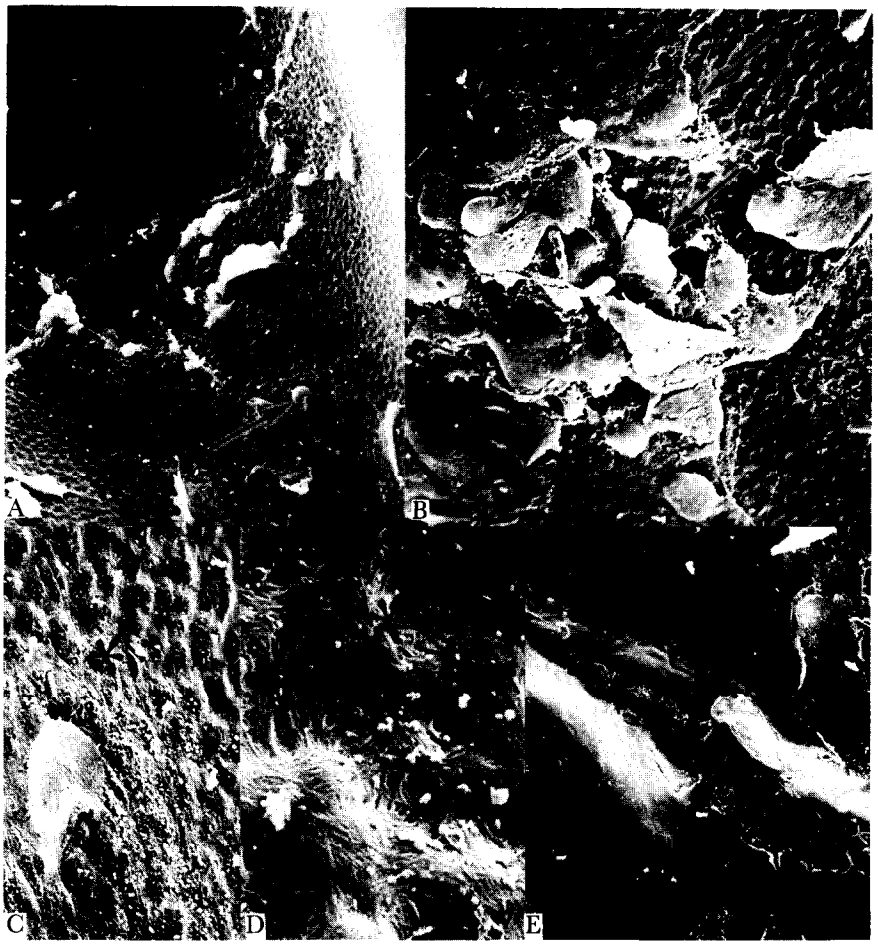

Fig. 2. Case 2. Scanning electron microscopic appearance of posterior surface of the cornea. The pitted appearance of the posterior fibrous tissue layer (asterisks) is evident and only few flattened, intact (arrows), and degenerated endothelial cells are present in some areas. In one area (lower right), a fairly normal pattern of endothelium was observed. (Left to right, × 500, × 1000, × 2,000, × 10,000, × 180)

this patient underwent an uneventful right trabeculectomy procedure with good immediate control of intraocular pressure (IOP). By October, 1981, her vision had dropped to count fingers and the IOP had risen to 38 mm Hg.

Light microscopy: Examination of semi-thin sections disclosed a coiled fragment of iris with a normal-appearing pigment epithelium and stroma. Examination of the trabeculectomy specimen disclosed a small fragment of normal-appearing peripheral corneal tissue and trabecular meshwork.

Transmission electron microscopy: Examination of the trabeculectomy specimen disclosed moderately attenuated endothelium and thickened Descemet's membrane. Fibrocytes, branching dendritic melanocytes, clumped cells, and (rarely) mast cells were present in the iris stroma. No cellular or basement membrane proliferations were observed on the trabecular meshwork or anterior surface of the iris.

CASE 2.

A 40-year-old man had a clinical diagnosis of Chandler's syndrome OD with corneal edema, elevated IOP, and broad peripheral anterior synechia. A penetrating keratoplasty was performed, with an initially clear graft that slowly became opaque.

Light microscopy: Examination of semi-thin sections of the corneal button disclosed epithelial edema, and a layer of fibrous tissue interposed between an attenuated endothelium and thickened Descemet's membrane.

Scanning electron microscopy: Examination disclosed that the posterior surface of the cornea was almost completely devoid of endothelial cells (Fig. 2A). An occasional clump of flattened pleomorphic endothelial cells that overlapped one another was seen (Fig. 2B). Some of the cells had long filamentous processes. The underlying surface was pitted and fibrous in appearance (Figs. 2C and D). In some areas a more nearly normal but pleomorphic cellular pattern was observed (Fig. 2E).

Transmission electron microscopy: Examination of the corneal button disclosed flat endothelial cells with abundant rough endoplasmic reticulum and aggregates of intracytoplasmic filaments that were 80 to 100 Å in diameter (Fig. 3). A 5-micron thick layer of

Fig. 3. Case 2. By transmission electron microscopy, Descemet's membrane consists of a 2.5 micron-thick anterior banded layer and a posterior non-banded layer that measures 3.7 microns in thickness. A fibrous tissue layer (between brackets) composed of collagen fibrils that measure up to 100 Å in diameter (upper right, inset) and contain patches of basement membrane (arrowheads) is interposed between Descemet's membrane and endothelium. One endothelial cell is fairly normal (arrow) but an adjacent cell (asterisk) appears to be degenerating. Prominent aggregates of filaments that measure up to 100 Å in diameter are present in the cytoplasm of most endothelial cells (upper left inset). (× 8,000; insets, × 50,000)

fibrous tissue containing collagen with fibril diameter of 100 Å and patches of basement membrane was interposed between Descemet's membrane and endothelium. Some endothelial cells appeared degenerated.

CASE 3.

A 45-year-old man was seen in 1979 for intermittent blurring of vision in the right eye. Vision was 20/15 OU and IOPs were 26 mm Hg OD and 14 mm Hg OS. Peripheral anterior synechia were present from the 4 to 7 o'clock position OD. The remainder of the ocular examination findings were normal, with a 0.3 cup/disc ratio and normal visual fields in both eyes. A peripheral iridectomy OD was later performed elsewhere, but the specimen was not studied pathologically.

Postoperatively the IOPs rose to the 30s OD, and therapy was begun with epinephrine, pilocarpine, and timolol. In October, 1980, visual acuity was 20/20 OD and 20/15 OS, and the IOPs were 32 mm Hg and 14 mm Hg, respectively. Slit-lamp examination disclosed much endothelial irregularity in cell size in the right eye, with a normal endothelial mosaic in the left eye. Two-thirds of the anterior angle was closed by peripheral anterior synechiae up to Schwalbe's line. The right iris showed patchy stromal atrophy, and fundus examination disclosed cup/disc ratios of 0.7 and 0.4 OS and OD. Visual field tests demonstrated an inferior nasal step and general contraction OD and a normal field OS.

Clinical specular microscopy of the involved cornea revealed grossly abnormal endothelial cells with bizarre shapes and intracellular blackout areas (Fig. 4A). In one area a very small area of persisting

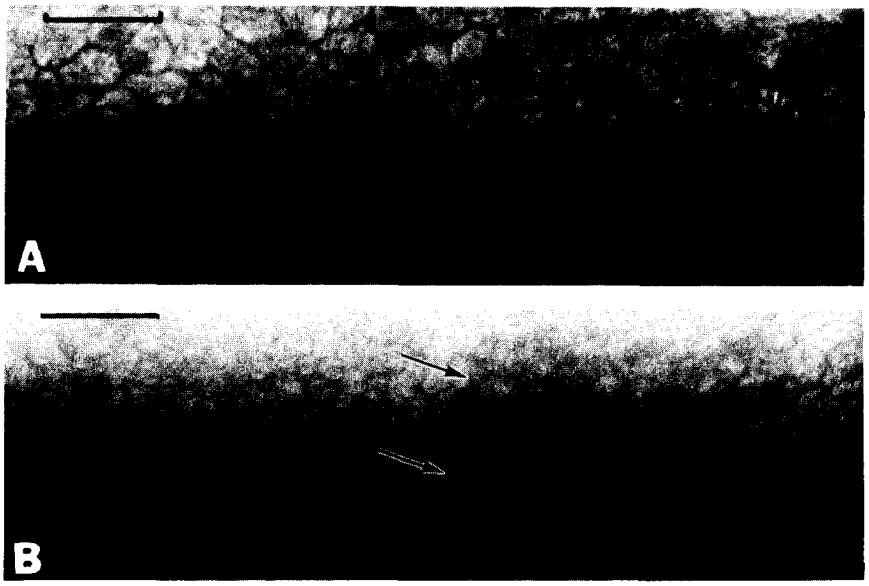

Fig. 4. Case 3. A: Small-field specular micrograph of endothelium of right cornea showing a well-preserved mosaic of irregular-shaped cells (mean cell size, 327 ± 90 square microns; n = 105). B: Small-field specular micrograph of endothelium of right cornea showing sharp interface (arrows) between abnormal pleomorphic cells to the right and a small array of more-regular cells to the left (bar = 50 microns).

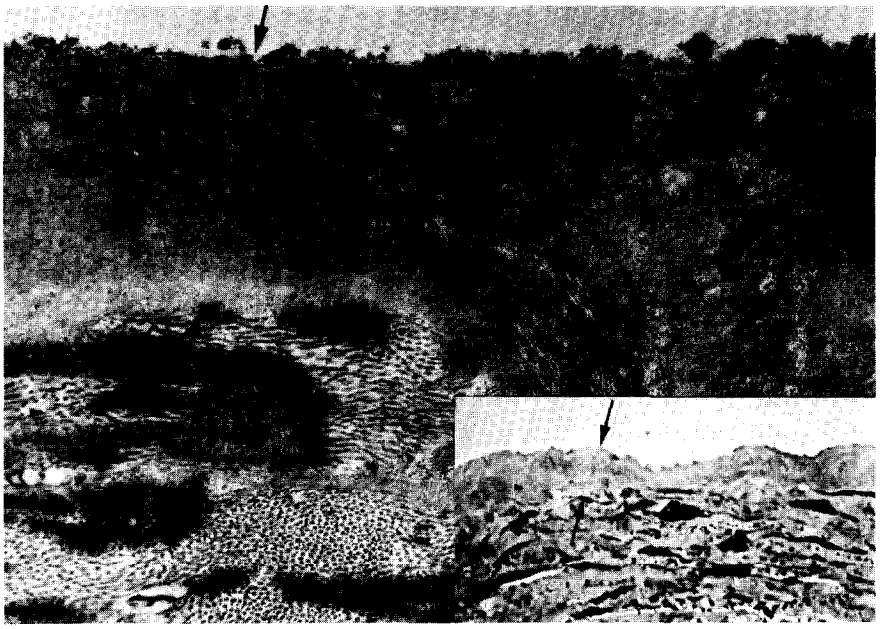

Fig. 5. Case 3. Trabeculum is covered by a basement membrane (between arrows) that measures up to 3 microns in thickness. (× 17,000; inset, paraphenylenediamine, × 480)

preserved endothelial mosaic was seen to have an abrupt interface with the area of abnormal endothelial cells (Fig. 4B).

In November, 1980, an uneventful trabeculectomy was performed in the right eye. Preoperative vision has been maintained, and the IOPs have been below 20 mm Hg without medications.

Light microscopy: The limbal inner-lamellar resection included a portion of trabecular meshwork that was covered by a basement membrane and rarely cells. A layer of cells covered the anterior surface of the iris.

Transmission electron microscopy: Examination of the trabeculectomy specimen showed an abnormal basement membrane on the anterior-chamber side of the meshwork (Fig. 5). Endothelium was present internal to this layer in only one small area.

The iris specimen showed cells on its anterior surface which were arranged in a monolayer with occasional overlap of some cells (Fig. 6). These cells had a prominent basement membrane adjacent to iris stroma and lacked any intracytoplasmic filaments, desmosomes or other cell junctions.

CASE 4.

A 47-year-old man had intermittent blurring of vision of his right eye for a year. When seen in August, 1978, he had IOPs of 27 mm Hg OD and 15

Fig. 6. Case 3. Inner surface of the peripheral iris is covered by multilayered cellular membrane with basement membrane production adjacent to iris stroma (circle and inset, arrow). (× 9000; inset, × 25,000)

Fig. 7. Case 4. Small-field specular micrograph of endothelium of right cornea showing very irregular cells (mean cell size, 488 ± 173 square microns; n = 111) and intracellular abnormalities (bar = 50 microns).

mm Hg OS, with scattered peripheral anterior synechiae. Minor guttae of Descemet's membrane were evident in both corneas. Therapy with timolol drops was begun in the right eye, and one year later the IOP was 36 mm Hg OD, with extensive corneal edema. Diamox and pilocarpine were added to the regimen. In December, 1979, IOPs were 32 mm Hg OD and 18 mm Hg OS. Broad peripheral anterior synechiae were present on the right, and some smaller peak-like adhesions were evident. There was a 0.8 cup/disc ratio with definite glaucomatous changes in the right eye and a 0.6 cup/disc ratio in the left. Scattered corneal guttae were noted bilaterally, but the right endothelial surface had a diffuse beaten-metal appearance. Epinephrine was added to the regimen.

Clinical specular microscopy disclosed grossly enlarged and irregular cells with loss of the normal hexagonal mosaic (Fig. 7). There were other areas where no endothelium was present. Except for occasional typical guttate excrescences, the endothelial mosaic of the left cornea was normal.

Because of continued uncontrolled IOP elevation, the patient underwent an uneventful trabeculectomy OD in October, 1980. Postoperatively he has maintained good vision with normal IOPs.

Light microscopy: The inner, lamellar limbal resection specimen contained peripheral Descemet's membrane and partially collapsed trabecular meshwork. The posterior half of the angle was closed by peripheral anterior synechia (Fig. 8). A thick basement membrane covered the inner surface of the trabecular meshwork throughout both the open anterior portion and the posterior portion to which the iris was adherent (Figs. 8A and C). A single layer of cells that was continuous with corneal endothelium extended over a portion of this membrane on the trabecular meshwork and on the anterior iris surface, where a basement membrane was also present (Fig. 8B).

Transmission electron microscopy: At the corneal periphery, Descemet's membrane was nodular and

was covered posteriorly by endothelial cells. A continuous basement membrane which measured up to 1.5 microns in thickness covered the internal surface of the trabecular meshwork (Fig. 9). In some areas, no cells were located internal to this membrane (Fig. 9). In other areas, intact and degenerated endothelial cells lined the inner aspect of this membrane (Fig. 10). A similar basement membrane and a single layer of endothelium also covered the anterior surface of the peripheral iris (Fig. 11). The cells were occasionally joined by poorly developed junctional complexes. Cytoplasmic filaments that measured 80 Å in diameter were present in these endothelial cells (Fig. 10, inset).

CASE 5.

A 51-year-old man had noted gradual decrease in vision in the right eye during a one-year period. When seen in August, 1972, his vision was 20/40 OD and 20/25 OS. Intraocular pressures were 34 mm Hg OD and 16 mm Hg OS, with a cup/disc ratio that was larger for the right eye than for the left. Epinephrine 1% twice a day gave good IOP control.

When examined in 1980, he had vision of 20/200 OD and 20/20 OS, with IOPs of 21 mm Hg OD and 19 mm Hg OS. Diffuse stromal and epithelial edema was apparent in the right cornea, with a normal cornea on the left. There was a small area of peripheral anterior synechia at the 5:30 o'clock position OD. The anterior chamber angle was open OS. There was mild bilateral nuclear sclerosis and 0.8 cup/disc ratio OD, with definite glaucomatous changes and 0.3 cup/disc ratio OS.

After partial clearing of the corneal edema, wide-field clinical specular microscopy disclosed no areas of normal endothelial mosaic. Small-field specular microscopy highlighted the grossly enlarged cells with pleomorphism and intracellular blackout areas (Fig. 12A). The endothelial mosaic on the unaffected left eye appeared normal (Fig. 12B).

The patient underwent an uneventful penetrating keratoplasty and extracapsular cataract extraction OD in July, 1981, and has maintained 20/40 vision with a clear graft.

Light microscopy: The corneal epithelium was uniformly thinned to two or three cell layers. Mild intracellular and intercellular edema was present. Bowman's membrane and the corneal stroma were not remarkable. Descemet's membrane was uniformly thickened. A thick layer of fibrous tissue was interposed between Descemet's membrane and the greatly attenuated endothelium. The lens had moderate cataractous changes.

Transmission electron microscopy: Descemet's membrane (Fig. 13) was composed of a 2.5-micron-thick and banded anterior portion and a 3.7-micron-thick posterior nonbanded layer. A 5.1-micron-thick fibrous tissue layer composed of fibrils that measured 120 Å in diameter was present between Descemet's membrane and the posterior cellular layer. The cells

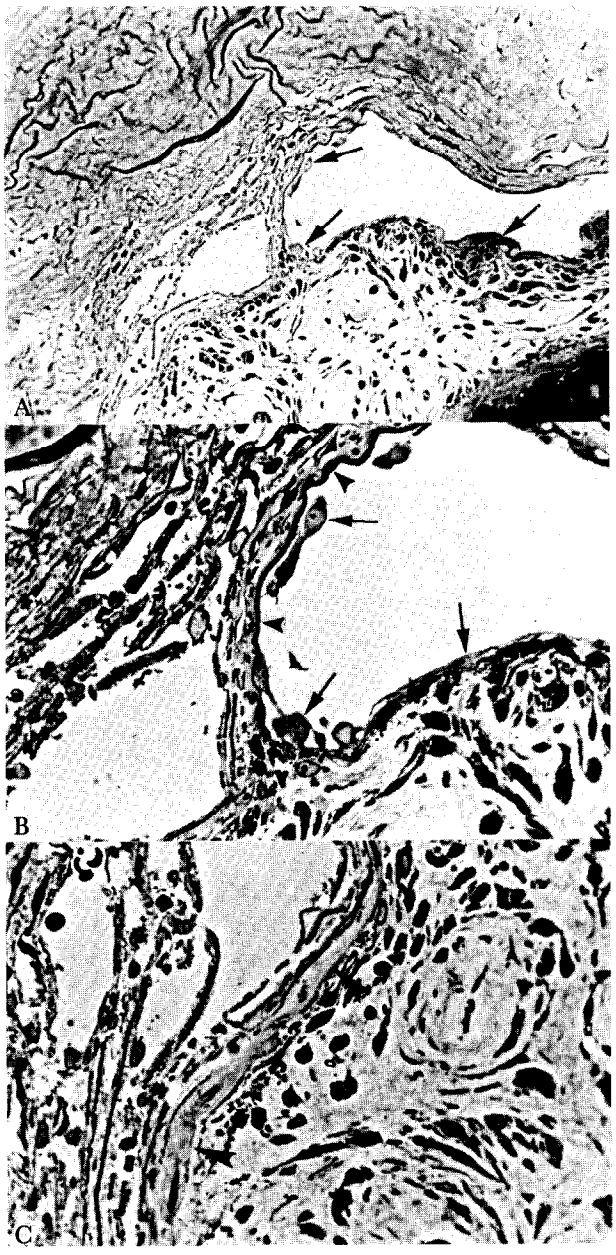

Fig. 8. Case 4. A and B: Trabeculectomy specimen showing peripheral synechia involving the posterior one-half of the trabeculum. Endothelium (arrows) extends over the inner surface of the trabecular meshwork, across the false angle, and onto the anterior iris surface. C: A thick basement membrane (arrowheads) is associated with the endothelium and is located on the inner surface of the posterior portion of trabecular meshwork that is covered by peripheral anterior synechia (paraphenylenediamine, phase-contrast). (A, × 192; B, × 480; C, × 12000)

lining the posterior surface of the cornea had microvilli and contained cytoplasmic filaments that measured 75 Å in diameter. Some cells overlapped each other and were joined by junctional complexes. An occasional macrophage was present on the posterior surface of the cornea.

Scanning electron microscopy: There was much variation in the shapes and sizes of the endothelial cells (Fig. 14). Two populations of cells appeared to be present: one with microvilli and the other without. A scattering of adherent macrophages and cellular debris was present on the endothelial surface.

CASE 6.

A 47-year-old woman was noted to have a slightly distorted left pupil in 1968. Because of intermittent pain and decreasing vision, she was seen in September, 1971, with an IOP of 37 mm Hg OS. Pilocar-

Fig. 9. Case 4. Transmission electron microscopy of trabeculectomy specimen shows thick basement membrane (between arrows) covering the inner surface of the trabecular meshwork. (× 8,000)

Fig. 10. Case 4. Transmission electron microscopy of different area of trabecular meshwork shows a thick overlying membrane (between arrows) that measured 1.5 microns in thickness, with a layer of endothelial-like cells (between arrowheads) containing cytoplasmic filaments of 80 Å size (lower right, inset) and joined by junctional complexes (lower left, inset). Some of these cells appeared degenerated (asterisk). (× 12,000; insets, × 40,000)

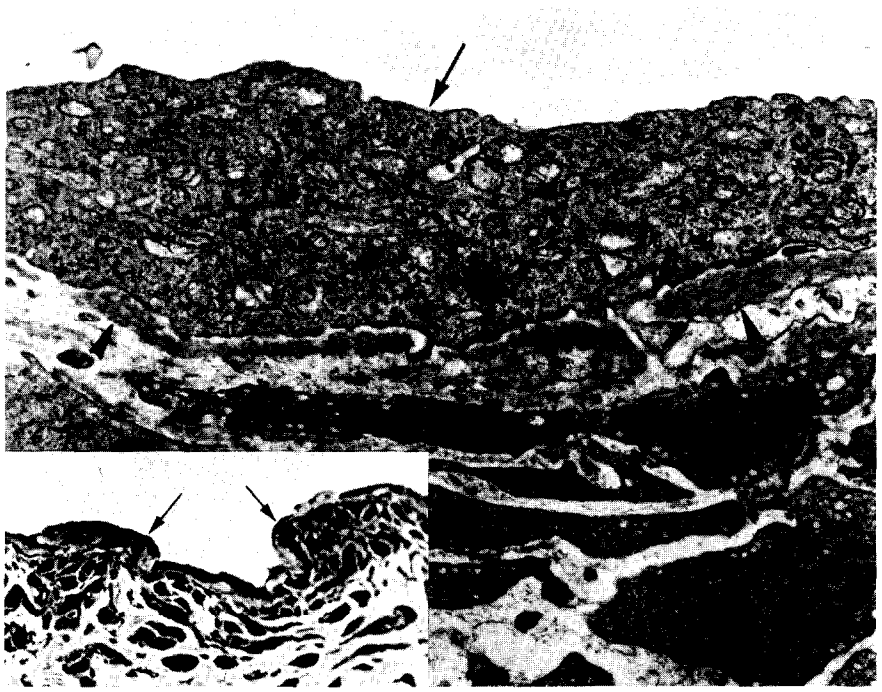

Fig. 11. Case 4. The anterior surface of the periphery of iris is covered by a single layer of cells containing numerous mitochondria, and by a basement membrane (arrowheads) that measured up to 0.3 microns in thickness. (× 17,000; inset, paraphenylenediamine, × 480)

pine 4% and epinephrine 1% were prescribed. In March, 1972, vision was 20/20 in both eyes and the IOPs were 12 mm Hg OD and 42 mm Hg OS. Tonography showed an outflow facility (C value) of 0.29 OD and 0.09 OS. The pupils were normal. Patchy iris stromal atrophy at the 2 o'clock and the 8 to 9 o'clock positions, and peripheral anterior synechia at the 2:00 to 4:30 position and the 8:00 to 10:30 position were present in the left eye. The cup/disc ratio was 0.3 OD and 0.4 OS. In August, 1974, vision was 20/200 with bullous keratopathy OS despite normal IOP. In September, 1978, she underwent an uneventful left penetrating keratoplasty and intracapsular cataract extraction OS. Postoperatively she did well, with vision improving to 20/40 and normal IOP.

Light Microscopy: The corneal epithelium was diffusely thinned to two cell-layers, and on one side was separated from Bowman's membrane by a thick, sparsely vascularized fibrous pannus (Fig. 15, inset). The stroma was normal, but Descemet's membrane was diffusely thickened. The endothelium was quite attenuated and had a few greatly flattened nuclei; a few flecks of pigment were present either on or within the endothelium. There was fibrous tissue proliferation beneath the endothelium (Fig. 15, inset). The iris, resected at the 12 o'clock position (an area devoid of synechia), was normal; no cells with epithelioid characteristics, or "descemetization" of the anterior iris surface, were observed.

Transmission electron microscopy: Descemet's membrane (Fig. 15) consisted of an anterior 1.6 micron-thick banded portion, and a posterior 3.9 micron-thick nonbanded portion. A 10.5 micron-thick collagenous layer, composed of widely spaced fibrils that measured 120 Å in diameter and multilaminated basement membrane, was present between Descemet's membrane and endothelium. The endothelial cells contained microvilli, abundant rough endoplasmic reticulum, and filaments of 80 Å thickness. Some endothelial cells overlapped one another and had junctional complexes along their margins of contact. An occasional macrophage was apparent.

Scanning electron microscopy: Diffuse endothelial cell loss was present (Fig. 16), and the remaining endothelial cells were attenuated and had a dendritiform configuration. The posterior collagenous layer was exposed in some areas.

CASE 7.

A 57-year-old woman had a history of blurring of vision in the right eye. She had no family history of glaucoma and had no past history of trauma. She had corneal edema OD, with an IOP of 69 mm Hg. The left eye was entirely normal. Because of failure to respond to medical therapy for IOP control, a peripheral iridectomy and thermal sclerotomy OD were performed (elsewhere), but the surgical specimen was not studied histopathologically. Topical

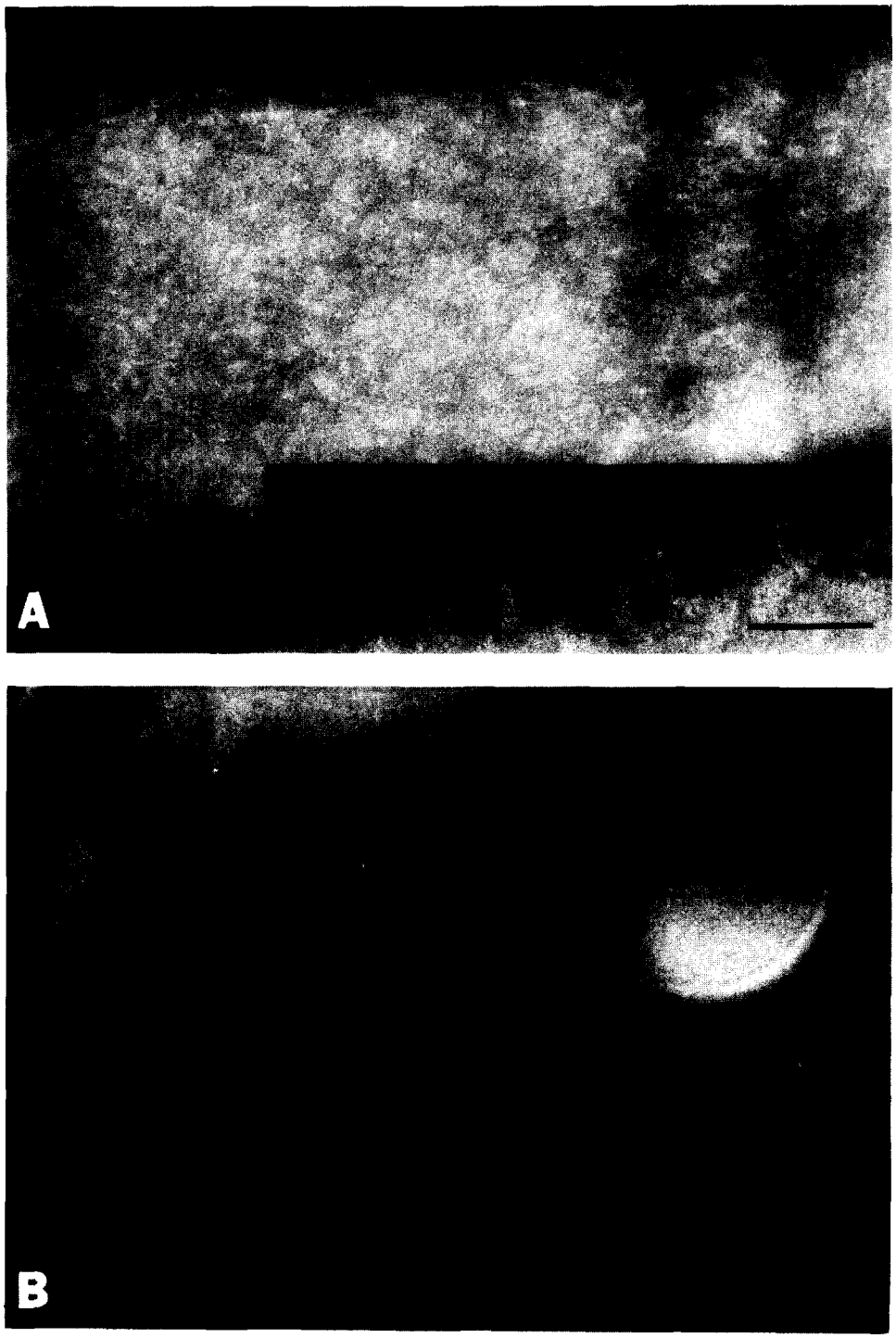

Fig. 12. Case 5. A: Wide-field specular micrograph of right corneal endothelium showing loss of cell outlines and bizarre cell types with no normal endothelial mosaic. Inset: High magnification highlighting the unusual cell shapes and sizes (mean cell size, 793 ± 445 square microns; n = 101). B: Wide-field specular micrograph of endothelium of left eye showing persistence of a relatively normal endothelial mosaic. Inset: High magnification of regular endothelial mosaic (bar = 50 microns).

medications were required to maintain IOP control postoperatively.

In February, 1975, vision was 20/25 in both eyes with IOP of 23 mm Hg OD and 16 mm Hg OS. Slit-lamp examination disclosed fine guttate excrescences over the right endothelial surface and a normal left endothelium. Gonioscopy showed a large peripheral iridectomy and several areas of peripheral anterior synechia. The lens had mild nuclear sclerotic changes, and the right eye had a 0.5 cup/disc ratio. Examination of the left eye was normal. Visual field tests disclosed a Bjerrum scotoma in the right eye and a normal field in the left. Trabeculectomy and peripheral iridectomy were performed OD because of poor control of IOP on maximum medication.

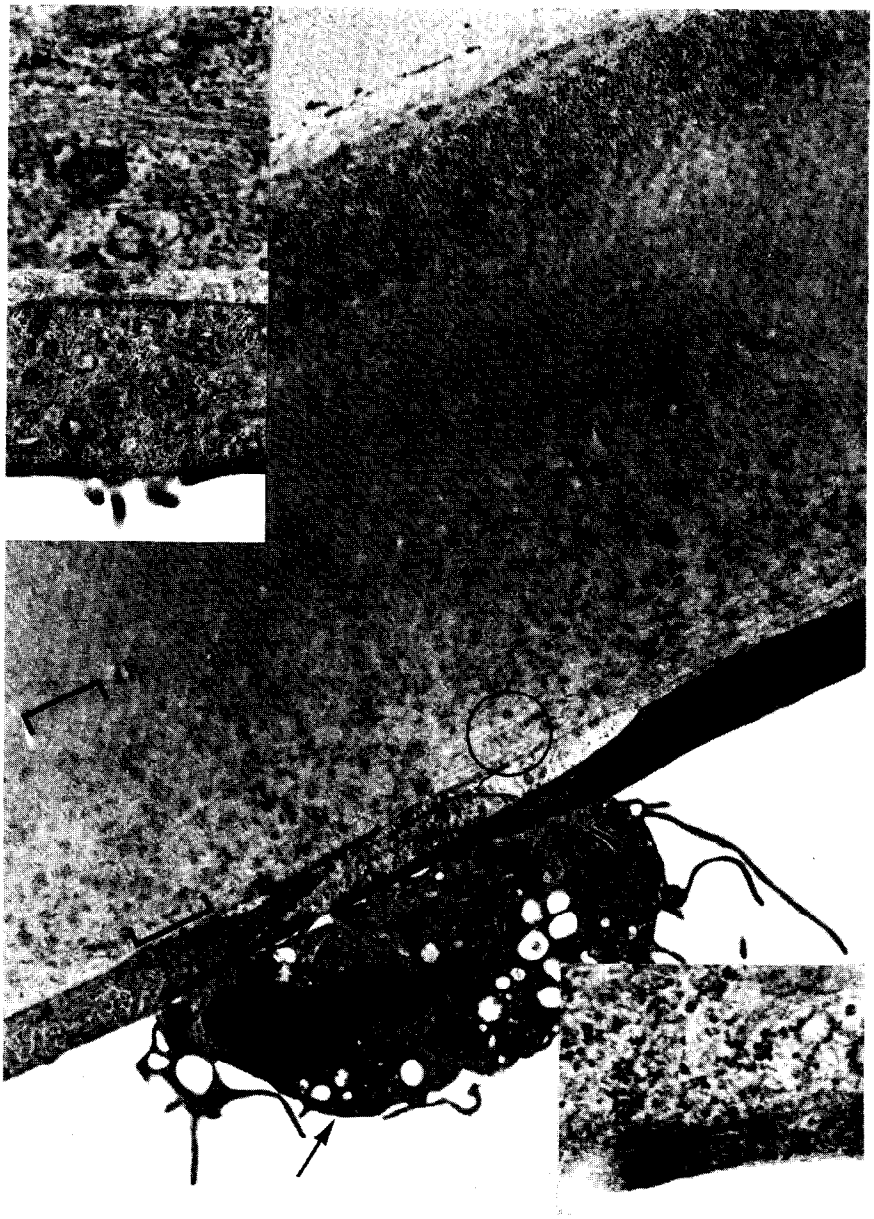

Fig. 13. Case 5. A 5-micron-thick layer of collagenous tissue (between brackets) contains basement-membrane-like material scattered in fragments (arrowheads) and arranged in multiple layers (circle) and is interposed between Descemet's membrane and endothelium. Endothelial cells contain 75 Å cytoplasmic filaments (upper top, left inset), have microvillous processes (lower top, left inset) and are joined by junctional complexes (lower right, inset). Overlapping of some cells is present, and some endothelial cells appeared degenerated (asterisk). A macrophage (arrow) clings to the endothelial surface. (× 8,000; insets: upper top left, × 60,000; lower top left, × 17,000; lower right, × 60,000)

Despite controlled IOP, vision was reduced to count fingers OD because of corneal edema, for which a bandage soft contact lens was prescribed. A dense nuclear sclerotic cataract was also present. In June, 1978, a penetrating keratoplasty with intracapsular cataract extraction was performed uneventfully in the right eye. The corneal button and a portion of iris were submitted for histopathologic study. The corneal graft has remained clear, and IOP has remained normal.

Light microscopy: The corneal epithelium was thinned and edematous. The stroma was thickened and vascularized. Descemet's membrane was variably thickened and multilaminated, and its posterior surface was lined by fibrous tissue which was about the thickness of Descemet's membrane (Fig. 17, inset). Rarely, extremely attenuated endothelial nuclei were present, and occasional pigment granules were seen on the posterior surface of the corneal endothelium (Fig. 17, inset). The anterior surface of the iris had normal morphology, and showed no corneal endothelialization or descemetization.

Transmission electron microscopy: The stroma contained blood vessels associated with lipid-laden histiocytes and polymorphonuclear leukocytes. Descemet's membrane was uniformly thickened, and was covered posteriorly by an acellular fibrous layer that was about 20 microns in thickness and was com-

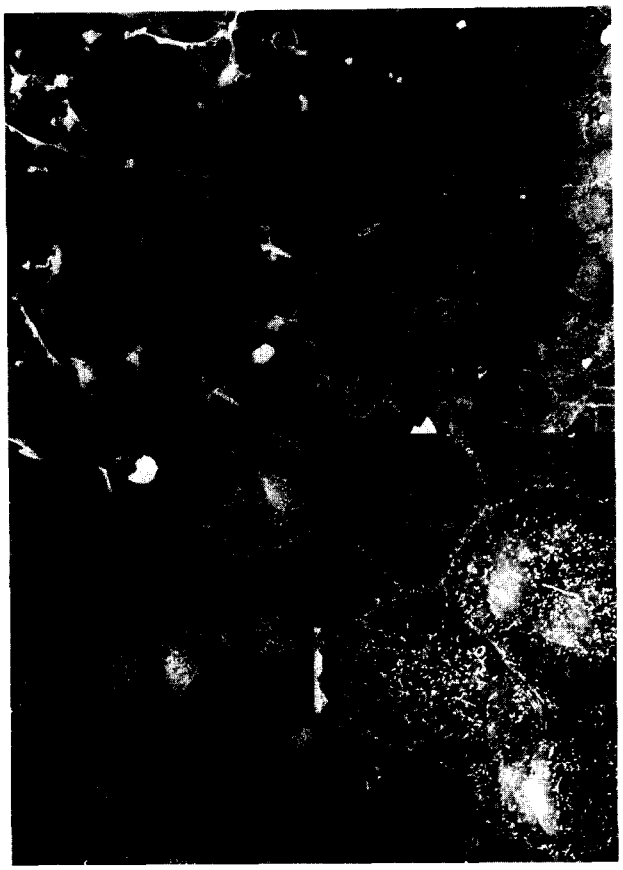

Fig. 14. Case 5. Scanning electron microscopic appearance of endothelial cell layer with much variation in size and shape of cells. Numerous microvilli are present on some cells. (Left to right: × 380, × 380, × 1,000, × 16,000)

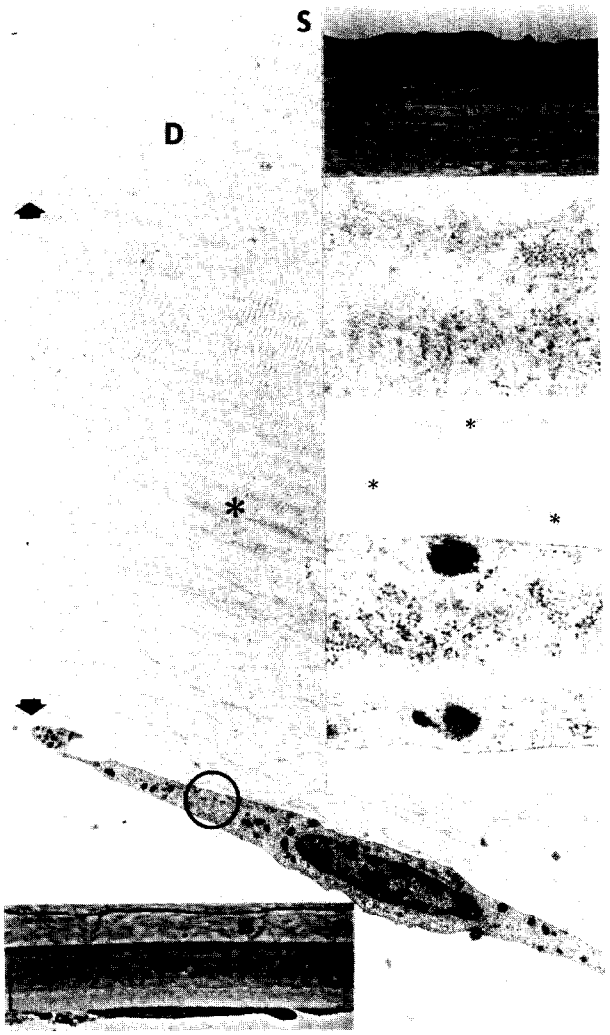

Fig. 15. Case 6. Inset (top right): Phase-contrast view of keratoplasty specimen shows fibrocellular pannus between the intact Bowman's layer (B) and irregular epithelium with intracellular edema (paraphenylenediamine, × 250). Inset (bottom left): Phase-contrast photomicrograph illustrates posterior stroma (S), relatively normal anterior Descemet's membrane (D), and the approximately 10-microns-thick posterior collagen layer (bracketed). The endothelial cell layer is irregular and discontinuous (paraphenylenediamine, × 400). Main figure: Transmission electron micrograph shows corresponding area with posterior stroma (S), ultrastructurally normal Descemet's membrane (D), thick posterior collagen layer (between arrows), and an attenuated endothelial cell (× 9,000). Inset (middle right) is higher magnification of area indicated by asterisk, to resolve basement-membrane-like material, fine filaments, and long-spaced banding patterns of the posterior collagen layer (× 50,000). Inset (lower right) resolves increased cytoplasmic filaments of endothelial cell (circled in main figure) and multiple layers of basement membrane material (asterisks) extracellularly (× 50,000).

posed of loose and randomly arranged collagenous fibrils of 130 Å diameter, interspersed among short discontinuous segments of multilaminar basement-membrane-like material (Fig. 17, inset). Occasional macrophages (Fig. 17) and endothelial cells contained phagocytosed pigment granules.

Scanning electron microscopy: Diffuse corneal endothelial loss was present, and scattered clusters of endothelial cells with exposed areas of the fibrous tissue layer were seen (Fig. 18). The endothelial cells were extremely attenuated and pleomorphic, some with surface microvilli, and were resting on a layer of a randomly interwoven pattern of filaments and fibrils, composing the posterior collagen layer.

CASE 8.

This 26-year-old woman noticed a distortion of the pupil into a vertically oval shape in her right eye. On examination one year later the visual acuity was 20/20 OU, the right pupil was vertically oval, and an afferent pupillary defect was present in this eye. There were zones of iris atrophy in the superior and

inferior iris, and iridocorneal adhesions were seen by slit-lamp in these areas. The entire anterior chamber angle was involved to various degrees by peripheral anterior synechiae that often extended anterior to Schwalbe's line. The IOP averaged 40 mm Hg and was not adequately lowered by maximum tolerated medical therapy. The optic disc had an 0.8 cup/disc ratio (compared to 0.3 in the fellow eye), and an inferior arcuate-zone field loss was detected by Goldmann perimetry. The left eye was entirely normal.

Clinical specular microscopy showed abnormal endothelial cells (identical to those in Cases 1, 4 and 5) without any normal areas.

She underwent uncomplicated trabeculectomy OD and has had normal IOP without medication for the six postoperative months.

Light microscopy and transmission electron microscopy: The trabeculum included an area of iris adhesion to the meshwork. Corneal endothelial cells containing dense intracellular filaments formed a continuous layer over the meshwork and onto the iris. A thin basement membrane underlay these cells. They were joined by typical endothelial gap junctions, and no desmosomes were found. No multilayerings or microvilli were seen.

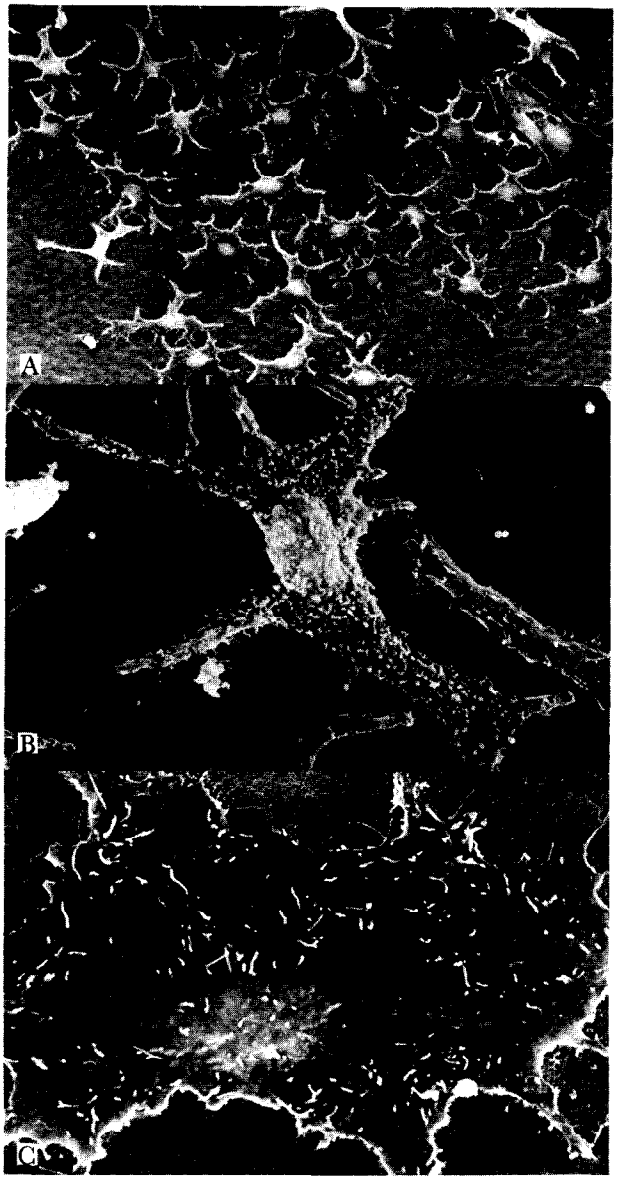

Fig. 16. Case 6. A: Scanning electron microscopy of keratoplasty specimen shows individual endothelial cells that fail to completely cover the exposed posterior fibrous tissue layer (asterisks). B: Higher power demonstrates the unusual dendritiform configuration of an attenuated endothelial cell. C: An adjacent cell has spread to dimensions of about 20 by 30 microns and shows numerous microvillous surface projections. The fibrous surface characteristics of the posterior collagen layers are also evident. (A, × 350; B, × 2,000; C, × 3,500)

CASE 9.

This 34-year-old woman noted hazy vision in the right eye and halos around lights. Examination at that time disclosed visual acuity of 20/40 OD and 20/20 OS. A right afferent pupillary defect was present. The cornea of the right eye had numerous fine dots at the level of the endothelium. The pupil was centrally placed, but diffuse iris stromal atrophy was present temporally and an iridocorneal adhesion extending into clear cornea was present in this zone. Nearly 75% of the angle was closed by peripheral anterior synechiae that varied greatly in their height, some extending anterior to Schwalbe's line. Intraocular pressure OD varied from 28 to 42 mm Hg while using various topical medications. The cup/disc ratio OD was 0.8, compared to 0.5 OS. There was visual field loss OD, both superiorly and inferiorly in the nasal field. For three years the patient was lost to follow-up, then was reexamined at age 37. All findings were unchanged except for further field loss and progression to total glaucomatous cupping OD. Visual acuity remained 20/40.

Clinical specular microscopy showed abnormal cells of the type seen in Cases 1, 4 and 5.

The patient recently underwent uncomplicated trabeculectomy after failure of IOP control by maximum tolerated medical therapy.

Light microscopy and transmission electron microscopy: The findings were identical to those of Case 8. Cells covered the trabecular meshwork and extended onto the iris at a zone of peripheral anterior synechia. The cells were similar in every respect to those described in Case 8. No abnormal cells were seen to cover the separate iridectomy specimen.

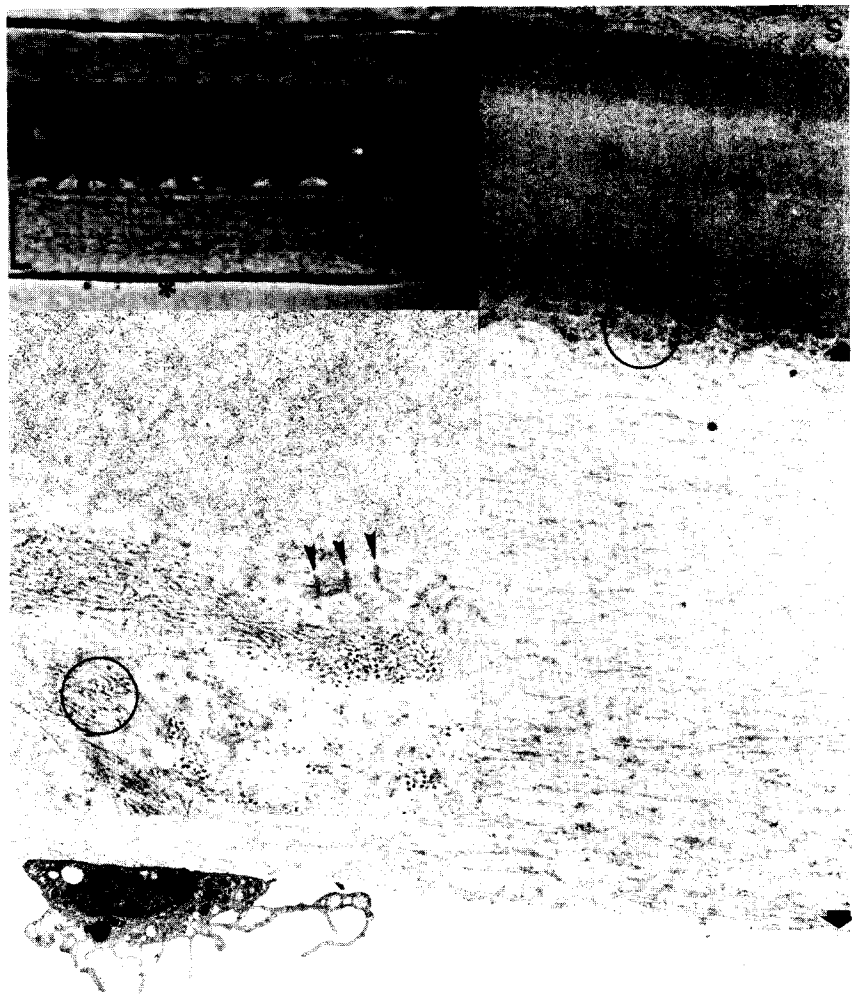

Fig. 17. Case 7. Inset (top left): Phase-contrast photomicrograph illustrates uniformly thickened Descemet's membrane (D) covered posteriorly by an acellular fibrous layer (bracketed) of about 20 microns thickness. An extremely attenuated endothelial layer (asterisk) is evident (S = stroma; paraphenylenediamine; × 800). Main figure: Transmission electron micrograph contrasts the normal ultrastructure of Descemet's membrane (D) with the loose fibrillar structure of the posterior collagen layer (between arrows). A single macrophage with phagocytosed pigment and extended cytoplasmic processes is present (× 5,000). Inset (middle left) shows circled area of main figure at higher magnification to resolve basement membrane material, long-spacing collagen figures (arrowheads) and small diameter filaments (circled). (× 45,000)

Discussion

Since Chandler's[4] original report, much new information has improved our knowledge of this disorder[13] and its relation to other similar syndromes. Although it appeared initially to represent a rare and unique set of findings, clinical similarities to essential iris atrophy and the iris-nevus syndrome have been pointed out.[6,21,22,25] All three entities show unilateral iris stromal abnormalities, iridocorneal adhesions, Descemet's membrane irregularities, and a strong tendency to develop glaucoma. The features that originally seemed unique to each group were: early corneal edema in Chandler's patients, the presence of full-thickness iris holes in essential iris atrophy, and multiple fine iris nodules in the iris-nevus syndrome.

Shields et al[21] discovered, however, that some patients who initially met the criteria for Chandler's syndrome subsequently developed full-thickness iris holes. Thus, if seen only later in the course of the disease, they would have been classified as having essential iris atrophy. The difference appears related to the stage of disease, not to different disease entities. Similarly, Shields et al[21] noted the presence of iris nodules in cases of essential atrophy, thereby establishing overlap with the so-called iris-nevus syndrome.[22] Hence, these three disorders are now considered together under the designation, iridocorneal endothelial (ICE) syndrome.[5]

Two types of evidence suggest that the primary pathogenetic event in Chandler's syndrome (and the other ICE syndrome types) is an abnormality in the corneal endothelium. First, the clinical specular microscope demonstrates that the endothelium in involved eyes is composed of cells that vary greatly in size and shape and have substantial differences in appearance from those of normal eyes.[7] The change is distinctive enough that it can be distinguished from other corneal disorders in a "masked" examination of photographs.[9] The entire endothelial mosaic is involved. Also, this major change in cellular structure is present even at the earliest stage of the

Fig. 18. Case 7. Scanning microscopy of keratoplasty specimen shows extremely attenuated and pleomorphic endothelial cells (top left) overlying irregular surface of posterior collagen layer (asterisk). A single endothelial cell (E) (top right) has enormously enlarged its surface area, measuring about 30 by 80 microns. Another attenuated endothelial cell (bottom left) has extended numerous cytoplasmic processes. At higher magnification (bottom right), the endothelial cell (above) is located on a layer of randomly oriented filaments and fibrils (arrowheads) that compose the posterior collagen layer. (× 550, × 1200, × 2,000, × 15,000)

disease — when only a small portion of the anterior chamber angle has synechia, and even before glaucoma develops. No substantial difference has been noted between Chandler's syndrome patients and essential iris atrophy patients in their endothelial abnormality. In the cases described here, specular microscopy confirmed the presence of abnormalities typical of Chandler's syndrome in the involved eyes, while a normal endothelial mosaic was noted in the uninvolved eye.

The second feature suggesting a primary endothelial disorder as the cause of much of the clinical picture of Chandler's syndrome is the finding of endothelium ectopically present on the trabecular meshwork and anterior iris.[7,17,18] Corneal endothelial growth over the angle, with descemetization, may be seen in several conditions in which the iris is brought into contact with the peripheral cornea, including the peripheral anterior synechiae caused by angle neovascularization. Descemetization over an open angle may occur in association with chronic iridocyclitis and post-contusion angle deformity. The striking feature of the ICE syndrome eyes studied by us and by others is the occurrence of endothelial migration without apparent cause. It is not likely, however, that every area of the angle will be involved in this process, at least not early in the course of the disease. In our material, ectopic endothelium was seen in four of five trabecular specimens, and in three of seven iris specimens (Table 1). Since these eyes were not at a late stage of the disease, and because each specimen represented only a minute sample of the total anterior segment trabecular and iris tissue, it is remarkably consistent that the presence of ectopic endothelium was so frequently evident.

In those eyes in our series that underwent trabeculectomy, the cornea in each case was clear, although glaucoma was present and medically uncontrolled. It is probably only later in some eyes that corneal endothelial dysfunction becomes so severe that corneal edema develops. If this sequence is the typical one, then glaucoma would usually precede corneal clouding, and eyes requiring keratoplasty would have already developed glaucoma. Certainly our cases followed this general pattern, because in all nine patients glaucoma developed first, with only four patients later progressing to corneal edema despite normalized intraocular pressure. It is unclear whether the migration and/or proliferation of endothelial cells onto the trabecular meshwork and iris actually deplete the residual corneal endothelial cell population, thereby precipitating corneal edema. On the contrary, in two of our patients requiring keratoplasty from whom iris specimens were obtained, no endothelial surface proliferation was observed, although the limited specimen sampling precluded a generalized conclusion. If, however, we are to assume this mechanism, then the intriguing paradox arises whereby there are migrating and presumably proliferating endothelial cells that extend over the angle and iris, and coexistent endothelial cells that remain on the cornea but are reduced in number and are so incapable of proliferation that they enlarge, attenuate, secrete posterior collagen layers, and degenerate. These pathologic findings have been confirmed in each morphologic report of corneal tissue in Chandler's syndrome[16–18] and other ICE syndrome patients,[3,5,6] and this is entirely consistent with the findings in the four keratoplasty specimens in our study.

There has been some recent controversy about the detailed ultrastructure of the corneal endothelial cells in Chandler's syndrome. Rodrigues and colleagues[17,18] have observed endothelial cells to be attenuated, degenerated, and possessing both microvilli and some junctional complexes, but they have not reported epithelial-like characteristics. Further, in performing immunochemical stains for keratin, the endothelium of Chandler's syndrome corneas showed no keratin, again lacking this epithelial feature.[19] In the recent case studied by Hirst et al,[8] several epithelial characteristics — including intracytoplasmic 8-nm filaments, desmosomes, microvillous projections, and immunohistochemically demonstrable keratin — were noted. Similar ultrastructural features had been described in the report by Quigley and Forster[15] in cases that shared other clinical aspects (dominant inheritance and bilateral involvement) consistent with posterior polymorphous dystrophy, a condition characterized by epithelial-like cells interspersed among more-typical corneal endothelial cells.[14,17,19] Perhaps this latter case represents a transitional point in a spectrum that includes both Chandler's syndrome and posterior polymorphous dystrophy.

In the Chandler's syndrome cornea reported by Richardson,[16] intracytoplasmic filaments were a consistent feature of the degenerating endothelial cells. Although such filaments can hardly be identified as keratin on the basis of ultrastructure alone, this possibility remains to be explored.

In our cases, such intracytoplasmic filaments were evident in the endothelial cells of three corneas (Cases 2, 5 and 6) and one iris specimen (Case 4). The specificity of this finding is in question, however, because the acquisition of increased intracytoplasmic filaments within aberrant endothelial cells might also be interpreted as nonspecific evidence of endothelial distress, similar findings being widely apparent in other degenerative and dystrophic endotheliopathies.[10,12]

Clearly, the abnormal endothelium of Chandler's syndrome can show various morphologic appearances, probably depending in part on the stage of the disease and the areas from which tissues are examined. Additional careful clinicopathologic studies will be required to determine whether proliferative and degenerative responses of the endothelium can occur sequentially or simultaneously within the same eye, and whether these epithelial-like characteristics represent a consistent mosaicism or transformation of the endothelial cell population. Regarding the latter, we think it may currently be appropriate to consider that Chandler's syndrome and posterior polymorphous dystrophy can have some cytologic, and hence pathogenetic, aspects in common. The cases of posterior polymorphous dystrophy that develop peripheral anterior synechiae, iris stromal abnormalities, and glaucoma show further how the clinical picture and pathogenesis of these disorders can be related.

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