

AGE RELATED MACULAR DEGENERATION

A MODERN EPIDEMIC

JIM RUNCIMAN

DISCLAIMER:

MEDICAL ADVISORY BOARDS AUST. [\$ PAID]

NOVARTIS:	VISUDYNE [Verteporfin] PDT	2000 – present
	LUCENTIS [Ranubizumab]	IVI
BAYER:	EYLEA [VEGF Trap] IVI	2011 – present
ALLERGAN :	OZURDEX	2013 – present
[PAST : Alcon – Retaane , Pfizer – Macugen]		

CONSULTANT ELLEX , ELLEX R&D

NFP BOARDS [UNPAID]

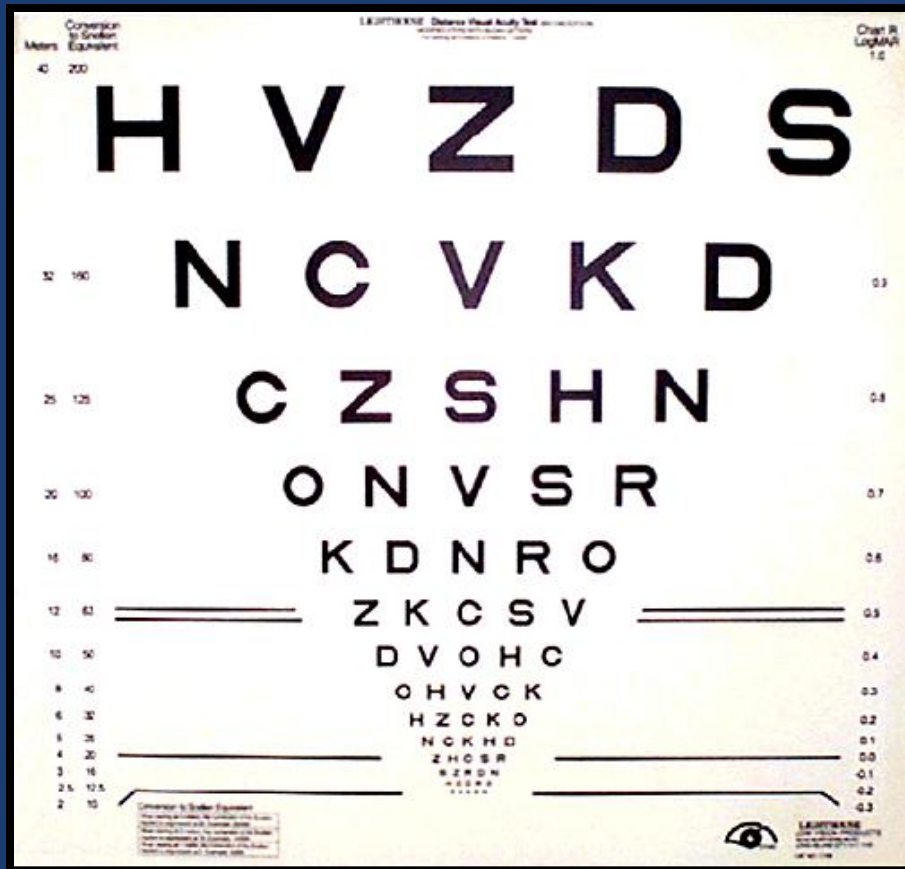
Royal Society for the Blind	1995 – present
Macular Degeneration Foundation	2004 – present
+ chairman med. advisory comm.	
+ research grant comm.	

What is Macular Degeneration (AMD)?

- **Progressive, chronic disease of central retina**
- **Loss of central vision**
- **Peripheral vision not affected**
- **Not black blind**



The eye chart



< 6/60 (legally blind)

6/12 (driving limit)

6/6 (normal vision)

Age-related Macular Degeneration in Australia

Responsible for over 2/3
of new cases of blindness
in people aged over 50

All other eye diseases
together comprise the other
1/3



Macular degeneration in Australia

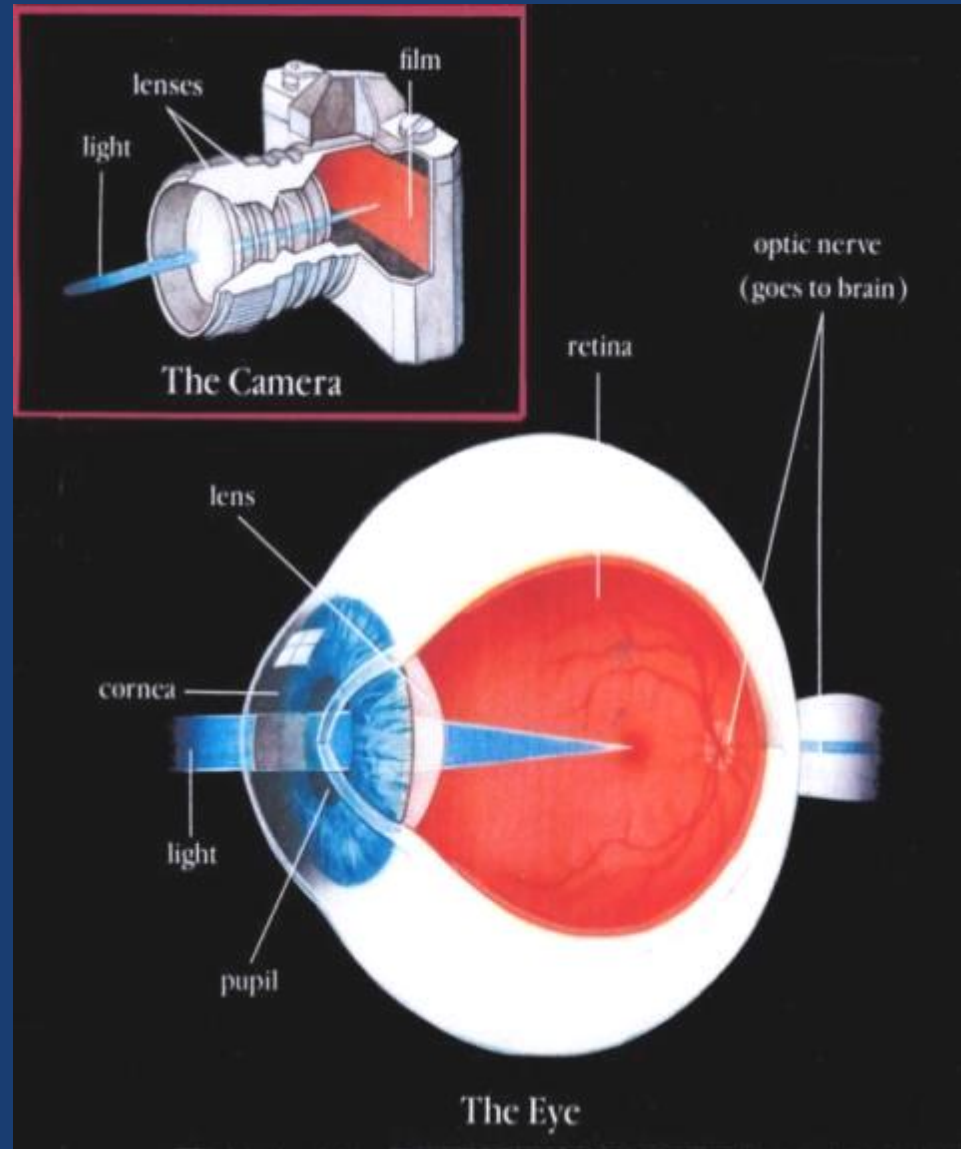
- Leading cause of blindness* and severe vision loss
- 1 in 7 people over 50 have some evidence of macular degeneration
- Incidence increases with age – 1/3 aged 75yrs have some AMD

* legal blindness

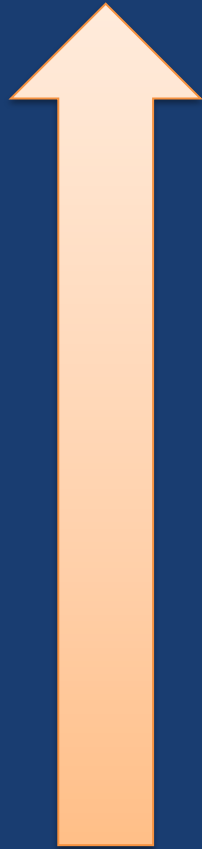
How the eye works

The eye works like a camera:

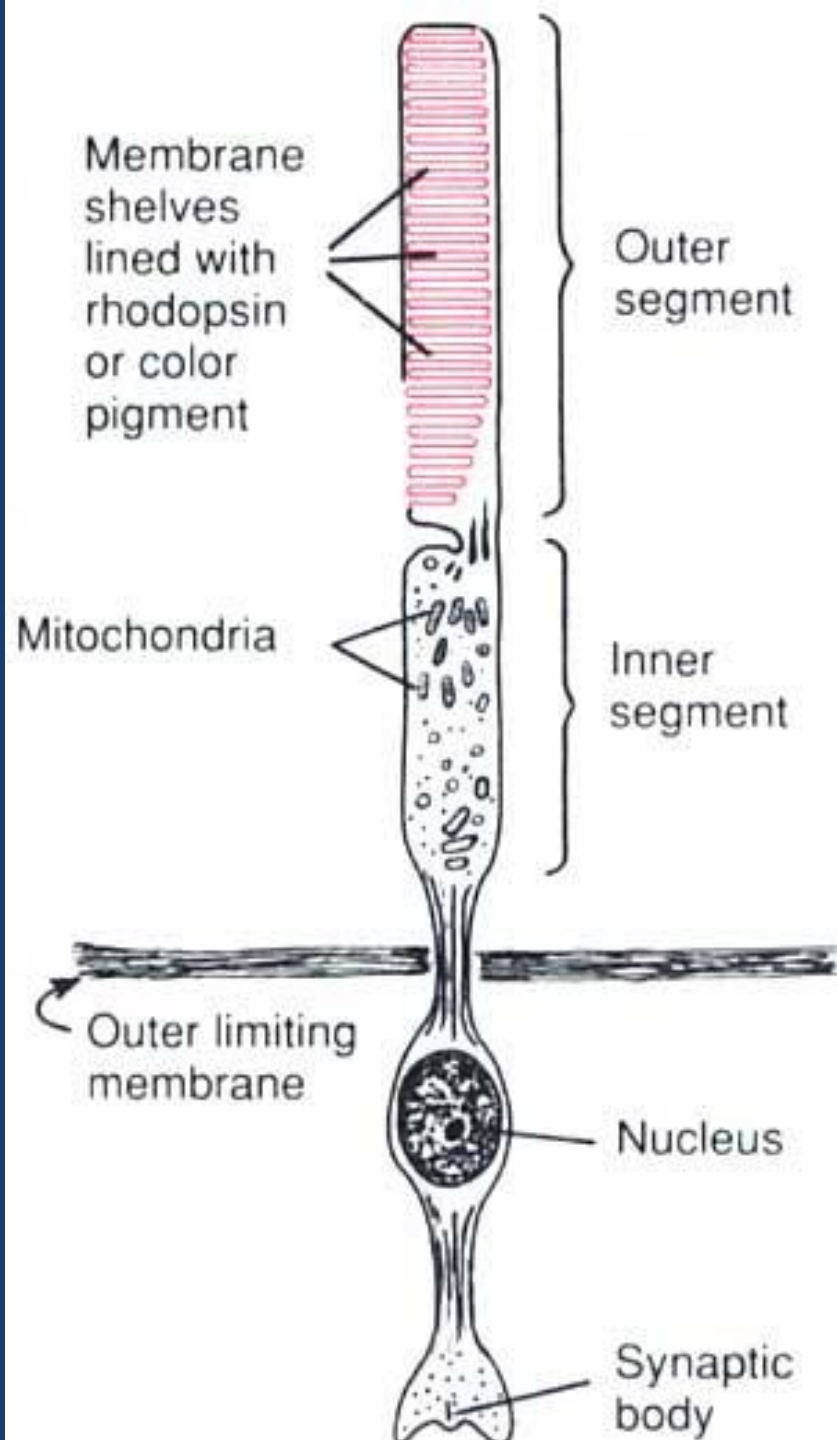
- Light passes through the pupil (shutter) and the eye lens (camera lens)
- It's focused on the retina (film) , detects and encodes
- Impulses sent along the optic nerve to the brain
- Brain interprets the impulses to form a picture



DISCS

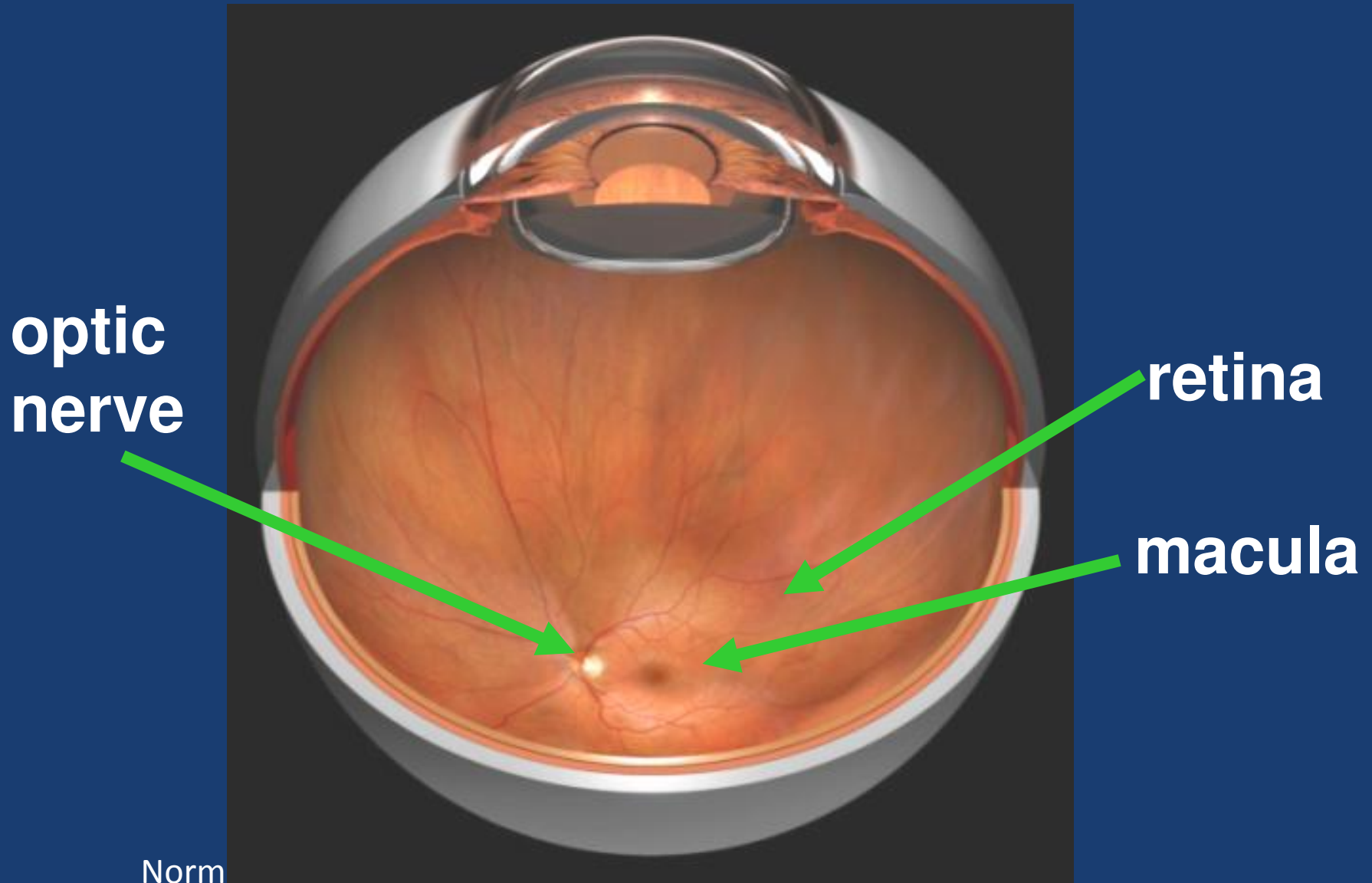


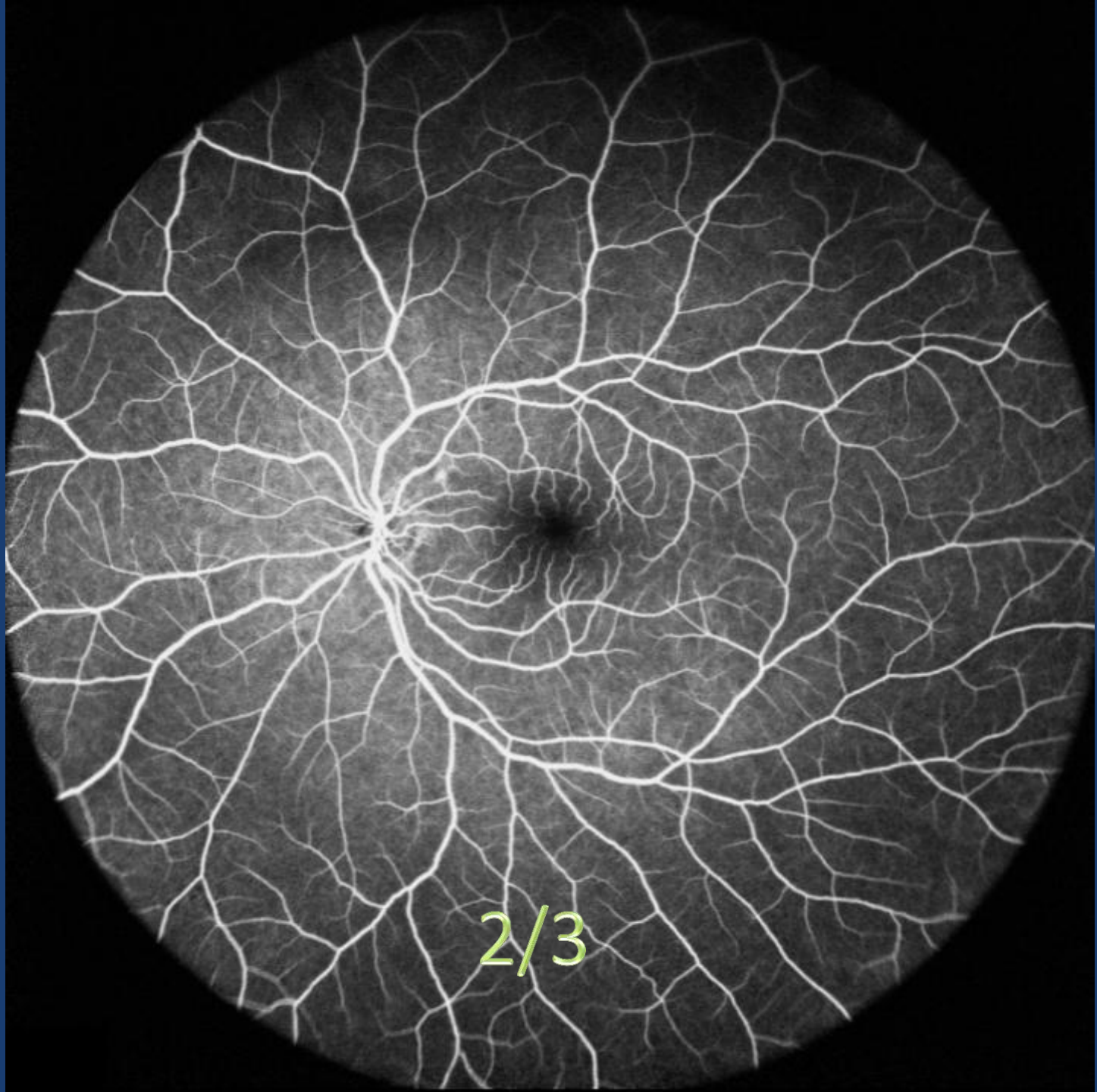
LIGHT



**ROD
PHOTORECEPTOR**

What is the Macula?

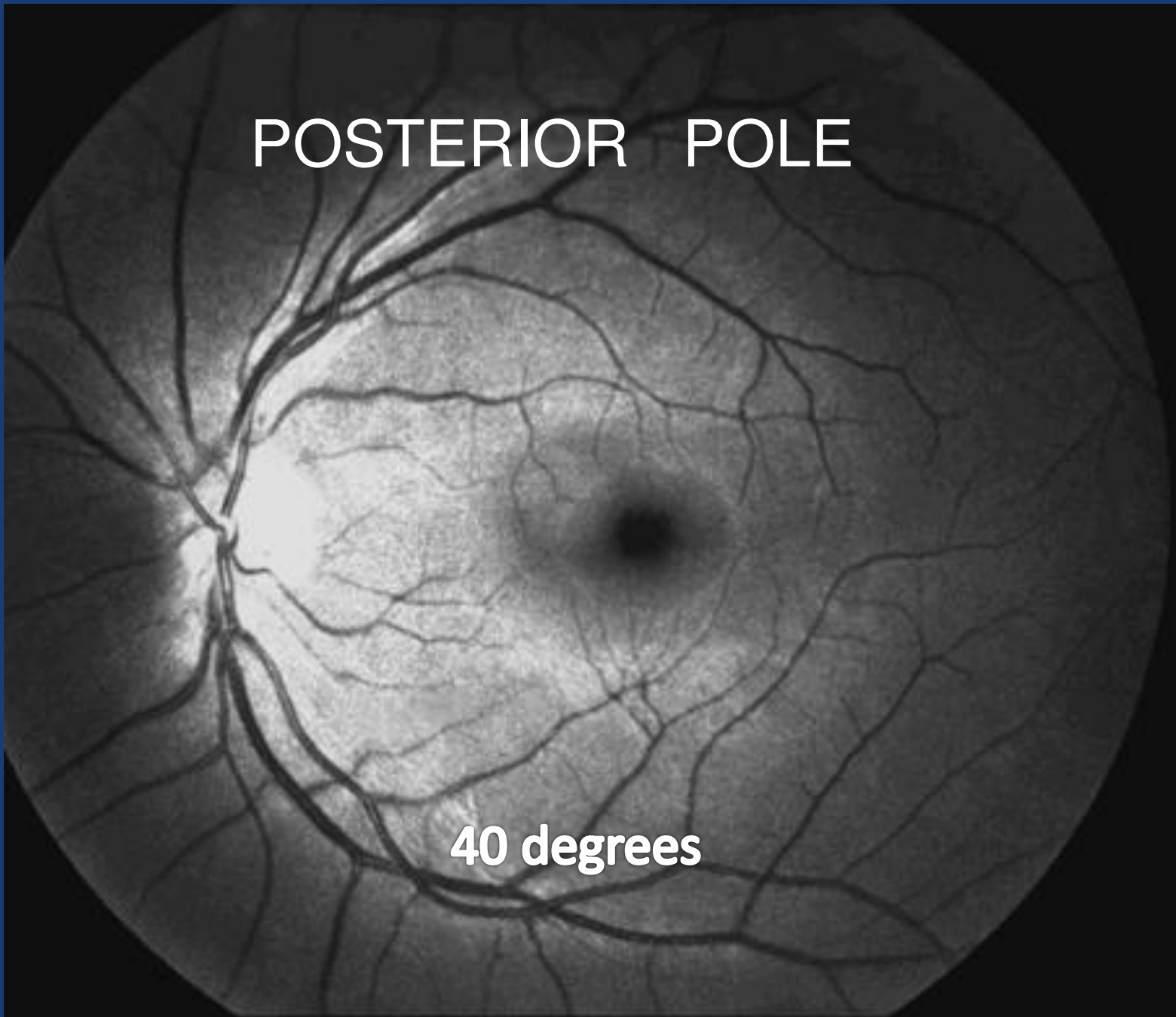


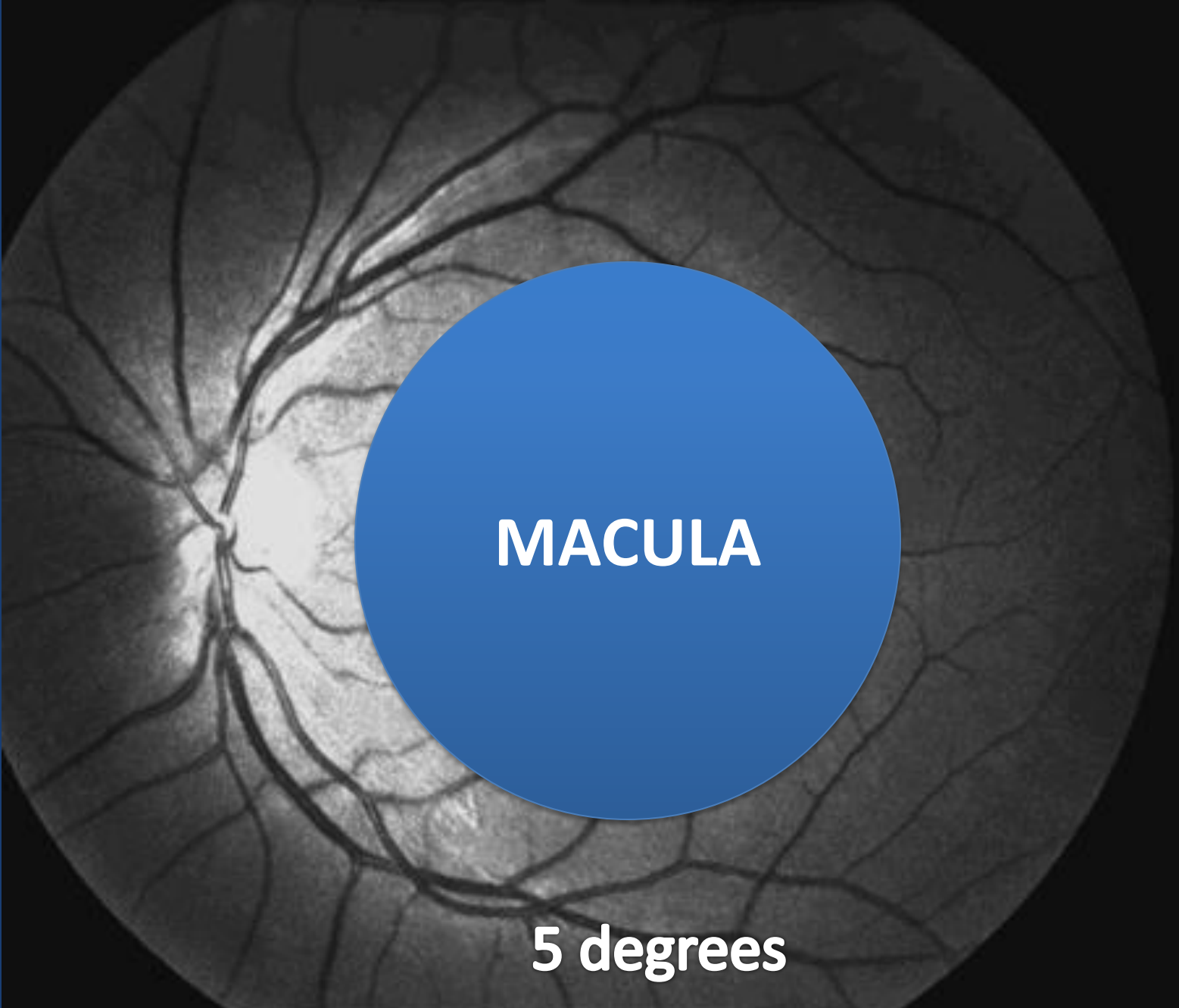


2/3

POSTERIOR POLE

40 degrees

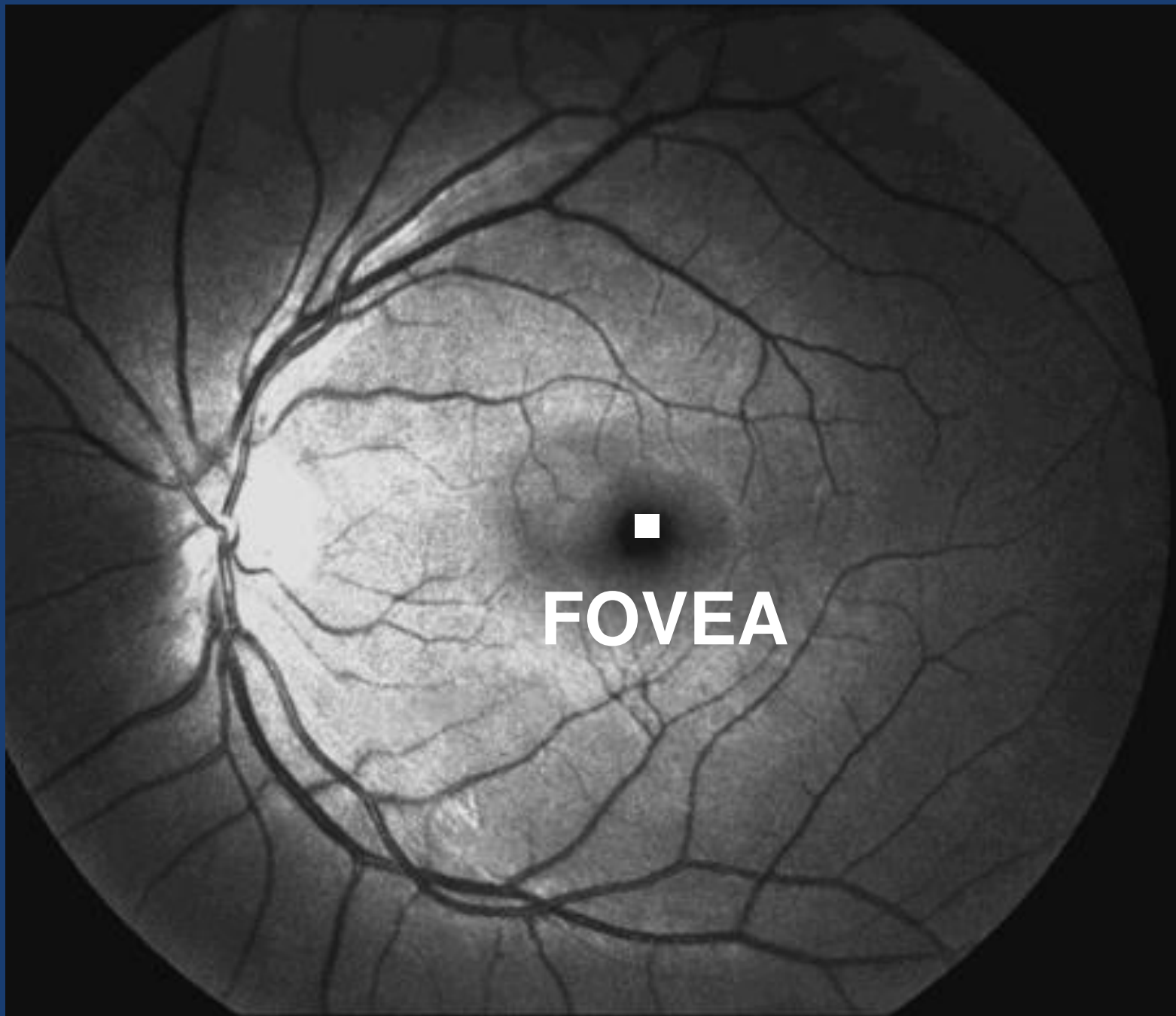




A fundus photograph of a human retina, showing the optic disc on the left and a network of retinal vessels. A blue circular overlay is centered on the macula. The text 'MACULA' is written in white inside the circle, and '5 degrees' is written in white below the circle.

MACULA

5 degrees



FOVEA

MACULA - FOVEA CRITICAL
VERY FINE VISUAL ACUITY

VISUAL ACUITY

VISUAL ACUITY

VISUAL ACUITY

VISUAL ACUITY

VISUAL ACUITY

VISUAL ACUITY

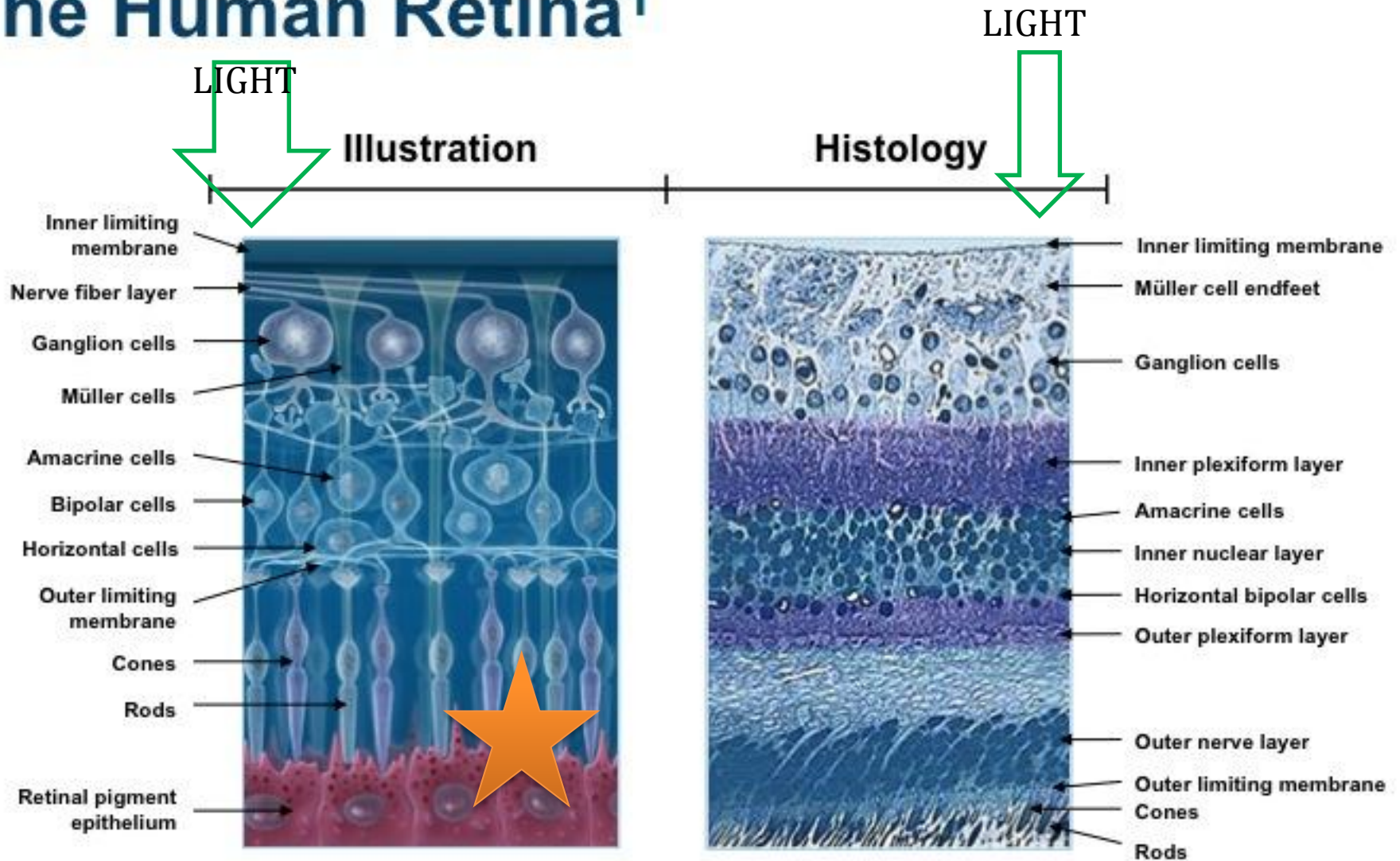
VISUAL ACUI

A fundus photograph of the retina, showing the optic disc on the left and the macula in the center. The fovea, the central point of the macula, is highlighted with a small blue star. The text 'FOVEA' is written in white serif font above the star.

FOVEA

**Very very highly specialized BUT
Extremely susceptible to any insult !!
Legally Blind <6/60**

The Human Retina¹



Micrograph image adapted from Kolb H. *The Organization of the Retina and Visual System*. 2012.¹

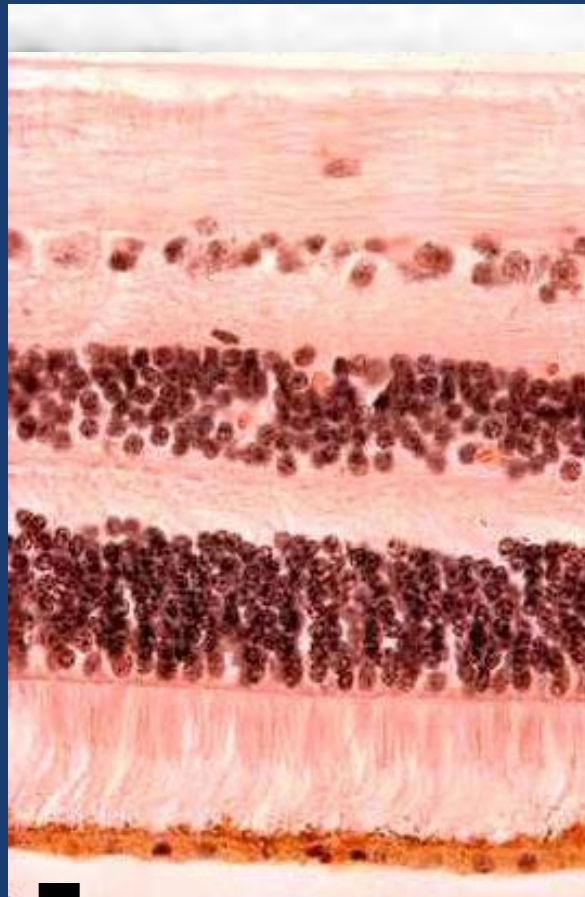
1. Kolb H. Simple anatomy of the retina. In: *The Organization of the Retina and Visual System*. 2012.

OCT

OPTICAL COHERENCE TOMOGRAPHY

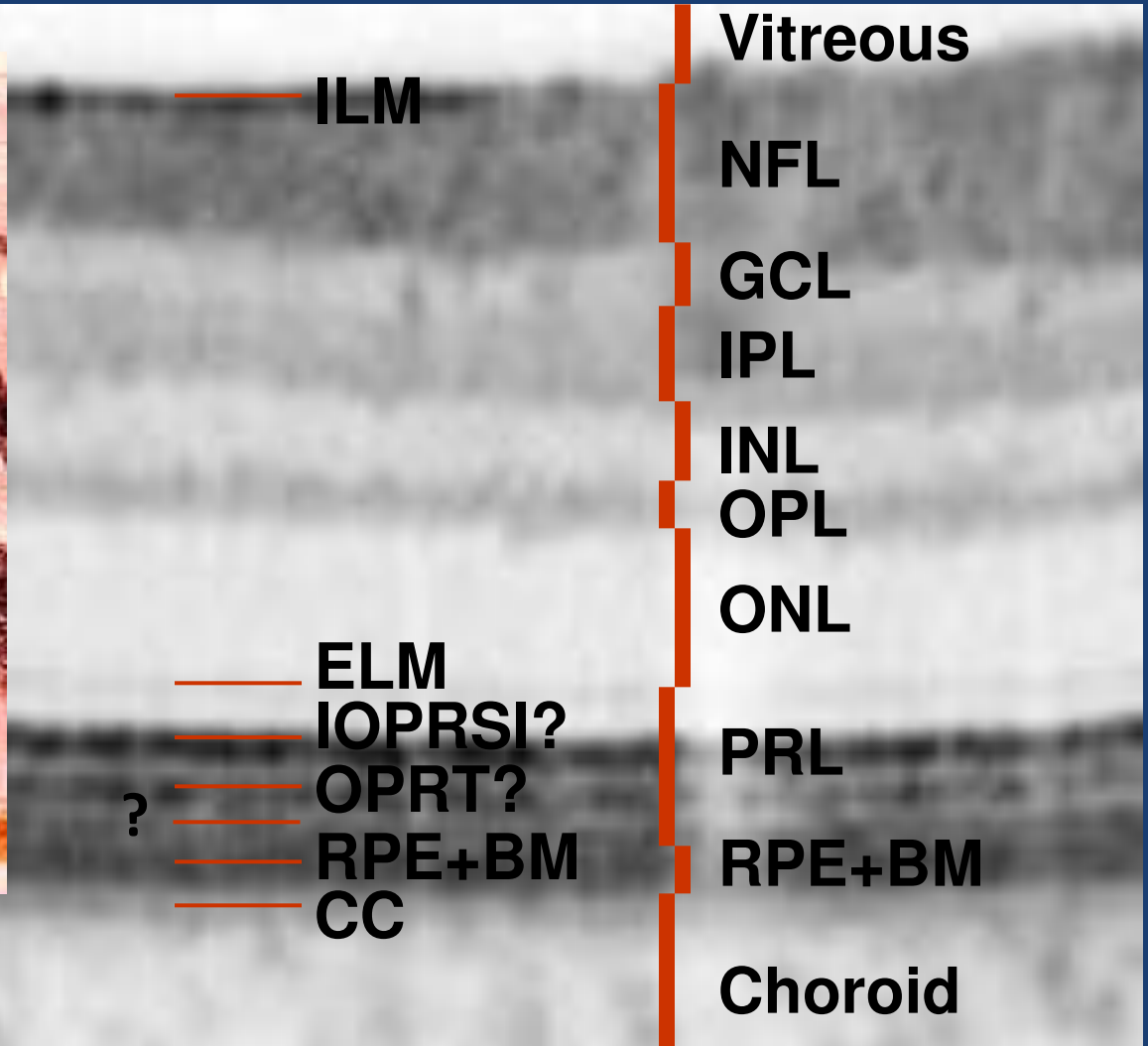
- **REVOLUTION** : in vivo high res optical biopsies
- 3-D OR 2-D IMAGING OF NEURO-RETINA
- RAPID , NONINVASIVE , NON-MYDRIATIC
- HIGHLY REPRODUCIBLE
- SERIAL COMPARISON
- NORMATIVE DATABASE
- ESSENTIAL
- BUT UNFUNDED !!

POST MORTEM HISTOLOGY



50 μm

IN VIVO OPTICAL COHERENCE TOMOGRAPHY



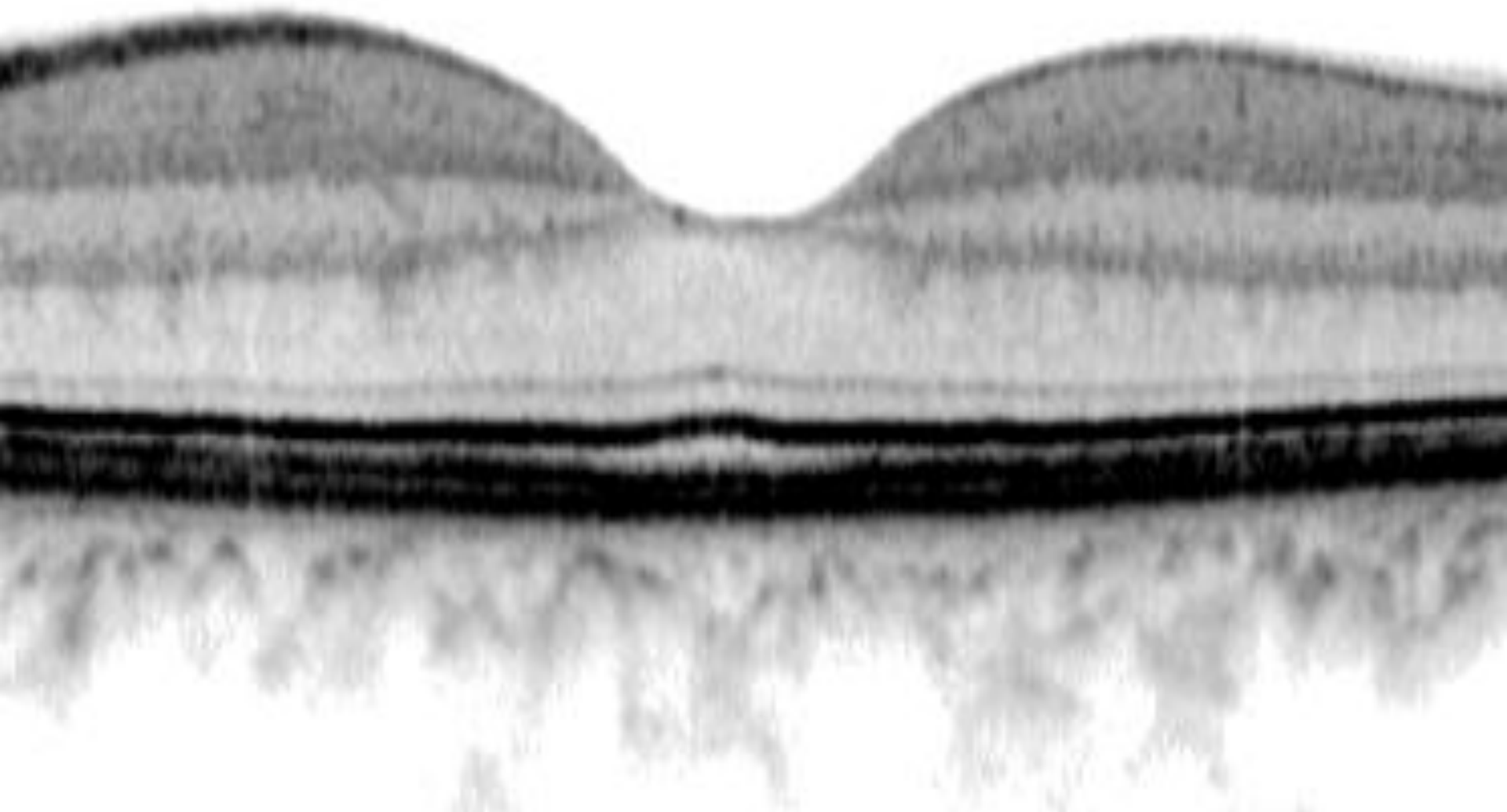
OPTICAL COHERENCE TOMOGRAPHY

UNFUNDED

SD OCT C/S CUTS < 10 microns

200 μm

Optical Coherence Tomography



FOVEA



foveola

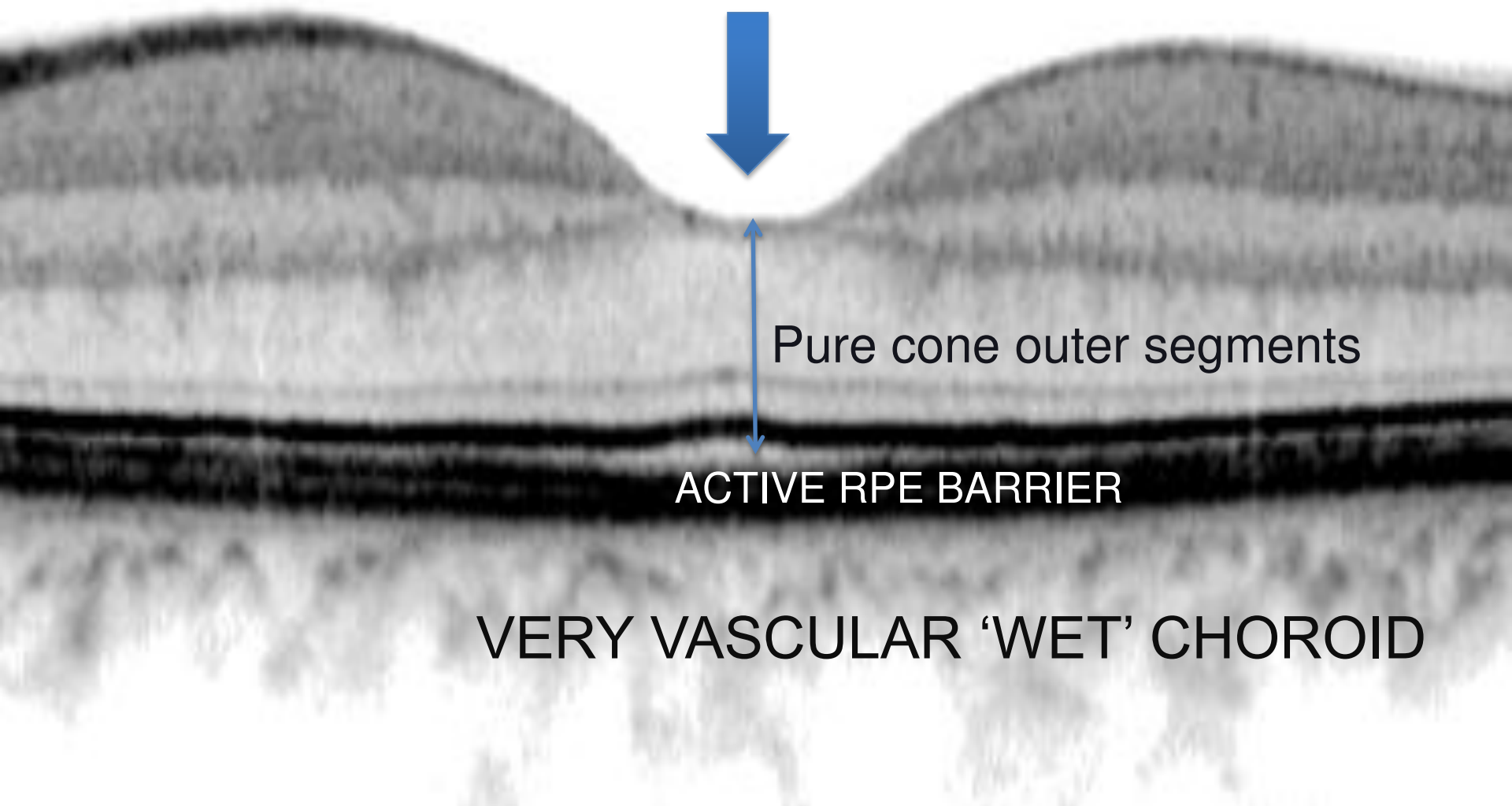


Pure cone outer segments



ACTIVE RPE BARRIER

VERY VASCULAR 'WET' CHOROID



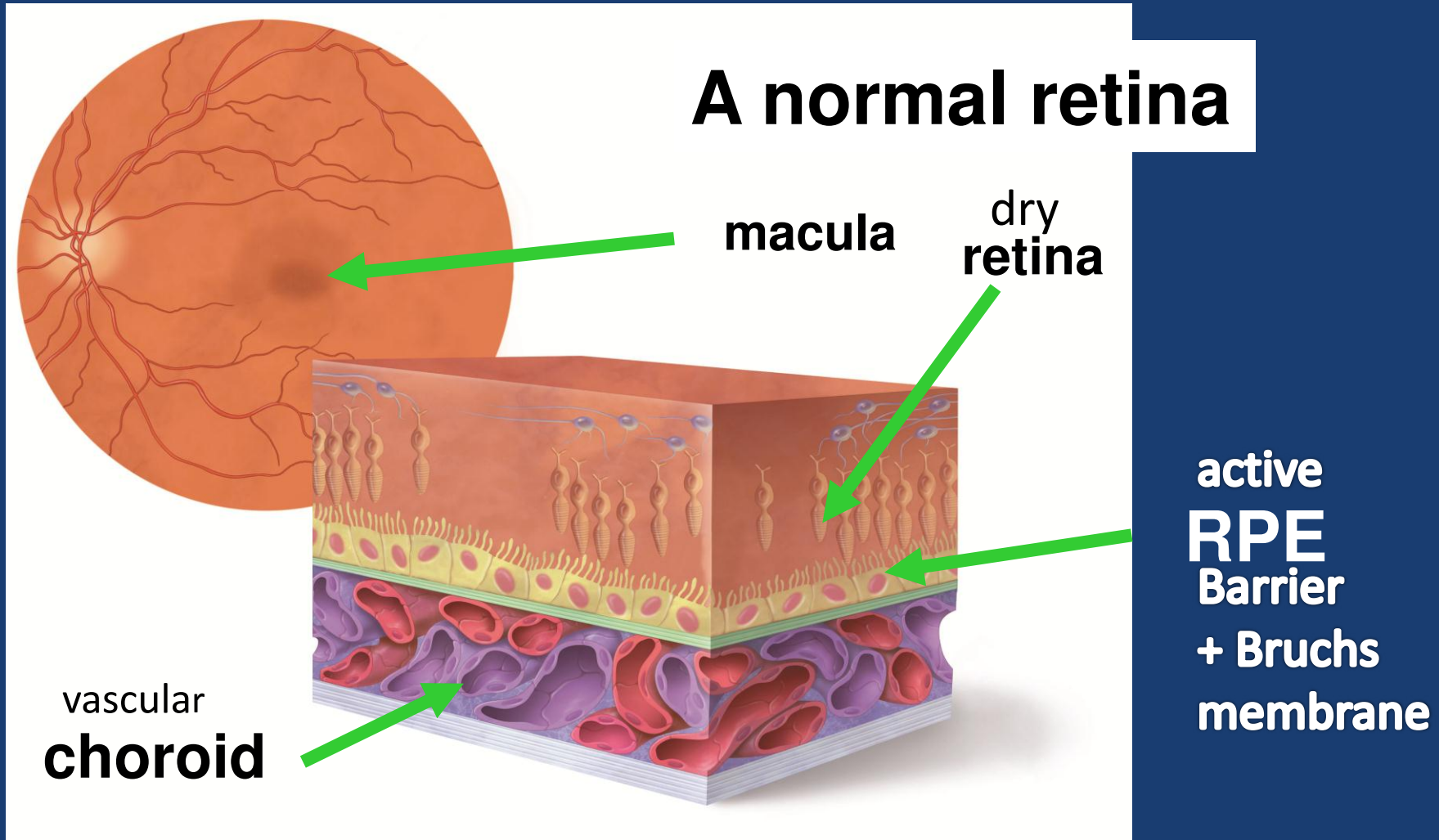
OCT



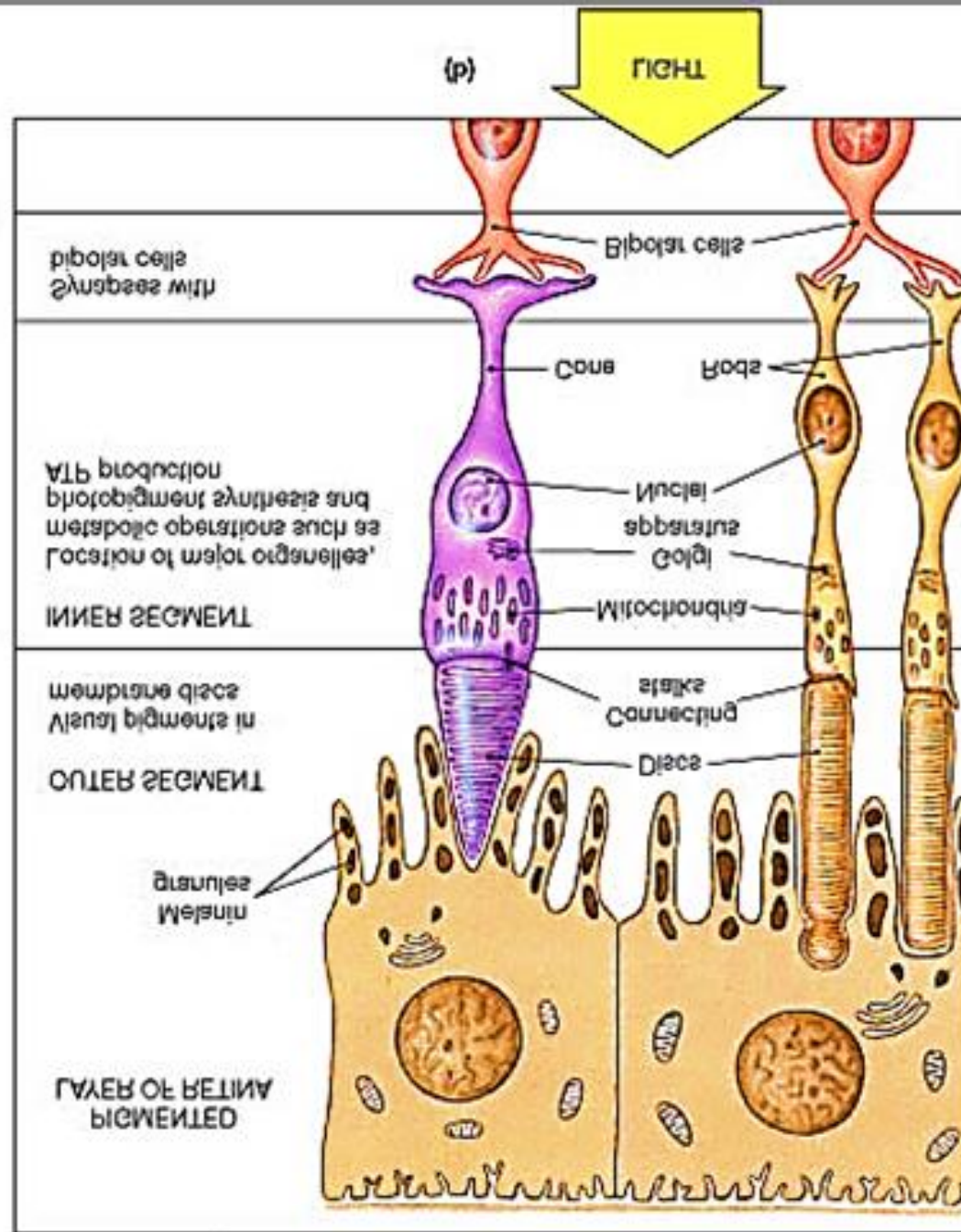
Quick easy non-mydriatic non-invasive acquisition

How AMD Develops

AMD is a disease of the Retinal Pigment Epithelium



**RODS
CONES**

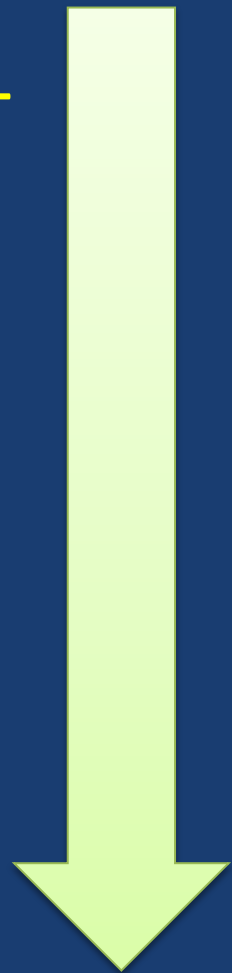


**VISUAL
PIGMENT
DISCS**

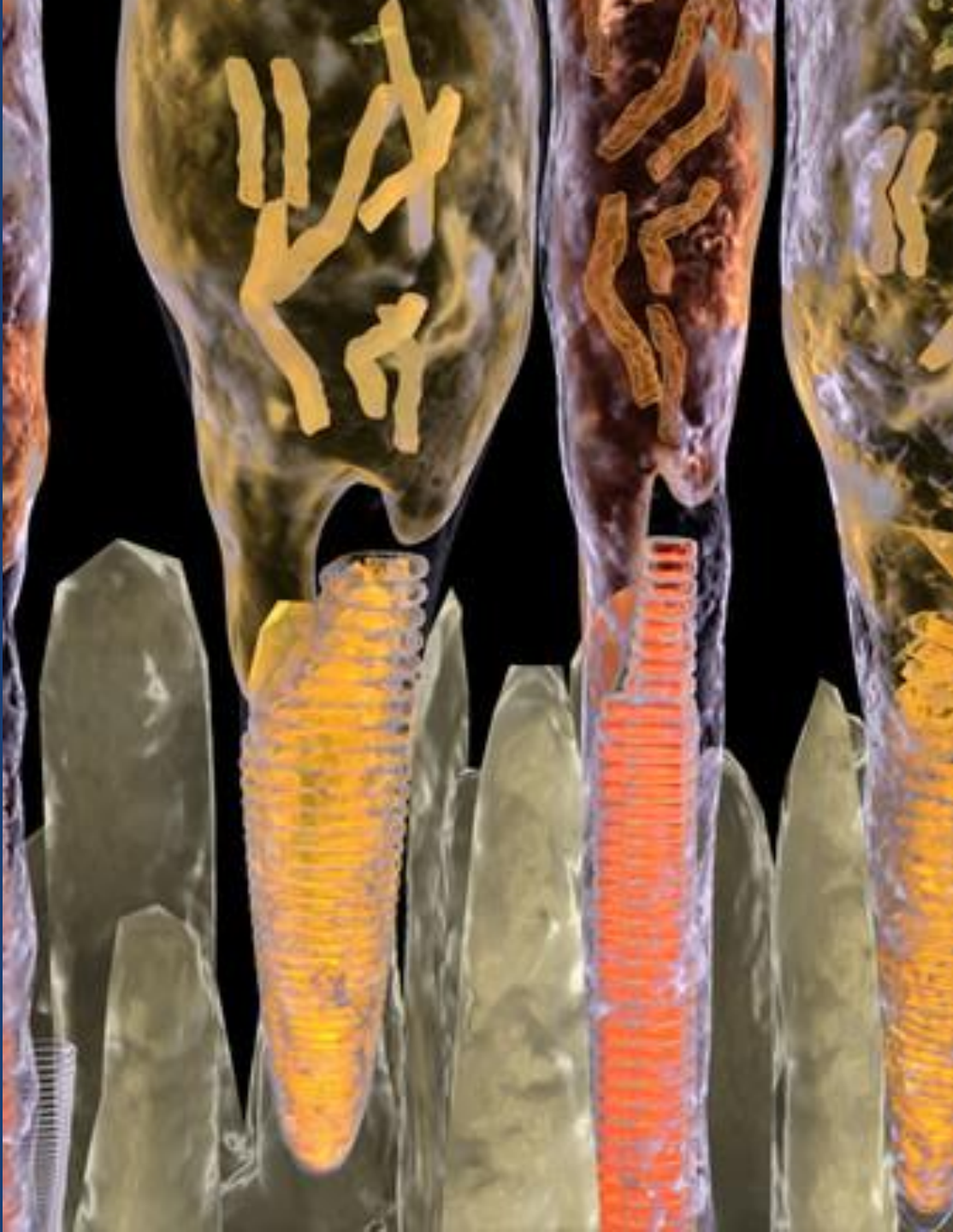
**RPE
MONOLAYER
CELLS**

**RETINAL
PIGMENT
EPITHELIUM**

LIGHT



RPE
MICROVILLI



ROD+CONE
OUTER
SEGMENT
DISCS

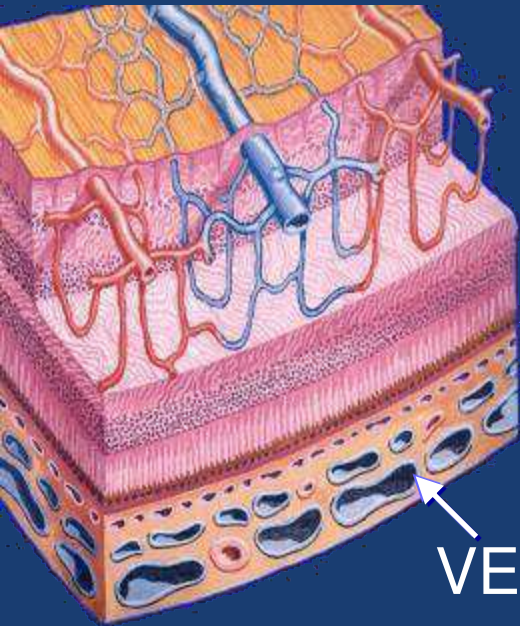
The role of the RPE

“ DRY “ NEURO - RETINA

Recycles discs

Nourishes

Removes waste products

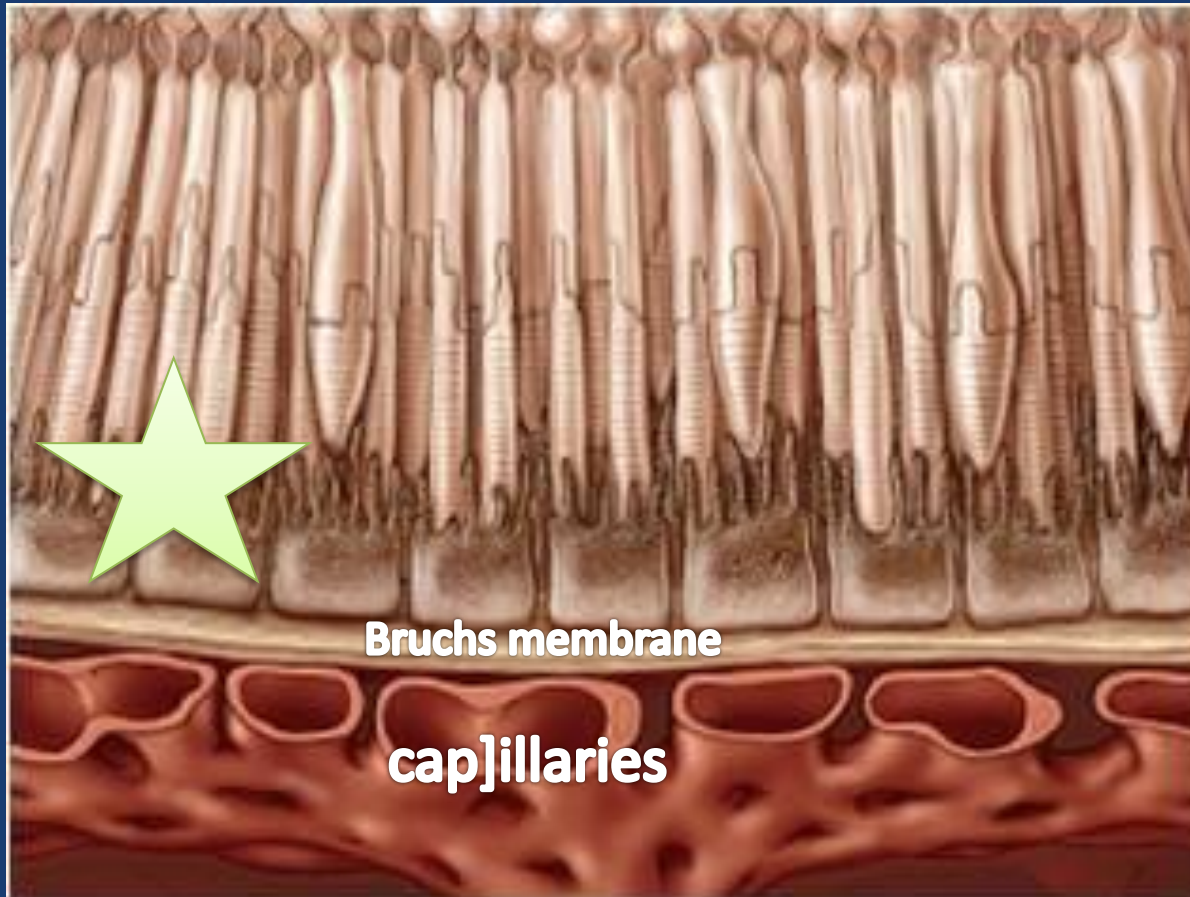


RPE

VERY VASCULAR CHOROID

Barrier stopping fluid and choroidal blood vessels from growing into retina

Outer retina in C/S



**Outer Retina
rods+cones**

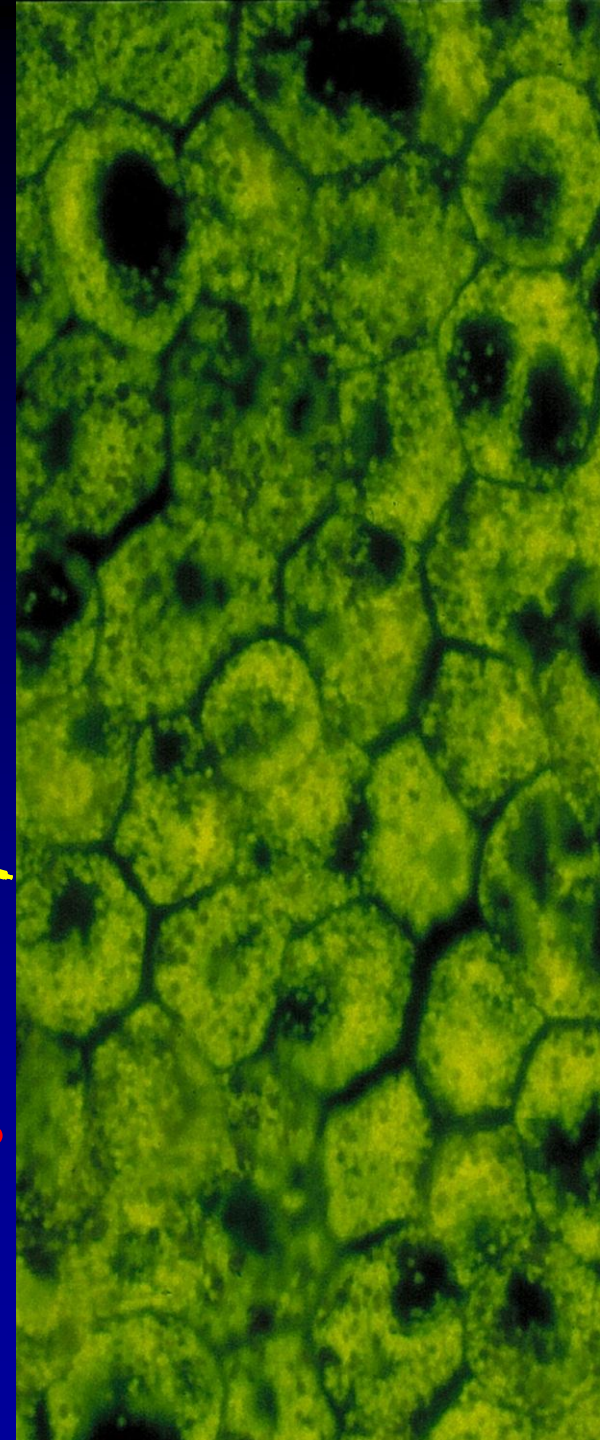
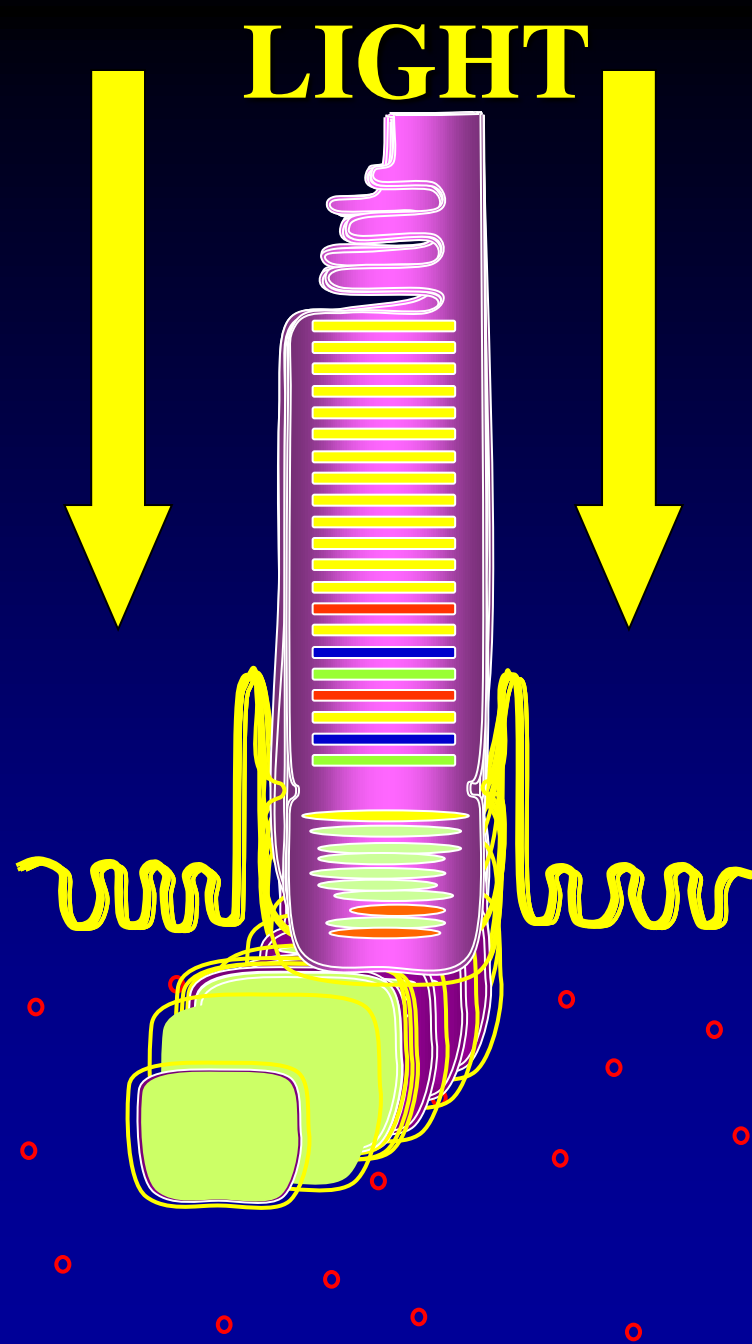
**active
RPE**

barrier

**Choroid
blood vessels**

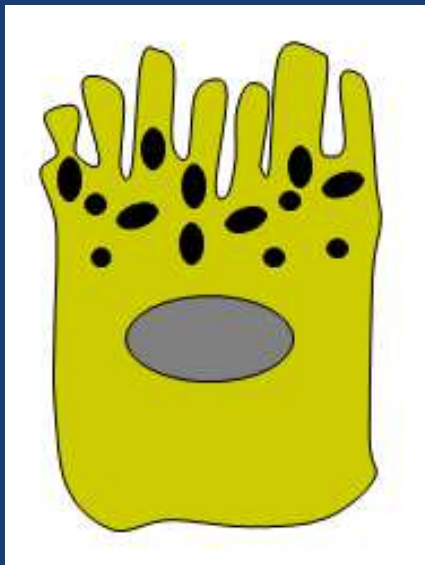
Bruchs membrane

cap]illaries

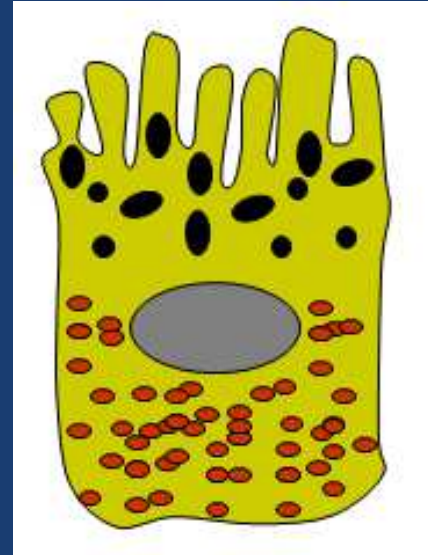
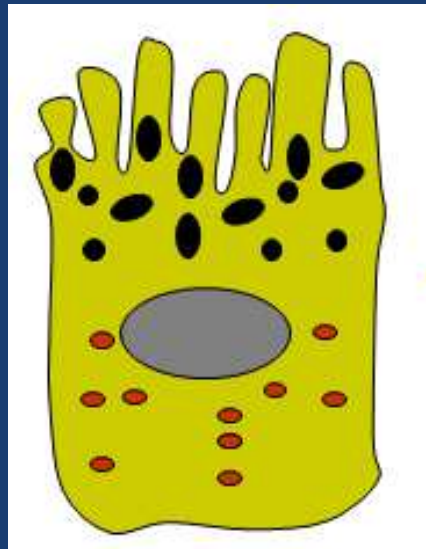


The role of the RPE

Waste builds up in the RPE as we age



Normal
RPE cell



“Garbage” builds up over time

LIPOFUSCIN

AGED EYE

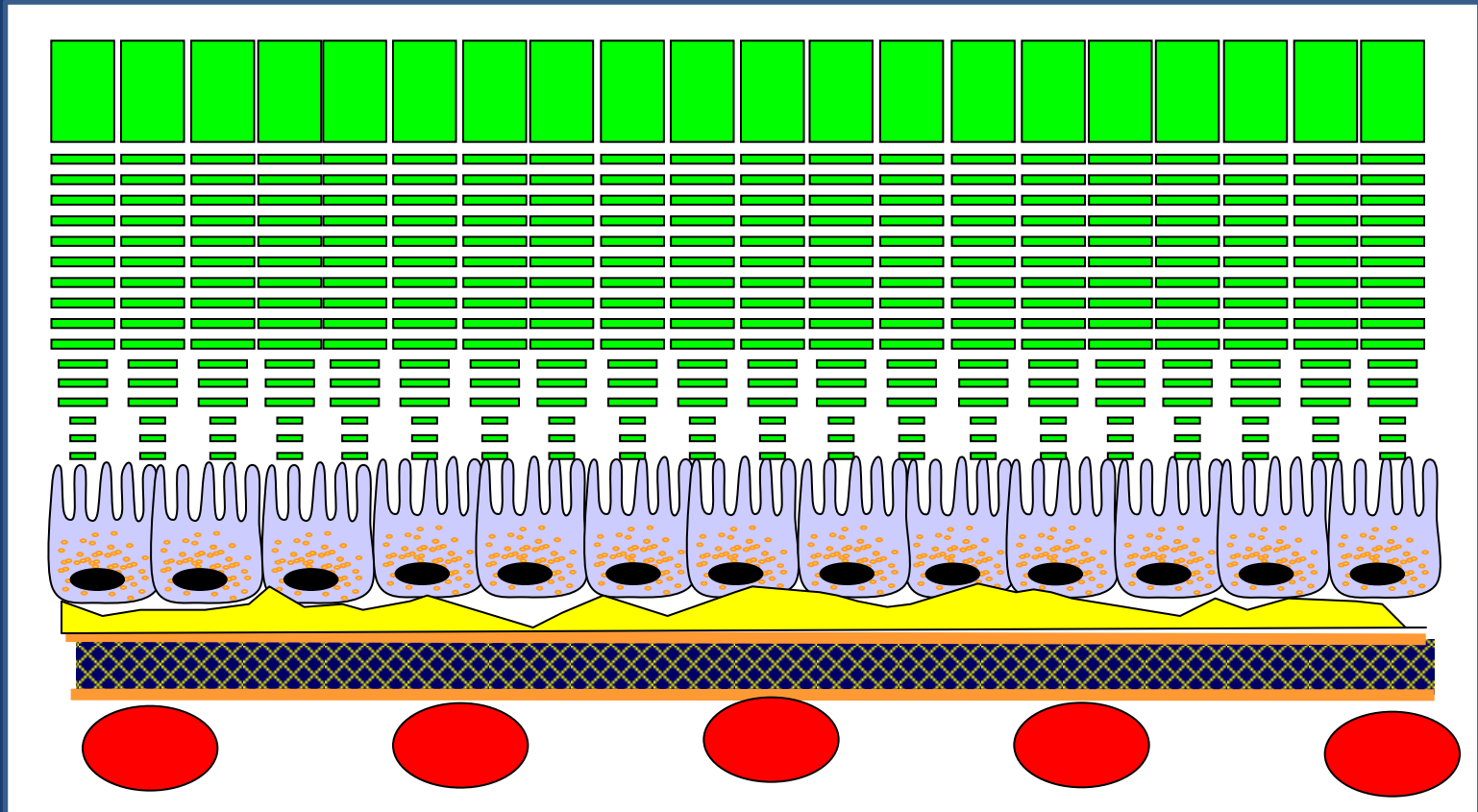
EM BLIND BLAMD DEBRIS

ROD
CONE
OUTER
SEGMENT
DISCS

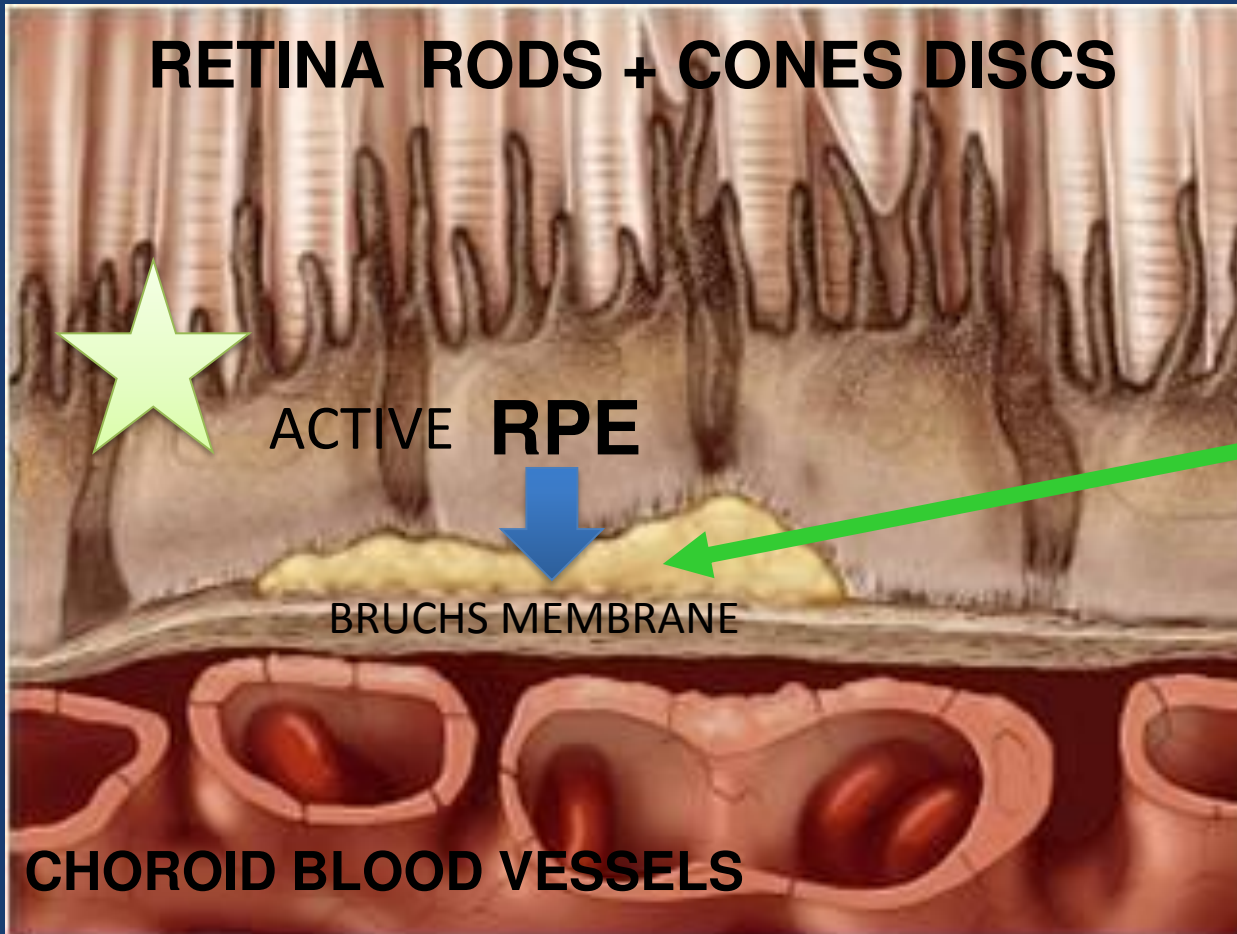
RPE

BM

CC



Early stage AMD

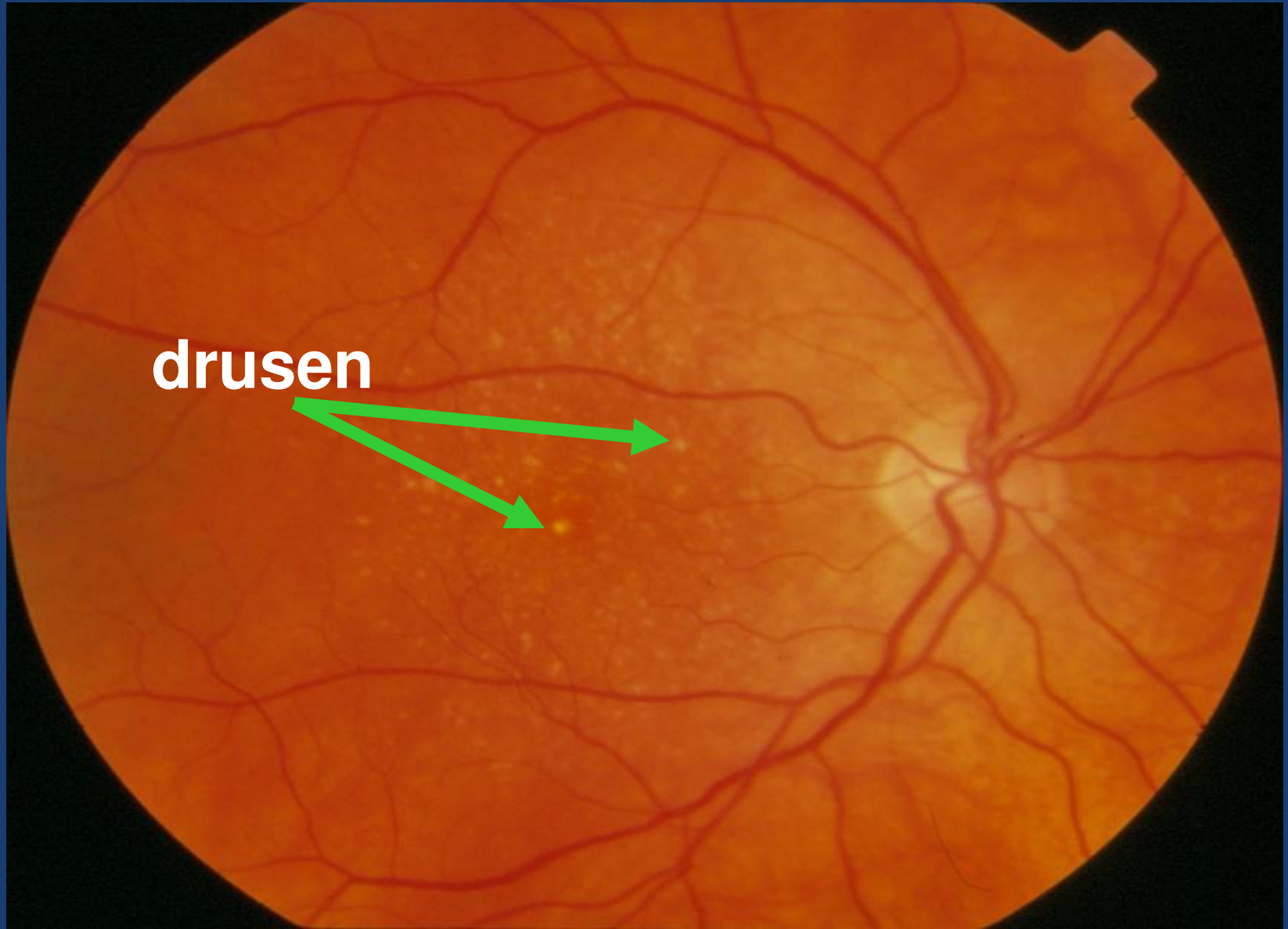


Drusen

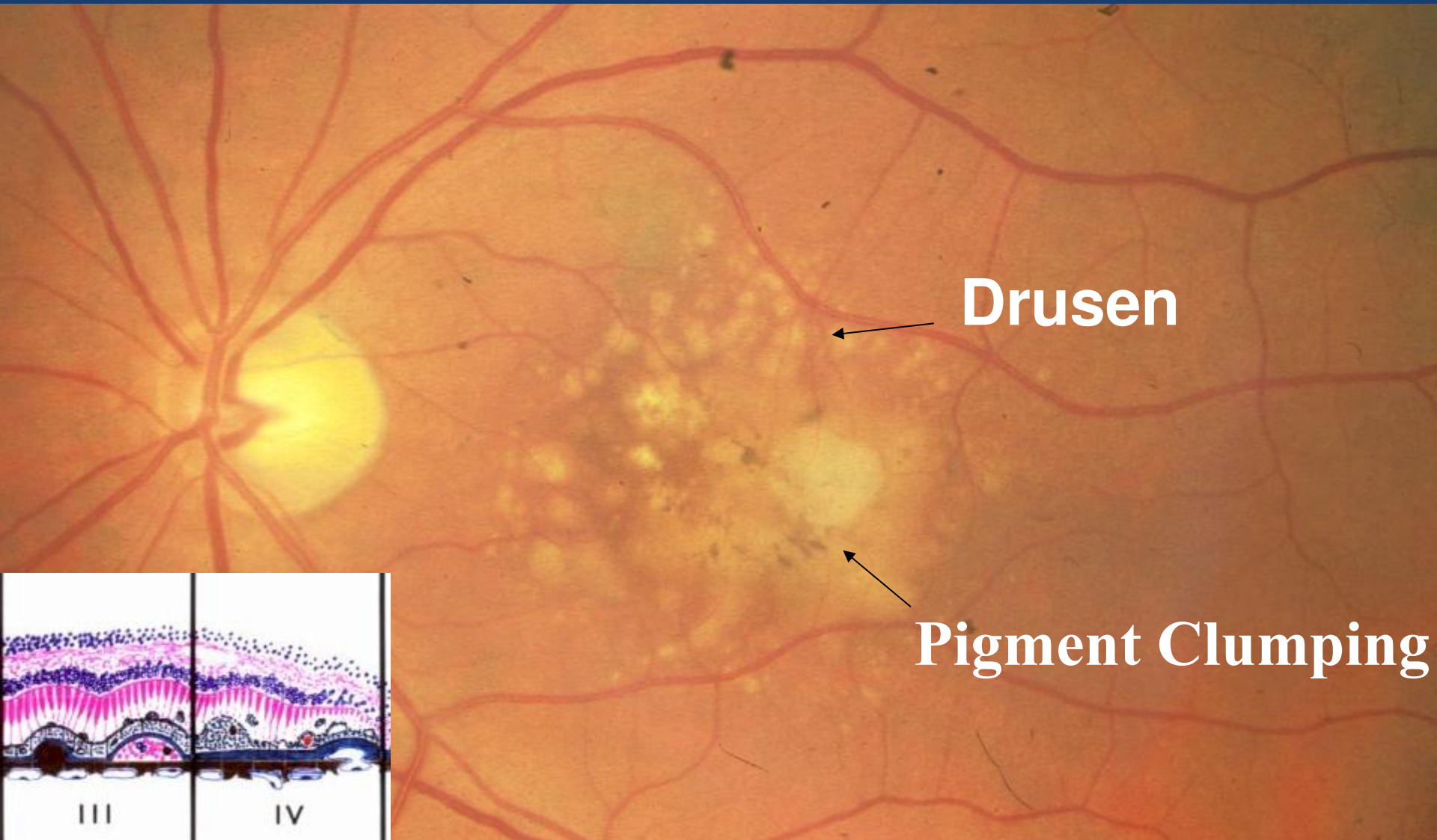
waste products
oxidative stress
Inflammation
MACs

C

Early stage AMD



AGE RELATED MACULOPATHY



Types of AMD

- **EARLY STAGES - asymptomatic**
- **LATE STAGES**

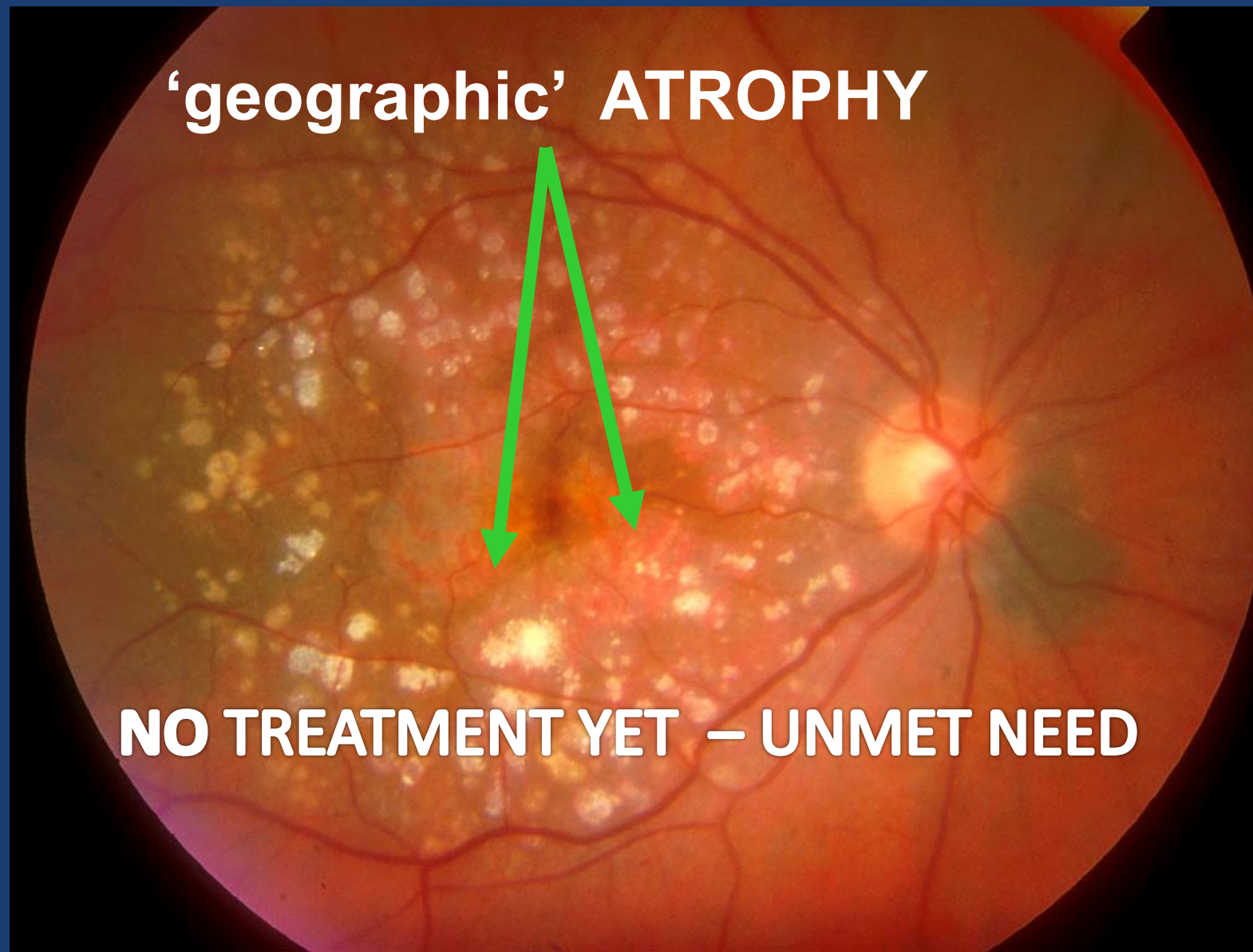
Dry MD common

- non-aggressive
- slow , progresses over years or decades
- end stage may have significant vision loss

Wet MD nasty

- rapid onset , aggressive, severe vision loss

Late stage “DRY” AMD



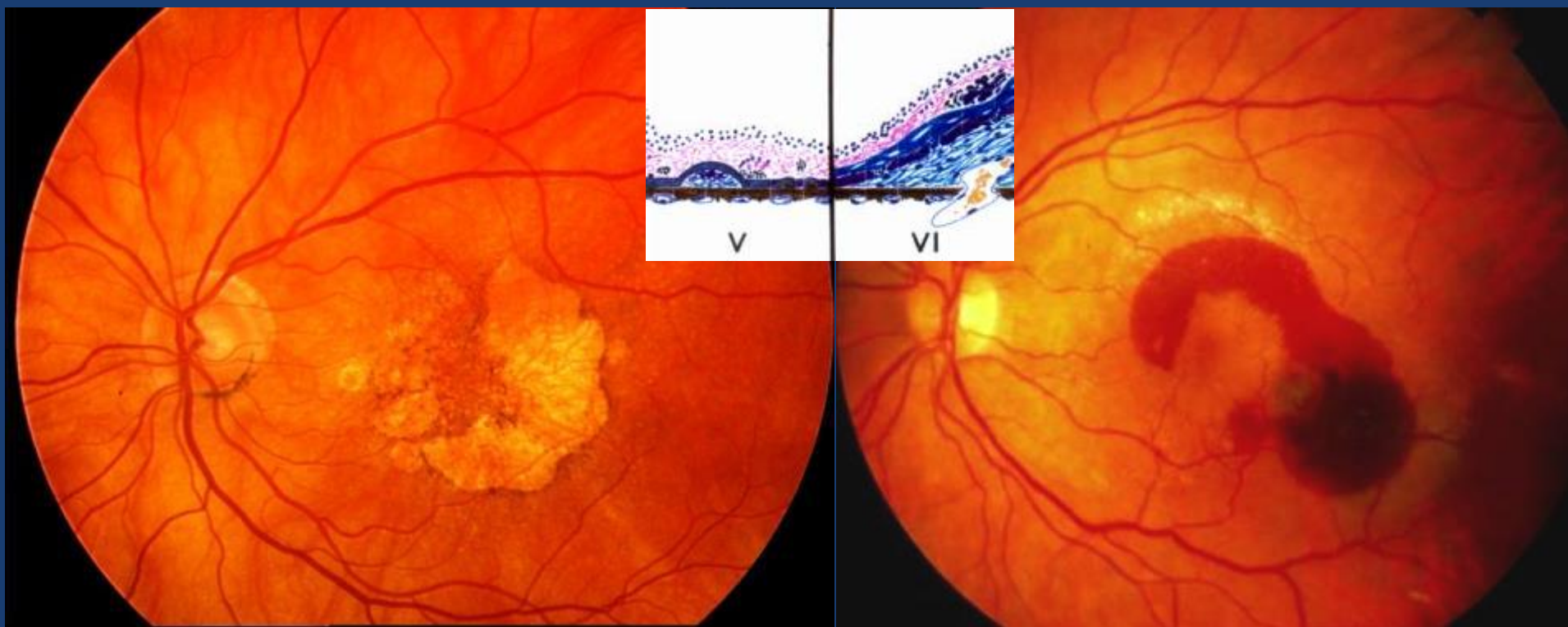
Late stage - Age related Macula Degeneration

DRY = atrophy

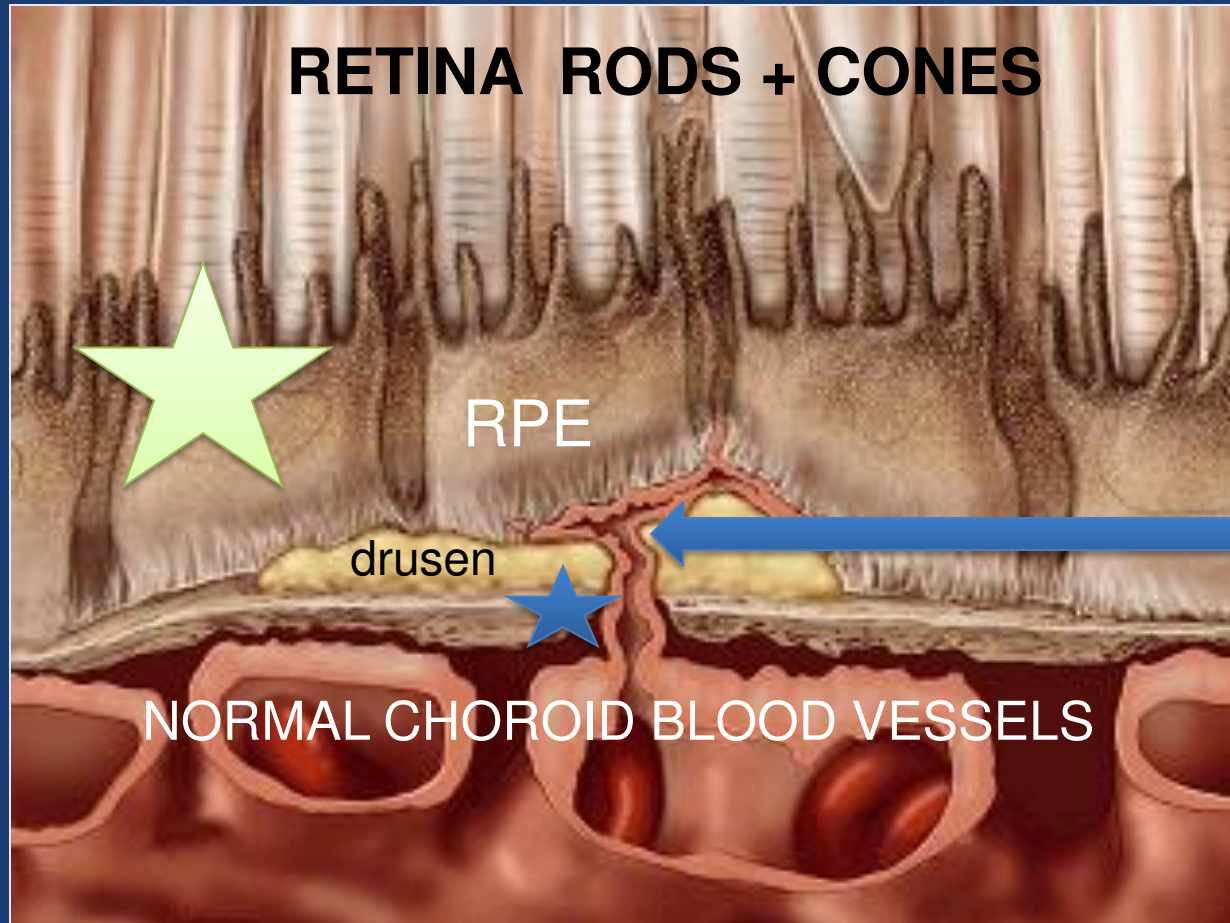
Gradual visual loss
RPE atrophy

WET = CNV

Haemorrhage + Fluid
Rapid visual loss



Initial stage “WET” AMD



CNV

“bad” new
blood vessel

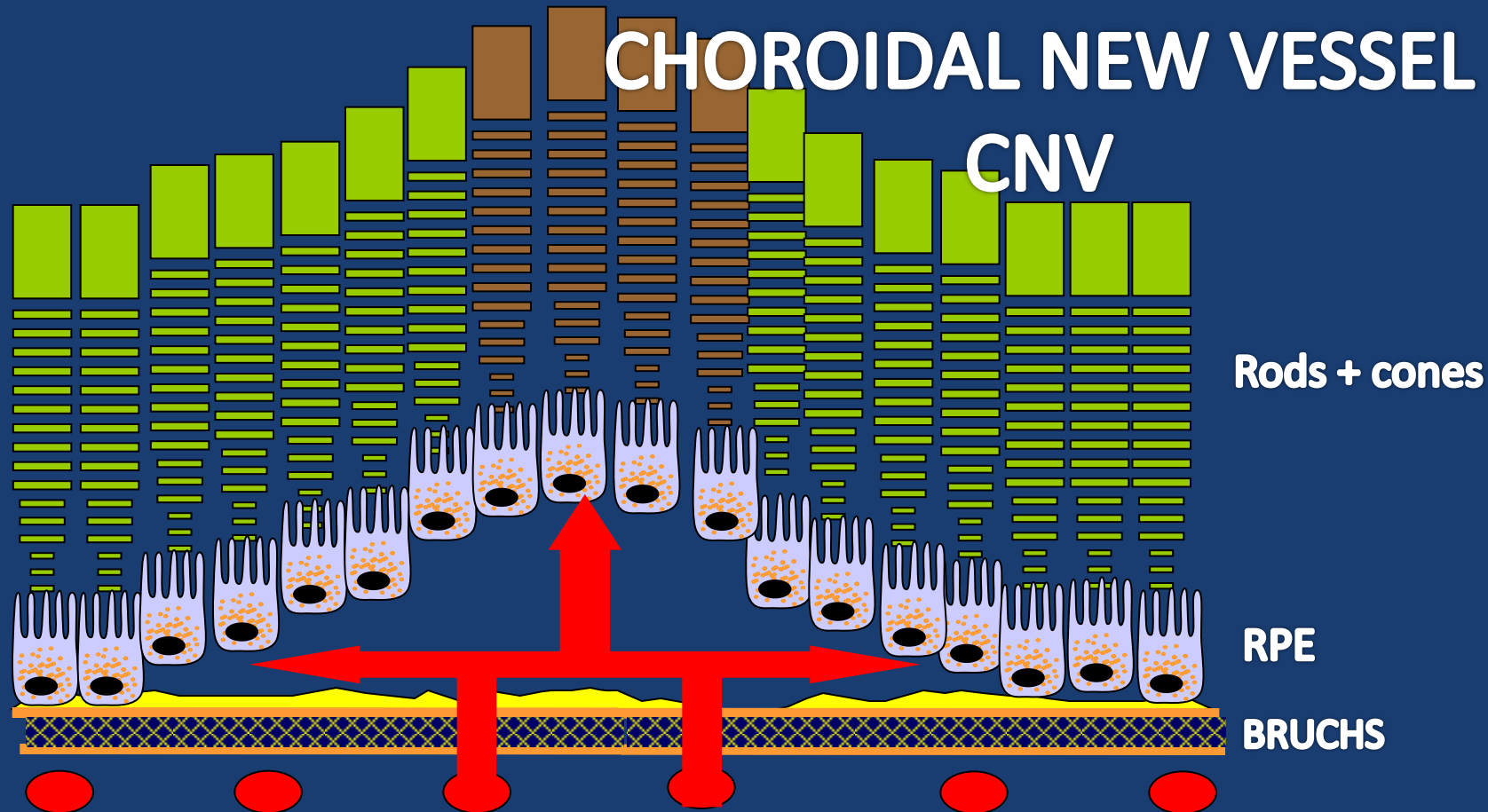


Leak
Bleed
Scar

Type 1 CNV : SUB-RPE WET AMD = CNV 1994

FRAGILE ABNORMAL
CHOROIDAL NEW VESSEL

CNV



Over expression of VEGF + C - bad choroidal new vessels

Wet Form Accounts for ~90% of Severe* Vision Loss Due to AMD¹

- Wet form is characterised by²
 - Subretinal fluid
 - Subretinal haemorrhage
 - RPE detachment
 - Hard exudates
- Wet AMD can be effectively treated with anti-angiogenic therapies^{3,4}

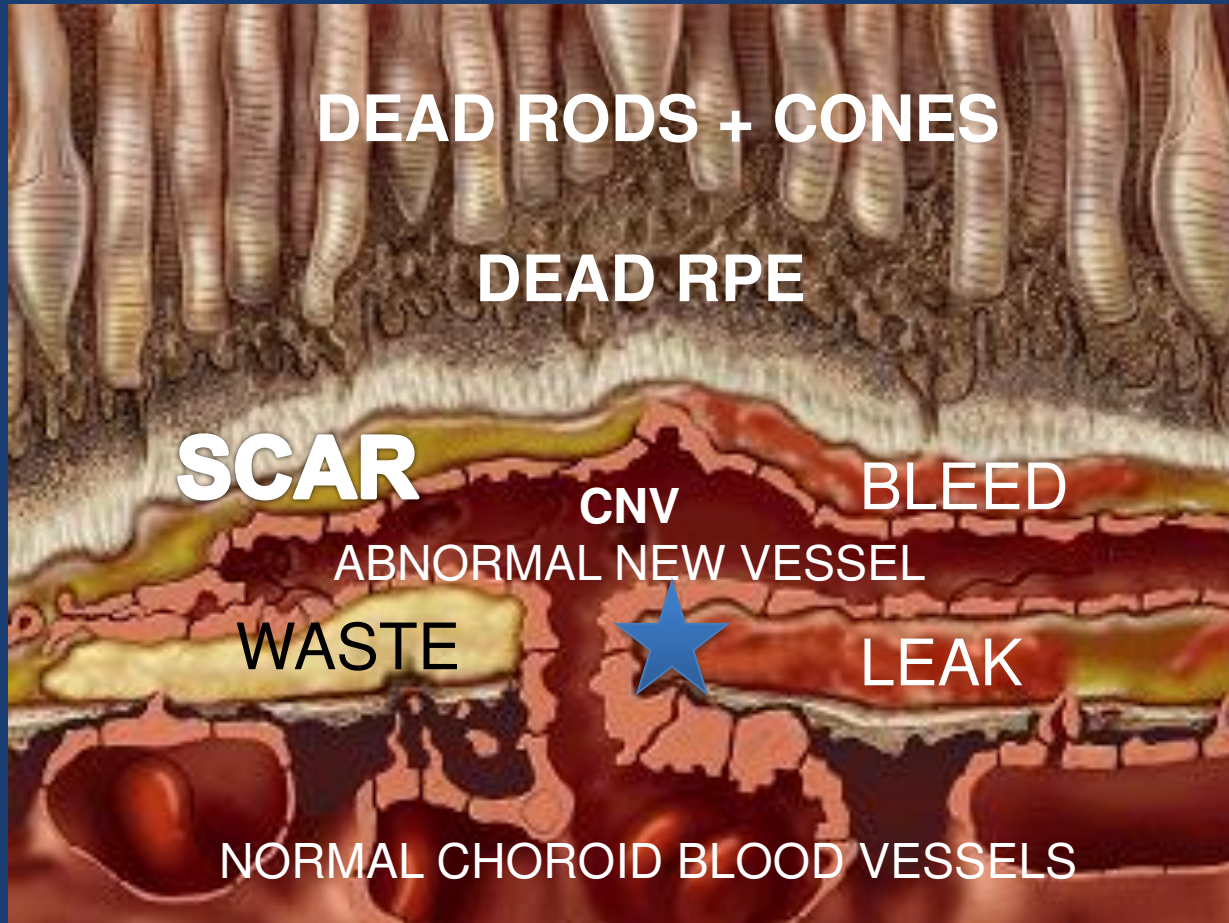
*Visual acuity 20/200 or worse.



Wet AMD in the central retina

1. Preferred Practice Pattern® Guidelines. American Academy of Ophthalmology; 2011
2. Lim JI, Tsong JW. In: *Age-Related Macular Degeneration*. 2007:125-157
3. EYLEA Product Information, 15 March 2012
4. Lucentis Product Information, 25 October 2011

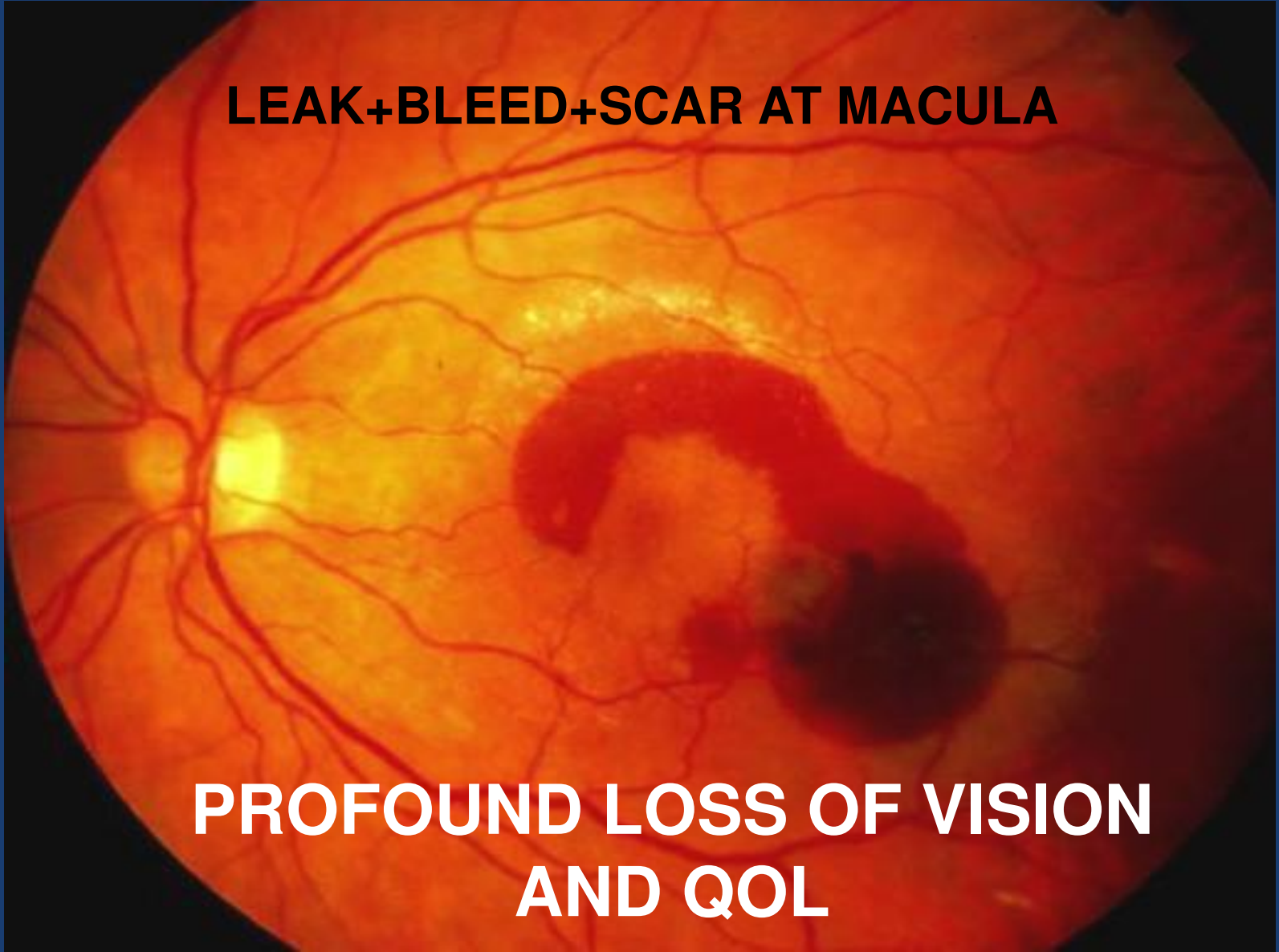
Late stage “WET” AMD



Late stage “WET” AMD

LEAK+BLEED+SCAR AT MACULA

**PROFOUND LOSS OF VISION
AND QOL**

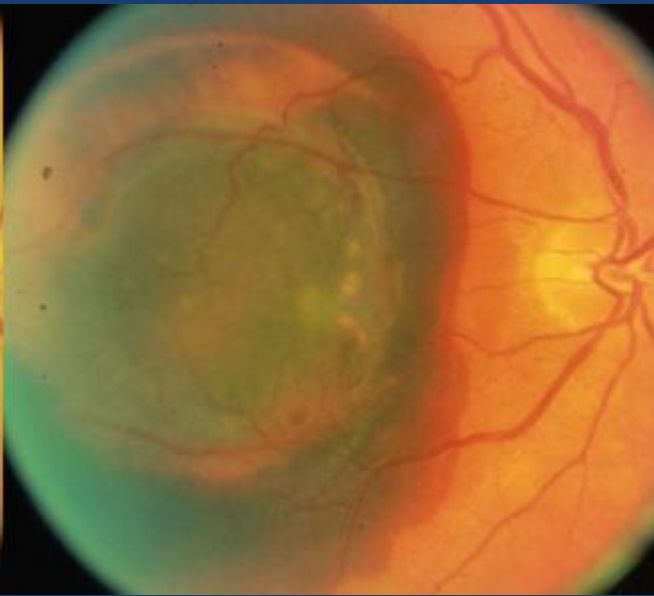


Evolution of macular degeneration

72 year old man seen after 2 months and 1 year



soft drusen,
pigment changes



bleed under
retina



scar formed
under retina

AMD TRIALS

- OBSERVATIONAL c/s or longitudinal

BMES Paul Mitchell

CERA Robyn Guymer

Genetic

- INTERVENTIONAL Therapeutic

AREDS 1 & 2

LEAD 2RT

WET : ANTIVEGF

DRY

METRICS: Efficacy vs SOC

- BCVA LogMar Letters
- MP , Light- Dark , SCS , Colour , etc
- PRO VFQ-25
- Ophthalmoscopy drusen , GA , RPE
- OCT drusen volume , GA area ,
fluid , PED , CRT etc
- FAF for GA
- FFA & ICGA cnv, polyps, area

SAFETY

- Serious Adverse Events
- Adverse Events

NON OCULAR

OCULAR

IMAGING MODALITIES

complement each other

- COLOR PHOTO non-mydratic 45 deg
- OPTICAL COHERENCE TOMOGRAPHY
- MYDRIATIC CLINICAL VIEW various
- FUNDUS FLUORESCEIN ANGIOGRAM
- RED FREE PHOTO
- INFRA RED IMAGE
- FUNDUS AUTO FLUORESCENCE

Symptoms of MD

- **Early stages = normally no symptoms!**
- **Distinguishing faces a problem**
- **Difficulty with detailed or fine vision**
- **Dark patches or empty spaces in central vision**

Symptoms of wet AMD

few things ne
s as they begin t
ds have been the
pear until early
nce, they are



wetAMD in one eye



TREATMENT for AMD

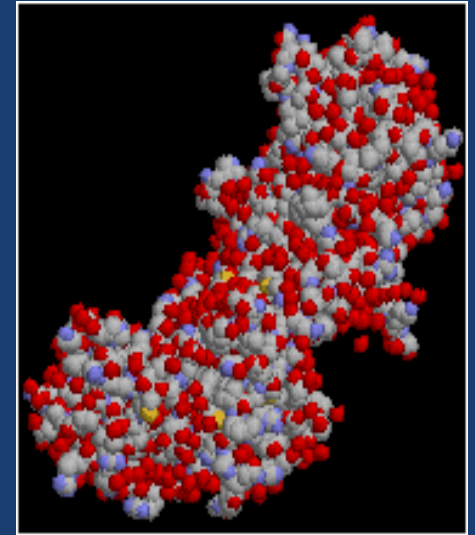
- **Presently no cure or prevention**
- **Dry MD = no treatment**
but diet and lifestyle important
- **Wet MD = treatment now available**

Treatments for WET AMD

- Laser: for new vessels not under the fovea
- **Anti-VEGF drugs**
 - but Intravitreal injection repeatedly

VEGF – Vascular Endothelial Growth Factor

- VEGF is a natural protein that acts on endothelial cells (the cells that line blood vessels)
- VEGF stimulates angiogenesis (new vessel growth)
- VEGF is a potent inducer of vascular permeability (leakiness of blood vessels)



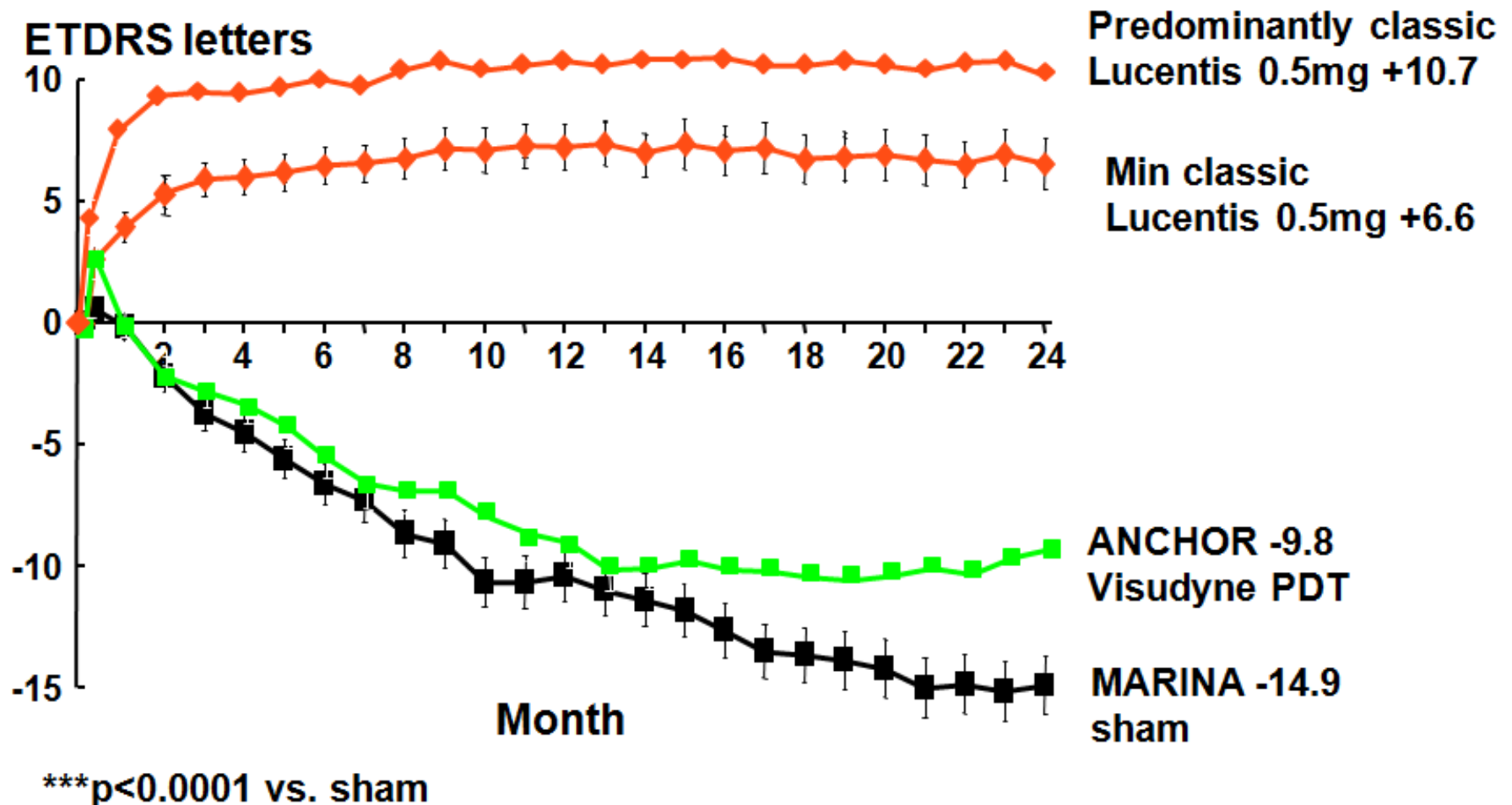
VEGF INHIBITORS / BLOCKERS

EFFECTS ARE :

- ANGIOGENESIS INHIBITED cancer
- LEAKAGE REVERSED / STABILIZED [VPF]
- DECREASE INFLAMMATION

Treatment for Wet MD

Initial Ranubizumab – Trial Outcomes 2005



Treatment for Wet MD

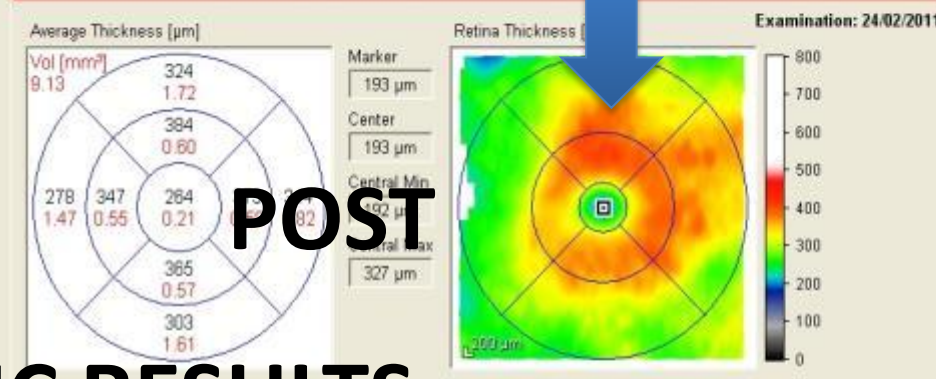
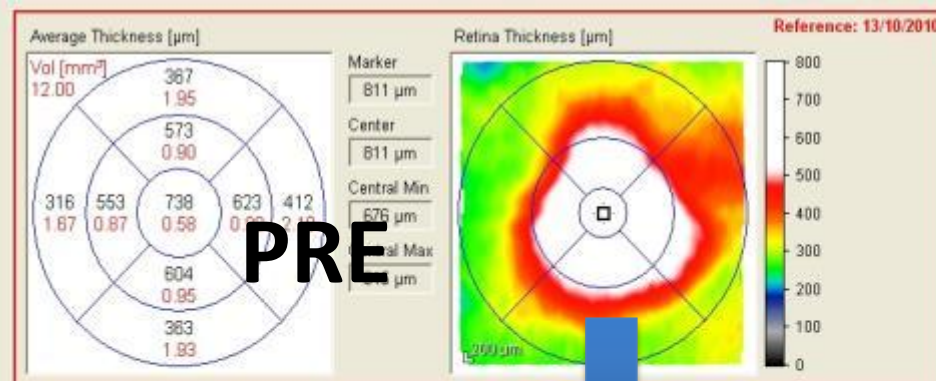
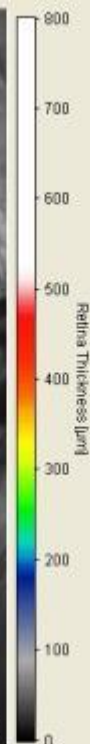
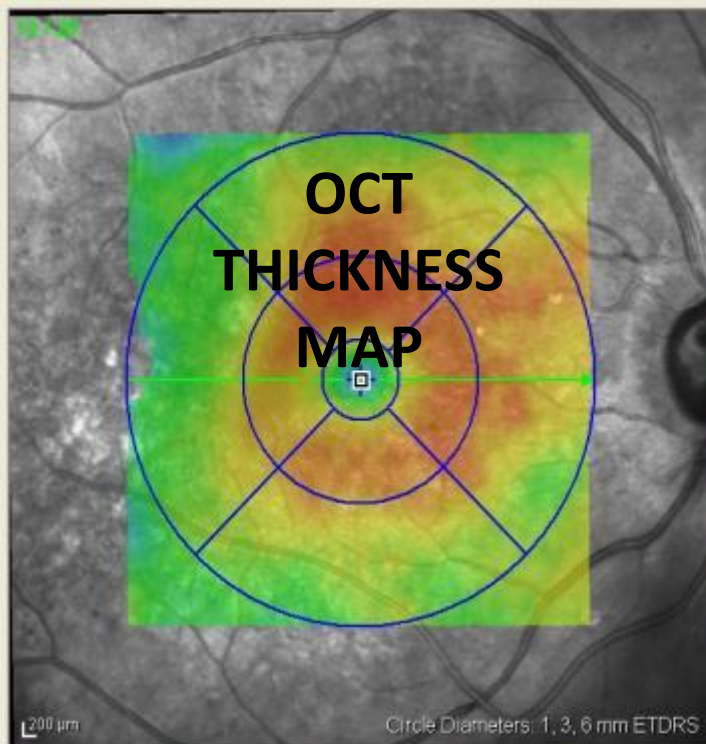
AntiVEGF treatment outcomes:

Old lesions do NOT respond to treatment !

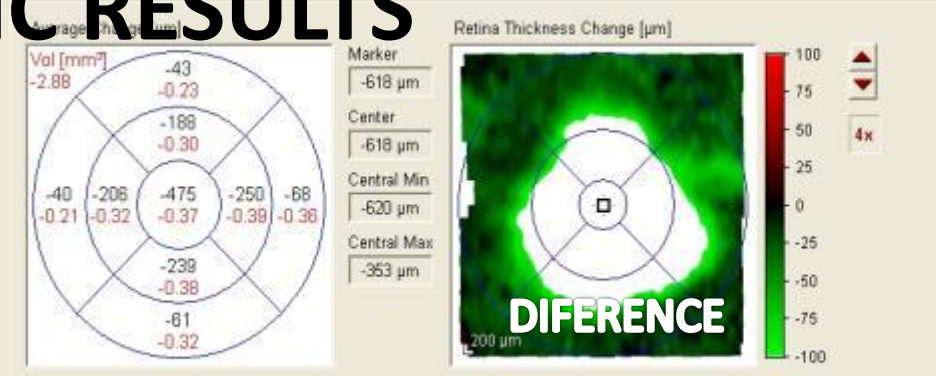
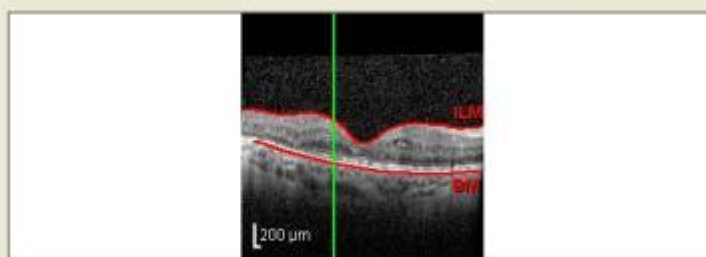
EARLY diagnosis and treatment is critical !



NEW ERA OF INTRA-VITREAL INJECTIONS



SOME DRAMATIC RESULTS



The evolution of evidence for anti-VEGF treatment in wet AMD

Ranibizumab
LUCENTIS

MARINA }
ANCHOR } HORIZON
FOCUS }
SAILOR
PIER
EXCITE
SUSTAIN → SECURE
HARBOR

Bevacizumab
AVASTIN

Aflibercept
EYLEA

← Lucentis comparator arm

CATT
IVAN

← Lucentis comparator arm

VIEW I
VIEW II

IVI ANTI-VEGF AGENTS



REPEATED!! REPEATED!! REPEATED!! REPEATED!!



BUT

MASSIVE

BURDEN OF ONGOING TREATMENT

Incidence of Legal Blindness in Denmark 2000–2010¹

- From 2000 to 2010 the incidence of legal blindness from AMD fell to half the baseline incidence
- The bulk of the reduction occurred after the introduction of intravitreally injected anti-VEGF treatments in 2006

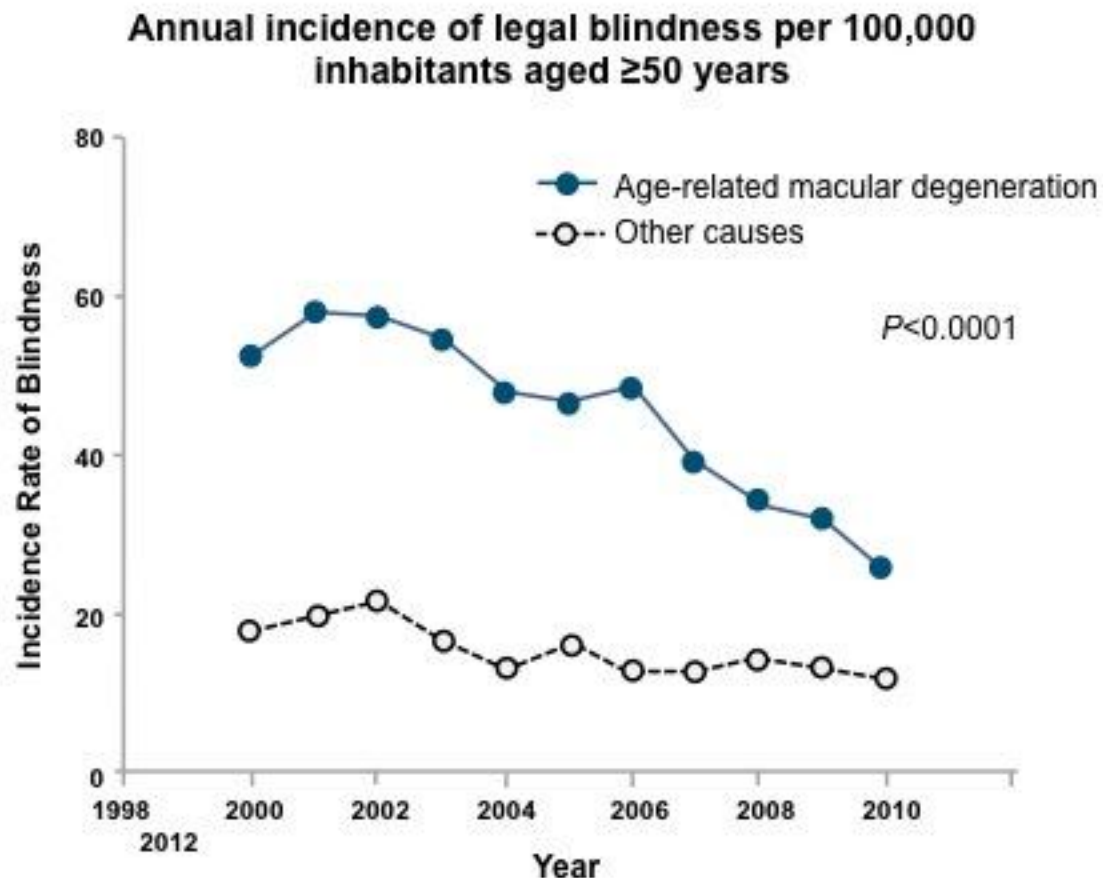


Figure adapted from Bloch SB et al. *Am J Ophthalmol.* 2012.¹

AMD: Key Risk Factors

- Non-modifiable^{1,2}
 - Age
 - Genetic factors
- Modifiable^{1,2}
 - Cigarette smoking
 - High BMI*
 - Low level dietary antioxidants



Images used with permission from Microsoft

Other risk factors described in the literature are still to be confirmed.

*BMI = body mass index

1. Eong KA et al. In: *Age-Related Macular Degeneration*. 2007:47-85.

2. Preferred Practice Pattern® Guidelines. American Academy of Ophthalmology; 2011.

Impact of LATE AMD on patients

— Loss of independence

- unable to work or travel
- loss of free-will, loss of purpose, feelings of guilt

— Loss of leisure activities

- difficulty enjoying hobbies (reading, bridge)
- feelings of boredom

— Loss of social activities

- lack of social connection
- difficulty monitoring own appearance
- unable to recognise faces of family & friends

Low vision optical aids help improve vision for people with macular degeneration. Many different types of magnifying devices are available. Spectacles, hand or stand magnifiers, telescopes, and closed circuit television for viewing objects are some of the available resources. Aids are either prescribed by your ophthalmologist or by referral to a low vision specialist or center. Special lamps with brighter illumination are often beneficial. Books, newspapers, and other items available in large print offer further help.



Vision Impairment Prevents Healthy and Independent Ageing

- Impact of vision loss on a patient's quality of life and psychological wellbeing is comparable to that of cancer or coronary heart disease, increasing the risk of depression and suicide
- Risk of **depression**: **3 X** more likely to experience depression compared to the general population

Vision Impairment Prevents Healthy and Independent Ageing

- Risk of **falls** increased **2 X**
- Risk of **hip fractures** is increased **4 to 8 X**
- Admission to **nursing homes** - **3 years** earlier
- **Social dependence** increased **2 X**
- **Social independence** decreased **2 X**
- **Lower employment rates**, a **higher** use of **social services** and **social isolation**

EFFECT OF LATE AMD

PROFOUND DECREASE
IN QUALITY OF LIFE

grossly underestimated

TRUE QOL IMPACT OF LATE WET ARMD IS GROSSLY UNDERESTIMATED

6/60 OR LESS =

SIGNIF. CVA

ADVANCED PROSTATIC CANCER

INTRACTABLE PAIN



SUPPORT AND REHAB

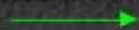
THANK YOU

SWEPT SOURCE OCT

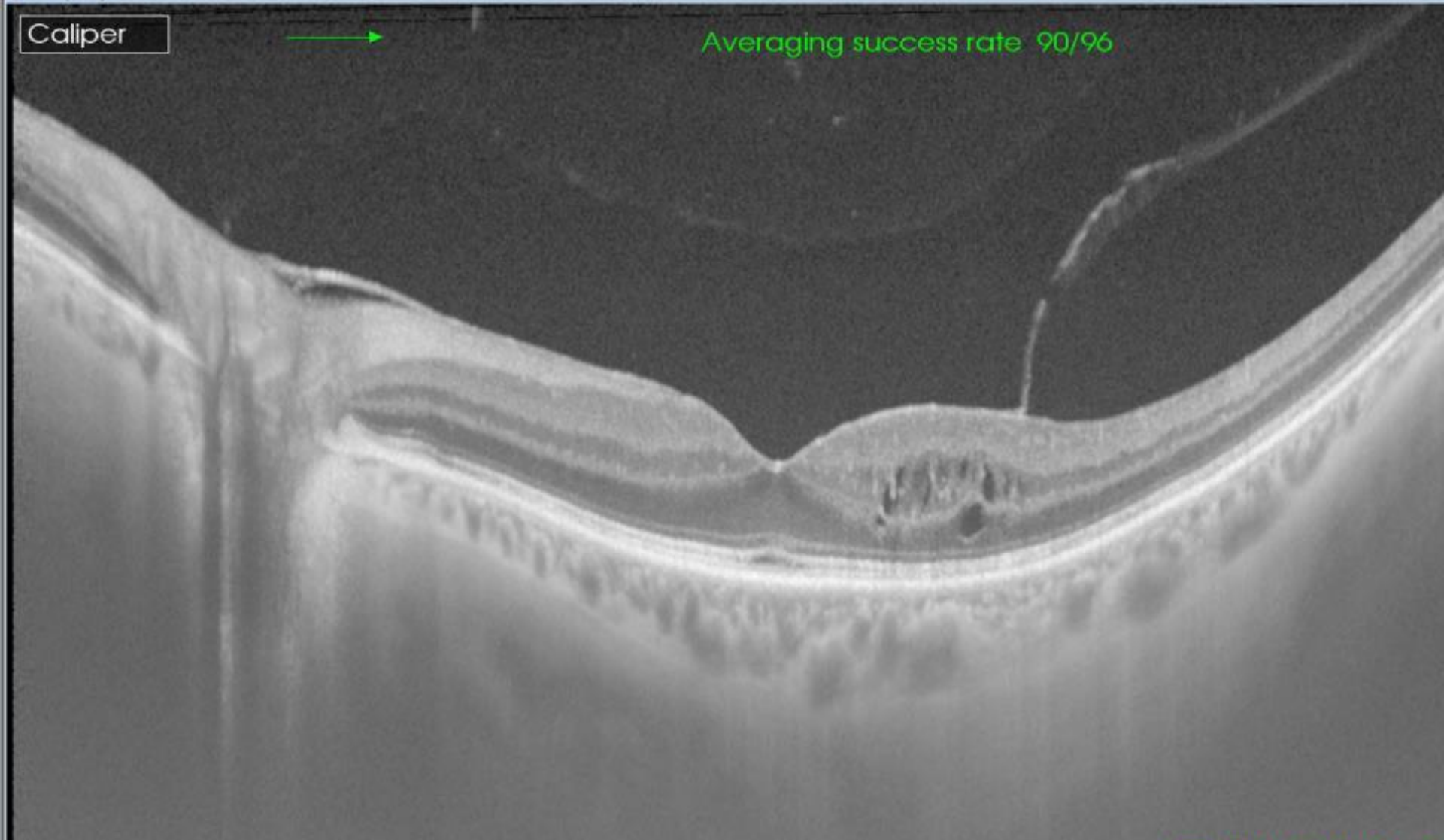
ID: 12 Name: T s t x x Segment: Retina Eye: OS(L) Date: 2014/04/05 Scan Length: 12.0 mm File Name: 2563.fda Analysis:

B-Scan (Axial)

Caliper

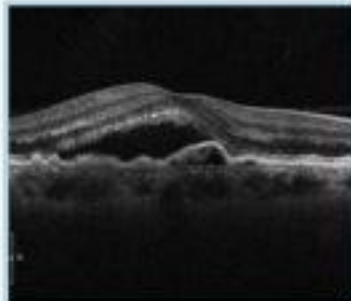


Averaging success rate 90/96



Retinal Imaging Quantifies AMD Disease, Progression and Treatment Response

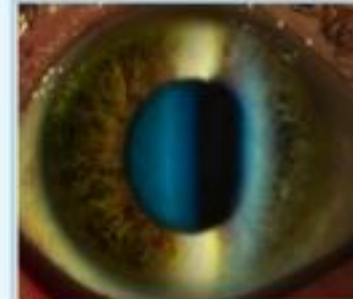
Different modalities can qualify the presence of disease and quantify the extent, progression and treatment response



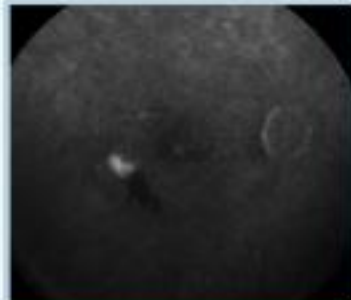
Optical Coherence Tomography (OCT)¹



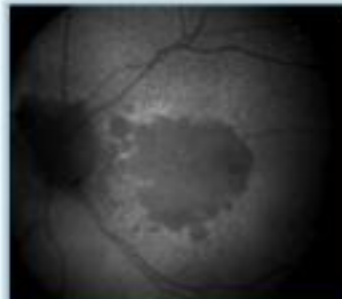
Colour Fundus Photography¹



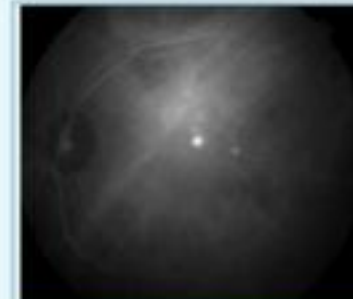
Slit-Lamp Microscopy¹



Fluorescein Angiography (FA)¹



Autofluorescence (AF)²



Indocyanine Green Angiography (ICG)¹

Images used with permission from Alex P Hunyor

Individual Impact of AMD¹

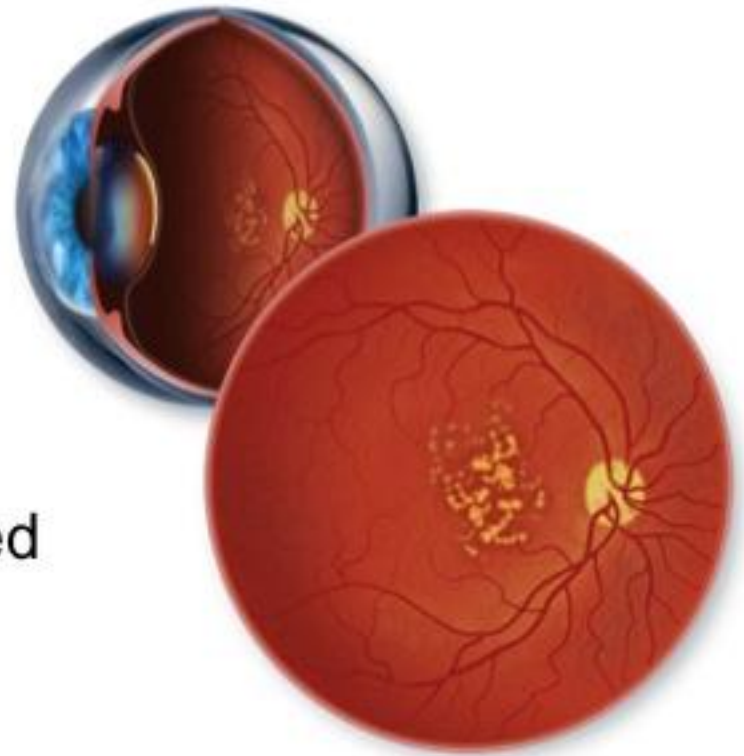
- Visual function impairment
 - Difficult to perform daily activities and pursue leisure activities
 - Increased financial burden
 - Impact on family
- Psychological well-being
 - Greater emotional distress and depressive disorder due to anxiety about the disease and fear of going blind
- Life satisfaction
 - Poor life satisfaction and social support, and greater stress

1. Mitchell J, Bradley C. *Health Qual Life Outcomes*. 2006;4:97.

Dry Form Accounts for ~80% of AMD Patients¹

- Dry form is characterised by²
 - Soft drusen
 - RPE* atrophy
 - Outer retinal atrophy
 - Loss of choriocapillaris
- There is a high unmet medical need
- Effective therapy is lacking

*RPE = retinal pigment epithelium



Dry AMD with characteristic drusen

phagosome retrieval into the pigment epithelial cell.

Fig. 15. Diagrammatic representation of disc shedding and

