Normal Tension Glaucoma:

Thoughts, Time, Testing and Treatment

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OPTOMETRIC MEETING

CONTINUING EDUCATION

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Normal Tension Glaucoma

Course Goal

To provide useful clinical information in the diagnosis and treatment of normal tension glaucoma.

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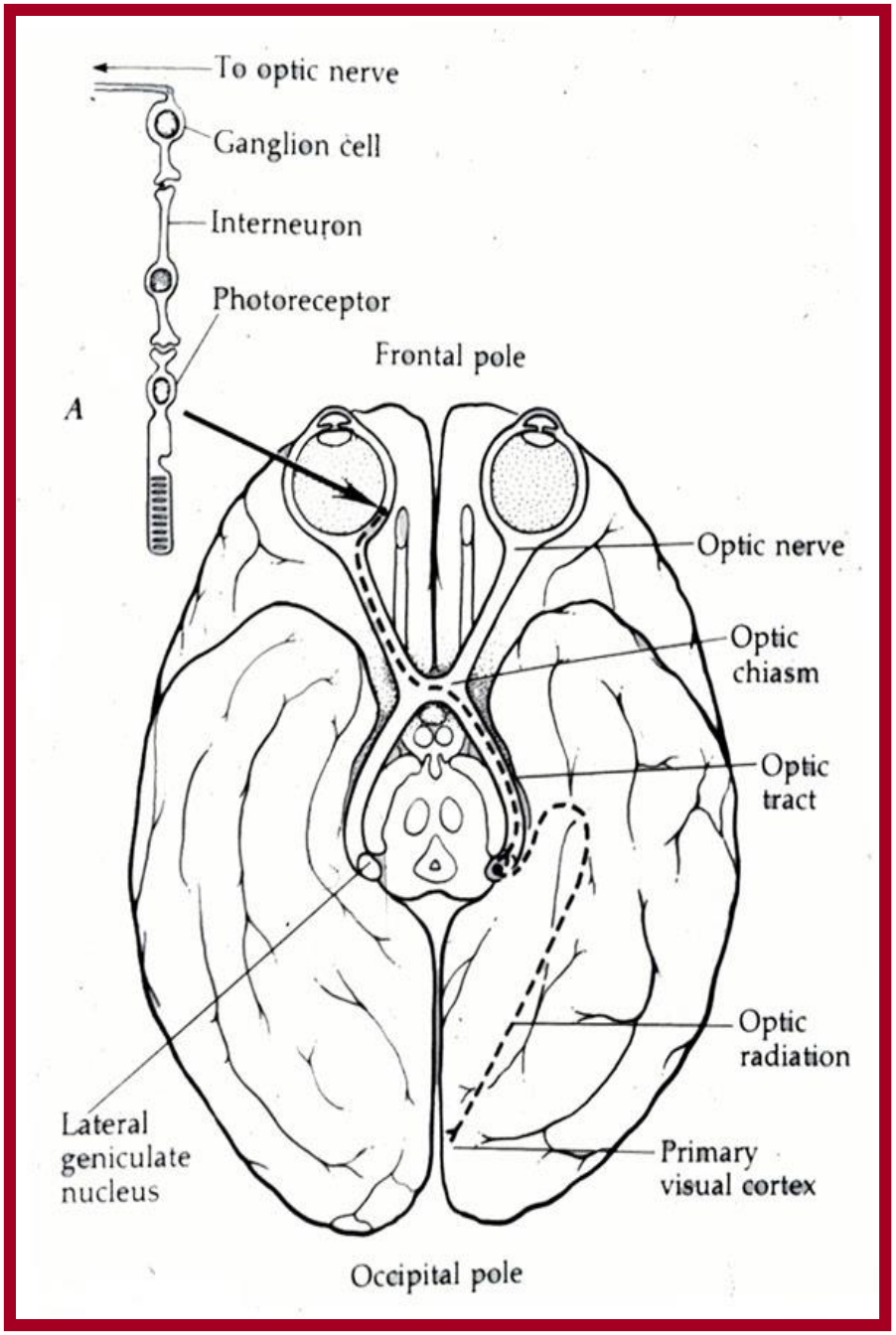
The Visual Pathway



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Intraocular Optic Nerve (Optic Nerve Head)

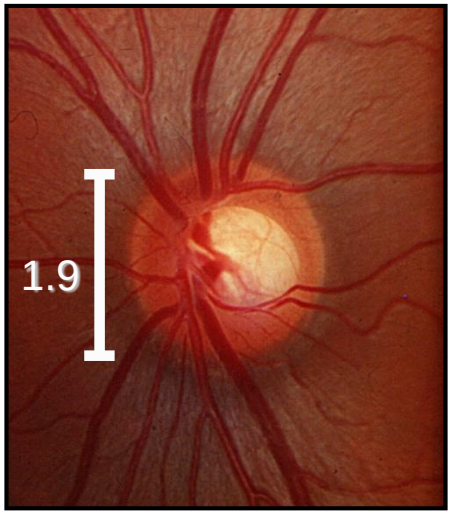
- 1.2 mill axons → lamina cribrosa
  - grouped in fascicles (1,000)

- Avg. diam = 1.8 mm

Optic Nerve Size

Size of cup varies with size of disc
Large discs have large cups in healthy eyes

Small



Average

Large

Identify small and large optic discs

Small discs: avg vertical diameter <1.5 mm

Large discs: avg vertical diameter >2.2 mm

Dr. Tom Lewis

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Definition of Glaucoma:

Glaucoma is an chronic progressive **optic neuropathy** (a neurodegenerative disease) that presents with a type of optic atrophy called **"cupping".**

It is a group of ocular conditions where the level of intraocular pressure damages the optic nerve. This in turn causes a loss of visual function (a visual field defect)

Classification of Glaucoma:

A. Congenital Glaucoma
B. Primary Open Angle Glaucoma (~ 70%) = **2.25 million US adults**
C. Secondary Open Angle Glaucoma
D. Primary Angle Closure Glaucoma
E. Secondary Angle Closure Glaucoma

Important Note:

- Primary open angle glaucoma is made by a diagnosis of exclusion
- Gonioscopy is the diagnostic test

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Low Tension Glaucoma:
An Oxymoron in Ophthalmology and Optometry

What this lecture will try to explain:

Is Low-tension Glaucoma a disease on the spectrum of primary open angle glaucoma ????

Is the optic disc appearance secondary to ON hypoperfusion due to vascular disease ????

Should low tension glaucoma be included in a spectrum of congenital and acquired optic neuropathies that can simulate a glaucomatous optic neuropathy ????

Should low tension glaucoma include a thorough systemic and neurological workup ????

Should this form of optic neuropathy be treated differently than high pressure OAG ????

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The Glaucoma Etiology Process

It appears that glaucoma is a “three – pressure” disease

A balance between :

- Intraocular pressure
- Intracranial pressure (aka CSF) = 10 mm Hg
- Ocular perfusion pressure (diastolic BP – IOP)
  - Should be above 55 during the day

Los Angeles Latino Eye Study (LALES) = Ocular Perfusion Pressure

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Intraocular pressure

Misnomer :

Intraocular pressure (IOP) because of the prefix “intra” meaning within in Latin has incorrectly led many individuals to view IOP as the pressure inside the eyeball.

When measuring IOP we are actually measuring the pressure difference across the cornea.

IOP is really a “transcorneal pressure difference”

Remember: glaucoma occurs at the optic nerve head and not in the cornea

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When scuba diving 30 feet below sea level the eye pressure is about **1500 mm Hg** as a result of 760 mm Hg pushing on the body.

When hiking in Colorado where the elevation is higher the absolute pressure inside the eye is **635** mm Hg as a result of 620 mmHG pushing on the body.

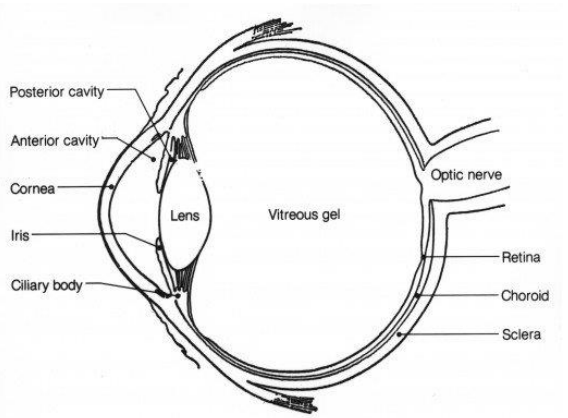
There is no research to show us that scuba divers have a higher incidence of glaucoma or those that live in lower atmospheric pressure zones have a reduced chance of glaucoma.

This may show that the absolute pressure inside the eye is less relevant to glaucoma than the pressure variance across the cornea.

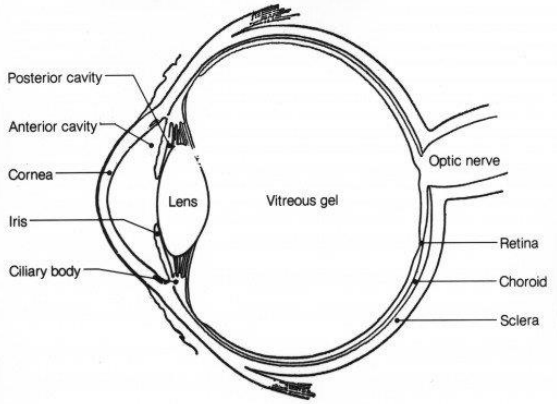
IOP (aka transcorneal pressure) is a surrogate measurement for the "Translaminar pressure" happing at the optic nerve head.

John Berdahl, MD

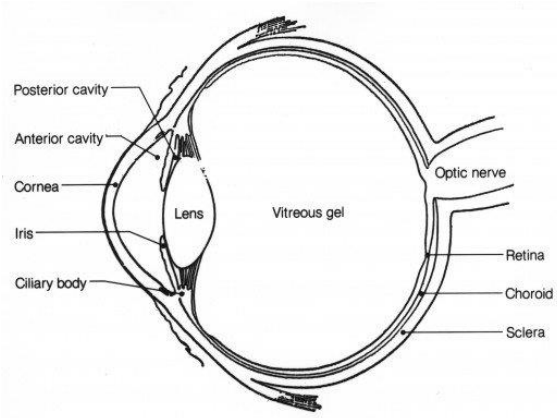
620 +15 = 635 mmHG



760 + 15 = 775 mm HG



1500 + 15 = 1515 mm HG



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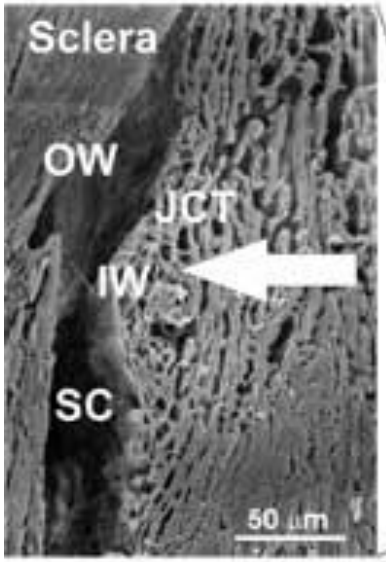
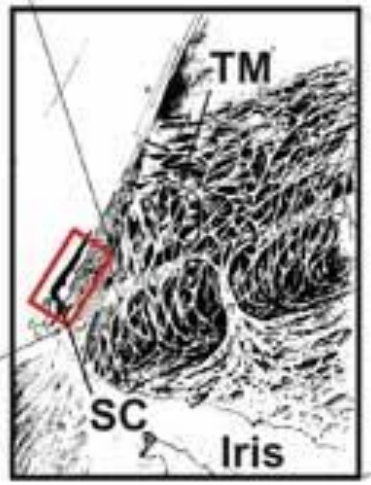
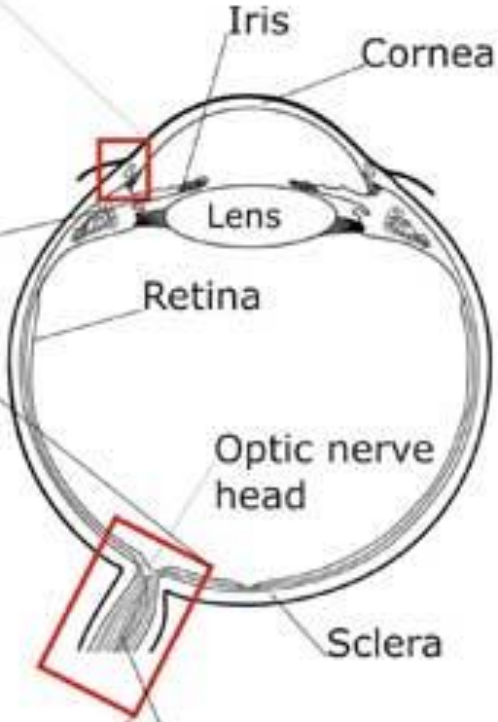
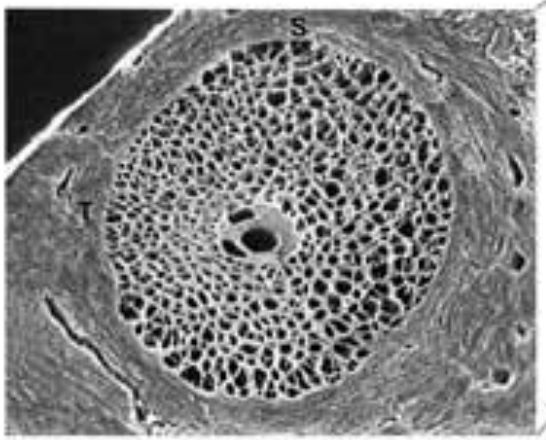
Tissues Involved in Glaucoma



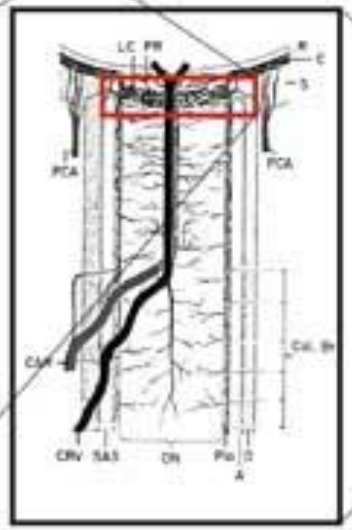
TM = trabecular meshwork
SC = Schlemm's canal
JCT = juxtacanalicular tissue
IW = inner wall
OW = outer wall
LC = lamina cribrosa







Lamina cribrosa, en face view



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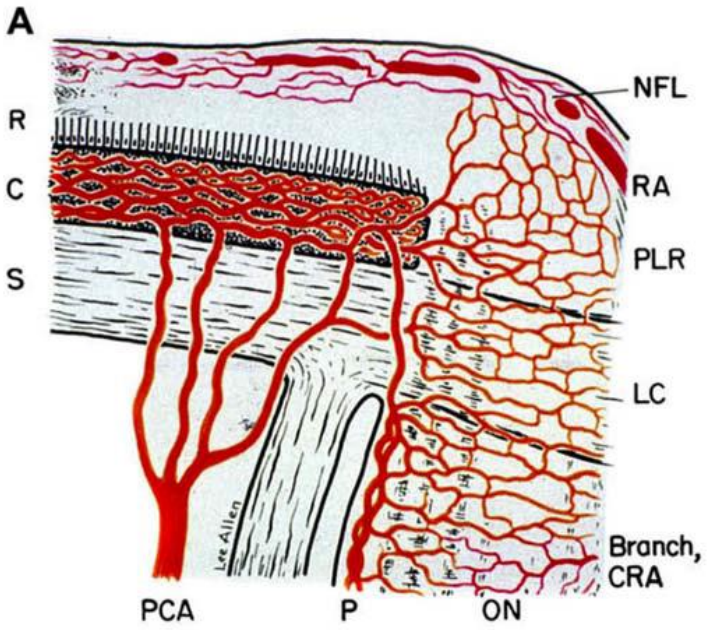
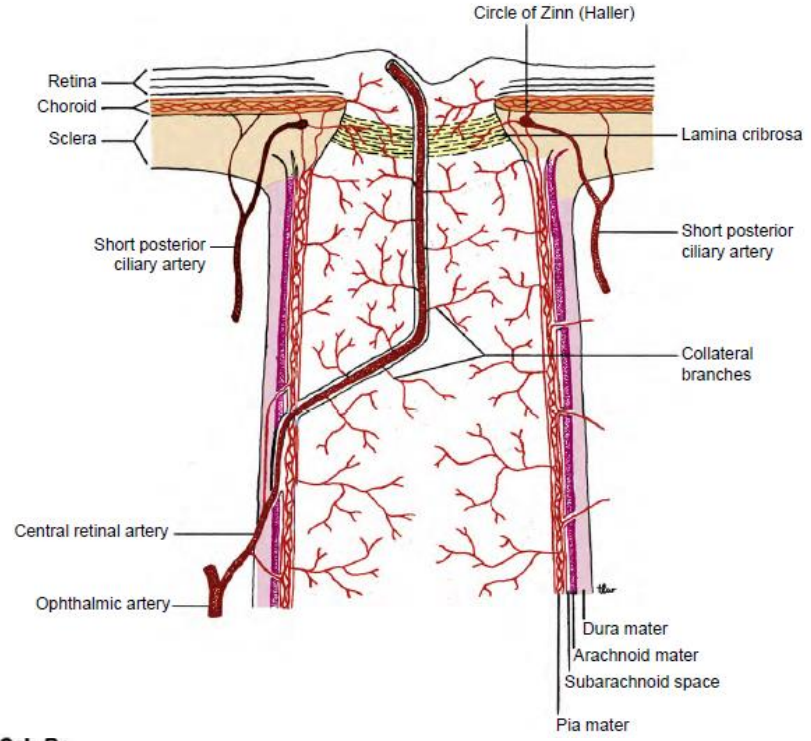
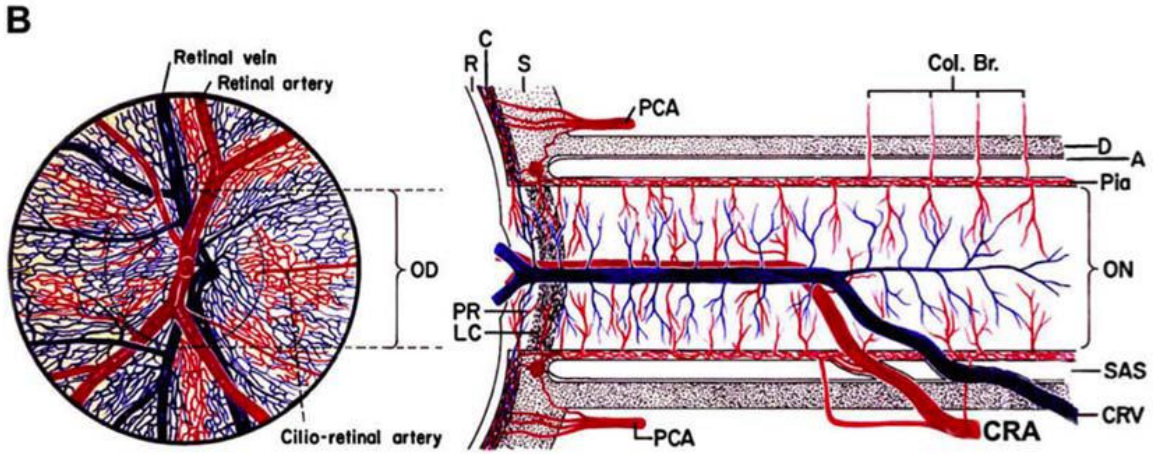
Optic Nerve Blood Supply







Ocular Perfusion Pressure =

Diastolic BP – IOP

80 – 25 = 55 mm Hg

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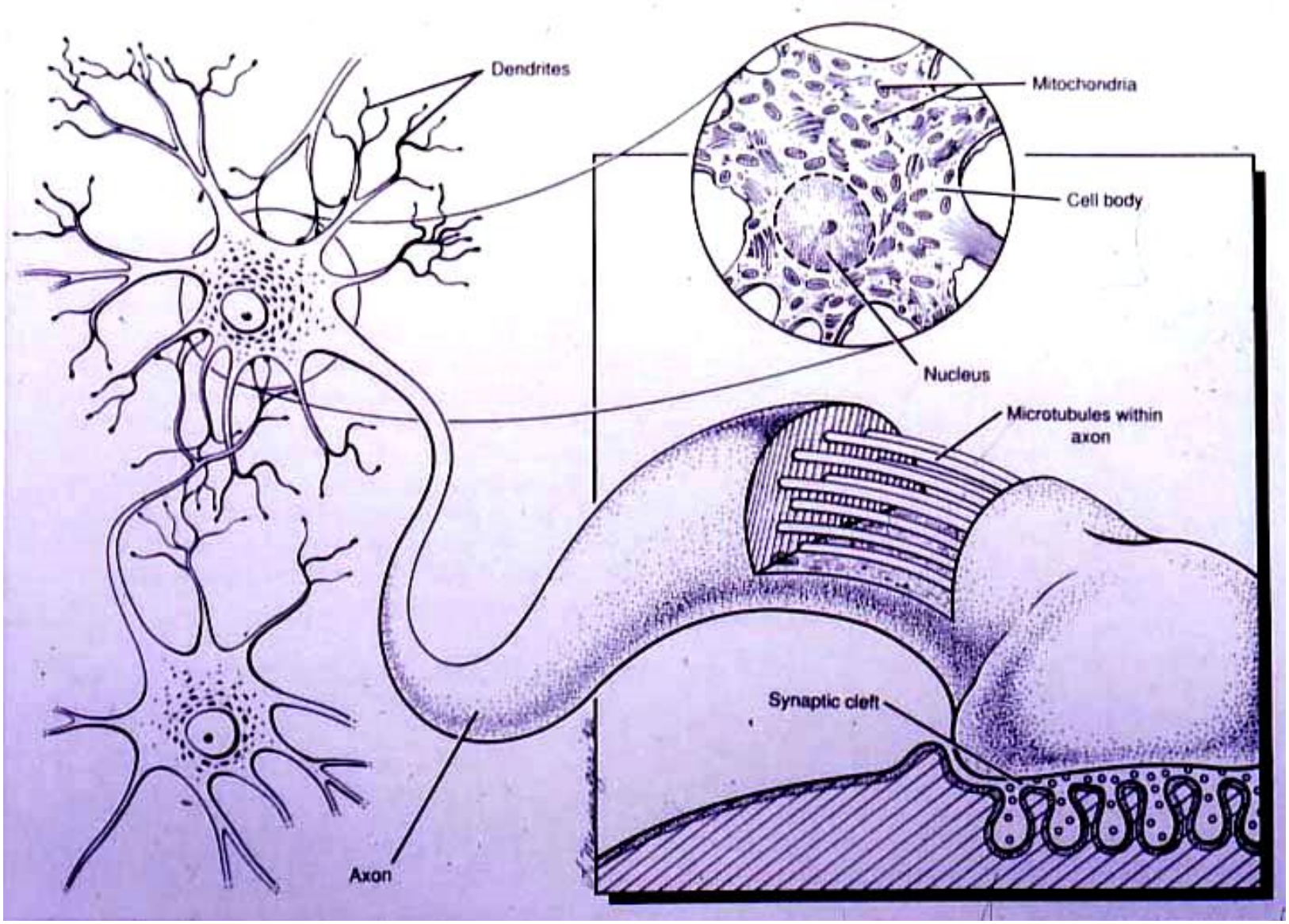
Brain Derived Neurotrophic Factor, nerve growth factor, NT 3 , NT 4



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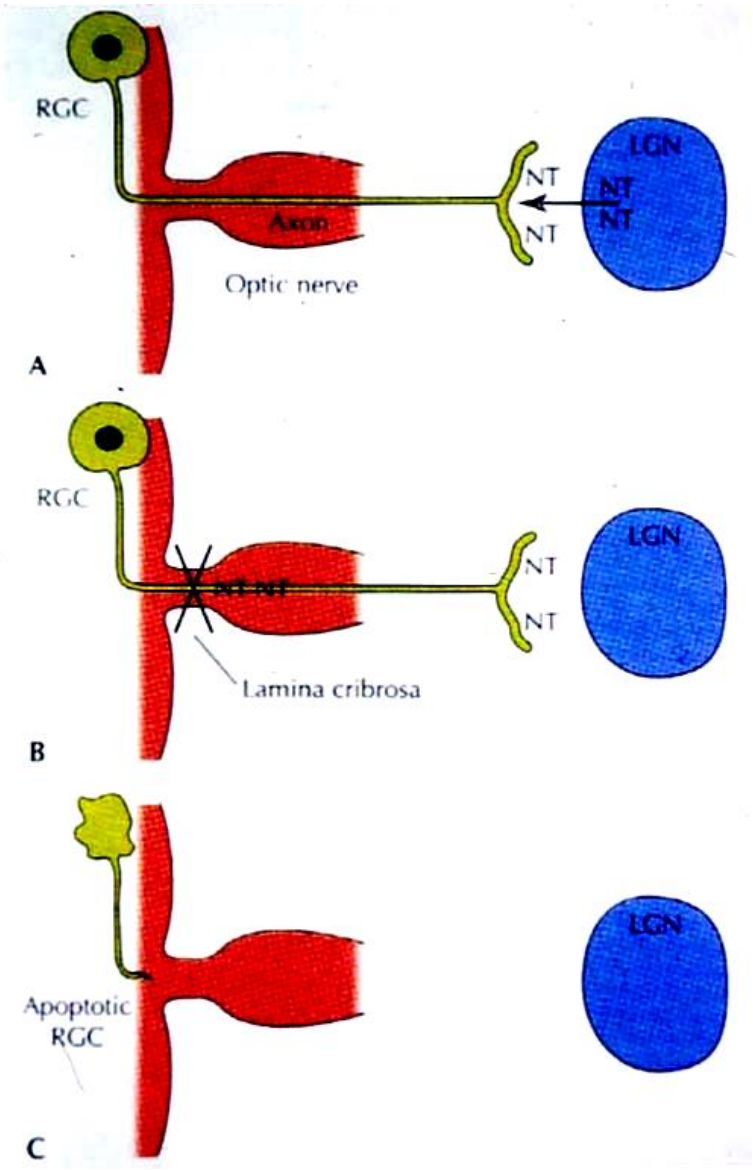
Neurotrophins

IOP 14

CSF 10

TLP 4

Trans laminar pressure



IOP 24

CSF 10

TLP 14

OPP

DBP – IOP

80 -25 = 55

In glaucoma patients, CSF pressure starts to drop around the age of 65. However nothing noteworthy happens to IOP at age 65.

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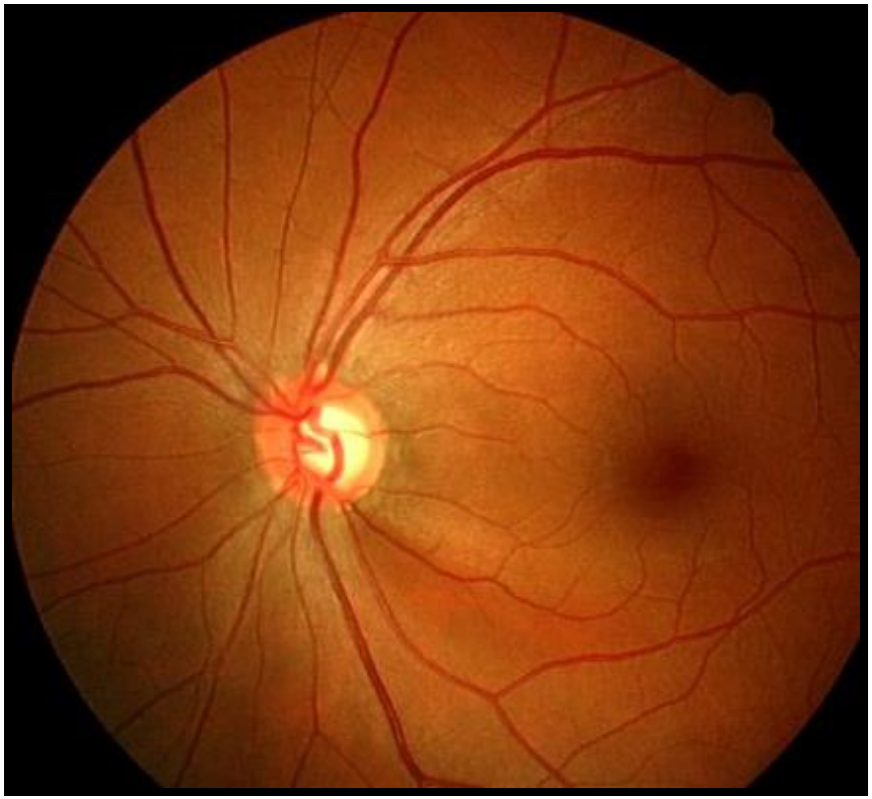
Glaucoma: A chronic progressive optic neuropathy

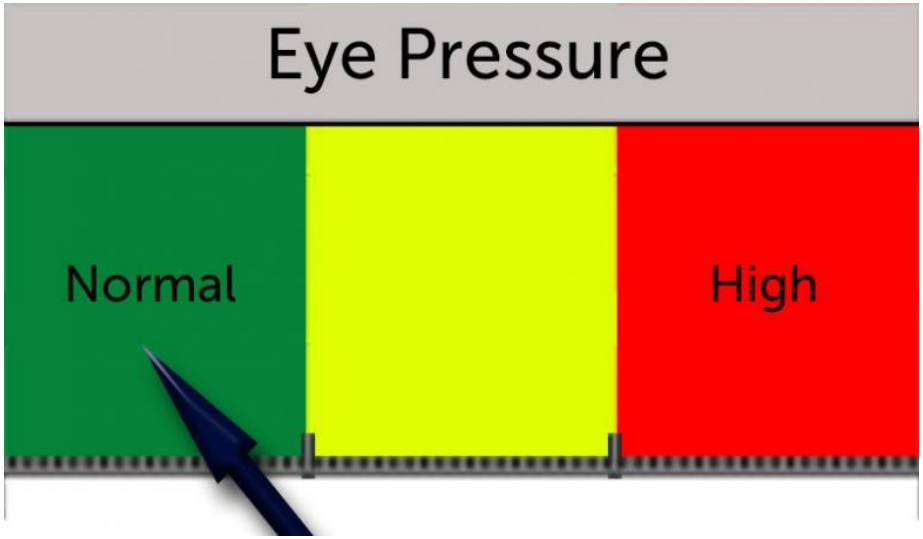
- Glaucoma is an “end stage” clinical presentation of many diseases

- Example: Heart failure is not a disease but a clinical end stage of many causes such as hypertension, coronary artery disease, etc.



Primary Open Angle Glaucoma (High and Low pressure)

- A chronic progressive optic neuropathy
- The most common form of glaucoma
- Open normal appearing anterior chamber angle
- Bilateral, but often asymmetric disease



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Primary Open Angle Glaucoma (Low pressure)

- Elevated IOP does not define glaucoma
- IOP is only a "risk factor" for developing glaucoma
- Research has shown that the highest IOP is in the early AM
- IOP then declines during the day and is at it's lowest at night
- "Baltimore Eye Survey": Up to **50 %** of patients with glaucoma had an initial IOP reading below 21 mm Hg
- Glaucoma with a "normal" IOP does exist
  - Normal tension glaucoma (14 -21 mmHg)
  - Low tension glaucoma (below 14 mmHg

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Ocular Hypertension and Normal tension are not clinical entities.
They are meaningless statistical constructs.

Von Graefe concluded that all glaucoma optic nerves were associated with high pressure based on finger tension.

Samples came from older European derived populations.

IOP without POAG had a mean of 15. Less than 2% of the general population was expected to have IOP greater than 21 or 22. Uncommon had become abnormal.

Population surveys found a number of patients normal IOP, NTG entered as a clinical entity

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Relationship Between Intraocular Pressure and Primary Open Angle Glaucoma Among White and Black Americans The Baltimore Eye Survey

Alfred Sommer, MD, MHS; James M. Tielsch, PhD; Joanne Katz, MS; et alHarry A. Quigley, MD; John D. Gottsch, MD; Jonathan Javitt, MD; Kuldev Singh, MD

Arch Ophthalmol. 1991;109(8):1090-1095.

- A detailed ocular examination, including perimetry, was conducted on 5308 black and white subjects aged 40 years and older in a population-based prevalence survey in east Baltimore, Md. Roughly half of all subjects with optic nerve damage from primary open angle glaucoma, regardless of race, were unaware that they had the condition.

The average intraocular pressure (IOP) among black patients with glaucoma who were receiving treatment was virtually identical to that in those black patients who were not receiving treatment (median IOP, 20 mm Hg); treated eyes of white patients had a lower IOP than those eyes of white patients who were not receiving treatment (mean[±SD] IOP, 18.69 ±3.23 mm Hg vs 24.15±5.23 mm Hg; *P*<.001).

The risk of glaucomatous optic nerve damage increased with the height of the screening IOP, particularly at levels of 22 to 29 and 30 mm Hg and above (relative rate compared with IOP of 15 mm Hg or lower, 12.8 and 40.1 mm Hg, respectively). **More than half of all glaucomatous eyes had a screening IOP below 21 mm Hg, whether these eyes were receiving treatment or not. T**he IOP in glaucomatous eyes tended to rise on follow-up, in contrast with non-glaucomatous eyes in which the IOP was as likely to rise as to fall.

Results confirmed that IOP is an important factor in glaucoma, but did not support the traditional distinction between "normal" and "elevated" pressure, nor its corollaries, "low-tension" glaucoma and "high-tension" glaucoma.

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Glaucoma and intraocular pressure in EPIC-Norfolk Eye Study: cross sectional study

Michelle P Y Chan, research fellow,[1] David C Broadway, professor,[3] Anthony P Khawaja, research fellow,[4] Jennifer L Y Yip, clinical lecturer,[4] David F Garway-Heath, professor,[5,6] Jennifer M Burr, reader,[7] Robert Luben, head of biomedical informatics,[4] Shabina Hayat, research coordinator,[4] Nichola Dalzell, study coordinator,[4] Kay-Tee Khaw, professor,[4] andPaul J Foster, professor[5,6]

Objectives To report the distribution of intraocular pressure (IOP) by age and sex and the prevalence of glaucoma.

Design Community based cross sectional observational study.

Setting EPIC-Norfolk cohort in Norwich and the surrounding rural and urban areas.

Participants 8623 participants aged 48-92 recruited from the community who underwent ocular examination to identify glaucoma.

Main outcome measures Prevalence and characteristics of glaucoma, distribution of IOP, and the sensitivity and specificity of IOP for case finding for glaucoma.

Results The mean IOP in 8401 participants was 16.3 mm Hg (95% confidence interval 16.2 mm Hg to 16.3 mm Hg; SD 3.6 mm Hg). In 363 participants (4%), glaucoma was present in either eye; 314 (87%) had primary open angle glaucoma. In the remaining participants, glaucoma was suspected in 607 (7%), and 863 (10.0%) had ocular hypertension. Two thirds (242) of those with glaucoma had previously already received the diagnosis. **In 76% of patients with newly diagnosed primary open angle glaucoma (83/107), the mean IOP was under the threshold for ocular hypertension (21 mm Hg)**. No one IOP threshold provided adequately high sensitivity and specificity for diagnosis of glaucoma.

Conclusions In this British community, cases of glaucoma, suspected glaucoma, and ocular hypertension represent a large number of potential referrals to the hospital eye service. **The use of IOP for detection of those with glaucoma is inaccurate and probably not viable.**

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Table showing the percentage of eyes with POAG and screening IOP lower than 22 mm Hg

Baltimore Eye Study	59%
Beaver Dam Eye Study	32%
Melbourne VI Project	39%
Rotterdam Study	39%

If the prevalence (risk) of glaucoma increases in patients with higher IOP, how can half the patients with POAG have a screening IOP lower than 22 mm Hg?

Because the vast majority of the population has low IOP

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Those at higher risk for this form of glaucoma (NTG) are:

- A family history of normal-tension glaucoma
- People of Japanese or Korean ancestry
- A history of systemic heart disease such as irregular heart rhythm.

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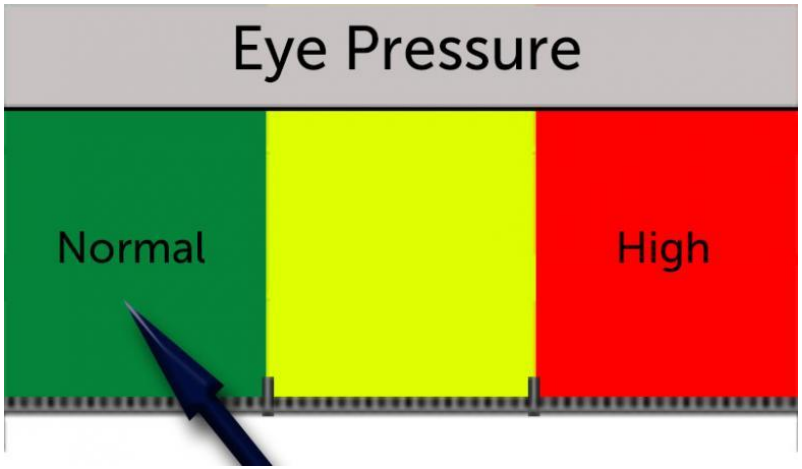
The history of low-tension glaucoma (LTG) may include the following



Steroid use

Trauma

Vasospasm (Raynaud syndrome)

Migraine headaches

Coagulopathies - Previous blood loss or shock-like episode

Systemic nocturnal hypotension (notably in older thin, white women)

Autoimmune disorders (evidence of other autoimmune diseases common)

Systemic vascular disease

Thyroid disease - Increased incidence of thyroid disease in patients with low-tension glaucoma (6 of 25 patients in 1 series)

Sleep apnea (particularly in heavy men)

Alzheimer disease

Family history of glaucoma or optic neuropathy

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Normal Tension Glaucoma

- Among patients with NTG, an elevated prevalence of vasospastic diseases (migraine and Raynaud's disease), ischemic vascular diseases, and hypotension is found.

- Evidence suggests a high prevalence of autoimmune diseases in patients with NTG compared to controls with ocular hypertension.

Goldberg I, Hollows FC, Kass MA, Becker B. Systemic factors in patients with low-tension glaucoma. *Br J Ophthalmol*. 1981;65:56-62.

Cartwright MJ, Grajewski AL, Friedberg ML, Anderson DR, Richards DW. Immune-related disease and normal-tension glaucoma: A case control study. *Arch Ophthalmol*. 1992;110:500-502.

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Normal Tension Glaucoma

• NTG accounts for 25% of the glaucomas. Patients commonly affected by this condition = **older women** and patients who are **Japanese**.

• The mean age is 60 years and patients with NTG are generally 10 years older than patients with high-tension glaucoma.

Shiose Y. Prevalence and clinical aspects of low-tension glaucoma. In: *TwentyFourth International Congress of Ophthalmology*. Henkind P, ed. Philadelphia, PaLippincott; 1983

Levene RZ. Low-tension glaucoma. In: *Glaucoma*. Cairns JE, ed. London: Grune and Stratton; 1986.

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Normal Tension Glaucoma

Although the occurrence of normal-tension glaucoma varies worldwide, it is very prevalent in Japan.

In the United States, up to **15-25%** of people with open-angle glaucoma experience normal-tension glaucoma.

According to the Baltimore Eye Study**, 50%** of individuals with changes in their optic disc and in their visual field had an IOP of less than 21 mm Hg on a single visit, and 33% had an IOP of less than 21 mm Hg on 2 measurements.

Normal-tension glaucoma is more common in women than in men.

Normal-tension glaucoma affects adults, with an average age of 60 years.

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Glaucoma in Women: The Estrogen Connection

Many studies in the 2000s uncovered risk surrounding reproductive factors and glaucoma

- **Early menopause**
- **Late menarche**
- **Oophorectomy** – removal of the ovaries before the age of 43 had a significant risk of POAG
- **Oral contraceptive use** – oral contraceptives differ from endogenous estrogens in many ways

Loss of estrogen at an early age may cause the optic nerve to age prematurely

The Rotterdam Study, the Blue Mountains Eye Study and the Nurses' Health Study support the theory that decreased lifetime estrogen exposure may increase the risk for glaucoma later in a woman's life.

Estrogen receptors are expressed on the retinal ganglion cells and have a maintenance effect.

Estrogen may stimulate more collagen fiber formation at the lamina cribrosa

It may also influence the flexibility of the entire eye and decrease IOP.

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Theories of Damage:

- **Mechanical Theory –** distortion of lamina cribrosa backward and compression of axons
- **Vascular Theory –** poor perfusion of blood to the optic nerve = (diastolic BP- IOP) should not be lower than 50 during the day
- **Toxicity Theory –** Glutamate toxicity to the ganglion cells
- **Fluctuation Theory** = differences of IOP throughout the day
- **Neurogenic Theory** = not IOP , susceptibility to the IOP

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Space Travel Applications

Astronauts who return from the International Space Station experience diminished vision for years.

Vision impairment and intracranial pressure (VIIP) also known as space-associated neuropathy Syndrome (SANDS), yields four main side effects:

- **Globe flattening**
- **Hyperopic shifts**
- **Choroidal folds**
- **Optic nerve edema**

Low IOP can cause corneal decompensation, accelerated cataract formation and maculopathy

At zero gravity, IOP is significantly lower than CSF and over time many astronauts get papilledema, optic atrophy and loss of visual acuity.

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Five Practical Rules:

#1. Observe the scleral ring to identify the limits of the optic disc and evaluate its size.

#2. Identify the size of the rim.

#3. Examine the retinal nerve fiber layer

#4. Examine the area outside the nerve for peripapillary atrophy

#5. Watch for optic disc and retinal hemorrhages

Susanna R, Vessani RM; New findings in the evaluation of the optic disc in Glaucoma diagnosis. Current Opinion in Ophthalmology 2007,18:122-128.

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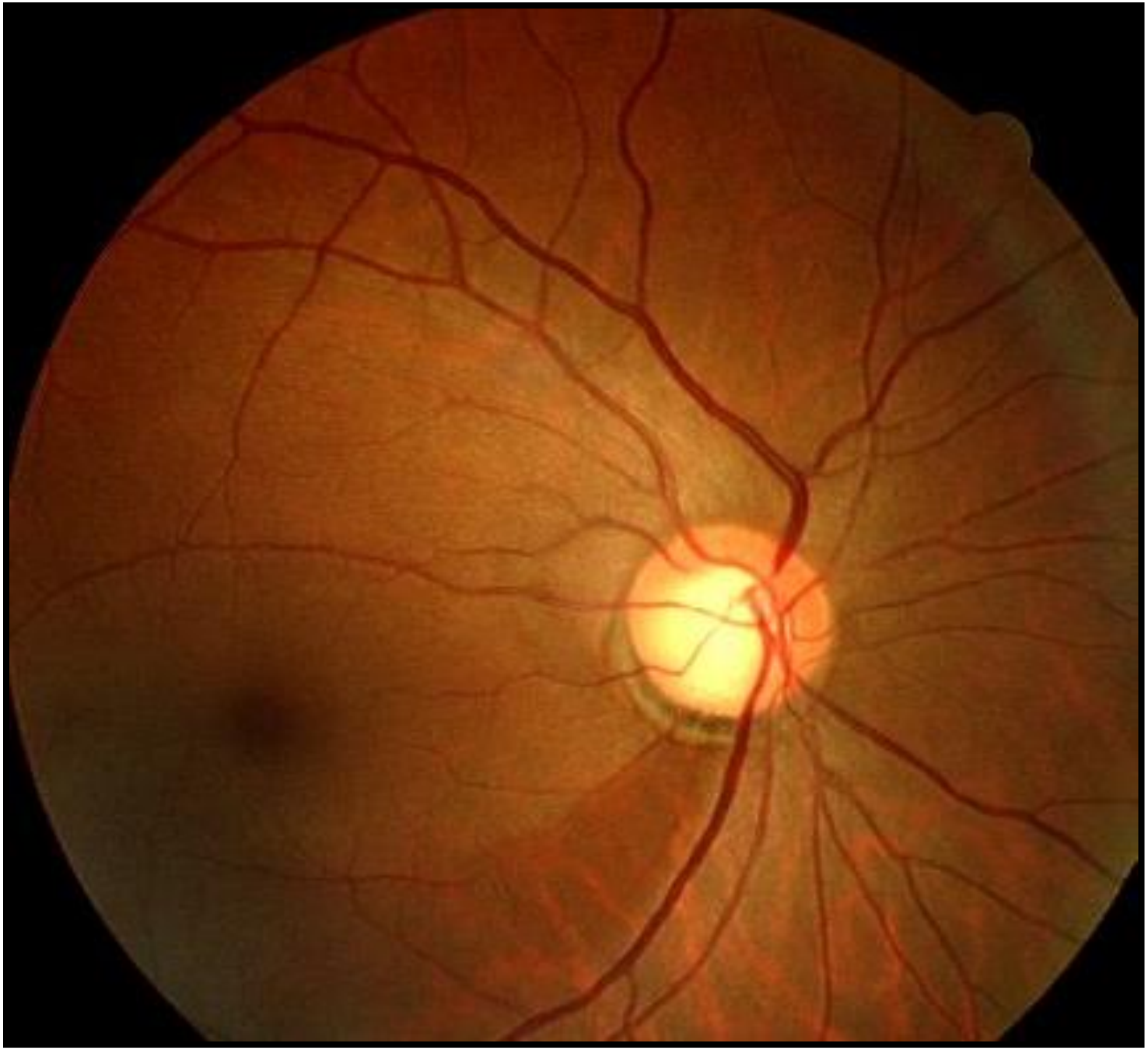

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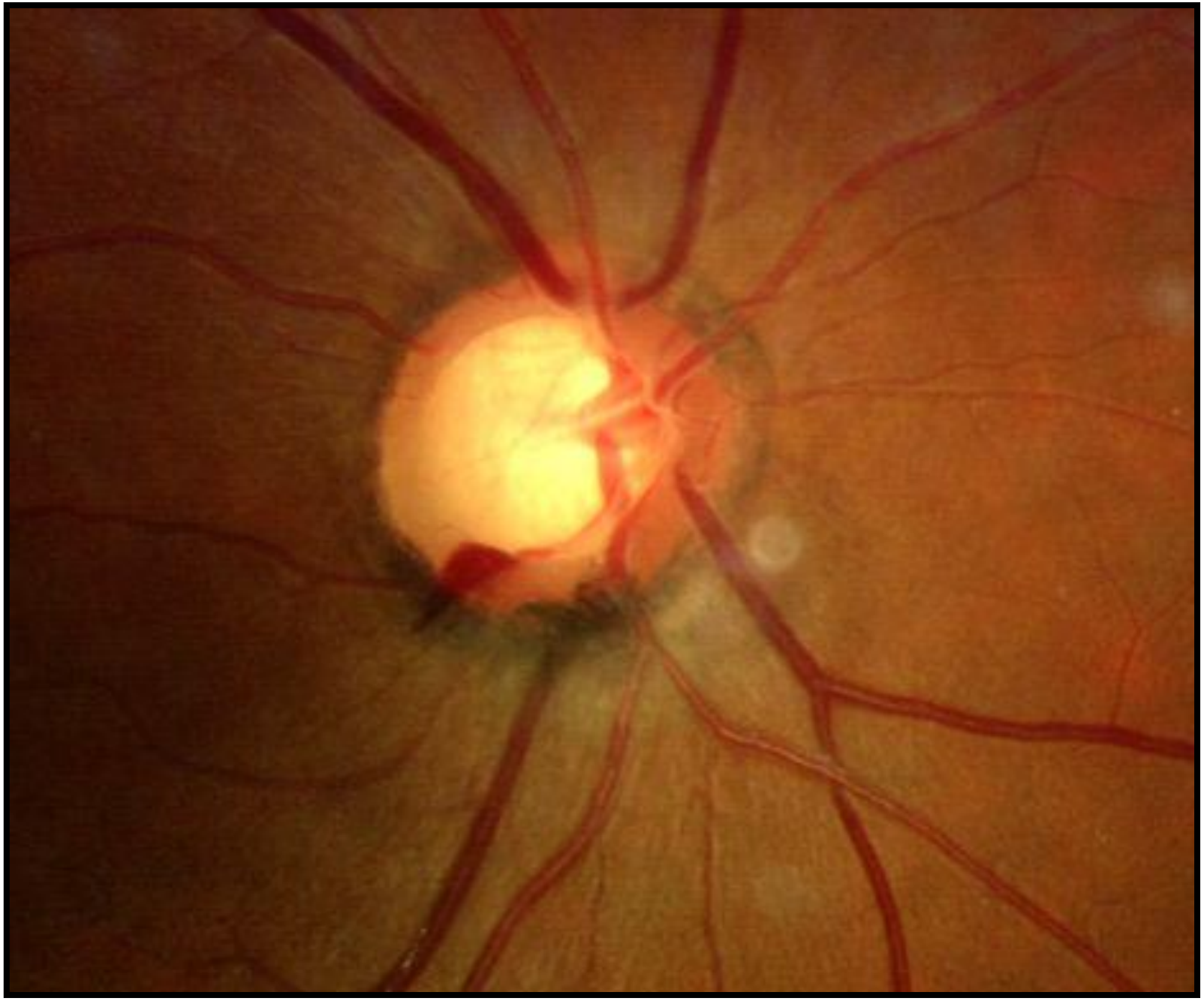

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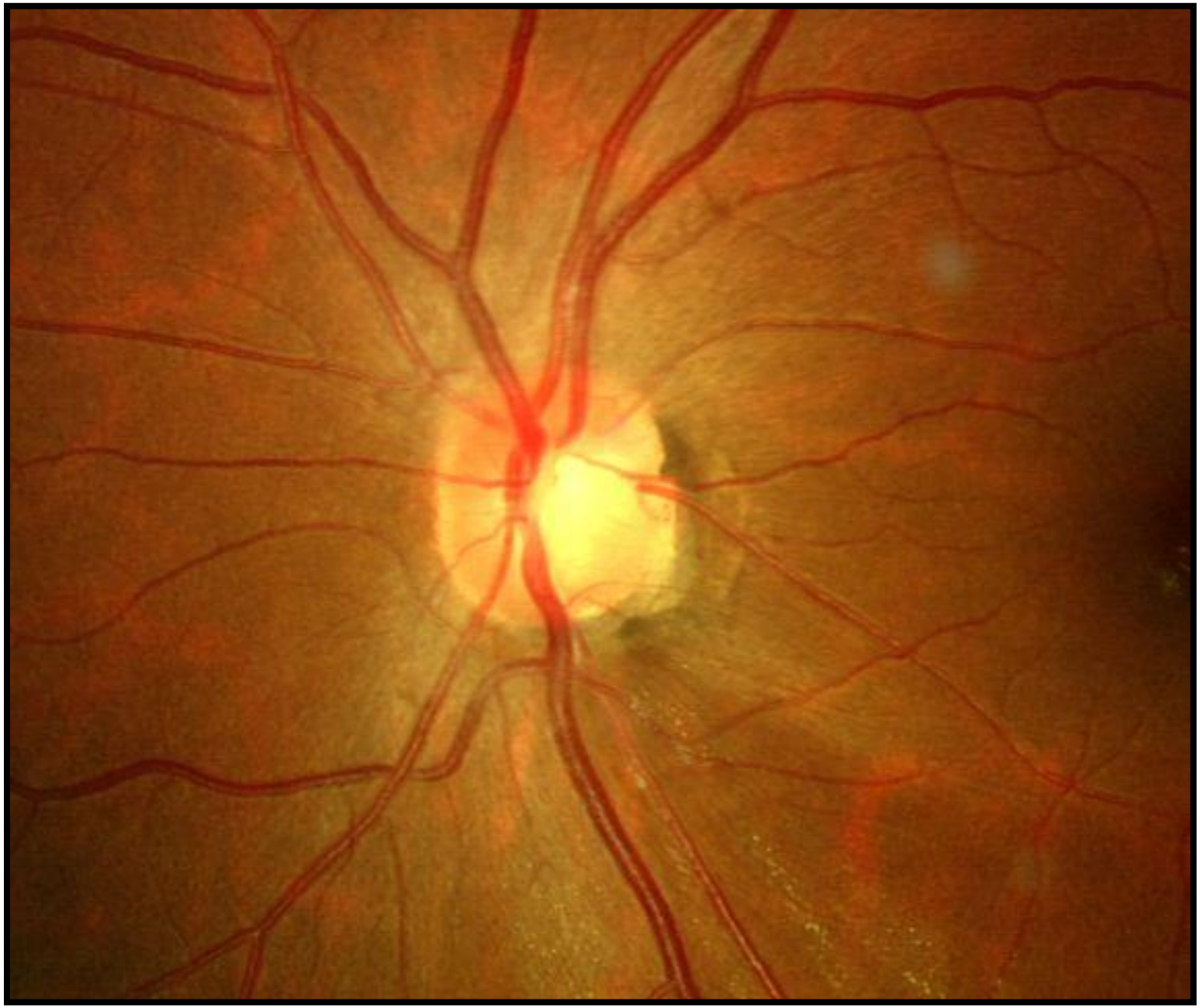

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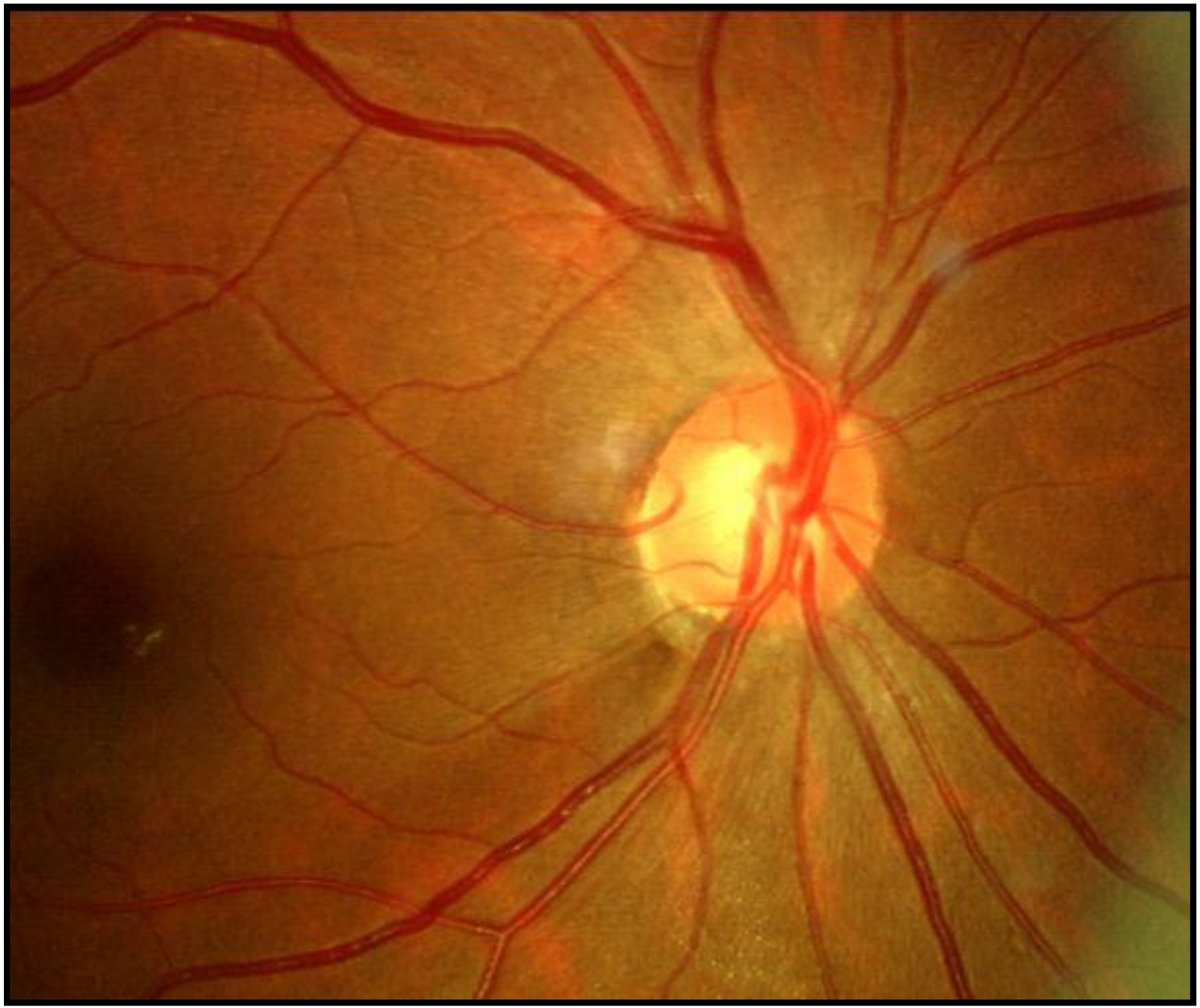

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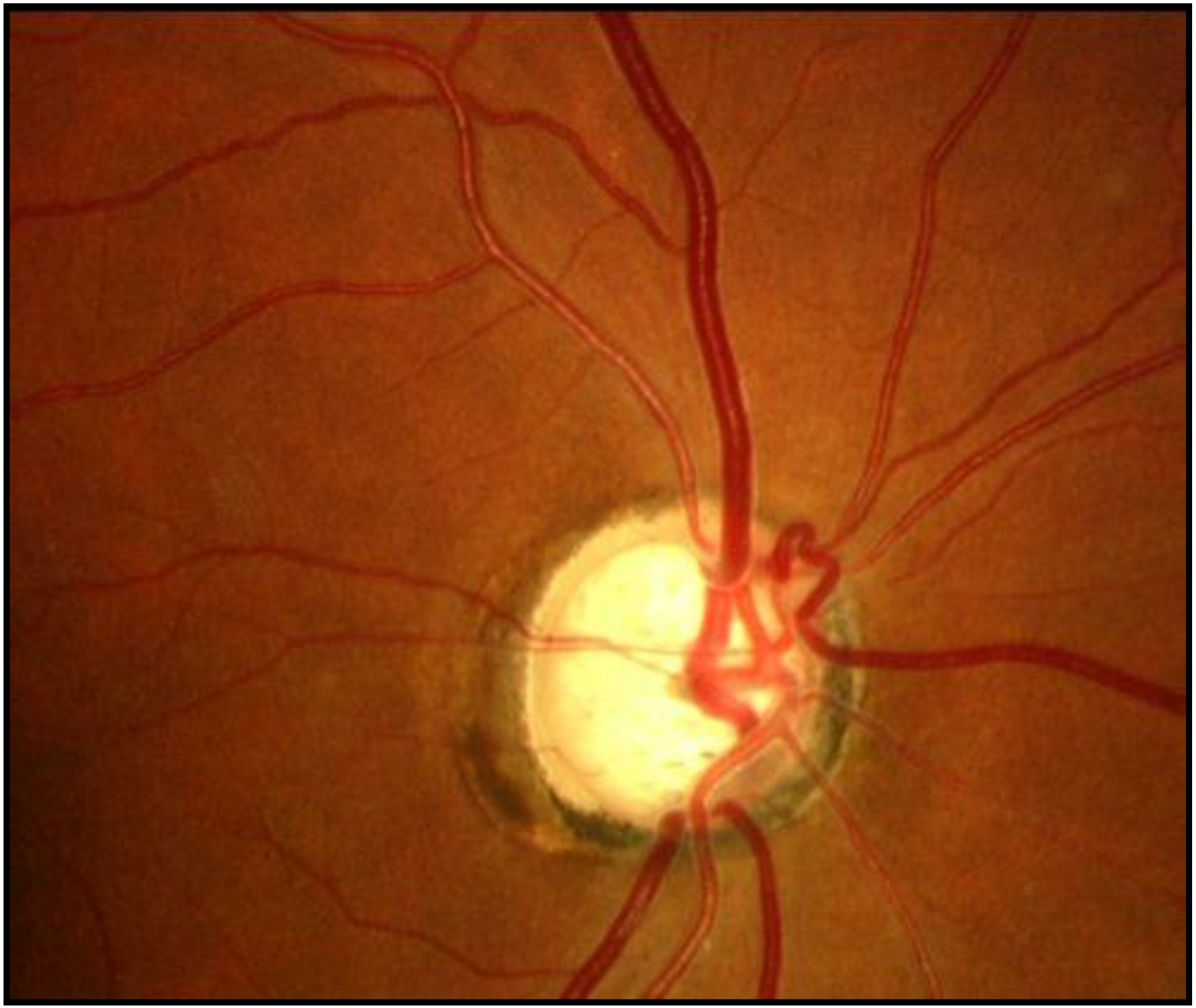

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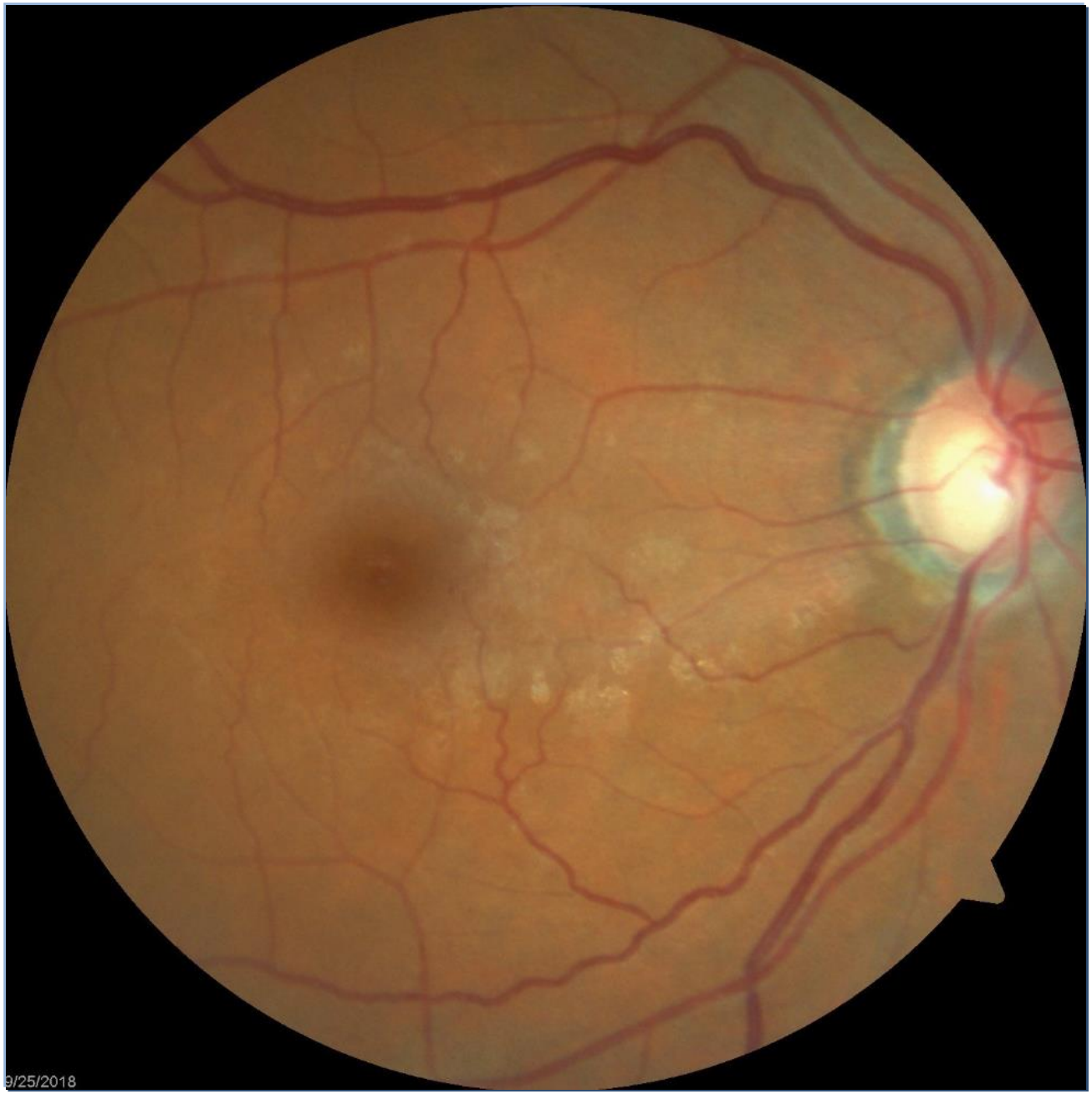

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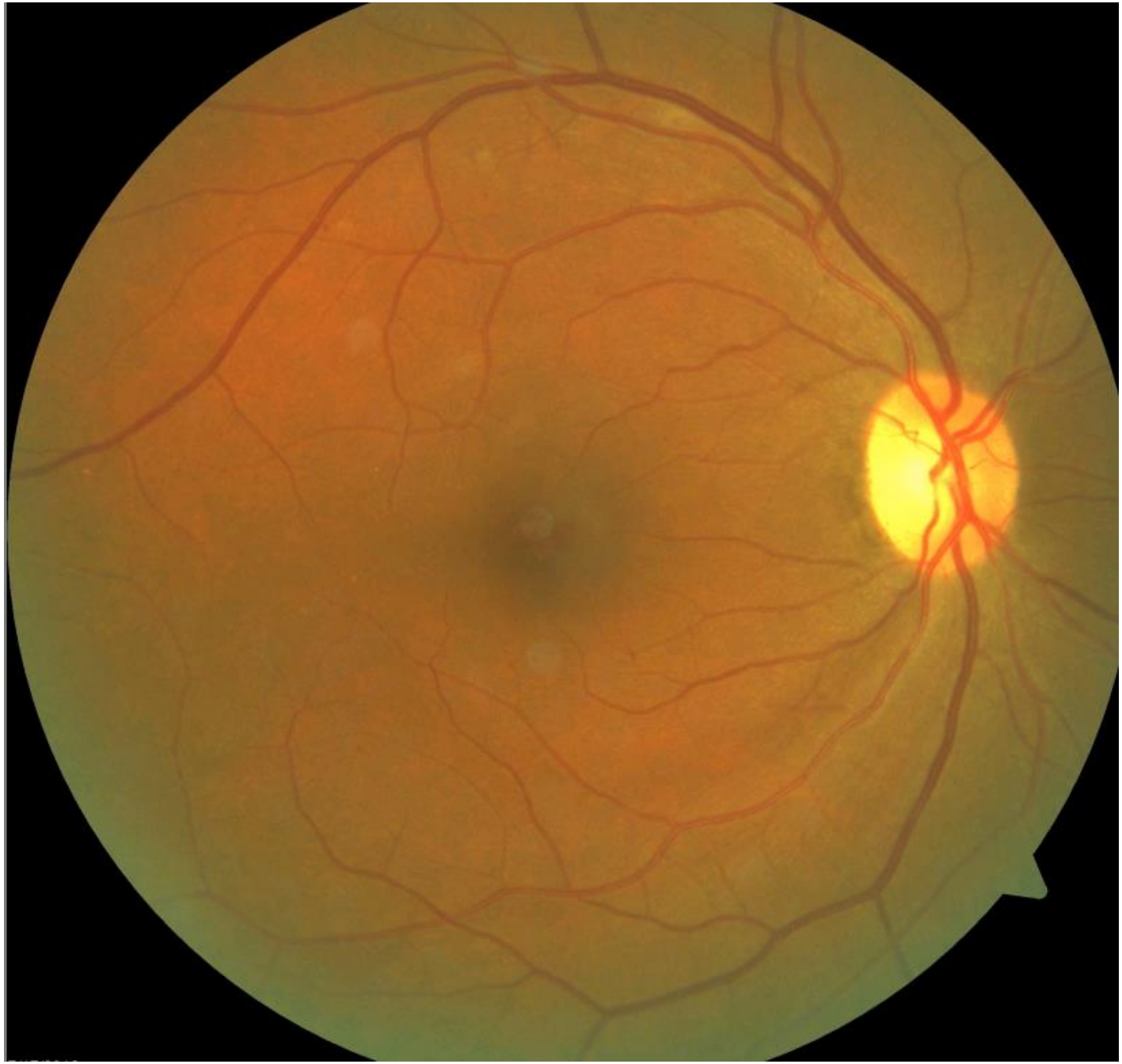

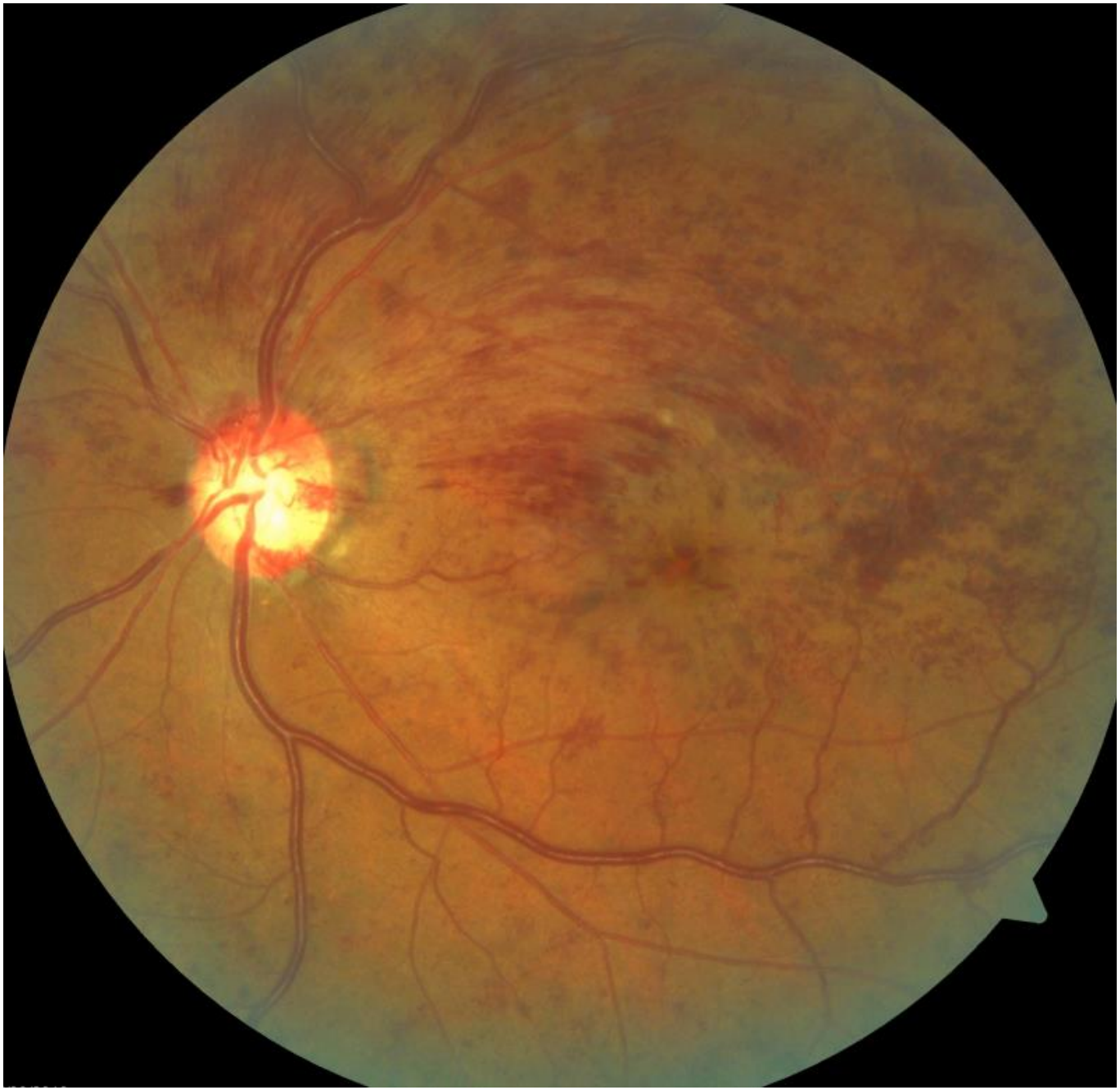

NANOS 2015 Annual Meeting
February 26, 2015
Hotel del Coronado | San Diego, CA

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IS NORMAL TENSION DIFFERENT THAN HIGH TENSION GLAUCOMA: OTHER POSSIBLE FACTORS

Martin B. Wax, MD *Dept Ophthalmology and Visual Sciences*
Rutgers, New Jersey Medical School, Newark, New Jersey

LABORATORY EVALUATION

Certainly, in order to rule out certain systemic considerations to help confirm the diagnosis of normal pressure glaucoma, it is reasonable to obtain several laboratory and/or radiologic tests. In general, there have always been two schools of thought which have tempered the clinical judgment of ophthalmologists regarding testing of these patients. There are those practitioners who will obtain almost no tests whatsoever.

Conversely, there are those that will obtain every test imaginable. We would advocate that in general it is reasonable to perform limited testing to detect certain obvious disorders which are either treatable, or require further medical evaluation to assess potential treatment, and therefore should be performed on all patients with normal pressure glaucoma. **The following tests should be viewed as the minimal essential testing to be performed, and their rationale are as follows:**

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A) **Complete blood count with differential and platelets**. There is no easier test to identify obvious blood dyscrasias, or common anemias, which may impair the delivery of oxygen to the high energy requirement tissues of the retina and
optic nerve.

(B) **Antinuclear antibody panel (ANA).** This test is a useful screen for collagen vascular disease, and other autoimmune abnormalities. A hospital generally offers ANA panels of varying complexity and we would advocate that the most complete panel offered, which typically tests for antibodies to extractable nuclear antigens such as Ro/SSA, La and Sm antibodies, are the most useful. Positive findings to the presence of these autoantibodies may signify the identification of the autoimmune subset of patients with normal pressure glaucoma.

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(C) **VDRL and FTA**. One of the great masqueraders of glaucomatous optic neuropathy is indeed luetic disease. In our experience two out of every 100 patients with optic atrophy that have been referred to us for normal pressure glaucoma have tertiary syphilis which requires treatment.

(D) **Serum immunofixation for paraproteins**.
In our experience in a tertiary care setting, approximately **10-15%** of patients with normal pressure glaucoma have a **monoclonal gammopathy** (paraproteinemia), which is a clonal expansion of B cells which produces excessive serum immunoglobulin. While the majority of monoclonal gammopathies in an older adult population generally represents a benign condition (called “monoclonal gammopathy of undetermined significance”), approximately one-third of these gammopathies will turn out to be caused by lymphoproliferative disorders such as **multiple myeloma or other neoplastic conditions**. It is recommended, therefore, that the ophthalmologist test for this condition and if a paraproteinemia is found, refer the patient to a hematologist for further workup which may include a bone marrow aspirate. Although paraproteinemias can often be determined by obtaining full **serum protein electrophoresis profiles**, a much easier and cheaper test is available in most laboratories in which immunofixation testing is performed in order to detect a serum monoclonal protein.

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Additional laboratory testing which may be useful in selected patients include the following:

(E) **SMA12**. It is not unreasonable to obtain electrolytes and studies of liver and renal function in patients in whom there is a high index of suspicion of such disease. We have found, however, that routine testing for these values has been rather unproductive in virtually all patients with normal pressure glaucoma.

(F) **Complement studies**. Testing for C3 and C4 complement has been unproductive in our hands as a assessment of potential collagen vascular disease.

(G) **B12 and folate**. These two have likewise been unrevealing. Although they are often obtained when there is a high degree of suspicion of an intrinsic neuropathy affecting central vision, we have not found them to be of value in assessing patients with normal pressure glaucoma.

(H) **Cryoglobins.** These may be useful in patients in whom there is Raynaud's phenomenon or evidence of marked peripheral vasospasm, but is otherwise not very helpful.

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Normal Tension Glaucoma Testing

Radiological studies:

There is considerable debate as to whether there is any utility in obtaining a CAT scan or MRI in patients with normal pressure glaucoma.

Obviously, these tests are more useful in patients in whom there is a loss of central vision with preservation of peripheral vision, or in patients in whom chiasmal lesions are suspect. On the other hand,one might argue that it is not unreasonable to leave “no stone unturned”

The odds of finding another problem with NTG ?

What is the statistical likelihood of uncovering
a serious non-glaucoma health isssue ????

How often does a horse turn out to be a zebra in disguise ????

Consider the cost to the patient !!!!

Consider the cost to the health-care system !!!!

Is there such a thing as too much information ????

“If it looks, walks and quacks like a duck, it is probably a duck”

Make the best choice !!!!

It comes down to the “Physician’s Philosophy”

Normal Tension Glaucoma Treatment

• As in primary open-angle glaucoma, medical treatment is the initial approach in reaching this goal.

• A 30% reduction in IOP was achieved and maintained in ~ half of the patients randomized to treatment in the Normal-Tension Glaucoma study with only topical drugs, or laser trabeculoplasty or both.

• The CNTGS showed faster rates of progression in women in those patients with migraine headaches or disc hemorrhages.

Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients therapeutically reduced intraocular pressures. *Am J Ophthalmol*. 1998;126:487-497.

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Normal Tension Glaucoma

• The Collaborative Normal-Tension Glaucoma Study (CNTGS) found that, by reducing the IOP by greater than 30%, the rate of visual field progression decreased from 35% to 12%.

• However, in 65% of patients, disease did not progress over the length of the study, despite having no treatment at all.

Collaborative normal-tension glaucoma study group. The effectiveness of intraocular pressure in the treatment of normal-tension glaucoma. *Am J Ophthalmol*. 1998;126:498-505.

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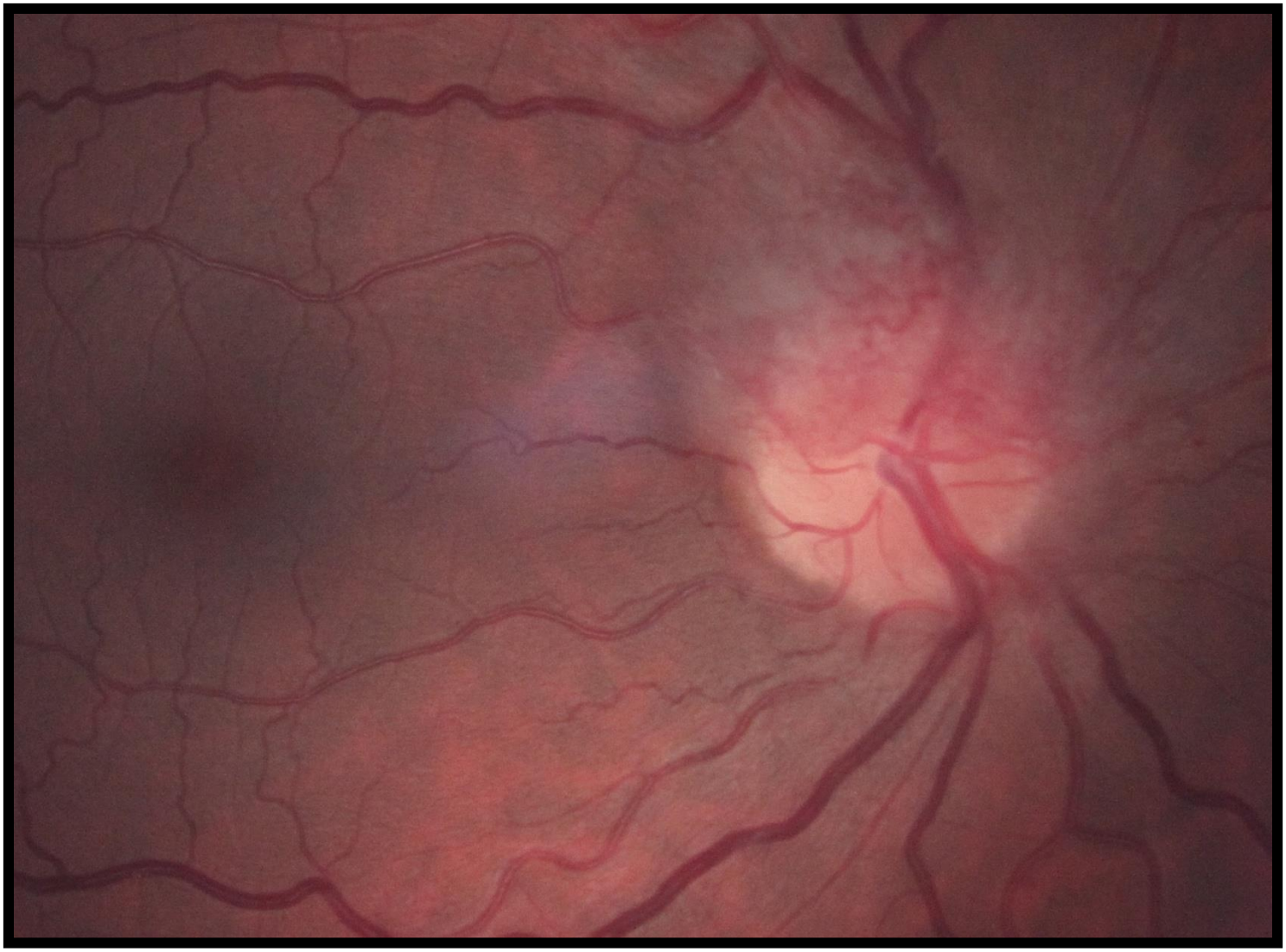

Pink Optic Nerve Swelling - NAAION

Dr. Trego

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Assessing the Optic Disc

- Optic nerve appearance alone can mislead the doctor

- One can not judge the function of the optic nerve by just appearance
- Optic nerve appearance must correlate to tests of afferent function
    - Visual Acuity
    - Color vision
    - Color desaturation
    - Relative afferent pupillary defect
    - Brightness sense
    - Visual fields

- History is extremely important in the assessment of the optic nerve
    - Weight gain
    - Trauma
    - Drug use – Alcohol / Tobacco
    - Nutrition

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The End!

- Thank you for your attendance
- My e-mail address:

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