Diabetes and the Eye

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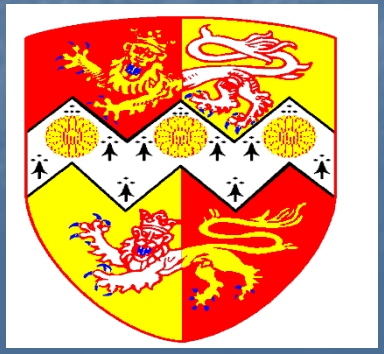
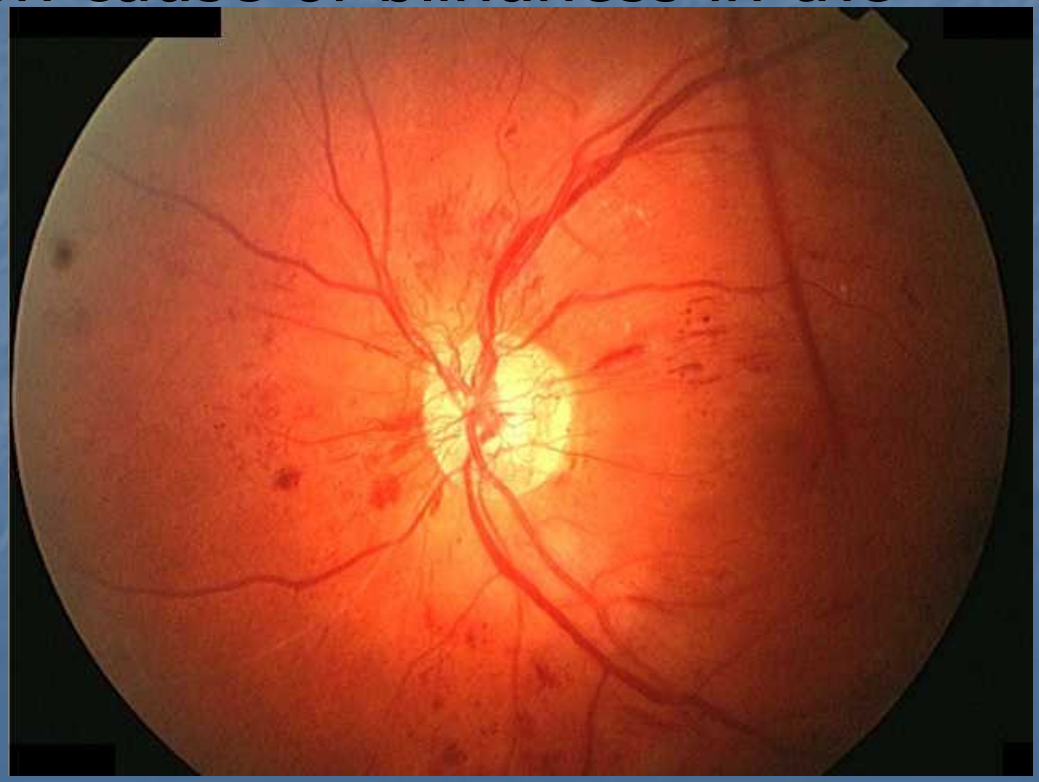


A Bit of Background

- Diabetes remains:
  - The most common cause of blindness in the developed world



Mechanisms

- Visual loss occurs due to
  - Macular oedema
  - Vitreous haemorrhage
  - Traction retinal detachment

Biochemistry

- Abnormalities have been described in the following:
  - Sorbitol pathway
  - Advanced glycation end-products (AGE)
  - Protein kinase C (PKC) activation
  - Oxidative stress
  - Inflammatory markers
  - Retinal blood flow
  - Growth factors, such as vascular endothelial growth factor (VEGF)

Silva PS et al Nat Rev Endocrinol 2010;6(9):494-507

Some History

- In the 1970's and 1980's diabetes was the lading cause of severe visual impairment
- People with diabetes were 25 times more likely to have a VA of 20/200 in their best eye due to
  - Haemorrhage
  - Tractional detachment of the macula due to proliferative diabetic retinopathy (PDR)
  - Macular oedema
  - Cataract
  - Glaucoma

Klein R & Klein BE Diabetes 2010;59(8):1853-1860

Some History

- There was no definitive evidence that achieving good glycaemic control would actually result in less DR
- Also, technology was not of a standard to allow easy optimisation of control
- In the early 1970's the efficacy of photocoagulation had not yet been demonstrated.
- Vitrectomy was in its developmental stages

Klein R & Klein BE Diabetes 2010;59(8):1853-1860

The Relationship Between Glycaemic Control and Retinopathy

- In 1978 Kelly M West wrote "The extent to which the level of hyperglycaemia determines the risk of retinopathy is not at all clear. This is the most important issue at hand and deserves high priority in epidemiologic research"

West KM. 1978. *Epidemiology of Diabetes and Its Vascular Lesions* . Elsevier, NY

WESDR

- It was the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) cohort data that first demonstrated a relationship between glycaemic control and the risk of retinopathy

Klein R et al JAMA 1988;260:2864-2871

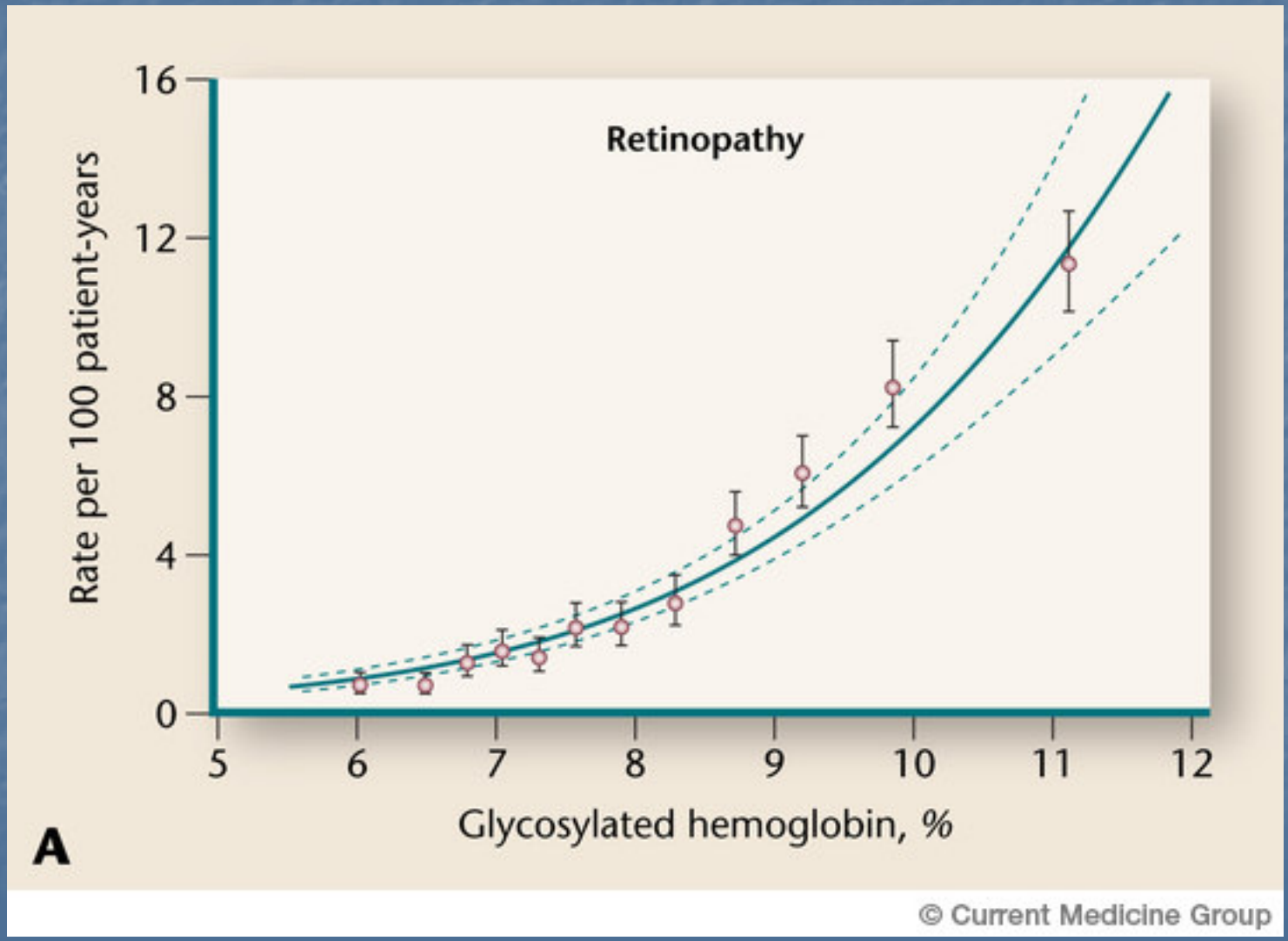
DCCT and UKPDS

- It was then the DCCT and UKPDS that showed that improving glycaemic control substantially reduced the risk of developing retinopathy
  - 76% reduction in the progression of retinopathy in the primary prevention cohort of the DCCT
  - 54% reduction in the progression of DR in the secondary prevention cohort of the DCCT
  - 21% reduction in the progression of DR in the UKPDS
  - 29% reduction in the need for laser photocoagulation in the UKPDS

DCCT Research Group NEJM 1993;329(14):977-986

UKPDS 33 Lancet 1998;352:837-853

Glycaemic Control and Retinopathy



DCCT Research Group NEJM 1993;329(14):977-986

Achieving Good Glycaemic Control – the Effects of Insulin on the Eye

- Tight glycaemic control using insulin is unequivocally associated with a long-term decreased risk of the development and progression of diabetic retinopathy in patients with either type 1 or type 2 diabetes mellitus

- If achieved early, this effect is maintained independently of glycaemic control

Silva PS et al Nat Rev Endocrinol 2010;6(9):494-507

What About 'Early Worsening'?

- In the first 2 years following the initiation of intensive insulin therapy, diabetic retinopathy can transiently worsen
- However, over the long term, intensive glycaemic control is associated with improved retinopathy and visual outcomes
- Early worsening has been shown to be more common in patients with poorly controlled, long-standing diabetes mellitus with moderate or more advanced non-proliferative diabetic retinopathy

Early Worsening

- Thus, this subgroup requires careful ophthalmologic monitoring before initiation of intensive treatment and for at least 6-12 months following initiation of intensive treatment, at a minimum of 3-monthly intervals

Early Worsening

- Manifests as the development of retinal cotton wool spots and is associated with a large decrease in HbA1c levels during the first 6 months of intensive insulin treatment
- The risk of a further sustained three-step progression in diabetic retinopathy on the (ETDRS) scale at 18 months was two to four times greater in patients who experienced early worsening compared with those who had not

Early Worsening

- Despite the fact that early worsening is sometimes apparent in the first period after the initiation of intensive insulin treatment, this increased risk of retinopathy progression disappears by 4 years

Early Worsening - Causes

- Possible alterations in retinal blood flow due to a decreased ability of the retinal circulation for autoregulation
- Transient ischaemia owing to a decrease in nutrient substrate and insulin-induced changes in retinal homeostasis that lead to an increase in growth factors such as VEGF

Silva PS et al Nat Rev Endocrinol 2010;6(9):494-507

Thiazolidinediones

- Pioglitazone
- Others in the class may delay progression of disease by anti-angiogenic mechanisms
- However, their use has been associated with a 2.6 fold increase in the risk of developing macular oedema

Silva PS et al Nat Rev Endocrinol 2010;6(9):494-507

Metformin

- Despite its clear CV benefits, it does not have clear benefits in protecting the eyes
- Theoretically it should help
  - It decreases concentrations of (PAI-1) and thereby increases fibrinolytic activity
  - It inhibits inflammatory mediated angiogenesis

Hypertension and Retinopathy

- Tight control of blood pressure reduces the progression of DR in subjects with type 2 diabetes
  - In the UKPDS aggressive BP control led to a 34% reduction in the progression of DR and a 47% reduction in the decrease in visual acuity of three lines or more

UKPDS 38 BMJ 1998;317:703-713

Schrier RW et al. Kidney Int 2002;61:1086-1097

Hypertension and Lipids

- ACE inhibitors and ARB's have been shown to be of benefit – possibly by their BP lowering effects, although the effects remain when BP has been factored out

- Fenofibrate has also been shown to be beneficial by reducing the incidence of CSMO and PDR by over 30% and slowing pre-existing retinopathy

Chaurvedi N et al Lancet 1998;351:28-31
Chaurvedi N et al Lancet 2008;372:1394-1402
Maur et al NEJM 2009;361:40-51
Keech AC et al Lancet 2007;370:1687-1697

RAAS Blockers

- In proliferative diabetic retinopathy, vitreous levels of VEGF are increased and positively correlated with the activity of ACE
- Thus the effects of ARB's and ACEI may be directly on the eye, and independent of BP control

Silva PS et al Nat Rev Endocrinol 2010;6(9):494-507

Lipid Lowering Agents

- High total cholesterol and LDL cholesterol, are risk factors for the development of retinal hard exudates and diabetic macular oedema

- Lipid deposition within the retina has been shown to be toxic to retinal endothelial cells in animal models, and both retinal hard exudates and elevated serum lipid levels increase the risk of visual impairment

Fibrates and Statins

- Fibrates suppress endothelial cell proliferation and inhibit VEGF production
- Statins have documented vasculoprotective effects due to antioxidant and anti-inflammatory properties independent of their cholesterol-lowering activity – their effect on retinopathy progression is far more modest than fibrates

Silva PS et al Nat Rev Endocrinol 2010;6(9):494-507

Aspirin & Other Antiplatelet Agents

- Hyperglycaemia leads to increase platelet adhesiveness and thus microthrombus formation
- This leads to increased retinal ischaemia and promoted retinopathy
- Aspirin and other antiplatelet agents have not shown to be of significant benefit in preventing or delaying retinopathy

Prevalence of Retinopathy in the USA

- Diabetic retinopathy was 28.5%
- Vision-threatening diabetic retinopathy was 4.4%
- Men vs Women 31.6% vs 25.7% (p=0.04)
- Hispanic black vs non-Hispanic white
  - Diabetic retinopathy 38.8% vs 26.4% (p=0.01)
  - STDR 9.3% vs 3.2% (p=0.01)

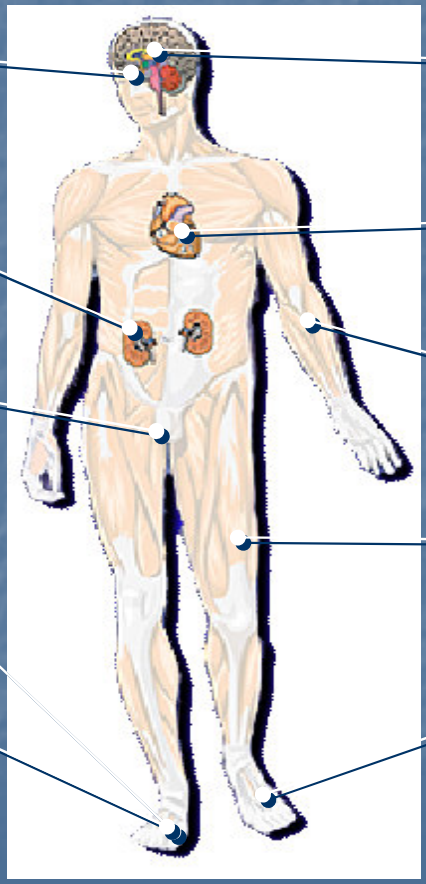
Zhang X et al JAMA 2010;304(6):649-656

Prevalence of Retinopathy in the USA

- Male vs female for the presence of diabetic retinopathy OR 2.07
- higher HbA1c OR 1.45
- Male vs female for longer duration of diabetes OR 1.06 per year duration
- Male vs female for insulin use OR 3.23
- Male vs female for higher systolic blood pressure OR 1.03 per mm Hg

Zhang X et al JAMA 2010;304(6):649-656

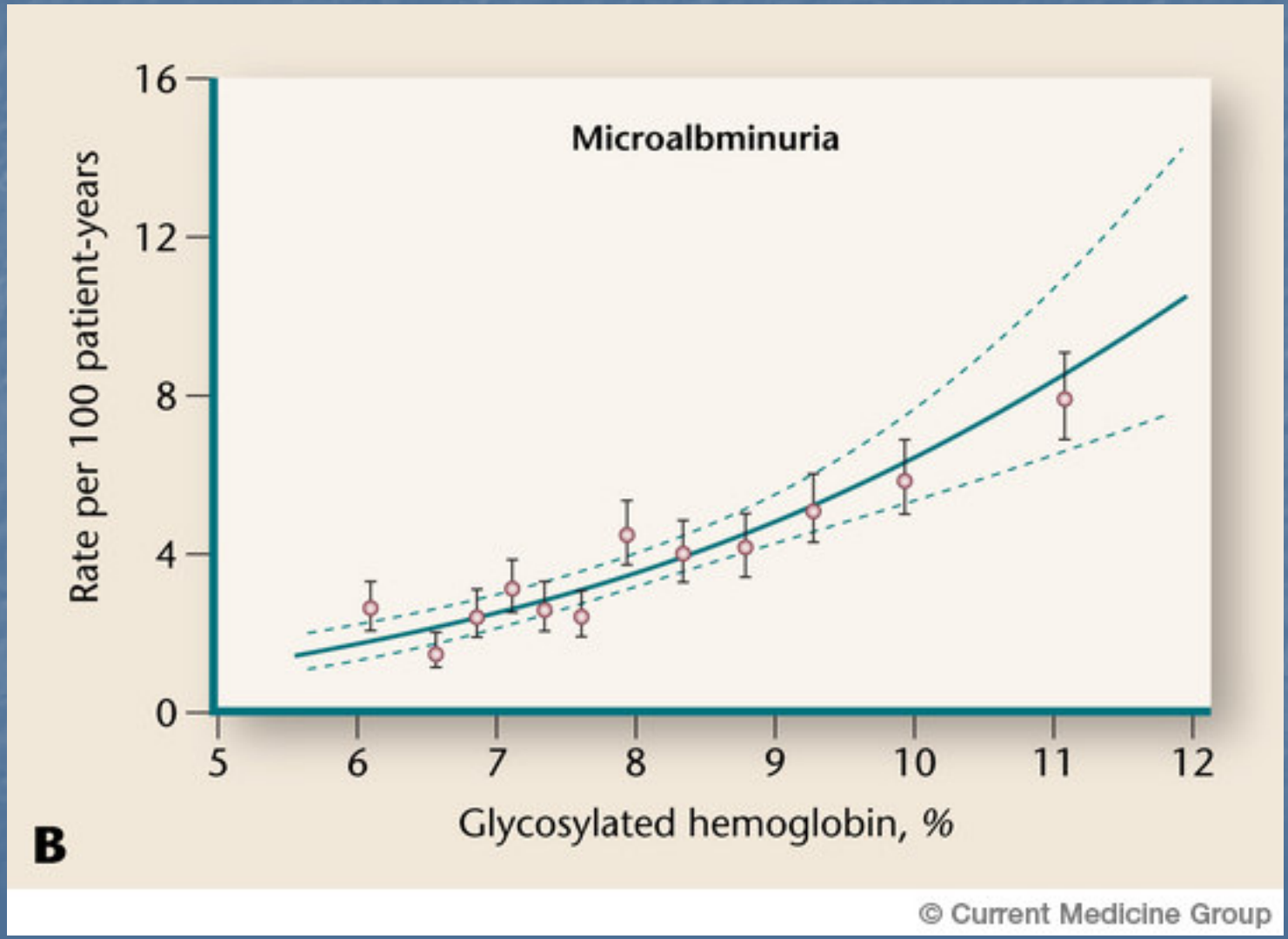
Vascular Complications Of Type 2 Diabetes At The Time Of Diagnosis



Retinopathy[1]	21%	7%	Cerebrovascular disease[3]
Nephropathy[2]	18%	18%	Abnormal ECG[1]
Erectile dysfunction[1]	20%	35%	Hypertension[1]
Ischaemic skin changes (foot)[1]	6%	4.5%	Intermittent claudication[3]
Abnormal vibration threshold (foot)[1]	7%	13%	Absent foot pulses[1]

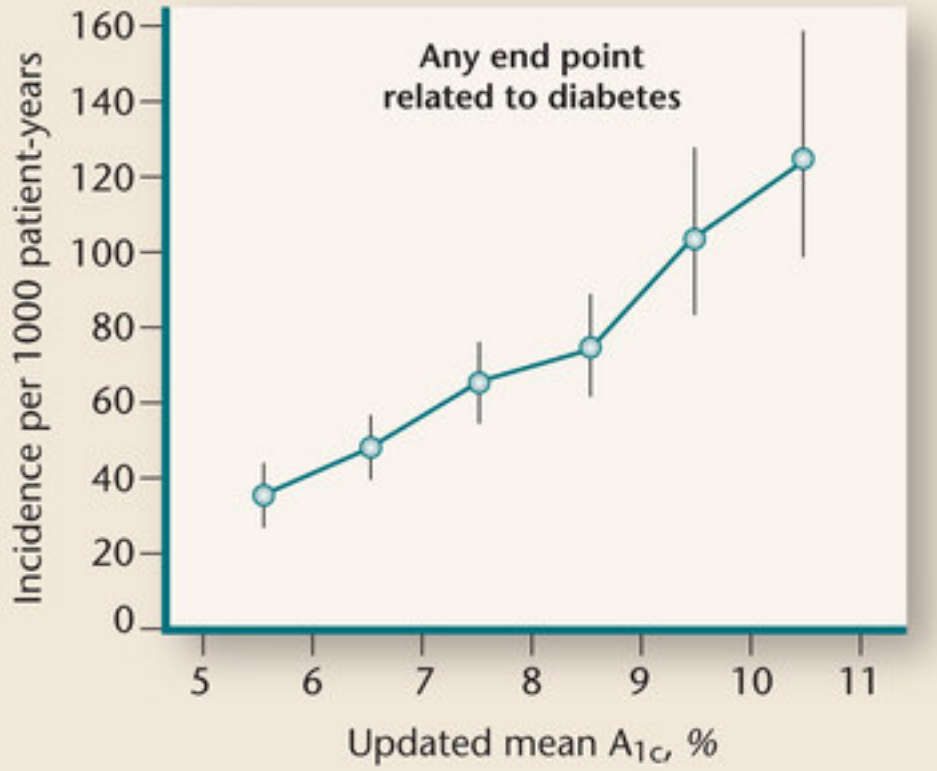
1. UKPDS Group. *Diabetes Res* 1990; **13**: 1–11. 2. The Hypertension in Diabetes Study Group. *J Hypertension* 1993; **11**: 30–17. 3. Wingard DL *et al. Diabetes Care* 1993; **16**: 1022–5.

Nephropathy and Glycaemic Control



DCCT Research Group NEJM 1993;329(14):977-986

Glycaemic Control is Important



Reduction in risk per 1% reduction in A_{1c} (9 mmol/mol)

- Overall: 21%*
- Diabetes mortality: 21%*
- MI: 14%
- Stroke: 12%†
- Microvascular: 37%*
- Heart failure: 16%†
- Cataract extraction: 19%*
- Amputations or PVD death: 43%*

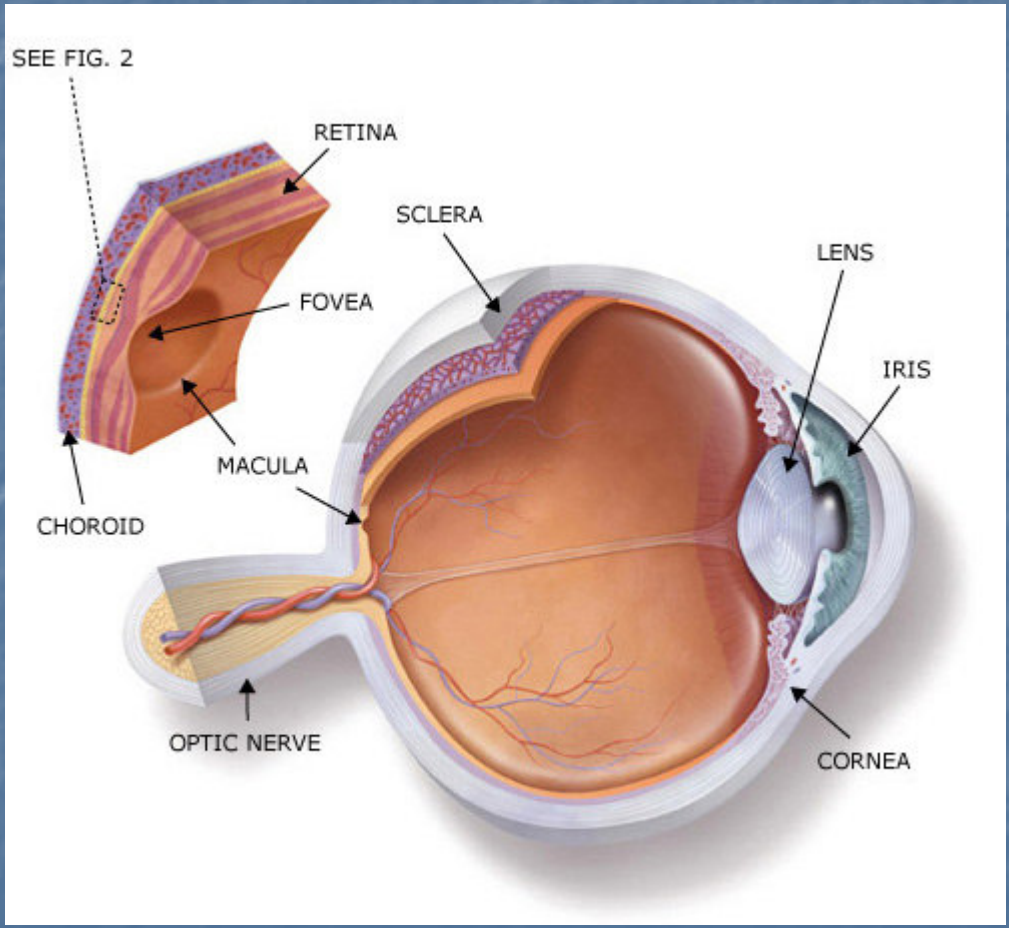
* $P < 0.0001$.
† $P < 0.05$.

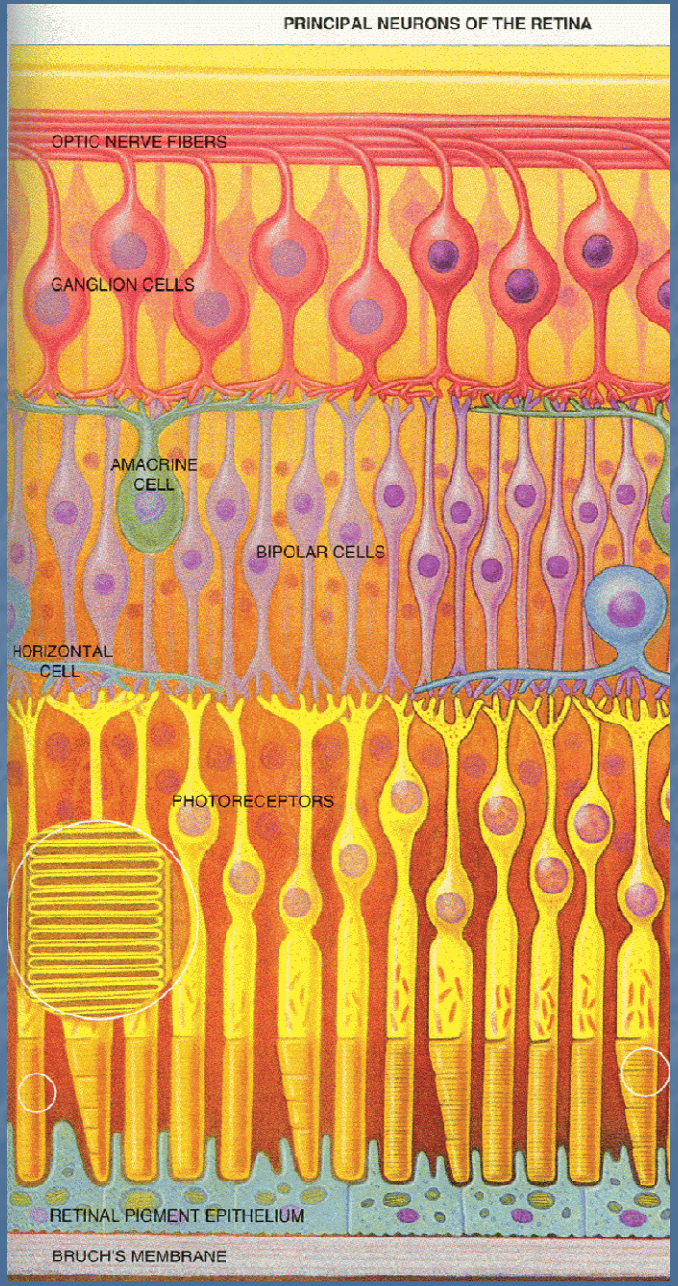
UKPDS Lancet 1998;352(9131):837-853

Overview

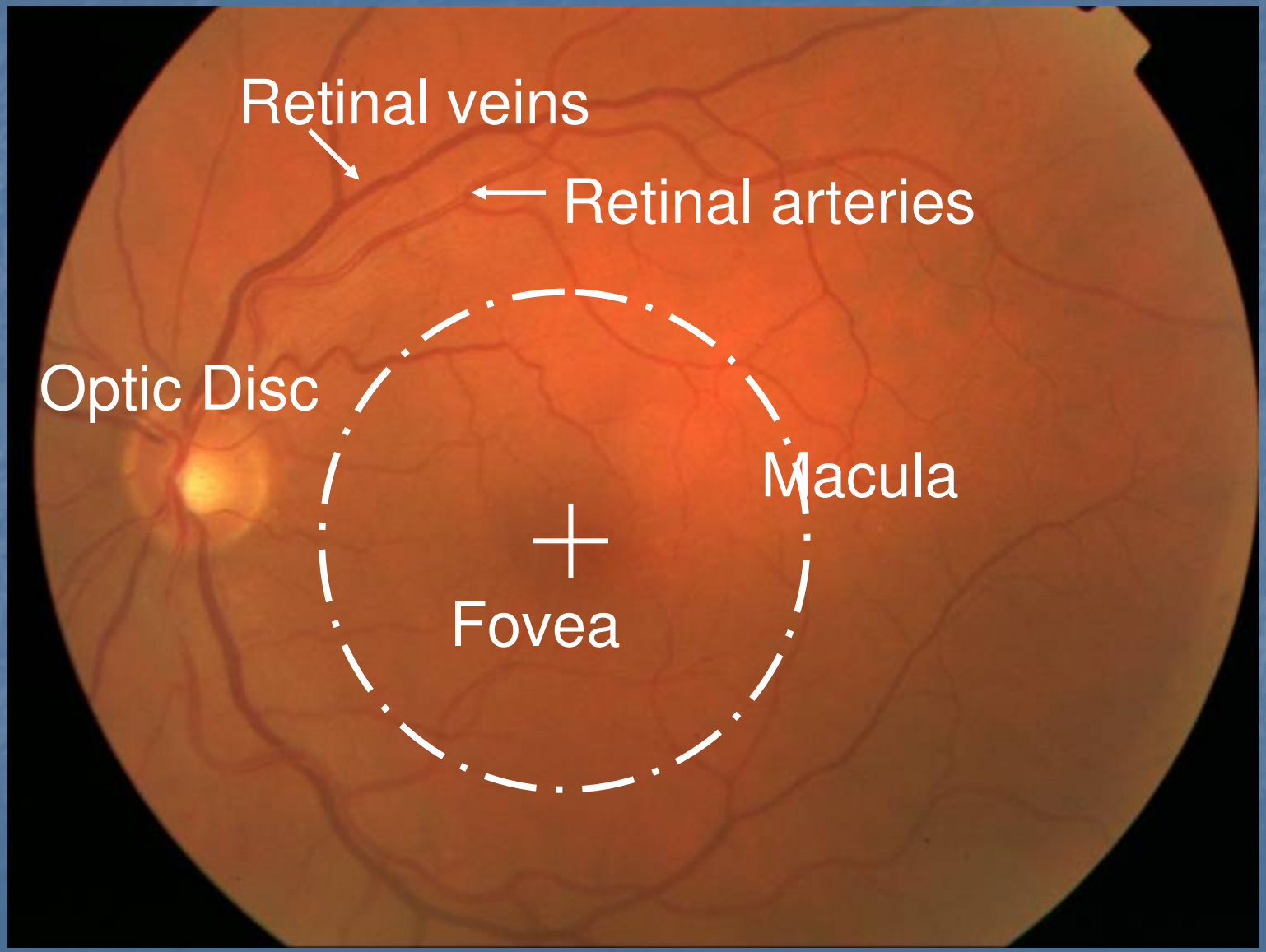
- The anatomy of the eye
- National Screening Committee grading system

Anatomy

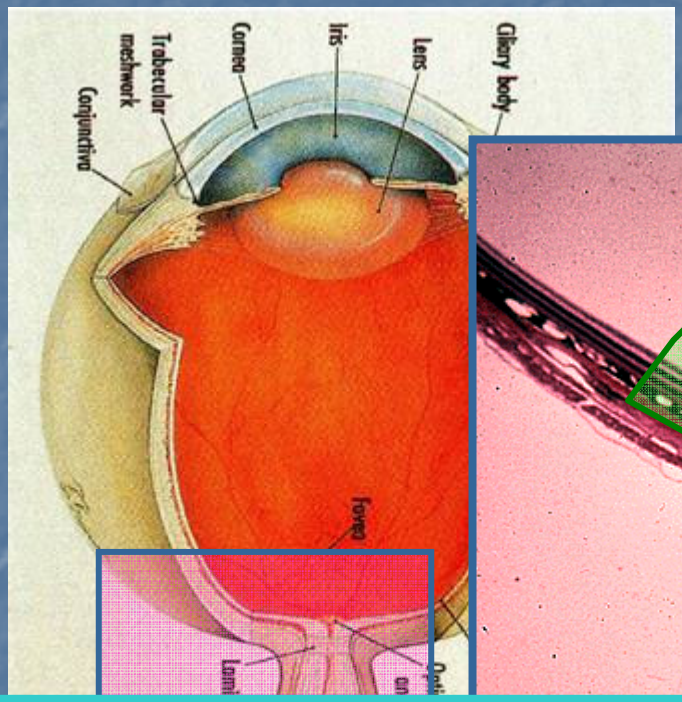

SEE FIG. 2
RETINA
SCLERA
LENS
FOVEA
IRIS
MACULA
CHOROID
OPTIC NERVE
CORNEA

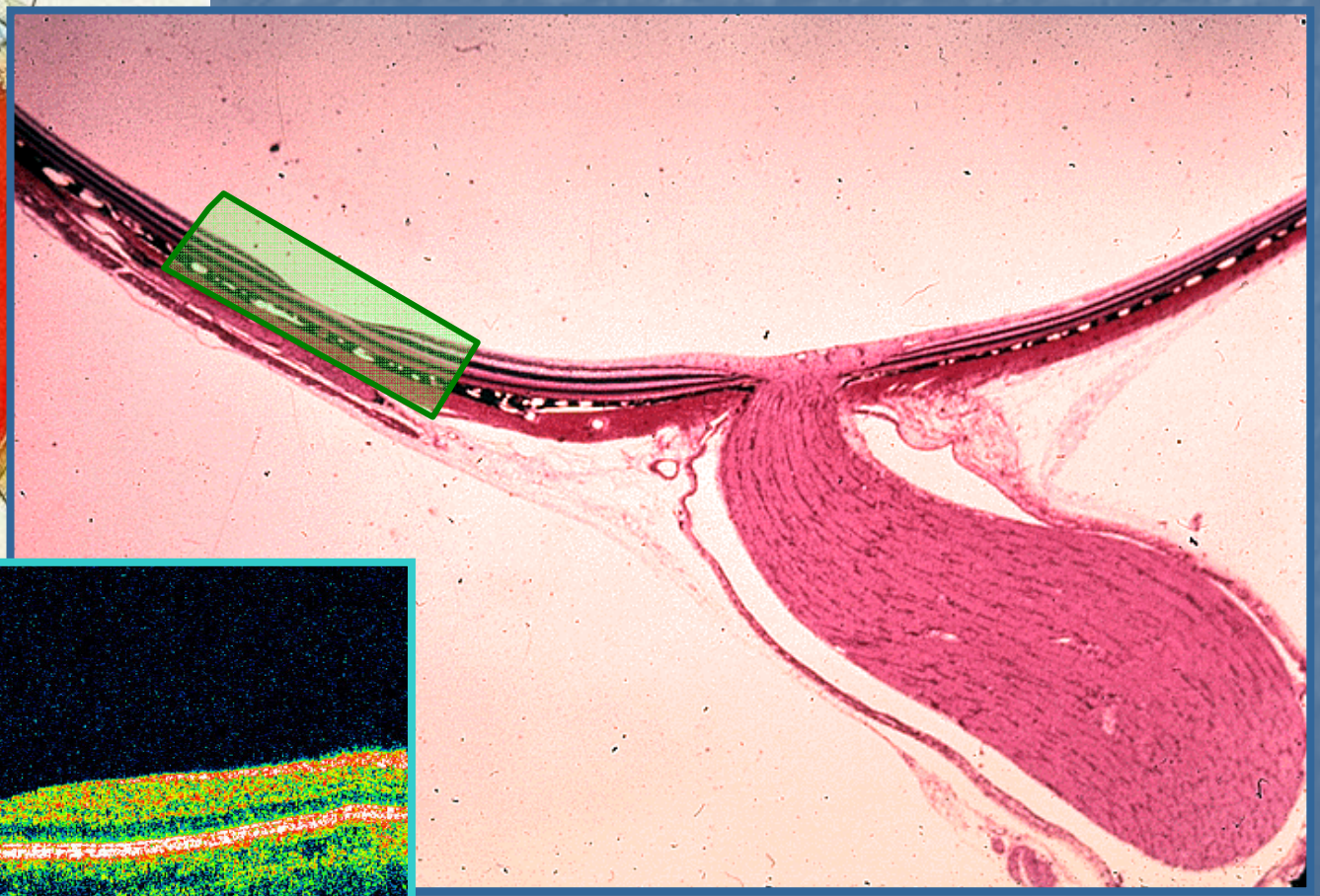

PRINCIPAL NEURONS OF THE RETINA
OPTIC NERVE FIBERS
GANGLION CELLS
AMACRINE CELL
BIPOLAR CELLS
HORIZONTAL CELL
PHOTORECEPTORS
RETINAL PIGMENT EPITHELIUM
BRUCH'S MEMBRANE

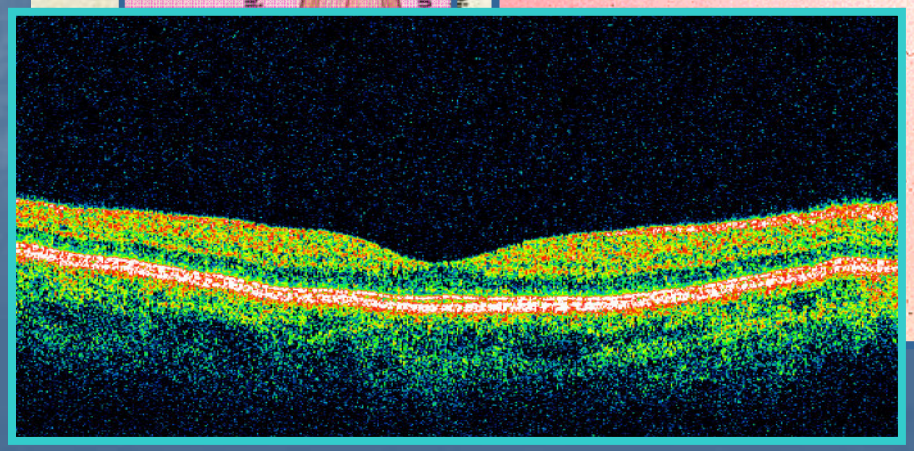
The Fundus



OCT: Ocular Coherence Tomography







National Screening Committee Grading System

Grading and disease management in national screening for diabetic retinopathy in England and Wales

S. Harding, R. Greenwood*, S. Aldington†, J. Gibson‡, D. Owens§, R. Taylor¶, E. Kohner**, P. Scanlon††, G. Leese‡‡. The Diabetic Retinopathy Grading and Disease Management Working Party

Diabet. Med. 20, 965–971 (2003)

Grading Classification

Retinopathy (R)		
Level 0	None	
Level 1	Background	Microaneurysm(s) Retinal haemorrhage(s) ± any exudate
Level 2	Preproliferative	Venous beading Venous loop or reduplication Intraretinal microvascular abnormality (IRMA) Multiple deep, round or blot haemorrhages (CWS—careful search for above features)
Level 3	Proliferative	New vessels on disc (NVD) New vessels elsewhere (NVE) Preretinal or vitreous haemorrhage Preretinal fibrosis ± tractional retinal detachment
Maculopathy (M)		Exudate within 1 disc diameter (DD) of the centre of the fovea Circinate or group of exudates within the macula Retinal thickening within 1 DD of the centre of the fovea (if stereo available) Any microaneurysm or haemorrhage within 1 DD of the centre of the fovea only if associated with a best VA of ≤ (if no stereo) 6/12
Photocoagulation (P)		Focal/grid to macula
Unclassifiable (U)		Peripheral scatter

Management of Each Grade

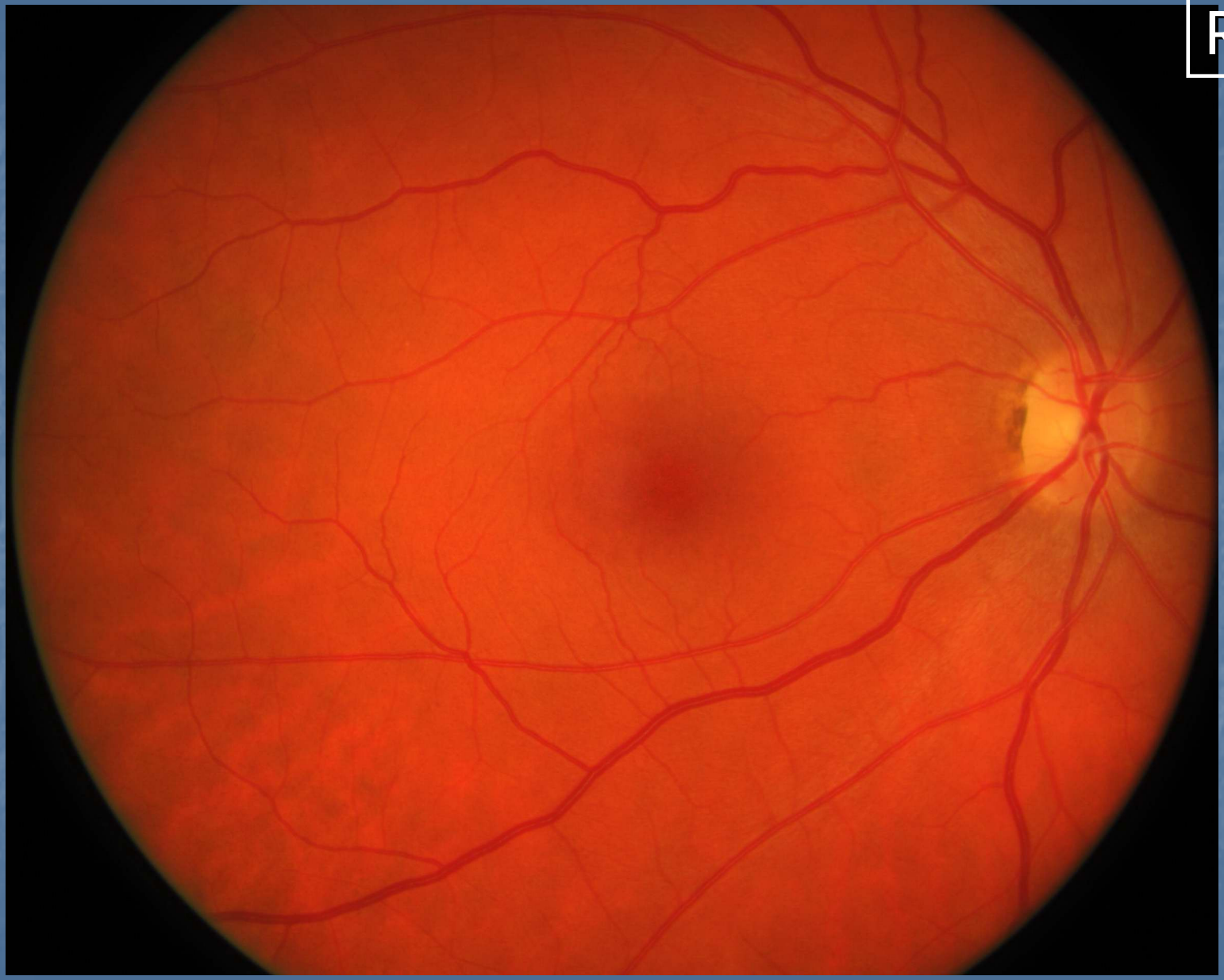
Retinopathy (R)	R0	Annual screening
	R1	Annual screening
	R2	Refer to hospital eye service
	R3	Fast-track referral to hospital eye service
Maculopathy (M)	M1	Refer hospital eye service
Photocoagulation (P)	P1	New screenee→refer hospital eye service Quiescent post treatment→annual screening
Other lesions (OL)		Refer to hospital eye service or inform primary physician
Ungradable/unobtainable (U)		Poor view but gradable on biomicroscopy→refer hospital eye service Unscreenable→discharge, inform GP (option to recall for further photos if purely technical failure)

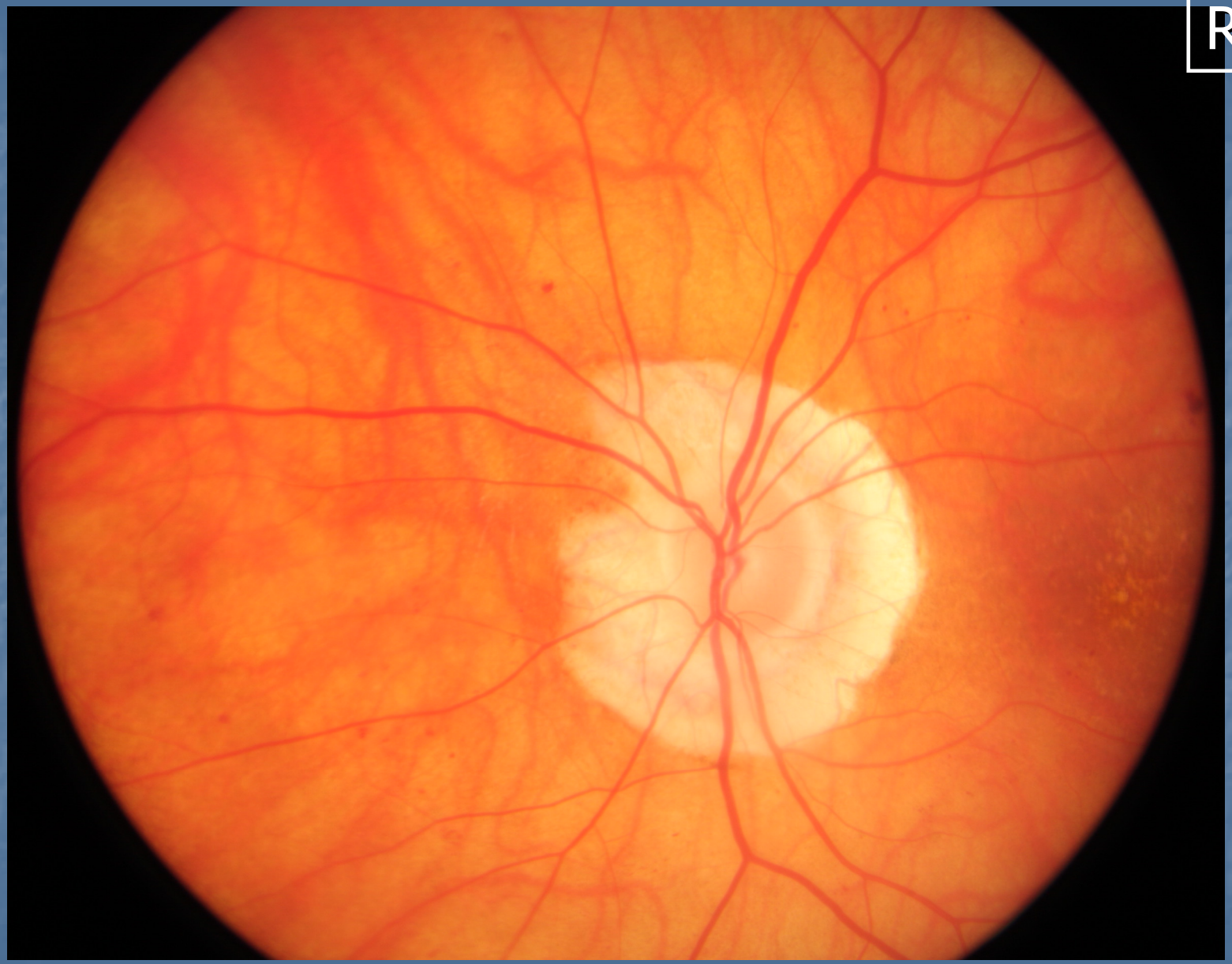
Retinopathy - R

R0 – None

R1 – Microaneurysms, retinal haemorrhages ± exudate

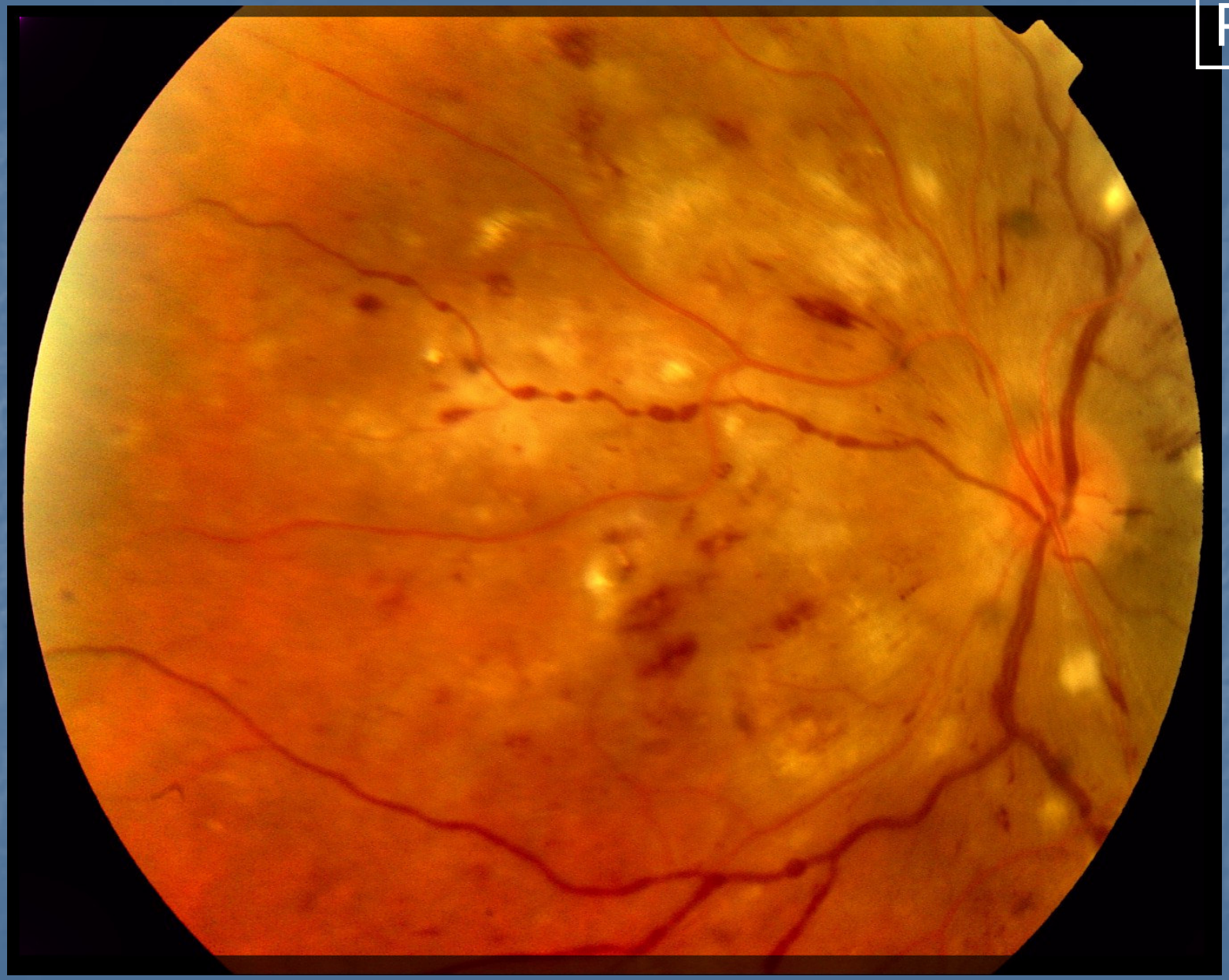
Both of these are annual recall

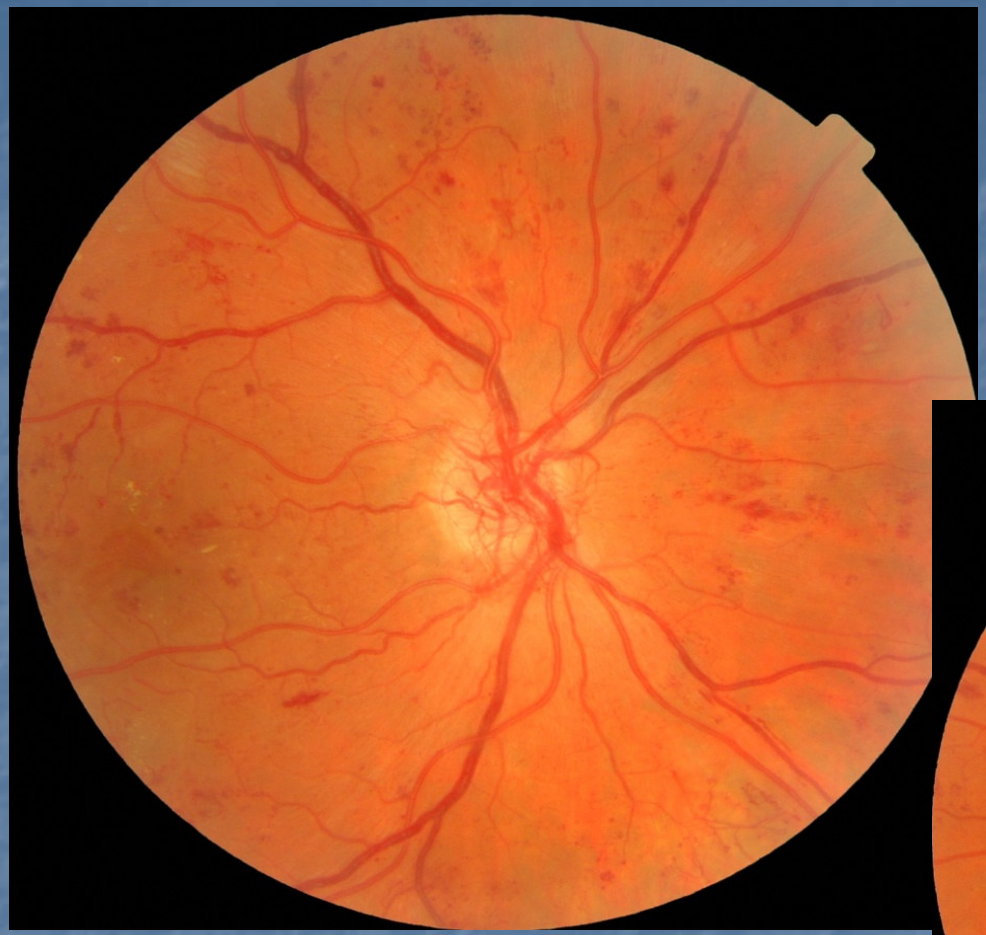

R0


R1

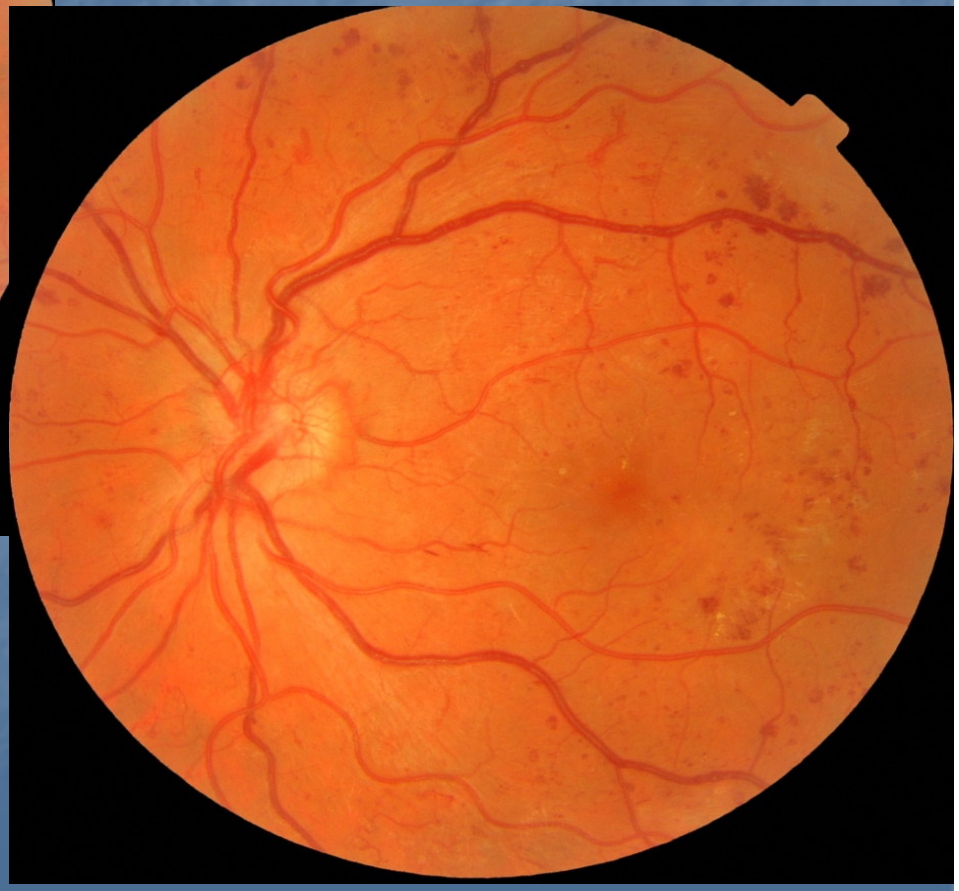
Referable Retinopathy - R

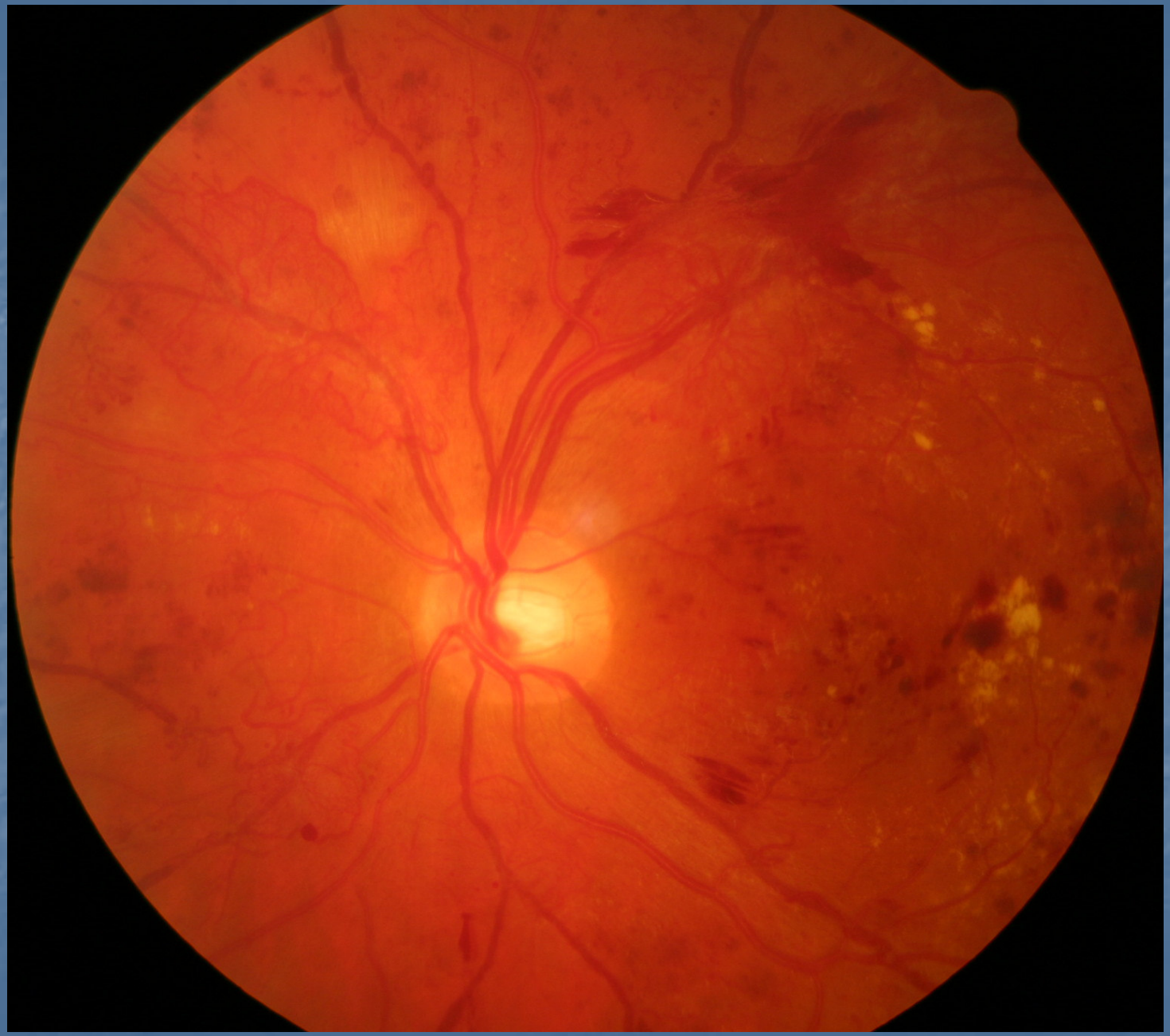
- R2 - Pre-proliferative
  - venous beading
  - venous loop
  - intraretinal microvascular abnormality (IRMA)
  - multiple deep, round or blot haemorrhages
- R3 - Proliferative
  - new vessels on disc (NVD)
  - new vessels elsewhere (NVE)
  - pre-retinal or vitreous haemorrhage
  - pre-retinal fibrosis ± tractional retinal detachment


R2



R3




R3

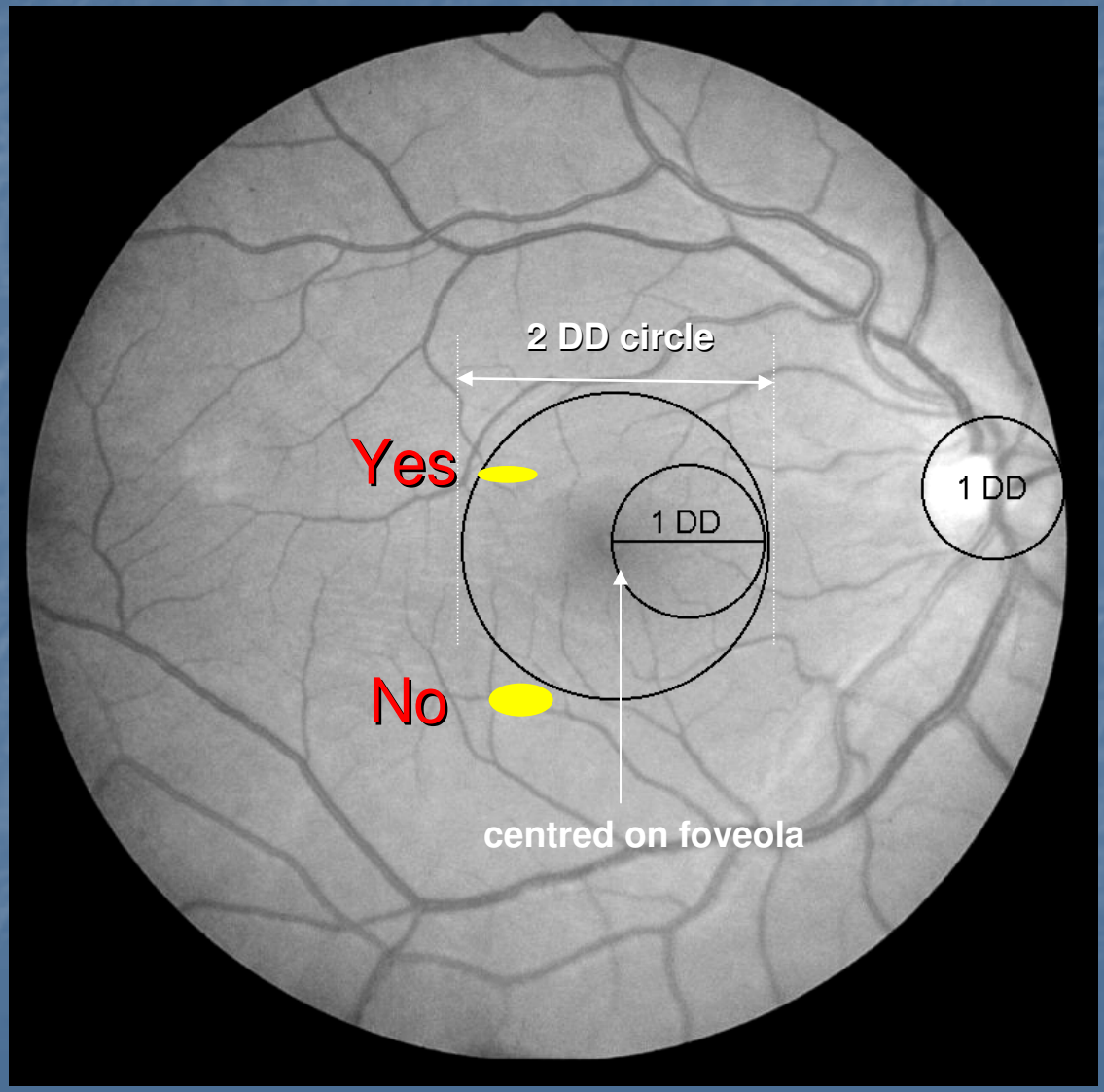
Visual Loss Can Occur Due To:

- Macular oedema affecting the fovea
- Macular ischaemia
- Vitreous haemorrhage
- Retinal / Vitreous scarring
- Tractional retinal detachment

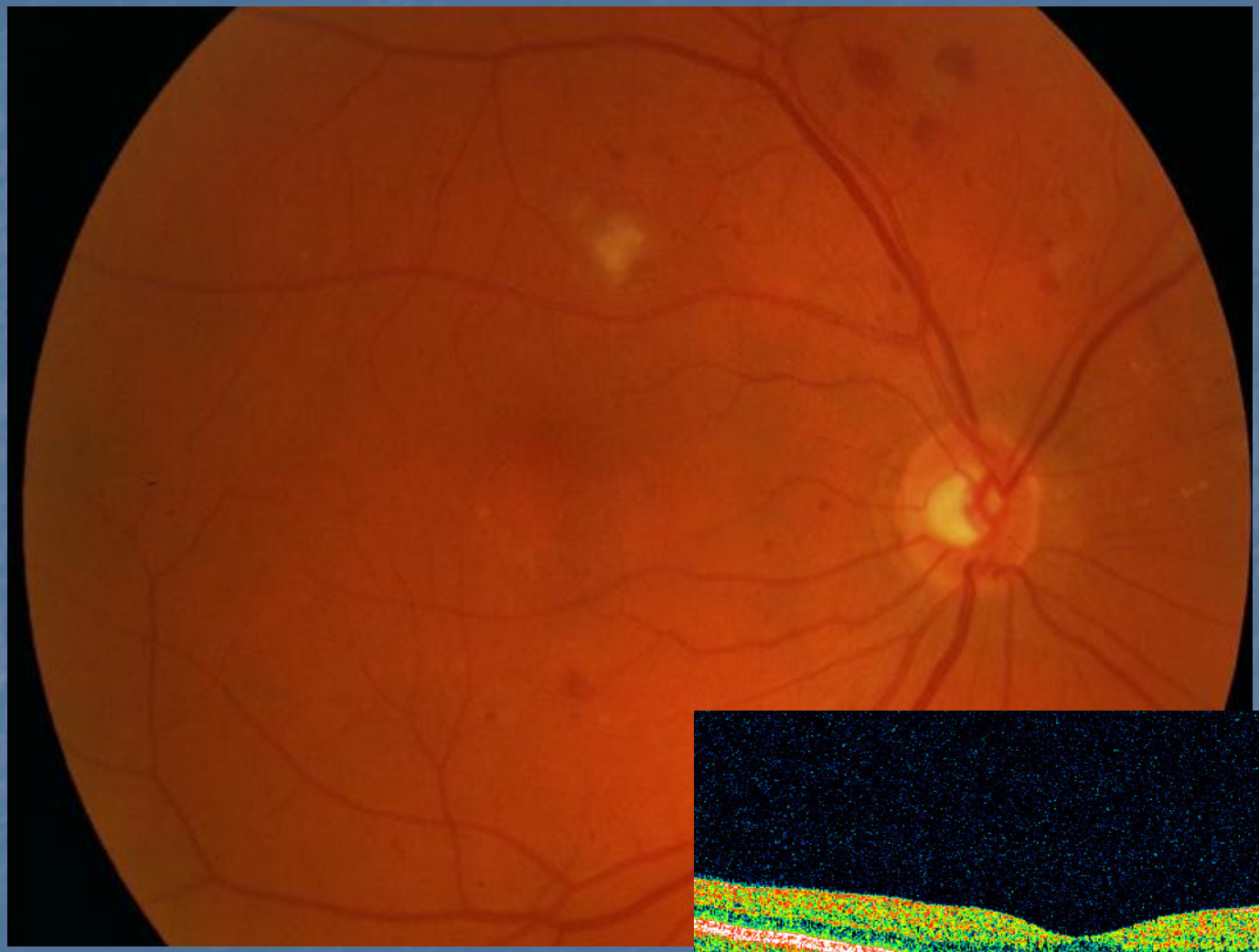
Maculopathy

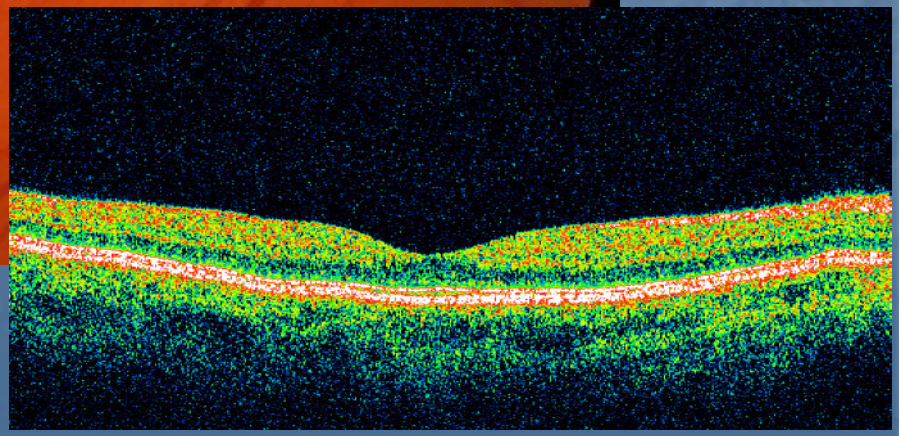
- M0 – No referable maculopathy
- M1 – presence of referable retinopathy
  - exudate within 1DD of centre of fovea
  - circinate or group of exudates within macula
  - any MA or haemorrhage within 1DD of centre of fovea associated with BCVA ≤ 6/12

Within 1DD of the Centre of the Fovea?

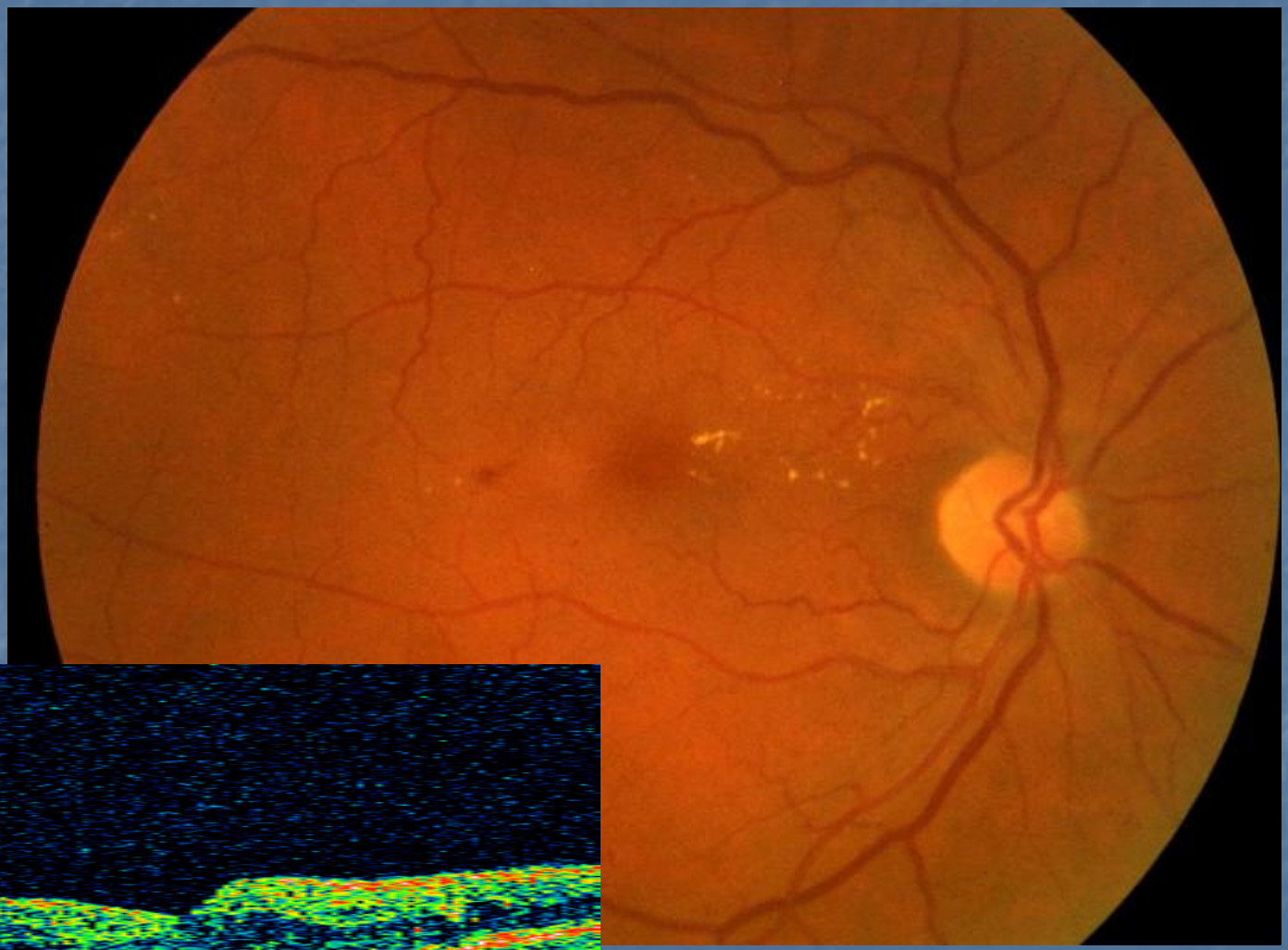


Observable

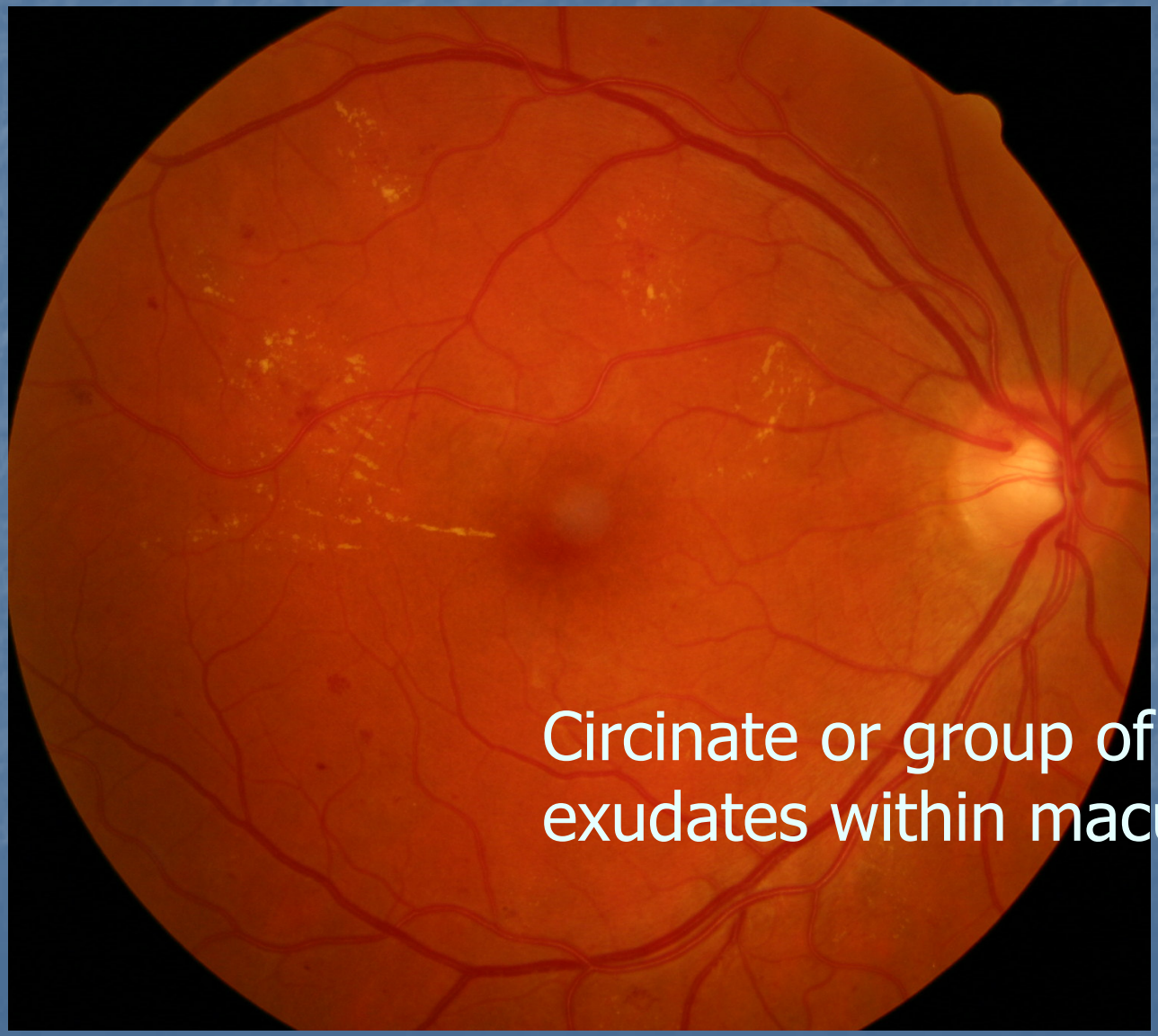




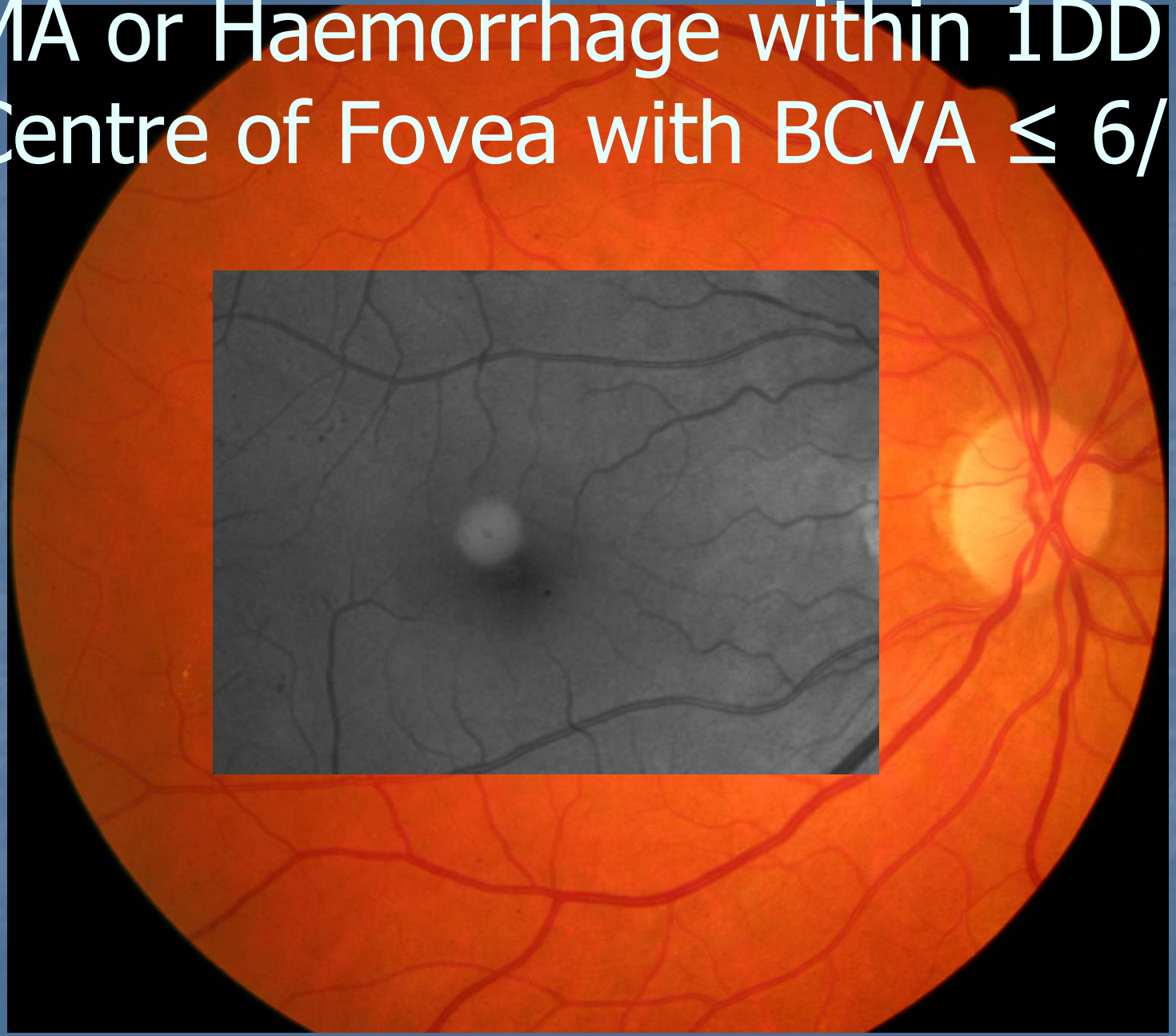
Exudate Within 1DD of Centre of Fovea



Exudate Within 1DD of Centre of Fovea

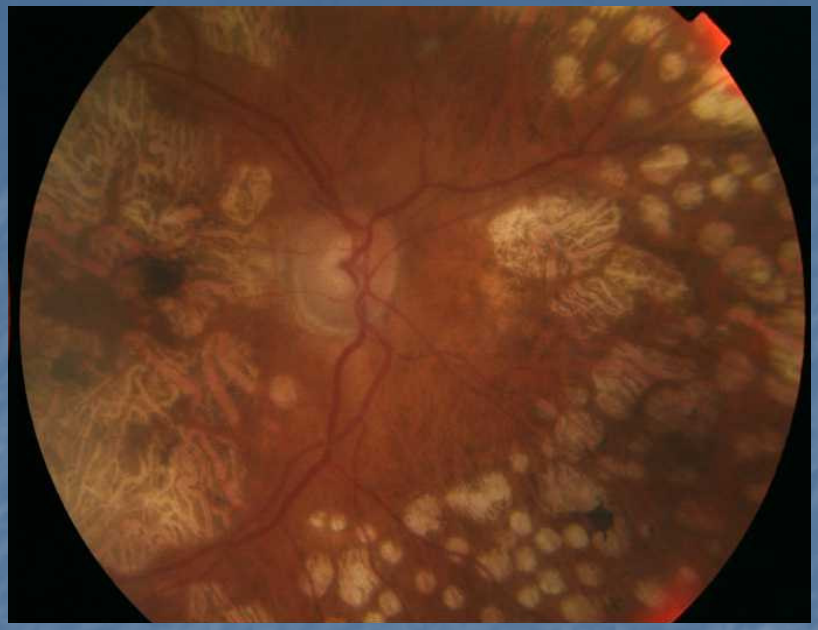


MA or Haemorrhage within 1DD of Centre of Fovea with BCVA ≤ 6/12



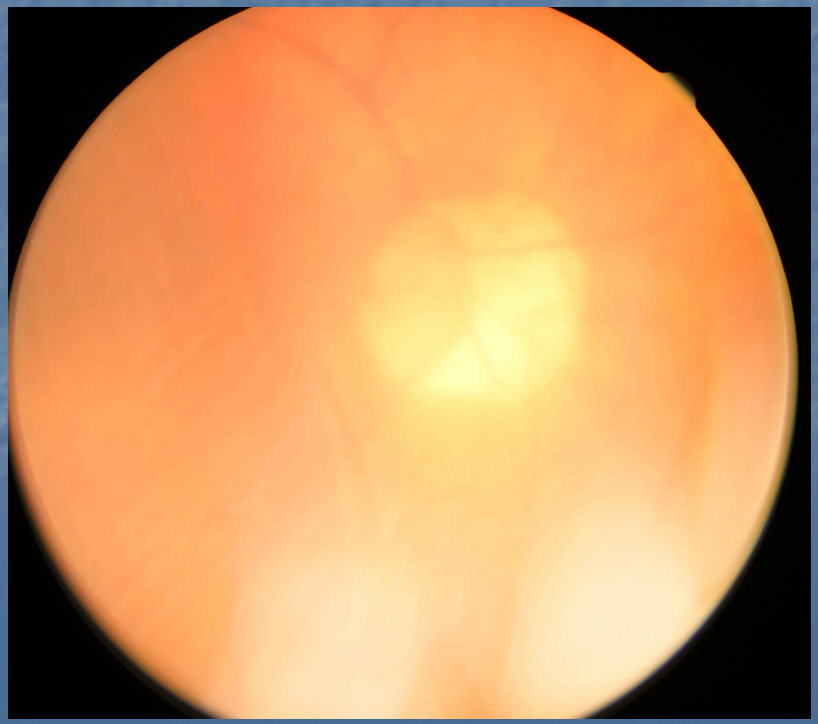
P

- Photocoagulation
  - Focal/grid macula
  - Peripheral scatter



U

- Unclassifiable
- Unobtainable
- Ungradeable



Finally – a Plug

- 3rd Annual Diabetes and the Eye Day
- Barnham Broom
- Tuesday the 9th of November 2010

- 09.25 – 09.30 Welcome and introduction to the day – Ketan Dhatariya
- 09.30 – 10.15 Diabetes – the basics
- 10.15 – 11.00 Interactive session – What do these images show, what is the grade of retinopathy and do you refer it? – Aseema Misra
- 11.00 – 11.15 Tea and coffee
- 11.15 – 12.00 "What on earth is that?" Eye conditions seen on routine screening unrelated to diabetes – diagnosis and treatment – Colin Jones
- 12.00 – 12.45 Update on the drugs used in diabetes – focus on insulin and newer agents – Swe Myint
- 12.45 – 13.45 Lunch
- 13.45 – 14.30 Vitreoretinal surgery for proliferate diabetic retinopathy - Ted Burton
- 14.30 – 15.15 Update in diabetes – why it isn't only about glucose – Jeremy Turner
- 15.15 – 15.30 Coffee and tea
- 15.30 – 16.15 Why diabetes related eye disease isn't just about the retina – Andy Glenn
- 16.15 – 17.00 Thyroid eye disease – Bijan Beigi