Herpetic Eye Disease

Brad Sutton, OD, FAAO

IU School of Optometry: Indianapolis Eye Care Center

Clinical Professor

Financial disclosures

- None

Epidemiology

- Eight known human herpes viruses
- Herpes simplex I (oral-facial-ocular), II (genital)
- Can cross infect
- Herpes viruses 6 & 7 (roseola infantum) and herpes virus 8 (Kaposi sarcoma and lymphoma)
- Varicella-Zoster, CMV, Epstein-Barr

Epidemiology

- Man is the only host
- DNA Virus
- HSK is a leading cause of corneal blindness worldwide
- 8 / 100,000 new ocular cases per year, 21 total new & recurrent per 100,000 per year (US)
- 50,000 cases of new or recurrent ocular disease each year in the US. Well over 400,000 total Americans afflicted

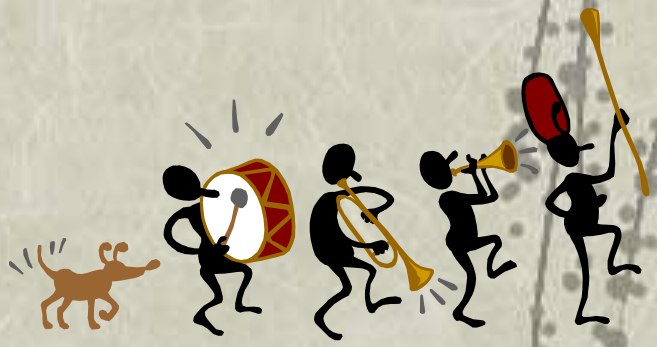
Epidemiology

- 80-90% of population in US over the age of 15 has antibodies to HSV
- Passive immunity up to 6 months old (neonatal infection still possible)
- Most have primary exposure by age 5: 5-10% clinical
- Spread by close personal contact

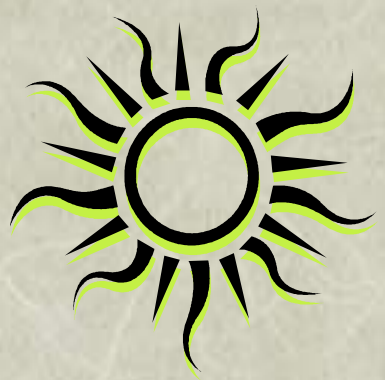
- 70% of trigeminal ganglia on autopsy harbor HSV

Epidemiology

- After primary exposure, virus lays dormant in neural ganglia (carried by axonal flow) including the trigeminal and sacral ganglia



Triggers for reactivation



- Dormant virus particles can be reactivated by various triggers
- These include stress, UV light (sun), trauma, fever, menstruation

Triggers

- Excimer laser treatment and prostaglandin eye drops have also been linked to recurrence.
- Original primary infection of trigeminal ganglion more commonly associated with gingivostomatitis than ocular disease
- Recurrence can then be either oral or ocular

Reactivation

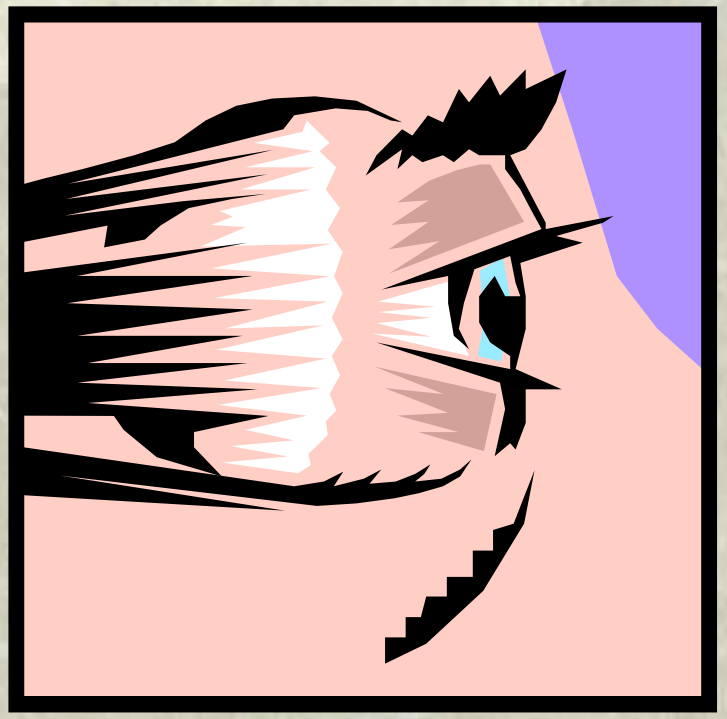
- Timolol, epinephrine, and Latanoprost have all been linked over the years to reactivation
- Several theories from decreased IOP causing retrograde axonal flow to corneal epithelial damage (trauma).
- Need to consider past herpetic infection when considering LASIK or PRK. Can perform procedure with pre and post operative antiviral therapy

Ocular findings

- There are several ocular findings associated with HSV infection. Some are more commonly seen in primary cases, others in cases of reactivation.

- Lid vesicles with edema
- Conjunctivitis
- Canaliculitis
- Epithelial lesions (dendritic, punctate, geographic)
- Stromal infiltrative disease (disciform, etc.)
- Endothelial inflammatory disease

Ocular findings



- Neurotrophic keratitis
- Uveitis
- Iris atrophy
- Acute retinal necrosis

Primary infection

- Lid lesions with edema, follicular conjunctivitis, and corneal epithelial lesions are commonly seen with primary infection. Most often blepharoconjunctivitis
- Corneal stromal disease is very rare in these instances as is iritis or endothelial disease
- Approximately 10% of cases can be bilateral…..usually in patients with atopic disease

Primary infection

- The initial ocular symptoms in adult patients usually are the result of recurrence in cases where the primary infection was asymptomatic (or at a very young age)
- Ocular symptoms in children or adolescents may represent primary infection

Primary infection

- Epithelial lesions may be in the form of a dendrite or may be fine punctate lesions which then go on to coalesce in to dendrites
- Geographic ulcers very rare in primary disease
- Dendrite formation follows a very similar course in both primary and recurrent disease

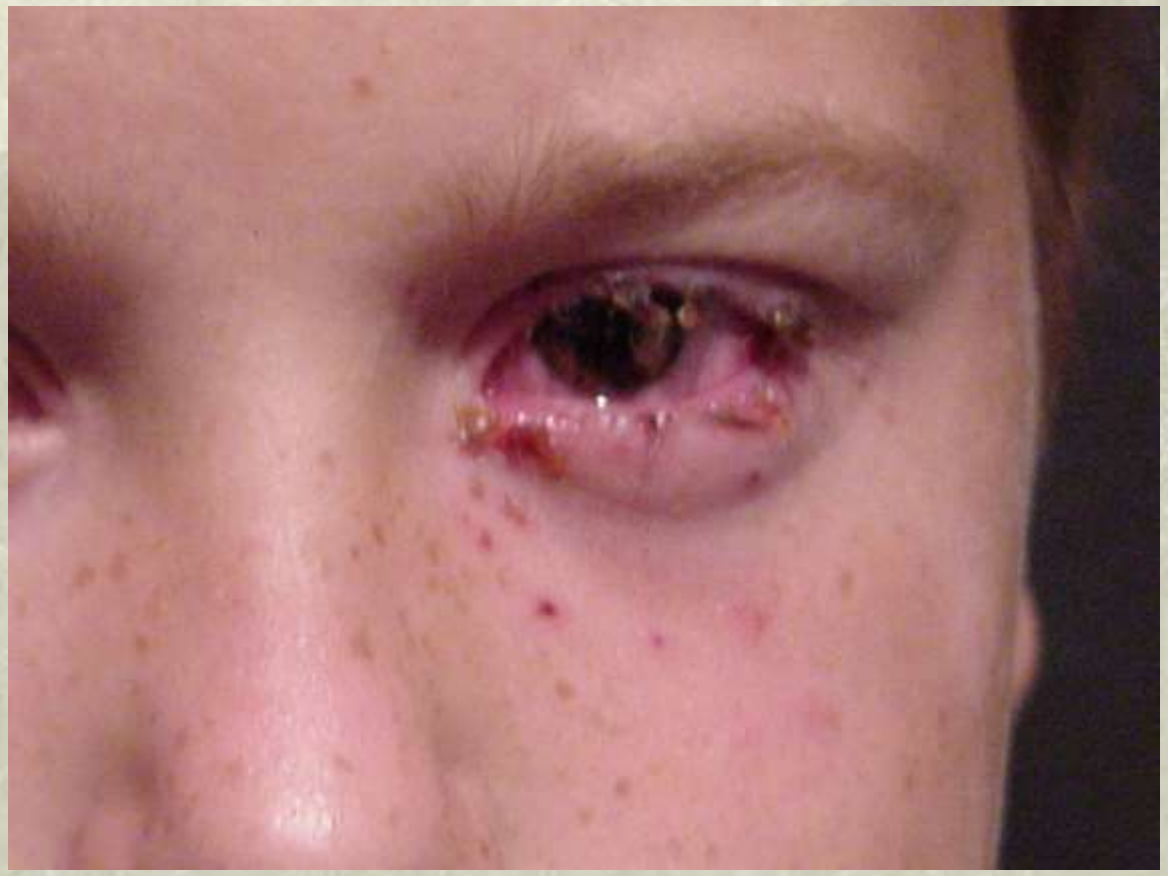
Primary infection

- Clinical symptoms occur 1-2 weeks after contact and are accompanied by fever, malaise, etc.
- Lid lesions are small, ulcerated vesicles often seen on lid margins. Can be hidden by lashes
- Fluorescein staining can help detect/outline them

Primary infection

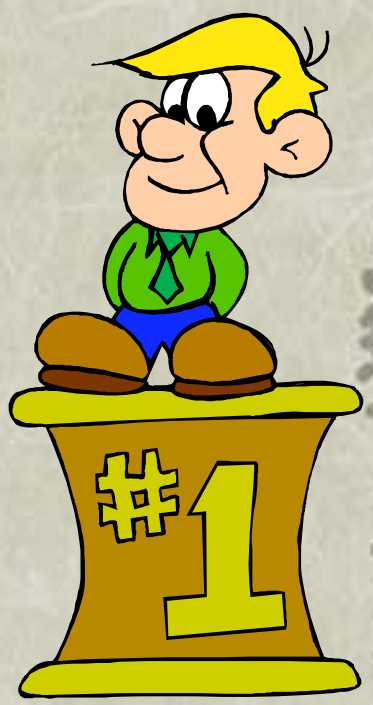
- Conjunctivitis is usually follicular with injection and chemosis
- Epithelial dendrites take on the traditional branching pattern with fluorescein staining of the center and rose bengal / lissamine green staining of the edges and terminal end bulbs

Lid lesions and conjunctivitis



Primary infection

- Diagnosis can be confirmed by the presence of corneal hypesthesia (takes time)
- Limbal dendrites are often more refractory to treatment than central dendrites
- Disease process is self limiting but treatment is usually undertaken to improve symptomotology and decrease the likelihood of sight-threatening corneal scarring



Secondary/recurrent infection

- Reactivation can lead to several ocular complications
- Epithelial disease mimics that seen in primary infection with the exception that geographic or “megaherpetic” lesions are possible
- Infected epithelial cells can release VEGF leading to corneal neovascularization

Secondary/recurrent infection

- Stromal inflammatory disease is common in secondary cases including disciform keratitis. Necrotizing more rare
- Stromal disease is an inflammatory reaction and is the main cause of scarring related vision loss……may not represent replicating virus
- CD4 T cell mediated inflammation

Recurrent infection

- Mild iritis is often seen
- Sectoral iris atrophy accompanied by iritis / trabeculitis and an increase in IOP can be seen even in the absence of corneal disease. Can present as Possner-Schlossman syndrome
- 80% of such cases caused by HSV, 20% by VZV. CMV also a cause
- Endothelitis (with or without trabeculitis)

Recurrent infection

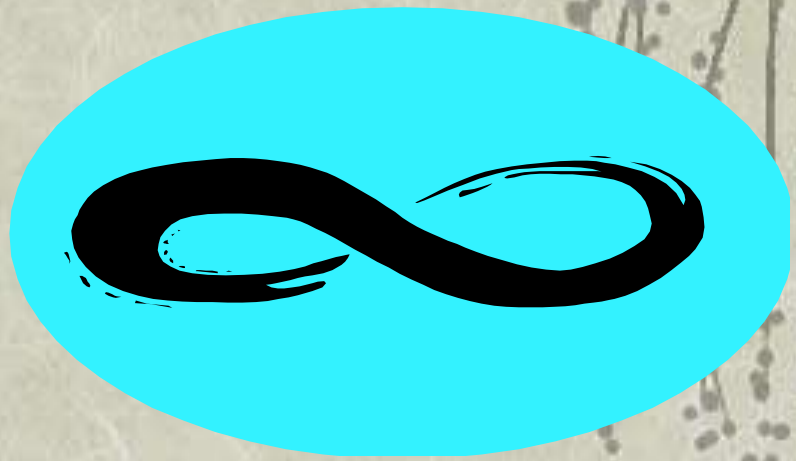
- Tear production is often reduced
- Due to decreased corneal sensitivity and inhibited feedback mechanism

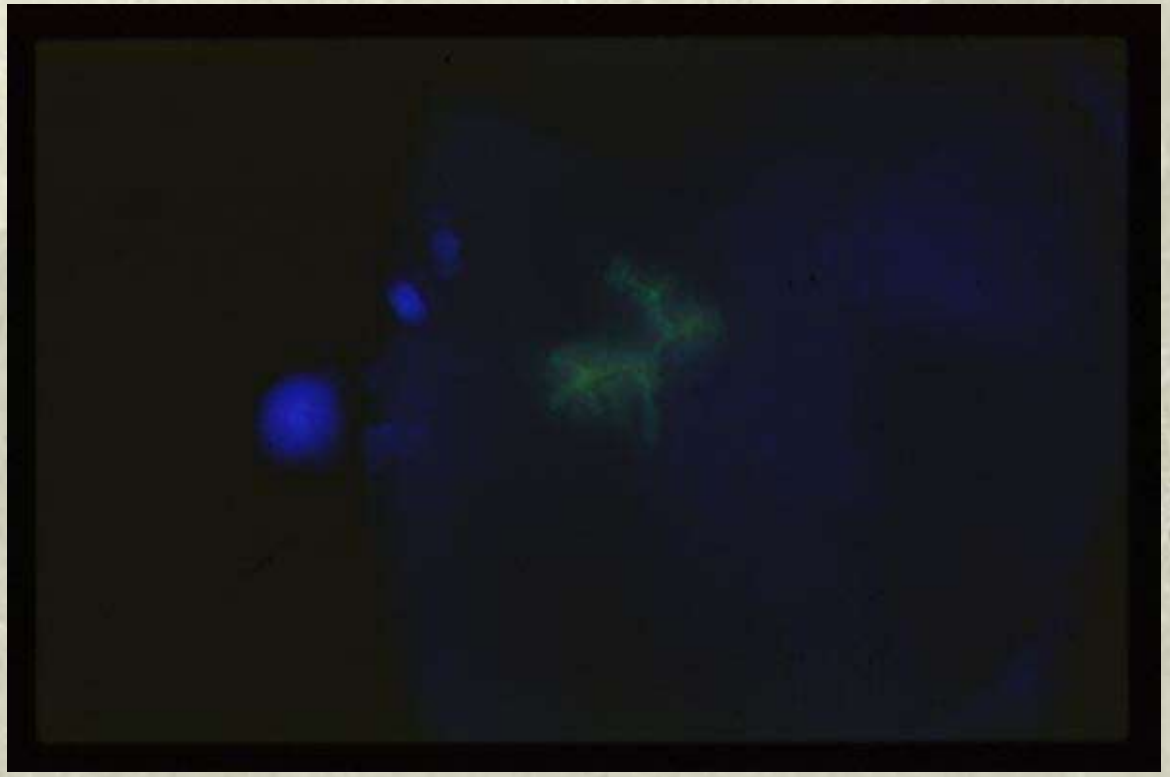
Recurrent infection

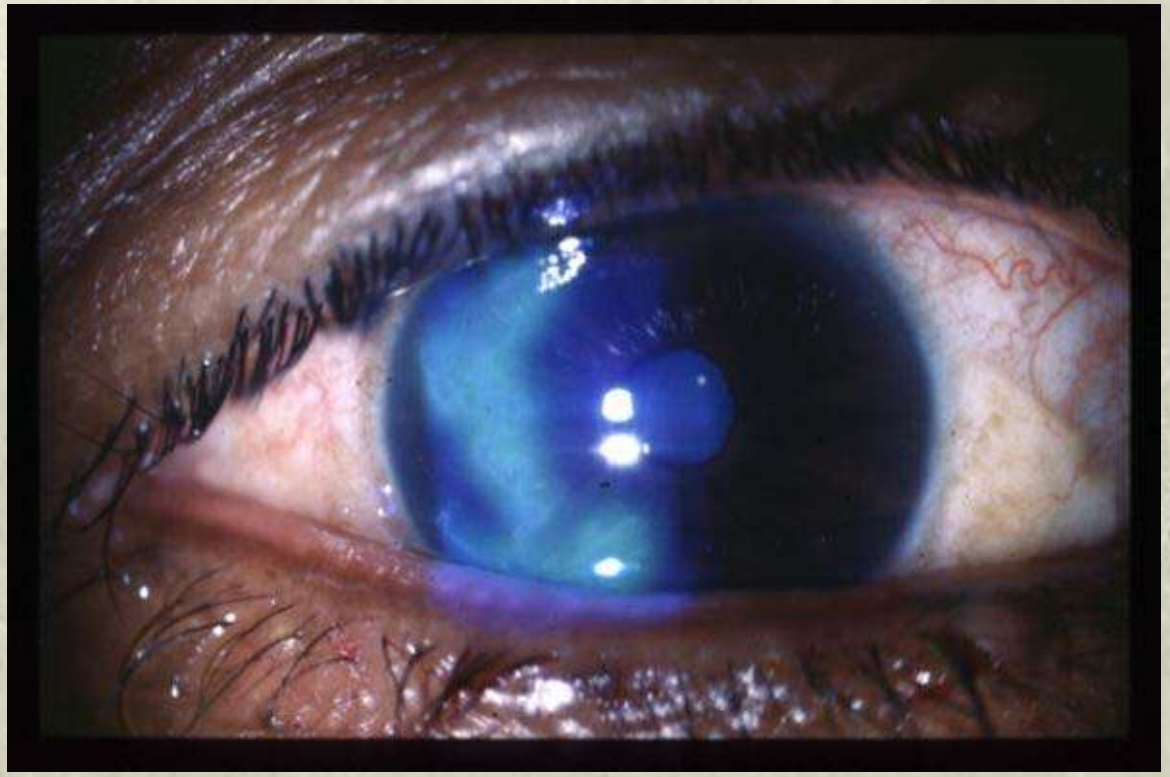
- This loss of sensory feedback can lead to neurotrophic corneal lesions (HS kills nerves)
- This is the breakdown of the corneal epithelium without trauma, infection, or severe desiccation
- Early signs include punctate RB / LG staining
- Severe cases lead to persistent, non-healing epithelial defects with ulceration

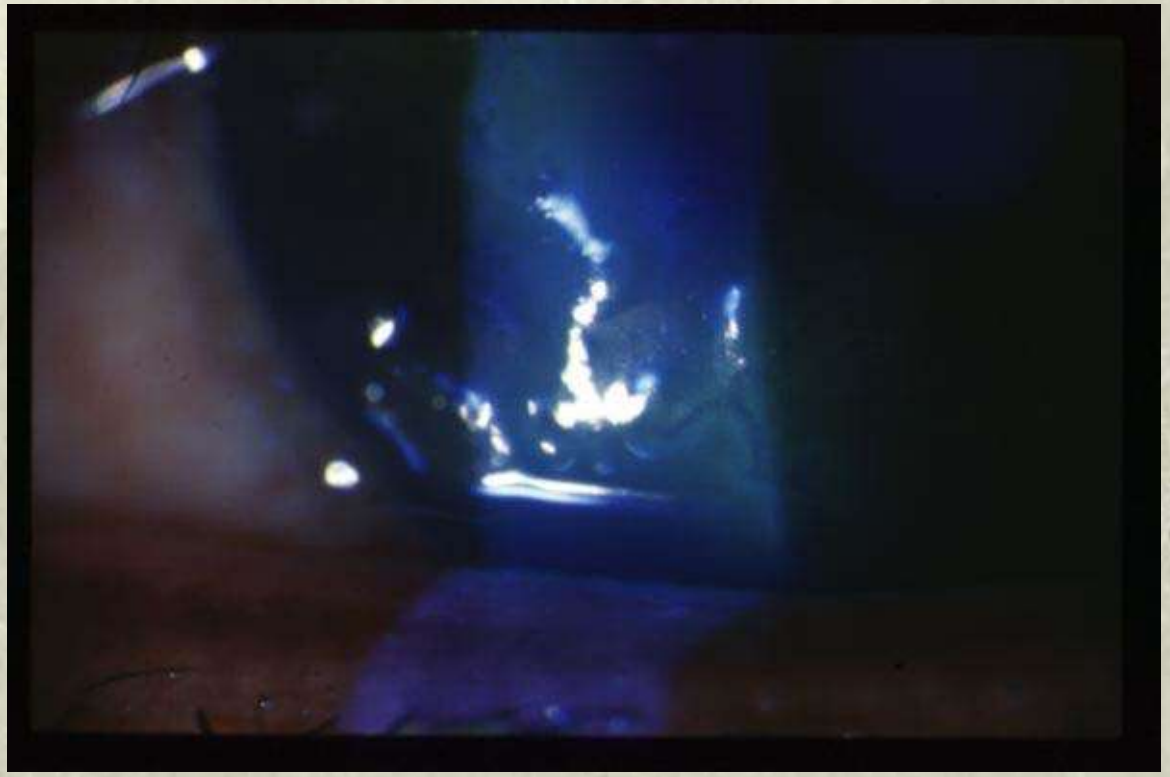
Recurrent infection

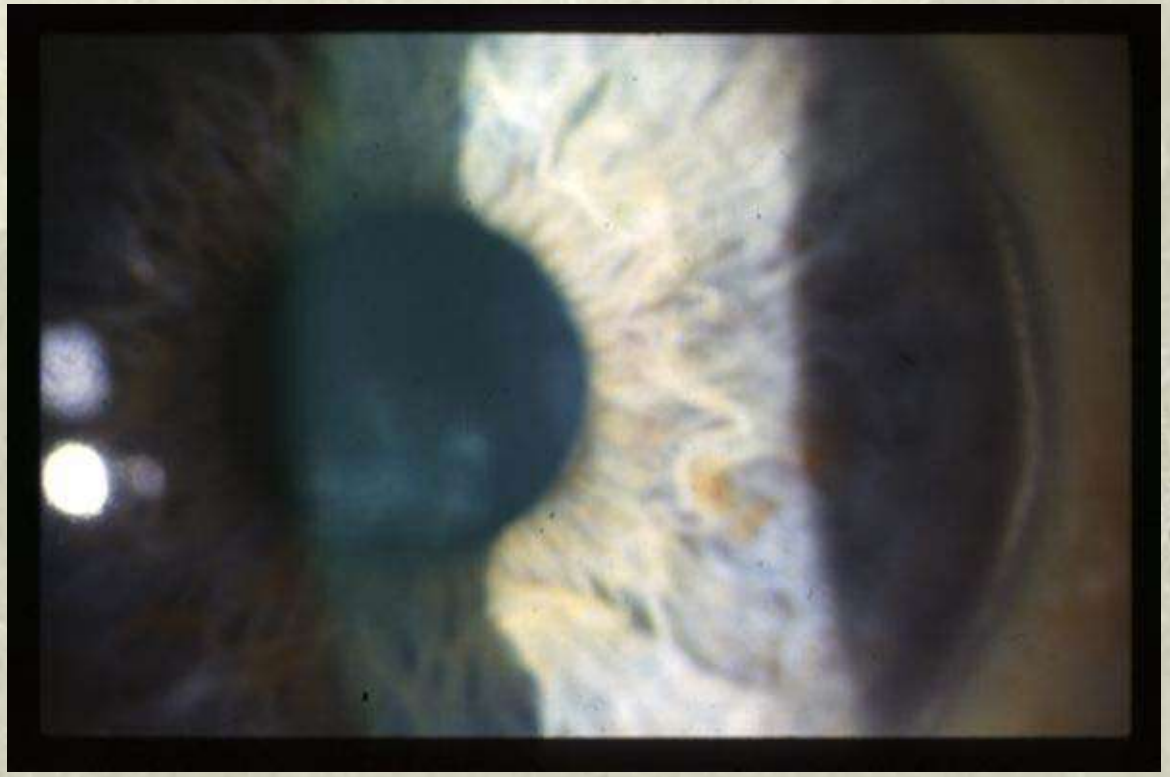
- Cases of reactivation can include stromal disease alone, epithelial disease alone, or the two in conjunction with one another
- The other associated findings can be present with or without corneal involvement





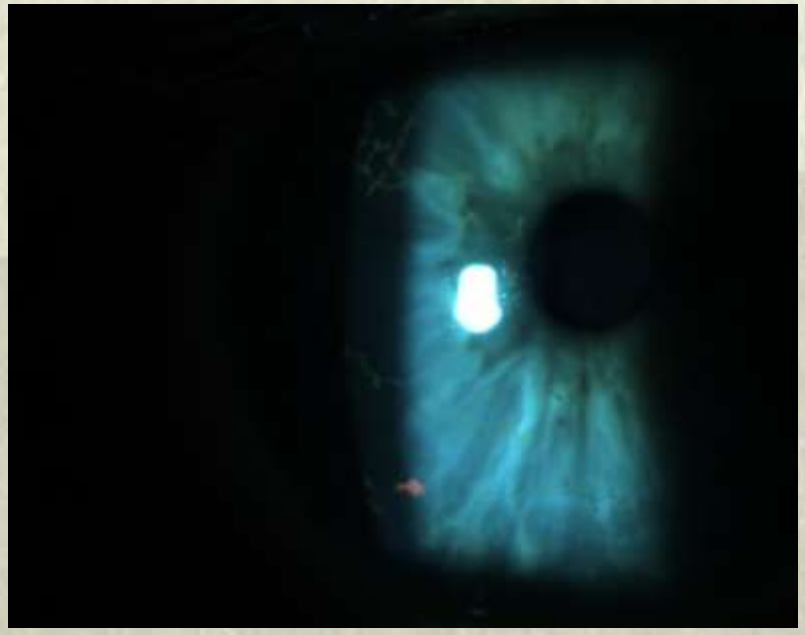


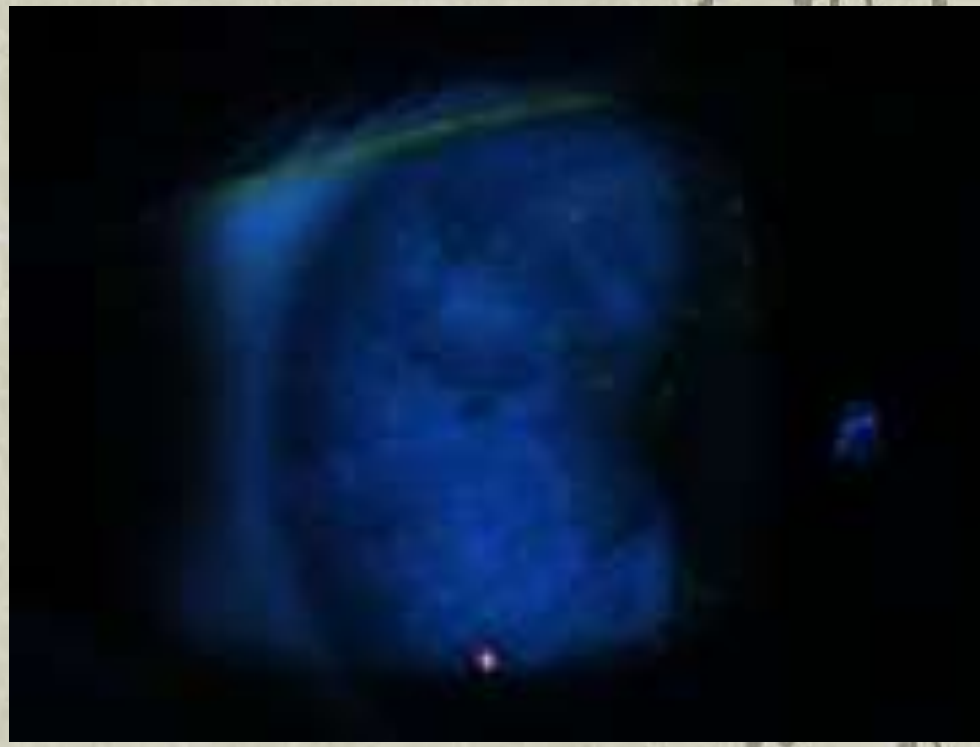




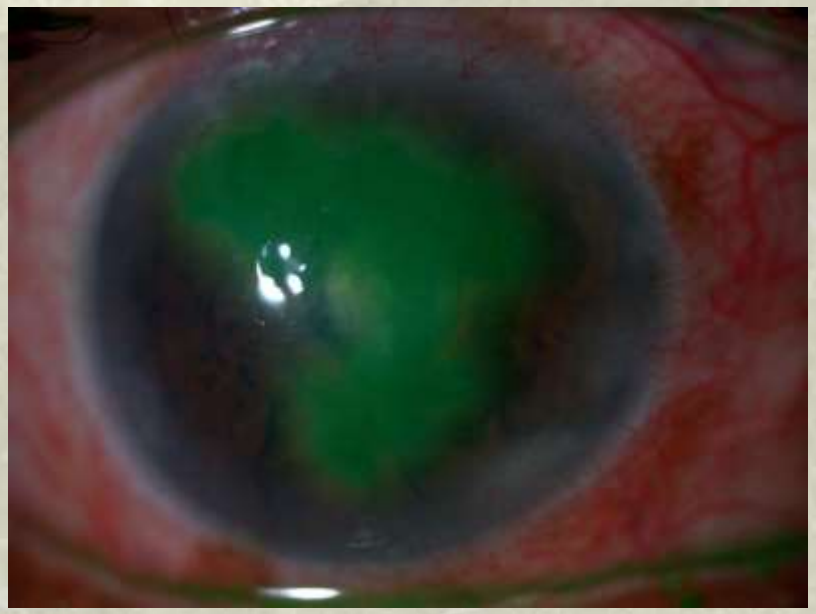
Exposure pseudodendrite

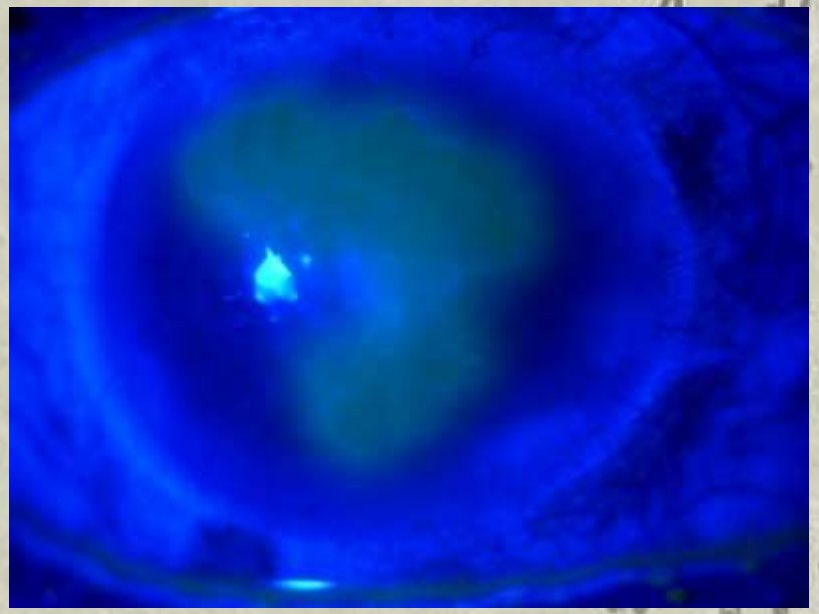
Zoster pseudodendrites

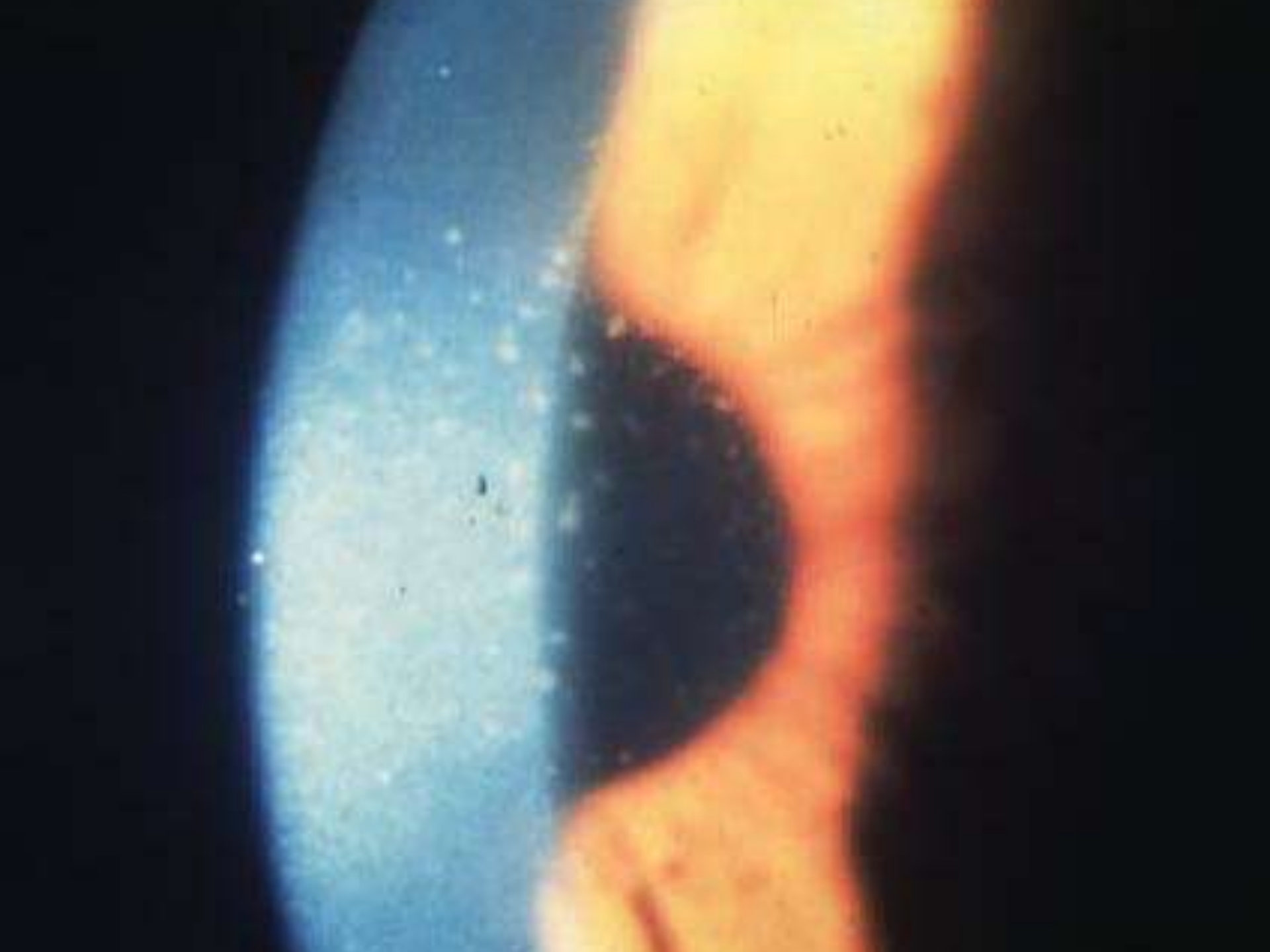




Geographic HSK





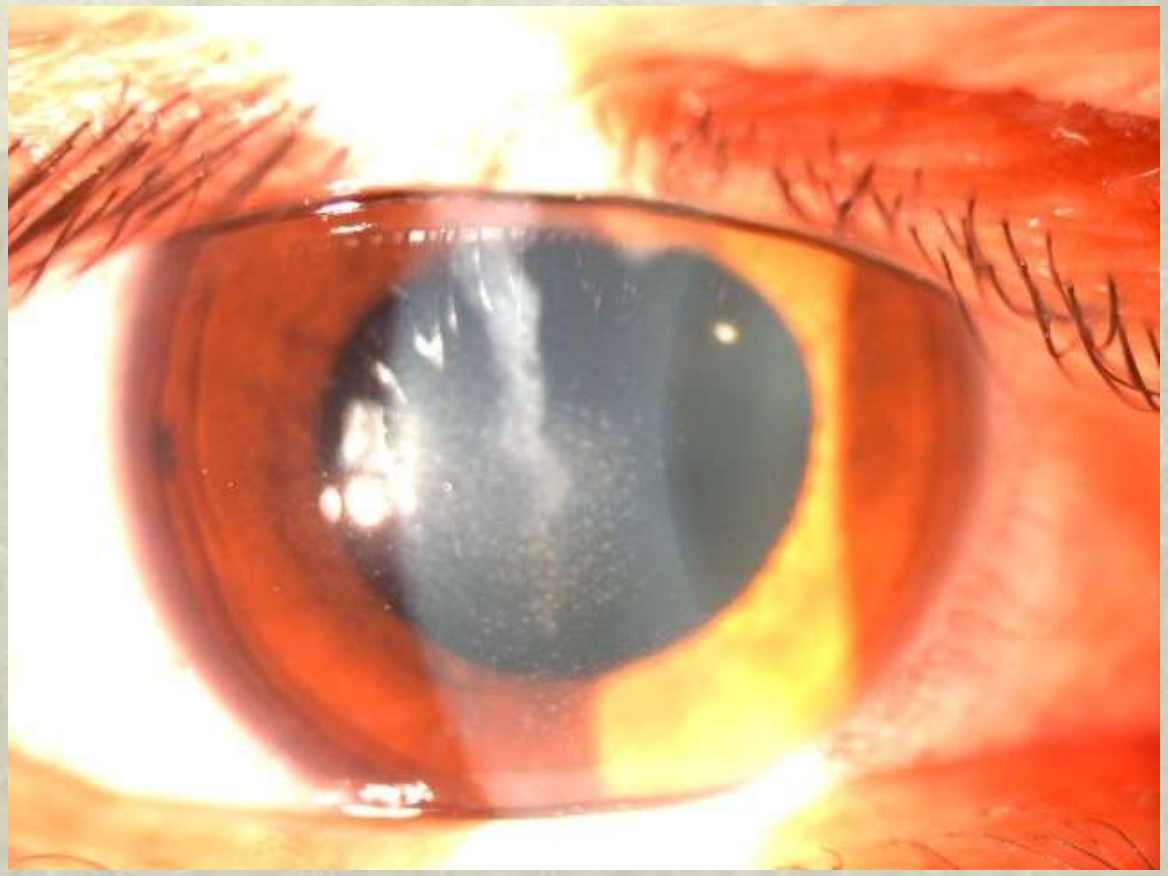


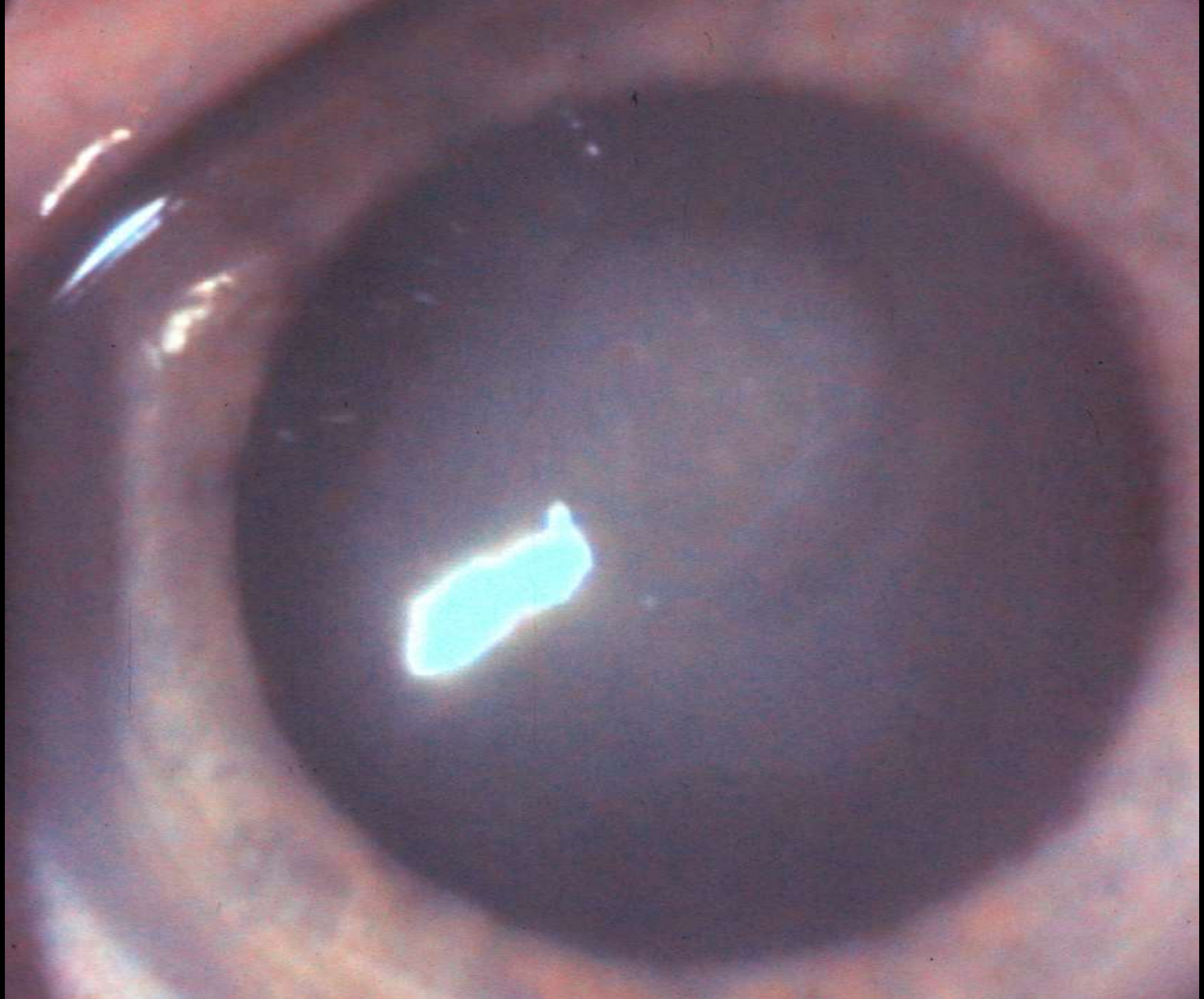
Endothelitis

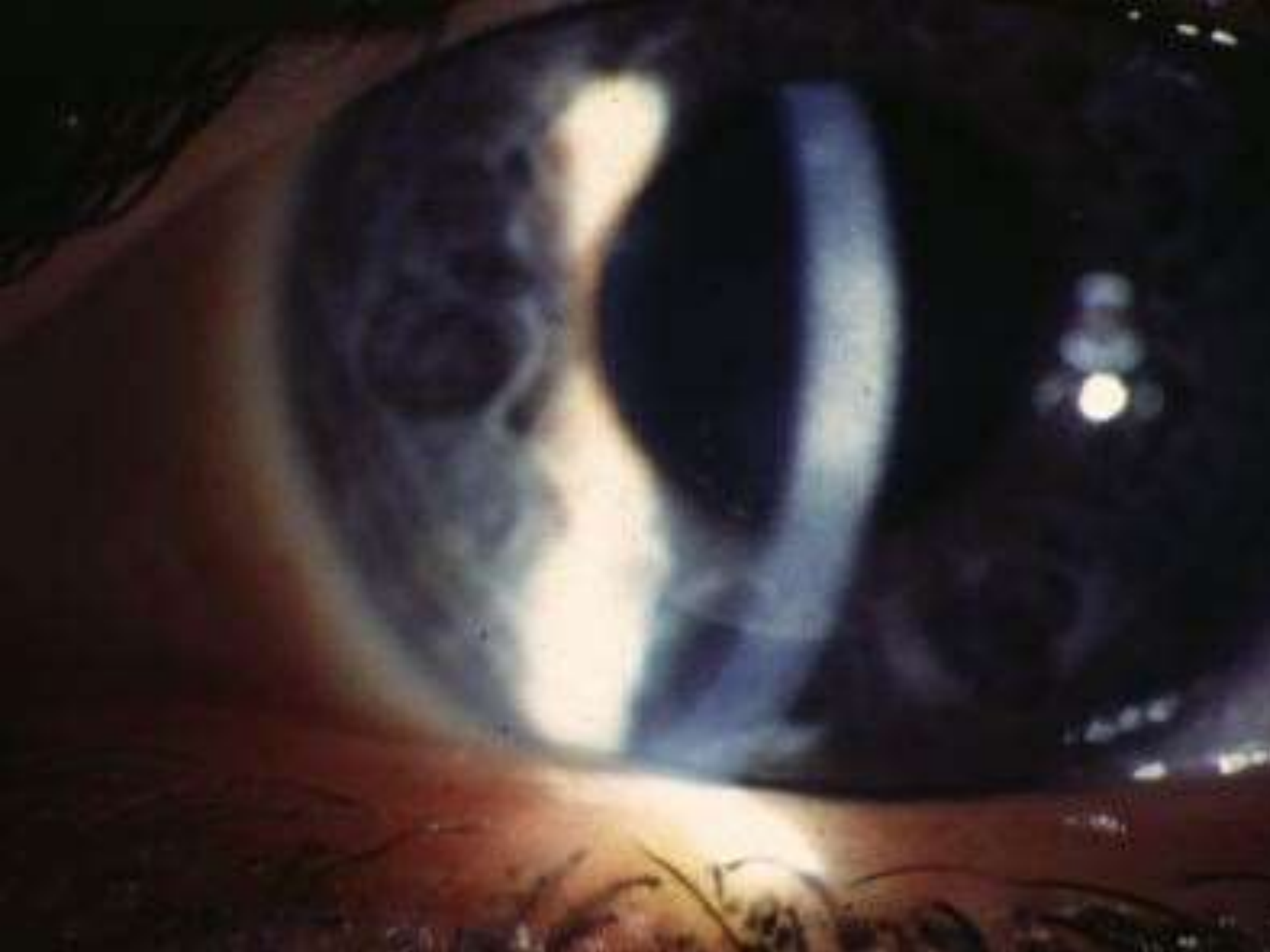
endothelitis

endothelitis

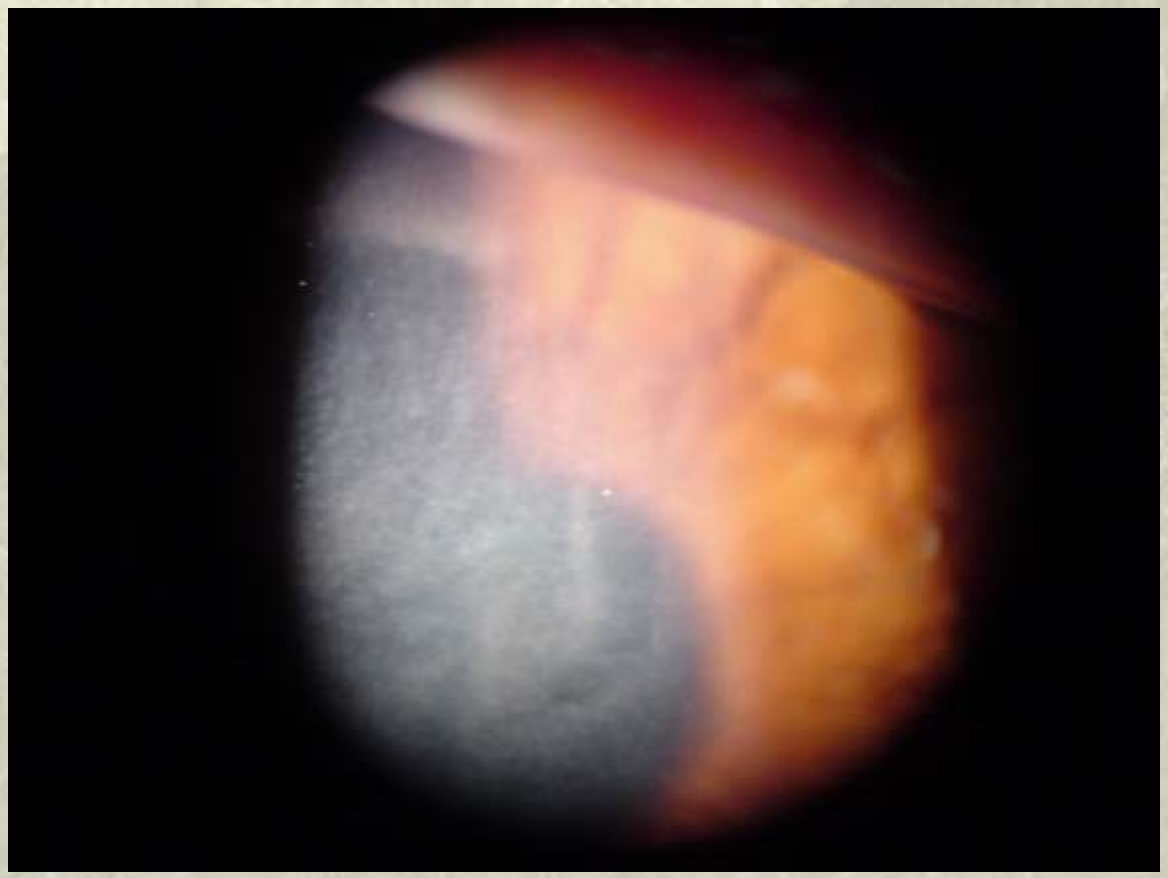
Stromal scar and iritis



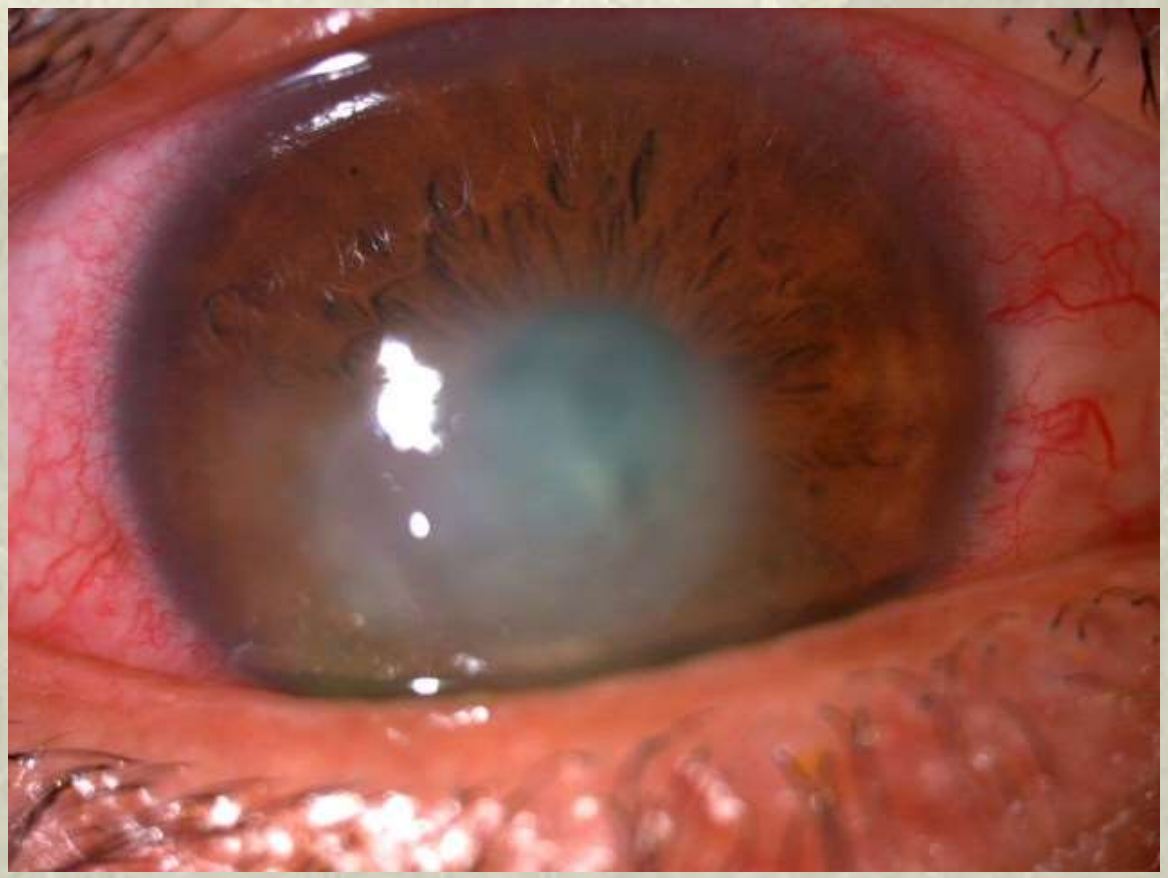




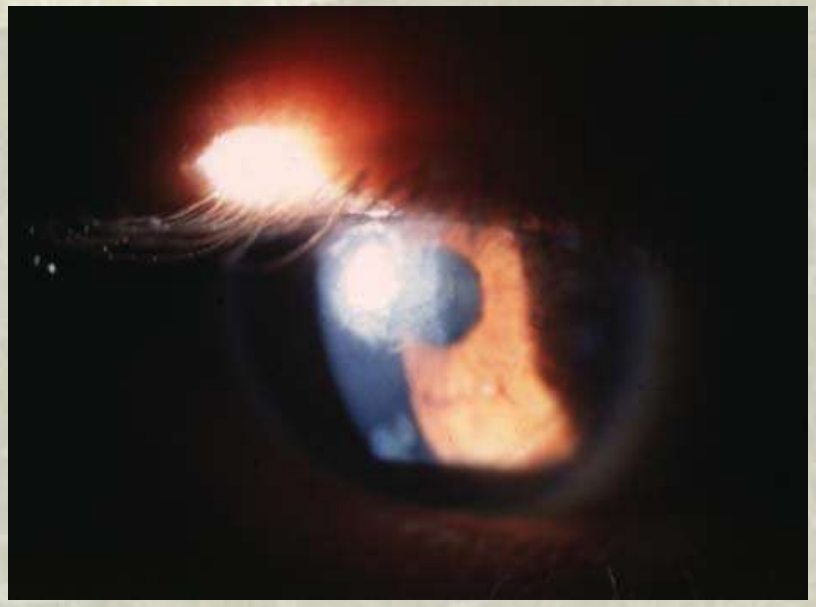
Disciform stromal keratitis

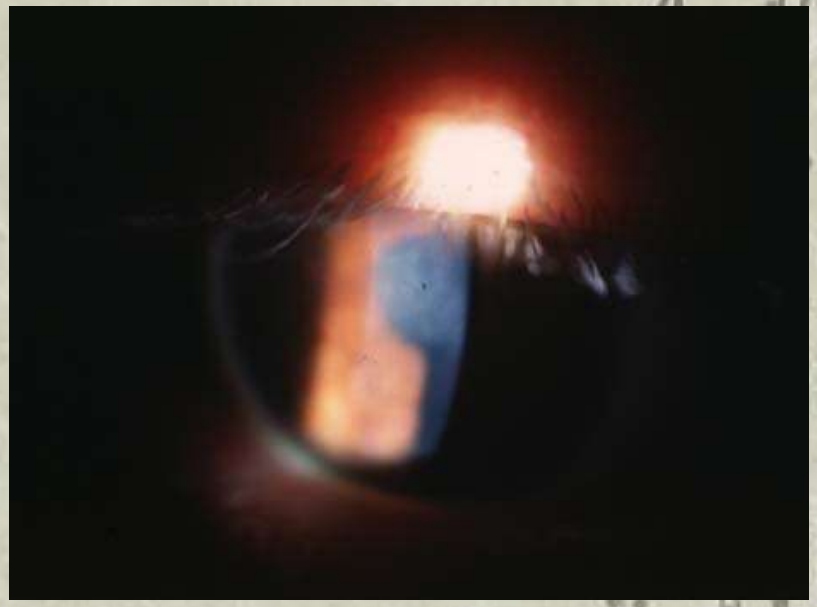


Disciform stromal keratitis

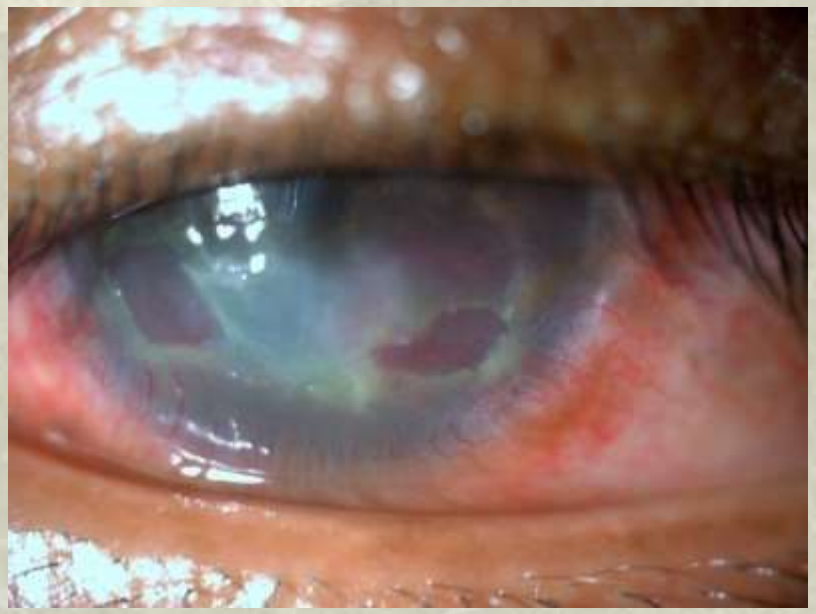


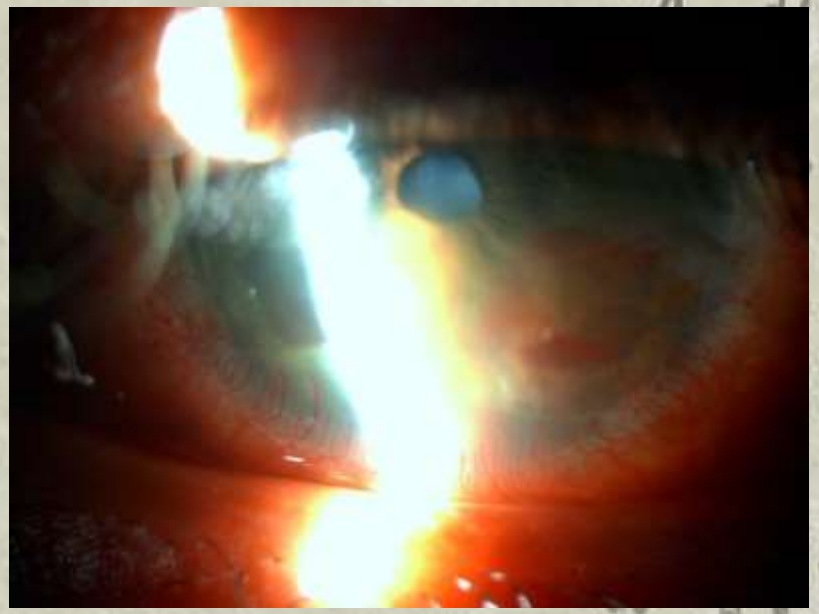
Stromal keratitis



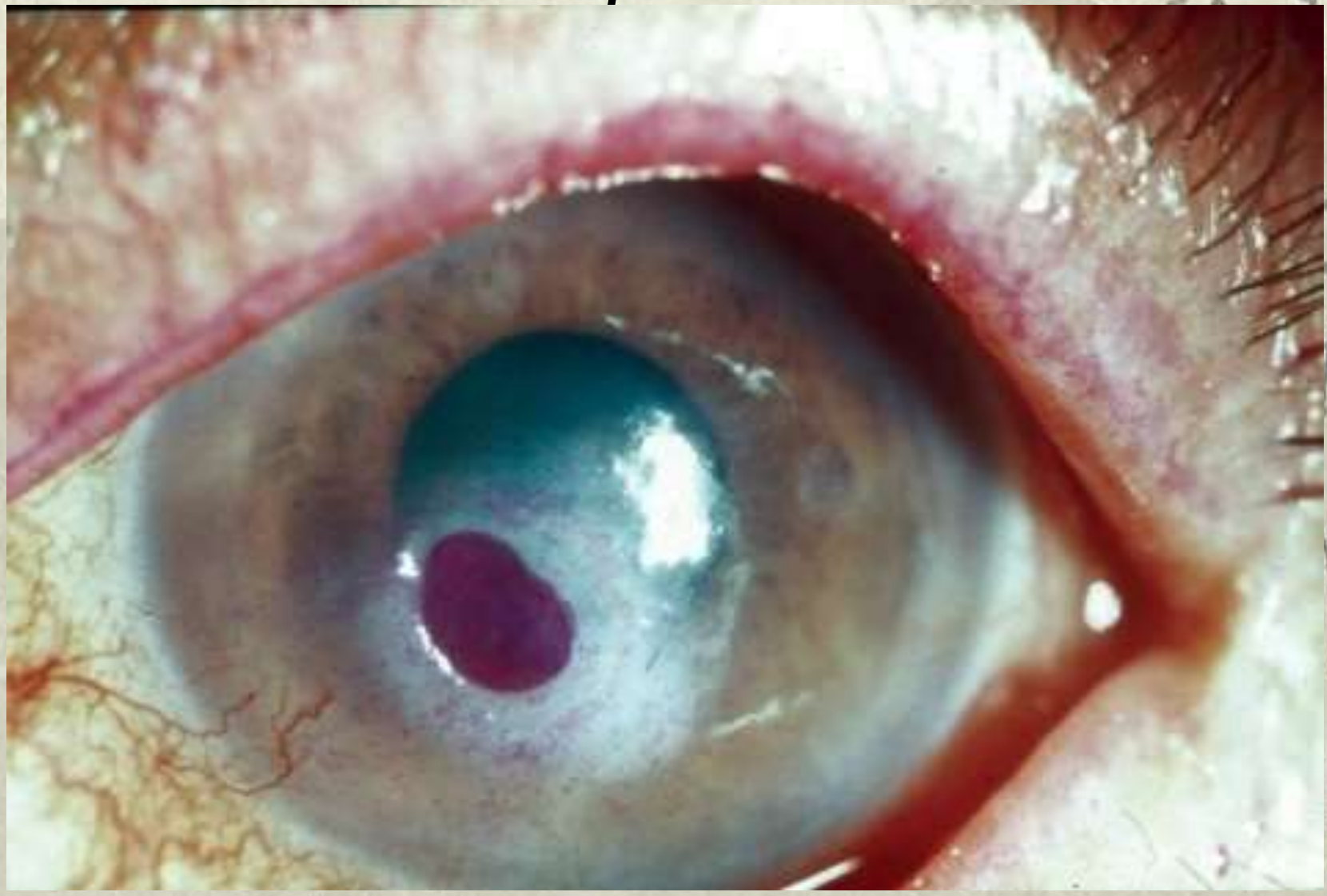


Stromal keratitis from Zoster

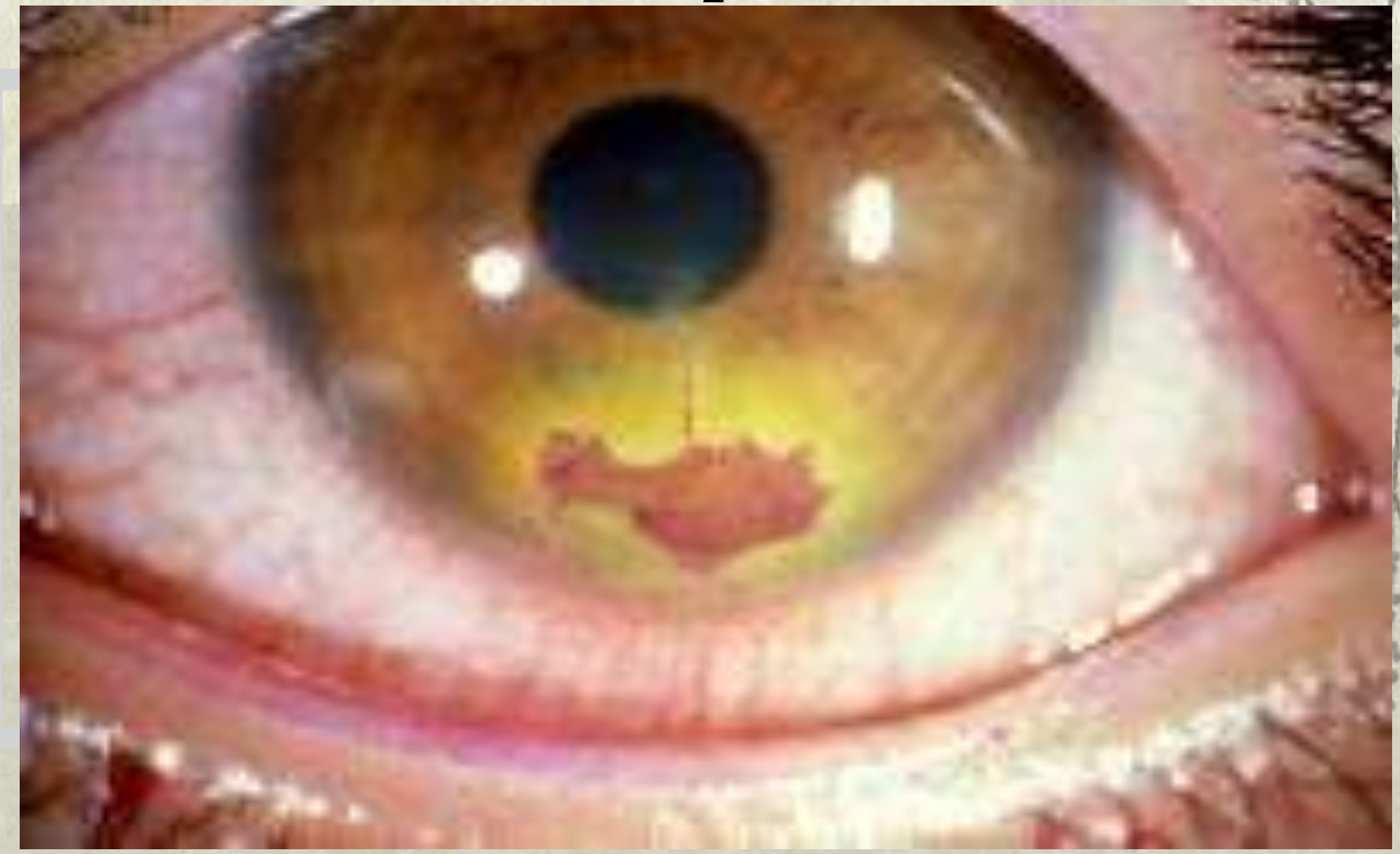




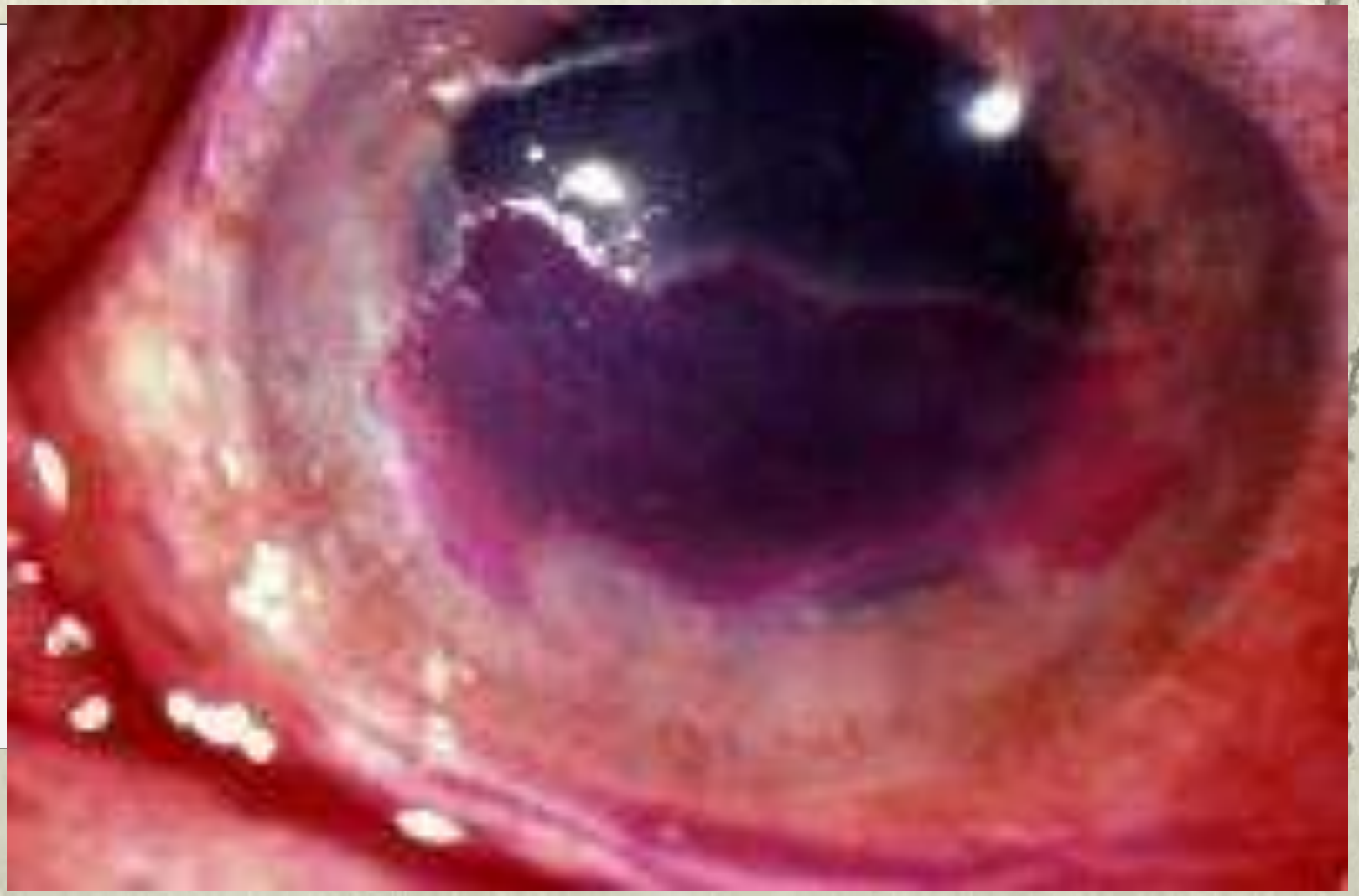
Neurotrophic Ulcer



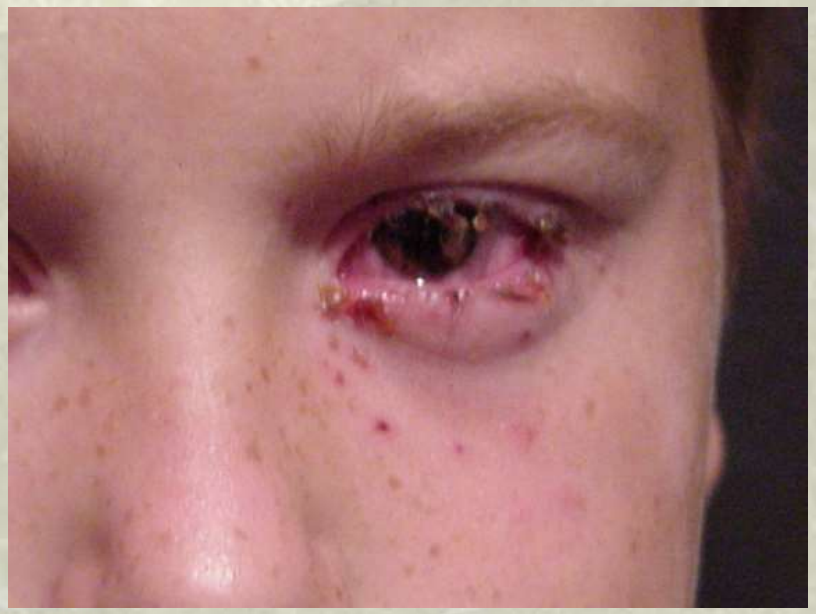
Neurotrophic ulcer



Neurotrophic Ulcer



Treatment of ocular disease



- Lid lesions and conjunctivitis can often be managed palliatively. Cool compresses and artificial tears helpful and oral agents can be used

Treatment

- Epithelial lesions respond extremely well to topical antiviral therapy. Historical mainstay of treatment is Viroptic (triflurodine).
- Topical drop that is extremely effective against HSV but very toxic to the cornea. Also, very expensive, even generic.

Treatment

- Viroptic is utilized Q 2-3h with an ideal maximum of around nine drops per day (toxicity). Once epithelium heals, decrease to QID for about 1 more week
- Medicamentosa is very common with secondary keratitis but the drug is almost universally effective in treating the infection
- Alternate with preservative free tears

Treatment

- Another topical option is Zirgan, a gel forming drop. May also be effective against adenovirus and is effective against Zoster dendrites.
- Prolonged contact time, so dosing is less: 5 times per day until the epithelium is intact, then TID for several more days. Also very expensive.
- Avaclyr 3% Acyclovir ointment. Fera pharmaceuticals. FDA approved in Summer of 2019. Same dosing as Zirgan
- Older agents that are no longer readily available include IDU (Idoxuridine) and Vira-A (vidaribine) ointment

Treatment

- A viable alternative to topical therapy is the use of oral antiviral agents
- Can be very effective, but may take a while longer to work
- Very, very cost effective if using Acyclovir. Dosing is 800mg TID (or 400 mg 5 X day). Cost of around $30
- Also available in 200mg pills on most $4 / $10 plans. Can run in to issues with supply (need 12 pills per day, and can only fill at that price once per month)

Oral agents-Simplex dosing

- Acyclovir (200,400,800) : 800mg TID or 400 mg 5 x day
- Also available in a pediatric suspension
- Famvir (125,250,500) : 500mg TID
- Valtrex (500,1000) : 500 mg TID. (It is a pro-drug of Acyclovir, so more bioavailability)

Oral antiviral agents

- Only contraindication is kidney disease
- Can be toxic in patients with kidney issues
- In elderly patients with kidney disease, Acyclovir can cause visual hallucinations and “death delusions”

Oral agents

- L-Lysine prophylaxis with 500mg daily. Also comes in a 1000 mg / day tablet as well
- Amino acid
- Works for cold sores, so….
- Sitavig for cold sore treatment: 50mg mucoadhesive acyclovir. One tablet, one time

Treatment

- Steroids hasten the progression of and worsen epithelial disease. Can be used for provocative testing of followed very closely
- However, they are often critical in the management of stromal lesions to prevent scarring

Treatment

- Treat stromal inflammation aggressively with topical steroids while concomitantly utilizing oral antiviral therapy

Treatment

- Topical steroids also indicated for iritis, trabeculitis, and endothelitis.
- Many patients with recurrent stromal disease require chronic low dose topical steroids (one drop per day or one drop every other day) to prevent flare ups
- Generally, need to stay on oral antivirals as well (acyclovir 400mg PO BID)

Topical steroids

- Generic PF most cost effective
- Can use brand PF, Lotemax, Durezol, etc. (watch IOP particularly closely with Durezol)

Treatment

- Neurotrophic keratitis is managed based upon its level of severity
- Mild cases can be handled with copious lubrication and/or punctal occlusion
- More severe cases may require patching, a bandage CL, or an amniotic membrane. Tarsorraphy is a last resort
- Tissue adhesives can be utilized in cases of stromal thinning or melting

Oxervate

- Completely unique agent to treat neurototrophic keratitis
- Dombe pharmaceuticals out of Italy
- Exactly mimics nerve growth factor proteins
- Dosed 6 X day for 8 weeks
- FDA approved summer 2018 as a treatment specifically for neurotrophic keratitis

Herpetic Eye Disease Study

- Originally undertaken to evaluate the usefulness of oral acyclovir in stromal HSV disease
- Became much more as it progressed from September of 1992 to December of 1996
- Looked at over 700 patients with various manifestations of ocular HSV infection
- Many sub-groups studied

H.E.D.S. - findings

- Several interesting findings
- Epithelial disease alone did not make future recurrences much more likely, but stromal disease definitely did
- Stromal disease was 8-10 times more likely over an 18-month study period in those with previous stromal episodes. More episodes = more risk

H.E.D.S. - findings

- 400 mg of oral Acyclovir twice per day for one year resulted in a 45% decrease in the rate of recurrence for all forms of ocular complications
- Over the six months after discontinuation, there was no rebound increase but no continued benefit…….so you have to keep taking it
- Could there be a role for Cyclosporin A , given the CD4 T cell mediated inflammation?

Another study

- Olmstead County, Minnesota (394 patients)
- Those NOT taking prophylactic antivirals were……
- 9.4 X more likely to have epithelial recurrence
- 8.4 X more likely to have stromal rec.
- 34.5 X more likely to have lid / conj. rec.

Prophylaxis

- So……

- At least discuss prophylaxis for all patients with stromal disease and patients with multiple attacks of epithelial disease
- Acyclovir 400mg PO BID
- Very safe, caution in severe kidney disease, monitor creatine and BUN levels

Prophylaxis

But…….

- Significant issue with resistance to prophylactic drug over tiime
- Must consider this very carefully when thinking about prophylaxis

The end!