

## Chapter 2

# Cornea

The cornea is a remarkable tissue; it can be thought of as “the window to the world.” Optimally – as with any window you are trying to see through – it must be clear and spotless. It is the eye’s main refractive element, and it normally is avascular.

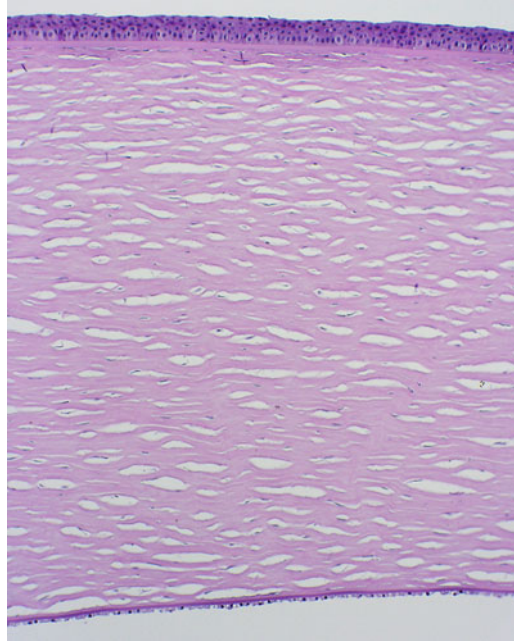
The cornea and its tear film layer typically are not recognized when we look in our own eyes or the eyes of others. The tear film layer protects and coats the corneal surface and is composed of three distinct layers: from outer to inner they are the lipid layer, aqueous layer, and mucous layer. The lipid layer is produced by the meibomian (sebaceous) glands of the eyelid; the aqueous layer is produced by the serous glands of the lacrimal gland, and the mucous layer is produced by the goblet cells of the conjunctiva. A defective tear film layer can result in dry eye, which is a leading cause of eye-related disease.

Scarring, infection, inflammation, vascularization of the stroma, congenital anomalies, dystrophies, and neoplasia can be detrimental to vision. This chapter will introduce some of the basic and common pathology affecting the cornea.

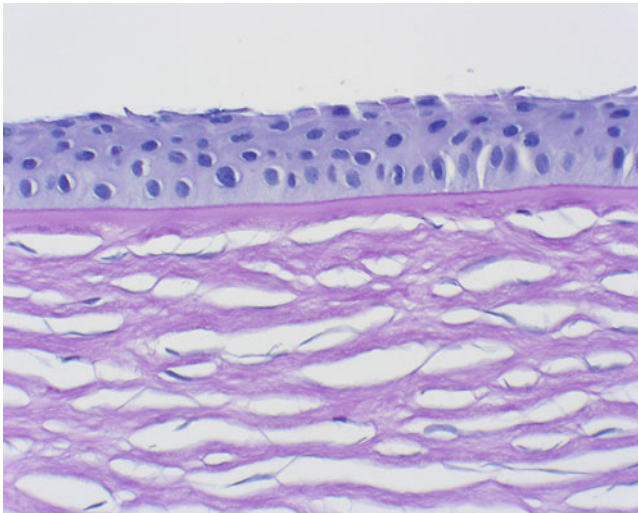
The normal cornea has five layers (Fig. 2.1). Let us examine the histology of each layer individually:

### 1. The surface epithelium (Fig. 2.2):

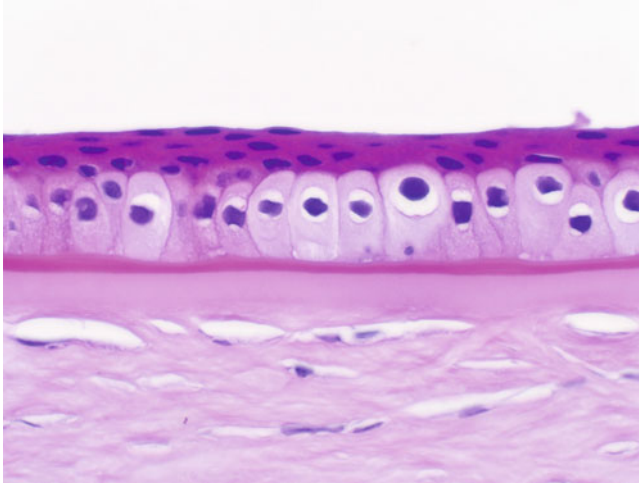
- Is normally four or five cell layers thick.
- Is a nonkeratinizing squamous epithelium.
- Has a smooth convex curvature.
- In cases of corneal swelling (bullous keratopathy), the basal layer of epithelium may undergo significant hydropic change (Fig. 2.3).
- There is a thin epithelial basement membrane which is often not recognizable histologically in normal corneas (although some authors may consider it to be its own layer). It can thicken in cases of trauma and diabetes (Fig. 2.3).
- Following injury, the epithelium may become thickened (acanthosis) (Fig. 2.4).



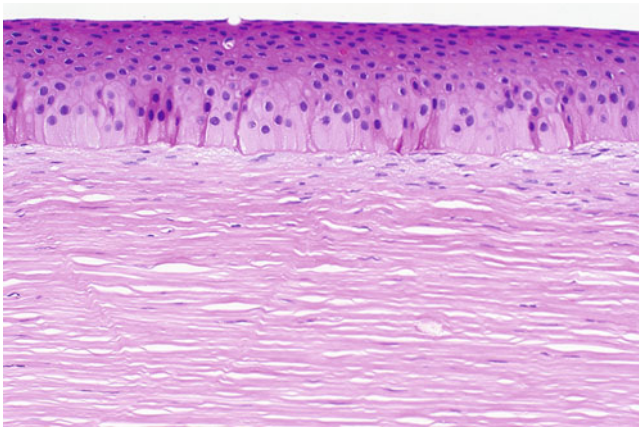
**Fig. 2.1** Normal cornea showing the epithelium at the *top of the field*, Bowman's layer, the corneal stroma, Descemet's membrane, and corneal endothelium. The normal corneal stroma has an artifactual clefted or cracked appearance



**Fig. 2.2** Anterior cornea showing a nonkeratinized layer of squamous epithelium, a very thin basement membrane, Bowman's layer, and the anterior stroma. The blue nuclei within the stroma are the nuclei of the keratocytes



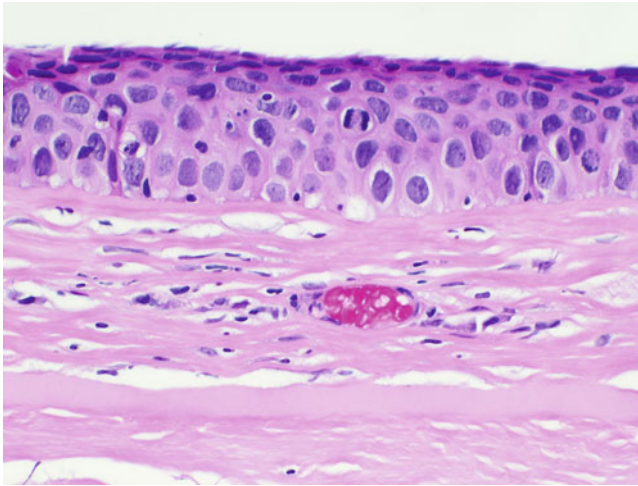
**Fig. 2.3** Anterior cornea with hydropic change in the basal epithelial cells in a case of bullous keratopathy (corneal edema). Beneath the epithelium is a bright pink thickened basement membrane. This epithelial basement membrane is often not seen in hematoxylin and eosin-stained sections, although it can be thickened in certain diseases such as diabetes. Underlying the bright pink basement membrane is the light pink Bowman's layer, and underneath that is the corneal stroma



**Fig. 2.4** Cornea with thickening or acanthosis of the epithelium, absence of Bowman's layer, and scarring

## 2. Bowman's layer:

- Named after Sir William Bowman, English ophthalmologist and anatomist (1816–1892). He also identified Bowman's capsule in the kidney.
- Bowman's layer is a smooth eosinophilic band which acts as a protective barrier for the stroma.
- Breaks or disruptions in Bowman's layer are typically seen in cases of keratoconus (discussed below).



**Fig. 2.5** Fibrovascular pannus between the cornea epithelium and Bowman's layer. In this case, the overlying epithelium shows carcinoma in situ

- Pannus is fibrocollagenous or fibrovascular scar tissue between the epithelium and Bowman's layer (see Fig. 2.5).
- Calcific band keratopathy is calcific stippling of Bowman's layer.

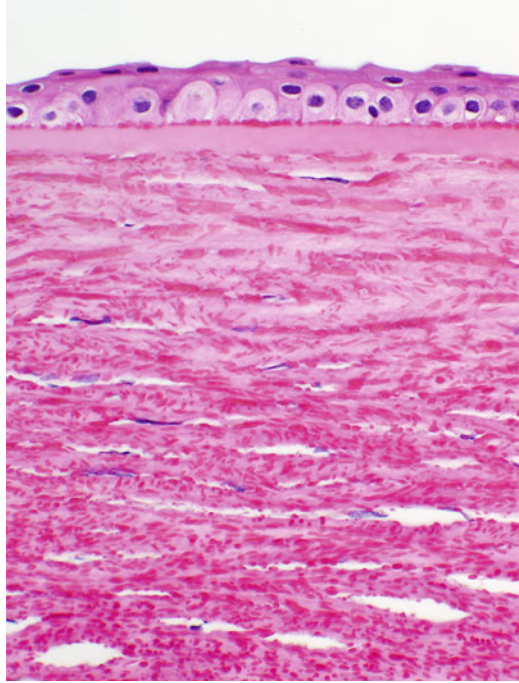
### 3. Stroma/substantia propria:

- The stroma accounts for approximately 90% of the cornea. It is mostly collagen fibers, which, when examined ultrastructurally, are found to be in an organized pattern of alignment to reduce refraction of light. In contrast, the collagen fibers of the sclera are arranged haphazardly.
- Identify the nuclei of the keratocytes. The keratocytes are the fibroblasts of the cornea, and they are not to be confused with the keratinocytes of the skin.
- The normal corneal stroma is characterized by numerous cleft-like spaces. These spaces are artifacts; they are not lymphatics or blood vessels (vascularization of the cornea is abnormal and is bad for vision). Absence of these cleft-like spaces might indicate corneal swelling.
- Following trauma, hemoglobin may stain the cornea and is known as corneal blood staining (Fig. 2.6).
- The cornea is innervated by the ophthalmic branch of the trigeminal nerve. Peripheral nerve twigs are not normally seen in the cornea; however, they may become enlarged in certain clinical conditions including neurofibromatosis type 1 (Figs. 2.7, 2.8, 2.9).

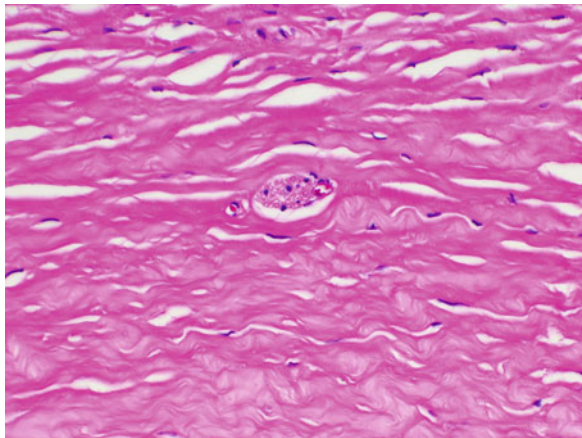
### 4. Descemet's membrane:

- Named after Jean Descemet, French physician (1732–1810).
- The anterior gray band denotes the fetal/gestational layer of Descemet's membrane (Fig. 2.10). This is a helpful clue in determining you are looking

**Fig. 2.6** Cornea with blood staining exhibiting innumerable blood fragments



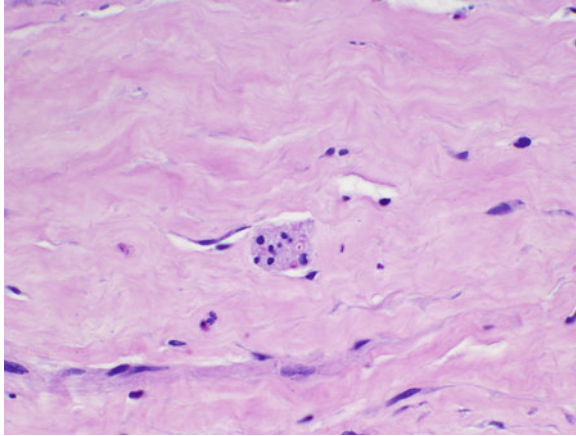
**Fig. 2.7** Cornea stroma with a visible peripheral nerve twig. Peripheral nerves are typically too small to be seen on light microscopy



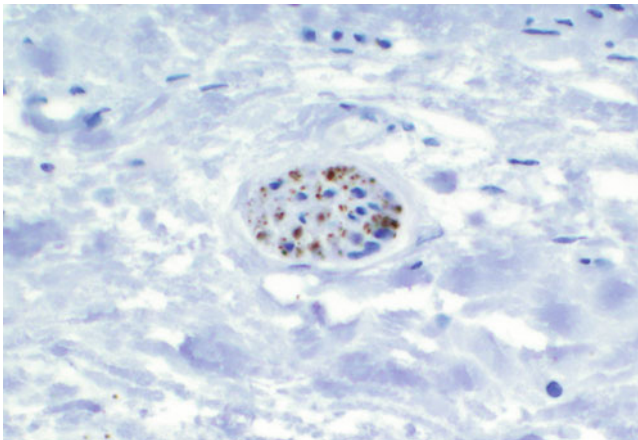
at Descemet's membrane and not Bowman's layer or the lens capsule. Additional nonbanded membrane is formed by the corneal endothelial cells throughout life.

- How do you know if Descemet's membrane is too thick? It is advantageous to examine normal autopsy eye controls over a wide range of ages. Thickening of Descemet's membrane and the presence of guttae are diagnostic features often seen in Fuchs' corneal dystrophy (discussed below).



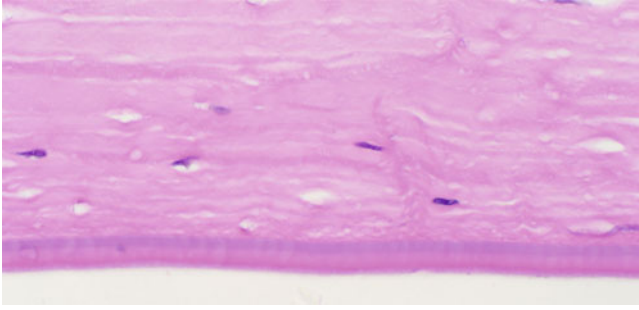


**Fig. 2.8** Cornea stroma with a visible peripheral nerve twig. An axon in cross section is seen as a red dot

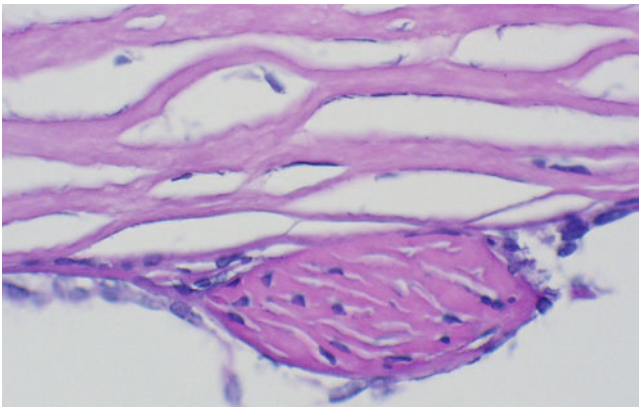


**Fig. 2.9** Cornea peripheral nerve twig highlighted with a synaptophysin immunohistochemical stain

- Posterior embryotoxon is a nodular prominence at the termination of Descemet's membrane (thickening of Schwalbe's line) (Fig. 2.11), but a fortuitous section is necessary to identify it in histological specimens.
- In Wilson's disease, deposition of copper in Descemet's membrane is known as a Kayser–Fleischer ring.



**Fig. 2.10** Posterior corneal stroma and Descemet's membrane. The gray band within the anterior aspect of Descemet's membrane is the fetal/gestational banded layer of Descemet's membrane. This is a useful clue to distinguish Descemet's membrane from lens capsule or Bowman's layer if the corneal epithelium is absent. Additional nonbanded Descemet's membrane is formed by the corneal endothelial cells throughout life. In this case, Descemet's membrane is markedly thickened, and there are no corneal endothelial cells



**Fig. 2.11** Posterior corneal stroma showing a nodular prominence known as posterior embryotoxon. These are identified with fortuitous sections of the peripheral cornea. They represent the demarcation of the termination of Descemet's membrane (Schwalbe's line)

## 5. Endothelial cell layer:

- The corneal endothelial cells line the posterior surface of Descemet's membrane and are thought to be derived from the neural crest; they are not related to the endothelial cells that line blood vessels.
- Corneal endothelial cells are important because they function to pump aqueous fluid from the cornea to prevent turgescence (swelling/bullous keratopathy) of the cornea which results in visual loss.
- Decreased numbers of corneal endothelial cells are typically seen in Fuchs' dystrophy and failed corneal grafts.



**Fig. 2.12** Low-magnification appearance of a specimen from a Descemet's stripping endothelial keratoplasty (DSEK)/Descemet's stripping automated endothelial keratoplasty (DSAEK) procedure

## Corneal Pathology to be Familiar With (and Which You Are Most Likely to See in a 1-Month Rotation)

### 1. Cornea transplants and failed cornea grafts:

- These are common cornea specimens in surgical pathology.
- Histological findings to look for in a full-thickness cornea button include:
  - A peripheral linear incision
  - Epithelial cell swelling
  - Swelling of the corneal stroma (characterized by loss of the normal artifactual cleft-like spaces)
  - Scarring and neovascularization of the stroma
  - A decreased number of corneal endothelial cells
- Descemet's stripping endothelial keratoplasty (DSEK)/Descemet's stripping automated endothelial keratoplasty (DSAEK) is a surgical technique whereby Descemet's membrane is removed from the host (Fig. 2.12) and replaced with a donor Descemet's membrane graft. This technique is commonly performed for Fuchs' corneal dystrophy.
- DSEK/DSAEK grafts can sometimes fail and need to be surgically removed. Failed DSEK/DSAEK grafts typically consist of a thin layer of posterior cornea stroma lamellae and Descemet's membrane with a markedly decreased number of corneal endothelial cells (Fig. 2.13).

### 2. Fuchs' corneal endothelial dystrophy:

- Ernst Fuchs was a Viennese ophthalmologist (1851–1930).
- Fuchs' dystrophy is a leading indication for corneal transplantation in the USA.
- It results from a primary loss of endothelial cells with loss of the ability to maintain stromal deturgescence.
- Pathology:
  - Bullae (small blister-like cystic spaces) may be seen between the epithelium and Bowman's layer. Rupture of bullae may result in pain.
  - Stromal edema (bullous keratopathy).



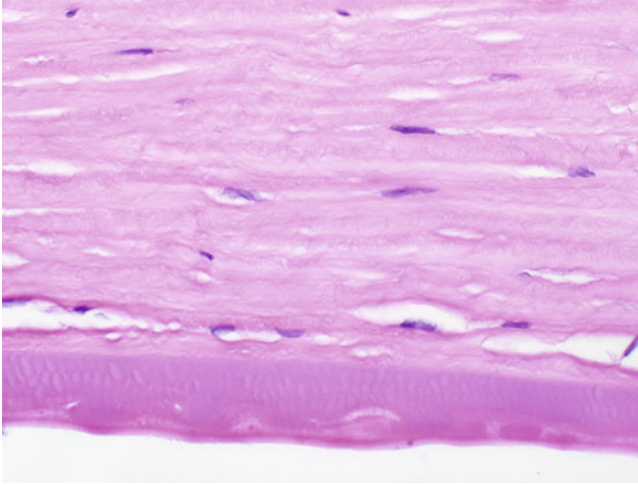


**Fig. 2.13** Failed corneal DSEK/DSAEK graft showing posterior cornea stroma and Descemet's membrane with absence of corneal endothelial cells

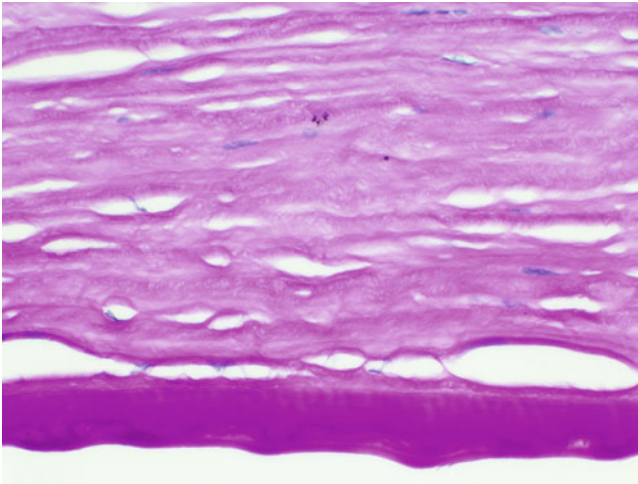


**Fig. 2.14** DSEK/DSAEK specimen in a case of Fuchs' corneal dystrophy characterized by thickening of Descemet's membrane, guttae, and absence of corneal endothelial cells. Some guttae in Fuchs' dystrophy are anvil shaped, as shown here

- Thickening of Descemet's membrane.
- Guttae:
  - Guttae are excrescences or drops of basement membrane material that protrude posteriorly from Descemet's membrane.
  - They are often box shaped or anvil shaped (Fig. 2.14).
  - Sometimes they are “buried” within Descemet's membrane (Fig. 2.15) and can be identified with a periodic acid-Schiff (PAS) histochemical stain (Fig. 2.16). In ophthalmic pathology, the PAS stain is excellent at highlighting Bowman's layer, Descemet's membrane, basement membrane in the ciliary body, and the lens capsule.
- A few other things about guttae:
  - Hassall-Henle warts are age-related guttae at the far periphery of Descemet's membrane, and they are not diagnostic of Fuchs' dystrophy. Corneal transplant procedures for Fuchs' dystrophy generally excise the central cornea; the guttae in these specimens are abnormal.
  - The word gutta is from Latin, meaning a drop or something resembling a drop. If you receive a prescription for eyedrops, it might be written as *ii gtt OS q 8 h x 7d*, meaning place two drops in the left eye every 8 h for a total of 7 days.



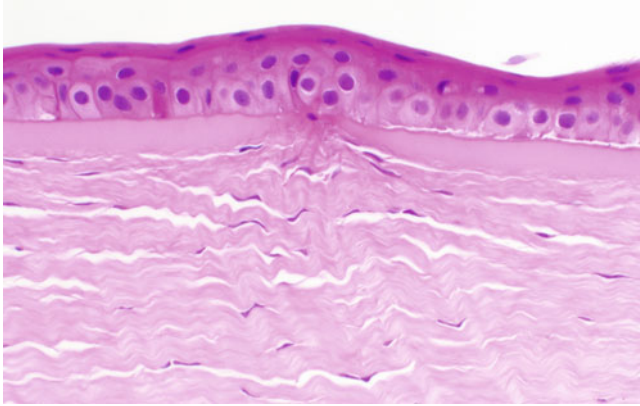
**Fig. 2.15** Guttae are sometimes “buried” within Descemet’s membrane rather than the more common “drop-like” excrescences



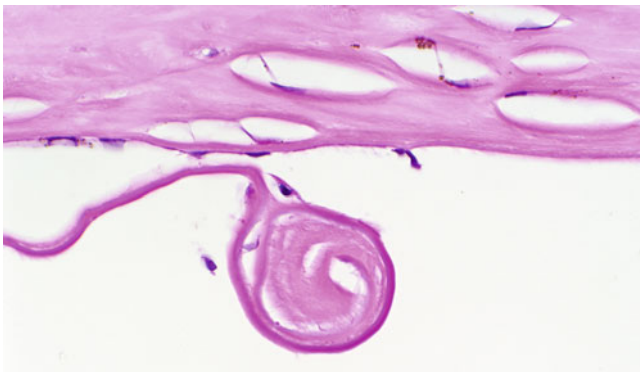
**Fig. 2.16** Periodic acid-Schiff (PAS) histochemical stain highlights “buried” guttae

### 3. Keratoconus:

- Keratoconus is a coning or ectasia of the cornea.
- The diagnosis can often be predicted by simply observing the shape of the tissue on the glass slide; the cornea has a characteristic wrinkled and thin appearance.
- Microscopic findings in keratoconus include breaks or disruptions in Bowman’s layer (Fig. 2.17) and thinning of the corneal stroma. The histological findings in keratoconus can vary from minimal to severe.

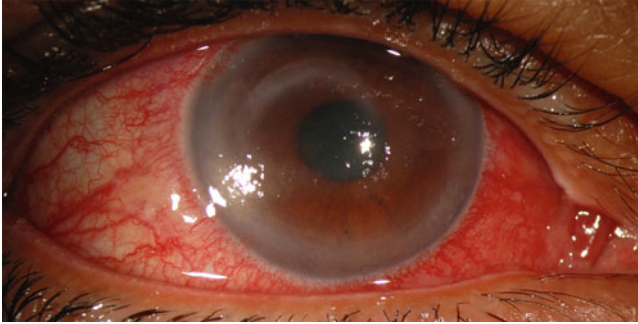


**Fig. 2.17** Keratoconus with a break in Bowman's layer

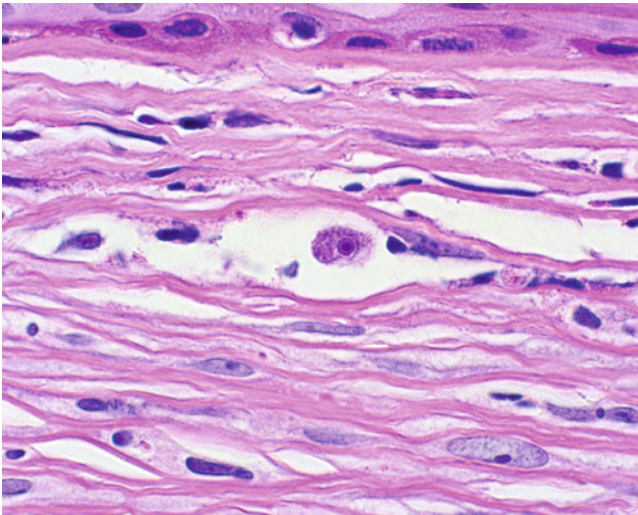


**Fig. 2.18** Keratoconus showing Descemet's layer with rupture and scroll formation

- Rupture of Descemet's membrane results in scrolls (Fig. 2.18) and corneal swelling (hydrops).
- Intraepithelial iron deposition in keratoconus is known as the Fleischer ring; this is to be distinguished from the Kayser–Fleischer ring of copper deposition in Descemet's membrane seen in Wilson's disease.
- Deep anterior lamellar keratoplasty (DALK) is a surgical procedure sometimes used for keratoconus. This often results in a “Swiss-cheese-like” stromal artifact from air injection as part of the surgical technique. DALK removes the central corneal stroma and spares the removal of Descemet's membrane and corneal endothelium; thus, they are not part of these specimens, unless the surgeon determines a complete PK (penetrating keratoplasty) is indicated.



**Fig. 2.19** Clinical image of a red eye with a corneal stromal infiltrate of *Acanthamoeba* keratitis

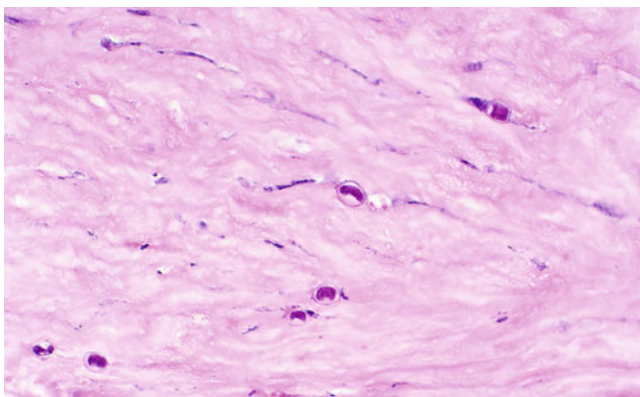


**Fig. 2.20** *Acanthamoeba* keratitis showing the classic appearance of the trophozoite

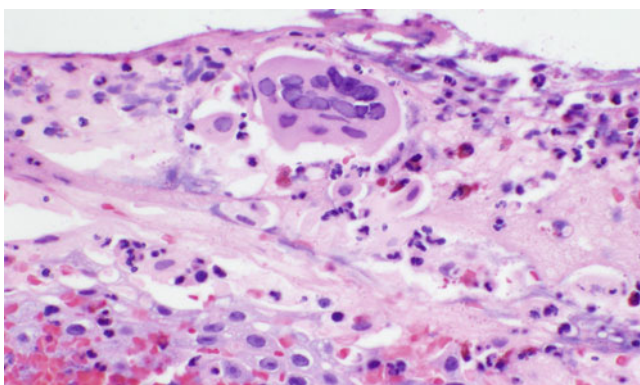
#### 4. Infectious disease of the cornea:

Keratitis refers to inflammation of the cornea. Keratitis can be infectious or noninfectious. These are some of the classical cases of infectious keratitis you might see or be asked about:

- *Acanthamoeba* keratitis (Figs. 2.19, 2.20, 2.21)
- Bacterial keratitis:
  - *Staphylococcus aureus*
  - *Streptococcus*
  - *Pseudomonas*



**Fig. 2.21** Multiple Acanthamoeba cysts are seen here

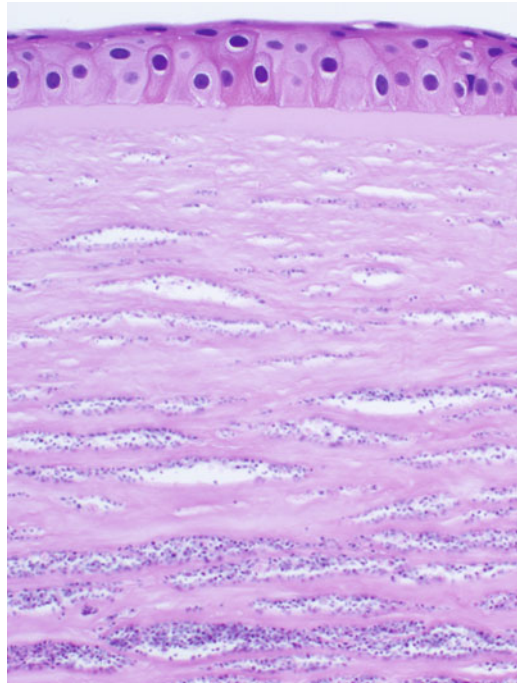


**Fig. 2.22** Herpes simplex keratitis. Shown is a multinucleated giant cell with a glassy appearance of the virally infected nuclei

- Fungal keratitis:
  - *Aspergillus*
  - *Candida*
  - *Fusarium*
- Herpes simplex keratitis (Fig. 2.22)
- Herpes zoster keratitis
- Microsporidiosis (Fig. 2.23)
- Mycobacterial keratitis: *Mycobacterium chelonae*
- Onchocerciasis



**Fig. 2.23** Cornea with microsporidiosis involving the stroma but sparing the epithelium. Note the absence of inflammation

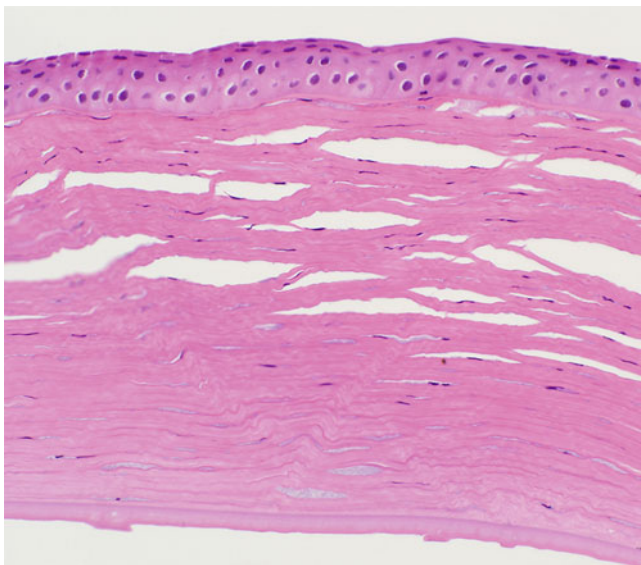


## 5. Corneal dystrophies:

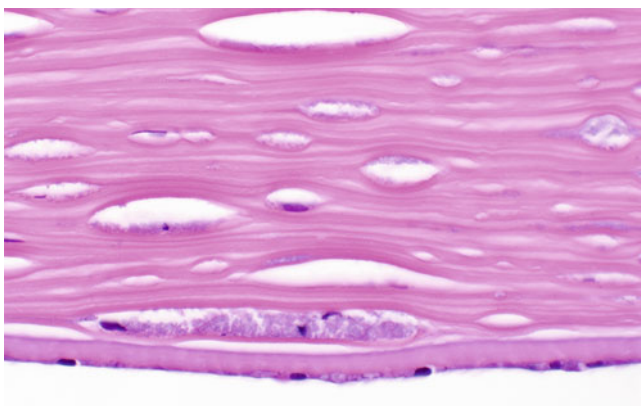
- The corneal dystrophies are a group of inherited disorders in which characteristic deposits accumulate within the cornea.
- The corneal dystrophies are typically bilateral.
- The transforming growth factor- $\beta$ -induced gene (*TGFBI*)/*BIGH3* maps to chromosome 5q31 and codes for the protein keratoepithelin. Mutations in this gene have been implicated in the pathogenesis of corneal dystrophies including some types of granular and lattice dystrophy. The molecular genetics of the corneal dystrophies is ever expanding.
- A few of the more commonly encountered corneal dystrophies are listed here with their characteristic deposit and histochemical stain:

### Dystrophy/deposit/histochemical stain:

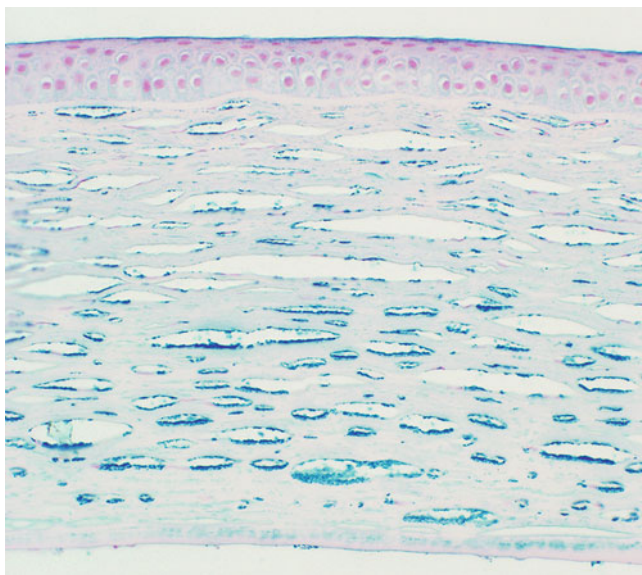
- Macular dystrophy/mucopolysaccharides/alcian blue (Figs. 2.24, 2.25, 2.26)
- Granular dystrophy/hyaline material/Masson trichrome (Figs. 2.27, 2.28, 2.29)
- Lattice dystrophy/amyloid/Congo red (Figs. 2.30, 2.31)



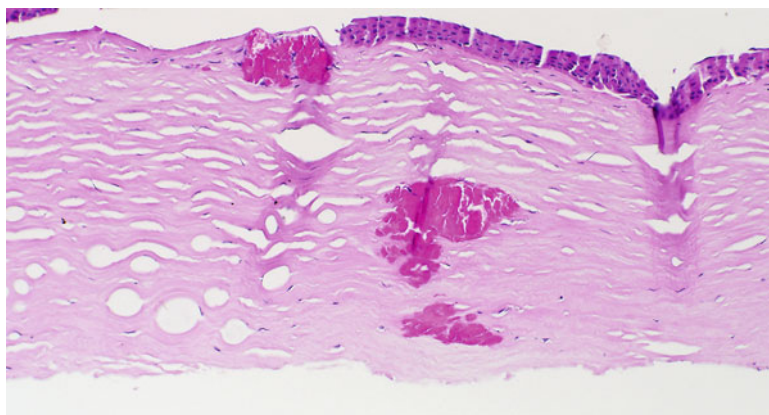
**Fig. 2.24** Macular corneal dystrophy showing stromal deposits. Guttae may be seen in cases of macular corneal dystrophy, and a few are present in this image



**Fig. 2.25** Macular corneal dystrophy showing stromal deposits at higher magnification

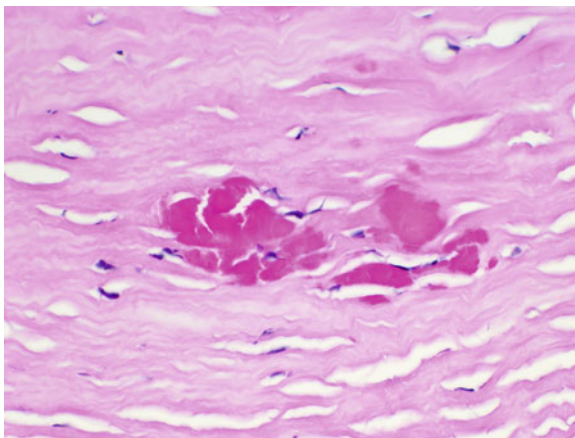


**Fig. 2.26** Alcian blue stain highlighting the mucopolysaccharide deposits in macular corneal dystrophy

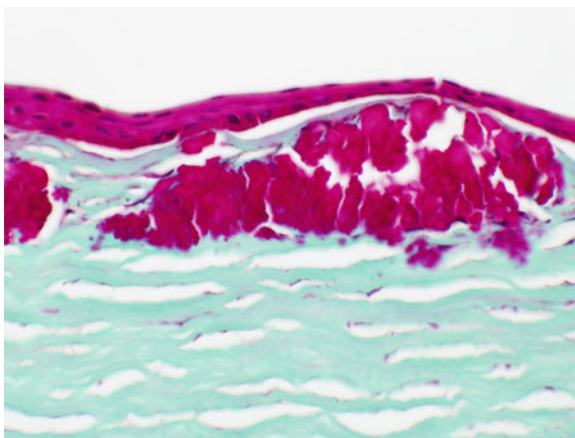


**Fig. 2.27** Granular corneal dystrophy showing typical stromal deposits

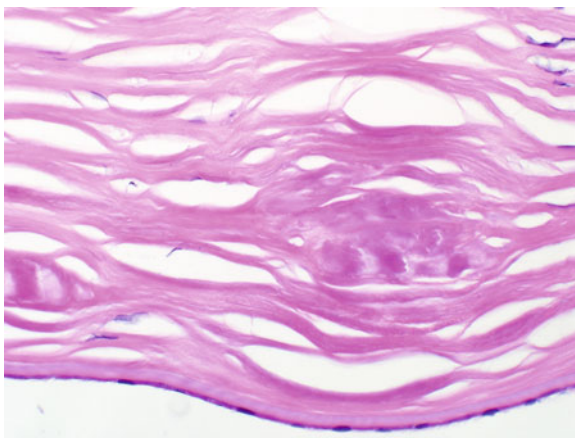
**Fig. 2.28** Granular corneal dystrophy stromal deposits



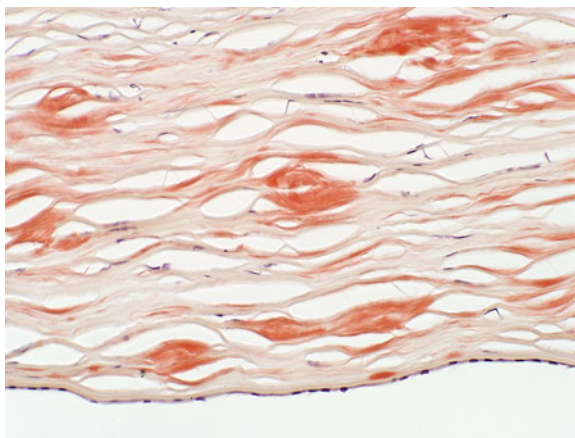
**Fig. 2.29** Masson trichrome stain highlights the hyaline deposits in granular corneal dystrophy



**Fig. 2.30** Lattice corneal dystrophy showing typical amyloid deposits in the deep stroma



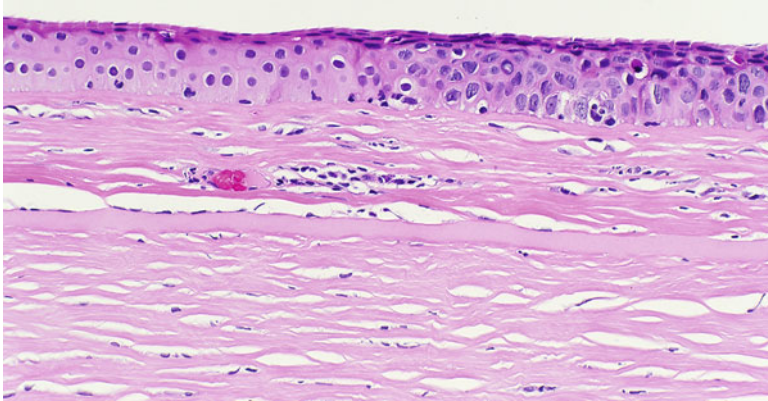
**Fig. 2.31** Congo red stain highlighting amyloid deposits in lattice corneal dystrophy



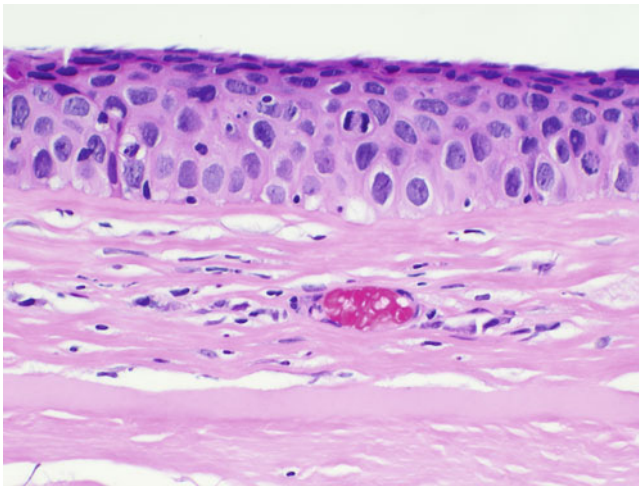
Corneal dystrophy pitfalls:

- Immunoglobulin deposits may accumulate in the cornea in cases of monoclonal gammopathy of unknown significance (MGUS). Some of the deposits may mimic those of granular corneal dystrophy. You need to be aware of the clinical history.
  - Not all amyloid deposition in the cornea is due to lattice corneal dystrophy. Amyloid deposition may occur in primary amyloidosis or as a secondary occurrence from trauma, infection, and other causes.
  - Granular corneal dystrophy type II (Avellino dystrophy) has features of both granular and lattice dystrophy.
6. Corneal neoplasia is rare. The cornea is usually secondarily involved from conjunctival or eyelid neoplasia. A few of the more common neoplasms you may encounter in the cornea include:
- Squamous cell carcinoma (Figs. 2.32, 2.33)
  - Malignant melanoma
  - Sebaceous carcinoma with intraepithelial spread
7. Retrocorneal pathology:
- Fibrous membranes adherent to Descemet's membrane.
  - Anterior synechiae (iris tissue adherent to Descemet's membrane).
  - Epithelial ingrowth or downgrowth. This is an often refractory and potentially blinding process whereby surface epithelium extends through a defect (e.g., a corneal incision) and proliferates along the posterior surface of Descemet's membrane (Fig. 2.34a, b). A cytokeratin immunohistochemical stain is useful to identify the epithelium (Fig. 2.35).





**Fig. 2.32** Low-magnification view of corneal intraepithelial neoplasia. Contrast the dysplastic epithelium on the right side of the figure with the normal epithelium on the left side of the figure

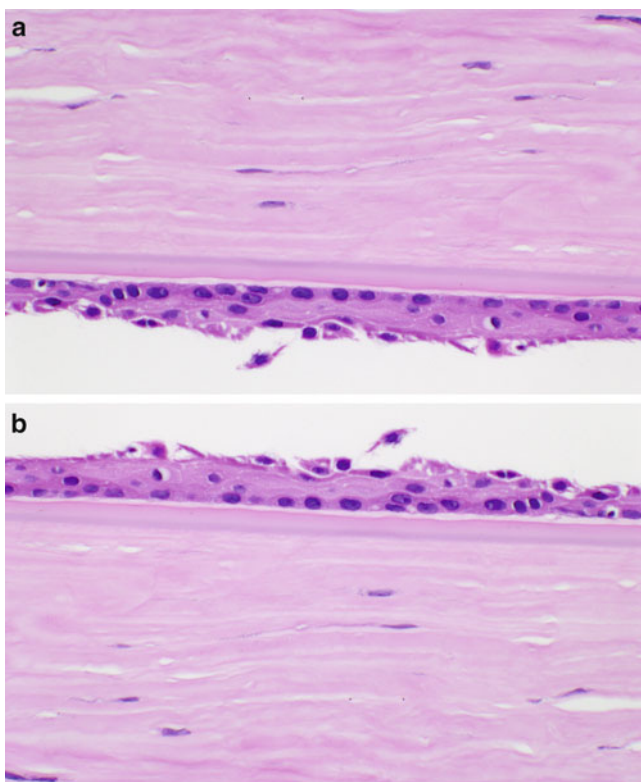


**Fig. 2.33** Higher-magnification view of cornea intraepithelial neoplasia showing cytological atypia and a mitotic figure. Also seen is a thick layer of fibrovascular pannus between the epithelium and the homogeneous pink Bowman's layer (same as Fig. 2.5)

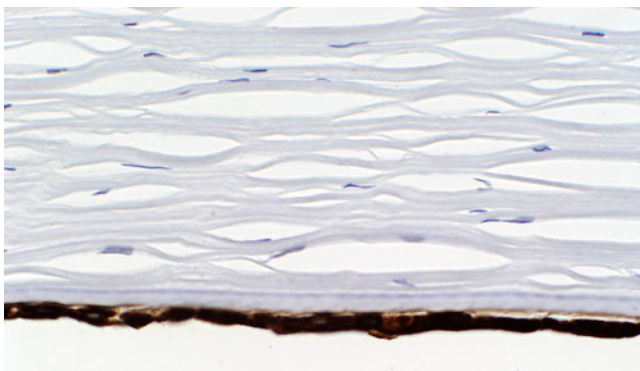
#### 8. Corneal incisions:

Penetrating keratoplasty, LASIK, and radial keratotomy are three corneal procedures, each of which is recognizable by a characteristic and histologically identifiable incisional scar:

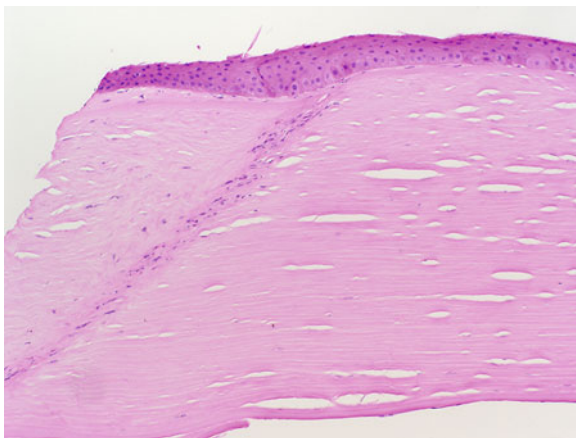
- Penetrating keratoplasty: peripheral linear incision (Fig. 2.36)
- LASIK incision: superficial/stromal horizontal incision (Figs. 2.37, 2.38)
- Radial keratotomy: multiple vertical incisions (Figs. 2.39, 2.40)



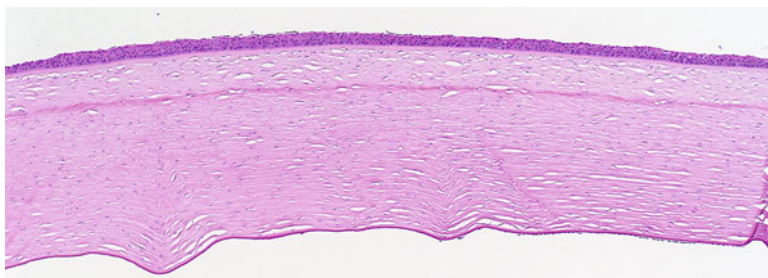
**Fig. 2.34** (a) Epithelial downgrowth showing posterior cornea stroma and Descemet's membrane with a retrocorneal layer of squamous epithelium. The grayish fetal/gestational banded layer of the anterior Descemet's membranes is a clue that it is Descemet's membrane and not Bowman's layer. The pitfall in this case is if the orientation is rotated (b) and you thought this was Bowman's layer, you might mistake this as normal surface corneal epithelium



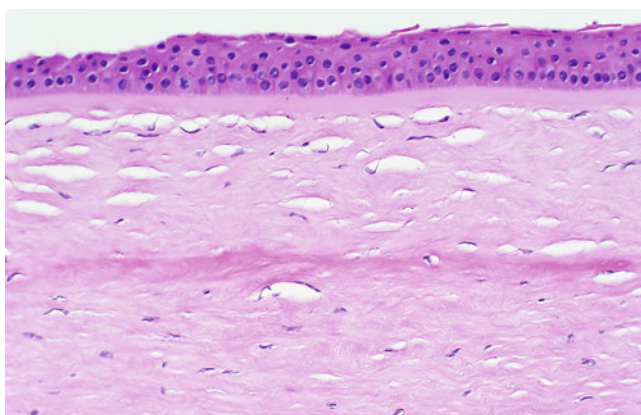
**Fig. 2.35** Squamous epithelium highlighted by a cyokeratin immunohistochemical stain in a case of epithelial downgrowth



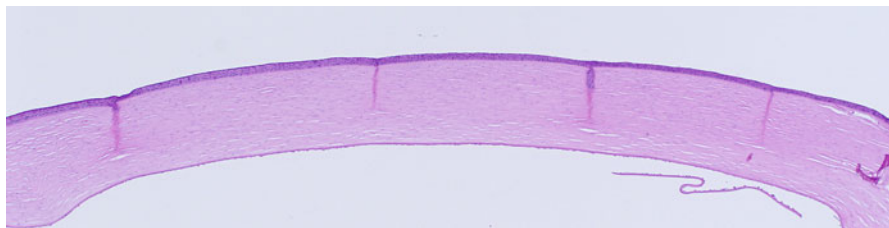
**Fig. 2.36** Failed corneal graft with a peripheral linear scar from a penetrating keratoplasty incision



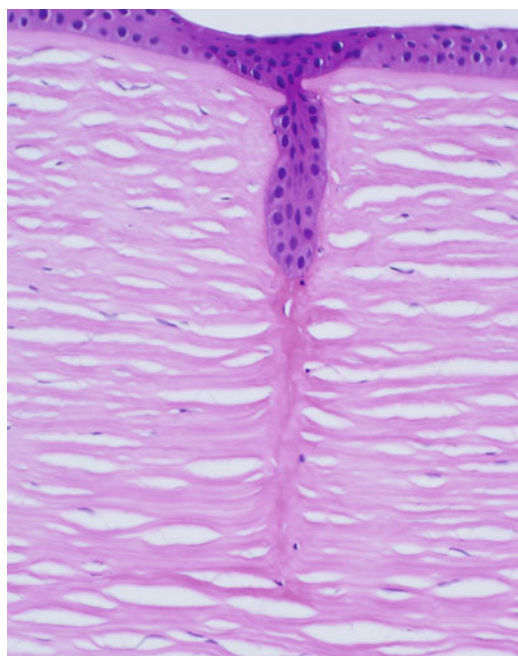
**Fig. 2.37** Cornea showing stroma with a horizontal scar in the stroma following LASIK procedure



**Fig. 2.38** Higher magnification showing a horizontal corneal stromal scar following LASIK procedure



**Fig. 2.39** Cornea with vertical scars (usually four) following the radial keratotomy procedure



**Fig. 2.40** Higher magnification of cornea with a vertical scar from the radial keratotomy procedure and with epithelial extension into the wound

Ophthalmic Pathology

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