Ophthalmic manifestations of Diabetes

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Financial Disclosures

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Presentation Objectives

At the end of this presentation, participants will be able to:

1. Examine the acute and chronic complications of eye health due to diabetes.
2. Discuss different treatment options for ophthalmic manifestations of diabetes.
3. Describe typical ocular changes caused from diabetes.

Prevalence of Diabetic Retinopathy

- 40.3% of adults older than 40 years old in the united states with Diabetes have diabetic retinopathy.
- Diabetic retinopathy is a leading cause of new vision impairment among working-age Americans.
- The incidence of diabetes-related vision loss is projected to triple by 2050 in the United States.
- Duration of diabetes is a major risk factor associated with the development of diabetic retinopathy
  - Type 1: 25% after 5 years, 60% after 10 years, 80% after 15 years
  - Type 2:
    - Insulin-dependent: 40% within the first 5 years and 84% within the first 19 years
    - Non insulin-dependent: 24% within the first 5 years and 53% within the first 19 years

Risk Factors of Diabetic Retinopathy

- Duration of diabetes and severity of hyperglycemia are the main risk factors for developing retinopathy.
- Blood sugar and blood pressure are important modifiable risk factors associated with the development of diabetic retinopathy.
  - Lipid-lowering agents have shown a protective effect on diabetic retinopathy progression

Prevalence of Diagnosed Diabetes Among Adults Aged 20 Years or Older

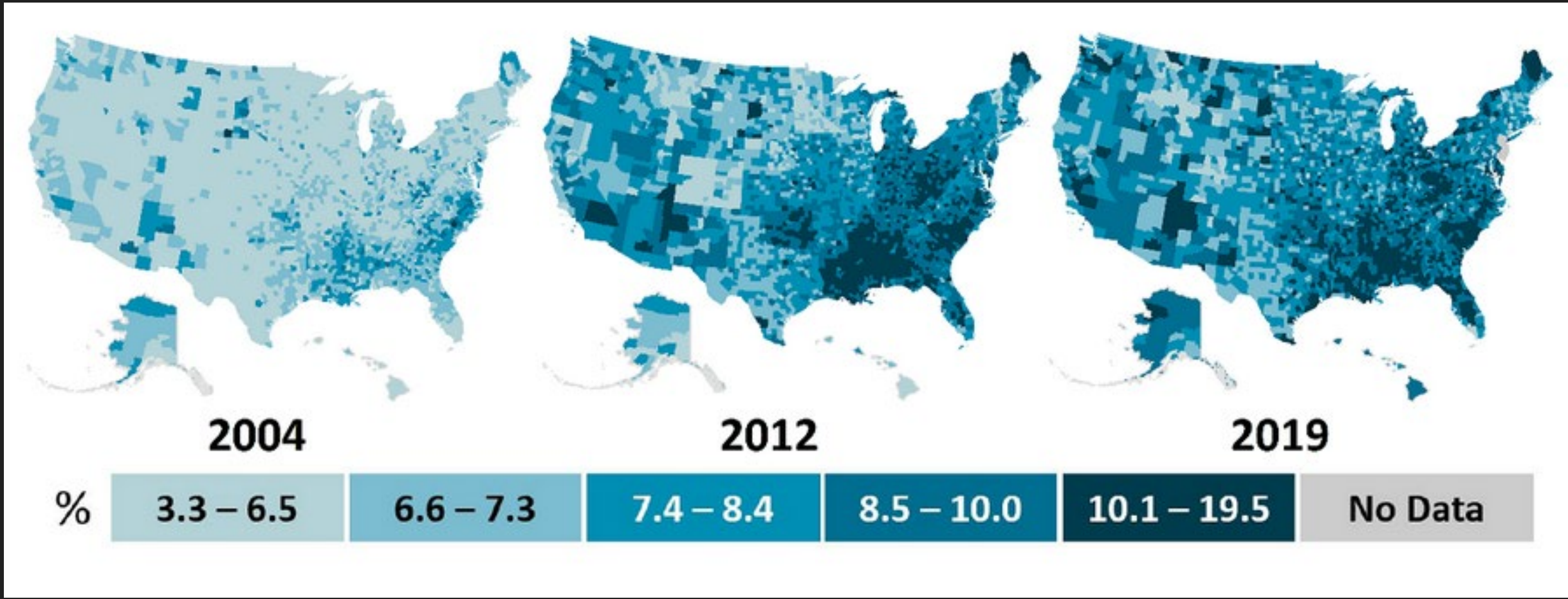


Image source: CDC

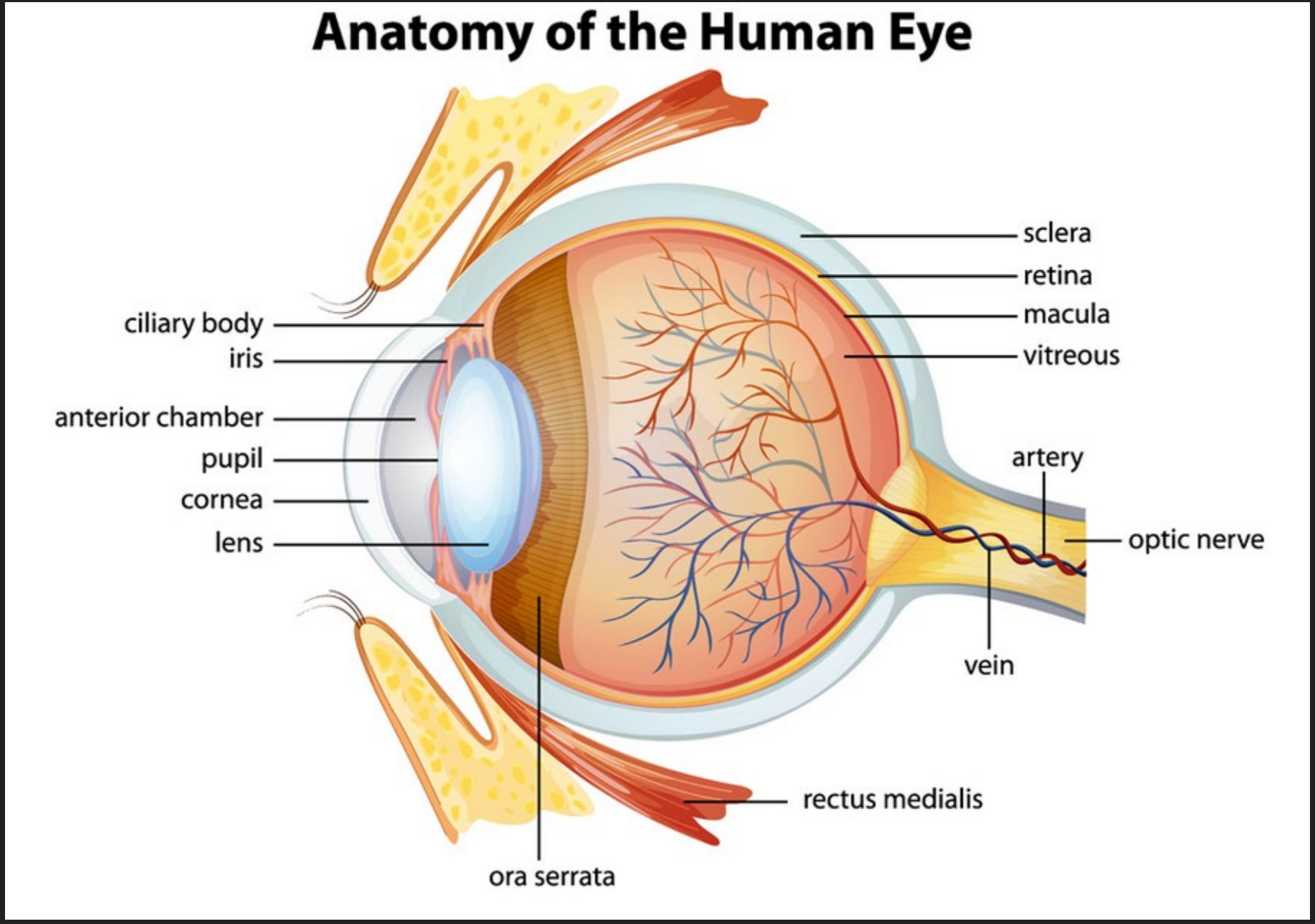


Image source: Exeter Eye

Possible Ocular Complications of Diabetes

- Neurotrophic keratitis
- Ischemic cranial nerve palsies
  - Oculomotor motor
  - Abducens
  - Trochlear
- Neovascular glaucoma
- Neovascularization / Proliferative Retinopathy
  - Iris
  - Retina
  - Optic Nerve
  - Tractional Retinal Detachment
- Diabetic cataracts

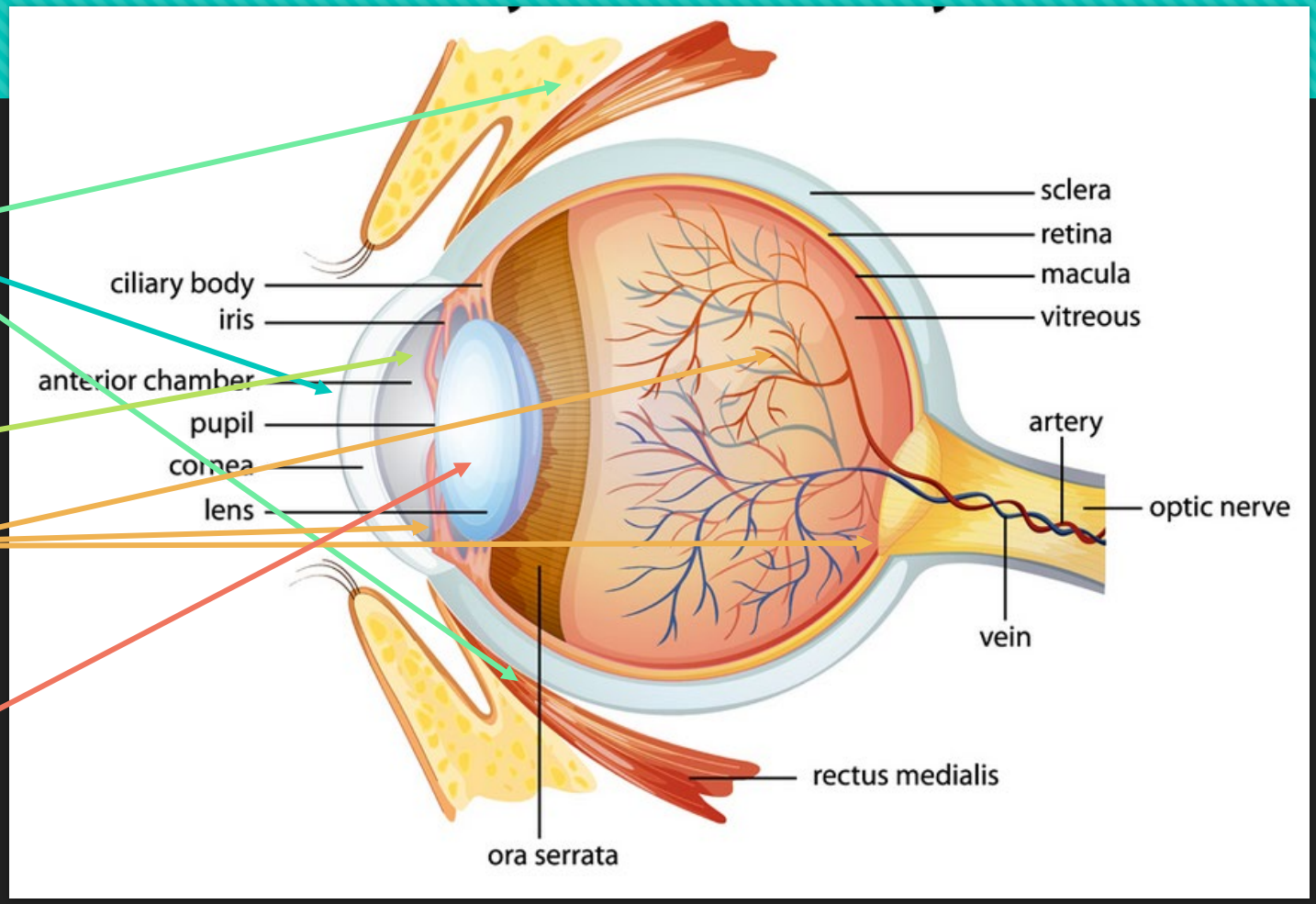


Image source: Exeter Eye

Possible Ocular Complications of Diabetes

- Refractive shifts
- Nonproliferative Retinopathy
  - Mild
  - Moderate
  - Severe
- Vitreous hemorrhage
- Diabetic papillitis
- Ocular vein and artery occlusions

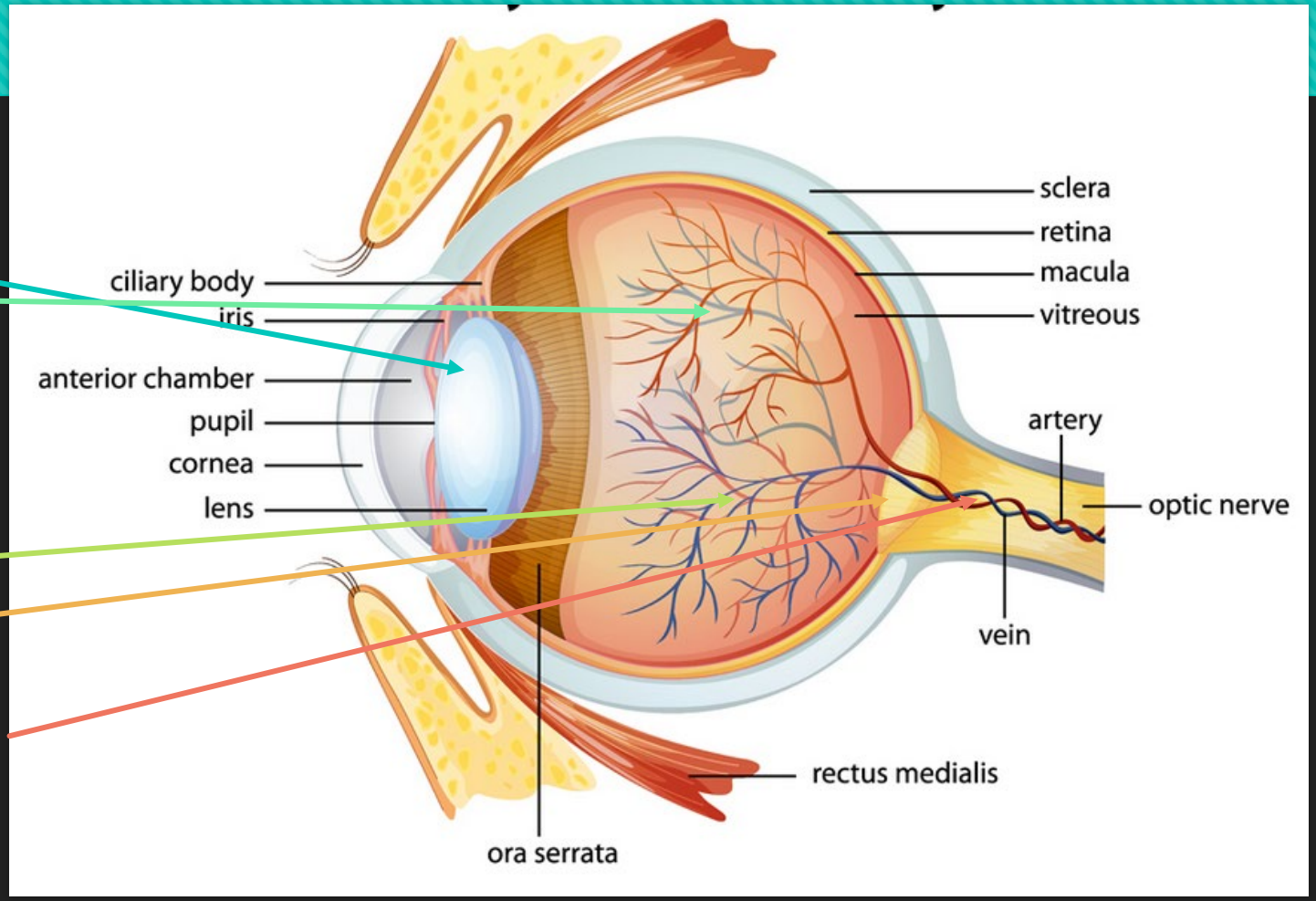


Image source: Exeter Eye

Neurotrophic Keratitis (NK)

- A degenerative corneal disease caused by damage of trigeminal innervation.
  - Loss of corneal sensitivity impairs wound healing leading to epithelial defects and possible corneal ulcers.
- The extent of trigeminal nerve damage in diabetes has been shown to be associated with the duration of hyperglycemia.
  - Corneal nerve evaluation has shown a reduction of sub-basal nerve density with abnormally tortuous nerve fiber bundles.

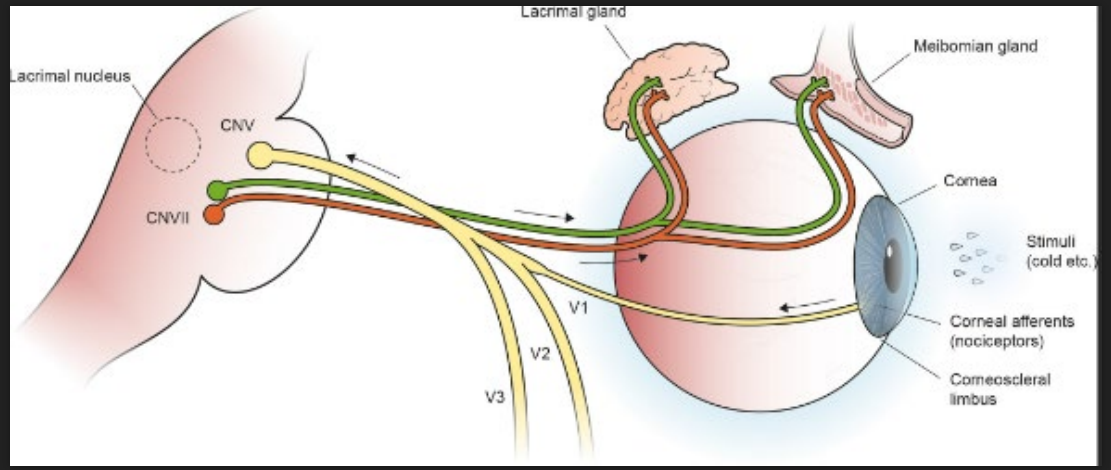


Image source: Labetoulle et al, 2018

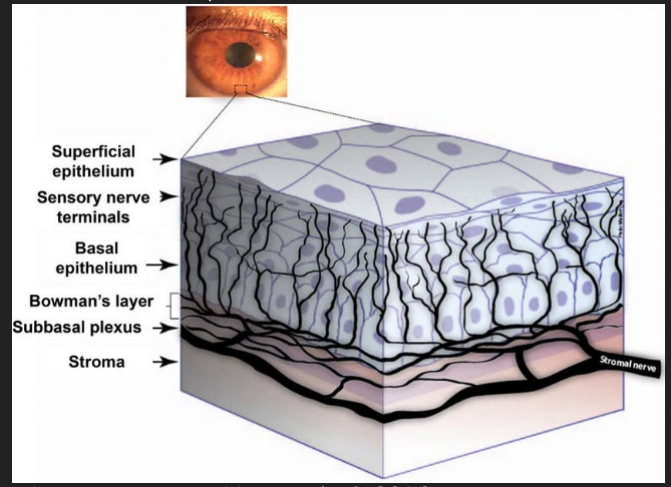
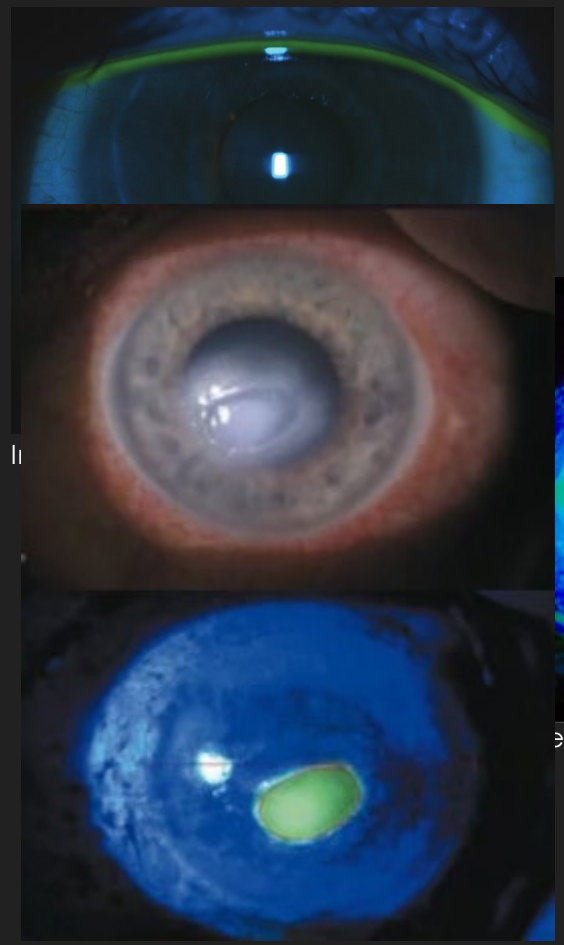


Image source: Yang et al, 2018

Clinical Presentation of NK

- 3 Stage Classification
  - Stage 1: Irregular corneal epithelium (punctate keratitis, hyperplasia, edema, neovascularization)
  - Stage 2: Recurrent or persistent confluent epithelial defect
  - Stage 3: Corneal ulcer and thinning with possible perforation
- Symptoms typically of blurry vision NOT pain.



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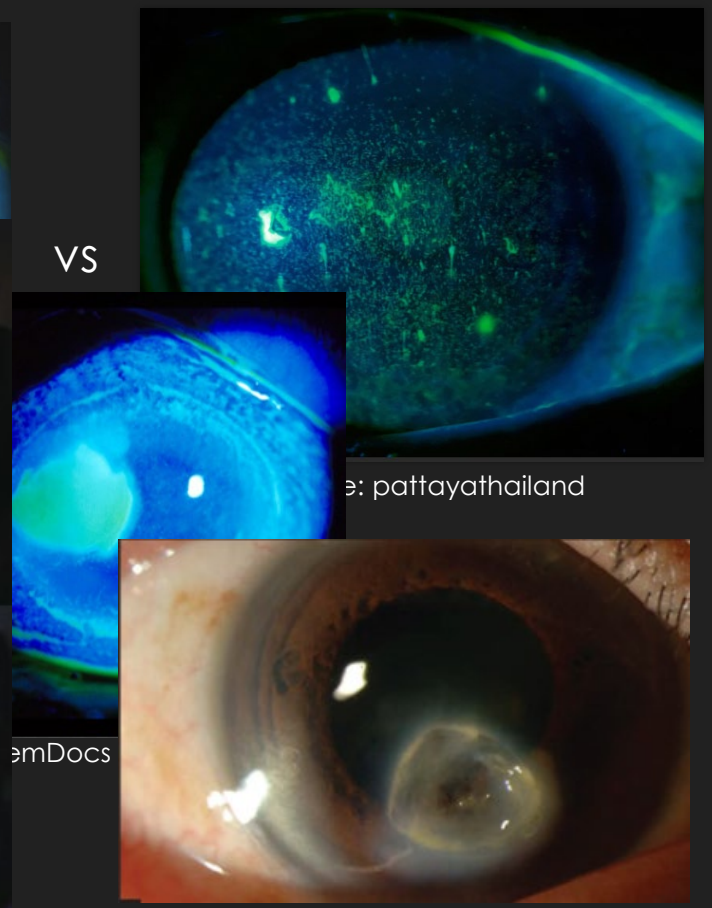

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Image source: Deshmukh et al, 2020

Treatment of NK

Traditional

- Stage 1
  - Preservative-free artificial tears
- Stage 2
  - Topical antibiotics to prevent secondary infections
  - Bandage contact lens
  - Autologous serum
- Stage 3
  - Surgical intervention
    - Tarsorraphy, conjunctival flap, amniotic membrane transplantation

New/On the Horizon

- Recombinant Human Nerve Growth Factor
  - A neurotrophin that stimulates corneal re-innervation by inducing epithelial cell proliferation and differentiation
  - Studies have shown staining less than 0.5mm at 8 weeks, dosing 6x/day, in 69.6-75.4% of patients
  - Cenegermin 0.002% ophthalmic solution is commercially available
    - Approx $30,000 for a 14 day supply 
- Insulin
  - A peptide that enhances cell migration
  - Human and rat studies have consistently shown complete corneal re-epithelialization at much faster rates compared to the controls.
  - Blood glucose levels and serum insulin levels remain unchanged
- Others: matrix regenerating agents, substance P + insulin-like growth factor 1, thymosin beta 4, connexin43 + antisense oligodeoxynucleotides

Ischemic Ocular Cranial Nerve Palsies

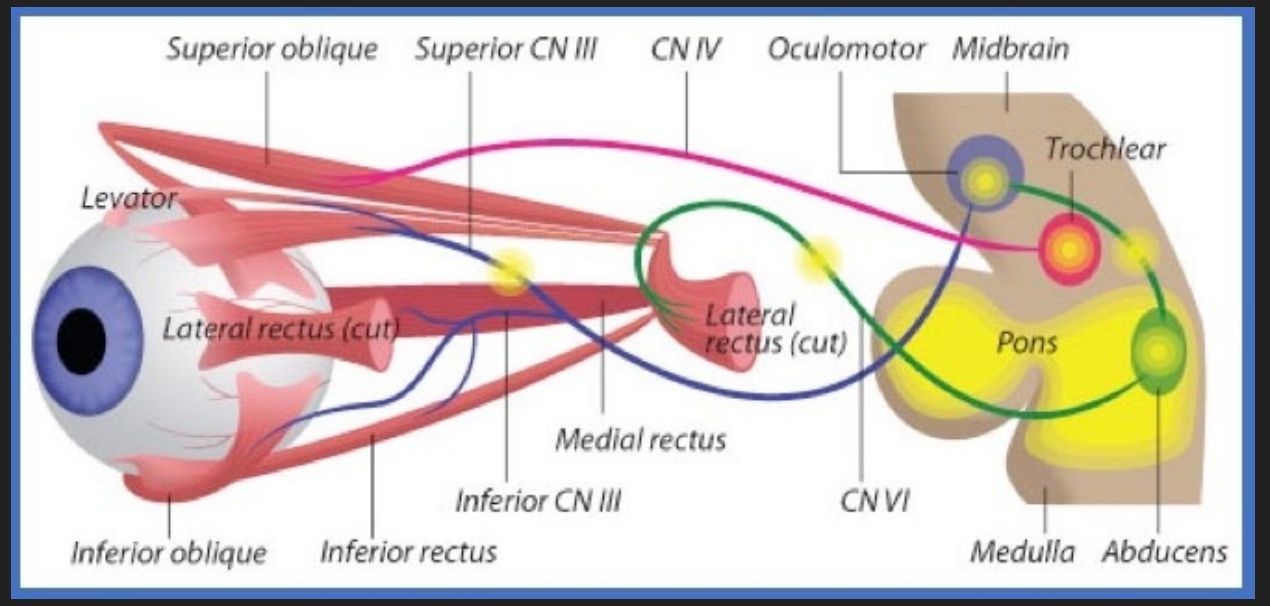


Image source: Elizabeth Engle

Ischemic Ocular Cranial Nerve Palsies

- Microvascular changes in diabetes affect the blood supply to ocular cranial nerves causing temporary paralysis.
- Main symptom is diplopia
  - Variable degrees in different gazes
  - Can also present with pain

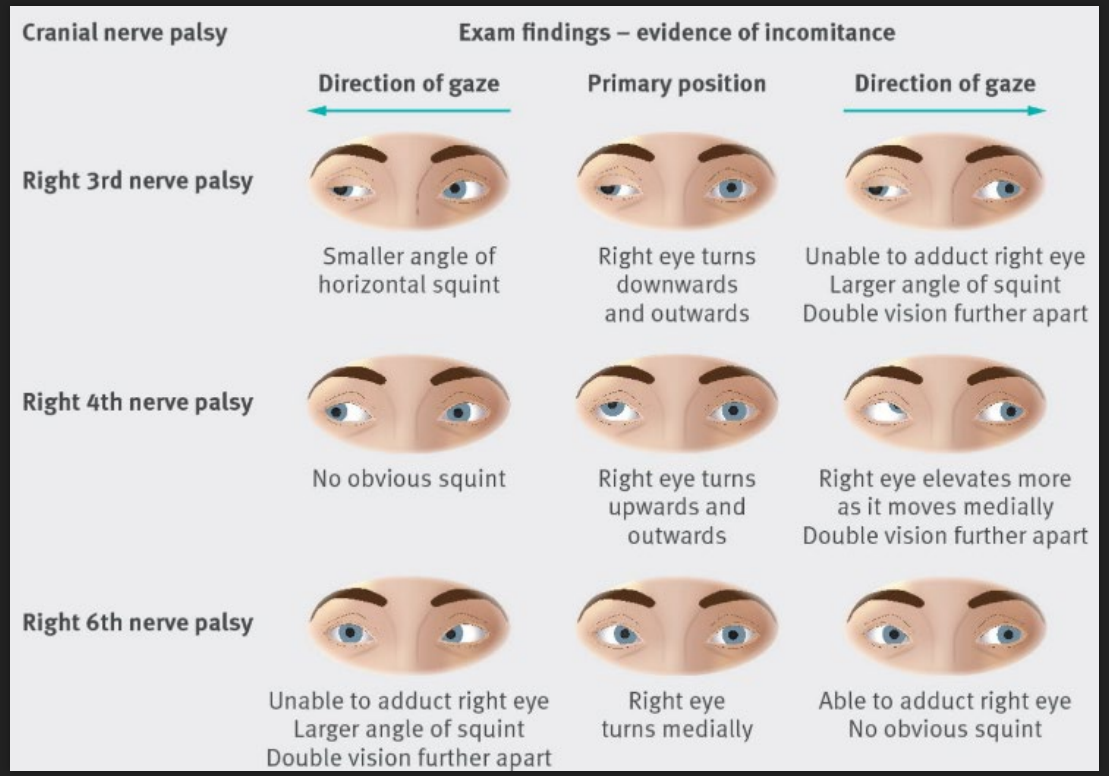
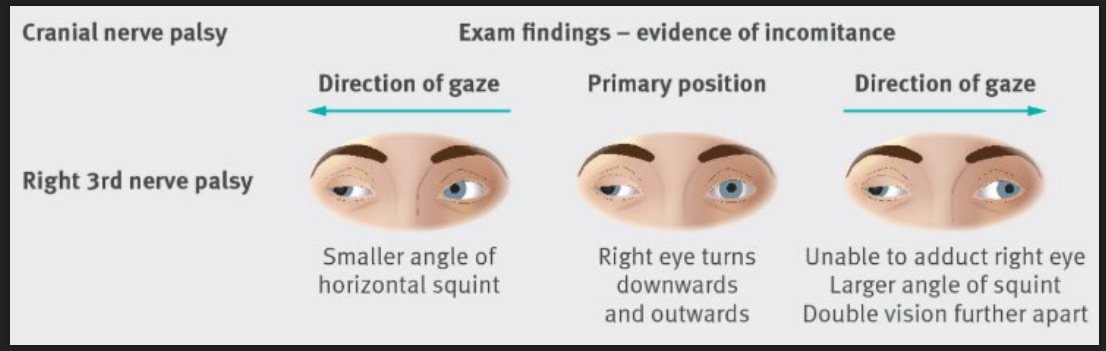


Image source: GrepMed

Oculomotor Nerve Palsy (III)

- Can be complete or incomplete
  - Complete palsies will present with a complete ptosis with the eye positioned down and out, and an inability to adduct, infraduct, and supraduct.
  - Patient will have horizontal and vertical diplopia
- Lack of pupil involvement is consistent with ischemic etiology
  - Pupil involved oculomotor palsies should promote high concern of compressive etiology
- Management
  - Neuroimaging
  - Monitor



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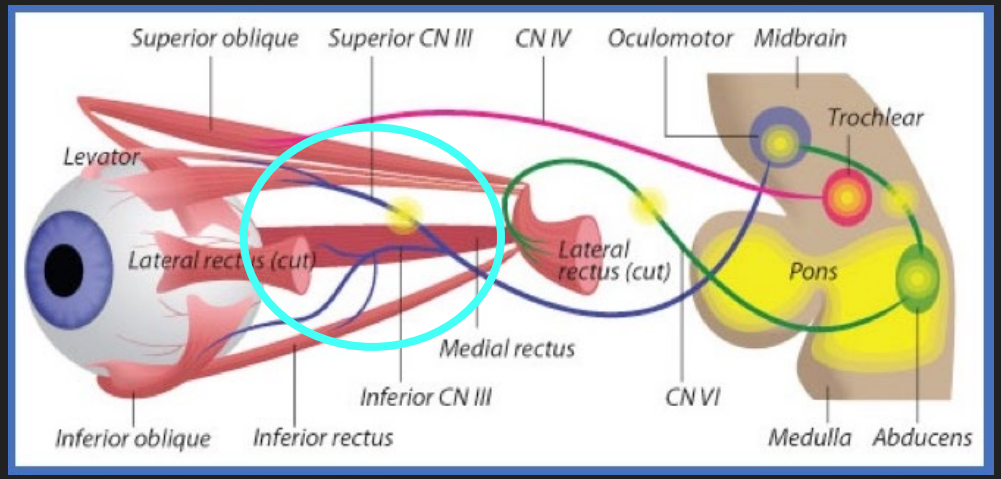

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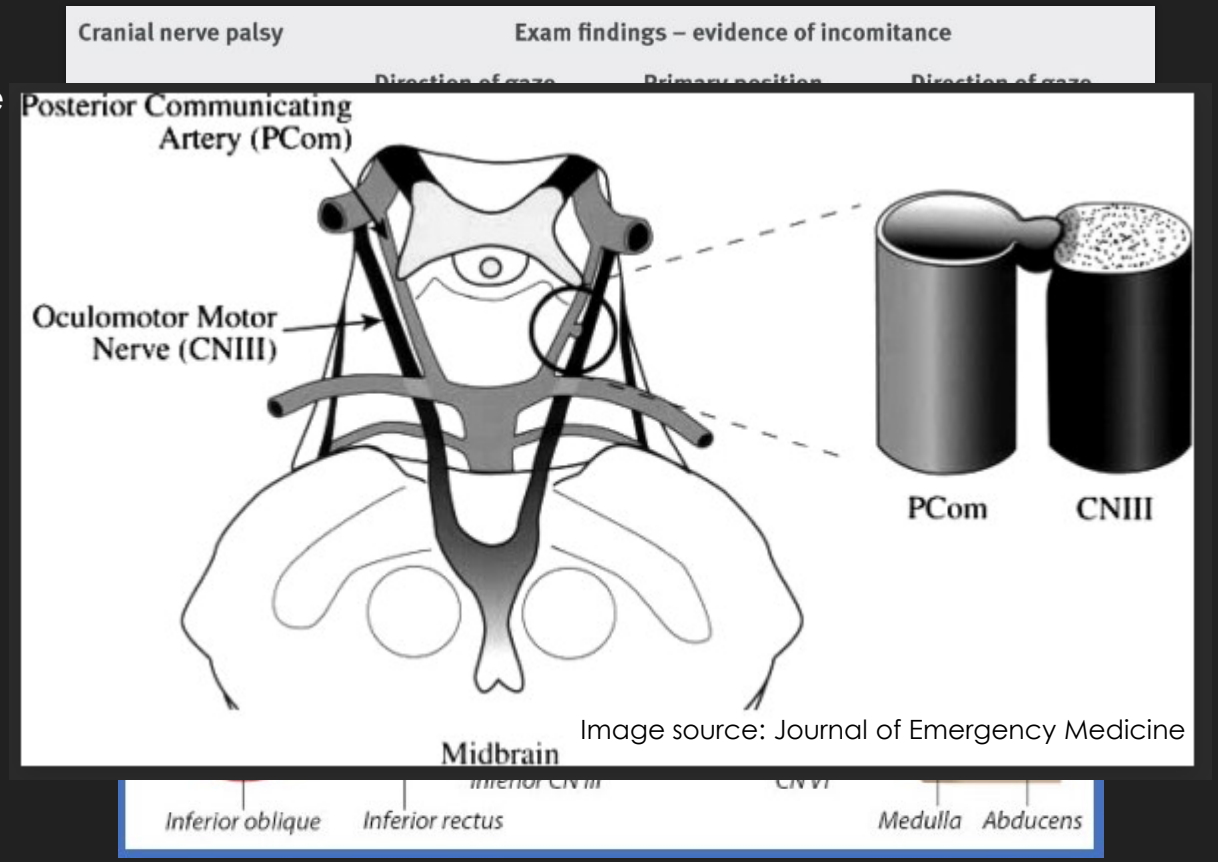
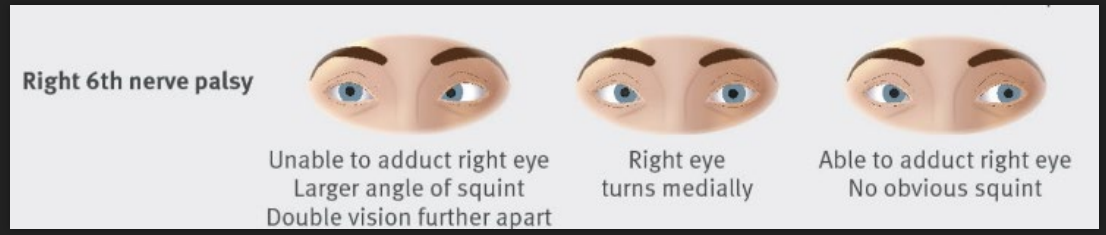


Image source: Journal of Emergency Medicine

Image source: Elizabeth Engle

Abducens Nerve Palsy (VI)

- The most common ocular motor paralysis in adults.
- Patients will typically present with an inward turned eye and the inability to abduct the affected eye.
  - Patients will have horizontal diplopia
- Management
  - Isolated palsy in the presence of vasculopathic condition(s) = Monitor
  - All others = neuroimaging and lab work



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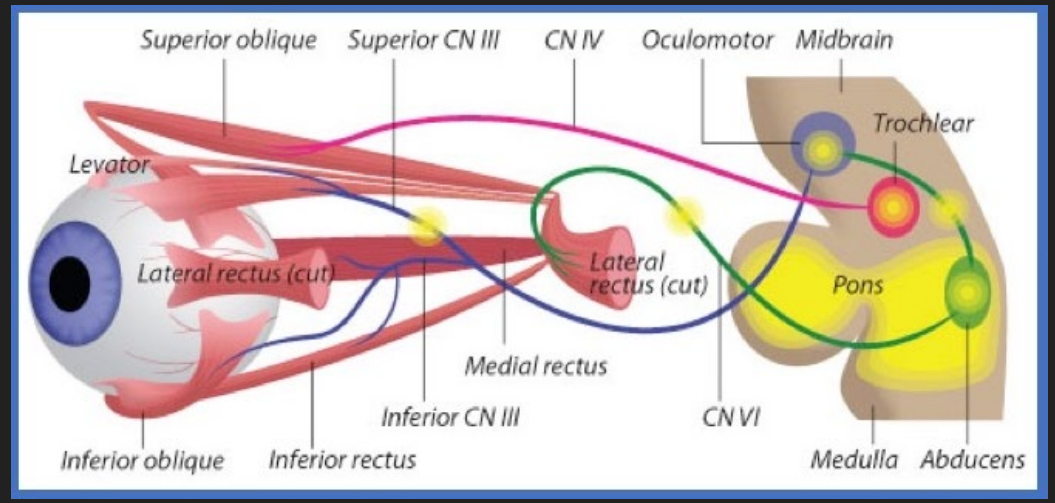
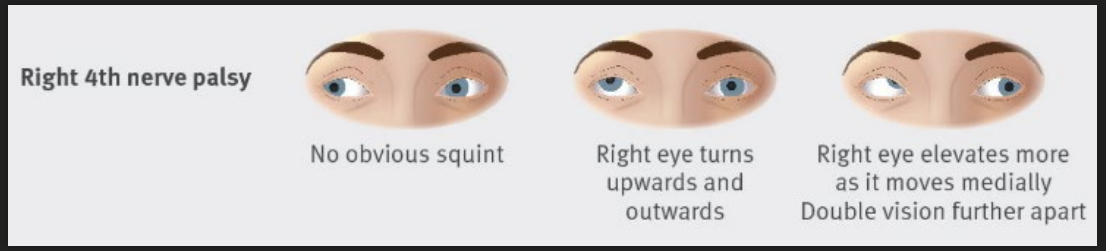


Image source: Elizabeth Engle

Trochlear Nerve Palsy (IV)

- Patients will typically present with a hypertropic eye that elevates when adducted.
  - Patient will have vertical diplopia
- Parks-Bielschowsky 3 step test
  - Which eye is hypertropic?
  - Gaze in which direction makes hypertropia worse?
  - Direction of head-tilt which makes hypertropia worse?
- Management
  - Isolated trochlear nerve palsies are typically related to trauma or microvascular disease and can be monitored.
    - Has the longest intracranial course making it vulnerable to trauma.
  - Non-isolated trochlear nerve palsies should be neuro-imaged and blood work should be acquired.



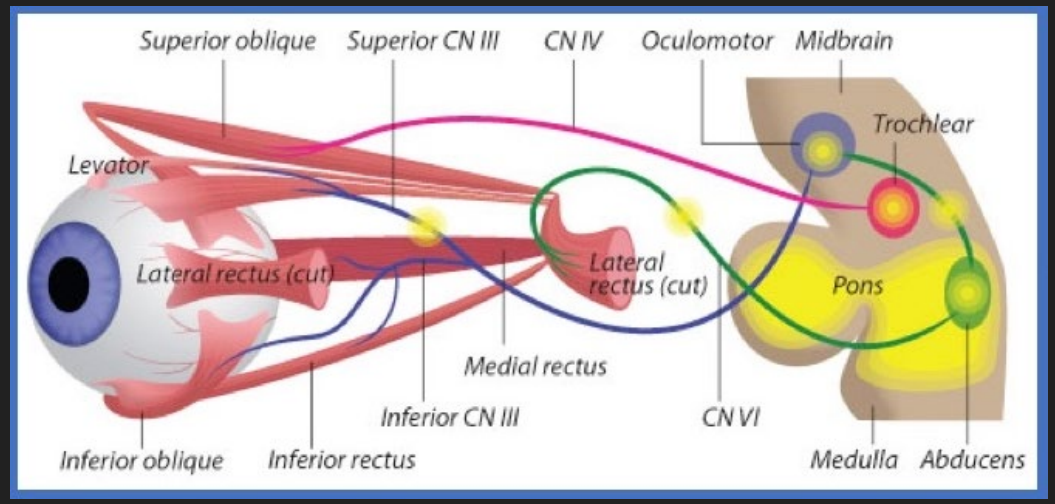


Image source: Researchgate

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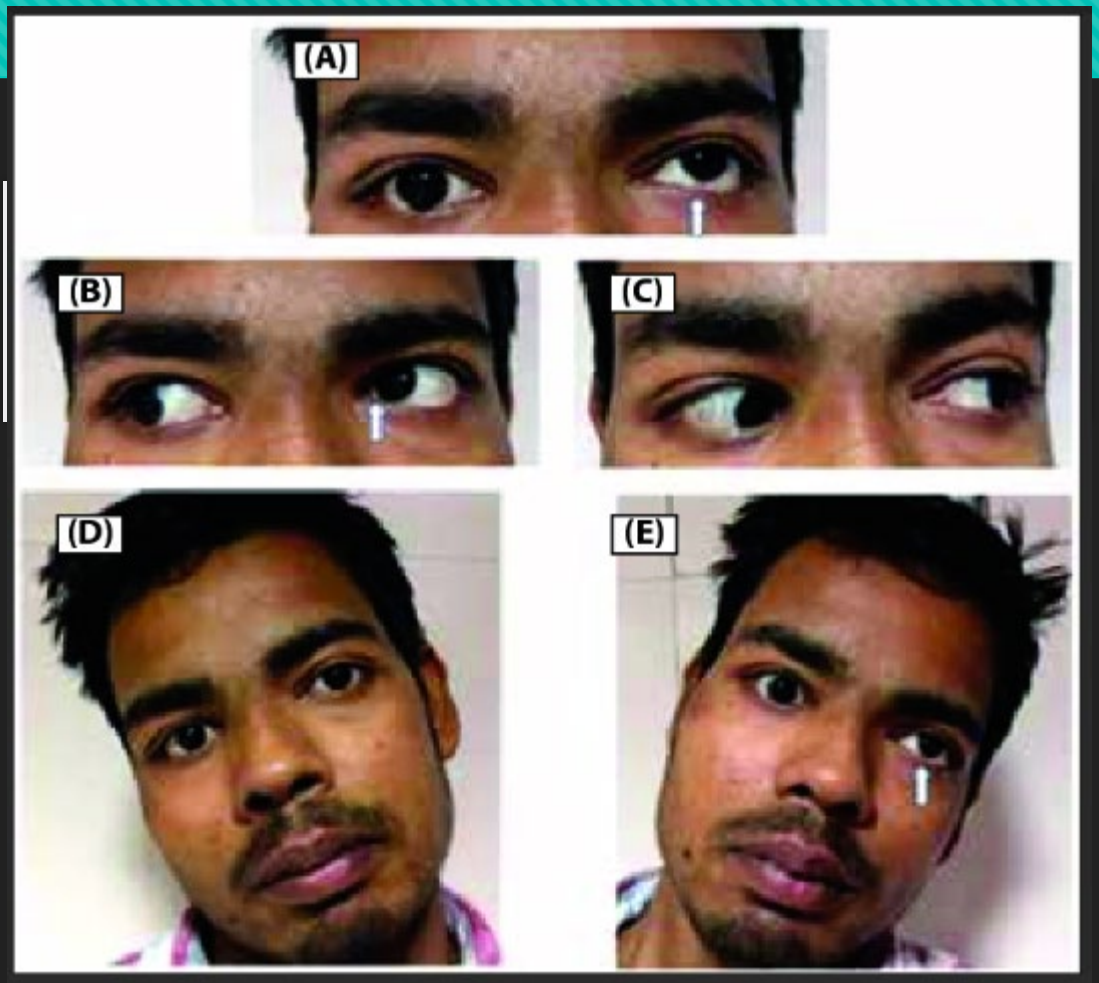


Image source: Researchgate

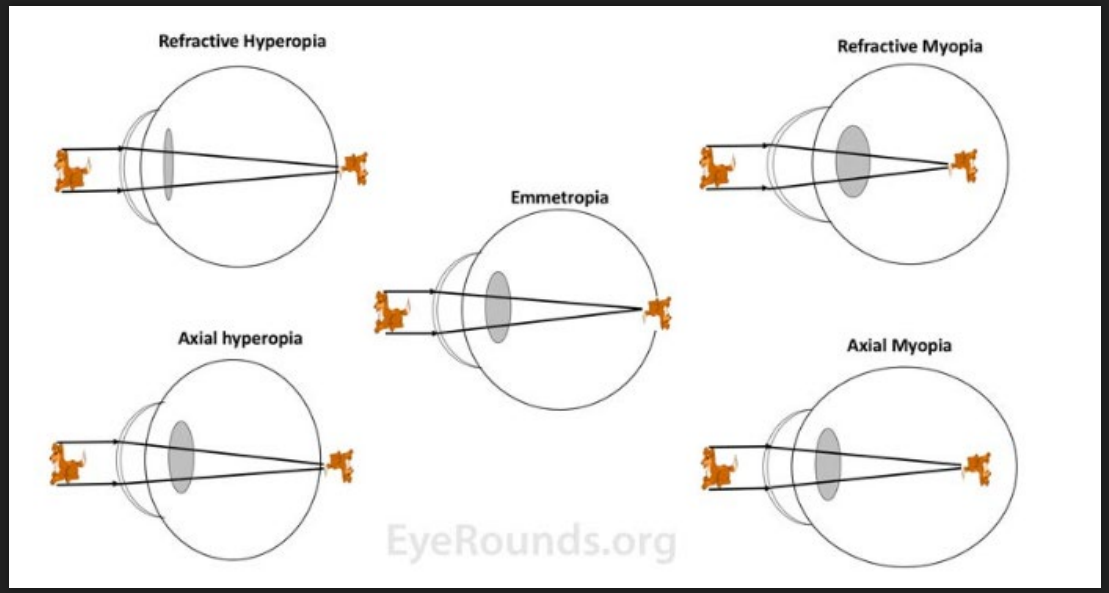
Diabetic Cataracts

- Clouding of the intraocular lens
- Pathogenesis is still not completely understood but it is known that the development is linked to sorbitol production through the polyol pathway.
  - Increased sorbitol production in the lens leads to a collapse and liquefaction of lens fibers resulting in lens opacities.
- Studies have shown a 3-4x increased prevalence of cataracts in patients with diabetes under the age of 65.
- Cataract surgery is safe and recommended in patients with vision 20/40 or worse.

Image source: Khanorkar et al, 2020

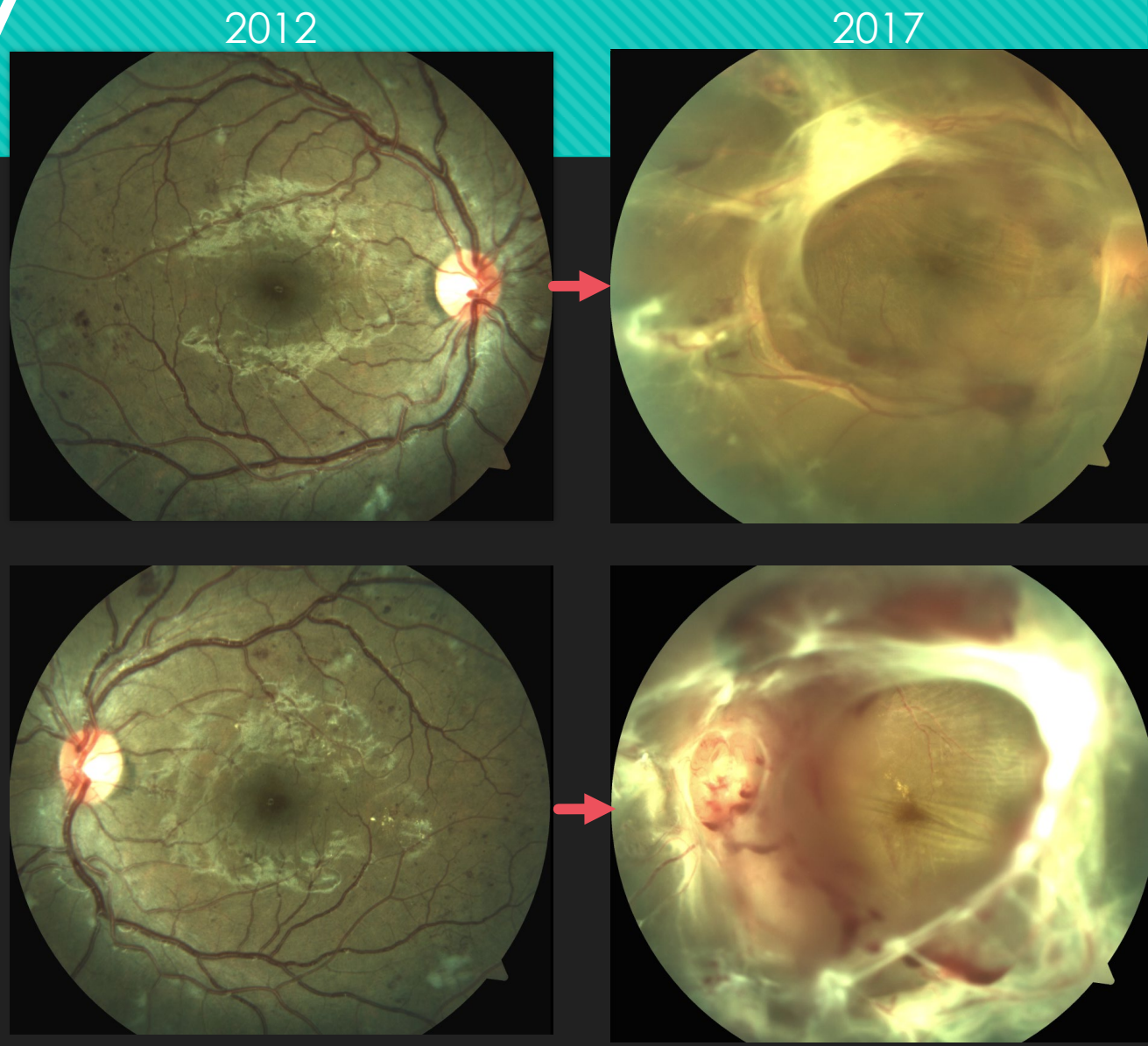
Refractive Shifts

- Hyperopia = distant objects are focused behind the retina
  - Shifts occur when either the effective axial length is decreased or the refractive power of the eye is reduced.
- Myopia = distant objects are focused in front of the retina
  - Shifts occur when either the axial length of the eye is increased or the refractive power of the eye is increased.
- Both myopic and hyperopic shifts can occur from hyperglycemia due to changes in water distribution within certain parts of the lens.
  - Sudden refractive changes are due to changes in osmotic pressure in the lens (swelling or dehydration)
  - BILATERAL

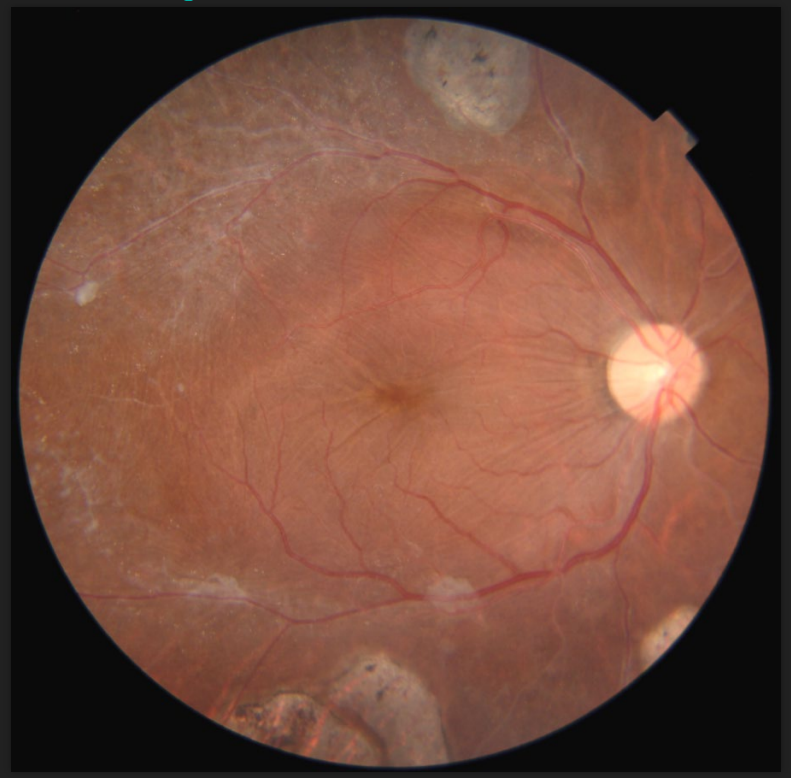


Diabetic Retinopathy

- Retinal vascular abnormalities that occur as a result of control and/or duration of diabetes.
  - Duration of disease and sustained hyperglycemia are primary risk factors
- In the United States, it is estimated that 40.3% of adults >/= 40 yo with diabetes have diabetic retinopathy.
  - The number of Americans >/= 40 yo with diabetic retinopathy is projected to triple by 2050
- Broadly classified as Nonproliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR).



Post Surgical



Characteristics of Diabetic Retinopathy

1. Retinal blood flow alterations
   - Not readily observed in a clinical setting
2. Microaneurysms – saccular outpouchings of retinal capillaries due to a loss of intramural pericytes
3. Hemorrhages – caused by ruptured or leaking microaneurysms
4. Hard exudates – lipid and proteinaceous material leaked from the impaired blood-retinal barrier
5. Cotton wool spots – an interruption of axoplasmic flow as a result of focal ischemia
6. Intraretinal microvascular abnormalities (IRMA) – proliferation of pre-existing retinal vessels that serve as shunts through areas of nonprofusion
7. Venous caliber abnormalities – indicators of severe retinal hypoxia that take the form of venous dilation, venous beading, or loop formation.
8. Neovascularization – new vessels signifying the presence of proliferative disease.

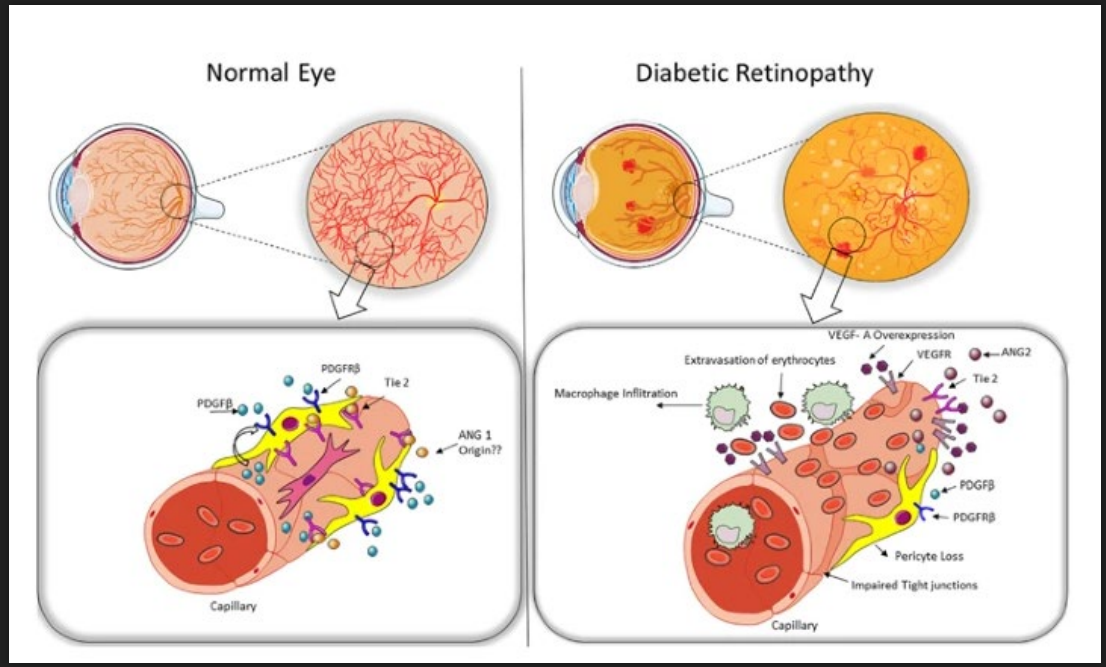
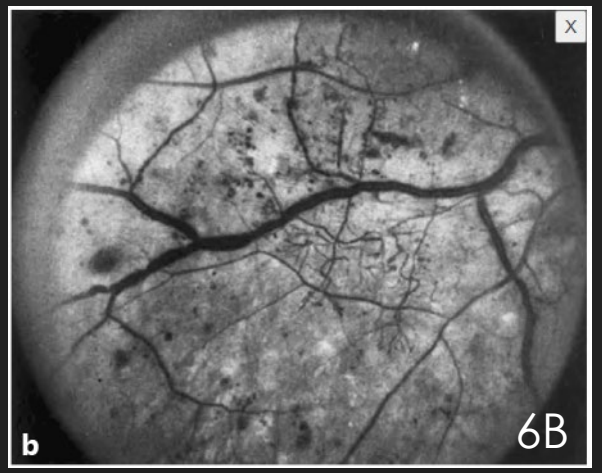


Image source: Santos et al, 2017

Nonproliferative Diabetic Retinopathy

- All diabetic retinal changes before the development of neovascularization.
- Divided into 4 levels
  - Mild NPDR: only hemorrhages and microaneurysms present
    - Severity less than ETDRS standard photograph 2A
  - Moderate NPDR: hemorrhages greater than that depicted in ETDRS standard photo 2A in 1 to 3 quadrants or presence of exudates, cotton wool spots, venous beading, and/or IRMA to a mild degree
  - Severe NPDR: presence of any 1 of the characteristics of the 4-2-1 rule
    - 4 retinal quadrants with hemorrhages greater than ETDRS standard photos 2A
    - 2 or more retinal quadrants with definite venous beading (ETDRS standard photos 6A and 6B)
    - 1 quadrant with prominent IRMA greater than or equal to ETDRS standard photo 8A
  - Very Severe NPDR: 2 or more characteristics of the 4-2-1 rule are met
- Patients may be, and typically are, asymptomatic

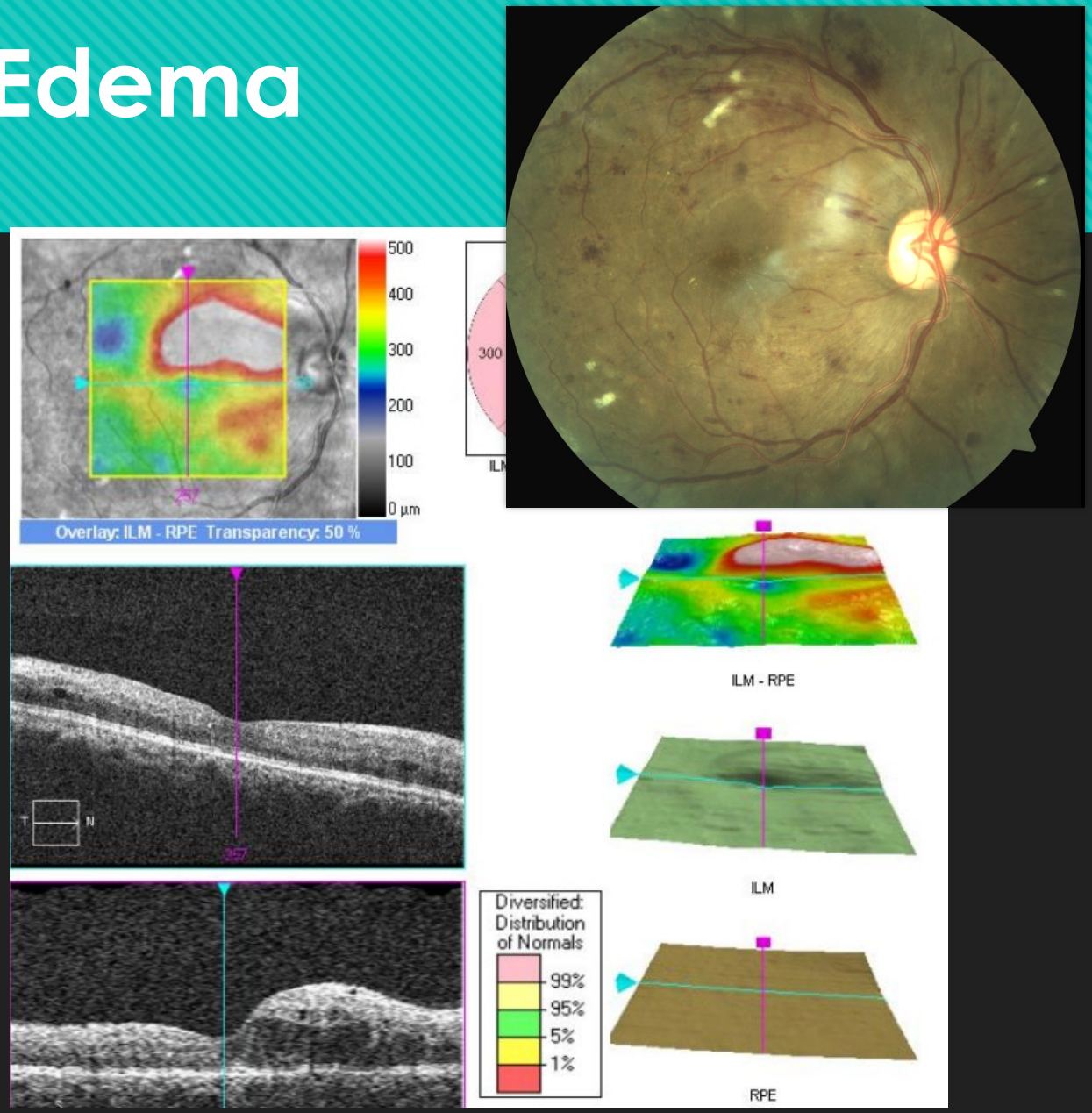


Proliferative Diabetic Retinopathy

- The most severe form of diabetic retinopathy.
- When neovascularization occurs on the iris, angle, optic disc, and/or retina.
- PDR is considered high risk when at least 3 of the following are present:
  - Pre-retinal or vitreous hemorrhage
  - New vessels anywhere
  - New vessels that are on or near the optic disc
  - New vessels on the optic disc that are >/=1/3 of the disc area (standard photo 10A)
- Pts may be asymptomatic

Diabetic Macular Edema

- A collection of intraretinal fluid in the macular area of the retina that can occur with any level of diabetic retinopathy.
- 2 general classifications
  - Non-central-involved
    - Patient may be asymptomatic
  - Central-involved
    - Patient will be symptomatic



Diabetic Retinopathy Management

- Nonproliferative disease without macular edema should be monitored at intervals consistent with severity of disease.
  - Mild NPDR q12months
    - 5% risk of PDR within 1 year
  - Moderate NPDR q6-9months
    - 12-27% risk of PDR within 1 year
  - Severe or very severe NPDR q3-4months
    - 52-75% risk of PDR within 1 year
- Non-central-involved macular edema should be monitored based on the background retinopathy present.
  - Mild NPDR w/ NCIME q4-6months
  - Moderate NPDR w/ NCIME q4-6months
  - Severe or very severe NPDR w/ NCIME q2-3months
- Central-involved macular edema
  - Should be monitored ***only if*** the vision is 20/25 or better at an interval of q2-4months.
  - Should be treated with anti-VEGF injections if the vision is 20/30 or worse
- Non-high risk proliferative disease can be monitored or treated based on the Ophthalmologist's discretion.
- High risk proliferative disease should always be treated.
  - Panretinal photocoagulation
  - Anti-VEGF injections
  - Vitrectomy

pathy Management

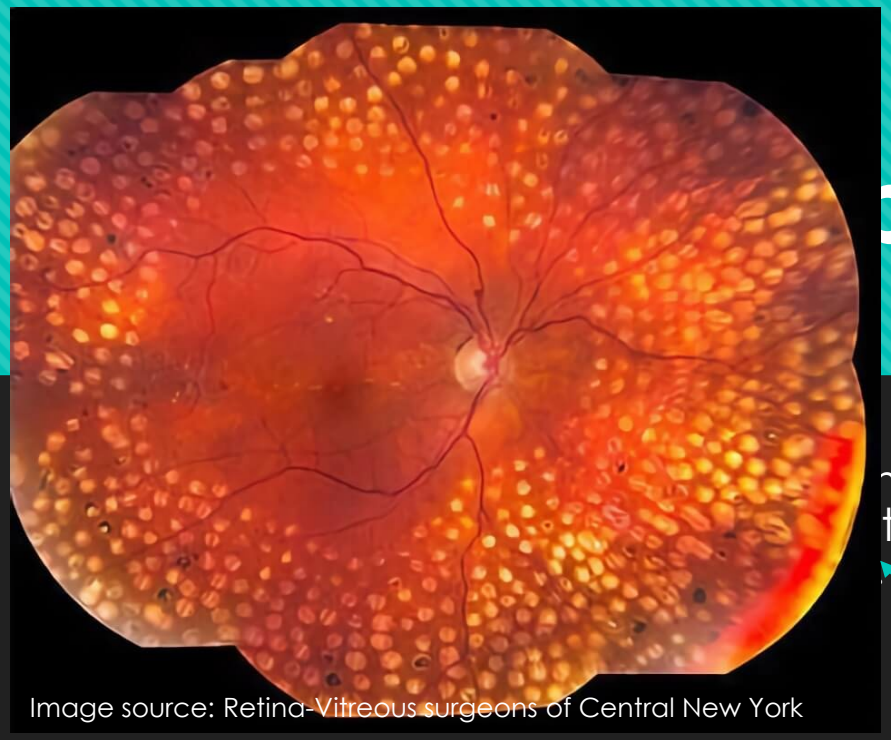


Image source: Retina-Vitreous surgeons of Central New York

- macular
- tervals
- Moderate NPDR q6-9months
  - 12-
- Severe
  - 52-
- Non-centr
  should be
  backgrou
  - Mild NF
  - Moder
  - Severe
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Image source: Eye Physicians and Surgeons of Ontario

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  - Anti-VEGF injections
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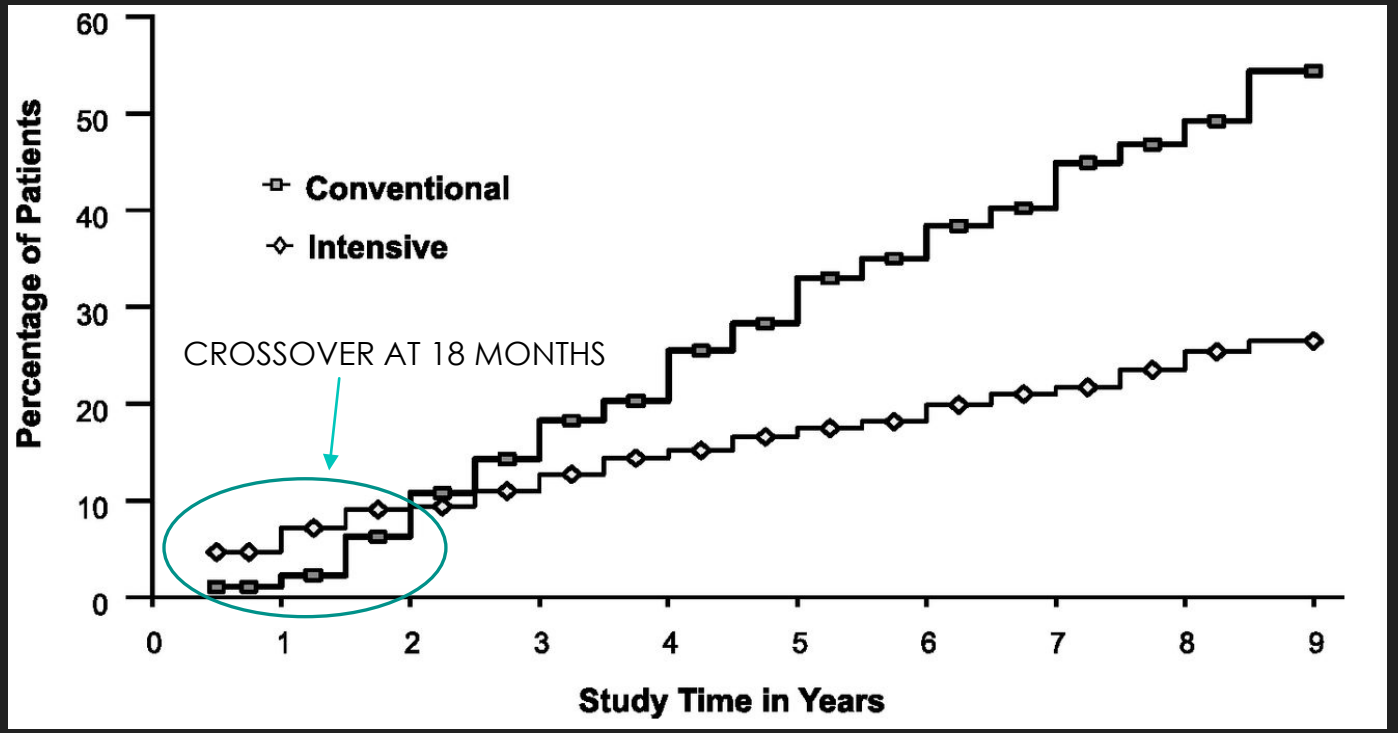
Image source: Retina Specialist in New York

Older, but Important Study

Diabetic Retinopathy and Other Ocular Findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study

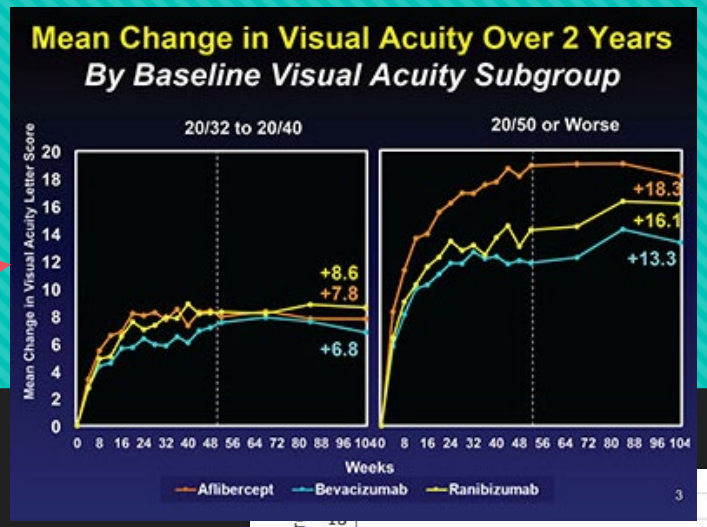
2014

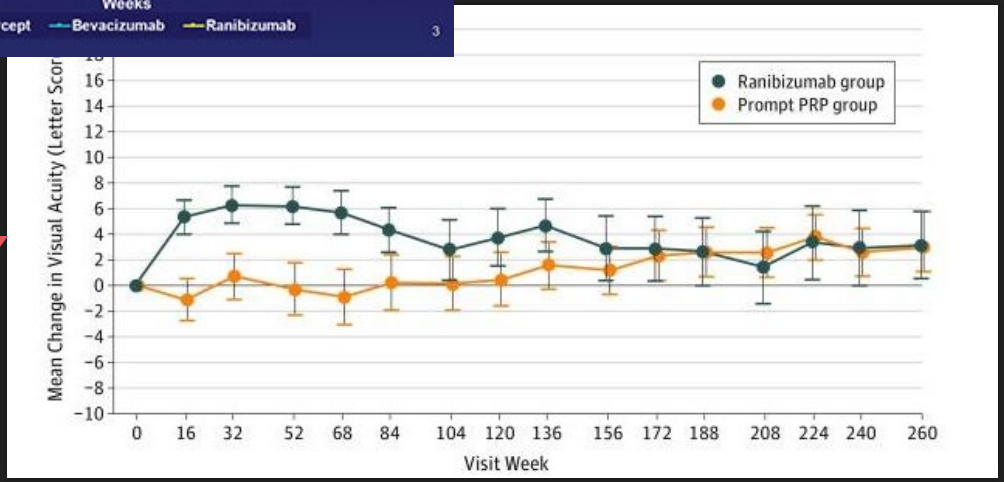
- Purpose: To evaluate whether intensive treatment reduces the risk of onset and progression of diabetic retinopathy in Type 1 diabetics.
- N=1441
- Subjects followed for an average of 6.5 years
- Intensive treatment resulted in long-term risk reduction in the progression of diabetic retinopathy HOWEVER increased progression did occur in the first year of follow-up.
  - Phenomenon termed "Early Worseneing"
  - Risk factors: high initial a1c, larger magnitude of a1c reduction, duration of DM, and bseline level of retinopathy

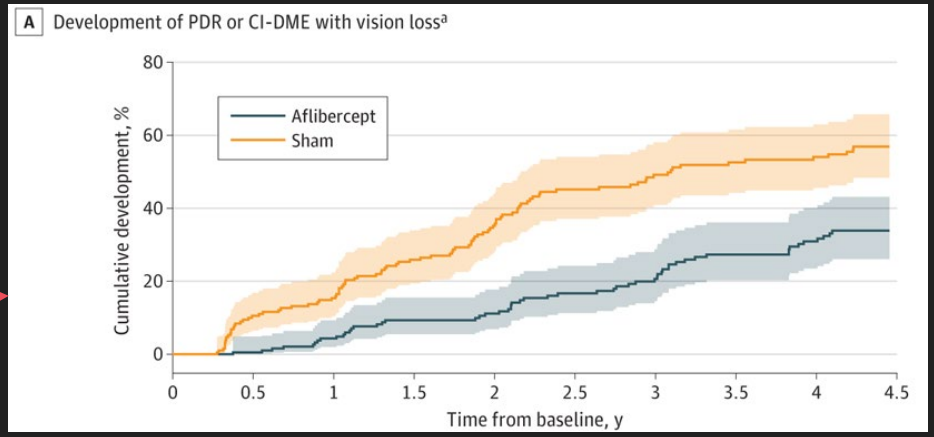


Research

- Protocol T
  - Comparing 3 intravitreal medications (aflibercept, bevacizumab, and ranibizumab) for the treatment of diabetic macular edema.
    - Found no statistically significant difference in patients with mild disease (initial BCVA of 20/40 or better)
    - Found aflibercept to have the most visual and anatomical improvement in patients with worse disease (initial BCVA of 20/50 or worse)
- Protocol S
  - Comparing PRP and anti-VEGF injections for the treatment of proliferative diabetic retinopathy.
    - At 2 years: anti-VEGF injections were found to have favorable results compared to PRP
    - At 5 years: anti-VEGF injections were still non-inferior to PRP but had lost initial favorable gains compared to PRP
- Protocol W
  - Designed to study if anti-VEGF injections are able to prevent proliferative diabetic retinopathy and diabetic macular edema before they happen
    - At 2 years: prophylactic anti-VEGF injections were shown to decrease likelihood of developing PDR or center-involved DME
      - Equal visual outcome if early initiation of anti-VEGF after development of PDR or center-involved DME
      - ~16% of treatment group still progressed to PDR and/or center-involved DME
    - At 4 years: similar results to 2 years
      - 33.9% vs 56.9% progression to PDR and/or center-involved DME in treatment group vs sham group, respectively
      - Ending visual outcome the same in both groups -> preventative anti-VEGF injections are generally not recommended.







Research Continued

- New treatment options being studied:
  - Photobiomodulation Therapy for DME
    - Irradiation by light in the far-red or near-infrared region of the spectrum thought to be able to reduce edema
  - Fenofibrate for prevention of retinopathy progression
    - A cholesterol-lowering medication that may have protective effects on the blood-retinal barrier
  - Tonabersat for DME
    - Connexin hemichannel blocker traditionally used for migraines and epilepsy
      - Increased connexin43 hemichannel opening is associated with diabetic macular edema

Neovascular Glaucoma

- Associated with any condition that causes retinal ischemia.
- A secondary glaucoma that occurs when there is proliferation of fibrovascular tissue in the anterior chamber angle (where the iris and the cornea meet).
  - Fibrovascular tissue causes an outflow issue of aqueous humor leading to significantly increased intraocular pressure
- Management
  - Panretinal photocoagulation
    - With or without anti-VEGF injections
  - Topical IOP lowering medications
  - Glaucoma drainage implant
- Prognosis is poor
  - Early detection is key

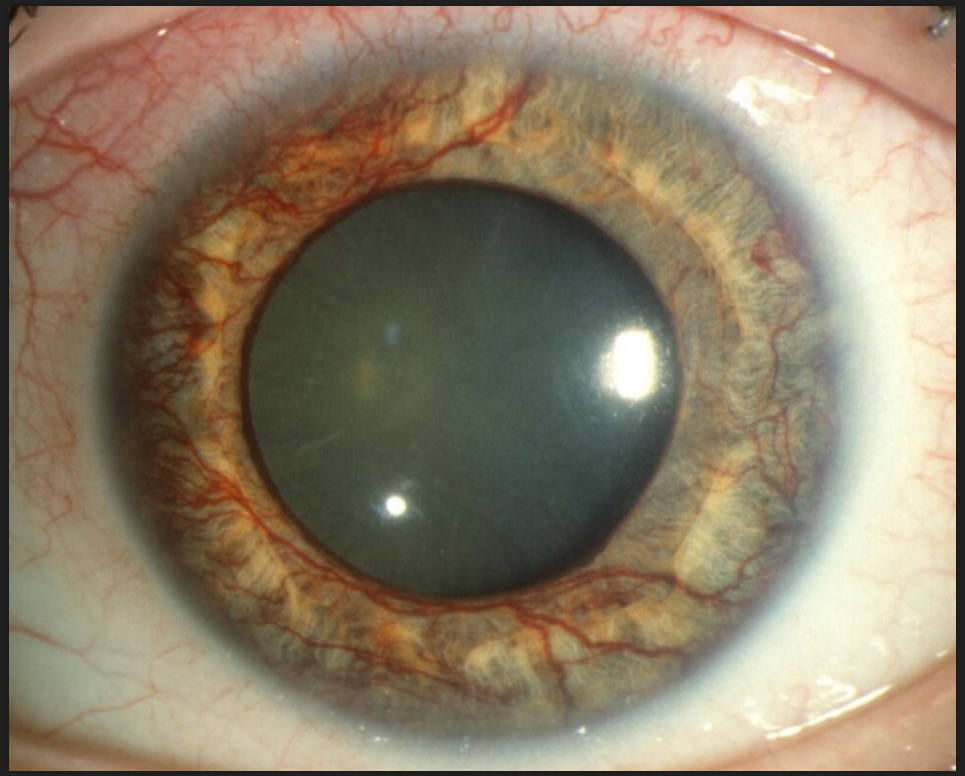
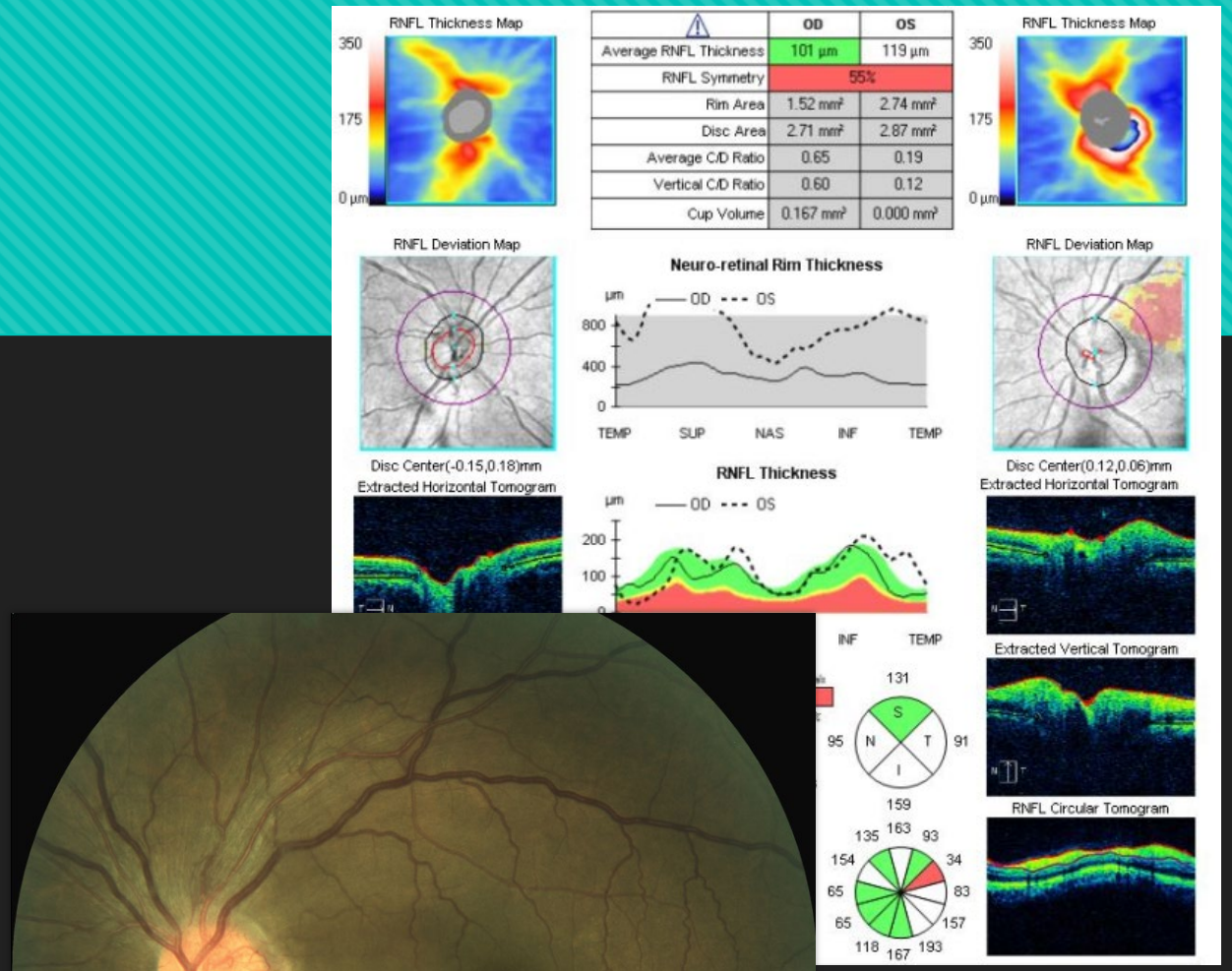


Image source: University of Utah

Diabetic Papillitis

- Optic nerve head edema that is typically unilateral and with minimal symptoms.
  - Estimated incidence: 0.5%
- Pathophysiology is not clearly understood but rapid changes in glycemic control is thought to be contributory.
- A diagnosis of exclusion
  - All inflammatory neuropathies, MRI imaging, and lumbar punctures should be ruled out
- Management: Observation
  - Approximately 1/3rd can progress to nonarteritic ischemic optic neuropathy
  - Spontaneous resolution is typically seen in 4-9 months
- Prognosis is good



Retinal Vascular Occlusions

- 2 Main types: artery occlusions and venous occlusions
- Artery Occlusions
  - Obstruction of the retinal vascular lumen by an embolus, thrombus, or inflammatory or traumatic vessel damage
  - Clinical appearance: retinal whitening
  - Patient will complain of sudden, painless vision loss if the central retinal artery is occluded
    - May have been preceded by episodes of transient vision loss
    - Branch retinal artery occlusions may result in no symptoms or nonspecific visual disturbances
  - Treatment: stroke work-up; very poor visual prognosis

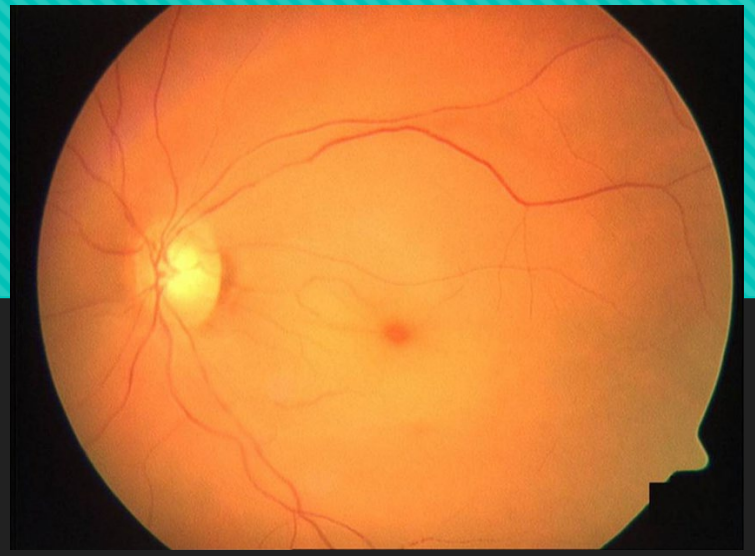
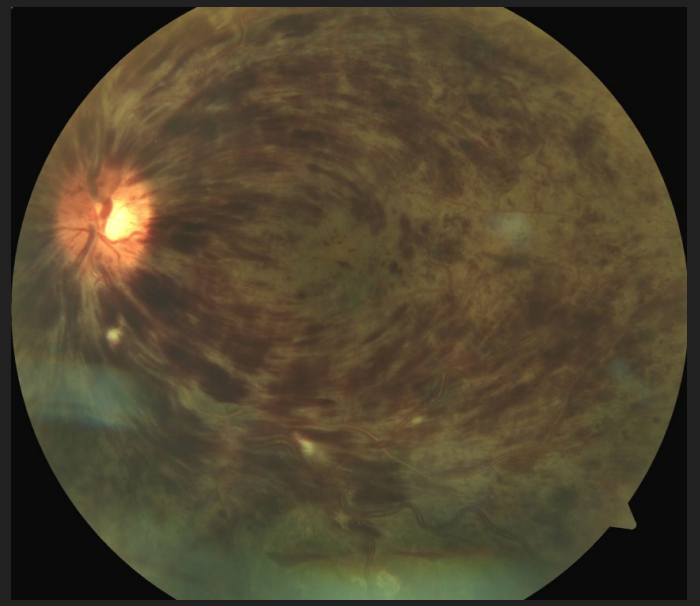


Image source: Researchgate

- Venous occlusions
  - Result from an obstruction of venous outflow typically secondary to atherosclerosis of overlying arterial vasculature
  - Clinical appearance: "Blood and thunder"
  - Patient will complain of sudden, painless blurred vision
  - Treatment: anti-VEGF injections, panretinal photocoagulation
- Can lead to neovascular glaucoma



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Thank You!

- Questions?