Age-related Macular Degeneration
Do you have a relative with macular degeneration?
YOU ARE NOT ALONE

800,000 Australians have some sign of AMD
Figure 2a. Prevalence of Drusen > 125 µm in Diameter in Whites

1/4 over 75 have signs of AMD
Figure 1a. Prevalence of Advanced AMD in Whites

1/10 over 75 have lost vision due to AMD

NEI dataset – AMD in white populations
Age-related Macular Degeneration in Australia

Is responsible for over 2/3 of new cases of blindness in people aged over 50
### CAUSES OF BLINDNESS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular Degeneration</td>
<td>58%</td>
</tr>
<tr>
<td>Retinal Vein Occlusion</td>
<td>12%</td>
</tr>
<tr>
<td>Cataract</td>
<td>10%</td>
</tr>
<tr>
<td>Diabetic Retinopathy</td>
<td>2%</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Beaver Dam Study Klein et al, Ophthalmology 2001
The initial Macular Degeneration Foundation Survey 2001

- 90% don’t know what it is
- 70% have never heard of it
- 5% know it is the major cause of blindness
Age-related Macular Degeneration

What is macular degeneration
What is its natural history
Why does it occur
How do we prevent it
What treatments are available
WHAT IS THE MACULA
What is AMD?

It is a disease of the RPE that separates the retina from the vascular layer called the choroid.
Choroid

RPE

- Is a barrier preventing choroidal blood vessels from growing into retina
- Nourishes
- Removes waste products
Removes waste products

Nourishes

Is a barrier preventing choroidal blood vessels from growing into retina

Drusen

Atrophy

Wet AMD
AGE RELATED MACULOPATHY

- Drusen
- Pigment Clumping
Late stage - Age related Macula Degeneration

**DRY**
- RPE atrophy
- Gradual visual loss

**WET**
- Haemorrhage
- Rapid visual loss
Age-related Macular Degeneration

What is macular degeneration

What is its natural history

Why does it occur

How do we prevent it

What treatments are available
Evolution of macular degeneration

72 year old man seen after 2 months and 1 year

- soft drusen, pigment changes
- bleed under retina
- scar formed under retina
Natural history (3 years) of wet AMD

- Normal 6/6
- 40% 6/60
- 10% 6/18
- 50% 1/60
Age-related Macular Degeneration

What is macular degeneration
What is its natural history
Why does it occur
How do we prevent it
What treatments are available
Cause of AMD

- Genetic Predisposition
- Environment
- Age
GENETIC FACTORS

Indirect evidence for many years has shown that AMD has a genetic predisposition

- There is high concordance for AMD among monozygotic twins & relatively lower concordance among dizygotic twins

- If your sibling has late AMD, your lifetime risk is around 50%. If you have sibs but no family history, your lifetime risk is around 15%.
GENETIC FACTORS

- Recently identified susceptibility genes
  - **Chromosome 1 [q31-32]**
    - Complement Factor H (CFH - Y402H)
    - Factor B (BF), complement component (C2, C3)
  - **Chromosome 10 [q26]**
    - LOC387715 - A69S
    - HTRA1

- In complex disease such as AMD, presence of a relevant gene alone does not cause the disease
**Y402H Haplotype**

- is associated with a 6 to 12 fold increased risk of developing AMD
- is responsible for 50% AMD in the population.
Age-related Macular Degeneration
GENETIC FACTORS HAVE NOT CHANGED THEREFORE THE ENVIRONMENT IS IMPORTANT
The retinal pigment epithelium (RPE)

Receptors

RPE

Choroid
Accumulation of lipofuscin increase with age

Okubo A et al. 1999
SUNLIGHT + ANTIOXIDANTS

DYSFUNCTIONAL MITOCHONDRIA

O-

DYSFUNCTIONAL OUTER SEGEMENTS

LIPOFUSCIN

UNSATURATED LIPID
SUNLIGHT EXPOSURE AND 10 YR INCIDENCE OF ARM

Those exposed to summer sun for >5 cf <2 hours in their teens and 30s

RR 3.17  \( p = 0.01 \) for pigment changes
RR 2.14  \( p = 0.05 \) for early ARM.......

And the use of hats or sunglasses for half the time decreased the risk

RR 0.51  \( p = 0.02 \) for pigment epith changes.
RR 0.55  \( p = 0.02 \) for soft indistinct drusen
Lutein and zeaxanthin in the macula act like internal pair of sunglasses absorbing blue light.
BMES

RISK RATIOS FOR INCIDENT WET AMD FOR THE TOP TERTILE OF FOOD INTAKE

- **LUTEIN**  RR 0.35  CI 0.13-0.92

- **BETA CAROTENE**  RR 2.68  CI 1.03-6.96

(P FOR TREND ON BETA CAROTENE WAS 0.027)
## Dietary Lutein/Zeaxanthin

highest versus lowest quintile

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographic atrophy</td>
<td>0.45</td>
<td>0.24-0.86</td>
</tr>
<tr>
<td>Neovascular AMD</td>
<td>0.65</td>
<td>0.45-0.93</td>
</tr>
<tr>
<td>Large Drusen</td>
<td>0.73</td>
<td>0.56-0.96</td>
</tr>
</tbody>
</table>

AREDS REPORT  No 22  
Arch Ophthalmol
## BETACAROTENENE or LUTEIN

### ODDS RATIOS FOR DIFFERING QUINTILES OF INTAKE

<table>
<thead>
<tr>
<th>SERVINGS PER WEEK</th>
<th>&lt; 0.25</th>
<th>0.25 to 0.75</th>
<th>1.0</th>
<th>2 to 4</th>
<th>5+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carrots</strong></td>
<td>1.0</td>
<td>1.2</td>
<td>1.0</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>spinach</strong></td>
<td>1.0</td>
<td>0.8</td>
<td>0.6</td>
<td>0.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Randomized participants
n=90

Consecutive, randomized into 3 groups on a 1:1:1 ratio

Lutein (10 mg)  
n=29

Lutein (10 mg) + additional antioxidants and nutrients  
n=30

Placebo (maltodextrin)  
n=31

Richer S et al. 2004
LAST: vision outcomes improved in patients receiving lutein

Improvement in Snellen equivalent visual acuity (letters)

- Lutein alone: +5.4
- Lutein plus antioxidants: +3.5
- Placebo: -0.2

Richer S et al. 2004
SUNLIGHT + ANTIOXIDANTS → O⁻ → DYSFUNCTIONAL MITOCHONDRIA

UNSATURATED LIPID OUTER SEGEMENTS

LIPOFUSCIN
BMES

RISK RATIOS FOR INCIDENT WET AMD FOR THE TOP TERTILE OF FOOD INTAKE

ZINC       RR 0.56    CI 0.32-0.92
High intake of vitamin C & E, beta carotene & zinc reduced the risk of AMD

- Dietary intake of above-median intake of vitamin C, vitamin E, β-carotene, and zinc was associated with a 35% reduced risk of AMD

Rotterdam study

van Leeuwen R et al. 2005
THE HOLY GRAIL IS A PROSPECTIVE CONTROLLED TRIAL OF SUFFICIENT DURATION WITH ADEQUATE DOCUMENTATION OF DISEASE PROGRESSION IN A LARGE NUMBER OF SUBJECTS
Randomized participants
N=4757

Placebo
n=1483
Antioxidant
n=1482
Zinc
n=904
Antioxidant plus zinc
n=888

AREDS Report No. 8. 2001
In patients at high risk of AMD, antioxidants plus zinc significantly delayed progression to advanced AMD ($P<0.01$ vs placebo)

AREDS Report No. 8. 2001
SUNLIGHT + ANTIOXIDANTS → O⁻ → UNSATURATED LIPID OUTER SEGMENTS → LIPOFUSCIN → DYSFUNCTIONAL MITOCHONDRIA
A 1 YR PROSPECTIVE PLACEBO CONTROLLED TRIAL OF:

ACETYL L CARNITINE 200MG
+ N-3FATTY ACIDS 1.06GM
+ COENZYM E Q10 20MG PER DAY

J. Feher et al. Improvement of Visual Functions and Fundus Alterations in Early Age-Related Macular Degeneration Treated with a Combination of Acetyl- L -Carnitine, n-3 Fatty Acids, and Coenzyme Q10 Ophthalmologica 2005;219:154–166
## PRIMARY EFFICACY VARIABLE

### THE VISUAL FIELD MEAN DEFECT

<table>
<thead>
<tr>
<th></th>
<th>Most affected eyes</th>
<th>Less affected eyes&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>treated (n = 48)</td>
<td>placebo (n = 53)</td>
</tr>
<tr>
<td>Improved or unchanged</td>
<td>47 (98%)</td>
<td>44 (83%)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>1 (2%)</td>
<td>9 (17%)</td>
</tr>
<tr>
<td>p</td>
<td>0.006</td>
<td>0.031</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>10.93</td>
<td>11.81</td>
</tr>
</tbody>
</table>

<sup>a</sup> ± 2.0 dB long-term fluctuation was applied.

<sup>b</sup> Data were modified by adding 0.5 to each value in the less affected eyes for odds ratio computing.
The effect of 12 months treatment with mitochondrial nutrients on drusen area

SUNLIGHT + ANTIOXIDANTS → O⁻ +

DYSFUNCTIONAL MITOCHONDRIA

UNSATURATED LIPID OUTER SEGEMENTS

LIPOFUSCIN

YOU ARE WHAT YOU EAT
LIPID RICH
OUTER
SEGEMENTS

LIPOFUSCIN
LIPID = FATS

FOOD
In Epidemiology, particularly Nutritional Epidemiology, you have to expect negative studies.

To evaluate the data you look for internal consistencies and repeatability in prospective and population based studies and the ability to control for bias.
CONFOUNDING VARIABLES

WATCHING TV CAUSES HEART ATTACKS

Walter Willett

INDICATION BIAS

EATING CARROTS CAUSES NIGHT BLINDNESS

Paul Mitchell
OR = 1500

PEOPLE WHO TAKE THE MACU-VISION ARE 1500 TIMES MORE LIKELY TO HAVE AMD

Paul Beaumont
Smoking and Subsequent Development of AMD

Odds ratio (95% CI)

- PHS*
- NHS**
- RS^*
- BDES†
- BMES†
- Pooled
- BDES, BMES & RS°

0 2 4 6 8 10 12 14 16 18 20

Odds ratio (95% CI)
case control study showed

VEGETABLE FAT INTAKE

was associated with AMD

OR = 2.84 (1.45-5.57)

P = 0.006

Professor Johanna Seddon
Linoleic acid reduces the beneficial effect of fish

Patients who eat 3 vs 1 serves of fish per week

<table>
<thead>
<tr>
<th></th>
<th>(-)</th>
<th>(0.54 \text{ (0.3-0.9)})</th>
<th>(p 0.02)</th>
<th>(0.82 \text{ (0.5-1.31)})</th>
<th>(p 0.36)</th>
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<tr>
<td>(\leq 5.6\text{gm linoleic acid})</td>
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A prospective study of the effect of diet on the progress of patients who already had AMD

261 patients were followed for an average of 4.6yrs

Seddon et al Arch Ophthalmol 2003
Quartiles of vegetable fat intake

RR 3.82 (1.58-9.28; p for trend 0.003)
INTERNAL CONSISTENCY

PROCESSED B FOODS RR 2.42 (1.21-4.84; p for trend 0.005)

POLYUNSATURATED FAT RR 2.28 (1.04-4.99; p for trend 0.05)

TRANS UNSATURATED RR 2.39 (1.1-6.17; p for trend 0.008)

Those eating > 1 serving of nuts per week compared to none had a **RR of progression of their AMD of 0.46** (**p trend .008**).
RR for progression 0.36 (0.14-0.95; p for trend 0.045) for > or equal to 2 cf. <1 serving of fish/wk and <5gm linoleic acid intake
Specific types of fat, rather than total fat intake, are potentially important factors related to the risk for AMD.
REPEATABILITY in a population based study

FISH 0.65 (0.46-0.91; p for trend = 0.009)
LINOLENIC ACID 1.41 (1.0-1.98; p for trend = 0.03)
MARGARINE 1.42 (1.01-2.00; p for trend = 0.03)
OIL + VINEGAR DR. 1.29 (1.0-1.66; p for trend 0.08)
VEGETABLE FAT 1.35(1.04-1.77;p for trend = 0.06)
## BETACAROTENE or LUTEIN

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FRUIT

RR FOR 3 OR MORE PIECES OF FRUIT VERSUS LESS THAN 1.5

0.64 (0.44-0.93; p for trend 0.004)

Bananas 3/wk cf. <2/mo RR 0.63 .....People who eat a lot of fruit often did not smoke

Cho E et al
VITAMIN D AND EARLY AMD

Highest versus the lowest quintile of serum vitamin D
OR 0.64 95% CI 0.5-0.8 p trend < 0.001

Milk intake was inversely associated, early AMD
OR 0.74 95% CI 0.6-0.9

In individuals who did not consume milk
the consistent intake of a vitamin D supplement
was inversely associated with early AMD
OR 0.67 95% CI 0.5-0.9

Fish OR 0.41 95% CI 0.2-0.9

Age-related Macular Degeneration

What is macular degeneration
What is its natural history
Why does it occur
How do we prevent it
What treatments are available
What do you tell people to eat?

EAT FISH 3 TIMES A WEEK
AND A HANDFUL OF NUTS
What do you tell people to eat?

EAT SPINACH, A CUP A DAY,

BUT DON’T EAT CARROTS
What do you tell people to eat?

FRUIT IS GOOD

AS IS OLIVE OIL WHICH IS A FRUIT OIL
What do you tell people to eat?

REDUCE ALL YOUR FAT INTAKE
PARTICULARLY
VEGETABLE OIL
What else do you tell people?

DON’T SMOKE

EXERSIZE

LOOSE WEIGHT

CONTROL BLOOD PRESSURE

AND AVOID SUNLIGHT

IF THEY HAVE SIGNIFICANT DRUSEN

TAKE MACUVISION 2/day
AREDS antioxidant/zinc formulation protects against visual acuity loss

Probability of at least a 3-line visual acuity loss after 5 years

- Placebo: 29%
- Antioxidants: 26%
- Antioxidants + zinc: 23%

Odds ratio 0.73 ($P=0.008$)

AREDS Report No. 8. 2001
Antioxidants and zinc from diet alone are not sufficient to slow the progression of AMD, for example

- **Oysters are one of the richest sources of zinc**
  - One medium-sized oyster contains 3.4 mg of zinc
  - More than 24 oysters would need to be consumed every day to provide 80 mg of zinc (the amount in the AREDS formulation)

- **Almonds are a premium dietary source of vitamin E**
  - But it takes 1400 nuts/day to give you the AREDS vitamin E dose of 400 mg/day
What do you tell those people who don’t like fish and spinach?

TAKE 2 capsules per day of LUTEIN-VISION ADVANCED

LUTEIN AND ZEAXANTHIN 12mg

DHEA/EPA CONCENTRATES 1gm

SELENIUM 100mcg
100g of Spinach costs $1.80

And contains: Lutein 10 mg
Zeaxanthin 0.3mg
Beta-carotene 5mg
LUTEIN-VISION ADVANCED

2 CAPSULES CONTAINS 1000 MG OF DHA/EPA

2 CAPSULES IS EQUIVALENT TO:

95gm OF SARDINES
120gm OF SWORDFISH
200gm OF SNAPPER
400gm OF YELLOW FIN TUNA

WHICH WOULD COST ROUGHLY $3 TO $6
To get the same daily Lutein, Se and EPA/DHA in food would cost 5 to $10/day

The 2 capsule/day cost is $1.25
Age-related Macular Degeneration

Why is this of importance to GPs
What is macular degeneration
What is its natural history
Why does it occur
How do we prevent it
What treatments are available
LUCENTIS....an anti VEGF
Angiogenesis and CNV

- Angiogenesis = growth (genesis) of blood vessels (angio)

- Angiogenesis is the process that leads to choroidal neovascularisation (CNV) in the retina

- Angiogenesis is induced by vascular endothelial growth factor (VEGF)
Ranibizumab (Lucentis ®)

- Anti-VEGF ... A humanised monoclonal AB that binds all isoforms of VEGF
  - Monthly intravitreal injections

30 gauge needle

Tuberculin Syringe
DEVIAE FROM THE MONTHLY REGIME AND YOU RISK VISION LOSS
CHRONIC LESIONS DO NOT RESPOND TO TREATMENT

EARLY DIAGNOSIS AND TREATMENT IS CRITICAL
• For information sheets etc contact the Macular Degeneration Foundation on 1800 111 709

• www.mdfoundation.com.au