OPTIC NEUROPATHIES

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KRESGE EYE INSTITUTE

I have nothing to disclose…but I wish I did.

Road map for this lecture:

1. Anatomy of the Afferent Visual Pathways
2. How we diagnose optic neuropathies
3. Optic Neuritis
4. Ischemic Optic Neuropathy
5. Leber's Hereditary Optic Neuropathy

The Visual System from a Neuro-ophthalmologist's Perspective*

- **Afferent** visual system: **visual perception**

  (incoming information)

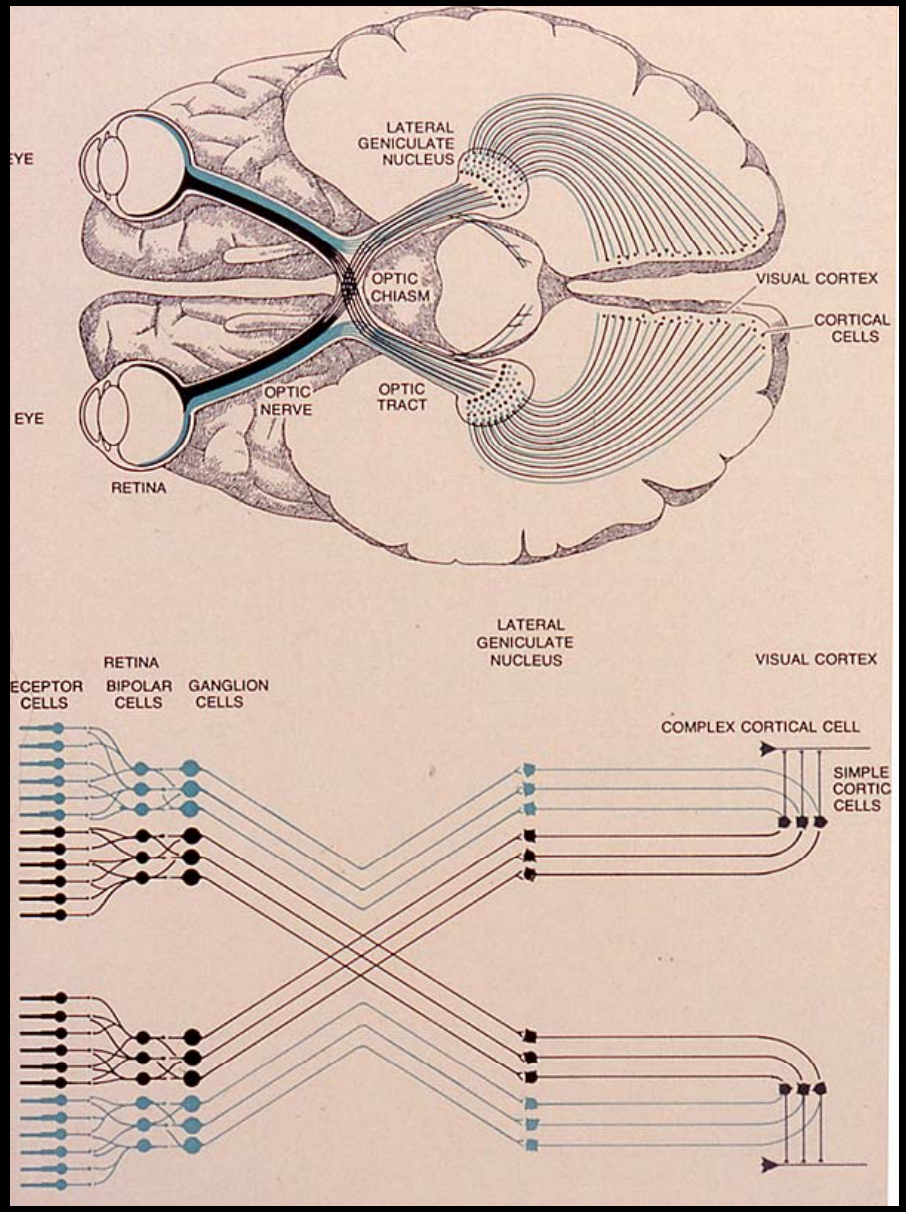
- **Efferent** visual system: **eye movements**

  (outgoing information)

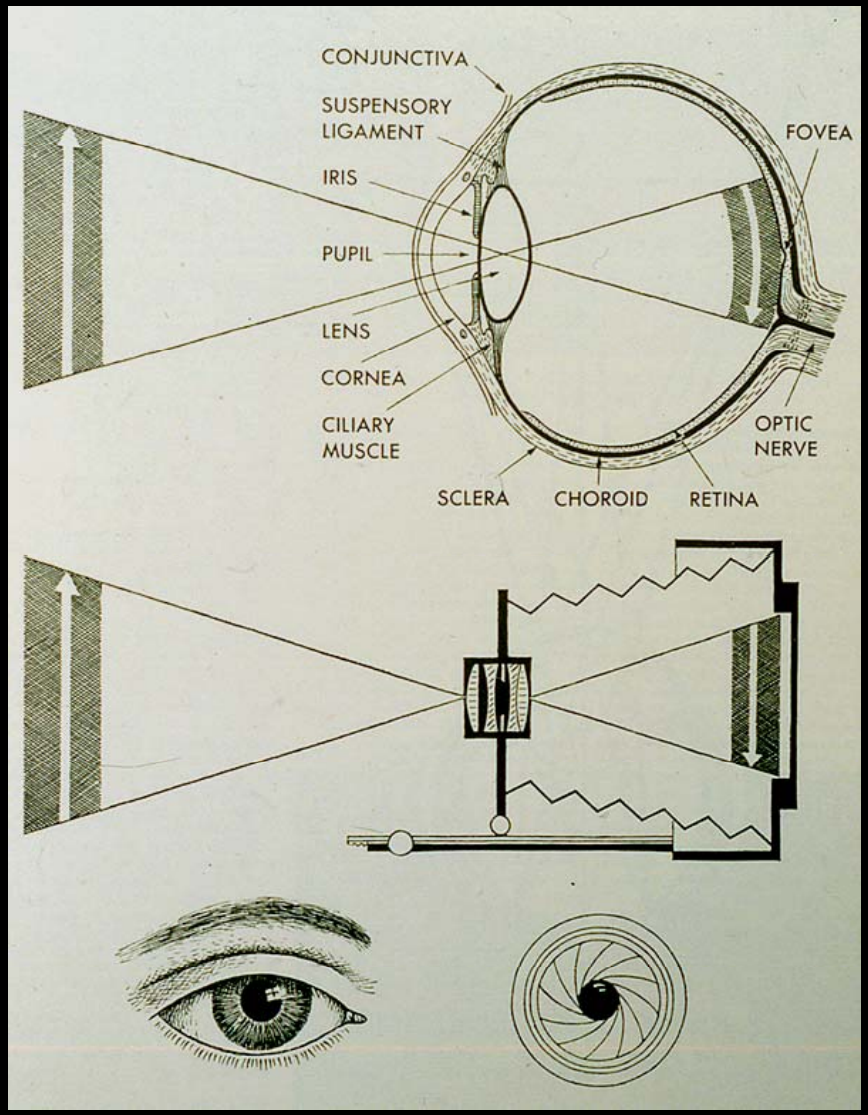
**A clinical neuro-ophthalmologist is a physician who uses ophthalmologic tools and techniques to arrive at neurologic diagnoses*

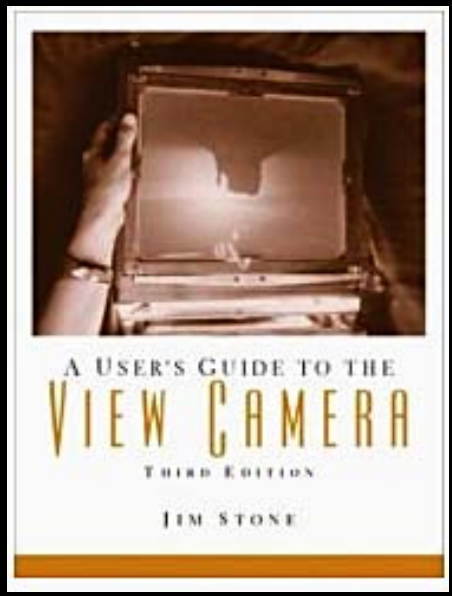
Anatomy of the Afferent Visual Pathways

Anatomy of Vision - 1

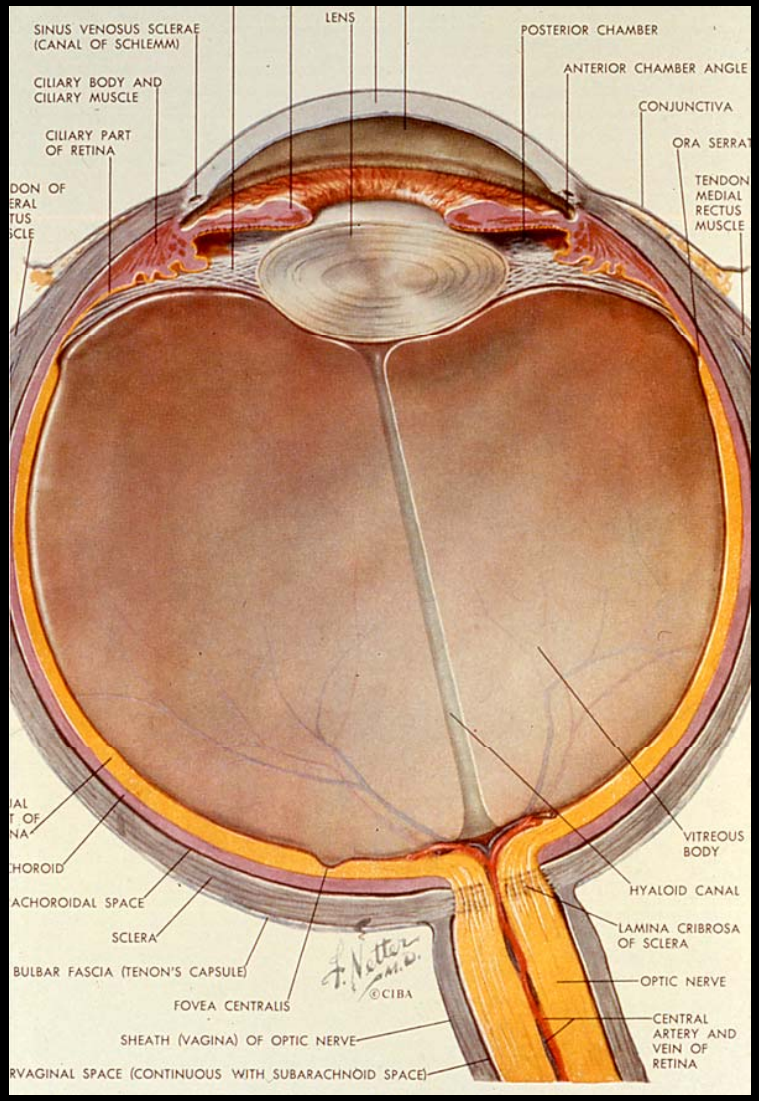


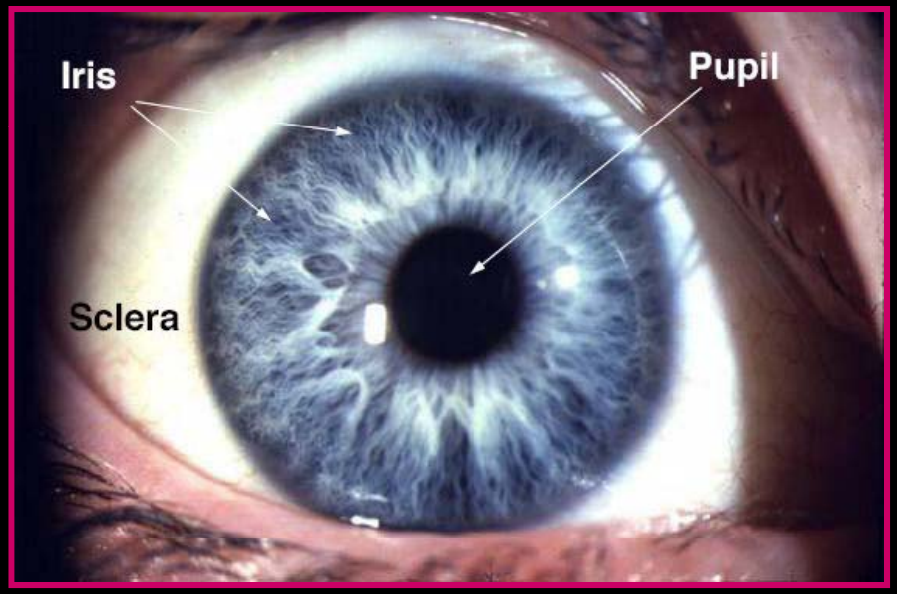
The Eye is Like a Simple Camera



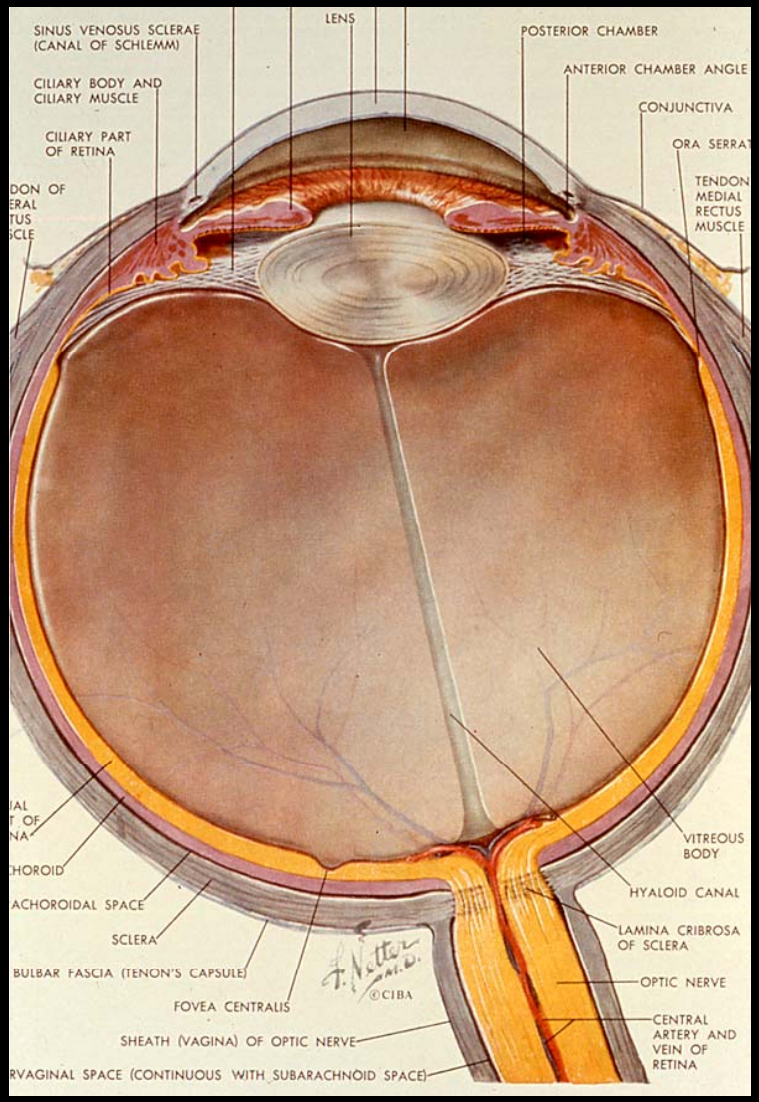


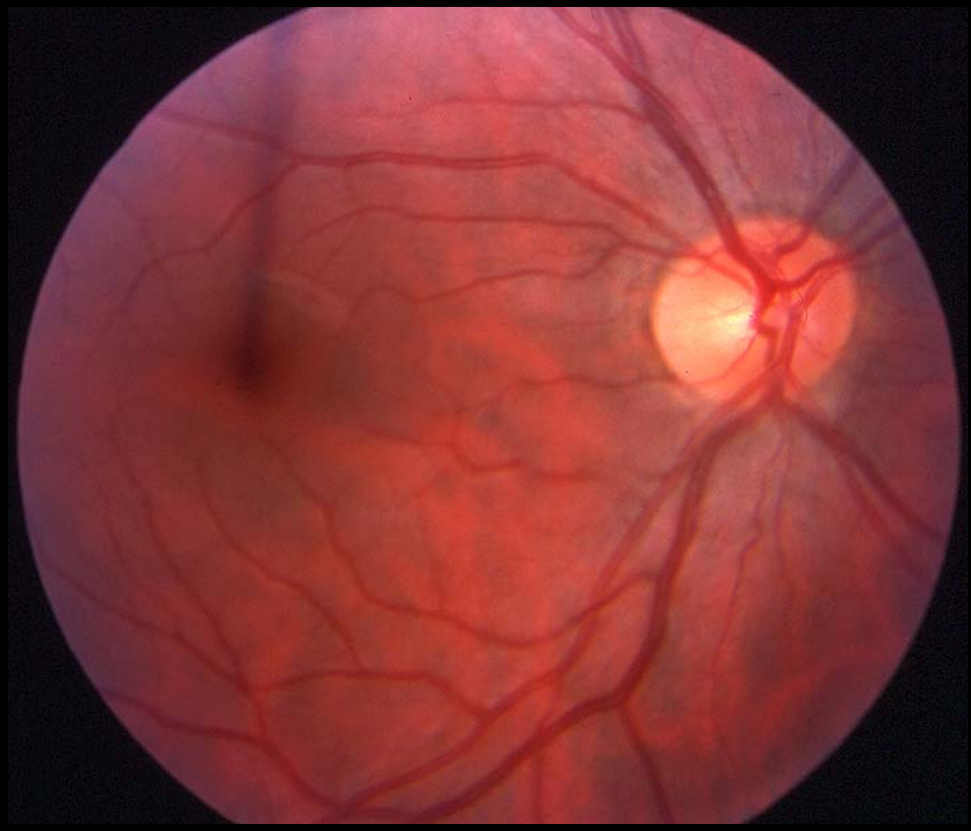
Anatomy of the Eye



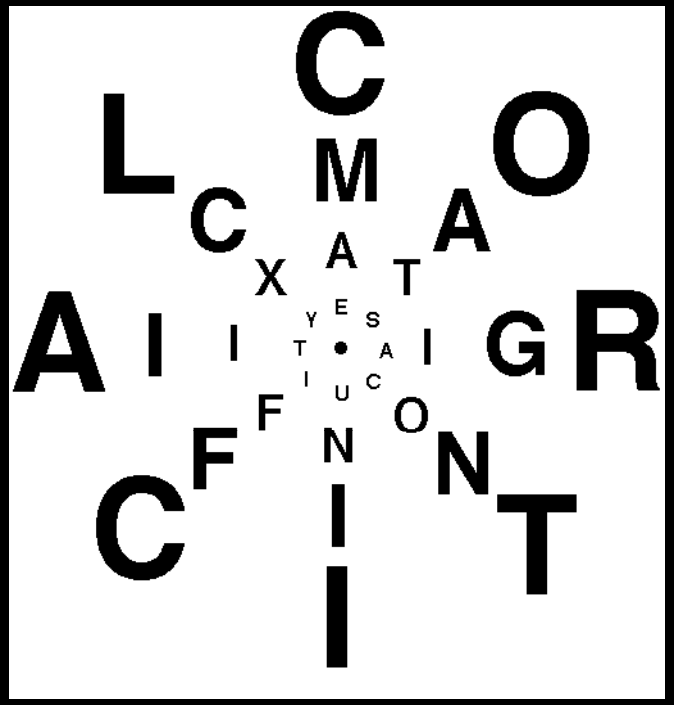


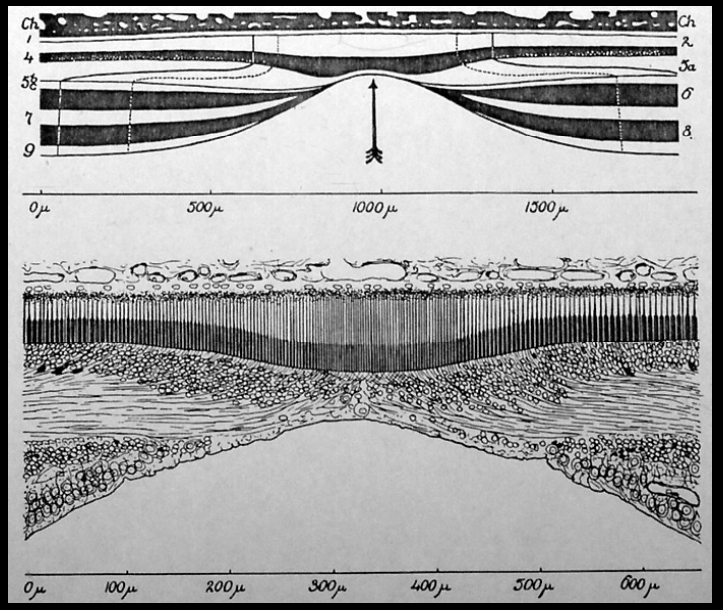
Anatomy of the Eye

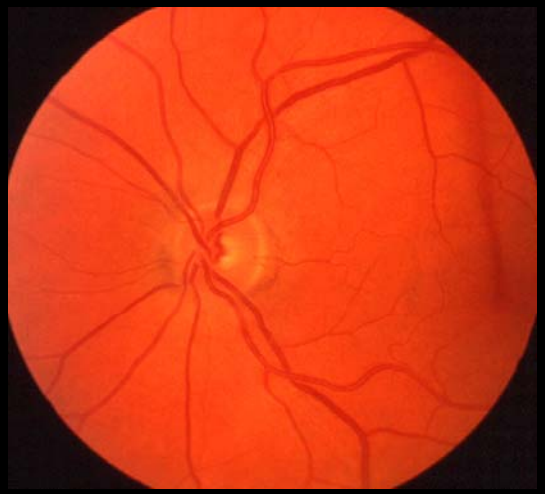


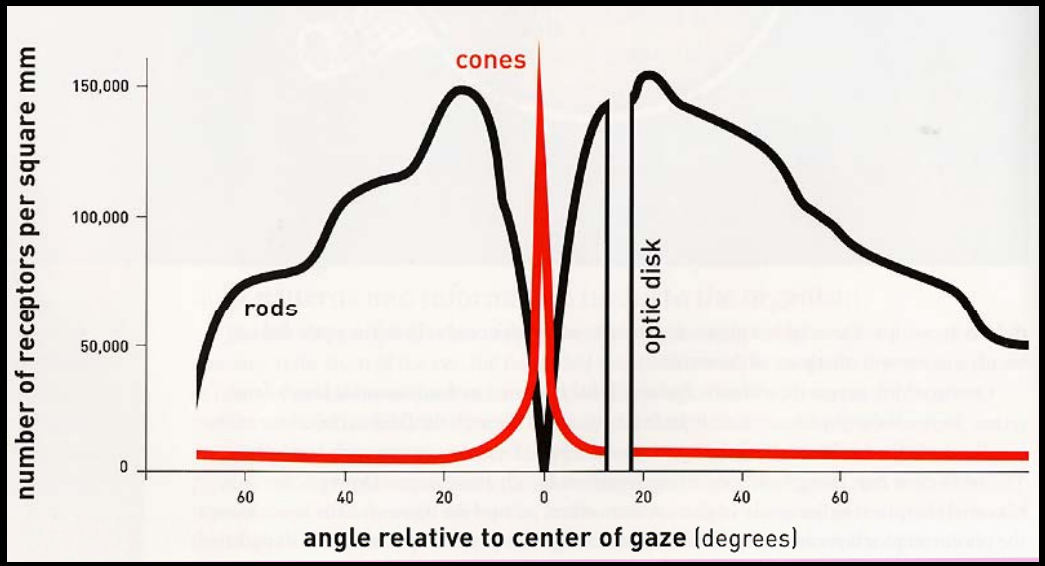


Scaled Acuity Chart



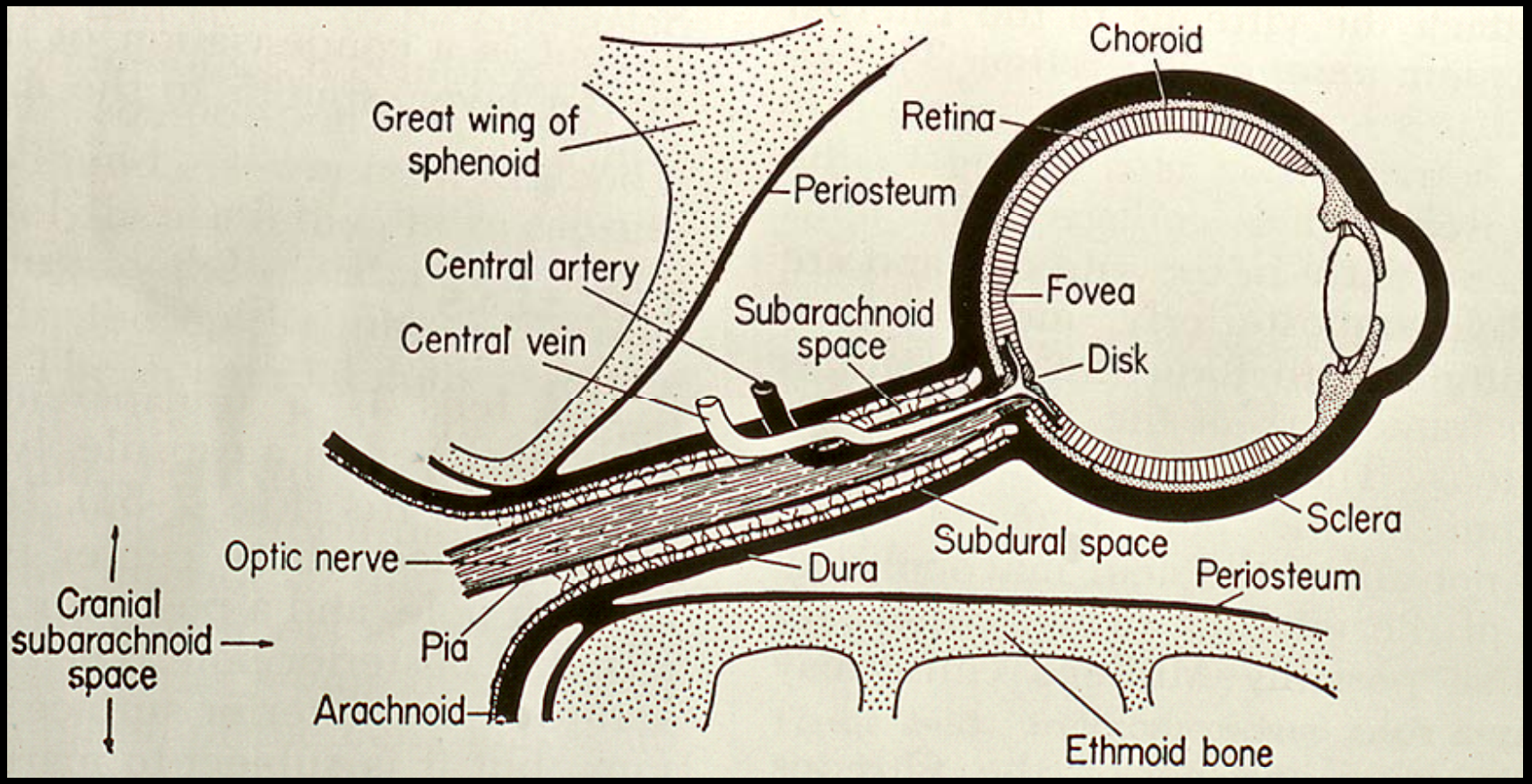




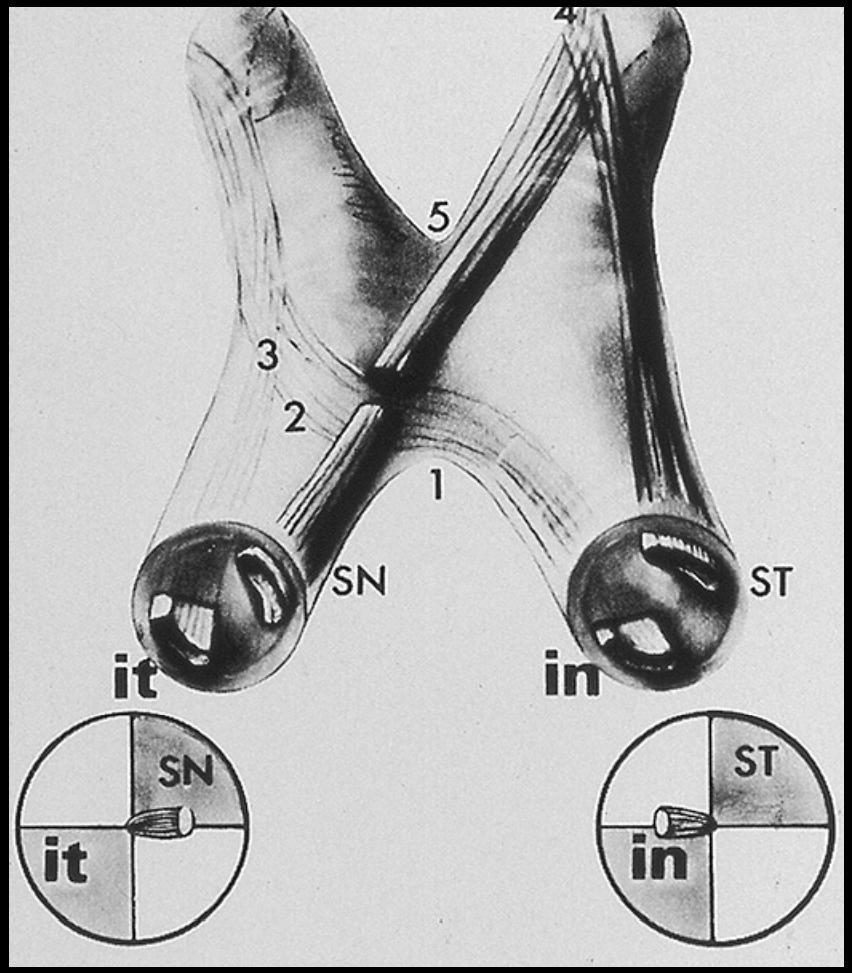


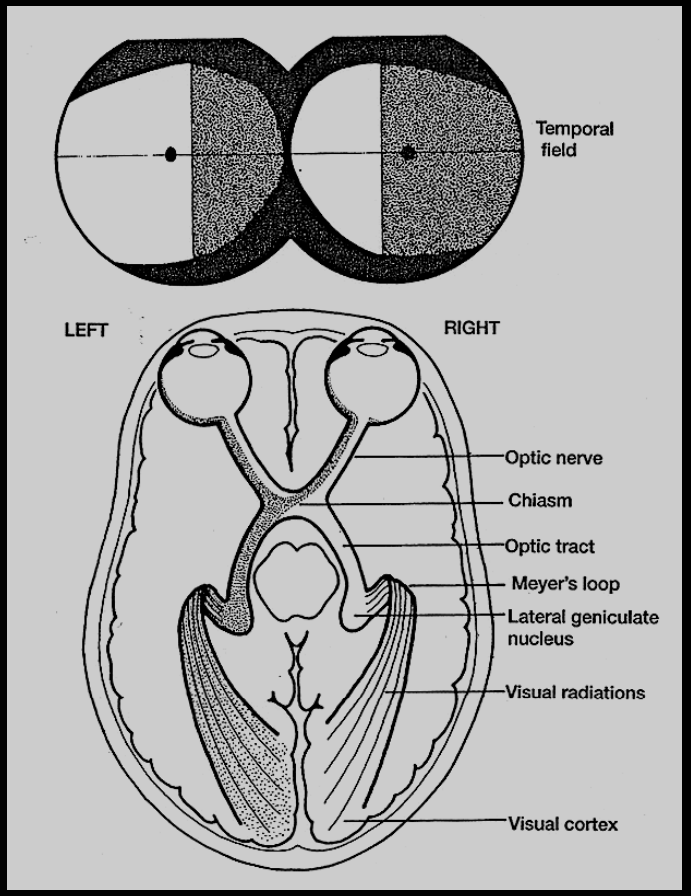
Visual acuity is directly related to cone density

Optic Nerve: Orbit



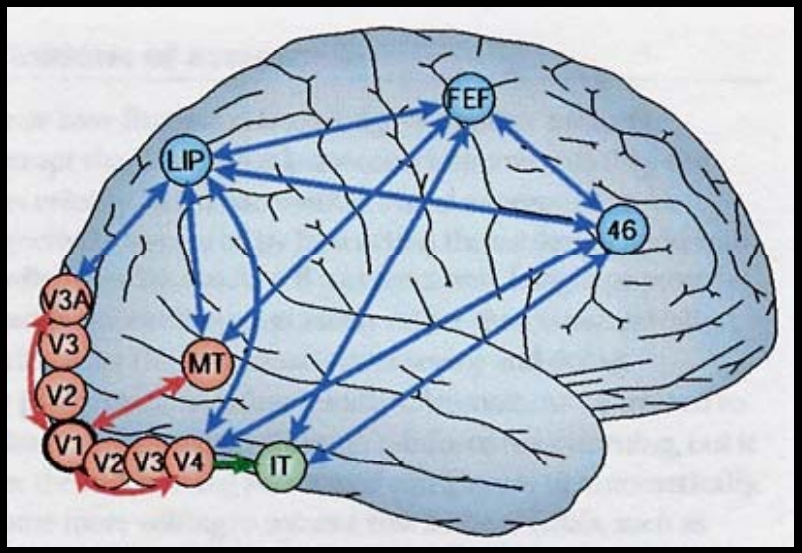
Optic Chiasm

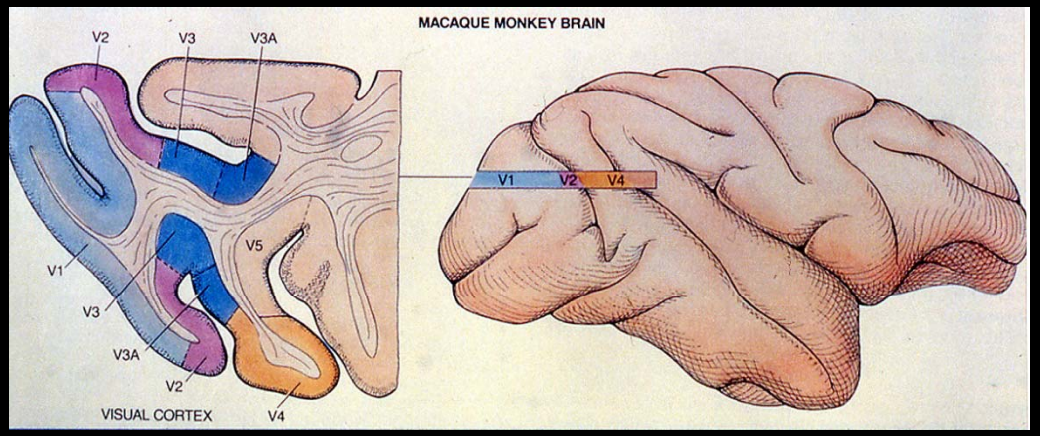


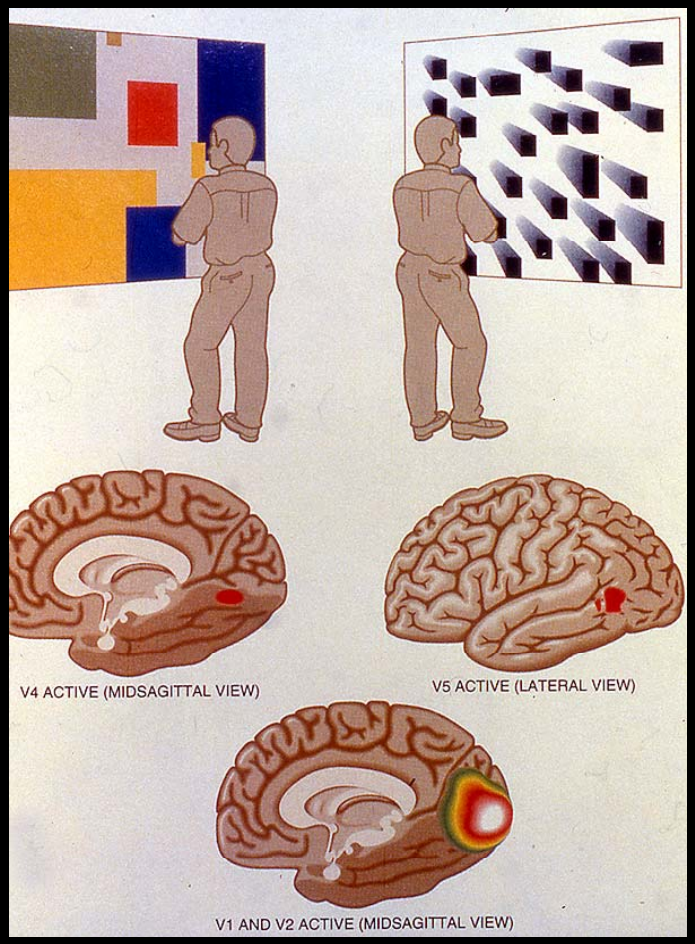


Crossed/Uncrossed = 53/47

The Visual System is Subdivided into Specialized Areas







To Diagnose Optic Neuropathies We Use the "Vital Signs" of Afferent Neuro-ophthalmology

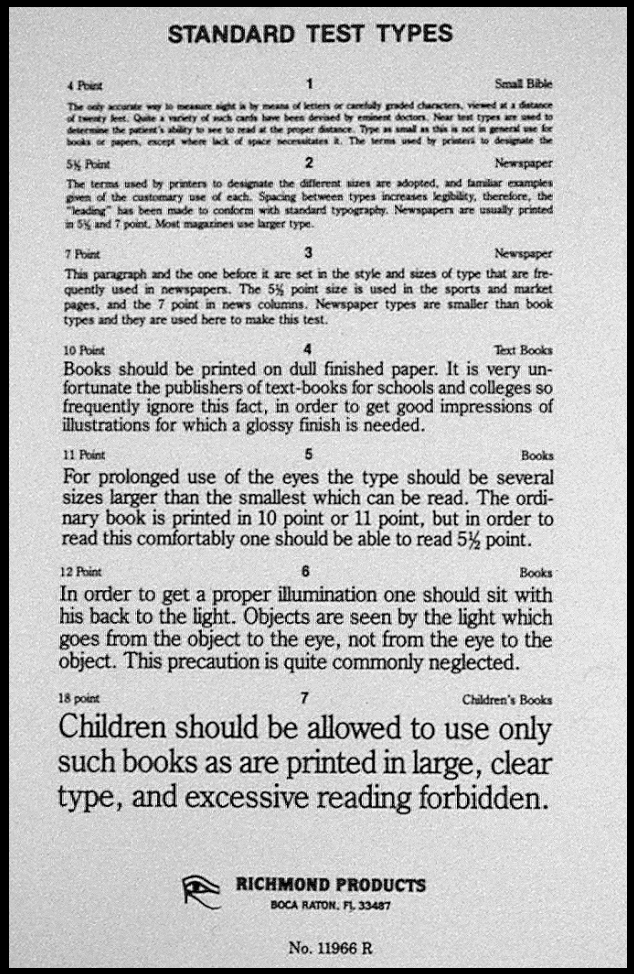
- Visual acuity
- Pupil reactions
  - Looking especially for RAPD
- Some measure of visual fields
- The appearance of the optic nerve
  - i.e. ophthalmoscopy

Examination - *Things You Can (and should) Do Yourself*

- Check near vision
- Check for relative afferent pupil defect
- Do confrontation visual field testing
- Do funduscopy with direct ophthalmoscope

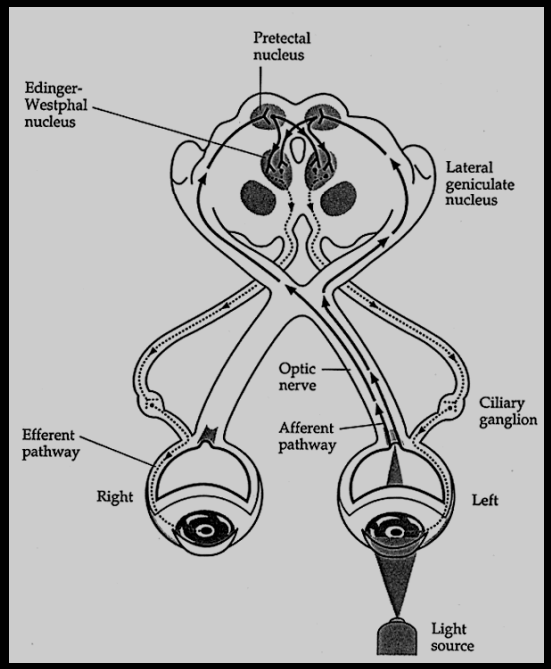
Measure Near Vision ***with Correction***

Tests how they see

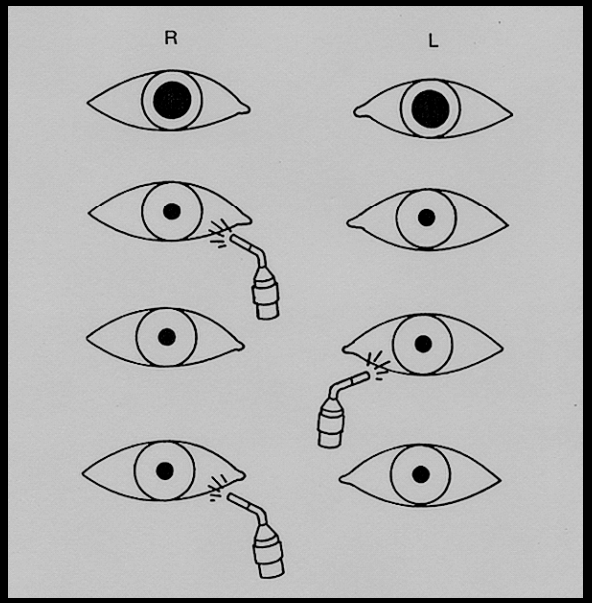


Tests how they see *and* how they read

Normal Pupil Response to Light and RAPD



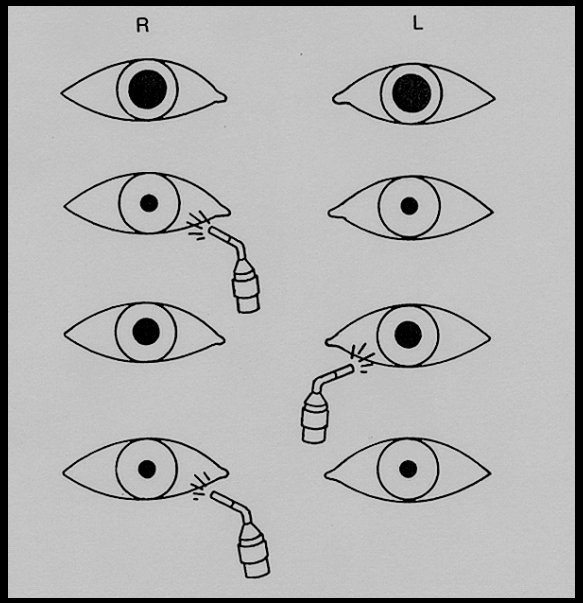
Pupil pathways



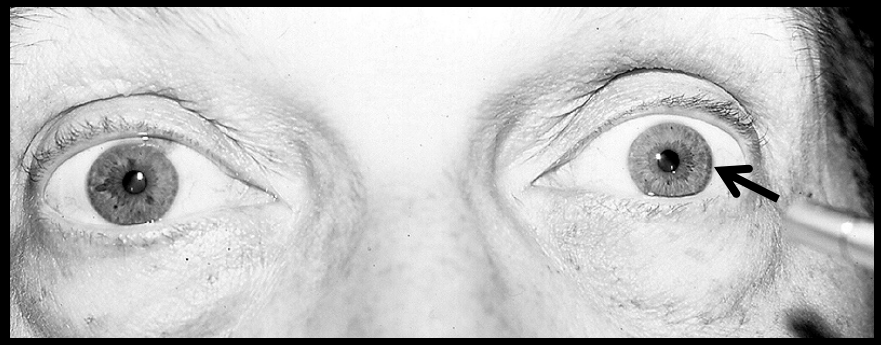
Normal direct and consensual light response

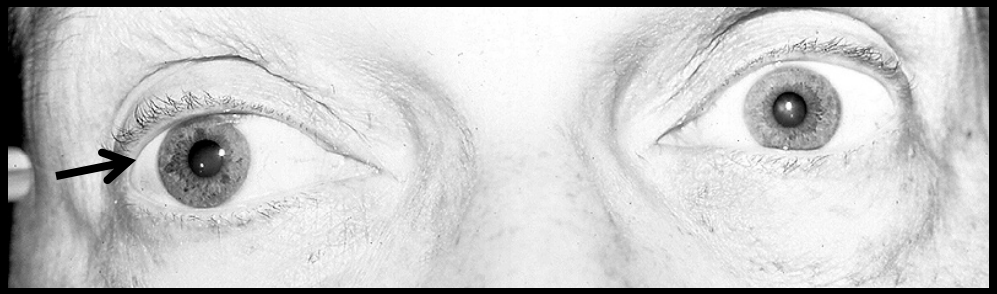
Left relative afferent pupillary defect (RAPD)

(Marcus Gunn Pupil)

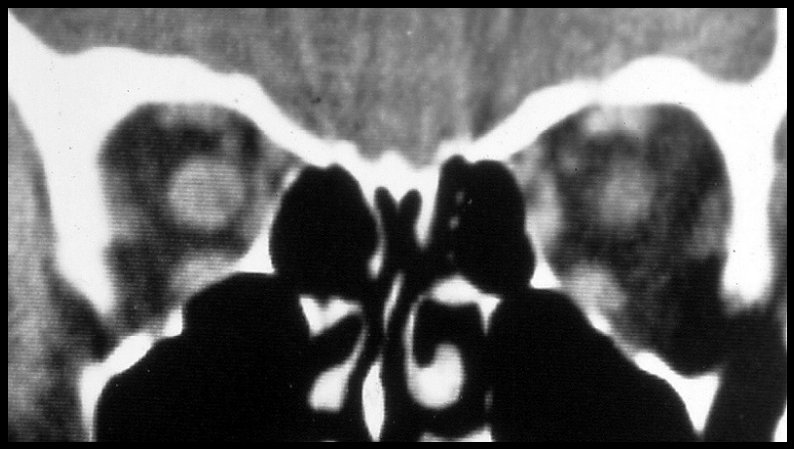


Right RAPD





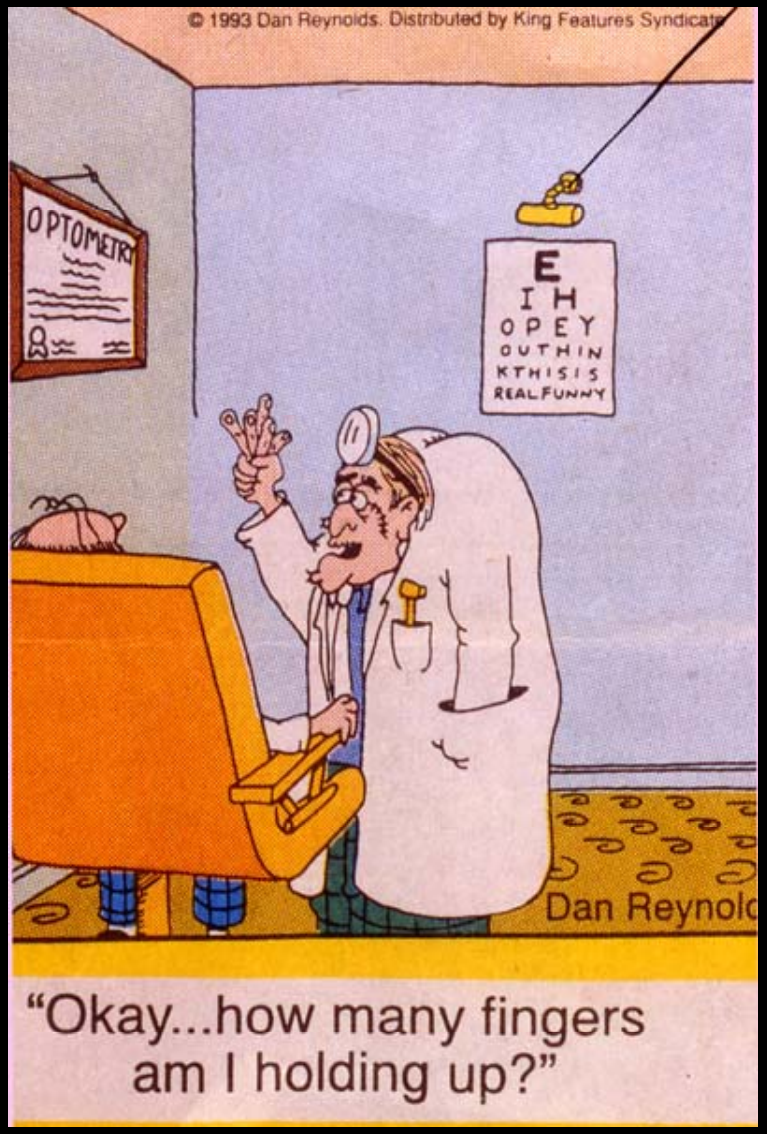
R



R optic n. sheath meningioma

Use a Bright Light

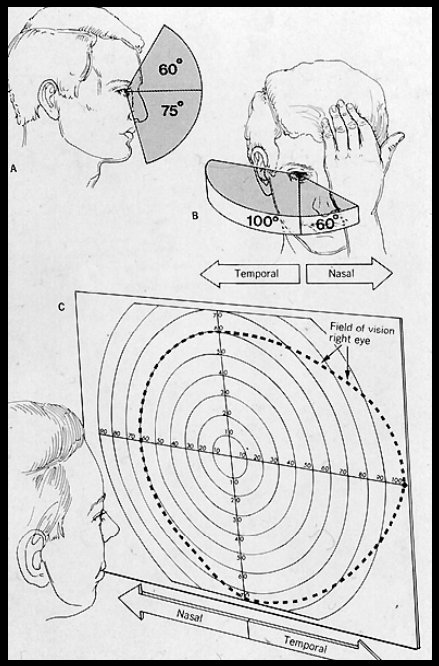
Confrontation Visual Field Testing

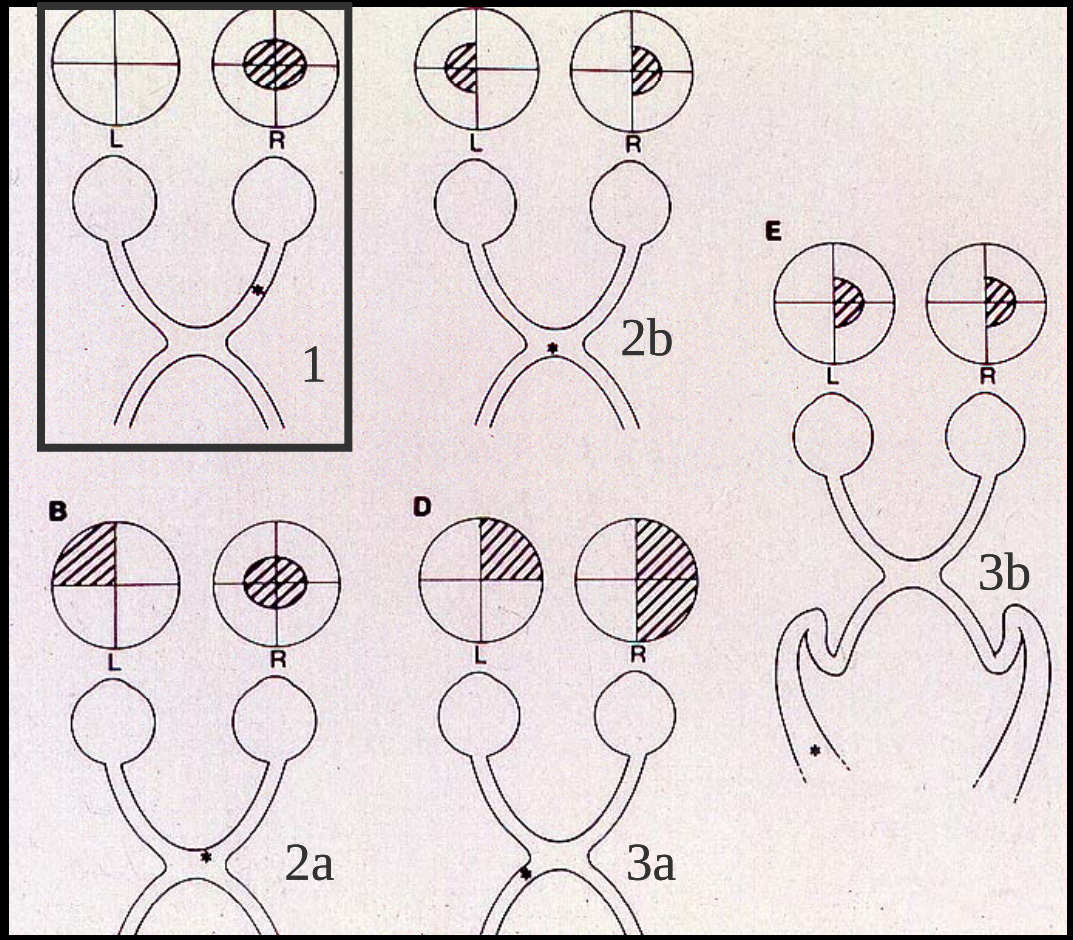


Visual Field Interpretation:

3 Basic Anatomic Regions

- **1. Prechiasmal**
- **2. Chiasmal**
- **3. Retrochiasmal**

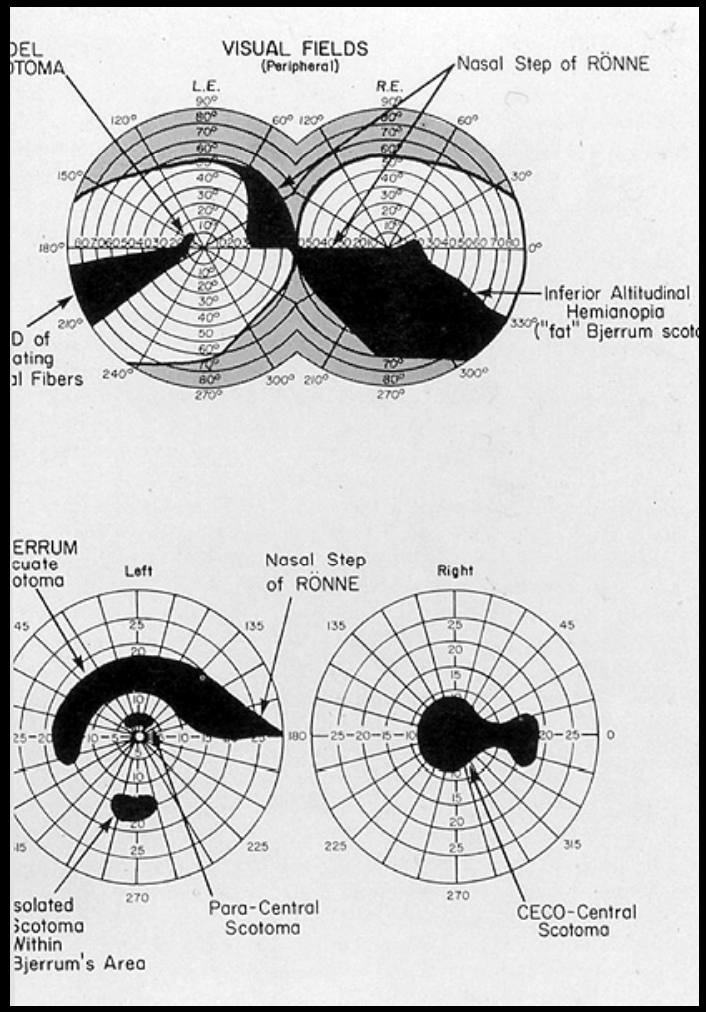




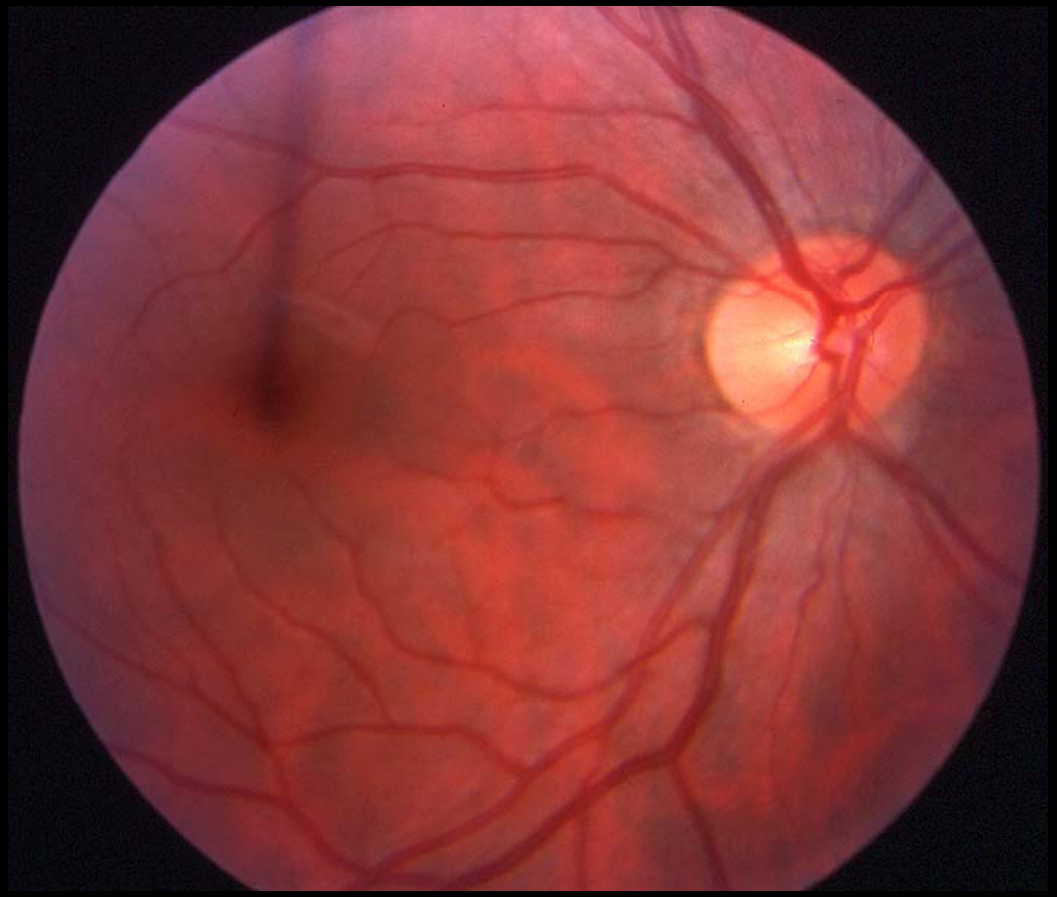
Central Visual Field Loss

- Scotoma ~ “darkness”
- ***Quickly noticed unless slow in onset and unilateral***
- Retina (*we can see the abnormality*) or optic nerve
- Less common: cortical

blindness (*pupils normal*) or chiasmal compromise

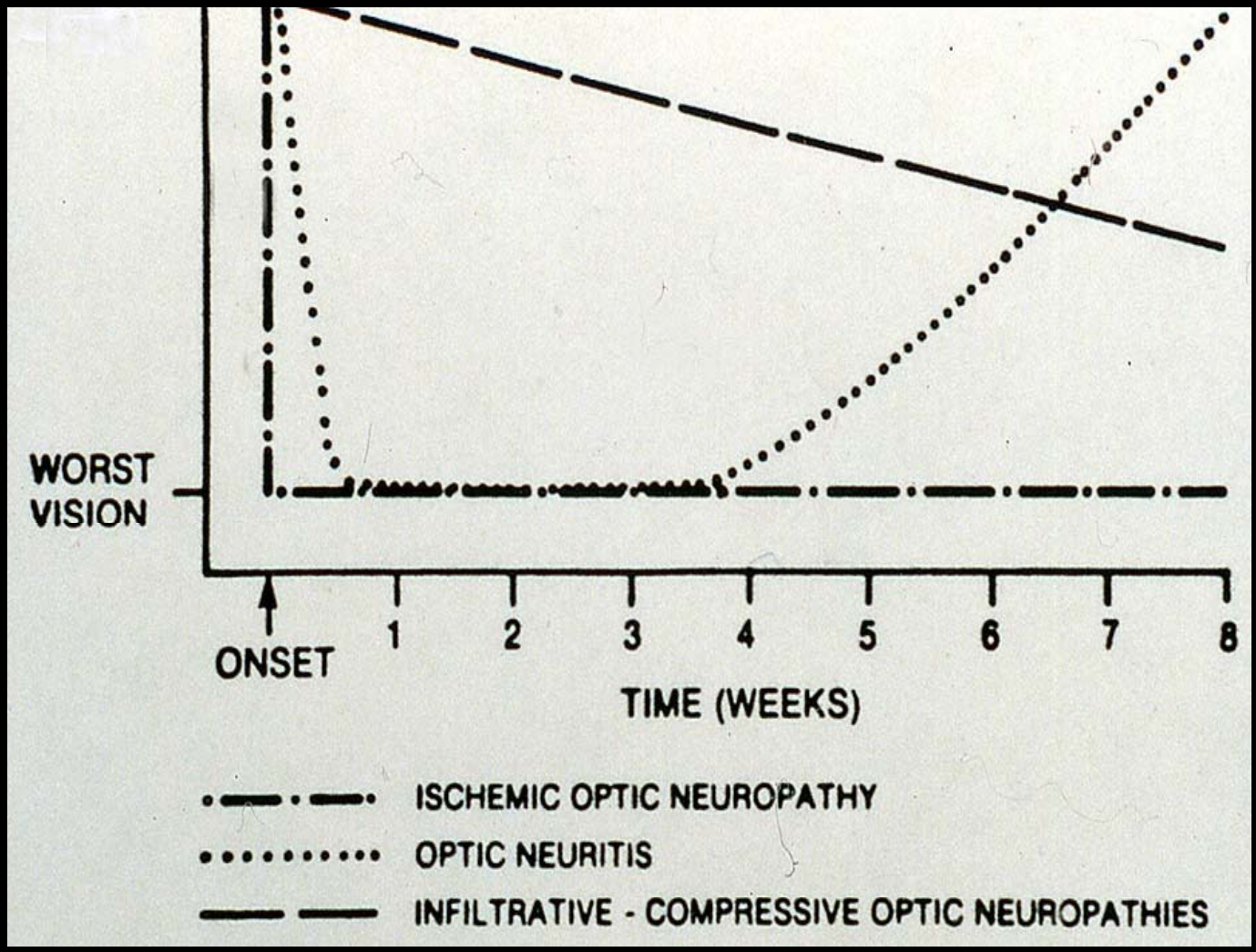


You should be able to see the optic nerve, posterior vessels and macula with the direct ophthalmoscope



Dilating the pupils helps *A LOT*

Temporal Profile of Optic Neuropathies



Lessell, 1968

Optic Neuritis

Clincial Features of Optic Neuritis

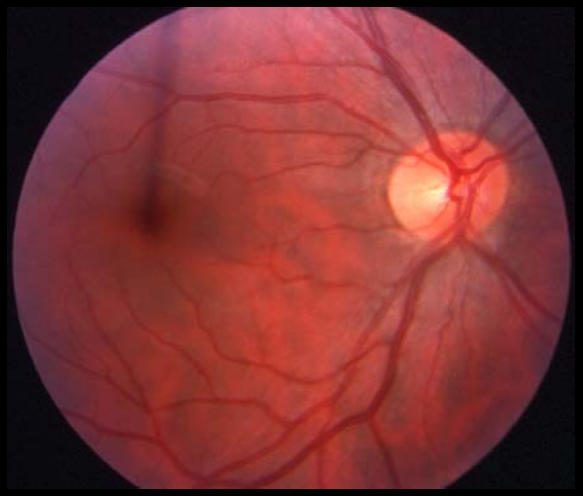
"The lesion of the central vision is usually the first, the most severe, and the last sign of the disease."

- Alfred Kestenbaum

Optic Neuritis - Clinical Profile

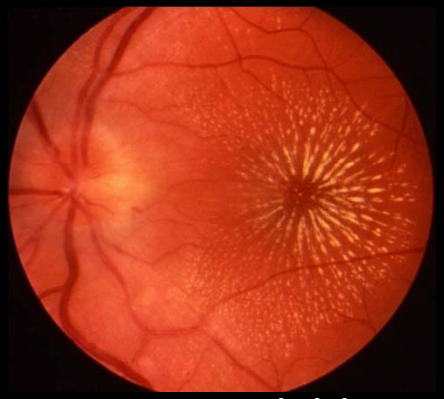
1. Unilateral loss of central vision over hours to days
2. Dyschromatopsia and loss of contrast sensitivity
3. Pain on eye movement (>90%)
4. Relative afferent pupillary defect (RAPD;Marcus Gunn pupil) if unilateral or asymmetric
5. Excellent prognosis for visual recovery in weeks to months, with or without treatment

Optic nerve looks normal on exam 2/3rds of the time , but functions abnormally

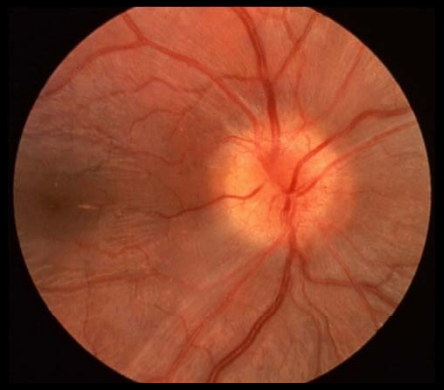


Classification of Optic Neuritis

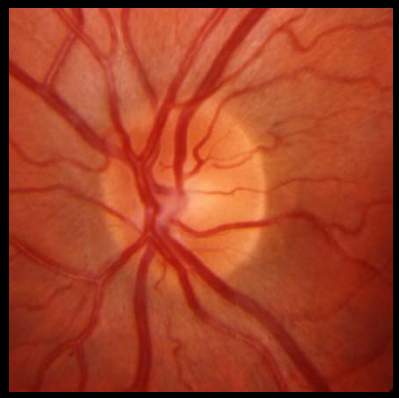
- ***By Site***
  - e.g. Neuroretinitis < papillitis < retrobulbar optic neuritis
- ***By Incidence***
  - Retrobulbar > papillitis > neuroretinitis
- ***By Cause***
  - MS > idiopathic/post-viral > other



Neuroretinitis



Papillitis



Retrobulbar optic neuritis

Differential Diagnosis for Optic Neuritis

- With normal disc:
- Compressive lesions
- Autoimmune
- Toxic/nutritional
- Paraneoplastic
- Retinal mimics

- With swollen disc:
- Ischemic optic neuropathy
- Impending retinal vein occlusion
- Optic nerve drusen
- Diabetic papillopathy
- Papilledema
- Leber's hereditary optic neuropathy

Optic Neuritis Treatment Trial (ONTT)

- Randomized, multicenter study
- 457 patients enrolled
- 15 year f/u
- All had MRI, LP, Chest X-ray, multiple blood tests, complete neurologic exam

Treatment groups:

1) placebo

2) oral prednisone, 1 mg/kg/day for 14 days

3) IV-methylprednisolone, 250 mg q.I.d. for 12 doses followed by oral prednisone 1 mg/kg/day for 11 days

Optic Neuritis Treatment Trial (ONTT)

- Most patients with optic neuritis begin to improve within the 18 days after onset, irrespective of treatment
- OP alone increased ON recurrence rate
- IV-MP + OP decreased ON recurrence rate over 2 year period
- IV-MP + OP decreased the incidence of CDMS occurring in the first 2 yrs by ~ 50%

Analysis of 15 yr ONTT Results

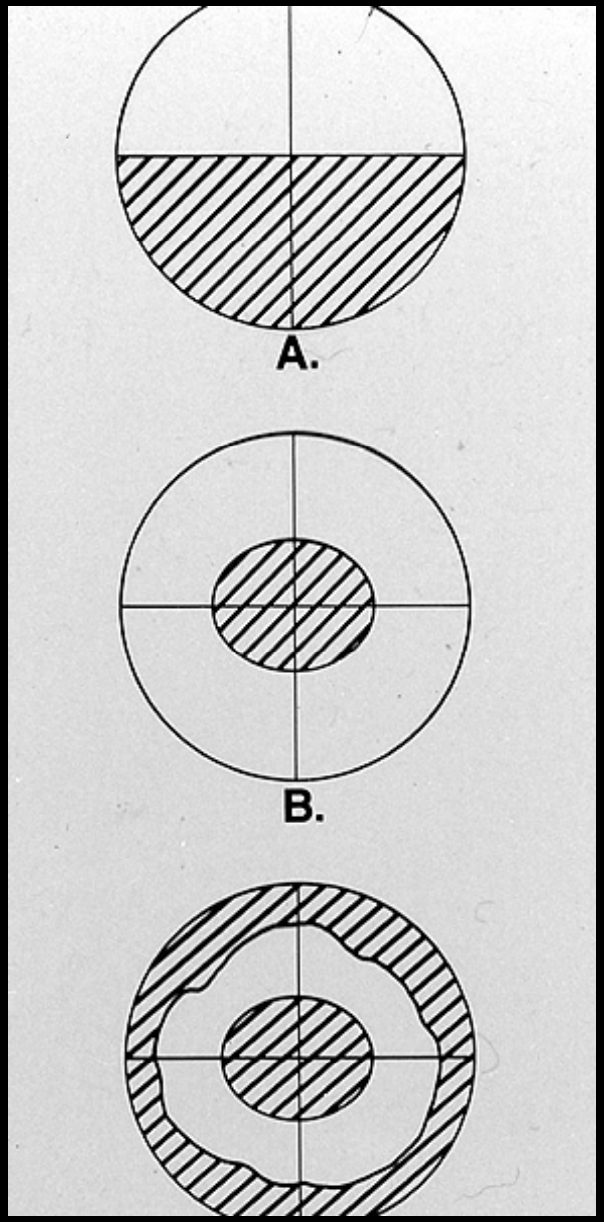
- 389 patients at final tally
- **Risk of CDMS 50% overall**
- **72% if one or more MRI lesion at entry**
- **25% if no MRI lesions at entry**
- VA: 20/20 or better in 72%
- No difference in 3 treatment groups
- Moderate to severe neurologic disability in 35%
- Development of CDMS unrelated to ONTT Rx

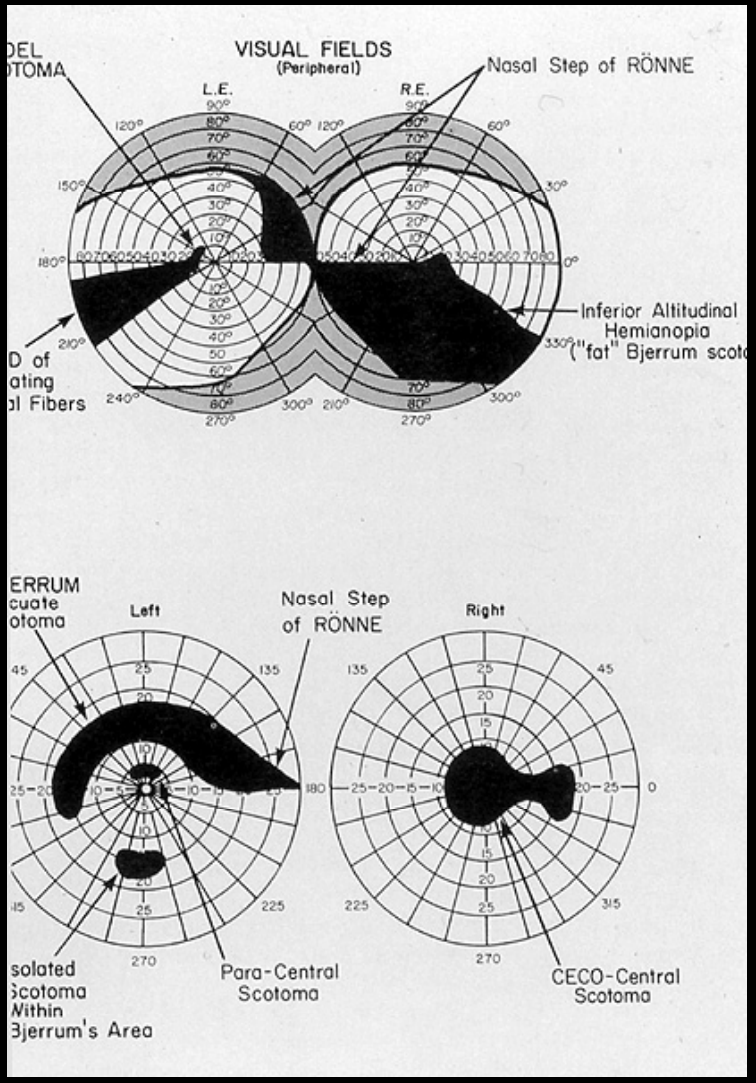
Prechiasmal Visual Field Defects

Altitudinal
Ischemic

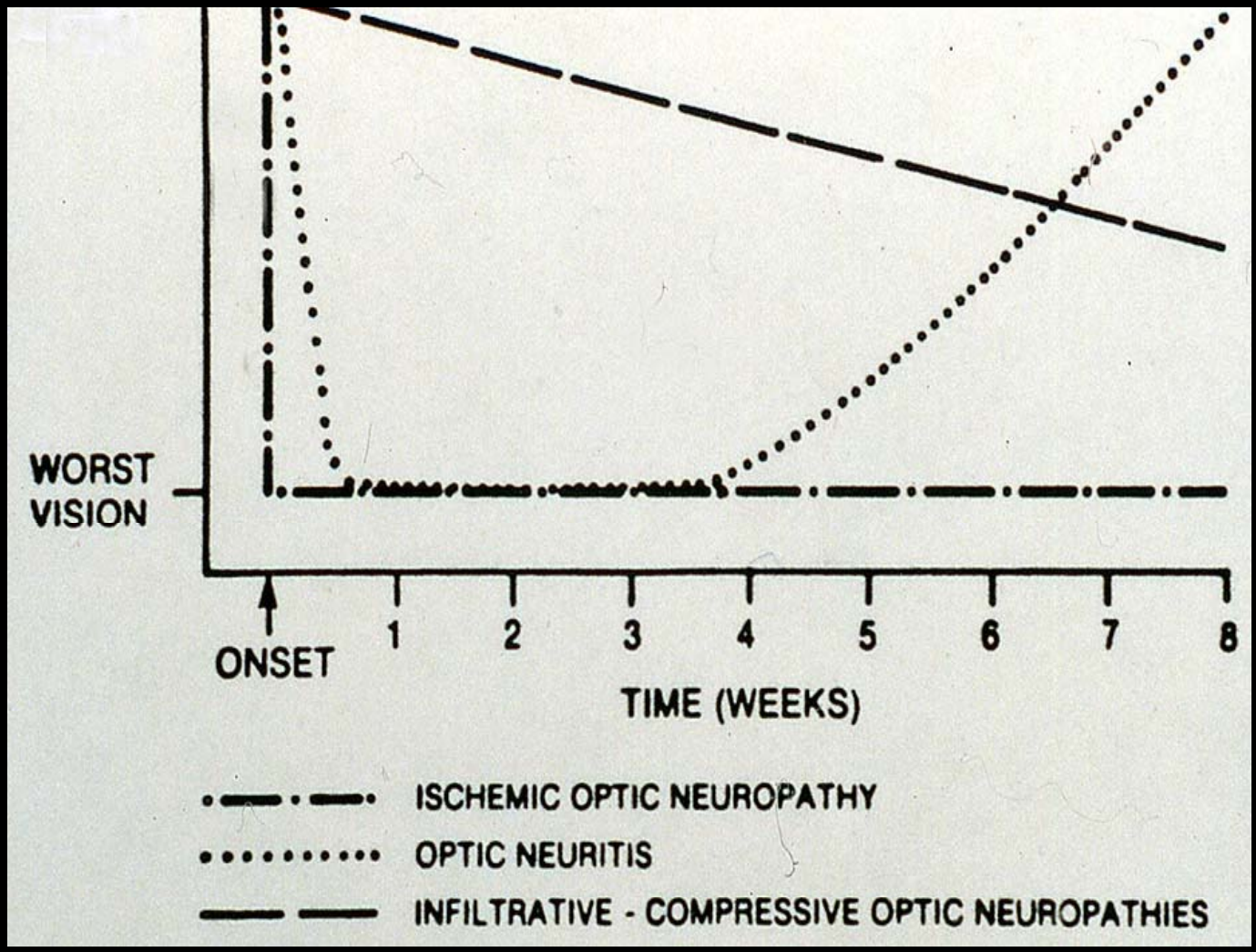
Cecocentral
Inflammatory

Combination
Compressive





Temporal Profile of Optic Neuropathies



Lessell, 1968

Ischemic Optic Neuropathy

- **Nonarteritic anterior ischemic optic neuropathy (NAION)**
- **Arteritic anterior ischemic optic neuropathy** (giant cell, or temporal, arteritis)
- **Posterior ischemic optic neuropathy (PION)**
  - Associated with surgery, especially spine operations
  - Associated with giant cell arteritis
  - Associated with ipsilateral carotid disease & general anesthesia

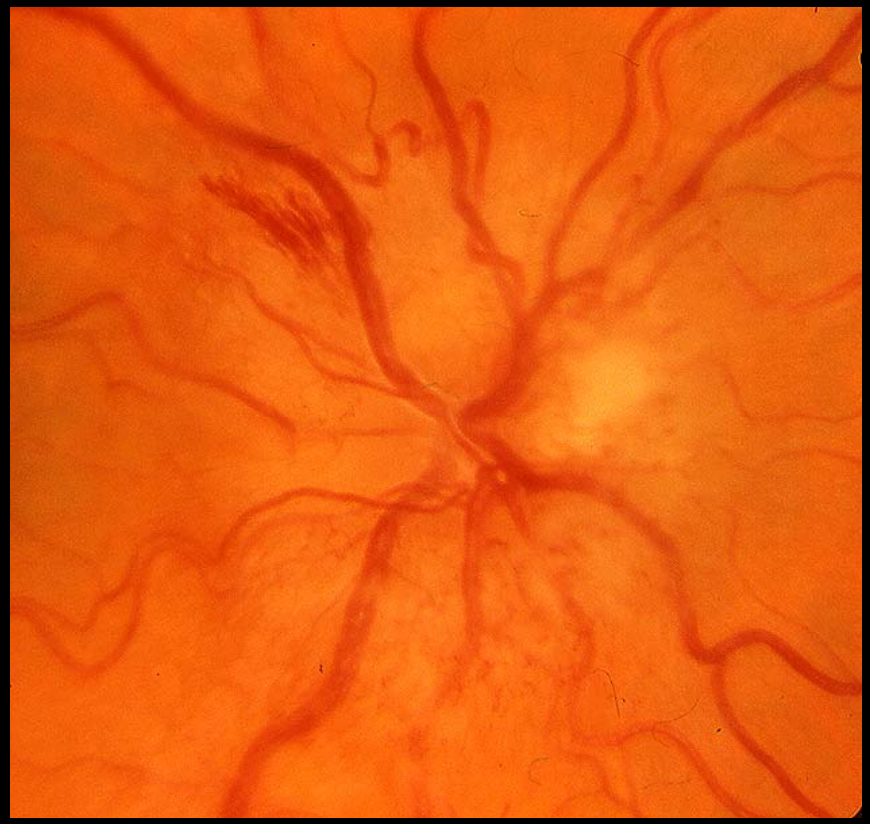
Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

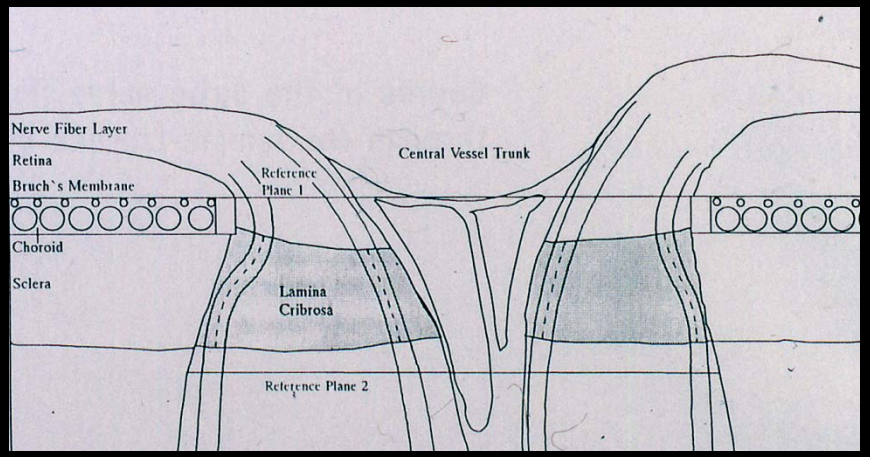
- Most common acute optic neuropathy in persons over 50 yrs of age
- Most common form of ION
- Sudden painless visual loss, often noted on awakening
- Altitudinal visual field loss (lower > upper field)
- Natural history of visual loss: 60% stable, 30% some improvement, 10% worsen over 6 weeks
- Other eye involvement about 15-40% in months to years

NAION

- 2-10/100,000
- Typical patient is 60-70 yrs old, but one study found 23% less than 50 yrs of age
- Caucasians represent ~ 95% of cases

Anterior Ischemic Optic Neuropathy





Caused by infarct in optic nerve at the level of the lamina cribrosa

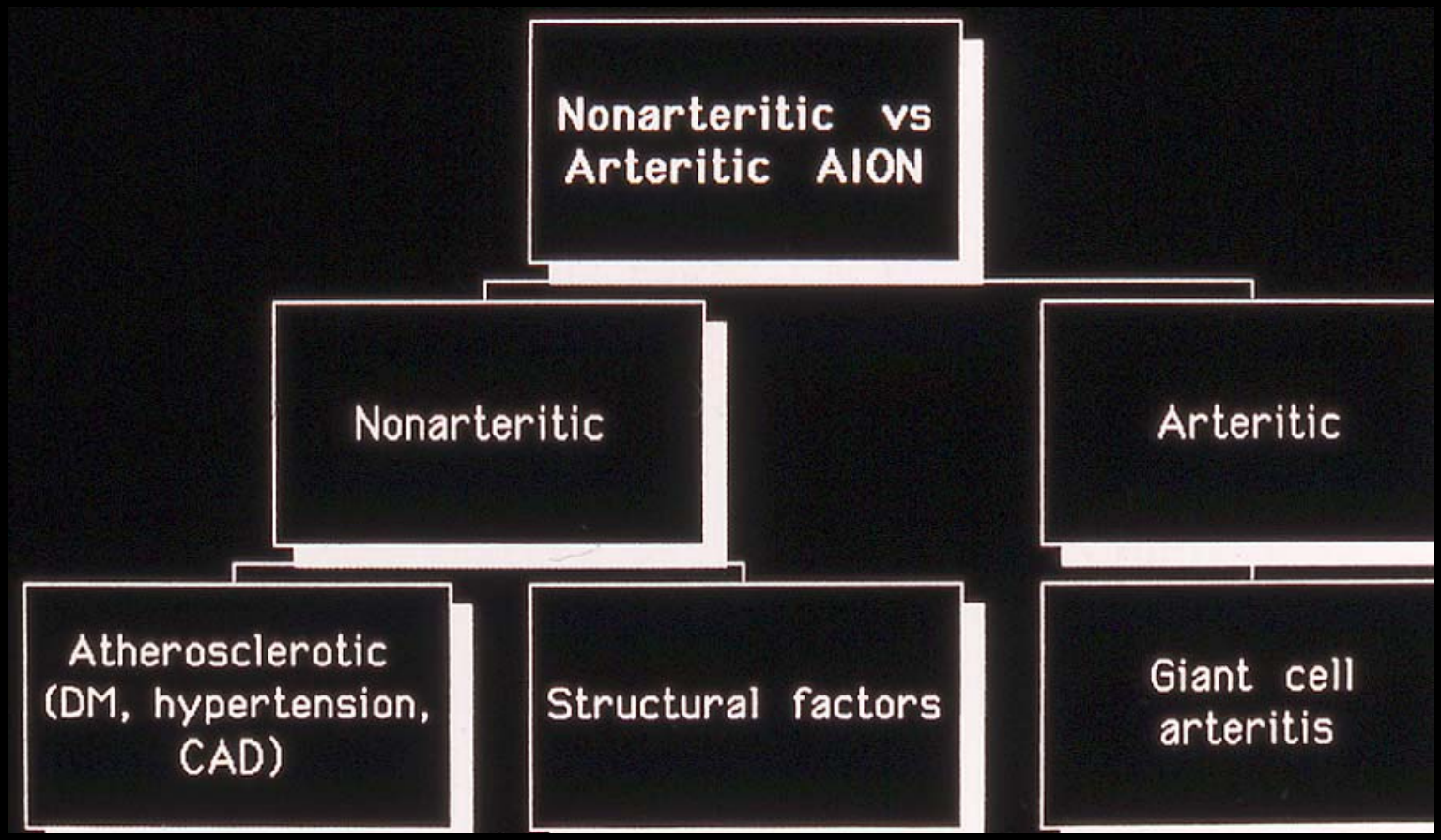
NAION - Etiology

- Optic nerve structure: ***"disk at risk"*** - small or absent physiologic cup
- Nocturnal hypotension/sleep apnea – 2/3 patients awaken with visual loss - possibly combined with nocturnal elevation of intraocular pressure
- Atherosclerotic risk factors, esp. DM
- Procedures which cause hypotension
- Medications, e.g. Viagra and Interferon-alpha
- Impaired autoregulation of disc vessels
- **NB: Thrombosis of vessels (SPCA) has never been demonstrated**

NAION - Treatment

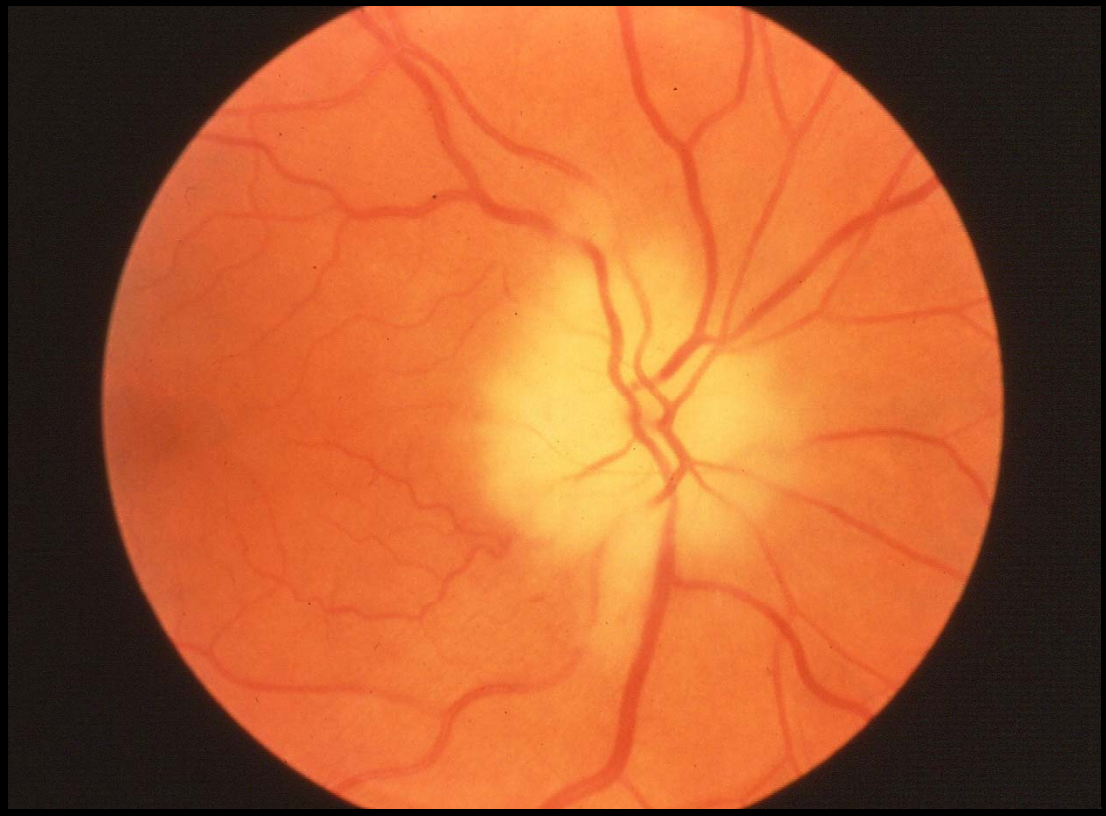
- No treatment has been shown to alter the course of the disease
- **Optic nerve sheath decompression is contraindicated**
- Risk factors for atherosclerotic complications should be addressed

Anterior Ischemic Optic Neuropathy



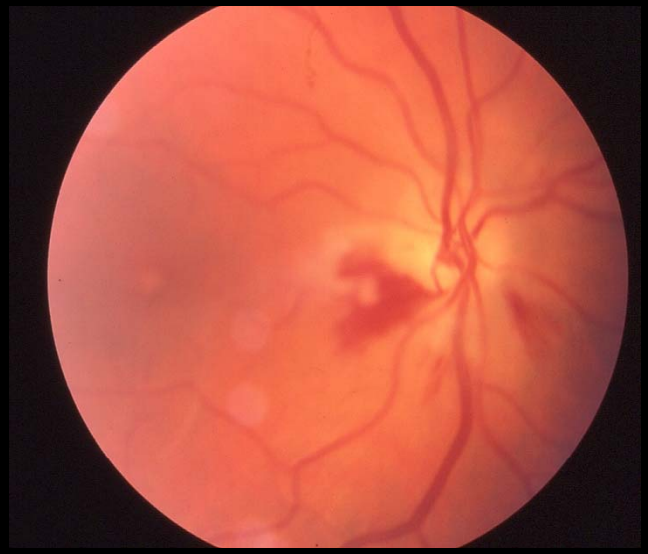
Ischemic Optic Neuropathy from Giant Cell (Temporal) Arteritis

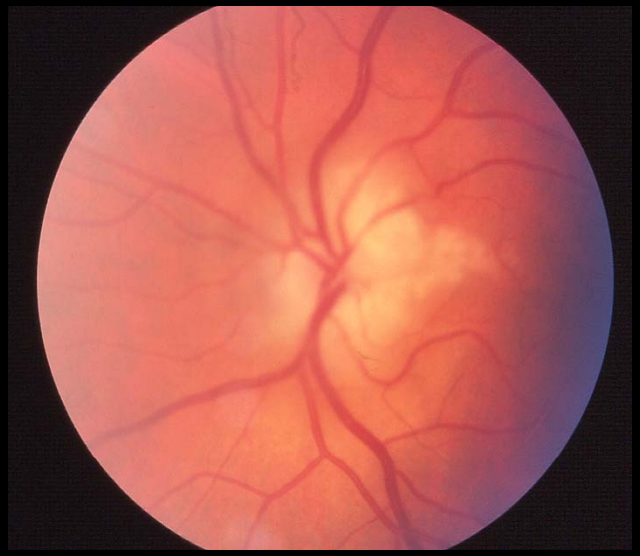
Pallid Edema in Arteritic Anterior Ischemic Optic Neuropathy



Nerve is pale because the degree of ischemia is profound

Bilateral Simultaneous Ischemic Optic Neuropathy In GCA

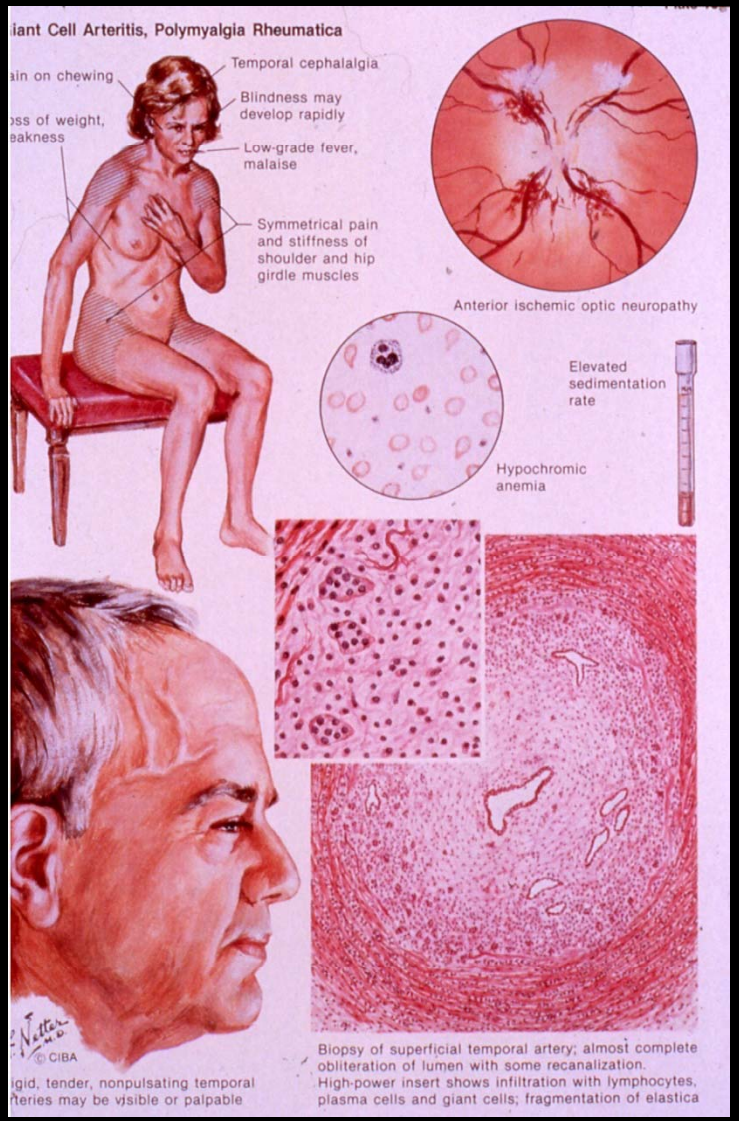




Temporal Arteritis - Overview

- Disease of the elderly - mean age of presentation is 70 years
- Women affected about twice as frequently as men
- Rare in blacks, Hispanics, Asians
- Chronic disease, may recur even if treated, **may be fatal**
- Pathogenesis is immunologic and inflammatory

GCA - Textbook Presentation



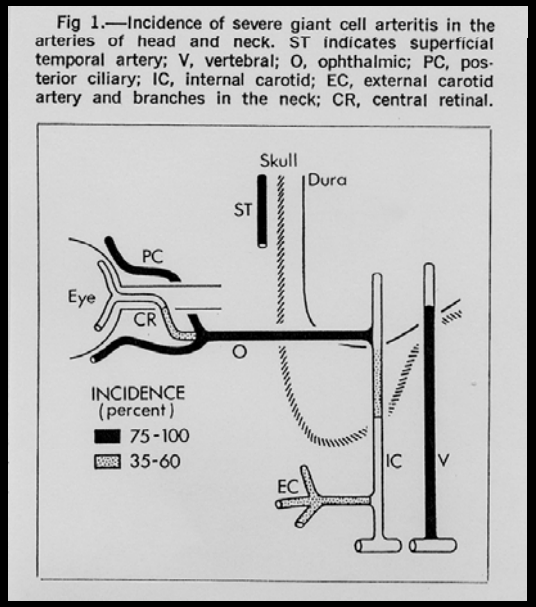
Pathology Textbook Definition Of Giant Cell Arteritis

- **Granulomatous inflammation affecting large and medium arteries in:**
- **Heart**
- **Breast**
- **Female genital tract**
- **Thyroid**
- **Liver**
- **Small bowel**
- **Gall bladder**
- **Kidney**
- **Pancreas**
- **Esophagus**
- **Bone marrow**
- **Spinal cord**
- **Prostate**

But …People Usually Go Blind
From Involvement of
Posterior Ciliary Arteries
Which Are About
250 microns in diameter or less!!
(the PCilAs do have elastic tissue, but not internal elastic laminae)

Neurologic Manifestations of GCA

- **Headache**
- Neuropathies
- **TIA/stroke**
- Neuro-otologic syndromes
- Tremor
- Neuropsychiatric syndromes (e.g., depression, visual hallucinations
- Myelopathies



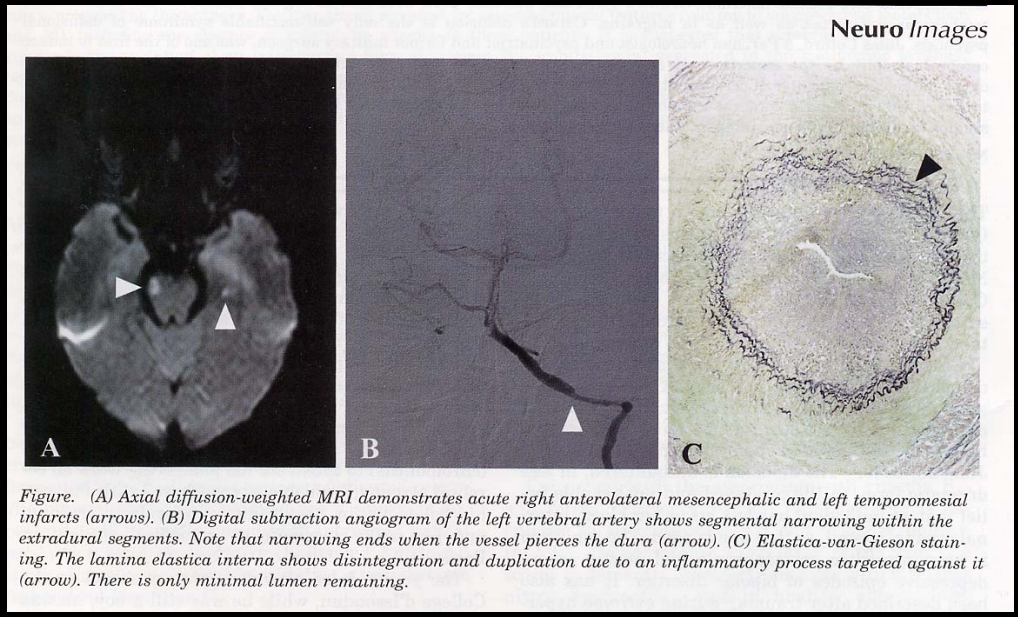


Figure. (A) Axial diffusion-weighted MRI demonstrates acute right anterolateral mesencephalic and left temporomesial infarcts (arrows). (B) Digital subtraction angiogram of the left vertebral artery shows segmental narrowing within the extradural segments. Note that narrowing ends when the vessel pierces the dura (arrow). (C) Elastica-van-Gieson staining. The lamina elastica interna shows disintegration and duplication due to an inflammatory process targeted against it (arrow). There is only minimal lumen remaining.

Acute Phase Reactants in GCA

- C-reactive protein: rises within hours of inflammatory stimulus
- Fibrinogen: peaks after about 2 weeks
- Platelet count: thrombocytosis takes months to develop

C-Reactive Protein and GCA

- C-reactive protein > 2.45 mg/dl AND Westergren sedimentation rate of 47 mm/hr or greater gave a specificity of diagnosis of 97%

(Hayreh et al, 1997)

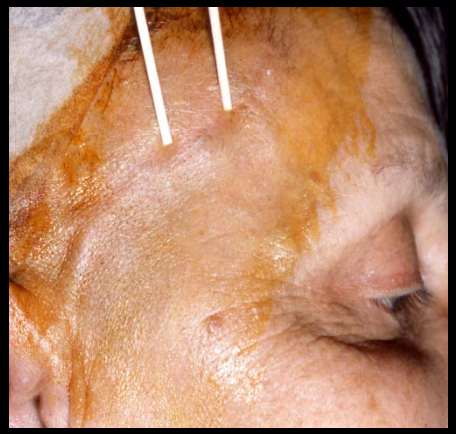
Panel of Tests for Presumed GCA

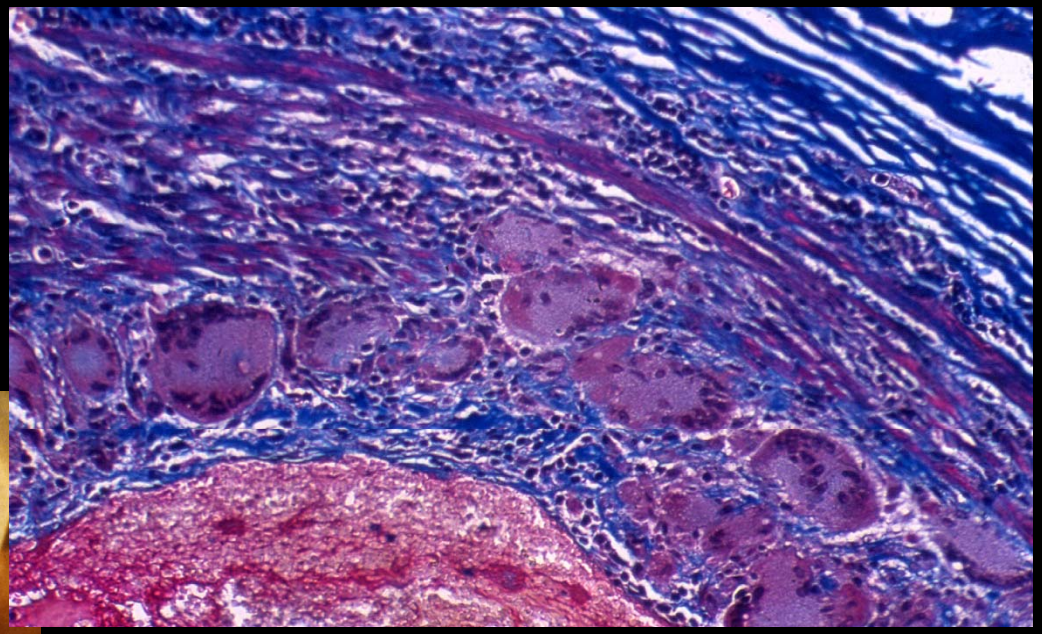
- Westergren sedimentation rate
- CBC w/differential and platelet count
- Fibrinogen
- C-reactive protein

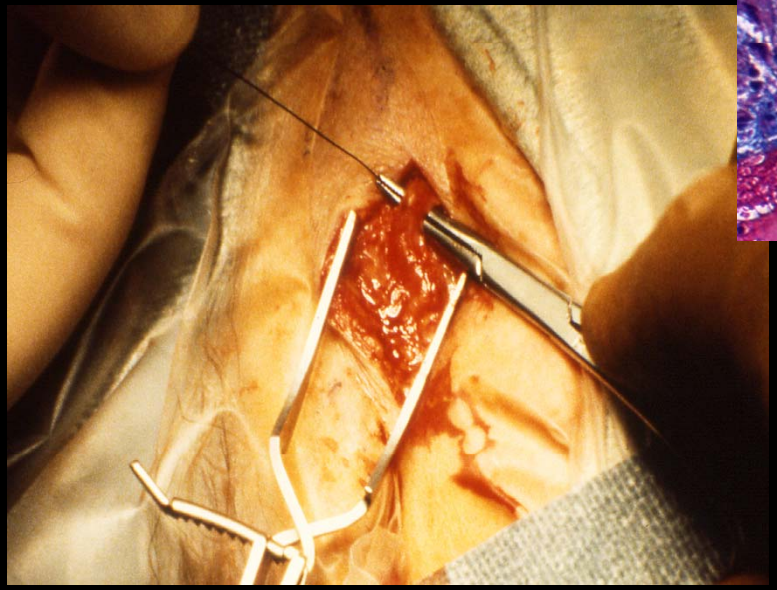
Question: Does a temporal artery biopsy need to be done as an emergency procedure?

Answer: **No**

Temporal Artery Biopsy







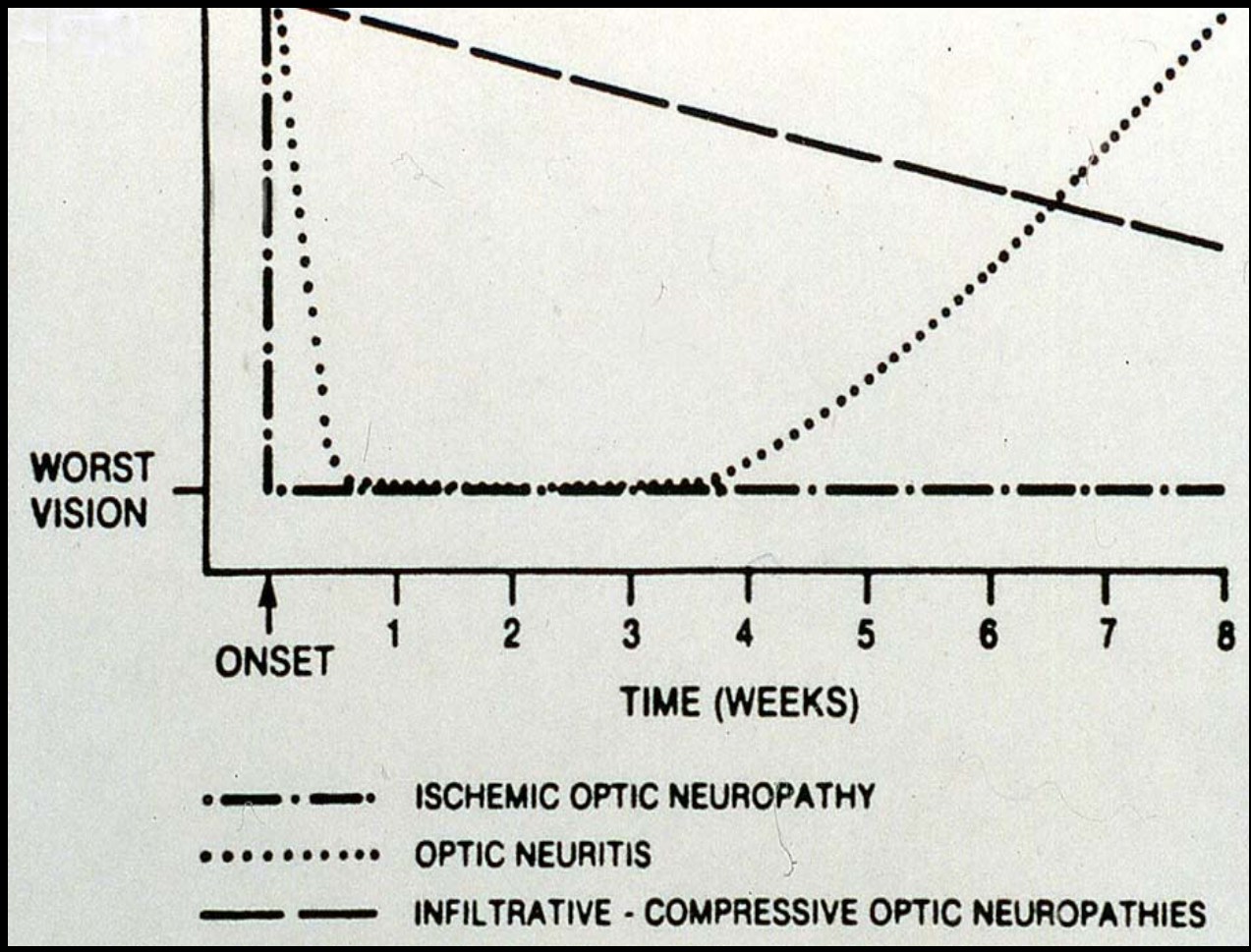
Question: If I suspect the diagnosis of temporal arteritis, do I have to start steroids on an emergency basis?

Answer: **Yes**

Treatment of Visual Loss in Giant Cell Arteritis

- Even when aggressively treated with high dose IV steroids, vision almost never improves significantly
- The fellow eye is at risk until the systemic inflammatory response is controlled

Temporal Profile of Optic Neuropathies



Lessell S. Optic Neuropathies NEJM 1978;299:533-6

Leber's Hereditary Optic Neuropathy (LHON)

- Described in 1871 by Theodore Leber
- First human disease to be etiologically linked to mtDNA mutation
- 80-90% of affected are males
- Age at presentation is usually 15-35 yrs (range: 2-87 yrs

The Neuro-ophthalmology of Mitochondrial Disease

J. Alexander Fraser, MD,[1] Valérie Biousse, MD,[1,2] and Nancy J. Newman, MD[1,2,3]

SURVEY OF OPHTHALMOLOGY VOLUME 55 • NUMBER 4 • JULY–AUGUST 2010

LHON: Clinical Presentation

- Rapid painless loss of central vision in one eye followed by loss of vision in fellow eye within days to months
- > 97% develop 2nd eye involvement within first year (median time: 6-8 wks)
- Final visual acuities 20/200 or worse
  - Some recovery with 14484 mutation (37-71%)
- Pupillary light reflexes often spared to some degree
  - Melanopsin containing RGCs are relatively spared in LHON

LHON: Early and Late

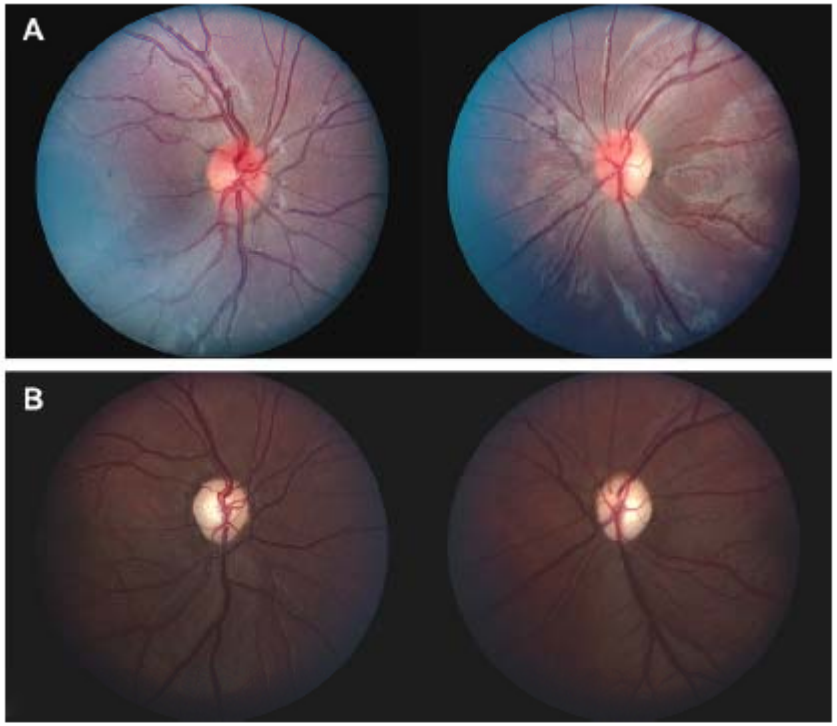


Fig. 5. Ocular fundus appearance in a patient with Leber hereditary optic neuropathy (LHON). *A*: Acute pattern: disk hyperemia, pseudoedema, and telangiectasias; the left eye was affected one month prior to the right eye, and early temporal optic disk pallor is evident in the left eye. *B*: Chronic pattern: diffuse optic atrophy, most apparent temporally, 3 years later.

Goldmann Visual Fields in LHON

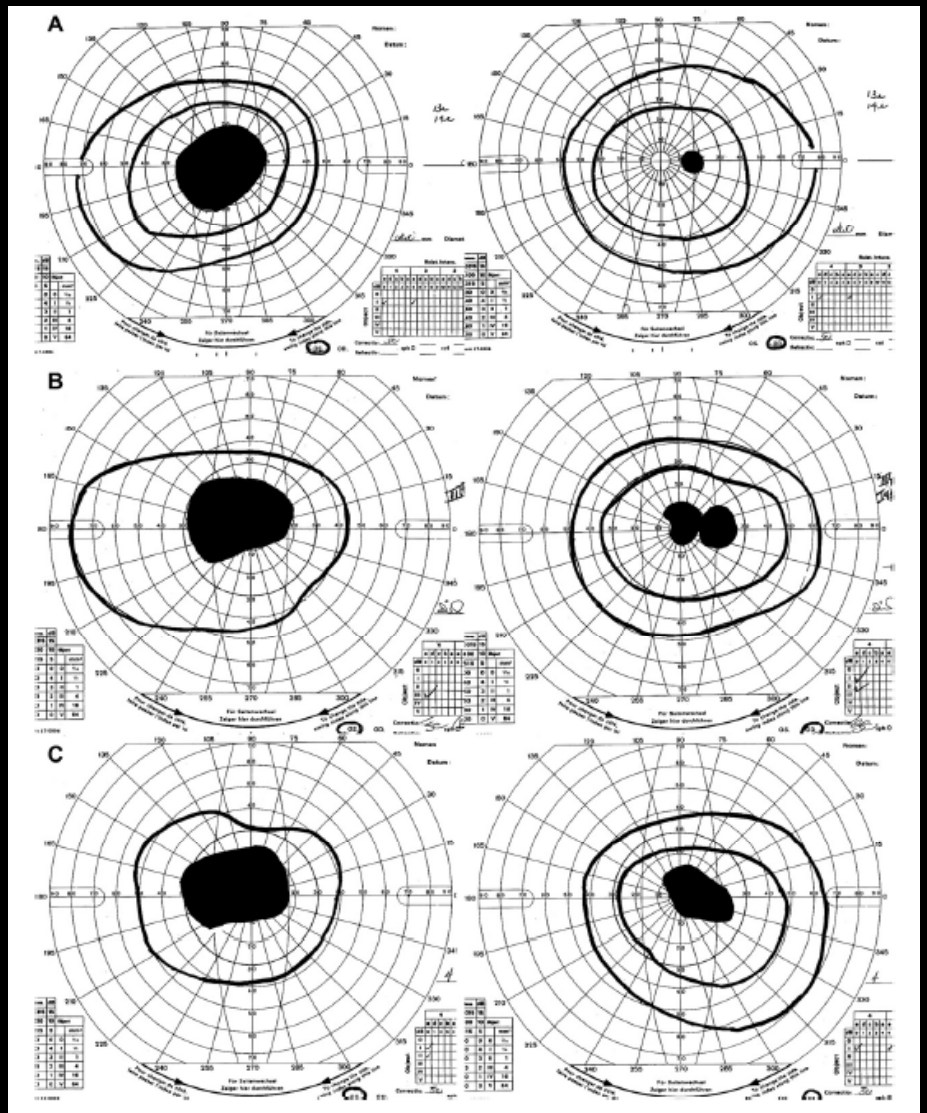


Fig. 4. Goldmann visual fields (GVF) in a patient with Leber hereditary optic neuropathy (LHON). Progressive central scotoma in the right eye of a 21-year-old man with the 11778 LHON mutation. He had suffered a painless central scotoma in the left eye three months prior. *A*: GVF from March 5, 2009. *B*: GVF from March 19, 2009. *C*: GVF from April 16, 2009.

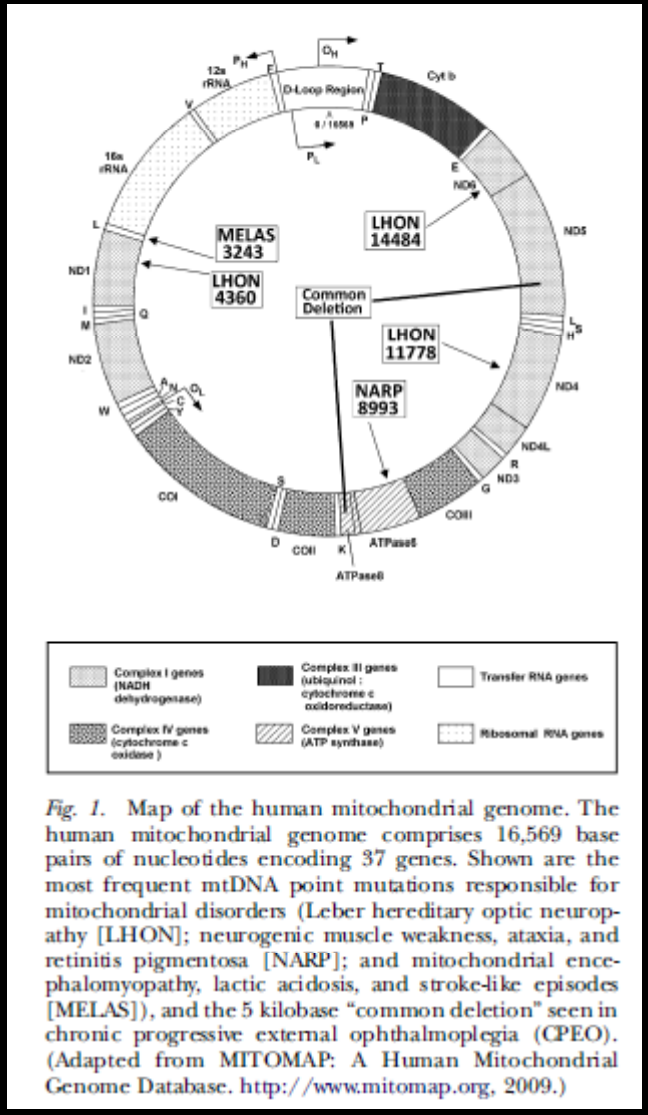


Fig. 1. Map of the human mitochondrial genome. The human mitochondrial genome comprises 16,569 base pairs of nucleotides encoding 37 genes. Shown are the most frequent mtDNA point mutations responsible for mitochondrial disorders (Leber hereditary optic neuropathy [LHON]; neurogenic muscle weakness, ataxia, and retinitis pigmentosa [NARP]; and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS]), and the 5 kilobase "common deletion" seen in chronic progressive external ophthalmoplegia (CPEO). (Adapted from MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2009.)

Primary LHON Mutations

11778: 69%

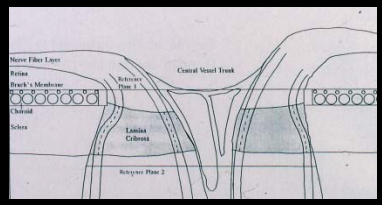
14484: 14%

3460: 13%

Map of Mitochondrial Genome

LHON

- Why is the ON involved?
  - Mitochondria are concentrated posterior to lamina cribrosa where myelination begins
- Factors affecting phenotypic expression
  - Heteroplasmy
    - mtDNA mutation disproportionately distributed to different tissues
  - Nuclear factors
    - Putative X chromosome susceptibility gene
  - Other mtDNA factors
    - Haplogroup background (11778-J [-] 11778-H [+])
  - Environmental; epigenetic factors
    - Nutritional, EtOH, tobacco
  - Lifetime risk of vision loss across all mutations ~ 46% M & 11% F



Leber's Plus Syndromes

1. Cardiac conduction defects

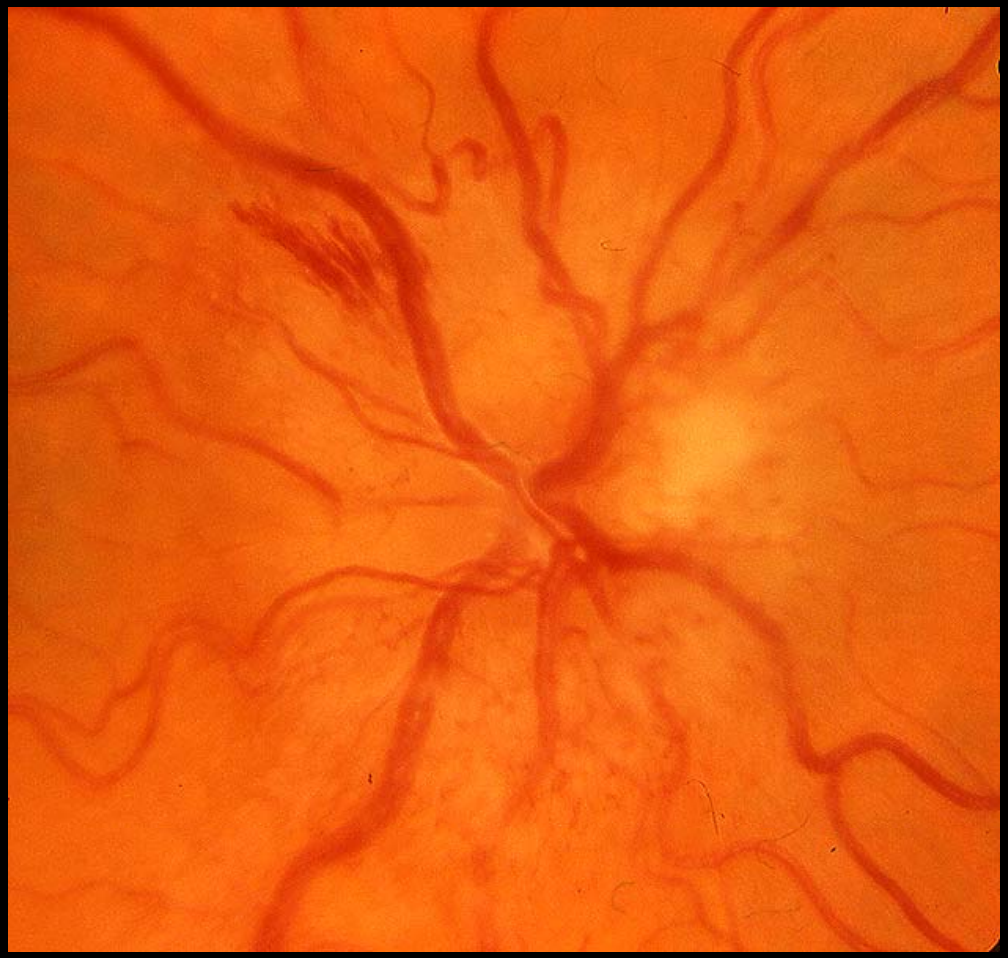
2. Basal ganglionic degeneration, psychiatric symptoms, encephalopathy

3. Multiple sclerosis

But wait!

There’s more…

Is this NAION or Papilledema?

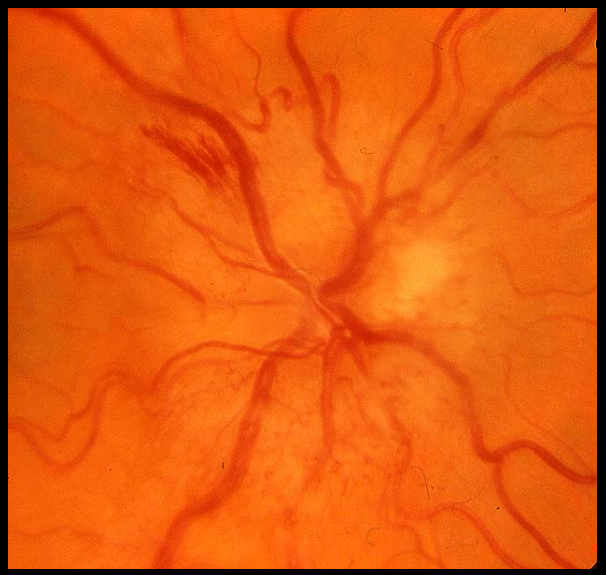


How would you go about finding out based on what we covered today?

"Vital Signs" of Afferent Neuro-ophthalmology

1. Best corrected visual acuity
    1. Distance and near
2. Pupillary light responses
   (Is there a RAPD?)
3. Visual fields

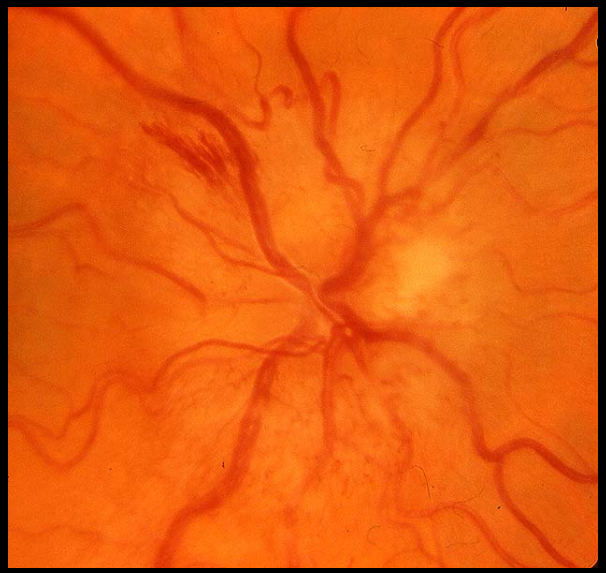
AION vs. Papilledema

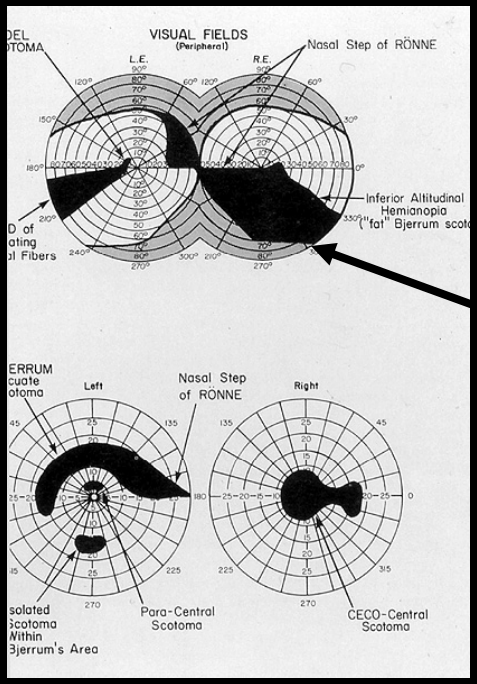


Visual acuity is decreased in majority of cases of AION, but spared in papilledema unless significant optic atrophy ensues

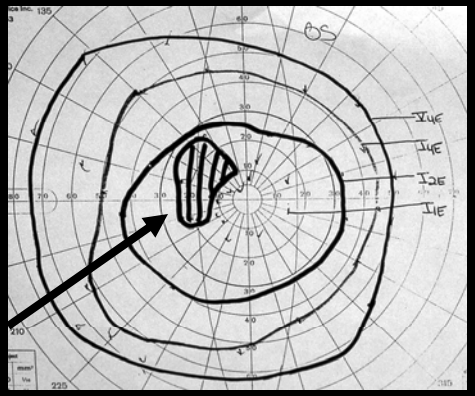
RAPD characteristically present with AION, but absent with papilledema

AION vs. Papilledema

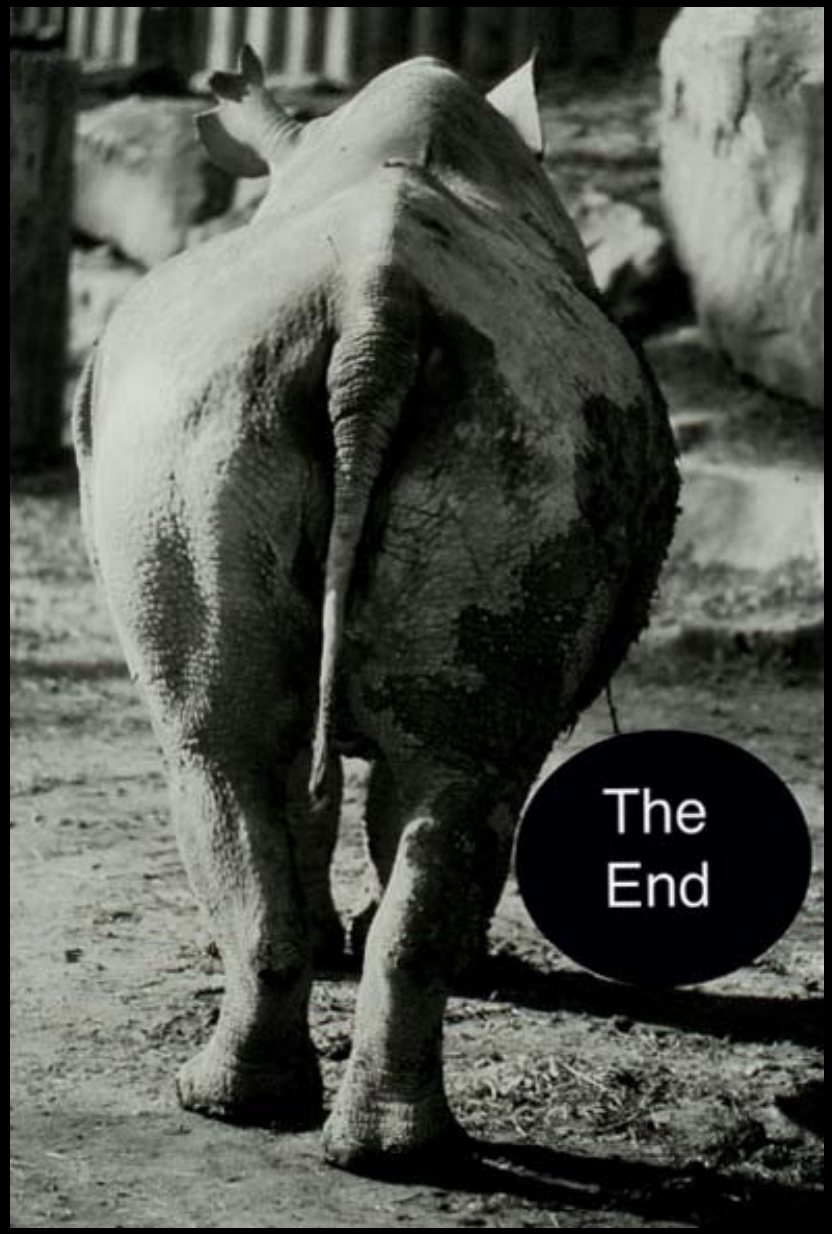




Inferior altitudinal VFD characteristic of AION



Enlargement of the blind spot is the earliest VFD with true papilledema (optic disc edema from elevated ICP)


The
End