



*Waldenström
and
the Eye
Maureen Hanley, OD
The New England College of
Optometry
Boston, Massachusetts*



Rhode Island

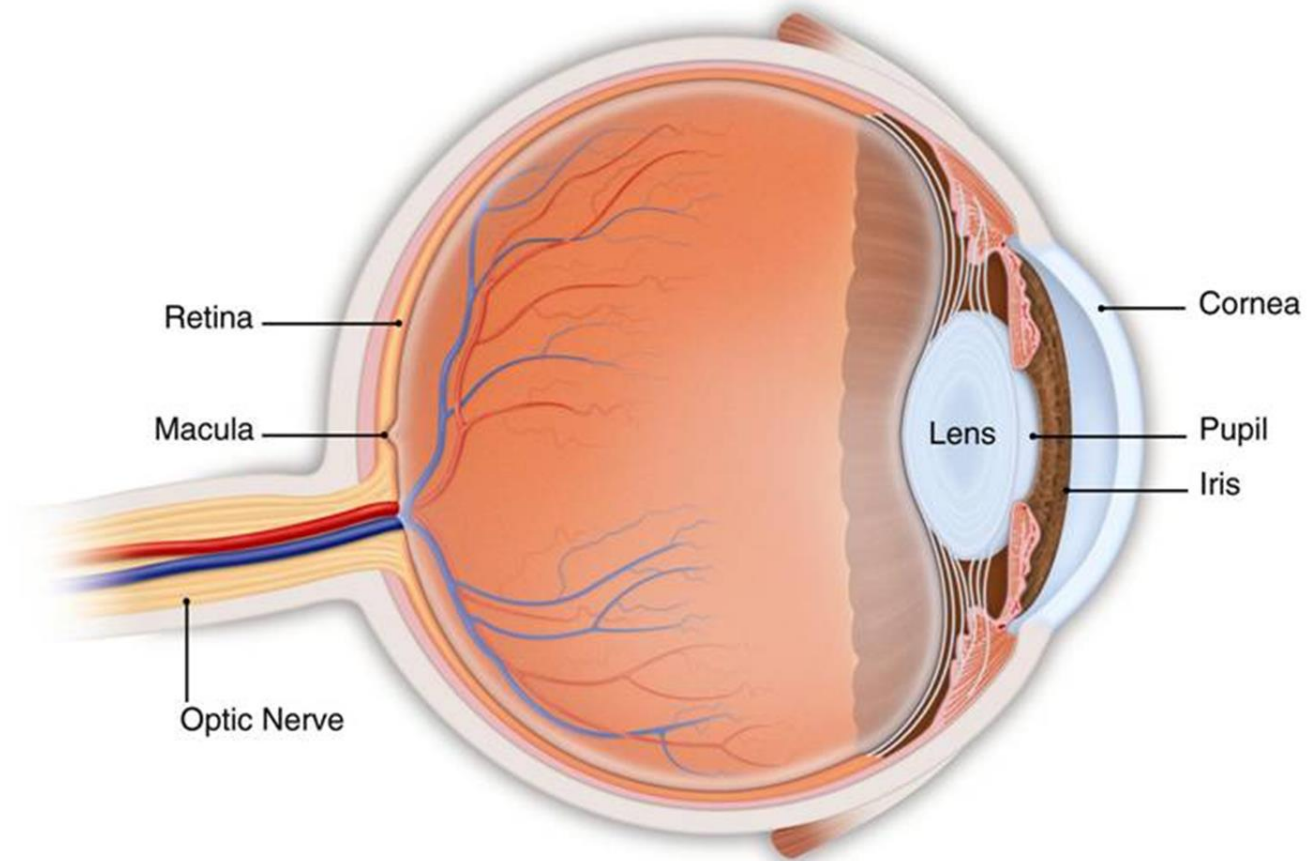


- ☞ Born and raised in this Great State
- ☞ Covers an area of 1,214 square miles. 48 miles North to South and 37 miles and East to West
- ☞ As we say the smallest state but yet so Great
- ☞ Bubblers, clam cakes, clear chowder
- ☞ Of course, we have the beaches therefore the Ocean State



Lets talk eye - front to back

∞ Lets talk normal aging versus Waldenström related issues.



Conjunctiva

- ∞ The conjunctiva is a clear mucous membrane with fine blood vessels which lines the inside of eyelids and also covers the sclera (the white part of the eye).
- ∞ The conjunctiva can be affected by WM, and in this case the blood within the vessels of the conjunctiva may appear segmented and sluggish. The change in the conjunctiva can only be seen under an instrument called a slit lamp.
- ∞ Such changes also happen with almost all types of anemia.

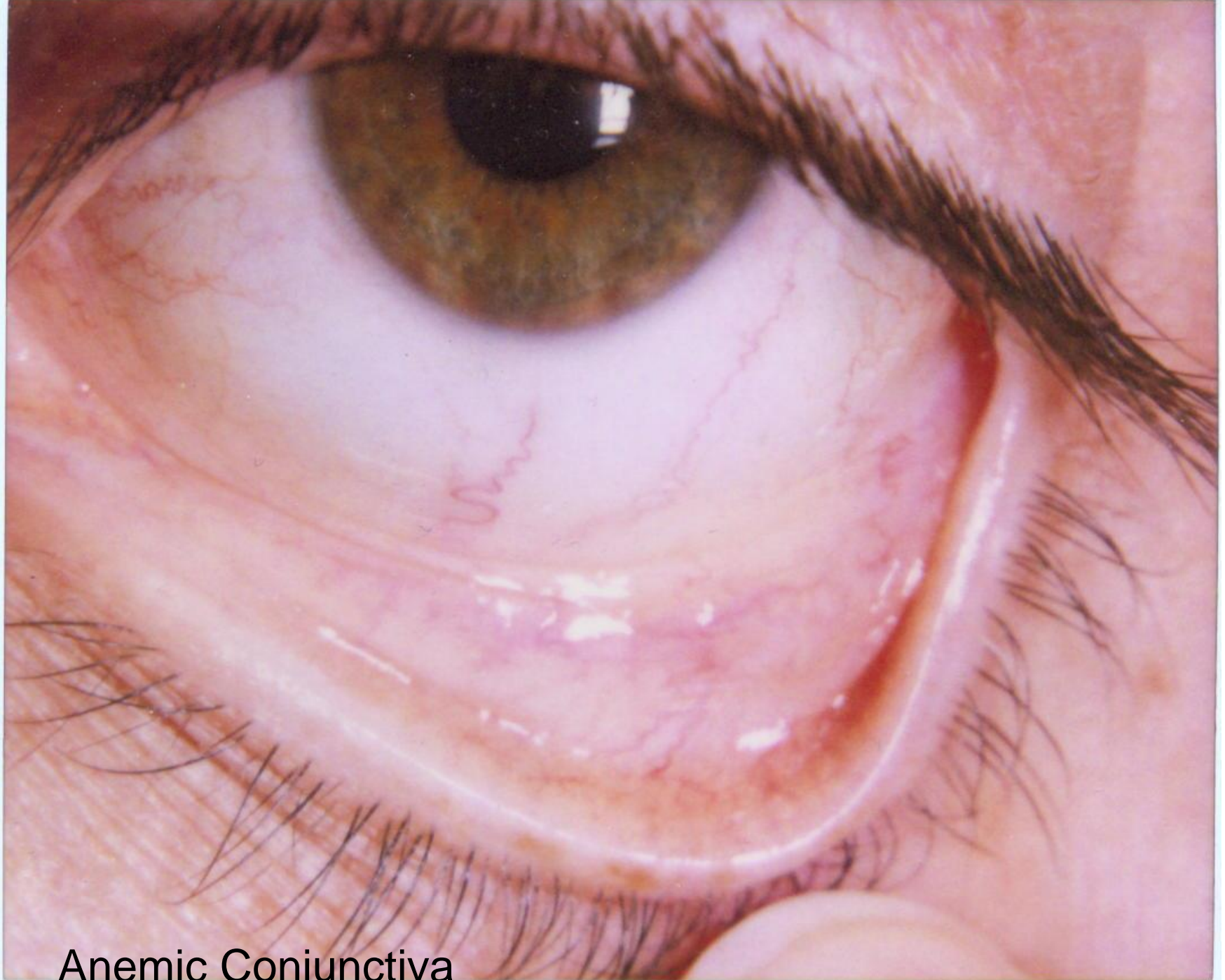
Conjunctival pallor

- ∞ May be a simple screen for the presence of anemia although studies vary on sensitivity and specificity.
- ∞ You can actually see gaps in between erythrocytes (red blood cells) when you do a careful slit lamp examination.



Normal conjunctival Coloring

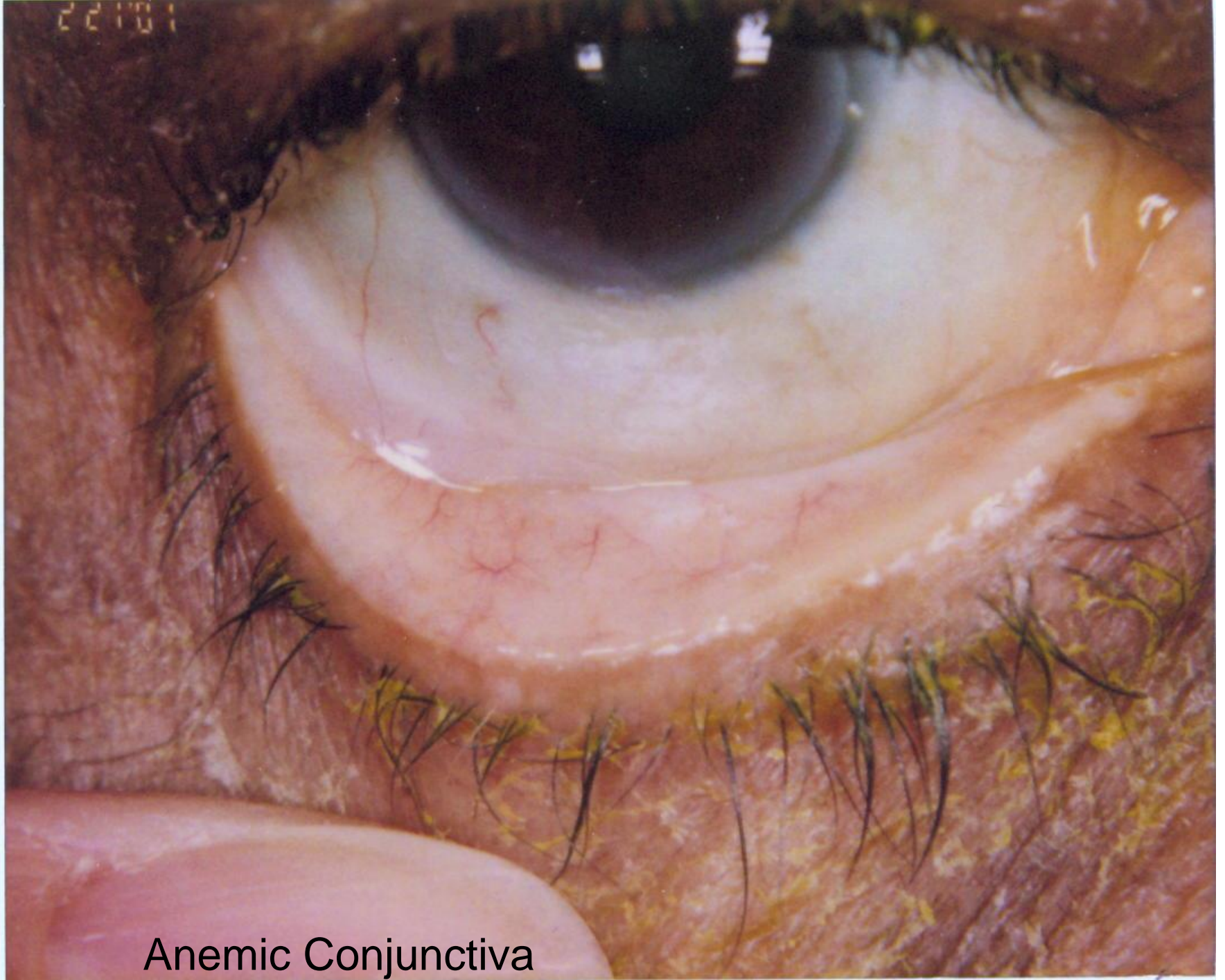




Anemic Conjunctiva



Anemic Conjunctiva



Anemic Conjunctiva



Anemic Conjunctiva – gaps

Subconjunctival hemorrhages

- ✧ Subconjunctival hemorrhages also occur commonly, whether or not you have WM.
- ✧ The hemorrhage occurs when a small blood vessel bleeds into the area of the eye between the sclera and the conjunctiva.
- ✧ When this happens, the sclera or whites of our eye look bright red.
- ✧ A subconjunctival hemorrhage is usually harmless however recurrent ones usually indicate a systemic issue and traumatic SCH always need to be addressed.
- ✧ ***However if you are on blood thinners such as coumadin or your platelet counts are low you should call your doctor.***
- ✧ ***Also if your vision is ever down from a subconjunctival hemorrhage you should call your doctor immediately.***



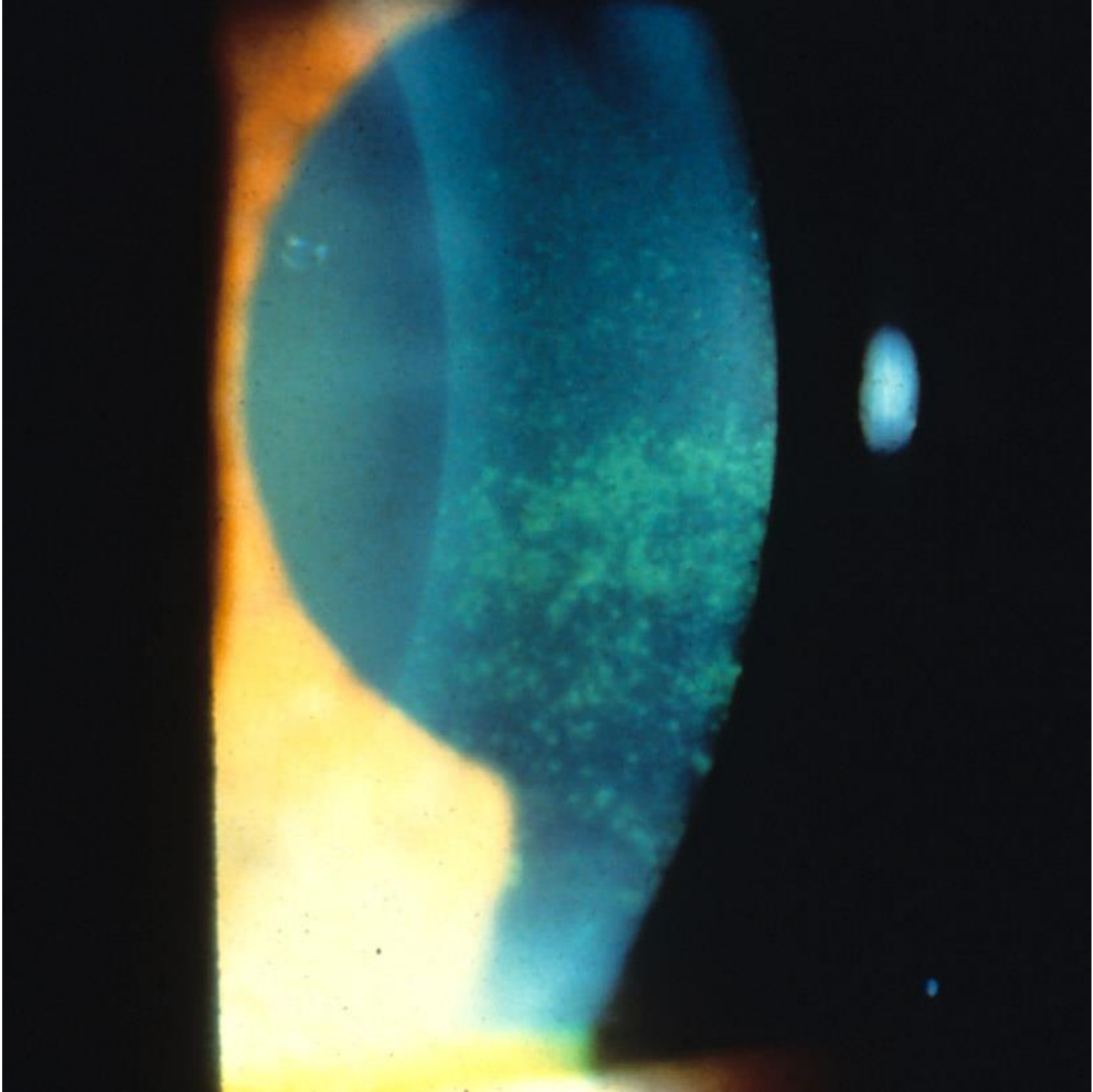


plasmapheresis

- Also, you should notify your doctor if you have a bright red eye after plasmapheresis since your PT (prothrombin time – a test for clotting ability) and PTT (partial thromboplastin time) may be dangerously off.
- This can not only cause a SCH but serious bleeding in the orbit which can lead to permanent vision loss

Dry Eye

- ∞ Dry eyes are a very common problem.
- ∞ Approximately twenty percent of all Americans suffer from dry eye symptoms.
- ∞ Dry eyes are even more prevalent in post-menopausal women, and WM may make this problem worse because it may have an autoimmune effect on the lacrimal gland



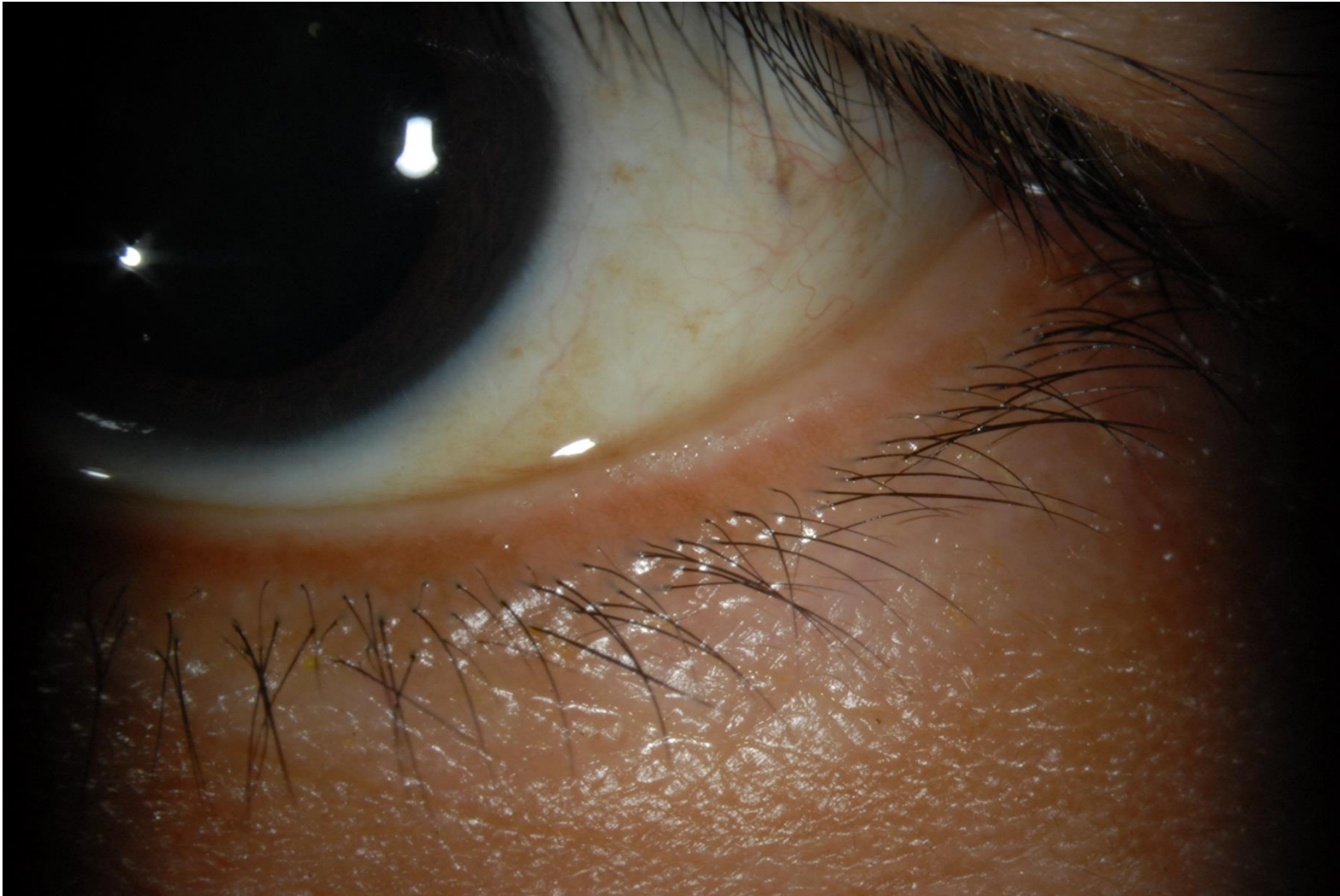
What can be done for a dry eye

- ∞ Need to find out what type of dry eye you have from your eye doctor and proceed from there
- ∞ Evaporative Dry
- ∞ Aqueous Deficient
- ∞ Mixed Etiology
- ∞ Systemic Medications

Treatment for Dry Eye

- ∞ It depends on the type of dry eye you have. But some of the treatments
- ∞ Artificial Tears
- ∞ Warm compresses and lid scrubs
- ∞ Moisture chamber spectacles
- ∞ Restasis
- ∞ Low dose steroid drops
- ∞ Punctal Plugs
- ∞ Scleral contact lenses
- ∞ autologous serum tears made from the plasma of your blood
- ∞ amniotic membrane

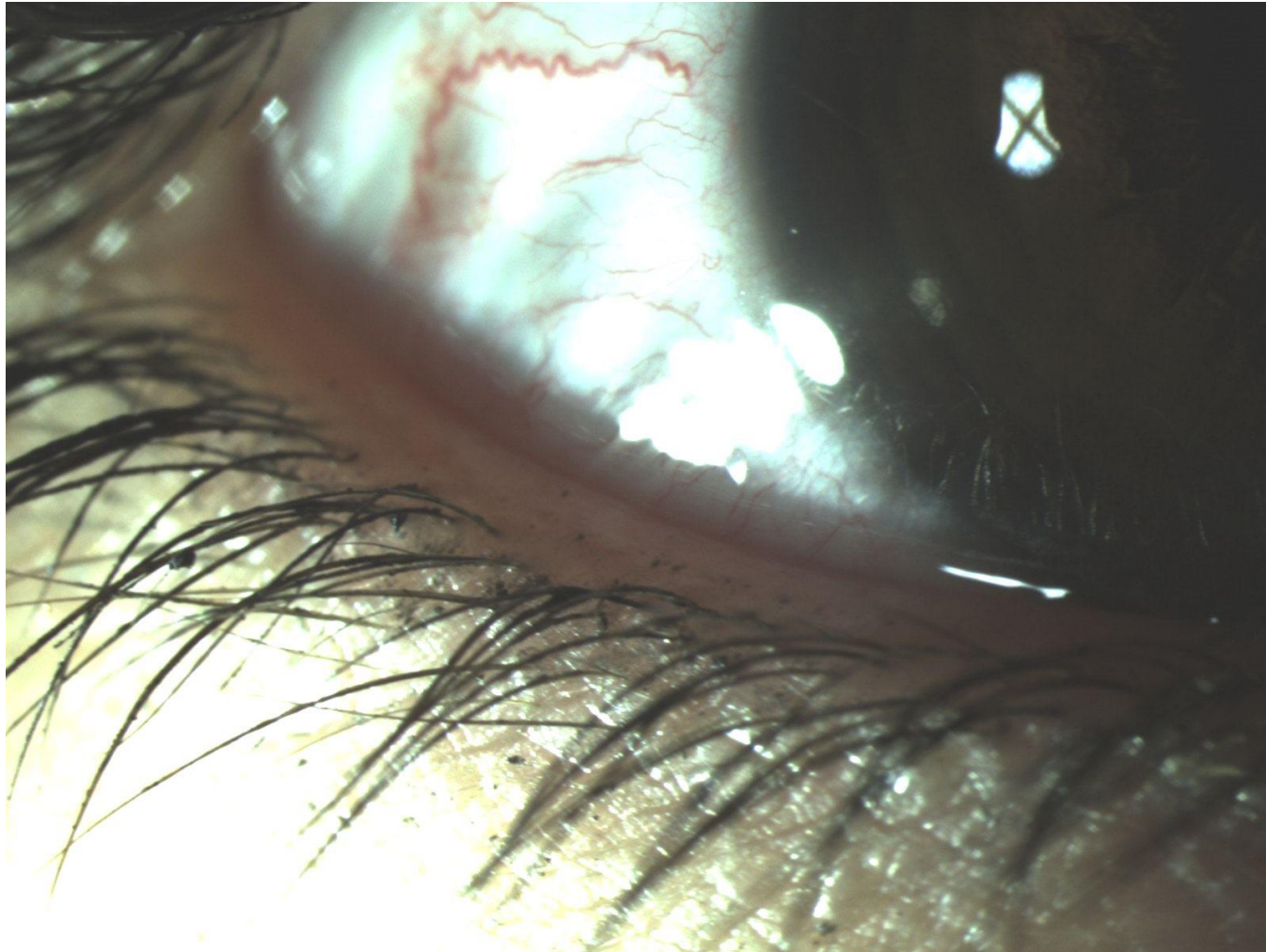
Meibomitis



Make up



Makeup on lower lid



Patient
Education

inferior puncta



Jordan M. Graff, MD
U of Iowa, 2004

Inferior puncta with a punctal plug



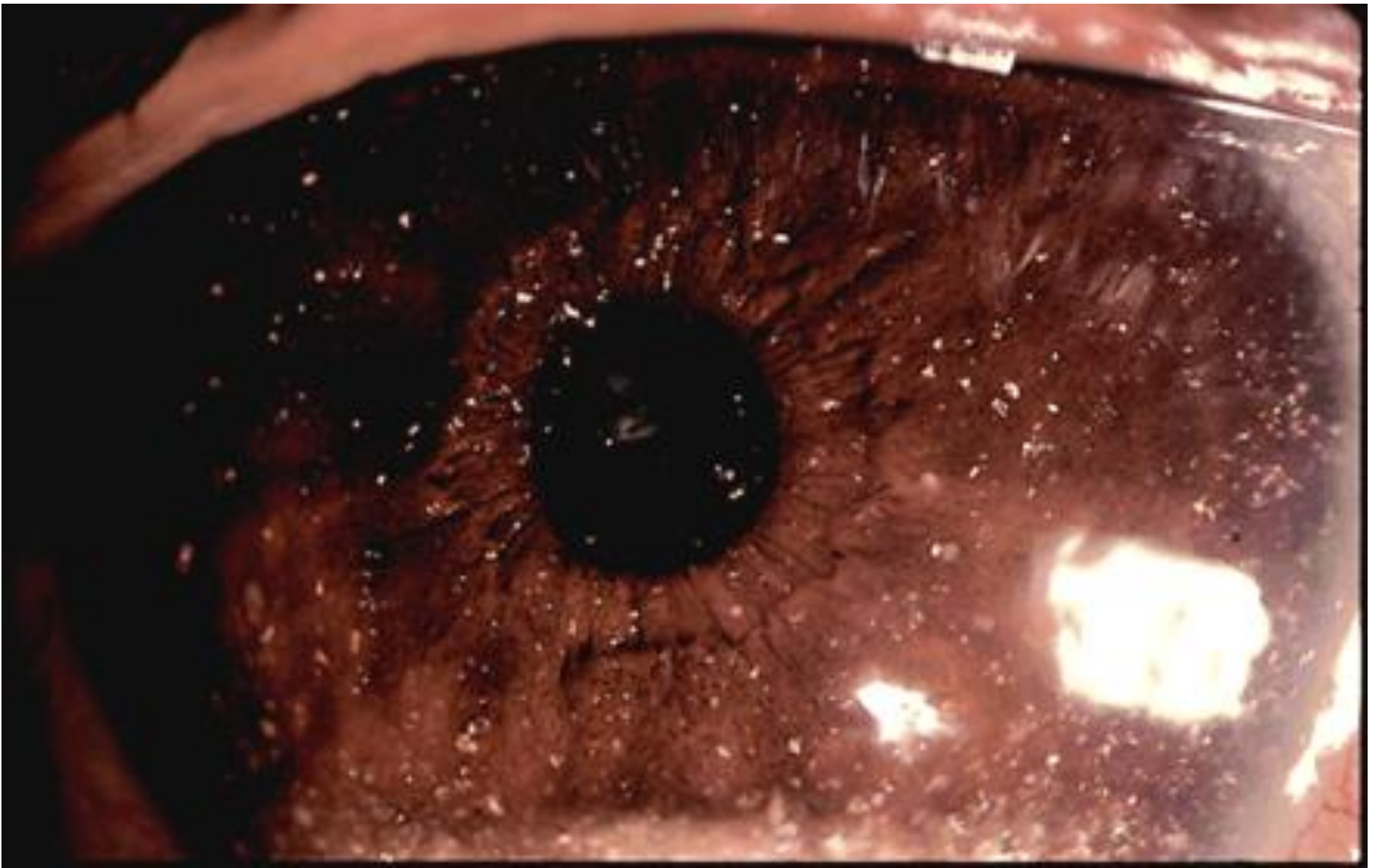
Why would you want to put a plug in the puncta?

Cornea

- ∞ Corneal crystalline deposits this is very rare
- ∞ Can happen in Multiple Myeloma and also just in MGUS

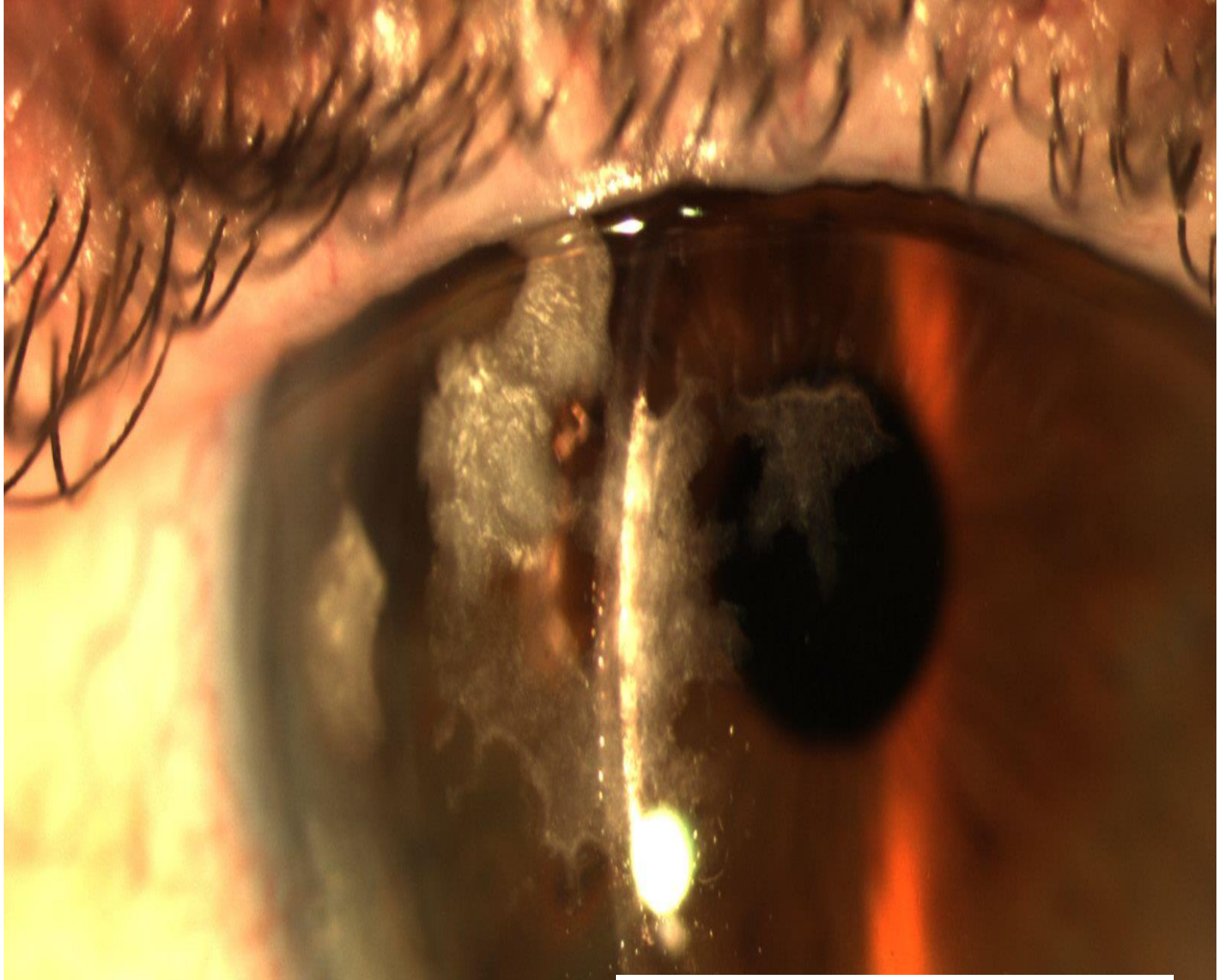
Corneal Crystals Secondary to Lymphoplasmacytic Lymphoma

Ryan Petrucci, BSc (Hons); Rebecca Stein, BSc (Hons); Raymond M. Stein, MD, FRCSC



Corneal crystalline deposits

Courtesy of Joseph P. Shovlin, OD, FAAO



Joseph P. Shovlin, OD, FAAO

Corneal crystalline deposits

Refractive

- Going from front to back we next have the lens
- If you are on high doses of steroid it can change the blood sugar levels in some patients. Increased blood sugar levels can markedly change your refractive error, usually making one more near sighted but in some individuals you can become more hyperopic . This happens to both eyes at the same time unless you have had cataract surgery



Lens

- ∞ Focusing - In our forties or early fifties we begin to lose the ability to focus. This is called presbyopia.
- ∞ With WM, presbyopia may become more pronounced because one tends to become more fatigued but we do not become presbyopic because of Waldenstrom.
- ∞ Anti-emetic medications, antihistamine drugs like Benadryl also decrease our ability to focus

Cataracts

- ∞ A cataract is an opacity of the lens. The lens is part of the focusing mechanism of the eye.
- ∞ The Framingham Heart study showed that the prevalence of cataracts occurring without vision loss was 41.7% in persons 55-64 years of age and 91.1% in those of ages 75-84.
- ∞ The prevalence of cataracts with vision loss was 4.5% in persons 55-64 years of age and 45.9% in persons of ages 75-84. Essentially, if we live long enough we all will develop a cataract.

Different kinds of Cataracts

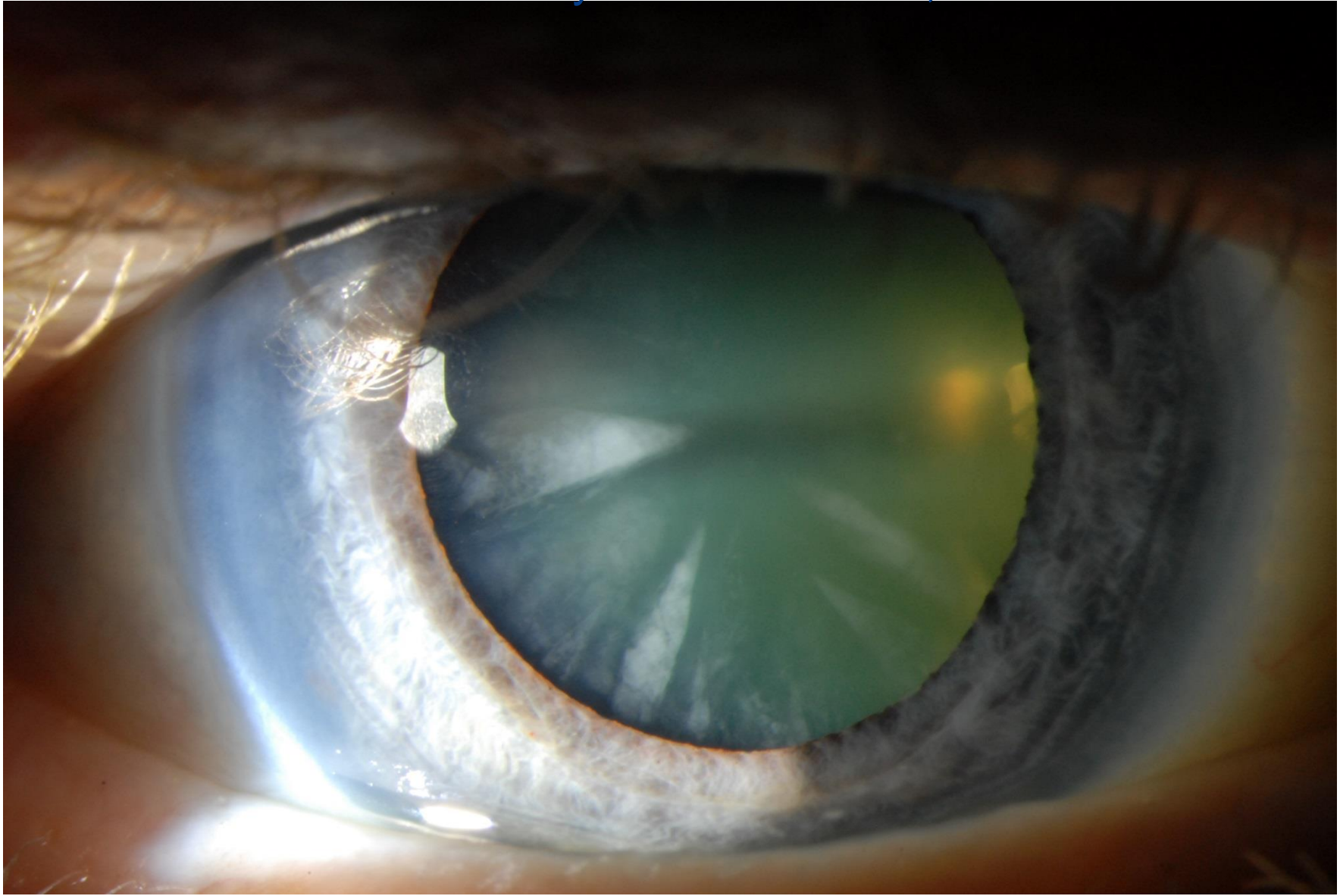
∞ The three main age related cataracts are

∞ Cortical

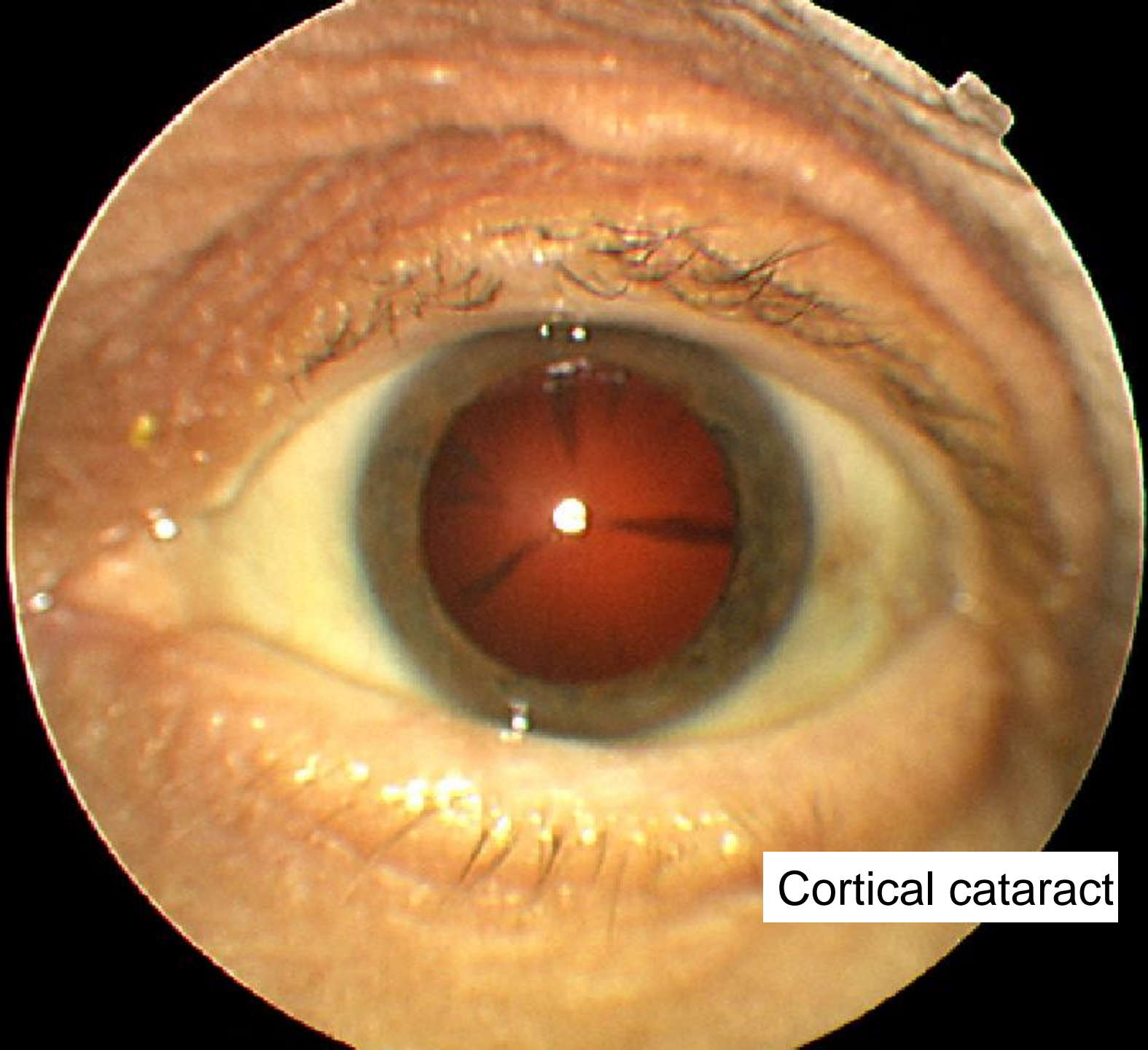
∞ Nuclear Sclerosis

∞ Posterior Subcapsular

Photo courtesy of Mike Barlow, OD

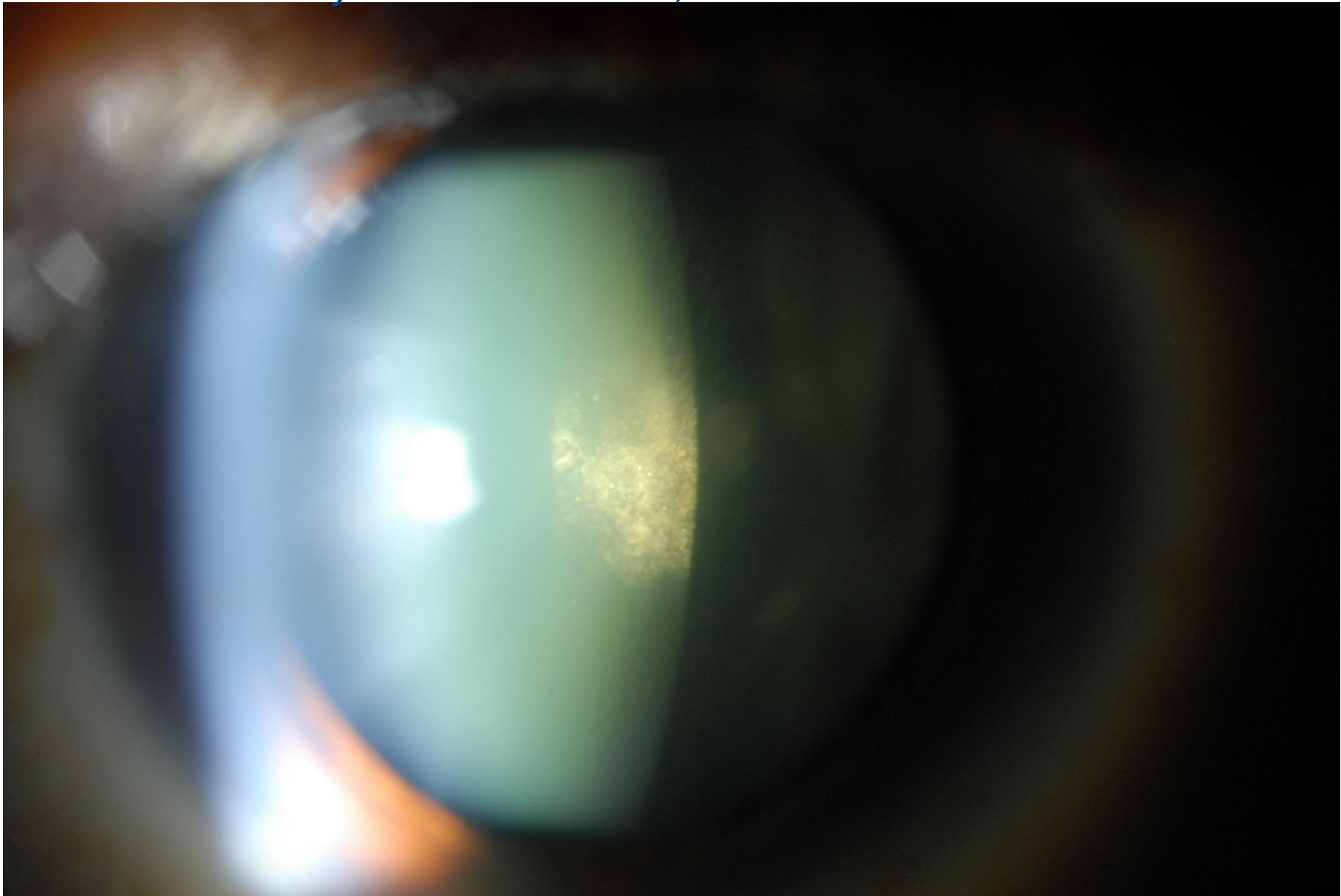


Anterior Cortical and Nuclear Sclerotic
Cataract



Cortical cataract

Photo courtesy of Mike Barlow, OD



Nuclear Sclerotic cataract and posterior subcapsular cataract

Cataracts: Posterior Subcapsular

Clinical Findings

- Dense granular appearance of posterior layers of lens cortex
- Early appearance described as iridescent sheen, which later becomes more granular and plaque-like
- Central opacities and vacuoles
- Often located along visual axis

∞ Pathophysiology

- Epithelial cell proliferation at pole with fluid filled areas within
- Associated with UV exposure and steroids
- Occurs earlier than NS or cortical

∞ Most visually distressing type

∞ Reduced acuity at near because as you age or read, the pupil gets small (Miosis effect) and with miosis many times you are looking right through the cataract

PSC

Controversial

- ⌘ A study found that 75% of the patients receiving more than 15 mg/day of prednisone for more than one year have PSC. JAMA 1960;174:166- 171
- ⌘ Certainly other studies vary in percentage to as low at 11%
- ⌘ Some studies suggest that the most important factor in steroid-induced posterior subcapsular cataract formation may be individual susceptibility.
- ⌘ Other studies suggest the cumulative amount of glucocorticosteroid taken is the determining factor.
- ⌘ The use of ocular or inhaled steroids has also been linked to cataract formation but does not pose as great of a risk for cataract formation

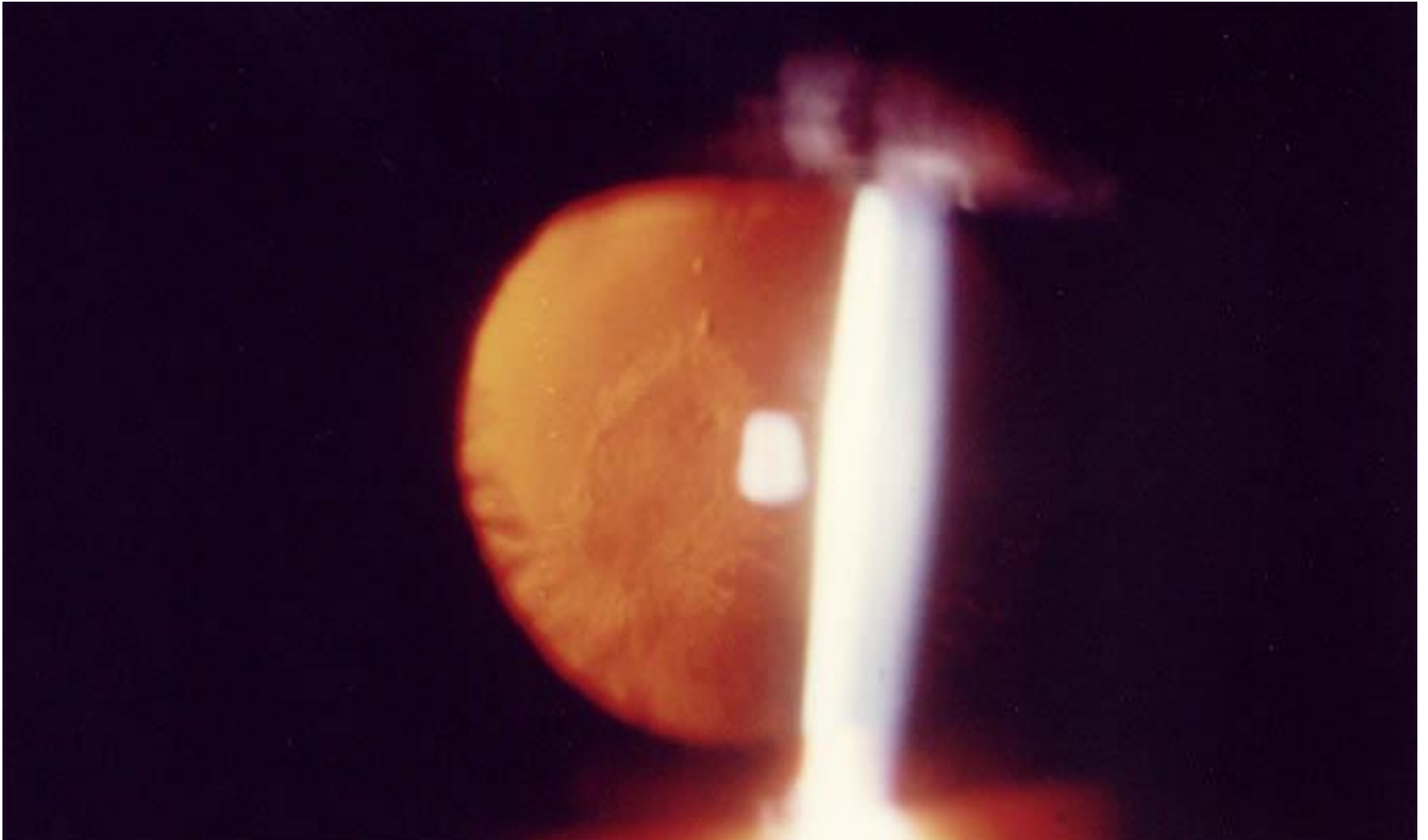
Steroids

- ∞ Intravitreal
 - ∞ Topical steroids
 - ∞ Oral
 - ∞ Inhaled
-
- ∞ Naturally dose and duration are important
 - ∞ Steroids are a definite for PSC

Steroids

- ✧ Lens epithelial cells seem to express a steroid binding protein and then gene expression occurs which appears to lead to
 - ✧ Cell proliferation
 - ✧ Cell differentiation
 - ✧ Cell apoptosis
 - ✧ Modulation of glucose metabolism
 - ✧ Modulation of membrane channels
 - ✧ Direct and indirect modulation of signal transduction
- ✧ In summary the etiology of steroid induced cataracts may be secondary to transactivation and transrepression of genes as well as modulation of the activity of proteins

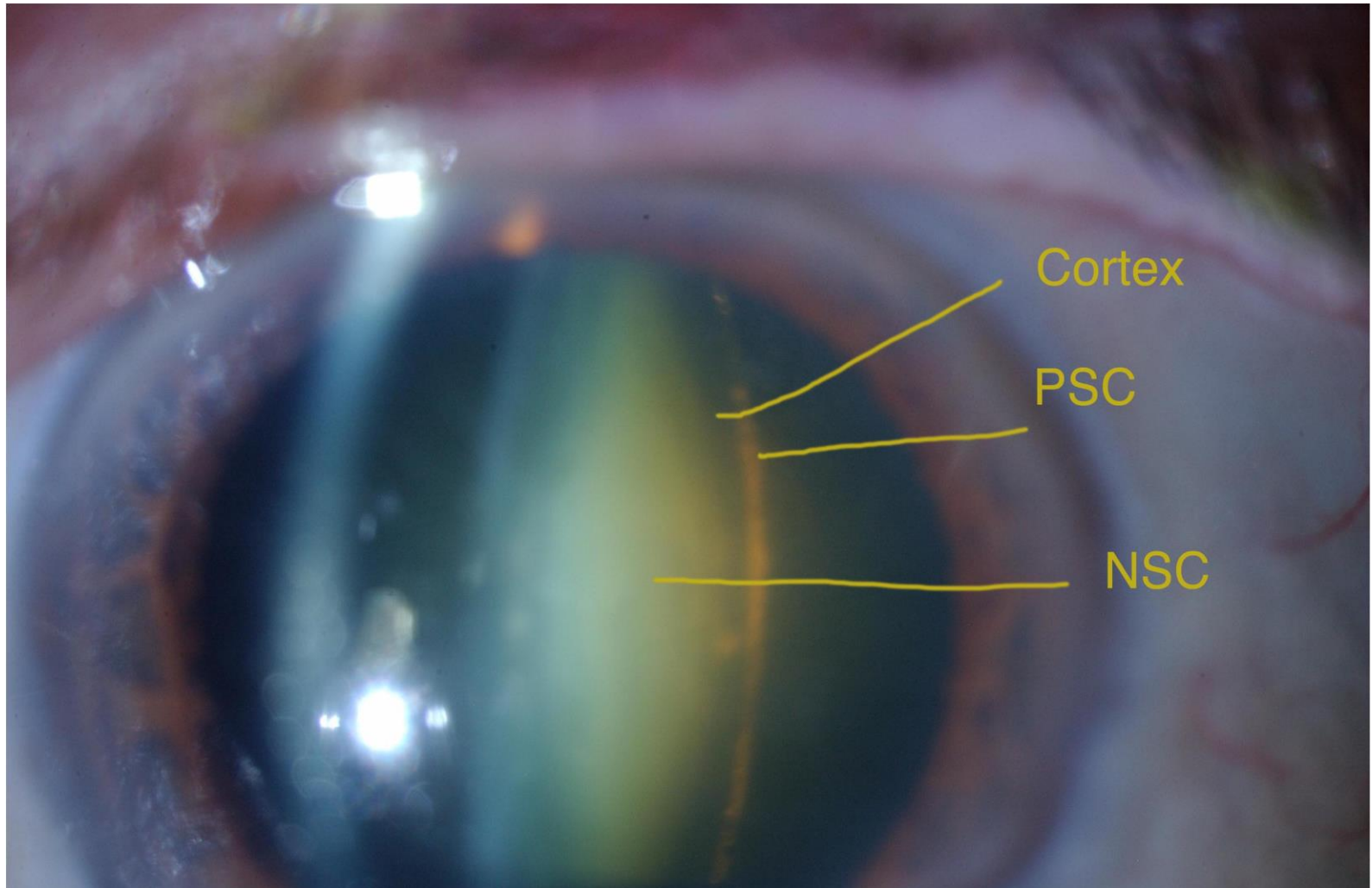
Cataracts: Posterior Subcapsular



Cataracts: Posterior Subcapsular



Combination Cataract



Retina

- ⌘ When eye doctors hear the term Waldenstrom they generally think of the retina.
- ⌘ Before discussing the retinal impacts of WM, it is important to know that hemorrhaging in the eye can also occur if one's hematocrit (HCT) is 50% below normal, especially if it is combined with thrombocytopenia (low platelets).
- ⌘ The cause of hemorrhage is secondary to the anoxic damage to the endothelial cells of the retinal capillaries and the decrease platelet counts may delay the sealing of the endothelial defect thereby causing a hemorrhage.
- ⌘ Thrombocytopenia by itself can cause retinal changes.
- ⌘ Hypertension and diabetes can also cause retinal hemorrhaging in the eye, as can carotid artery blockage

Retinal Hemorrhages with Anemia

- Retinal hemorrhages from severe anemia may be flame shaped (occasionally with Roth's spots) or dot and blot hemorrhages.

Roth Spots are flame shaped hemes with white centers The white center are either CWS or white blood cells

- Cotton wool spots, hard exudates and venous tortuosity may be present.

Severe Anemia



Photo by
Jeff Ho
OD

Severe Anemia

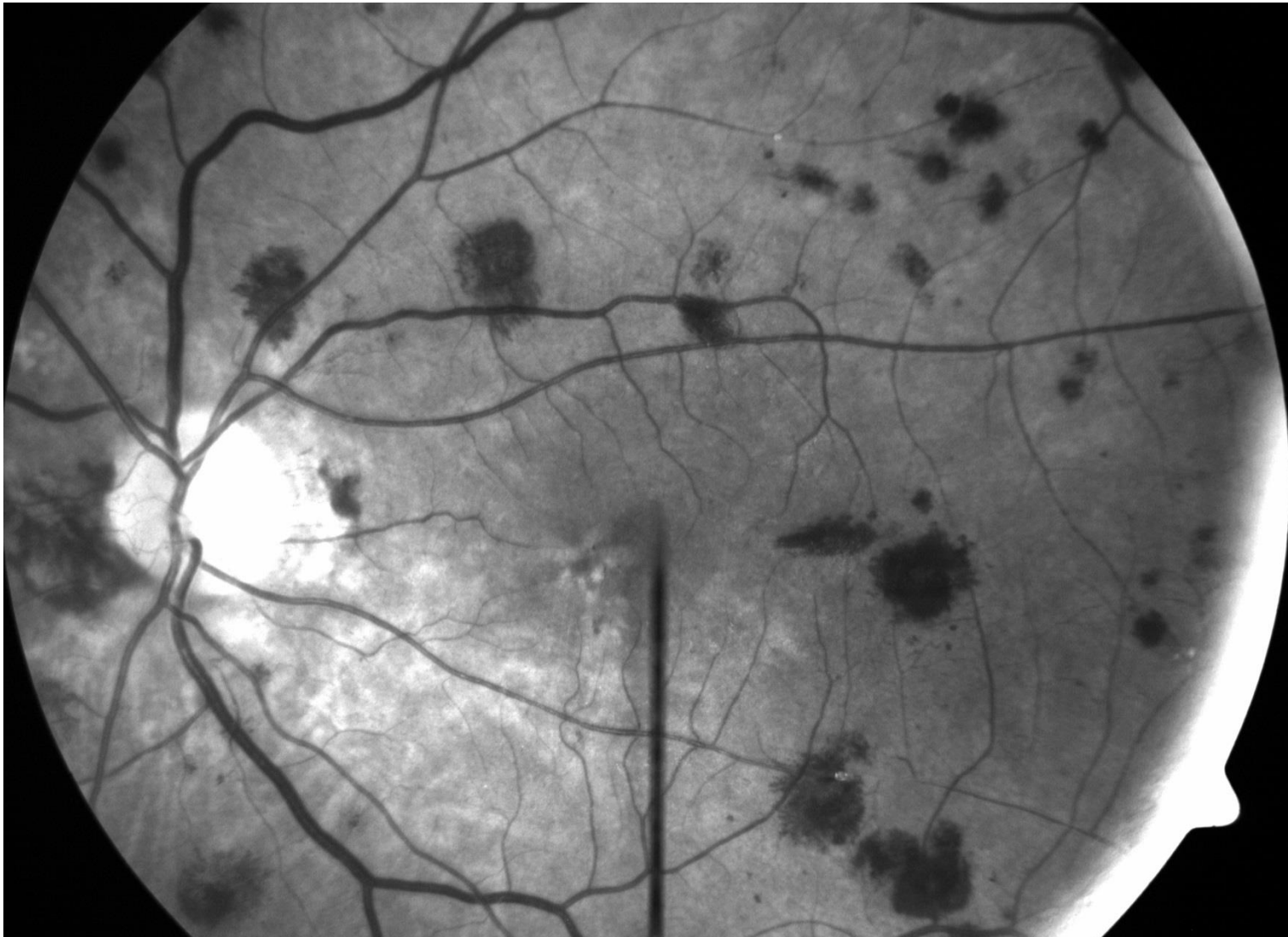


Photo by Jeff
Ho, OD

Severe Anemia

Photo by Jeff Ho
OD

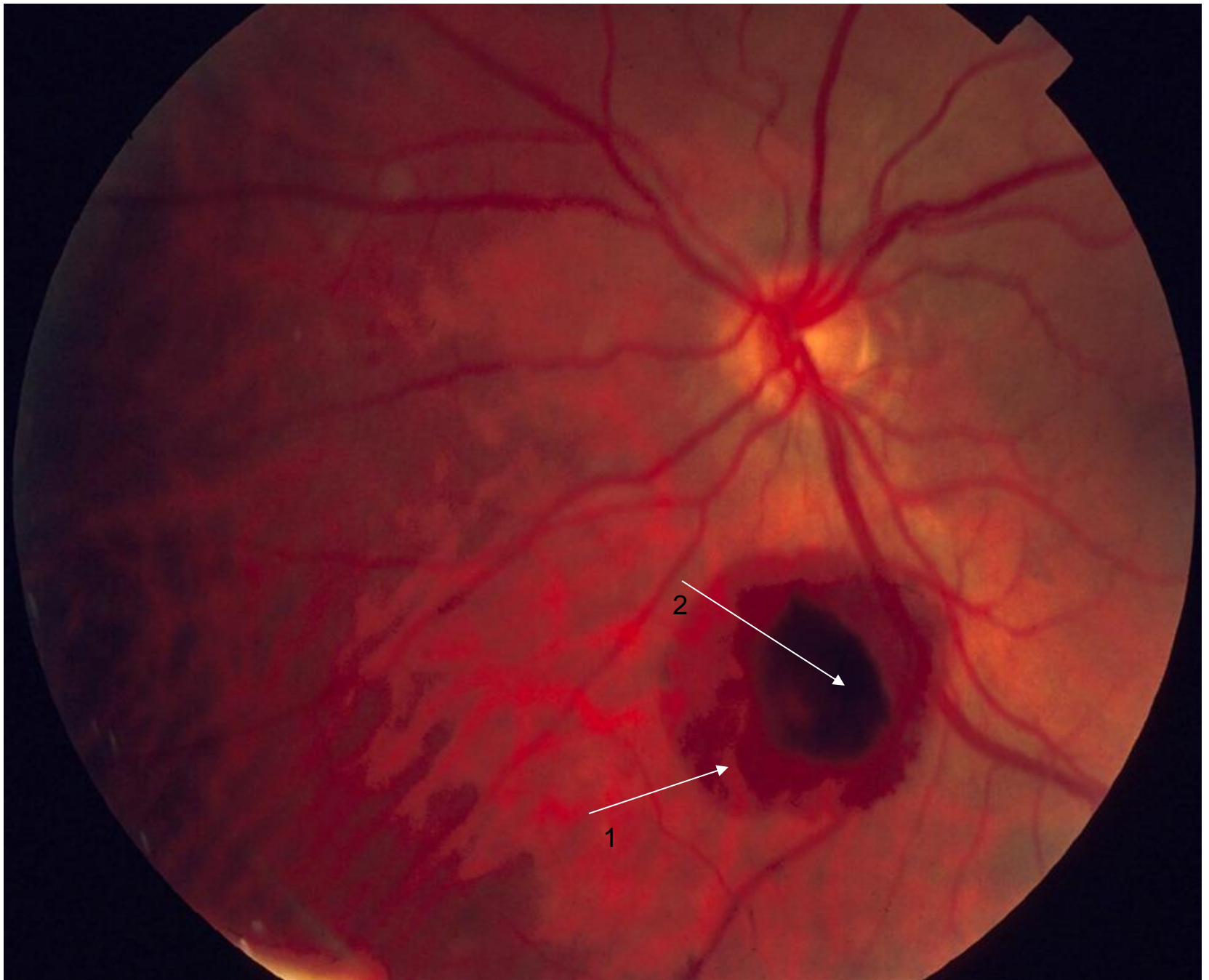
Roth spot

Slide courtesy of
Dr. Bina Patel





Leukemia retinopathy – exudates and large intraretinal heme



Leukemia retinopathy – 1.subretinal heme 2.sub RPE heme

Waldenstrom Macroglobulinemia

- Small B cell lymphoma secretes monoclonal Ig M which is a large protein molecule and increases the blood viscosity resulting in venous dilation, segmentation, tortuosity, and sludging. You can get superficial and deep hemorrhages and you can also get disc edema. Retinal artery and vein occlusions can result.
- Although it varies, patients with an IgM of over 3,000 are at risk for retinal bleeding but in some cases peripheral hemorrhaging has been noted with lower IGM
- Normal serum viscosity is 1.4- 1.8 times that of water - in WM it can go > 6. Retinopathy has been noted as low as 2.1 (far periphery) however the average s.v. associated with retinopathy in the posterior pole is 5.6 Arch Ophthalmol. 2006 Nov;124(11):1601-6. **Hyperviscosity-related retinopathy in waldenstrom macroglobulinemia.Menke et al**



The earliest changes may be seen only with scleral depression looking at hemorrhages in the periphery

The earliest retinal changes can occur at SV and IgM levels that are lower than previously reported in other studies. Clinically, indirect ophthalmoscopy with scleral depression provides a straightforward means of evaluating the earliest structural damage due to HVS.

Marcel N. Menke, MD; Gilbert T. Fekke, PhD;

J. Wallace McMeel, MD; Andrew Branagan,

BS; Zachary Hunter, BS; Steven P. Treon, MD, PhD

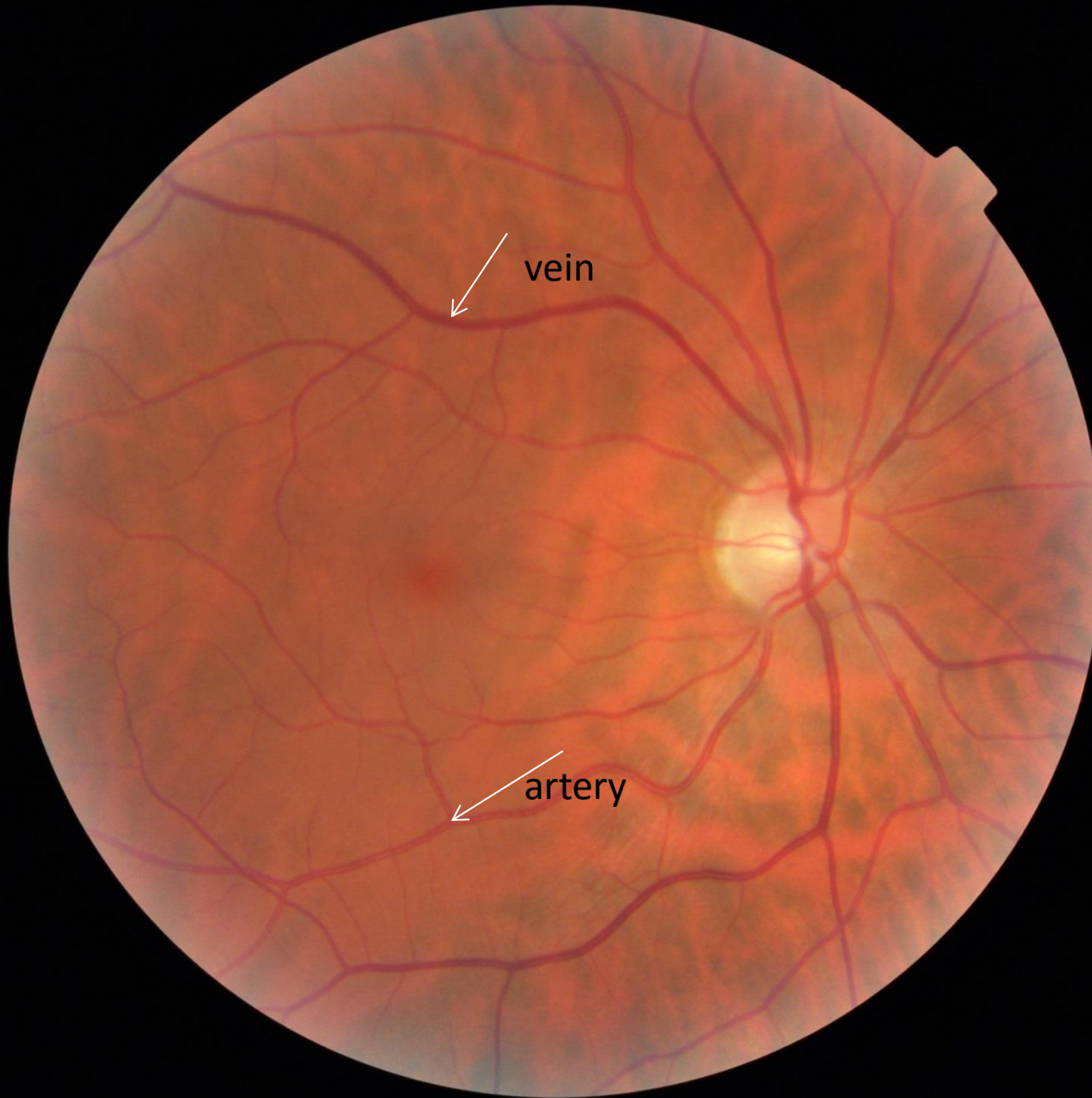


Hyperviscosity causing Peripheral Hemorrhages near the ora
However these can also occur in patients with DM and in patient with carotid artery stenosis

Retina

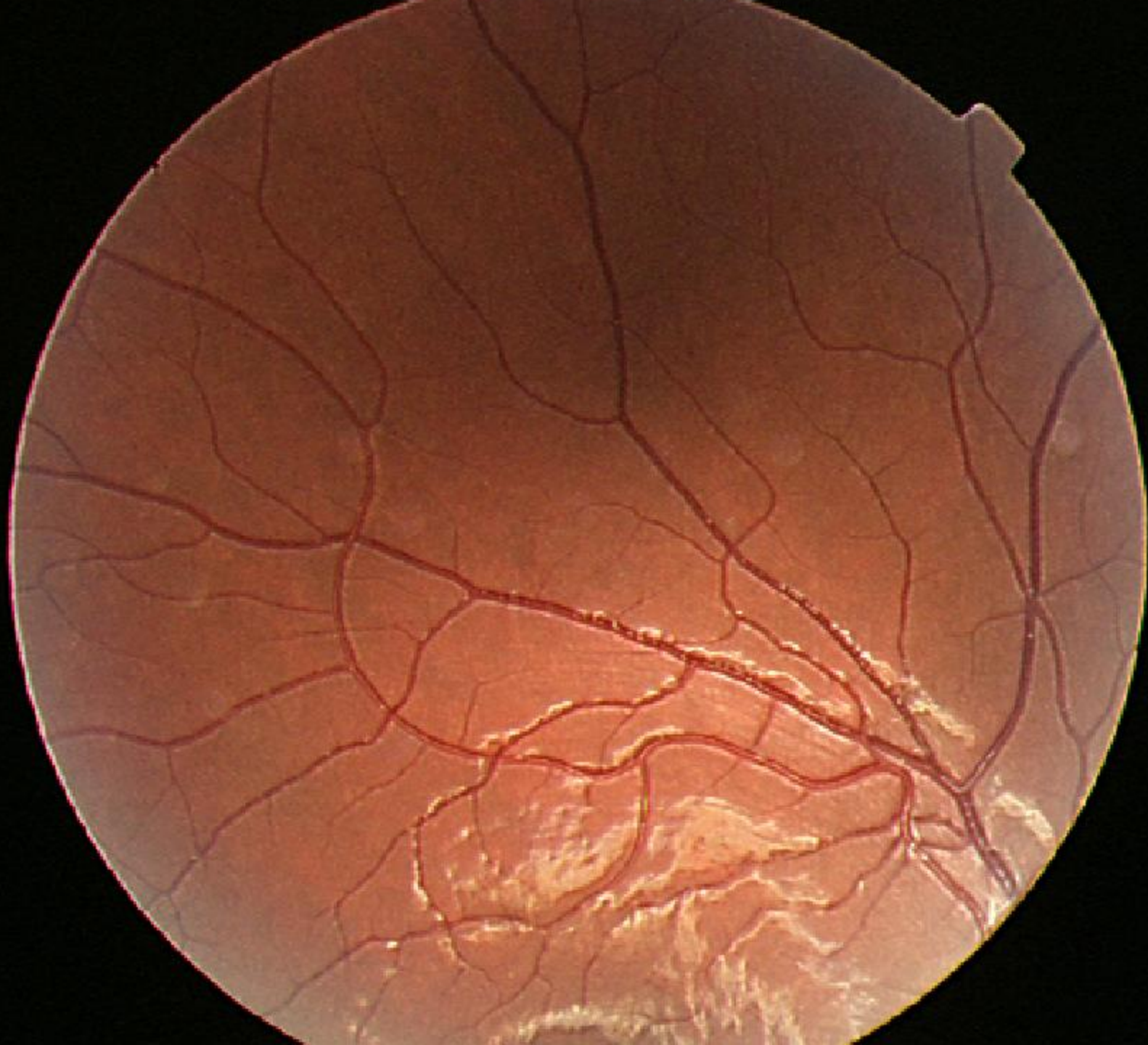
- ∞ In WM the earliest sign of a problem is usually venous dilation.
- ∞ Venous dilation and increased venous tortuosity can be difficult to recognize in their earliest state because many patients have congenital tortuous vessels.
- ∞ Congenital tortuosity is not associated with retinal hemorrhaging.

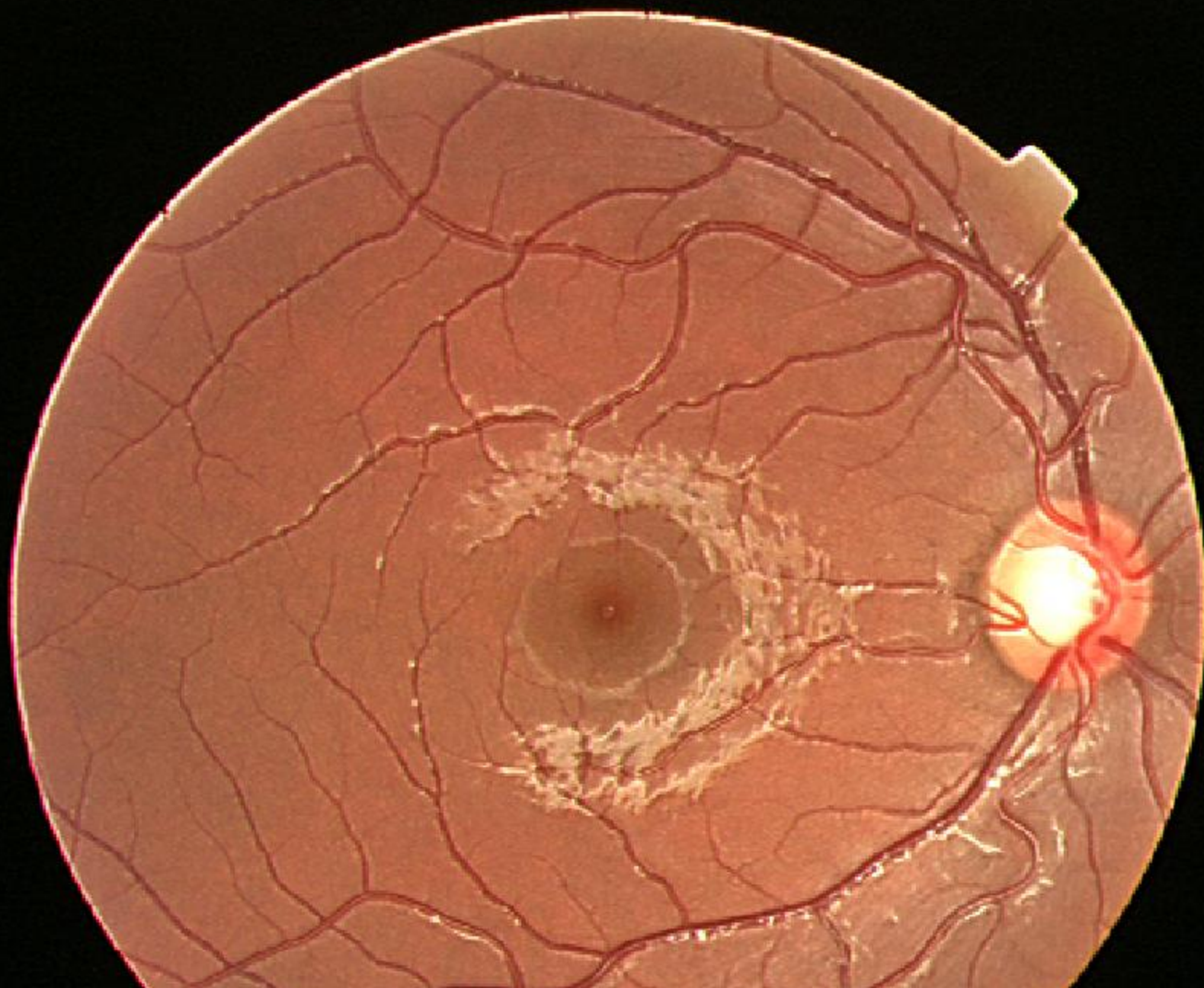
Normal Right Eye

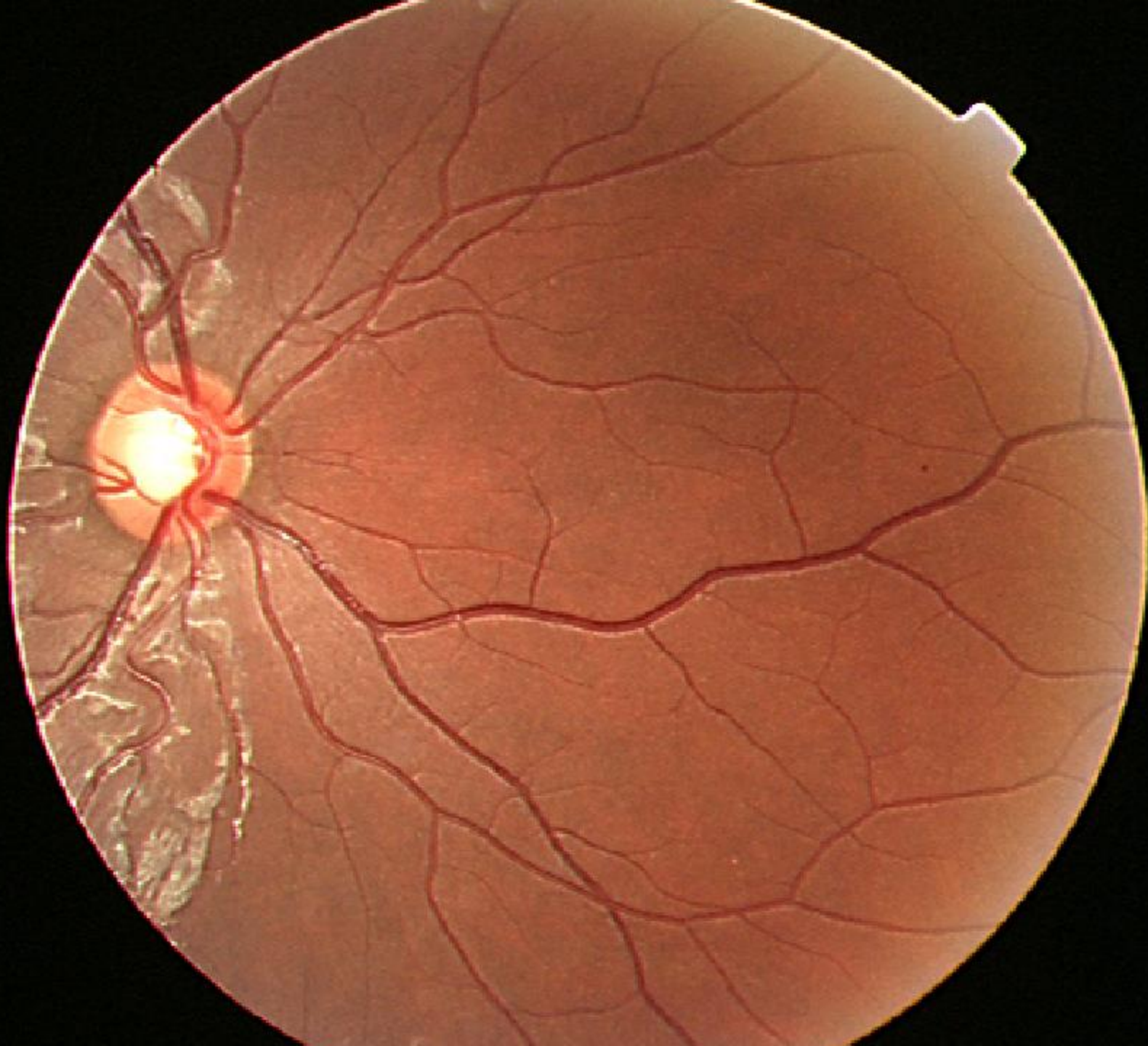


Normal Left eye









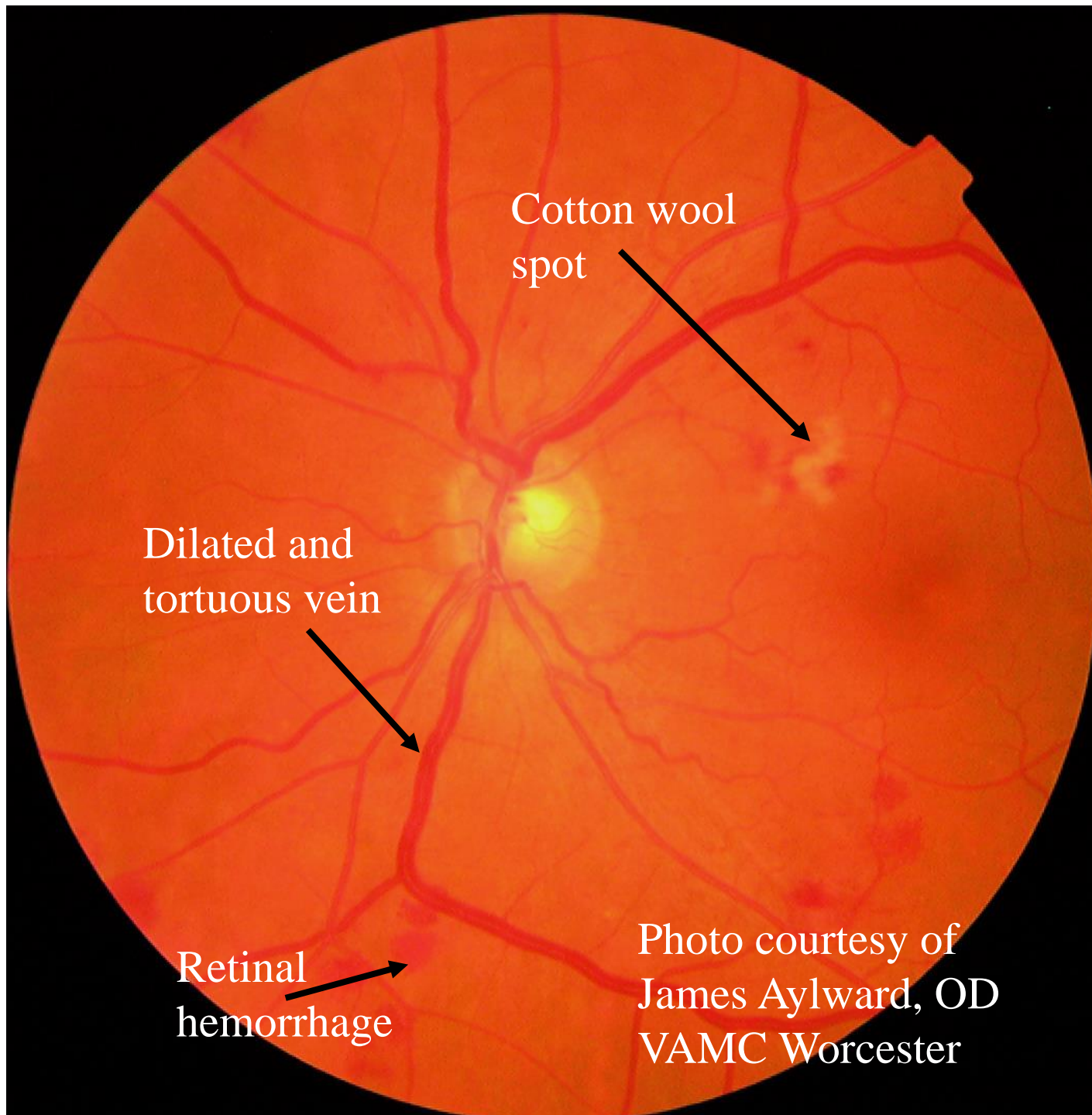


Courtesy of Dr. Bina Patel



AV Nicking

Patient with
Retinopathy
From WM



Cotton wool
spot

Dilated and
tortuous vein

Retinal
hemorrhage

Photo courtesy of
James Aylward, OD
VAMC Worcester



WM





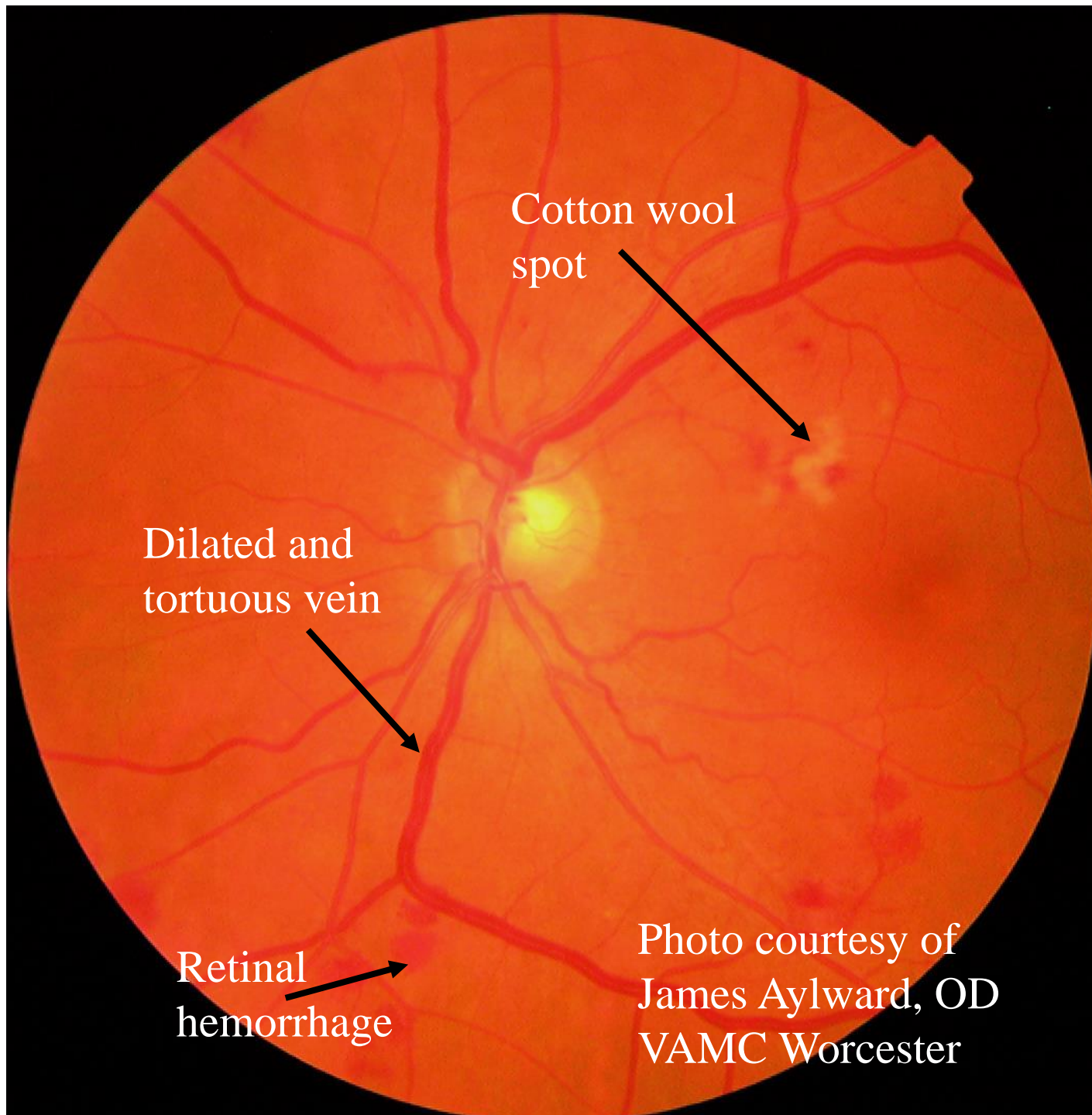
BRVO

Donated by Dr. Patti Landry

Waldenstrom

- ∞ In the early stages of WM-related retinopathy,
 - Small hemorrhages in the peripheral retina. Scleral depression is usually needed to see these peripheral hemorrhages.
 - As the WM-related retinopathy becomes more evident
 - hemorrhages increase in number, appearing in the posterior pole, exudates, and cotton wool spots can occur in addition to hemorrhages.
 - The venous system becomes engorged via compression at arteriovenous crossings in the eye near the optic nerve. This can lead to branch-vein occlusions. Further engorgement or swelling of the veins can lead to optic nerve congestion and a central retinal vein occlusion.
 - Not all individuals progress from one hemorrhage to a full-blown central vein occlusion.

Patient with
Retinopathy
From WM



Cotton wool
spot

Dilated and
tortuous vein

Retinal
hemorrhage

Photo courtesy of
James Aylward, OD
VAMC Worcester

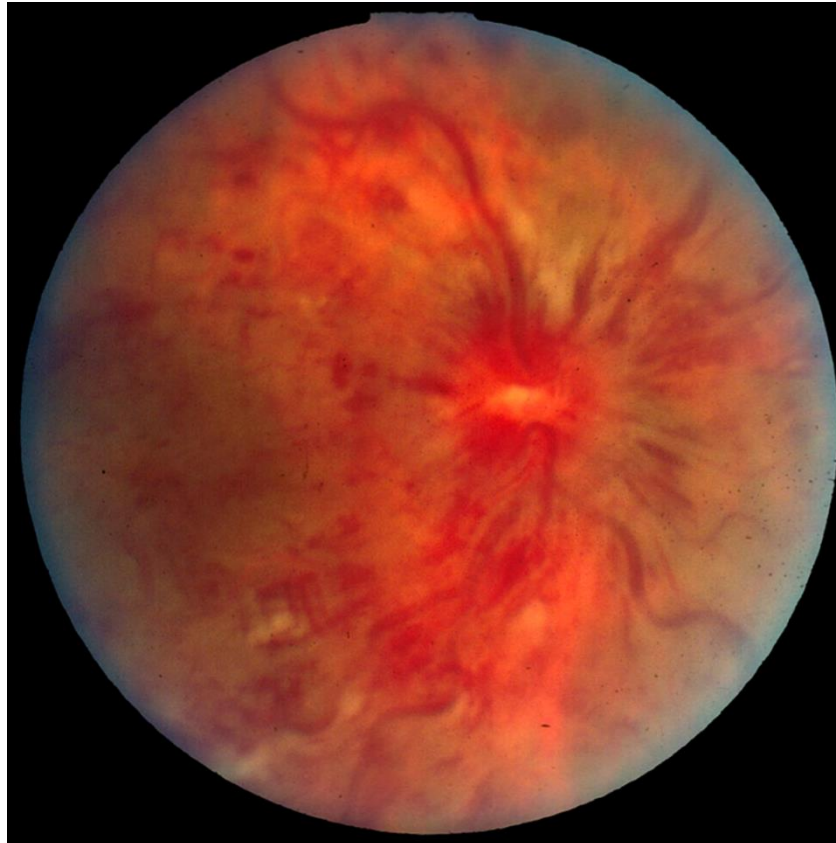
Variability of WM

- Some individuals can have a clean retinal evaluation and later have a central vein occlusion in just weeks or months following the exam.
- It is very important to realize that while not everyone with WM will have retinal problems, it is estimated that about 40% will, and these cases appear to be related to SV, which in turn depends somewhat on the concentration of monoclonal IgM.
- However some patients can have a s.v. of 8 and not have retinopathy.

Central Retinal Vein Occlusion

- Thrombus of the Central Retinal Vein in the area of the lamina cribrosa causing increased venous resistance

Patient could have
been 20/20 the day before
And is now CFF

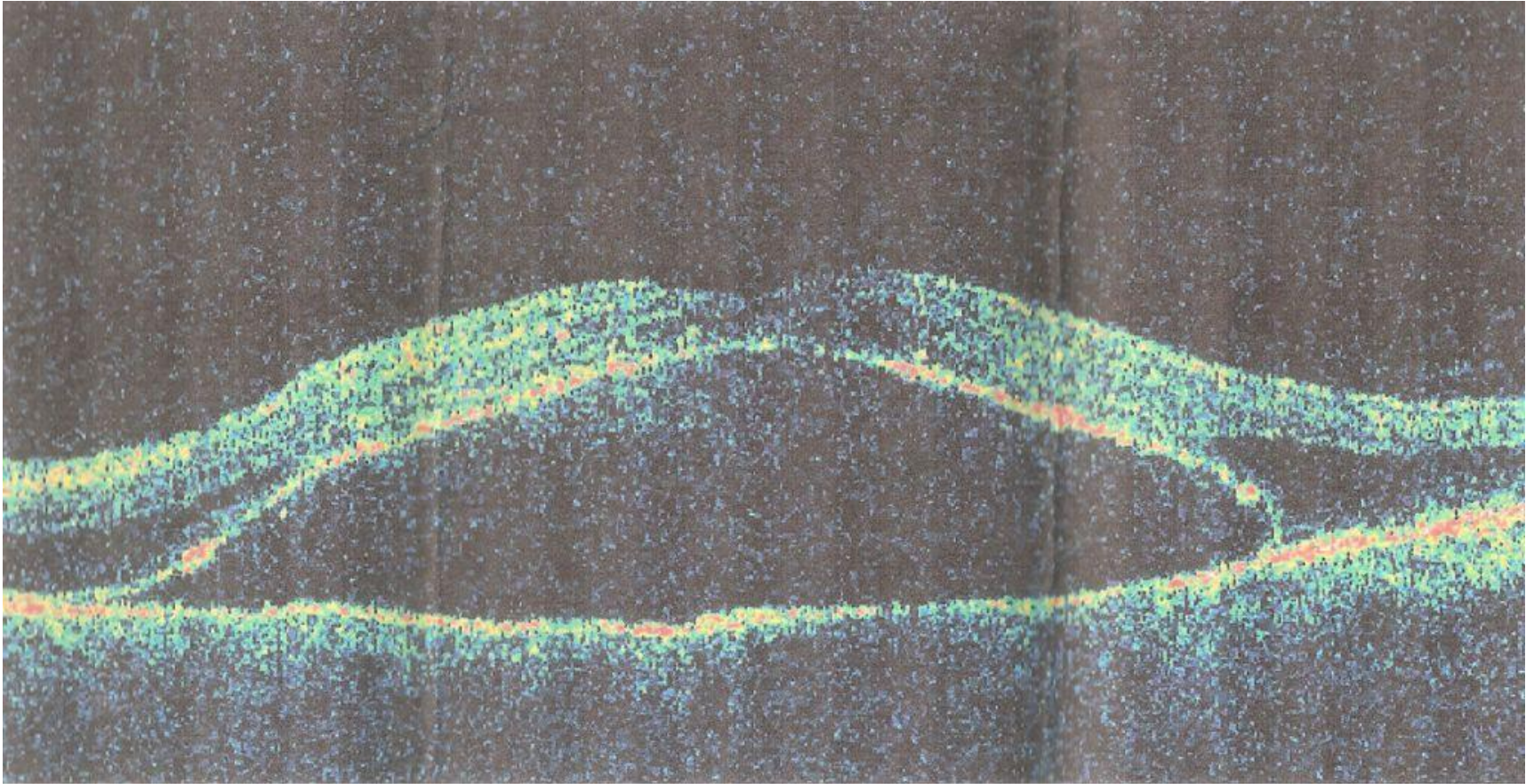


Also with Waldenstrom

- ∞ You can also get a “central serous type “ maculopathy - a serous detachment of the macula
 - It is believed that the high IGM may actually seep fluid out of the retina.
- ∞ Central serous is a split in the sensory retina
- ∞ Other causes of this sensory detachment can be idiopathic, steroids, subretinal neovascularization



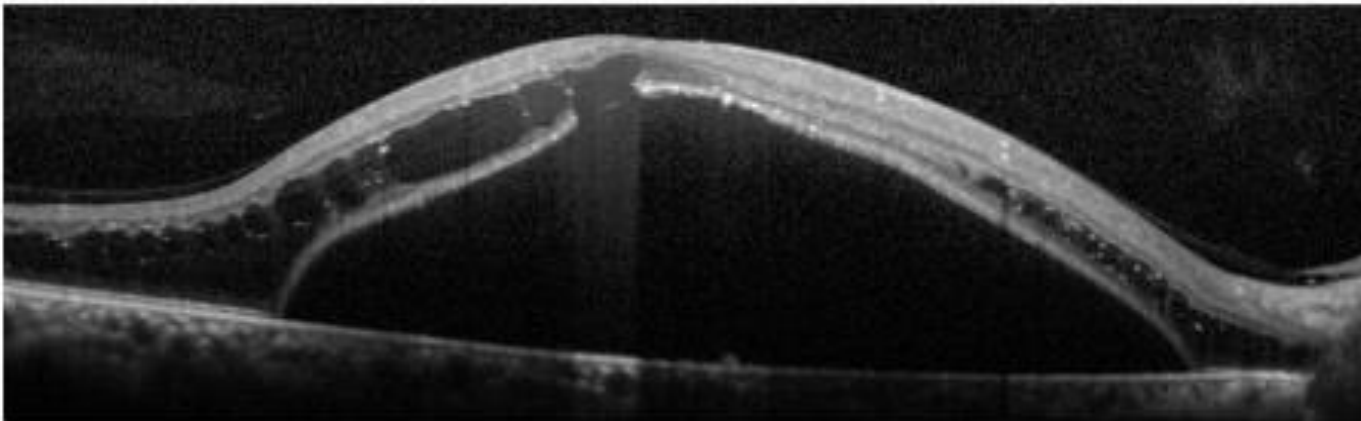
Cataract



OCT of a serous macular detachment from a WM patient

OCT of a patient who actually was operated on for cataracts but indeed the patient had WM maculopathy

- ∞ Serous Macular Detachment in Waldenstrom
Macroglobulinemia: A Report of Four Cases PAUL S. BAKER,
SUNIR J. GARG, MITCHELL S. FINEMAN, ALLEN CHIANG, RAYAN
A. ALSHAREEF, JONATHAN BELMONT, AND GARY C. BROWN
- ∞ Wills Eye Institute



Hyperviscosity-Related Retinopathy in Waldenstrom Macroglobulinemia

Marcel N. Menke, MD; Gilbert T. Feke, PhD; J. Wallace McMeel, MD; Andrew Branagan, BS; Zachary Hunter, BS; Steven P. Treon, MD, PhD

- Patients with WM were evaluated using indirect ophthalmoscopy with scleral depression, laser Doppler retinal blood flow measurements, and serum IgM and SV determinations. Hemodynamic findings were compared with those of a group of age-matched controls. A retinopathy severity scale was developed, and the associated IgM and SV values were related to particular morphologic changes.
- A total of 46 patients with WM and 14 age matched, healthy controls participated in the study. Patients exhibited far-peripheral hemorrhages and venous dilation with increasing SV and IgM values. Central retinal changes were associated with significantly higher SV values. Retinal vessel diameter increased with increasing serum IgM and SV levels. The mean IgM level of patients with the earliest retinal changes was 5442 mg/dL. The mean SV level was 3.1 cP.

Study continued

- Retinal hemodynamics were assessed using a Canon Laser Doppler Blood Flow Meter (CLBF100; Canon Inc, Tokyo), an instrument that simultaneously measures the centerline red blood cell speed and the blood column diameter in individual retinal vessels. The retinal blood flow rate is automatically calculated at each measurement site
- Venous diameter and venous blood flow

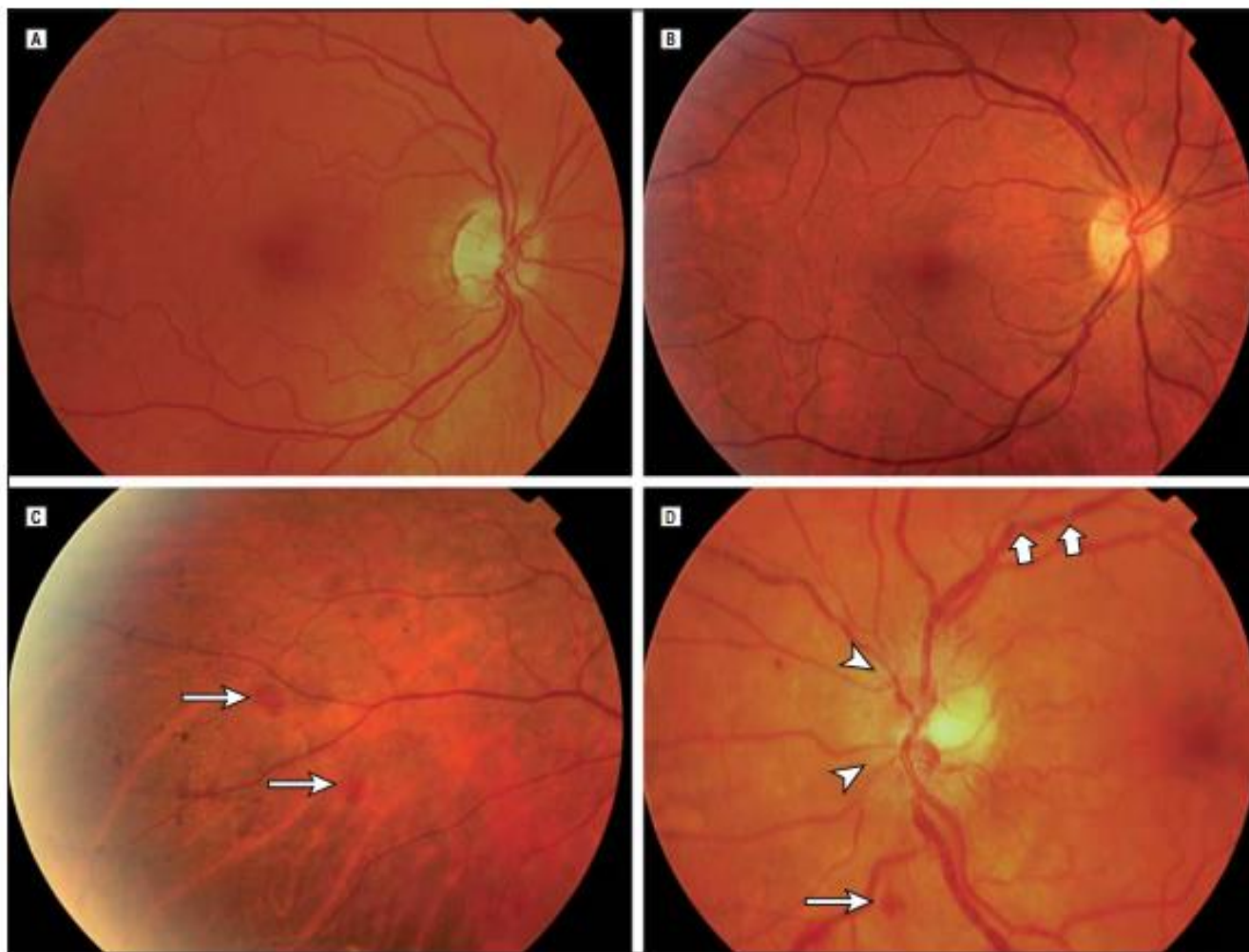


Figure 3. Fundus images of patients with Waldenström macroglobulinemia. A, No retinopathy (group 1); B, dilated veins (group 2); C, peripheral retinal hemorrhages in a group 2 patient (arrows); and D, central retinal hemorrhage (thin arrow), optic disc edema (arrowheads), and venous saussaging (thick arrows) in a group 3 patient.

Hyperviscosity-Related Retinopathy in Waldenstrom Macroglobulinemia Marcel N. Menke, MD;
 Gilbert T. Feke, PhD; J. Wallace McMeel, MD; Andrew Branagan, BS; Zachary Hunter, BS;
 Steven P. Treon, MD, PhD

- ⌘ A study by Menke evaluated 46 patients with WM along with 14 age-matched adults without WM. The mean IgM level of 4,732 mg/dL and a mean SV of 3.0 cp (centipoise).
- ⌘ Patients were divided into 3 groups:
- ⌘ Group 1: no retinopathy. 24 patients
- ⌘ Group 2: dilated veins and /or peripheral hemorrhages; a mean serum IgM of 5,442 mg/dL (range of 2,950 to 8,440 mg/dL) and a mean SV of 3.1 cp range was 2.1 -3.7cp. 18 patients
- ⌘ Group 3: peripheral and central retinal hemorrhages accompanied by dilated veins, optic nerve head edema, and venous sausageing; a mean serum IgM of 8,515 mg/dL (range of 5700 to 12,400 mg/dL) and a mean SV of 5.6 cp. Range 3.8 to 8cp 4patients

- ∞ This study concluded that retinal changes were found in patients with SV values as low as 2.1; however, these changes produced no symptoms for the patient since the hemorrhages were in the far periphery.
- ∞ In addition, the major retinal arteries and veins showed increasing dilation with increasing serum IgM levels and the correlation between increasing retinal vein diameter and increasing SV levels was also significant.
- ∞ Clinically, the hemorrhages represent structural damage secondary to hyperviscosity.
- ∞ The hyperviscosity-related changes in the eye become symptomatic when the posterior pole becomes involved; the average SV associated with that effect was 5.6 cp.
- ∞ Another study by the same group showed that plasmapheresis helped reduce the hyperviscosity-related retinopathy

Questions do we have the Answers???

- ∞ The question becomes, “Should a patient be treated if their IgM is 4,000 mg/dL and there are only one or two retinal hemorrhages observed at the far periphery by scleral depression and the patient has no other signs or symptoms?”
- ∞ It appears that doctors have no consistent answer to this question of whether to treat or not under the circumstances described. What if a patient has an IgM concentration of 10,000 and both eyes look fine??????

Discuss WM case

- ✎ 80 year old routine eye examination just wanted glasses
- ✎ Hemorrhage in far periphery
- ✎ HCT of 26.5 and living on transfusions
- ✎ Past HX of MGUS (monoclonal gammopathy of unknown significance)
- ✎ IGM 1990 and also IGG and IGA were low
- ✎ He was living on 80mg of steroids a day secondary to hemolytic anemia and had steroid induced diabetes
- ✎ I called oncologist- discuss results in lecture

Glaucoma

- ∞ Optic Neuropathy
- ∞ 2% of patients over 40 have glaucoma
- ∞ About 1/3 of patients on steroids will have an increase in eye pressure
- ∞ Low tension glaucoma is thought to be a vascular problem of blood insufficiency or an autoimmune problem rather than a glaucoma resulting from increased IOP. Patients who are more prone to low tension glaucoma include patients who have systemic hypotension, anemia, cardiovascular problems, and sleep apnea. High serum viscosity (SV) also appears to be a risk factor
- ∞ ?? Low tension and autoimmune neuropathy

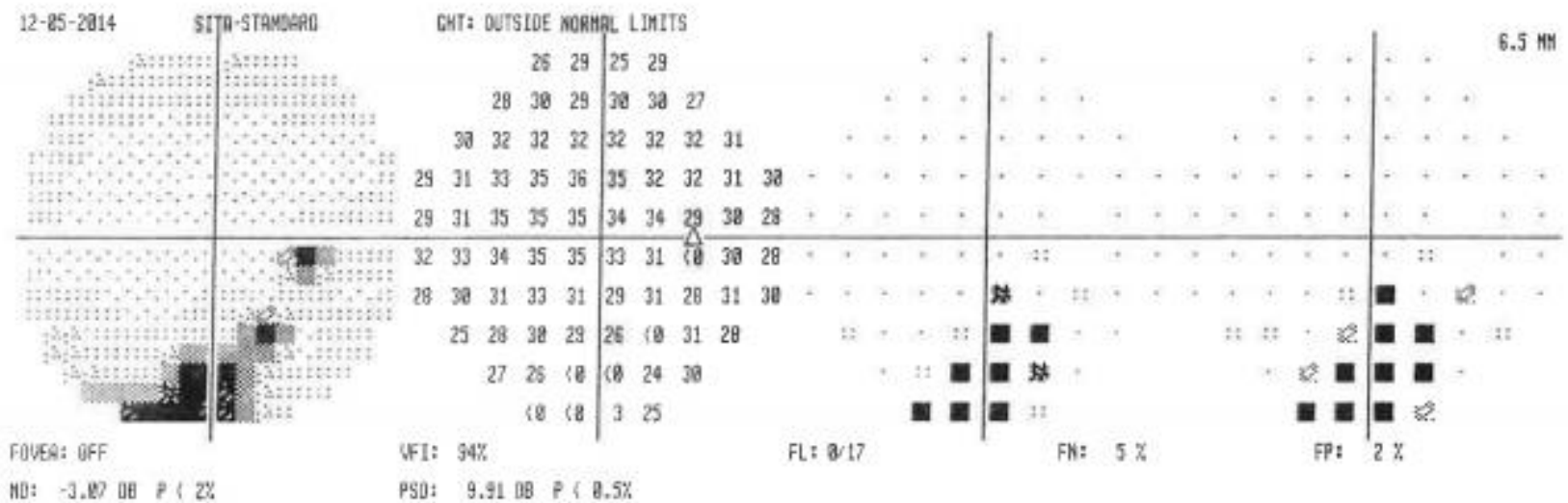
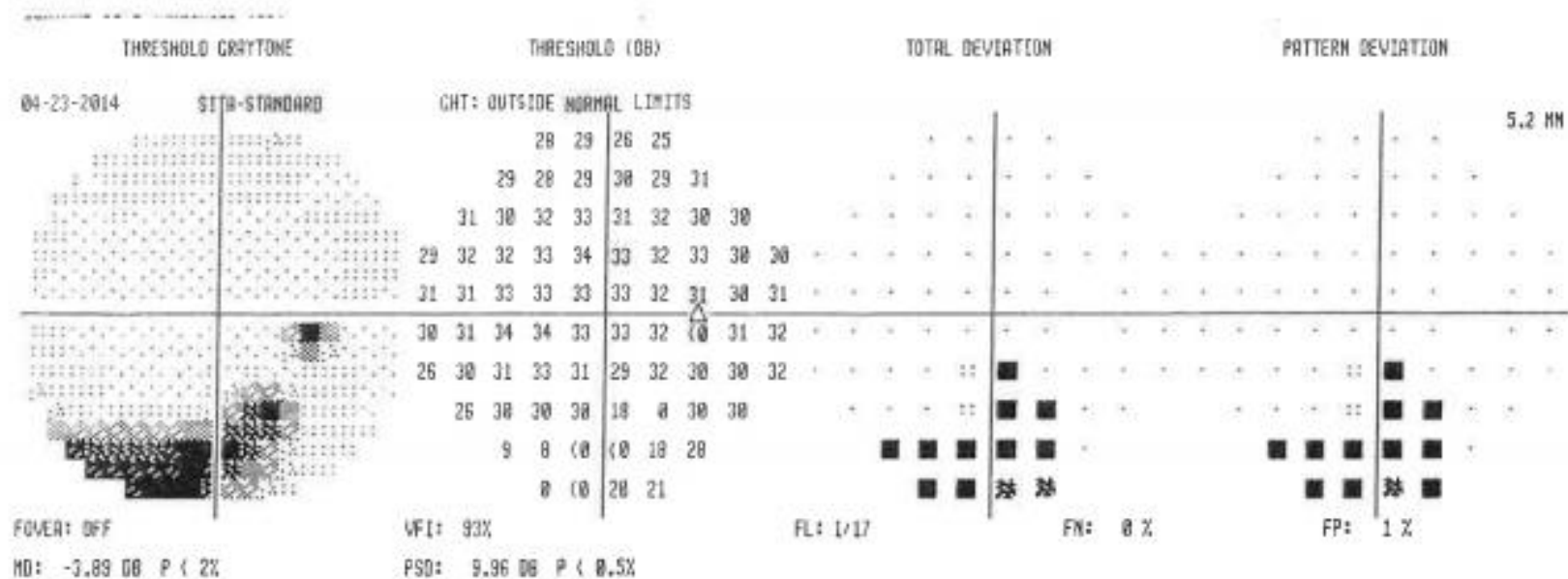
Let us discuss these nerves



. © Heiko Philippin (left and middle), Rupert Bourne (right)









LEFT EYE



RIGHT EYE

5-01



LEFT EYE



RIGHT EYE

7-16-03



LEFT EYE



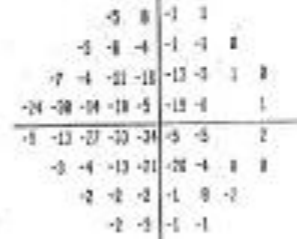
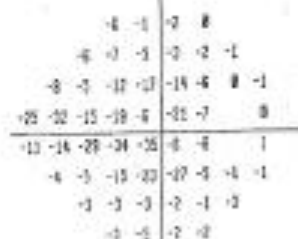
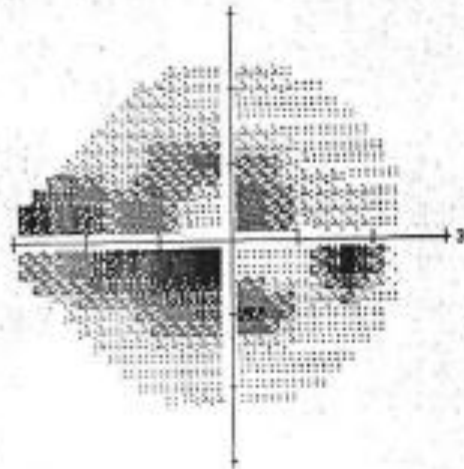
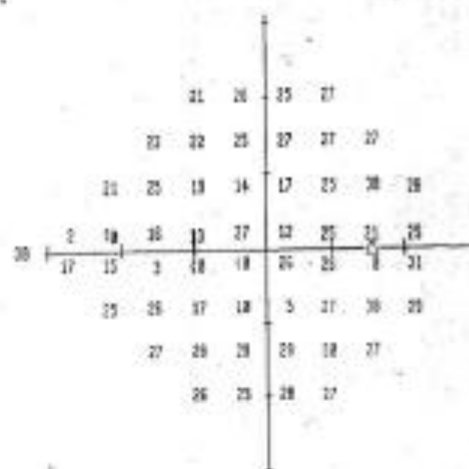
RIGHT EYE

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 FALSE NEG ERRORS: 5.0
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 FEARS: OFF

STIMULUS: DIT, WHITE
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 STRATEGY: STD-STANDARD

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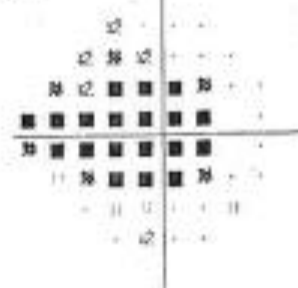
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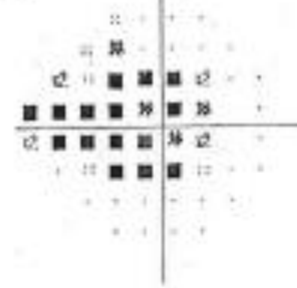
DIT
 OUTSIDE NORMAL LIMITS

MD -18.52 DB P < 0.5%
 PSD 18.55 DB P < 0.5%

TOTAL
 REACTION



PATTERN
 DEVIATION



11 4.00
 12 4.00
 38 1.00
 38 1.00

FIXATION MONITOR: GAZE-BLINDSPOT

FIXATION TARGET: CENTRAL

FIXATION LASSES: 2/23

FALSE POS ERRORS: 4 %

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BACKGROUND: 31.5 ASD

STRATEGY: SITH-STANDARD

PUPIL DIAMETER: 5.1 MM

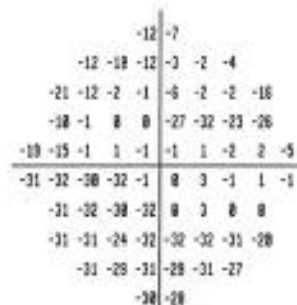
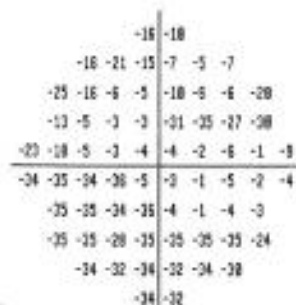
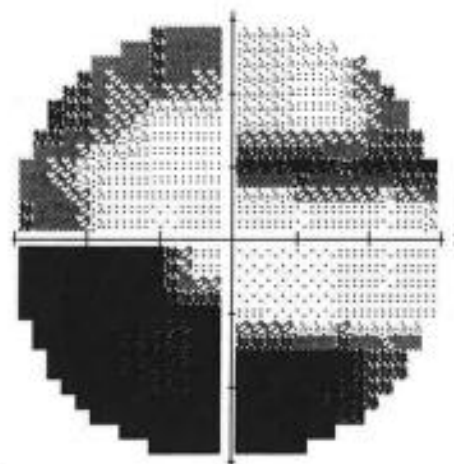
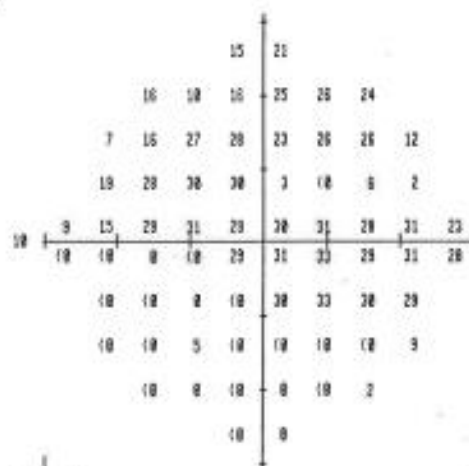
VISUAL ACUITY:

NR: 43.00 DB DC X

DATE: 09-22-2003

TIME: 11:00 AM

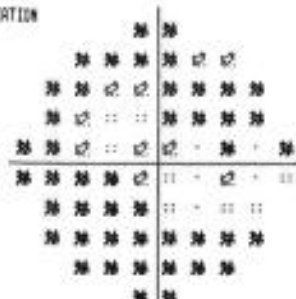
AGE: 55



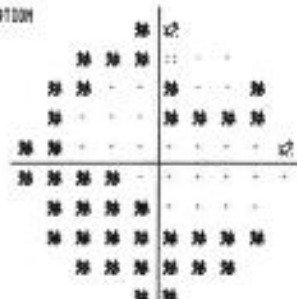
NR -10.00 DB P < 1%

PSD 13.94 DB P < 1%

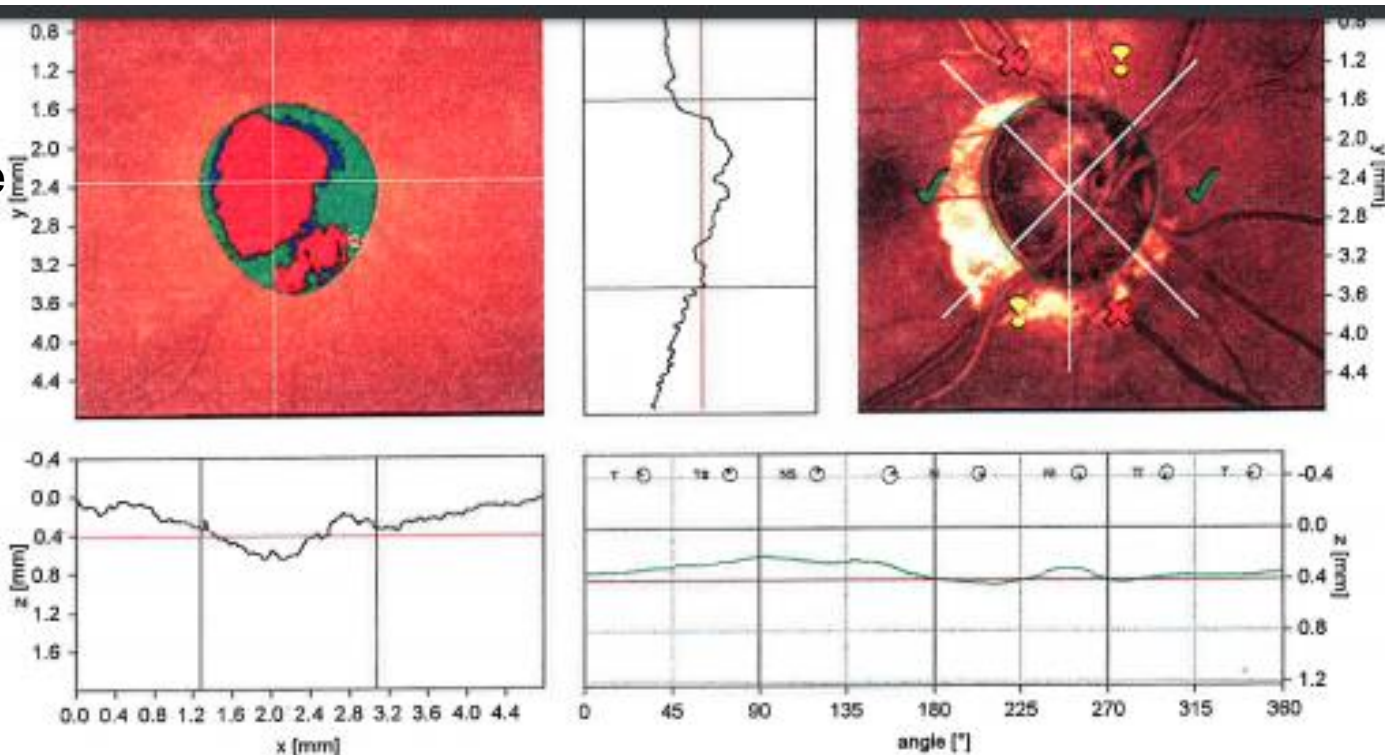
TOTAL
DEVIATION



PATTERN
DEVIATION



Right eye

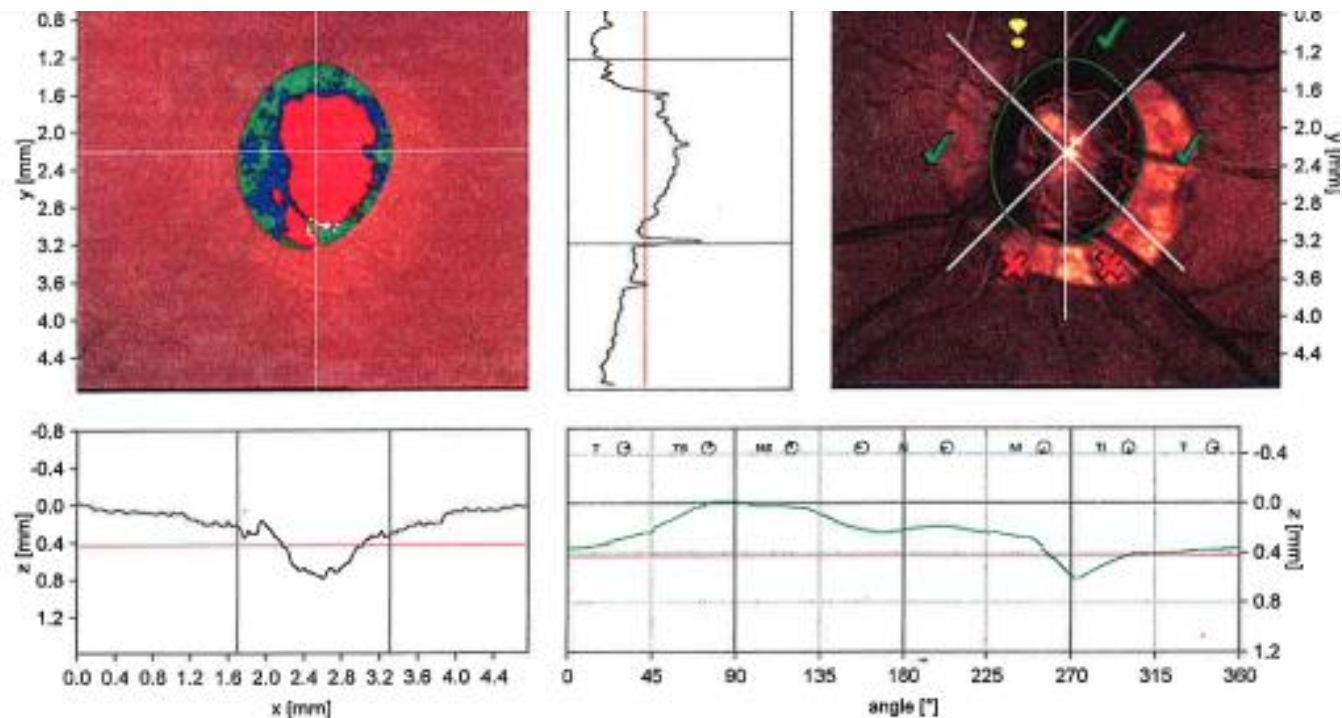


Stereometric Analysis ONH	
Disk Area	2.729 mm ²
Cup Area	1.532 mm ²
Rim Area	1.198 mm ²
Cup Volume	0.181 cmm
Rim Volume	0.122 cmm
Cup/Disk Area Ratio	0.561
Linear Cup/Disk Ratio	0.749
Mean Cup Depth	0.162 mm
Maximum Cup Depth	0.402 mm
Cup Shape Measure	-0.099
Height Variation Contour	0.220 mm
Mean RNFL Thickness	0.067 mm
RNFL Cross Sectional Area	0.396 mm ²
Reference Height	0.404 mm
Superior Pole Area	0.22 mm ²

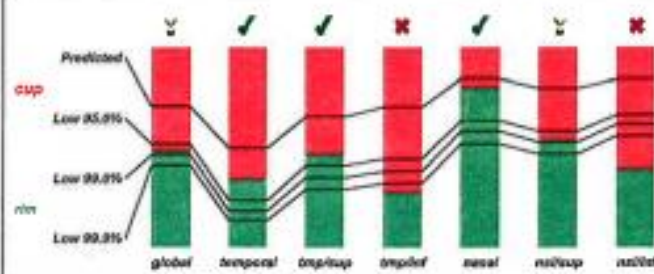
<p>global</p> <p>temporal</p> <p>temp/sup</p> <p>temp/inf</p> <p>nasal</p> <p>nas/sup</p> <p>nas/inf</p>	<p>✓</p> <p>✓</p> <p>✗</p> <p>✓</p> <p>✓</p> <p>✗</p>
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Comments:

Date: Sep/29/2003 Signature:



Stereometric Analysis ONH	
Disk Area	2.469 mm ²
Cup Area	1.263 mm ²
Rim Area	1.206 mm ²
Cup Volume	0.226 mm ³
Rim Volume	0.231 mm ³
Cup/Disk Area Ratio	0.511
Linear Cup/Disk Ratio	0.715
Mean Cup Depth	0.237 mm
Maximum Cup Depth	0.610 mm
Cup Shape Measure	-0.142
Height Variation Contour	0.629 mm
Mean RNFL Thickness	0.169 mm
RNFL Cross Sectional Area	0.944 mm ²
Reference Height	0.419 mm



Comments:

My Recommendations

- ∞ Get an annual or semi-annual complete dilated eye exam with a doctor who is comfortable examining a WM patient
- ∞ Try to get a digital copy of retinal photos
- ∞ Remember that you may be prone to low tension glaucoma even if your IgM is not high. Your optic nerve should be carefully examined, and if there is any question, a glaucoma workup should be done.
- ∞ Have an OCT before cataract surgery
- ∞ Any sudden loss of vision call your eye doctor immediately