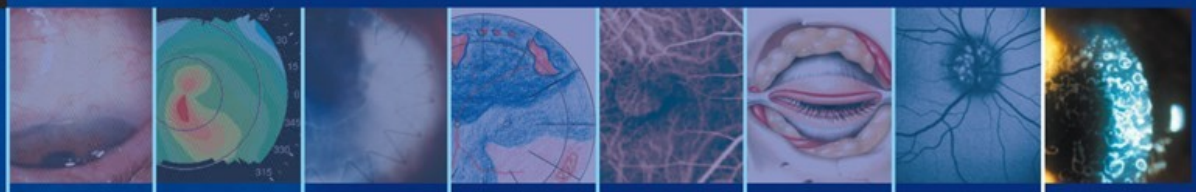
ESSENTIALS IN OPHTHALMOLOGY

G. K. KRIEGLSTEIN · R. N. WEINREB

Series Editors



Glaucoma | Cataract and Refractive Surgery | Uveitis and Immunological Disorders | Vitreo-retinal Surgery | Medical Retina | Oculoplastics and Orbit | Pediatric Ophthalmology, Neuro-Ophthalmology, Genetics | **Cornea and External Eye Disease**

Cornea and External Eye Disease

Edited by

T. REINHARD

F. LARKIN

Springer

Essentials in Ophthalmology

Cornea and External Eye Disease

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Cornea and External Eye Disease

Editors Thomas Reinhard
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Cornea and External Eye Disease

With 103 Figures, Mostly in Colour
and 14 Tables

Springer

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Foreword

The series *Essentials in Ophthalmology* was initiated two years ago to expedite the timely transfer of new information in vision science and evidence-based medicine into clinical practice. We thought that this prospicient idea would be moved and guided by a resolute commitment to excellence. It is reasonable to now update our readers with what has been achieved.

The immediate goal was to transfer information through a high quality quarterly publication in which ophthalmology would be represented by eight subspecialties. In this regard, each issue has had a subspecialty theme and has been overseen by two internationally recognized volume editors, who in turn have invited a bevy of experts to discuss clinically relevant and appropriate topics. Summaries of clinically relevant information have been provided throughout each chapter.

Each subspecialty area now has been covered once, and the response to the first eight volumes in the series has been enthusiastically positive. With the start of the second cycle of subspecialty coverage, the dissemination of practical information will be continued as we learn more about the emerging advances in various ophthalmic subspecialties that can be applied to obtain the best possible care of our patients. Moreover, we will continue to highlight clinically relevant information and maintain our commitment to excellence.

G. K. Krieglstein
R. N. Weinreb
Series Editors

Preface

The second volume covers a broad range of conjunctival and corneal diseases, again with particular emphasis being placed on problem management.

Various new surgical approaches are currently being evaluated in the clinical setting, an example of which is posterior lamellar keratoplasty in Fuchs endothelial disease. While amniotic membrane transplantation has been in use for some years and for a range of indications, it is now becoming more and more popular for the treatment of ulceration in infectious keratitis. Tissue-engineered scaffolds as templates for corneal reconstruction are being investigated for possible future surgical approaches. Phototherapeutic keratectomy has been established for some years in the therapeutic repertoire for various phenotypes of corneal dystrophy: this intervention is now safe and effective in many patients with superficial dystrophic corneal opacities or recurrent erosion.

Molecular genetic evidence of corneal dystrophies is fascinating and has led to a completely new classification.

The chapter on corneal preservation shows the challenge for tissue banking behind the new surgical approaches. Inflammatory diseases of the cornea and conjunctiva remain a continuing challenge in every external eye disease clinic, described in the chapters on herpes simplex keratitis, ocular pemphigoid, adult inclusion conjunctivitis, and chronic blepharitis. Understanding of the biology of conjunctival melanoma is improving and confocal microscopy may become established as a new diagnostic aid and follow-up technique.

We hope you enjoy reading this book.

Thomas Reinhard
Frank Larkin

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Chapter 1

Fuchs Endothelial Dystrophy: Pathogenesis and Management

1

Leejee H. Suh, M. Vaughn Emerson, Albert S. Jun

Core Messages

- Fuchs endothelial dystrophy (FED) is a progressive disorder of the corneal endothelium with accumulation of focal excrescences called guttae and thickening of Descemet's membrane, leading to stromal edema and loss of vision
- The inheritance of FED is autosomal dominant, with modifiers such as increased prevalence in the elderly and in females
- Corneal endothelial cells are the major "pump" cells of the cornea that allow for stromal clarity
- Descemet's membrane is grossly thickened in FED, with accumulation of abnormal wide-spaced collagen and numerous guttae
- Corneal endothelial cells in end-stage FED are reduced in number and appear attenuated, causing progressive stromal edema
- Symptoms include visual blurring predominantly in the morning with stromal and epithelial edema from relatively low tear film osmolality
- FED can be classified into four stages, from early signs of guttae formation to end-stage subepithelial scarring
- Diagnosis is made by biomicroscopic examination; other modalities, such as corneal pachymetry, confocal microscopy, and specular microscopy can be used in conjunction
- Exact pathogenesis is unknown, but possible factors include endothelial cell apoptosis, sex hormones, inflammation, and aqueous humor flow and composition
- Mutations in collagen VIII, a major component of Descemet's membrane secreted by endothelial cells, have been linked to FED
- Medical management includes topical hypertonic saline, the use of a hairdryer to dehydrate the precorneal tear film, and therapeutic soft contact lenses
- Definitive treatment is surgical in the form of penetrating keratoplasty (PK)
- New surgical modalities such as various forms of endothelial keratoplasty are gaining popularity in the treatment of FED
- DLEK and DSEK avoid the surgical complications of PK, such as wound dehiscence, suture breakage/infection and high postoperative astigmatism
- Future directions in the treatment of FED include gene or cell therapy and continued advances in endothelial keratoplasty

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1.1 Introduction

Fuchs endothelial dystrophy (FED) is a primary, progressive disorder of the corneal endothelium that results in corneal edema and loss of vision. The initial stages of FED typically begin in the fifth through seventh decades of life and are characterized by progressive accumulation of focal excrescences, termed "guttae," and thickening of Descemet's membrane, a collagen-rich layer secreted by endothelial cells. Eventually, there is loss of endothelial cell density and functionality as the "pump" of the cornea, causing vision-threatening corneal edema. Although corneal guttae are not pathognomonic for FED, the development of stromal edema defines this disorder.

1.2 Historical Perspective

In 1902 Ernst Fuchs initially described the disorder that would later bear his name, and he postulated that this disease of the elderly was related to changes in the posterior cornea that allowed for increased fluid movement from the aqueous into the corneal stroma [11]. He later published a case series of 13 patients with FED in which he suggested pathologic involvement of both the endothelial and epithelial corneal layers [12]. After the introduction of the slit-lamp biomicroscope in 1911, Vogt was the first to report detailed biomicroscopic observations of FED and coined the term "cornea guttata," in reference to focal excrescences on the endothelial surface, which when confluent, resembled beaten bronze [58]. The natural progression of FED from isolated, asymptomatic guttae to the formation of corneal edema with painful loss of vision was first noted in 1953 [53]. These and other important observations led to the understanding of FED as a primary disease of the corneal endothelium with secondary involvement of the other layers of the cornea.

1.3 Epidemiology and Inheritance

The prevalence of FED is difficult to estimate given its later onset, slow progression, and lack of symptoms in the early stages. Furthermore, mild guttae can occur in normal individuals in such conditions as aging, ocular trauma, ocular inflammation, and glaucoma. In a large study of 2002 normal individuals, Lorenzetti et al. found scattered central guttae in 0.18% of eyes in those between the ages of 20 and 39, and in 3.9% of eyes in those above 40 years of age [33]. Despite the lack of an accurate estimate of the prevalence of FED, it remains one of the most common indications for corneal transplantation, accounting for up to 29% of cases [1].

Fuchs endothelial dystrophy can be either sporadic or hereditary. In hereditary cases, the inheritance of FED has been demonstrated to be autosomal dominant, with penetrance as high as 100% [10, 35]. In a large study of 228 relatives from 64 pedigrees with FED, Krachmer et al. observed that 38% of first-degree relatives over 40 years of age were affected, suggesting autosomal dominant inheritance with possible genetic or environmental modifiers [30]. Some studies, including Fuchs' original case series, also report an increased prevalence and severity in female patients [12, 30, 49]. This may reflect a possible recruitment bias or a physiologic effect of sex hormones on corneal endothelial cell function and survival [1, 62]. The incidence of FED has been reported to be similar among white and black patients, and much lower in Japanese individuals [17]. Central corneal guttae have been reported in Japanese individuals and significant vision loss is rare in these patients [29].

Summary for the Clinician

- Corneal guttae can be present in non-affected individuals and are associated with conditions such as aging, inflammation, trauma, and glaucoma
- Fuchs endothelial dystrophy is defined as the accumulation of corneal guttae with stromal edema
- Inheritance of FED is autosomal dominant, but sporadic forms can occur

1.4 Pathology

The corneal endothelium is a neural crest-derived cellular monolayer that utilizes an ATP-dependent pump to maintain physiologic stromal hydration necessary for corneal clarity [13, 61]. Corneal endothelial cells in humans do not normally proliferate in vivo [25, 26]. Corneal endothelial cells are normally lost throughout life at an estimated rate of 0.6% per year, although higher rates of cell loss occur in the settings of trauma (both surgical and nonsurgical) and primary endotheliopathies [3, 7]. Corneal endothelial cell loss is compensated for through flattening and enlargement of remaining cells without cell division in order to maintain a continuous monolayer [61].

The corneal endothelial cells in end-stage FED are reduced in number and appear thinned with attenuated nuclei, as seen by light microscopy (Fig. 1.1) [17]. With scanning electron microscopy, corneal endothelial cells show evidence of degeneration with large vacuoles and swollen organelles with disrupted membranes [17]. Corneal endothelial cells also demonstrate dilated sacs of endoplasmic reticulum filled with a finely granular material along with a marked increase in cytoplasmic filaments and ribosomes, suggesting transformation to a fibroblastic cell type [17, 20, 62].

Normal corneal endothelial cells produce Descemet's membrane, beginning in utero and continuing throughout postnatal life [34]. Histologically and ultrastructurally, Descemet's membrane consists of an anterior "banded" zone subjacent to the corneal stroma and containing 110 nm of banded collagen and a posterior "nonbanded" zone that lies anterior to the corneal endothelium [62]. At birth, the thickness of the anterior banded zone is approximately 3 μm, and this varies little throughout life [62]. In contrast, the thickness of the posterior nonbanded zone increases from approximately 3 μm at age 20 to 10 μm at age 80 [9], reflecting the ongoing synthesis and deposition of Descemet's membrane by the corneal endothelium [22].

Normal Descemet's membrane contains collagen IV, collagen VIII, fibronectin, entactin, laminin, and perlecan [31, 32]. The supramolecular structure of Descemet's membrane resembles stacks of hexagonal lattices arranged parallel to the surface of the membrane [52]. Monoclonal antibody analysis has shown the lattice array of Descemet's membrane to be composed of collagen VIII, a nonfibrillar short chain collagen [50, 52].

The abnormalities of Descemet's membrane are a striking feature of FED. Descemet's membrane is invariably thickened in FED up to 20 μm or greater [62]. Thickened Descemet's membrane also contains numerous focal excrescences (guttae) along its posterior surface (Fig. 1.2a).

Descemet's membrane also differs strikingly from normal on electron microscopy. In addition to a relatively normal anterior banded zone produced in fetal life, the posterior nonbanded zone of Descemet's membrane is attenuated or absent in FED and is replaced by a markedly thickened posterior collagenous layer with an average thickness of 16.6 μm (Fig. 1.3a) [7, 20]. The posterior collagenous layer is characterized by a diffuse, granular banding pattern, focal posterior guttae, and the accumulation of spindle-shaped bundles with 110-nm collagen banding, known as wide-spaced collagen (Fig. 1.3b) [7]. The composition of wide-spaced collagen in the posterior collagenous layer of FED corneas was shown by immunoelectron microscopy to be collagen VIII [31].

Summary for the Clinician

- Corneal endothelium is a monolayer of cells that acts as the major pump to deturgesce the cornea and ensure clarity
- There is a normal attrition rate of endothelial cells of 0.6% per year; the rate is accelerated in FED
- Normal endothelial cells produce Descemet's membrane, made up of an anterior banded zone and posterior nonbanded zone, the latter of which expands with age
- In FED, Descemet's membrane is abnormally thickened, with attenuation or absence of the posterior nonbanded zone and replacement with abnormal collagen, known as wide-spaced collagen

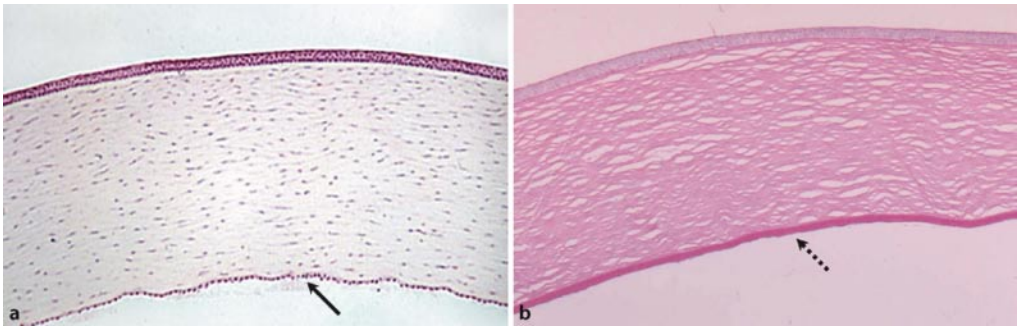

Fig. 1.1 **a** Light microscopy section of a normal human cornea. Note numerous endothelial cell nuclei lining the posterior surface (*arrow*). **b** Light microscopy section of FED cornea. Note the markedly thickened Descemet's membrane and the absence of endothelial cell nuclei on the posterior surface (*dashed arrow*). (Photos courtesy of W. Richard Green, M.D.)

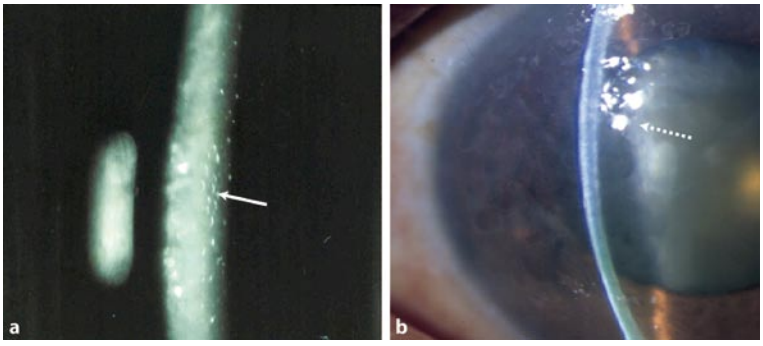

Fig. 1.2 **a** Slit-lamp biomicroscopy of stage I Fuchs endothelial dystrophy (FED; see Table 1.1). Note scattered, punctate, refractile endothelial guttae to the left of the *arrow*. **b** Stage III FED. Note thickening of the cornea, with the irregular surface and epithelial bullae indicated by scattered surface reflection (*dashed arrow*). (Photos courtesy of Walter J. Stark, M.D.)

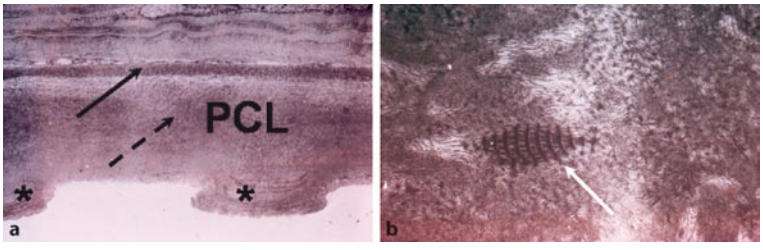

Fig. 1.3 **a** Low power electron micrograph of Descemet's membrane from a FED patient. Note the normal anterior banded zone (*arrow*), the markedly thickened and diffusely banded posterior collagenous zone (*PCL; dashed arrow*), and the focal posterior excrescences (guttae, *asterisks*). **b** High-power electron micrograph of PCL showing a spindle-shaped bundle with 110-nm collagen banding (wide-spaced collagen, *white arrow*). (Photos courtesy of W. Richard Green, M.D.)

1.5 Clinical Findings

The earliest clinical signs of FED include few (<10), central, focal excrescences (guttae) of Descemet's membrane (Fig. 1.2a). Over decades, accumulation of guttae coincides with the normal, gradual attrition of corneal endothelial cells occurring throughout postnatal life. Normal adult central corneal endothelial cell density is approximately 2,500 cells/mm², and a density of approximately 500–1,000 cells/mm² is the minimum threshold for physiologic corneal deturgescence. Once this threshold is crossed, corneal edema occurs, resulting in loss of vision and pain due to formation of epithelial bullae (Fig. 1.2b).

The clinical course of FED can be divided into four stages (Table 1.1) [1]. Stage I is characterized by biomicroscopic evidence of central corneal guttae, with a possibly thickened, grayish Descemet's membrane (Fig. 1.2a). At this stage, the patient is asymptomatic. In stage II disease, the vision may be predominantly blurred in the morning because of decreased tear evaporation, which lowers tear film osmolality when the eyes are closed [36]. Stromal and epithelial edema is notable on biomicroscopy. Stage III and IV disease are characterized by the presence of epithelial bullae, which cause pain upon rupture (Fig. 1.2b). Stage IV is distinguished by the presence of subepithelial scar tissue, resulting in further worsening of visual acuity, but relief from pain.

The diagnosis of FED is made principally on the basis of the biomicroscopic examination. Other modalities that have been used in conjunction with slit-lamp biomicroscopy include corneal pachymetry, confocal microscopy, and noncontact specular microscopy. Corneal pachymetry measures are of limited utility given the wide variation in corneal thickness of normal individuals. The greatest utility of pachymetry is in the consideration of penetrating keratoplasty (PK) in known or suspected FED patients being evaluated for cataract surgery (see Sect. 1.8).

Confocal microscopy and noncontact specular microscopy rely on slightly different methods of light emission and different patterns of light reflection at the interface between Descemet's membrane and corneal endothelial cells. The absence of corneal endothelial cells adjacent to and overlying guttae leads to transmission of light without reflection in these areas. Corneal endothelial cells (Fig. 1.4a) and corneal guttae (Fig. 1.4b) can be easily demonstrated with confocal microscopy. Both confocal and specular microscopy can aid in demonstrating corneal endothelial cell polymorphism and pleomorphism, as well as measuring endothelial cell density. These characteristics have potential clinical and research applications as markers of disease progression.

Confocal microscopy is superior to specular microscopy for evaluating the corneal endothelial layer in the setting of corneal stromal edema [8, 16]. However, the benefits of specular mi-

Table 1.1 Clinical stages of Fuchs endothelial dystrophy[a]

Stage	Symptoms	Clinical findings	Visual acuity
Stage I	No symptoms	Few to moderate corneal guttae	Normal (20/20)
Stage II	Mild to moderate loss of vision, no pain	Moderate to numerous corneal guttae, mild corneal edema	Mild to moderate reduction (20/20 to 20/80)
Stage III	Moderate to severe loss of vision and pain	Confluent corneal guttae, moderate to severe corneal edema, epithelial bullae	Moderate to severe reduction (20/100 to 20/400)
Stage IV	Severe loss of vision, reduced pain	Subepithelial scar, fewer epithelial bullae	Severe reduction (20/400 or worse)

[a]Adapted from [1].

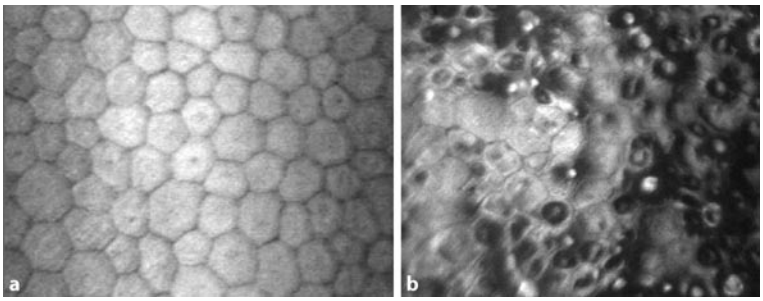

Fig. 1.4 **a** In vivo confocal microscopy image of normal corneal endothelial cells (CECs). Note ordered, hexagonal array of cells. **b** Confocal microscopy image of CECs in FED. Note the numerous excrescences (guttae) of Descemet's membrane as well as the irregular size and shape of the cells

croscopy over confocal microscopy include its relative cost-effectiveness and its ease of use [8]. Neither modality is effective in cases of extreme corneal edema or stromal opacity [16]. In addition, the utility of these auxiliary tests in the diagnosis of FED is primarily in unusual cases, as the diagnosis can usually be made on the basis of slit-lamp biomicroscopy.

Summary for the Clinician

- Diagnosis of FED is primarily made by the appearance of guttae with or without corneal edema on biomicroscopy
- Fuchs endothelial dystrophy can be classified into four stages: (I) presence of subclinical central guttae; (II) presence of stromal and epithelial edema; (III) presence of epithelial bullae; (IV) presence of subepithelial scarring

1.6 Pathophysiology and Genetics

Studies of FED have been predominantly limited to end-stage corneas because milder cases are asymptomatic and therefore less readily available for clinicopathologic correlation. Many of the observations likely reflect complex secondary changes occurring as a result of corneal endothelial cell decompensation. Furthermore, initiating events are largely unexplored, and virtually no information exists about early cellular and extracellular matrix changes leading to corneal endothelial cell loss.

Using scanning fluorophotometry, Wilson et al. demonstrated a decreased endothelial pump rate in corneas with advanced FED [63]. McCartney et al. demonstrated a decline in the density of ATPase pump sites in the basolateral corneal endothelial cell membranes [39]. Nucleus labeling, transmission electron microscopy, and TUNEL assays were used to demonstrate apoptosis in corneal endothelial cells of advanced stage FED corneas [6]. Serial analysis of gene expression studies of FED corneal endothelial cells demonstrated decreased transcripts related to apoptosis defense and mitochondrial energy production [14]. Whether corneal endothelial cell apoptosis is primary in the pathogenesis of FED or secondary to an abnormality of the basement membrane remains to be elucidated. Other proposed factors with unclear relevance include fibrinogen/fibrin, reduced sulfur content and increased calcium of Descemet's membrane, aqueous humor flow/composition, sex hormones, and inflammation [5].

To date, only mutations in the α2 collagen VIII (COL8A2) gene have been identified as causing FED [4, 15]. Biswas et al. performed genetic linkage analysis of a pedigree with three affected generations and identified an FED locus on chromosome 1p34.2-p32. DNA sequencing revealed a mutation in the COL8A2 gene resulting in a substitution of glutamine with lysine at amino acid 455 (Q455K). This

mutation cosegregated with FED in this pedigree and was absent in 244 ethnically matched control individuals [4]. The COL8A2 gene was sequenced in 115 additional unrelated FED patients, with a total of 8 individuals demonstrating mutations in the COL8A2 gene [4]. Gottsch et al. performed genetic linkage analysis in a large early-onset FED pedigree originally described by Magovern [35] and identified a second point mutation in COL8A2 at amino acid 450, resulting in a substitution of leucine with tryptophan (L450W) [15]. In contrast to common FED, members of this pedigree had an earlier onset of disease with children as young as 3 years of age affected and with distinct features such as a fine, patchy distribution of guttae.

Collagen VIII is a major component of normal Descemet's membrane and forms the abnormally thick posterior collagenous layer in FED corneas. Furthermore, the characteristic aggregates of wide-spaced collagen in Descemet's membrane of FED consist of collagen VIII [31]. Based on the implied functional effects of these mutations, one pathophysiologic hypothesis is that amino acid substitutions reduce the turnover of COL8A2, resulting in the abnormal accumulation of collagen VIII and abnormalities of Descemet's membrane. These abnormalities eventually become incompatible with endothelial cell function and survival, resulting in apoptosis. If this model proves accurate, additional candidate genes for FED could include other protein constituents of Descemet's membrane. To date, however, no published reports have associated mutations in these genes with FED.

Alternatively, the accumulation of collagen VIII in FED may occur as a secondary response to another primary insult to the endothelium. This possibility is consistent with the observation that a posterior collagenous layer of Descemet's membrane, presumably composed of collagen VIII, is present in other hereditary and acquired diseases of the corneal endothelium [23, 31, 38, 48]. Thus, a more complex relationship may exist between corneal endothelial cell dysfunction and abnormal accumulations of collagenous material in Descemet's membrane [15, 31].

Summary for the Clinician

- The pathogenesis of FED is unclear. Possible factors include sex hormones, inflammation, and endothelial cell apoptosis
- Collagen VIII is a major component of Descemet's membrane and is secreted by healthy and pathologic corneal endothelial cells
- Mutations in collagen VIII have been linked to FED

1.7 Differential Diagnosis

The diagnosis of FED is based on clinical findings, mainly slit-lamp biomicroscopy. Distinguishing FED from other entities is important because the diagnosis has implications for treatment and prognosis of both patients and their family members. Other entities that must be differentiated from FED include other posterior dystrophies, including posterior polymorphous dystrophy. In this autosomal dominant condition, groups of small round vesicles are found at the level of the endothelium, interspersed with sheets of gray material within Descemet's membrane [60]. This condition is not generally associated with stromal or epithelial edema or corneal guttae.

Another form of endothelial dystrophy, congenital hereditary endothelial dystrophy, is present at birth or early in postnatal life and is characterized by edema of the entire cornea and severe visual impairment [60]. Hassall-Henle bodies have the same appearance as guttae, but are located only in the peripheral cornea and are not associated with progressive visual loss or corneal edema [23]. Aphakic and pseudophakic bullous keratopathies are caused by endothelial cell dysfunction related to trauma during or after cataract extraction and presuppose a normal corneal endothelium prior to cataract extraction [23]. Inflammatory diseases, such as anterior uveitis or interstitial keratitis, may be mistaken for FED and can be differentiated by resolution of keratic precipitates with proper treatment in the case of anterior uveitis, or on the basis of se-

rologic testing for syphilis in the case of interstitial keratitis [59].

1.8 Management

1.8.1 Medical

Early treatment modalities are not specific for FED, but are commonly applied to all etiologies of corneal epithelial and stromal edema. These approaches involve artificially raising the osmolality of the tear film and include hypertonic saline solutions and ointments, as well as the use of a hairdryer in the morning to dehydrate the precorneal tear film [62]. The use of therapeutic soft contact lenses may help in relieving the pain from recurrent epithelial erosions, while decreasing irregular astigmatism in cases that have progressed to bullous keratopathy [62]. The use of cycloplegics and nonsteroidal anti-inflammatory agents may also aid in diminishing corneal pain from bullous keratopathy. The use of intraocular pressure-lowering medications may reduce corneal edema in patients with elevated or even normal intraocular pressure [1].

1.8.2 Surgical

If conservative management options do not provide adequate clarity of the visual axis or alleviation of discomfort or pain, surgical options may be considered [37]. PK has been regarded as the definitive procedure in patients with corneal decompensation due to FED. In one study of PK in patients with FED, the proportion of patients with visual acuity of 20/40 or better was 50% at 3 months postoperatively, and increased to 80% by 24 months [47]. The authors attribute this improvement over time to corneal healing, suture removal, and fitting of rigid contact lenses. A 10-year follow-up study of 908 patients who underwent PK for FED found a graft survival rate of 97% at 5 years and 90% at 10 years [56]. The most common cause of graft failure in these patients was endothelial rejection, followed by nonimmunologic endothelial failure. Uncorrectable irregular astigmatism was another leading cause of poor postoperative visual acuity. Others have reported graft survival rates of 89% at a mean follow-up of 8.4 years [44], and 81% after 10 years' follow-up [18] in patients with FED.

However, visual function after PK may not be dramatically improved, as one study found 42% of patients who had undergone corneal transplant for FED had visual acuities of worse than 20/200 at an average of 50 months after surgery [42]. The disparity between these results suggests that outcomes may be operator-dependent, and surgeons with more experience tend to have better results [57].

Because many patients with FED and corneal decompensation also have cataracts, attention has turned toward combined versus staged surgical management of the cataract and cornea. It has been suggested that combined procedures in the hands of an experienced surgeon have the same outcome as staged procedures with PK preceding cataract extraction [2]. The American Academy of Ophthalmology suggests that corneal thickness measurements greater than 600 μm portend a poor prognosis following cataract surgery and recommends consideration of combined cataract extraction and PK in these patients [21]. However, in the hands of a skilled surgeon, one study suggests that cataract extraction may be safely performed in patients with corneal thickness measurements up to 640 μm [51].

New posterior lamellar techniques to selectively replace diseased endothelium, as in FED, have been developed and are gaining popularity over traditional PK. In 1998, Melles described "posterior lamellar keratoplasty," or PLK, which consisted of manually dissecting both recipient and donor tissues at 80–90% stromal depth and transplanting the donor posterior lamellar disc through a scleral incision [40]. This technique was later modified and popularized as deep lamellar endothelial keratoplasty (DLEK) by Terry and Ousley [54].

Deep lamellar endothelial keratoplasty has the advantage over PK of being a "sutureless" technique, thereby avoiding the potential infectious and refractive complications associated with sutures. This technique also has the advantage of maintaining the tensile strength of the cornea, which is not possible with PK. The largest disadvantage of DLEK is its technical difficulty, even for highly-experienced anterior segment sur-