

Fluorescein Angiography

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Learning Objectives

- Understand basic principles behind FA
- Explain common complications associated with FA
- Identify normal features of FA imaging
- Identify pathological patterns of hyperfluorescence and hypofluorescence

Fluorescein Angiography

Applications

- Diabetic retinopathy
- Age related macular degeneration
- Central retinal vein occlusion
- Branch retinal vein occlusion
- Central serous chorioretinopathy
- Cystoid macular edema
- Hypertensive retinopathy
- Central retinal artery occlusion
- Branch retinal artery occlusion
- Retinal arterial macroaneurysm
- Subretinal neovascular membrane
- Choroidal tumors
- Chorioretinal inflammatory conditions

Should only be performed if the findings are likely to influence management

History

1871: Fluorescein was synthesized by Nobel laureate Johann Baeyer

1881: Ehrlich observed fluorescence in the anterior chamber after an injection of fluorescein

1950s: Flock and co-workers investigated methods to determine retinal circulation times with various dyes, including fluorescein

1961: Fluorescein was introduced to ophthalmic imaging by Novotny and Alvis (2 medical students)



What's the Science?

When light energy is absorbed into a luminescent material, free electrons are elevated into higher energy states. This energy is then re-emitted by spontaneous decay of the electrons into their lower energy states. When this decay occurs in the visible spectrum, it is called **luminescence**.

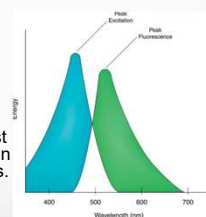
Peak Absorption: 490nm

Peak Emission: 520nm

Excitation and Barrier filter

Two filter system:

- Excitation filter: transmits 490nm which is the **absorption peak** of fluorescein excitation
- Barrier filter: transmits 520nm which is the **emitted peak** of fluorescein



When choosing a camera, one should request the transmission curve of the filter combination to make sure that no significant overlap exists. (otherwise other items would "fluoresce")

After several years, the filters become thin, emitting more light and increasing the incidence of pseudofluorescence.

Quillen, David A., and James D. Strong. "Principles of Fluorescein Angiography." Albert & Jakobiec's Principles & Practice of Ophthalmology. By Timothy J. Renshaw. 3rd ed. 2000.

Fluorescein Solution

Sodium Fluorescein $C_{20}H_{12}O_5Na$

- Orange-Red crystalline hydrocarbon
- When injected 80% is bound to protein, 20% remains in free bloodstream
- It is eliminated by the liver and kidneys within 24 hours, though traces may be found in the body for up to a week
- Available solutions:
 - 10mL of 5% fluorescein
 - 5mL of 10% fluorescein
 - 3mL of 25% fluorescein
 - The larger the volume, the longer the injection
 - The smaller the volume, the more solution remains in the venous dead space between the arm and the heart

Alternative if venous line could not be established or injection is refused:

Oral administration of dose 30mg/kg

Won't see rush of fluorescein enter the eye

Pictures are taken 20-60 minutes following ingestion



Complications

Mild Reactions <5%	Injection site reaction Nausea Vomiting
Moderately Severe Reactions <1%	Urticaria Shortness of breath Vasovagal reaction Skin necrosis
Life-threatening reactions (<0.001%)	Anaphylactic shock Seizure Cardiovascular collapse

- Avoid angiography in pregnant women, especially in the first trimester
- Premedication with antihistamine and/or corticosteroids can be used for patients with a history of moderately severe reactions. (depending on the situation)
- All units performing fluorescein angiography should have a crash cart available

Complications

Extravasation of fluorescein under the skin

- Accidental administration of fluorescein into the extravascular space/tissue around the infusion site
 - Side effects:
 - Can be extremely painful
 - Necrosis and sloughing of skin (rare)
 - Subcutaneous granuloma (rare)
 - Apply ice pack

A common cause is the use of a large, long needle directly attached to a syringe.

*Use scalp vein needle instead

Procedure

Material:

- Fundus camera and auxiliary equipment
- Matched fluorescein filters (barrier and excitation)
- Digital photoprocessing unit (computer-based) and software user interface
- 23 gauge scalp vein needle
- 5 mL syringe
- Needle to draw the dye
- Armrest for fluorescein injection
- Tourniquet
- Alcohol swabs
- Bandage
- Standard emergency equipment

Emergency Kit:

- Airway bag
- Automated external defibrillator
- Oral or intramuscular antihistamines
- Autoinjectors for epinephrine

Procedure

Explanation: PARQ

- Procedures
- Alternatives
- Risks
- Questions

Procedure

Set up:

- Maximal dilation
 - 6mm or more is best
- Preparation of fluorescein and scalp-vein needle
- Identification photo
- Set up patient
- Color photos
- Red free photos
- Filter in place, flash and camera ready
- Check which eye is the **transit** eye



Procedure

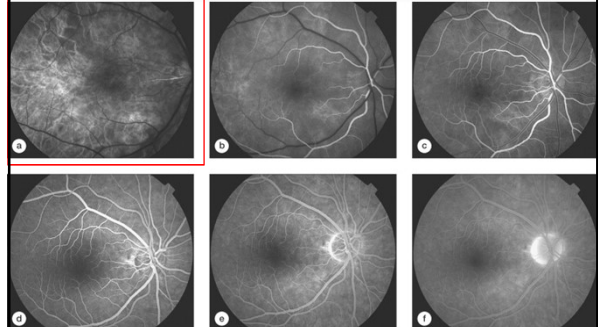


- Establish a venous line
- Start timer and inject 5mL of 10% Fluorescein rapidly (~10 sec)
 - Make sure not to overload the vein and inject the fluorescein under the skin
- Fluorescein should start appearing in the eye in about 8-12 seconds
 - 8 seconds for younger individuals
 - 12 seconds for older individuals
- Take photos every 1.5-2 seconds in the transit eye for about 30 seconds until the initial transit is complete
 - After, the fluorescein recirculates and the concentration of fluorescein begins to decrease
- Option of taking photos of fellow eye & periphery
- Wait (for late staining) ~3-5 minutes, take additional photo
- Option of taking 10 minute photo

Early phase

CHOROIDAL FLUSH (8-12s): choriocapillaris leaks dye freely through the space. Usually little detail as the RPE acts as an irregular filter that obscures view of choroid. When present, cilioretinal arteries fill at the same time.

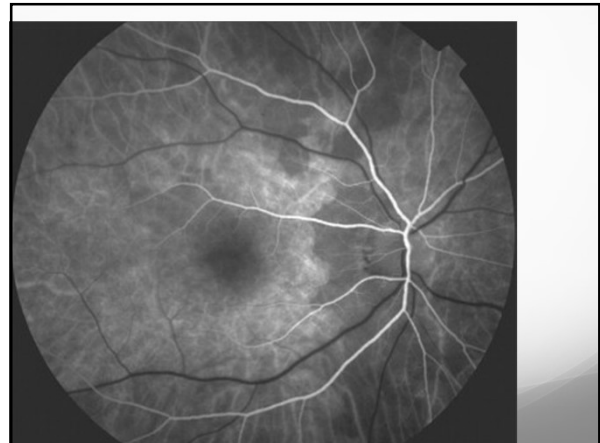
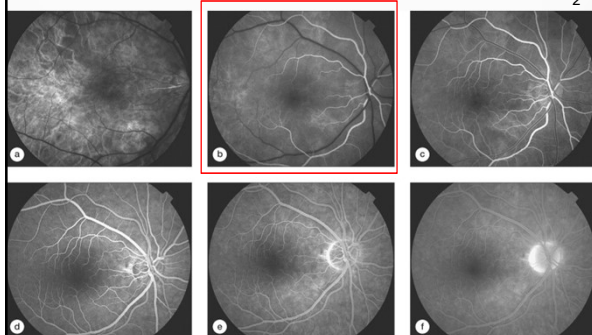
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Early phase

ARTERIAL PHASE (2s after the choroidal phase): Retinal arteries fill

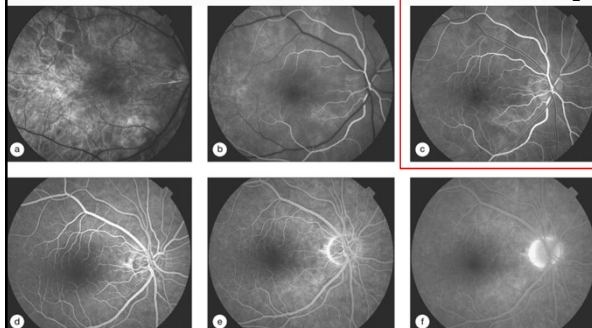
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Early phase

ARTERIOVENOUS PHASE: When the retinal arteries, capillaries, and veins contain fluorescein. The early part of this phase is the laminar phase when fluorescein is visualized in the walls of the larger veins.

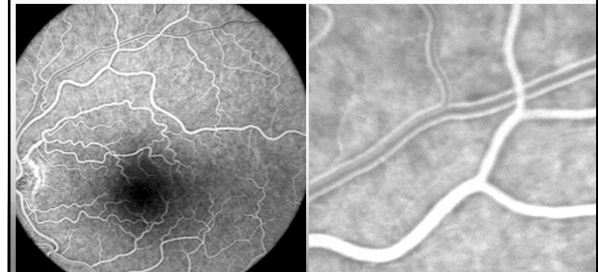
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Ateriovenous phase

Laminar phase when the fluorescein is in the laminar walls of the vein.

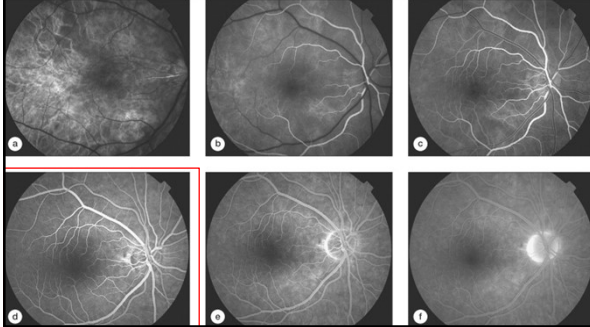
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Early phase

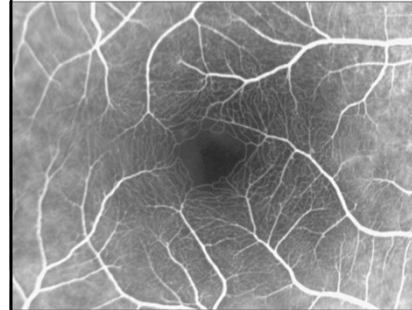
VENOUS PHASE (about 30 s after injection): as the fluorescein leaves the arteries, the veins have an increase in fluorescein. Perifoveal capillary network best visualized during the venous phase.

2



Normal Macular Filling

Dark macula area: 2

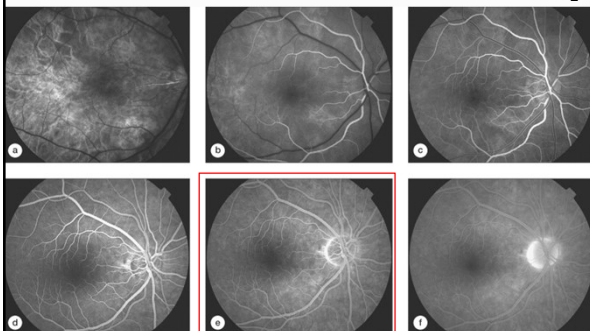


- Taller, more pigmented RPE
- Xanthophyll pigment
- Absence of retinal capillaries in foveal center

Mid phase

Mid Phase: Recirculation occurs 2-4 min after injection. The arteries and veins are roughly equal in brightness.

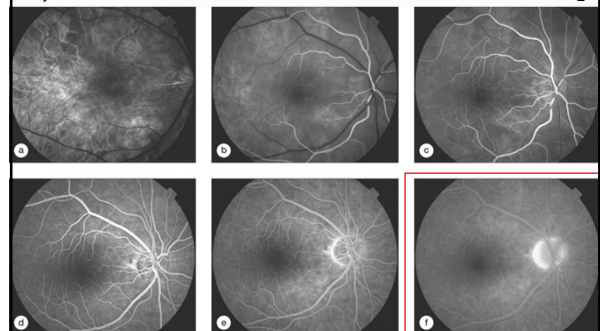
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Late Phase

Late Phase: Gradual elimination of the dye from the retina and choroid. Staining of the optic disc is normal. Photos normally taken 7-15 min after injection

2



Review of Vasculature

Retinal circulation supplies the inner 2/3 of the retina

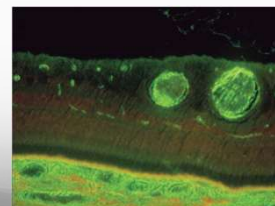
- Non-fenestrated
- Blood-retinal barrier via tight junctions

Choroidal circulation supplies the outer 1/3 of the retina

- Fenestrated, low resistance
- Blood-retinal barrier via tight junctions at the RPE

Review of Vasculature

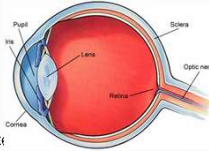
Sodium Fluorescein readily diffused through the fenestrated vessels of the choriocapillaris but does not pass through healthy endothelial cells of non-fenestrated retinal vessels or through the RPE



2

Hypofluorescence

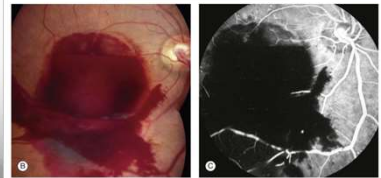
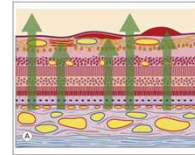
- Reduction or absence of normal fluorescence
- **BLOCKAGE**
 - Hemorrhage
 - Pigment
- **VASCULAR FILLING DEFECT**
 - Absence of vascular tissue or by a complete or partial obstruction of the vessels



Key: correlate the hypofluorescence on the angiogram with the fundus view. If the size/shape/location corresponds, its blockage. If not, it is a vascular filling defect.

Hypofluorescence

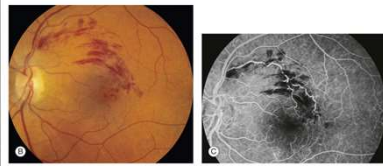
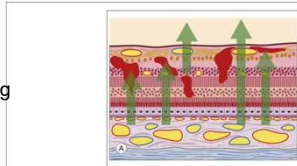
Preretinal hemorrhage causing hypofluorescent blockage of all retina and choroid



Hypofluorescence

Intraretinal hemorrhage causing blockage.

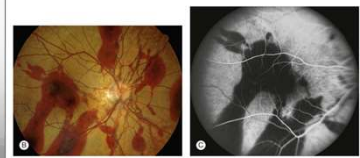
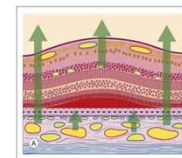
Hemorrhages located in most of the layers of the retina



Hypofluorescence

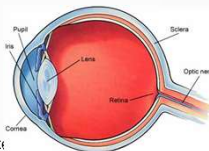
Subretinal hemorrhage causing hypofluorescence.

Blockage of the choroid but no blockage of the retinal vessels.



Hypofluorescence

- Reduction or absence of normal fluorescence
- **BLOCKAGE**
 - Hemorrhage
 - **Pigment**
- **VASCULAR FILLING DEFECT**
 - Absence of vascular tissue or by a complete or partial obstruction of the vessels

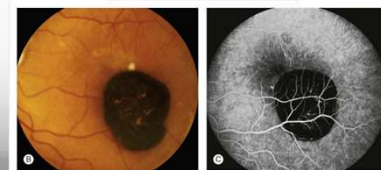
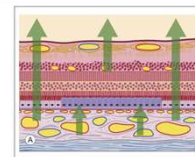


Key: correlate the hypofluorescence on the angiogram with the fundus view. If the size/shape/location corresponds, its blockage. If not, it is a vascular filling defect.

Hypofluorescence

Subretinal hypertrophy of the retinal pigmented epithelium.

Blocked choroidal fluorescence and normal retinal fluorescence.



Hypofluorescence

Choroidal nevus causing blockage of choroidal fluorescence

Choriocapillaris seen over the nevus

1

Hypofluorescence

- Reduction or absence of normal fluorescence
 - BLOCKAGE**
 - Hemorrhage
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 - Absence of vascular tissue or by a complete or partial obstruction of the vessels

Key: correlate the hypofluorescence on the angiogram with the fundus view. If the size/shape/location corresponds, its blockage. If not, it is a vascular filling defect.

Retinal capillary non-perfusion from diabetic retinopathy

A

Hyperfluorescence

Abnormally excessive fluorescence

- PREINJECTION FLUORESCENCE**
 - Pseudofluorescence
 - Autofluorescence
- EARLY (vascular)**
 - Retinal
 - Abnormal vessels
 - Choroidal
 - RPE window defect
 - Abnormal vessels
- LATE (leak, extravascular)**
 - Leakage
 - Neovascularization
 - Pooling
 - Staining
 - Tumors

To determine the type of hyperfluorescence, we must determine the time at which the hyperfluorescence appears

Pseudofluorescence

Preinjection

Pseudofluorescence (fake fluorescence)

- Nonfluorescent structures appear fluorescent
- Causes decreased contrast and resolution

Therefore, the two filters should be carefully matched so that the overlap of light is minimal

Autofluorescence

1

Preinjection

Occurs naturally in some pathologic entities
Optic disc drusen
Astrocytic hamartomas

Hyperfluorescence

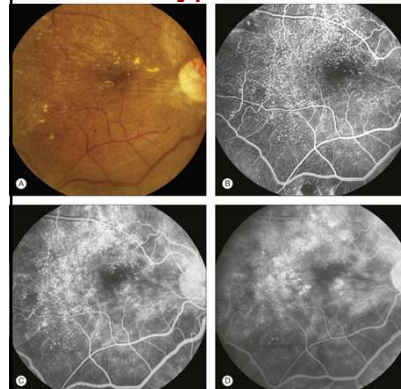
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Hyperfluorescence



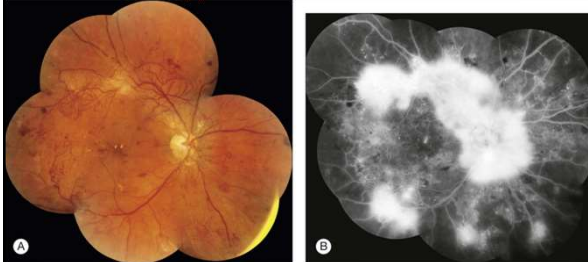
Early Defect

Abnormal retinal vessels with hyperfluorescence of microaneurysms from diabetic retinopathy

Arterovenous phase of extensive hyperfluorescence

Late leakage from vessels

Hyperfluorescence



Early Defect

Hyperfluorescence from abnormal retinal vessels: retinal neovascularization.

Early hyperfluorescence and late leakage.

Hyperfluorescence

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Hyperfluorescence

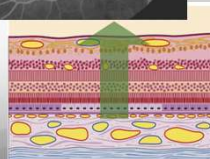
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Early Defect:

Window defect where the transmission of hyperfluorescence is seen in the **choroid** due to damage of the RPE.



The size remains uniform throughout angiogram

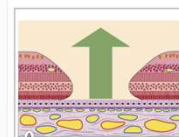


Hyperfluorescence

1

Early Defect:

Window defect due to loss of retina: macular hole.



The choriocapillaris is intact and shows early hyperfluorescence in the center of the fovea and fading in the late phase angiogram.



Hyperfluorescence

Abnormally excessive fluorescence

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Hyperfluorescence

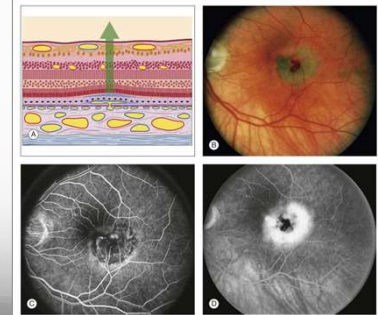
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Early and Late Defect:

Hyperfluorescence due to abnormal choroidal vessels: choroidal neovascularization.

Early fine lacy hyperfluorescence from the choroidal neovascularization.

Late leakage of the vessels.



Hyperfluorescence

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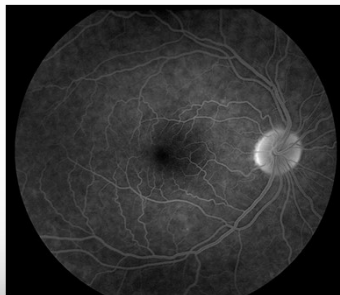
To determine the type of hyperfluorescence, we must determine the time at which the hyperfluorescence appears

Hyperfluorescence

- **Leakage:** dye is leaks from an intravascular space into an extravascular space
The area of leakage increases in size and intensity as the angiogram progresses
- **Pooling:** dye fills an anatomical space
Cysts, subretinal space, etc
- **Staining:** deposition of dye within involved tissue
Normal: optic nerve & sclera
• Pathologic: scars

Fluorescein empties almost completely from retinal vasculature and choroid about **10-15 minutes** after injection. Normal staining:

1. Fluorescence of the disc margins
2. Fluorescence of the lamina cribosa
3. Fluorescence of the sclera at the disc margin (scleral crescent)
4. Fluorescence of the scleral in a lightly pigmented fundus



Hyperfluorescence

Abnormally excessive fluorescence

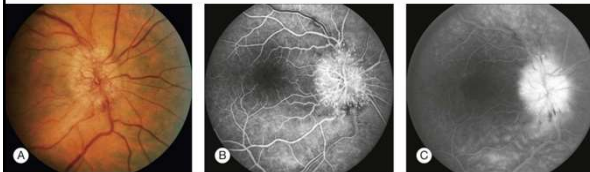
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To determine the type of hyperfluorescence, we must determine the time at which the hyperfluorescence appears

Hyperfluorescence

1



Early and Late Defect

Disc leakage from optic disc swelling.

Early hyperfluorescence from dilated vessels

Late leakage. Dilated vessels leak.

Hyperfluorescence

1

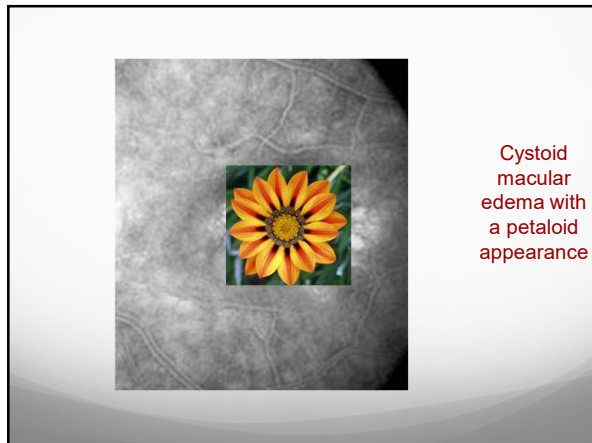
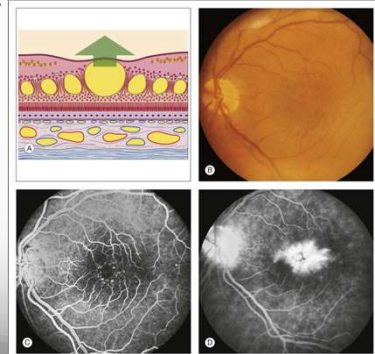
Early & Late Defect

Retinal leak from retinal vessels.

Early AV phase of dilation of fine capillaries in the macula.

Late phase of fluorescein accumulating in the cystic spaces.

Cystoid macular edema (petaloid)



Cystoid
macular
edema with
a petaloid
appearance



Hyperfluorescence from leakage

Hyperfluorescence

Abnormally excessive fluorescence

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Hyperfluorescence: pooling of subretinal fluid

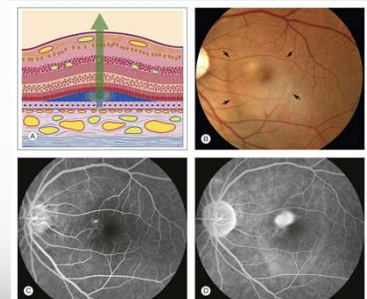
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Early and Late Defect

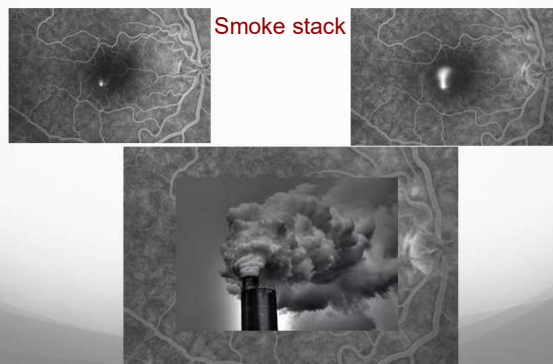
Choroidal leakage and pooling into subretinal space

Early phase shows small hyperfluorescent spot

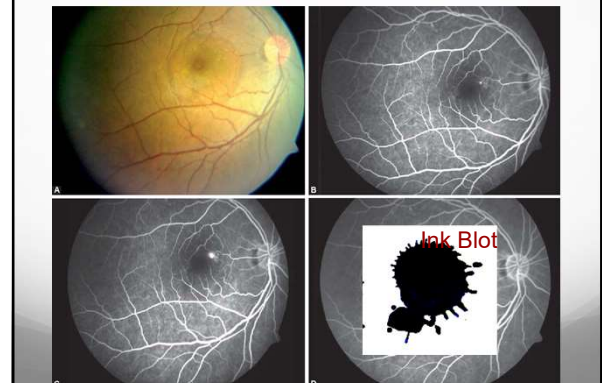
Late phase show pooling of the fluorescein. With pooling there is a defined space so the fluorescein will stop at the border of the central serous retinopathy.



Hyperfluorescence: pooling of subretinal fluid



Hyperfluorescence: pooling of subretinal fluid



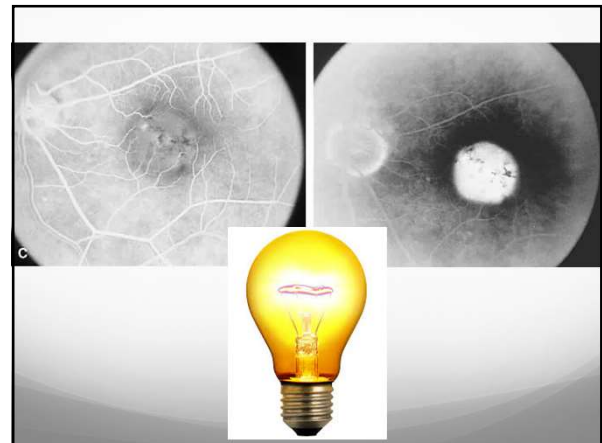
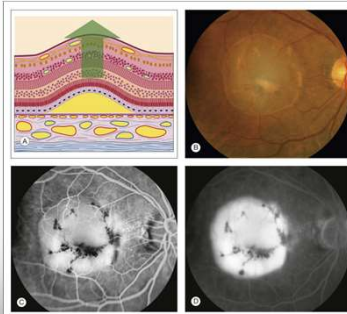
Hyperfluorescence: pooling

Early and Late Defect

Early AV phase showing early fluorescence from the area of detached RPE.

Late phase showing well-demarcated hyperfluorescent borders.

In Pigment Epithelial Detachment (PED), fluorescein flows freely through Bruch's membrane into the sub-RPE space



Hyperfluorescence

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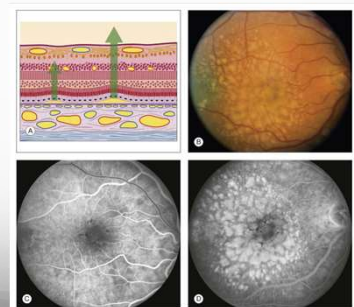
Hyperfluorescence from staining

Late Defect

Drusenoid PED allowing staining or pooling of fluorescein.

Early: drusen not very apparent

Late staining of drusen (more common in large drusen)

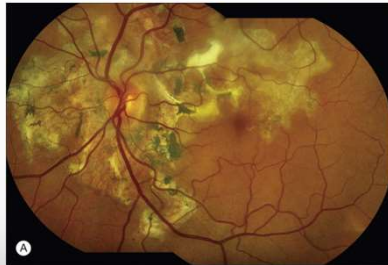


Hyperfluorescence: staining of fibrous scar ¹

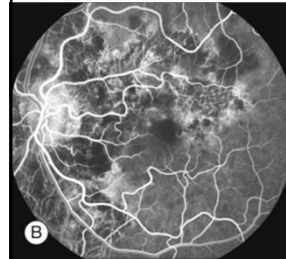
Late defect

Fibrous scar (white lesions)

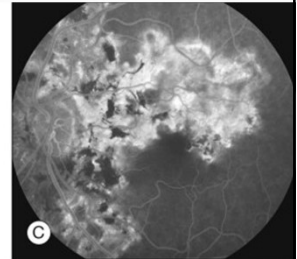
Most common location is subretinal



Hyperfluorescence: staining of fibrous scar ¹



Early hypofluorescence from blockage



Late hyperfluorescence from staining of fibrous tissue

Hyperfluorescence

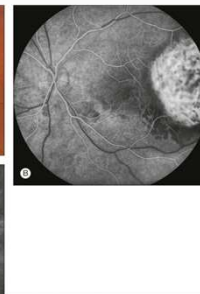
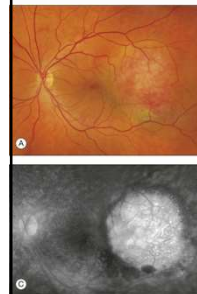
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Hyperfluorescence ¹



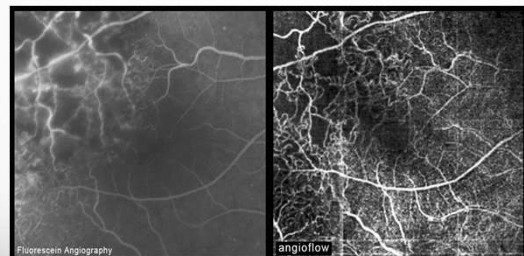
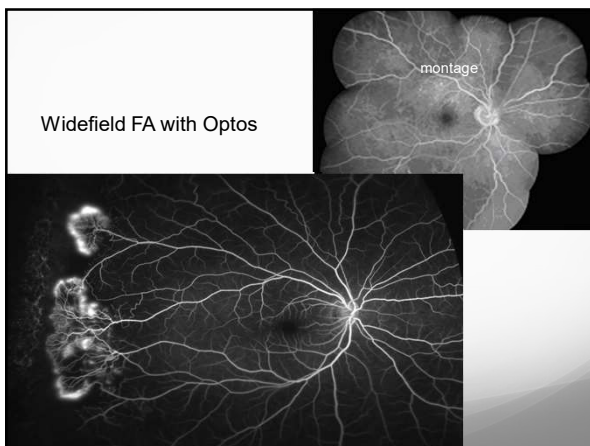
Early Phase & Late Phase

Hyperfluorescence due to abnormal choroidal vessels from a choroidal hemangioma.

Early filling from tumor vessels.

Late leakage.

Widefield FA with Optos



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