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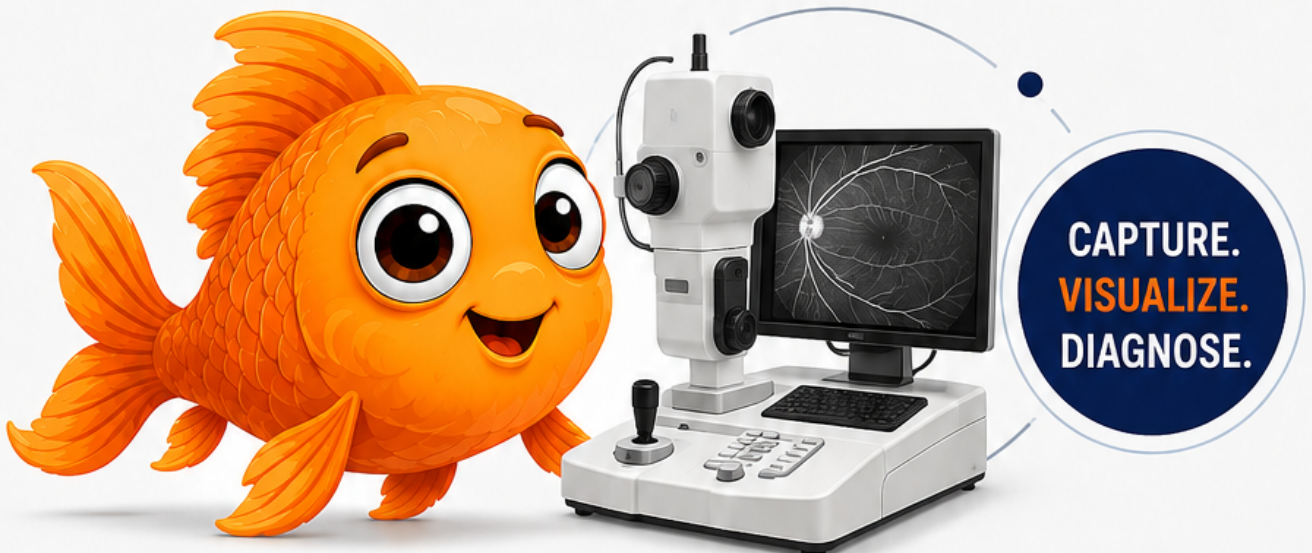
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GOLDFISH MEMORY SERIES

FLUORESCCEIN ANGIOGRAPHY (FFA)

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**HIGH-YIELD
CONTENT**



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Fundus Fluorescein Angiography (FFA)

PG Consultant-Level Revision Sheet — Ophthalmology Residency | Based on Kanski, Yanoff & Duker, Shields, Atul Kumar & Ryan's Retina

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1. The Clinical Analogy — "The Leaky Garden Hose"

Analogy: Imagine the retinal vasculature as a network of garden hoses with intact rubber walls (tight junctions = blood-retinal barrier). Sodium fluorescein dye is like a coloured water tracer injected into the hose system.

- If a hose wall has a **hole** (breakdown of tight junctions) → water sprays out and keeps spreading → this is **leakage**.
- If a hose is missing its opaque outer casing at one spot but the wall is intact (a bald patch in the RPE) → you simply **see the background flow through** more brightly, without any extra water escaping → this is a **window defect**.
- If water pools into a bucket with no walls (sub-RPE or subretinal space) and stays there, increasing in a fixed shape → this is **pooling**.
- If the water gets absorbed into a sponge and stains it permanently → this is **staining** (e.g., drusen, sclera, optic disc).
- If a rock sits on top of the hose and blocks your view of water at all → this is **blocked fluorescence** (blood, pigment, exudate).

This single analogy resolves 80% of confusing hyperfluorescence questions in viva.

2. Principles & Pharmacology of Sodium Fluorescein

Parameter	Detail
Molecular weight	376.27 Da (hydrocarbon dye)
Dose	5 mL of 10% or 3 mL of 25% sodium fluorescein IV, rapid bolus (antecubital vein)
Excitation wavelength	465–490 nm (blue light)
Emission wavelength	520–530 nm (yellow-green)
Protein binding	~80% bound to plasma albumin (bound fraction does NOT fluoresce — only free 20% fluoresces)
Excretion	Hepatic conjugation (glucuronide) + renal excretion; urine stays yellow-orange for 24–36 h
Arm-to-retina time	Normally 8–15 seconds (delayed in carotid occlusive disease, cardiac failure)

Viva Pearl: Fluorescein crosses an *intact* inner blood-retinal barrier only at the RPE tight junctions level being the limiting factor — the choriocapillaris is normally leaky (fenestrated), which is why choroidal fluorescence appears diffusely early and is normally "masked" by the RPE monolayer (a natural pigment epithelial window filter).

3. Instrumentation — Filters

The fundus camera uses two filters that must be matched to fluorescein's excitation/emission spectra:

Filter	Function	Wavelength
Excitation (blue) filter	Placed in front of flash; allows only blue light to strike the fundus	465–490 nm
Barrier (yellow-green) filter	Placed in front of camera lens; blocks reflected blue light, transmits only emitted yellow-green fluorescence	520–530 nm

MCQ Trap: If the barrier filter is defective/absent, the image looks falsely hyperfluorescent everywhere due to reflected blue light — a classic "trick" question mimicking pseudofluorescence (autofluorescence must not be confused with this artifact).

4. Normal Phases of FFA — The Timeline

Phase	Time (approx.)	Description
Choroidal (pre-arterial) flush	8-12 sec (~1 sec before arterial)	Patchy, mottled early choroidal filling from short posterior ciliary arteries; peripapillary areas fill first
Arterial phase	within 1 sec after choroidal flush	Retinal arterioles fill completely, "laminar flow" may be seen
Arteriovenous (capillary) phase	~ +2-3 sec	Arterioles fully filled, venous lamellar flow begins (dye first along walls of veins)
Venous phase	~ +3-5 sec	Complete venous filling
Late/recirculation phase	up to 10 min	Progressive dye dilution; leakage, staining, and pooling become evident/increase

Pearl: Cilioretinal artery, if present, fills WITH the choroidal flush (since it is a branch of posterior ciliary circulation) — a useful discriminator in CRAO where the retinal arterial tree is delayed/absent but a cilioretinal-supplied wedge fills normally and early.

5. Fundamentals: Hyper- vs Hypofluorescence

A. Hyperfluorescence — Mechanisms

Type	Mechanism	Behaviour over time	Classic Example
Window defect (transmission defect)	RPE atrophy/thinning unmasks normal choroidal fluorescence	Appears early, ↑ in intensity with choroidal flush, fades with choroidal dye washout, size constant, no leakage (borders stay sharp)	Geographic atrophy, RPE atrophy in high myopia
Leakage (true leak)	Breakdown of inner (retinal capillary tight junction) or outer (RPE) blood-retinal barrier	Increases in size AND intensity with time; blurred/fuzzy margins	CNV, disc edema, CME, vasculitis
Pooling	Dye accumulates in an anatomic space (sub-RPE or subretinal)	Fixed borders that fill in progressively (like a glass filling with water) — shape unchanged, intensity increases	PED, CSCR (subretinal fluid)
Staining	Dye binds to a structure/tissue	Appears late, persists into late phase, does NOT change in size	Drusen, disc staining, scleral staining, sclerosed vessels

B. Hypofluorescence — Mechanisms

Type	Mechanism	Classic Example
Blocked fluorescence (masking)	Opaque material anterior to retinal/choroidal circulation prevents transmission of fluorescence	Sub/intraretinal hemorrhage, hyperpigmentation (RPE hypertrophy), hard exudates, media opacity
Filling defect (vascular non-perfusion)	Absence of blood flow — vessel occluded or absent	Capillary non-perfusion in DR/BRVO, CRAO, choroidal ischemia

Classic Trap: Differentiate blocked fluorescence from a filling defect — inject dye and look at the AREA: in blocked fluorescence, the vessels are present but obscured (an overlying hemorrhage will "silhouette" the vessels irregularly, often with hyperfluorescent rim as hemorrhage resolves); in a filling defect, the vascular bed itself is absent/non-perfused with sharply demarcated capillary dropout, often with surrounding telangiectasia/shunt vessels (in DR).

6. Blood-Retinal Barrier — Anatomical Correlation

Barrier	Location	Component	Clinical relevance
Inner BRB	Retinal capillary endothelium	Tight junctions (zonula occludens) between non-fenestrated endothelial cells	Breakdown → diabetic macular edema, RVO, vasculitis leakage

Outer BRB	RPE	Tight junctions between RPE cells (zonula occludens); choriocapillaris is fenestrated and normally leaky	Breakdown → CSCR, CNV-related leakage, AMD
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Surgical/Anatomical Correlation: The RPE monolayer functions as both an active pump (fluid transport choroid-ward) and a passive barrier. In CSCR, focal RPE barrier breakdown classically produces the "smokestack" (dye rises vertically then mushrooms under the neurosensory detachment) or "inkblot" (round expanding spot) pattern on FFA — this dual pattern is a favourite viva question.

7. Indications & Contraindications

Indications	Contraindications
Diabetic retinopathy — grading, PRP planning, macular edema evaluation	Absolute: known anaphylaxis to fluorescein
AMD — CNV detection, classification (classic vs occult), PDT planning	Relative: pregnancy (Category C — avoid unless essential), severe renal/hepatic impairment, breastfeeding (dye in milk for 24-76h — pump & discard advised)
Retinal vascular occlusions (BRVO/CRVO) — ischemic vs non-ischemic grading (10 disc-area rule)	Uncontrolled asthma / severe cardiovascular disease (relative — risk of severe reaction)
Uveitis — vasculitis mapping, macular edema, disc leakage	-
Inherited retinal disease phenotyping	-
Tumours — choroidal hemangioma, melanoma differentiation	-
Pre-laser/pre-PDT/anti-VEGF planning & post-treatment monitoring	-

8. Complications & Mechanisms

Reaction	Incidence	Mechanism	Management
Nausea/vomiting	~5-10% (most common)	Direct chemotoxic/vasovagal effect, rate-of-injection dependent	Slow injection; reassurance; usually self-limiting
Transient skin discoloration, yellow urine	Universal, benign	Pharmacokinetic — expected	Reassure patient in advance (informed consent pearl)
Urticaria/pruritus	~1%	Anaphylactoid (non-IgE mediated, direct mast cell degranulation) — NOT true allergy in most cases	Antihistamines
Vasovagal syncope	Uncommon	Reflex response to needle/anxiety	Supine position, reassurance
Severe anaphylaxis, laryngeal edema, bronchospasm	Rare (~1 in 2000)	Anaphylactoid reaction	Adrenaline IM, airway support, emergency protocol — resuscitation trolley MANDATORY in every FFA room
Death	Extremely rare (~1 in 220,000)	Cardiac arrest/anaphylaxis	-
Extravasation	Uncommon	Perivascular leak at injection site — chemical irritant	Cold compress, elevation; rarely tissue necrosis if severe

MCQ Trap: Fluorescein reactions are classified as **anaphylactoid** (direct non-immune mast cell/complement activation), NOT true IgE-mediated anaphylaxis — hence a negative reaction on first exposure does NOT guarantee safety, and skin testing is unreliable and not recommended before FFA.

9. FFA vs ICG vs OCT-Angiography

Feature	FFA	ICG Angiography	OCT-A
Dye/method	Sodium fluorescein	Indocyanine green	No dye — motion contrast of erythrocytes
Protein binding	~80%	~98% (larger molecule, stays intravascular longer)	N/A

Excitation/emission	465–490 / 520–530 nm (visible)	790–805 / 835 nm (near-infrared — penetrates RPE/pigment/blood better)	N/A
Best for	Retinal vasculature, inner BRB breakdown	Choroidal vasculature — CNV in AMD (esp. occult/PCV), tumours through hemorrhage/pigment	Rapid, depth-resolved layer-specific flow (SVP, DVP, choriocapillaris) — non-invasive
Leakage detection	Yes (dynamic, functional)	Yes, but less leakage (larger protein-bound molecule)	No — cannot show leakage/pooling/staining (major limitation)
Safety	Anaphylactoid reactions	Contraindicated in iodine/shellfish allergy (iodide component)	No dye risk at all

Consultant Pearl: OCT-A cannot distinguish "leakage" as a phenomenon since it is a static structural/flow map — this is the single biggest limitation examiners love to test, especially in differentiating active vs quiescent CNV.

10. Disease-wise Classic FFA Patterns — High-Yield Table

Disease	Classic FFA Finding
Diabetic retinopathy	Microaneurysms (early hyperfluorescent dots, leak late), capillary non-perfusion, IRMA (no leak, unlike NVE which leaks profusely), NVE/NVD leakage in late phase
CSCR	"Smokestack" or "inkblot" pattern — focal RPE leak with pooling into subretinal fluid
Classic CNV (AMD)	Well-demarcated early hyperfluorescence with progressive leakage obscuring margins in late phase ("lacy/lace-like" pattern)
Occult CNV	Fibrovascular PED — irregular stippled hyperfluorescence, late leakage of undetermined source; best seen on ICG
BRVO/CRVO (ischemic)	Capillary non-perfusion >10 disc areas (BRVO) / extensive non-perfusion with delayed AV transit (CRVO); blocked fluorescence from hemorrhage
CRAO	Delayed/patchy arterial filling, prolonged arm-retina and AV transit time, boxcarring; cilioretinal artery filling if present (choroidal-timed)
Central serous vs PCV vs occult CNV	Best differentiated on ICG — PCV shows nodular polypoidal hyperfluorescence with branching vascular network
Macroaneurysm	Discrete saccular hyperfluorescence, may show surrounding blocked fluorescence from hemorrhage/exudate
Coats disease	Massive telangiectatic vessels with light-bulb aneurysmal dilatations, marked leakage
Choroidal melanoma	"Dual circulation" — intrinsic tumour vessels + retinal circulation; diffuse late staining
Choroidal hemangioma	Early diffuse choroidal hyperfluorescence, "lacy" pattern, late diffuse staining
Papilledema/disc vasculitis	Progressive disc leakage in late frames (vs. pseudopapilledema which shows NO leak — key differentiator!)
Best disease (vitelliform)	Blocked fluorescence in vitelliform stage; window defect in "scrambled egg"/atrophic stage
Angioid streaks	Early hyperfluorescence (window-like) of streaks radiating from disc, may show CNV leakage

11. Landmark Trials Using FFA

Trial	Relevance to FFA
ETDRS (Early Treatment Diabetic Retinopathy Study)	Defined clinically significant macular edema (CSME) partly using FFA leakage patterns; established focal/grid laser protocols
DRCR.net Protocols (various)	Used FFA for baseline non-perfusion assessment before anti-VEGF/laser decisions in DME
MPS (Macular Photocoagulation Study)	Classified CNV as classic/occult based on FFA characteristics; guided laser photocoagulation in AMD
TAP & VIP studies	Used FFA/ICG classification of CNV (predominantly classic) to determine PDT eligibility
BVOS/CVOS (Branch/Central Vein Occlusion Studies)	Defined ischemic vs non-ischemic RVO using disc-area non-perfusion criteria on FFA

12. Emerging Concepts (Forward-Looking)

- **Widefield/Ultra-widefield FFA** (Optos, Heidelberg widefield) — detects peripheral non-perfusion in DR/RVO missed by conventional 30–50° fields; peripheral ischemic index now studied as a biomarker for treatment response.
- **OCT-Angiography** increasingly replacing FFA for CNV detection/monitoring in AMD follow-up (non-invasive, faster) —

though FFA remains gold standard for demonstrating *leakage/activity*.

- **AI-based automated FFA image analysis** for non-perfusion area quantification and predicting anti-VEGF response.
- **Dye-based multimodal fusion imaging** (FFA + ICG + OCT-A registration) for complex neovascular membrane characterization (PCV, RAP lesions).

13. Consultant-Level MCQ Traps

1. A geographic atrophy patch appears hyperfluorescent from the earliest choroidal phase, increases in *intensity* but NOT in *size*, and fades with the late choroidal flush. What is this?
Answer: Window defect — NOT leakage (a common trap is calling any increase in intensity "leakage"; the key discriminator is SIZE, not intensity).
2. Pseudopapilledema (crowded disc/disc drusen) vs true papilledema — the single best FFA discriminator?
Answer: Absence of late leakage in pseudopapilledema; true papilledema shows progressive late-phase disc hyperfluorescence/leakage.
3. Why does IRMA not leak on FFA while NVE does?
Answer: IRMA are intraretinal dilated pre-existing capillary shunts within the retina, still covered by an intact (though abnormal) inner BRB-like endothelium; NVE are new vessels growing through/breaking the internal limiting membrane into the vitreous with fenestrated, incompetent walls lacking tight junctions → hence profuse leakage.
4. Patient develops urticaria on second FFA despite an uneventful first FFA — is this a true allergic (IgE) response?
Answer: No — it is anaphylactoid (idiosyncratic non-IgE mast cell degranulation); prior tolerance does not predict future safety, hence resuscitation readiness is mandatory every single time.
5. A cilioretinal artery fills earlier than the central retinal artery branches in a patient with CRAO — why?
Answer: Because the cilioretinal artery arises from the posterior ciliary/choroidal circulation, not the central retinal artery, so it fills during the choroidal flush phase, unaffected by CRAO.

14. Viva Pearls & Follow-up Question

Rapid-fire viva pearls:

- Autofluorescence must always be checked with a pre-injection "red-free"/blue-light-only frame before dye injection — true autofluorescent lesions (e.g., optic disc drusen, astrocytic hamartoma) will fluoresce even before dye reaches the fundus.
- "Staining" never changes shape or size in late frames — differentiates it from pooling (fills a fixed space over time) and leakage (expands progressively).
- Always correlate the FFA leakage pattern with OCT structural findings in real exam vivas — examiners frequently ask you to "predict the OCT" from a given FFA image and vice versa.
- 10-disc-area rule for BRVO ischemia and >10 disc areas (or 30-45° widefield equivalent) for CRVO ischemia are classic numbers to remember for viva.

Consultant-Level Follow-up Question for Extension:

In a patient with type 2 PCV (polypoidal choroidal vasculopathy) misdiagnosed as classic CNV on FFA due to a hemorrhage obscuring the polyps, explain — using the anatomical basis of choroidal vs retinal circulation and the dye properties of fluorescein vs ICG — why ICG angiography, not repeat FFA, is the correct next investigation to confirm the diagnosis, and how this would alter your treatment algorithm (anti-VEGF monotherapy vs combination PDT).

Prepared as a structured PG revision aid. Cross-verify with current editions of Kanski's Clinical Ophthalmology, Yanoff & Duker's Ophthalmology, Ryan's Retina, and Shields' Atlas before exams, as classification criteria and trial data may be periodically updated.



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