Brit. J. Ophthal. (1973) **57**, 376

Cystic disorders of the corneal epithelium

II. Pathogenesis

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Epithelial cysts have been observed in histological and ultrastructural studies of various kerato-conjunctival disorders (Cogan, 1941; Hogan and Zimmerman, 1962; Cogan, Donaldson, Kuwabara, and Marshall, 1964; Kuwabara and Ciccarelli, 1964; Guerry, 1965; Duke-Elder and Leigh, 1965; Wolter and Fralick, 1966; Burns, 1968; Khodadoust, Silverstein, Kenyon, and Dowling, 1968; Goldman, Dohlman, and Kravitt, 1969; Kenyon and Dowling, 1968; Goldman, Dohlman, and Kravitt, 1969; Kenyon, 1969; Ashton, 1971; Iwamoto and DeVoe, 1971; Dohlman, 1971; Schroder and Hanna, 1971; Tripathi and Bron, 1972; Trobe and Laibson, 1972). Our knowledge of the morphogenesis of such cysts, however, remains limited. In the preceding paper (Bron and Tripathi, 1973), the clinical features of various cystic disorders of corneal epithelium have been presented. The present study by light and electron microscopy has been undertaken with a view to providing a clinico-pathological correlation of some cystic epithelial lesions, and on the basis of our findings a unified hypothesis is presented underlining the pathogenesis of cystic disorders of the epithelium.

Material and methods

The specimens (Table) were obtained surgically either as a stripped piece of the corneal epithelium or after a partial or full-thickness keratectomy. The conjunctival epithelium was excised as biopsy material.

Table *Specimens obtained from 46 cases*

Corneal epithelial biopsies		*Full- or partial-thickness corneal discs*		*Conjunctival biopsies*	
Clinical diagnosis	*No. of cases*	*Clinical diagnosis*	*No. of cases*	*Clinical diagnosis*	*No. of cases*
Recurrent erosion syndrome	3	Fuchs's endothelial dystrophy	8	Conjunctival chemosis (? Epidemic virus conjunctivitis)	2
Cogan's cystic dystrophy	2	Posterior polymorphous dystrophy	2	Episcleritis nodules	4
?Meesmann's dystrophy	2	Folds in Descemet's membrane	1		
Other unspecified epithelial keratopathies	5	Congenital endothelial dystrophy	2		
		Reis-Bücklers' dystrophy	4		
		Macular dystrophy	2		
		Granular dystrophy	4		
		Lattice dystrophy	5		

Received for publication November 28, 1972
Presented in part at the meeting of the Ophthalmological Section of the Royal Society of Medicine, London, December 9, 1971
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For a precise clinico-pathological correlation, the orientation and topography of the epithelial lesions were carefully checked. The tissue was divided into two halves; one half was fixed in formol saline for conventional histology and the other half in either 2·5 per cent. glutaraldehyde or 1 per cent. osmium tetroxide for electron microscopy.

The formol saline-fixed specimens were used for frozen sections and for paraffin wax or celloidin embedding; sections were stained with haematoxylin and eosin, periodic acid-Schiff (PAS) and haematoxylin, Masson trichrome, Alcian blue, Gomori silver technique, Hale's colloidal iron, and toluidine blue. The specimens for electron microscopy were embedded in Araldite, semi-thin sections (1–2μm.), cut on an LKB ultramicrotome using glass knives, and stained with toluidine blue for light microscopy. Thin sections (50–90 nm) were cut from selected areas of the block and stained with uranyl acetate and lead citrate, and electron micrographs were taken using an AEI EM6 electron microscope.

Structure and ultrastructure

There appear to be three cardinal features common to most specimens studied—cysts, "pale" cells, and spongiosis. The degree of severity of these and other associated changes, however, varied in individual specimens and this will be emphasized where appropriate.

CYSTS*

In the corneal epithelium, cysts had two distinct locations:

(*a*) *Intraepithelial*

The cysts, which were seen clinically as having a globular profile and a smooth outline, presented a similar appearance in histological sections, and were mostly located in the mid and superficial regions of the epithelium (Fig. 1).

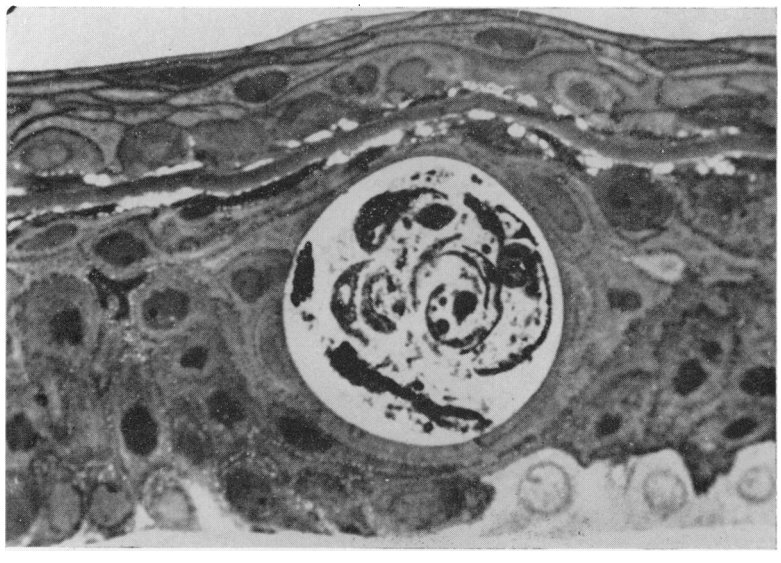

FIG. 1 *Intraepithelial cyst, containing cellular debris is seen in the midepithelial region. In the basal region (bottom-right) there are a few "pale" cells. Cogan's cystic dystrophy. Osmium-fixed, Araldite-embedded, semi-thin section, toluidine blue stained. Photomicrograph.* ×930

The central region of the cyst was usually occupied by degenerate epithelial cells and cellular debris which were moderately PAS-positive. The cysts were lined by the plasma membrane of adjacent epithelial cells which in many instances showed a corrugated appear-

* Cyst (from Greek *kustis*, bladder) — A sac with a distinct wall, containing fluid or other material.

ance apparently representing the preservation of the surface configuration of the epithelial cell membrane (Figs 2 and 3).

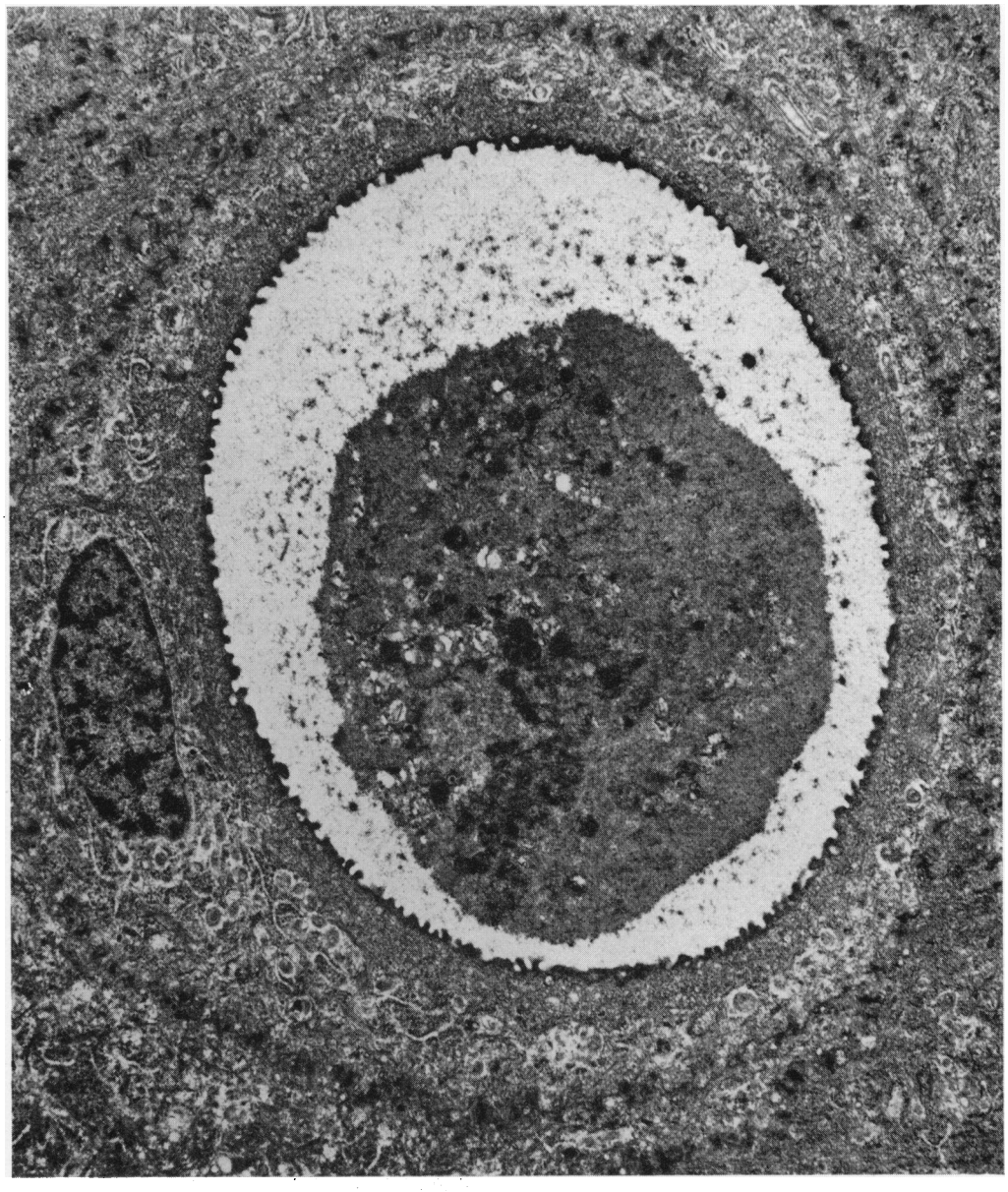

FIG. 2 *Intraepithelial cyst, containing cellular debris. Note concentric arrangement of surrounding epithelial cells and corrugated appearance of cell surfaces forming wall of cyst. Recurrent erosion syndrome. Osmium-fixed, Araldite-embedded, uranyl acetate and lead citrate stained. Electron micrograph.* × 10,000

In some instances, especially where the cysts were smaller in size, the surrounding epithelial cells had assumed a flattened and concentric profile characteristically arranged in an onion-skin fashion (Figs 2 and 4). Occasionally, a multi-nucleate giant cell encircled

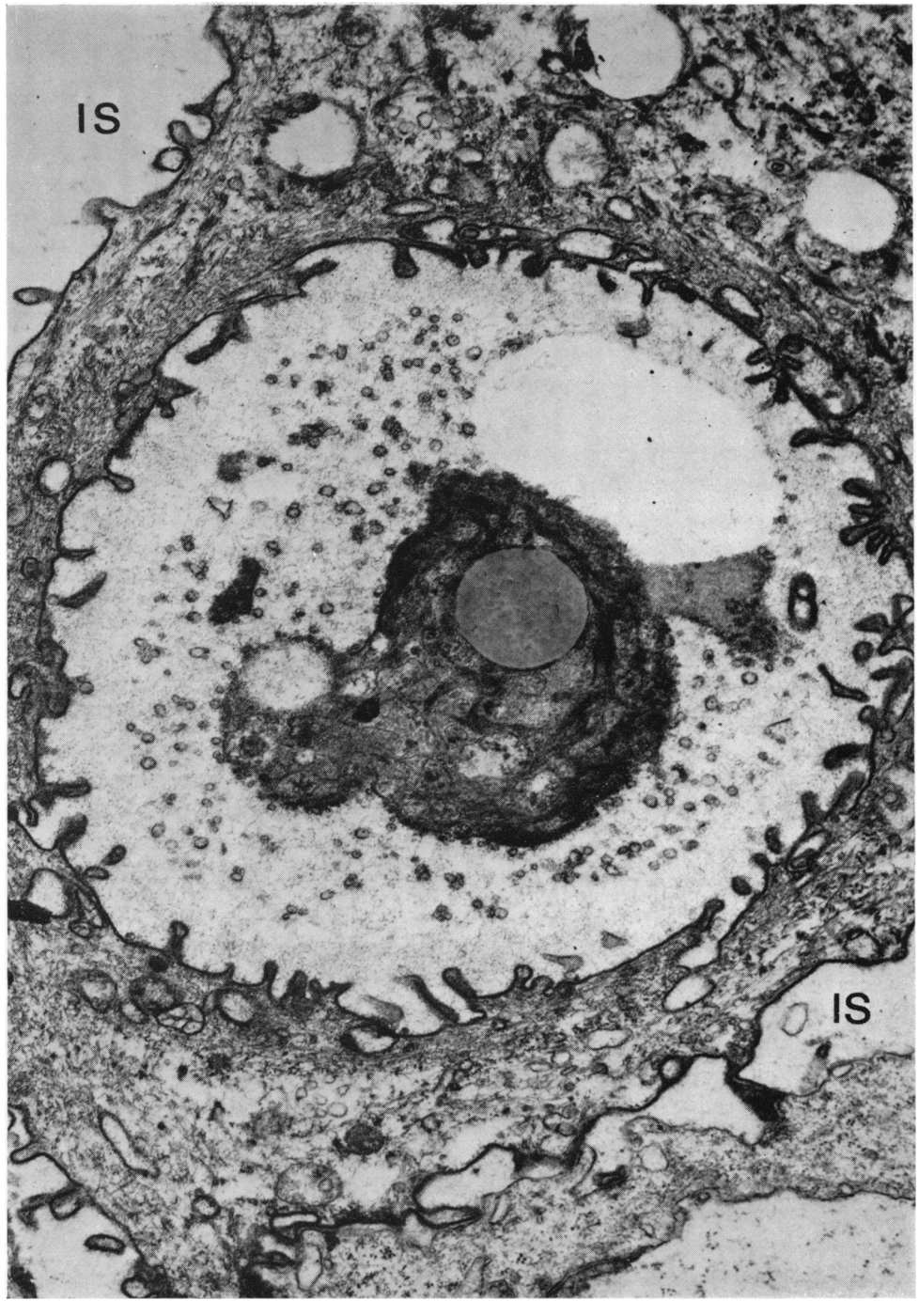

FIG. 3 *Intraepithelial conjunctival cyst, containing cellular debris. Note corrugated appearance of cell surfaces forming wall of cyst and widening of intercellular spaces (IS). Conjunctival chemosis (? epidemic keratoconjunctivitis). Osmium-fixed, Araldite-embedded, uranyl acetate and lead citrate stained. Electron micrograph.* ×25,000

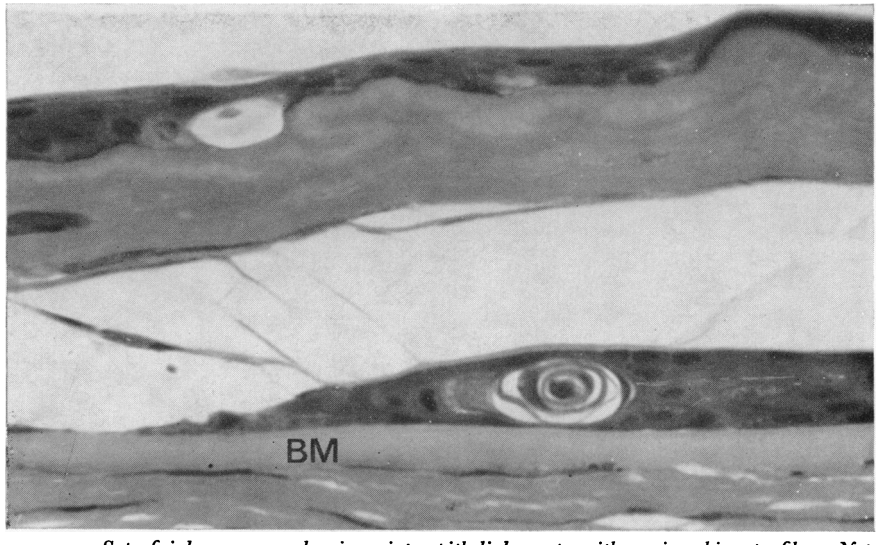

FIG. 4 *Superficial cornea, showing intraepithelial cyst with onion-skin profile. Note irregularity of epithelial thickness and proliferation of fibrous tissue artefactually separated from underlying epithelium. BM=Original Bowman's zone. Hydrokeratopathy of Fuchs's dystrophy. Formol saline-fixed, paraffin-embedded, Masson trichrome stained. Photomicrograph.* ×560

the microcyst. The size of the cysts generally corresponded to the clinical measurements as described in the previous paper (Bron and Tripathi, 1973). Examples of such cysts were seen in the recurrent erosion syndrome, Meesmann's dystrophy, Cogan's dystrophy, and other undefined epithelial dystrophies, and in some cases of hydrokeratopathy following endothelial decompensation. It should be noted, however, that the cysts in Cogan's dystrophy were very variable in size and densely packed with degenerating epithelial cells and PAS-positive material.

The cysts seen clinically as having an elongated horizontal profile were due to a separation of different epithelial layers (Fig. 5). The cysts which appeared "clear"

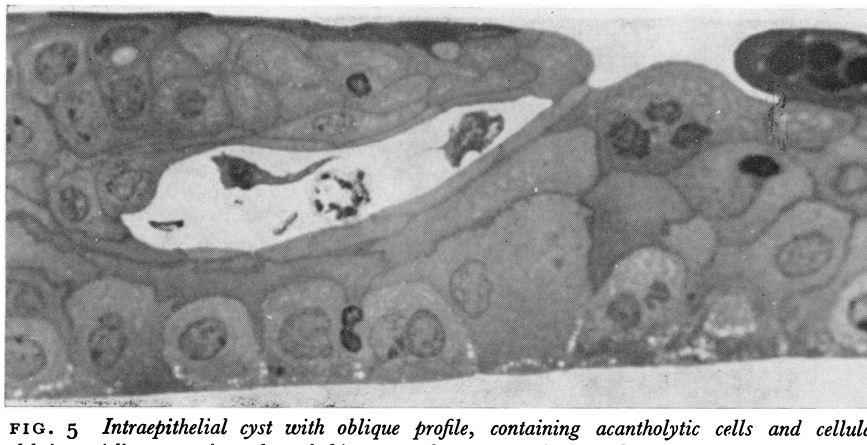

FIG. 5 *Intraepithelial cyst with oblique profile, containing acantholytic cells and cellular debris. Adjacent sections showed this cyst to be open on the superficial surface. Note also an early spongiotic change in the basal region. Recurrent erosion syndrome. Osmium-fixed, Araldite-embedded, semi-thin section, toluidine blue stained. Photomicrograph.* ×1,050

clinically when examined in electron microscopical preparations were seen to contain a sparse amount of flocculent material presumably derived from oedematous fluid, and, not infrequently, a few acantholytic cells and/or some cellular debris were also seen (Fig. 5). Occasional cysts were seen to open onto the surface. Examples of such intraepithelial cysts were seen in hydrokeratopathies following an endothelial decompensation, recurrent erosion syndrome, other ill-defined epithelial dystrophies and disorders, and occasionally in Cogan's dystrophy. In some instances of hydrokeratopathies following endothelial decompensation, the intraepithelial cysts were located between the most superficial adjacent squamous cell layers of the epithelium and these were essentially clear bleb-like vesicles.

(*b*) *Subepithelial*

In such instances, there was a complete separation of the basal epithelium from Bowman's zone of the stroma and, depending on the extent of fluid accumulation and degree of separation, this produced either a flattened or a dome-shaped elevation of the epithelial surface. These cysts were recognized clinically as bullae*, a typical feature of hydrokeratopathy following endothelial decompensation as seen in Fuchs's endothelial dystrophy and allied conditions. They usually contained flocculent material, oedematous fluid, and occasionally some cellular debris and basement membrane material.

The cysts which had opened onto the surface of the cornea produced a variable degree of irregularity of the corneal epithelium (Fig. 6). In some instances, loss of the entire thickness of the epithelium occurred in localized areas, as typically seen in the recurrent erosion syndrome and in hydrokeratopathies following endothelial decompensation.

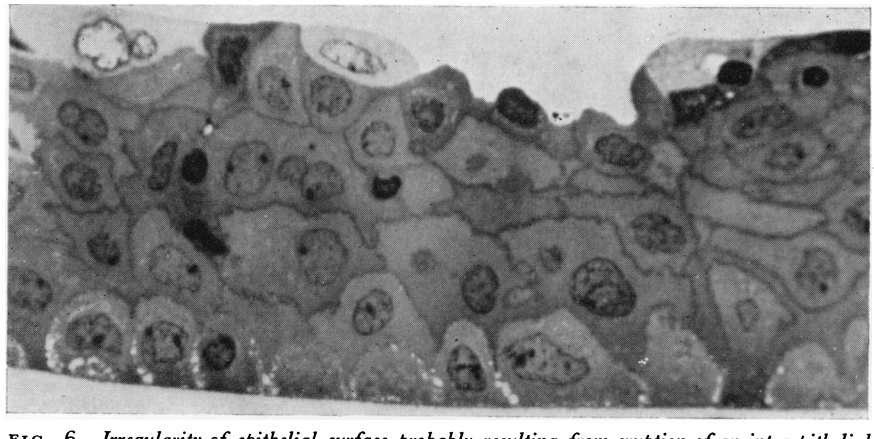

FIG. 6 *Irregularity of epithelial surface probably resulting from eruption of an intraepithelial cyst. Note also the presence of a few "pale" cells in the superficial region and some degree of spongiosis in the basal region. Unspecified epithelial dystrophy. Osmium-fixed, Araldite-embedded, semi-thin section, toluidine blue stained. Photomicrograph.* ×1,050

"PALE" CELLS

Examination of both unstained and stained sections (paraffin wax and epoxy-resin embedded) showed the majority of the epithelial cells to be fairly uniform in cellular density and staining reaction. Isolated or small groups of epithelial cells in the basal layer and occasionally in the middle and superficial layers were, however, swollen in appearance and had a low cellular density; they also reacted poorly with the stains used (Figs 1, 6, 7, 8, and 9). The nuclei of these "pale" cells were often poorly basophilic while the cytoplasm

* Bulla (Latin) — A large bleb or blister, forming either within or beneath the epidermis and filled with lymph.

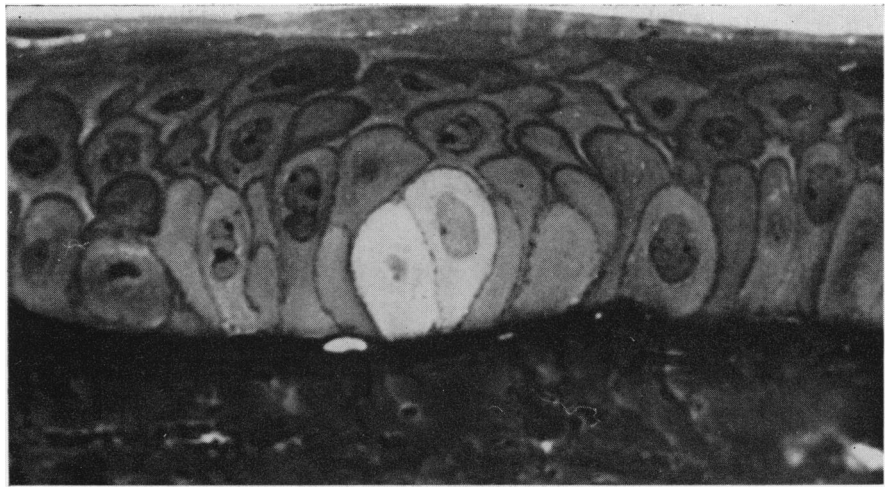

FIG. 7 *Corneal epithelium, showing two swollen "pale" cells in basal region invaginating into surrounding epithelial cells. Hydrokeratopathy of congenital folds in Descemet's membrane. Osmium-fixed, Araldite-embedded, semi-thin section, toluidine blue stained. Photomicrograph.* × 1,050

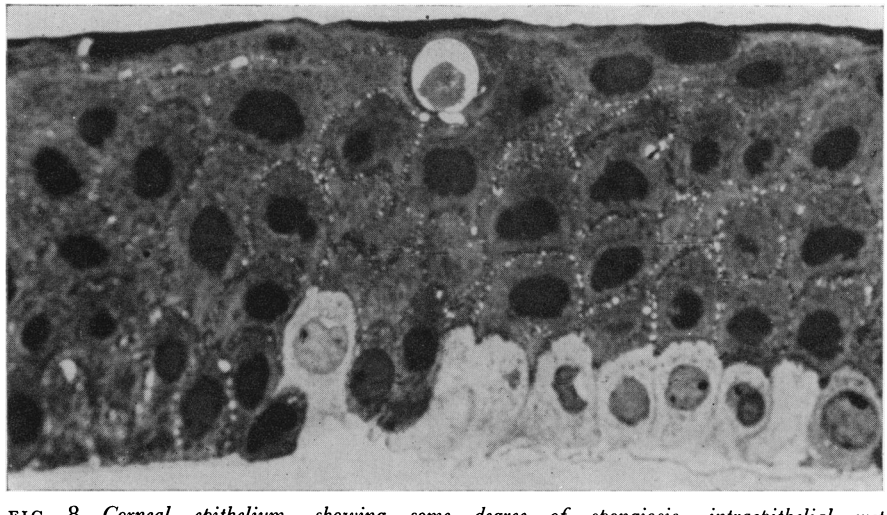

FIG. 8 *Corneal epithelium, showing some degree of spongiosis, intraepithelial cyst, and many "pale" cells in basal region. Note separation of basement membrane in region of "pale" basal cells. Recurrent erosion syndrome. Osmium-fixed, Araldite-embedded, semi-thin section, toluidine blue stained. Photomicrograph.* × 1,050

showed small vacuoles and faint eosinophilia. Electron microscopy confirmed the low cellular density and predominant basal location of the "pale" cells seen by light microscopy. The desmosomal attachments of these cells were ill-defined and adjacent cells of the same group showed fewer interdigitations and intercellular clefts (Fig. 10). The cell membrane was poorly demarcated and occasionally interrupted in places. The cell was relatively depleted of its glycogen content, and the cytoplasmic matrix and tonofilaments were of low electron density, hence the "pale" appearance. The intracellular organelles showed degenerative changes, such as swollen mitochondria, dilated endoplasmic reticulum,

FIG. 9 *Corneal epithelium, showing swollen "pale" basal cells in various stages of hydrolysis. Hydrokeratopathy of Fuchs's dystrophy.*
Formol saline-fixed, celloidin-embedded, Masson trichrome stained. Photomicrograph. × 1,050

nuclear blebs, and coarsely granular chromatin. Some cells showed advanced vacuolar degeneration and others a variable degree of cellular lysis (Fig. 9). Examples of "pale" cells were seen in many epithelial disorders (*e.g.* recurrent erosion syndrome, Meesmann's dystrophy, Cogan's dystrophy, and other epithelial keratopathies), in stromal disorders (*e.g.* granular dystrophy, lattice dystrophy, Reis-Bücklers' dystrophy, etc.), and in hydrokeratopathies following endothelial decompensation.

SPONGIOSIS

A variable degree of spongiosis was seen in most specimens, being characterized by an increase in width of the intercellular spaces of adjacent epithelial cells (Figs 3, 5, 6, 8, and 11). The degree of spongiosis varied from specimen to specimen and from the basal to the superficial layers of the epithelium, but in some regions the entire epithelium was involved. In instances where spongiosis occurred around an individual cell, such partially or completely acantholytic cells usually exhibited a shrunken profile and a somewhat increased electron density (Fig. 12). The intercellular spaces of spongiotic epithelium contained a flocculent material, probably proteinaceous elements of oedema fluid (Fig. 13). In most places the intercellular junctions were intact, while elsewhere the intercellular spaces were excessively widened and a loss of cohesion and separation of intercellular bridges (acantholysis) had occurred. Examples of spongiosis were typically seen in the vesicular stage of hydrokeratopathy following endothelial decompensation, recurrent erosion syndrome, Meesmann's dystrophy, Cogan's dystrophy, and other epithelial keratopathies.

Associated features

Certain other features are seen in association with various cystic epithelial disorders. In some cases, these could constitute a distinguishing feature of a particular epithelial disorder, *e.g.* an abnormal deposition of glycogen and/or mucopolysaccharide complex as seen in Meesmann's epithelial dystrophy, an intraepithelial proliferation of basement membrane-like material and fibrous tissue, either following endothelial decompensation, as seen in the late stages of hydrokeratopathy, or following spontaneous epithelial defect, as seen in Cogan's dystrophy. A detailed consideration of these and other associated features is, however, beyond the scope of this paper and will be the subject of a future report.

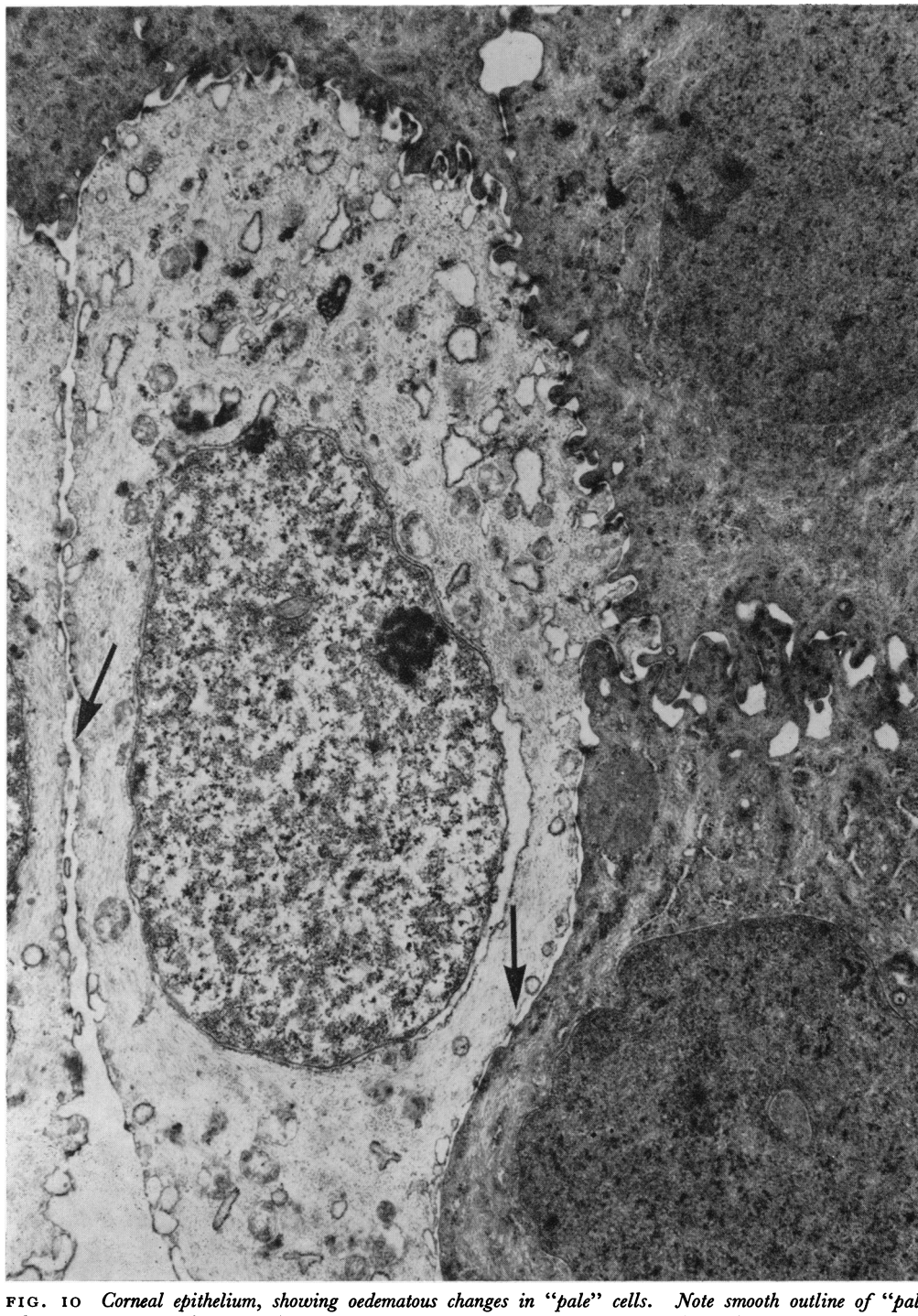

FIG. 10 *Corneal epithelium, showing oedematous changes in "pale" cells. Note smooth outline of "pale" cells in some regions (arrows), breaks in cell membrane, low electron density of cytoplasmic matrix and tonofilaments, early nuclear bleb, dilated endoplasmic reticulum, decreased glycogen granules, swollen mitochondria, granular nuclear chromatin, etc. These changes can be compared with the relatively normal appearing epithelial cells on the right. Recurrent erosion syndrome. Osmium-fixed, Araldite-embedded, uranyl acetate and lead citrate stained. Electron micrograph.* × 15,000

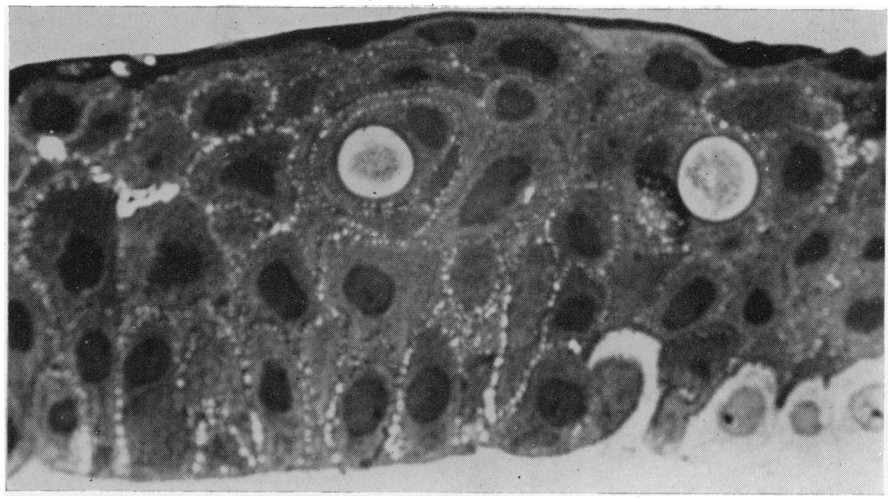

FIG. 11 *Corneal epithelium, showing a variable degree of diffuse epithelial spongiosis. Note also the presence of two intraepithelial cysts; that towards the left shows a concentric arrangement of adjacent epithelial cells, and a few "pale" cells in the basal region. Atypical Meesmann's dystrophy. Osmium-fixed, Araldite-embedded, semi-thin section, toluidine blue stained. Photomicrograph.* ×1,050

Discussion

Whereas the spongiotic appearance of the epithelium represents a state of extracellular oedema, the morphological appearances of the "pale" epithelial cells are consistent with the manifestations of intracellular oedema (see Tripathi and Bron, 1972). It would also appear that the morphogenesis of most epithelial cysts is intimately related to both of these oedematous processes. In many instances, however, it is difficult to distinguish whether a particular cyst has arisen from intra- or extracellular oedema, although the early sequence of events in either case can be considered to be fairly characteristic.

"Pale" cells would seem to be the precursors of the cysts arising from intracellular oedema. With the progression of this oedema, the cell undergoes an irreversible hydropic degeneration. After vacuolar and liquefying degeneration, the intracellular fluid is eventually released from the cell into the extracellular space through the functionally defective and/or interrupted plasmalemma. The end-result is cellular lysis with the formation of a cyst containing some cellular debris. The small cysts arising in this way usually show a circular or oval profile and, depending on the size, location, and the level of origin of the cyst, the surrounding epithelial cells assume a concentric arrangement. Judging from the morphological appearances, it would appear that this arrangement primarily results from the swelling of the "pale" cells which invaginate into the surrounding epithelium. This process may be further accentuated after cellular lysis, since additional fluid could accumulate within the cyst because of the ionic and osmotic imbalance thereby created. Larger cysts of varying sizes and shapes may be formed either by the disintegration of a group of "pale" cells or by the coalescence of small cysts.

The earliest sequence of events in the formation of an intraepithelial cyst after extracellular oedema seems to be an accumulation of fluid in the extracellular spaces. This may give rise to cysts having varying profiles (globular, elongated, or sinuous). Subepithelial bullae are formed because of the massive accumulation of fluid between the basal layer of the epithelium and Bowman's zone of the stroma.

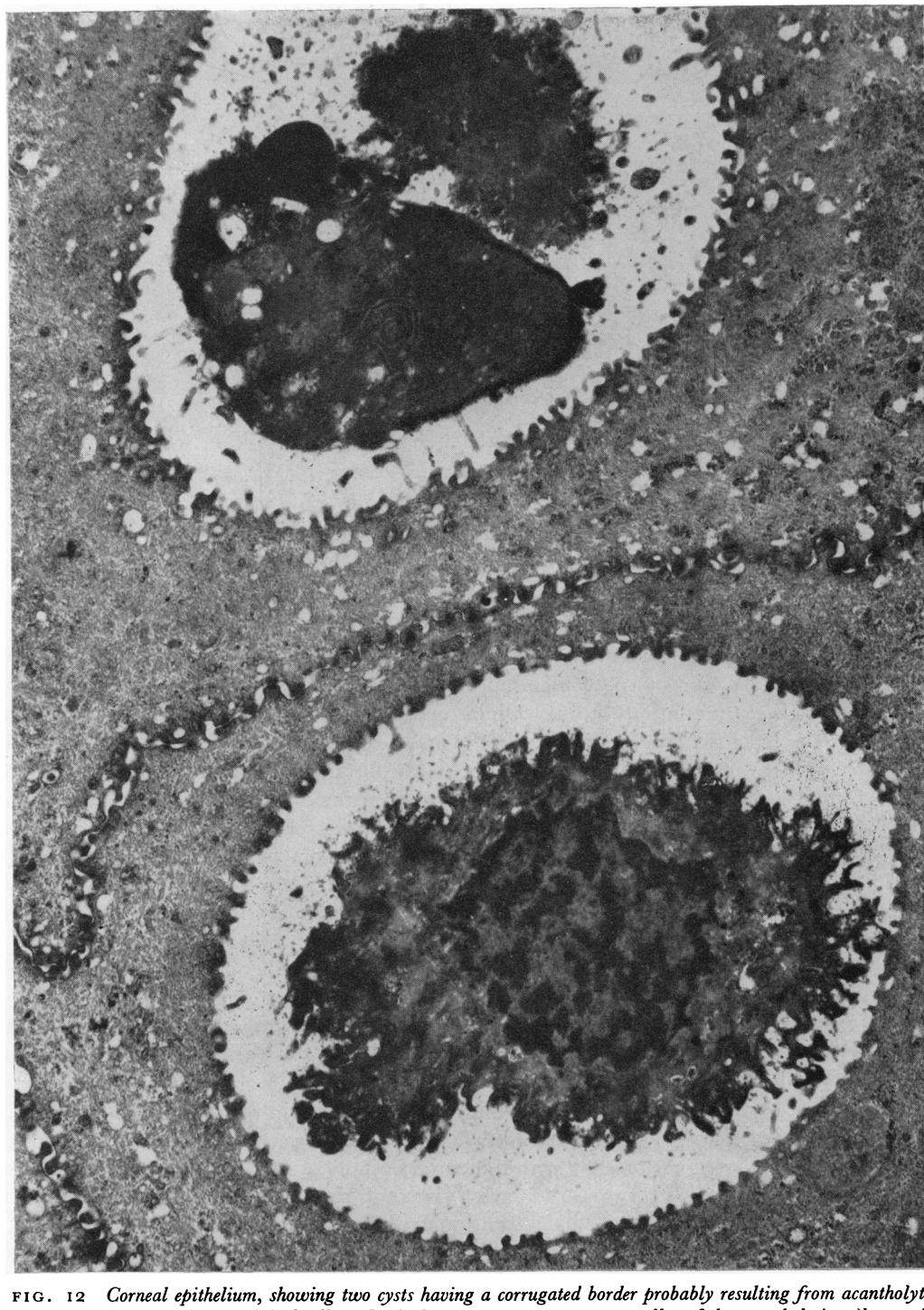

FIG. 12 *Corneal epithelium, showing two cysts having a corrugated border probably resulting from acantholytic change around individual epithelial cells. In the lowermost cyst, some organelles of the acantholytic cell are still recognizable. Recurrent erosion syndrome. Osmium-fixed, Araldite-embedded, uranyl acetate and lead citrate stained. Electron micrograph.* × 14,000

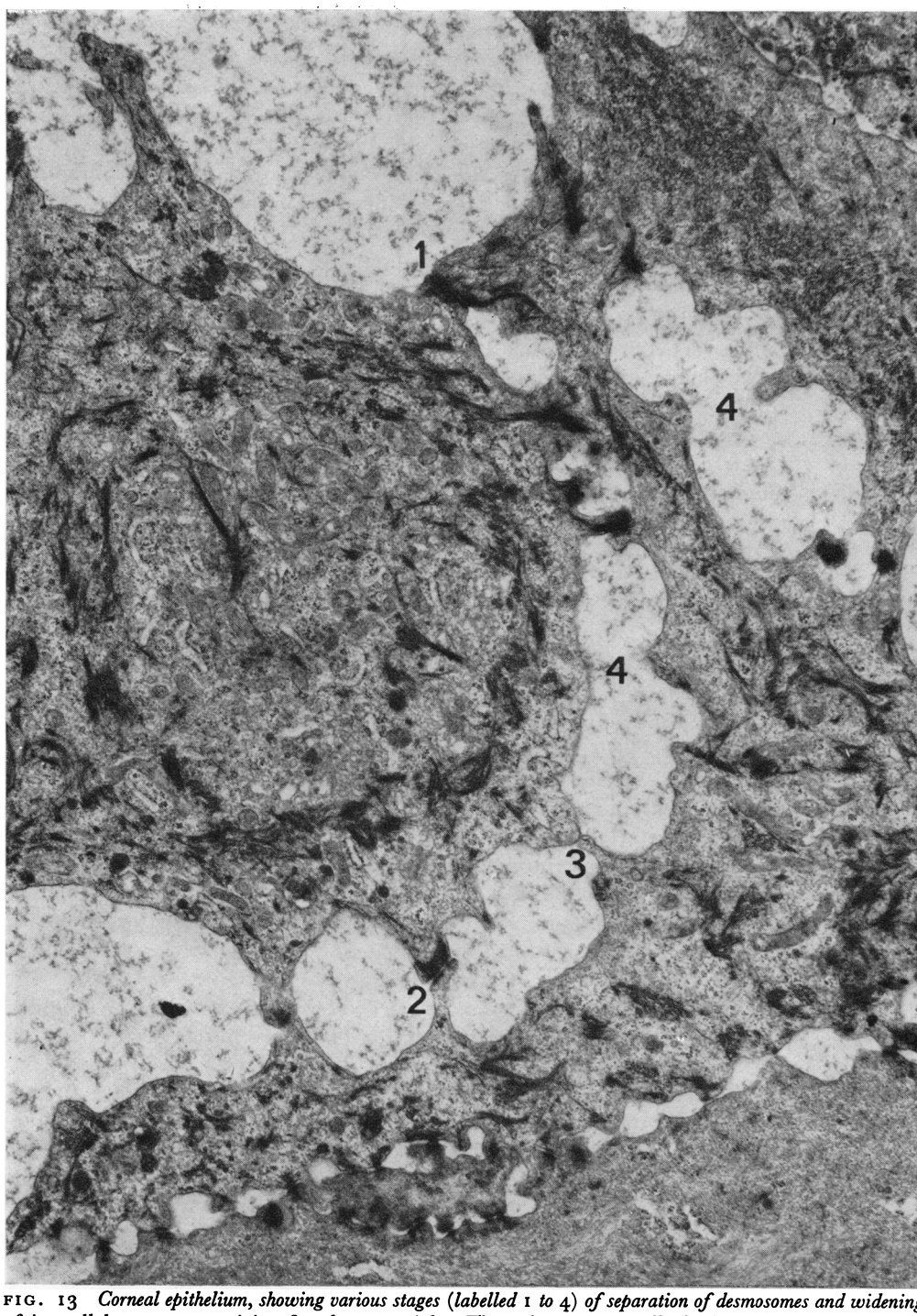

FIG. 13 *Corneal epithelium, showing various stages (labelled 1 to 4) of separation of desmosomes and widening of intercellular spaces containing flocculent material. These changes eventually lead to complete acantholysis. Cogan's cystic dystrophy. Osmium-fixed, Araldite-embedded, uranyl acetate and lead citrate stained. Electron micrograph.* ×15,000

A small globular cyst appears to originate from fluid accumulation initially around one cell or a group of cells and this leads to the complete acantholysis of these cells. It is interesting to note that, in some bullous diseases of the skin, antibodies reacting with the intercellular substance of the epidermis have been shown to be responsible for the acantholytic changes (1) (Beutner and Jordon, 1964; Beutner, Lever, Witebsky, Jordon, and Chertock, 1965; Chorzelski and Beutner, 1971). The acantholytic cells show a shrunken profile, indicating a loss of intracellular fluid (probably because of the higher tonicity of the surrounding extracellular fluid). The flattened and concentric arrangement of the surrounding epithelial cells, similar to that seen in small cysts originating from "pale" cells, would suggest the expanding nature of the cyst. The acantholytic and shrunken cell or cells within the cyst eventually disintegrate, and the remains are seen as cellular debris. The fusion of smaller cysts could give rise to a larger cyst.

An elongated or sinuous cyst probably originates from fluid accumulation between epithelial cells of different or successive layers. The early stages of the cyst appear to be localized enlargements of extracellular spaces (epithelial bedewing seen clinically). Later, either the individual clefts or lacunae enlarge enormously, separating a large number of cells, or many smaller clefts join together giving rise to large cysts. The resulting shape and size of these cysts is obviously determined by the location of the clefts. These are usually clear cysts, but it is not uncommon to see some acantholytic cells within their fluid content.

The cysts which were distinguishable clinically as bullae or large dome-shaped elevations of epithelium, and which were seen histologically to contain extracellular fluid in the subepithelial region, would appear to arise from a massive accumulation of fluid from a posterior route.

It should be noted that the characteristic appearance and fate of a cyst would seem to depend on its level of origin, location, rate of size increase, and the turnover rate of the epithelium. Smaller cysts containing cellular debris, whether surrounded by a group of epithelial cells, or enveloped by a single giant epithelial cell, gradually evolve and with the migrating epithelial cells eventually burst on the epithelial surface releasing their contents. Larger cysts, located intraepithelially, either burst at a localized spot releasing the fluid on the surface in the form of a sinus, or erupt causing loss of partial epithelial thickness. Similarly, subepithelial bullae may subside, either by bursting through a localized opening or epithelial crack, or by causing frank loss of the full-thickness epithelium in the affected area.

Although it is apparent that the oedematous processes play a dominant role in the morphogenesis of cysts, the earlier events giving rise to intra- or extracellular oedema are not absolutely clear in every instance. In hydrokeratopathy secondary to endothelial dysfunction or raised intraocular pressure, a positive fluid pressure in the stroma would appear to be the cause of epithelial over-hydration. Here, one may assume extracellular oedema to be the primary event and intracellular oedema to be a secondary change, perhaps related to a change in composition as well as amount of extracellular fluid. On the other hand, where endothelial function is normal and the barrier function of the epithelium is disturbed (*e.g.* owing to an epithelial defect or to constitutional abnormality of the tear fluid), then it is likely that the tear fluid may make a significant contribution to the extracellular oedema. Where both endothelial and epithelial barriers are intact, then it seems that occurrence of spongiosis could be explained on the basis of a defect in the cells and/or their ground substance.

Many factors could be responsible for the above epithelial defects, *e.g.* dystrophic,

1 The possibility that a similar autoimmune reaction (antibodies directed against basement membrane) may be responsible for the spontaneous loss of hemidesmosomal attachment of the basal cells in some cases of epithelial erosion needs further investigation. The role of other factors, such as subepithelial fluid accumulation, weakness of hemidesmosomes (either as inherent defect or following basal cell oedema), and a defective constitution of the basement membrane, have been discussed elsewhere (Tripathi and Bron, 1972). In addition, as Cogan (1941) has postulated, dystrophic changes in corneal nerves (see Sugiura and Matsuda, 1967) and diseases of Bowman's zone may be of significance in some cases.

toxic, infective, allergic, or neurogenic insult, etc. The cellular defect evident as "pale" cells, representing a state of intracellular oedema, may also result from these factors, although the possibility remains that some "pale" cells could occur secondary to extracellular oedema. The predominance of "pale" cells in the basal layer of the epithelium may be related to their germinal property, higher metabolic requirements, and susceptibility to abnormal constituents of the surrounding fluid.

In the cystic epithelial disorders presented in the preceding paper (Bron and Tripathi, 1973), the co-existence of cysts, spongiosis, and "pale" cells is a common feature. It is, however, not necessary that every case of spongiosis and "pale" cells should be followed by cyst formation; there may be conditions where these features could exist independently. In the early stages of spongiosis not associated with acantholytic changes, the extracellular oedema is reversible. Similarly, intracellular oedema is reversible if it has not progressed to the late stages of hydropic degeneration with the rupture of cell membranes.

There are many gaps in our knowledge of the physiology of the epithelium, including its role as a permeability barrier (see Dohlman, 1971; Tripathi, 1973). Our study, however, supports the concept that the epithelium forms a barrier to a transcorneal flux of water from the anterior route as well as from the anterior chamber and stroma. The reason why some regions of the oedematous and cystic epithelium take up topically instilled fluorescein would seem to be related to the breakdown of the anterior barrier function of the epithelium. There is increasing ultrastructural evidence that in the main this barrier is formed by the intact and viable squamous cells on the surface. These cells have a thickened outer leaf of the plasma-membrane on their exposed surfaces and are joined laterally with the cells of the same layer by occluding zonules which extend around the entire circumference of the individual cells. The deeper layers of the epithelium do not form such an effective barrier since the cells are joined by desmosomes and maculae occludentes. The intercellular passage of the molecules is slowed down, mainly because they have to pass through the long, narrow, and tortuous intercellular spaces filled with ground substance.

From the present work it is clear that the corneal epithelium, like many other squamous epithelia of the body, has a limited number of reaction patterns with which it can respond to pathological stimuli that give rise to or result from oedema. This explains why clinically different cystic epithelial disorders may show essentially similar histological patterns, differing mainly in the severity of the response and its consequences or in having certain associated features (as occurs in Meesmann's dystrophy, Cogan's dystrophy, and hydrokeratopathy following endothelial decompensation). For a pathological diagnosis, therefore, it is necessary to have a knowledge, not only of the histology and ultrastructural morphology of the cysts, the affected epithelium, and other associated changes, but also of the fullest possible clinical details of the case.

Summary

Specimens from a wide variety of cystic epithelial disorders of the cornea were studied by light and electron microscopy to provide a clinico-pathological correlation of the cystic lesions. On the basis of this study, a unified hypothesis is presented underlining the pathogenesis of cystic disorders of the epithelium.

Structurally and ultrastructurally, there seem to be three cardinal features common to most specimens studied—cysts, "pale" cells, and spongiosis. The degree of severity of these changes varied in individual specimens. On morphological appearances, it would seem that "pale" cells represent a state of intracellular oedema, while the spongiotic

appearance of the epithelium is due to extracellular oedema. The role of various factors in giving rise to spongiosis and "pale" cells is discussed. Both these oedematous processes contribute to the morphogenesis of the cysts, and this is described and discussed in detail. It is concluded that the cystic disorders of the epithelium may occur as a result of one or more of the following factors:

(*a*) An abnormality of the epithelial cells and their ground substance as a result of dystrophic, toxic, infective, allergic, or neurogenic insults, etc.

(*b*) Excessive entry of fluid into the epithelium either from the anterior route (*e.g.* tear fluid whether or not of an abnormal composition) or from the posterior route (*e.g.* the aqueous fluid) following endothelial decompensation of the cornea.

From the present study, it is apparent that the corneal epithelium has a limited number of reaction patterns with which it can respond to the pathological stimuli that give rise to or result from oedema.

Our thanks are due to Prof. Norman Ashton, F.R.S., for his advice, constructive criticism, and support in this work.

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