DIABETIC RETINOPATHY

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DIABETIC RETINOPATHY

- INTRODUCTION
- RISK FACTORS
- AETIOPATHOGENESIS
- CLASSIFICATION
- AIDS TO DIAGNOSIS AND ASSESSING SEVERITY

INTRODUCTION

- **The adult diabetic population in Africa will double in 20 years, from 12 million in 2010 to 24 million in 2030**
  - **Rural–urban drift: sedentary life-style,**
  - **less physically demanding jobs**
  - **Dietary changes**
  - **Increasing longevity**

Shaw JE, Sicree RA, Zimmet PZ: Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010, 87:4–14.

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INTRODUCTION CON'T

- **DM induced microvascular disease of the retina characterised by increased vascular permeability, ischaemia, and neovascular proliferation**

INTRODUCTION CON'T

- Common long term microvascular complication of DM
- Diabetic retinopathy is a leading cause of new cases of blindness in people aged 20 to 74 years .
- It has a considerable impact on both the patient and the society because it typically affects individuals in their most productive years .

INTRODUCTION CON'T

- Blindness is 25 times more common in diabetics than non diabetics.
- Blindness is due to:
  - Non-clearing vitreous hemorrhage
  - Neovascular glaucoma
  - Tractional retinal detachment
  - Macular ischemia

INTRO CON'T - Prevalence

- The overall global prevalence of diabetic retinopathy from a total of 35 studies (1980–2008) is 34.6%[1]

- DR prevalence in sub-Saharan Africa DM population: 15 - 17%.[2, 3]

[1]Yau JWY, et al. Global Prevalence and Major Risk Factors of Diabetic Retinopathy. Dia Care. 2012 Mar 1;35(3):556–64.

[2]Erasmus RT, Alanamu RA, Bojuwoye B, et al. East Afr Med J.1989;66:248—54

[3]Rotimi C, Daniel H, Zhou J, et al. Ethn Dis. 2003;13:S110—7

Prevalence

- The 25-year cumulative rate of progression of DR in Type I was:
  - progression of DR was 83%.
  - progression to PDR was 42%.
  - macular edema was 26%.

(WESDR Ophthalmology. 2008 Nov;115(11):1859-68)

RISK FACTORS

- Duration
- Glycaemic control
- Systemic hypertension
- Hyperlipidaemia
- Nephropathy
- Pregnancy
- Anaemia
- Carotid artery occlusive disease
- Alcohol ?
- Cigarette smoking?
- Obesity

RISK FACTORS

1. **Duration of diabetes** :

- is the most important independent factor.
- In patients diagnosed as having diabetes before the age of 30 years, the incidence of DR :
  - after 10 years is 50%
  - after 30 years is 90%

WESDR

RISK FACTORS

- It is extremely rare for DR to develop within 5 years of the onset of Type I diabetes.

- About 5% of Type II have NPDR at presentation perhaps due to the lag between onset and diagnosis.
  - Type II: it may take 9 – 12 years before diagnosed with DM

RISK FACTORS

2. Glycaemic control : determined by the level of HbA1c

- Good metabolic control of diabetes will not prevent DR, although it may delay its development by a few years.
- increased severity of diabetic retinopathy is associated with poorer glucose control.
- insulin treatment is associated with a decreased risk of either the development or progression of diabetic retinopathy in patients with type 1 diabetes.
- Insulin use in type II indicates poor prognosis

RISK FACTORS

- With strict control of DM:

  - risk of developing retinopathy was reduced by 75% .

  - 50% reduction in the rate of progression of retinopathy in existing retinopathy

  - early worsening of retinopathy is unlikely to threaten vision .

Diabetes Control and Complications Trial Research Group N Engl J Med 1993; 329:977-986.

RISK FACTORS

- ~~Duration~~
- ~~Glycaemic control~~
- Systemic hypertension
- Hyperlipidaemia
- Nephropathy
- Pregnancy
- Anaemia
- Carotid artery occlusive disease
- Alcohol ?
- Cigarette smoking?
- Obesity

Ocular Risk Factors

Posterior Vitreous Detachment (PVD) :

- due to degenerative changes in the vitreous.
- significantly more common in diabetic subjects.
- complete PVD may prevent the development of PDR because the hyaloid is needed as a scaffold for retinal neovascularization.
- attached posterior hyaloid has also been associated with an increased risk for DME

Ocular Risk Factors

High myopia :

- choroidal degeneration and extensive old chorioretinopathy protect against DR.
- believed to act in the same manner as pan retinal photocoagulation by reducing the metabolic needs of the retina

Ocular Risk Factors

Removal of cataract :

- DR may progress after cataract surgery.
- Patients who have CSME, SNPDR or PDR should undergo photocoagulation if the media is sufficiently clear.
- If the cataract preclude retina evaluation and treatment, prompt postoperative retinal evaluation and treatment should considered.

  - **Benson WE, Brown GC, Tasman W, et al. Extracapsular Cataract Extraction with placement of a Posterior Chamber Lens in Patients with Diabetic Retinopathy. *Ophthalmology*. 1993; 100:730-738**

AETIOPATHOGENESIS

- Diabetic retinopathy is a microangiopathy affecting the retinal precapillary arterioles, capillaries and venules .
- Retinopathy has features of both:

  - microvascular leakage. (mild- mod NPDR)

  - microvascular occlusion .(severe NPDR-PDR)
- Larger vessels could be affected

AETIOPATHOGENESIS

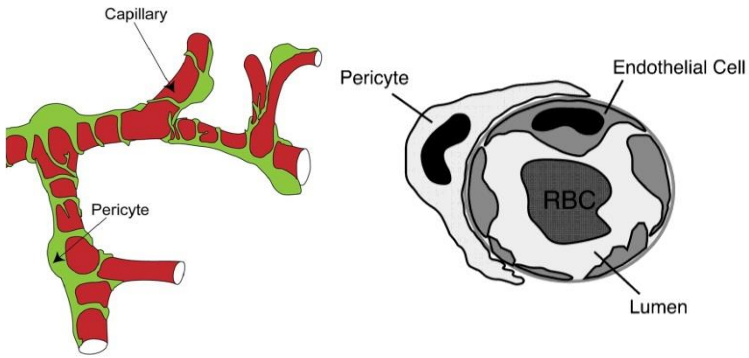
- Microvascular leakage :

- due to reduction in the number of pericytes .

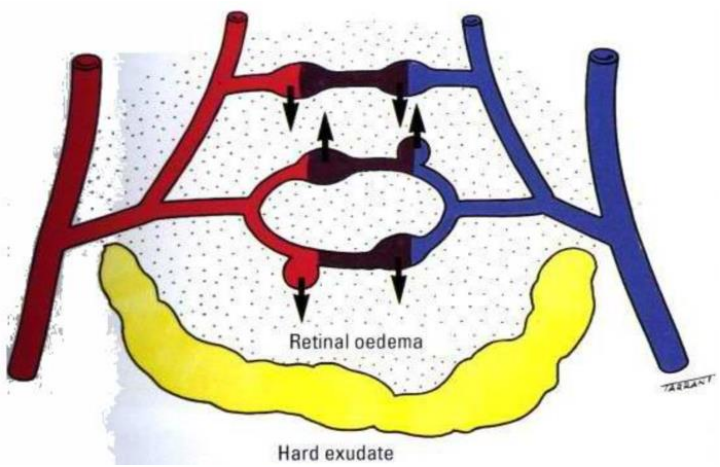
- The pericytes are wrapped around the capillaries and are thought to be responsible for the structural integrity of the vessel wall.

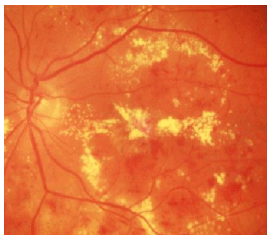
Microvascular leakage

Degeneration and loss of pericytes → Capillary wall weakening

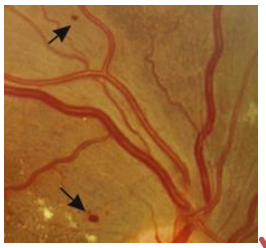


Capillary wall weakening → Plasma leakage → Retinal edema → Hard exudate (Circinate pattern)





Capillary wall weakening → microaneurysm → Intraretinal hemorrhage



AETIOPATHOGENESIS

Microvascular occlusion :

1. thickening of the capillary basement membrane.
2. capillary endothelial cell damage and proliferation.
3. changes in red blood cells leading to defective oxygen transport, and increased stickiness and aggregation of platelets

Microvascular occlusion

Endothelial cell damage and proliferation

Capillary basement membrane thickening

Increased plasma viscosity
Deformation of RBC
Increased platelets stickiness

Decreased capillary blood flow and perfusion

Retinal hypoxia

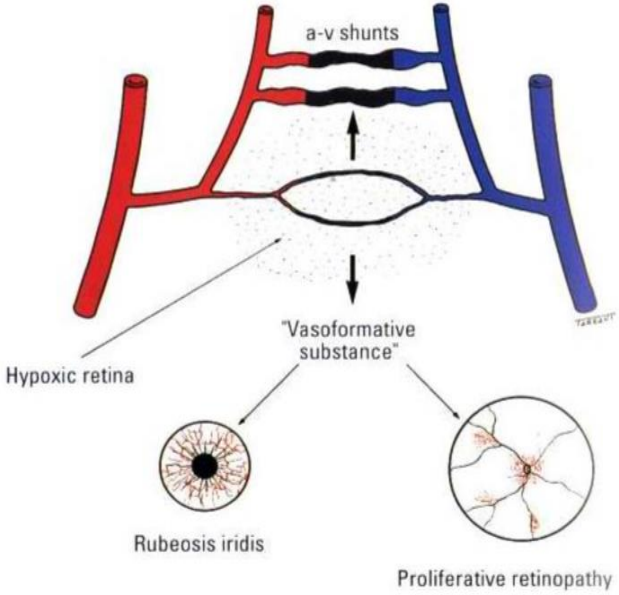
VEGF

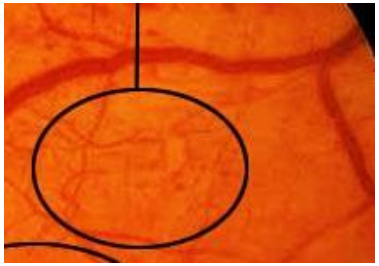
A-V shunt
IRMA*

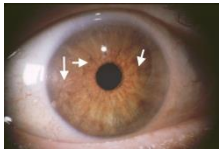
Neovascularization and fibrovascular proliferation

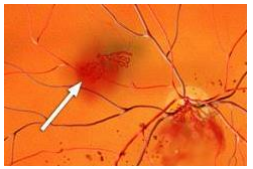
Rubeosis iridis

Proliferative retinopathy

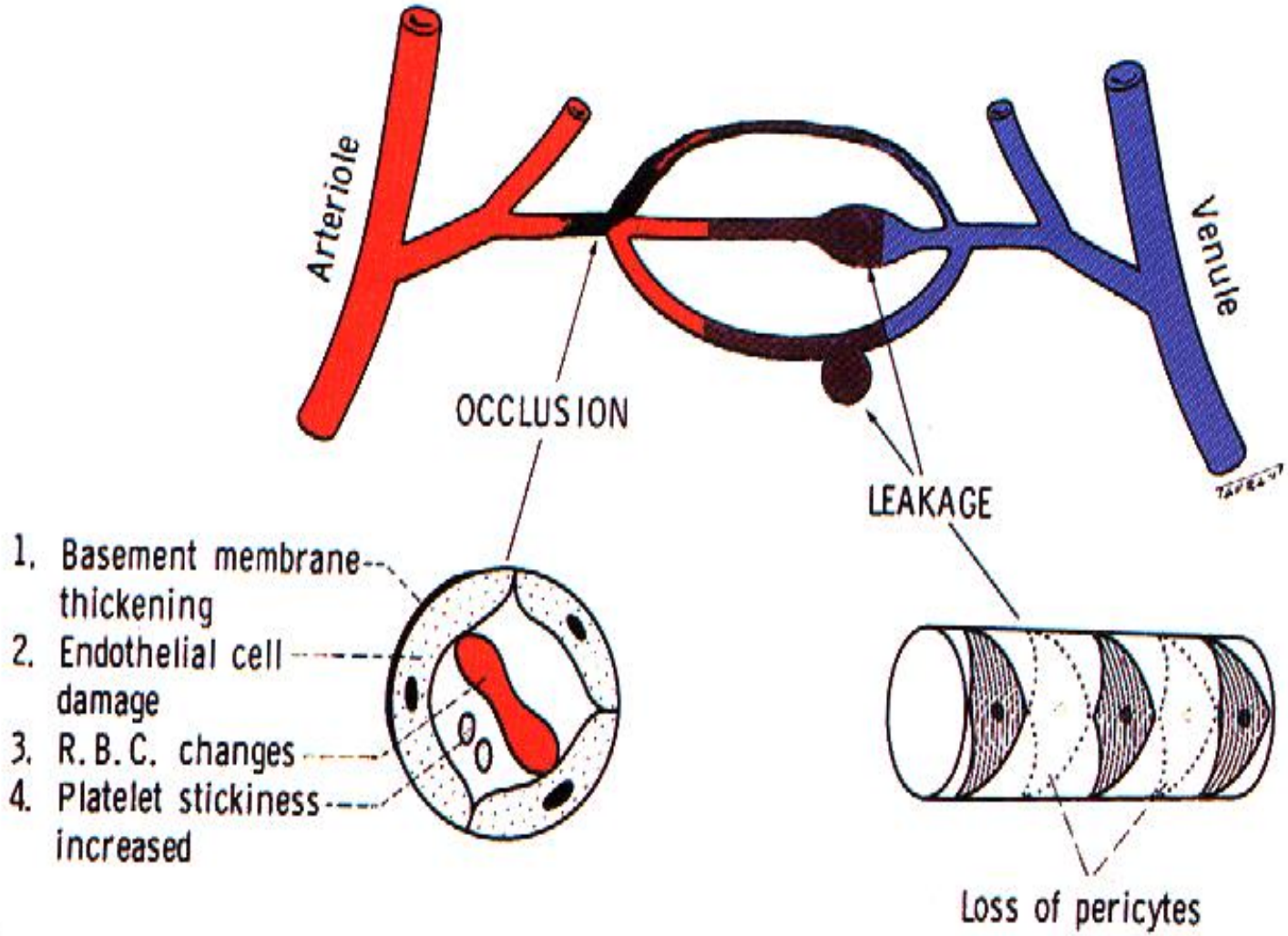








*intraretinal microvascular abnormalities


Arteriole
Venule
OCCLUSION
LEAKAGE
1. Basement membrane thickening
2. Endothelial cell damage
3. R.B.C. changes
4. Platelet stickiness increased
Loss of pericytes

1.SORBITOL(POLYOL) PATHWAY

- Glucose → Sorbitol

  Aldose Reductase

- Intracellular hyperosmosis → cell damage

- Little conclusive proof found to support the hypothesis
- Effect of *aldose reductase* inhibitors on progress of DR showed no beneficial effect

2. ADVAVCED GLYCATION END PRODUCTS(AGEs)

- Hyperglycaemia causes non-enzymatic glucose interaction with lysine residue of protein side chains(Glycated proteins); eg glycated haemoglobin(Hb A1c)
- AGEs affect protein function – enzymes, regulatory proteins – autoregulation is affected leading to retinopathy, nephropathy etc.
- Glygated Hb has high oxygen affinity – less oxygen to tissues

3. OXIDATIVE DAMAGE

- Hyperglycaemia – oxidation radicals, eg protein oxidation, superoxide anions, glucose oxidation

- Antioxidants trials in humans inconclusive

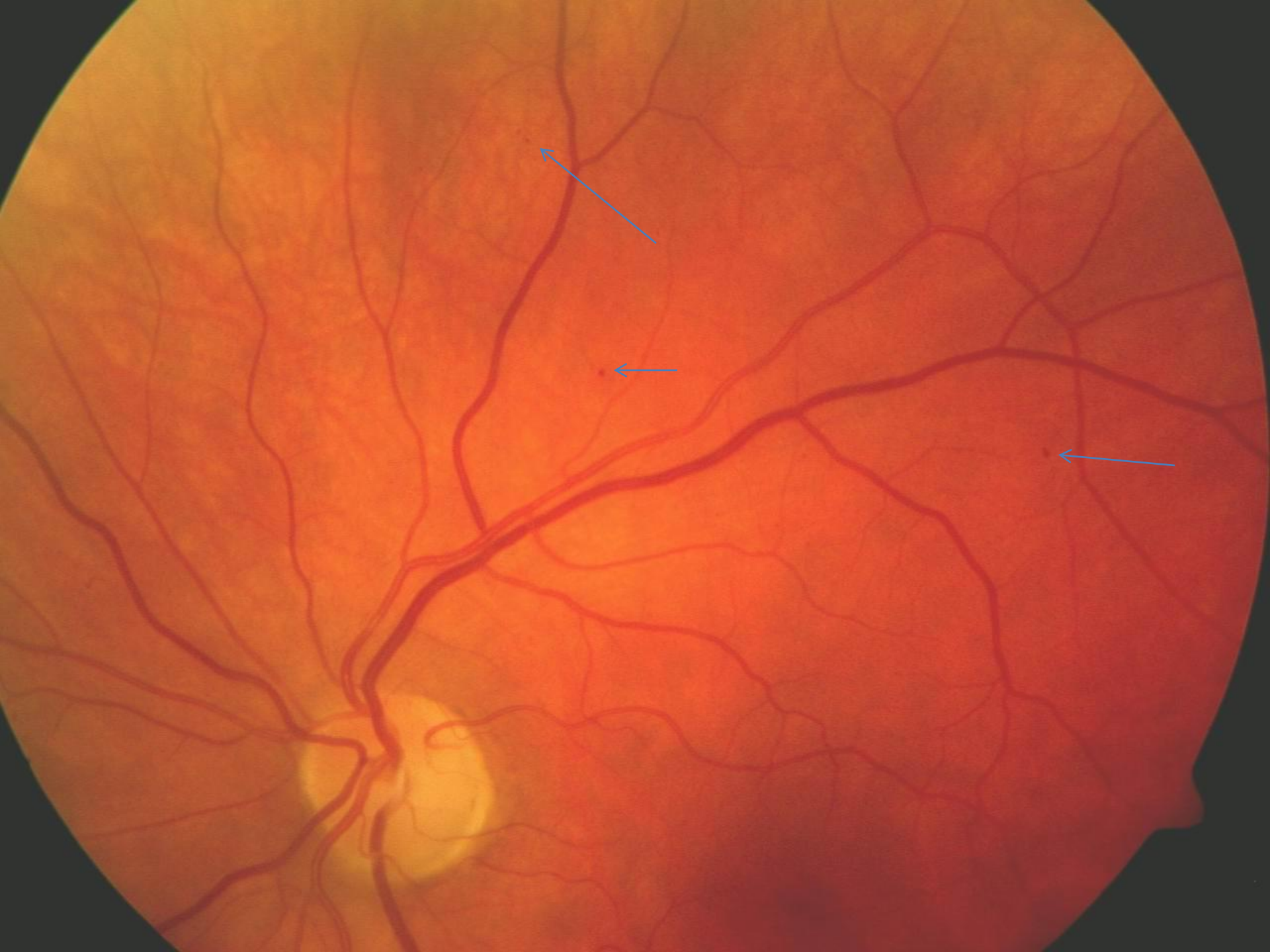
PROTEIN KINASE C & VEGF

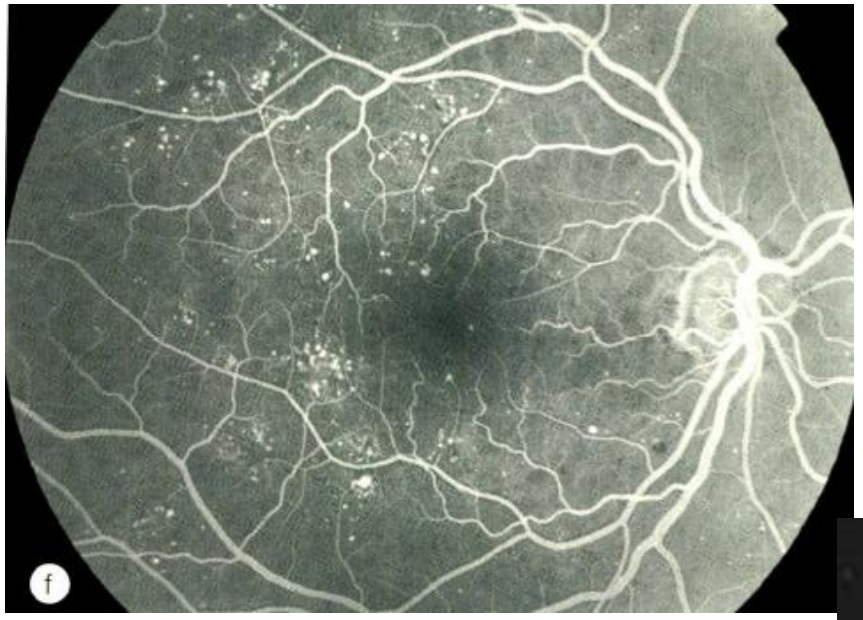
- Protein kinase C β2 isoform – implicated in hyperglycaemia-related microvascular damage – retinal leakage, ischaemia and neovascularisation
- implicated in pericytes damage in early DR
- VEGF(cytokine) – angiogenic and mitogenic. Involved in increased permeability and neovascularisation.
- Intravitreal injection of anti-VEGF antibodies attenuates angiogenic response to VEGF in experimental models

CLINICAL PRESENTATION

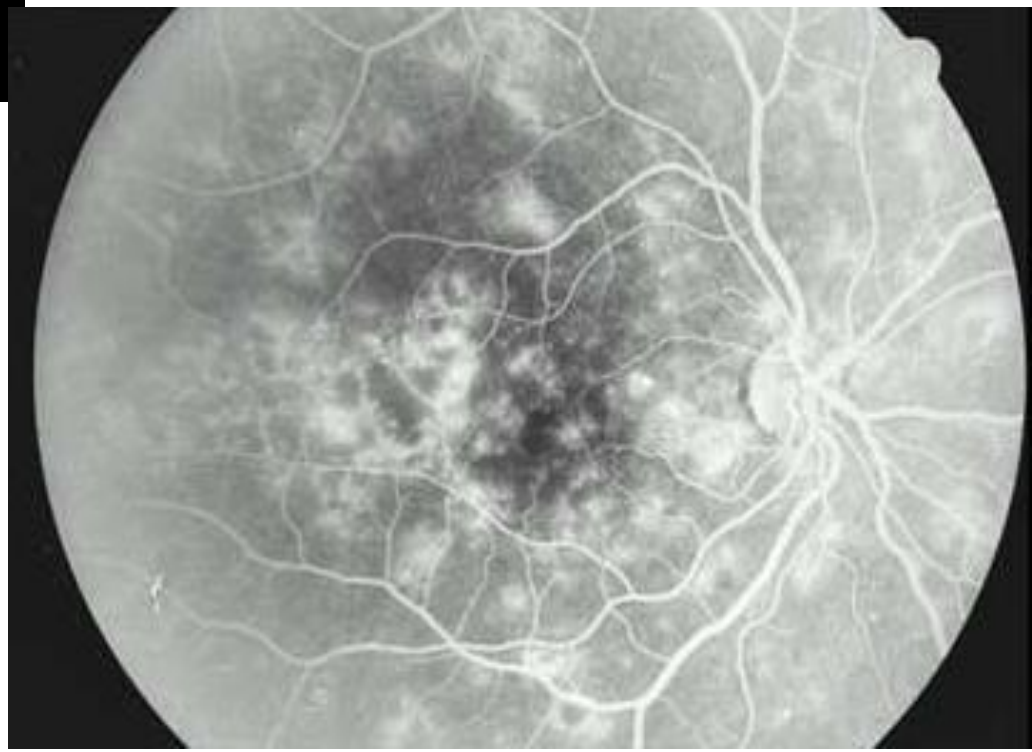
- **Microaneurysms** :

  - located in the inner nuclear layer .
  - the first clinically detectable lesions .
  - small round dots .(20-200 µm)
  - mostly located near and temporal to the macula.
  - When coated with blood they may be indistinguishable from dot haemorrhages.





Scattered hyperfluorescent



Microaneurysms may leak plasma constituents into the retina

CLINICAL PRESENTATION

- **Haemorrhages** :

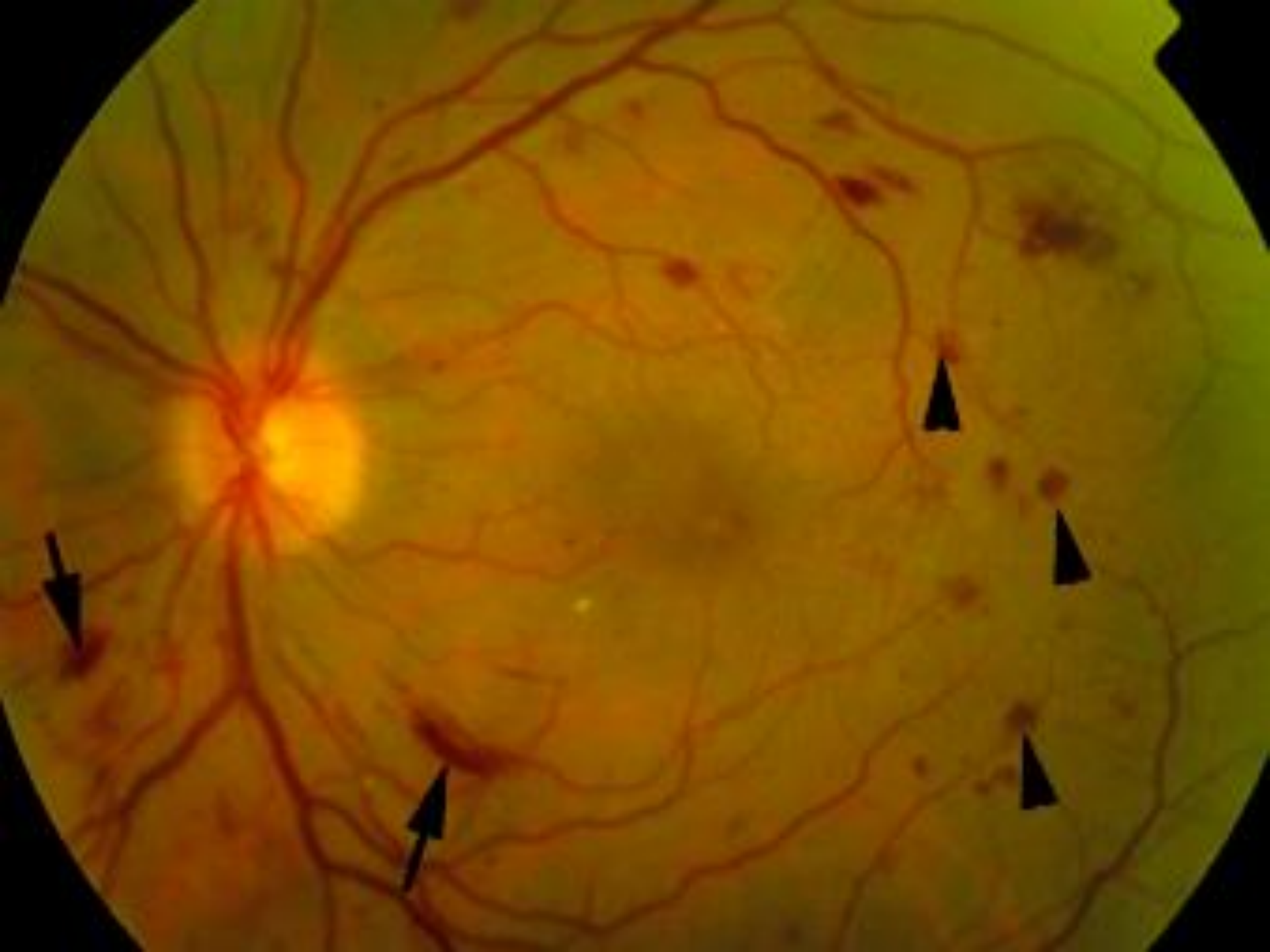
  The clinical appearance depending on location

  - 'dot' and 'blot' :

    * originating from the venous end of the capillaries. *located in the compact middle layers of the retina .

  - Flame-shaped :

    * originate from the more superficial precapillary arterioles, follow the course of the retinal nerve fibre layer. (liner distribution)



CLINICAL PRESENTATION

- **Hard exudates** :

  - located between the inner plexiform and inner nuclear layers of the retina.

  - They are often distributed in a (circinate pattern) .

  - The centres of rings of hard exudates usually contain microaneurysms .

  - Made up of accumulated lipoproteins .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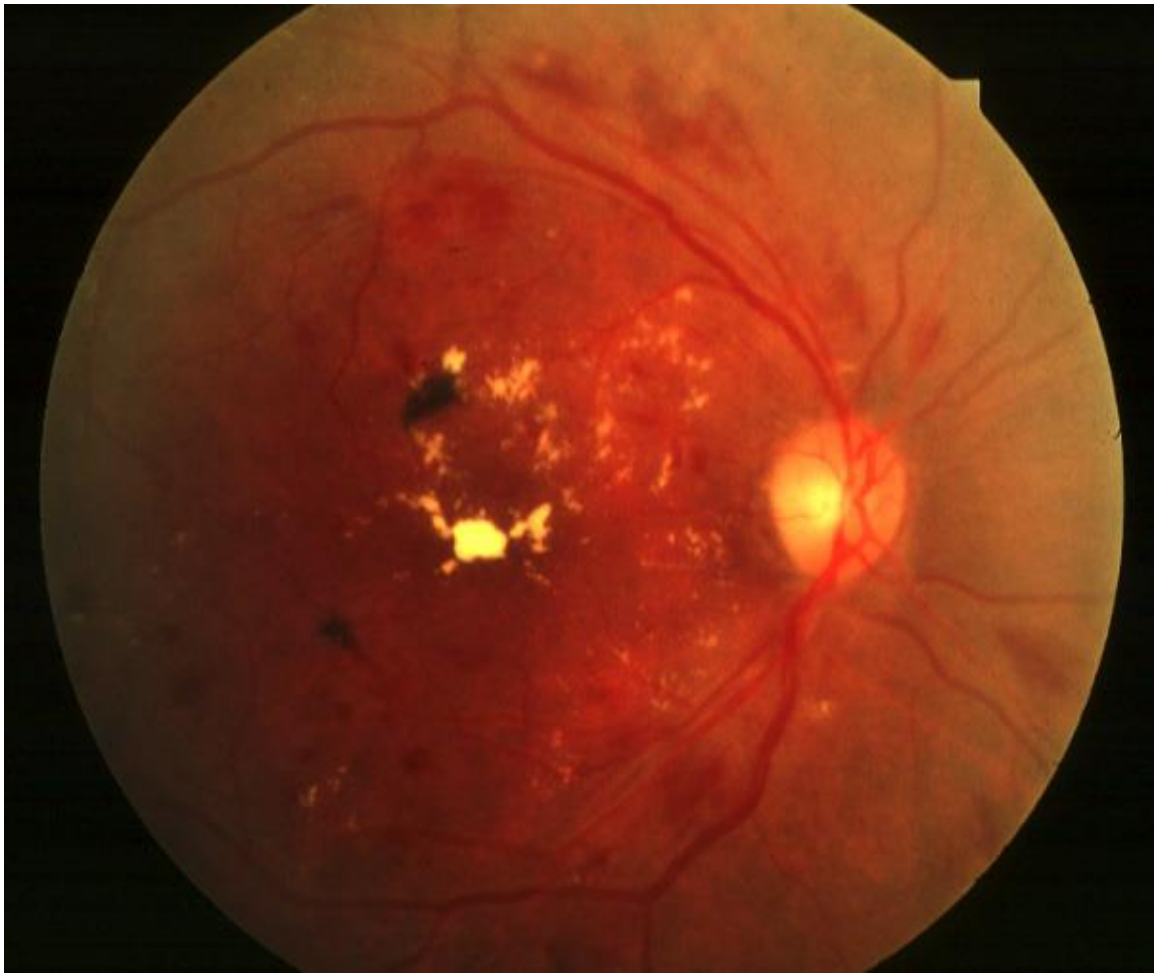
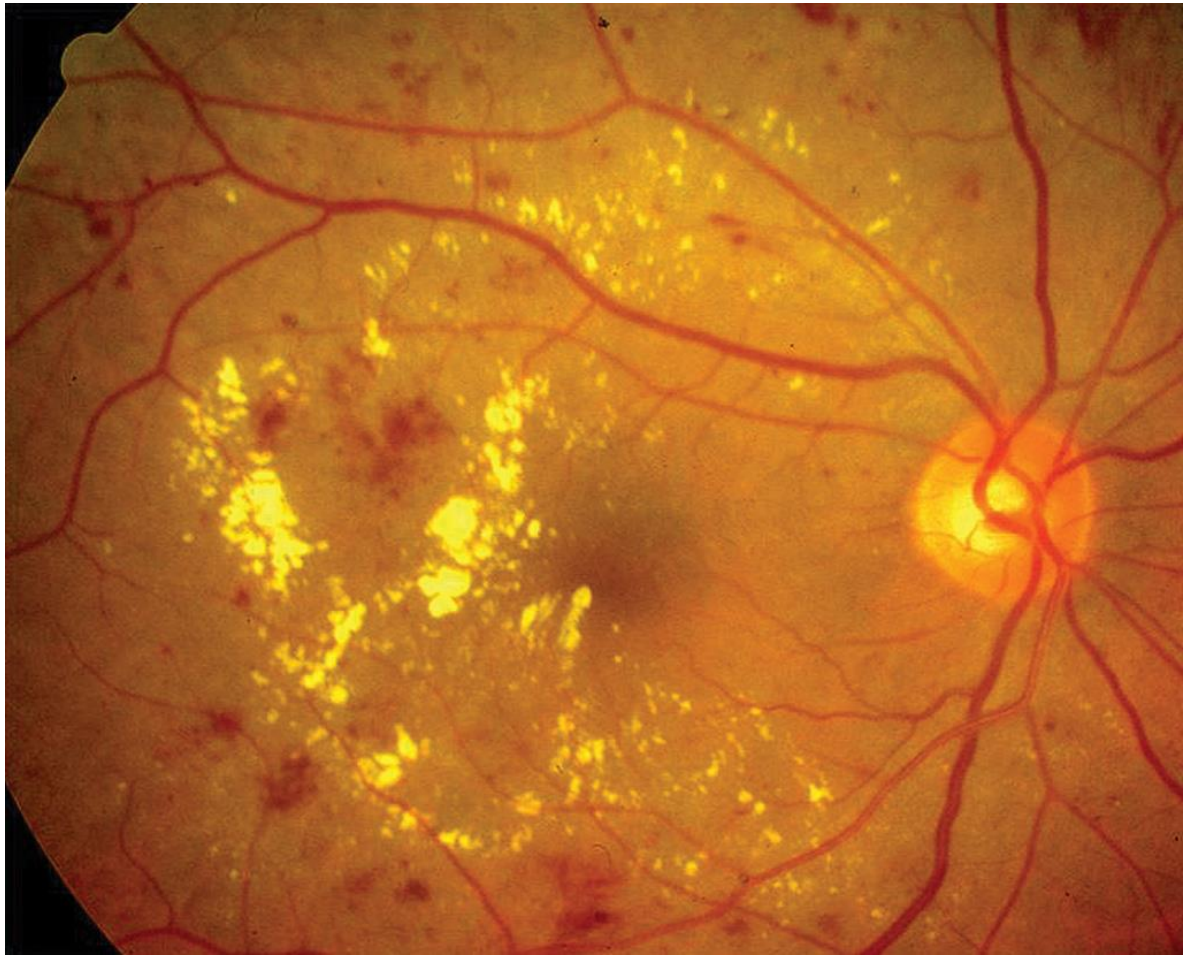
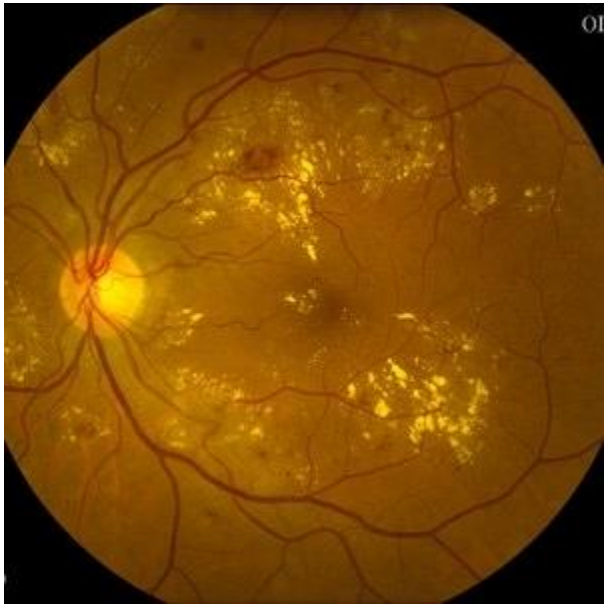
Columbia University







CLINICAL PRESENTATION

- **Retinal oedema** :

- located between the outer plexiform and inner nuclear layers.
- Later it may involve the inner plexiform and nerve fibre layers, until eventually the entire thickness of the retina may become oedematous.
- with further accumulation of fluid, the fovea assumes a cystoid appearance .

- Macular oedema types: (FFA + Clinical)

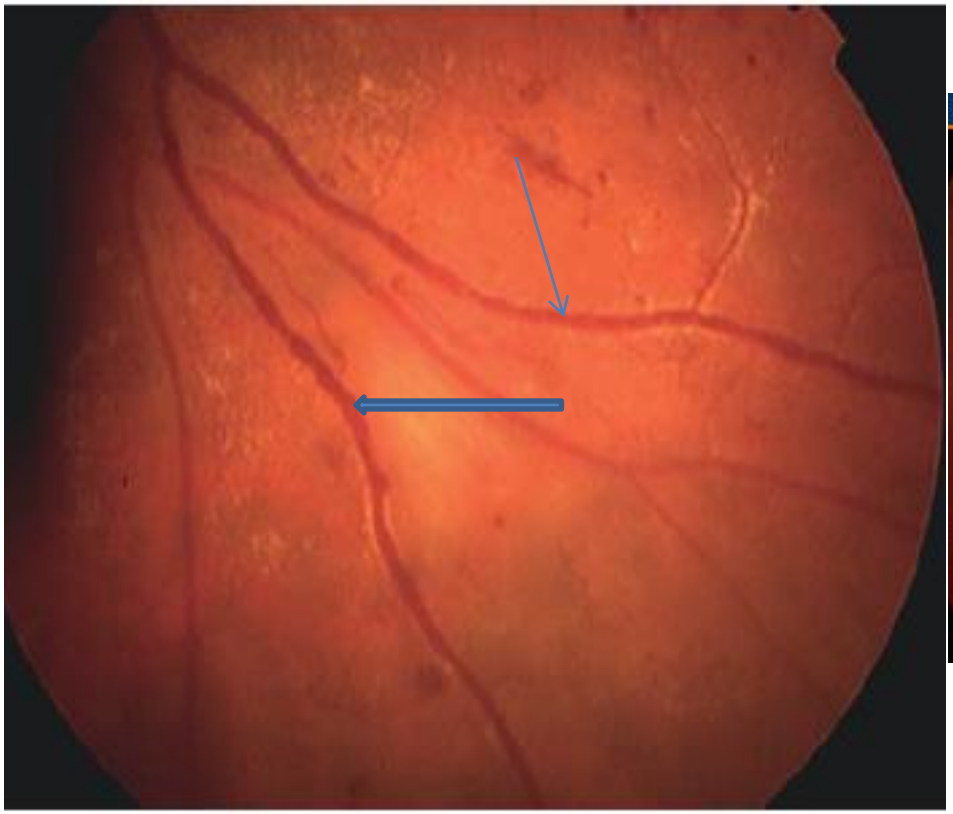
1. Focal MO :which has identifiable leakage source.
2. Diffuse MO: which has multiple unidentifiable source of leakage.
3. Cystoid MO: in which fluid accumulate in OPL and INL to form cystoid spaces.

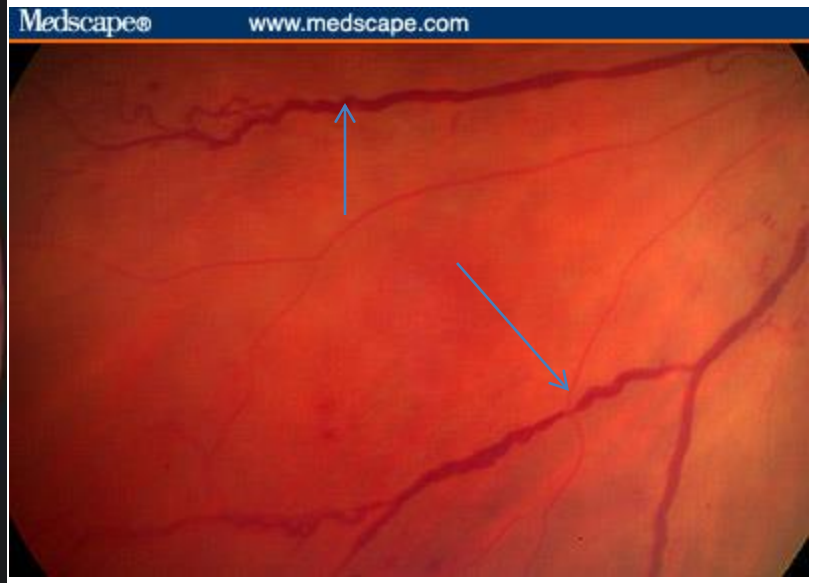
CLINICAL PRESENTATION

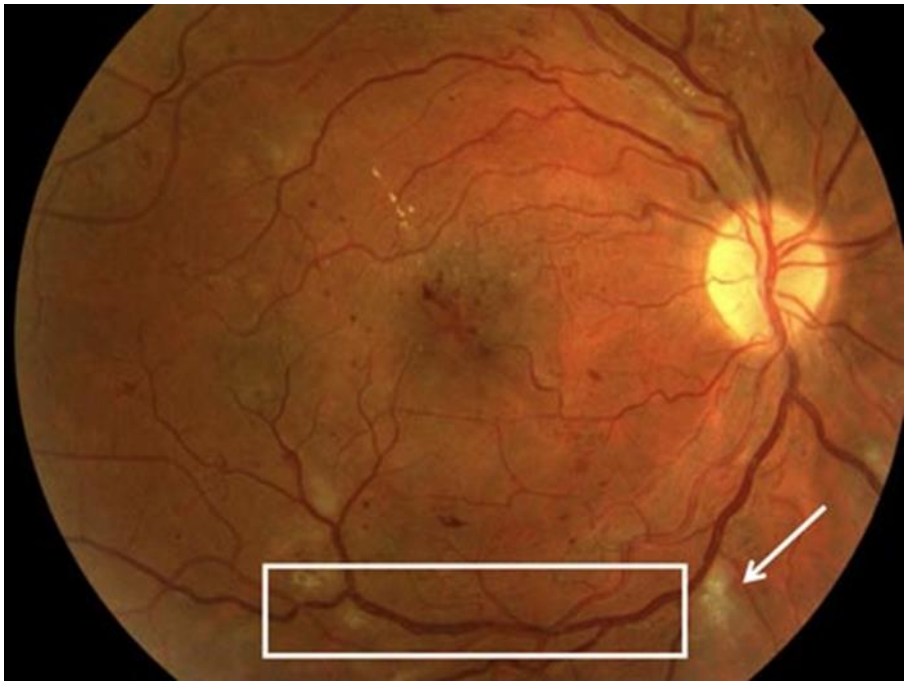
- **Vascular changes** :

- venous changes :in the form of 'beading', 'looping' and 'sausage-like' segmentation.
- It represent endothelial cell proliferation.
- arterioles may also be narrowed and even obliterated, resembling a BRAO .
- The most powerful predictors for development of PDR.

Venous beading



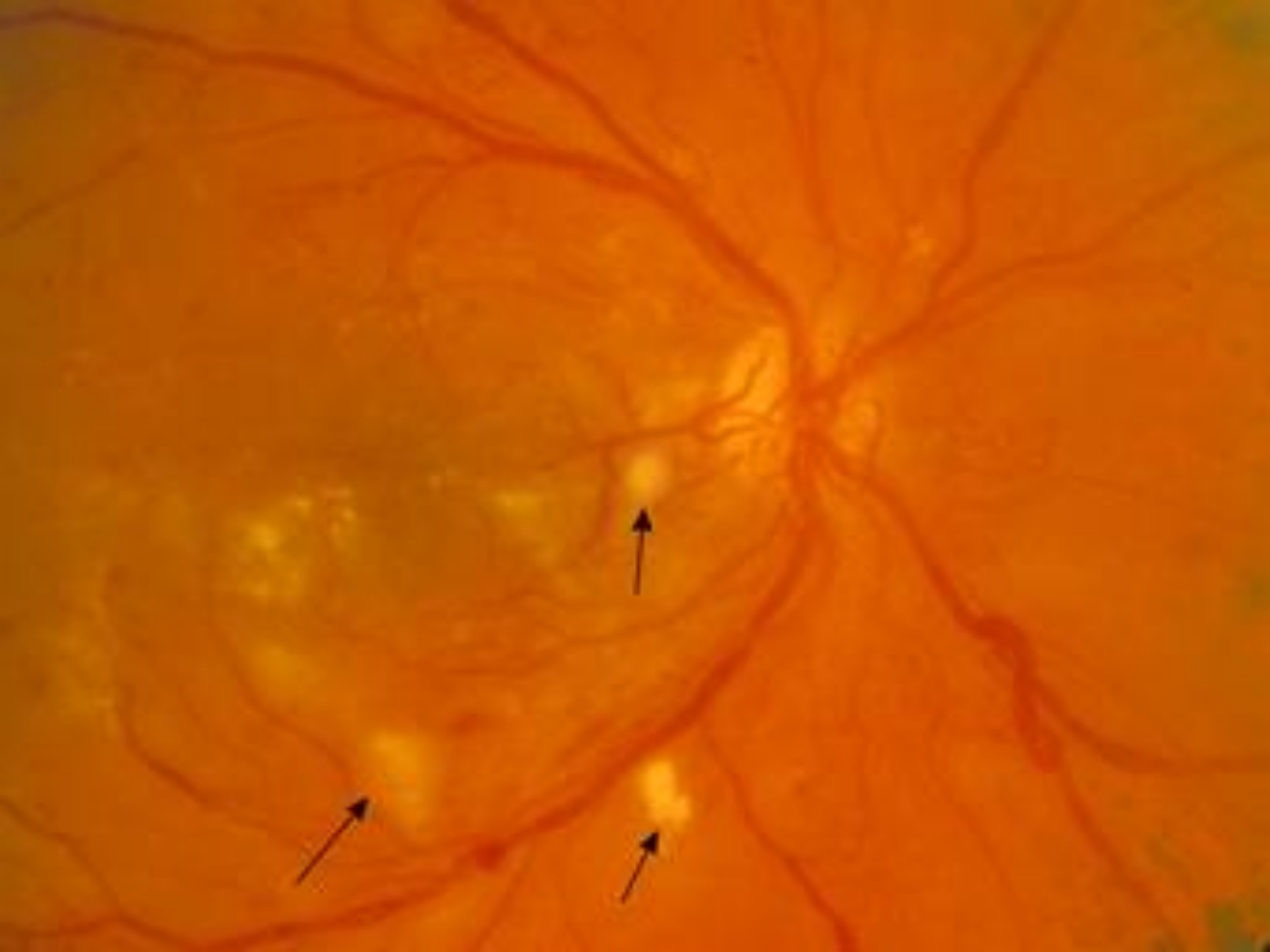


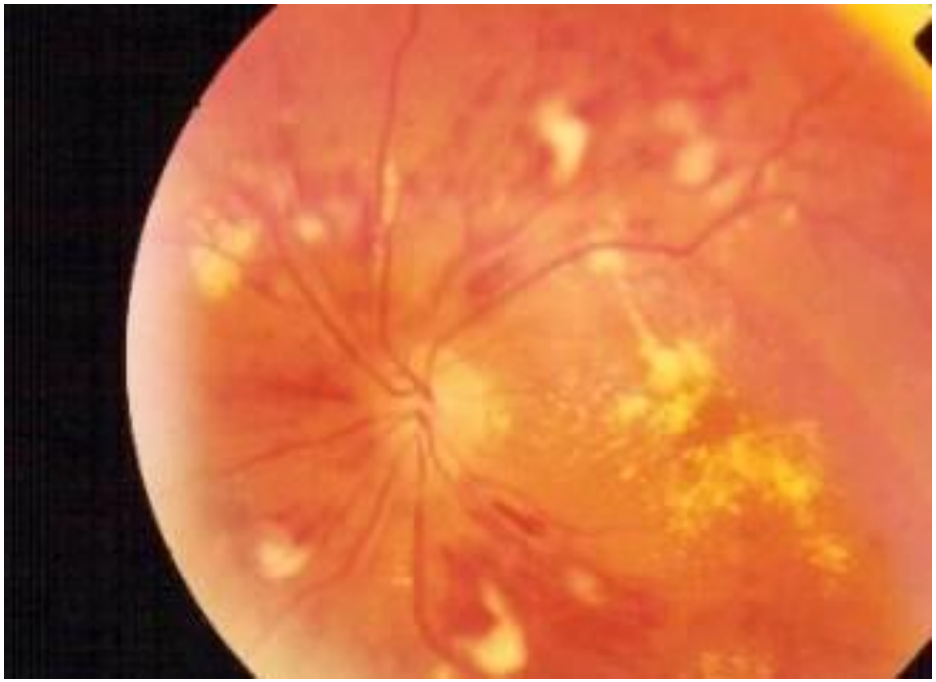


CLINICAL PRESENTATION

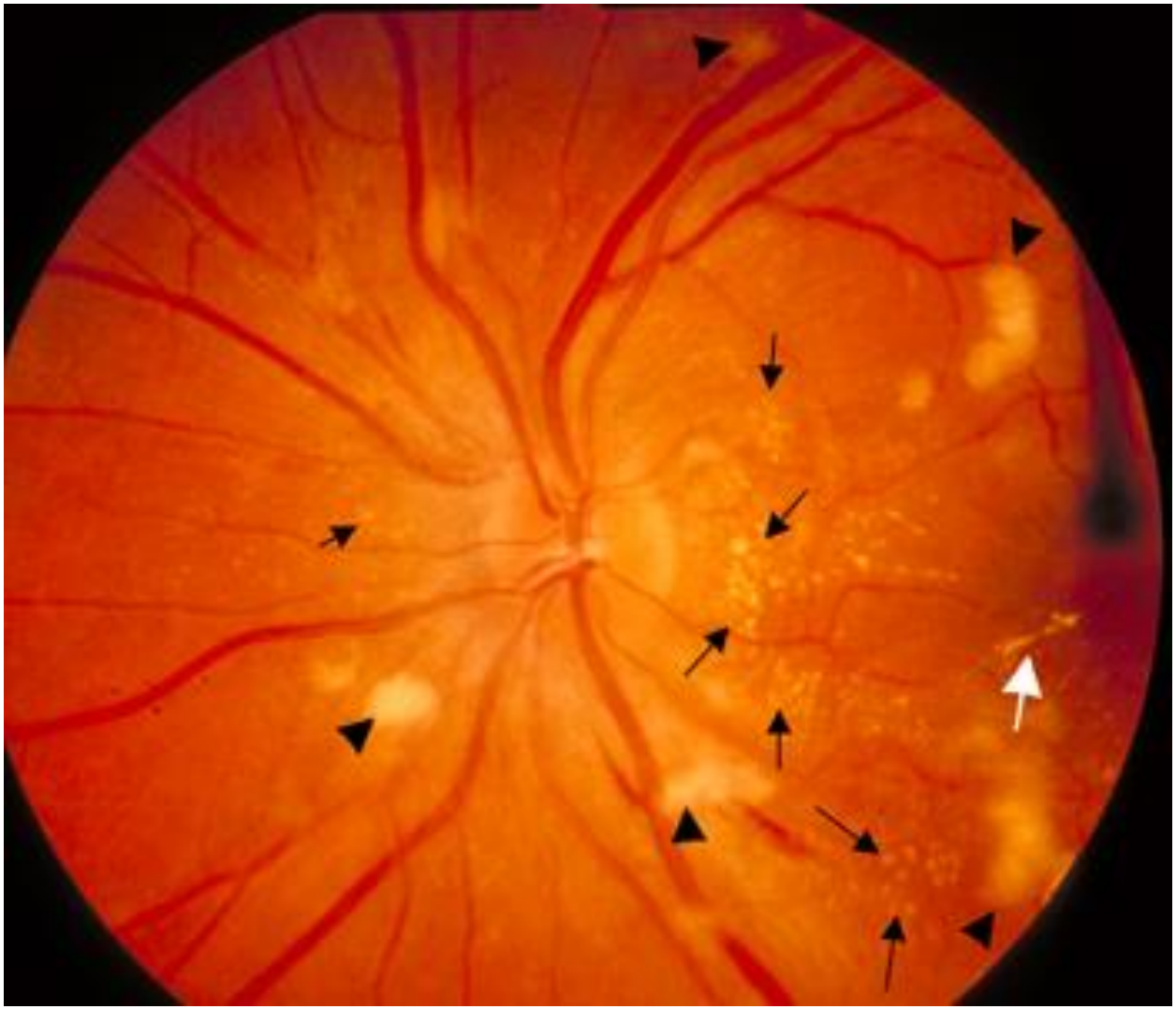
- **Cotton-wool spots** (CWS):

- Nerve fiber layer infarction.
- caused by capillary occlusion in the retinal nerve fibre layer.
- The interruption of axoplasmic flow caused by the ischaemia, and subsequent build-up of transported material within the nerve axons, is responsible for the white and opaque appearance of these lesions.
- Disappear within weeks to months.





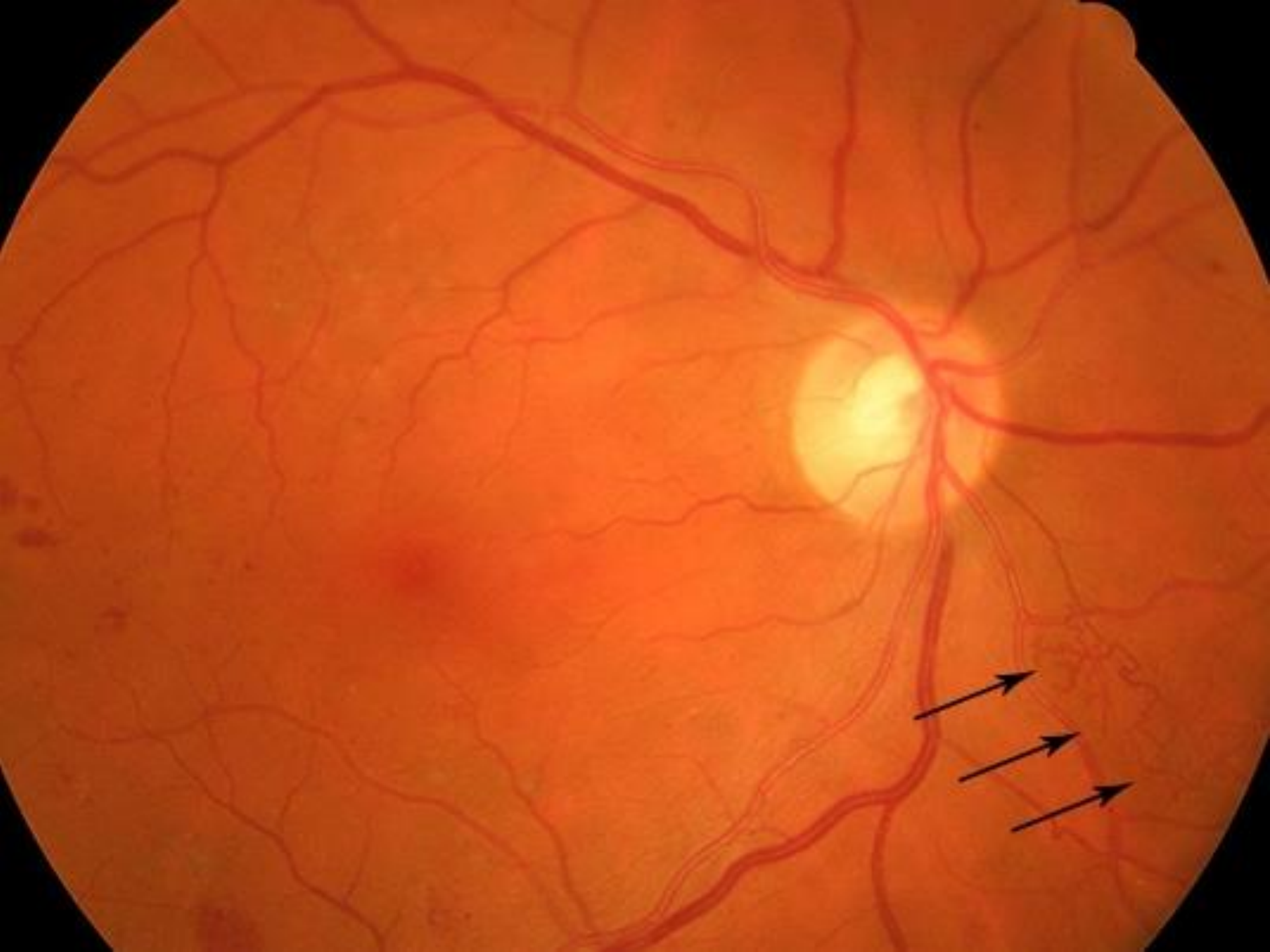
Exudates vs CWS



CLINICAL PRESENTATION

- **Intraretinal microvascular abnormalities** (IRMA) :
- Dilated, tortous retinal capillaries that act as a shunt between arterioles and venules.
- frequently seen adjacent to areas of capillary closure.
- IRMA may resemble focal areas of flat NVE . But in IRMA :

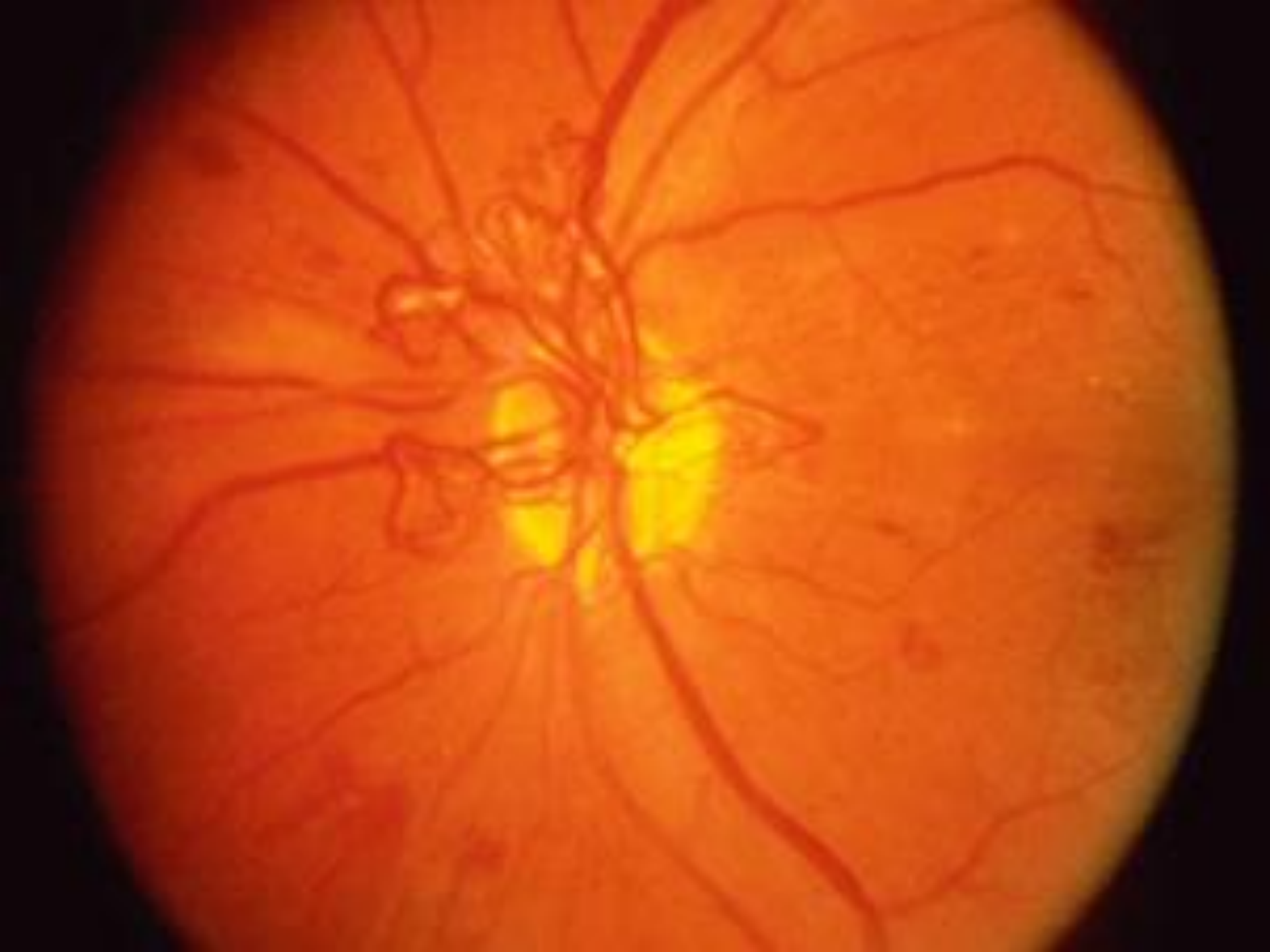
1. intraretinal location.
2. absence of profuse leakage on fluorescein angiography.
3. failure to cross over major retinal blood vessels.

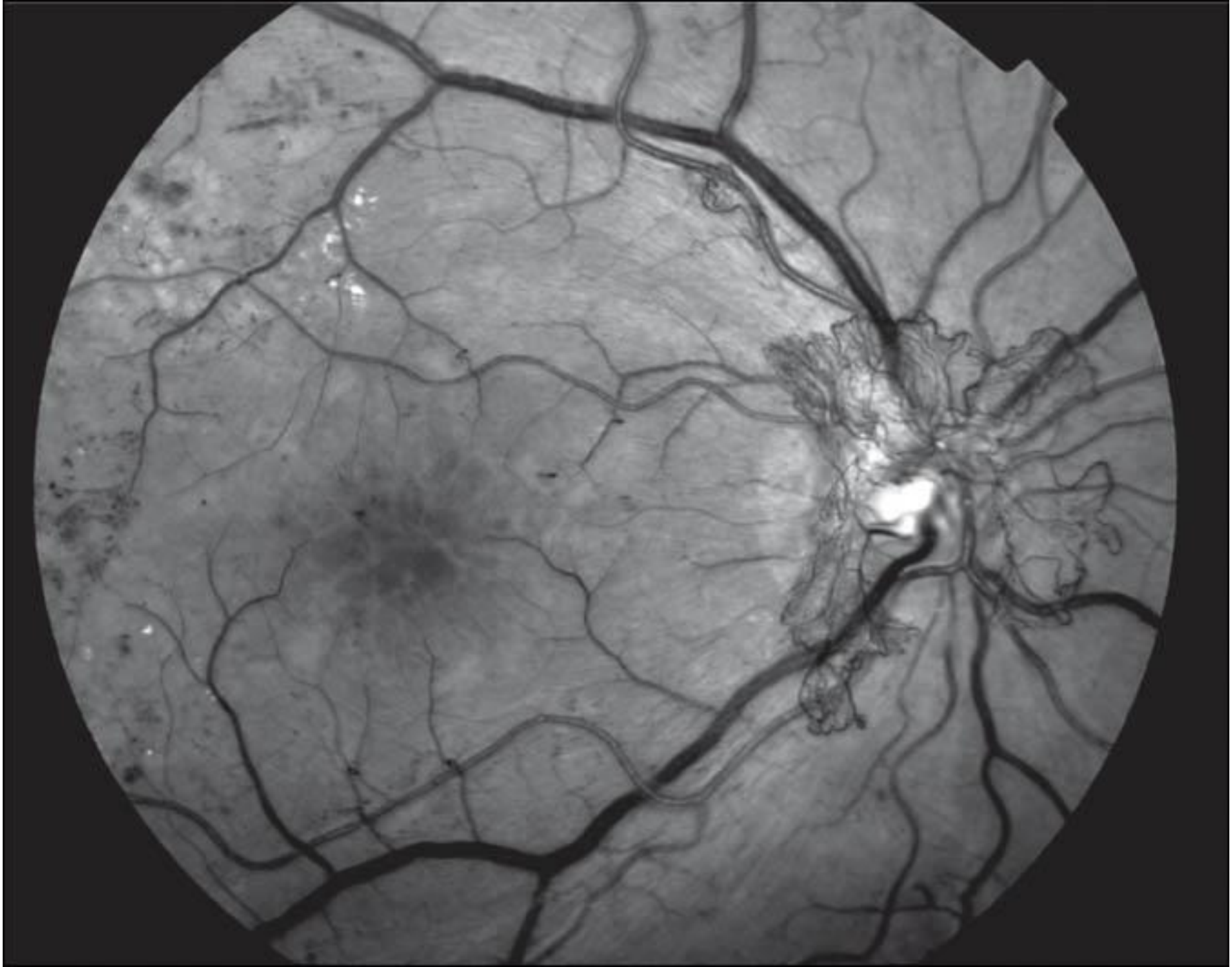


CLINICAL PRESENTATION

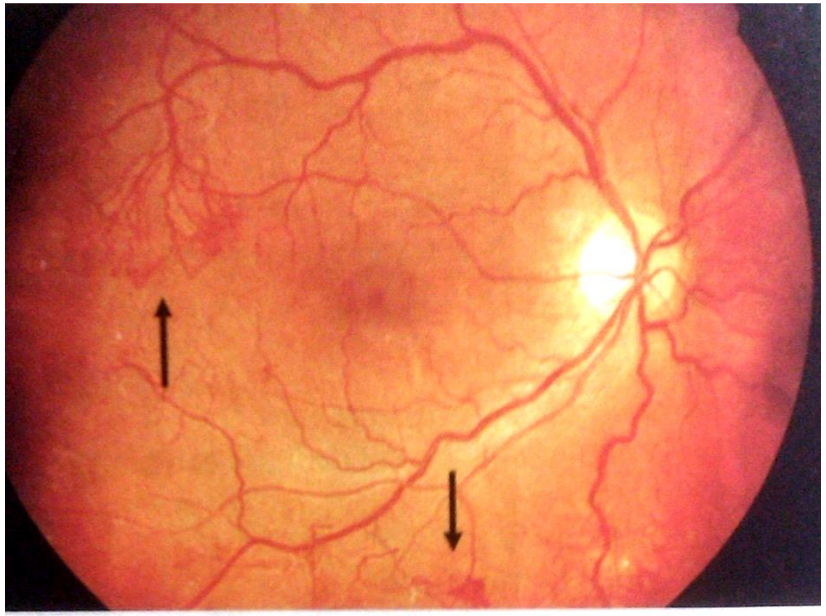
- **New Vessels:**

- Unlike IRMA, they arise on the retinal surface and may extend or be pulled into the vitreous cavity.
- NVD : NV appears on or within one DD of disc margin .
- NVE : any other location .

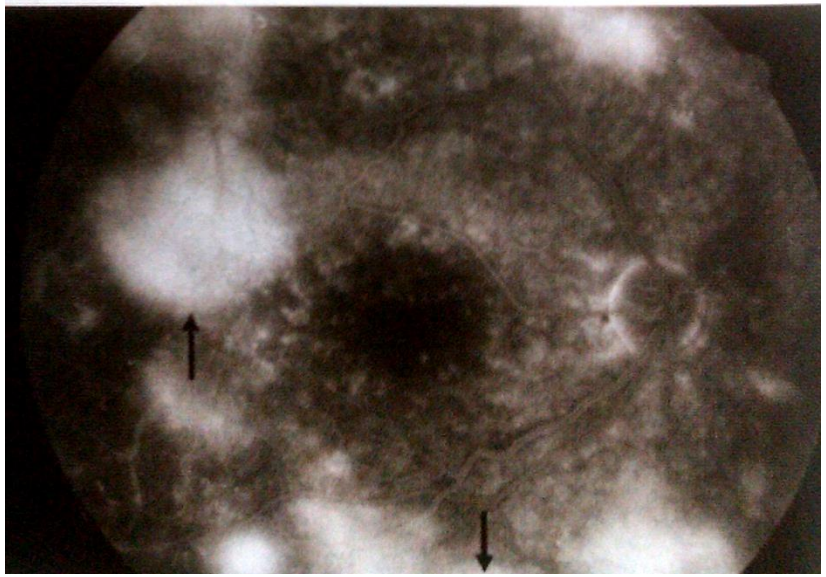


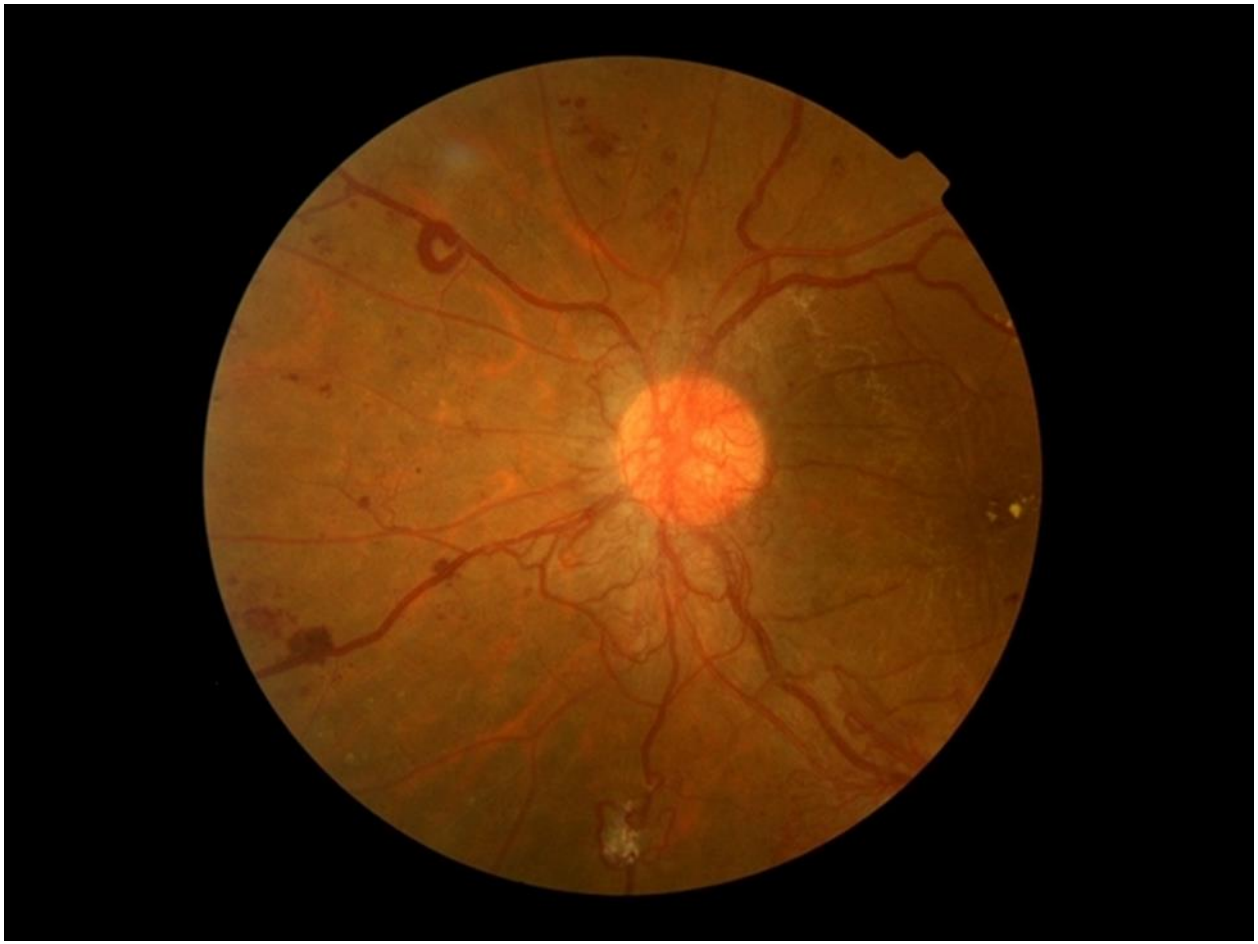


Neovascularization of elsewhere



Fluorescein dye leakage is seen in neovascularized area



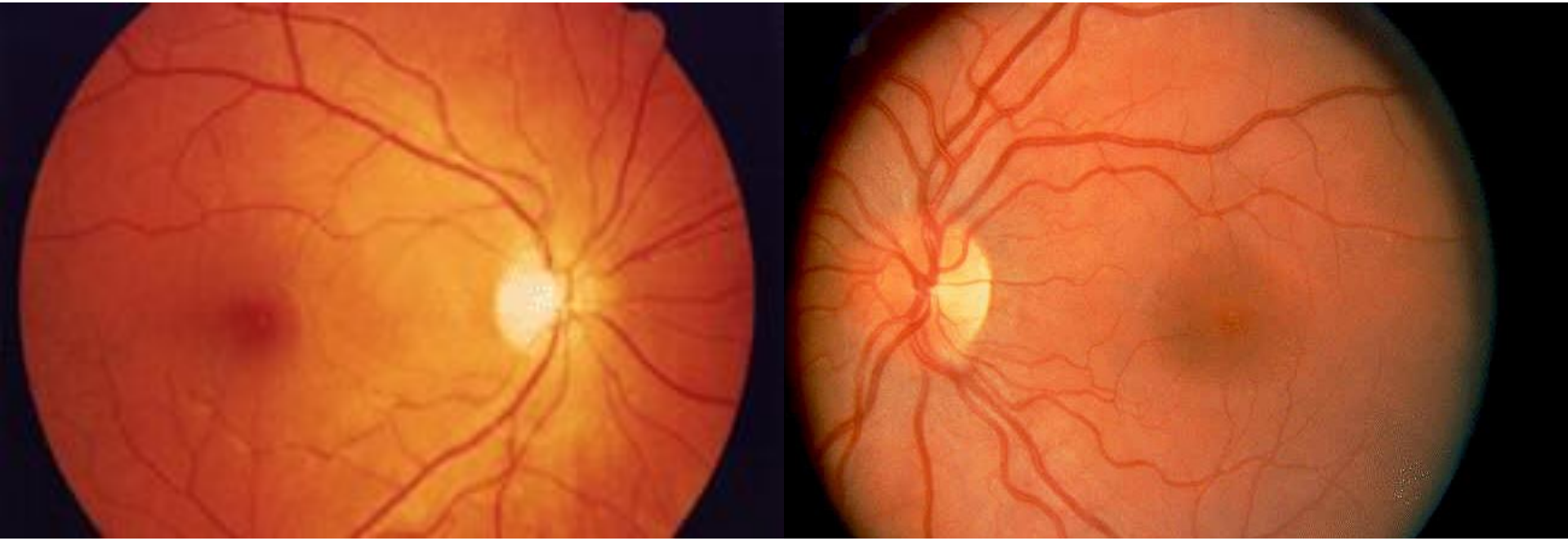


CLINICAL PRESENTATION

- **Fibrous Glial proliferation :**

- Accompained growth of new vessels.
- It is proliferation between the posterior vitreous gel and the ILM.
- Derived from retinal glial cells and fibrocytes.

NO DR



Classification of DR

- Non proliferative DR
- Proliferative DR
- Maculopathy
- Papillopathy

Classification of Severity of Diabetic Retinopathy

Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS Report 9. *Ophthalmology*. 1991;98:766–785.

Nonproliferative DR

Mild NPDR	**Microaneurysms, retinal hemorrhage and hard exudate**
Moderate NPDR	**Microaneuryams , haemorrhages in at least one quadrant plus cotton wool spots /IRMA.**
Severe NPDR **4 : 2 : 1** **Rule**	**Moderate NPDR plus one of :** 1. **Intraretinal Hges in four quadrants .** 2. **marked venous beading in two or more quadrants** 3. **IRMA one or more quadrants.**
Very severe NPDR	**Two or more of the above features described in severe NPDR**

Classification of severity of diabetic retinopathy

- *Proliferative DR*

Early PDR	**New vessels and/or fibrous proliferations; or preretinal and/or vitreous hemorrhage**
PDR with HRC	**1. NVD ≥ 1/3 of DD.** **2. less extensive NVD, if vitreous or preretinal hemorrhage is present .** **3. NVE ≥ half disc area, if vitreous or preretinal hemorrhage is present**
Advanced PDR	**1. Extensive vitreous hemorrhage precluding grading.** **2. retinal detachment involving the macula.** **3. phthisis bulbi .**

Macular oedema

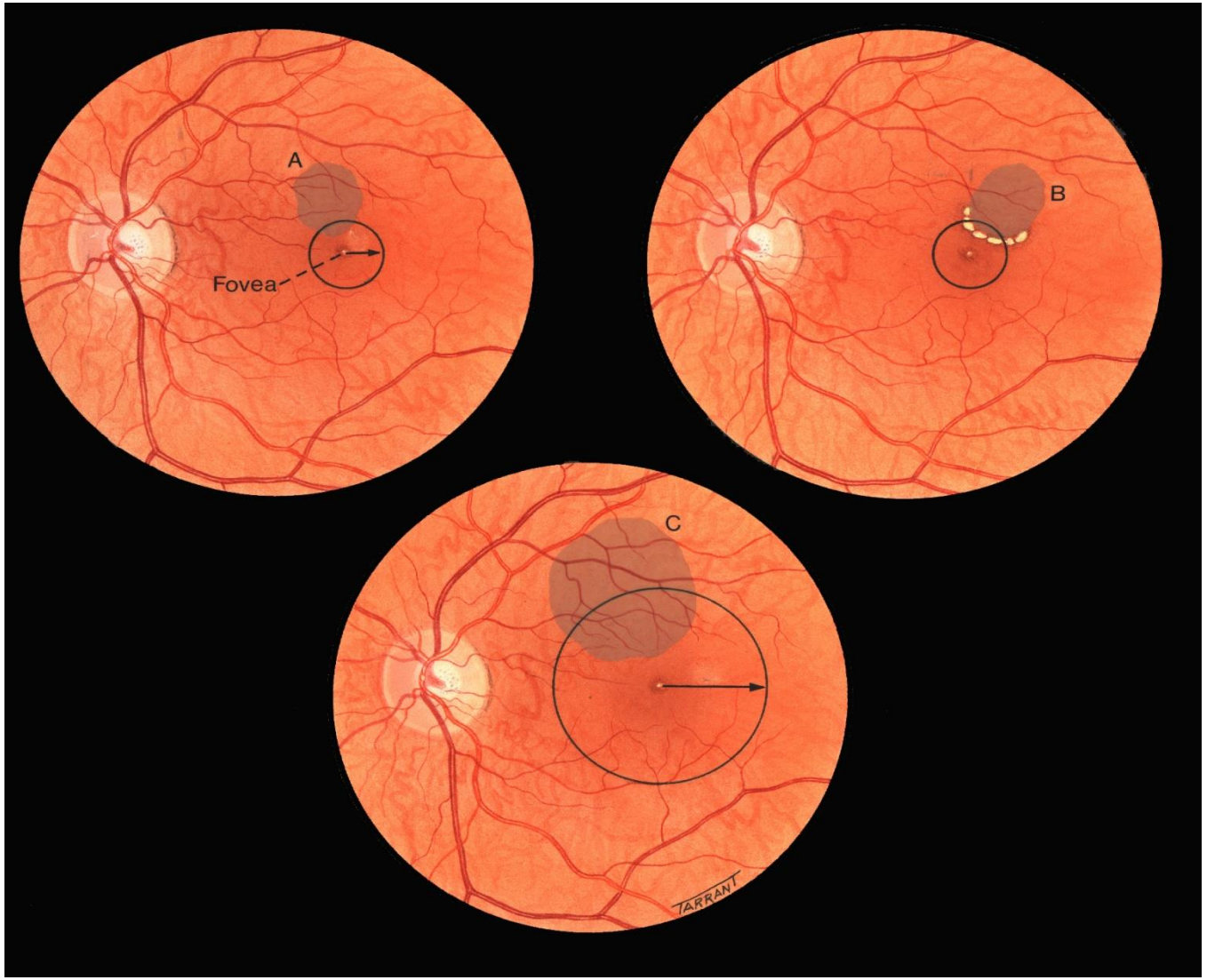
- defined as the presence of any retinal thickening or hard exudates within one disc diameter (i.e. 1500 µm) of the centre of the fovea.
- clinically insignificant macular oedema do not require treatment, only should be followed up at 6 monthly intervals.

Clinically significant macular oedema (CSMO)

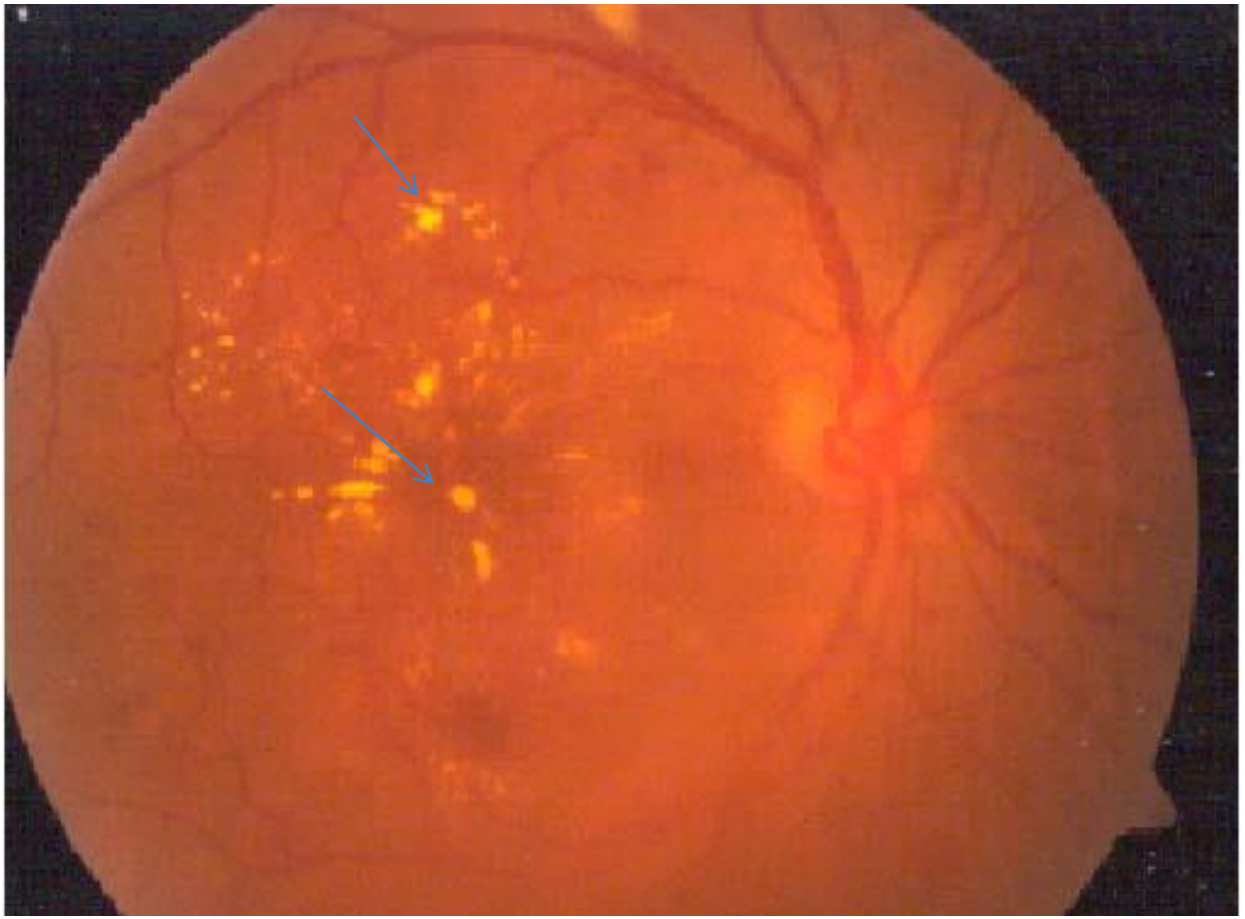
defined as the presence of one or more of the following features:

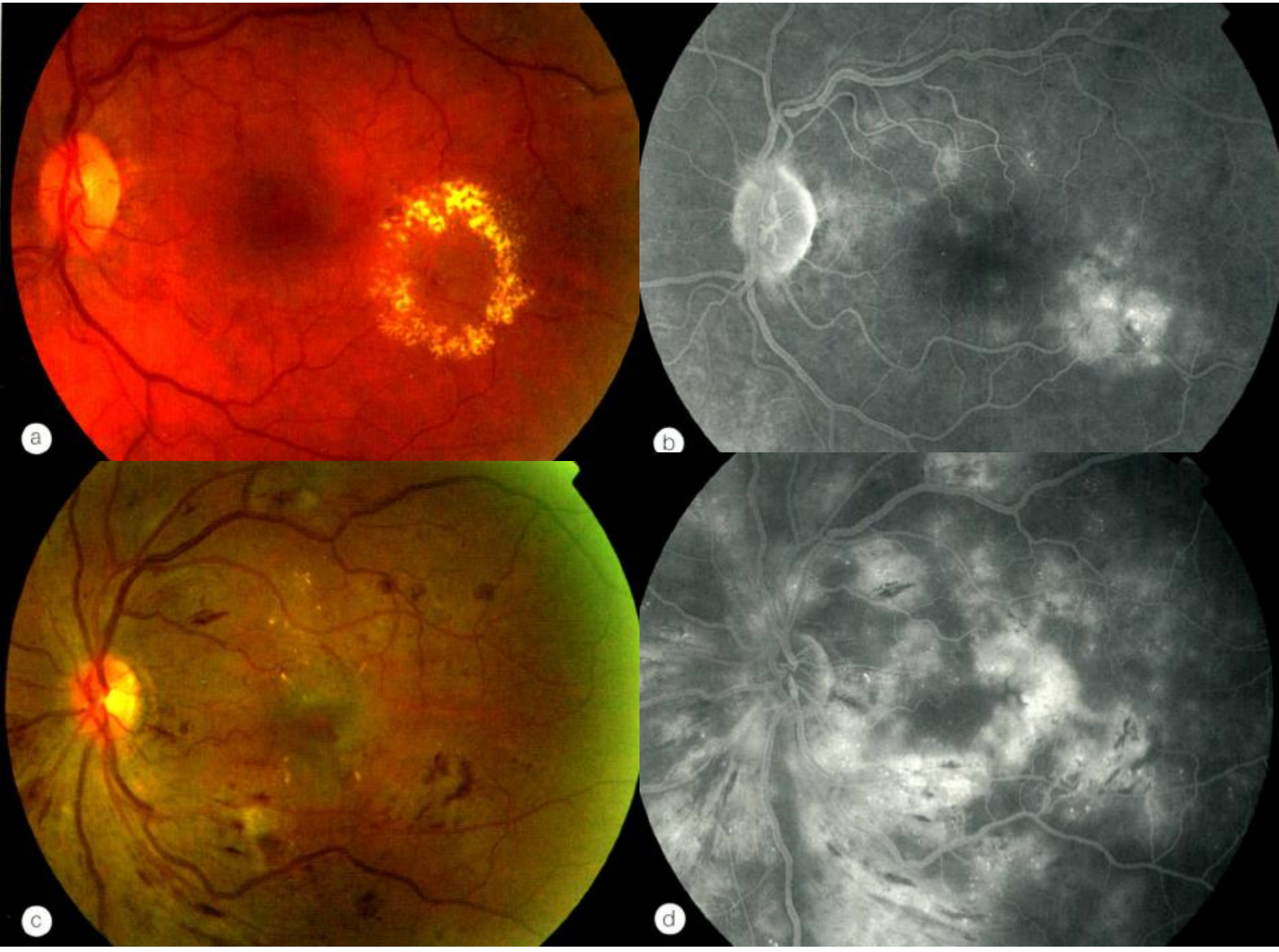
1. Retinal oedema within 500 µm of the centre of the fovea .
2. Hard exudates within 500 µm of the fovea, if associated with adjacent retinal thickening (which may be outside the 500 µm limit) .
3. Retinal oedema that is one disc area (1500 µm) or larger, any part of which is within one disc diameter of the centre of the fovea.

- **Early Treatment Diabetic Retinopathy Study Research Group. Early Photocoagulation for Diabetic Retinopathy. ETDRS report 9*. Ophthalmology* 1991;98:766-785**

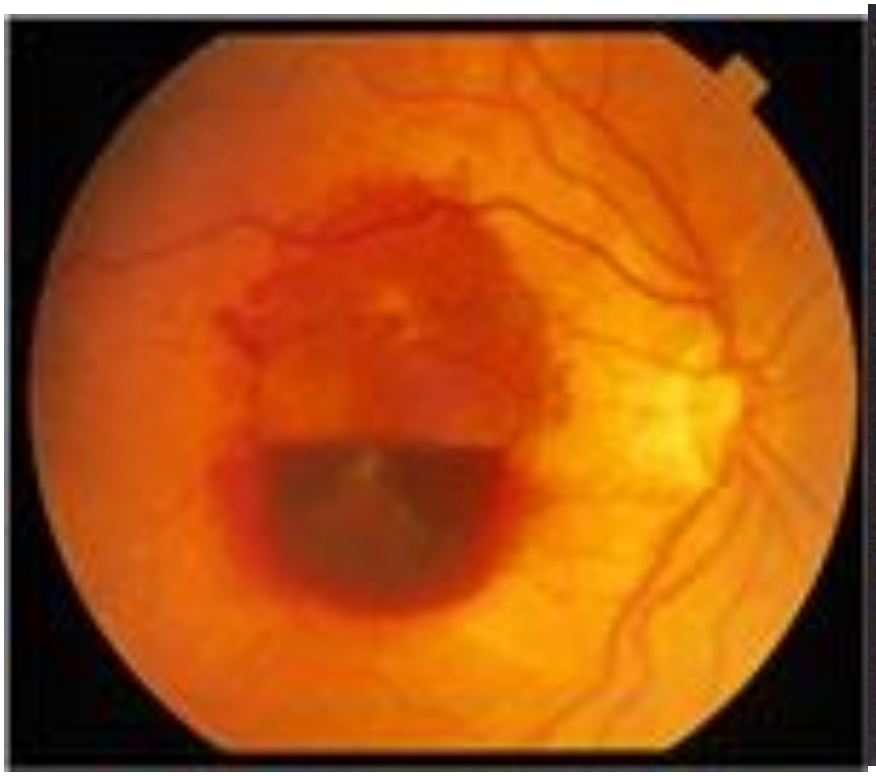

A
Fovea
B
C
TARRANT

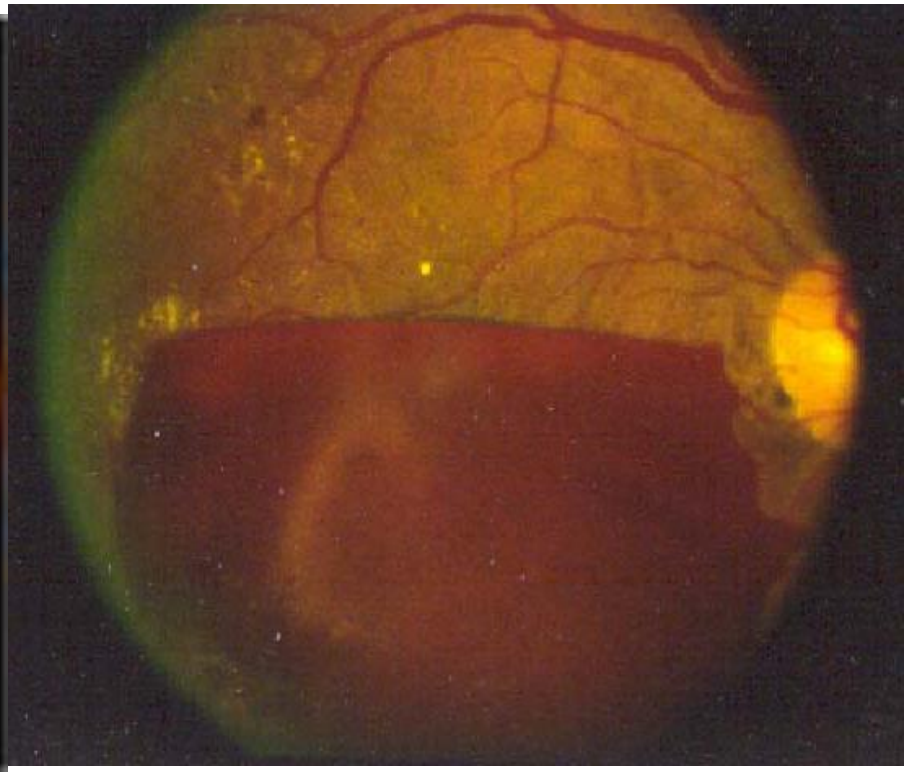
CSMO



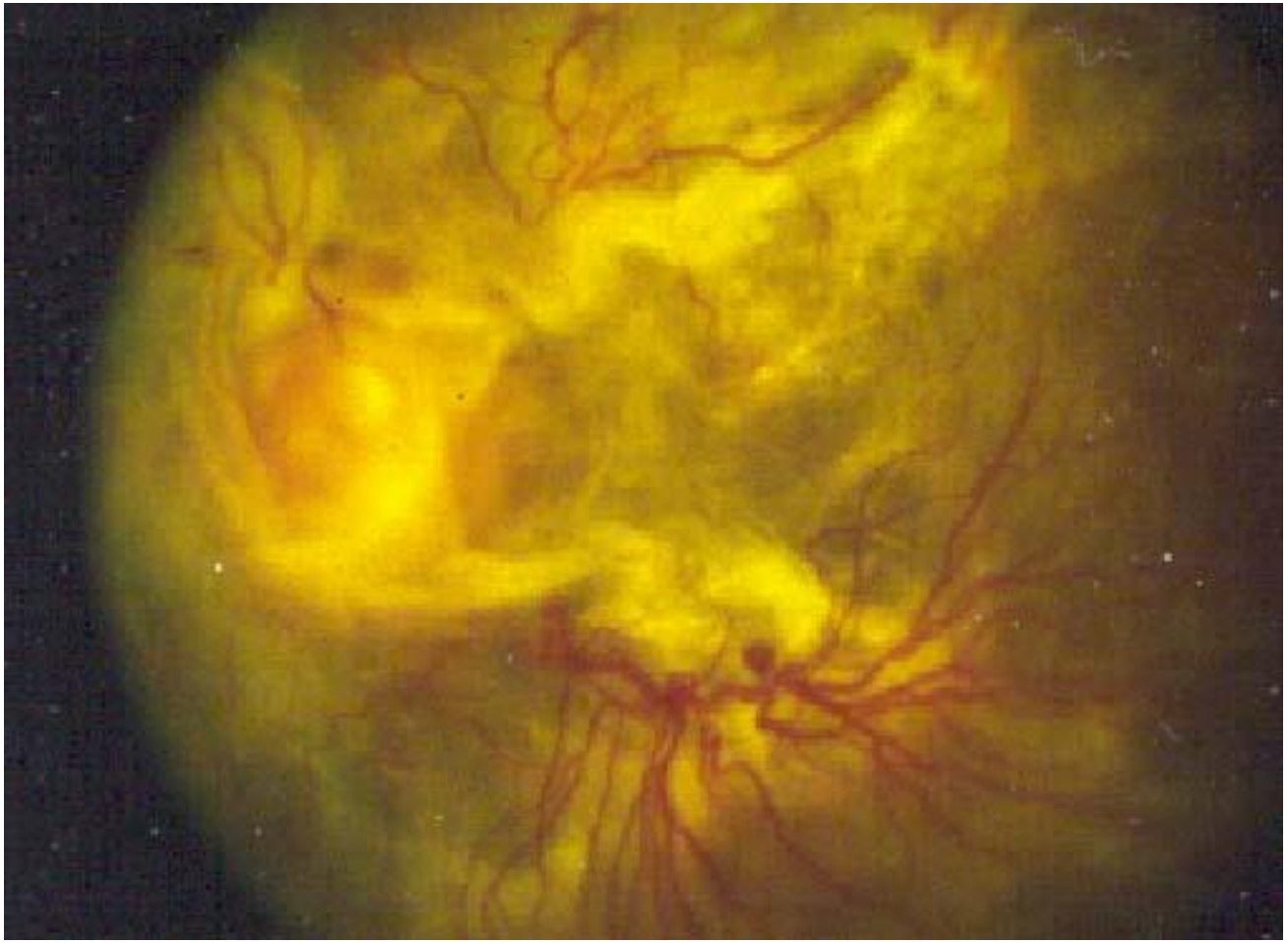

a
b
c
d

Subhyaloid haemorrhage

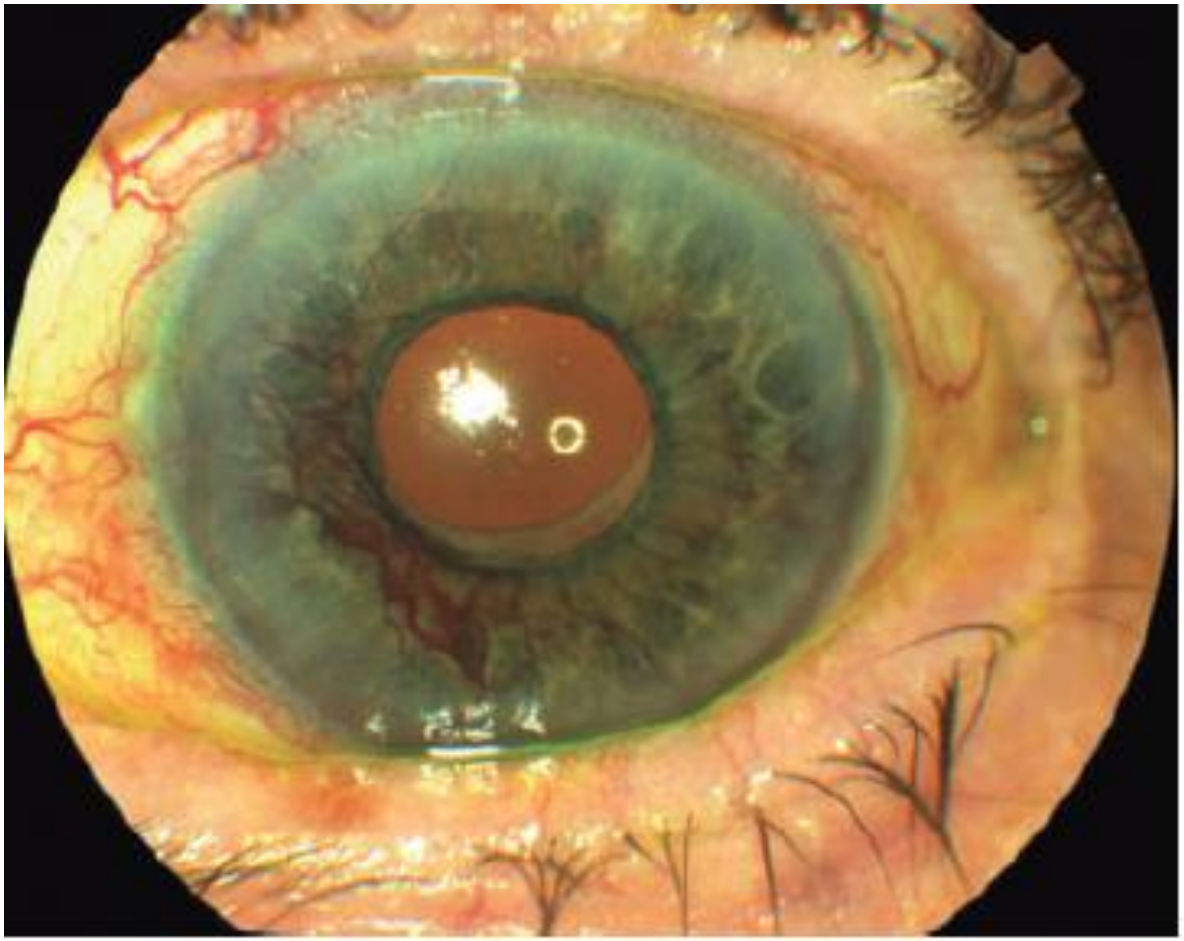




Tractional retinal detachment



Rubeosis iridis



AIDS TO DIAGNOSIS

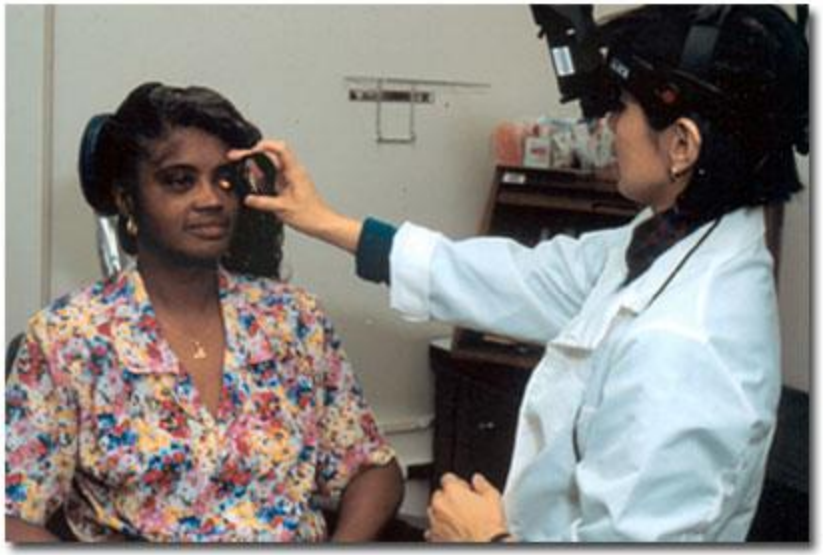
- Anterior segment:
  - Slitlamp exam

AIDS TO DIAGNOSIS

- Dilated Fundus Exam:
  - Slitlamp with 90D/78D/Superfield:

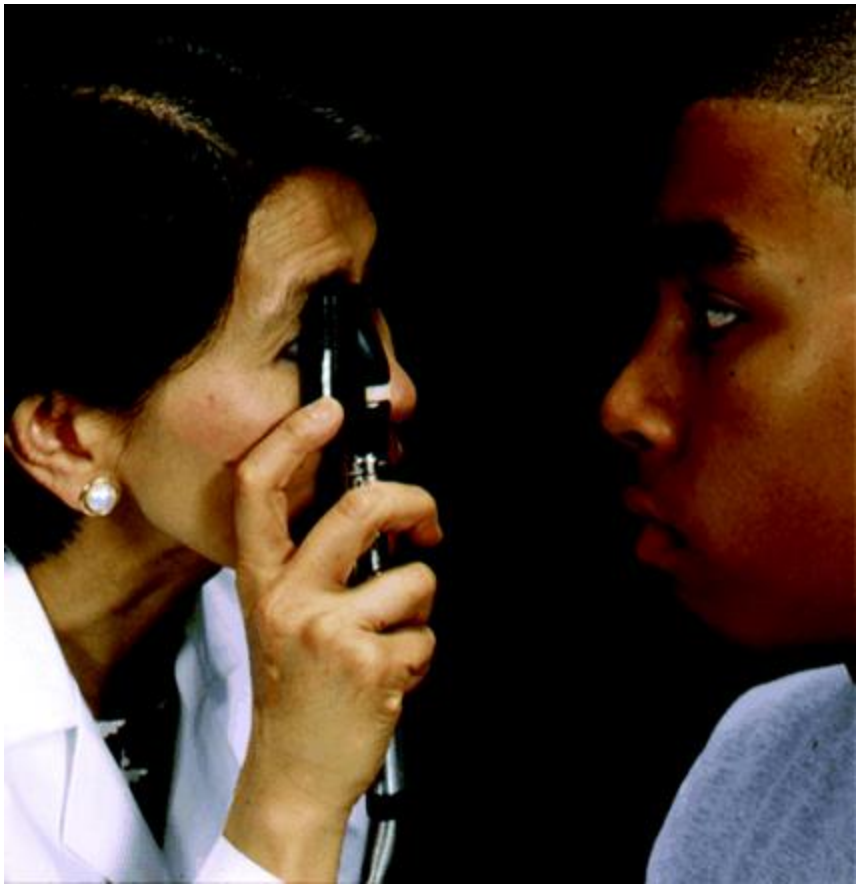
AIDS TO DIAGNOSIS

- Dilated fundus exam:
  - Indirect ophthalmoscopy with 20D/28D

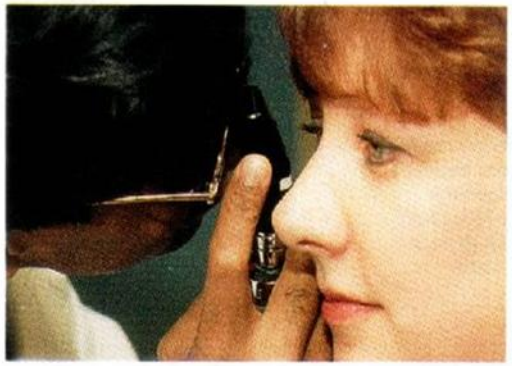


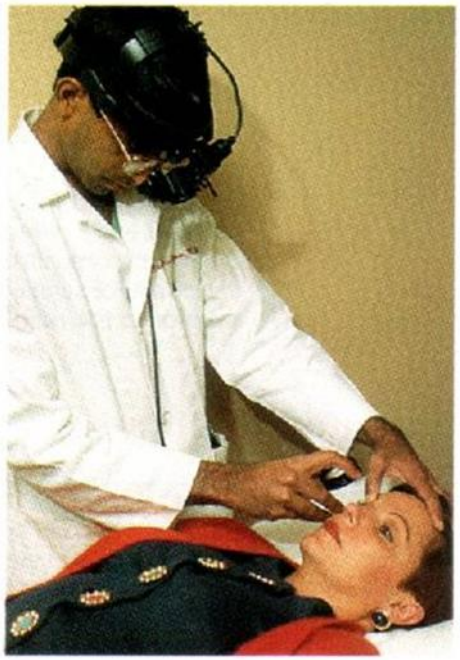
AIDS TO DIAGNOSIS

- Direct Ophthalmoscopy:



AIDS TO DIAGNOSIS





THANK YOU