# Age Related Macular Degeneration

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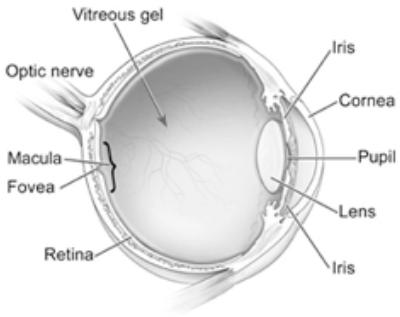
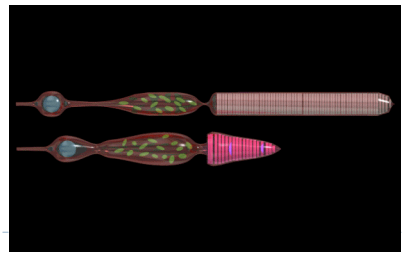
## Why do we care?

- 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)

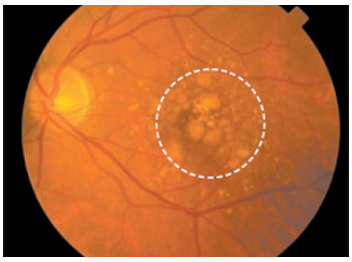


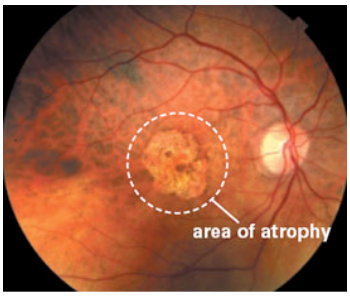
## Dry AMD

- 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: ≈ 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)

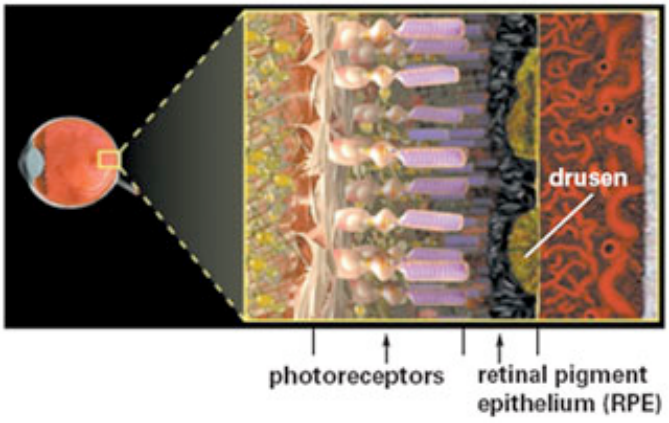





### Drusen

- 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

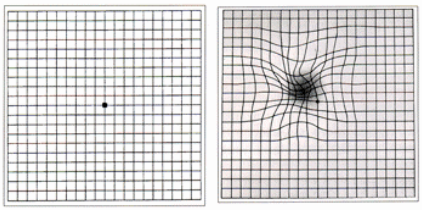
## Drusen




## 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 damn 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 of antioxidants correlated with a lower incidence of AMD (West et al, 1994)
  - Absorbic 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)

## 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

## 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

## Treatments: Photodynamic Therapy

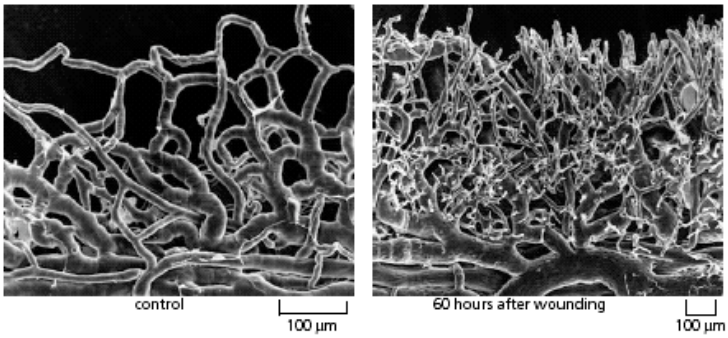
- A.K.A. PDT
- First demonstrated in a mouse model in which verteporfin was injected and activated in the eye (TAP, 1999)
- Human system uses visudyne to target wet AMD by specifically preventing CNV
- Drawbacks:
  - Only abrogates existing blood vessel formation = repeated treatments necessary

## 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.
- 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

## 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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