The cornea

Gross Anatomy:

The cornea is the anterior continuation of the sclera; it forms 1/6th of the outer layer of eyeball. It is a transparent structure; its function is facilitating entrance and focusing the light rays on the retina. It represents the most important refractive organ in the eye.

Applied anatomy:

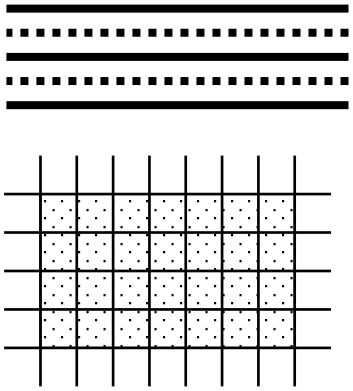
The cornea consists of the six following layers: (from anterior to posterior or from external to internal)

1- The epithelium: is stratified (multiple cell layers), squamous and non-keratinized. If, there is any damage, it regenerates *without any scarring.*

This layer is composed of basement membrane posteriorly and attaching to it a layer of columnar cells by hemidesmosomes, then 2-3 layers of wing cells and at anterior-most, there are 2 layers of squamous cells.

2- Bowman's layer:

This is acellular superficial layer of the stroma which *scars* when damaged.



3- The Stroma: makes up 90% of the corneal thickness. It is composed of regularly oriented layers of collagen fibrils whose spacing is maintained by glycosaminoglycan (GAG) ground substance, the distance between the fibrils is slightly less than half of the wave length of incident light, so the reflected rays from the cornea will one cancel the other by the process of *destructive interference* and the cornea appears transparent as long as the lattice arrangement was maintained (Maurice theory).

4- Dua's Layer: new layer discovered recently by Harminder Singh Dua's, university of Nottingham in 2013 during corneal graft surgery. It is 15 micrometers in thickness, fourth caudal layer, and located between the corneal Stroma and Descemet**'s** membrane. Anatomically, it is like Stroma and can be separated with the Descemet's membrane from the anterior part of stroma if air is injected within stromal layer. Rapture of this layer lead to passage of

aqueous from AC into Stroma in a condition called acute hydrops of patients with keratoconus.

5- Descemet's membrane: it is composed of a fine latticework of collagen fibrils. It is the basement membrane of the endothelial cells.

6- The endothelium:

It consists of a single layer of hexagonal cells. It *plays a vital role in maintaining corneal transparency & deturgescence*, as water composes 70% of cornea that makes it relatively dehydrated as compared with other body tissues where water might composes even 98% of them. It has an *active pump mechanism* that removes the fluid from Stroma. Normal cell count is 2500-3000 cell/ mm^2. With advancing age, the number of endothelial cells decreases and they are non-regenerative cells, therefore the neighboring cells enlarge to fill the gaping space.

The cornea is transparent for the following reasons:

1- The epithelium is not keratinized.

2- The stroma is regularly oriented. (Maurice theory)

3- The endothelium has active pump, it pushes the fluid into aqueous and it acts as barrier to prevent entrance of aqueous inside the cornea.

4- The corneal nerves are unmylinated.

5- It contains NO blood vessels.

6- It contains NO pigments (as melanin).

Signs of corneal diseases:

1- Epithelial signs:

a- Punctate epithelial erosions (PEE):

Are tiny, slightly depressed, epithelial defects (micro-ulcers seen by slit-lamp), which stain with fluorescein.

***** Fluorescein is vital extracellular stain. It stains living tissue e.g. the base of ulcer, while Rose-Bengal is non-vital intracellular stain. It stains dead cells at the margin of ulcer and mucus.

causes: vernal keratoconjunctivitis, poorly fitting contact lens, dry eyes, decreases corneal sensation (as in trigeminal nerve palsy or after herpes simplex viral keratitis), exposure to ultraviolet (e.g. in wilding flash), corneal exposure and toxicity from drops (e.g. Amino glycosides).

b- Punctate epithelial keratitis (PEK):

Is the hallmark of viral infections, it is characterized by granular, opalescent, swollen epithelial cells stained with rose Bengal stain but not fluorescein.

c- Epithelial edema:

It is a sign of *endothelial* decompensation or *severe and sudden* elevation of intraocular pressure (as that occurring in acute glaucoma as IOP is raised leading to edema that affects the vision).

d- Filaments:

Small, comma-shaped mucus strands lined with epithelium (one end attached to the epithelial cornea and the other is free), which stain well with Rose-Bengal stains.

Causes:

Keratoconjunctivitis sicca (dry eye), recurrent erosion syndrome, prolong eye patching, corneal exposure, diminished corneal sensation and herpes zoster ophthalmicus.

e- Pannus:

It is inflammatory or degenerative sub-epithelial ingrowths of fibrovascular tissue from limbus.

2- Stromal signs:

a- Stromal infiltration:

Focal areas of active stromal inflammation composed of accumulations leucocytes and cellular debris. These focal areas are granular, gray-white opacities within the stroma.

Causes:

i- Non-infectious (Antigen sensitivity): e.g. contact lens wear and marginal keratitis.

ii- Infectious keratitis: e.g. bacteria, viruses, fungi and protozoa.

b- Stromal oedema:

Causing disturbance of regularly arranged collagen fibers (or fibrils) that affects eye vision by disturbance of corneal transparency (according to Maurice theory), so it affects optically empty spaces between stromal lamellae associated with increase corneal thickness and decreased its transparency.

Causes:

Keratoconus, Fuch's dystrophy (Hereditary abnormal endothelium or decreased number of endothelium cells) and surgical damage to the corneal endothelium (iatrogenic).

c- Vascularization:

Causes: Wide variety of corneal disorders, e.g. microbial keratitis, chemical burns, trauma, TB, syphilis and autoimmune Keratoconjunctivitis (Cicatricial Pemphigoid and Stevens Johnson syndrome).

3- Descemet's membrane signs:

a- Breaks in the Descemet's membrane:

Causes: Corneal enlargement e.g. congenital glaucoma, birth trauma and keratoconus. It leads to influx of aqueous causing stromal oedema.

b- Folds in the Descemet's membrane (Striate keratopathy):

Causes: Surgical trauma, ocular hypotony, stromal inflammation and oedema.

***** Normal IOP is 10-21 mm Hg, if it is less than 6 mm Hg then it is hypotony.

Microbial keratitis

1- Bacterial Keratitis:

Predisposing factors:

- Bacteria capable of penetrating intact epithelium include Neisseria gonorrhoea and H. influenzae.
- Other bacteria are capable of producing keratitis only after compromisation of *epithelial integrity* with the following factors:

a- Contact lens wear: is the most common predisposing factor in patients with previously normal eye therefore meticulous lens hygiene is vital.

b- Pre-existing corneal disease: such as trauma (usually after surgery of cataracts), bullous keratopathy (if there is endothelial decompensation it leads to oedema that may persist and leads to formation of bullae of fluid in the stroma), exposure keratopathy and diminished corneal sensation.

c- Other factors: chronic blepharoconjunctivitis, chronic dacryocystitis, dry eyes, topical steroid therapy and hypovitaminosis A.

Clinical Features:

Symptoms:

These are: foreign body sensation, photophobia, *blurring of vision*, pain, eyelid oedema and discharge.

Signs:

- Conjunctival and circumcorneal injection (almost always some sort of anterior uveitis is associated with Keratitis).
- Epithelial defects associated with an infiltrate around the margin and base.
- Enlargement of the infiltrate associated with stromal oedema.
- Secondary sterile anterior uveitis with hypopyon.
- Progressive ulceration may lead to corneal perforation and bacterial endophthalmitis (involvement of all intraocular tissues).

Differential diagnosis of bacterial keratitis:

a- Fungal keratitis.

b- Acanthamoeba keratitis.

c- Stromal necrotic herpes simplex keratitis.

d- Marginal keratitis.

e- Sterile inflammatory corneal infiltrates associated with contact lens wear.

Treatment:

a- Topical antibiotics:

- Initial instillation of fortified antibiotic is at hourly intervals.
- If response is favourable, frequency is decreased to 2-hourly during waking hours.
- Then fortified drops can be replaced by weaker commercial preparations, which are then tapered and eventually discontinued.

b- Oral ciprofloxacin (750mg twice daily):

- Copious secreted in the tears.
- Lipid soluble and has excellent intraocular penetration.

c- Atropine: it prevents the formation of posterior synechiae (adhesions between papillary margin and lens).

- Reduce pain from ciliary spasm and associated uveitis.

d- Steroid therapy: It is controversial, the potential benefits of topical steroids in reducing stromal necrosis and scaring should be

weighed against decreased fibroblast activity and increased risk of perforation.

We can use it only when cultures become sterile and there is clear evidence of improvement (7-10 days after initial treatment).

2- Fungal keratitis:

Rare infection but have devastating effects, the most common pathogens are:

- Filamentous fungi (Asperigillus and Fusarium species): Infection occurs after trauma by wood usually.
- Candida albicans: Usually infects immuno-compromised patients.

Clinical features:

Symptoms:

- Gradual onset of foreign body sensation, Photophobia, Blurred vision (due to opacification of cornea, whether due to epithelial or stromal edema) and discharge (mucopurulent).

**** Progression is much slower and less painful than in bacterial keratitis.***

Signs:

Filamentous keratitis:

- A grayish, stromal infiltration with indistinct margin.
- Surrounding, satellite, feathery, finger-like lesions (extensions).
- Hypopyon (pus in the anterior chamber).

***** There is always some sort of iritis associating keratitis.

Candida keratitis:

- A yellow-white, stromal infiltration associated with dense suppuration similar to bacterial keratitis.

Treatment:

a- Topical treatment:

Filamentous: Natamycin 5%, and may add Amphotericin 0.15%.
Candida: Imidazole 1% or Flucytosine 1%.
} **for 6 weeks**

b- Systemic antimycotics: e.g. Ketoconazole (tablets) or Itraconazole in severe keratitis or endophthalmitis.

c- Therapeutic penetrating keratopathy: In unresponsive cases (if there is resistant infection).

3- Viral keratitis:

<u>A- Herpes simplex keratitis</u>:

Basic concepts:

- HSV is a DNA virus, which infects only human.
- Infection with HSV is common, up to 90% of the population is sero-positive for HSV-1 antibodies although most infections are sub-clinical.
- HSV-1 predominantly causes infection above the waist (face, lips and eyes).
- HSV-2 typically causes venereally acquired infection below the waist (genital herpes).
- Rarely HSV-2 may be transmitted to the eye through infected genital secretions, either venereal or at birth.

i- Primary infection:

It is usually occur in early childhood through droplet (the most common route) or direct inoculation. It may be sub-clinical or may cause mild fever, malaise and URT infection. In immuno-compromised subject, the infection may become generalized and life threatening.

ii- Recurrent disease:

- Following primary infection, the virus travels up to the ganglion (trigeminal **"Gasserian"** for HSV-1 and spinal for HSV-2), where it lies in a latent state.
- This latent state may subsequently reverse and the virus re-activates, replicates & travels down to its target tissue causing recurrent disease (genital herpes, herpes labialis & herpes keratitis).

Primary ocular infection:

- Typically occurs in children between ages of *6 months- 5 years*, and may be associated with generalized symptoms.

Signs:

- Skin vesicles typically involve the lids and periorbital area.
- Acute, unilateral, follicular conjunctivitis associated with tender lymphadenopathy.
- Secondary canalicular obstruction may occur (the infection by itself causes lacrimation, but if it is complicated by secondary canalicular obstruction this will cause epiphora).
- Keratitis is uncommon.

Treatment:

- Aciclovir (Zovirax®) eye ointment five times a day for three weeks to prevent keratitis.

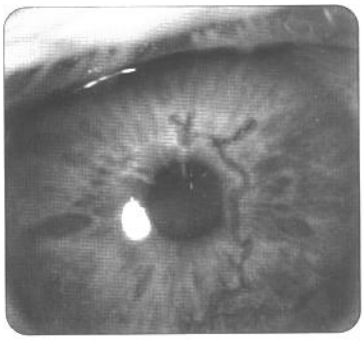
Recurrent herpes simplex ocular disease (Epithelial keratitis):

Presentation:

- Occurs at *any age*.
- Mild discomfort.
- Watering eye.
- Blurring of vision.

Signs: (in chronological)

- Opaque epithelial cells or punctuate epithelial keratitis.
- Central desquamation results in a linear-branching (dendritic) ulcer. ☛



- Decreased corneal sensation (as it involves the nerves).
- Anterior stromal infiltration under the ulcer.
- Progressive centrifugal (from the center outwards) enlargement may result in a large epithelial defect with a geographical or amoeboid configuration, especially in the context of injudicious topical steroid therapy.
- Following healing, there are persistent linear-branching shapes, which represent waves of healing epithelial cells.

Differential diagnosis of dendritic ulceration: (pseudo-dendritic ulceration)

a- Herpes Zoster keratitis.
b- Healing corneal abrasion.
c- Soft contact lens wear.
d- Acanthamoeba keratitis.
e- Toxic keratopathies (kertitis medicamentosa).

Treatment of Herpes simplex epithelial keratitis:

a- Topical: without treatment, 50% resolves spontaneously, with treatment, the cure rate is 95%.

i- Aciclovir 3% ointment, five times daily for 2 weeks.
ii- Ganciclovir 0.15% (Virgan®) gel: it is a new preparation which is used five times daily and is as effective as Aciclovir.
iii- Trifluorothymidine 1% drops: it is used every 2 hours during the day for 2 weeks , like Aciclovir, it has a cure rate of 95%, but it is more toxic.
b- Debridement: Which is used in dendritic but not geographic ulcers in patients who are: non-compliant, allergic to drugs, when antiviral agents are not available and resistant cases. Drugs are ideally used after debridement. Cure rate is above 50% and below 95%.

B- Herpes Zoster ophthalmicus (HZO):

It is a disease caused by Varicella Zoster virus (VZV), which is morphologically identical to HSV but different antigenically and clinically.
Chickenpox (Varicella) and Zoster are different conditions caused by the same virus, Zoster mainly affects elderly patients. Primary disease occurs during childhood is usually chickenpox after an attack of chickenpox, virus remains dormant in sensory root ganglia. Later, it reactivates and migrates back down sensory nerves to the skin and eye causes the characteristic lesions. Herpes zoster in a young person makes us to think about either immune compromised patient or one with AIDS.
- Approximately, 15% of all cases of herpes zoster affect the ophthalmic division of the trigeminal nerve (HZO).
***** If we have crust lesion at the tip of the nose "Hutchinson sign", it indicates ocular involvement (Because the distribution of the ophthalmic division of the trigeminal nerve)
Ocular involvements occur by the following mechanisms:
i- Direct viral invasion, which results in epithelial keratitis and conjunctivitis.
ii- Secondary inflammation.
iii- Occlusive vasculitis.
iv- Autoimmune: stromal keratitis, uveitis, scleritis and episcleritis, all are not due to invasion of the virus directly.
v- Hypoaesthesia (due to denervation of the cornea) may result in neurotrophic keratitis.

systemic features:

 Influenza-like illness: Fever, malaise, headache and depression.

 Herpetic neuralgia: Varies from a superficial itching or burning sensation to severe deep boring or lancing pain.

 Skin rash: Progress rapidly from papules →vesicles →pustules → crust and scar formation.

Ocular Features:

Keratitis, conjunctivitis, episcleritis, scleritis and anterior uveitis.

Neurological Complication:

 Cranial nerve palsies: 3rd, 4th or 6th cranial nerve palsy.

 Optic neuritis.

 Encephalitis.

 Contralateral hemiplegia.

Treatment:

 Systemic: Valaciclovir 1g t.i.d for 7 days

Or Famciclovir 250mg t.i.d for 7 days.

 Topical: **a- Skin:** Steroid + Antibiotics skin cream, e.g. Hydrocortisone 1% with Fusidic acid 2%.

b- Eye: Herpetic ulcer →Aciclovir ointment.

Autoimmune → Topical steroid. Sometimes, both of them are used.

* Unlike herpes simplex keratitis, here we can use steroids from the beginning of the treatment accompanying other medications, as the mechanisms of inflammation are different (points 2 to 5 in mechanisms of ocular involvements).

Keratoconus

It is a progressive disorder in which the cornea assumes an irregular conical shape. The onset is at around puberty with slow progression thereafter and become stationary at any time (age).

In keratoconus, there is progressive and irregular changes in the cornea making it more convex and make it have a more conical shape, also there is severe thinning of the cornea that the cornea may reach 1/3 its original thickness (about 0.16mm). These deformities will

affect the visual acuity (as the cornea is the most important focusing power) leading to myopia and irregular astigmatism.

Presentation:

1- Unilateral impairment of vision due to progressive myopia and regular astigmatism, which subsequently becomes irregular.

2- Frequent changes in spectacle prescription or decrease tolerance to contact lens (due changes in the shape of cornea).

3- The fellow eye usually has normal vision with negligible astigmatism at presentation because of the asymmetrical nature of the condition. Most ***[not all]*** of the cases are bilateral.

Signs of keratoconus:

The hallmarks are: **1-** Central or paracentral stromal thinning.
2- Apical protrusion.
3- Irregular astigmatism.

1- Direct ophthalmoscope from a distance of one foot shows an oil droplet reflex.

2- Retinoscpoy (used for diagnosis of refraction errors) shows an irregular reflex.

3- Slit-lamp shows very fine, vertical, deep **stromal** striae "Vogt's lines" due to protrusion of cornea.

4- Epithelial iron deposits, best seen with a cobalt blue filter, may surround the base of the cone (Fleischer ring).

5- Later, there is progressive corneal thinning as little as one third of normal thickness, associated with poor visual acuity (irregular myopic astigmatism).

6- Bulging of the lower lid in down gaze "Munson sign".

7- Acute hydrops: It is an acute influx of aqueous into the cornea as a result of a rupture in Descemet's membrane and Dua's layer →sudden decrease in visual acuity associated with discomfort and watering (lacrimation).

The break usually heals within 6-10 weeks and the corneal oedema clears, but a variable amount of stromal scarring may develop.

Management:

1- Spectacles: In early cases to correct regular and mild irregular astigmatism.

2- Rigid contact lenses: For higher degree of irregular astigmatism, they only reshape the cornea, there refractive power is zero.

3- Keratoplasty: In advanced progressive disease, especially with significant corneal scarring.

4- intracorneal ring segment (Intacs) implantation: which is done by using laser or mechanical channel creation. These rings which are inserted inside these corneal channels can change the abnormality in the curvature of cornea and causing moderate visual improvement.

5- corneal collagen cross-linking: is done by using riboflavin (vitamin B2) drops to photosensitizer the eye followed by exposure to ultraviolet-A light. This a newer treatment which offers promise of stabilization or reversal of ectasia in at least some patients. It can combined with Intacts insertion.

Note: lasik is contraindicated in correction of myopia and astigmatism induced by keratoconus because it lead to more thinning and ectasia of the cornea and sever deterioration of vision later on.

Keratoplasty (Corneal transplantation, Grafting)

It is an operation in which abnormal corneal host tissue is replaces by healthy donor cornea, it is either ***Full-thickness*** (Penetrating Keratoplasty) or ***Partial thickness*** (Lamellar Keratoplasty and endothelial Keratoplasty).

1-Penetrating keratoplasty: *Indications:*

a- Optical keratoplasty: To improve visual acuity indicated in e.g. keratoconus, dystrophies, degenerations, scarring of cornea and pseudophakic bullous keratopathy (oedema due damage of the endothelium after implantation of intraocular lens).

***** The most common indication in western countries is pseudophakic bullous keratopathy.

b- Tectonic keratoplasty: To restore corneal integrity, indicated in stromal thinning and descemetoceles (A **descemetocele** is an outward displacement, or ectasia, of Descemet's membrane in an area where the overlying corneal stroma has been destroyed by inflammation).

c- Therapeutic keratoplasty: Removal of infected corneal tissue in eye unresponsive to antimicrobial therapy.

d- Cosmetic keratoplasty: Rare indication, to improve the appearance of the eye.

2- Lamellar keratoplasty:

It involves partial-thickness excision of the corneal epithelium and stroma so that the endothelium and part of the deep stroma are left behind.

Indications:

a- Opacification of the superficial one-third of the corneal stroma.

b- Marginal corneal thinning or infiltration as in recurrent pterygium.

c- Local thinning or Descemetocele formation.

d- keratoconus because the endothelium is normal in this condition.

3- Endothelial Keratoplasty:

It involves partial thickness excision of the corneal endothelium, Descemet's membrane and very thin part of stroma (Dua's layer). It is indicated when there endothelial damage e.g. pseudophakic bullus keratopathy and Fuchs endothelial dystrophy.