CNV Variations and Masqueraders

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- Honoraria
  - Alcon
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  - Reichert
- Scientific Advisory Boards
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  - Carl Zeiss Meditec
- Proprietary Interests
  - None
- CEO/Founder
  - Optometryboardcertified.com
- CE Companies
  - CEinItaly.com
  - EyeSkiUtah.com

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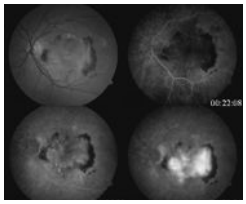
- CE Companies
  - CEinItaly.com
- Dr. Pelino has no proprietary interests or other financial relationships to disclose.

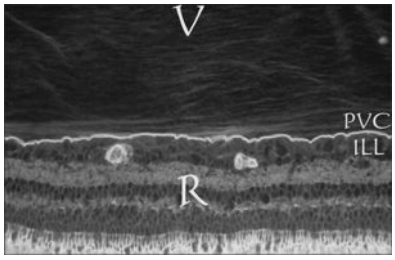
Course Goal

- To provide useful clinical information about variations and masqueraders of CNV.
  - Classification, diagnosis, treatment/management



Evaluate the vitreoretinal interface routinely.

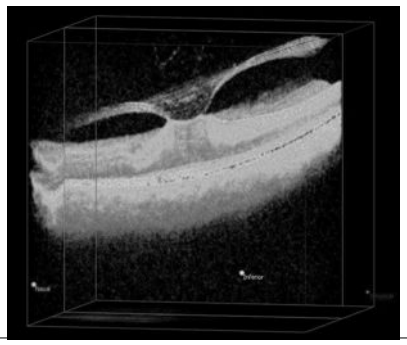
The Vitreoretinal Interface



retinalphysician.com

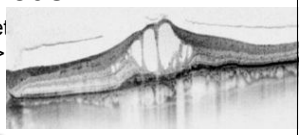
Persistent Vitreomacular Adhesions (VMA)

Anomalous PVD



Anomalous PVD

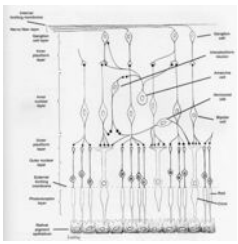
- May hasten the Wet AMD process. ---->



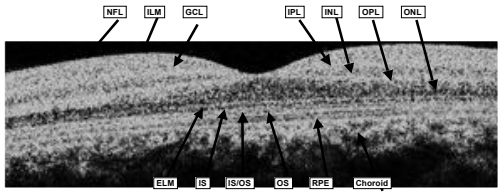
Jetrea (ocriplasmin)

The Retina

- RPE
- Neurosensory
- 6 million Cones
  - Detailed vision
  - Color vision
- 120 million Rods
  - Peripheral retinal receptors
  - Great sensitivity to light



SD-OCT Healthy Macula



NFL: Nerve Fiber Layer
ILM: Inner Limiting Membrane
GCL: Ganglion Cell Layer
IPL: Inner Plexiform Layer
INL: Inner Nuclear Layer

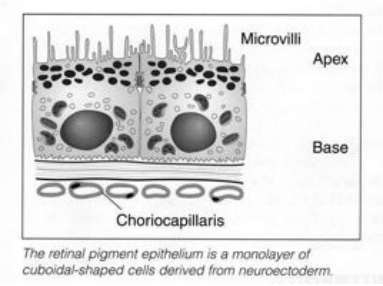
OPL: Outer Plexiform Layer
ONL: Outer Nuclear Layer
ELM: External limiting membrane
IS: Photoreceptor Inner Segment

IS/OS: Junction of inner and outer photoreceptor segments
OS: Photoreceptor Outer Segment
RPE: Retinal Pigment Epithelium

Retina

- The Pigment Epithelium
  - Monolayer
  - Cuboidal cells
  - Function of RPE
  - Tight junctions form outer blood-retina barrier

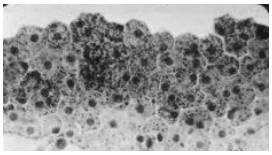
RPE



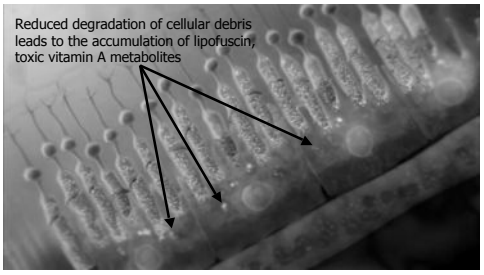
The retinal pigment epithelium is a monolayer of cuboidal-shaped cells derived from neuroectoderm.

Retinal Pigment Epithelium

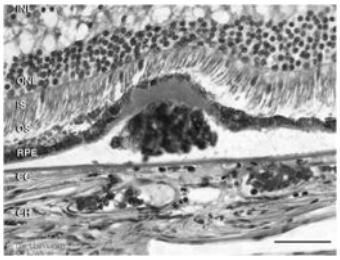
- 120 million cells in monolayer
- Functions of RPE
  - Phagocytosis of renewable discs of PRs
  - O-2 diffusion to PRs
  - Provision of nutrients to PRs



Early AMD: Accumulation of Lipofuscin and Vitamin A Metabolites



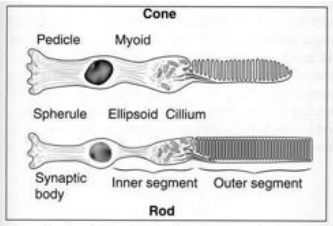
Drusen



Retina

- The Neurosensory Retina
  - The Photoreceptors
    - Structure and function of cones and rods
  - Inner and outer segment junction
    - Importance of structural integrity to visual function
  - Outer limiting membrane
  - Outer nuclei
  - Synaptic layer (plexiform)

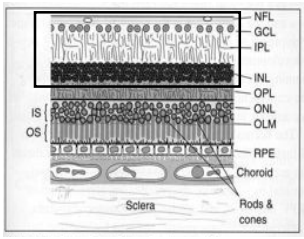
Photoreceptors



The ratio of rods to cones is 20:1. In cones, the outer segment discs are attached to the cell membrane whereas in rods the discs are arranged like a "stack of coins."

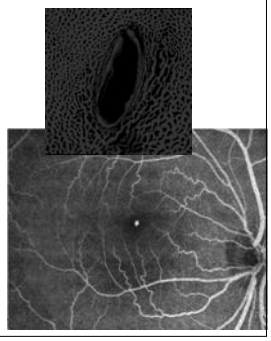
Neuro-sensory Retina

- Inner nuclei
- Synaptic layer (plexiform)
- Ganglion cells
- Nerve fiber layer
- Internal limiting membrane



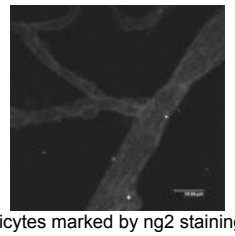
Retinal Vasculature

- 2 main sources of blood supply:
- Choroidal BV
  - Supplies outer retinal layers, including PRs
- CRA
  - 4 branches nourish inner retina
  - Run radially toward fovea



Retinal Capillaries

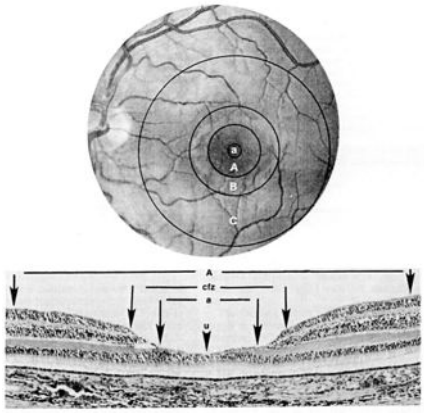
- Pericytes surround each endothelial cell
  - provide support
- Tight junctions between endothelial cells
- Pericytes + tight junctions form inner blood-retinal barrier.



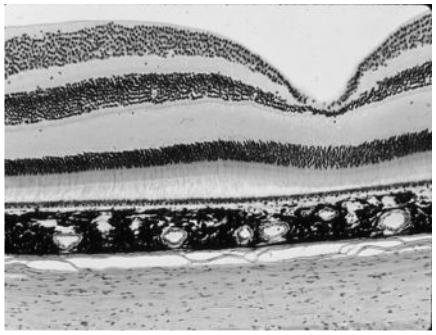
Pericytes marked by ng2 staining (blue) and endothelial cells are marked by PECAM (red).

Retina

- Photransduction
  - conversion of light into an electrical impulse
- The retina is damaged by it's own operation.
- Autoregulation of blood flow



Functional Anatomy: The Fovea



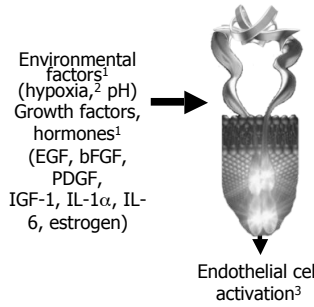
The Choroid

- Vascular layers
- Melanocytes
- Bruch's membrane
- Sympathetic regulation of blood flow
- Function of choriocapillaris
  - Supply of nutrients
  - Absorption of light

Diagnostic Dilemma

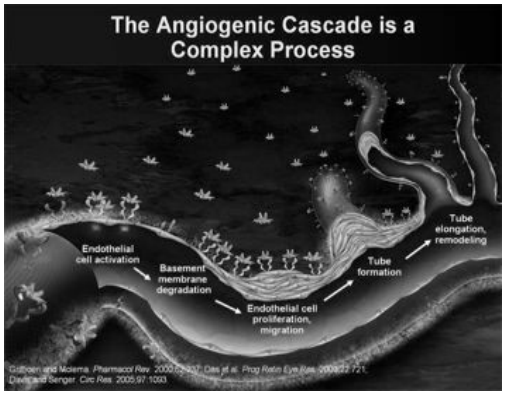
Choroidal
Neovascularization

Angiogenesis

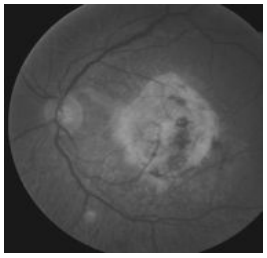


VEGF-A = vascular endothelial growth factor A; EGF = epidermal growth factor; bFGF = basic fibroblast growth factor; PDGF = platelet-derived growth factor; IGF = insulin-like growth factor; IL= interleukin.

1. Dvorak HF. *J Clin Oncol*. 2002;20:4368. 2. Aiello LP, et al. *Arch Ophthalmol*. 1995;113:1538.
3. Ferrara N, et al. *Nat Med*. 2003;9:669. 4. Griffioen AW and Molema G. *Pharmacol Rev*. 2000;52:237.



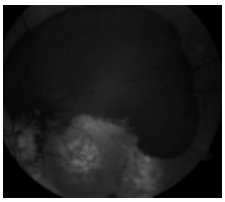
CNV ---> FV Scar



CNV has several variations, causes, and masqueraders.

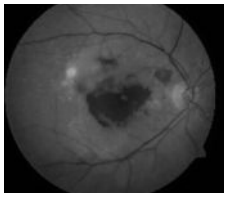
Choroidal Neovascularization

- Subjective symptoms
- Objective data
- Diagnostic Workup
- Making the diagnosis

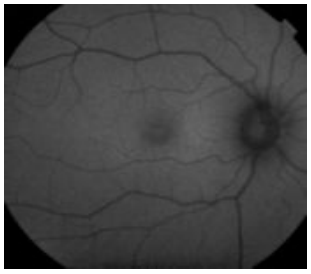


Common Causes of CNV

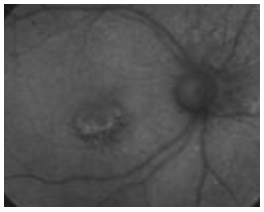
- Exudative AMD
- Ocular Histoplasmosis
- High Myopia
- Angioid Streaks



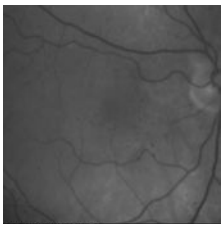
Fundus Autofluorescence

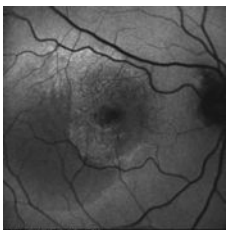


Fundus Autofluorescence

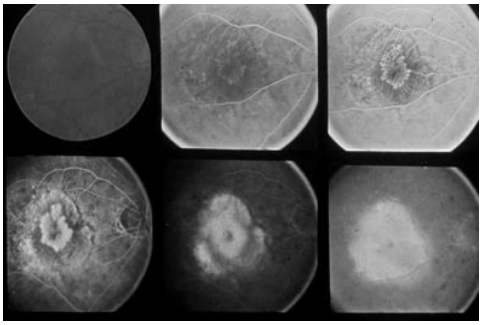


Fundus Autofluorescence Wet AMD



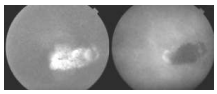


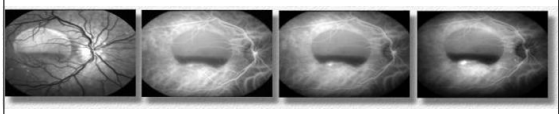
Fluorescein Angiography



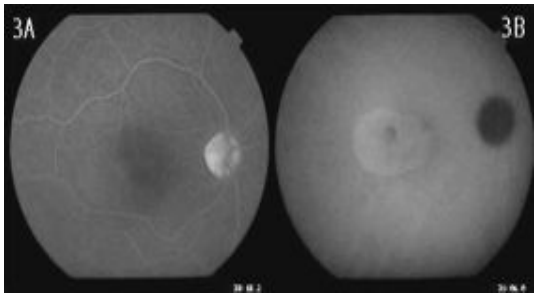
Indocyanine Green Angiography (ICGA)

- Uses digital imaging systems
- Dye properties
- "Sees" through blood
- Delineates choroidal circulation better than fluorescein angiography
- Boundaries of occult membranes imaged

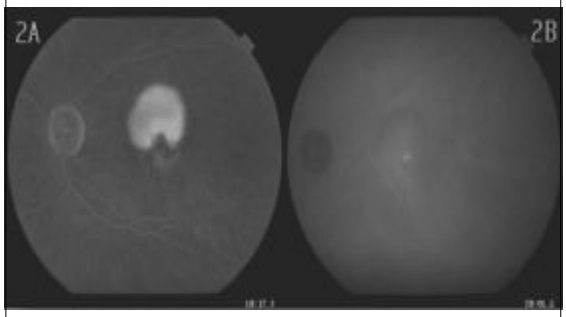




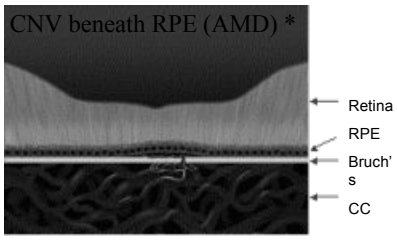
Occult CNV



Classic CNV

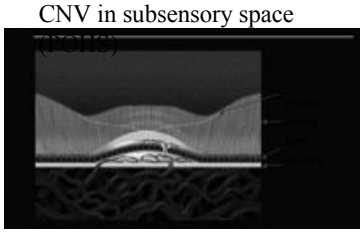


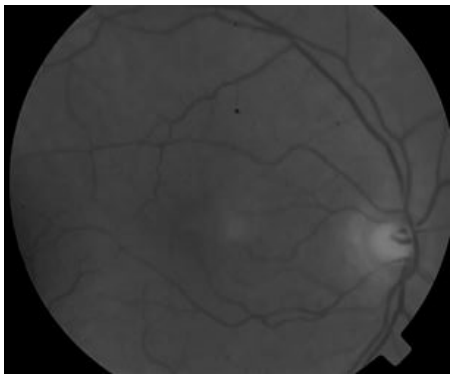
Type I CNVM

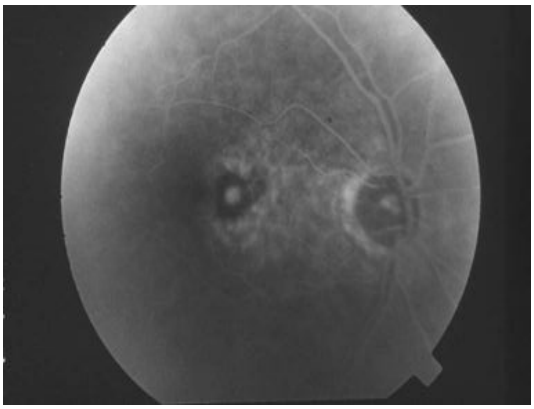


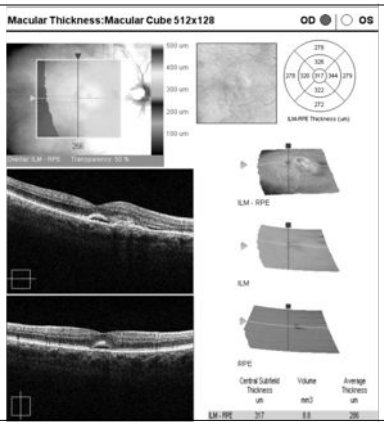
Type II CNVM

CNV in subsensory space (PCV?)

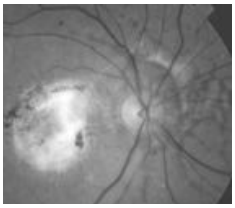


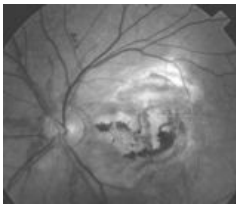






ANGIOID STREAKS





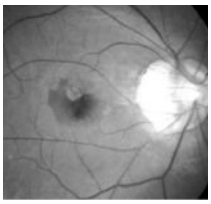
- Note Angioid Streaks radiating from the optic discs and macular laser scarring

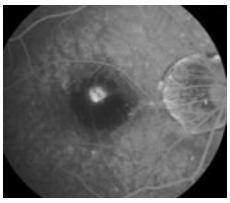
Differential Dx. of Angioid Streaks: PEPSI

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

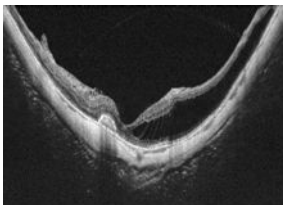
Causes of CNV

- High Myopia in a 52 y/o WM
- CNV w/heme





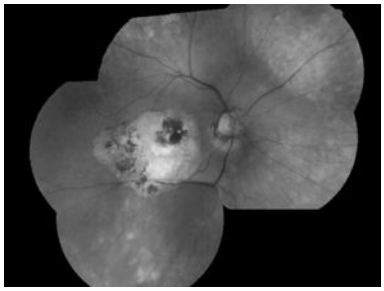
48 y/o WM
-12.00D



Concave fundus, CNV, schisis

Causes of CNV

- OHS



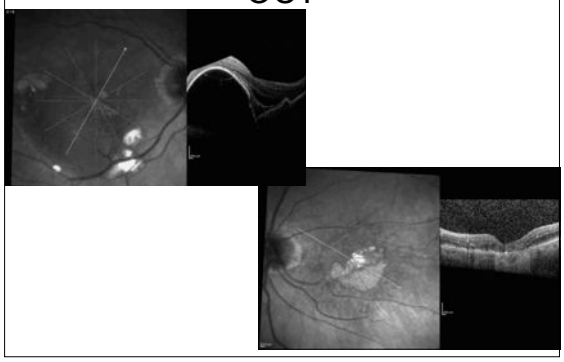
Case

- 81 Year old Female with a history of arthritis.
- 7 year history of injections with Avastin or Lucentis
- PMH: AMD OU, Cataracts OU
- OcHx: Injections for AMD.

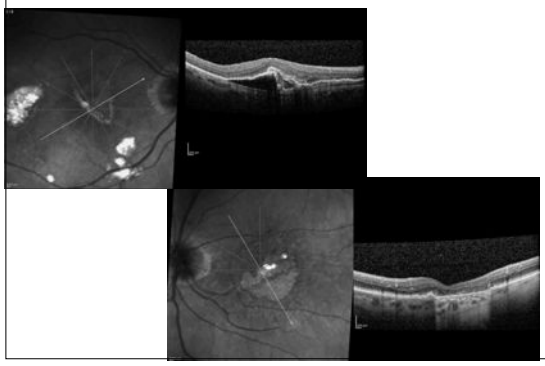
Ophthalmic Exam

- VA:
  - OD: 20/400 OS: 20/80
- IOP
  - OD: 11 OS: 12
- SLE:
  - OD: NS +1 OS: NS + 1
- DFE:
  - PED OD and Geo Atrophy OS

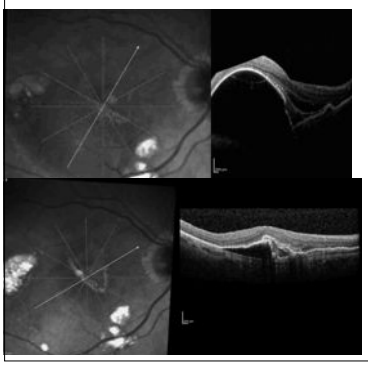
OCT



After Switching to Eyelea



Comparison



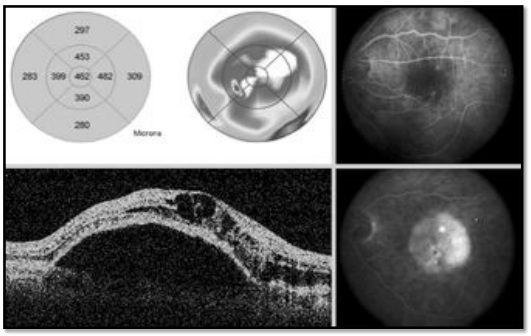
7 Years of Avastin and Lucentis

20/400

2 Injections of Eyelea

20/50

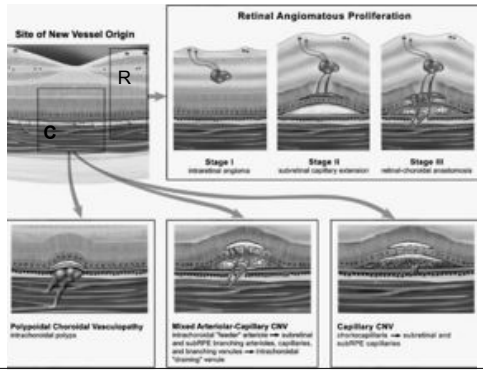
Another PED example



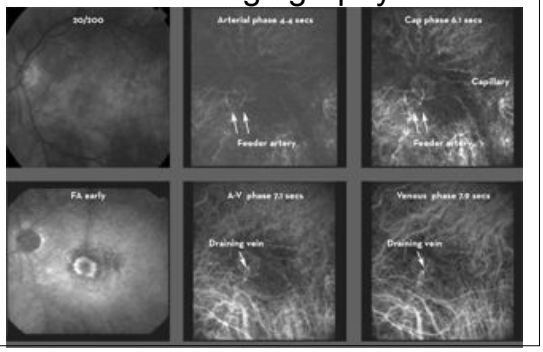
Variations and Masqueraders of CNV

- Polypoidal Choroidal Vasculopathy (PCV)
- Retinal Angiomatous Proliferation (RAP)
- Masqueraders of CNV
  - Choroidal Neoplastic Disease
  - Primary Tumors of the Choroid
    - Nevus vs. melanoma
  - Metastatic Tumors to the Choroid
    - Common primary sites
    - Breast
    - Lung
  - Central Serous Chorioretinopathy (CSC)

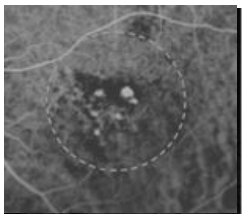
CNV Variants



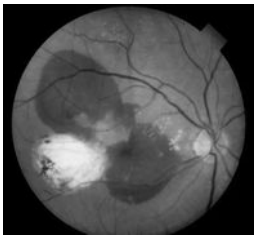
ICG Angiography



AMD vs PCV

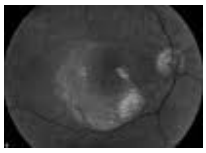
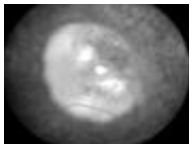


SUSPICIOUS POLYPOIDAL



AMD -SUBRETINAAL HEMORRHAGE

Retinal Angiomatous Proliferation

- Sub retinal neovascularization ensues.

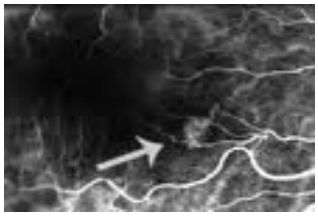
Retinal Angiomatous Proliferation

- First described by Yannuzzi in 1991, RAP is a retino-choridal anastamosis.
- Intraretinal capillary proliferation, which extends throughout the sensory retina and then into the sub retinal space.

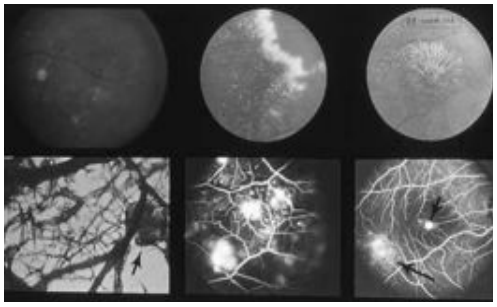
Retinal Angiomatous Proliferation

- 10-20 % of neovascular AMD patients start with RAP.
- The age group is thought to be slightly older.
- ICGA aids in confirming diagnosis, identifying "hot spots" of ICG dye pools in the sub retinal space.

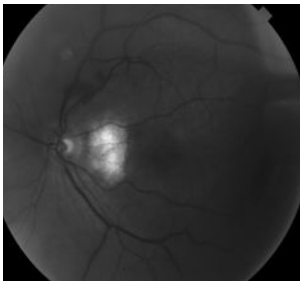
Retinal Angiomatous Proliferation "Hot Spot"

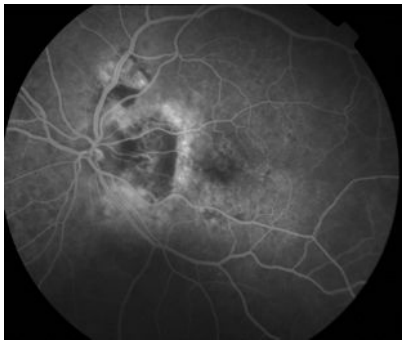


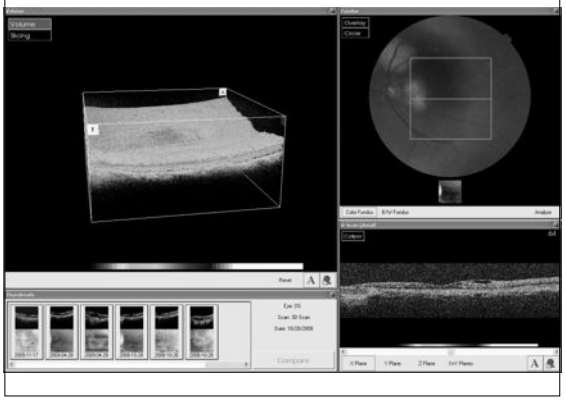
Retinal Angiomatous Proliferation

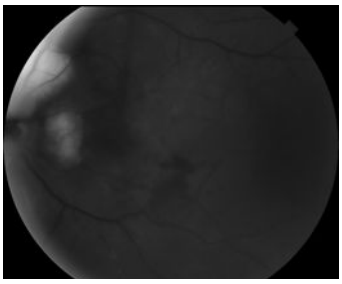


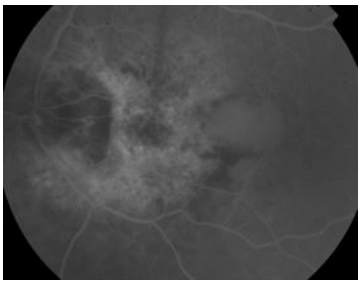
82 y/o WM w/drusen

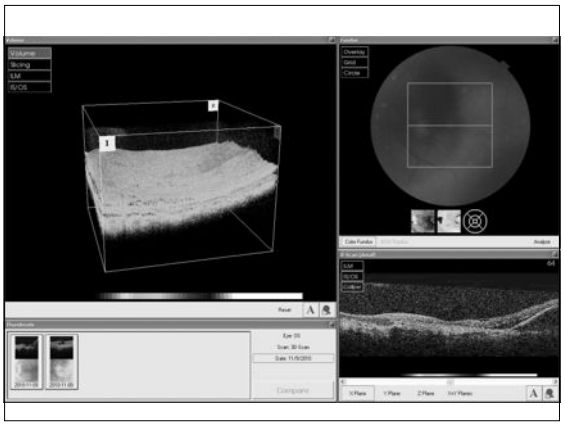


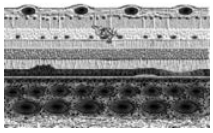




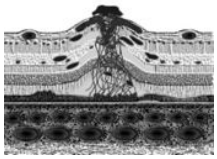




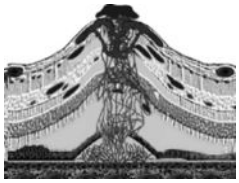




RAP Stage I: intraretinal neovascularization.



RAP Stage II: subretinal NV w/retinal-retinal anastomosis.



RAP Stage III: subretinal NV w/vascularized RPED and retina-choroid anastomosis.

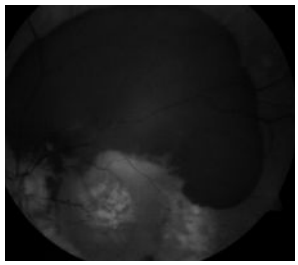
RAP: Current Treatment Options

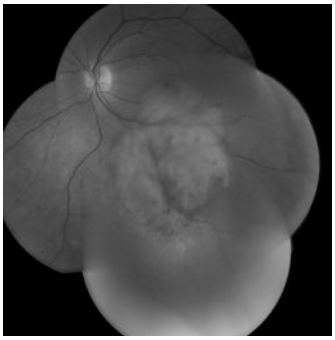
- Thermal Laser
- Photodynamic Therapy
- Anti VEGF Therapy

CNV Masquerador:

Neoplastic Disease

CNV or Mass?



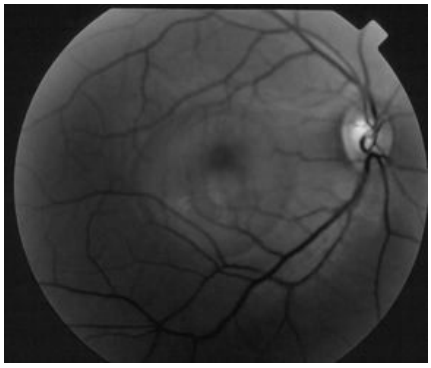


CNV Masquerador:

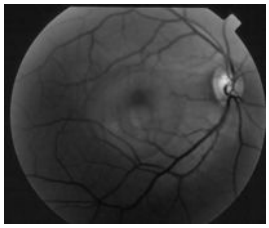
Central Serous
Chorioretinopathy

Mystery Macula

- Subjective
  - 35 y/o WM
  - sudden, unilateral blur OD
  - no pain or trauma
  - "Type A"
- Objective
  - VA
    - OD 20/60
    - OS 20/20
  - Hyperopic shift



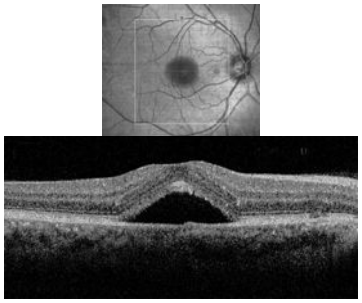
Describe That Fundus!

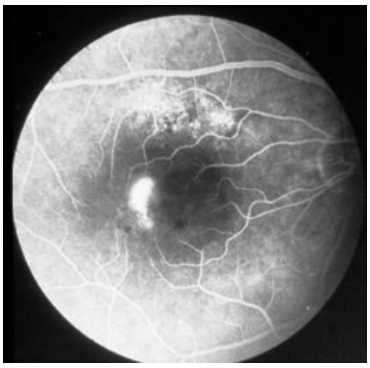


- DFE shows large, serous elevation
- Focal detachment of sensory retina

What other tests would you like to perform?

OCT

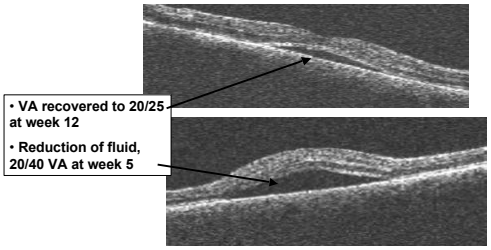




(Idiopathic) Central Serous Chorioretinopathy

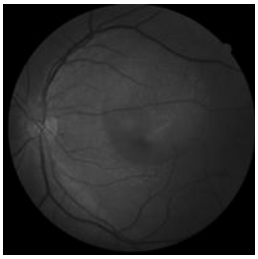
(ICSC)

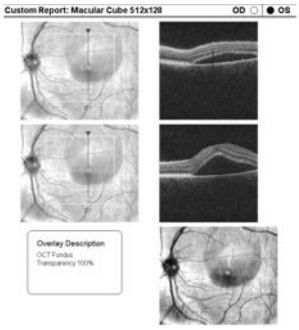
Patient Outcome



Central Serous Chorioretinopathy

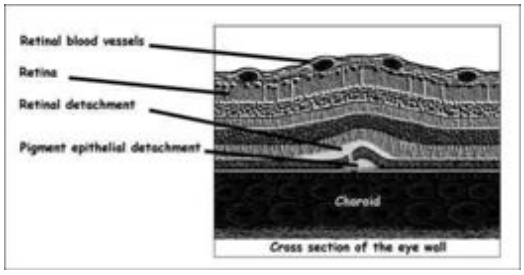
- 36 y/o WM
- CC: Sudden central blur OS
- VA OD 20/20
- VA OS 20/200



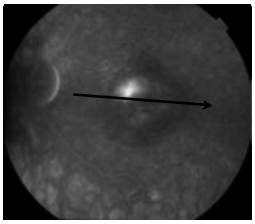


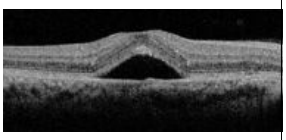
ICSC

- Objective
  - Breakdown of outer blood-retina barrier
  - FA shows classic "smoke-stack"
    - Pooling beneath RPE detachment
    - Dye ascends vertically, then laterally in SRS
- Differential Diagnosis
  - Tumor
  - RPE detachment/CNVM
  - Steroid-induced CSC



ICSC



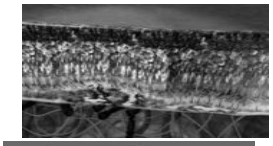


Plan

- Observation
  - 60% regain 20/20 w/no intervention
  - monitor q4wks for 6 mon
- Focal Laser
  - Unresolved after 4-6 mon
  - Recurrent
  - Focal, direct treatment
  - Leak must be outside FAZ (500 um)

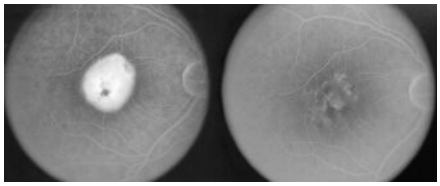
Treatments for CSC

- Thermal laser



- Photodynamic Therapy
  - Visudyne (Verteporfin)
  - A light-activated drug

Photodynamic Therapy for CSC

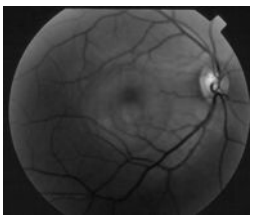


- Serous detachment before PDT.

Resolution of detachment with residual RPE mottling after PDT.

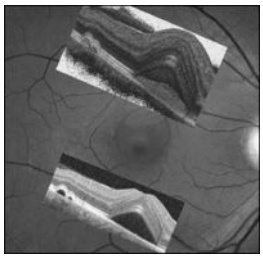
What's new in CSC Treatment?

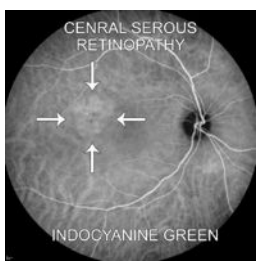
- Intravitreal bevacizumab (Avastin) has shown some benefit in small case series.



Low-fluence PDT

ICGA-guided, lower flow, lighter dosage resulted in less hypoperfusion of the choriocapillaris





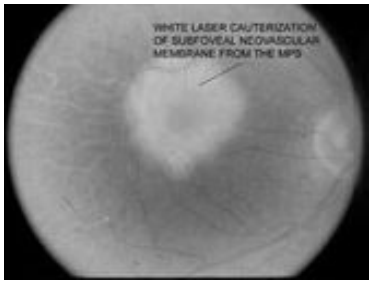
Current and Future Treatment of CNV

Laser

- Now reserved for extrafoveal disease
- Ectopic disciform
- Poylpoidal demarcation

Concern had been expressed over some practitioners of 'laser eye surgery'.

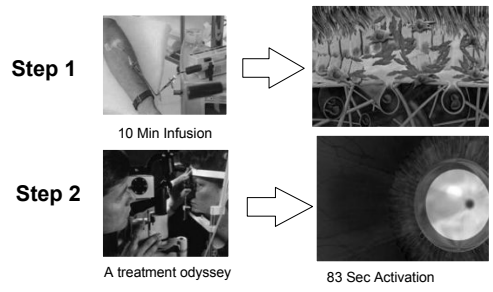
Limitations of Laser

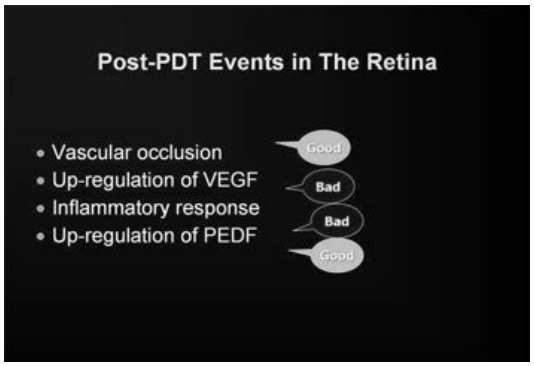


PDT

- Poylpoidal choroidal vasculopathy
- Used in conjunction with anti VEGF
- Cental Serous Chorioretinopathy

Photodynamic (Visudyne) Therapy: A 2-Step Process

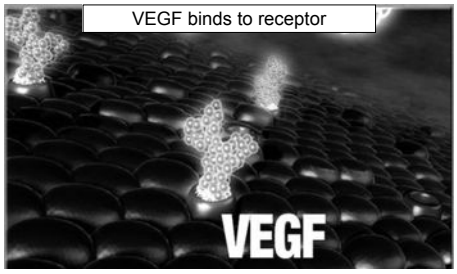




Vascular endothelial growth factor (VEGF)

- VEGF was found to be essential in normal and pathological angiogenesis.
- Hypoxia (ischemia) and inflammation induce secretion of VEGF.
- VEGF binds to its receptors, promoting endothelial cell migration and proliferation, which are required to develop new vessels.
- VEGF breaks down the blood retina barrier which increases vascular permeability (edema).
- Maximum expression of VEGF at border of vascular and avascular tissue.

Antiangiogenic Drugs: VEGF Inhibitors

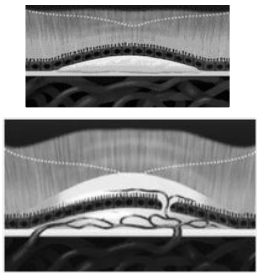


Anti VEGF

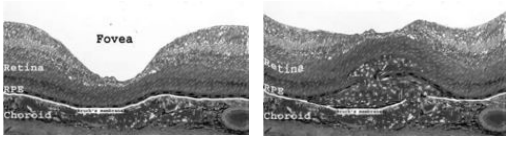
- The mainstay of CNV treatment at this point
- Requires intravitreal injection
- Post operative care

Pathogenesis of CNVM

- Breaks in Bruch's Theory
  - Diffuse thickening of Bruch's w/soft drusen
  - Predisposes Bruch's to breaks
  - New BV's from CC grow and proliferate



Wet AMD Pathology



Anti VEGF Treatment

- Concept of antiangiogenesis was first proposed by Judah Folkman as a cancer treatment
- The concept has been extended to ocular proliferative retinopathies
- Three anti-VEGF treatments currently being used (Avastin, Lucentis, Eyelea)

VEGF-A

- VEGF-A has 3 isoforms which differ in their solubility and receptor binding properties
- VEGF 121
- VEGF 188
- VEGF 165

VEGF Inhibition for Wet AMD

VEGF Inhibitors

- Pegaptanib sodium-***Macugen*** (Pfizer/Eyetech)
  - FDA Approved
  - *Aptamer (decoy):* inhibits protein activity
- Ranibizumab- ***Lucentis*** (Genentech) $2,000.00
  - FDA Approved
  - Antibody-based
  - Compared favorably to PDT in ANCHOR study
- Bevacizumab- ***Avastin*** (Genentech) $40.00
  - Off label
  - Anti-neoplastic
  - Intravitreal injection
  - 1 injection/mon x 3 mon

Pegaptanib

- Macugen (Pfizer)
- RNA aptamer (decoy) that binds the isoform VEGF 165
- Received FDA approval in December 2004 for treatment of neovascular macular degeneration
- First ocular VEGF therapy
  - Seldom used today

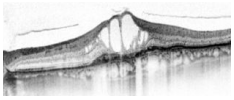
Ranibizumab

- Lucentis (Genetech, Inc.)
- Recombinant humanized monoclonal antibody fragment
- Low molecular weight for better retinal penetration
- Binds and inactivates all 3 isoforms of VEGF
- FDA approved in June 2006 for treatment of neovascular macular degeneration

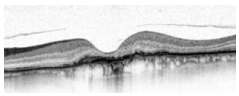
Bevacizumab

- Avastin (Genetech, Inc.)
- Full length humanized monoclonal antibody
- Binds all 3 isoforms of VEGF and inhibits its interaction with receptors on endothelial cells
- FDA approved for IV treatment of metastatic colorectal cancer in 2004
- Used off label for ocular neovascularization
- Less expensive than Lucentis
- Longer half life than Lucentis due to larger molecule weight

Pre and Post Avastin Treatment



VA 55 L



VA 78 L

Treatment Studies

- VISION => VEGF Inhibition Study in Ocular Neovascularization
- MARINA => Minimally Classic/Occult Trial of he Anti VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD
- ANCHOR => Anti VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD Study
- PrONTO; CATT (ongoing), SAILOR, and more

Intravitreal Injections for Wet AMD
Anti-VEGF Agents

Antiangiogenic therapy

- Pegaptanib (Macugen)
  - Dec 2004, for neovascular (wet) AMD
- Bevacizumab (Avastin)
  - For metastatic colorectal cancer
- Ranibizumab (Lucentis)
  - June 2006, for neovascular (wet) AMD

AMD = age-related macular degeneration; VEGF = vascular endothelial growth factor.

- Eylea (Regeneron)
  - Aflibercept intravitreal injection
  - Approved for CNV/AMD.
  - Binds all forms of Vascular Endothelial Growth Factor-A (VEGF-A) and Placental Growth Factor (PlGF).
  - Binds tightly to VEGF receptors
  - Rapid decrease in foveal thickening, improved visual function.

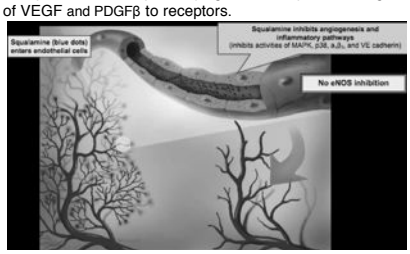
Wet AMD Treatments on the Horizon

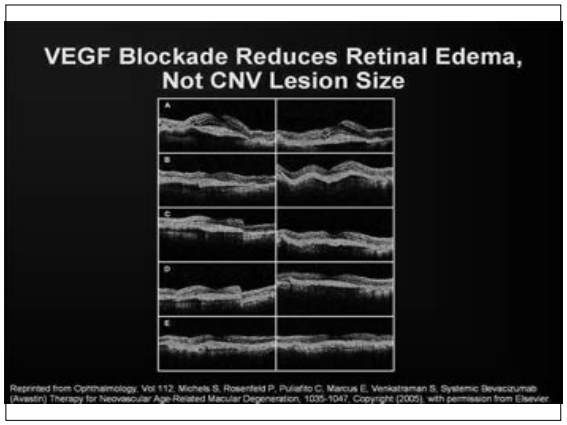
VEGF Inhibitors

- Squalamine lactate- ***Envizon*** (Genaera): Phase II
  - Isloated from dogfish shark tissue
  - Originally developed for oncology
  - Aminosterol
    - Inhibits plasma membrane ion channels
    - Blocks proliferation of endothelial cells
  - Administered Intravenously
    - Weekly x 4 wks
  - Small sample showed improved or stabilized VA
  - Low systemic toxicity
  - Topical drug delivery??

Squalamine lactate- ***Envizon*** (Genaera)

Squalamine works INSIDE endothelial cells to block multiple intracellular pathways generated by the binding of VEGF and PDGFβ to receptors.

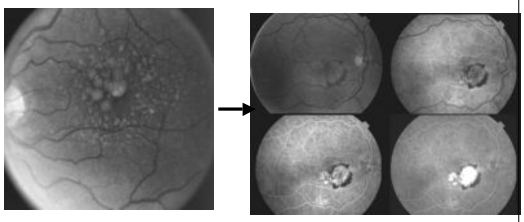




Fovista (Ophthotech)

- Anti-PDGF
  - Platelet derived GF
- To be used with Anti-VEGF
- Decreases size of CNV when used w/Lucentis
- Better efficacy than Lucentis alone
- No adverse events at 6 mon
- Phase 3 under way

Conversion to Exudative AMD



Can we prevent this?

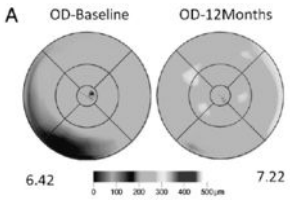
Dry AMD Treatments on the Horizon

Future Dry AMD Treatments?

- Neuroprotection
- Prevention of oxidative stress/damage
- Inflammation inhibition

Future Dry AMD Treatments?

- Ciliary neurotrophic factor (CNTF) delivered via intraocular encapsulated cell technology implant.
- CNTF retards PR loss.
- Right, an 84 y/o subject with GA.

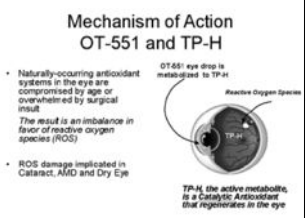


Future Dry AMD Treatments?

- Neuroprotection
- Prevention of oxidative stress/damage
- Inflammation inhibition

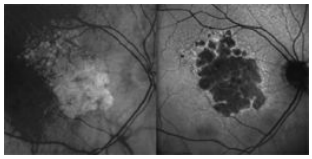
OT-551 (Othera)

- Topical Anti-
  - -oxidant
  - -inflammatory
  - -angiogenic
- Tested in combo w/L & Z



Future Dry AMD Treatments?

- Fenretinide po
  - Synthetic Vitamin A derivative
  - Reduces amount of lipofuscin accumulation



Future AMD Treatments

- Visual Cycle Modulation:
- ACU - 4429 (Acucela and Otsuka) - can modulate, slow down, the visual cycle. Oral drug targets the rod system by inhibiting a key enzyme. Does not affect the cones.
- Reduces the amount of A2E and lipofuscin accumulating in the RPE.
- Fenretinide aka RT-101 (Sirion Therapeutics) - reduces the amount of A2E and lipofuscin by modifying the visual cycle. Oral administration.

Future Dry AMD Treatments?

- Neuroprotection
- Prevention of oxidative stress/damage
- Inflammation inhibition

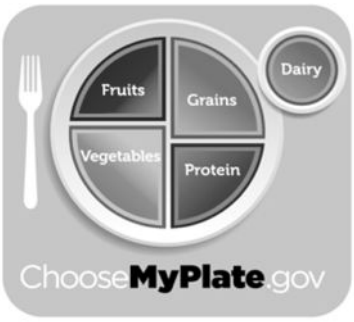
Future Dry AMD Treatments?

- Complement inhibition
  - Intravitreal (ARC 1905)
  - Sub-conj (Soliris)
- Toxic RNA (Alu RNA) inhibition
- Increase "Dicer" enzyme

Future AMD Treatments

- Complement Inhibition:
- POT-4 (Potentia Pharmaceuticals)
- Inhibits complement component C3. Single intravitreal injection
- Neuroprotection:
- NT-501 intraocular implant (Neurotech)
- Delivers human cells that have been genetically modified to secrete ciliary neurotrohic factor (CNTF).
  - CNTF is a neuroprotectant cytokine under investigation for neurodegenerative diseases like ALS.

A Nutritional Approach



AMD Risk Factors

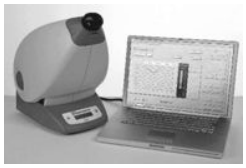
- **Age**
  - **Gender -** F > M
- **AMD Family History**
- **Smoking**
- **Iris Color -** lighter iris
- **Obesity**
- **CV Disease**
- **Poor nutrition**
- **Dietary and Serum Levels -** Complex analyses (most, but not all) show a relationship.
- **Low Macular Pigment**
- MPOD- Most (but not all) studies have shown reduced MPOD in AMD (by multiple measurement techniques).

Macular Pigment Optical Density (MPOD)

HFP

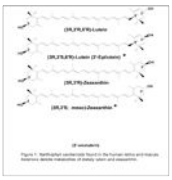
Risk assessment, early detection and monitoring of AMD

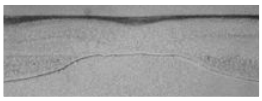
- Macular Pigment Optical Density
  - MPOD



Xanthophylls and AMD

- Lutein and zeaxanthin form the macular pigment
- Dietary sources include green leafy vegetables and orange-yellow fruits
- Act as antioxidants or light screening compounds





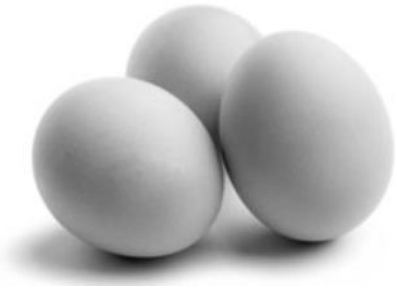
Macular Pigment Optical Density (du)

Low	Average	High
0.1- 0.25	0.25- 0.45	> 0.45

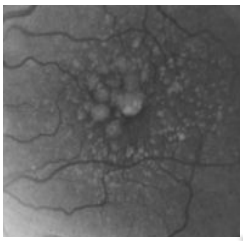
Lutein

Zeaxanthin

Dietary Lutein and Zeaxanthin: Eggs



AREDS 1 and 2

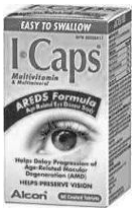


Daily Dosage in AREDS 1

Supplements were manufactured to have the following minimum contents:

Supplement	Dosage
Antioxidants	
Beta-carotene	15 mg
Vitamin C	500 mg
Vitamin E	400 IU
Essential Trace Elements	
Copper	2 mg
Zinc	80 mg

AREDS 1



AREDS Grading Scale

1. No drusen or a few small drusen.
2. Pigment abnormalities or non-extensive small or intermediate drusen.
3. Extensive intermediate drusen or any large drusen or non-central atrophy.
4. Good acuity and no advanced AMD in the study eye. Advanced AMD in the fellow eye (choroidal neovacularization or geographic atrophy).

"AREDS 1 resulted in a formulation of vitamin C, beta carotene, zinc, and vitamin E that reduced the risk of progression of advanced disease by 25%" at 5 years."

Emily Chew, MD, from the National Eye Institute in Bethesda, Maryland,

AREDS 2: NEI Trial Overview

Feature	Description
Objective	To evaluate the effect of high-dose vitamin supplementation on age-related macular degeneration (AMD) progression and visual acuity.
Design	Double-masked, randomized, placebo-controlled trial
Population	3640 high risk patients (55-80 years)
Duration	6.3 years supplementation and follow up

A AREDS report no. 8. *Arch Ophthalmol* 2001.119(10): 1417-36.

AREDS 2

- **Lutein (10mg)**
- **Zeaxanthin (2mg)**
- **Omega-3 fatty acids (350 mg DHA, 650 mg EPA)**
- **With and without β-carotene (15 mg vs 0 mg)**
- **High vs low zinc levels (80mg vs 25mg)**

Lutein/Zeaxanthin

- Antioxidant activity
  - **Prevent free radical damage in the retina**
  - More effective than Beta-carotene
- Filter blue light
  - Most damaging type of light due to it short wavelength
- Selectively binds to tubulin
  - Improves structure integrity
  - Maintains eye health and quality of vision

AREDS 2

Multi-center, multi-factorial, randomized, control-group trial.

AREDS 2

- Lutein/Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration. The Age-Related Eye Disease Study 2 (AREDS2) Controlled Randomized Clinical Trial. AREDS2 Research Group. JAMA, May 5, 2013 Online.
- Lutein/Zeaxanthin for the Treatment of Age-Related Cataract. AREDS2 Research Group. JAMA Ophthalmology, May 5, 2013 Online.

AREDS 2 2006-2012

4203 participants aged 50 to 85
with bilateral large drusen
or
large drusen in 1 eye and
advanced AMD in the fellow eye.

AREDS 2: Purpose

- To determine if adding lutein/zeaxanthin, omega-3s, or a combination could improve upon the positive results found in the AREDS 1.
- To evaluate the effect of eliminating beta carotene, lowering zinc, or both.

AREDS 2 Design

- 4203 participants were randomized to placebo with no additional supplementation or to 1 of 3 treatment groups:
  - Group 1 tablet w/10 mg L + 2 mg Z
  - Group 2 gel cap w/350 mg DHA + 650 mg EPA
  - Group 3 both the tablet and gel cap
- On a daily basis

AREDS 2: Primary Study Outcome

- An additional 25% decrease in the risk of progression to advanced AMD in the three treatment groups over the study subjects taking the original AREDS1 supplement.

Study Subjects: AREDS 1 vs AREDS 2

- All stages of AMD
- Average age = 69
- 67% took Centrum (no L)
- Varied diets
- Varied serum L and Z

- More advanced stage
- average age = 74
- 89% taking Centrum Silver (w/minimal L)
- diet high in carotenoids and vegetables
- higher serum L and Z

These differences could impact the ability to detect a more significant reduction in progression!

AREDS 2 First Results

"In the overall analysis, using 3 treatment groups, we found no significant difference in rates of macular degeneration," Dr. Chew said.

AREDS 2 Sub-group Analysis

- 10% reduction in progression to advanced AMD w/L & Z compared to no L&Z
- 18% reduction in progression in subjects who received L&Z + AREDS 1 supplement (without beta carotene) compared to those who took the original AREDS 1 supplement with beta carotene
- 26% reduction in progression in the participants taking L&Z that were in the lowest quintile of dietary L&Z intake

AREDS 2 Conclusions: First, the Bad News

- Overall, the addition of 10 mg L and 2 mg Z, 1g DHA + EPA, or both to the AREDS formulation did not further reduce risk of progression to advanced AMD.

AREDS 2 Conclusions

- Results reaffirm previous epidemiological data that high dietary intakes of L&Z reduce the risk of AMD.
- Results support the safety and treatment benefits of substituting 10 mg L and 2 mg Z for beta carotene in AREDS formulations.

What about omega-3 EFAs?

- Fish oil supplement did not significantly alter the progression of AMD in AREDS 2.

AREDS 2 Limitations

- A greater reduction in AMD progression may have been demonstrated if the subject's diet had been more representative to that of the general US population.
- Inability to determine if the null findings are attributable to lack of efficacy of the supplements, inadequate dosing, inadequate Tx. duration, or a combination of these.

Conclusions

- Choroidal Neovascularization (CNV) is a leading cause of vision impairment worldwide.
- An understanding of the functional anatomy of the posterior segment is essential in understanding CNV.
- CNV has several causes, variants, and masqueraders.
- Early diagnosis of CNV enables early treatment with today's effective therapies, thereby preserving visual function.

Thank you!

Carlo and Joe

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