



Age Related Macular Degeneration

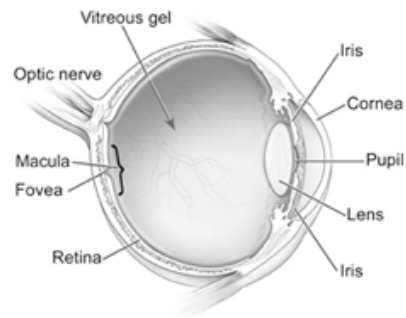
Presentation by Alex Akerberg

Why do we care?

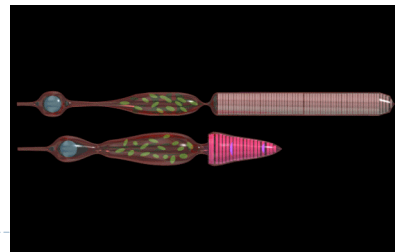
- ▶ AMD destroys central vision resulting in symptoms ranging from decreased visual acuity to complete loss of central vision
- ▶ AMD inhibits the vision of an estimated 1.75 million people in the U.S.
- ▶ Occurs primarily in people over the age of 60
- ▶ Now considered the leading cause of blindness in developed countries



Background: The Eye



- ▶ **Retina: rod dense**
 - ▶ Dim light
 - ▶ Peripheral vision
- ▶ **Macula: Cone dense**
 - ▶ Color
 - ▶ Fine details (visual acuity)

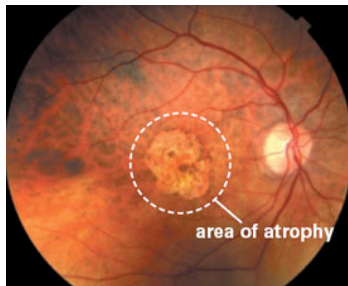
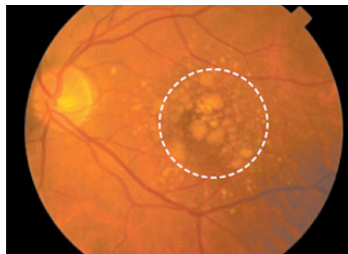


Dry AMD

- ▶ Non neovascular form (atrophic)
- ▶ Macula loses function due to:
 - ▶ Unhealthy aging of cells
 - ▶ Abnormal cell loss
 - ▶ Accumulation of cellular material (drusen) between the RPE and inner collagenous zone of the Bruchs membrane (fovea)
- ▶ Most common: $\approx 85\%$ of all AMD
- ▶ Progression patterns not known!

Wet AMD

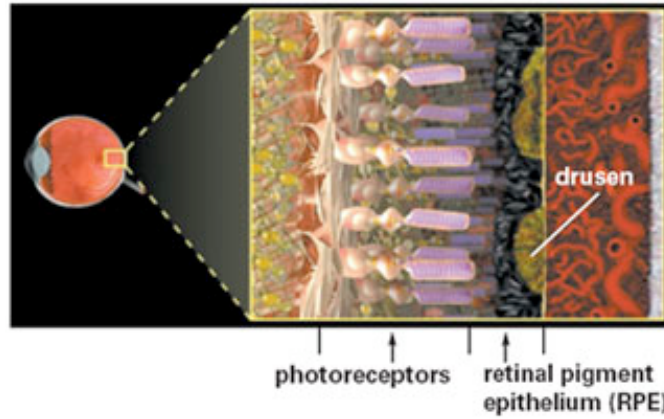
- ▶ More advanced form of AMD
- ▶ Characterized by neovascularization beneath the retina
 - ▶ Permanent damage to and displacement of retinal cells resulting in “blind spots”
- ▶ Neovascularization
 - ▶ Occult
 - ▶ Classic (choroidal neovascularization or CNV)



Drusen

- Buildup of extracellular material
- Common in most people over the age of 40
- Larger and more numerous drusen is often the first sign of AMD

Drusen



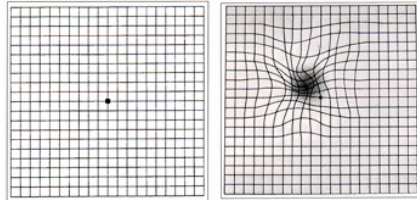
Symptoms



- Severe case of AMD resulting in little to no central vision



How is AMD screened for?



- ▶ Official detection and classification require a photographic assessment of the eye

- ▶ Amsler grid
- ▶ Progression of AMD is correlated with central vision loss



Other risk factors aside from age?

- ▶ Large scale population studies: Beaver dam eye study (1996), Rotterdam eye study (1995) and the Blue Mountain eye study (1998)
- ▶ AREDS confirmed risk factors:
 - ▶ Age
 - ▶ Gender
 - ▶ Smoking
 - ▶ Race
 - ▶ heredity



Other Initial studies

- ▶ Molecular factors contributing to atrophy
 - ▶ Oxidative stress?
 - ▶ High endogenous plasma levels of antioxidants correlated with a lower incidence of AMD (West et al, 1994)
 - ▶ Ascorbic acid, alpha tocopherol and beta carotene
 - ▶ “plausible but unproven” (Seddon et al. 1996)
 - ▶ Zn concentrations in retinal cells also showed link to healthy cell function (Cho et al. 2001)
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AREDS to the rescue... again

- ▶ Randomized placebo controlled clinical trial exploring supplementations containing Zn, vitamin A, E and beta carotene
 - ▶ Initial results: general attenuation of progression in certain cohorts
 - ▶ Analysis: people >55 with intermediate or large drusen, central geographic atrophy, or AMD in **one** eye would benefit from supplementation.

 - ▶ AREDS formula: Currently the least invasive method of slowing AMD progression
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Treatments: Photocoagulation

- ▶ Target: blood vessels under the retina
 - ▶ Implementation: A fine laser is used to destroy blood vessels and thus prevent leakage

 - ▶ Drawbacks:
 - ▶ sufficiently destroyed existing blood vessels however, did nothing to prevent new ones from forming
 - ▶ Resulted in scarring of surrounding retinal tissue which only exacerbated symptoms
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Treatments: Photodynamic Therapy

- ▶ A.K.A. PDT
 - ▶ First demonstrated in a mouse model in which verteporfin was injected and activated in the eye (TAP, 1999)
 - ▶ Human system uses visudyne to target wet AMD by specifically preventing CNV

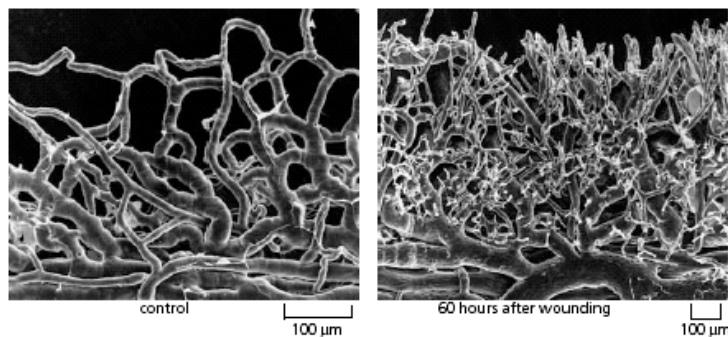
 - ▶ Drawbacks:
 - ▶ Only abrogates existing blood vessel formation = repeated treatments necessary
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Treatments: VEGF inhibitors

- ▶ VEGF is a key growth factor that promotes angiogenesis throughout the body
- ▶ In-situ hybridization and immunohistochemistry were used to isolate and stain subfoveal membranes for the presence of VEGF (Kvanta et al. 1996)
- ▶ Human treatment: ranibizumab antibody fragment
- ▶ Drawbacks: Only prevents formation of *new* blood vessels but does little to destroy existing ones

VEGF

- ▶ Capillary response to wounding (Alberts 5th ed.)



▶

Current research

- ▶ Focus has shifted to genetic analysis of risk factors
 - ▶ Researchers have recently identified SNPs at several locations that strongly correlate with AMD formation
 - ▶ Complement Factor H (CFH): functions as an inhibitor of the complement pathway
 - ▶ A single Tyr-His SNP at position 402 increased risk of AMD by 2.7 fold (Edwards et al. 2005)
 - ▶ CFH emerges as a molecular target and implicates complement pathway.
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- ▶ Rohrer et al. 2009

Drusen provides clues

- ▶ Analysis of drusen revealed the presence of many complement factors such as C3 (complement component 3)
 - ▶ C3 was subsequently correlated to both wet and dry AMD via meta-analysis of data gathered from the Rotterdam study.
 - ▶ Next step will be to investigate the downstream effects of a mutated C3 gene
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- ▶

Future experiments

Experimental

- ▶ RPE protection via EPO
 - ▶ Wang et al 2008
- ▶ VEGF trap
 - ▶ Nguyen et al. 2006
- ▶ Heat Shock Proteins
 - ▶ Kaarniranta et al. 2009

Clinical

- ▶ PDT combined with VEGF inhibitors (bevacizumab)



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