Mastering Endothelial Keratoplasty

DSAEK, DMEK, E-DMEK, PDEK, Air pump-assisted PDEK and others
Volume I

Soosan Jacob
Editor

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ISBN 978-81-322-2816-5 ISBN 978-81-322-2818-9 (eBook)
DOI 10.1007/978-81-322-2818-9

Library of Congress Control Number: 2016945973

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer (India) Pvt. Ltd.

For Abe – you are the reason I am!

For Ashwin and Riya – you are the reason for me!

"The strongest and sweetest songs yet remain to be sung."

-Walt Whitman

Foreword

We are now witnessing the natural progression of the management of corneal endothelial disease from full thickness penetrating keratoplasty to endothelial transplantation. With any new disruptive surgical technique there are pioneers who provide the leadership and direction to take an innovative idea and create the transformation that will change the future of our specialty. Dr. Soosan Jacob is one of these individuals. She is an undisputed innovator, educator and international leader in anterior segment surgery who constantly looks at surgical dilemmas and discovers solutions to the most difficult problems facing anterior segment surgeons today. Her surgical techniques have changed the face of ophthalmology and have been adapted worldwide to the betterment of our patients. Her videos, often in collaboration with her mentor Dr. Amar Agarwal, are masterpieces of innovation that have helped educate an entire generation of ophthalmologists and have won numerous international awards. In addition she is a prolific writer editing 15 textbooks, writing 200 book chapters and authoring 80 peer-reviewed publications. She is a superb surgeon with many innovative instrumentations and surgical techniques to her credit, but most remarkably she possesses the rarest of all personal attributes, she is an original thinker. Dr. Jacob is creative, analytical, pioneering, and her advances are built on the foundation that no matter what we do, our patients come first and we should do everything to maximize their visual outcome. No case is too complex for Dr. Jacob. In addition, Dr. Jacob, despite all of her accomplishments, is humble and self-effacing, always giving credit to anyone who has in anyway been associated with her success. There is a small group of surgeons around the world that I call on for advice in managing my most demanding surgical cases and Dr. Jacob is at the pinnacle of this elite group.

Over little more than a decade there has been a revolution in advancing our management of corneal endothelial disease. Just a few short years ago penetrating keratoplasty was the routine management of bullous keratopathy, pseudophakic bullous keratopathy and Fuchs' dystrophy. The visual rehabilitation was painfully slow with high postoperative astigmatism, surgically induced glaucoma and a lifetime risk of even mild ocular trauma resulting in a vision threatening wound dehiscence. Endothelial keratoplasty has changed the course of the most common causes of

corneal transplantation. Beginning with DSAEK and advancing to DMEK and now PDEK, visual rehabilitation for endothelial disease has now become safer with more rapid visual rehabilitation and incredible improvement in quality of vision and quality of life over full thickness penetrating keratoplasty. Dr. Soosan Jacob has been at the forefront of these advances with multiple innovations to her credit including the endo-illuminator assisted Descemet's membrane endothelial keratoplasty devised to enhance visualization and three-dimensional depth perception during DMEK and air-pump assisted pre-Descemet's endothelial keratoplasty (PDEK) that makes PDEK surgery easier and more adoptable by surgeons.

Dr. Jacob's new book, *Mastering Endothelial Keratoplasty*, is a comprehensive tour de force of the surgical management of endothelial disease beginning with the history and anatomy, advancing through corneal transplantation, Descemet's stripping automated endothelial keratoplasty (DSAEK), ultrathin DSAEK, Descemet's membrane endothelial keratoplasty (DMEK) and finally pre-Descemet's endothelial keratoplasty (PDEK). The book is a comprehensive analysis of the management of endothelial disease and summarizes all of the best and most useful and practical pearls that she and her authors have developed. Dr. Jacob has brought together an extraordinary internationally recognized group of authors who have changed the face of endothelial management. This book will be widely read by anterior segment surgeons who wish to add to their surgical skill and will be an important contribution to ophthalmology.

Eric Donnenfeld, MD
Clinical Professor of Ophthalmology, NYU
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Editor-in-Chief, EyeWorld

Preface

The landscape of cornea as a sub-speciality has changed significantly from the past. Technology has improved by leaps and bounds and new techniques are constantly evolving. Interlinking of technology, newer surgical techniques, and basic research has brought about rapid shifts in our approach to corneal surgery, especially keratoplasty. Lamellar keratoplasty, both anterior and posterior, have shown such improved results that they have become the standard of care. The last two decades have seen the introduction of posterior lamellar keratoplasty as well as many changes in the way it has been performed. Endothelial keratoplasty has today become the most popular of choices for endothelial dysfunction requiring surgery. In 2011, about half the corneal transplants performed in the USA were Descemet stripping automated endothelial keratoplasty (DSAEK), and in 2012 it overtook penetrating keratoplasty in terms of the number of corneas being used. The acceptance is similar in many other parts of the world. The reason DSAEK is finding favor with both surgeons and patients is because of the improved recovery times and visual outcomes as well as the numerous intra-operative advantages. However, despite the even greater perceived advantages of the two more recent forms of endothelial keratoplasty – Descemet membrane endothelial keratoplasty (DMEK) and Pre-Descemet endothelial keratoplasty (PDEK) – there is still hesitancy on the part of many corneal surgeons to the inclusion of these into their surgical armamentarium. This is because these are perceived as more challenging techniques with a greater learning curve.

This two-volume book on endothelial keratoplasty (EK) serves to fill up a vacuum in this space as there is at present no book that covers all kinds of EK including DSAEK, ultra-thin DSAEK (UT-DSAEK), DMEK, and PDEK. It has been aimed to serve as an excellent guide for DSAEK to both the beginning surgeon as well as those who need a refresher to sharpen their skills further. It also at the same time serves as a stepping stone for successfully, and with minimal heartburn, mastering the more challenging newer endothelial keratoplasties, viz., DMEK and PDEK. The various minute steps that are essential for these as well as for newer ancillary techniques which help make surgery easy such as endoilluminator assisted DMEK (E-DMEK) and the air-pump assisted PDEK have been described in detail. The

original pioneers for the various techniques as well as eminent specialists in this area have contributed their knowledge as well as given their tips and tricks for increasing surgical success. The two volumes have been designed to comprehensively cover the pre-, intra-, and post-operative period. The presence of numerous high-quality photographs, illustrations, and linked videos help make understanding easier and make this two volume book a must-have for all corneal surgeons. Despite the amount of educational material in it, the size and format has been kept to allow easy reading. The electronic format of the book helps carry it around for easy and quick reference at any place or time.

I would like to thank many people for making this labor of love possible. My co-authors who have contributed so much of their valuable time and effort to writing excellent chapters and have become dear friends; my friends and colleagues for their constant support in innumerable ways, and Saijimol AI for helping me with everyday work that otherwise would have overwhelmed me. I would also like to thank Naren Aggarwal and Teena Bedi from Springer for encouraging me to take on this task, for being immensely helpful at every step and for keeping this book to such high standards. I would like to thank all my patients from whom I have learnt so much and all the teachers in my life who have taught me so much. I would like to especially thank my two mentors, Drs. Amar and Athiya Agarwal who have pushed me ever forwards and always encouraged me to keep raising the bar further and further, always more than I would think possible for myself. I would also like to thank my parents – Mary Jacob and Lt. Col Jacob Mathai – for guiding me and molding me into what I am and my brother Alex Jacob and my sister Asha Jacob for always being there for me. Finally, I would like to thank Dr. Abraham Oomman, my husband, my best friend, my confidante, and my sounding board for his unflinching support and constant love, for making me keep at it and complete it, and lastly my children, Ashwin and Riya, who tolerated me throughout and kept me smiling through all the long hours spent.

Finally, as Oliver Wendell Holmes said, “Great things in this world depends not so much on where we stand but which direction we are moving.” This book is an attempt to throw a light to illuminate the path and make it easier to travel. I hope you the reader will enjoy this book and glean from it pearls that you will be able to incorporate into your practice.

Chennai, India Soosan Jacob

About the Editor

Dr. Soosan Jacob, MS, FRCS, DNB, MNAMS is Director & Chief; Dr. Agarwal's Refractive and Cornea Foundation (DARCF) and Senior Consultant, Cataract and Glaucoma Services, Dr. Agarwal's Group of Eye Hospitals, Chennai, India. She is a noted speaker widely respected for her innovative techniques and management of complex surgical scenarios. She conducts courses and delivers lectures in numerous national and international conferences; has been the recipient of IIRSI Special Gold medal, Innovator's award (Connecticut Society of Eye Physicians), ESCRS John Henahan award for Young Ophthalmologist, AAO Achievement award and two time recipient of ASCRS Golden Apple award. She has special interest in cutting-edge cataract, cornea, glaucoma, and refractive surgery and has won more than 40 international awards for videos on her surgeries, innovations and challenging cases at prestigious international conferences in United States and Europe. Her innovations, many of which have won international awards, include anterior segment transplantation, where cornea, sclera, artifical iris, pupil and IOL are transplanted enbloc for anterior staphyloma; suprabrow single stab incision ptosis surgery to enhance postoperative cosmesis; turnaround techniques for false channel dissection during Intacs implantation; Glued Endo-Capsular Ring and Glued Capsular Hook for subluxated cataracts; Stab Incision Glaucoma Surgery (SIGS) as a guarded filtration surgery technique; Contact lens assisted crosslinking (CACXL) for safely crosslinking thin keratoconic corneas; Endo-illuminator assisted DMEK (E-DMEK) and Air Pump Assisted PDEK for easier and better surgical results; and the PrEsbyopic Allogenic Refractive Lenticule (PEARL) Inlay for treating presbyopia. She has proposed a new classification of Descemet's membrane detachments into rhegmatogenous, tractional, bullous and complex detachments with a suitable treatment algorithm and a new technique of relaxing descemetotomy for tractional Descemet's detachment. Her surgeries and surgical techniques have often been Editor's Choice in prestigious International Ophthalmic websites (AAO/ ONE network, ISRS, Eyetube etc). Her video blog "Journey into the Eye - A surgeon's Video blog" in the prestigious Ocular Surgery News, USA features her surgical videos. She also has her own surgical educational YouTube channel: Dr. Soosan Jacob with more than 2500 subscribers. Dr. Jacob is senior faculty for training postgraduate, fellowship

and overseas doctors. She has authored more than 80 peer reviewed articles, numerous chapters in more than 30 textbooks by international publishers, is editor for 15 textbooks in ophthalmology and reviewer for many prestigious journals. She has two popular columns, "Eye on Technology" and "Everything you want to know about" in the prestigious Eurotimes magazine published by ESCRS. She is a committee member of ISRS/AAO Multimedia Library and is on the editorial board of the Ocular Surgery News–Asia Pacific Edition, Cataract and Refractive Surgery Today- Europe, Glaucoma Today and the EuroTimes Magazines. Her life and work have been featured on the Ocular Surgery News cover page, "5Q" interview (prestigious Cataract and Refractive Surgery Today), "Sound off" column (CRST) and is the first researcher internationally to be interviewed in the prestigious CRST "Researcher's Column." She can be contacted at dr_soosanj@hotmail.com

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Chapter 1
Anatomy of the Cornea

Soosan Jacob and Preethi Naveen

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S. Jacob (ed.), *Mastering Endothelial Keratoplasty*,
DOI 10.1007/978-81-322-2818-9_1

1.1 Introduction

The cornea is a transparent dome-shaped structure covering the iris, lens, and anterior chamber (AC) of the eye. It accounts for nearly two-thirds of the total refractive power of the eye (Fig. 1.1a, b). The adult cornea measures 11–12 mm horizontally and 9–11 mm vertically. The thickness varies from 0.5 mm in the central cornea and gradually increases to around 1 mm near the limbus [1]. The periphery is more aspheric as the curvature decreases from the center toward the periphery. Refractive index of the cornea is 1.376. The radius of curvature anteriorly is 7.8 mm and posteriorly 6.5 mm. The refractive power of the cornea is +48D on the anterior surface and −5D on the posterior surface accounting for a net power of +43 D. The normal keratometric value for the cornea is within the range of 42–45 D. Transparency, avascularity, and immunological privilege are unique properties of the cornea. It derives its nutrition from tears, aqueous, and the perilimbal vasculature. Oxygen supply is from the atmosphere through the tear film and also from the perilimbal capillaries. Aqueous humor is the main source of glucose for all layers of the cornea, while amino acids required for protein synthesis are acquired by passive diffusion from the aqueous.

1.2 Embryology

Corneal development begins from the 22nd day of gestation. The layers of the cornea develop from different cell lineages. The epithelium is derived from surface ectoderm. The corneal stroma, Bowman's layer, and endothelium are derived from the mesenchymal cells of neural crest origin. The Descemet's membrane is laid down by the endothelial cells of neural crest origin from the 6th month onward. The cornea starts becoming transparent around this time. Cell migration occurs in three waves between the ectoderm and lens vesicle [2]. The first wave gives rise to corneal endothelium. The second wave of cells is between the epithelium and endothelium giving rise to keratocytes which form the stroma. The third wave of cells migrates between endothelium and lens giving rise to stroma of the iris. The corneal epithelium

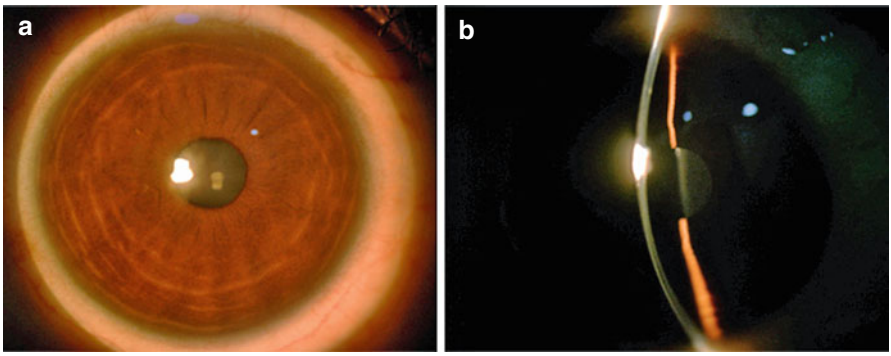

Fig. 1.1 (**a**) The human cornea is a six-layered structure which is transparent and optically clear. It contributes to majority of the refractive power of the eye. (**b**) The normal cornea seen in slit view

develops during the 6th week when the ectoderm detaches from lens vesicle. The junctional complexes in the epithelium also form by the 6th week. The cornea is well developed by the 7th month of gestation when the epithelium has clearly demarcated basal, wing, and superficial cells and stroma is almost fully developed with accumulation of keratan sulfate among collagen fibers [3]. The glycosaminoglycan chains bind to core protein from the proteoglycans which occupy the space between the collagen fibers. At birth the corneal epithelium has only two layers which gradually keeps increasing to reach adult thickness of five to seven layers. Anterior segment anomalies arise due to defective migration of neural crest derived cells.

1.3 Layers of Cornea

The cornea has six layers and the Dua's layer or the pre-Descemet's layer (PDL) which is present between the stroma and Descemet's membrane is a new addition to the traditional classification of corneal layers into five (Fig. 1.2).

1. Epithelium
2. Bowman's membrane
3. Stroma
4. Dua's layer
5. Descemet's membrane
6. Endothelium

1.3.1 Epithelium

This is the outermost layer of the cornea and is derived from the surface ectoderm. It's a non-keratinized stratified squamous epithelium measuring 50 μm in thickness composed of five to seven layers of cells [3]. The epithelium plays a crucial role in maintaining a smooth refractive surface along with the tear film. It also provides a mechanical

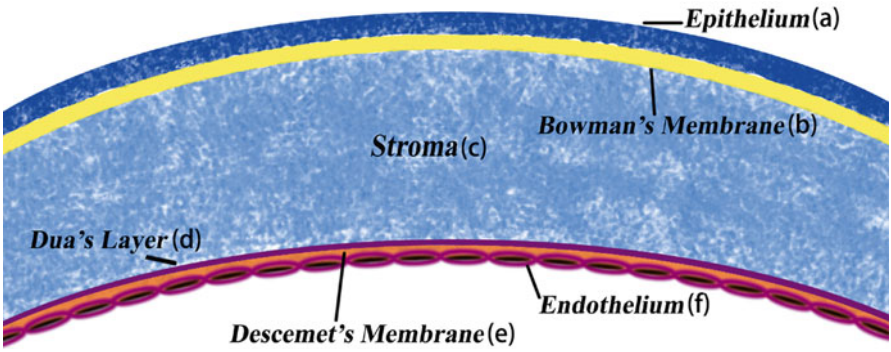

Fig. 1.2 Layers of the cornea (not to scale): (**a**) epithelium, (**b**) Bowman's layer, (**c**) stroma, (**d**) Dua's layer, (**e**) Descemet's membrane, (**f**) endothelium

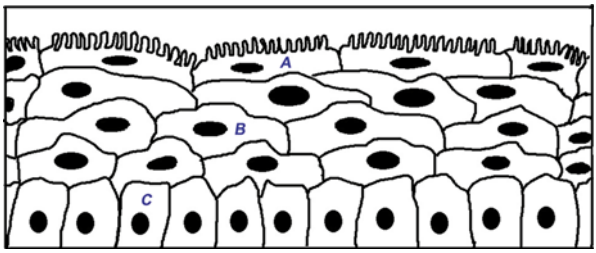

Fig. 1.3 Normal epithelial cells of the cornea (*A* superficial cells, *B* wing cells, *C* basal cells)

barrier to all external pathogens. The superficial cells are two to three layers, flat, polygonal with numerous microvilli and microplicae on their surface that secrete glycocalyx which play a role in maintaining stability of the tear film. These cells are well differentiated (Fig. 1.3A). The next layer-the wing cell layer, so named because of the typical wing shape of the cells, consists of two to three layers, and these cells are in an intermediate state of differentiation (Fig. 1.3B). The basal layer is the only layer where the cells have mitotic activity and differentiate into wing and superficial cells. The basal layer is attached by hemidesmosomes to the basal lamina (Fig. 1.3C).

There are different types of intercellular junctions between the epithelium. The superficial cells have desmosomes and tight junctions (zonula occludens) which are mostly present along the apical surface of the superficial cells providing an effective barrier to penetration of tears. The wing cells and basal cells have desmosomes, gap junctions, and hemidesmosomes [3].

The epithelium regenerates every 7–14 days. The daughter cells differentiate into wing cells and migrate toward the surface as superficial cells. Thoft and Friend postulated the X,Y,Z hypothesis where X-mitosis, Y-cellular migration, and Z-shedding of superficial cells suggests that there exists an equilibrium between these three factors which play a major role in epithelial regeneration [2]. The epithelial stem cells are found in the palisades of Vogt which form a 1 mm zone around the limbus. The stem cells give rise to transient amplifying cells which later migrate and form well-differentiated epithelial cells. The limbal stem cells have a high proliferative capacity but are poorly differentiated.

Diabetes causes the corneal epithelium to show reduced corneal sensitivity with increased susceptibility to delayed healing of epithelial defects. There is a decrease in the density of the subbasal nerve plexus which is noted to be related to the severity of diabetic retinopathy. There is also increased permeability of the epithelium which could be due to abnormality in the tight junctions.

1.3.2 Bowman's Layer

This is an acellular, tough membrane measuring 10 μm situated between the epithelium and stroma [3]. It is not a true basement membrane unlike the Descemet's membrane. It is composed of randomly arranged collagen fibers which are continuous with that of the anterior stroma. This layer primarily contains collagen types 1

and 3. The Bowman's layer helps maintain the shape and is also resistant to trauma. Unlike epithelium, it does not have the property to regenerate once destroyed and can form a fibrous scar following injury.

Melles et al. have recently come up with a novel technique for treatment of eyes with advanced keratoconus [4]. In keratoconus, there is fragmentation of the Bowman's layer, and hence Bowman's layer transplantation into the mid-stromal region could cause flattening of the anterior corneal surface and also an increase in the tensile strength. The flattening of the cone post-surgery was due to fibrosis and stromal compression. Their study has shown an average reduction of 6–7 D in corneal power post-surgery. As there are theoretically lesser risks of allograft rejection as compared to a PK/DALK, this procedure offers promising results in the treatment of advanced keratoconus which might require a transplant.

1.3.3 Stroma

This layer contributes to almost 90% of corneal thickness [2]. It is derived from the mesenchyme. There are approximately 200–250 lamellae of collagen fibers arranged parallel to one another which run from limbus to limbus. The stroma may be divided into anterior one-third and posterior two-thirds both of which have distinct features that play a role in the biomechanical strength of the cornea. The prominent collagens are type 1 with smaller amounts of types 3, 5, and 6 [3]. The proteoglycans in the stroma are dermatan sulfate, keratan sulfate and chondroitin sulfate. Most abundant among them is keratan sulfate. In the anterior one-third, the lamellar arrangement is oblique to each other and interlacing providing more strength. It contains less water, glucose, and more dermatan sulfate. The posterior two-thirds of the stroma has collagen fibers which are parallel to one another and contain more keratan sulfate. Posterior stroma has poor interlamellar connections. This difference in fiber arrangement offers more tensile strength to the anterior one-third of stroma as compared to the posterior stroma.

The keratocytes are highly metabolically active cells which are spindle shaped and lie scattered among the lamellae. They synthesize collagen and proteoglycans of the stroma. The anterior stroma has a higher density of keratocytes as compared to posterior stroma.

1.3.4 Pre-Descemet's Layer (PDL) or Dua's Layer

The recent discovery of the pre-Descemet's layer or the Dua's layer has changed the understanding of lamellar corneal surgeries. This previously unrecognized distinct layer of cornea is located between the posterior stroma and the Descemet's membrane (Fig. 1.4).

The Dua's layer is a tough, acellular layer measuring between 6 and 15 μm in thickness and composed of 5–8 thin lamellae of tightly packed collagen bundles

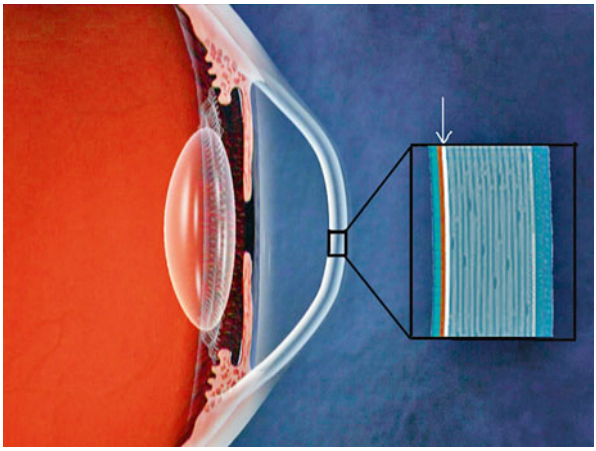

Fig. 1.4 Figure showing schematic cross section of the cornea. Inset is the zoomed view of the microscopic structure. *Arrow* points to the pre-Descemet's layer

which run in longitudinal, transverse, and oblique directions [5]. The fibrils are much thicker in this layer. The collagen bundles on the anterior surface of the Dua's layer are more regularly arranged and parallel. The posterior surface has coarse bands of collagen arranged in a pleated pattern. This layer is impervious to air which can be attributed to the tightly packed lamellae and greater space between fibrils possible accommodating greater amounts of proteoglycan.

The type 1 bubble in lamellar surgery is well circumscribed and dome shaped and starts from the center of the cornea and expands toward the periphery. It typically forms between the stroma and PDL. The type 2 bubble occurs when air enters the space between the posterior surface of Dua's layer and the Descemet's membrane. This occurs because the PDL ends before the Descemet's membrane and air escaping beyond the edge of the PDL into the periphery gains access to this plane [5].

This plane between the Dua's and stroma can be used to generate tissue for endothelial transplant. This layer may also be involved in posterior corneal pathologies like acute hydrops and descemetocele.

Recent studies [6] have also postulated that the collagen matrix of the trabecular meshwork (TBM) is an extension of the Dua's layer and that the broad beams of the TBM take origin from the peripheral termination of the collagen lamellae of the Dua's layer. The presence of collagen 6 in both TBM and Dua's layer as well as trabecular cells in the Dua's layer has been presented by the authors as lending support to the theory that formation of TBM commences in the peripheral part of Dua's layer anterior to termination of DM.

1.3.5 Descemet's Membrane

This is secreted by the endothelial cells which are derived from the neural crest. It is composed primarily of collagen types 4 and 8 and laminin. The membrane is divided into an anterior banded zone which is laid during fetal development and a posterior non-banded zone which is laid throughout life. Thickness is around 8–10

μm. It is a true basement membrane and not a continuation of stroma like the Bowman's layer [2]. The peripheral termination of the DM forms the Schwalbe's line. The natural excrescences found in the periphery of the membrane are called Hassall-Henle bodies which do not interfere with vision. The elasticity of this layer is due to particular arrangement of collagen fibers and glycoproteins (fibronectin, laminin, thrombospondin). It is a tough layer which resists enzymatic degradation. The DM has strong attachments to post surface of stroma. In corneal ulcers as a result of high IOP, it herniates forming a descemetocele.

1.3.6 Endothelium

This is a single layer of hexagonal cells arranged in a mosaic pattern around 5 μm thick with a density of 3000–4000 cells/mm^2 at birth which gradually keeps decreasing with age. Average cell count for adults is between 1500 and 3500 cells/mm^2. Primary function of the endothelium is to maintain corneal transparency by keeping the stroma in a dehydrated state. Normal cornea has 70–80 % of hexagonal cells [2]. The coefficient of variation (CV) normally is 0.25. The CV is the most sensitive index of endothelial dysfunction. It is the standard deviation of cell area/mean cell area. Polymegathism refers to increased variability in cell area and pleomorphism is the deviation from hexagonality. Loss of endothelial cells due to an insult is compensated for by enlargement and spreading of adjacent cells. A fall in the endothelial cell count below a critical value results in corneal decompensation (Figs. 1.5 and 1.6).

1.3.6.1 Endothelial Pump

The endothelial pump plays a major role in corneal transparency. There exists a pump-leak mechanism in the endothelium. Passive movement of solutes from aqueous occurs through gap junctions in the endothelial layer. The endothelium

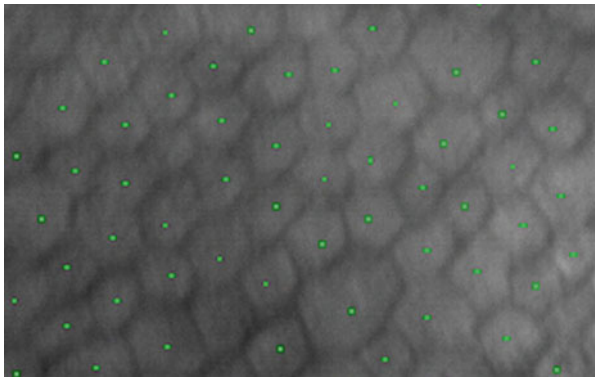

Fig. 1.5 Specular microscopic picture of corneal endothelium

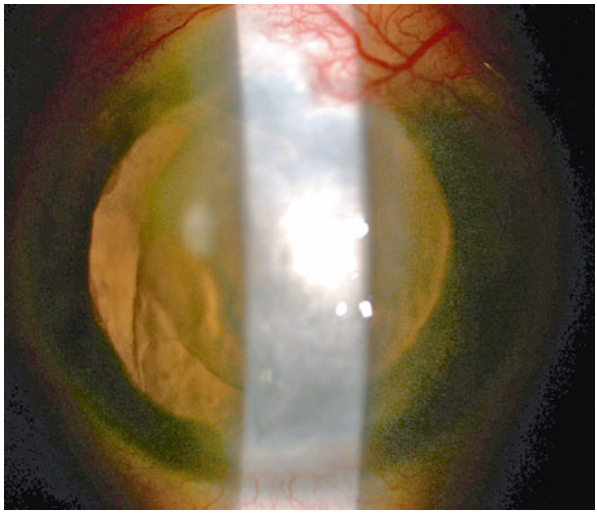

Fig. 1.6 Pseudophakic bullous keratopathy

Table 1.1 Causes of corneal edema

Fuchs endothelial dystrophy
Aphakic and pseudophakic bullous keratopathy
Cornea guttata
Other endothelial dystrophies
Trauma
ICE syndrome
Glaucoma
Advanced age
Uveitis
Contact lens wear

has a Na+ and K+ dependent ATPase and a sodium/hydrogen exchange pump in its basolateral membrane [3]. These cells contain numerous mitochondria and cytoplasmic organelles as they are very metabolically active. There exists an osmotic gradient between the aqueous and the stroma allowing sodium movement from the aqueous to stroma and potassium in the opposite direction. Carbon dioxide diffuses into the cytoplasm of these cells along with water and generates bicarbonate. This reaction is catalyzed by carbonic anhydrase enzyme. The movement of bicarbonate into aqueous is coupled with water entry across the endothelial cells. This pump mechanism is partly dependent on cellular energy. Cooling of cornea causes swelling and opaque cornea which reverts back to normal once body temperature is normal known as the temperature reversal phenomenon. When there is a failure in this pump mechanism, there is entry of aqueous into the stroma resulting in corneal edema, widening of space between collagen fibers and loss of transparency (Table 1.1).

1.3.6.2 Specular Microscopy

It is a noninvasive method to evaluate the endothelial status. It captures images which are reflected from the optical interface between the endothelium and aqueous humor [3]. The parameters analyzed are endothelial cell density, mean cell area, coefficient of variation, and hexagonality. There are two methods of analyzing the cells – the fixed frame and the variable frame analysis, with the latter being more reliable. Donor corneas should have a count of at least 2000 cells/mm^2 for optimal functioning.

1.4 Nerve Supply of the Cornea

The cornea is a highly innervated tissue. Sensory nerves are derived from the long ciliary nerve which is a branch of the ophthalmic division of the trigeminal nerve [1]. The long ciliary nerves run in the suprachoroidal space and pierce the sclera a little away from the limbus, where they branch and along with the conjunctival nerves form the pericorneal plexus of nerves. From the perilimbal plexus, the nerves penetrate the cornea in the deep peripheral stroma. The bulk of the corneal nerves enter at 3 and 9 o'clock positions. They ascend upward in the stroma losing their myelin sheath and form three plexuses of nerves, namely, stromal plexus in the mid-stroma, the subbasal plexus, and the intraepithelial plexus. The nerves penetrate the Bowman's layer and terminate at wing cell level. The sensitivity is maximum at the apex and minimum at periphery and further drops at the limbus. Loss of corneal epithelium leads to increased pain sensitivity due to exposed nerve endings.

Amongst other causes, post Lasik dry eye symptoms are also directly related to the transection of corneal nerves during flap creation. It is a temporary phenomenon as the nerves regenerate within a period of 3–6 months. The superiorly hinged flap is found to sever more nerves as compared to a nasally or a temporally hinged flap as the bulk of corneal nerves enter at 3 and 9 o'clock positions.

1.5 Vascular Supply of the Cornea

The cornea is an avascular structure. Anterior ciliary artery from the ophthalmic artery forms a vascular arcade and anastomoses with vessels from facial branch of the external carotid artery to form the perilimbal plexus of blood vessels [3]. In normal corneas, there are no blood vessels because of the compact arrangement of fibers, whereas in pathological conditions when the cornea swells and creates space, vessels grow in between. In conditions of infection or inflammation there is growth of new vessels which aid in repair. Corneal hypoxia is also a stimulus for neovascularization. In superficial vascularization, vessels arise from the conjunctival plexus and can be traced beyond the limbus. Deep vessels arise from anterior ciliary arteries and traverse deep in the stroma. Once the inflammatory stimulus is lost, these

vessels regress leaving them as ghost vessels. The corneal epithelium has high expression of VEGFR-3 receptor which has an anti-angiogenic effect [2].

The success of corneal transplants is largely attributed to the avascular nature of cornea which offers it an immune privilege. The presence of vascularization is one of the main factors which interfere with graft survival. The presence of more than two quadrants of deep vascularization poses a high risk of graft rejection. Subconjunctival bevacizumab may be useful for regression of neovascularization prior to transplant.

1.6 Transparency of the Cornea

Corneal transparency is contributed to by various factors both anatomical and physiological.

These include the smooth surface of epithelium along with tear film, regular arrangement of collagen fibers, the absence of blood vessels, and the presence of nonmyelinated nerve fibers. Physiological factors like the role of stromal swelling pressure, endothelial pump mechanism, and the barrier function of corneal epithelium all play a key role in maintaining a dehydrated state of the cornea.

The arrangement of collagen fibers in the stroma plays a major role in maintaining corneal transparency. The lattice theory of Maurice (1957) [3] postulates that the collagen fibers are equal in diameter and the space between each fiber is less than half the wavelength of light. This arrangement causes destructive interference of scattered light rays thereby maintaining transparency (Fig. 1.7). The Goldman

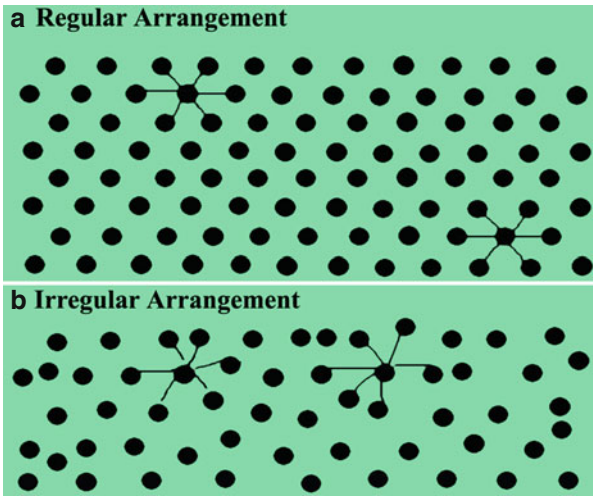

Fig. 1.7 Lattice theory. (**a**) Cross-sectional view showing regular arrangement of collagen fibers in corneal stroma. (**b**) Picture showing irregular arrangement of collagen fibers in sclera

theory states that fiber diameter less than one-third of the wavelength of light is enough to maintain transparency. When there is fibrosis or edema, there is an increase in fiber spacing leading to a loss in transparency.

Following any insult to corneal stroma, the keratocytes transform into myofibroblasts [3] and produce extracellular matrix, collagen-degrading enzyme, matrix metalloproteases, and cytokines for tissue repair leading to wound closure.

Stromal swelling pressure plays a role in maintaining the dehydrated state of the cornea. The tendency of the stroma to swell is called swelling pressure (SP). Imbibition pressure is the property of collagen lamella to draw in fluid. This is also due to the repulsive forces between the negative charges on keratin and chondroitin sulfate. The correlation between the imbibition pressure, swelling pressure, and intraocular pressure (IOP) is expressed as IP = IOP − SP [3]. The IP is lower than swelling pressure due to the compressive effect of IOP. In an excised cornea, the imbibition pressure is equal to swelling pressure.

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