CONTENTS

I. BASIC SCIENCE ASPECTS

1. PHYSIOLOGY

Physiology of the Cornea: CORNEAL EDEMA

Claes H. Dohlman

Edema of the cornea is a major problem in ophthalmology. Only moderately common in occurrence, it can very quickly result in discomfort and marked reduction of vision, and it is frequently bilateral. Fortunately, in the last few decades great therapeutic advances have been made in treating corneal edema as a result of increased understanding of the basic physiology of the regulation of corneal water content, as well as the development of sophisticated diagnostic and therapeutic methods.

Edema of the cornea is the result of excess water in the epithelium, in the stroma, or in both of these layers simultaneously. It is important to consider epithelial edema and stromal edema separately since they arise from somewhat different pathophysiologic mechanisms and have different clinical effects. This section will discuss the normal regulation of corneal hydration, the pathophysiology of a variety of abnormalities that cause edema, and the medical and surgical approaches to the treatment of edema.

REGULATION OF STROMAL HYDRATION

For convenience, the term *stromal hydration* (H) has been used to quantitate the water content of the stroma. Hydration is defined as the weight of water in the stroma, divided by the stroma's dry weight (gm H_2O/gm dry weight). This value is about 3.4 in human and rabbit corneas.

The water content can also be expressed as percentage of water. The normal cornea is 78 percent water. However, a cornea of double normal thickness is about 87 percent water, whereas the H values have gone from 3.4 to 6.8 in the edematous cornea. The advantage of using H is that increases or decreases in hydration are linearly related to the thickness of the cornea, which can be measured clinically.

Regulation of corneal water content depends upon a variety of factors. These include the swelling pressure of the stroma, the barrier function of the epithelium and endothelium, and the water pumping mechanism located in the endothelium. Of lesser importance are the roles of evaporation from the corneal surface and the intraocular pressure. In Figure 1-1, these factors are shown in schematic fashion to indicate that all of them have an influence on the resultant corneal stromal thickness.

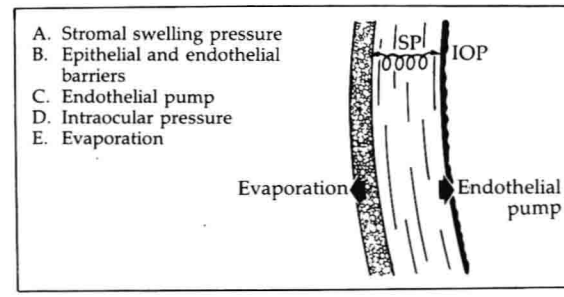

FIGURE 1-1. *Factors affecting hydration of the cornea. The tendency of the stroma to swell (swelling pressure [SP]) is balanced by the barriers imposed by the epithelium and endothelium, as well as by endothelial pumping. Evaporation plays a minor role, and intraocular pressure (IOP) has almost no effect over a wide range of pressures.*

STROMAL SWELLING PRESSURE

The corneal stroma normally has a higher water content than most connective tissue elsewhere in the body. This relatively high hydration is ascribed to the water-binding capacity of the proteoglycans that fill the space between the collagen fibrils. The glycosaminoglycans characteristic of the cornea are keratan sulfate and chondroitin sulfate (of varying degrees of sulfation). Together they constitute about 1 percent of the corneal wet weight. These proteoglycans are thought to be responsible for the swelling of the corneal stroma when the endothelium and epithelium are absent. The degree of swelling is related to the parallel and poorly cross-linked configuration of the collagen fibrils, which allows swelling to several times normal thickness.

This tendency to swell has been called the *stromal swelling pressure*. It can be measured by using a manometer to determine the pressure the stroma can overcome yet still imbibe water. A more accurate method of measuring the stromal swelling pressure is to clamp isolated stroma between two glass filters and immerse it in saline. The force generated against the clamps can be converted into the swelling pressure. The swelling pressure has been measured in rabbit, bovine, and human corneal stroma and has been found to be 40 to 50 mm Hg at normal corneal thickness [15, 19, 28]. Although there are other constraints that help determine the ultimate thickness of a swollen cornea, the swelling pressure decreases as the cornea swells (Fig. 1-2). Thus when the stroma has swelled by 50 percent, its swelling pressure has dropped to about a third of its normal value. It is clear that, in vivo, the stromal swelling pressure and the dehydrating mechanism are in constant equilibrium. If dehydration becomes less effective because of trauma or disease, the stroma swells until a new equilibrium is found.

Also apparent from Figure 1-2 is the fact that compression of the stroma is associated with a greatly increased tendency to imbibe water, a feature that

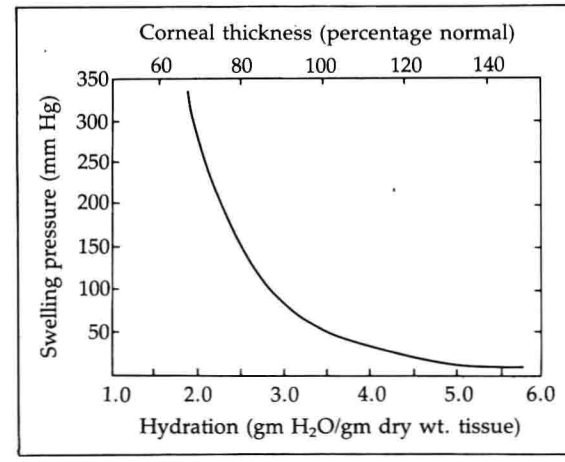

FIGURE 1-2. *Swelling pressure, hydration, and thickness of the cornea. As corneal thickness and hydration increase, the tendency to swell decreases.*

works against the thinning of the cornea by mechanical or physiologic means. The swelling pressure of the stroma therefore tends to set a limit on the minimum thickness of the cornea, while at the same time it tends to swell the cornea beyond its normal thickness.

The swelling pressure is due primarily to the glycosaminoglycans, which have a great tendency to expand their molecular volume [27]. As polyelectrolytes, their fixed negative charges repel each other, causing stretching of the molecules, which thereby occupy a larger volume than uncharged molecules would. In addition, the colloid-osmotic pressure of the tissue also contributes to the swelling pressure to a small degree.

EPITHELIAL AND ENDOTHELIAL BARRIERS

The tendency of the stroma to absorb water and swell must be constantly counteracted to keep the tissue dehydrated and transparent. It is well established that both the epithelium and the endothelium act as barriers to rapid fluid movement [43, 46, 51]. This is accomplished primarily by the high resistance to diffusion of electrolytes rather than by the resistance to water flow across these layers. The resistance of the epithelium to ions is about 2000 times that of the total stroma, and since the movement of ions is therefore restricted, the resulting osmotic pressure tends to retain water in the stroma. The relative thickness of epithelium, stroma, and endothelium is 0.1 : 1.0 : 0.01; the relative resistance to diffusion of electrolytes of these structures is 2,000 : 1.0 : 10.0 [43, 46, 51]. More recently, it has been shown that the barrier properties lie primarily at the level of the surface cells of the epithelium [35]. Thus, the epithelium constitutes an almost perfect semipermeable membrane but one that is quite vulnerable to trauma, inflammatory products, drug toxicity, and contact lens overwear. The single-cell endothelial layer is only slightly more leaky than the epithelium, its resistance to ions being about 10 times higher than that of the total stroma [46].

ENDOTHELIAL PUMP

Eventually the limiting cellular layers could not resist the stromal swelling pressure simply by their impermeability to solutes. In addition, some fluid undoubtedly enters the stroma across the limbus. A constant removal of a small volume of water from the stroma must therefore be postulated, but the mechanism for this dehydration is not entirely clear. The classic temperature reversal experiments showed that corneas will swell at low temperature but will again dehydrate if body temperature is restored [12, 26]. This metabolically related dehydration is blocked by inhibitors of anaerobic glycolysis such as iodoacetate, inhibitors of the respiratory chain of enzymes such as cyanide, inhibitors of Na-K ATPase such as ouabain, and deficiencies of essential nutrients such as oxygen and glucose [46].

Current information clearly identifies the endothelium as the layer across which the water transport takes place. Experimental demonstration of a fluid transport ability of great magnitude clearly implicates the endothelium as the layer responsible for the active dehydration of the cornea [45, 52]. Thus, the endothelium is capable of transporting at least 6.5 ml/cm^2/hour against normal hydrostatic pressure [45]. However, the mechanism by which this metabolic pump operates is not entirely clear. Of several hypotheses, the concept of a bicarbonate pump is presently in favor. An active transport of bicarbonate by the endothelium has been demonstrated [29, 31], and it may provide the missing link between cell metabolism and endothelial fluid transport. Whatever the exact mechanism, the cornea is definitely dependent on an intact, viable endothelial layer to keep the stroma from swelling excessively (Fig. 1-3).

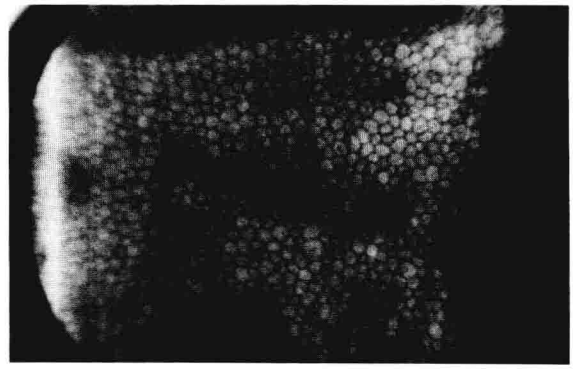

FIGURE 1-3. *Wide-angle specular microscopy showing normal endothelial mosaic. (Courtesy Calvin W. Roberts, M.D.)*

Transport of certain ions has also been shown to occur across the epithelium. For example, chloride is transported from the stroma to the tear film; this transport is modulated by adenosine 3′,5′-cyclic phosphate (cAMP) and stimulated by beta-adrenergic agonists [36]. However, the amount of water transported by this mechanism would be far too small compared with what leaks in to maintain normal hydration [37].

INTRAOCULAR PRESSURE

Intraocular pressure cannot be ignored in considering the fluid dynamics of the cornea. However, in the normal eye, variations in pressure from almost zero to 40 to 50 mm Hg have virtually no influence on stromal thickness and do not create any epithelial edema [63]. On the other hand, when endothelial abnormalities are present, intraocular pressure is an important causal factor in the development of epithelial edema.

EVAPORATION

Evaporation of water from the corneal surface occurs constantly between blinks. The resulting hypertonicity of the tear film causes water to move forward through the cornea to make up for the loss. This evaporation and tear film hypertonicity can have disastrous consequences in the diseased eye,

especially if corneal sensation is reduced. In the normal eye, evaporation has no other influence than causing a slight thinning of the cornea during daytime compared with the night when the lids are closed [41]. The healthy cornea with intact innervation protects itself against evaporative damage by registering tear hypertonicity as a slight sting, which in turn elicits a blink to restore isotonicity.

DEVELOPMENT OF EDEMA

TYPES OF EDEMA

As mentioned earlier, epithelial and stromal edema deserve to be discussed separately since their pathophysiology and their influence on vision differ. In most situations, stromal edema precedes epithelial edema but stromal edema is usually symptom-free until epithelial edema occurs. It is only when epithelial edema ensues that vision, and sometimes patient comfort, become severely affected. Understanding of the causal factors involved and the sequence of events is important for clinicians in diagnosis, prognostication, and treatment of corneal edema.

STROMAL EDEMA

Stromal edema results in a thickening of the tissue in proportion to the increase in stromal hydration. The diameter of the collagen fibrils seems to remain the same; the additional fluid accumulates in the interfibrillar space. On swelling, corneal diameter does not change, and no anteriorly directed swelling takes place, as evidenced by the lack of change in the outer corneal radius. Swelling is directed posteriorly, with shortening and folding of Descemet's membrane, producing striae of the posterior surface, for which the clinical term is *striate keratitis*. In later stages a varying degree of scarring can develop in the stroma, particularly in the posterior folds (see Chapter 2, Morphology and Pathologic Response of the Cornea to Disease).

Stromal edema is always caused by the malfunctioning of one or both of the limiting cellular layers. If the epithelium is damaged or removed, tears are imbibed, but the resulting stromal thickening is slight and usually restricted to the tissue just beneath the area of damage. On the other hand, if corresponding damage occurs to the endothelium, the resulting stromal edema is much greater. Injury or disease of the endothelium has two adverse consequences: the loss of the barrier function and interference with the active pump mechanism. This combination of effects accounts for the profound effect of endothelial dysfunction on stromal hydration.

EPITHELIAL EDEMA

In most clinical conditions associated with stromal edema, the endothelium is the site of the primary abnormality. Nevertheless, epithelial involvement can develop nearly immediately; this involvement generally alarms the patient because of decreased vision or pain. Intercellular epithelial edema begins as fluid accumulation between the cells, particularly between the basal cells (Fig. 1-4). Depending on the degree of edema, the size and form of these accumulations vary, in advanced stages developing into blisters typical of bullous keratopathy. As distortion and elevation of the epithelial cells proceeds, interference with maintenance of normal cell permeability may lead to abnormalities of cation pumping, with subsequent development of intracellular edema (Fig. 1-5). This chain of events is quite different from that seen in the metabolic edema found after inappropriate contact lens wear, in which anoxia leads first to a failure of cation pumping and intracellular edema, with virtually no extracellular edema or bullae formation (see Chapter 17, Therapeutic Soft Contact Lenses).

The pathophysiology of epithelial edema differs to some extent from that of stromal edema. Epithelial edema is not only related to the state of the endothelium, but is also dependent upon intraocular pressure [63]. In fact, fluid accumulates in the epithelium only when the intraocular pressure has overcome the endothelial pump pressure and there is a forward bulk flow of fluid toward the epithelium. Owing to the great resistance to the movement of water across the anterior portion of the epithelium, the fluid is trapped primarily in the posterior or midportion of this layer, resulting in the clinical signs of epithelial edema. Thus, epithelial edema can occur with normal endothelial function but very high intraocular pressure (e.g., in acute glaucoma), with poorly functioning endothelium but normal pressure (e.g., Fuchs' dystrophy), or with a combination of both factors. Under any circumstance, intraocular pressure is the driving force; in phthisis with pressure near zero, no matter how damaged the endothelium is, epithelial edema never occurs.

Evaporation can have a considerable influence on epithelial edema, with almost no effect on stromal edema. It is a well-known clinical phenomenon that, in the early stages of epithelial edema, vision is worst in the morning after a night's lid closure and absence of evaporation from the ocular surface. As the day goes on, however, fluid is extracted from the epithelium because the tear film is intermittently made hyperosmotic by evaporation between blinks, and vision gradually clears. Sometimes epithelial edema is visible only in the upper part of the

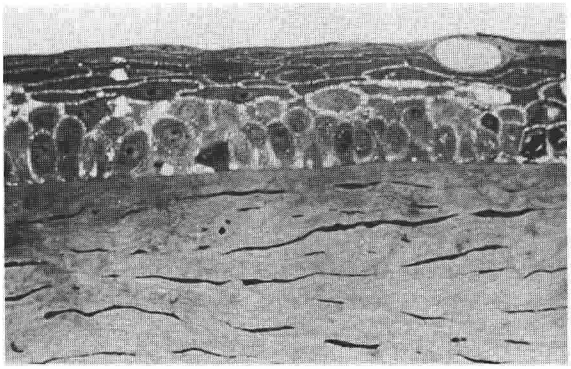

FIGURE 1-4. *Intercellular edema. This accumulation of fluid between the cells is frequently the result of endothelial damage. (×500.)*

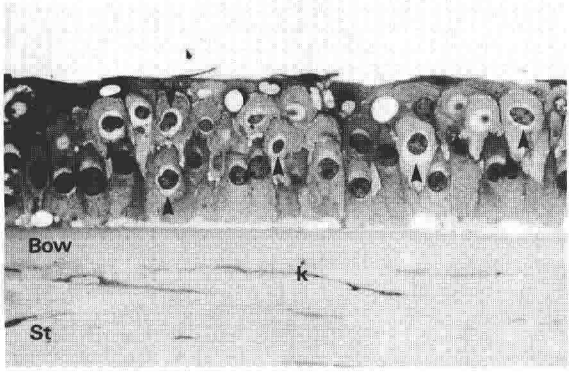

FIGURE 1-5. *Intracellular edema* (arrows) *occurs as the result of distortion of cell walls by edema fluid or by abnormalities of cation pumping. (×500.) (Bow = Bowman's layer, St = stroma, k = keratocyte) (Courtesy Yasuo Ishii, M.D.)*

cornea, where the upper lid permanently prevents evaporation. In more advanced edema, however, fluid flows into the epithelial layers so fast that evaporation does not clear the epithelium of excess fluid.

EFFECT ON VISUAL ACUITY

The transparency of the normal cornea is not readily explained in terms of geometric optics [47]. Rather, it has been proposed that the fluctuations in refractive index across the stroma and the cellular layers are so small that scattering of light is kept to a minimum. It is known from the field of optics that if such refractive index heterogeneities are distanced less than half the wavelength of light (about 2000 Å) apart, transparency is preserved. Normally, the collagen fibrils of the cornea are closer together than half the wavelength of light, satisfying this criterion for transparency. However, theoretically, abnormal fluid accumulation between the fibrils should increase light scattering and decrease transparency. In support of this theory, such fluid accumulations with dimensions far greater than the wavelength of light can be seen in edema, not only in the corneal epithelium but also in the stroma, where irregular collections can form, especially around the keratocytes [22].

Epithelial and stromal edema differ in their effect on visual acuity, as already mentioned, with stromal edema far less important. A moderate swelling of the stroma without epithelial involvement has little influence on vision. For example, when bovine stroma is excised and evenly hydrated, a transparency equivalent to 20/30 vision still persists at a 60 percent increase in thickness [64]. However, later in the development of chronic edema, stromal scarring and posterior irregular astigmatism from the Descemet's folds result in more marked reduction of vision.

Epithelial edema, in contrast, affects vision early. The patient may report either colored haloes around lights or decreased acuity even though the edema can be seen only with the slit lamp. The reasons for this early and profound effect on vision are twofold: increased light scattering within and between the epithelial cells themselves, and, even more important, the microscopic irregularity of the surface. This latter effect can be thought of as conversion of the optically smooth epithelium into a mosaic of fine irregularities, each of which tends to refract the light rays that impinge on it in a different direction. The retinal image produced by such multiple refracting surface elements is not only blurred but is also characterized by color separation because of prismatic effects.

PATHOLOGIC PROCESSES LEADING TO EDEMA

Most causes of corneal edema have a direct adverse effect on the endothelial layer. These causes include inflammation, endothelial dystrophies, keratoconus, and trauma. Elevated intraocular pressure alone can also lead to edema, although the stromal component is much less prominent than the epithelial portion in this case. The basic pathophysiology of each of these conditions is described in the following paragraphs.

INFLAMMATION

Corneal edema can accompany any severe inflammation of the anterior segment. Unidentified inflammatory mediators or inflammatory cells seem to interfere with endothelial cell function in a manner

that can be localized or generalized, reversible or irreversible. Certainly, the presence of keratitic precipitates (KP) on the surface of the endothelium would be expected to interfere with the metabolically active fluid pump. Even in herpetic keratouveitis the endothelium might be expected to suffer by being covered in part by inflammatory cells. This adverse influence of inflammatory cells and possible mediators of inflammation is probably the cause of corneal edema in acute herpes zoster or herpes simplex, bacterial and fungal infection, and some forms of uveitis.

However, the relationship of corneal edema to uveitis is a peculiar one. Chronic uveitis (e.g., rheumatic or idiopathic) can exist for years or decades without corneal damage, despite the intermittent presence of abundant KP on the back of the cornea. One can postulate that there are inflammatory mediators whose adverse effect on the endothelium is greater than that of the physical presence of KP.

The mechanism by which disciform edema in herpes simplex occurs may also depend in some way on humoral influences. Certainly, the development of such edema appears to be secondary to immunologic processes. Observations supporting such a pathogenesis include the presence in the stroma of remnants of herpes virus that might serve as antigens, the presence of lymphocytes, and the remarkable therapeutic effect of steroids. How this immunologic process leads to dysfunction of the endothelium is unknown. The development of stromal edema is so common in herpes simplex infection that the finding of edema with or without uveitis in one eye, the other being normal, must always lead to the consideration of herpes as the cause, even in the absence of a history of epithelial or stromal disease.

CORNEAL GRAFT REACTION

Immunologic graft rejection is a form of inflammation. After the recipient's immune system is triggered, lymphocytes can find their way to the corneal graft and attack its cells. Although rejection of both epithelial and stromal cells can occur, involvement of these two cell layers does not produce corneal edema. Rather, it is the damage to the endothelium that leads to edema of the graft (but not of the surrounding host cornea) and reduced vision [42]. In the early massive rejection of a graft in a vascularized recipient cornea, the lymphocytes appear to escape from the graft wound and migrate to the posterior surface, forming a line that slowly advances toward the center of the cornea, destroying the endothelium in the process [34] (Fig. 1-6). Edema is initially localized to the overlying area. Later (about 3 months after surgery) a rejection line is rarely seen, and damage takes a more diffuse form, with numerous KP and uniform graft edema. Presumably the lymphocytes derive from the iris via the aqueous in this form (see Chapter 3, Immunology).

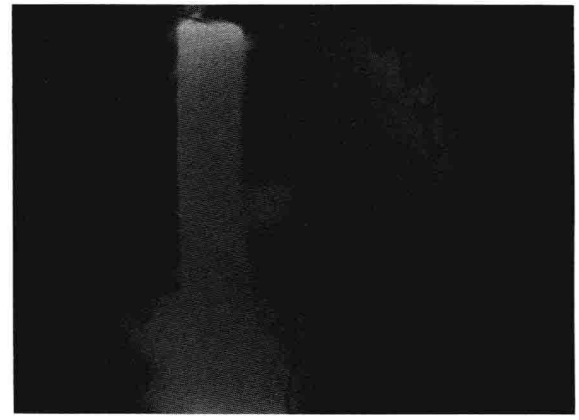

FIGURE 1-6. *Immunologic graft reaction showing a line of keratitic precipitates (Khodadoust line) on the endothelial surface.*

ENDOTHELIAL DYSTROPHIES

FUCHS' DYSTROPHY

In 1910 Ernst Fuchs described the dystrophy that bears his name [21]. At that time only the epithelial manifestations of the advanced stage were recognized. Decades later it was realized that this form of dystrophy stems from a primary malfunction of the endothelium rather than of the epithelium (see Chapter 9, Dystrophies and Degenerations).

The first clinical sign of Fuchs' dystrophy is the appearance of guttata in the slit lamp when using specular reflection of the Descemet's membrane region (Fig. 1-7). The appearance, which has been likened to beaten silver or orange peel, begins centrally in both corneas. Sometimes a diffuse, golden brown pigmentation of the central posterior surface is also seen. Specular microscopy reveals decreased cell density, irregular-sized cells, and dark spots that presumably correspond to the guttate lesions [2]. Histologically the endothelial cells show degeneration and deposition of abnormal Descemet's membrane material to form the wartlike excrescences on the posterior surface of that membrane. The cells gradually thin over these prominences, and, on further deterioration, the apical junctions break up, which readily explains the concomitant decline in the barrier function of the endothelial layer.

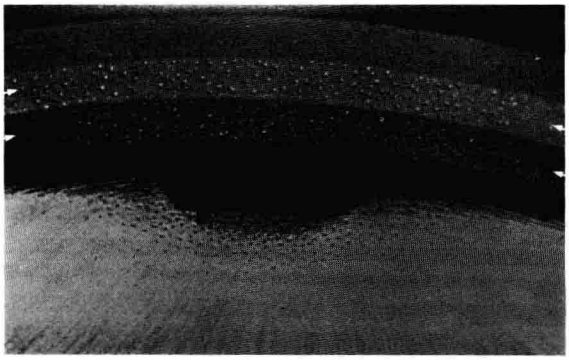

FIGURE 1-7. *Artist's conception of endothelial guttate changes. Posterior corneal surface shows the guttate changes seen in Fuchs' dystrophy* (white arrows).

The guttata often appear in early middle life and progress very slowly. In early stages there is no epithelial edema, and visual acuity is usually 20/30 or better. It is difficult to predict the rate of development of edema based merely on the guttate appearance in the slit lamp. Large and widespread guttate lesions may be compatible with many years of good vision. Thus, there can be a considerable discrepancy between the anatomic appearance (extent of guttata) and endothelial function. The degree of stromal edema (measured by pachometry) is the most reliable indicator of how close the cornea has come to the stage of epithelial edema. Such measurements are particularly important if surgery (e.g., cataract extraction) may be needed in the future.

Sooner or later, often decades after the guttate appearance was first observed, epithelial edema gradually develops, first as a fine bedewing and later as frank bullae. The edema begins centrally in the optical zone, and vision fails rapidly. Characteristically, vision is worse in the morning owing to the lack of evaporation from the tear film during sleep. Eventually the benefit of better vision late in the day is lost, the epithelium becomes more bullous, and photophobia or pain develops. Finally, in long-standing severe edema, connective tissue is formed between epithelium and stroma; at this point discomfort has disappeared, but vision has dropped to hand movements. This end stage is now less commonly encountered, since the natural history of the disease is usually interrupted by therapeutic measures.

Fuchs' dystrophy with epithelial edema is a relatively rare disease, although firm epidemiologic data on its frequency are lacking. Familial transmission of the disease is rare, but a dominant inheritance pattern has been reported [10]. Cataract and glaucoma are slightly more common in patients with Fuchs' dystrophy than in the general population, but there are no known systemic abnormalities.

CONGENITAL HEREDITARY ENDOTHELIAL DYSTROPHY

Congenital hereditary endothelial dystrophy (CHED) is an entity distinctly different from Fuchs' dystrophy. In CHED, the corneas are already hazy at birth. They are often extremely swollen, but epithelial edema is minimal. Keratoplasty specimens show markedly degenerated endothelium; sometimes this layer is almost absent. There is no vascularization or other signs of inflammation. Since the disease is already present at birth, deep amblyopia, nystagmus, and esotropia commonly occur. Also, glaucoma is not uncommon in severe cases (see Chapter 10, Congenital Anomalies).

CHED is autosomally hereditary, and both dominant and recessive forms have been reported. In the dominant form, the corneas are often less cloudy at birth, but the disease is still progressive. Because of the severity of this disease and the limited success of therapy for it, genetic counseling is advised.

CHANDLER'S SYNDROME

Chandler's syndrome is a rare ocular disease manifested by essential iris atrophy (often with distortion of the pupil), glaucoma, and corneal edema [8]. The condition is always unilateral and easy to diagnose. Fine guttata are visible early in the course of the disease, and peripheral anterior synechiae develop from an abnormal endothelial membrane that grows over the angle and the iris [6]. The corneal stroma is not very swollen, and the epithelial edema characteristically appears as a fine bedewing of the whole cornea (in contrast to Fuchs' dystrophy, in which the edema begins centrally). There is no evidence of a genetic basis in Chandler's syndrome. The Cogan-Reese syndrome seems to be a variant of Chandler's syndrome in that it exhibits similar characteristics, plus nevi, heterochromia, and ectropion uveae (see Chapter 9, Dystrophies and Degenerations).

KERATOCONUS

In a minority of patients with keratoconus, usually in those with advanced thinning, Descemet's membrane can suddenly break centrally. The edges roll up and aqueous enters the area, which is now devoid of endothelium, thus creating massive edema. The endothelium soon heals, presumably by cells sliding in and covering the defect, and the edema is

cleared within 2 months. The edema usually leaves a small stromal scar, which is often located slightly eccentric to the visual axis. There is no treatment of this temporary edema, although a soft lens may ameliorate discomfort. Frequently the patient regains the vision he had before the episode.

TRAUMA

INTRAOCULAR SURGERY

Cataract extraction is the most frequent type of surgery associated with corneal endothelial cell damage. Currently, more than 400,000 cataract extractions are performed annually in the United States. In about a quarter of them, an intraocular lens is also inserted. The incidence of irreversible corneal edema after cataract surgery is not known with certainty; however, recent data compiled by the Food and Drug Administration have indicated an incidence of about 1 percent [62]. Also, many patients who developed edema postoperatively show guttate changes in the other eye, which suggests the presence of preoperative endothelial dystrophy in the edematous eye. This also explains why so many patients develop edema in both eyes after bilateral surgery.

It is often hard to pinpoint in retrospect what maneuver has damaged the endothelium during a seemingly uneventful and successful cataract extraction. Some damage is probably unavoidable and can be detected only by sophisticated methods such as specular microscopy. The average postoperative cell loss in clinically successful cases, as measured by specular microscopy, is less than 20 percent [60]. In less experienced hands, cataract surgery commonly results in some permanent increase in stromal thickness as well, but usually short of epithelial edema and without interference with vision [48]. When a polymethylmethacrylate intraocular lens is inserted, flat contact between the plastic material and the endothelium can result in surface adhesion and subsequent rupture of the posterior cell walls, resulting in widespread damage [4].

In the postoperative period, vitreous touch to the cornea can be another cause of edema. If the vitreous is solid and adhering to the corneal back surface, stromal swelling over the affected area, followed by total decompensation, can occur. On the other hand, loose vitreous, even filling the whole anterior chamber, is not likely to cause corneal decompensation. In fact, the role of vitreous contact in causing corneal edema seems to have been overestimated [3].

OTHER TRAUMA

Any injury, if severe enough, can cause either immediate or delayed corneal edema. In perforating injuries, permanent edema is common. Of interest is the slit lamp appearance of the eye after blunt trauma. The posterior surface can show temporary guttata indistinguishable from the permanent guttata of Fuchs' dystrophy [39]. After a few days these temporary guttata usually disappear, and there are no further consequences. However, this phenomenon raises questions about the exact anatomic nature of what is seen in the slit lamp as guttata.

ELEVATED INTRAOCULAR PRESSURE

In contrast to the clinical conditions described above, increased intraocular pressure does not directly injure the endothelium. However, elevation of pressure, especially acutely, may overwhelm the fluid transport mechanism of the endothelium, resulting in a bulk flow of aqueous into the stroma. The fluid separates and elevates the epithelial cells, giving rise to epithelial edema very soon after the pressure elevation.

The most striking condition producing corneal changes as a result of intraocular pressure elevation is acute glaucoma. A patient with epithelial edema, normal stromal thickness, pain, narrow chamber angles, and a fixed, semidilated pupil does not pose any diagnotic difficulties. Usually a pressure of more than 60 mm Hg is found. On normalization of the pressure, the epithelial edema clears very rapidly. However, in rare circumstances with long-standing high pressure, irreversible endothelial damage can occur and result in chronic edema.

Even mild elevation of pressure can lead to corneal edema in the presence of preexistent endothelial damage. Such vulnerability of the cornea can occur after cataract extraction or trauma or as a result of partial endothelial loss following endothelial graft reaction. Lowering the intraocular pressure usually eliminates the edema. However, in the long run, progressive deterioration of the endothelium often gradually lowers the pressure level above which epithelial edema occurs. Finally the edema becomes irreversible, even when ocular pressure is normal.

Even in open-angle glaucoma, stromal thickness is slightly increased, although it does not produce clinically detectable edema [13].

CLINICAL EVALUATION OF THE ENDOTHELIUM

Until recently, evaluation of the corneal endothelium was limited to biomicroscopic examination for guttata, folds, or KP. Such limited observa-

tion made it difficult to evaluate endothelial function and functional reserve, to predict the future course of a disease, or to determine the eye's ability to withstand surgery. It is also difficult by mere slit lamp examination to compare the relative merits of different surgical procedures or to diagnose drug toxicity in terms of endothelial damage. More recently, however, better techniques for in vivo evaluation of the endothelium have been introduced or simplified. These include specular microscopy, pachometry, and fluorophotometry. Endothelial morphology, pump function, and permeability characteristics can be quantitated with these aids, although there are still problems with accuracy, simplicity, and interpretation.

SPECULAR MICROSCOPY

The introduction of specular microscopy made possible the direct visual inspection of the endothelium [44] (see Fig. 1-3). Further development of the instrumentation [4, 40] has made in vivo observation relatively easy and permitted valuable clinical correlations. Noncontact and wide-angle instruments (encompassing a field of over 1 mm^2) have added versatility to this technique [30, 38].

The cells of the human corneal endothelium seem to have no ability to divide after birth. Therefore, any injury, mechanical or inflammatory, to this cellular layer heals only by the sliding, rearrangement, and enlargement of existing cells (see Chapter 2, Morphology and Pathologic Response of the Cornea to Disease). A large number of cells in the area around the defect are affected by this migration. Finally, new cell junctions are formed, and the dehydrating function of the endothelium regains its full efficiency. If the total cell loss is too great, however, irreversible corneal edema may result, although the critical cell density below which edema occurs is not well known.

The normal endothelial cell count is 3000 to 3500 cells per square millimeter in the young adult, decreasing to about two-thirds of that value in old age. This decrease in number is coupled with increased cell size and pleomorphism [4]. Drastic cell loss, to less than 400 cells per square millimeter, has been observed with clear corneal grafts. On the other hand, many cases of edema have a much higher cell count. In general, it has proved impossible to predict physiologic function merely on the basis of endothelial cell density and morphology [57].

Endothelial disease and trauma can be followed quite accurately with specular microscopy. Thus, in early Fuchs' dystrophy, endothelial abnormalities and Descemet's membrane excrescenses can be diagnosed by specular microscopy before they become visible by slit lamp observation [2]. The guttate excrescenses are seen as irregular dark areas where the endothelial cell contours cannot be distinguished (Fig. 1-8). Similarly, larger or smaller KP deposited on the endothelium can be readily observed by specular microscopy, and any gradual cell loss can be followed [54].

Specular microscopy has its greatest value in determining the relative trauma to the endothelium resulting from various surgical procedures, particularly cataract extraction techniques, intraocular lens implantations, and penetrating keratoplasty. Most studies indicate that uncomplicated intracapsular cataract extraction causes only minor cell loss (4–21 percent) [60]. Phacoemulsification is more traumatic, according to most accounts, and intraocular lens implantation can result in a very marked cell loss. These observations have led to substantial improvements in surgical technique and greater care in treating the endothelium. For instance, specular microscopy has proven the protective value of introducing sodium hyaluronate into the anterior chamber during intraocular lens implantation [49].

Using specular microscopy, corneal transplantation can also be evaluated in terms of endothelial cell loss during and after the surgery. Several studies have reported mean cell counts in clear grafts to be about 1000 to 2000 cells per square millimeter. As would be expected, a graft into a recipient with abnormal endothelium in edema undergoes greater cell loss than does a graft into a cornea with normal endothelium (e.g., in keratoconus) [11]. Specular microscopy may also find routine use in the in vitro evaluation of endothelial quality in donor tissue for keratoplasty [54, 55]. In general, this valuable technique will undoubtedly continue to be applied to studies of surgical procedures, corneal dystrophies and inflammations, and drug toxicity. In addition, specular microscopy may be a useful clinical tool for the routine evaluation of many patients.

PACHOMETRY

Since corneal swelling occurs only in the posterior direction, and since stromal hydration is regulated by the endothelium, it follows that measurement of corneal thickness should be an accurate indicator of endothelial function. Corneal (or stromal) thickness can be measured with an optical device called a pachometer, using a technique that was made practical after World War II [50]. In spite of later simplifications and marketing of slit lamp–attached

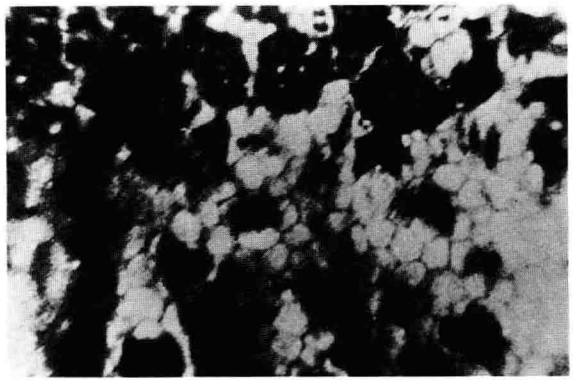

FIGURE 1-8. *Fuchs' dystrophy. The presence of guttata interferes with the normal imaging of the endothelial cells overlying the guttata. In advanced cases of Fuchs' dystrophy, the endothelial cells may be absent over the guttata. (Courtesy Calvin W. Roberts, M.D.)*

units, the technique is not as frequently used in routine ophthalmology as it should be, mainly because a good deal of practice is required to obtain reliable readings. With skill, the reading error is about ± 2 percent. New devices based on ultrasound and specular microscopy principles may eventually surpass the present split-image optical pachometer in accuracy. Such accuracy is of great importance in the performance of radial keratotomy, in which the depth of the corneal incision is determined by pachometry before the operation (see Refractive Keratoplasty in Chapter 15, Keratoplasty).

Measuring corneal thickness is often a useful maneuver when subclinical edema is suspected in the presence of guttata or after disease or surgery. The normal thickness is about 0.50 mm; a higher value indicates some endothelial dysfunction. Epithelial edema, with consequent decrease in vision, usually does not occur until the cornea has swelled to a thickness of 0.65 to 0.75 mm, provided the intraocular pressure is normal. If the pressure is elevated, epithelial edema occurs at lesser thicknesses [63]. The value of pachometry lies in estimating the functional reserve of the endothelium in a clear cornea: A reading close to 0.50 mm is reassuring for the future, whereas one around 0.70 mm means borderline decompensation and risk of imminent epithelial edema.

FLUOROPHOTOMETRY

A technique that allows measurements of fluorescein exchange between cornea and aqueous humor can be utilized to determine endothelial permeability [53]. The fluorescein can be ingested, injected intravenously, or driven into the corneal stroma from the surface by means of iontophoresis, and the diffusion across the endothelium can be followed. In this way it has been shown that patients with guttata and some corneal thickness increase also have increased permeability to fluorescein, suggesting that in early Fuchs' dystrophy swelling is due to a breakdown of the barrier function rather than to a low endothelial pump rate [5]. Fluorophotometry definitely offers promise for the future as a useful diagnostic tool.

MEDICAL TREATMENT OF EDEMA

Nonsurgical treatment of corneal edema can be directed toward improving endothelial function itself, or toward either reducing epithelial edema or making such edema less troublesome for the patient. Reduction of stromal or anterior chamber inflammation, for example, is thought to reestablish more normal endothelial function. On the other hand, the use of hypertonic agents for epithelial dehydration and the application of a soft contact lens both serve to overcome the adverse consequences of epithelial edema. Depending upon the particular underlying disease state, any of these maneuvers may serve to make more complex surgical therapy unnecessary.

SUPPRESSION OF INFLAMMATION

When endothelial function is compromised as a result of inflammation in the cornea itself or in the anterior chamber, the use of topical corticosteroids may be considered. Corneal edema secondary to a variety of diseases, including traumatic keratouveitis, infectious keratouveitis as seen in herpes simplex, and immunologic corneal graft reaction, frequently responds to such therapy. Most practitioners feel that severe keratouveitis in the presence of known herpes simplex is an indication for the use of corticosteroids. However, active viral proliferation is usually a contraindication for topical steroid use, although systemic steroids may still be used when severe uveitis is present [32] (see Herpetic Diseases in Chapter 5, Infectious Diseases).

In obscure cases without a clear history of herpetic infections, a trial of topical steroids (e.g., 0.1% dexamethasone drops 5 times daily) may be carried out for 2 weeks, which should be enough time to indicate whether the edema is reversible or not. Smaller doses of antivirals and antibiotics may be added prophylactically.

REDUCTION OF INTRAOCULAR PRESSURE

Since it is intraocular pressure that pushes fluid into the epithelium, causing epithelial edema, it makes

sense to try to reduce the pressure. However, in most cases of chronic edema the pressure is normal and the usual antiglaucomatous medications have little effect.

The most effective use of pressure reduction is in the case of marginally compensated corneal grafts, where even mildly elevated pressure can cause epithelial edema. A parallel condition is that seen in the endothelial dystrophies, such as Chandler's syndrome, in which a very modest reduction in pressure can restore good visual acuity.

The reduction of high pressure in acute glaucoma is also followed by prompt reduction of epithelial edema. In this case, of course, the endothelium may not be at fault, except that it cannot transport the much greater bulk of fluid that is forced across the posterior boundary.

To date, there are no known medications or maneuvers that can directly stimulate the rate of endothelial fluid transport. However, some attention is being given to determining whether or not the endothelium has a variable rate of pumping and whether or not this rate can be accelerated by cellular stimulation.

HYPERTONIC AGENTS

Since epithelial edema is reduced somewhat by evaporation during waking hours, it is not surprising that hypertonic solutions instilled in the eye have similar effects. This treatment was introduced in 1942 [9]. Since that time, 5% sodium chloride drops 3 or 4 times per day and sodium chloride ointment of the same strength at night has been the therapeutic mainstay. The exact dosage regimen can be determined by the patient himself according to the severity of his symptoms. Anhydrous glycerol is useful for clearing the cornea of epithelial edema before gonioscopy but is too painful for routine use.

Other methods can be used to dehydrate the epithelium. Hot, dry air from a hair dryer held at arm's length can be quite helpful in clearing early morning epithelial edema, although care must be taken not to irritate the ocular surface by overdoing the treatment. Regardless of which technique is chosen to render the precorneal tear film hypertonic and thereby extract water from the epithelium, many patients with irreversible epithelial edema benefit from this type of osmotherapy for months or even years.

Hypertonic agents are not useful in reducing stromal edema. The reason is that stromal water volume is quite large compared with the tear volume, so that hypertonicity of the tear film can extract only a small amount of stromal fluid, which is readily replenished from the aqueous across the leaky endothelium.

SOFT CONTACT LENSES

As mentioned earlier, advanced corneal edema with large bullae can be quite painful, and hypertonic agents may have no ameliorating effect. If comfort, rather than vision, is the objective in such cases, a hydrophilic soft contact lens can be tried (see Chapter 17, Therapeutic Soft Contact Lenses). Thus, for an elderly person with good vision in the other eye, there is no need for keratoplasty, and a soft lens in the uncomfortable edematous eye can be quite successful. The lens should not be too thin and flimsy but rather rigid, and it should be left in the eye around the clock. Vision may become slightly worse, but the objective of comfort is achieved in about three-quarters of the cases [14]. Topical antibiotics (e.g., 0.5% chloramphenicol drops 1–3 times daily) may be given during the first few weeks, although the value of this prophylaxis is not proven. The lenses can remain in place for months without cleaning. The incidence of infection is very small, less than 1 percent (Fig. 1-9).

SURGICAL TREATMENT OF EDEMA

PENETRATING KERATOPLASTY

When corneal edema has reached an irreversible state with markedly reduced vision and perhaps pain, keratoplasty is often the treatment of choice. It was not always so, with the first successful transplants in edema reported only in 1952 [59]. Since that time progress has been rapid, owing to the use of larger grafts, greater attention to the endothelium, the availability of corticosteroids, and finer suture material [1]. Today the majority of people with severe corneal edema uncomplicated by other disease can be helped by surgery (see Chapter 15, Keratoplasty). However, some specific features of corneal edema warrant special consideration when keratoplasty is contemplated.

The indications for keratoplasty in edema cannot be stated with complete precision. However, in a patient with bilateral edema and visual acuity between 20/80 and 20/200, it is reasonable to graft the worse eye, especially if the condition has been rapidly deteriorating. If the visual acuity in the better eye is still 20/50 or better, surgery in the opposite eye can be postponed. If the better eye is completely normal, no surgery is indicated, especially if the patient is elderly and would not be expected to tolerate a contact lens or aniseikonia well. If the edematous cornea is painful, a permanent soft contact lens is usually a less complicated therapy than keratoplasty. Finally, if the patient has only one remaining eye, it is prudent to postpone keratoplasty until vi-

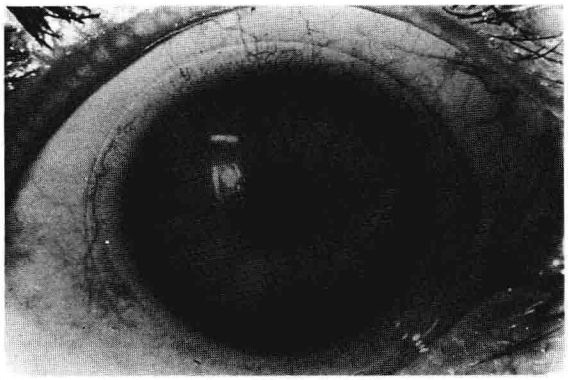

FIGURE 1-9. *A large soft contact lens can improve comfort in bullous keratopathy but does not improve vision in most cases.*

sion has fallen to 20/200 to 20/400. Needless to say, the patient's age and occupation, as well as any extracorneal pathologic conditions, will influence the decision concerning if and when to operate.

The presence of a significant cataract in addition to the corneal edema is normally an indication for the combined procedure of keratoplasty and cataract extraction. If the cornea exhibits only guttata and stromal swelling but no epithelial edema, standard intracapsular cataract extraction without transplantation is recommended. Even a borderline decompensated cornea often shows an unexpected resiliency and can remain clear for many years. Intraocular lens implantation in combination with keratoplasty for edema and cataract extraction (triple procedure) must be expected to entail a larger risk of damage to the graft endothelium, although several studies have disclosed remarkably good short-term results [61]. At present, it seems reasonable to reserve this procedure for situations in which preoperative hyperopia in combination with the aphakia would otherwise require an unacceptably high plus correction in glasses or contact lenses.

The keratoplasty technique for edema is the same as for other corneal diseases, except that a large graft (which carries a larger number of donor endothelial cells) is of greater importance than in situations in which the recipient's endothelium is normal. My technique for edema uses an 8.2- or 8.5-mm donor button, punched from the endothelial side on a silicone block. An 8.0-mm trephine is used for the recipient. In the elderly aphakic patient with a deep anterior chamber and massive corneal edema, a 9.0-mm graft into an 8.5-mm recipient opening might be recommended.

Postoperatively, the treatment relies heavily on the use of topical steroids to prevent an immune graft reaction. A substantial number of patients with edema are also aphakic, providing the surgeon with the opportunity to use more corticosteroids without causing a cataract [18]. In aphakic edema cases, I prefer to give steroids (0.1% dexamethasone drops) topically at the conclusion of the surgery and every 2 to 3 hours for the first day, and then taper the dosage over a period of a month or so to once daily. Most important, this once-daily regimen should be continued for the rest of the patient's life. Eyes that have been inflamed in the past may require a more intense steroid regimen.

Keratoplasty in uncomplicated edema now achieves clear grafts in 70 to 90 percent of cases [20], although some cases exhibit late failure many years postoperatively. Vascularization of the recipient cornea worsens the prognosis moderately, whereas chronic uveitis has a drastically unfavorable influence. Grafts in aphakia have slightly better expectations than do grafts in phakic eyes, probably because in aphakia the endothelium is usually protected during suturing by loose vitreous whereas in phakic eyes it is rubbed against the bulging iris. Keratoplasty for edema in children has notoriously poor prognosis, although encouraging results have been presented recently [58].

OTHER SURGICAL PROCEDURES

With the rising success rate of keratoplasty in edema and with the introduction of soft contact lenses for comfort, other surgical techniques are being employed less frequently. A total conjunctival flap is effective in eliminating all pain caused by bullous keratopathy and still is occasionally indicated in an elderly patient with a good opposite eye and difficulty in tolerating a soft contact lens [24, 25] (see Chapter 16, Conjunctival Surgery for Corneal Disease). The disadvantages of a total conjunctival flap are poor vision (usually finger counting), a poor appearance, and difficulty in examining deeper structures postoperatively.

Cautery of the corneal surface is another procedure aimed at providing comfort in painful edema. A large number of mild diathermy burns are applied to the whole surface, resulting in subepithelial scarring and marked corneal anesthesia [56]. A drawback of such cautery is the persistent epithelial defect that frequently follows it.

Several experimental and surgical procedures of considerable theoretical interest have been suggested for the amelioration of massive corneal edema. One approach has been to remove the edematous epithelium and bond a large polymethylmethacrylate contact lens to the basement

membrane with the aid of cyanoacrylate adhesive applied peripherally. This greatly improves vision; however, in the long run the bond loosens and the epithelium finds an opening to grow back in and cause irritation and diminution of vision. Another procedure utilizes a transparent, water-impermeable membrane, implanted intrastromally or attached to the posterior surface, that acts as a barrier to aqueous inflow. The cornea anterior to the membrane dehydrates, but interference with the supply routes of nutrients from the aqueous to the cornea causes frequent complications [16]. Finally, through-and-through keratoprostheses have been tried in corneal edema [7]. They have usually consisted of a methylmethacrylate stem attached to a supporting plate that anchors the device in the stroma. The advantage of these techniques is rapid restoration of very good vision, but complications are frequent and often severe. Ulceration around the stem can cause leaks, extrusion, infection, and retinal detachment [17]. In general, the procedures described have remained experimental owing to the rapid advances of corneal allografting.

Recent research in the surgical treatment of corneal edema has taken a more biologic turn and has explored the possibility of replacing malfunctioning endothelium with new cells that have been grown in tissue culture [33]. Cultured endothelial cells can be made to adhere in vitro to the denuded Descemet's membrane of a graft, and the cells coalesce and rearrange themselves into a layer indistinguishable from normal endothelium. Such a graft can be transplanted in the normal way and remain clear, indicating satisfactory dehydrating function of the new endothelium [23]. It even seems possible to grow noncorneal cells (e.g., vascular endothelium) from the recipient and make them function as a new corneal endothelium, thus possibly bypassing the otherwise severely limiting transplantation immunity problem. Undoubtedly these interesting techniques have great potential for the future.

REFERENCES

1. Abbott, R. L., and Forster, R. K. Determinants of graft clarity in penetrating keratoplasty. *Arch. Ophthalmol.* 97:1071, 1979.
2. Bigar, F., Schimmelpfenning, B., and Hurzeler, R. Cornea guttata in donor material. *Arch. Ophthalmol.* 96:653, 1978.
3. Boruchoff, S. A. Keratoplasty. In G. Spaeth (Ed.), *Ophthalmic Surgery*. Philadelphia: Saunders, in press.
4. Bourne, W. M., and Kaufman, H. E. Specular microscopy of human corneal endothelium in vivo. *Am. J. Ophthalmol.* 81:319, 1976.

5. Burns, R. R., Bourne, W. M., and Brubaker, R. F. Endothelial function in patients with cornea guttata. *Invest. Ophthalmol. Vis. Sci.* 20:77, 1981.
6. Campbell, D. B., Shields, M. B., and Smith, T. R. The corneal endothelium and the spectrum of essential iris atrophy. *Am. J. Ophthalmol.* 86:317, 1978.
7. Castroviejo, R., Cardona, H., and DeVoe, A. G. Present status of prosthokeratoplasty. *Am. J. Ophthalmol.* 68:613, 1969.
8. Chandler, P. A. Atrophy of the stroma of the iris, endothelial dystrophy, corneal edema and glaucoma. *Am. J. Ophthalmol.* 41:607, 1956.
9. Cogan, D. G., and Kinsey, V. E. The cornea: V. Physiologic aspects. *Arch. Ophthalmol.* 28:661, 1942.
10. Cross, H. E., Maumenee, A. E., and Cantolino, S. J. Inheritance of Fuchs' endothelial dystrophy. *Arch. Ophthalmol.* 85:268, 1971.
11. Culbertson, W., Forster, R., and Abbott, R. Endothelial cell loss in penetrating keratoplasty. *Ophthalmology* (Rochester). In press.
12. Davson, H. The hydration of the cornea. *Biochem. J.* 59:24, 1955.
13. DeCevallos, E., Dohlman, C. H., and Reinhart, W. J. Corneal thickness in glaucoma. *Ann. Ophthalmol.* 8:177, 1976.
14. Dohlman, C. H., Boruchoff, S. A., and Mobilia, E. F. Complications in the use of soft contact lenses in corneal disease. *Arch. Ophthalmol.* 90:267, 1973.
15. Dohlman, C. H., Hedbys, B. O., and Mishima, S. The swelling pressure of the corneal stroma. *Invest. Ophthalmol.* 1:158, 1962.
16. Dohlman, C. H., Brown, S. I., and Martola, E. L. Replacement of endothelium with alloplastic materials: A new technique in corneal surgery. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 71:851, 1967.
17. Dohlman, C. H., Schneider, H. A., and Doane, M. G. Prosthokeratoplasty. *Am. J. Ophthalmol.* 77:694, 1974.
18. Donshik, P. C., et al. Posterior subcapsular cataracts induced by topical corticosteroids following keratoplasty for keratoconus. *Ann. Ophthalmol.* 12:29, 1981.
19. Fatt, I., and Goldstick, T. K. Dynamics of water transport in swelling membranes. *J. Colloidoidal Sci.* 20:434, 1965.
20. Fine, M., and West, C. E. Late results of keratoplasty for Fuchs' dystrophy. *Am. J. Ophthalmol.* 72:109, 1971.
21. Fuchs, E. Dystrophia epithelialis corneae. *Arch. f. Ophthalmol.* 76:478, 1910.
22. Goldman, J., et al. Structural alterations af-