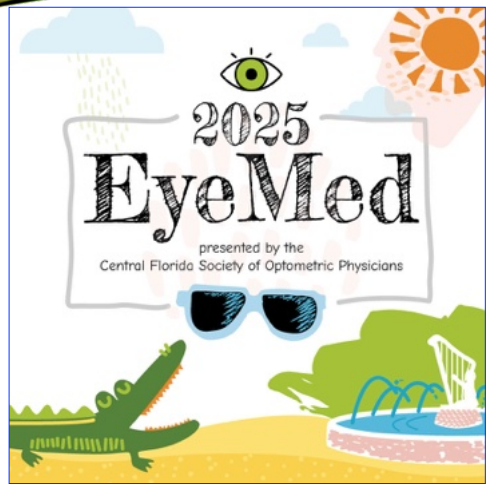
WELCOME!



OCULOSYSTEMIC DISEASES

And The Drugs That Treat Them

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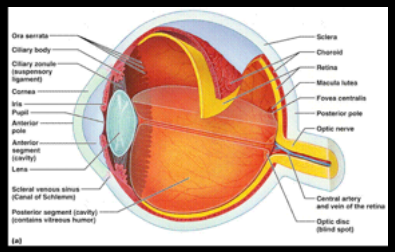
FINANCIAL DISCLOSURES

With respect to this course, I have no relevant financial relationships to declare.

E-Newsletter

optometricretinasociety.org

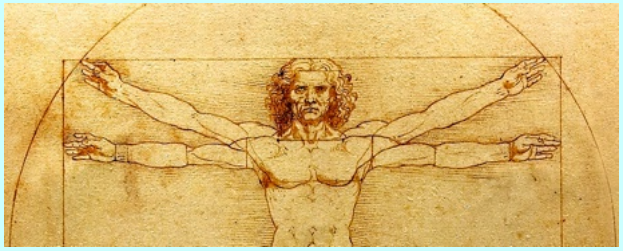
Check out our E-newsletter



Questions?

2 MINUTE STRETCH

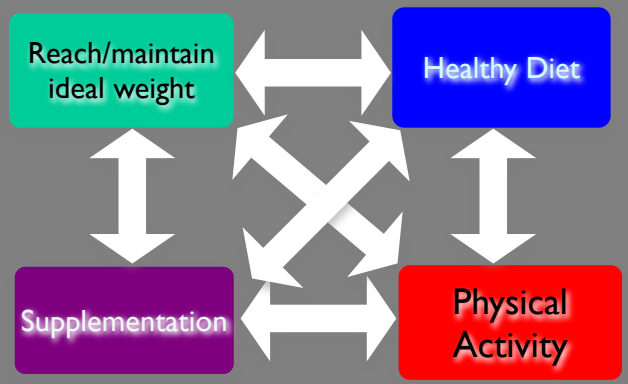
Every eye I've ever examined was attached to a whole person.



The Eye in Systemic Disease

- Inflammatory
- Infectious
- Vascular
- Endocrine
- Neurologic
- Collagen-vascular
- Neoplastic
- Autoimmune

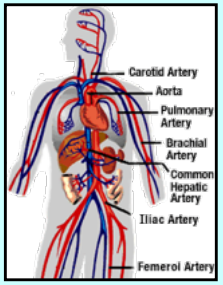
4 Pillars of Wellness



❑ The eye does not exist in isolation. It is an extension of the brain/CNS.*

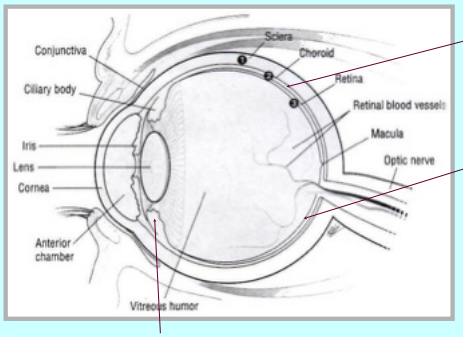
❑ The anatomy of the eye is structured to serve the functions of the retina.

❑ Primary reason for dilation is to detect systemic disease.



The eye is the only part of the body where neurological and vascular tissues can be directly and simultaneously viewed.

Ocular Blood Flow



Choroid 80%

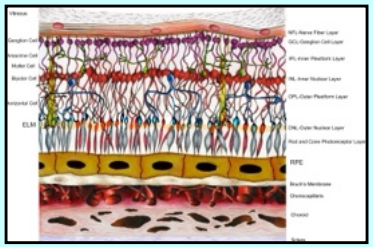
Sympathetic NS

Retina 5 %

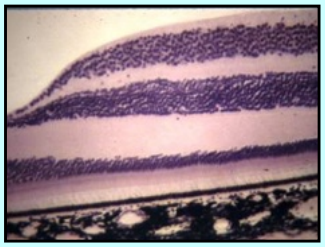
Auto-regulated

Iris / Ciliary Body 15%

The Eye in Systemic Disease

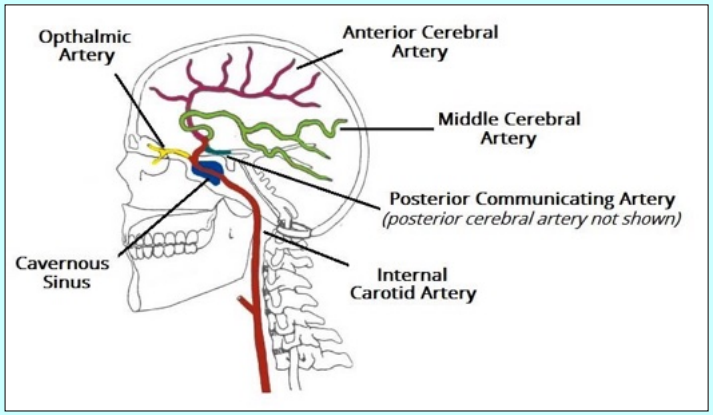


Inner and Outer Blood Retinal Barriers

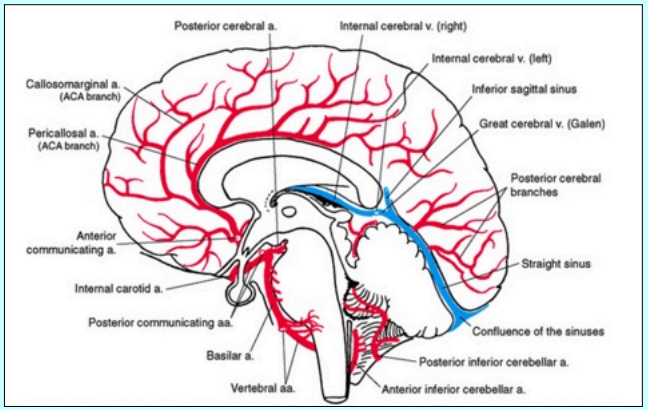


Retina/RPE, Choroidal Pigmentation

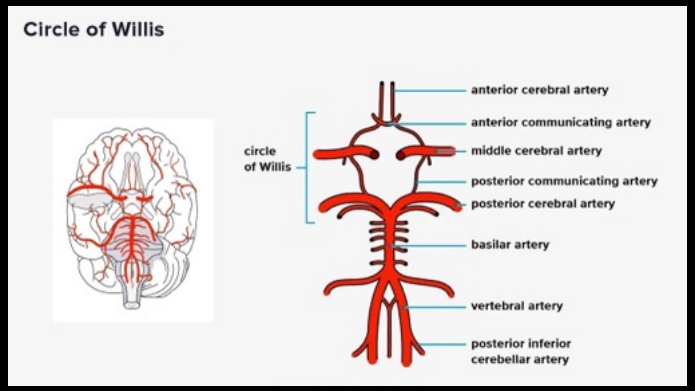
The Eye in Systemic Disease



The Eye in Systemic Disease



The Eye in Systemic Disease



Epidemics, Pandemics and Other Major Public Health Challenges

Obesity/Excess Weight/type 2 DM
Smoking
COVID and other viral
Autoimmune Disease
Age-related Eye Disease
(Sick Longevity)

Public Health
Prevent. Promote. Protect.

The Pathology of Obesity

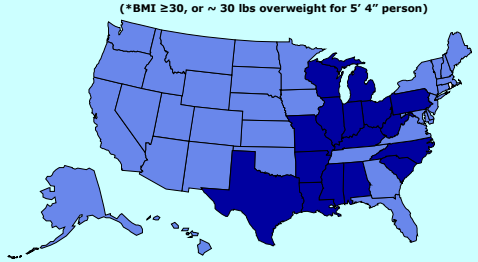
Skin	Yeast Infections, Gout
Endocrine	Polycystic Ovarian Syndrome, Low Testosterone, High Estrogen, type 2 DM
Heart	Heart Attack, Stroke, CHF
Pulmonary	Sleep Apnea
GI	Gallstones, GERD
Urinary	Incontinence
Gyno	Abnormal Menses, Infertility
Neuro	Depression, Memory Problems
Cancer	Breast, Colon, Prostate, Bladder, Esophagus
Post-Op	Pulmonary Embolism

Diabesity

- M_____ S_____ is characterized by central (abdominal) obesity, dyslipidemia, raised blood pressure, and insulin resistance
- *"Diabesity"*
  - Up to 97% of type 2 caused by excessive weight
  - Obesity = Increased weight caused by excess accumulation of fat.
  - "Over-fat" = normal BMI w/large waist
    - Visceral fat versus sub-cutaneous

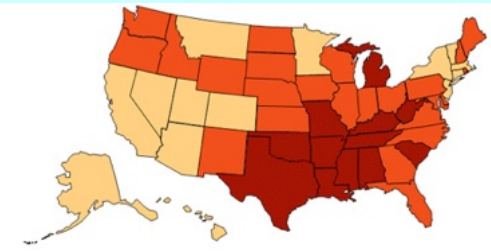
Obesity Trends* Among U.S. Adults
BRFSS, 1994

(*BMI ≥30, or ~ 30 lbs overweight for 5′ 4″ person)



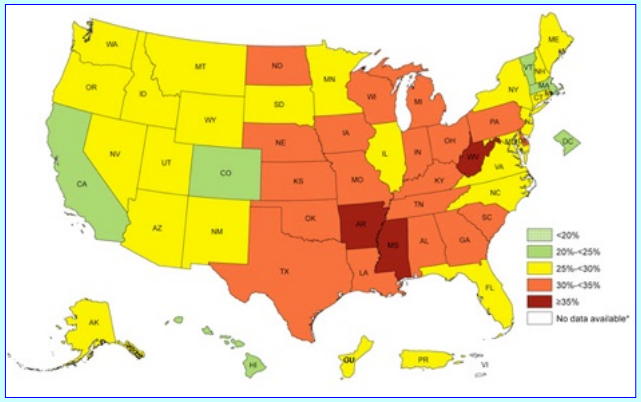
No Data <10% 10%–14% 15%–19% 20%–24% ≥25%

Obesity Trends-2012

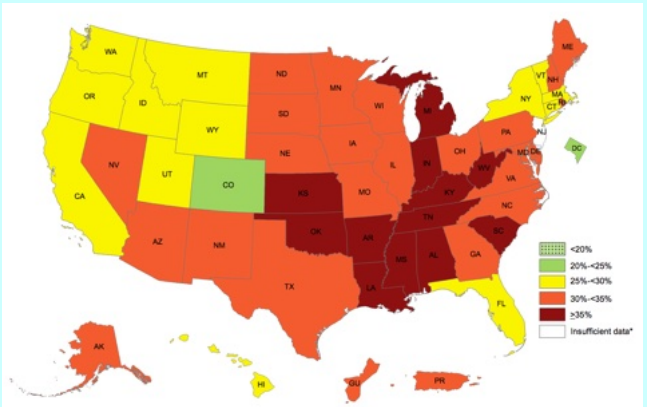


Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity Trends-2014

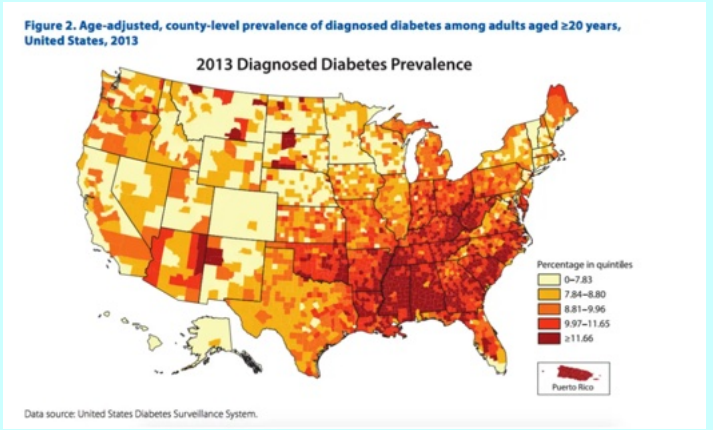


Obesity Trends-2019



Source: Behavioral Risk Factor Surveillance System

"Diabesity Belt"

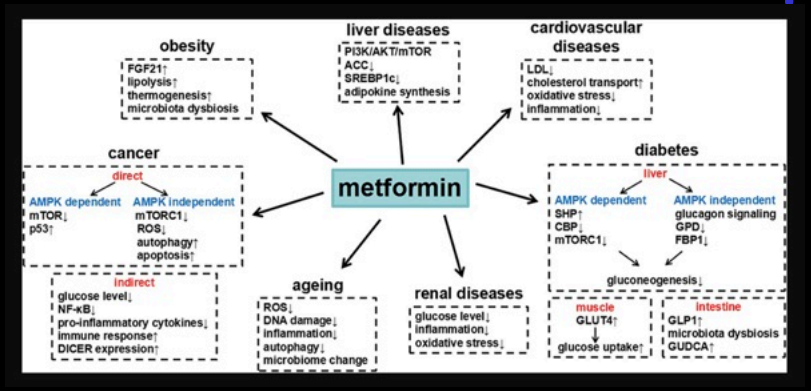


QUESTIONS

AND ANSWERS

PHARMACOTHERAPY OF DIABESITY

- Metformin (Fortamet, Glumetza, others)
- Action
  - Limit the liver's ability to release sugar
  - Improve cells' sensitivity to insulin
- Advantages: Very effective* glycemic control
  - May lead to minor weight loss
  - Low cost
  - Longevity and cognition



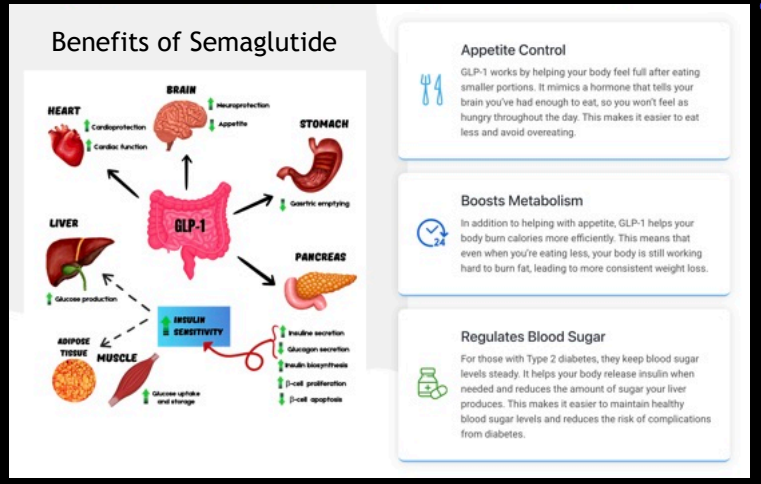
https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2020.00191

PHARMACOTHERAPY OF DIABESITY

- Metformin (Fortamet, Glumetza, others)
- Side effects
  - Temporary blur in older patients until BS stabilizes
  - Nausea
  - Stomach pain
  - Diarrhea
  - Rarely, harmful buildup of lactic acid — lactic acidosis — occurs in people with kidney failure or liver failure

PHARMACOTHERAPY OF DIABESITY

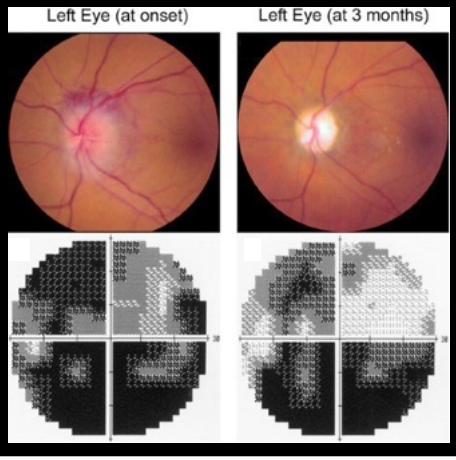
- Incretin mimetics (GLP-1 receptor agonists)
- Medications
  - Dulaglutide (Trulicity)
  - Exenatide (Byetta, Bydureon Bcise)
  - Liraglutide (Saxenda, Victoza)
  - Lixisenatide (Adlyxin)
  - Semaglutide (Ozempic, Rybelsus, Wegovy, Zepbound)
- Action
  - Cause the release of insulin as blood sugar levels are rising



PHARMACOTHERAPY OF DIABESITY

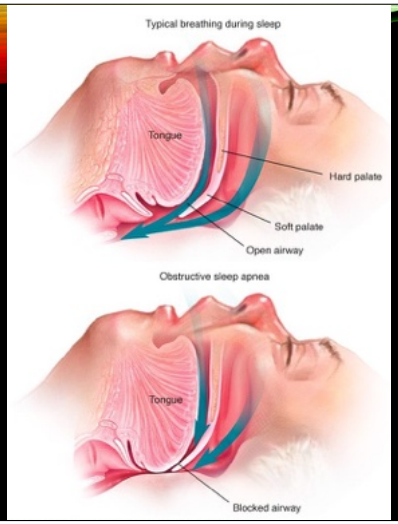
- Incretin mimetics (GLP-1 receptor agonists)
- Semaglutide (Ozempic, Rybelsus, Wegovy, Zepbound)
- Advantages
  - Decrease hunger
  - Leads to weight loss
  - May be used with metformin, basal insulin or a sulfonylurea
- Possible side effects: NAION?
  - Nausea
  - Vomiting
  - Diarrhea
  - Abdominal pain*
  - Increased risk of inflamed pancreas — pancreatitis

Semaglutide and NAION



SEMAGLUTIDE AND NAION

- July 3, 2024 in JAMA
- Researchers identified a potential link between these meds and NAION.
  - Association does not prove causation
- Subjects in the study were overweight/obese or had type 2 DM and are therefore at risk for NAION. Others at risk include those with:
  - Heart disease/MI
  - HTN
  - Sleep apnea
- A post-marketing surveillance study to determine safety/efficacy after a drug is released to patients may be helpful.



FDA APPROVES FIRST MED FOR OBSTRUCTIVE SLEEP APNEA

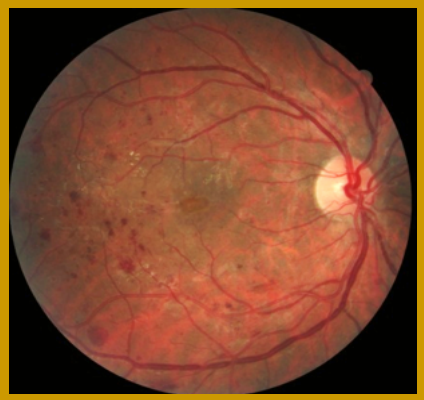
FDA APPROVES FIRST MED FOR OBSTRUCTIVE SLEEP APNEA

- December, 2024
- FDA approved Zepbound (tirzepatide) for mod-severe OSA.
- To be used with diet, increases physical activity.
- Works by activating receptors of hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino-tropic polypeptide (GIP).
- This reduces appetite, food intake, leading to weight loss.
- By reducing body weight, two studies showed improvements in OSA.

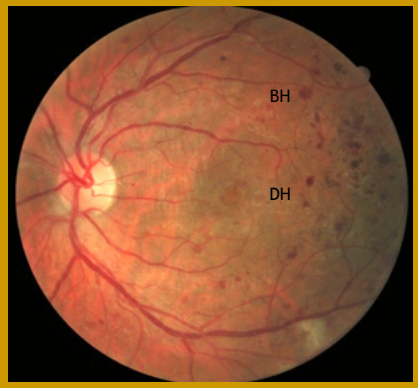
Case: 55 YOHM

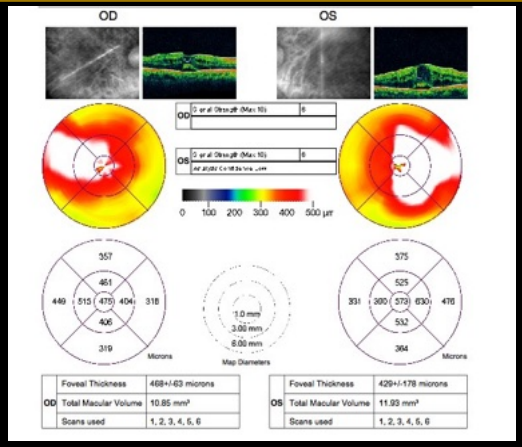
5 ft 10 in, 295 lbs
Central blur OD/OS
Type 2 DM x 3 yrs
+OSA, +HTN, +Dyslipidemia

OD: 20/100



OS: 20/200





QUESTION:

WHICH FACTORS MOST INFLUENCE THE ONSET, PROGRESSION AND VISUAL OUTCOME OF DIABETIC RETINOPATHY?

Systemic Conditions that May Exacerbate DR

- Dyslipidemia
- Hypertension
- Carotid occlusive dx
- Kidney disease
- Sleep apnea
- Anemia
- Obesity
- Vasculitis
- Neuropathy
- Nephropathy
- Vitamin D deficiency

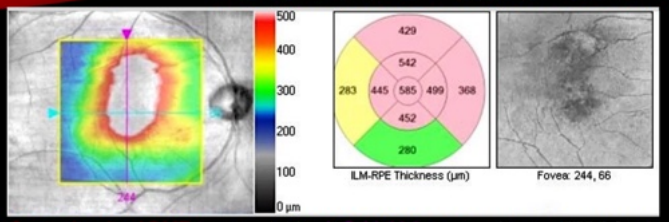
Sleep Apnea and DR/DME

- DME
  - Higher prevalence
  - Recurrence rate higher
  - Unresponsive to Anti-VEGF
- PDR
  - Higher prevalence
  - Worsening
- Improvement of DME, PDR w/CPAP

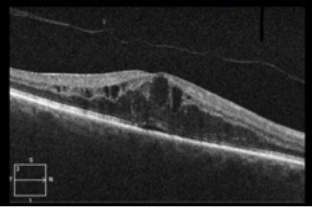
West, S. D., et al. "The prevalence of retinopathy in men with Type 2 diabetes and obstructive sleep apnea." Diabetic Medicine 27.4 (2010): 423-430.

OCT has forever changed the classification and management of DR, and especially DME.

VOLUMETRIC "CUBE" SCAN

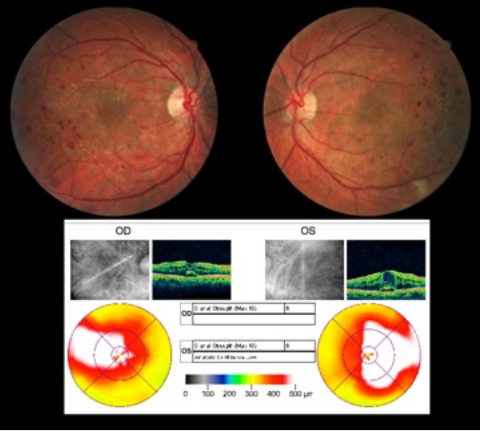


Center-involved DME: note central sub-field thickness on 9-zone ETDRS grid.



Temporal-to-nasal B-scan through foveal center shows Cystoid DME.

DME may occur at ANY stage of DR!

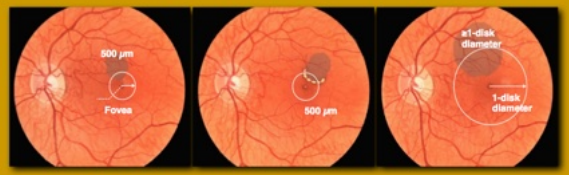


Clinically Significant Diabetic Macular Edema

Retinal thickening within 500 µm of macular center

Hard exudates within 500 µm of the center of the macula if associated with thickening of adjacent retina

Retinal thickening of >1-disk area in size, any part of which is located within 1-disk diameter of the center of the macula



CSME = clinically significant macular edema.
ETDRS Research Group. *Arch Ophthalmol.* 1985;103:1796-1806; Bandello F, et al. *Eye (Lond).* 2012;26:485-493.

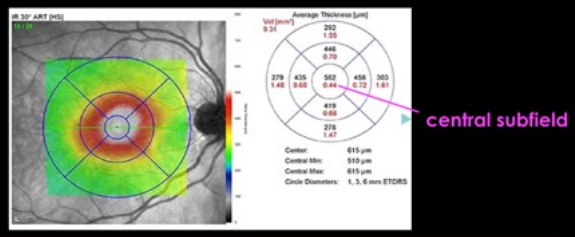
Clinically Significant Diabetic Macular Edema

OLD CRITERIA

CSME = clinically significant macular edema.
ETDRS Research Group. *Arch Ophthalmol.* 1985;103:1796-1806; Bandello F, et al. *Eye (Lond).* 2012;26:485-493.

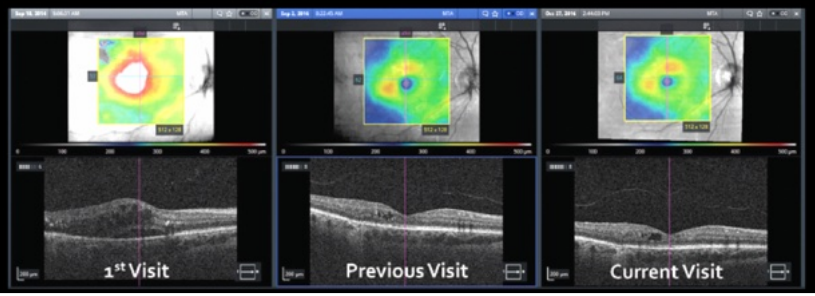
DME Classification & Management: Center Involved or Not?

- Randomized clinical trials of anti-VEGF agents used the presence of DME in **OCT central subfield.**
- Older ETDRS definition of "clinically significant macular edema" modified in era of OCT.



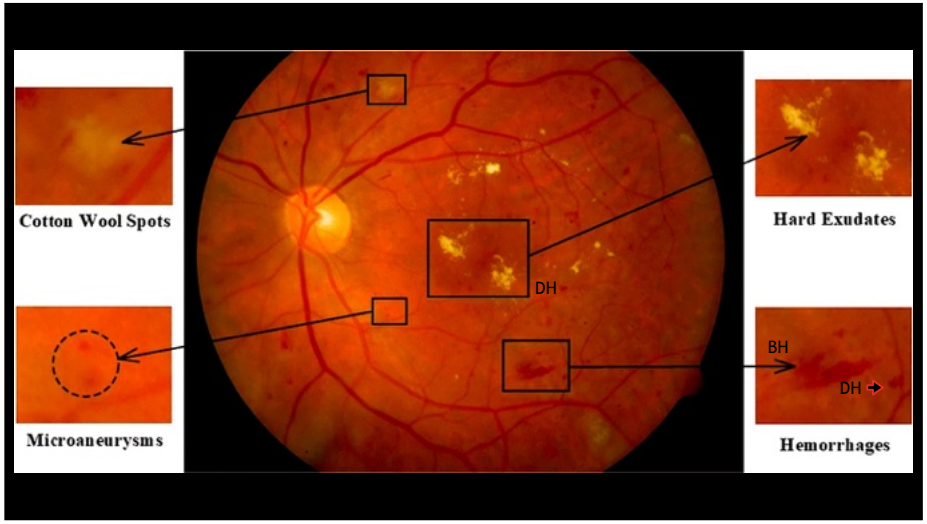
Nguyen, Quan Dong, et al. Ophthalmology 119.4 (2012): 789-801.
Brown, David M., et al. Ophthalmology 122.10 (2015): 2044-2052.

IS THE TREATMENT WORKING?



MA, DOT HEME, BLOT HEME

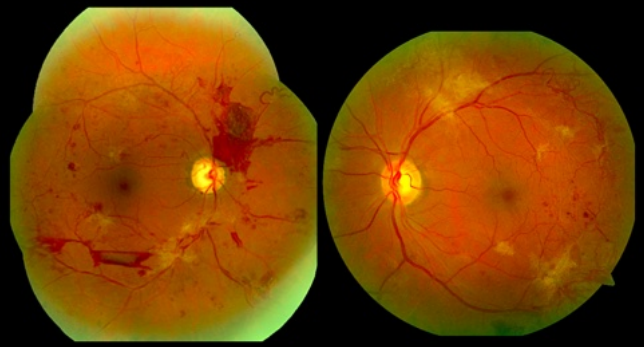
- All are red spots in the retina, but they differ in mechanism, size, location, and appearance.
- MAs are not hemes, but an out-pouching of the BV wall. MAs may or may not be accompanied by DH and/or BH. "MAs only"
  - Typically the first visible sign of DR.
  - They may leak exudate, heme, fluid.
  - Most common/visible within in the posterior pole.
  - Use a DO, red-free!



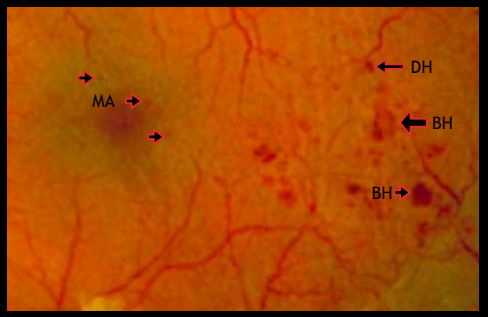
MA, DOT HEME, BLOT HEME

- A dot heme is a small, distinct round bleed, while a blot hemorrhage is a larger, less well-defined area of bleeding.
- Dot hemes are larger than MAs, usually more than 125 microns in diameter.
  - When DH is present, MAs are also usually visible.
  - DH may occur with or w/o BH. Specify this in your record!
- Dot hemes and blot hemes are located deeper in the retina than MAs, usually in the inner nuclear or outer plexiform layers.

DR is NOT exclusive to the central retina.



- BH indicates more extensive damage to the inner BRB Than DH.



MA, DOT HEME, BLOT HEME

- On FA, MAs appear hyperfluorescent, while dot hemes and blot hemes appear hypofluorescent.
- A blot heme is essentially a larger version of a dot heme. It indicates more extensive damage to the inner BRB.
  - Although BH may occur w/o DH, this is less common than the opposite.
  - When BH are present there are usually DH and MAs as well.
- The key difference between DH and BH is their size and more diffuse borders in a blot heme, compared to the sharp edges of a dot heme.

QUESTIONS

AND ANSWERS

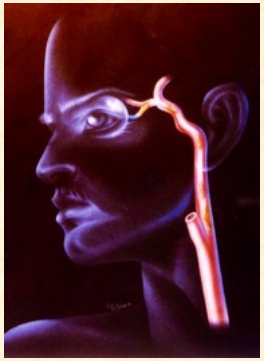
CFSOP

Central Florida Society of Optometric Physicians

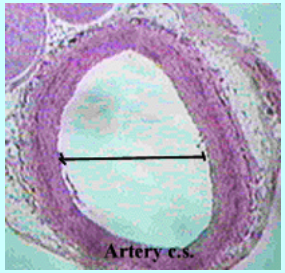
DM + Smoking = Blindness

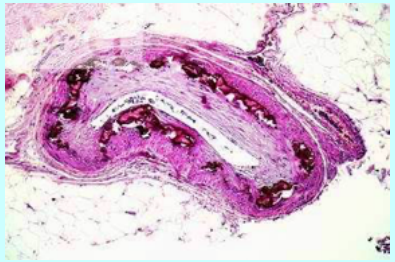
Cigarette Smoking, Ocular & Vascular Disease

- Increased arteriolar stiffness (sclerosis)
- Increased Vascular Endothelial Growth Factor (VEGF)
- Development/worsening of DR
- Development/worsening of AMD



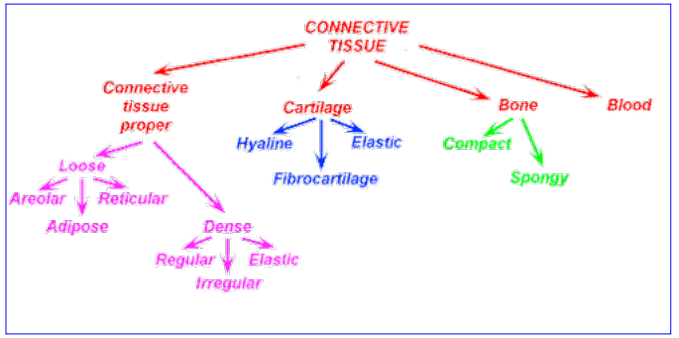
Arteriosclerosis with calcification of vessel wall.





AMD + Smoking = Blindness

The Eye in Connective Tissue Disease



What is connective tissue?

"Cellular glue" that gives tissues their shape and helps them do their work. Cartilage and fat are examples.

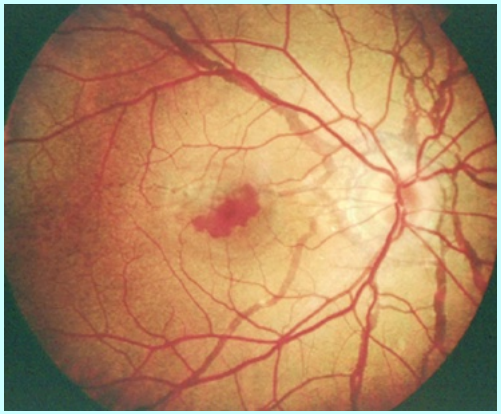
*There are over 200 disorders that impact connective tissue!

Connective Tissue Disorders

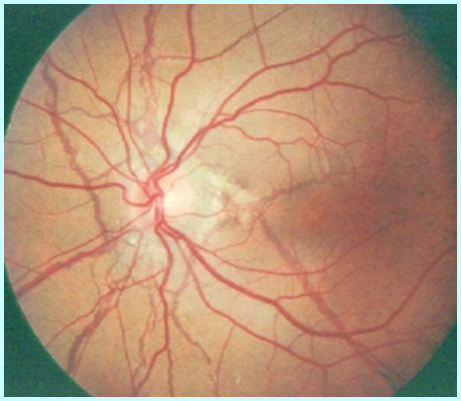
- Ankylosing Spondylitis
- Sjogren Syndrome
- Pseudoxanthoma Elasticum
- Ehlers Danlos Syndrome
- Paget's Disease
- Marfan Syndrome
- Systemic Lupus Erythematosus

Angioid streaks are present in 85% of patients with PXE.

The Eye in Systemic Disease



The Eye in Systemic Disease

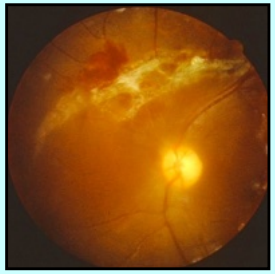


Masqueraders of Angioid Streaks

High Myopia

• **Lacquer Cracks**

Trauma



• **Choroidal Rupture**

Differential Dx. of Angioid Streaks: PEPSI

Diagnosis	**Key Clinical Features**
Pseudoxanthoma	redundant, "plucked chicken" skin hypertension weak peripheral pulses gastrointestinal bleeding
Ehlers-Danlos syndrome	blue sclera joint hyperextensibility fragile, elastic skin excessive bruising
Paget's disease	extraskeletal calcification bony erosion and abnormal formation osteoarthritis hearing loss, vertigo, tinnitus slurred speech, difficulty swallowing
Sickle cell disease	hemoglobin SS (most frequently) anemia
Idiopathic	vaso-occlusive crises

QUESTIONS

AND ANSWERS

2 MINUTE STRETCH

HYDROXYCHLOROQUINE
HCQ: TRADE NAME, PLAQUENIL
USED FOR SLE, RA, AI DX

CHLOROQUINE
CQ: TRADE NAME, ARALEN

HCQ TOXICITY

- Perform DFE annually.
- What additional testing/work-up is appropriate?

What is the recommended maximum daily HCQ dose?

- Calculate Max Dose in mg/day
- 2.3 x weight (in lbs.) = Max daily dose
- At recommended dose, risk of toxicity is < 1% after 5 years, < 2% after 10 yrs.
- Risk rises to almost 20% after 20 years. **
  - Our patient VY (~110-120 lbs) was taking 400 mg/d for 15 yrs, or nearly double the MDD!
- Risk for HCQ maculopathy depends on daily dose, duration of use*

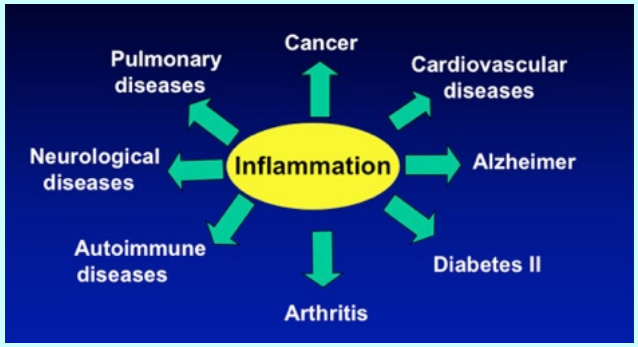
PLAQUENIL KERATOPATHY

SCREEN ANNUALLY

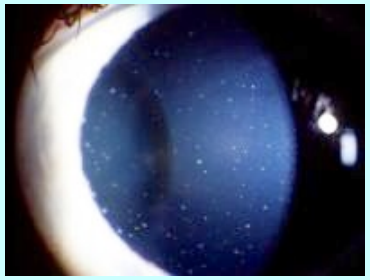
PLAQUENIL VORTEX KERATOPATHY

- While HCQ maculopathy is not reversible, even following drug cessation, keratopathy has been reported to be fully reversible.
- Another drug cause of vortex keratopathy is the antiarrhythmic amiodarone.

Inflammatory Disease

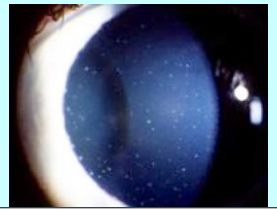


A Word About Uveitis



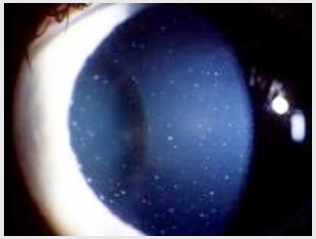
What is uveitis?

- Defined as inflammation of the uveal tract.
- For decades, considered a single disease.
- Fact: Uveitis entails a multitude of diseases.
  - Some are local, ocular immune
  - Many are systemic diseases with ocular manifestations.

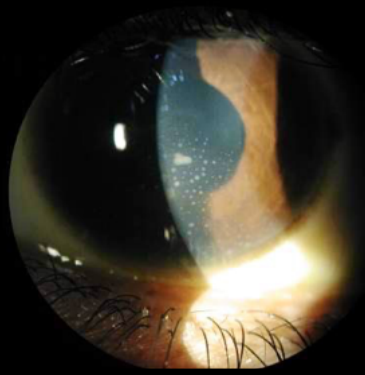


What is uveitis?

- Because the spectrum of pathogenesis ranges from autoimmunity to neoplasia to viruses, management requires an understanding of:
  - Internal medicine
  - Infectious diseases
  - Rheumatology
  - Immunology



Uveitis is an Immunological Process

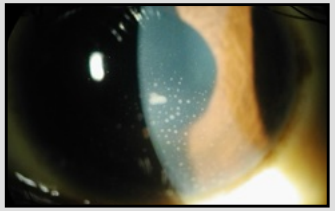


Immune Privilege

- The eye has a special relationship with the immune system.
  - Ability to quench unwanted immune-mediated inflammation.
  - This ability is known as immune privilege.
- Immune privilege enables ocular tissues to remain clear.

Common Etiologies of Anterior Uveitis

- In uveitis, immune privilege is overcome
- Idiopathic (post-viral syndrome)
- Human leukocyte antigen (HLA)-B27–positive or HLA-B27–associated
- Trauma or s/p intraocular surgery



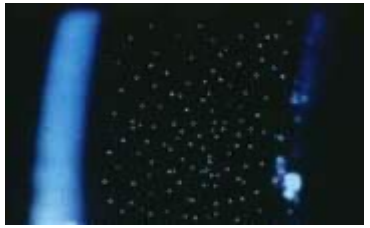
HLA-B27

- HLA-B27 is present in 1.4-8% of the general population.
- However, it is present in 50-60% of patients with acute iritis.
- HLA-B27 diseases include:
  - Ankylosing spondylitis
  - Reiter syndrome
  - Inflammatory bowel disease
  - Psoriatic post-infectious arthritis

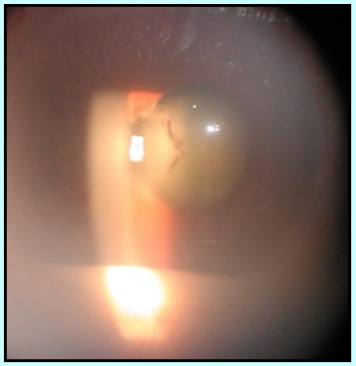
Hypopyon w/+ HLA-B27

Find the Cells

- Dark adapt
- SL on max illum
- Start w/Low mag*
- Optic section (long)*
- Increase mag
- ID the cells
- Shorten to short optic section or conic beam
- Count the cells

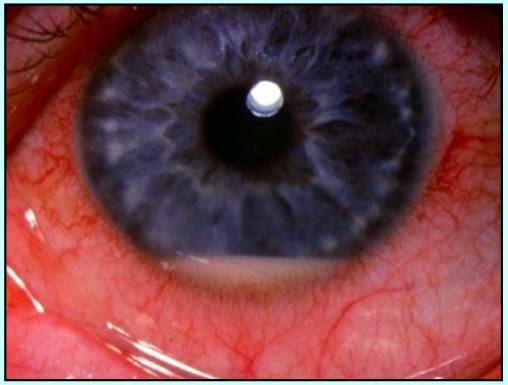


Hypopyon with 4+ cell and 3+ flare



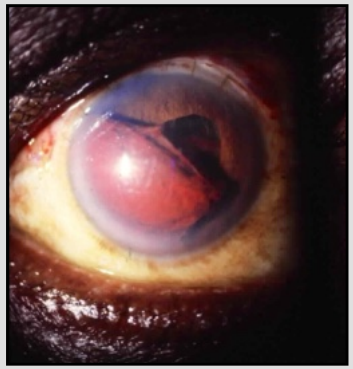
Hypopyon

- A collection of leukocytes that settle in the inferior anterior chamber angle.
- Related to amount of fibrin which allows WBCs to clump and settle.
- Highly suggestive of HLA-B27 disease, Behçet disease, or endophthalmitis.



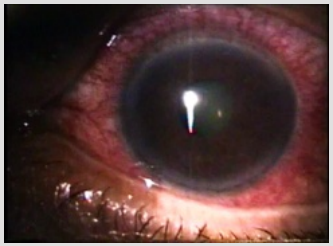
Hyphema

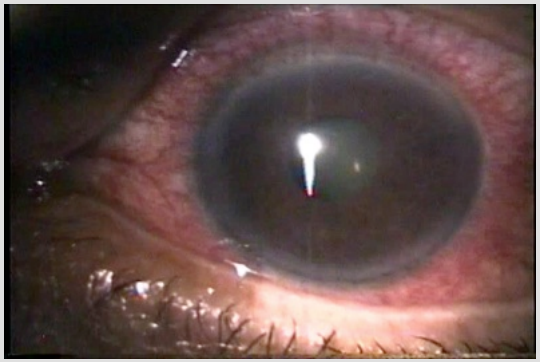
- Can occur in eyes with a chronic uveitis (UGH Syndrome)
- Can result from NVI/NVA
  - DR
  - RVO
  - IOS



KPs and Iris Nodules

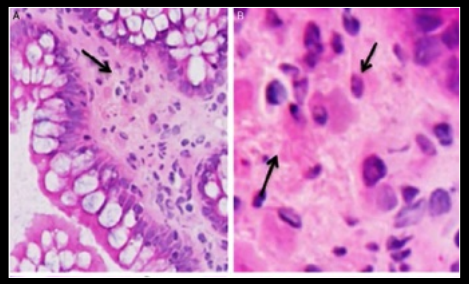
Serous/Exudative RD in Posterior Scleritis: Mainstay scleritis treatment is po steroid





GRANULOMATOUS UVEITIS

- An organized collection of macrophages.
  - A type of WBC that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells.



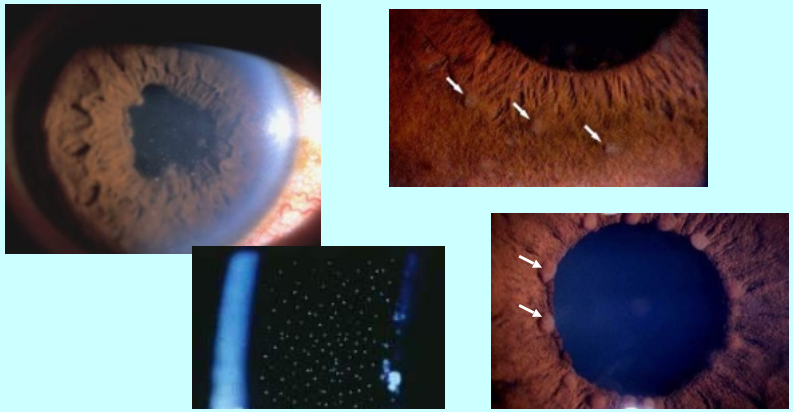
History

- A 34 year-old black female presents symptoms of bilateral redness x 7 days
- Gradual onset, gradual worsening
- Mild pain, mild photophobia OU
- Ocular history positive for previous episodes OU

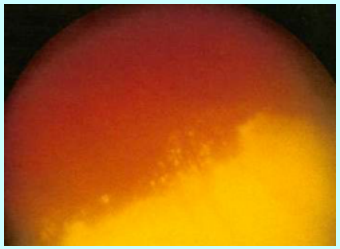
Clinical Findings

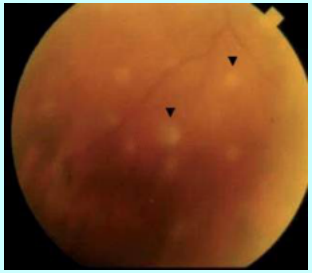
- Biomicroscopy
  - 2+ cells in AC OU
  - "Mutton fat" deposits on endothelium OU
  - Iris nodules OU
  - Areas of posterior synechia OU
- TAP: 9 mmHg OD/11 mmHg OS
- DFE
  - "Snowbanking"
  - Gray/white (old) vitreous "puff balls" inferior PP OU

Anterior Seg Findings



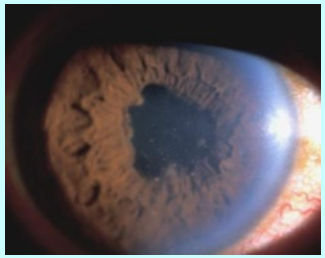
Posterior Seg "Puff-balls" and "Snowbanking"





What is your ocular diagnosis?

Assessment



- Bilateral anterior uveitis
  - Probably recurrent/chronic
- Granulomatous
  - Mutton-fat KPs
  - Iris nodules
- Prior posterior segment inflammation

What is your plan?

Ocular management?
Systemic testing?
Consultation?

A granulomatous uveitis has an increased likelihood of being part of a s_____ disease process.

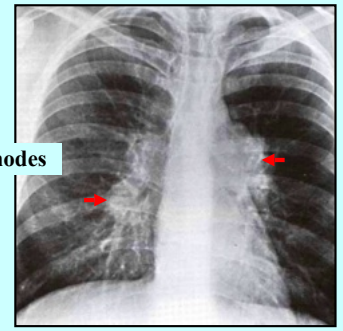
Actual Management

- Treated anterior uveitis using conventional topical meds.
  - Steroid
  - Cycloplegic (atropine)
- Ordered targeted systemic "uveitis" work-up
  - Serum lysozyme
  - ACE will be elevated in up to 80% of patients with active S_____ .
- Chest imaging

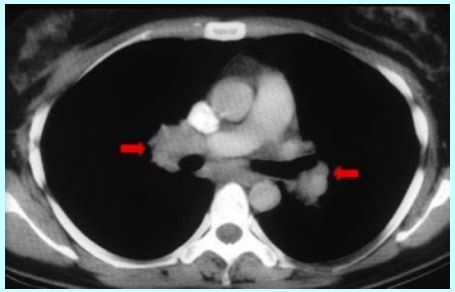
Corticosteroids

- Topical steroids are the mainstay to treat ocular inflammatory conditions.
- Systemic steroids also useful, especially in recalcitrant cases of uveitis, scleritis.
- Choosing which medication to use depends on the severity and location of the ocular inflammation.

Bilateral Hilar Lymphadenopathy on Chest X-Ray in Pulmonary Sarcoid



Bilateral Hilar Lymphadenopathy on CT Scan of Chest

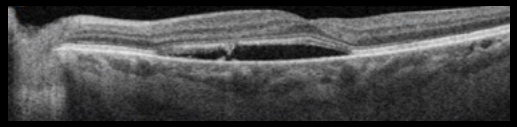


Outcome

- Sarcoidosis
  - Patient was also placed on po Prednisone (short-term)
  - Good ocular response to medical therapy
- What imaging tests to order:
  - Chest X-ray
  - CT of chest and abdomen

SIDE EFFECTS OF STEROID TREATMENT

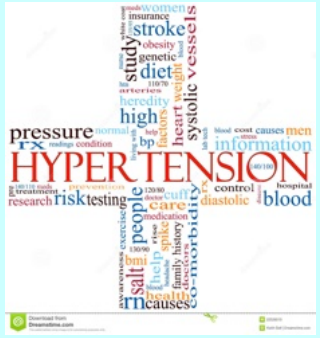
- By any route of administration:
  - Weight gain
  - PSC
  - CSC
  - GLC



Key Points: Sarcoidosis**

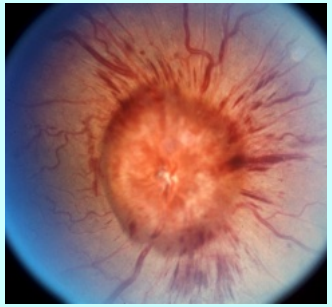
- A multi-system disease.
- Most often occurs between 20-40 years of age, with women being diagnosed more frequently than men.
- 10 to 17 times more common in African-Americans than in Caucasians.

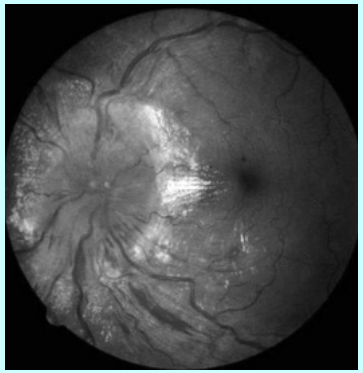
Questions and Answers



The Eye in Systemic Disease

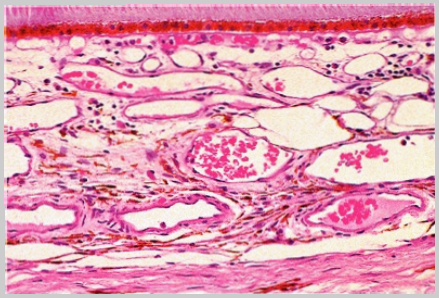
Malignant Hypertension





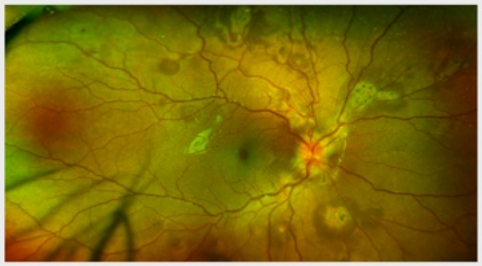
Choroid Microstructure

- Choriocapillaris
- Sattler's layer
- Haller's layer
- Supra - choroid

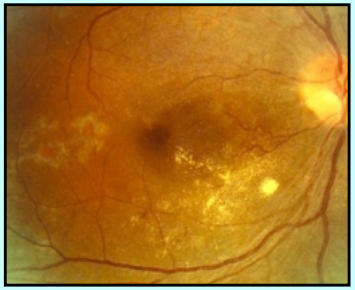


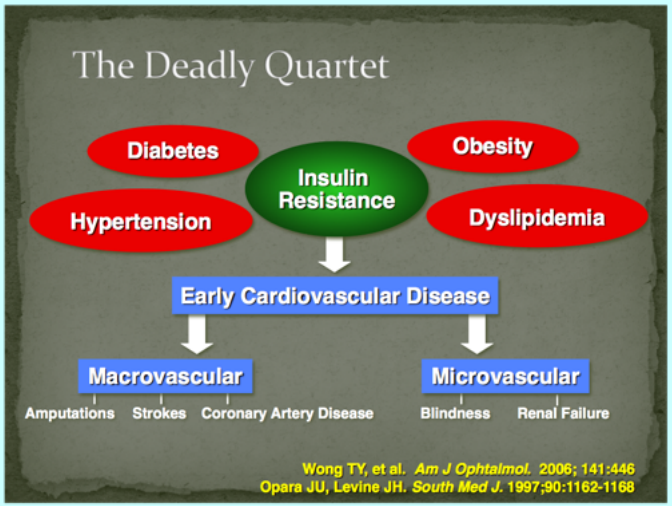
Hypertensive Choroidopathy

Elschnig spots



Elschnig Spots in Hypertensive Choroidopathy





Treatments

- Step 1:
  - Lifestyle modifications
    - Diet and exercise
    - Limit alcohol and tobacco use
    - Reduce stress factors
- Step 2:
  - If lifestyle changes are not enough, drug therapy will be introduced
- Step 3:
  - If previous steps don't work, drug dose or type will be changed or another drug is added
- Step 4:
  - More medications are added until blood pressure is controlled

Goals in Hypertension Therapy

- Lower blood pressure
- Facilitate regression of LV hypertrophy
- Reduce risk of coronary athero and myocardial infarct
- Mitigate renal damage
- Avoid stroke and CNS hemorrhage
- Prevent peripheral vascular and carotid athero
- **PROTECT THE EYES!!!**

Summary – Benefits of Lowering BP

	Average % Risk Reduction
Stroke Incidence	35-40%
Heart Attack	20-25%
Congestive Heart Failure	50%

Hypoperfusion Retinopathy

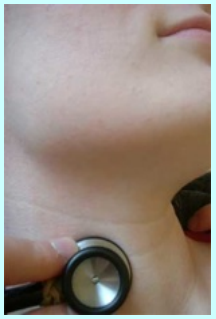
and the

Ocular Ischemic Syndrome

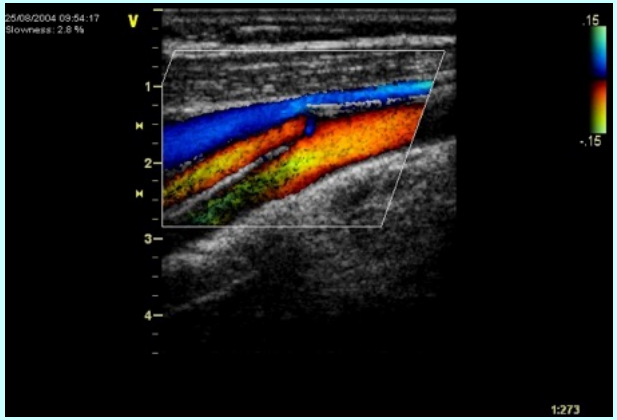
Carotid Artery Occlusive Disease

**Dot hemes and Blot hemes in mid-peripheral retina

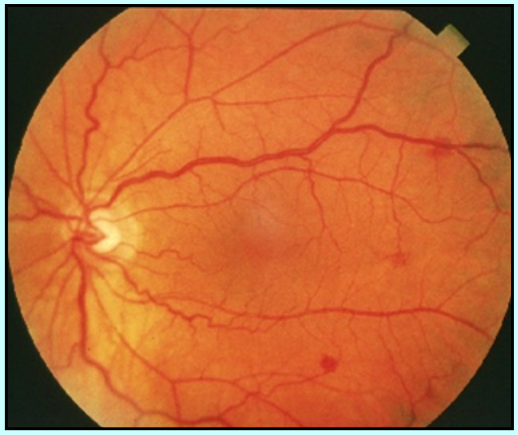
Carotid Occlusive Dx: Bruit



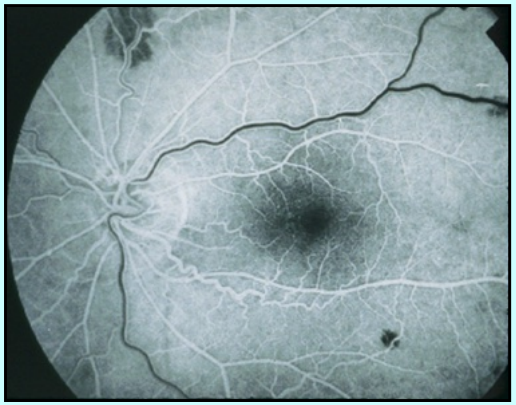
Carotid Doppler (Duplex) is noninvasive*



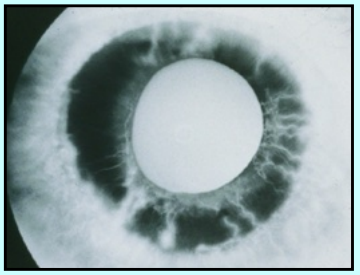
Mid-peripheral Hemes in Hypoperfusion Retinopathy



Hypoperfusion Retinopathy—same eye



NVI and Cataract in Ocular Ischemic Syndrome



The Ocular Ischemic Syndrome (OIS)

Key Point ▲

- Bilateral involvement in patients with ocular ischemic syndrome may occur in up to ~20% of all cases.

The Eye in Systemic Disease

Pathogenesis: Ocular Ischemic Syndrome

Non-invasive Carotid Doppler (Duplex) ultrasound**

- Atheromatous ulceration and stenosis at the bifurcation of the common carotid artery. The embolus usually travels upstream to occlude the ICA.

Key Point▲

- The most common etiology of the ocular ischemic syndrome is severe unilateral or bilateral atherosclerotic disease of the Internal Carotid A.

The Eye in Systemic Disease

OIS Work Up:

- Carotid artery evaluation (Carotid – Duplex Scanning)–ICA, ECA, CCA
- Color Trans-cranial Doppler (TCD) – ocular arteries
- Possible MRA (Magnetic Resonance Angiography)
- Computed Tomography (CT) Angiography
- Cardiology work up (Echocardiogram) – Transesophogeal/Transthoracic
- HTN, DM, Lipid Panel, ESR, C-reactive protein

The Eye in Sytemic Disease

Ocular Ischemic Syndrome

Cholesterol Plaques, disc pallor, non-GLC cupping

The Eye in Systemic Disease

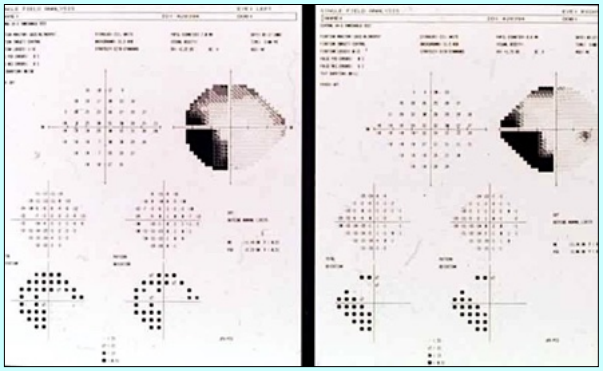
Ocular Ischemic Syndrome

Treatment:

- Consider carotid surgery if warranted (Endarterectomy)
  - ➢ European Carotid Surgery Trial (ECST)
  - ➢ North American Symptomatic Carotid End. Trial (NASCET)
- Therapeutic approach – Aspirin (325 mg QD or BID), Plavix
- Control modifiable vascular risk factors (HTN, DM, dyslipidemia)
- Stop smoking
- Panretinal photocoagulation (PRP) if neovascularization

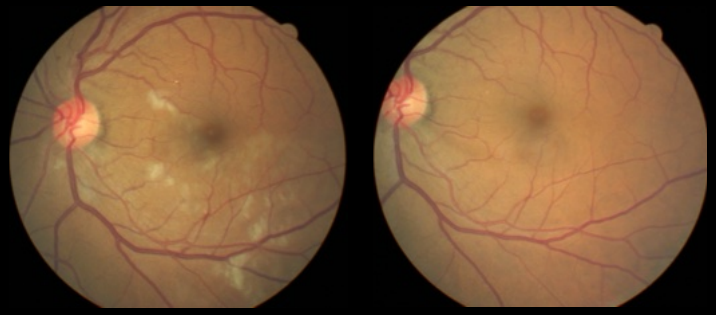
**Important Note:
Leading cause of death in OIS = Ischemic heart disease
Second leading cause of death = Stroke

The Eye in Systemic Disease



R Occipital Lobe Infarct

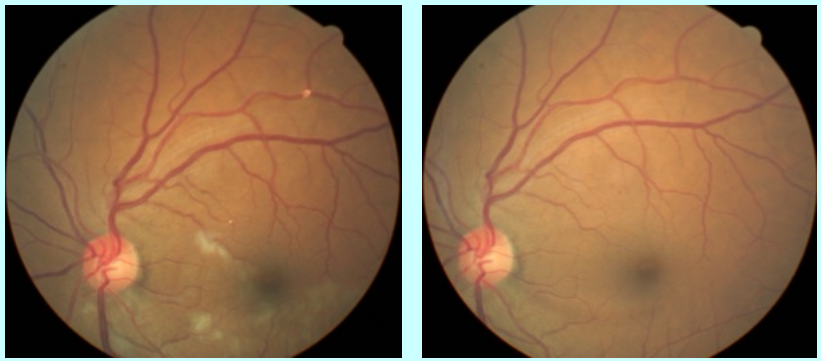
The Eye in Systemic Disease



Pre/post Endarterectomy

The Eye in Systemic Disease

Pre/post Endarterectomy



Causes of Embolism

I Cardiac Disease

- Arrhythmias
- Valvular disease
- Endocarditis
- Ischemic lesions
- Tumors

II Carotid Disease

The Eye in Systemic Disease

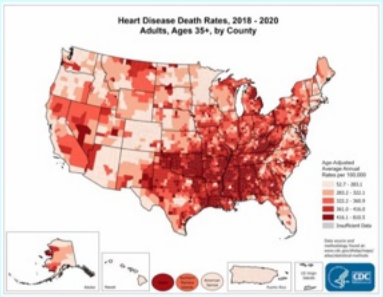
55 yo AA male
BRAO OD

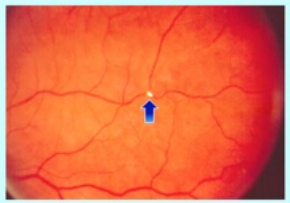
The Eye in Systemic Disease

55 yo AA male OS

Key Points

- Myocardial Infarction is the most common cause of death in USA.
  - Over 1 million deaths in the US*
  - ~~697,000~~ per year
- Cardiac valve disease is the most common cause of cardiac emboli to the eye.**





Warning Signs | Volunteer | Donate

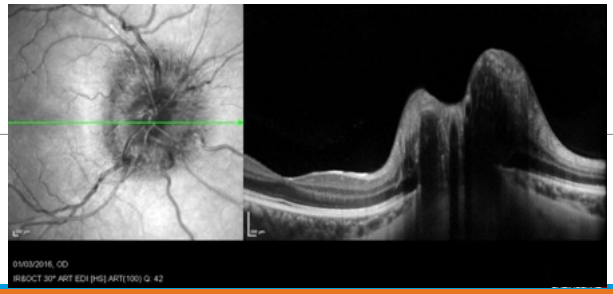
Newsroom

Categories: Advisories & Comments, Heart News, Program News, Stroke News, Diversity/Health Equity |
Published: June 29, 2022

American Heart Association adds sleep to cardiovascular health checklist

American Heart Association Presidential Advisory

- 28 yo WM w/TVO OD/OS:
- BMI = 29
- MRI/MRV, followed by LP, extensive serology



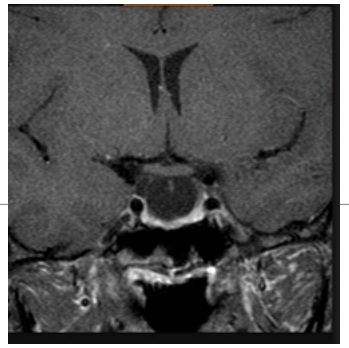
- Empty Sella
- T-1 sag

- IIH + OSA

Treatment of IIH

- 5-10% weight loss: diet w/inc physical activity
- Acetazolamide or topiramate to help the body produce less CSF
- Pain relievers for headaches
- Acetazolamide (Diamox)
  - Paresthesias, GI symptoms
  - Sulfa allergy?
  - Myopic shift
  - Ciliochoroidal effusions and acute angle-closure glaucoma (ACG)
    - Topical steroids, cycloplegics, and aqueous suppressant

- Empty Sella
- T-1 coronal



- IIH + OSA

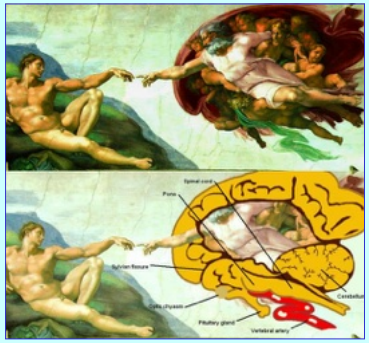
Topiramate (Topamax)

- Avoid prescribing topiramate if patient has narrow angles
  - Cilio-choroidal effusions and acute angle-closure glaucoma (ACG)
- Discontinue topiramate if angle closure glaucoma—especially with a myopic shift— is confirmed
  - Topical steroids, cycloplegics, and aqueous suppressant

Questions?

Conclusion

- The eye does not exist in isolation, but is a mirror of systemic health.
- Prescribe wisely.



The Creation of Adam (1508-12). Michelangelo Buonarroti. Sistine Chapel.
Source: Journal of the Royal Society of Medicine

Thank you!

Joe

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