The Corneal Endothelium

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Summary
The endothelium is a monolayer of cells on the posterior corneal surface that transports water from the stroma into the anterior chamber. This movement of water counters a natural tendency for the stroma to swell and is necessary to maintain a transparent cornea. Embryologic studies, in particular the demonstration of the derivation of the endothelium from the neural crest, have provided insight into the factors that govern the response of this tissue to disease. In some species the endothelium can regenerate after injury, but in man cellular enlargement is the main mechanism of repair after cell loss. A clinical estimate of endothelial cell density and function is provided by specular microscopy, fluorophotometry and pachymetry. In this paper we review the development, structure and function of the corneal endothelium, and then consider the pathological processes that can affect this tissue.

There have been considerable advances towards an understanding of the physiology of the endothelium since its role in maintaining corneal clarity was first recognised. Clinical interest has been spurred by the refinement of complex intraocular surgical techniques, appreciation of the susceptability of the endothelium to surgical trauma and the development of *in vivo* methods of evaluation that can demonstrate the dramatic changes in morphology which follow seemingly minor injuries. In addition, a reassessment of the embryogenesis of the corneal endothelium has influenced our interpretation of endothelial pathology. We are at a point where the current understanding of the development, structure and function of the corneal endothelium is providing an appreciation of the surprisingly diverse pathology which can affect this apparently simply monolayer of cells.

The Normal Endothelium
1. *Embryology*

The eye and periocular structures are formed from cells that are derived from four distinct embryologic tissues—surface ectoderm, mesoderm, neural tube and the neural crest (Fig. 1).[1] Many of the structural roles of mesoderm in the rest of the body are assumed by
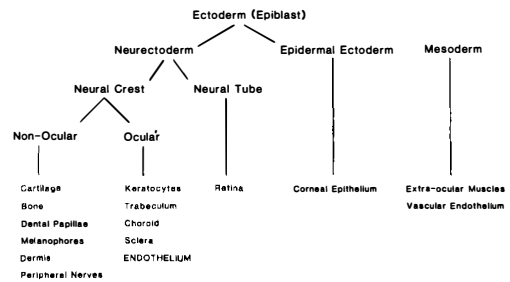

Fig. 1. *A diagramatic representation of the derivation of ocular tissues from embryonic precursors. The corneal endothelium is a product of the neural crest.*

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the neural crest in the head and neck, and the neural crest has a crucial role in the development of the eye.[2,3,4,5]

The fundamental studies of ocular embryology have been performed in birds, with movement of the neural crest being mapped by transplanting labelled cells between embryos and following their development in the resulting chimera.[6] Radioactively labelled cells can be identified for a few cell divisions during early oculogenesis,[7] but, by using quail cells that contain an intrinsic nuclear marker which can be identified after transplantation into chick embryos, it has been possible to follow subsequent stages.[8] This type of experiment has demonstrated the remarkable mobility of neural crest cells in the embryo and has shown that it is a population of these cells that ultimately forms the corneal endothelium.

Neural crest cells can first be identified as they separate from the neural plate, a thickening of the dorsal surface ectoderm. Prior to the closure of the neural folds at the anterior neuropore, the neural crest cells begin to move peripherally as primary mesenchyme (Fig. 2). In the primate, part of the migrating wave of neural crest cells comes to lie in a loose matrix at the rim of the optic cup and, at 40 days post-ovulation, these cells stream centrally through the loose fibrillar material of the primary cornea that has formed in the cleft between the lens vesicle and the surface ectoderm.[9,10,11,12] This centripetal movement of neural crest cells is termed the first wave of mesenchymal migration; a second wave later contributes cells that form the keratocytes and stromal cells of the iris.[13] Macrophages precede the migration of crest cells, which move over a layer of fibronectin into the primary corneal stroma to form a loosely arranged sheet of overlapping cells.[14] This layer thins to a monolayer of endothelium by the eighth week of human gestation. Developmentally, it is not a true endothelium and should more correctly be called the posterior cell layer of the cornea or the posterior epithelium[15] because its derivation is quite distinct from that of vascular endothelium. Cells of a similar origin cover the anterior surface of the iris and those in the anterior chamber angle migrate peripherally to form the lining of the trabecular meshwork.[16,17]

The inducers that mediate these complex cellular interactions have not been identified but it appears that the histogenesis of each migrating cell is in part determined by its locus of origin on the neural crest, with later modification by glycoproteins in the environment through which it moves.[18,19,20] Needless to say, such a complex pattern may be modifed at several levels. The eventual formation of a monolayer appears to be determined by contact inhibition, with the lens and the primary cornea acting as substrata.[21,22] Experiments show that the cells can move over any surface made available to them, to the extent that an intact junction between the lens equator and the optic cup is required to prevent backward migration of endothelial cells over the neuroretina.[23] Removal of the lens vesicle results in a loss of maturation control with persistent multilayering of the endothelial cells on the posterior corneal surface.[24]

Intercellular junctions begin to form when the endothelial monolayer is complete. Gap junctions develop first, the apical band is in place by the sixteenth week of gestation and an adult configuration is achieved by twenty weeks.[25] The formation of intercellular junctions corresponds with the beginning of aqueous secretion and the maturation of the barrier and transport functions of the corneal endothelium. In the avian model, the gradual increase in corneal transparency during the second half of gestation is dependent upon normal thyroid function.[26,27] Thyroid hormones may control the deposition of ground substance, and thus the ability of the stroma to bind water, or they may regulate the maturation of the endothelial pump function.

Beginning at the eighth week of gestation, endothelial cells deposit Descemet's membrane.[28] This first appears as patches of lamellar material and forms a complete layer by sixteen weeks. Collagen is continuously deposited thereafter until the eighth month of gestation, by which time the membrane forms a layer approximately 3 μm thick. The collagen of Descemet's membrane formed *in utero* has a banded appearance by electron microscopy, with a microperiodicity of 110 μm.[29] In contrast, Descemet's membrane that is secreted subsequently is finely granular and consists largely of non-banded basement
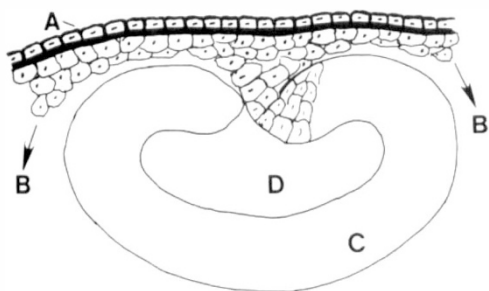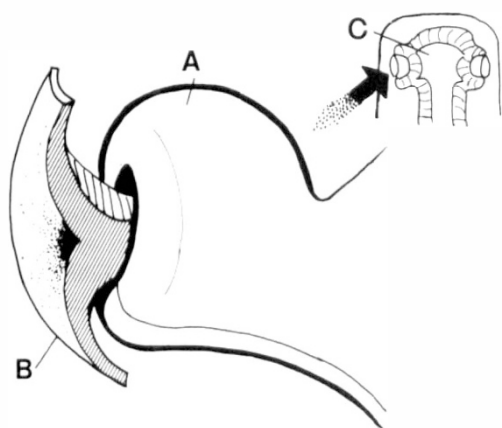
Fig. 2a.

Fig. 2b.

Fig. 2c.

Fig. 2. (a) Diagramatic representation of the migration of neural crest cells from a position dorsal to the neural tube to the posterior surface of the cornea, showing ectoderm (A), neural crest cells (B), neural ectoderm (C) and neural tube (D). (b) Outpouchings of the neuralectoderm at the level of the diencephalon form the optic vesicles which grow toward the surface ectoderm and induce the surface cells to elongate and form the lens placode. The diagram shows the optic vesicle (A), surface ectoderm (B) and diencephalon (C). By a complex process of differential growth, the optic vesicles then invaginate to form the optic cups. The lens placode also invaginates and separates from the surface ectoderm to form the lens vesicle lying within the rim of the optic cup. The inner and outer cellular layers of the optic vesicles form the neuroretina and the retinal pigment epithelium respectively, and extend forward with the advancing rim of the optic cup to form elements of the iris. The epithelium of the cornea develops (following lens invagination) from surface ectoderm. (c) Crest cells move from a position between the surface ectoderm and the neural tube to lie at the tip of the optic cup. They migrate over the posterior surface of the cornea to form the corneal endothelium. The diagram shows the cornea (A), neural crest cells (B) and the lens (C).

membrane. The granular portion of the membrane accumulates throughout life and may reach a thickness of between 10 and 40 µm. There is, however, a wide variation in the rate at which Descemet's membrane is deposited, and a measurement of its thickness does not provide an accurate gauge as to a patients age.[30]

2. Morphology

At birth, the human endothelium comprises a monolayer of up to 500,000 cells, with a density as high as 7,500 cells/mm^2. During life, cell density progressively reduces (Fig. 3).[31,32,33] An initial rapid decline occurs in the first year, reflecting hypertrophy of a fixed population of endothelial cells in response to continued corneal growth.[34,35,36] Cell density continues to fall at a reduced rate until the mid-twenties due to endothelial cell loss, and there follows a more gradual decline
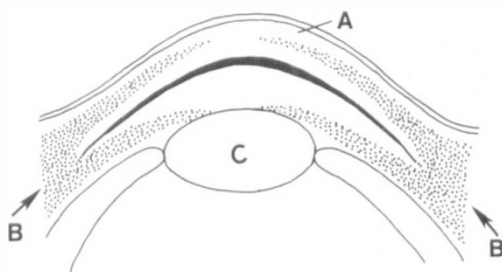
into old age.[37,38,39] It has been estimated that between the ages of 20 and 80 years the reduction in cell density averages 0.52% per year.[40] As the mean age of a population sample increases, there is a spread in the range of their endothelial cell density counts,[31] so that the measurement of cell density is not a reliable index of the chronological age of a cornea. Longitudinal data on the change of cell density with age for individual corneas are not yet available. Concurrent with an observed reduction in cell numbers, the mean cell area of the surviving cells increases[33,41] and there is an increased variation of cell size. These changes in cell density and shape with age have been observed to occur in the monkey,[42] rat,[43] cat,[44] dog[45] and rabbit,[46] but in each of these species the adult mean cell
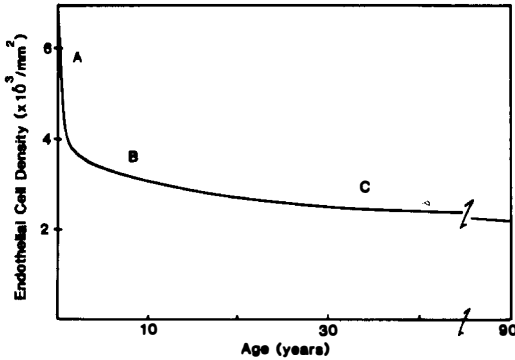
Fig. 3. *Graphical representation of the fall in endothelial cell density that occurs with age. An initial very rapid decline in infancy (A) levels off in the teens (B) to be followed by a gradual decline into old age (C). Details of the fall in density that occurs in childhood are sketchy, but available data suggests that there is approximately a 45% reduction in cell density by the age of one year, and that this figure is further reduced by 25% by the age of twenty years, with 50% of this loss occurring by the age of five years.*

density (about 2,500 cells/mm²) is remarkably constant.[35] Interestingly, it has been noted that in the rat the total reduction in endothelial cell numbers is of the same order of magnitude as occurs in humans, but the cell loss is compressed into the shorter life span of the species.[43]

A typical human endothelial cell measures 5 μm in height, is between 18 and 20 μm in width and has a round nucleus 7 μm in diameter. The posterior surface is covered by a variable number of microvilli that project between 0.5 and 0.6 μm into the anterior chamber.[47] Oligocilia, projecting 2 to 7 μm from a pair of centrioles in the posterior cytoplasm, are present on some cells (Fig. 4), particularly toward the corneal periphery.[48,49] Transmission electron microscopy has shown that cells are separated laterally by a gap of about 30 μm, which is reduced to 3 μm at the site of a gap junction toward the anterior chamber.[50] Focal tight junctions join the cells at the apical third of the cell, but there are no desmosomal junctions.[51] When the cells are viewed from the posterior surface there is an overall hexagonal pattern with fine marginal folds, but surface parallel histological sections reveal that there are extensive and irregular interdigitations between cells.[52] The anterior cell membrane of each cell is in direct contact with Descemet's membrane and, because no junctional complexes are present, endothelial cells are readily dislodged by mechanical injury.[53]

The endothelial cell cytoplasm is rich in organelles, suggesting active transport and protein synthesis, with large numbers of mitochondria, both rough and smooth endoplasmic reticulum, and a well developed perinuclear Golgi apparatus. Pinocytotic vesicles pass from the posterior cell membrane to be released either into the lateral cell space or through the anterior cell membrane. Their formation is temperature dependent and they are presumably concerned with the active transport of water and metabolites. Pigment granules are occasionally seen in the cytoplasm of corneal endothelial cells and are probably derived from phagocytosed melanin that has been dispersed from the iris stroma or pigment epithelium.[54]

A circumferential band of actin filaments localised at the apical junction may facilitate cell movement to cover endothelial defects after injury (Fig. 5) and there is an extracellular glycoprotein matrix containing fibronectin and laminin.[55,56] Plasminogen activator has been detected in the cytoplasm of cultured bovine endothelial cells after injury; this may function *in vivo* in a fibrinolytic system to maintain aqueous circulation by dissolving fibrin clots that threaten endothelial function.[57] Protein macromolecules 'float' within the lipid bilayer of the cell membrane.[58] These proteins may act as antigenic sites, ion pumps or enzymes.

3. Physiology
The endothelial pump
The maintenance of a transparent cornea depends upon the endothelium producing a state of relative stromal dehydration.[59] The proteoglycan matrix that surrounds each collagen fibre of the stroma produces an imbibition pressure (60 mm Hg) which tends to draw water into the cornea. Tight junctions between epithelial cells form a barrier to reduce the flow of water from the tear film into the stroma, but the absence of a continuous tight junction between endothelial cells permits the free flow of aqueous into the stroma. If this water is allowed to accumulate
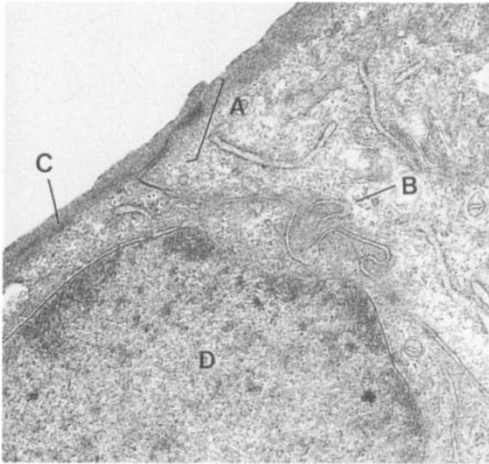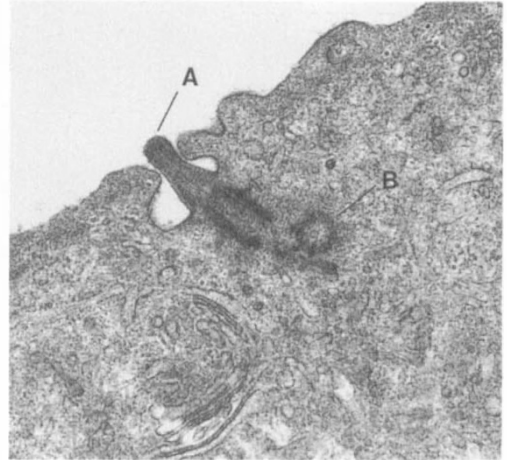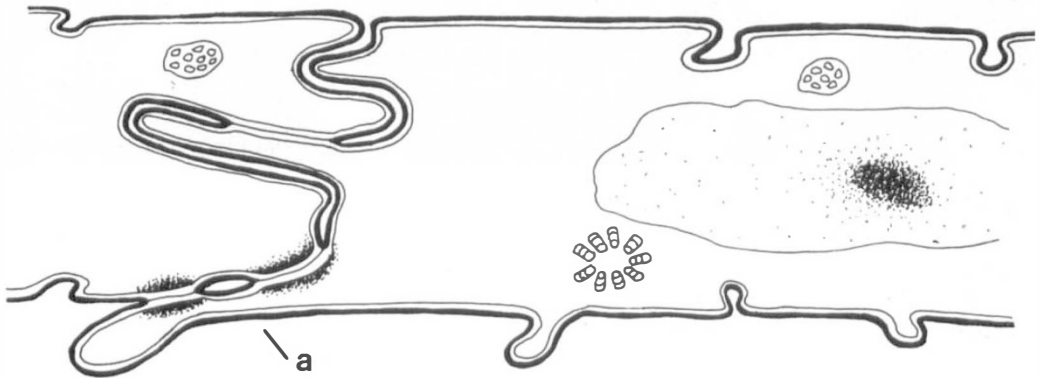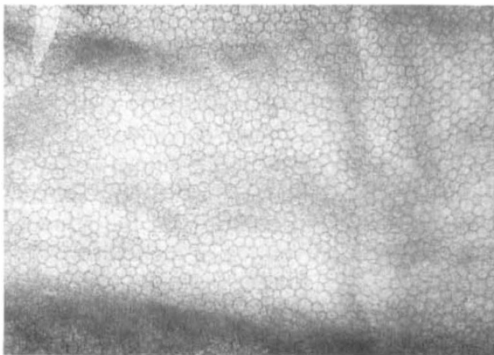
Fig. 4a.

Fig. 4b.

Fig. 4e.

Fig. 4c.

Fig. 4d.

Fig. 4. *The structure of corneal endothelium. A schematic representation of a cross-section of a typical endothelial cell (centre). (a) Details of the apical junction complex showing apical complex (A), gap junction (B), terminal web (C) and nucleus (D). (b) The basal structure of a cilium showing cilium (A) and basal complex (B). (c) Details of the surface features by specular microscopy and (d) by scanning electron microscopy.*
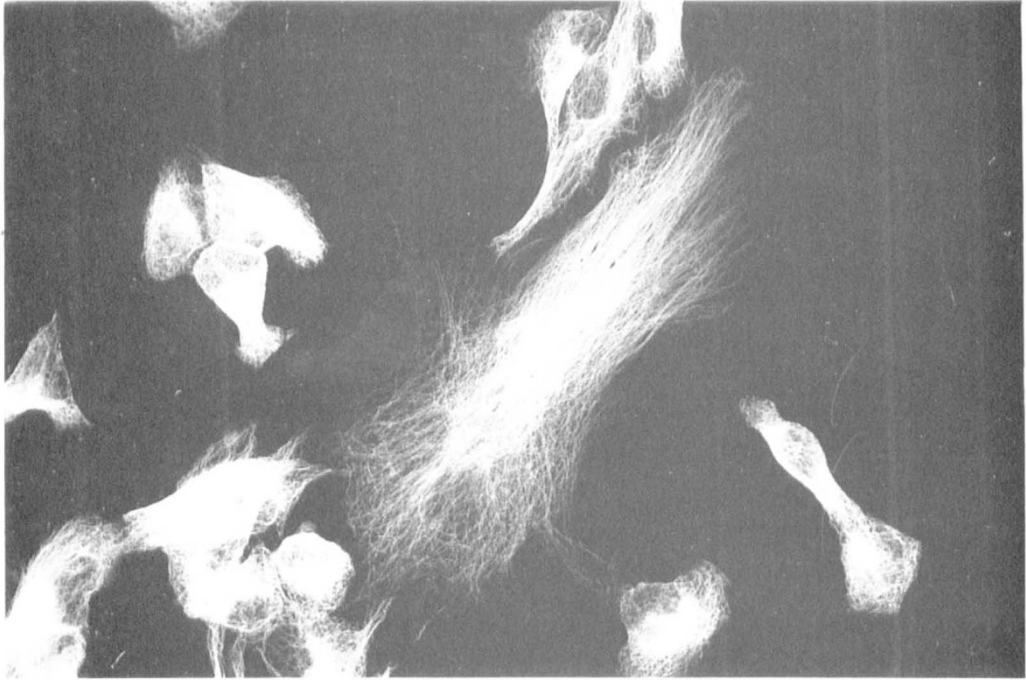
Fig. 5. *Polymerized microtubules crossing the cytoplasm of migrating endothelial cells* in vitro, *demonstrated by immunofluorescent labelling. Nuclei appear as dark intracellular areas.*

it produces stromal swelling and clouding.[60] The pump-leak concept of corneal hydration proposes that there is a dynamic equilibrium between the tendency of the stroma to swell and the active transport of ions by an endothelial pump to oppose the inward movement of water.[60]

Fluid transport by the endothelium depends upon aerobic metabolism which can be reversibly inhibited by cooling the cornea.[61] Mitochondria provide the energy to drive the system, producing ATP from glucose via the tricarboxylic acid cycle and the hexosemonophosphate shunt; the required oxygen is thought to diffuse into the endothelial cells from the anterior chamber ($pO_2 = 55$ mm Hg) rather than from the tear film ($pO_2 = 155$ mm Hg).[62] Movement of water across the endothelium is passive, and follows the flux of actively transported ions across the posterior cell membrane.[60]

The metabolically active processes of deturgescence are assisted by passive mechanisms. Evaporation can increase the osmolality of the tear film and draw water from the corneal stroma[63] and, in the presence of an intact endothelium, intraocular pressure is thought to compress the stroma and force water out.[64].

Research has recently been directed to identify the sequence of metabolic events that determine the transparency of the cornea (Fig. 6). Insight into the selective transport of ions by the endothelium has been gained by *in vivo* experimentation which has either measured the trans-endothelial potential or the degree of corneal swelling induced by changes of the ionic gradient across isolated perfused corneas.[65,66] Under these conditions a short circuit current (a measure of the flux of an actively transported ion) of $27\ \mu A\ cm^{-2}$ is established across the membrane. This current is reduced by about a third either by the removal of exogenous carbon dioxide from the perfusing solution on the aqueous side or by the prevention of the hydrolysis of carbon dioxide with a carbonic anhydrase inhibitor.[67] It is further reduced by the removal of exogenous bicarbonate, but it appears that the contribution of metabolically derived CO_2 is insignificant.[68]

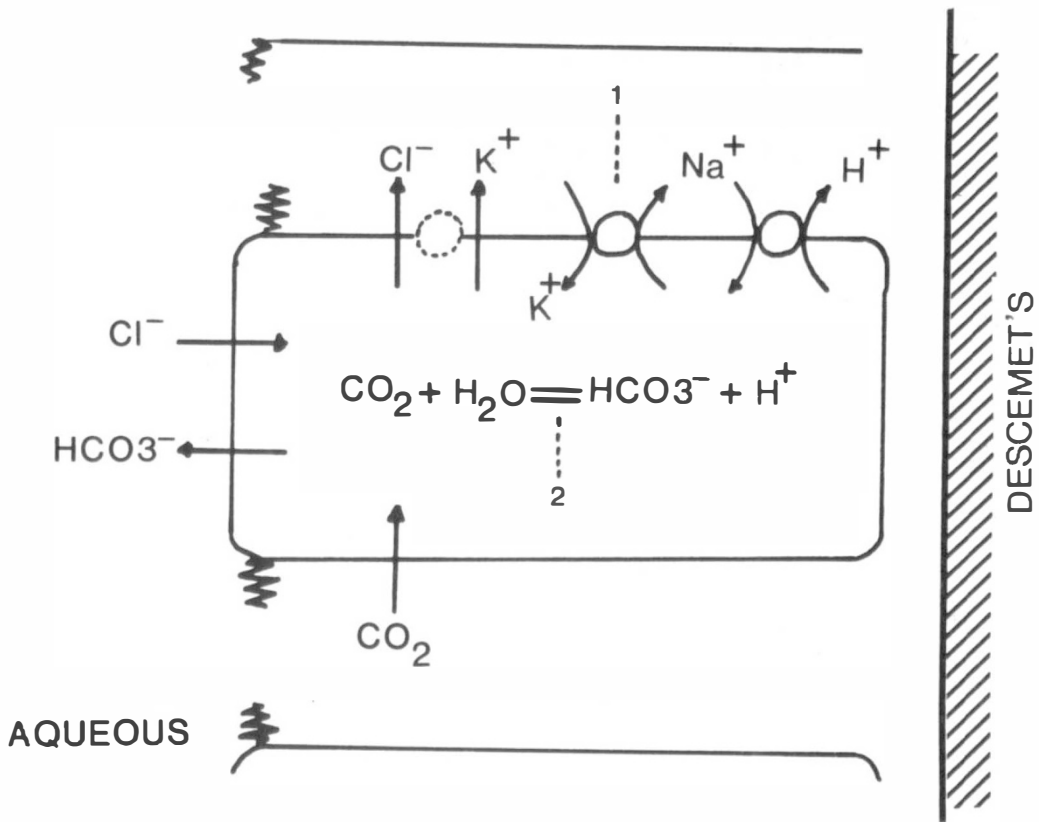Bicarbonate is required on the stromal side

Fig. 6. *Endothelial pump mechanisms. The linkage between ion flux and the mass movement of water from the stroma to the aqueous cannot be adequately explained. Although it is impossible to provide a definitive model of endothelial pumping, the following scheme summarizes aspects of our present understanding of ion transport. The pump can be inhibited by carbonic anhydrase inhibitors (1) or by ouabain (2).*

of the endothelium to maintain endothelial pump function and there is a net flux of bicarbonate ions from the stroma to the aqueous.[64,65,66,67] Such data has led to the concept that the movement of bicarbonate is the substrate for the endothelial pump,[65,67,69,70,71,72] although it is recognised that sodium and potassium could influence fluid transport (Fig. 6).[73,74] A specific bicarbonate-dependent ATPase pump has been identified, but it is associated with mitochondrial membranes,[75,76] and it is thus difficult to envisage a contribution by this pump to transcellular ion flux. The mechanism of the linkage of this anionic pump to an energy source, and hence to bulk fluid flow, is not understood.

Two observations argue against a simple bicarbonate pump model. Firstly, the removal of sodium from the aqueous humour inhibits fluid flow across the endothelium and causes a significant decrease in the short circuit current.[65,71] Secondly, ouabain, which irreversibly blocks the sodium-potassium ATPase pump, abolishes the short circuit current.[75,77,78] Thus sodium undoubtedly has an important role. If a cation such as sodium were to be pumped into the aqueous as a primary substrate, a standing potential would be established across the endothelium, with the aqueous side positive, but in the rabbit there is a standing potential of the order of $580\,\mu V$ of the opposite polarity across the intact endothelium. If sodium were to be pumped into the aqueous, but could diffuse back into the stroma, it would be possible for a sodium-potassium ATPase pump to drive

the transport of bicarbonate.[79] However, an understanding of the nature of the linkage between the sodium and bicarbonate systems awaits elucidation.[80,81] An alternative theory of enzymatically mediated sodium-bicarbonate exchange at the anterior cell membrane is currently attracting interest, while the active transport of sodium at the baso-lateral membrane by an ouabain-sensitive sodium-potassium ATPase pump is being reappraised.[82,83]

The number of ionic pump sites per endothelial cell may vary in certain circumstances. In Fuchs' dystrophy, there is an increase in the pump function of the endothelium in the early stages of the disease, despite a gradual deterioration in cell density, but pump sites are markedly reduced in the end stages coinciding with the onset of corneal oedema.[84,85,86]

Water normally enters the stroma transcellularly or via the intercellular space.[87] The removal of calcium from the aqueous results in a rapid influx of water and stromal swelling, which corresponds with the rapid disintegration of the microfilaments of the junctional complex.[88,89] The absence of glutathione, a tripeptide, has a similar effect.[90] Glutathione also appears to stimulate the endothelial pump, possibly by preventing the reduction of intracellular ATP.

4. The assessment of endothelial function

Light and electron microscopy can demonstrate the morphology of endothelial cells, but other techniques are required to assess the endothelium as a living tissue.[91] Tests of endothelial function may be broadly divided into morphological techniques, for guaging the number and shape of endothelial cells, and functional tests that measure their metabolic capacity. Qualitative tests may be further divided into tests of the pump or barrier mechanisms of the endothelium.

Specular microscopy

In 1919, Vogt described the specular appearance of normal and diseased corneal endothelium.[92] Routine slit-lamp examination of the endothelium is simple and adequate in most clinical situations, but in more demanding circumstances, modern specular or confocal microscopes permit study of the endothelium from a high resolution photographic image.[93,94] The surface detail and extra-cellular features may be visualised, and posterior corneal rings, an artefact of applanation, permit the relocation of individual cells.[95]

As already stated, cell density measurements in isolation correlate poorly with patient age or the ability of the endothelium to maintain corneal deturgescence, but computer-assisted morphometric analysis of a digitised image is a more sensitive indicator of endothelial damage. As part of a morphometric analysis, individual cell areas can be plotted against their frequency in a given population to give a distribution curve. An increase in the frequency of abnormally large cells produces a curve skewed to the right, and a 'coefficient of skewness' can be quantified.[96] Other new terms have been introduced to describe features of the cell mosaic: 'polymegathism' refers to irregularity of the mosaic due to the presence of abnormally large cells and 'hexagonality' refers to a tendency toward a regular hexagonal pattern that affords the greatest packing with optimum cell to membrane ratio.[97,98] There is a positive correlation between these two parameters whereby larger endothelial cells also have a more variable shape. A departure from a homogeneous population appears to be associated with a reduced ability to withstand trauma but further studies are being conducted to determine which parameter best reflects endothelial function.

Specular microscopy has greatly increased our understanding of endothelial pathology by providing an estimate of cell density before and after surgery. The impact of this information upon anterior segment surgical techniques, the design of intraocular lenses, and the constitution of intraocular irrigating fluids and medications has been marked. However, specular microscopy does have limitations, most notably the degradation of the image by stromal oedema when an estimate of cell morphology would be most useful. Serious sampling errors may occur because of regional variations in cell density, particularly when using the small image size of some non-contact microscopes.[99] Sampling error has been partly overcome by using wide field (1 mm^2)

examination and by relocation of the image using posterior corneal rings. A good correlation between endothelial morphology and functional performance has not been identified. Certainly, until cell numbers become low, there is a poor correlation between density and corneal thickness. Therefore, although specular morphometry has helped identify some of the caveats of intraocular surgery, it does not have a role in routine preoperative examinations, where an assessment of endothelial density made from visualisation of the specular image at the slit-lamp is adequate.[100]

Endothelia function and hypoxic stress testing

The linear relationship between stromal hydration and thickness means that corneal thickness can be used as an index of endothelial damage after surgery.[101,102,103,104] Similarly, the physiological function of the endothelium can be assessed experimentally by measuring changes in corneal thickness following hypoxic stress. Corneal hypoxia is produced by exposing the anterior surface of the cornea to an atmosphere of nitrogen or by placing a thick contact lens onto the eye.[105] Anaerobic metabolism by the epithelium leads to an accumulation of lactic acid which causes the corneal stroma to swell, either by directly inhibiting the endothelial pump or by creating an osmotic imbalance.[106,107] Upon restoration of air to the anterior surface, the cornea thins over the following one to two hours at a rate consistent with endothelial cell pumping (Fig. 7). Evaporation augments the deturgescence response by increasing the osmolarity of the tear film; ideally, the relative humidity during the experiment should be controlled. The induced changes in corneal thickness are small and require accurate pachymetry,[108] but if careful sequential measurements are made the technique can provide an indication of the capacity for deturgescence.[109]

The results of such studies have shown that, where there is a low endothelial cell density, a large corneal swelling response to hypoxia and a slow recovery occur. There is also a reduced recovery with increasing age.[110] Nevertheless, the correlation between the rate of recovery and endothelial cell morphology is poor. The corneal swelling response is slightly reduced by aphakia, which may reflect an increased oxygen availability to the anterior chamber following cataract extraction or reduced corneal innervation.[111,112]

The main reservation about the use of induced hypoxia to study corneal function concerns the fear that it may precipitate irreversible corneal oedema in some patients with low endothelial cell counts.

Corneal fluorophotometry

A quantitative assessment of the endothelium may be made by measuring the passage of fluorescein across the endothelial layer. This is said to be a test of the endothelial 'barrier', but it is uncertain which physiological function of the endothelium this test measures as the normal endothelium does not provide a significant barrier to the diffusion of water. If fluorescein is taken orally, the rate of transit from the anterior chamber into the stroma of the cornea can be measured with a modified fluorophotometer. Alternatively, fluorescein may be drawn into the corneal stroma by iontophoresis and its appearance in the anterior chamber observed.[113] In normal subjects, the values for fluorescein transfer appear to remain constant with increasing age but there
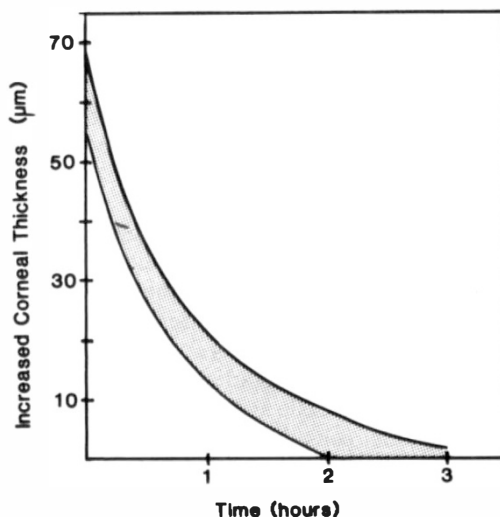

Fig. 7. *Representation of the fall in central corneal thickness that occurs in the recovery phase following corneal hypoxia. Increased humidity will shift the curve to the right.*

is a correlation between an increased transfer coefficient and corneal thickness.[114]

Although the results of this test in the study of disease have produced some conflicting results, trends have emerged. A high fluorescein transfer has been consistently demonstrated in Fuchs' dystrophy[115] and a reduced transfer in the iridocorneal endothelial syndrome.[116] In general, the permeability of the endothelium to fluorescein is increased after an injury and, although an intact cell layer recovers over a period of days, the recovery of full endothelial function, as adjudged by this technique, may require months.[117,118,119,120]

5. The endothelial response to injury

Although endothelial cells are slowly lost from the cornea throughout life, decompensation seldom occurs. If episodes of injury or inflammation reduce the density below a level critical to the maintenance of corneal deturgescence, physiological function fails and corneal oedema ensues. This critical density has been estimated to be 10–15% of the normal cell count or between 300 and 500 cells mm^2.[121,122] There is, therefore, a considerable physiological reserve; 500 cells mm^2 is as effective as 3,000 cells mm^2 in achieving corneal transparency in the short term. The mechanisms by which cell function adapts to the increased demands that follow cell loss are not understood but it may be that the number of transport sites on the membrane of each endothelial cell increases.[123]

Endothelial repair has been most extensively studied in the rabbit but the events of repair are similar in all species.[124,125,126] A localised endothelial injury initially stimulates repair by cells in the immediate vicinity of the wound; these cells flatten and slide to cover the defect and damaged endothelial cells are desquamated into the anterior chamber (Fig. 8).[127,128] As cells more distant become involved, a density gradient is established, with the largest cells at the site of the injury. Surrounding cells break their intercellular connections, develop pseudopodia and migrate at a rate of 0.5 to 1.0 mm per day to cover the defect, becoming flattened and attenuated in the process.[129,130] These cell movements are facilitated by f-actin that polymerises across the cell cytoplasm after injury,

a process that is inhibited by cytochalasin B.[131,132,133] Migrating cells have an increased number of intracellular organelles, fewer endocytotic vesicles and the cells do not appear to possess a fibronectin coat.[134]

When cells meet in the centre of the wound, further movement is prevented by contact inhibition and a wave of cell rearrangement spreads outward.[135] Mitotic figures appear at the wound edge at 16 hours, reach a peak at 24–36 hours and reduce again to zero within five days.[129,130,136] Division is a major component of endothelial repair in the young rabbit[137] but in species where endothelial mitotic figures are rarely observed, such as the cat and primates,[137,138,139] cell slide continues for up to one year. This complex process of cell reorganisation has been closely observed. Between four and seven days after injury, the large elongated cells at the wound margin begin to regain their original size and shape by moving relative to one another, thereby 'pulling' the more peripheral cells inwards. This sequence requires the repeated breaking and reformation of junctions between neighbouring cells, and, although a cell may become separated from its previous neighbour, macroscopic gaps do not appear in the extracellular matrix (Fig. 8).[140,141]

Mitotic figures have been demonstrated in the endothelium of cultured human corneas,[142,143,144,145] and it is claimed that mitotic figures may be visualised in vivo with the specular microscope.[146] Mitosis, however, does not occur in vivo at a rate sufficient to replace cells that are lost by ageing or injury and therefore, for all intents and purposes, the human endothelium must be regarded as a finite and irreplaceable resource. As a result of the inability to replace cells, a uniform cell distribution across the cornea may never be re-established and a vertical cell disparity, with a reduced number of cells near the wound, has been observed to persist for up to 20 years.[147,148,149] In contrast, the coefficients of variation and hexagonality return towards normal within five months, suggesting the new matrix has attained stability.[149] Amitotic cell division (division of the interphase nucleus without subsequent cell division[146,150]) and cell coalescence have been observed in man,[151] and giant multinucleated cells can
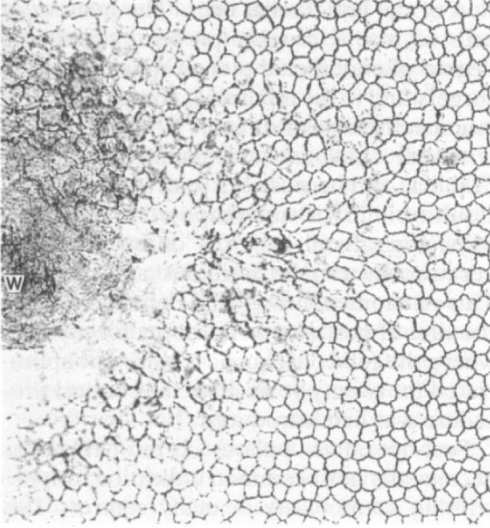
Fig. 8a.

Fig. 8b.

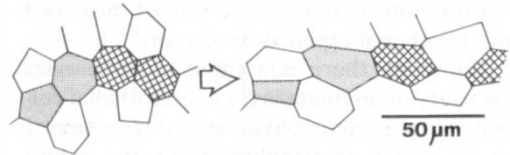**Fig. 8.** *Endothelial repair occurs by endothelial cell slide, followed by some cell division to replace cells that have been lost. (a) Cells elongate and slide toward the wound (W). (b) In the process, they undergo intercellular re-arrangement.*[140] *(c) Nuclear division may be demonstrated by the uptake of tritiated thymidine (labelled cells arrowed).*
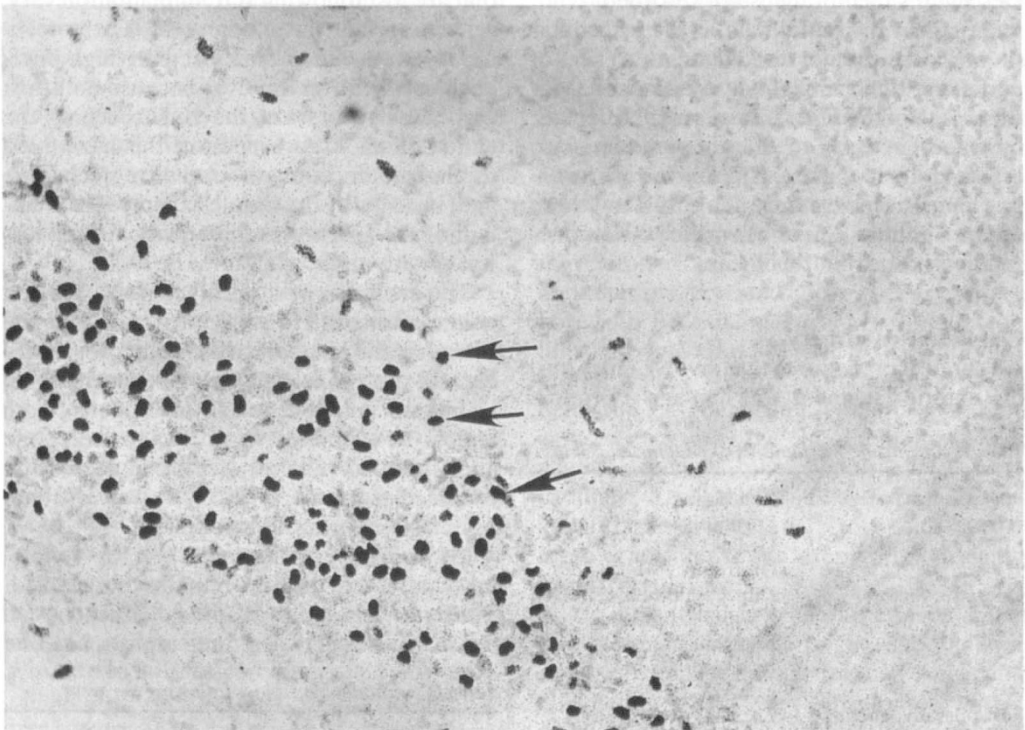

Fig. 8c.

form following injury. The role of these cells in endothelial repair is uncertain.[152]

Although there is a rapid morphological recovery of an intact layer of endothelial cells following injury, physiological function is more slowly re-established. In the rabbit, where endothelial proliferation occurs, the permeability to fluorescein returns to normal within 14 days of transcorneal freezing, but there is a further delay of up to seven days before the stroma returns to normal thickness.[153,154,155] In the cat, which like the human has little endothelial regenerative capacity, functional recovery may be delayed several months.[156]

If Descemet's membrane is damaged at the time of surgery, the cut edges retract elastically and curl toward the stroma. A fibrin clot forms on the exposed stroma, which is then covered by migrating endothelial cells. The cells covering the stromal bed secrete a new basement membrane but the damaged Descemet's membrane is not resorbed.[157]

Repair of the endothelial layer by cellular sliding has one major disadvantage. At sites of persistent mechanical injury caused, for example, by the leg of an intraocular lens or by a foreign body in the anterior chamber, cells migrate to the site of injury and are lost—like lemmings streaming off a cliff—and there can be a gradual spread of corneal decompensation arising from this focus.

Cell loss after surgery
All surgical procedures that involve entry into the anterior segment will damage a propor-

tion of the endothelial cells. The number of cells so lost is roughly proportional to the degree of endothelial pleomorphism prior to surgery and to the amount of corneal manipulation at the time of surgery.[158,159,160] If cell loss is severe, bullous keratopathy may ensue (Table I), but because cell rearrangement as a result of injury is superimposed upon a slow physiological cell loss, the onset of bullous keratopathy can be insidious and delayed. This phenomenon was well demonstrated in the case of posterior keratotomy for myopia, where the full consequences were not appreciated for twenty years after the surgical procedure was first introduced.[163]

Post-operative bullous keratopathy has become the most common indication for penetrating keratoplasty in many centres. This has been associated with the widespread adoption of intraocular lens implantation (IOL) following cataract removal. Although figures for the percentage of endothelial cells that are lost following IOL implantation vary, certain trends have emerged. Early techniques produced an unexpectedly high operative cell loss (up to 70%) because no effort was made to prevent the IOL touching the endothelium.[164] Awareness of this hazard led to the modification of operative technique and, initially, by the simple expedient of maintaining the anterior chamber with air, cell loss was greatly reduced (Table II).

The evolution of surgical techniques aimed at minimising cell loss has been steady. If one considers the numbers of eyes that progress to corneal decompensation, improvements in technique have reduced the figure from almost 10% in early trials[175] to between one and 2%, or even less if iris-clip lenses are excluded from the series.[176] However, long-term follow-up is still incomplete.

The question of continued cell loss following cataract extraction remains unresolved. The data suggest that a rapid fall in central cell density ceases between three months and one

Table I *Interacting mechanisms of endothelial cell loss*

Pre-existing corneal disease	Concussion
	Previous surgery
	Uveitis
	Dystrophy
Operative factors	Direct endothelial contact with instruments
	Intraocular lenses
	Inappropriate irrigating fluids
Post-operative factors	Corneo-vitreal touch
	Persistent inflammation
	Elevated intraocular pressure
	Intermittent intraocular lens touch[161,162]

Table II *Estimated cell loss following surgery*

Intracapsular extraction	6 to 15%[165,166,167,168]
Extracapsular extraction	14 to 23%[166,169,170,171]
ECCE+IOL	13 to 20%[168]
Phacoextraction AC	27%[172,173]
Phacoextraction PC	10 to 15%[167,171,174]

year after simple extraction[177] but that cell loss continues at a rate that is slightly higher than normal if an IOL is implanted, particularly if an iris supported lens is used.[178,179,180,181]

Mechanical trauma to the endothelium and incompatible irrigating fluids are the major contributory factors to operative cell loss. Contact with instruments,[172,182] crystalline lens fragments,[183] or the 'biophysical' adhesive effect between the endothelial cell membrane and the IOL[184] are the most frequent mechanical insults. The polymethylmethacrylate (PMMA) of an IOL was thought to adhere to the lipid of the endothelial cell membrane and cause cellular disruption on contact,[185] but this has not been confirmed.[186] Intact endothelial cells have been seen on the surface of IOLs removed from cases of pseudophakic bullous keratopathy, but it is uncertain whether these represent cells dislodged at the time of the original surgery or cells that have subsequently migrated onto the surface of the lens.[187,188] Interestingly, a coating of protein and cells on the surface of an IOL may alter the surface characteristics of the PMMA, making it less lipophilic and providing some degree of protection should there be inadvertent contact with the endothelium during subsequent surgery.[189] By coating a hydrophobic IOL with hydrophilic substances,[190] such as autologous plasma,[191,192] methylcellulose,[184,193] chondroitin sulphate,[194] or hyaluronic acid,[195,196] this adhesive effect is reduced. An alternative approach toward safer IOL insertion is to make lenses of a hydrophilic polymer, such as hydroxymethylmethacrylate (HMMA).[185,197]

Penetrating keratoplasty for aphakic bullous keratopathy is generally technically successful, with up to 95% clear grafts at two years.[198,199,200] The visual results are less encouraging, with only between 15 and 40% of patients achieving a best corrected visual acuity of 6/12 because of associated cystoid macular oedema and glaucoma.[198,199,200] Likewise, up to 80% of corneal grafts for pseudophakic bullous keratopathy remain clear at two years, with between 17 and 50% of patients having a visual acuity of 6/12 or better.[176,201,202,203] The visual prognosis is worse with iris supported lenses[204] but, in the absence of intraocular inflammation or cystoid macular oedema, there is no evidence that removal of a securely fixed lens will improve the final visual outcome or affect graft survival.[201,205,206] Meticulous anterior vitrectomy may be required at the time of grafting to prevent vitreocorneal touch and continued endothelial cell loss.[207]

Prolonged intraocular manipulation usually requires the intracameral use of potentially harmful substances that may contribute to cell loss. To avoid damaging the endothelium special care must be taken to ensure that irrigating fluids have a correct ionic balance (200 to 400 mOsm), a correct pH (6.8 to 8.2), and that calcium and glutathione are present. Preferably, an energy source should also be available.[208,209,210] Because the endothelial pump is temperature dependent, cooling by irrigating fluids can slow the metabolism and produce corneal oedema which obscures the surgeon's view, but even prolonged irrigation with cold physiological fluids (4 °C) produces few permanent changes. The preservatives for medications intended for ocular use have a dose-dependent toxicity. Sodium bisulphite, the buffer and antioxidant frequently used with adrenalin, is toxic to rabbit endothelium after intracameral injection or perfusion at concentrations of greater than 1 : 5,000,[210,211] while thimerosol and benzalkonium chloride may damage the endothelium at the accepted antimicrobial concentrations.[212] Toxic effects have also been demonstrated after sub-conjunctival injection.[213] The toxicity of antibiotics varies widely, gentamicin probably being the least damaging. Other preparations whose effect upon the endothelium has been studied include phenylephrine,[214] acetylcholine,[215] carbechol[216] and urokinase.[217] As a general rule, it is unsatisfactory to use any of these drugs unless in a preparation designed for intraocular use.

Air introduced into the anterior chamber during surgery is toxic to the endothelium. Animal studies demonstrate a reversible effect after contact for 30 minutes, with a more marked effect if the anterior chamber is filled with air that is allowed to resorb. Agents introduced into the eye following vitrectomy can damage the endothelium; the effects of sulphur hexafluoride (SF_6) gas are probably

similar to those of air, but perfluoropentane (C_3F_8) is more toxic because it is only slowly resorbed.[218,219,220,221,222] The presence of the lens provides protection against intraocular gas during pars plana vitrectomy.[223] If silicone oil passes into the anterior chamber it has a markedly toxic effect upon endothelium.[224]

Acute local endothelial damage undoubtedly occurs following 'minor' surgical procedures to the anterior segment, for example peripheral iridectomy or trabeculectomy, but it is rare for there to be a reduction in central endothelial cell density. Mechanical damage to the endothelium has been recorded following both continuous wave (Argon and Krypton) and short-pulsed (Nd/YAG or excimer) laser irradiation, but the long-term clinical significance of this is uncertain. Continuous wave lasers most frequently cause damage during peripheral iridectomy and trabeculoplasty,[225,226] when heat is conducted from adjacent pigmented structures.[227] Short-pulsed lasers produce damage when generated shock waves travel through the tissue or when high velocity tissue debris is emitted from the point of focus.[228,229,230,231]

6. The endothelium and penetrating keratoplasty

An essential objective of penetrating keratoplasty is the transfer of viable endothelial cells, and their subsequent preservation is the necessary preoccupation of the corneal transplant surgeon. The number of endothelial cells transferred on a graft is related to the status of the donor, in particular the donor age, and whether the eye has suffered any previous trauma. Endothelial cell numbers are also affected by the way the cornea is treated at the time of removal, the time elapsing between death and storage, the nature of the storage medium, and the time in storage. Subsequent cell loss occurs as a direct consequence of surgical manipulation, post-operative inflammation or allograft rejection.

The assessment of excised corneas prior to corneal grafting

In the absence of an accurate method for assessing the functional capacity of the endothelium of donor corneas, young donors are usually selected. This preference hinges upon the belief that a high cell density provides a reserve against subsequent cell loss, although there is a wide variation in endothelial cell density within any age group and a young donor does not guarantee a high initial endothelial cell count or an improved long-term cell density. However it has been noted that grafts from older donors usually require a longer post-operative period to attain their final thickness,[232,233] an observation that may reflect the reduced ability of the ageing endothelium to re-form intercellular junctions. Although advanced donor age does not preclude the use of a cornea for grafting, the life span of a transplanted endothelial cell is, as yet, unknown.

The accurate prediction of the functional performance of a donor cornea is a desirable but, as yet, unattainable goal. Specular microscopy permits a direct measurement of pre-operative cell density and the identification of pathology such as cornea guttata, keratic precipitates, Descemet's folds and areas of cell loss, each of which may adversely affect graft outcome. The metabolic state of tissue prior to grafting has been investigated using the nuclear magnetic resonance (NMR) of ^{31}P-Phosphorus to assess the abundance of organic high energy phosphate metabolites (ATP) in donor corneas.[234] Unfortunately, because of the low tissue mass of the endothelium and the high signal from the metabolically active epithelium, the technique does not resolve the endothelial response as distinct from the response of the whole cornea. The NMR of de-epithelialised corneas labelled by incubation with ^{13}C-Glucose could provide a more sensitive alternative.[235]

The endothelial cell response to grafting

Endothelial cells are readily dislodged from a donor button by surgical manipulation, and longitudinal studies show an exponential fall in the central cell density as cells migrate to cover gaps in the endothelial layer. Following grafting for keratoconus, where there is a high endothelial cell count on the recipient cornea, a central cell loss of at least 20 to 30% occurs on the graft during the first three post-operative months. This rises to between 50 and 60% by the end of the second

year.[236,237,238,239,240,241,242,243] The rate of cell loss in subsequent years is slower, but is still greater than would be expected to occur by ageing processes alone.[244] This cell loss is not the result of sub-clinical rejection and it is not prevented by topical steroids.[242] When the recipient endothelial cell count is low, as in bullous keratopathy, endothelial cell loss continues at an accelerated rate which is reflected in the poor long-term results for grafting of the condition.[245] Whether this is due to a late re-distribution of cells from the graft to the host cornea or continued inflammation is unclear.

The mechanisms of endothelial repair following the insertion of a corneal graft are not fully understood. Nuclear labelling experiments and sex chromatin studies demonstrate that the host and donor populations of endothelial cells move in both directions across the corneal wound but do not intermingle.[246,247,248,249] In the rabbit there is extensive migration,[250] and the available data suggests that a similar mechanism is present in humans. However, following grafting for keratoconus there is usually a higher final cell density on the host than on the donor cornea and a uniform cell density is never attained.[251,252,253,254]

Allograft rejection is the commonest cause of corneal graft failure.[255] Although grafts placed into corneas which have never been inflamed or vascularised seldom reject, unlike grafts for keratoconus, grafts placed in a recipient bed which has been inflamed or vascularised are often rejected.[256,257] The basis of this loss of corneal privilege is related to the accumulation of immunocompetent cells, particularly interstitial dendritic cells, in the diseased recipient cornea.[258] These 'passenger cells' present foreign antigens to the host immunocytes—the first step on the afferent path of the allograft response.[259] Following sensitisation, the efferent response is largely directed at the endothelium. Endothelial rejection appears clinically as either a diffuse uveitis with scattered keratic precipitates or as a rejection line enclosing a specific point of sensitisation, such as an iris synechia or vascular ingrowth.[255] Treated promptly and aggressively with steroids or antimetabolites, the rejection may be halted, with the

reappearance of a clear graft, but an abnormal appearance of the specular image persists.[260] Following severe rejection, a posterior collagenous layer is deposited beneath the endothelium and extensive cell loss may result in persistent oedema.[261,262]

Despite the role of the endothelium as a target for the allograft reaction, there is doubt as to the identity of the target antigens. Although most studies have reported that class I antigens are absent from adult corneal endothelium,[263,264,265,266,267] there are notable exceptions.[268,269] There is agreement, however, that class I antigens can be found on the endothelium of donors younger than two years of age.[263,269] Class II antigens are not expressed on healthy endothelium, but there is evidence that they can be induced under the influence of regulatory cytokines[270,271] and in rejected corneas.[272] Increased expression of class I and class II antigens has previously been shown to occur in other tissues during rejection[273,274,275] and class I antigens can be upregulated after surgery alone.[275] It would therefore appear that the endothelium does hold the target major histocompatibility antigens for rejection but that they are only expressed under certain conditions which predispose to allograft rejection.

The transplantation of endothelial cells onto a patient's own cornea has been proposed as a technique to reduce the antigenic load of a penetrating keratoplasty. In rabbits, cultured endothelial cells can be seeded onto thin gelatine sheets and, when a confluent monolayer has grown, the sheet affixed to the back of a donor cornea.[276] Alternatively, the cultured endothelial cells may be seeded directly onto exposed Descemet's membrane.[277] Both homografts and xenografts of corneal endothelium have had short-term success in experimental animals, but the clinical applications remain distant. It should be noted that endothelial cells express class I antigens after culture.[263,278] Experiments to seed the posterior corneal surface of cats with autologous vascular endothelial cells have not produced grafts that remain clear,[279] and there is no evidence that vascular endothelium can assume a pump capacity comparable to corneal endothelium.

The synthesis of peptide mitogens that

stimulate the proliferation and differentiation of endothelial cells after injury has been demonstrated in cell culture.[280] Although these peptides appear to have developed as a local regulatory system, cells can also respond to added growth factors and these have been used to stimulate the low replicative capacity of human corneal endothelium. A mitogenic effect upon endothelium in culture has been demonstrated for fibroblastic and epidermal growth factors,[281,282,283] and priming tissue with these polypeptides may yield a higher final endothelial cell density after grafting.[276] This has not been used clinically.

General Considerations of Endothelial Pathology

Despite the structural simplicity of the corneal endothelium, it is involved in a bewildering range of diverse but often interrelated pathologies. For the clinician, the precise classification of a particular case can be difficult. This is partly because any classification tends to be descriptive as so little is known of the aetiology of these conditions. Furthermore, the terminology of general pathology is not always appropriate.

For the general pathologist, a dystrophy may be defined as a disorder, usually congenital, of the structure or function of an organ or tissue due to a perverted nutrition. In its widest sense it includes agenesis, atrophy, hypertrophy, hyperplasia, and metaplasia, but in practice the term is usually applied to those disorders which do not fit into any other category. In ophthalmology, the corneal dystrophies are primary conditions although they may not manifest until adult life.

Several other terms deserve classification. Dysgenesis refers to conditions that are the result of an abnormal migration of formative elements. Dysplasia is a descriptive term that has been loosely applied. At times it is used as an alternative term for dystrophy, describing an abnormal growth of tissue, although it should only be applied to developmental disorders. This convention is usually followed by ophthalmologists, an exception being its use to describe changes found in the corneal epithelium that are considered to be pre-malignant. Within this framework, efforts have been made to group primary endothelial dis-

eases (dystrophies) in terms of the migration (dysgenesis) or differentiation (dysplasia) of a common neural crest precursor,[284,285,286,287] and thus to link the ocular and the systemic neurocristopathies (Table III).

Any of these disease processes may be accompanied by endothelial metaplasia. Metaplasia describes a change in which one cell type assumes the phenotype of another similarly differentiated tissue (Fig. 9). This may occur in the endothelium as part of a developmental disorder or it may occur in response to injury. Epithelioid metaplasia is accompanied by the loss of contact inhibition, an increased expression of keratin, and the proliferation of surface microvilli; posterior polymorphous dystrophy is the best example, but similar changes occur in the irido-corneal endothelial syndrome.[288] In fibroblastic metaplasia, the normally polygonal cells become fusiform and develop prominent cytoplasmic organelles. This appears to be a non-specific manifestation of endothelial distress and attempted repair and is observed after such varied stimuli as alkali burns, transcorneal freezing, graft rejection, vitreous touch and experimental uveitis.[289,290] Both types of metaplasia can be accompanied by the deposition of a posterior collagenous layer formed of long-spaced collagen.[291] Although the primary source of the abnormal collagen is the endothelial cell,[292,293] stromal keratocytes may contribute following rupture of Descemet's membrane.[294]

A peripheral migration of endothelial cells can accompany dystrophic disease (primary proliferation) or ocular injury (secondary proliferation). Primary endothelial proliferation most typically occurs in the iridocorneal endothelial syndrome,[295] while secondary proliferation may follow concussive injuries.

Special Pathology of the Endothelium

The time-honored convention of classifying

Table III   *The neurochristopathies*

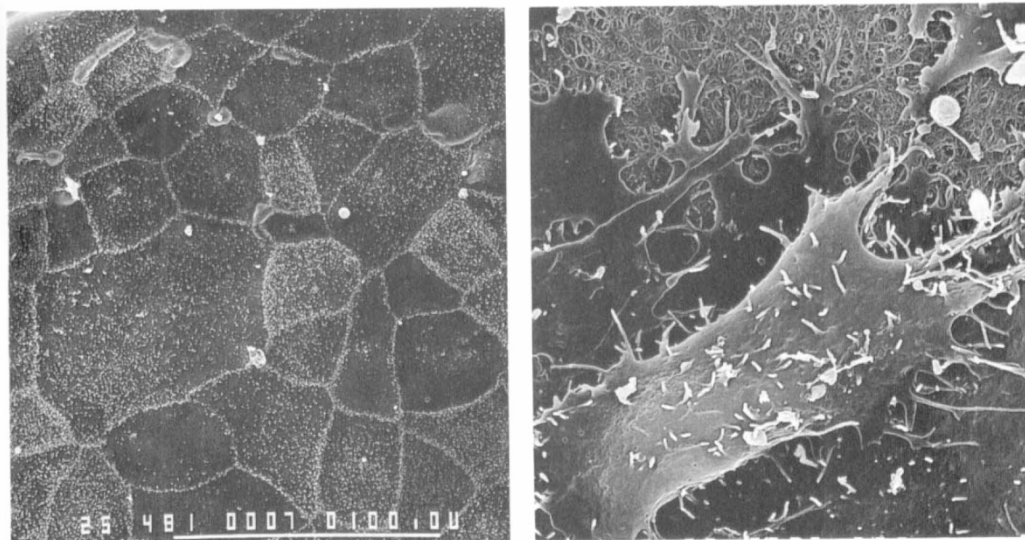|	
Abnormal migration	Axenfeld-Rieger' anomaly
	Peter's anomaly
Abnormal proliferation	ICE syndrome
Abnormal differentiation	CHED
	PPMD
	Fuchs' dystrophy
Acquired abnormality	Metaplasia

Fig. 9. *(a) Diseased endothelium may develop an irregular mosaic with numerous microvilli on each cell, an appearance that may superficailly resemble epithelium. (b) A fibroblastic configuration with the deposition of collagen is a non-specific feature of endothelial distress.*

disorders as developmental or acquired is appropriate for the conditions which specifically affect the normal endothelium.

Developmental Conditions

Mesenchymal dysgenesis (Anterior chamber cleavage syndrome)

Mesenchymal dysgenesis presents as bilateral malformations of the anterior segment which are transmitted with an autosomal dominant or sporadic mode of inheritance. A radially symmetric arrangement points to an anomaly of the first wave of neural crest migration as the cause for the ocular signs,[296,297] but the presence of non-ocular features involving the teeth, facial bones and melanocytes indicates a more generalised abnormality of neural crest derivatives.[298] A combination of several structural abnormalities produces a gradation of related syndromes: the Axenfeld-Rieger syndrome; posterior keratoconus; Peter's anomaly; sclerocornea; and trabeculodysgenesis (congenital glaucoma). Each incorporates a degree of dysplasia of the endothelium with an abnormal Descemet's membrane. Individuals often exhibit features that suggest an overlap between the syndromes which emphasises their common aetiology.[299]

The Axenfeld-Rieger syndrome is the least severely affected variant. There is only mild pleomorphism of the size and shape of the endothelial cells, Descemet's membrane can be attenuated, and an abnormal layer of collagen covers the prominent Schwalbe's line. These defects could represent an abnormal retention of primordial portions of the iris and anterior chamber angle (Table IV).

At the other end of the spectrum of disease, Peter's anomaly demonstrates the most severe form of dysgenesis with widespread maldevelopment of the anterior segment. Up to 80% of patients with Peter's anomaly have bilateral involvement[300] and between 50 and 70% of cases develop a secondary glau-

Table IV *Features of mesenchymal dysgenesis[296,297,300]*

Axenfeld-Rieger syndrome	Prominent and anteriorly displaced Schwalbe's line
	High insertion of iris
	Corectopia
	Hypoplasia of iris with holes
Peter's Anomaly	Corneal leukoma
	Corneal-lenticular adhesions
	Anterior polar cataract
	Shallow anterior chamber
	Scleralisation of cornea

coma.[296] A more detailed review of the syndromes within this group is presented elsewhere.[301,302,303,304]

Histological examination of the posterior cornea in Peter's anomaly demonstrates an attenuation of the endothelial layer centrally, while the peripheral endothelium may be normal. Descemet's membrane is absent or represented by multiple laminations of basement membrane interspersed with collagen fibrils.[305,306,307,308] Giant collagen fibrils, up to 60 μm in diameter, have been noted,[309] and similar fibrils have been demonstrated in both CHED[310] and following experimental lensectomy in the chick embryo.[311]

Treatment is required in only a minority of patients. Keratoplasty and lensectomy may be required to clear the visual axis if there are corneolenticular adhesions and cataract, but the visual prognosis is poor.

Endothelial Dystrophies

1. *Congenital hereditary endothelial dystrophy (CHED)*

This is a rare disorder that presents in children or young adults as a bilaterally symmetric diffuse corneal oedema varying from a mild stromal haze to gross opacification of the cornea (Fig. 10).[312,313] Judisch and Maumenee recognised differences in expression between the autosomal recessive and the autosomal dominant forms of the disease.[314] The recessive variant tends to present earlier, have more severe corneal opacification, and visual deprivation can produce a pendular nystagmus. The cornea in the dominant variant may appear to be normal in infancy but oedema usually begins to develop in the first two years, although visual deterioration may be delayed. Oedema is not always progressive, but epithelial breakdown can result in photophobia and tearing, and secondary changes can produce band keratopathy and spheroidal degeneration. Associated abnormalities of the anterior segment are not a prominent feature of CHED and the primary differential diagnosis is between congenital glaucoma and a mucopolysaccharidosis. The corneal diameter in congenital glaucoma is usually larger than normal and there is a raised intraocular pressure with Descemet's breaks; the opacity in a mucopolysaccharidosis tends to be an infiltration rather than oedema.

Histological examination reveals a range of endothelial morphology. The endothelial cells demonstrate fibroblast-like changes and may be absent from the central cornea. Descemet's membrane is often represented by only the anterior banded zone and a disorganised posterior collagenous layer can be grossly thickened and beaded.[315] The peripheral endothelium and Descemet's membrane are relatively unaffected. This distribution suggests that the disease is due to an incomplete central migration of endothelial precursors, with secondary endothelial metaplasia and hypersecretion of collagen.

The diameter of the stromal collagen fibres is increased and they show non-specific changes of long-standing corneal oedema.[316,317] Histological similarities between CHED and posterior polymorphous dystrophy suggest that there is an overlap between the two conditions, indeed it has been proposed that the two syndromes represent the clinical spectrum of a single congenital endothelial dystrophy.[318,319]

The decision to perform penetrating keratoplasty depends upon the degree of stromal opacity., If there is marked opacity from birth, the operation should be performed early and an appropriate optical correction provided to reduce the period of visual deprivation and the risk of amblyopia. This type of surgery can be difficult and requires careful follow-up as graft rejection may be insidious and develop rapidly in the infant. Even with the most meticulous care, the prognosis for graft survival in young children is poor, with only about 40% of long-term grafts remaining

Fig. 10. *Congenital hereditary endothelial dystrophy. Central corneal clouding presented at birth; the anterior segment was otherwise normal.*

clear.[320] If the degree of opacity permits a delay, the prospects for successful grafting improve markedly.[321]

2. Posterior polymorphous dystrophy (PPMD)

This is a slowly progressive disorder that is most often innerited as an autosomal dominant trait, although in some instances the inheritance appears to be autosomal recessive.[322,323] Involvement is bilateral, but the expression of the disease can be highly variable and asymmetric, such that early cases may appear to be unilateral. Vision is usually well preserved and only rarely does stromal and epithelial oedema develop. In some family studies vesicles and corneal oedema have been'noted at birth.

Corneal changes are best visualised with a slit-lamp using a broad tangential beam or retro-illumination (Fig. 11). At the level of Descemet's membrane, clusters of vesicular lesions are arranged in groups, scalloped geographic areas, or bands that may superficially resemble traumatic breaks in Descemet's membrane.[324] A faint grey stromal haze surrounds these lesions. Two separate populations of endothelial cells can be seen at specular microscopy: large pleomorphic cells and small cells that have indistinct boundaries.[325]

The benign non-familial occurrence of small clusters of posterior corneal vesicles has been reported.[326] These do not affect vision and are non-progressive.

The occurrence of features of mesenchymal dysgenesis, the iridocorneal endothelial syndrome (ICE), and CHED in some families with PPMD suggests a related aetiology.[319,324,327] The basic anomaly of both PPMD and ICE seems to be a proliferation of metaplastic epithelioid cells, although proliferation onto the anterior iris is not common in PPMD and the two conditions vary in their morphology, transmission and natural history.[328] Broad peripheral iridocorneal adhesions, a feature of some cases of PPMD, are more substantial than the finer adhesions that occur in the Axenfeld-Rieger syndrome and they are not associated with a prominent Schwalbe's line. Glaucoma rarely occurs in patients with PPMD, but when it appears it is thought to result from a proliferation of endothelium over the open angle or an anterior insertion of the iris into the trabecular meshwork—an abnormality that is more typically seen in primary congenital glaucoma (trabeculodysgenesis).[329]

Histopathological studies of PPMD are limited to the few cases that progress to corneal oedema. The presence of endothelial cells with epithelioid characteristics is remarkable.[330] Affected cells form multiple layers and overgrow the normal endothelial cells,[331] have desmosomal junctions and numerous microvilli facing the anterior chamber.

Endothelial cultures from affected corneas produce two distinct populations: cells of a normal appearance and cells having multiple microvilli.[332] An increased expression of the keratin cytoskeleton has been demonstrated by immunohistochemistry in PPMD,[333,334] indicating that the epithelioid cells are probably not derived from ectopic surface ectoderm but are metaplastic endothelial cells.[335] The presence of only a thin posterior non-banded Descemet's membrane suggests an onset of disease in the perinatal period.[331,335,336,337,338,339,340] A thick posterior collagenous layer is deposited later and may be heaped into fusiform swellings that project into the anterior chamber or form loose fibrocellular material which fills infoldings of Descemet's membrane. Both changes can produce the clinical appearance of vesicles.[341]

3. Fuchs' endothelial dystrophy

This is the most common of the endothelial dystrophies. It is characterised in its earliest stages by guttata which appear as non-reflecting points in the specular image of the endothelium or as refractile particles on retro-illumination[342] (Fig. 12). Primary ·guttata appear in two patterns: isolated central guttata as part of the normal ageing process or confluent guttata accompanied by corneal oedema and reduced vision which constitutes Fuchs' endothelial dystrophy. There is a continuum of disease between these two extremes. Secondary corneal guttata may appear after corneal inflammatory disease, such as syphilitic interstitial keratitis.[343]

Fuchs' endothelial dystrophy is typically inherited as an autosomal dominant trait with

Fig. 11a.

Fig. 11. *Posterior polymorphous dystrophy. (a) Numerous 'vesicles' may be seen on the red reflex. (b) On specular microscopy, these appear as localised groups of abnormal cells (arrows) amidst a mosaic that has moderate polymegathism.*
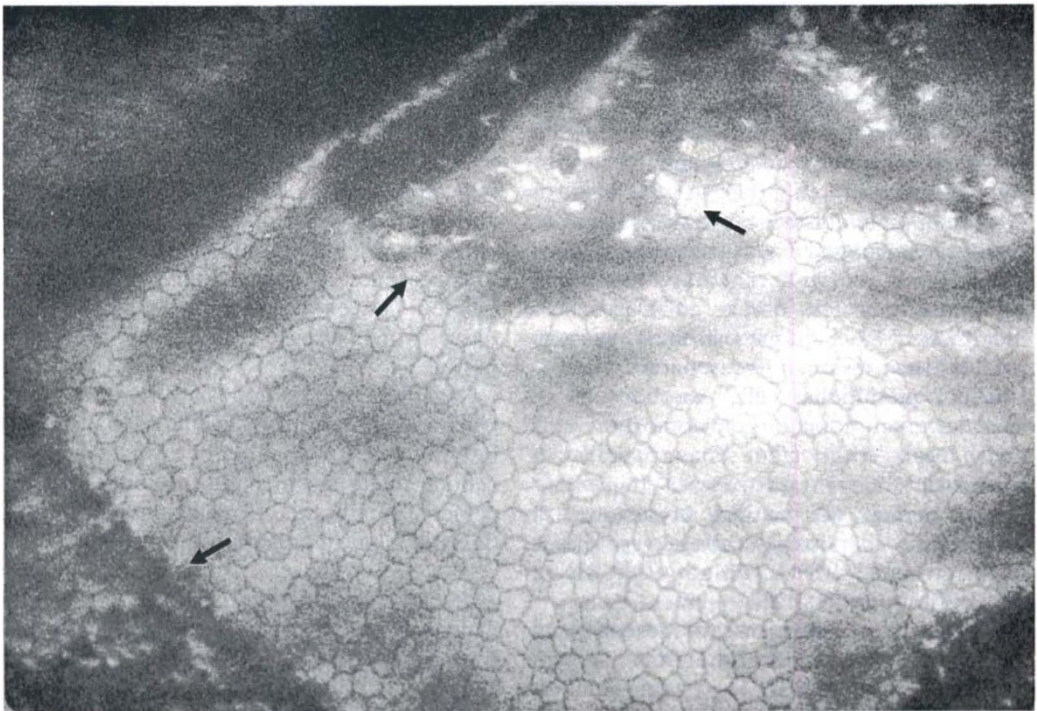

Fig. 11b.

incomplete penetrance, although in some series up to 50% of cases are sporadic.[344] In one large series, guttata were seen in 70% of individuals over the age of 40 years, but were confluent in only 3.7%.[345] The overall female to male ratio in this series was 2.5 to one but, when only the patients progressing to surgery were considered, the ratio increased to six to one.[344] Thus the disease is more common in females and the phenotypic expression is more severe.[346,347] An association of Fuchs'

endothelial dystrophy with chronic simple glaucoma, ocular hypertension and acute closed angle glaucoma would imply a generalised abnormality of the anterior segment,[348] but other authors report an incidence of chronic simple glaucoma of only 1.4%[344] and a normal outflow facility.

Abnormalities of the endothelium are evident many years before symptoms manifest. Symptoms typically develop slowly through three stages over a period of up to twenty

Fig. 12a.

Fig. 12b.

Fig. 12. *Fuchs' endothelial dystrophy. (a) Numerous guttata and localised stromal oedema may be seen on retroillumination. (b) Scanning electron microscopy graphically demonstrates the protruberent nature of the guttata and the way the remaining endothelial cells are at first stretched to cover them and are eventually lost.*

years. The eye is initially asymptomatic as guttata appear centrally, the thickened Descemet's membrane becomes visible on tangential illumination, and pigment that has been phagocytosed by endothelial cells forms geographic patterns. During a second stage of the disease, stromal and epithelial oedema produces glare and visual loss due to irregular astigmatism and the rupture of sub-epithelial vesicles can be painful. In the final stage, central sub-epithelial scarring results in an opaque cornea that may become secondarily vascularised.

Histological examination of Descemet's membrane shows a normal 110 nm banded layer anteriorly with a thin amorphous layer posteriorly. Excrescences formed of long-spaced collagen protrude into the anterior chamber, although these may be subsequently buried by the deposition of a posterior collagenous layer.[349] Endothelial cell loss results in an increase in the surface area of the remaining cells which become thinned.[350] The intercellular spaces are widened with the loss of occluding junctions, and the development of desmosomes could represent fibroblastic metaplasia.[350,351,352] Despite the loss of junctional complexes and a decrease in the endothelial cell numbers, endothelial pump function may be significantly increased in the early stages of disease, which would delay the onset of stromal oedema.[353,354]

Treatment aims to control discomfort and blurred vision. Increasing the tonicity of the tear film with hypertonic drops or blowing with a hair drier may help to clear vision, and a temporary bandage contact lens can lessen the discomfort from ruptured bullae. Topical steroids have no proven beneficial effect.[355] Penetrating keratoplasty should be considered when visual acuity falls to an unacceptable level. Despite the high percentage of graft successes in the early post-operative period, the long-term prognosis for keratoplasty has been reported to be poor;[356] this is based on one study in which all uncomplicated grafts had become cloudy at nine years follow-up.[357] Other long-term series, however, have reported success rates of up to 85% at 8 years.[358,359]

Viral particles have been demonstrated in one case of Fuchs' dystrophy,[360] but the aetiology of the majority of cases remains unknown. Fibrinogen and fibrin deposition have been demonstrated in the posterior collagenous layer by immunofluorescence and it is possible that the fibrinolytic system of the aqueous humour adversely affects the endothelial cells. Systemic tranexamic acid, an anti-fibrinolytic agent, has been used with some success in clinical experiments to induce stromal thinning in Fuchs' dystrophy,[361] but the mechanism of its action is undetermined.[362]

4. The irido-corneal endothelial (ICE) syndrome (Primary proliferative endotheliopathy)

The ICE syndrome is particularly difficult to classify as it does not completely satisfy the criteria for both dystrophy and dysplasia. The condition is essentially unilateral with minimal changes in the other eye; it is usually sporadic but family clusters have been described and it has a characteristic clinical appearance, with dysplastic endothelium the dominant histologic feature. Whether the condition should be considered with the dystrophies or whether it represents a true dysplasia (but grossly delayed) of the neural crest remains to be decided. For our purposes it is appropriate to consider the syndrome along with the endothelial dystrophies.

Essential iris atrophy, Chandler's syndrome and the Cogan-Reese syndrome are probably variants of a single disease process in which secondary corneal oedema, peripheral anterior synechiae and changes in the iris architecture are the main clinical features[363] (Table V). They form a group of progressive disorders collectively called the irido-corneal endothelial (ICE) syndrome[364] (Fig. 13). The endothelium in this syndrome has a characteristically hammered-silver appearance in specular reflection.[365]

Patients with the ICE syndrome are typically young white females in their third to fifth decade.[369] The female to male ratio is estimated to be as high as $5:1$[370] and, interestingly, affected males tend to have bilateral involvement. Although most cases are sporadic, a familial bilaterally symmetric variant has also been described.[371] Minor abnormal-

Table V *The iridocorneal endothelial syndrome*[366,367,368]

Essential iris atrophy	Broad iris synechiae
	Distortion of pupil
	Ectropion uvea
	Iris holes
	Sphincter pupillae preserved
	Corneal oedema over synechiae
Chandler's syndrome	Few iris features
	Diffuse corneal oedema
	Secondary glaucoma
Cogan-Reese syndrome	Pigmented iris nodules in addition to the above features

ities of the endothelium in the contralateral eye, iris transillumination defects and a reduction in the outflow facility all suggest that this is a bilateral disease with asymmetrical involvement.[372,373,374]

Specular microscopic examination has demonstrated that there are two cell populations: a unique 'ICE cell' that has a very irregular shape and reversed cell highlights and cells of normal appearance that may be at either a greater or lesser density than the cells of the unaffected eye.[373,375,376] There are marked regional variations, with cells of normal configuration and areas of gross pleomorphism.[377,378,379,380] When first examined, corneal involvement can be incomplete, in which case there is a sharp interface between the two populations of cells. Dystrophic cells can gradually replace the normal cells, an event that is frequently followed by an increase in intraocular pressure.

At histological examination, the striking feature is the wide variety of endothelial change, filopodia formation, multilayering of cells and localised cell necrosis. A collagenous layer forms posterior to normal Descemet's membrane and beneath ectopic endothelium on the iris surface—the 'glass membrane' seen by light microscopy.[381] Iris nodules of modified melanocytes can protrude through gaps in this ectopic membrane.[382] Features suggestive of epithelialisation of the posterior corneal surface have been demonstrated in cases of Chandler's syndrome[383,384] and, while the original diagnosis of ICE syndrome must be carefully considered, the increased expression of cytokeratins (epithelioid metaplasia) suggests a link between the ICE syndrome and PPMD.[385]

The features of the ICE syndrome result from degeneration of the endothelial cells on the posterior cornea. There is an associated, but paradoxical, proliferation of the remaining cells onto the iris,[364,385] although mitotic division is rarely observed.[379,380] A reduction in outflow facility is presumably the result of the growth of endothelial cells onto the trabecular meshwork.[386,387] Contraction of the collagen formed beneath the ectopic endothelium then produces peripheral anterior synechiae, an ectopic pupil, and traction tears of the iris. Evidence for vascular occlusion
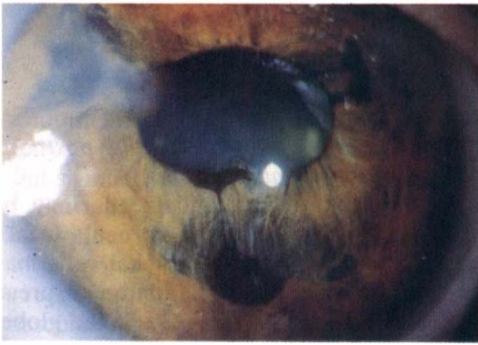
Fig. 13a.

Fig. 13. *ICE syndrome. (a) Clinical photograph demonstrating areas of corneal clouding, broad anterior synechiae, and an iris hole. Chandler's syndrome presenting as diffuse corneal oedema in an otherwise asymptomatic eye. (b) On specular microscopy, the endothelial mosaic is irregular and there are several ICE cells with reversed highlights (arrows). (c) A line of demarkation may be seen in cases of incomplete endothelial involvement.*
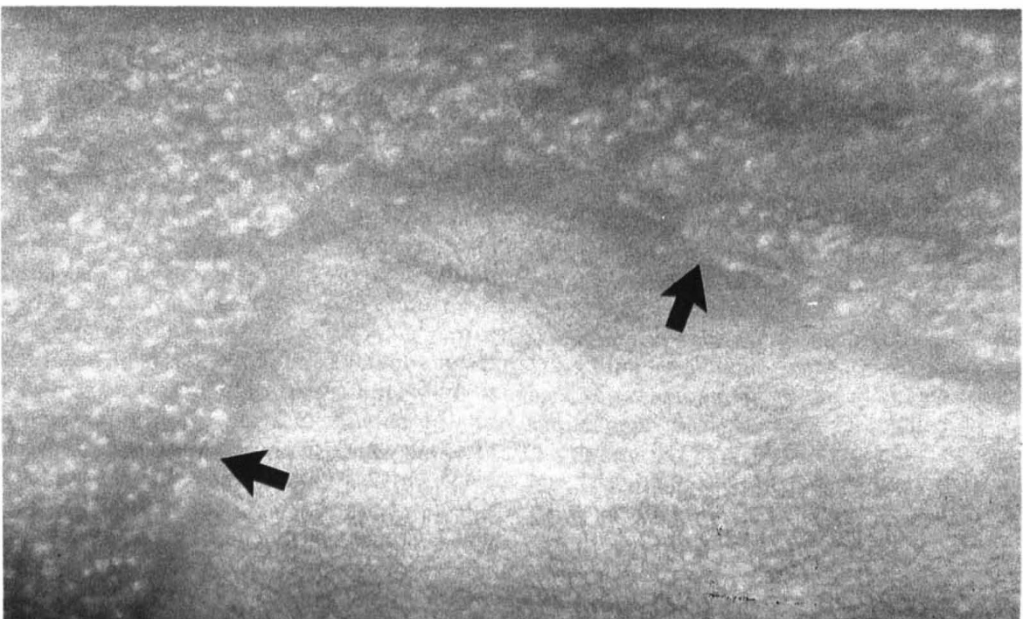

Fig. 13b.

Fig. 13c.

producing the iris holes in this disease is conflicting; some studies have failed to demonstrate any occlusion[372] while others have demonstrated widespread vascular change.[388,389] It is tempting to postulate that differences in the relative contribution of the three basic features of this condition—endothelial cell loss, endothelial migration and the deposition of an ectopic Descemet's membrane—could be reflected as three clinical variants.[390] The presence of normal Descemet's tissue beneath a posterior collagenous layer points to a post-natal onset of disease,[379] interpreted as either the delayed expression of abnormal neural crest development or an acquired inflammatory lesion.

Most patients with ICE syndrome maintain excellent vision and require only periodic review. The breakdown of the syndrome into three groups is of little clinical significance, particularly as patients may progress between groups.[369] However, it is important to make the distinction from other causes of iris tumour, for example iris melanoma, and to recognise a tendency to develop a raised intraocular pressure. In the presence of glaucoma, management should initially be directed toward control of aqueous production by medical means, but filtering surgery is eventually required in about 50% of cases.[391] Subsequent proliferation of endothelium into the filtering bleb may cause failure of some operations, but surgery can be repeated. Symptoms of early corneal oedema may be controlled by hypertonic drops or a soft contact lens, but penetrating keratoplasty, following the control of raised intraocular pressure, may be required if corneal oedema produces significant visual loss or ocular discomfort. There are no histological reports of recurrence of the primary disease in the donor corneal button.[392,393]

Acquired Disorders—the Endothelial Response to External Influences

The corneal endothelium has a limited repertoire of responses to challenge. Sub-lethal injury results in minor pleomorphic changes in the cellular array, more damaging injury may produce metaplasia, but cell loss is the most common response to trauma. Surgical intervention is the most common noxious stimulus experienced by the cornea.

Surgical Injuries

1. Epithelial downgrowth and other post-surgical retrocorneal membranes

Cells other than endothelial cells may be seeded onto the posterior corneal surface where they may grow. Epithelial cells may spread after traumatic implantation or spread through a gap in the integrity of the globe. Study of organ cultured corneas suggests that epithelium will not overgrow healthy endothelium,[394,395] and progressive endothelial disease seems to be a prerequisite for clinical disease.[396,397,398,399] However, in an inverted keratoplasty model of epithelial downgrowth developed in the cat, epithelial cells grow across residual endothelium onto the iris.[400] Iris pigment epithelial cells, iris stromal melanocytes or pigment-containing macrophages can also be seeded onto the back of the cornea, where they develop into pigmented retrocorneal membranes.[401,402] Melanocytes in this location may cover a large area, but such membranes do not invariably induce corneal oedema. It has been suggested that, as they are of neural crest origin, they are able to develop a pumping facility.[403,404] Alternatively, functioning endothelial cells may survive beneath the melanocytic layer. These hypotheses require further study.

2. Post-Surgical Endothelial Cell Loss

Loss of some endothelial cells after intraocular surgery is inevitable. This subject has been discussed in detail in a previous section.

Non-Surgical Injuries to the Endothelium

1. Concussive injuries

Breaks in Descemet's membrane can produce endothelial damage after forceps injuries, in congenital glaucoma and keratoconus, and in high myopia.[405] The cell loss after a blunt injury is then exacerbated by an associated hyphaema, uveitis or raised intraocular pressure.[406,407] A condition termed traumatic posterior annular keratopathy has been observed to follow the impact of high velocity particles on the superficial stroma, most frequently after powder flash or sand blasting injuries: as particles strike the cornea they generate a shock wave that passes backward from the point of impact producing a ring of vacuolated

endothelial cells with an adherent plaque of leukocytes and fibrin. This usually heals without significant endothelial cell loss.[408]

Secondary proliferation of the endothelium can follow blunt ocular injury, especially if the blow is of sufficient force to produce an angle recession;[409,410,411] less frequently it is seen in association with rubeosis iridis.[412] There is a reduction in the density of the remaining endothelial cells and obstruction of the anterior chamber angle.[295]

2. Hypoxia

Transient bleb-like structures in the specular image develop after overnight lid closure,[413] or within minutes of placing a low oxygen transmission contact lens onto the unadapted eye.[414] These changes, and a co-existent increase in corneal thickness, could be the direct result of endothelial hypoxia,[415] but more probably are the result of epithelial hypoxia, the retention of CO_2 and the accumulation of lactic acid producing an osmotic imbalance.[416,417] Although the acute changes persist for only one to two hours after removal of the contact lens, a reduced regularity of the endothelial matrix has been documented after the long-term use of both daily wear and extended wear contact lenses wearers.[418,419,420,421,422,423] Although there is no convincing evidence of a resulting abnormality of endothelial function, PMMA contact lenses may increase endothelial cells loss if worn after penetrating keratoplasty.[424]

Anterior segment hypoxia could contribute directly to the endothelial cell loss and corneal oedema that can follow temporal arteritis, anterior segment necrosis, herpes zoster ophthalmicus and acute closed-angle glaucoma.[425] This is supported by experimental observation in which ablation of the long posterior ciliary arteries in the rabbit produces a sharp drop in the anterior chamber oxygen tension and glucose concentration, which is followed by corneal oedema.[426]

3. Raised intraocular pressure

In the presence of an intact endothelial layer, an increase in intraocular pressure (IOP) will initially produce corneal thinning; corneal oedema is produced only if the endothelial pump is overwhelmed.[427,428,429] The endothelium can adapt to a gradual increase in IOP,[430,431] but rapid rises in IOP result in endothelial cell damage. The cell loss after an acute angle-closure attack is roughly proportional to the duration of stromal swelling during the attack; a mean cell loss of 23% has been reported.[432,433] In contrast, cell loss has not been consistently demonstrated in primary open angle glaucoma or pigmentary dispersion glaucoma,[434] although there appears to be a tendency for cell loss in pseudexfoliative glaucoma.[435,436,437] In other situations it is difficult to isolate the effect of increased IOP; for example, a 10% cell loss has been reported following glaucomatico-cyclitic crises,[435] but this may be due in part to associated inflammation. A similarly complex pattern occurs in herpes zoster ophthalmicus, where there can be a considerable cell loss but the relative contributions of viral endotheliitis, inflammation, and ischaemia are not known.[438]

4. Electromagnetic radiation

The cornea is effectively opaque to radiation of less than 290 nm, but prolonged exposure to broad band UV-B has been documented to induce endothelial swelling, desquamation and the development of microvilli.[439,440] Whether this is a direct effect upon the endothelium or subsequent to inflammation induced by epithelial damage is unclear. Other wavelengths have no demonstrated effect.

Effects of Ocular Disease

1. Uveitis

Leukocytes that enter the anterior chamber can migrate between and beneath endothelial cells where they appear as pseudoguttata on the specular image.[441,442] Following mild uveitis, these changes are reversible, but marked cell loss can follow severe uveitis, especially beneath mutton fat keratin precipitates.[443] This may be the result of mononuclear cells, which have been observed to penetrate apical junctions in experimental uveitis and to dislodge endothelial cells into the anterior chamber.[444] Polymorphonuclear leukocytes in the anterior chamber can also produce toxic endothelial damage and oedema.[445] Similar

changes have been produced by the hydrolytic enzyme cathepsin and by neutral proteases that digest cell surface proteins and glycoproteins.[446]

2. Viral infection

The herpes simplex virus can be cultured from the stroma of a percentage of patients with disciform keratitis and it is probable that the virus can invade endothelial cells directly. The resulting endotheliitis and secondary attack by immunocompetent leukocytes produces pseudoguttata and oedema of the overlying stromal and epithelium.[447]

A bilateral and symmetric stromal oedema that moves centrally behind a line of keratic precipitates has been termed presumed auto-immune endotheliopathy.[448] Although it responds readily to topical steroid, the aetiology of this rare condition remains an enigma. Similar, but unilateral, cases that do not respond to steroid have been reported.[449] The anterior chamber in these cases contains macrophages and lymphocytes, but attempts to isolate viruses have been unsuccessful.

Endothelial cells may also be involved by disease processes that have their primary effect upon other corneal layers. For example, there may be endothelial deposition of acid mucopolysaccharide in macular corneal dystrophy.[450]

Systemic Metabolic Disease
Diabetes

Human diabetic corneal endothelium appears to have a normal cell density but it is more susceptible to stress than normal endothelium and stromal oedema following surgical procedures may be slow to resolve.[451] The endothelium of both juvenile and adult onset diabetic patients is often abnormal on morphometric analysis[452] and has a higher permeability to fluorescein.[453] A failure to demonstrate an increase in the thickness of the basement membrane of the endothelium (Descemet's membrane) comparable to increases demonstrated elsewhere in diabetics is thought to reflect the low turn-over of these cells.[454,455]

Conclusion

That so much attention has been directed to studies of the corneal endothelium by laboratory-based and clinical scientists is an indication of the importance and complexity of disorders affecting this seemingly simple monolayer of cells. The pathway to a complete understanding of the disorders of the endothelium extends before us. Much has been learned in the last two decades, and is the subject of this review, however much remains to be learned in the years to come. With the advances in basic science, particularly molecular biology, transplantation and immunology, powerful tools have been developed which are being used to increase an understanding of the biology of the corneal endothelial cell. Progress in this area of research is accelerating and the prospects of conquering the common disorders of the endothelium in the forseeable future are very real.

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