CLINICAL PATHOLOGICAL REVIEW

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Morphologic Characteristics of Posterior Polymorphous Dystrophy. A Study of Nine Corneas and Review of the Literature

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Abstract. Based on their own study of nine corneas with clinically documented posterior polymorphous dystrophy and a review of the literature, the authors describe the morphologic features of this entity. Study by phase contrast light microscopy and transmission and scanning electron microscopy found that changes were primarily in the endothelium and consisted of endothelial cell degeneration and loss with focal fibroblastic and epithelial-like cell transformation. Secondary alterations of Descemet's membrane were seen; they consisted of abnormal lamination with deposition of abnormal collagen material, particularly in the posterior collagen layer, and formation of guttate excrescences and pits. (**Surv Ophthalmol 29:**139–147, 1984)

Key words. cornea • corneal endothelial cells • Descemet's membrane • histopathology • phase contrast light microscopy • posterior polymorphous dystrophy • scanning electron microscopy • transmission electron microscopy

Posterior polymorphous dystrophy (PPMD) of the cornea is a bilateral, autosomal dominantly determined, usually nonprogressive condition that basically affects the deepest layers of the cornea. Clinically, the lesions may appear as geographic and vesicular grayish patches at the level of the endothelium, sometimes accompanied by excrescences projecting into the anterior chamber and by localized infoldings or pits of Descemet's membrane. The disease often evolves without visual impairment unless secondary changes, such as epithelial and stromal edema, occur as a result of endothelial decompensation. For this reason, relatively few cases have been studied histopathologically.[1–7,9,11–13,15,17–19] The first pathologic descriptions[7,12] illustrated abnormalities in Descemet's membrane consisting of fusiform excrescences.[7] Subsequently, attention has been given to substantial abnormalities at the level of the corneal endothelium consisting of fibroblastic and epithelial-like cell transformation.[1,2,6,11,15–17] All these reports are based on single corneal specimens except two,[2,6] which describe two and three cases, respectively. In addition, Rodrigues and associates[14,16] have com-

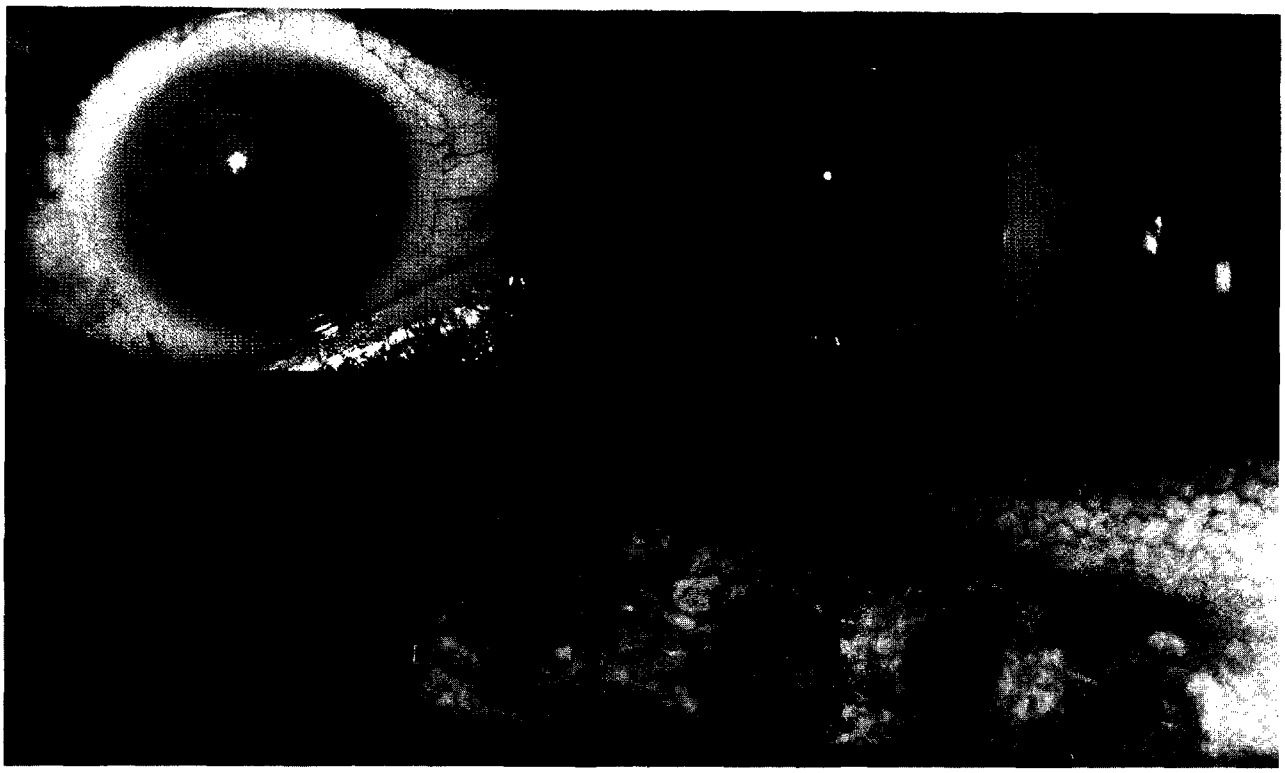

Fig. 1. Clinical photographs of patients with PPMD. Top left: Case 3 — Right eye exhibits advanced stage with corneal opacification due to stromal and epithelial edema. Top middle: Case 3 — Left eye shows Descemet's membrane alterations but without stromal edema. Top right: In a similar case, retroillumination best highlights polymorphous opacities. Bottom: Wide field specular microscopy resolves grouped vesicle-like Descemet's membrane thickenings with associated focal abnormalities of underlying endothelial cells. Note morphologic normal appearance of surrounding endothelium. (Photos courtesy of Philip Ruderman)

TABLE 1

Morphologic Features of Nine Posterior Polymorphous Dystrophy Corneas

Case #, age (yr), sex, eye	Epithelial edema	Focal Bowman's membrane disruption	Stromal edema	Descemet's membrane				
				Thickness (μm)	Abnormal lamination	Abnormal collagen deposition	Guttate excrescences	Pits
1,74,M,OS	+	+	+	7.5	+	+	+	−
2,54,F,OS	+	−	+	10	+	+	+	−
2,54,F,OD	+	−	+	7.5	+	+	+	−
3,35,M,OD	+	+	+	20	+	+	+	−
3,35,M,OS	+	−	+	15	+	+	+	−
4,45,M,OD	+	+	+	15	+	+	+	+
5,32,M,OS	+	+	+	7.5	+	+	−	−
6,42,M,OD	+	−	+	7.5	+	+	−	−
7,52,M,OS	+	+	+	8	+	+	−	−
Total	9	5	9		9	9	6	1

+ = present; − = not present; ND = not done.

pared ultrastructural pathology and in vitro morphology in four cases.

In this review, we summarize the morphologic changes in nine corneas of seven patients with clinically documented PPMD and compare our findings in this series with the previously reported cases.

Study Design

The nine corneas studied were from seven patients, six male and one female, whose ages ranged from 25 to 74 years with an average of 50 years. All had bilateral, typical changes of PPMD.[1,6,7] In each eye requiring corneal transplantation, stromal and epithelial edema had also developed (Fig. 1). At surgery, each corneal button was immediately placed in a solution of 2.5% buffered glutaraldehyde with 2% formaldehyde, where it remained for at least two hours. It was then removed and divided, and the segments processed for transmission electron microscopy (TEM) and scanning electron microscopy (SEM).

All tissue for TEM was postfixed in 1% cacodylate-buffered osmium tetroxide, dehydrated in graded alcohols, and embedded in araldite epoxy resin. Thick sections of about 1 μm were cut, stained with paraphenylenediamine, and examined by phase contrast for orientation and photomicrography. Representative areas were selected for TEM examination. Ultrathin sections were doubly stained with uranyl acetate and lead citrate and examined with a Philips 300 transmission electron microscope.

Specimens for SEM were also postfixed in 1% buffered osmium tetroxide. After fixation, tissues were dehydrated in graded alcohols followed by four changes of Freon-113 for one hour and subsequently critical-point dried utilizing Freon-113 gas. Then the specimens were affixed to aluminum mounts with silver conductive paint, coated with gold palladium in a vacuum evaporator equipped with a rotating stage, and examined with a Jeol-JSM35 or AMR 1000-A scanning electron microscope operated at 25 Kv.

TABLE 1
(Continued)

Endothelium				
Attenuation	Cell size variation (by SEM)	Focal cell loss	Fibroblastic proliferation	Epithelialization
+	+	–	–	–
+	+	+	+	–
+	+	+	–	+
+	+	+	+	+
+	+	+	+	+
+	+	+	+	+
+	+	+	–	+
+	ND	–	–	+
+	ND	+	–	+
9	7	7	4	7

Morphologic Features

The morphologic features of the nine corneas are summarized in Table 1. They are described in more detail below.

SCANNING ELECTRON MICROSCOPY

Seven specimens were examined by SEM. The posterior corneal surface was lined by polygonal endothelial cells of variable size with a diameter ranging from normal (~15 μm) to greatly enlarged (>40 μm). Most cells showed scant microvillous projections (Fig. 2A), prominent round or oval nuclei, and collapsed cytoplasm that connected with neighboring cells by numerous interdigitations. Although all specimens exhibited considerable endothelial pleomorphism, only one showed extensive areas without endothelial cells (Fig. 2B), as the remaining cells were enlarged, attenuated, and bizarrely extended, ranging in diameter from about 30 to 95 μm. In areas devoid of cells, a finely fibrillar posterior collagen layer subjacent to Descemet's membrane was exposed (Fig. 2B).

In six corneas, extensive areas exhibited large, epithelial-like cells covered by many microvillous surface projections (Figs. 2C–F). Most striking was the abrupt transition between endothelial- and epithelial-appearing cells (Figs. 2D, F).

PHASE CONTRAST MICROSCOPY

In all nine corneas, the epithelium was irregularly thickened, with an edematous basal cell layer. In five instances, Bowman's layer showed focal disruption with penetration of epithelial cells into the superficial stroma. There was diffuse edematous thickening of the stroma in all cases. In all corneas, Descemet's membrane appeared to be abnormally laminated (Figs. 3–6, insets). It was 7.5–10 μm in thickness in six instances, and 15–20 μm in three. In six corneas, guttate-like excrescences of Descemet's membrane were seen (Fig. 4); the excrescences ranged in height from 2.5 to 15 μm. One specimen showed pits formed by infolding of Descemet's membrane (Fig. 6). The infolded portion was filled with fibrous tissue.

The posterior surface of all corneas had areas of attenuation or discontinuity of the endothelial cell layer (Fig. 5). In some instances, focal areas of endothelium were replaced by multilayered clusters of fusiform cells (Fig. 3).

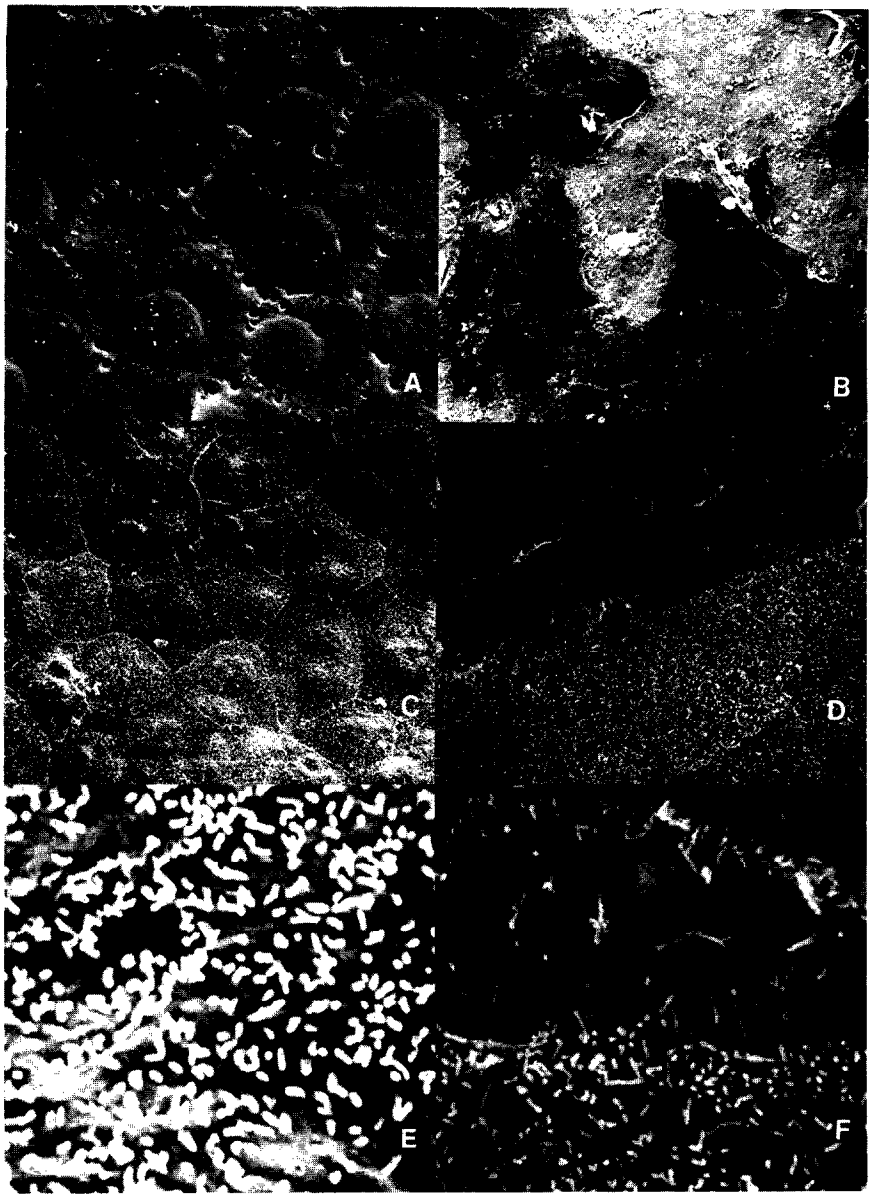

Fig. 2. Endothelial surface in PPMD as seen by SEM. A: Case 3, left eye. Endothelial cells vary markedly in size (× 2000). B: Case 4. Geographic area of endothelial cell degeneration (upper right) exposes fibrillar posterior collagen layer. Remaining cells are configured bizarrely, with extended cytoplasmic processes (× 540). C: Case 5. Epithelial-like cells line posterior corneal surface (× 1,000). D: Case 5. Typical polygonal endothelial cells (above) contrast with adjacent epithelial-like cells displaying numerous microvilli (below) (× 3,000). E: Case 5. Higher magnification of C; myriad microvilli cover posterior surface membrane of the epithelial-like cells (× 10,000). F: Case 5. Higher magnification of D details abrupt transitional zone between epithelial-like cells (below) and more normal-appearing endothelial cell surface (above) (× 9,400).

TRANSMISSION ELECTRON MICROSCOPY

Important TEM findings were limited to Descemet's membrane and endothelium. In all instances, Descemet's membrane displayed abnormal lamination and abnormal deposition of fibrillar and basement membrane collagenous material in its posterior portion (Figs. 3–5). This posterior collagenous layer was often interrupted by irregular thickenings or excrescences (Fig. 4), which showed the ultrastructural features of typical guttata, as small-diameter collagen fibrils 20 to 30 nm in diameter were interspersed with larger aggregates of about 100 nm macroperiodicity. Fibroblastic cells with prominent rough endoplasmic reticulum were numerous within the fibrocellular proliferation filling the Descemet's membrane pits and within the posterior collagenous layers (Fig. 6).

In all instances, thin, attenuated endothelial cells were found (Fig. 5). In seven specimens there was evidence of endothelial cell degeneration with disorganization of organelles, phagosomal inclusions, and destruction of the cell membrane (Fig. 4). Cells with the characteristics of fibroblasts (four corneas) and epithelial-appearing cells (seven corneas) were present lining the posterior aspect of Descemet's membrane. The epithelial-like cells were often mul-

Fig. 3. Case 3, right eye. Inset A: Phase contrast photomicrograph illustrates markedly thickened, multilaminated Descemet's membrane. Arrows delineate anterior boundaries of Descemet's membrane. The endothelium appears replaced by multilayered fusiform cells (paraphenylenediamine, × 400). Main figure TEM shows Descemet's membrane to have a normal-appearing anterior-banded zone with long-spacing 110 nm collagen (Da), and an extremely thickened (~15 μm) posterior portion (Dp) composed of several layers of abnormal collagen material of different electron density and band periodicity. Normal endothelium is absent; instead, epithelial-like cells with numerous microvillous projections, desmosomal attachments (arrows), and aggregates of keratofibrils are seen (× 12,800). Inset B: Higher-magnification TEM of area indicated by asterisk in main figure resolves randomly arranged collagen fibrils of large diameter (~60 nm) (× 43,400).

tilayered and showed numerous microvillous projections on the surface facing the anterior chamber. Desmosomal attachments and keratofibrils were particularly prominent (Fig. 7). In one of the two cases studied bilaterally, the left eye showed fibrous tissue proliferation as a posterior collagen layer, and the right eye had extensive epithelial-like cell transformation of the endothelium.

Discussion

This histopathologic study of nine PPMD corneas presents the largest currently available series of this relatively rare disease. The diagnosis of PPMD was based on biomicroscopic and clinical observations, which were supported by the characteristic slow progress of the disease with relatively good vision until endothelial decompensation occurred. Changes in Descemet's membrane consisting of deposition of abnormal collagen material[1–5,9,11,13–19] with pathologic lamination was by far the most constant finding. In all instances, these changes resulted in variable thickening of Descemet's membrane; in no instance was attenuation noted as described by Hanna and coworkers.[3] Similarly, none of our cases showed abnormal calcification of Descemet's membrane.[7] On the other hand, excrescences in

Fig. 4. Case 2, left eye. Inset (top left): Phase contrast photomicrograph of guttate changes in Descemet's membrane with many irregularly shaped excrescences and deteriorating endothelial cells (paraphenylenediamine, × 400). Main figure TEM illustrates ultrastructural details of these lesions as remnants of a degenerating endothelial cell (E) seen between two excrescences (*) of Descemet's membrane. Da, anterior banded zone of Descemet's membrane (× 13, 500). Inset (top middle): Higher-magnification TEM of areas indicated by arrows in main figure discloses fusiform configuration of long-spacing collagen with 100 nm macroperiod typical of guttata (× 74,800).

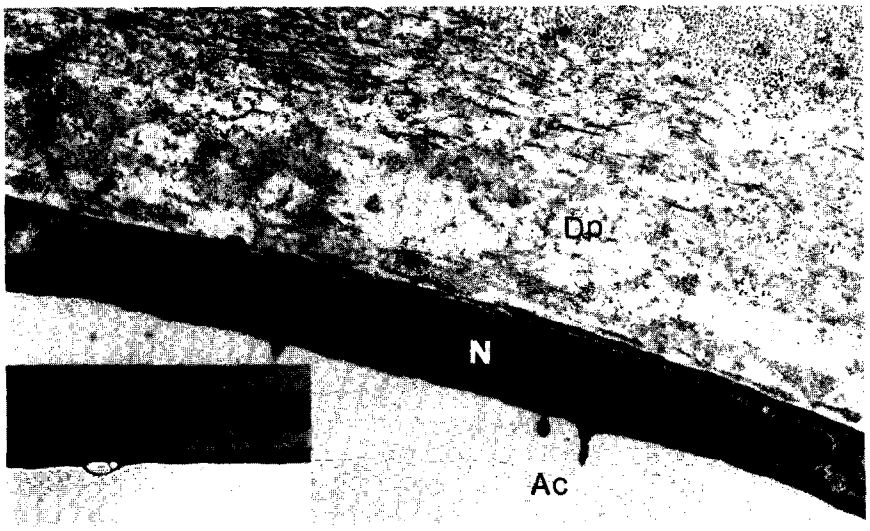

Fig. 5. Case 4. Inset: Phase contrast photomicrograph shows attenuated endothelial cells with intercellular vacuolar formation (paraphenylenediamine, × 400). Main picture illustrates fusiform nucleus (N) of a flattened endothelial cell lining abnormal posterior collagen region (Dp) of Descemet's membrane. Ac, anterior chamber (× 19,000).

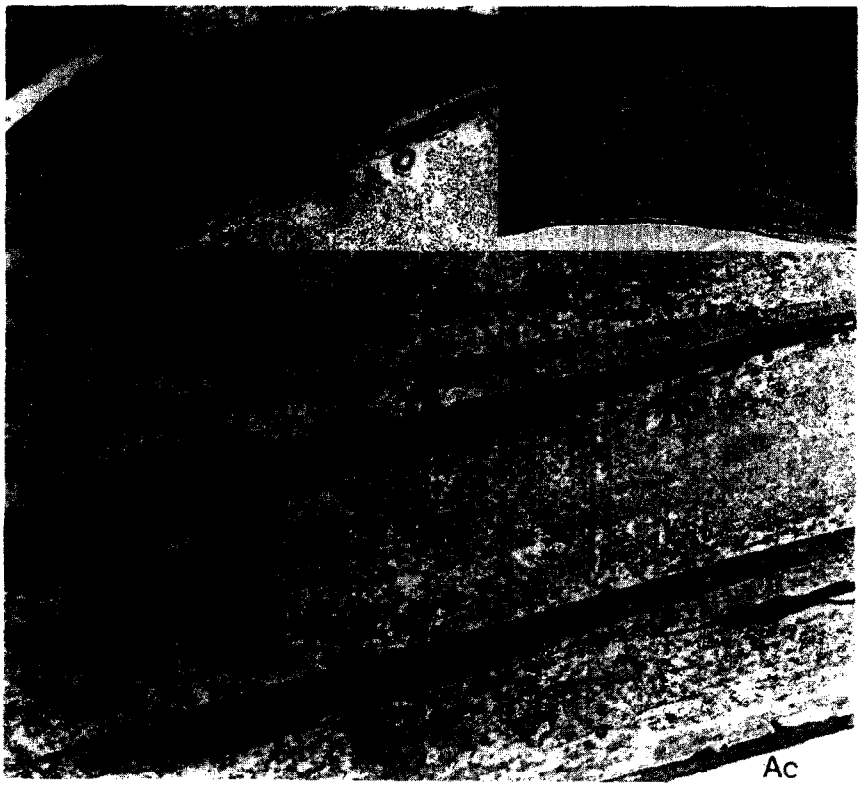

Fig. 6. Case 4. Inset (upper right): Phase contrast photomicrograph shows a posterior stromal pit as an infolding of Descemet's membrane. Note continuity of fibrocellular tissue (filling central cavity) with posterior collagen layer of Descemet's membrane (paraphenylenediamine, × 400). Main-figure TEM of posterior collagen layer demonstrates several fibroblastic-appearing cells (F) interposed among loose collagenous tissue (Co). The endothelial cell (lower right) is extremely attenuated. Ac, anterior chamber (× 8,900). Inset (upper left) details a fibroblastic cell, particularly its abundant, rough-surfaced endoplasmic reticulum (× 13,400).

Fig. 7. Case 3, right eye. Survey TEM illustrates multilayered, stratified epithelial-like cells with microvillous surface projections, desmosomal attachments (arrowheads), and bundles of cytoplasmic filaments (arrows). Ac, anterior chamber; Dm, Descemet's membrane (× 7,500). Insets: (A) Detail of cytoplasmic filaments (× 46,500). (B), (C) Detail of microvilli as seen in transverse and longitudinal sections, respectively. Note resolution of central filamentous core typical of cilia (B, × 87,500; C, × 75,000).

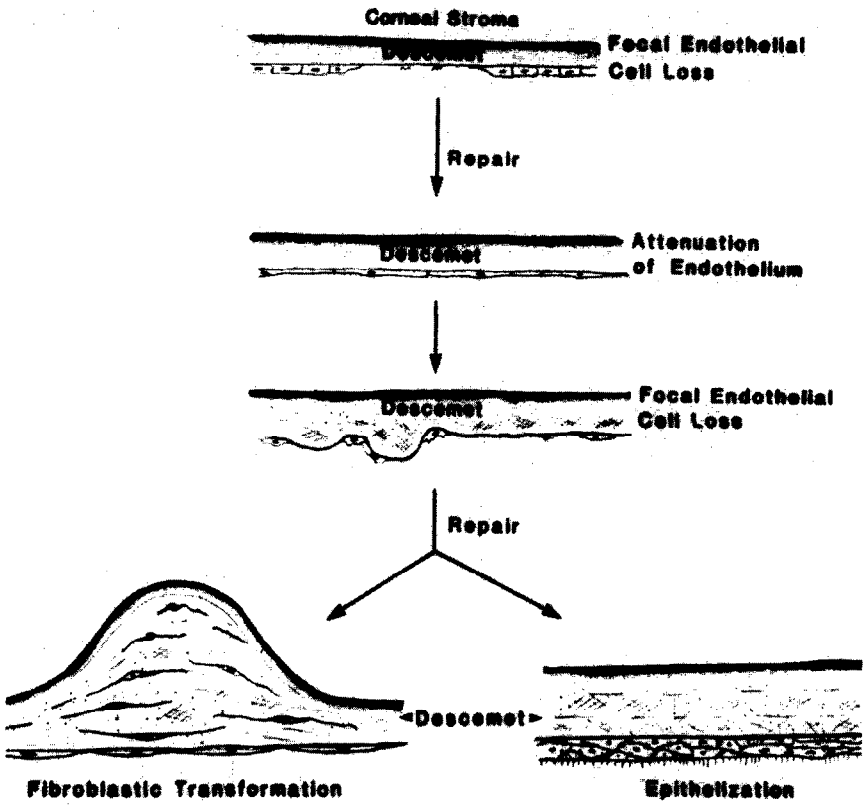

Fig. 8. Schematic hypothesis of pathogenesis of posterior polymorphous corneal dystrophy.

Descemet's membrane made of intermixed abnormal collagen and basement membrane material were common, being present in six of the specimens. These excrescences most commonly appeared similar to typical cornea guttata[7,14] rather than to the fusiform excrescences originally described by Morgan and Patterson[12] and later by others.[4,9] Pits in Descemet's membrane as described by Polack and coworkers[13] were found in only one instance.

Pleomorphism and attenuation of the endothelium, with flattened, elongated, and widely spaced cells,[2–4,6,7,9] was also a common finding and was usually accompanied by areas of focal endothelial cell loss,[2,4,7,13] as would be expected since corneal edema is the sole indication for keratoplasty in these cases. Pigmented endothelial cells[11] were not found. Hyperplastic, multilayered endothelium, as described by Tripathi and co-workers in one case of PPMD,[18] was not observed, although we believe that this might conceivably represent one stage or variation in the transformation of endothelium to epithelium. Similarly, the TEM illustrations in the case described by Polack and co-workers[13] suggest epithelial tissue lining the posterior surface of Descemet's membrane rather than multilayered endothelium.

Focal epithelialization of corneal endothelium, one of our most interesting findings, was present in seven of the nine specimens. This observation has also been emphasized by others.[6,14–16] Whether this represents a real transformation of endothelium into epithelial cells or embryonic mosaicism remains to be elucidated. At any rate, the epithelial nature of these "transformed" endothelial cells seems beyond doubt, based on recent demonstration by the same investigators of the presence of epithelial keratins with the epithelial-like PPMD cells.[14–16] Fibrocellular tissue proliferation as a posterior collagen layer, found in three instances, was particularly prominent in the case exhibiting pits in Descemet's membrane. Both fibroblastic and epithelial transformations are consistent with the cellular differentiation potential of the endothelium, as Johnson and Brown[9] and Rodrigues et al[17] have suggested.

Because combinations and variations within this range of abnormalities were seen among several cases of our series, we conclude that changes reported in these individual cases are undoubtedly part of the pathologic spectrum occurring in this syndrome. We think that the primary abnormality in PPMD is in the endothelium and that the changes in other structures, such as Descemet's membrane, stroma, and epithelium, are secondary.

The pathogenesis of PPMD remains entirely unknown. On the basis of our observations and those

of others, however, we propose the following speculative hypothesis (Fig. 8). For unknown reasons, focal areas of endothelium degenerate. The abnormal secretion of basement membrane and fibrillar collagen material as a posterior collagen layer is evidence of the usual secretory response of stressed endothelium.[10,19] As the process of abnormal collagen formation and cellular degeneration progresses, it leads to the formation of fusiform guttata or irregularly shaped excrescences on the posterior collagen layer of Descemet's membrane. Attempts at repair are made by neighboring endothelial cells which spread to cover the defect, resulting in an attenuated appearance of these cells. In some cases, there may be a fibroblastic transformation of endothelial cells with the formation of a fibrocellular posterior collagen layer.[2,19] Alternatively, the attempts at regeneration and repair from endothelial cells may result in an epithelial-like transformation with multilayered cells, desmosomal attachments, keratofibrils, and microvillous projections. At some point, an insufficient number of endothelial cells are present to cover the defects, leading to clinically manifest corneal edema. Although this hypothesis provides a consistent explanation of the observed clinical and pathological alterations in PPMD, the fundamental issue of whether this dystrophy represents an abnormal endothelial differentiation with subsequent degeneration and/or a true epithelial mosaicism of the endothelogenic mesenchyme remains to be resolved.

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