Macular Degeneration

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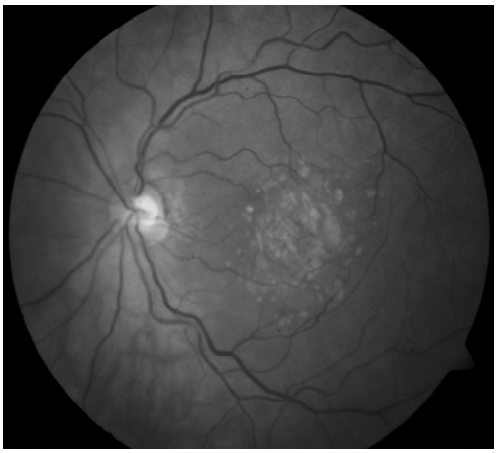
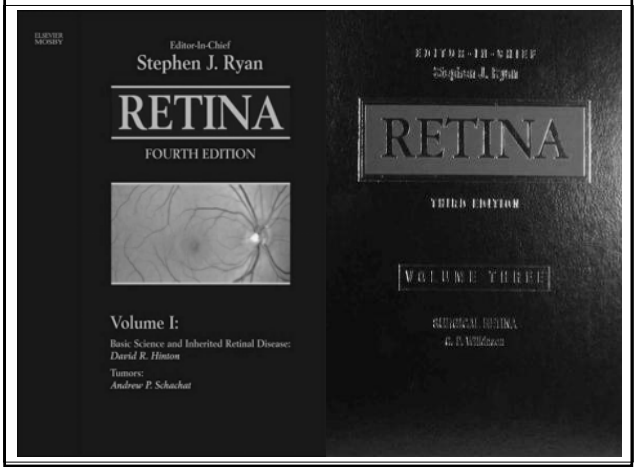
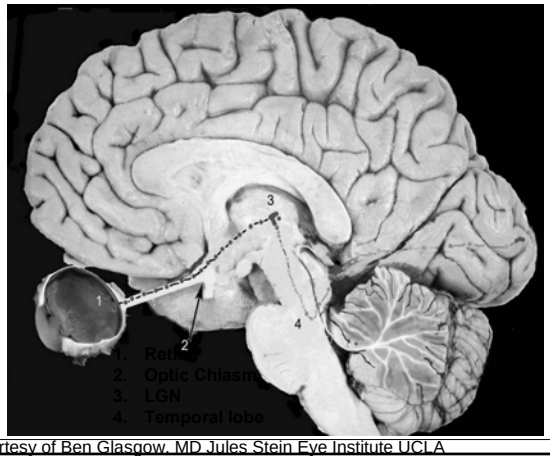
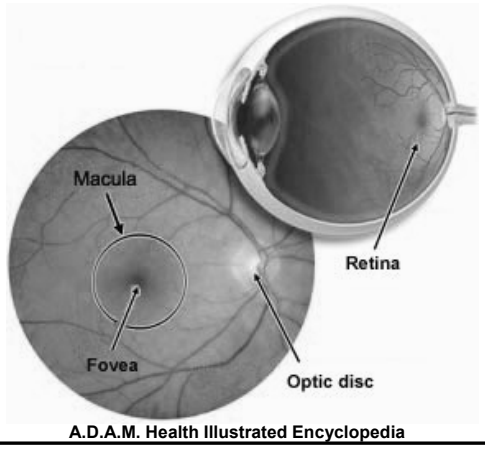






Courtesy of Ben Glasgow, MD Jules Stein Eye Institute UCLA



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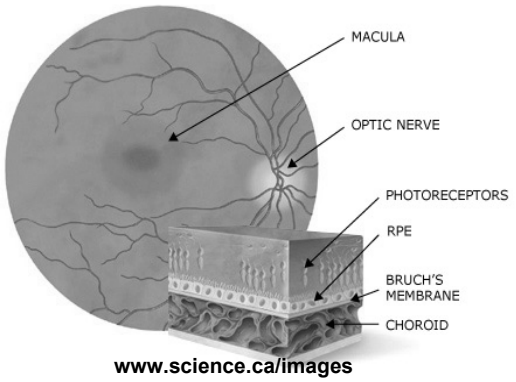

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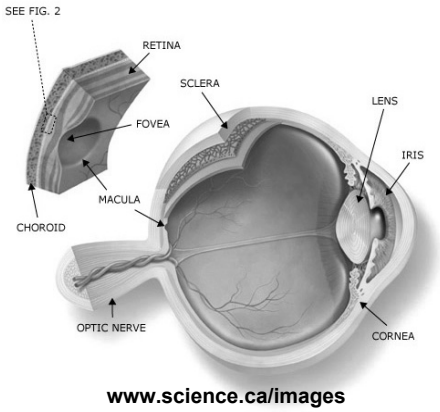

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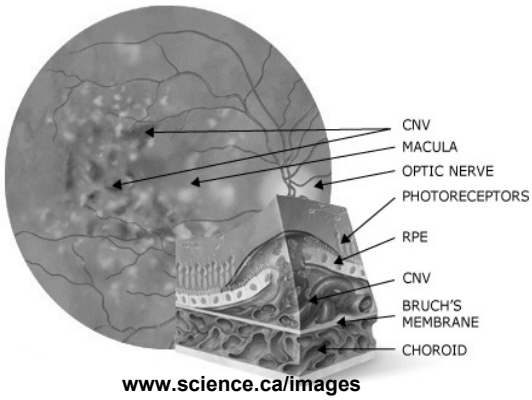

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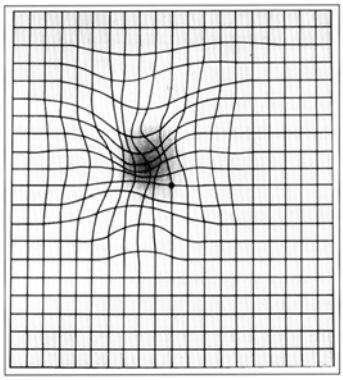
Dry Macular Degeneration (Non-neovascular AMD)

- Aging and thinning of macular tissue with pigmentary changes in the macula
- Gradual loss of central vision may occur but is usually not as severe as the symptoms associated with wet AMD

Courtesy of National Eye Institute

Courtesy of National Eye Institute

Amsler Grid



Epidemiology of AMD in USA

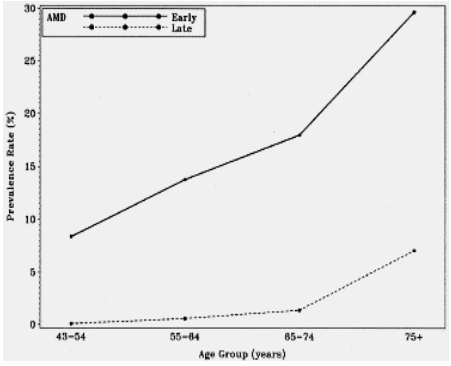
- With aging of population AMD is reaching epidemic proportions.
- Currently
  - ✓ Accounts for 16% of all causes of blindness
  - ✓ 7.3 million with some form of AMD
  - ✓ 1.75 million with wet or advanced AMD
  - ✓ Annual direct cost of AMD in USA estimated at $10 billion
- Projection for 2020
  - ✓ 2.95 million with wet or advanced AMD

(Venkataraman K et al. *Invest Ophthalmol Vis Sci* E-Abstract 3089 2003)
The Eye Diseases Prevalence Research Group *Arch Ophthalmol* 122: 564-572 2004

Risk Factors

1. Age
   - ✓ Advanced AMD: 60s- <1%
     90s- 15%
2. Female gender
3. Caucasian, Oriental Race more likely to progress to neovascular AMD
4. Smoking (>10 pack-years)
   - ✓ Directly related with 15% of cases
   - ✓ Living with a smoker doubles risk of developing AMD

Prevalence of all (dry and wet) AMD by Age Group



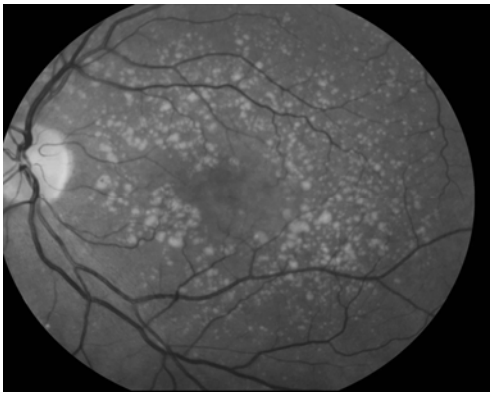
Klein R et al. *Amer J Ophthalmol* 137 (3): 486-95 2004

Risk Factors

5. Positive family history
6. Hypertension
7. Obesity and Inactivity-higher BMI more than double risk compared with vigourous activity 3x/week
8. Inflammatory biomarkers
   - ✓ C-reactive protein, interleukin 6
   - ✓ Complement Factor H variant

Not Risk Factors

- Light Eye Color
- People age 60 and over with no AMD have very low risk for developing AMD progression after 10 years of follow-up



Components of Dry AMD

1. Soft drusen
2. RPE hyperpigmentation
3. RPE hypopigmentation/atrophy
4. Geographic atrophy

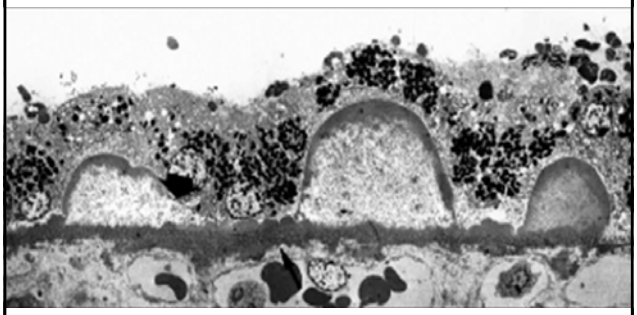
Soft Drusen

- Yellow deposits which lie under the RPE within Bruch's membrane
- Represent accumulated waste products from outer retinal layers
- A marker for macular degeneration
- There is increased risk for developing AMD as the number of drusen increases

Normal

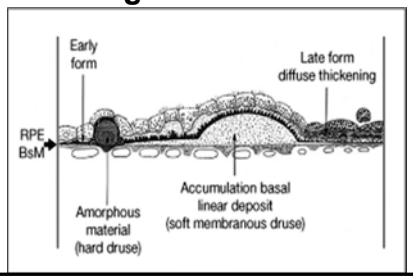
Drusen

Hard Drusen

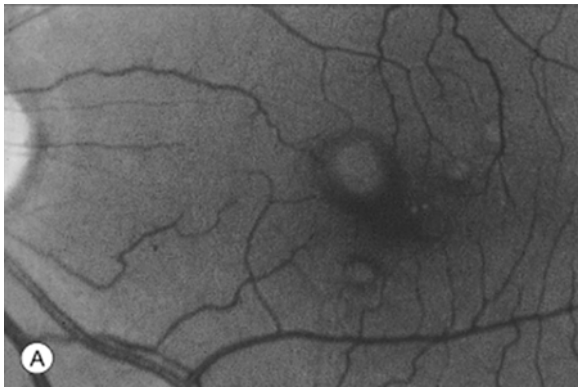


Hard Drusen

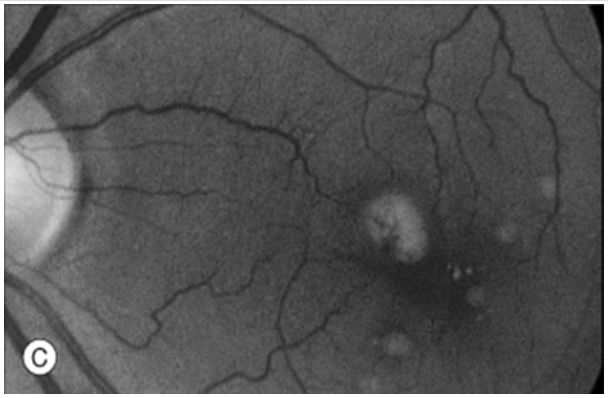
- **Small in size (<63 microns), not part of AMD definition because a constant retinal finding after 5th decade**



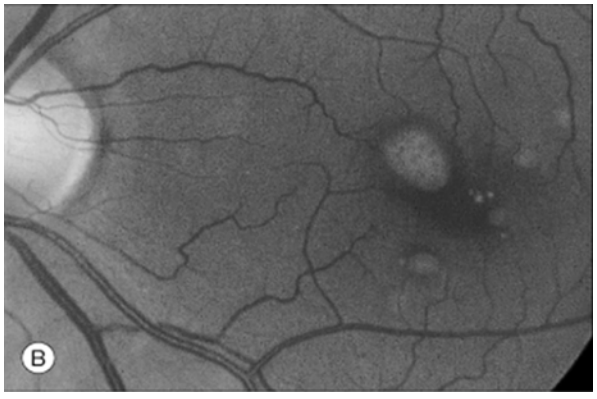
Soft Drusen



Age 48



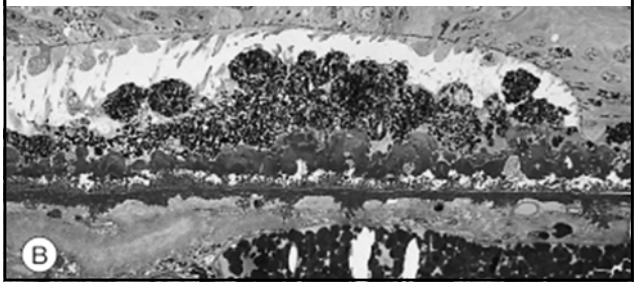
Age 57

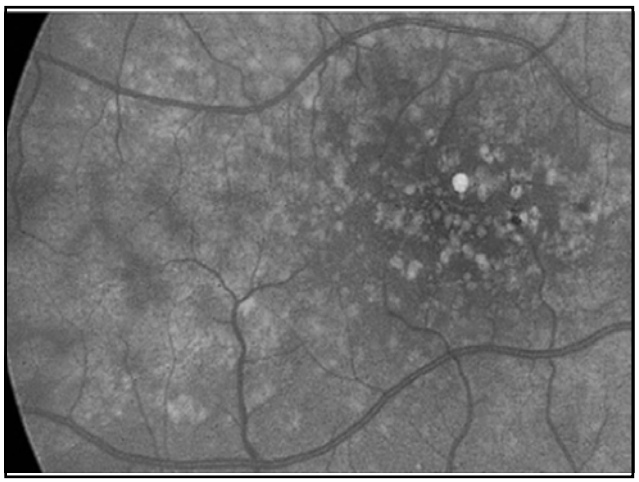


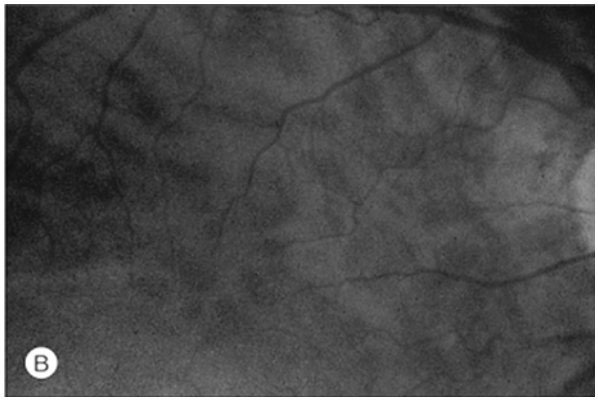
Age 52

RPE Hyperpigmentation

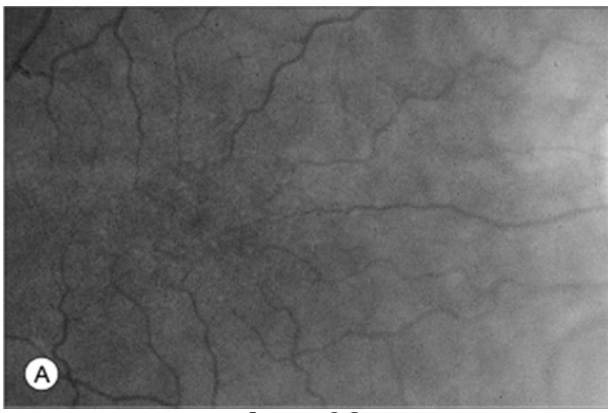
- Pigment clumping within the retinal pigment epithelium



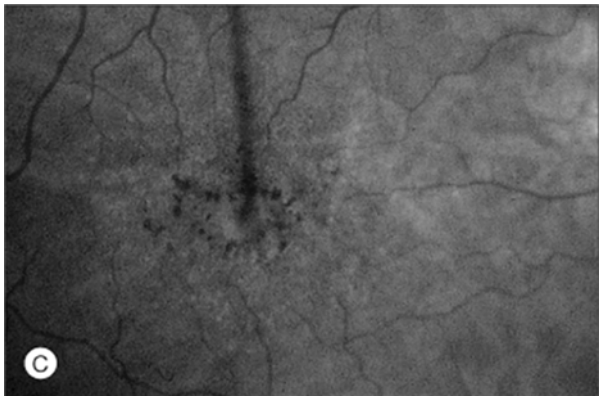




Age 73



Age 68



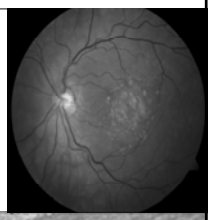
Age 77

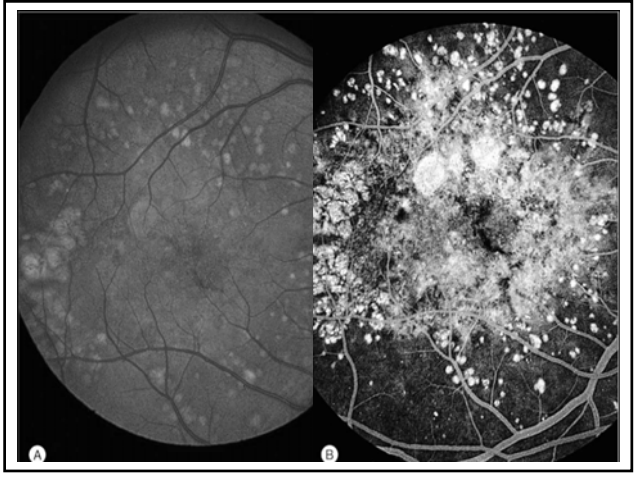
RPE Hypopigmentation

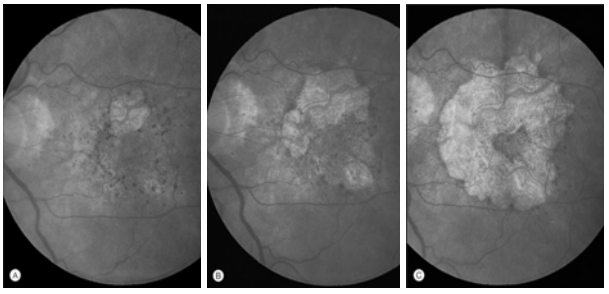
•Atrophy of the retinal pigment epithelium

Geographic Atrophy

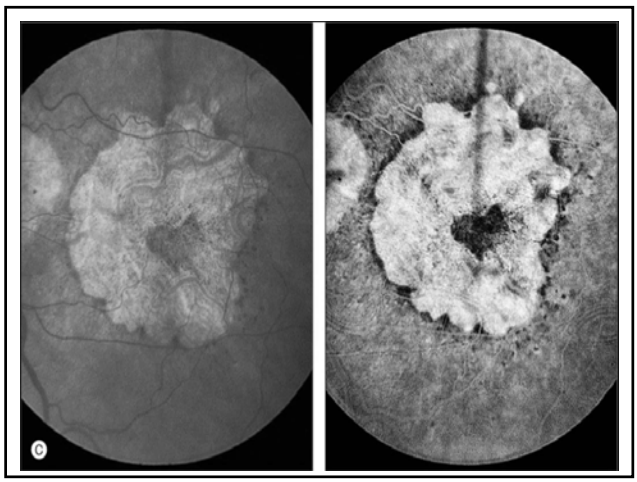
- Sharply delineated area of hypo- or depigmentation with absence of the RPE





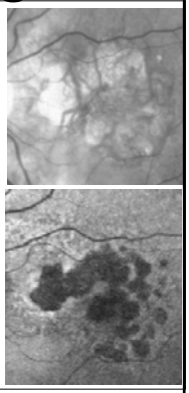


Age 68 20/25 **Age 69 20/30** **Age 73 20/80**



FAF Imaging

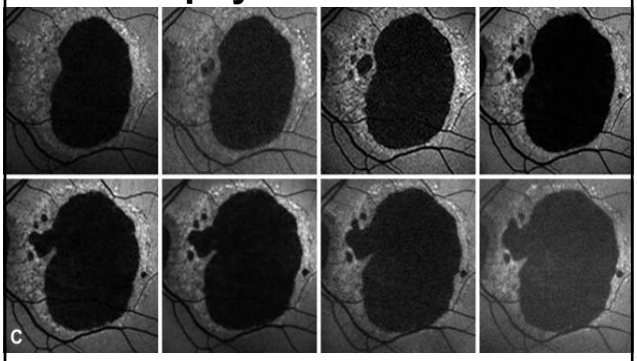
- Permits mapping of atrophic changes as well as lipofuscin accumulation in the RPE layer
- Lipofuscin in RPE cells represents a common pathogenetic pathway for various retinal dystrophies and degenerations including AMD
- FAF RPE lesion characteristics and their progression has prognostic implications



Schmitz-Valckenber S, Holz F et al. *Survey of Ophthalmol* 54 (1): 96-117 2009

FUNDUS AUTOFLUORESCENCE (FAF)

Progression of Geographic Atrophy Over 6.5 Years



Schmitz-Valckenber S, Holz F et al. *Survey of Ophthalmol* 54 (1): 96-117 2009

Definition of Early Age-Related Maculopathy

1. Age >50
2. Soft drusen (>63 microns). Those with indistinct margins, drusen >125 microns are more significant
3. Areas of RPE hyperpigmentation associated with drusen
4. Areas of RPE hypopigmentation associated with drusen

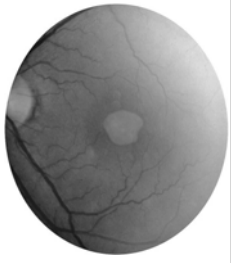
Differential Diagnosis of Dry Macular Degeneration

Not in Definition of Early Age-Related Maculopathy

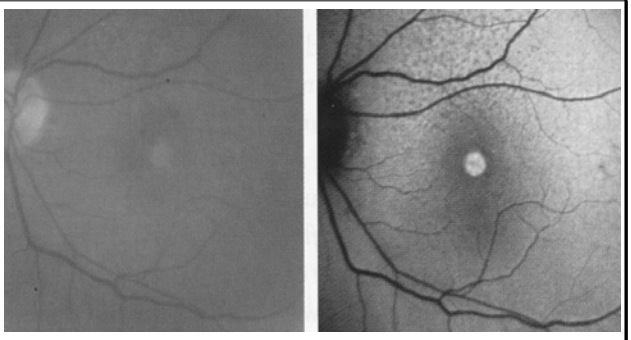
- Visual acuity since advanced changes may be present without affecting visual acuity
- Small hard drusen (<63 microns) since a constant finding after 5th decade
- Pigmentary changes unassociated with drusen since other processes can cause these

Foveomacular Pattern Dystrophy (Adult Vitelliform)

- Autosomal dominant
- Bilateral and symmetric
- Very slowly progressive
- Age of onset of symptoms is between 30-50 years
- Excellent visual prognosis (VA: 20/20 to 20/40)



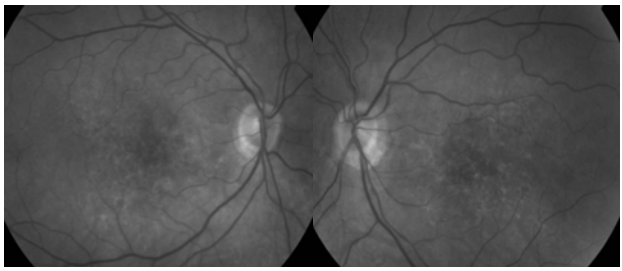
Autofluorescence



Central Hyperfluorescent Lesion

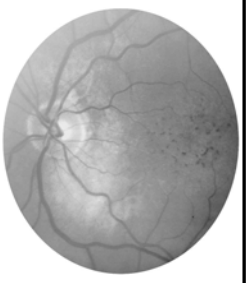
HolzFG et al. *Atlas of Fundus Autofluorescence Imaging*, p. 91 2007 Springer

- **62 YOF with VA: 20/25 OU**
  - ✓**Had been diagnosed with dry AMD for previous 10 years but wanted a second opinion**

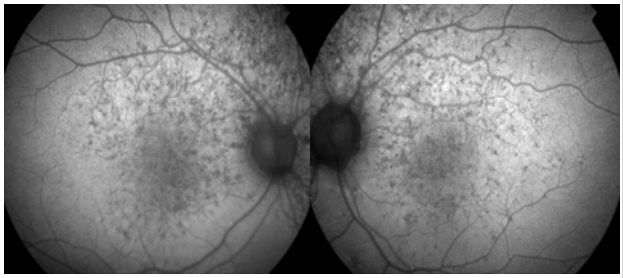


RPE Pattern Dystrophy

- **Autosomal dominant**
- **Bilateral and symmetric**
- **Very slowly progressive**
- **Age of onset of symptoms is between 30-50 years**
- **Excellent visual prognosis (VA: 20/20 to 20/40)**

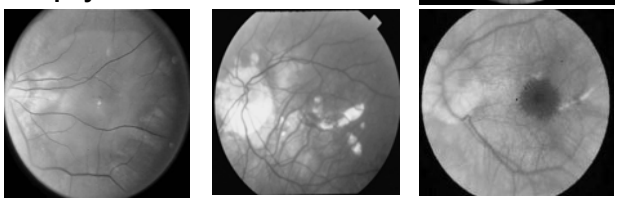


Autofluorescence



MYOPIC DEGENERATION

- Progressive elongation of the eye with thinning of choroid and RPE
- High myopia: >-6.00 D
- Often excellent acuity despite extensive chorioretinal atrophy

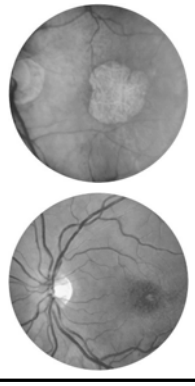


Therapeutic Strategies for Dry AMD

- Since retinal cells are neural cells, we can't substitute them
- Therefore, currently our best therapeutic strategy is to maintain the available retinal cells in a healthy state
- Antioxidant vitamins and zinc have previously shown promise in retarding AMD progression in several pilot trials

CENTRAL AREOLAR CHOROIDAL DYSTROPHY (CACD)

- Autosomal dominant
- Bilateral and symmetric
- Slowly progressive
- Age of onset: 2nd-4th decades
- Central vision affected 4th-5th decades
- VA: 20/100-20/200 by 7th to 8th decades



AREDS

National Eye Institute
NATIONAL INSTITUTES OF HEALTH

AREDS

Age-Related Eye Disease Study

Goals

- Clinical Trial
  - ✓ To evaluate the effects of nutritional supplements on the progression of both AMD and cataract

AREDS

- Took 2 tablets twice a day
- Followed an average of 6.7 years
- Randomly assigned to 1 of 4 different treatment groups

AREDS

- 4757 participants (Sept 1990-Jan 1998)
- Largest randomized clinical eye trial ever conducted
- Findings have had an enormous public health impact on the treatment of dry AMD globally

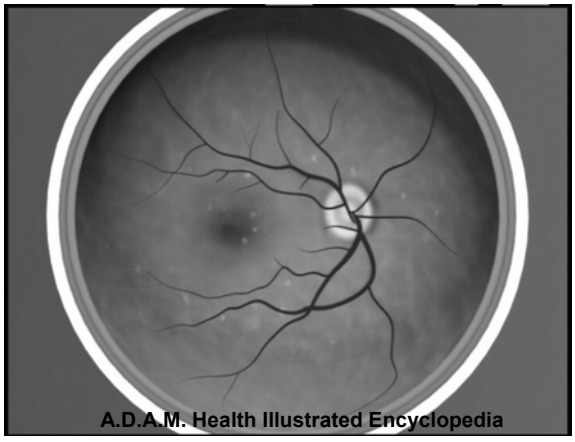
The Treatment Groups

1. Zinc and copper alone (copper used since high zinc levels can cause Cu deficiency)
2. Antioxidants alone: b-carotene (vitamin A), Vitamins C and E
3. Combination of antioxidants and zinc
4. Placebo (a look-a-like pill that had no active ingredient)

Supplement Facts

Serving Size 2 Capsules
Servings Per Container 30

	Amount Per Serving	%Daily Value
Vitamin A	25,000 IU	500%
(100% as beta-carotene)	15 mg	
Vitamin C (ascorbic acid)	500 mg	833%
Vitamin E (d-alpha tocopheryl succinate)	400 IU	1333%
Zinc (zinc oxide)	80 mg	533%
Copper (cupric oxide)	2 mg	100%



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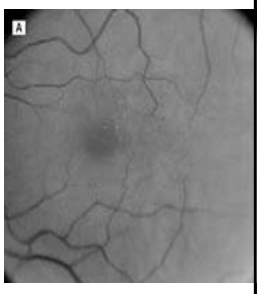
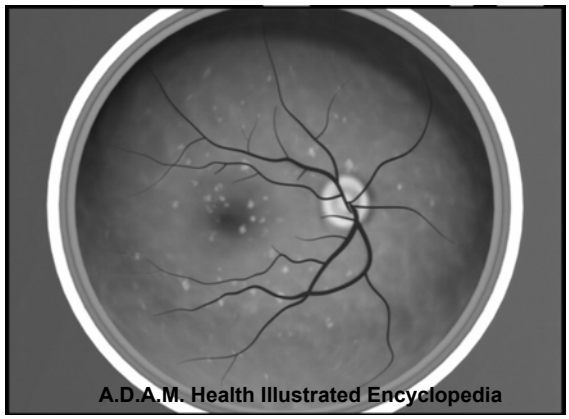
Category 1 – No AMD

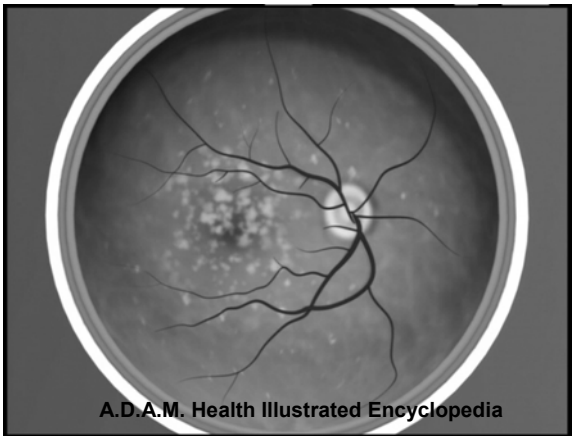
- **These participants had no drusen or only a few small drusen (<63 microns) in one or both eyes**

Category 2 – Early AMD

- **These participants had several small drusen or a few medium-sized drusen (63-125 microns), in one or both eyes**

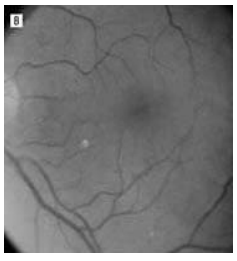






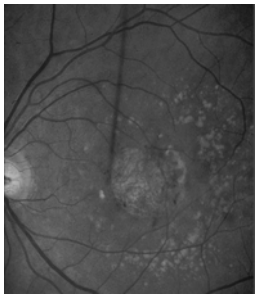
Category 3 – Intermediate AMD

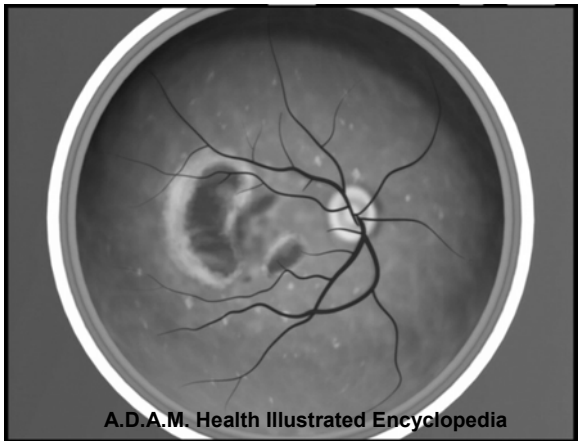
- These participants had many medium drusen or one or more large drusen (>125 microns), or areas of atrophy (thinning) of the tissue outside the central macula in one or both eyes



Category 4 – Advanced Unilateral AMD

- These patients had
  - ✓Geographic atrophy involving macula center
  - ✓Neovascular AMD in one eye





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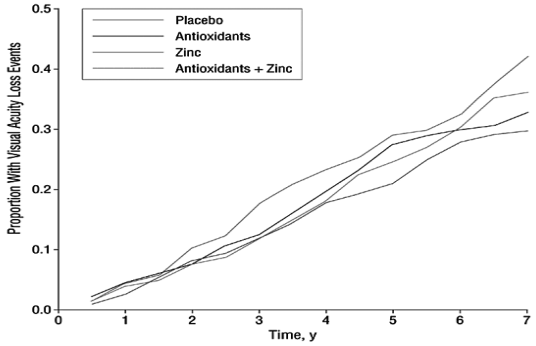
Chances of Developing Advanced AMD

- Category 2 (Early AMD), less than 2%
- Category 3 (Intermediate AMD), 18%
- Category 4 (Advanced AMD one eye), 43%

5 Year Results

Proportion of Participants with Loss of 15 or More Letters in At Least 1 Study Eye in Categories 3 and 4



AREDS Report no. 8 *Arch Ophthalmol* 119 (10):1417-36 2001

Conclusions of AREDS

- Early AMD-No benefit of Rx, observe
- Intermediate or advanced AMD: recommend AREDS supplements

Other General Recommendations:

- Stop smoking
- Control hypertension
- Wear ultraviolet lens protection
- Amsler grid self-testing

After Cataract Surgery

- AREDS did not show
  - ✓ Increased risk of developing wet AMD
  - ✓ Development of geographic atrophy

Side Effects of Vitamins

- Beta-carotene
  - ✓ Yellowing of skin
  - ✓ Increased risk of death in smokers
  - ✓ High levels may lead to osteoporosis
- Zinc
  - ✓ Genitourinary problems requiring hospitalization-UTI, stress incontinence and prostatic hyperplasia (7.5% vs 5%)
  - ✓ Anemia (13% vs 11% not taking Zn)
- Vitamin E
  - ✓ Avoid if on anticoagulants or bleeding diathesis

Supplement Comparisons

	Ocuvite PreserVision /ICaps (4/day)	PreserVision Lutein GelCaps (2/day)	Ocular Nutrition (4/day)	Ocuvite with Lutein (1/day)	Centrum Silver (1/day)
Vitamin A	28,640	None	20,000	1,000	5000
Vitamin C	452 mg	452 mg	1200 mg	200 mg	60 mg
Vitamin E	400 IU	400 IU	440 IU	60 IU	45 IU
Zinc	69.6 mg	69.6 mg	60 mg	40 mg	15 mg
Copper	1.6 mg	1.6 mg	None	2 mg	2 mg
Lutein*	None	10 mg	10 mg	2 mg	0.25 mg

AREDS 2
Age-Related Eye Disease Study 2

AREDS 2 Trial

Retinal Xanthophylls: Lutein and Zeoxanthin

- Lutein represents 36%, zeoxanthin 18% of natural caretenoids in the macula
- Not used in AREDS I since they were not readily available for research formulation at the time
- Shown to protect against progression of AMD in 5/6 pilot studies

Goals

1. Evaluate the effects of dietary xanthophylls and omega-3 fatty acids on the development of advanced AMD
2. Study the effects of eliminating beta-carotene in the original AREDS formula on AMD development and progression
3. Study the effects of reducing zinc in the original AREDS formula on AMD development and progression
4. Study the effects on cataract and moderate visual loss

Highest Dietary Sources of Lutein and Zeaxanthin

- Kale
  Collard Greens
  Orange peppers
  Spinach
  Fresh parsley
  Orange Juice
  Egg yolk
  Various squash
  Kiwi
  Zucchini
  Mustard greens
  Grapes
- *In general, the most colorful fruits (dark green, orange, yellow) have the highest caretonoids

Omega-3 Fatty Acids: Docosahexaenoic acid (DHA) Eicosapentaenoic acid (EPA)

- AREDS found an association between greater fish intake and 40% reduced AMD progression
- Mouse retinopathy model
  - ✓ Mice on omega-3-rich diet had 40-50% decrease in pathologic vessel growth

AREDS 2 Clinical Trial

- 4,000 participants
- Recruitment completed on June 30, 2008
- 5-year follow-up

Highest Dietary Sources of Omega-3 Fatty acids

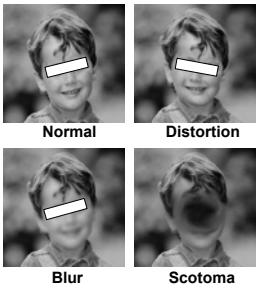
- Wild salmon
- Herring
- Mackerel
- Anchovies
- Sardines
- Fish oil supplements

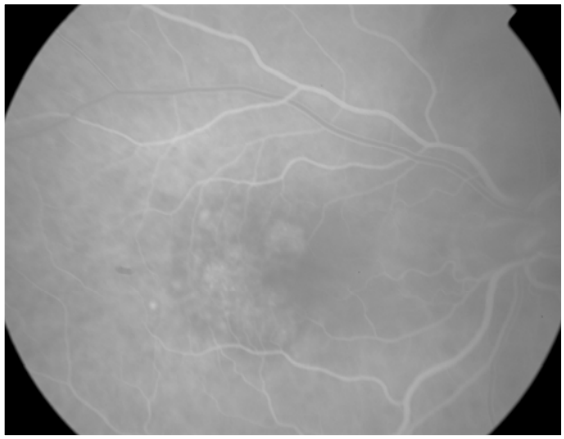
Wet AMD

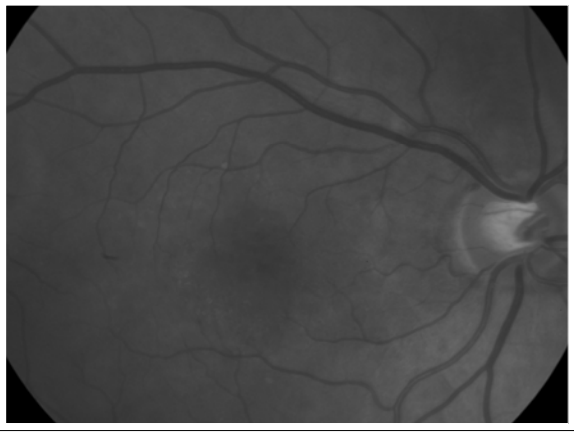
- Neovascular (wet) AMD:
  - ✓ Leading cause of vision loss in elderly
- Choroidal neovascularization (CNV)
- Vascular leakage
- Progressive loss of central vision
- 10% have wet AMD
- 153,000 new advanced cases each year in US
  - ✓ Advanced: geographic atrophy, Neovascularization

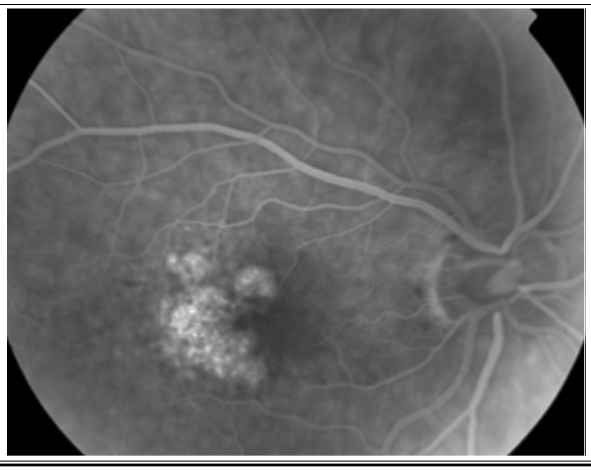
Wet AMD

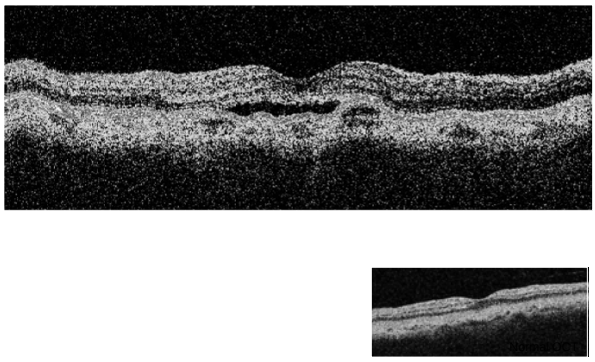
- Symptoms
  - ✓ Blurred vision
  - ✓ Scotoma
  - ✓ Metamorphopsia
  - ✓ Micropsia
  - ✓ Dyschromatopsia

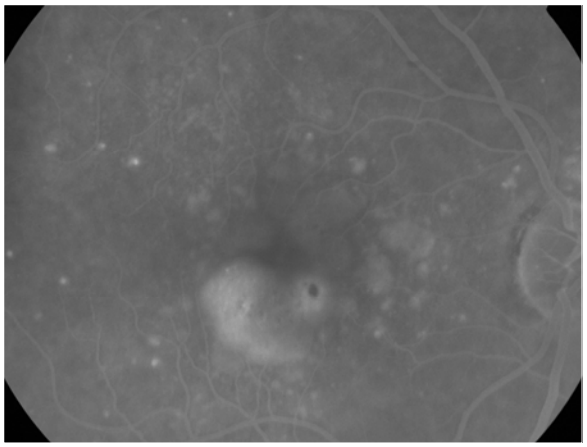


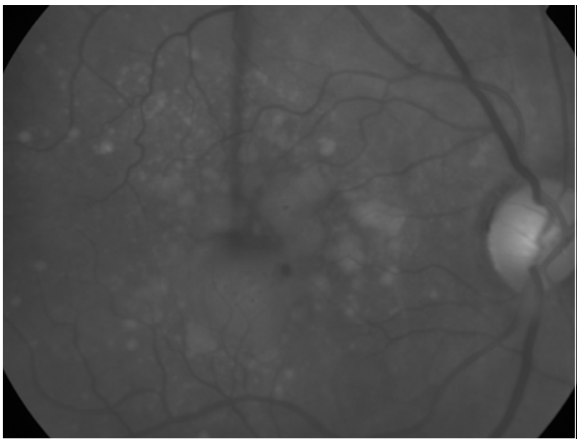


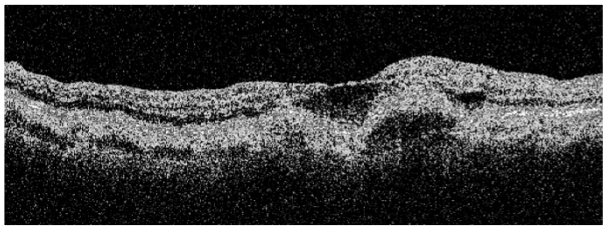


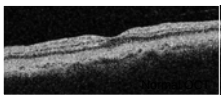


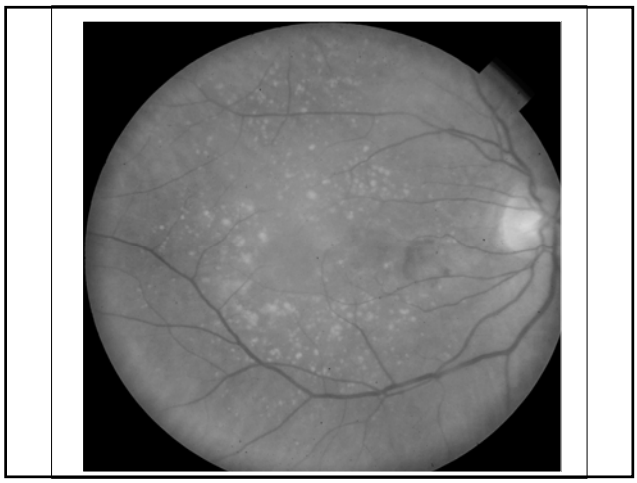


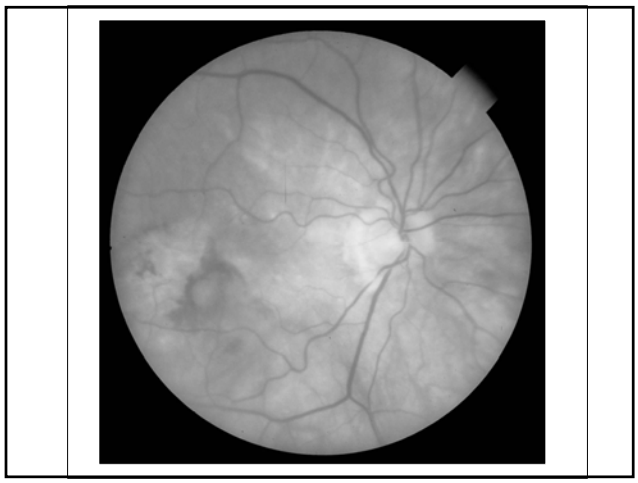


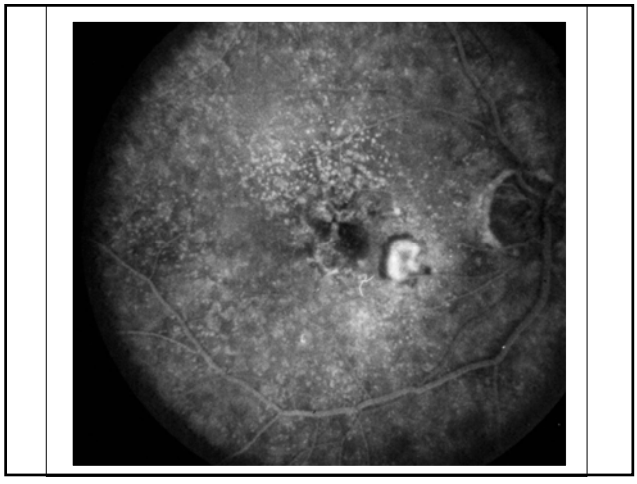


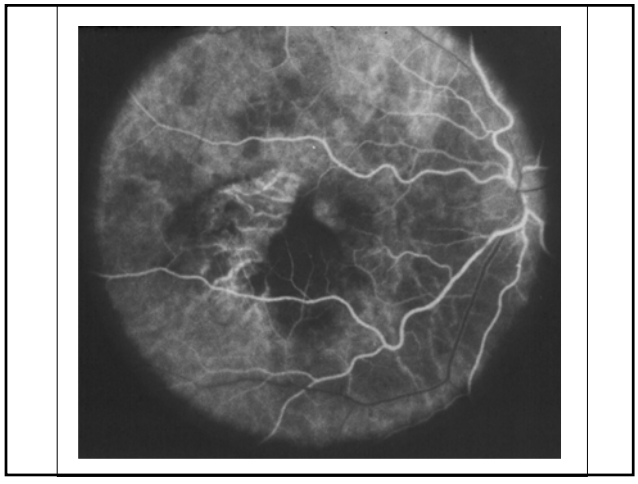


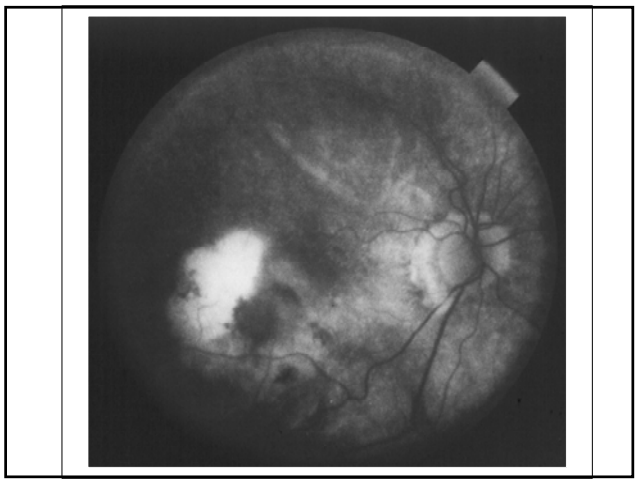


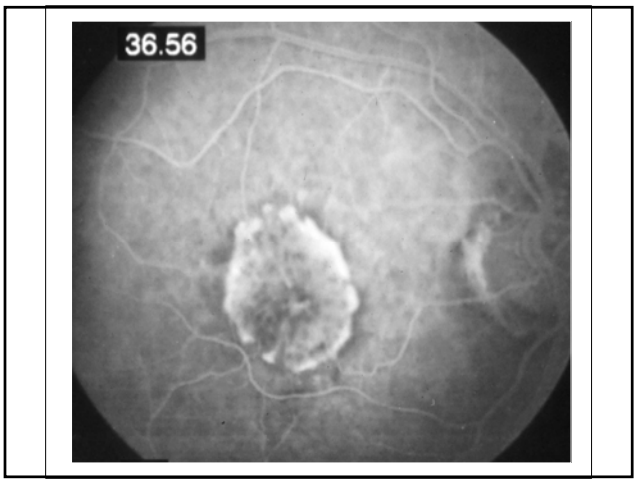








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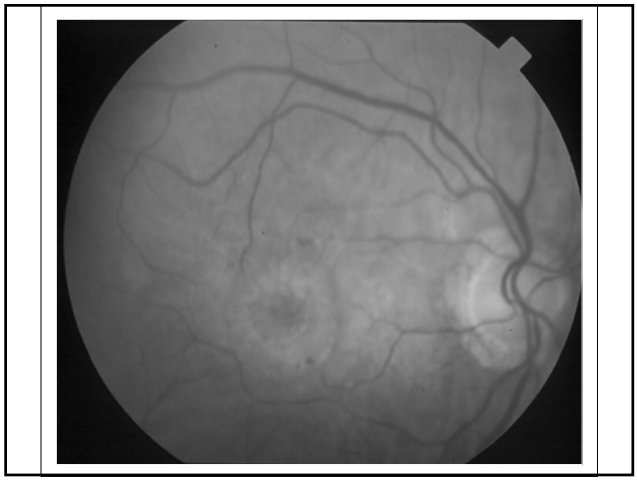
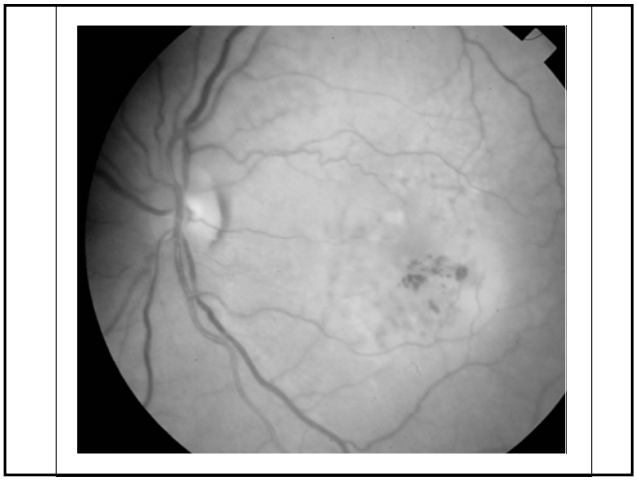
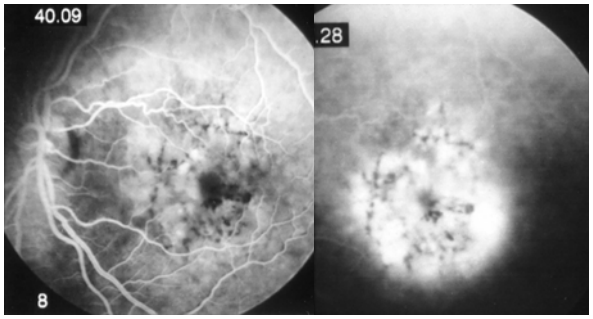
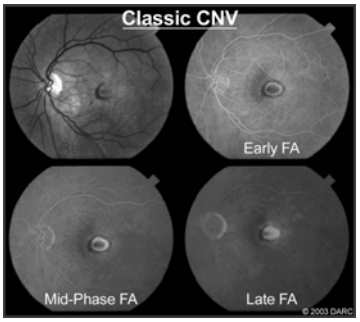






Classic CNV

- Well defined
- Early hyperfluorescence
- Progressive hyperfluorescence
- Fluorescence extends beyond initial boundaries
- Pooling of Fluorescein late



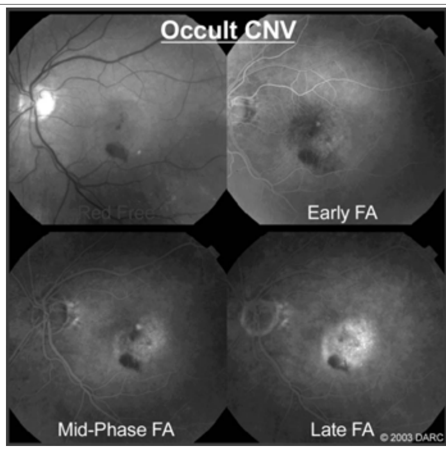
Courtesy of Digital Angiography Reading Center (DARC), New York NY

Choroidal Neovascular Membrane

- Composition
  - ✓ Classic: well defined pattern
  - ✓ Predominantly classic ≥ 50% classic CNV
  - ✓ Minimally classic < 50% classic CNV
  - ✓ Occult: poorly defined pattern
- Size and Boundaries
- Location
  - ✓ Extrafoveal ≥ 200 microns from foveal center
  - ✓ Juxtafoveal 1-199 microns from foveal center
  - ✓ Subfoveal

Occult CNV

- Fibrovascular Pigment Epithelial Detachment
  - ✓ Irregular elevation of retinal pigment epithelium
  - ✓ Hyperfluorescent stippling 1-2 minutes into FA
  - ✓ May or may not show leak in lates
- CNV
  - ✓ Late leakage of undetermined source
  - ✓ Speckled hyperfluorecence in lates
  - ✓ Pooling around speckles

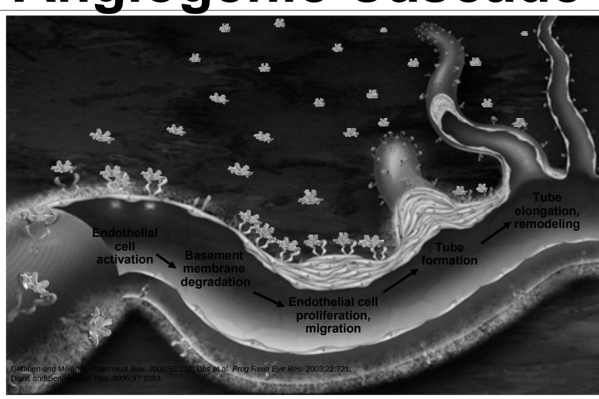


Courtesy of Digital Angiography Reading Center (DARC), New York NY

Pharmacologic Treatment of Wet AMD

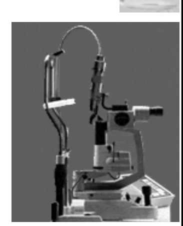
- Photodynamic Therapy with Verteporfin
- Anti-VEGF Therapy (Macugen, Lucentis and Avastin)

Angiogenic Cascade



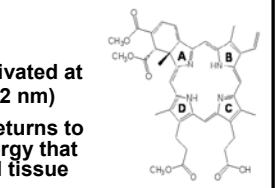
Photodynamic Therapy (PDT)

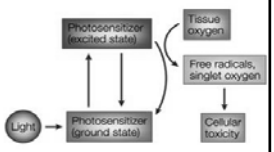
- Effect based on photosensitivity of verteporfin and its selective uptake by neovascular or neoplastic cells
- Visudyne was approved by FDA in 2000: the first drug treatment for wet AMD
- Other uses: esophageal, lung, pancreatic and bile duct CA, acne, rosacea and psoriasis
- Other FDA-approved photosensitizers include Metvix, LS11, Photofrin and Levulan



Mechanism Of PDT

- The photosensitive molecule (Verteporfin) or a metabolic precursor is activated at its maximum absorbance λ (692 nm)
- The photosensitive molecule returns to a grounded state releasing energy that excites oxygen present in local tissue
- Highly reactive singlet and superoxide oxygen radicals are formed which destroy the proliferative tissue that has absorbed the photosensitive molecules (vascular endothelium)

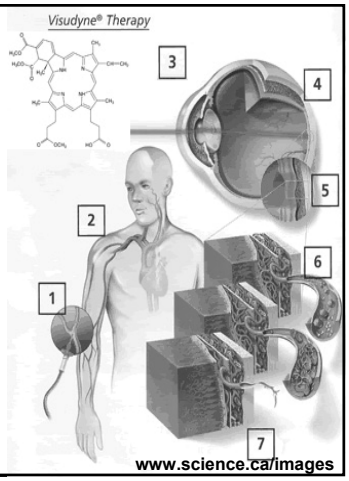




Dennis EJ et al. *Nature Reviews Cancer.* 3: 380-387, May 2003

2 Clinical Trials: TAP and VIP

- Visudyne (6 mg/m2) is injected into brachial vein
- Complexes with LDL (90%) for intravascular transport
- CNV endothelial cells absorb the LDL-Visudyne complex (10X normal cells)
- After 15 minutes a red laser beam is delivered at 690 nm for 83 sec and activates the verteporfin (energy: 50J/cm² and power: 600 mW/cm²)
- Oxygen radicals are then created and these react with and damage the neovascular endothelial tissue



www.science.ca/images

TAP Trial: Treatment of ARMD with PDT

- PDT reduced risk of moderate vision loss in predominantly classic lesions
- Rx was q 3 months: indicated by presence of leakage on FA
- n=609 (207 placebo)
- Lost greater than 3 lines of visual acuity

	PDT-treated	Placebo
At 12 months:	39%	54%
At 24 months:	47%	62%

- *Greater benefit if classic portion occupied >50% of lesion
- *Trial continued to 60 months as uncontrolled, open-label treatment and showed sustainment of 24 month outcomes

VIP Trial: Verteporfin in PDT

- PDT reduced the risk of moderate to severe vision loss in cases of occult with no classic CNVM
- n=225 Occult CNV (not originally eligible for TAP study)

Lost greater than 3 lines of visual acuity:

	PDT-treated	Placebo
At 12 months:	49%	45%
At 24 months:	55%	68%

Lost greater than 6 lines of visual acuity:

	PDT-treated	Placebo
At 12 months:	22%	33%
At 24 months:	29%	47%

- *Greater benefit with smaller lesions or VA > 20/50
- *Trial continued to 60 months as uncontrolled, open-label treatment and showed sustainment of 24 month outcomes

PDT Video

Side Effects of Visudyne PDT

- Mild to moderate, transient and include
  - ✓ Injection site reactions: pain, edema, extravasation,
  - ✓ Severe vision decrease: > 4 lines due to choroidal ischemia reported in 1%-5%. Incidence greatly decreased with reduced fluence PDT
  - ✓ Skin Photosensitivity to sunlight, halogen light
  - ✓ Back pain resolves by end of infusion

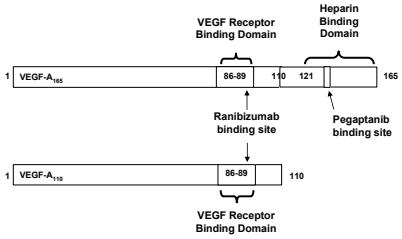
After Treatment

- Since verteporfin can cause porphyrin-induced skin damage and photosensitivity (due to reactive O_2 species), we ask patients to avoid exposure to sun or bright indoor lighting for 5 days and wear
  - ✓ Long-sleeved shirt
  - ✓ Long pants shoes and socks
  - ✓ Dark sunglasses
  - ✓ Wide-brimmed hat
  - ✓ Gloves
- *Exposure to normal indoor light is needed to help inactivate Visudyne in the skin.

Anti-VEGF Therapy

Pegaptanib Sodium

- Macugen
- Selective VEGF-A_{165} inhibitor
- Indicated for neovascular AMD
- FDA approved December 2004

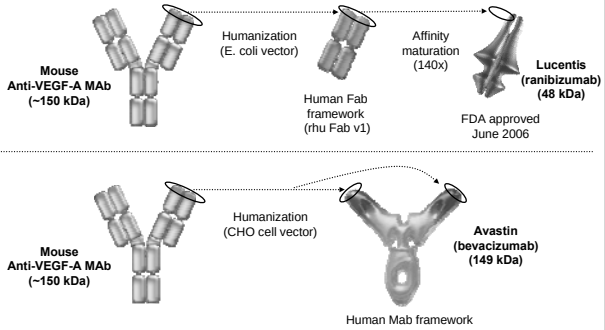


Vascular Endothelial Growth Factor

- Member of a family of growth factors
  - ✓ VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and PlGF
- Homodimeric glycoprotein secreted by a variety of cells
- Receptor-binding domain: essential for receptor-VEGF-A interaction and its role in triggering angiogenesis
- Initiates the angiogenic cascade by binding to VEGF receptors on the surface of endothelial cells

Ferrara et al. *Nat Med*. 2003;9:669; Robinson and Stringer. *J Cell Sci*. 2001;114:853.

Ranibizumab and Bevacizumab



Presta, LG, 1997. *Cancer Res*.57:4593; Chen Y. 1999 *J.Mol. Biol*.293:865

MARINA and ANCHOR Trials

MARINA: Phase III, multicenter, randomized, double-masked, sham-controlled study

Patients with minimally classic or occult lesions (N=716)

- Sham injection monthly (n=238)
- LUCENTIS 0.3 mg monthly (n=238)
- LUCENTIS 0.5 mg monthly (n=240)

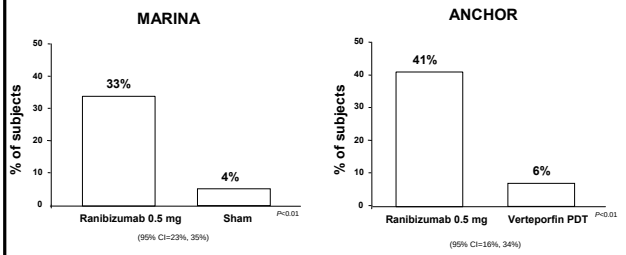
ANCHOR: Phase III, multicenter, randomized, double-masked, active-controlled study

Patients with predominantly classic lesions (N=423)

- Verteporfin PDT on day 0 and every 3 months as needed + injection monthly (n=143)
- LUCENTIS 0.3 mg monthly + sham PDT every 3 months as needed (n=140)
- LUCENTIS 0.5 mg monthly + sham PDT every 3 months as needed (n=140)

The 0.3 mg dose was not included in the FDA label. Therefore, efficacy results on the following slides reflect only the 0.5 mg dose.

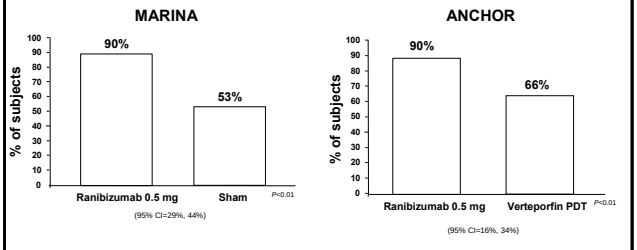
Up to 41% Improved Vision at 2 Years



Secondary endpoint: ≥3 line gain from baseline

Rosenfeld PJ et al. *N Engl J Med.* 2006;355:1419-31.
Brown DM et al. *N Engl J Med.* 2006;355:1432-44.

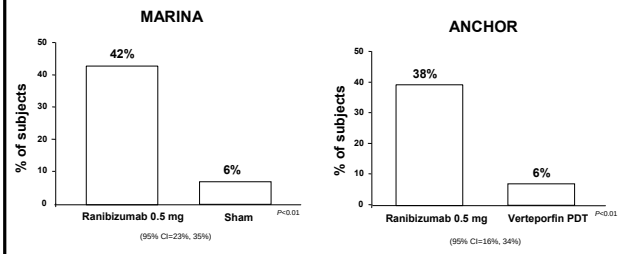
90% Maintained Vision at 2 Years



Primary endpoint: <15-letter loss from baseline

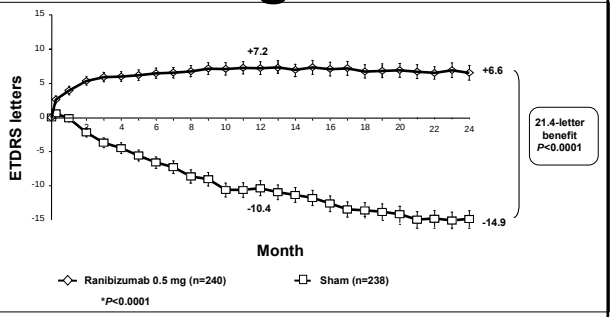
Rosenfeld PJ et al. *N Engl J Med.* 2006;355:1419-31.

Up to 42% with 20/40 or better, 2 Years



Rosenfeld PJ et al. *N Engl J Med.* 2006;355:1419-31.
Brown DM et al. *N Engl J Med.* 2006;355:1432-44.

MARINA: Mean Change in VA



Rosenfeld PJ et al. *N Engl J Med.* 2006;355:1419-31.

PIER Trial Design

Phase IIIb, multicenter, randomized, double-masked, sham-controlled study

Subfoveal CNV ± Classic component (N=184)

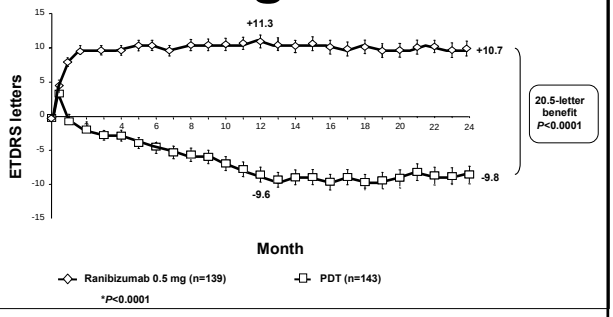
Randomization 1:1:1

Monthly x 3, then every 3 months

- Sham injection (n=63)
- Ranibizumab 0.3 mg (n=60)
- Ranibizumab 0.5 mg (n=61)

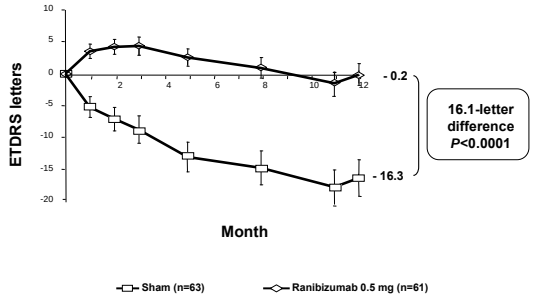
Rosenfeld PJ et al. *Ophthalmol Clin North Am.* 2006;19:361-72.

ANCHOR: Mean Change in VA



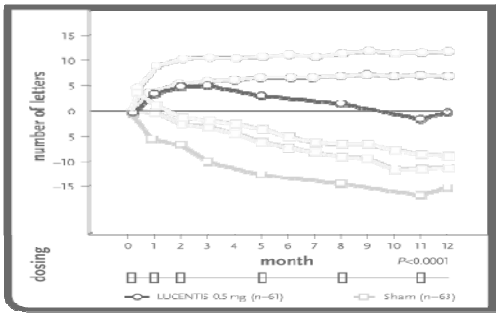
Brown DM et al. *N Engl J Med.* 2006;355:1432-44.

PIER: Mean Change in VA



Regillo CD et al. *Am J Ophthalmol.* 2008;145:239-48.

MARINA **ANCHOR** **PIER**



Rosenfeld PJ et al. *N Engl J Med.* 2006;355:1419-31.
Brown DM et al. *N Engl J Med.* 2006;355:1432-44.
Regillo CD et al. *Am J Ophthalmol.* 2008;145:239-48.

Serious Ocular Events

Adverse event	MARINA (Year 2)		ANCHOR (Year 2)		PIER (Year 1)	
	Sham (n=236)	Ranibizumab (n=477)	PDT (n=143)	Ranibizumab (n=277)	Sham (n=63)	Ranibizumab (n=120)
Endophthalmitis	0	1.0% (5)	0	1.1% (3)	0	0
Retinal detachment	0.4% (1)	0	0.7% (1)	0.7% (2)	0	0
Iatrogenic traumatic cataract	0	0.2% (1)	0	0	0	0

Ocular Adverse Events

Adverse event	Ranibizumab	Control
Conjunctival hemorrhage	43 - 77%	29 - 66%
Eye pain	17 - 37%	11 - 33%
Vitreous Floaters	3 - 32%	3 - 10%
Increased intraocular pressure	8 - 25%	3 - 8%
Vitreous detachment	7 - 22%	13 - 22%
Intraocular inflammation	5 - 18%	3 - 11%
Cataract	5 - 20%	6 - 16%
Foreign body sensation	6 - 19%	6 - 14%
Eye irritation	4 - 19%	6 - 20%
Increased lacrimation	3 - 17%	0 - 16%

Safety data pooled from MARINA (month 24), ANCHOR (month 24) and PIER (month 12)

Arterial Thromboembolic Events

Adverse event	MARINA (Year 2)		ANCHOR (Year 2)		PIER (Year 1)	
	Sham (n=236)	Ranibizumab (n=477)	PDT (n=143)	Ranibizumab (n=277)	Sham (n=63)	Ranibizumab (n=120)
Vascular death	1.7% (4)	1.3% (6)	2.1% (3)	1.4% (4)	0	0
Nonfatal myocardial infarction	1.7% (4)	1.9% (9)	1.4% (2)	2.2% (6)	0	0
Nonfatal ischemic stroke	0.8% (2)	1.7% (8)	1.4% (2)	1.1% (3)	0	0
Nonfatal hemorrhagic stroke	0	0.2% (1)	0	0	0	0
Total patients	3.8% (9)	4.6% (22)	4.2% (6)	4.7% (13)	0	0

Summary: Clinical Trials

- All CNV lesions types
- At up to 2 years with monthly dosing,
  - ✓ Vision maintained in up to 90% of patients
  - ✓ Vision improved (≥15 letters) in up to 42% of patients
- Reduced-interval dosing better than natural history
- Low incidence of serious ocular events (<0.1%)

- With the advent of anti-VEGF agents patients with wet AMD are receiving better treatment than ever
- Pan-anti-VEGF agents alone have been shown to be far superior to PDT alone in treating wet AMD

Injection Video

Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration

- 1:1:1 (0.3 or 0.5 mg of lucentis or PDT)
- n=423
- Lost greater than 15 letters:
  - ✓ 5.7% given 0.3 mg of lucentis
  - ✓ 3.6% given 0.5 mg of lucentis
  - ✓ 35.7% given verteporfin
- Gained by 15 or more letters:
  - ✓ 35.7% given 0.3 mg of lucentis
  - ✓ 40.3% given 0.5 mg of lucentis
  - ✓ 5.6% given verteporfin
- Conclusion: Ranibizumab was far superior to verteporfin

(Brown D et al. *NEJM* 355:1432-1444 Oct 2006)

- However, intravitreal injections are required in 4-6 week intervals with frequent follow-up visits
- There are substantial 3rd party payer expenses
- As a result, PDT has been revisited as a complementary treatment to anti-VEGF monotherapy

Current Clinical Trials

- Novartis: n=323, 43 centers; avastin/PDT vs avastin alone
- RADICAL Study: n=160, 26 centers; lucentis vs double Rx vs triple Rx (IVD)
- Oklahoma State University: n=30, lucentis vs double Rx
- Texas Retina Associates: n=60, lucentis vs double Rx
- Basel, Switzerland: n=40, lucentis vs double Rx
- San Francisco (Bay Area Associates): n=60, triple RX (IVD) vs lucentis alone
- Houston (Greater Houston Retina): n=30, avastin vs double Rx

Combination Treatment with PDT and Intravitreal Anti-VEGF Agents

- Gives two synergistic mechanisms of action
- Can reduce treatment frequency vs anti-VEGF monotherapy
- Reduced (half) fluence (25 Joules / 300 mW per cm2) is used to minimize collateral damage