ULSS 13
Divisione oculistica Dolo-Mirano
Direttore Dr. Romeo Altafini

Retinopatie e Maculopatie

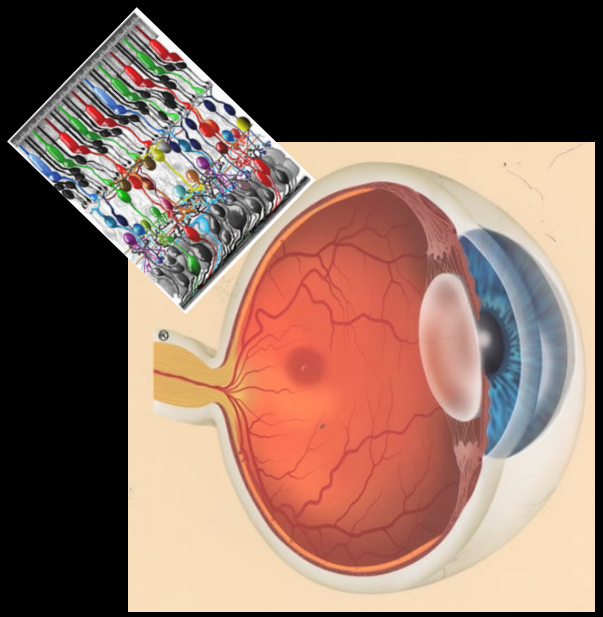
Dott.ssa Giorgia Sanguinetti

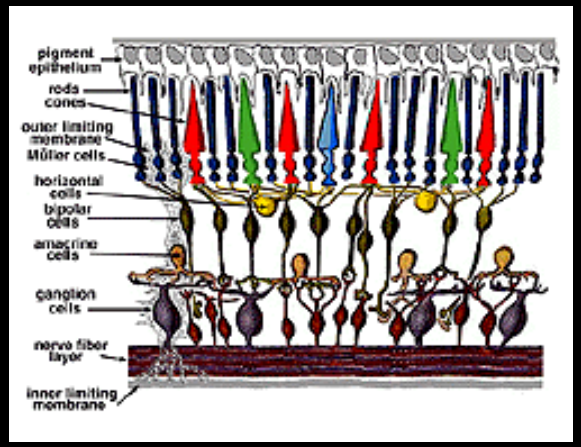
16 Ottobre 2016

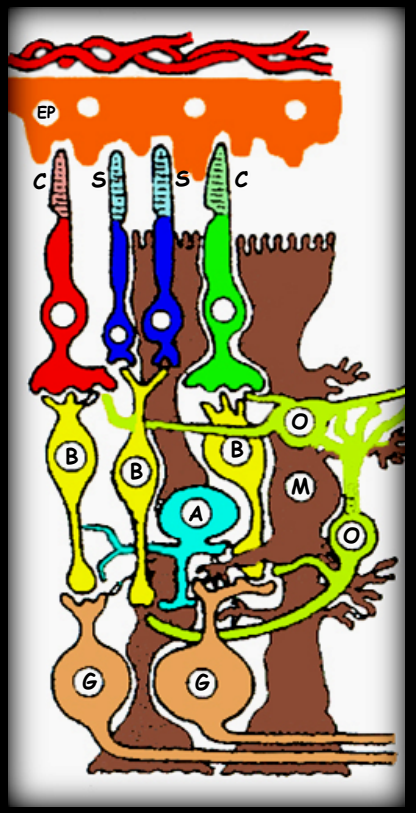
La retina

Sottilissima membrana che riveste internamente l'occhio

Costituita di cellule nervose





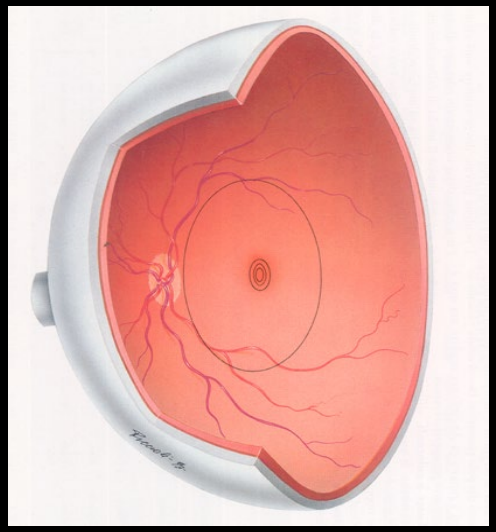


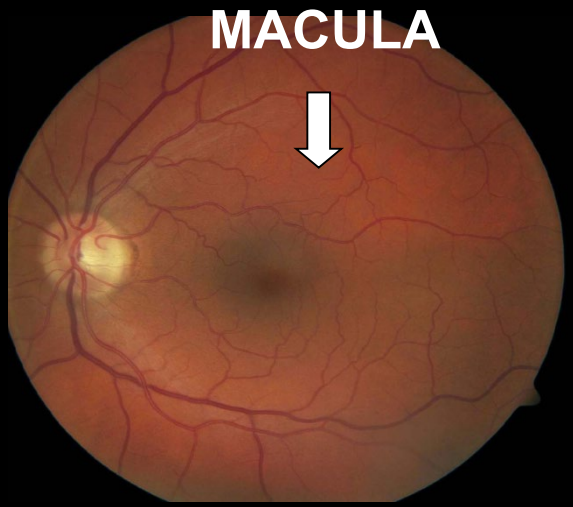
EP – epitelio pigmentato
B – cellule bipolari
O – cellule orizzontali
M – cellule di Muller

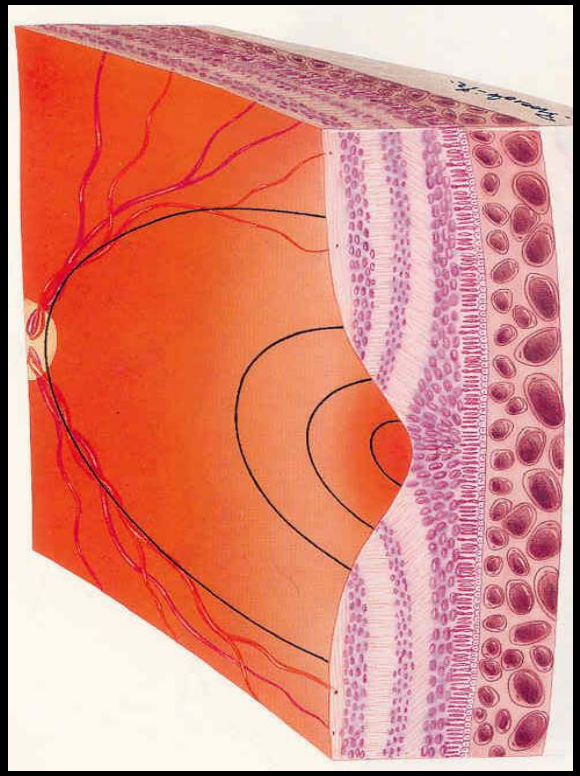
C – fotorecettori(coni)
S – fotorecettori(bastoncelli)
A – cellule amacrine
G – cellule ganglionari

La macula

Deputata alla percezione delle immagini



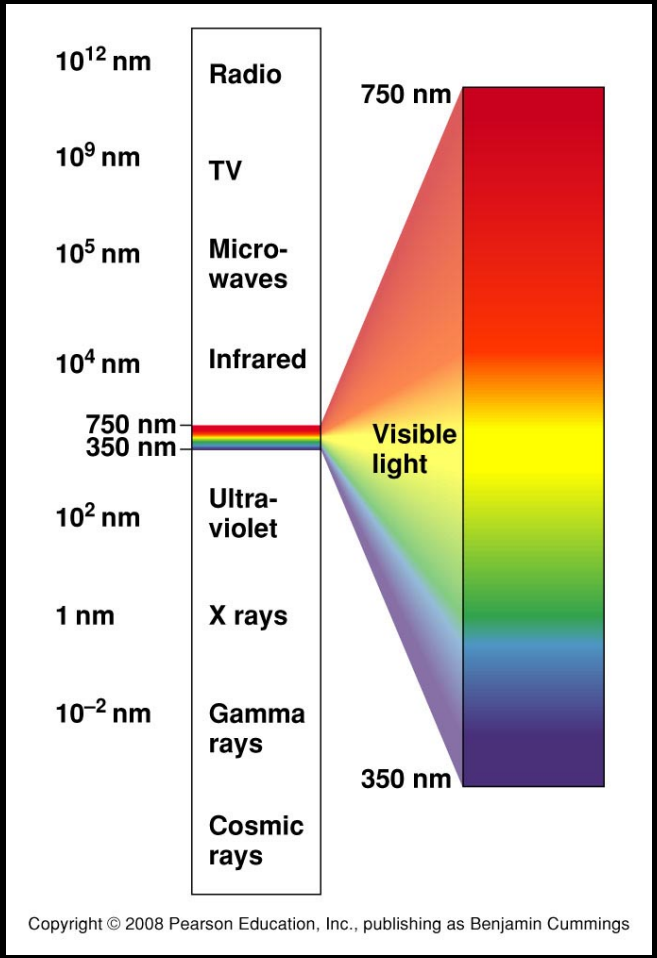




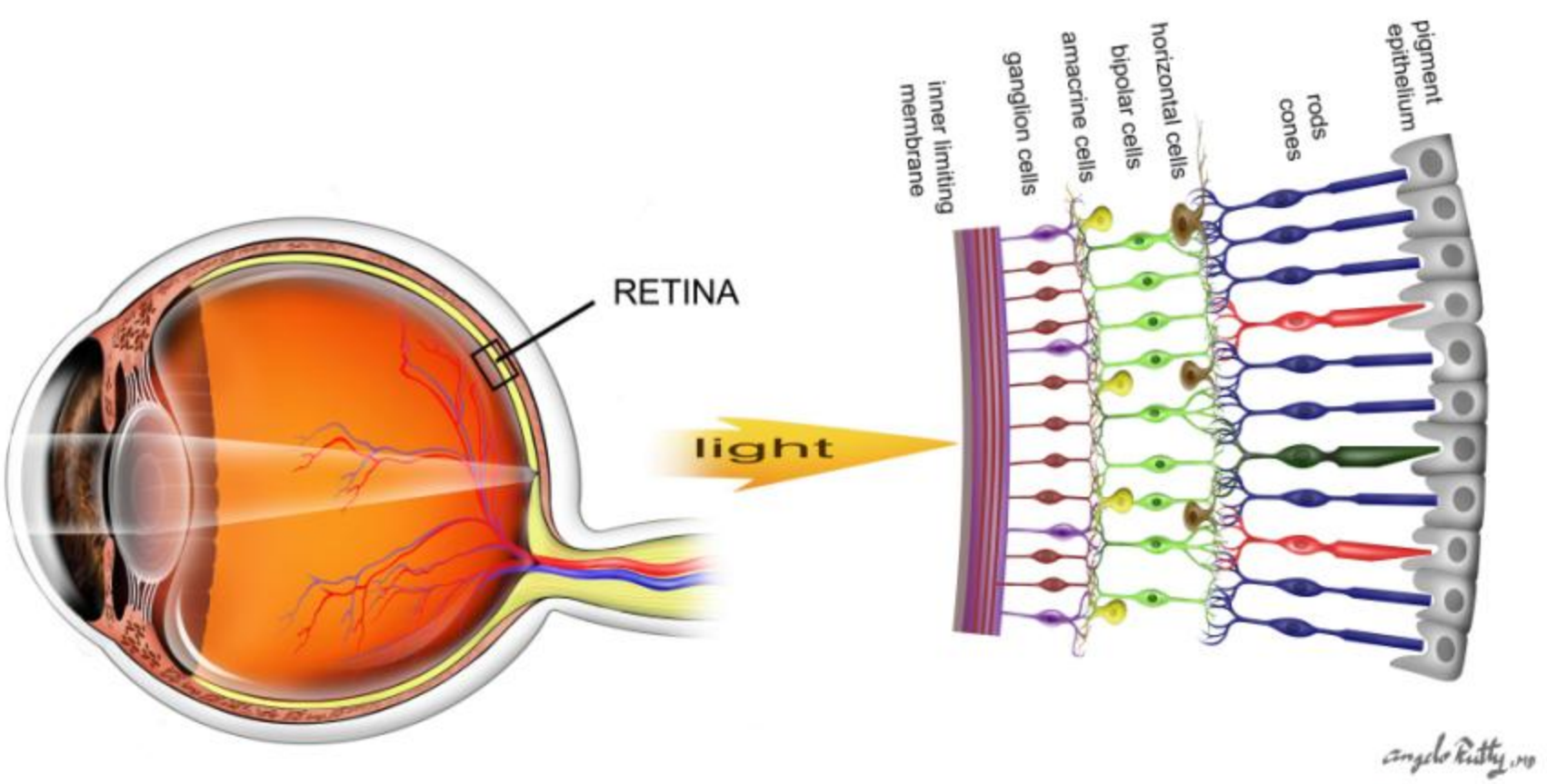
La retina

- La luce visibile:

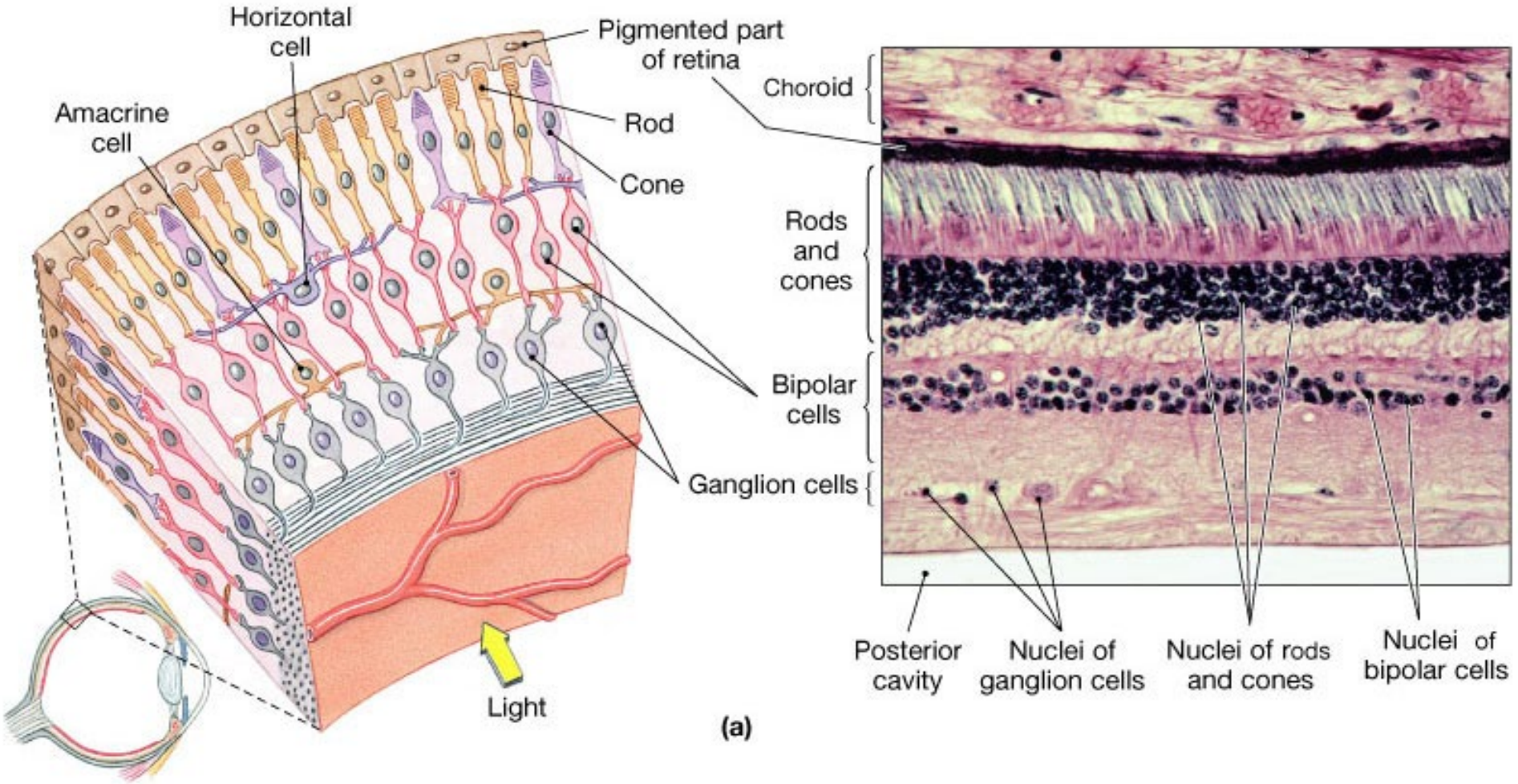
  porzione dello spettro elettromagnetico visibile dall'occhio umano, approssimativamente compresa tra 400 e 700 nanometri di lunghezza d'onda



La retina


RETINA
light
pigment epithelium
rods
cones
horizontal cells
bipolar cells
amacrine cells
ganglion cells
inner limiting membrane

La retina


Horizontal cell
Pigmented part of retina
Amacrine cell
Rod
Cone
Choroid
Rods and cones
Bipolar cells
Ganglion cells
Light
(a)
Posterior cavity
Nuclei of ganglion cells
Nuclei of rods and cones
Nuclei of bipolar cells

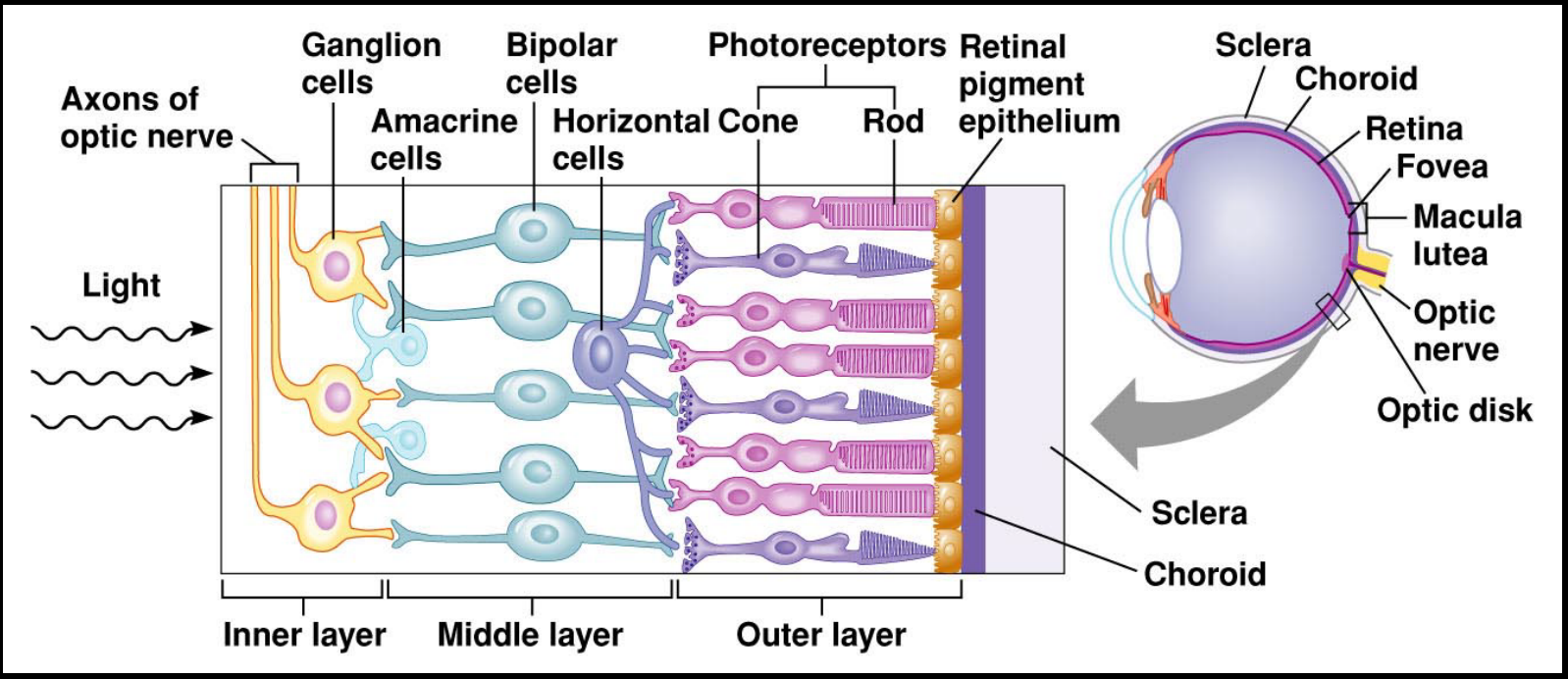
La retina

- Stazioni neurofunzionali:

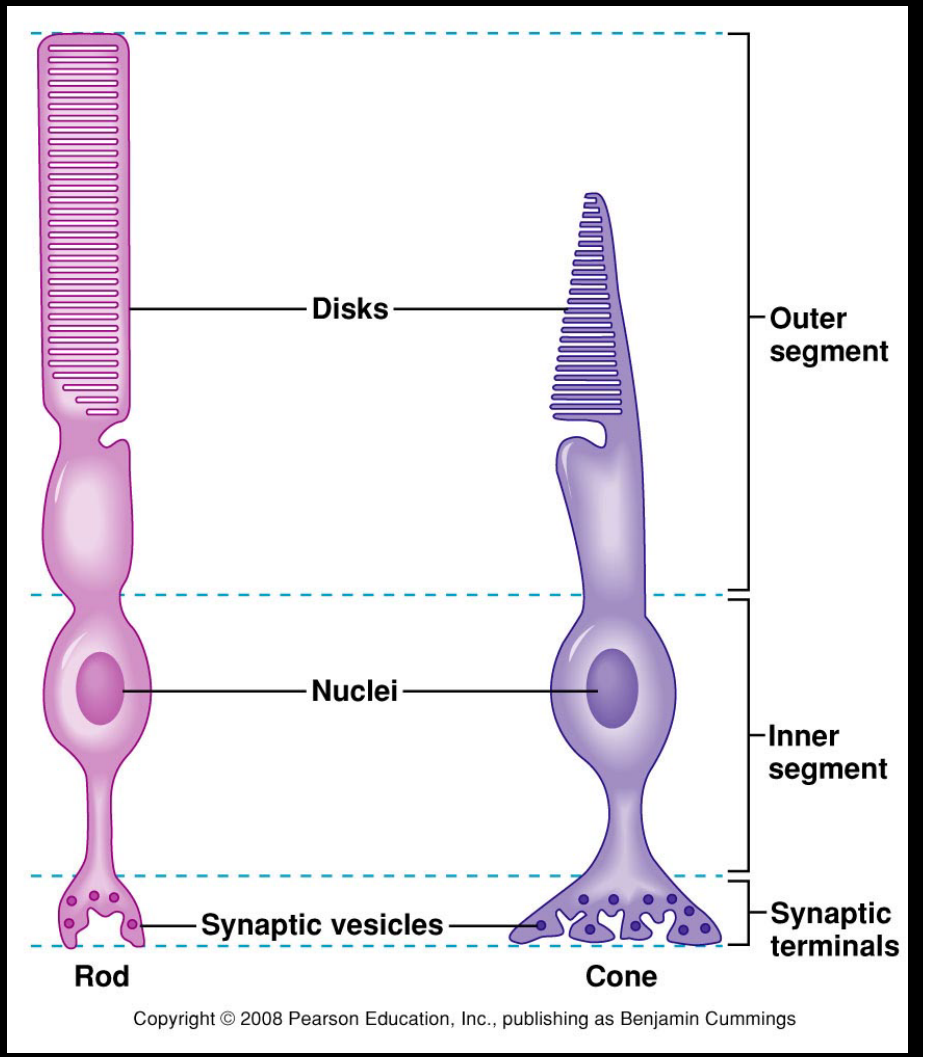
-- fotorecettori (coni e bastoncelli)

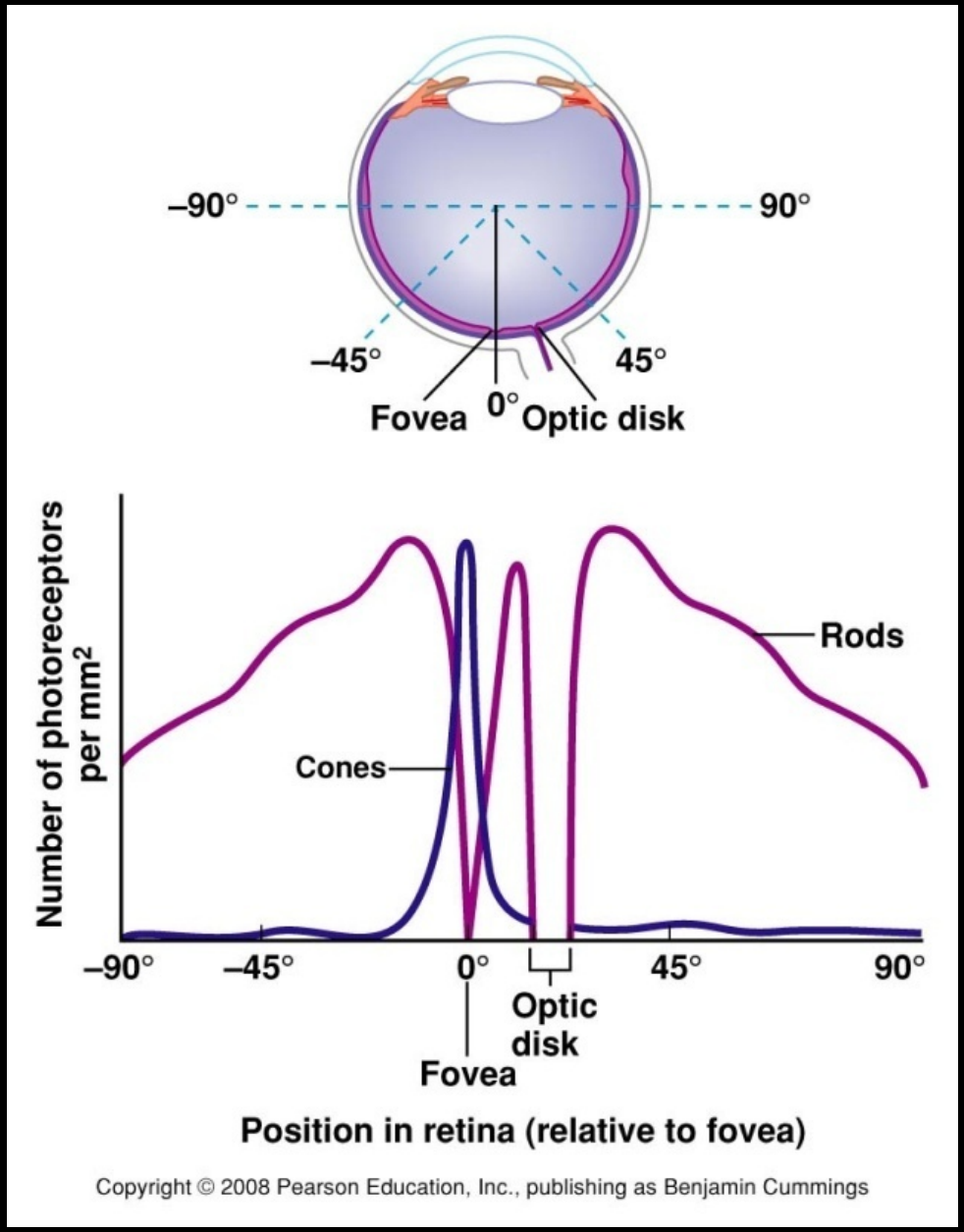
-- cellule bipolari

-- cellule ganglionari

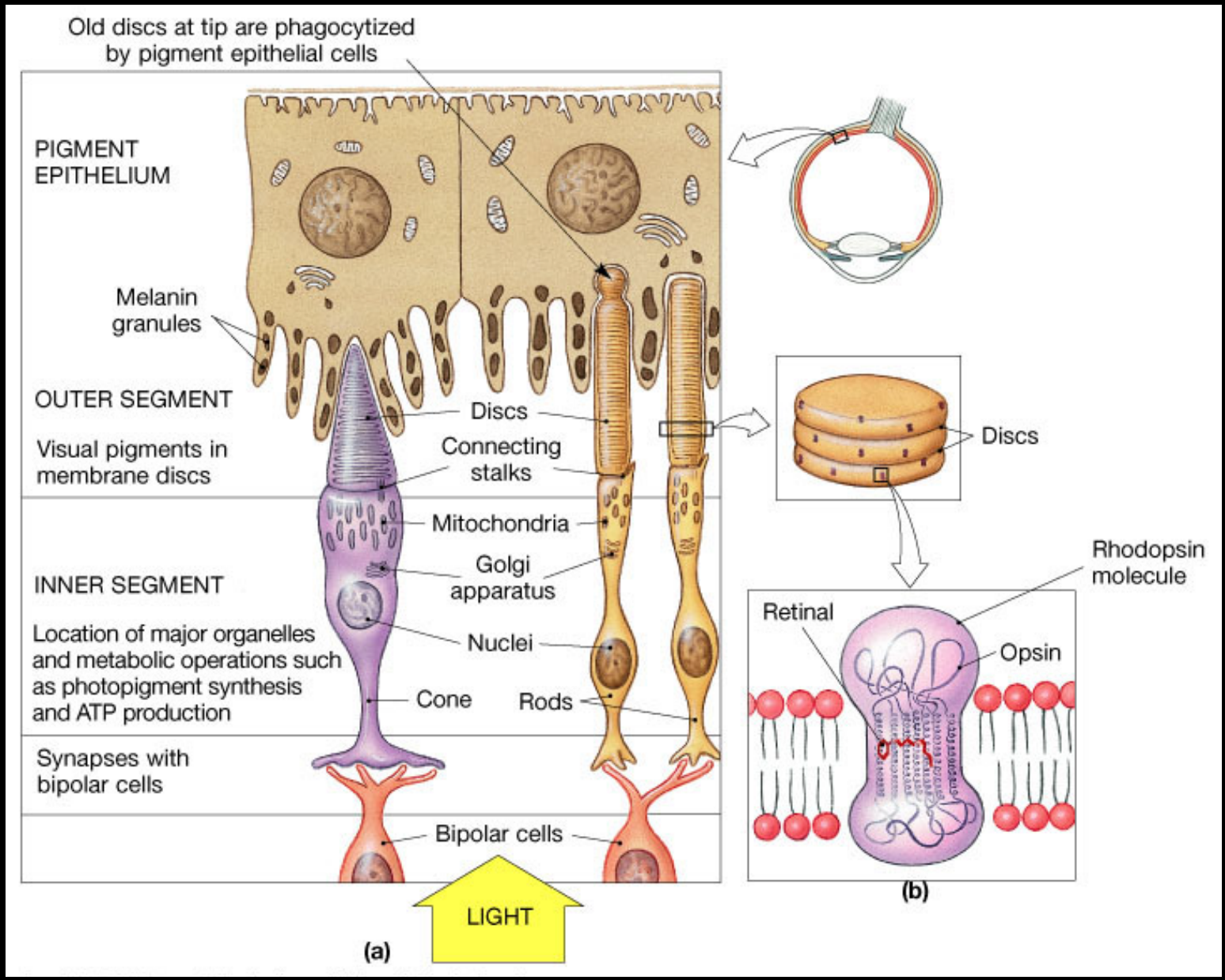


CONI e BASTONCELLI



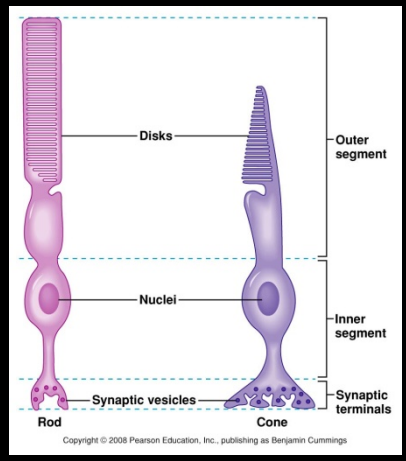


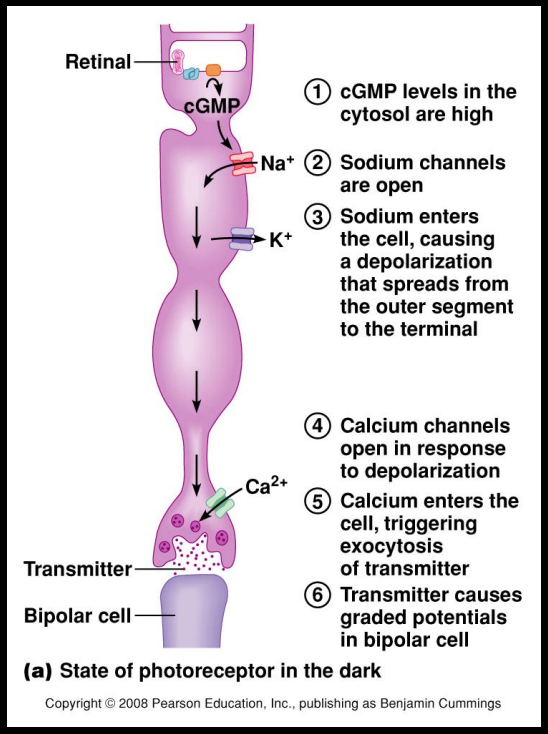
CONI e BASTONCELLI

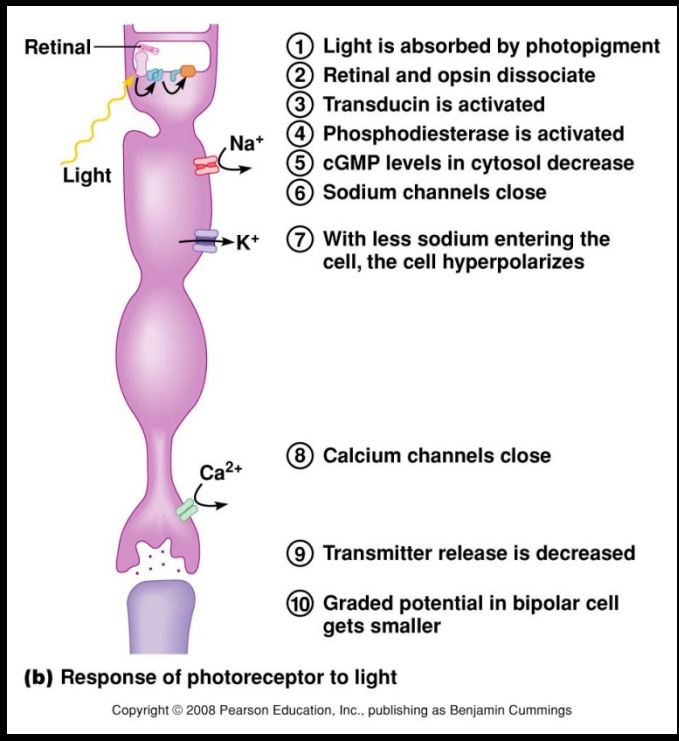


Phototransduction

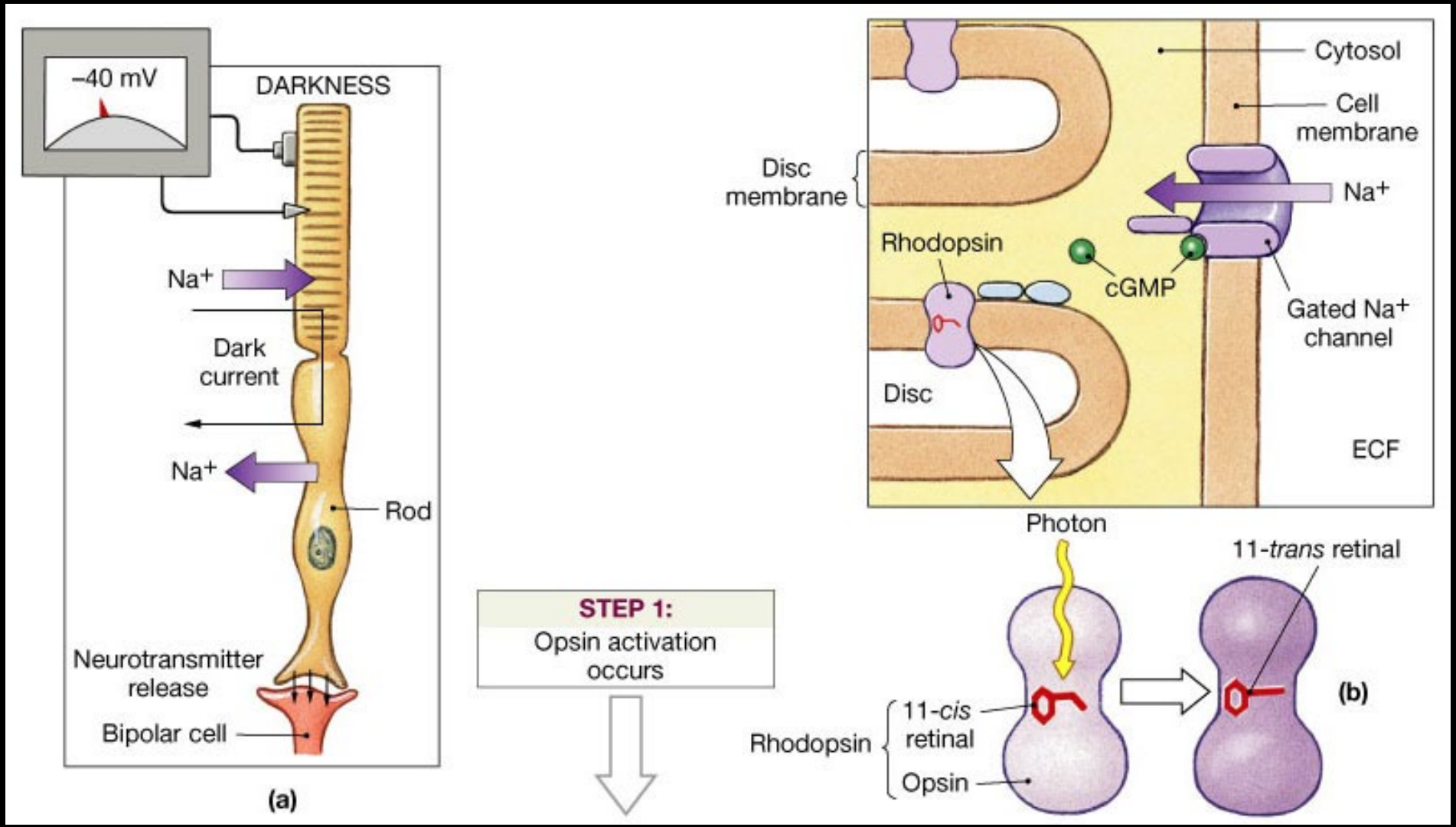
- Photons hit the pigment of a photoreceptor → → → enzymes are activated in the cell which modify its state of polarization



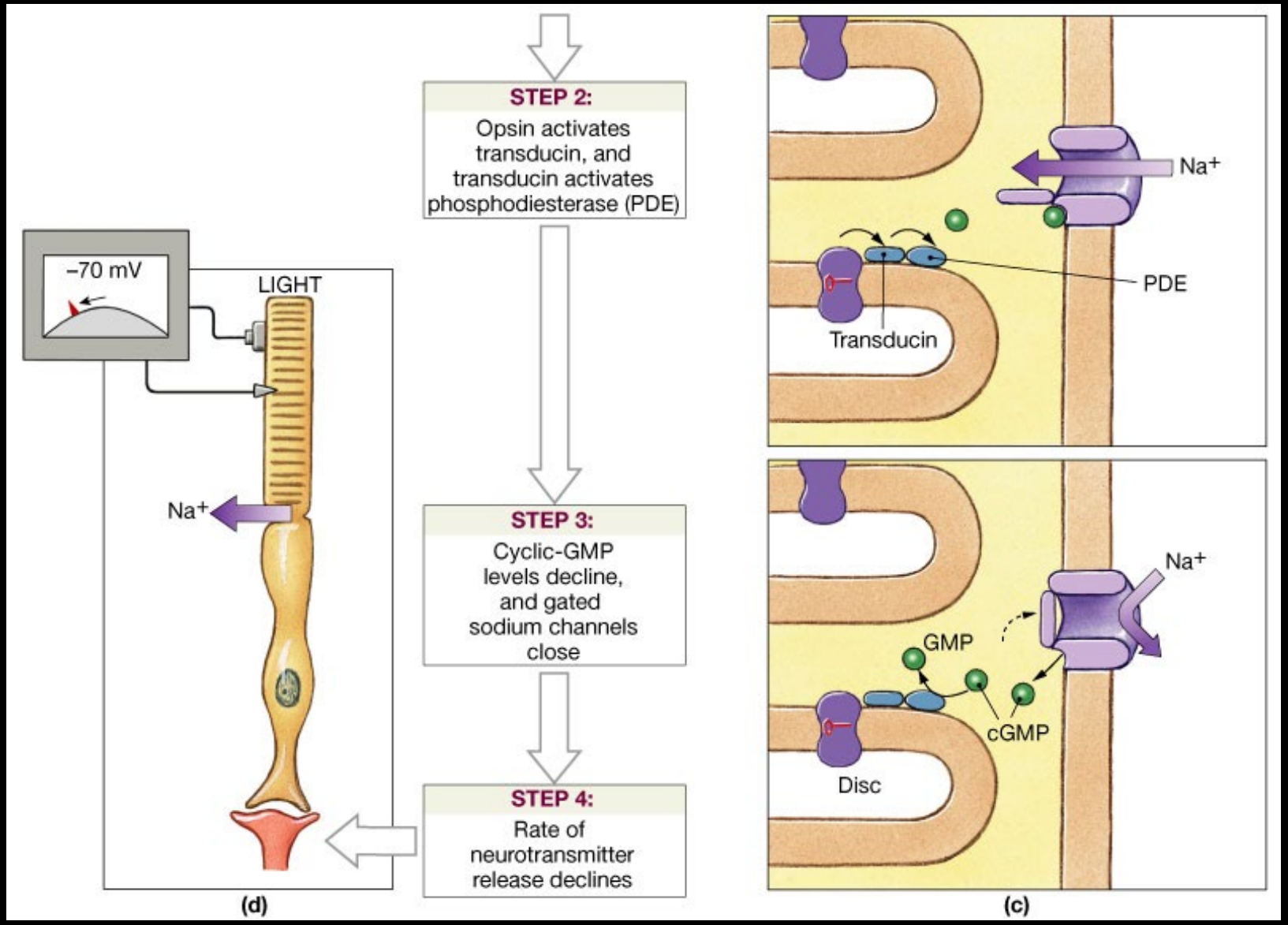




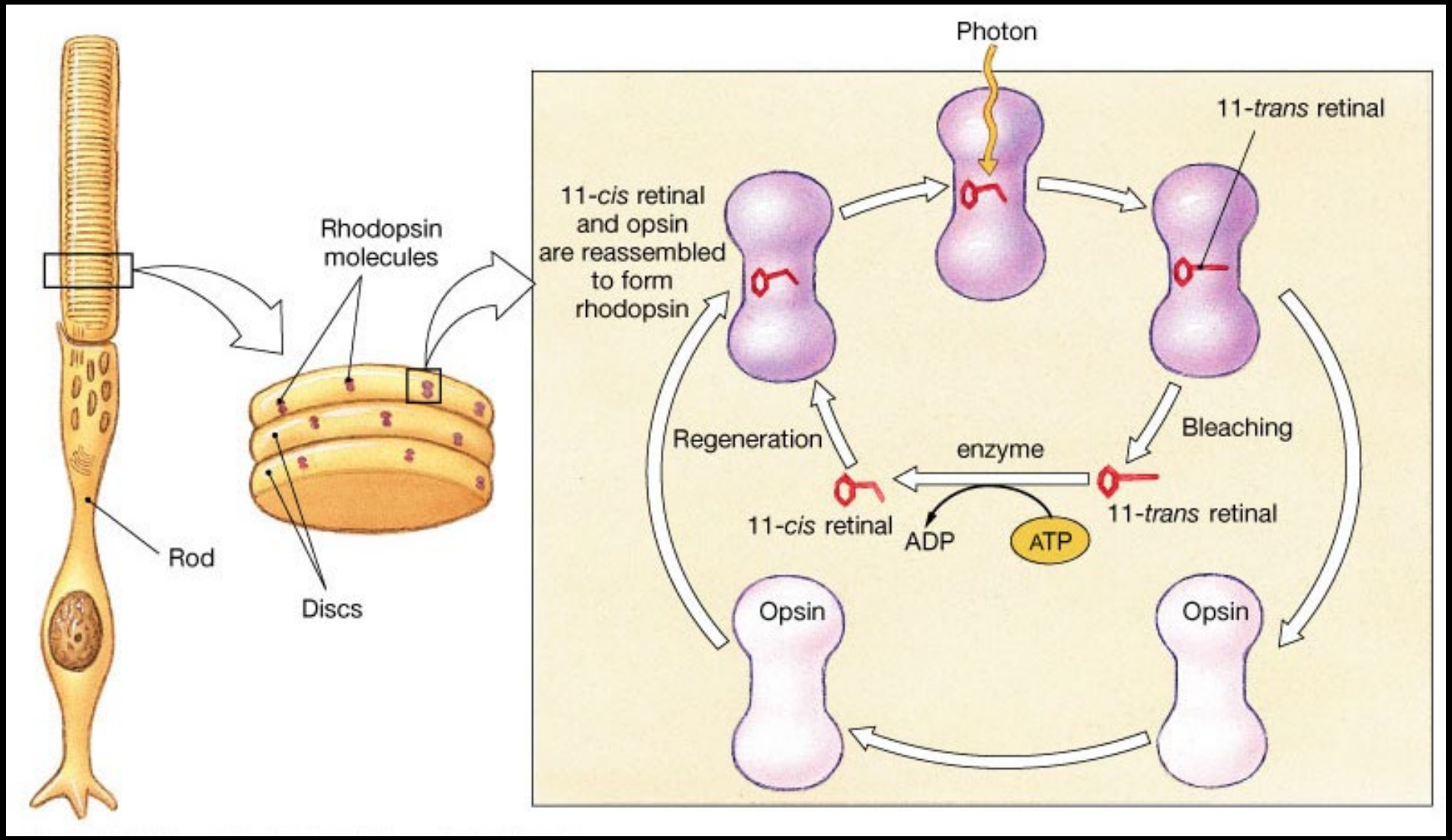
Photoreception - In More Detail



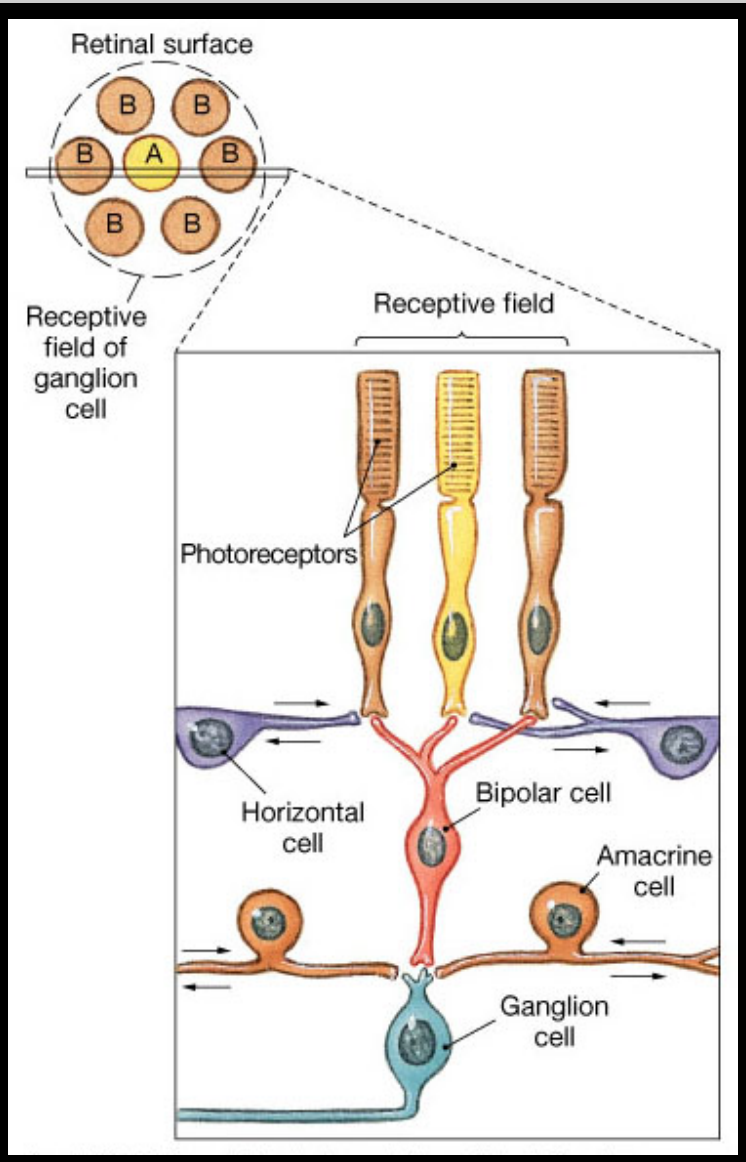
Photoreception



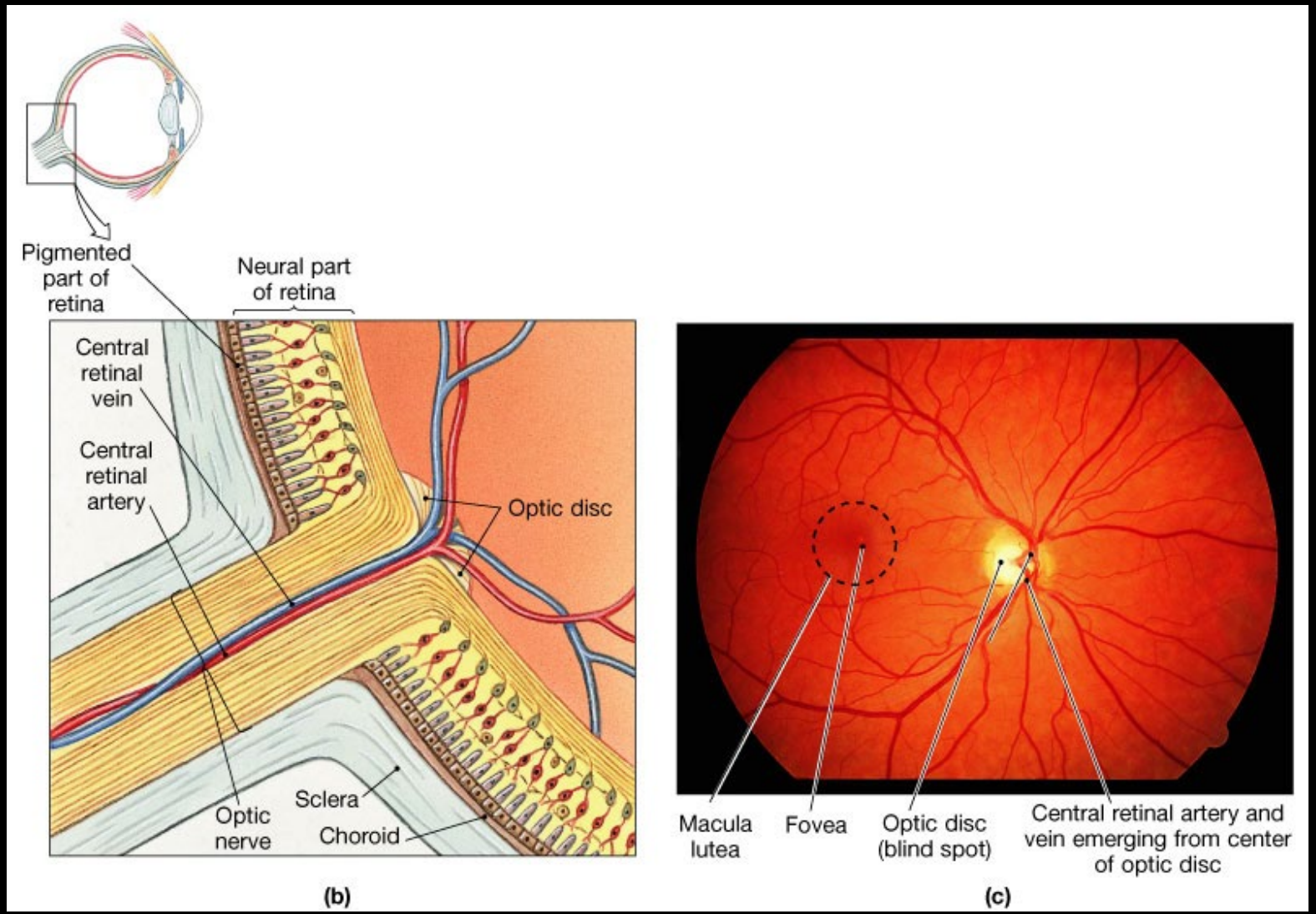
Bleaching and Regeneration of Visual Pigments



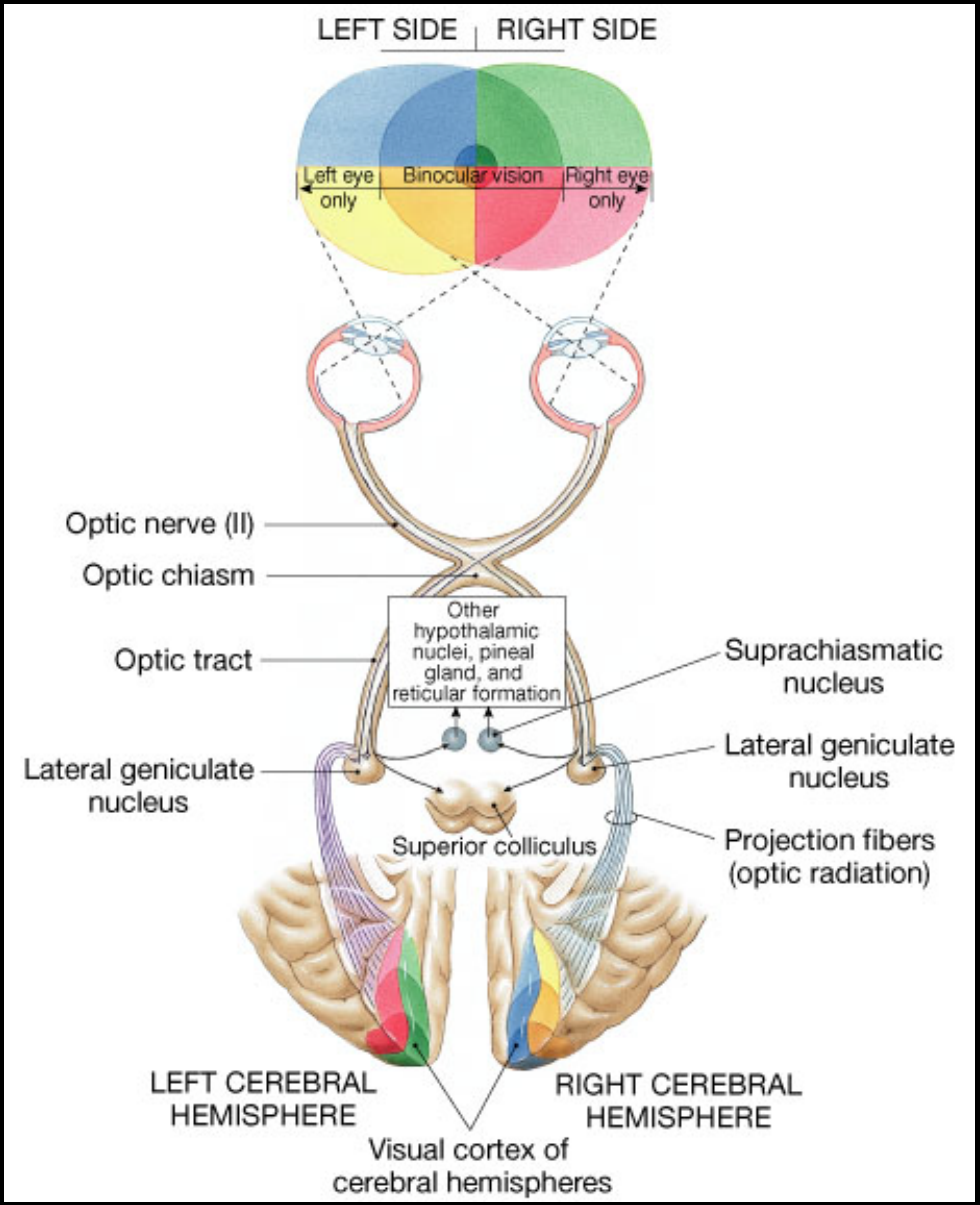
Convergence and Ganglion Cell Function



Il nervo ottico

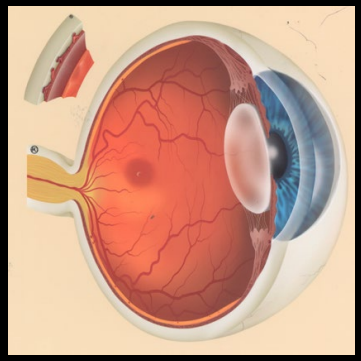


The Visual Pathways



Cecità e ipovisione

CECITA' E IPOVISIONE
www.cprnonvedenti.it



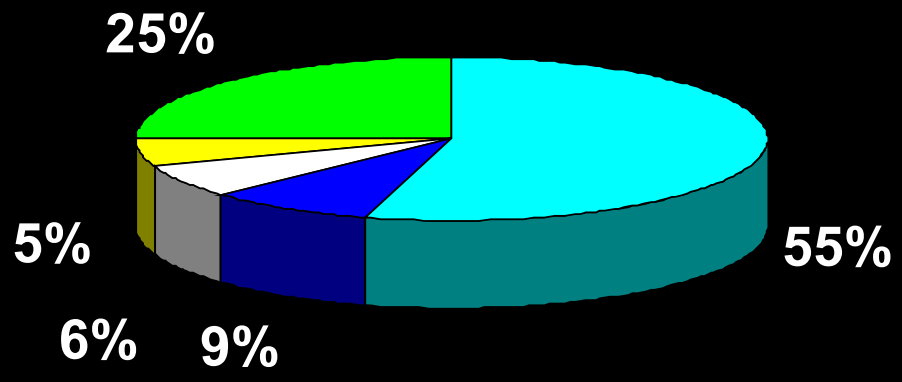
CIECHI TOTALI: AV ≤ MOTU MANUS
CAMPO VISIVO < 3%
CIECHI PARZIALI: AV ≤ 1/20
CAMPO VISIVO < 10%

IPOVEDENTI GRAVI: AV ≤ 1/10
CAMPO VISIVO <30%
IPOVEDENTI MEDIO-GRAVI: AV ≤ 2/10
CAMPO VISIVO <50%
IPOVEDENTI LIEVI: AV ≤ 3/10
CAMPO VISIVO <60%

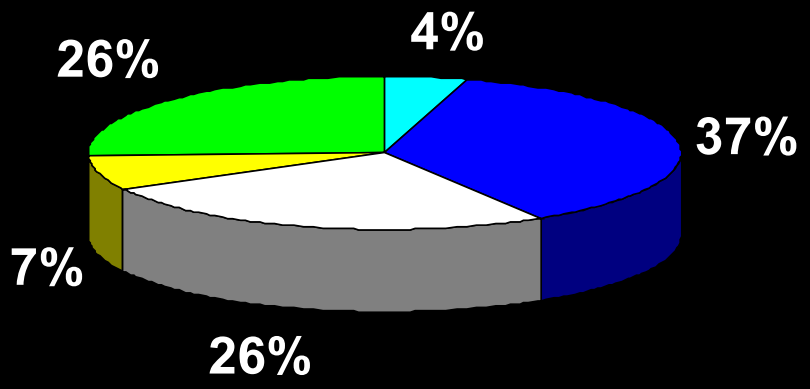
Cause di cecità per gruppi etnici

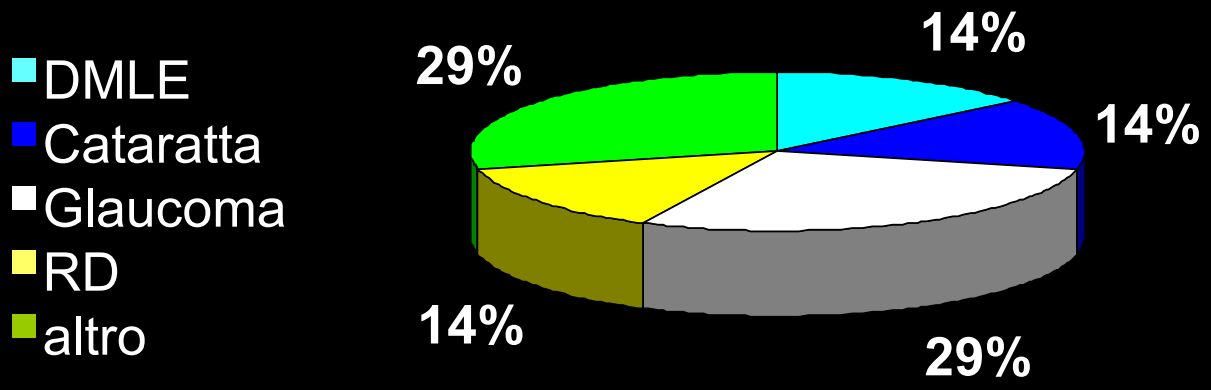
AV ≤ 1/20

Razza bianca



Razza nera





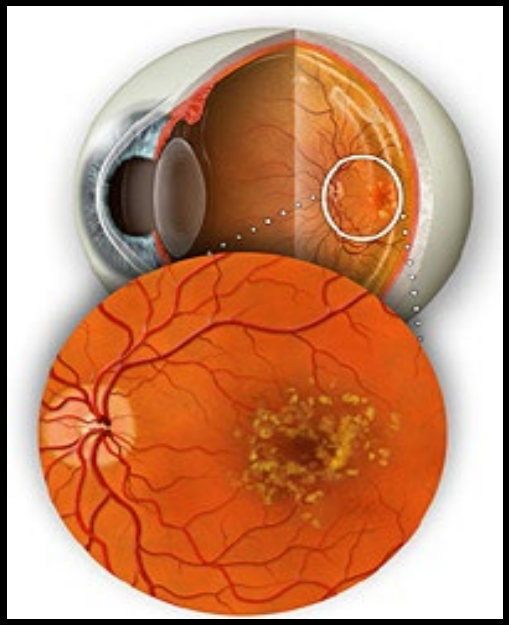
Razza ispanica

Cause di cecità

AV ≤ 1/20

Nei paesi industrializzati
la retinopatia diabetica
è la prima causa di cecità
in età lavorativa

Degenerazione maculare legata all'età (DMLE)



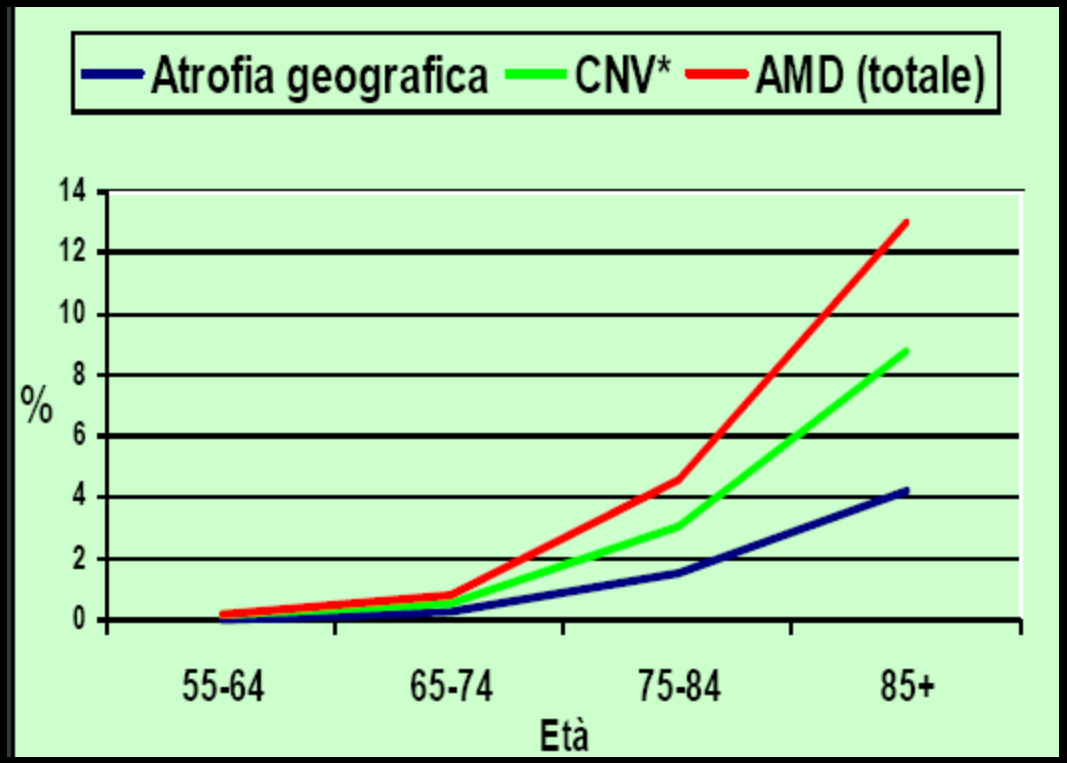
- La **Degenerazione Maculare Legata all'Età** (DMLE o AMD) è una patologia cronica che colpisce la porzione più importante della retina (***macula***), sede della visione distinta [1]

Incidenza DMLE

- **DMLE iniziale: 1.3% – 2.2% x anno**
- **DMLE evoluta: 0.01% – 1% x anno**

Hisayama study 2005
Copenhagen City Eye Study 2005
Visual Impairment Project 2004
Barbados Eye Study 2004
Blue Mountains Eye Study 2003
Beaver Dam Eye study 2002

Prevalenza DMLE



AMD: prevalenza (in almeno 1 occhio) come % della popolazione per fascia d'età

Degenerazione maculare legata all'età (DMLE)

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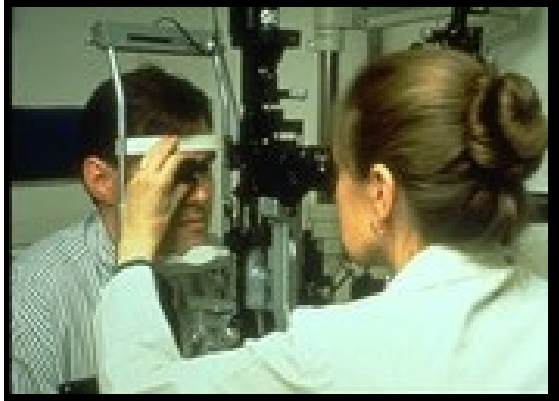
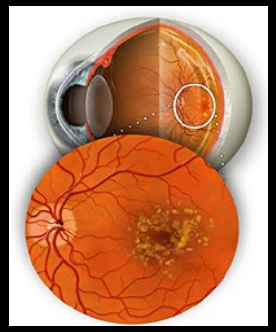
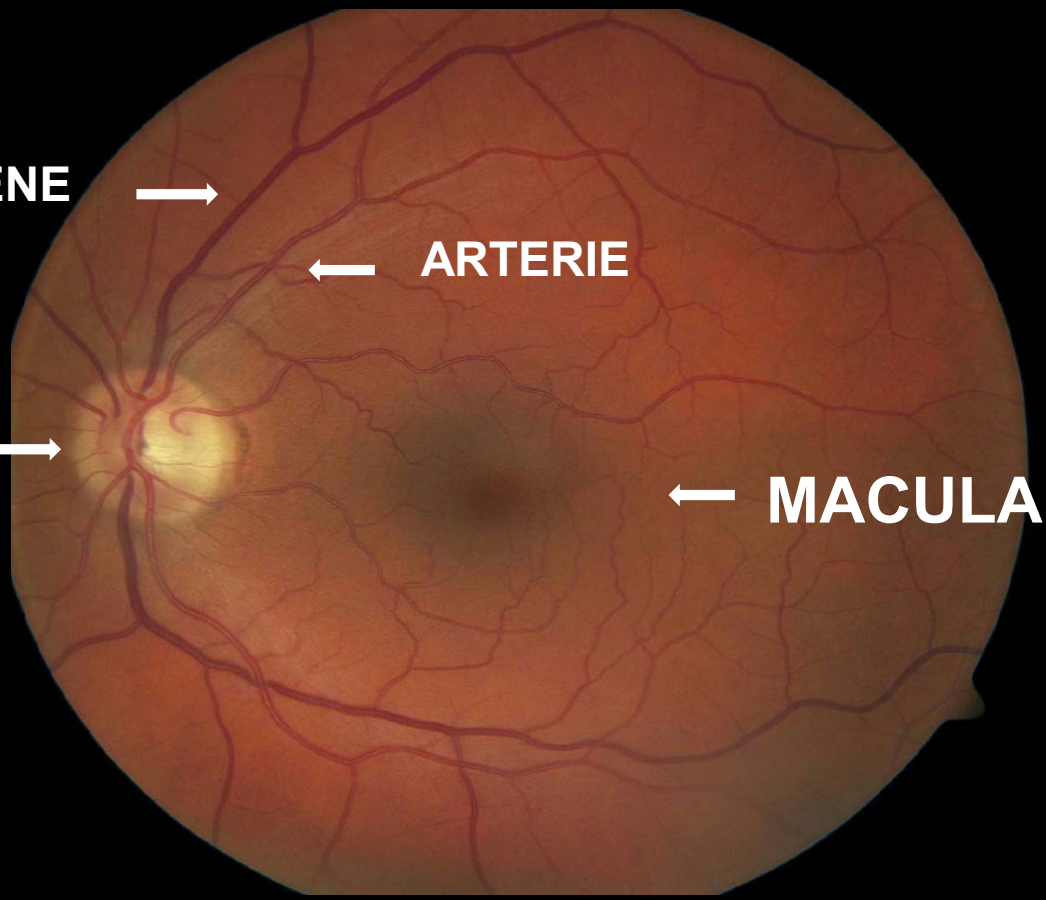
-OFTALMOSCOPIA

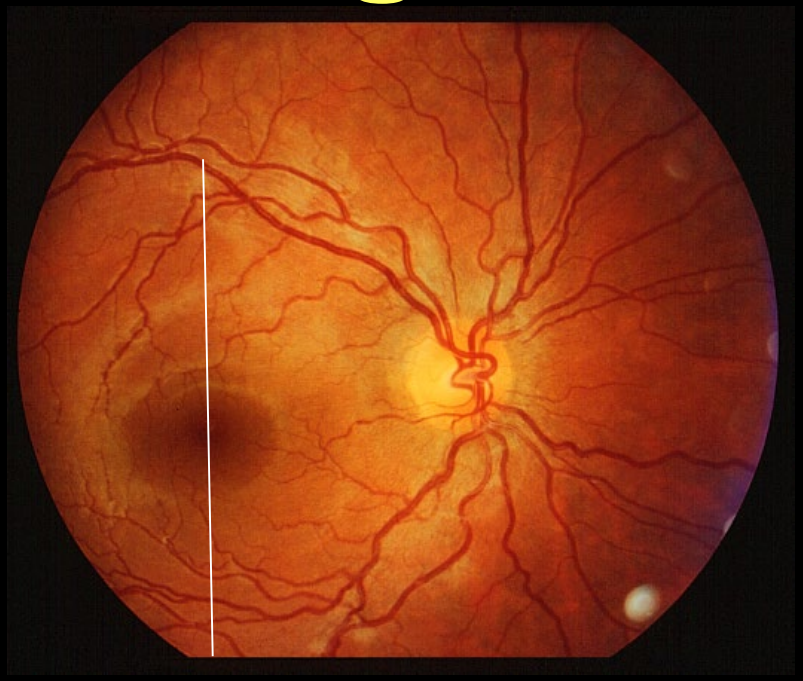


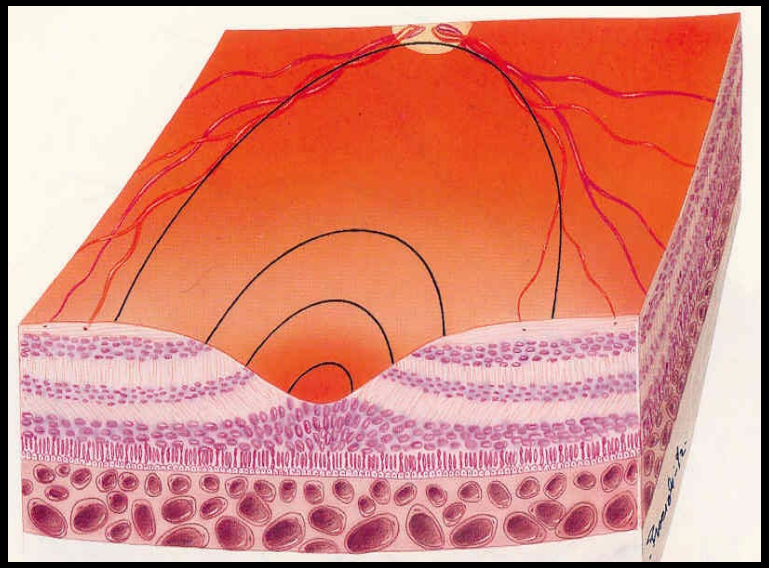
Degenerazione maculare legata all'età (DMLE)





Degenerazione maculare legata all'età (DMLE)

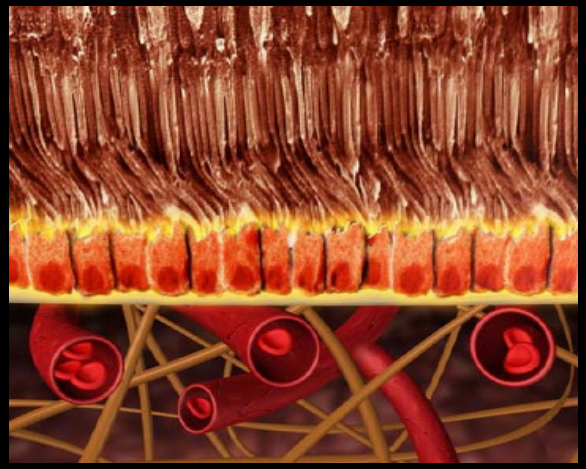




FOTORECETTORI

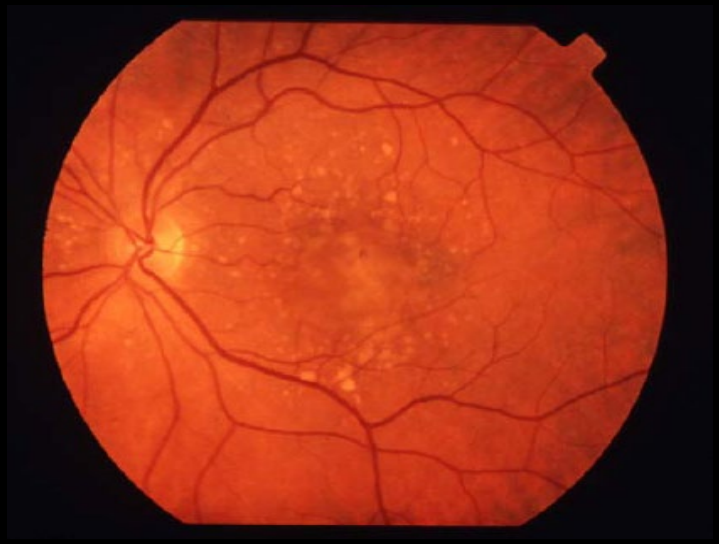
EPITELIO PIGMENTATO RETINICO

COROIDE



Degenerazione maculare legata all'età (DMLE)

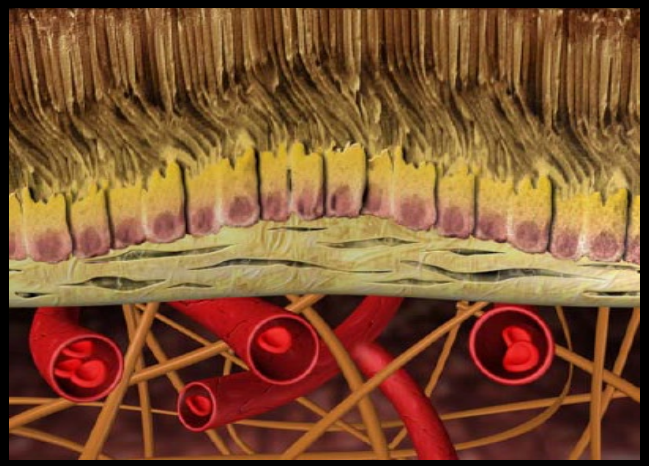
DRUSEN



FOTORECETTORI

EPITELIO PIGMENTATO RETINICO

COROIDE



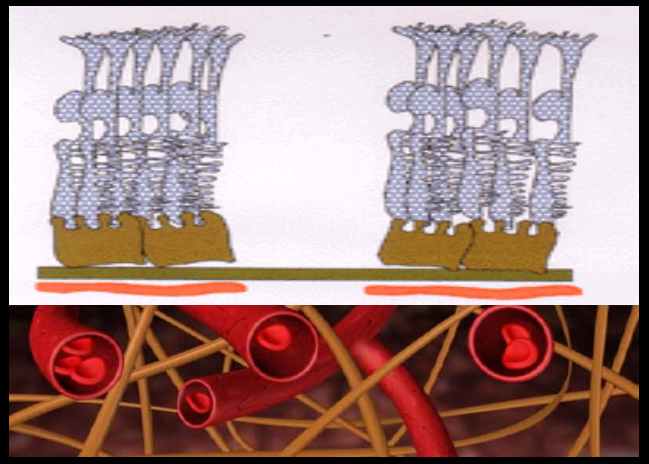
Degenerazione maculare legata all'età (DMLE)

ATROFIA

FOTORECETTORI →

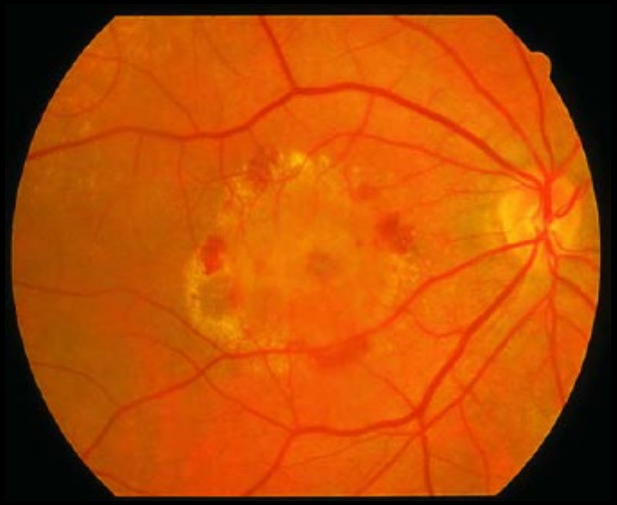
EPITELIO PIGMENTATO RETINICO →

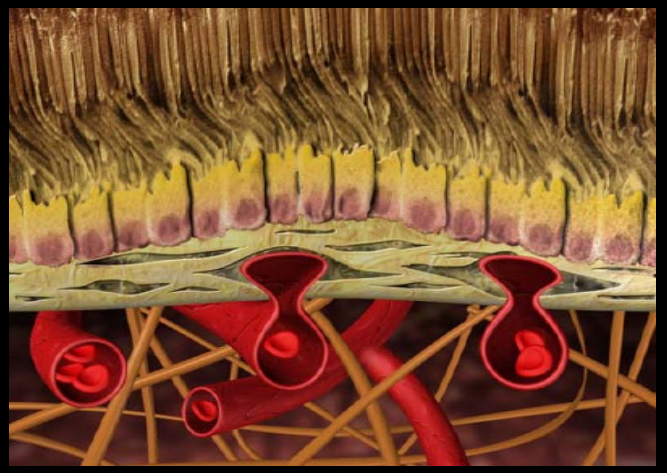
COROIDE →



Degenerazione maculare legata all'età (DMLE)

NEOVASCOLARIZZAZIONE COROIDEALE (CNV)





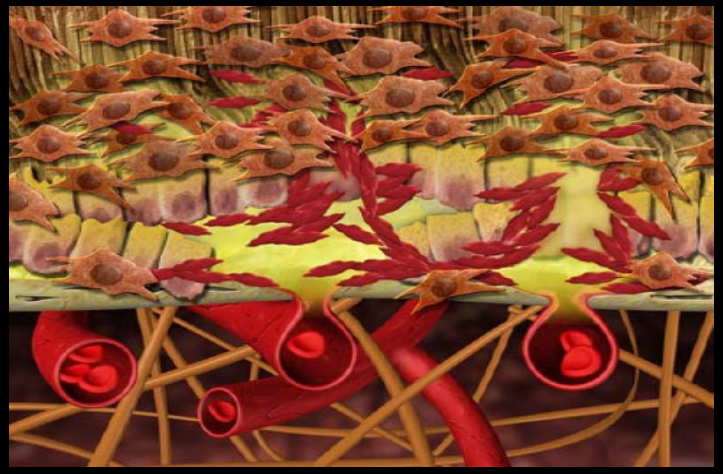
Degenerazione maculare legata all'età (DMLE)

DMLE EVOLUTA:
CICATRICE
FIBROVASCOLARE

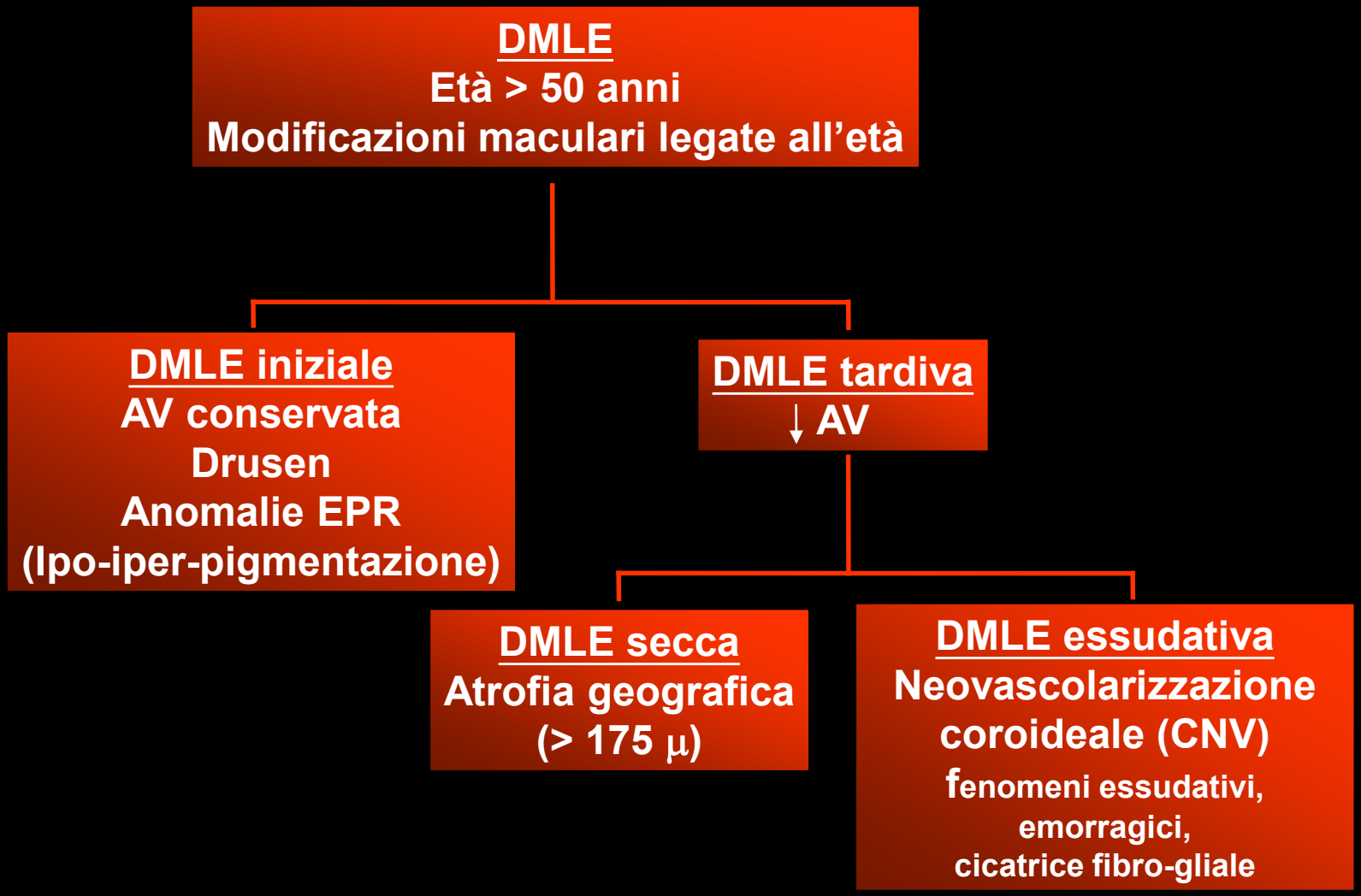
FOTORECETTORI →

EPITELIO PIGMENTATO RETINICO →

COROIDE →



Degenerazione maculare legata all'età (DMLE)



Degenerazione maculare legata all'età (DMLE)

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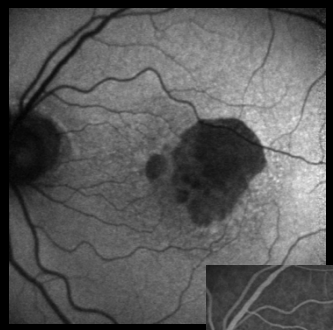
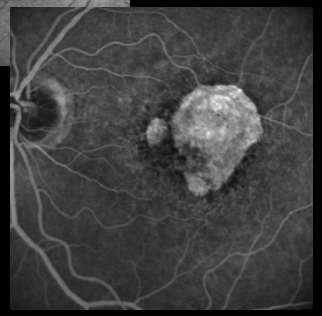
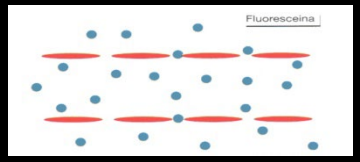


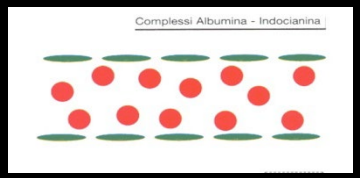
-AUTOFLUORESCENZA



-FLUORANGIOGRAFIA



- ANGIOGRAFIA AL VERDE INDOCIANINA

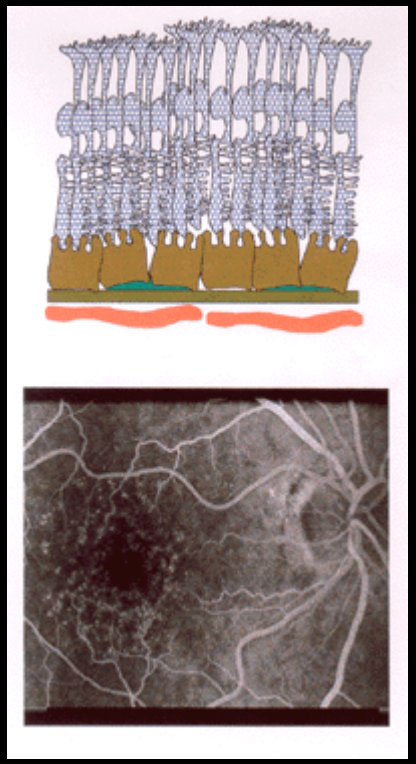


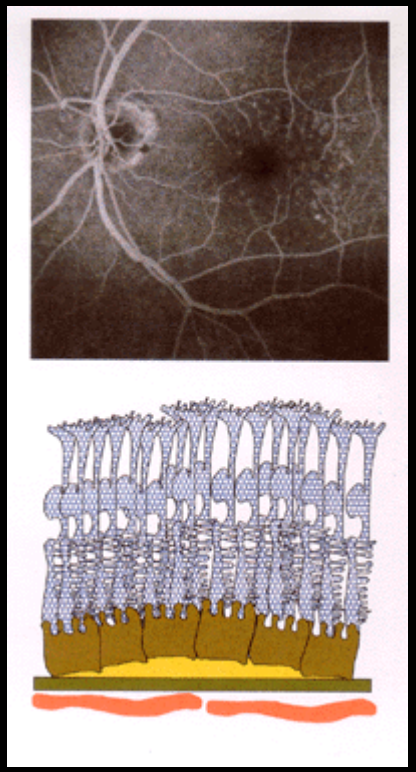
Degenerazione maculare legata all'età (DMLE)

STUDIO MORFO-FUNZIONALE

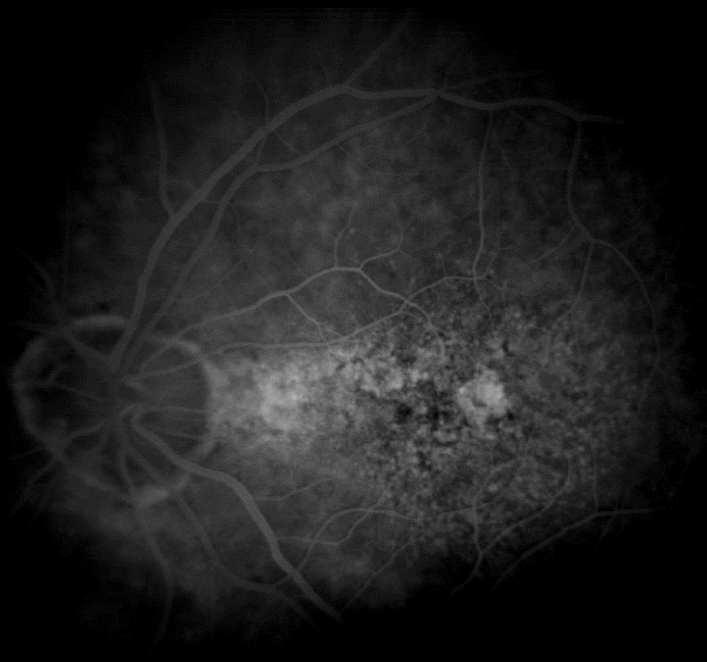
-FLUORANGIOGRAFIA

DRUSEN





Degenerazione maculare legata all'età (DMLE)

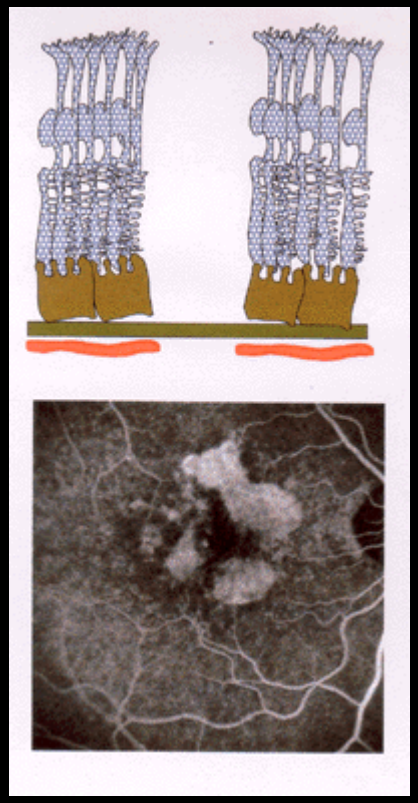


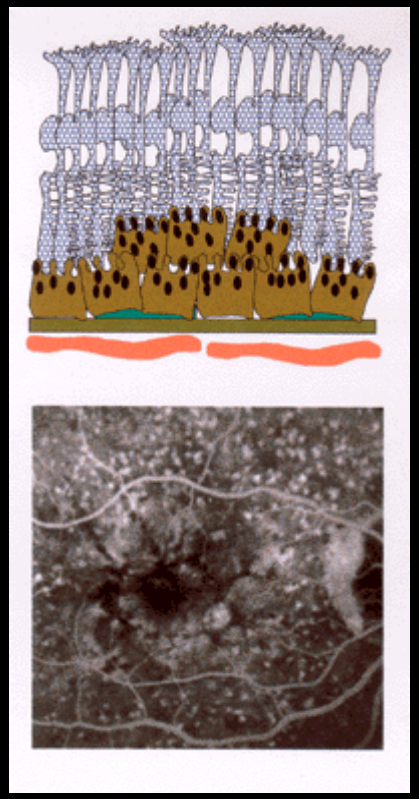
Degenerazione maculare legata all'età (DMLE)

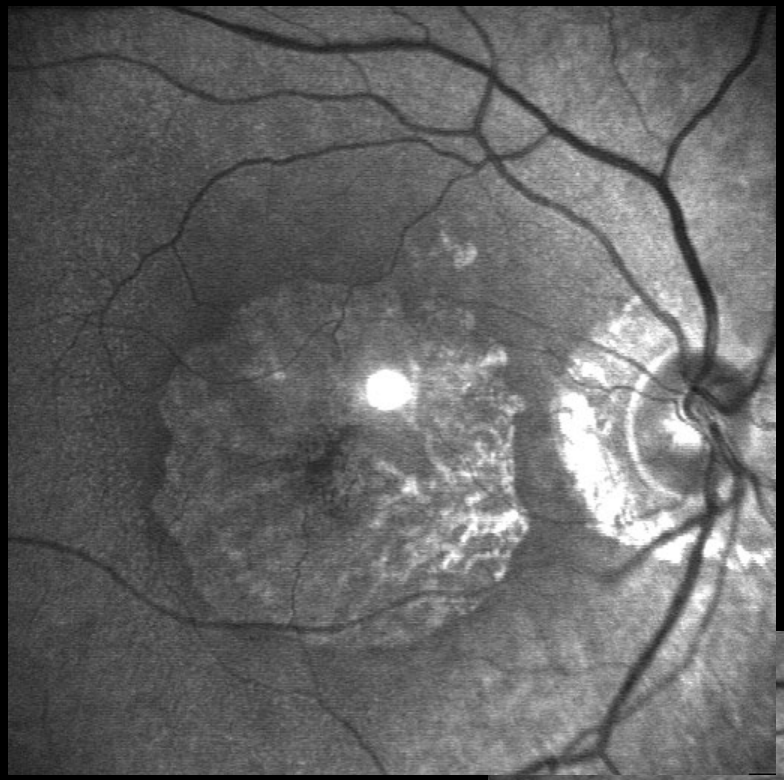
STUDIO MORFO-FUNZIONALE

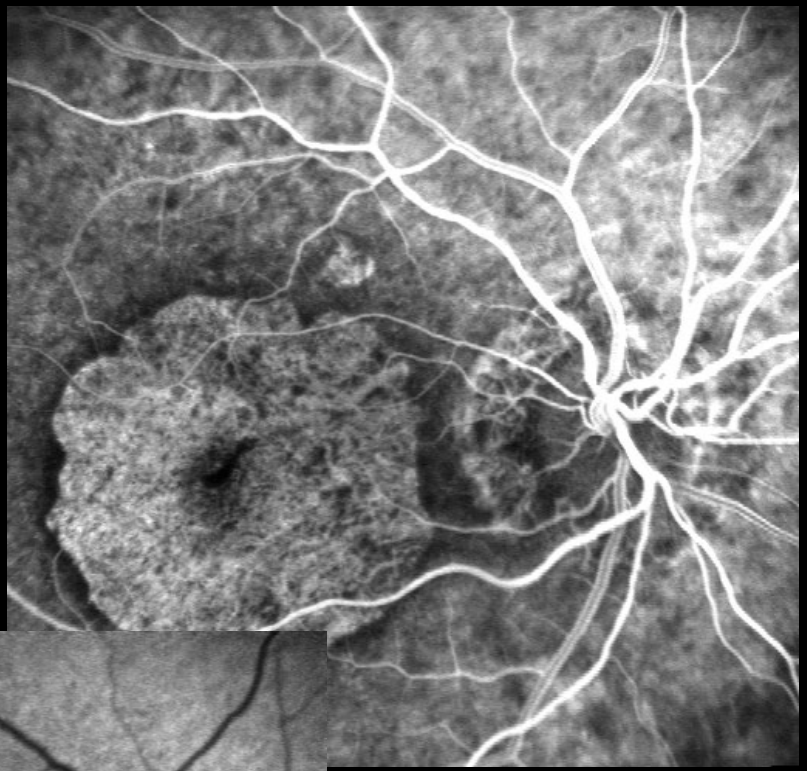
-FLUORANGIOGRAFIA

ATROFIA / PIGMENTO



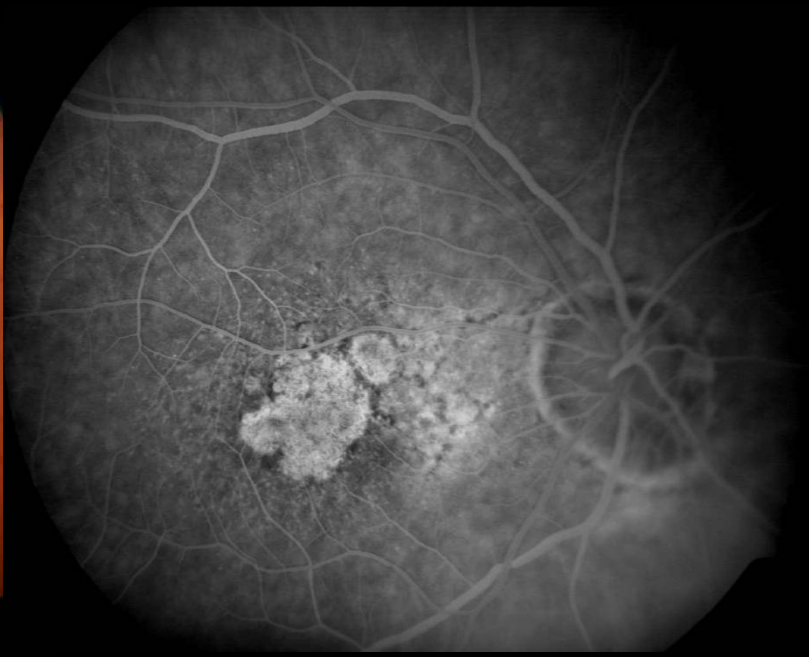







TRC-50EX

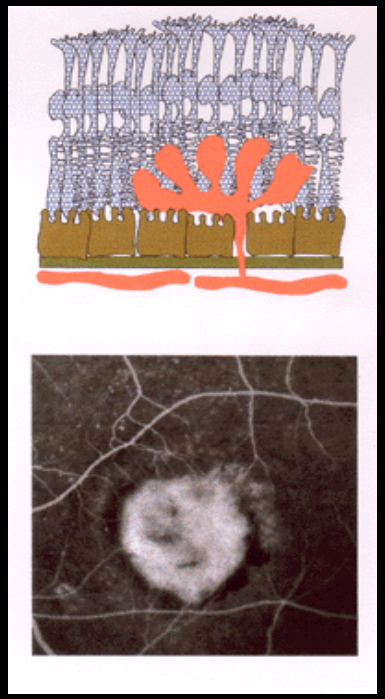
Degenerazione maculare legata all'età (DMLE)

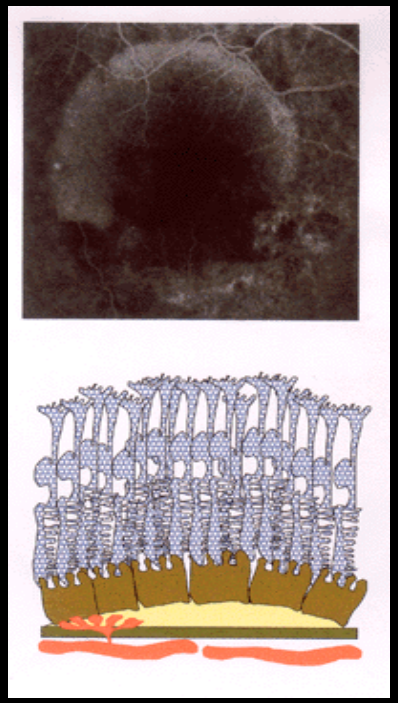


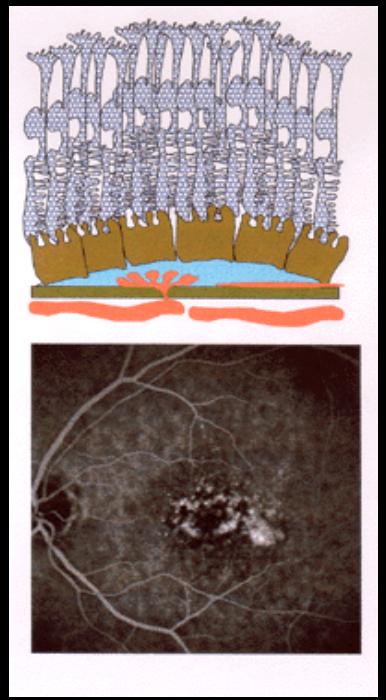
Degenerazione maculare legata all'età (DMLE)

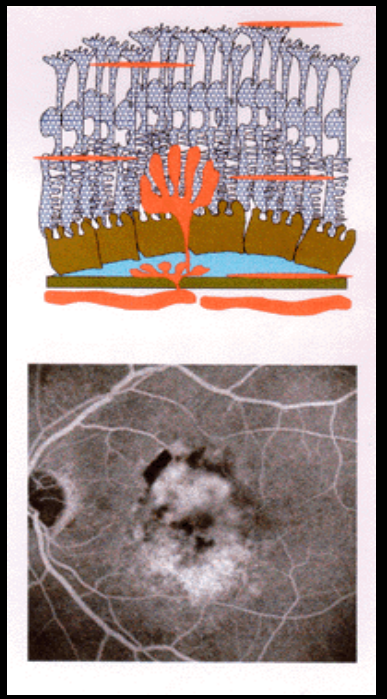
FLUORANGIOGRAFIA

NEOVASCOLARIZZAZIONE COROIDEALE







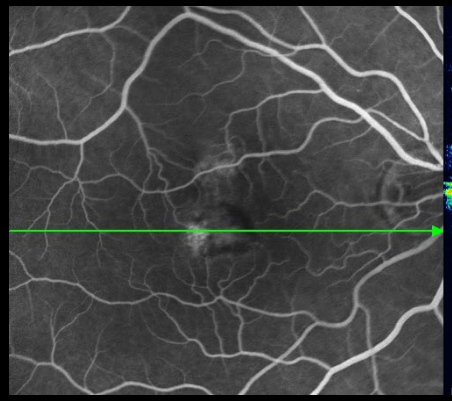


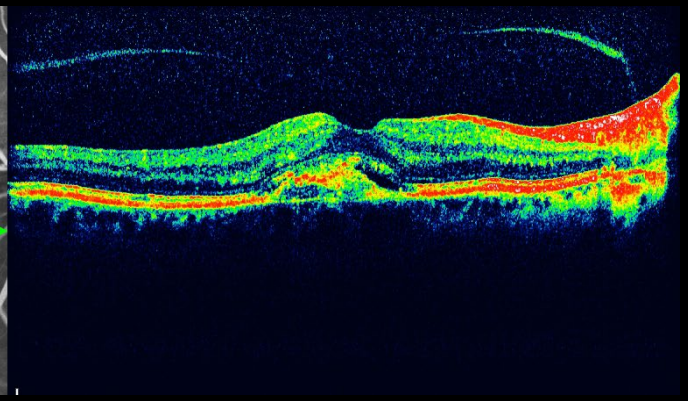
Degenerazione maculare legata all'età (DMLE)

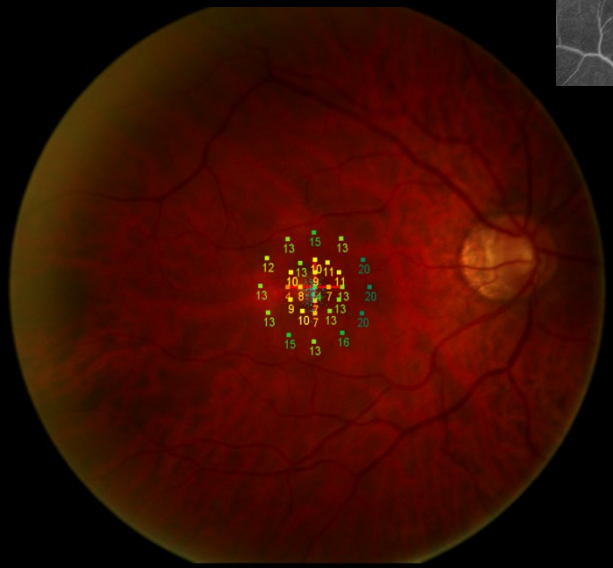
STUDIO MORFO-FUNZIONALE

- OCT

- MICROPERIMETRIA







DIAGNOSTICA "*DI SUPERFICIE*"

Oftalmoscopia

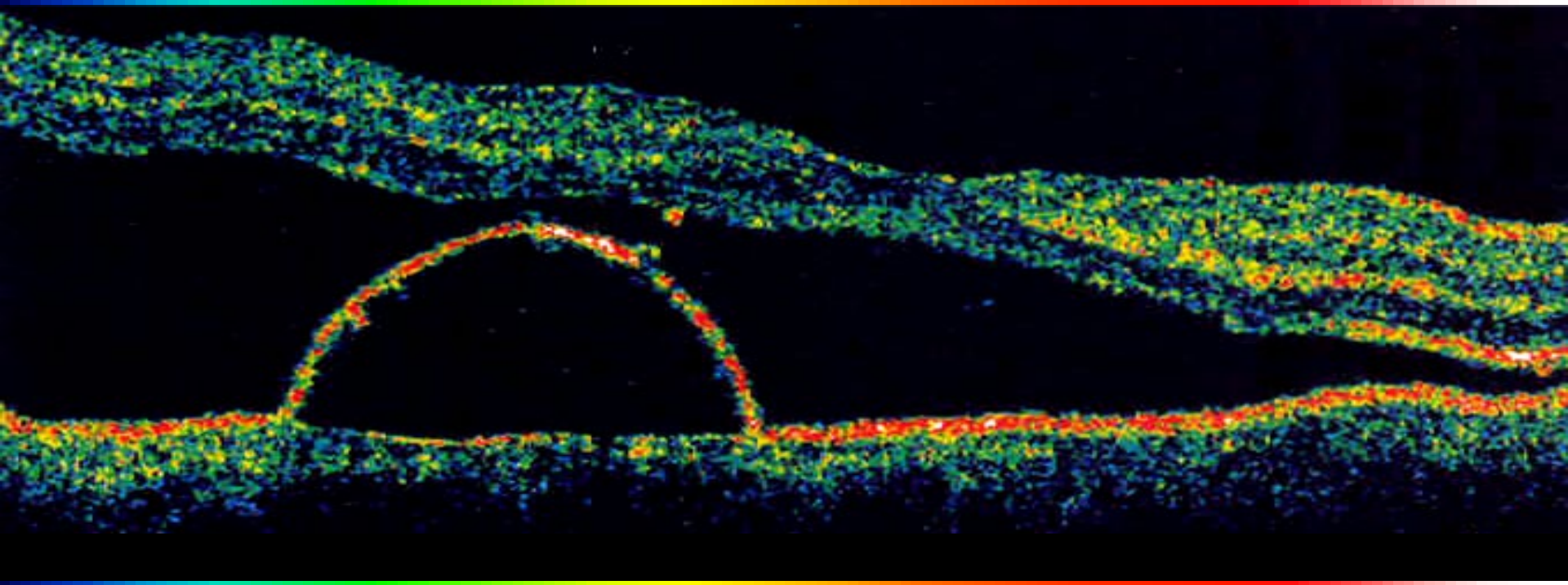
Fluorangiografia

DIAGNOSTICA "*DI SPESSORE*"

Ecografia: **Risoluzione: 150 μ**

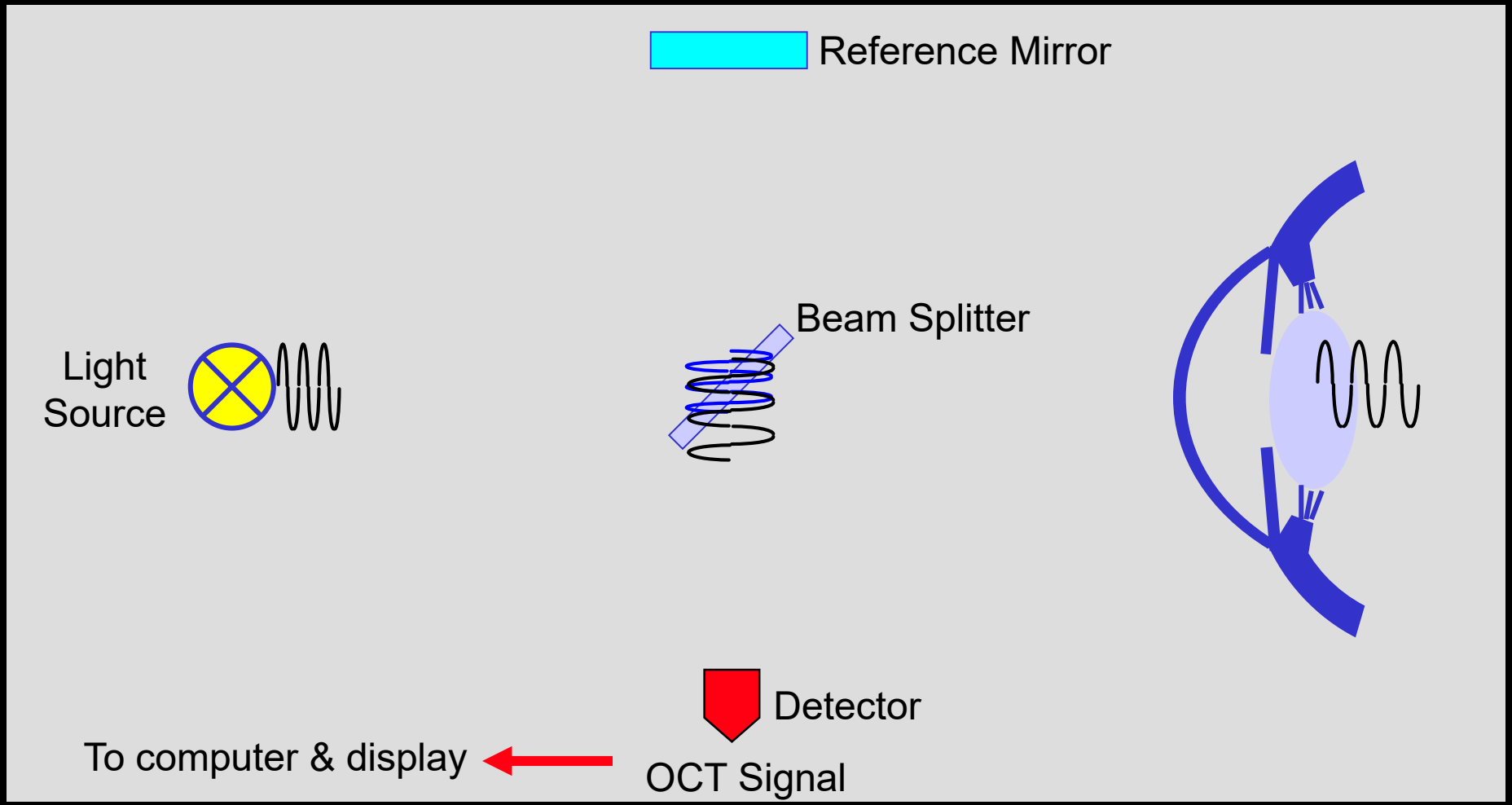
OCT: **Risoluzione: 7 - 15 μ**

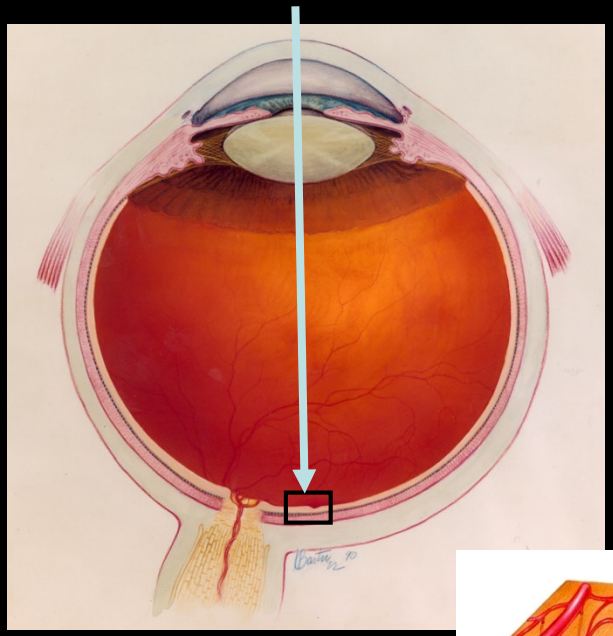
OCT

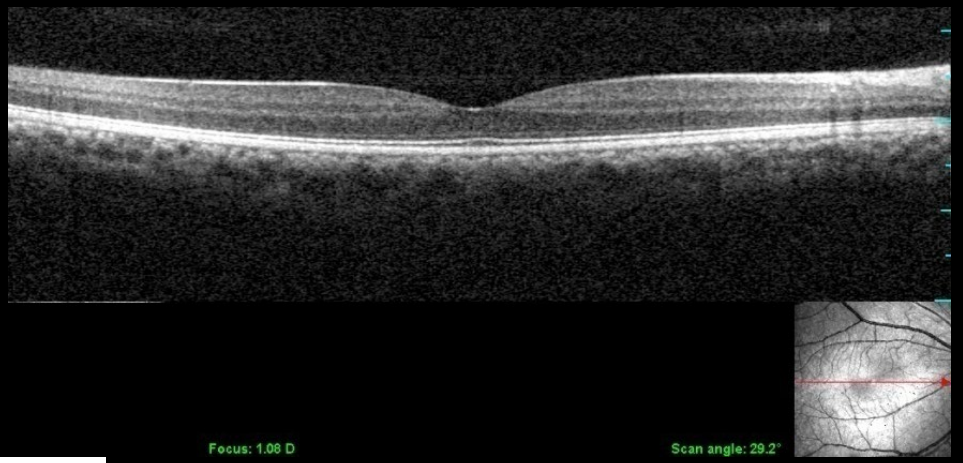


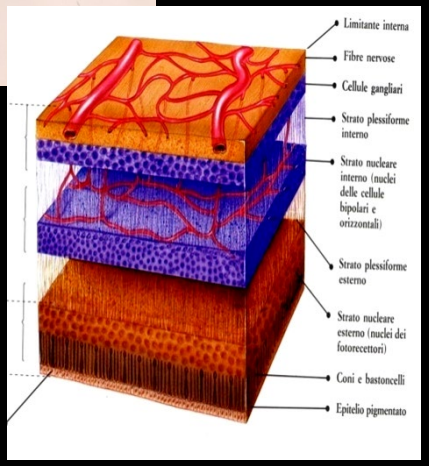
TOMOGRAFIA
A COERENZA OTTICA

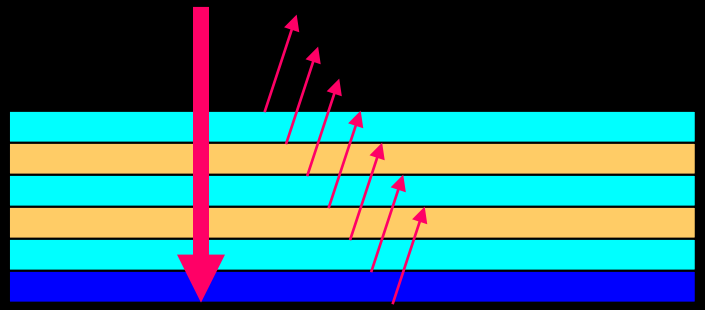
PRINCIPI DI FUNZIONAMENTO DELL'OCT



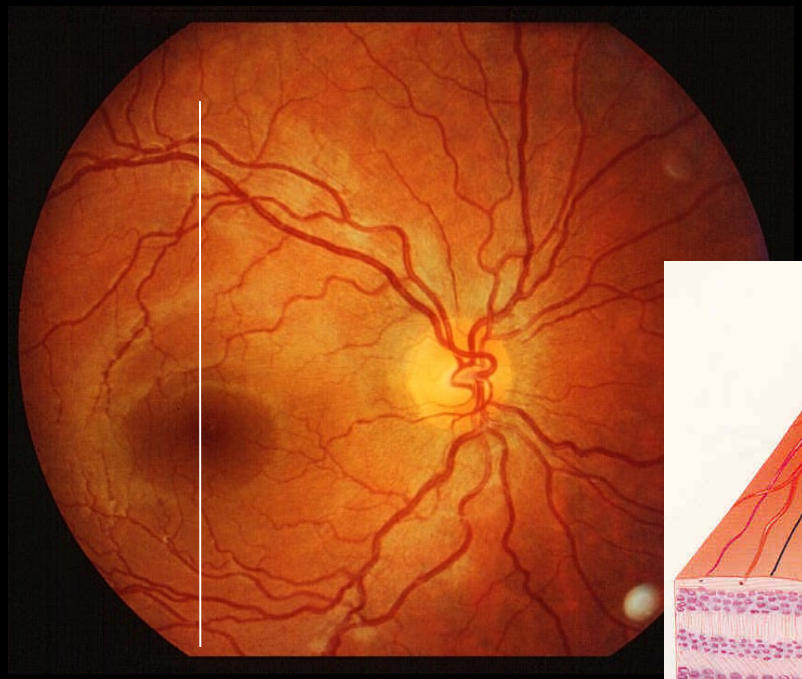


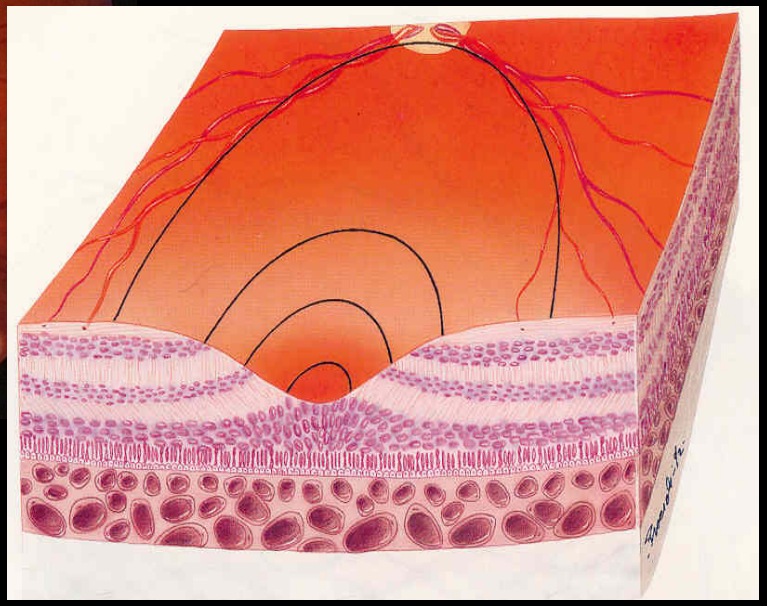


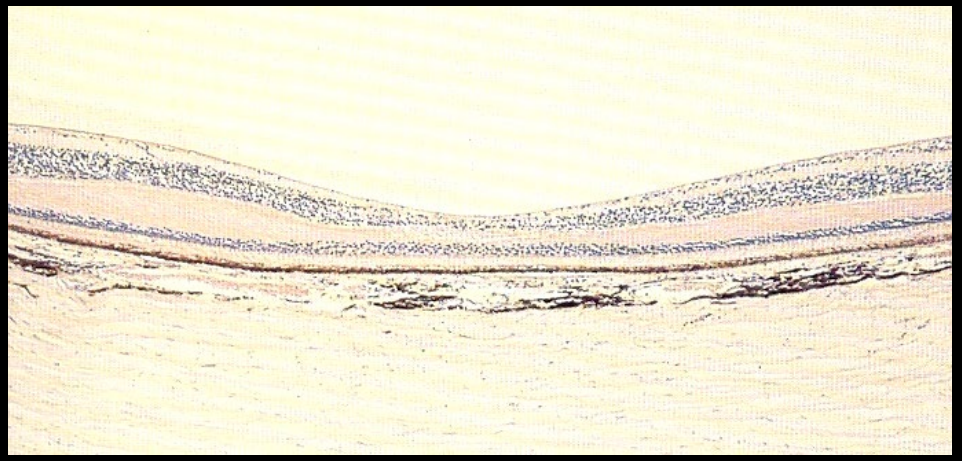




Partial coherent light is projected into the retina
The light scatter and reflects back from different layers of the vitreo-retina, retina and choroid

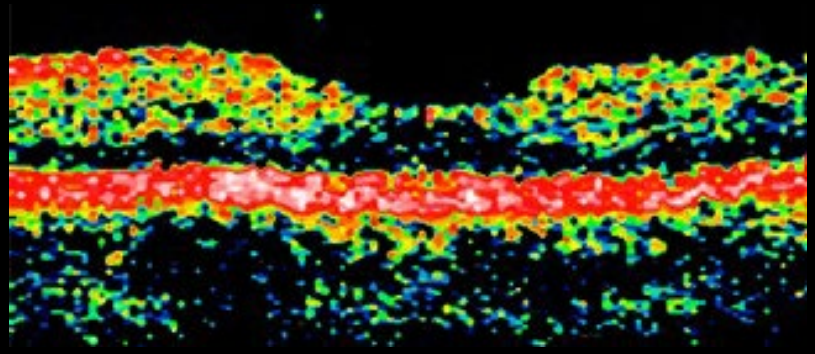




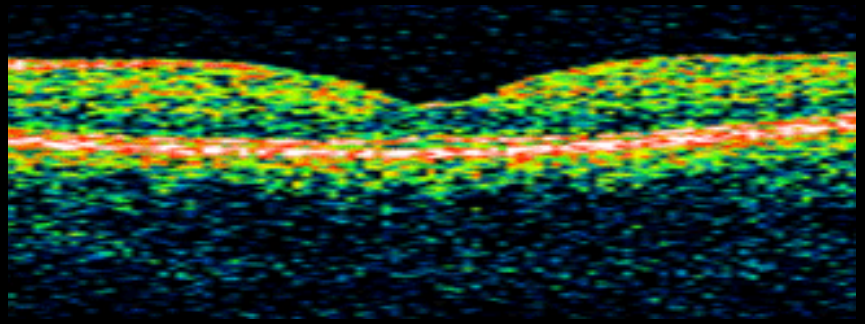



Focus: -1.28 D
Averaging 20 of 20
Scan angle: 29.2°

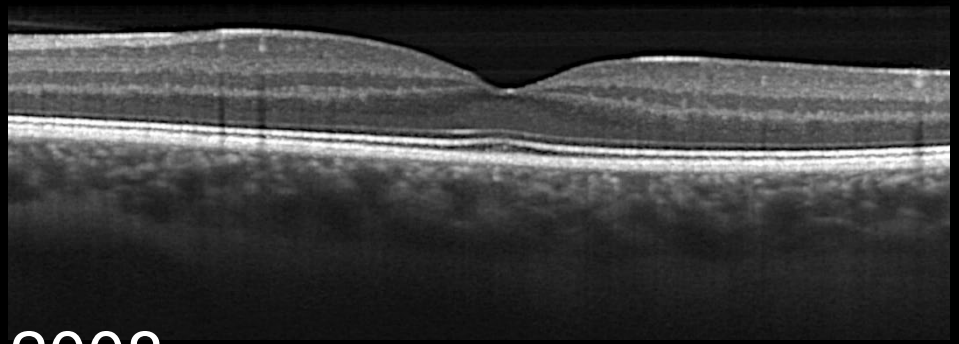
OCT has become progressively more focused since its introduction into clinical ophthalmology



1996

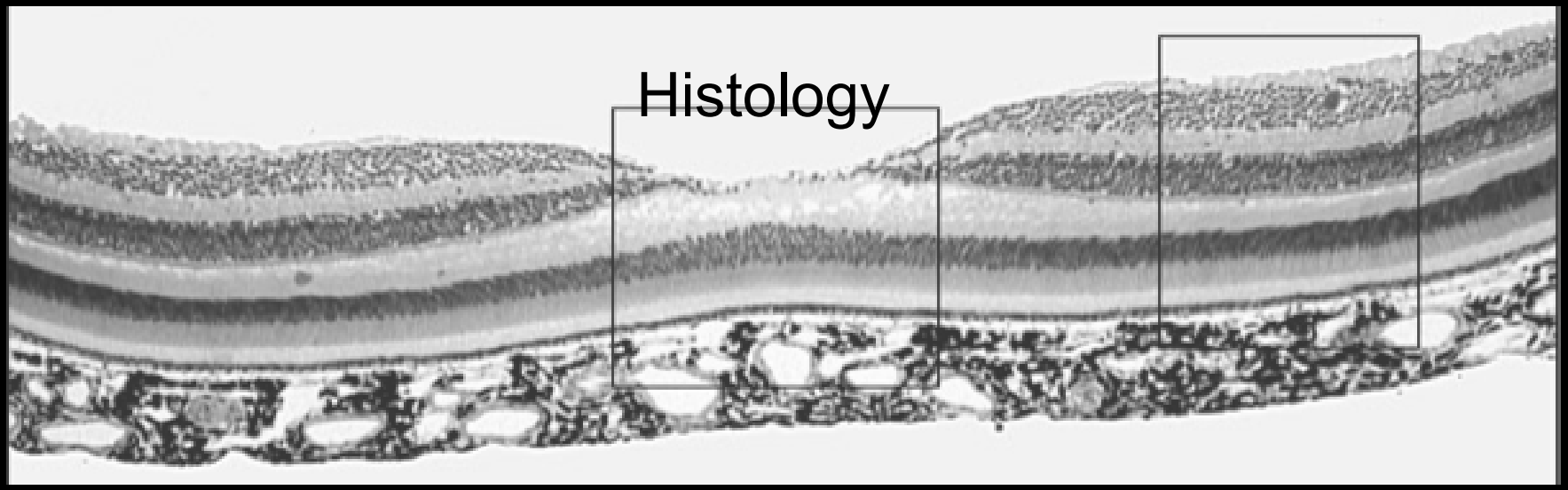


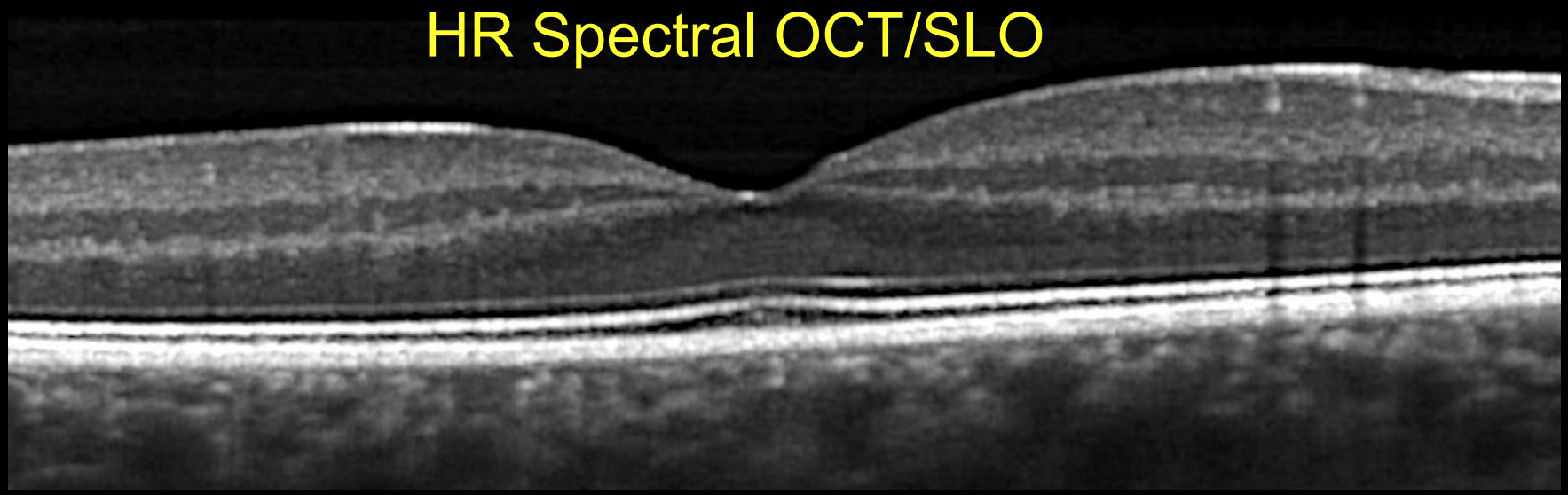
2001

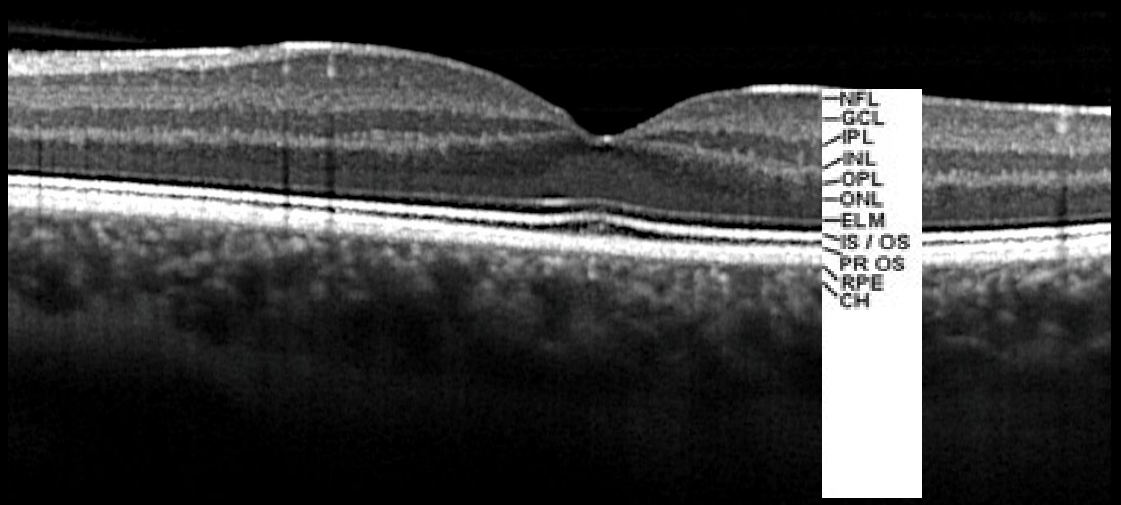


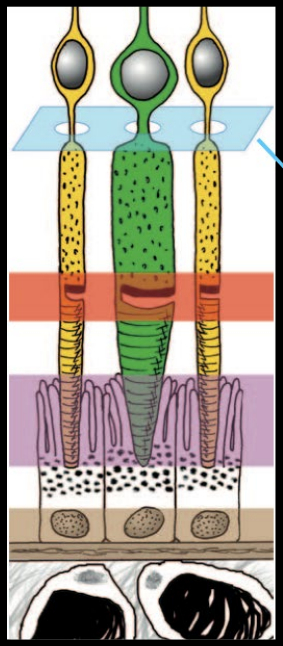
2008

Currently commercial OCTs map the macular anatomy to a level of detail approaching *in vivo* optical biopsy

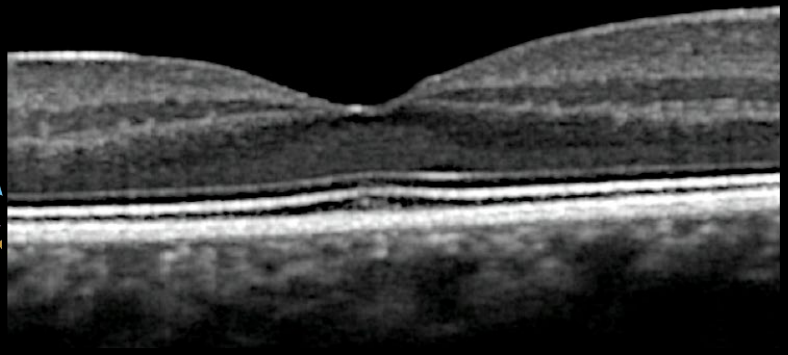








Outer Retinal Layers

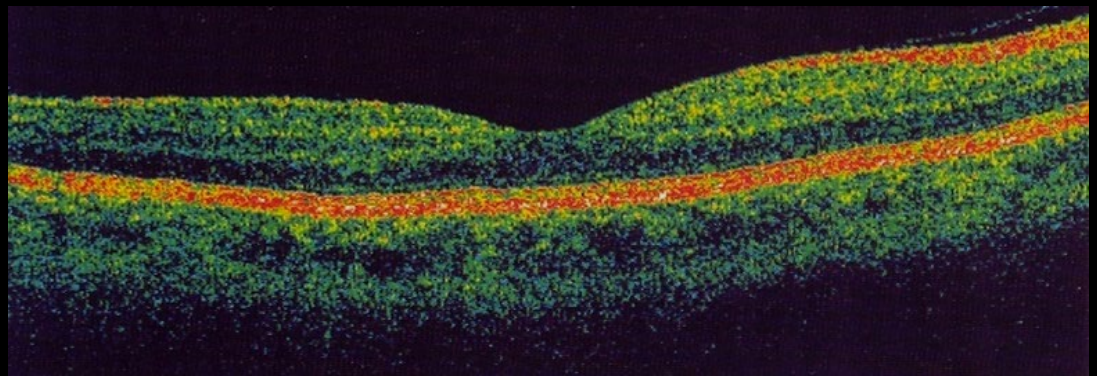


REFLETTIVITA' DI STRUTTURE F*ISIOLOGICHE*

ALTA:
Strato delle fibre nervose, membrana limitante esterna, giunzione SE/SI fotorecettori, EPR-coriocapillare

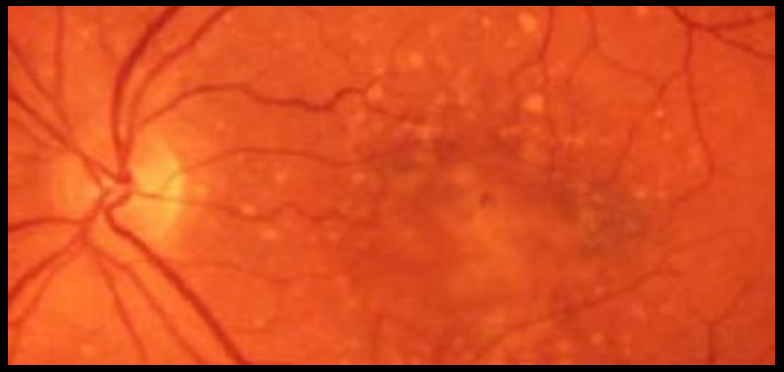
MEDIA:
Strati plessiformi interno ed esterno

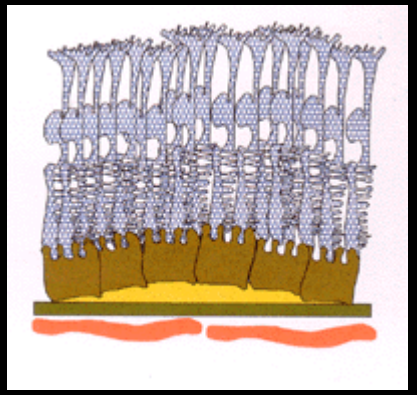
BASSA:
Strati nucleari interno ed esterno, fotorecettori

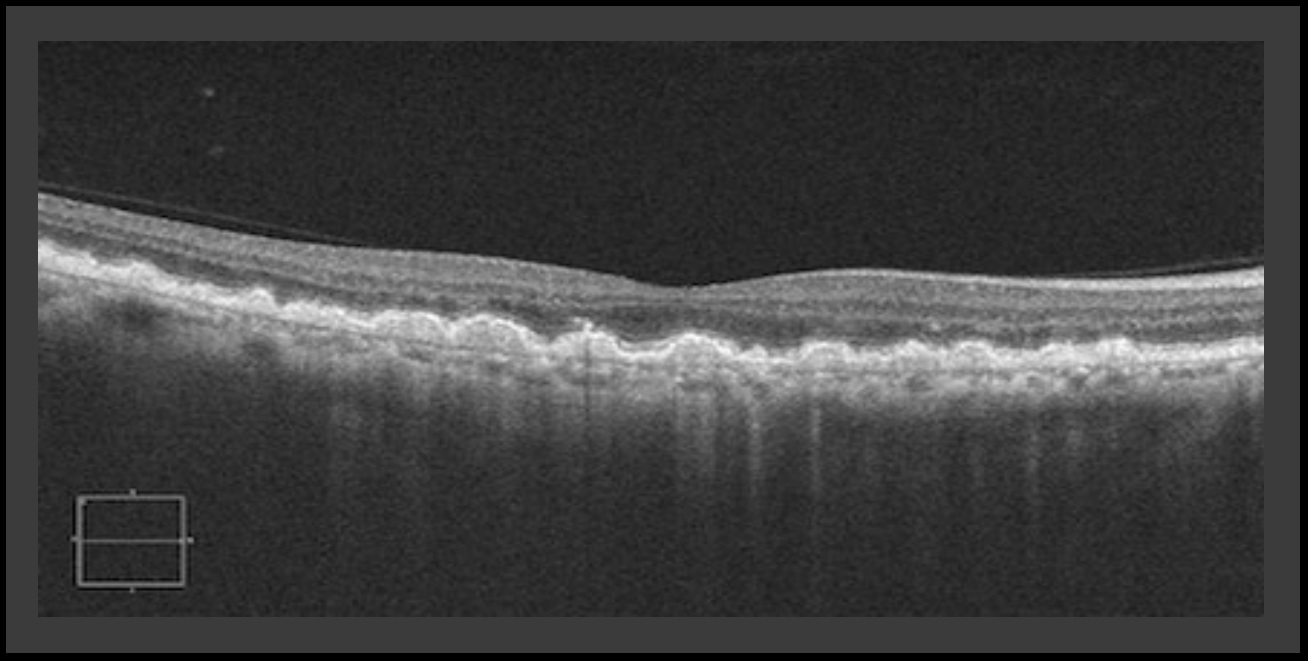


REFLETTIVITA' DI STRUTTURE PATOLOGICHE

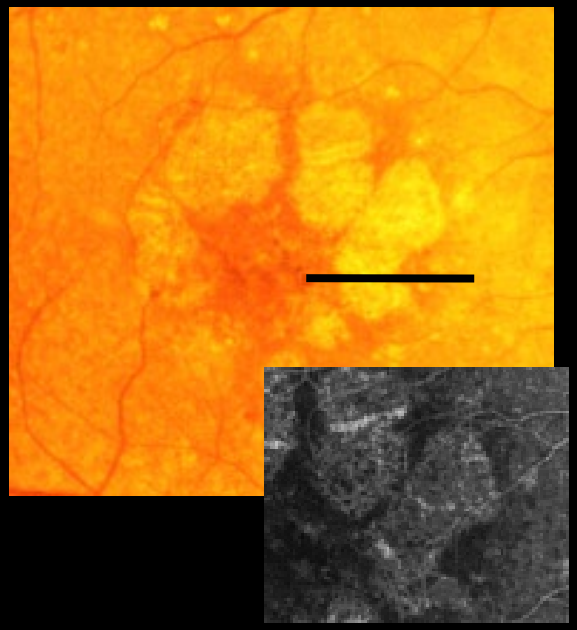
DRUSEN

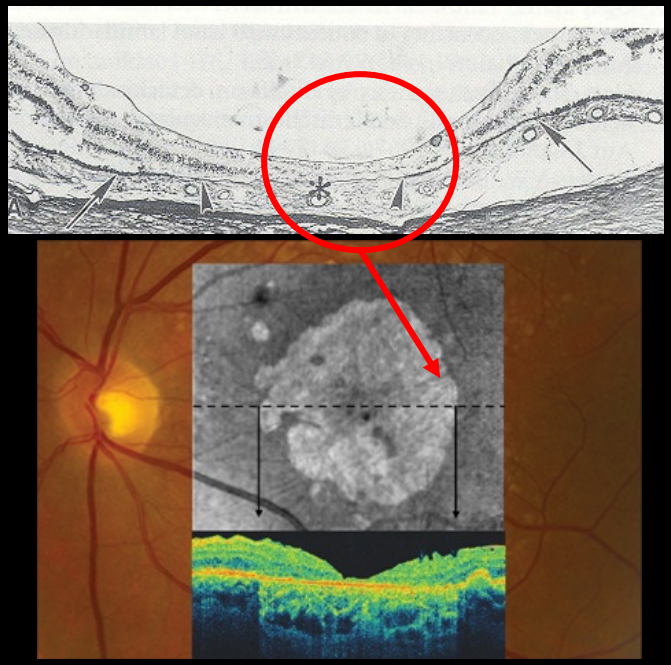


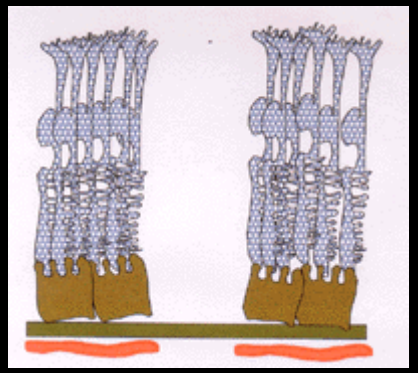




ATROFIA CORIORETINICA







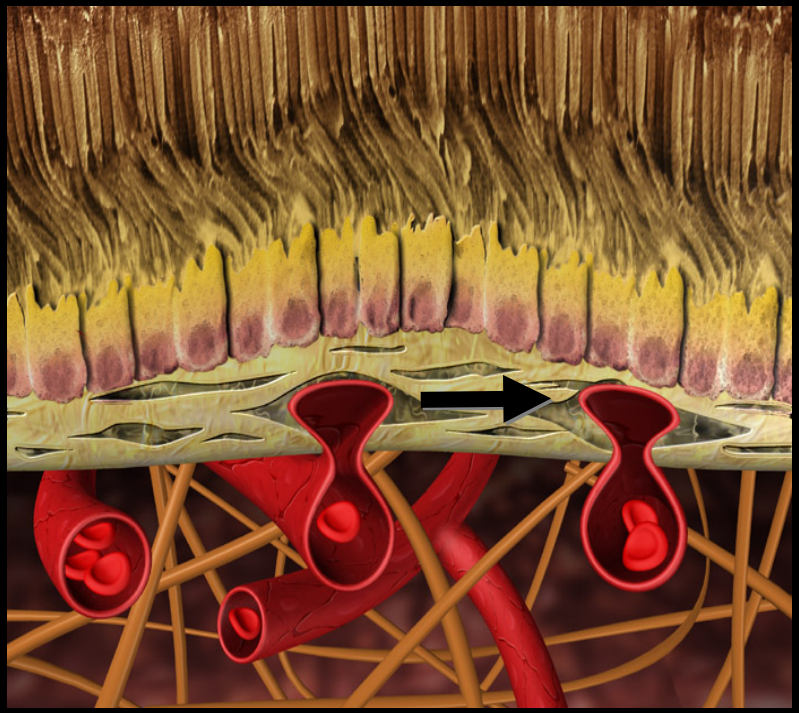
RIDUZIONE DI SPESSORE DI RETINA, EPR E CORIOCAPILLARE =

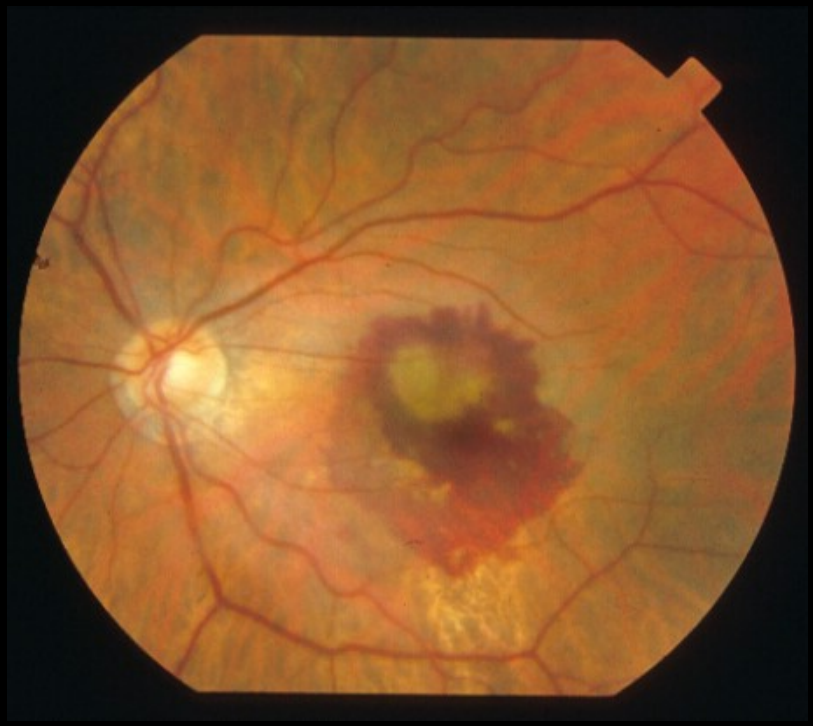
MINORE ATTENUAZIONE =

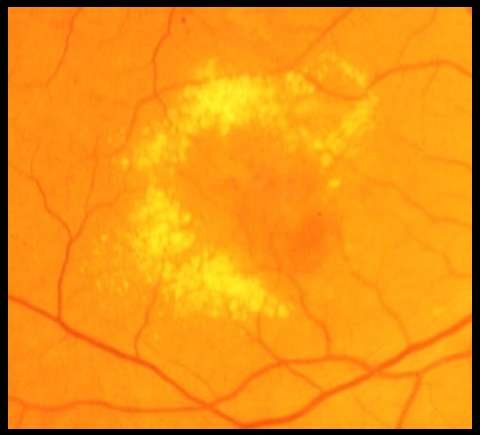
MAGGIORE ESPOSIZIONE COROIDEALE =

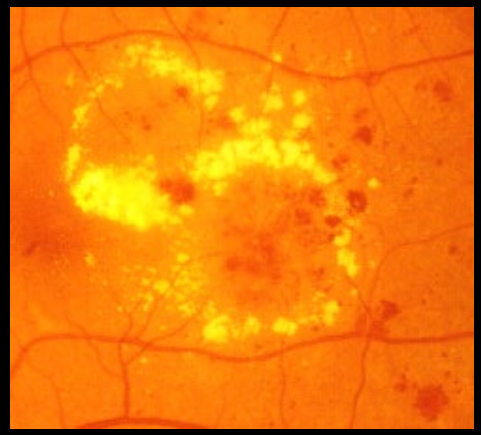
IPERREFLETTIVITA' + BACKSCATTERING

Neovascolarizzazione coroideale nella DMLE

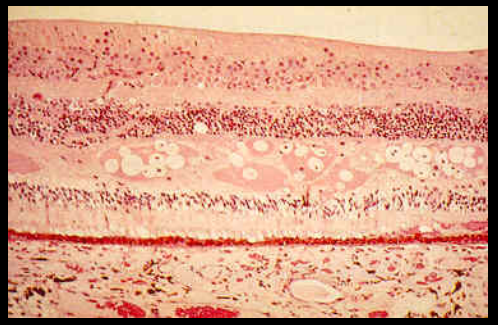


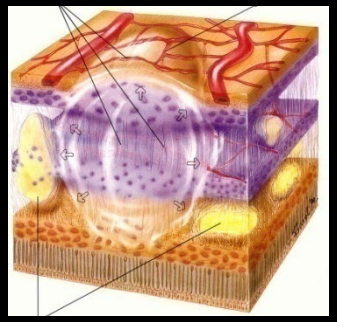


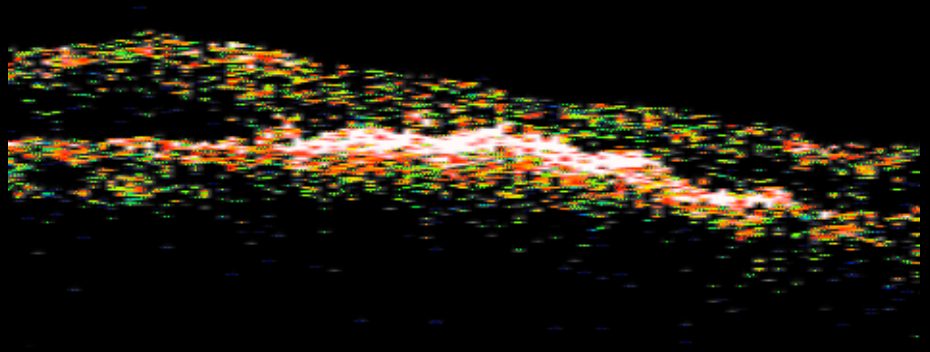


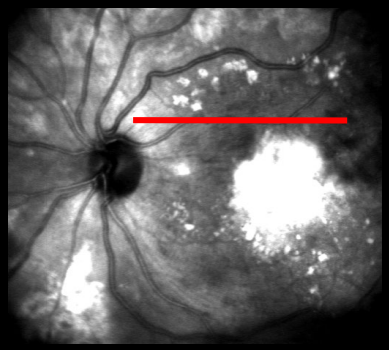


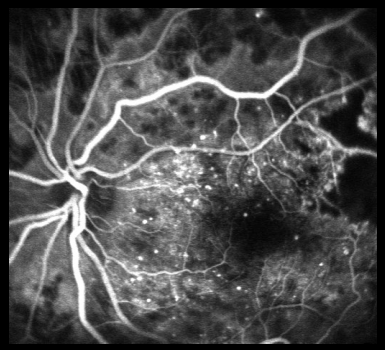
ESSUDATI DURI







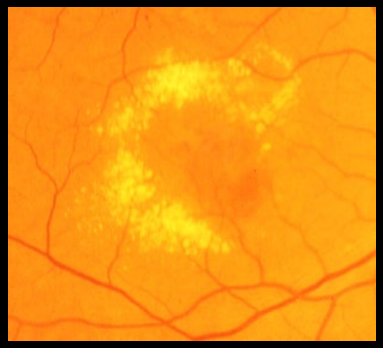


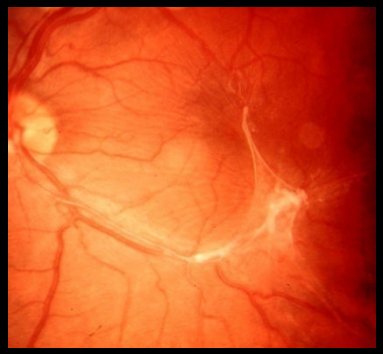


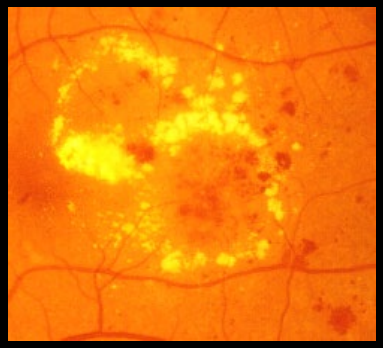
STRUTTURE INTRARETINICHE DENSE =

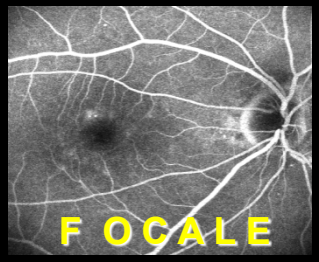
IPERRIFLETTIVITA' INTRARETINICA - EVENTUALE CONO D'OMBRA

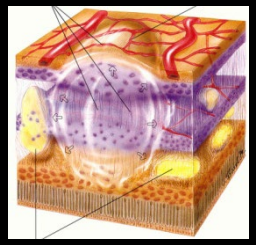
LIQUIDO *INTRA*RETINICO

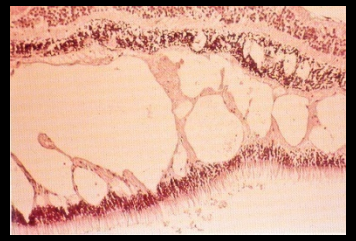


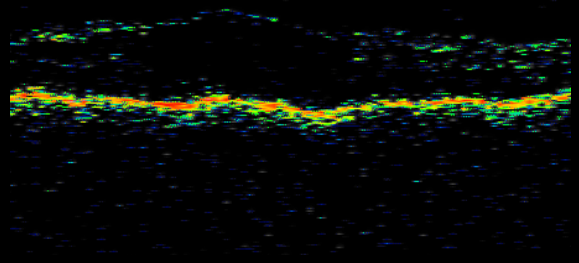


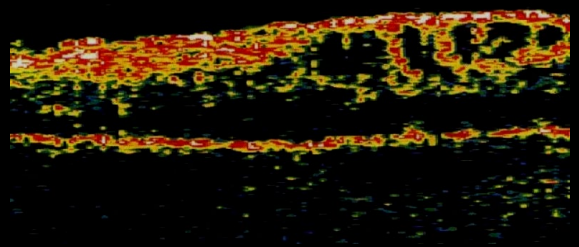


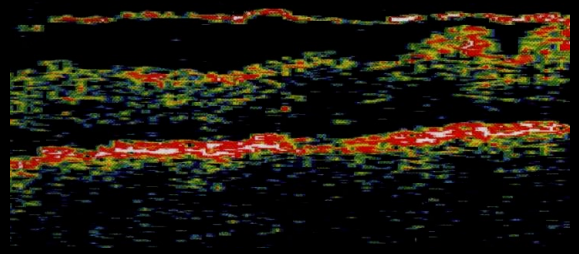












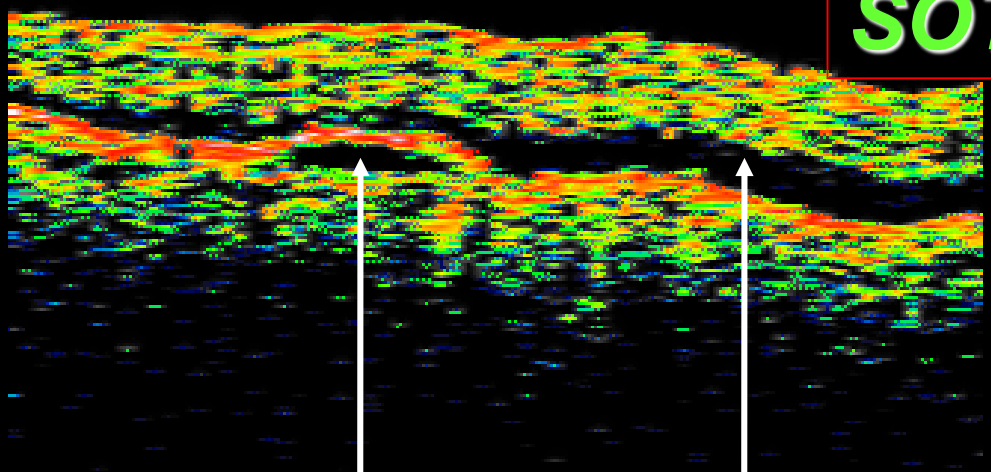
FLUIDO INTRARETINICO IPO-ARIFLETTENTE =

SPAZI VUOTI INTRARETINICI

CONSERVAZIONE DELLE CELLULE DI MULLER (EDEMA CISTOIDE) =

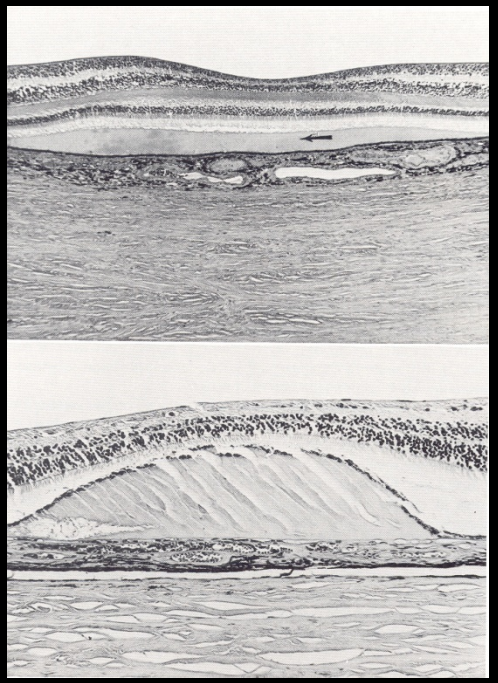
SEPIMENTAZIONE DEGLI SPAZI

LIQUIDO *SOTTONEURO*RETINICO



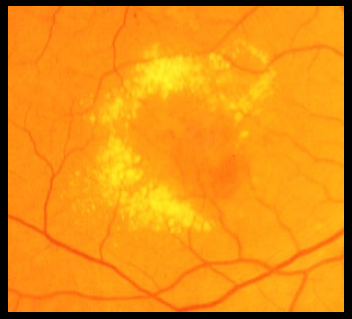
DISTACCO

DELL'EPR DEL NEUROEPITELIO

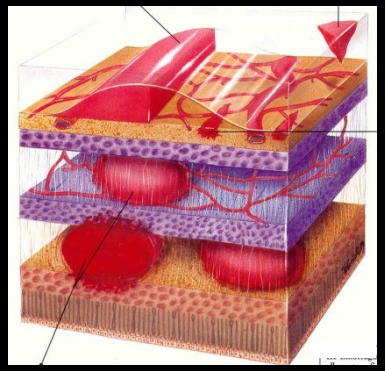


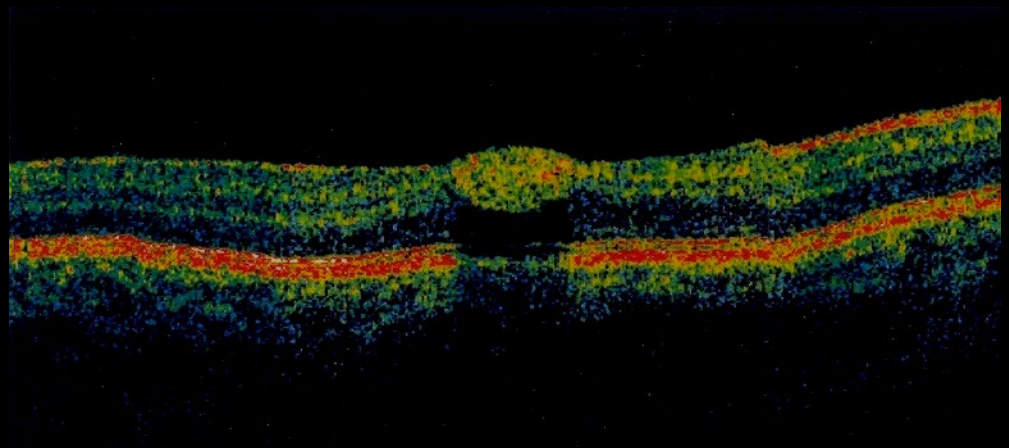
FLUIDO IPO-ARIFLETTENTE ***SOPRA*** LA BANDA IPERRIFLETTENTE =
DISTACCO NEUROEPITELIALE

FLUIDO IPO-ARIFLETTENTE ***SOTTO*** LA BANDA IPERRIFLETTENTE =
DISTACCO DELL'EPR (tendenzialmente cupoliforme)



EMORRAGIA





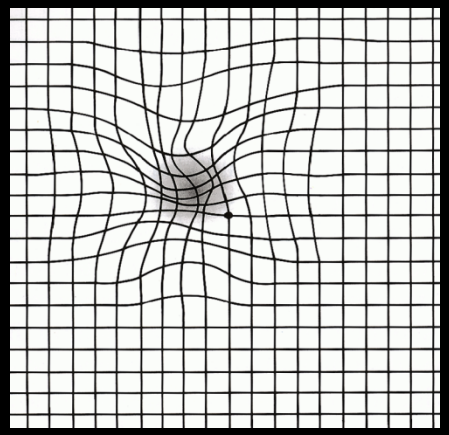
EMOGLOBINA - ELEVATA DENSITA' =

IPERREFLETTIVITA' CON CONO D'OMBRA

Degenerazione maculare legata all'età (DMLE)

Raccolta attenta dei segni e sintomi riferiti dal paziente:

- Riduzione visiva

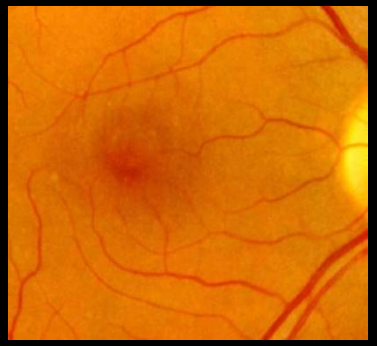


- Metamorfopsie

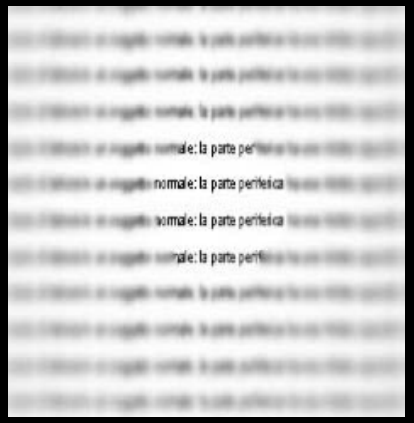
- Scotoma campo visivo centrale

Degenerazione maculare legata all'età (DMLE)

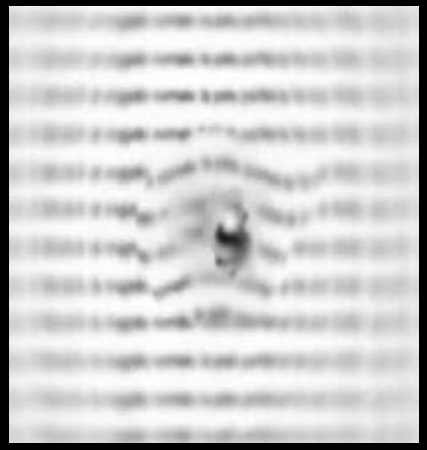
Scotoma campo visivo centrale



Visione normale di un testo: solo la regione maculare riconosce i dettagli più piccoli



La cicatrice maculare dovuta alla neovascolarizzazione corideale causa una macchia o scotoma centrale e distorsione dell'immagine.



EZIOPATOGENESI

Fattori genetici

Fattori ambientali

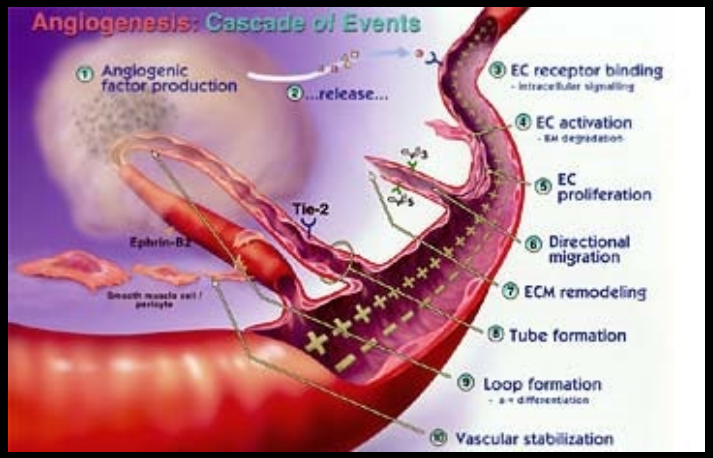
Invecchiamento

Radicali liberi

Alterato metabolismo fotorecettori e EPR

Fattori flogogeni

Formazione delle drusen



CNV

Alterato equilibrio fattori angiogenici

- **Ereditarietà DMLE: 46%**
- **Ereditarietà DMLE evoluta: 71%**

Seddon, 2005

Fumo di sigaretta

- Aumenta fino a 2.4 volte il rischio (fumatori > 25 sigarette/die)
- Stress ossidativo
- Riduce pigmento maculare
- Danno microcircolo

Hisayama Study 2005
AREDS report n.19 2005
Blue Mountains Eye Study 2002
AREDS report n. 3 2000
Physicians' Health Study 1996
Nurses' Health Study 1995-1996

Fattori nutrizionali

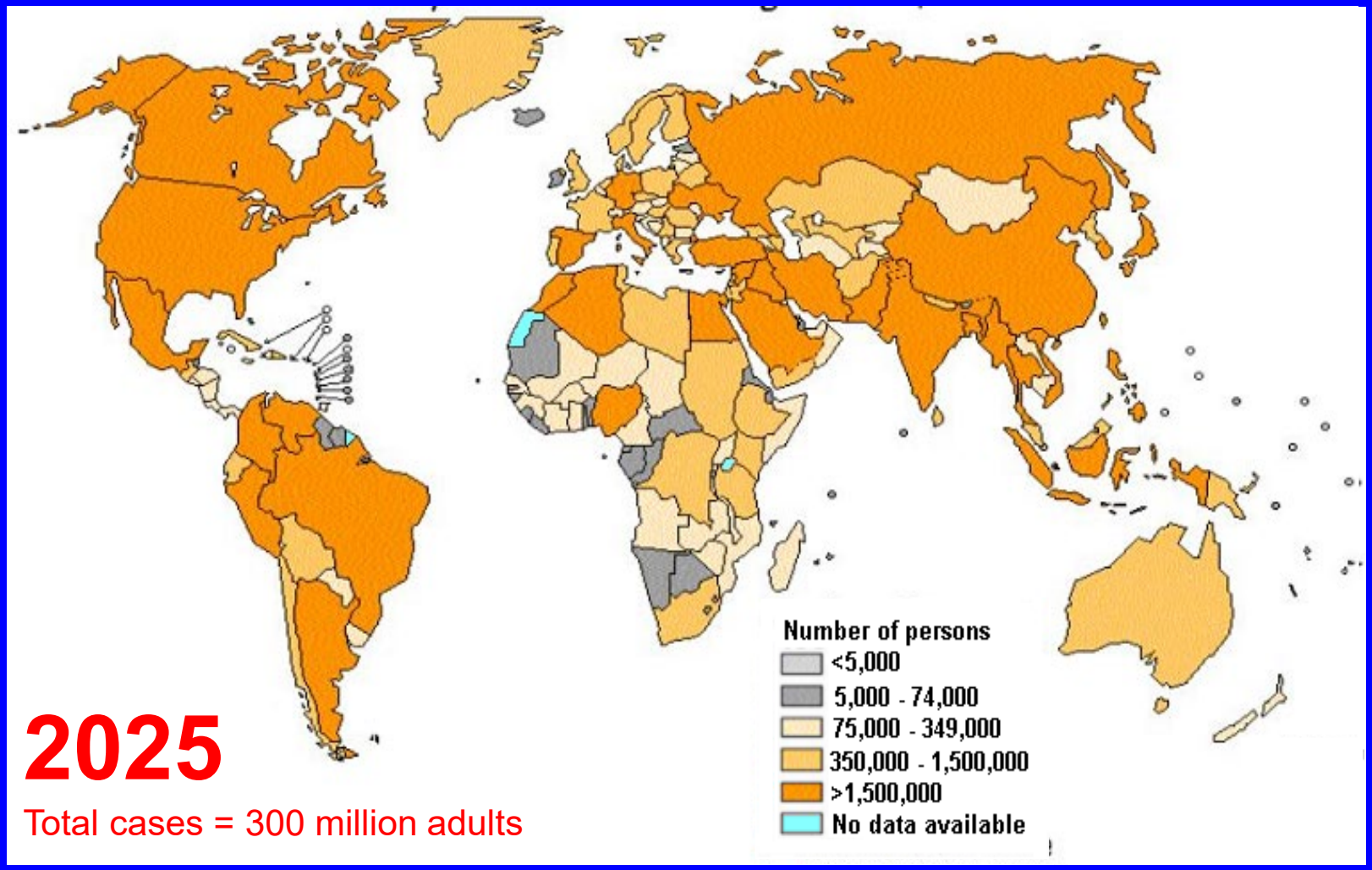
- Elevato introito di grassi aumenta fino a 2.9 volte il rischio di progressione DMLE
- Pesce e frutta secca riducono rischio
- Obesità associata a progressione DMLE
- Stress ossidativo
- Infiammazione
- Ruolo antiossidanti

AREDS report n.19 2005
Seddon 2003
AREDS report n. 3 2000

La Retinopatia Diabetica

Nel nostro paese la retinopatia diabetica rappresenta la principale complicanza oculare del diabete mellito, e la maggiore causa di cecità nella popolazione in età lavorativa

Stima di crescita (nel mondo) dei diabetici entro il 2025



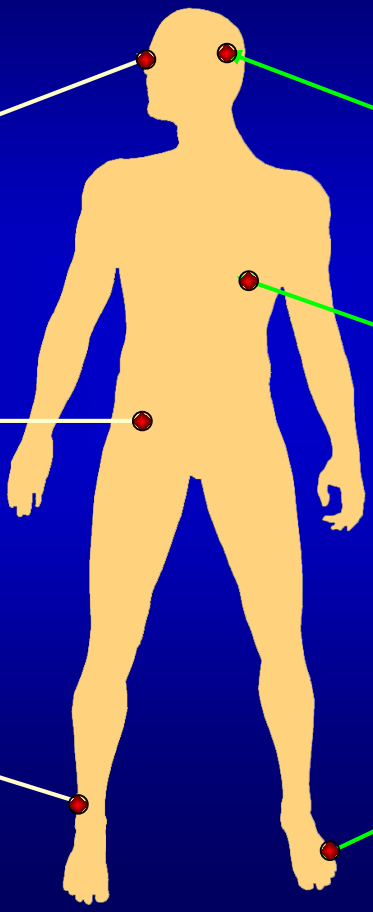
World Health Organisation. The World Health Report: life in the 21st century, a vision for all. Geneva: WHO, 1998

Il diabete è causa di gravi complicanze invalidanti che coinvolgono principalmente occhio, rene, sistema nervoso periferico e sistema cardio-circolatorio

(Microangiopatia e Macroangiopatia)

Microangiopatia

Macroangiopatia



Retinopatia

Nefropatia

Neuropatia

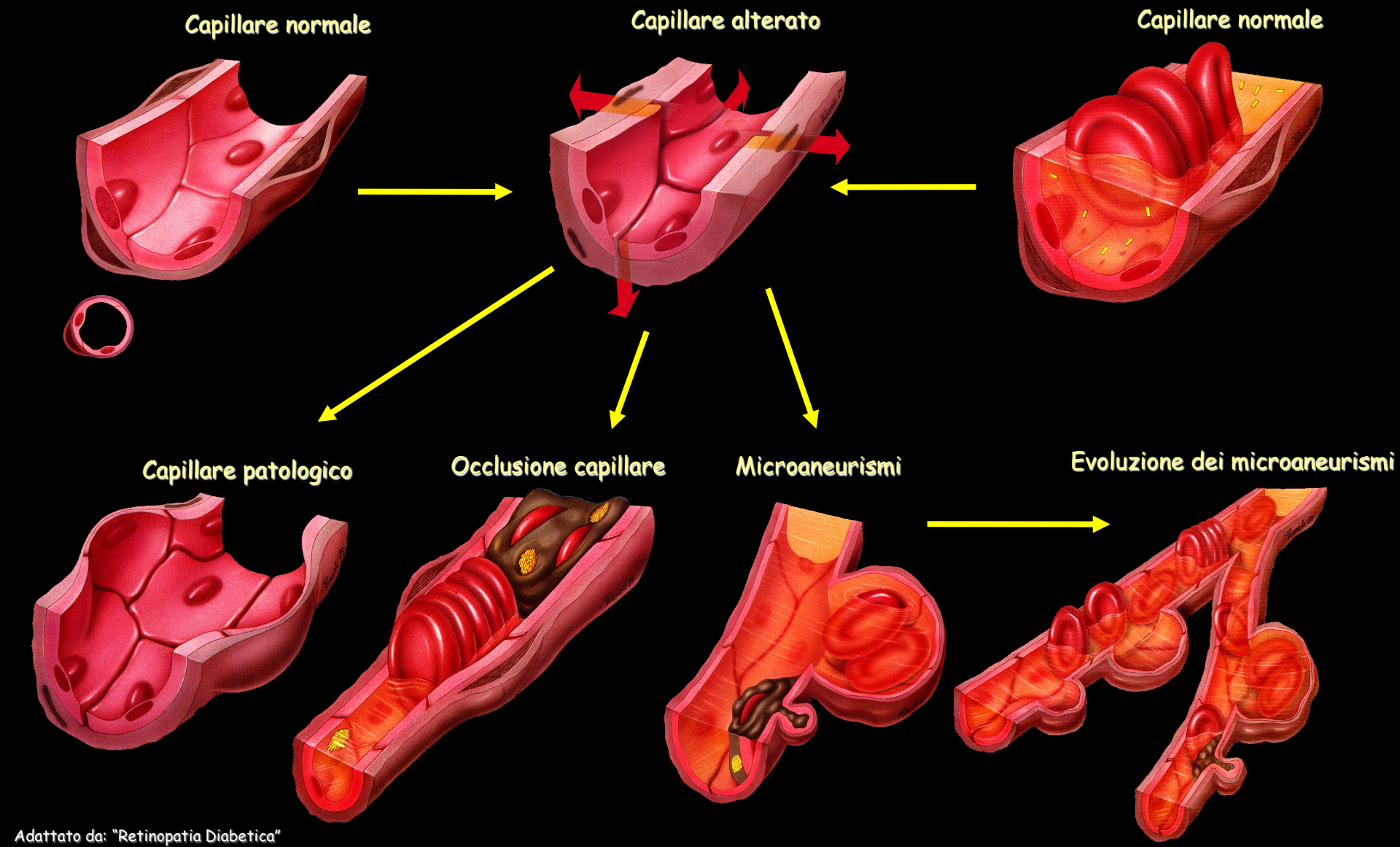
Malattie cerebro vascolari

Coronaropatie

Vasculiti periferiche

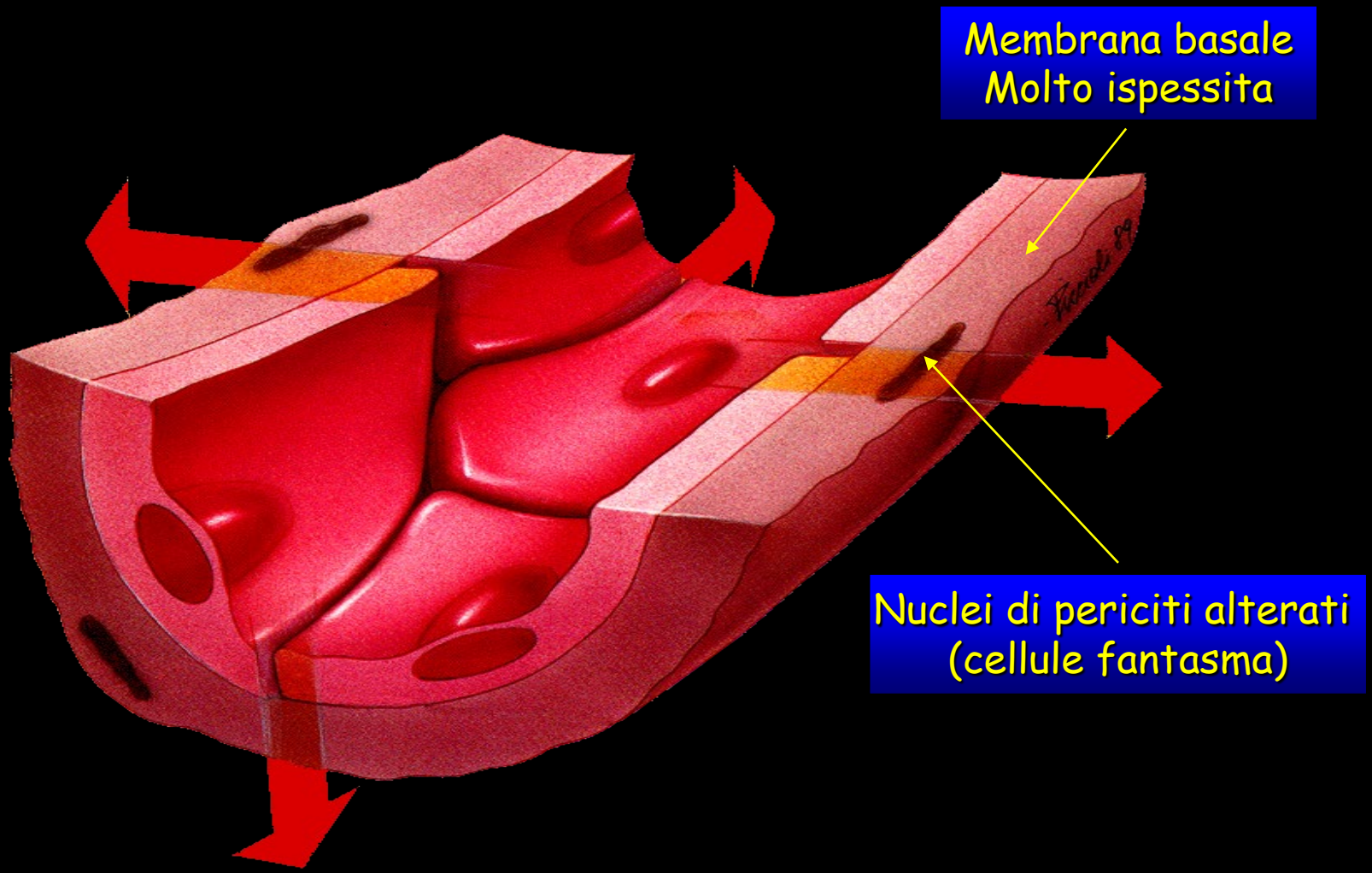
The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2001; **24** (Suppl. 1): S5-S20

Lesioni dei capillari



Adattato da: "Retinopatia Diabetica"
Del Prof. B. Lumbroso

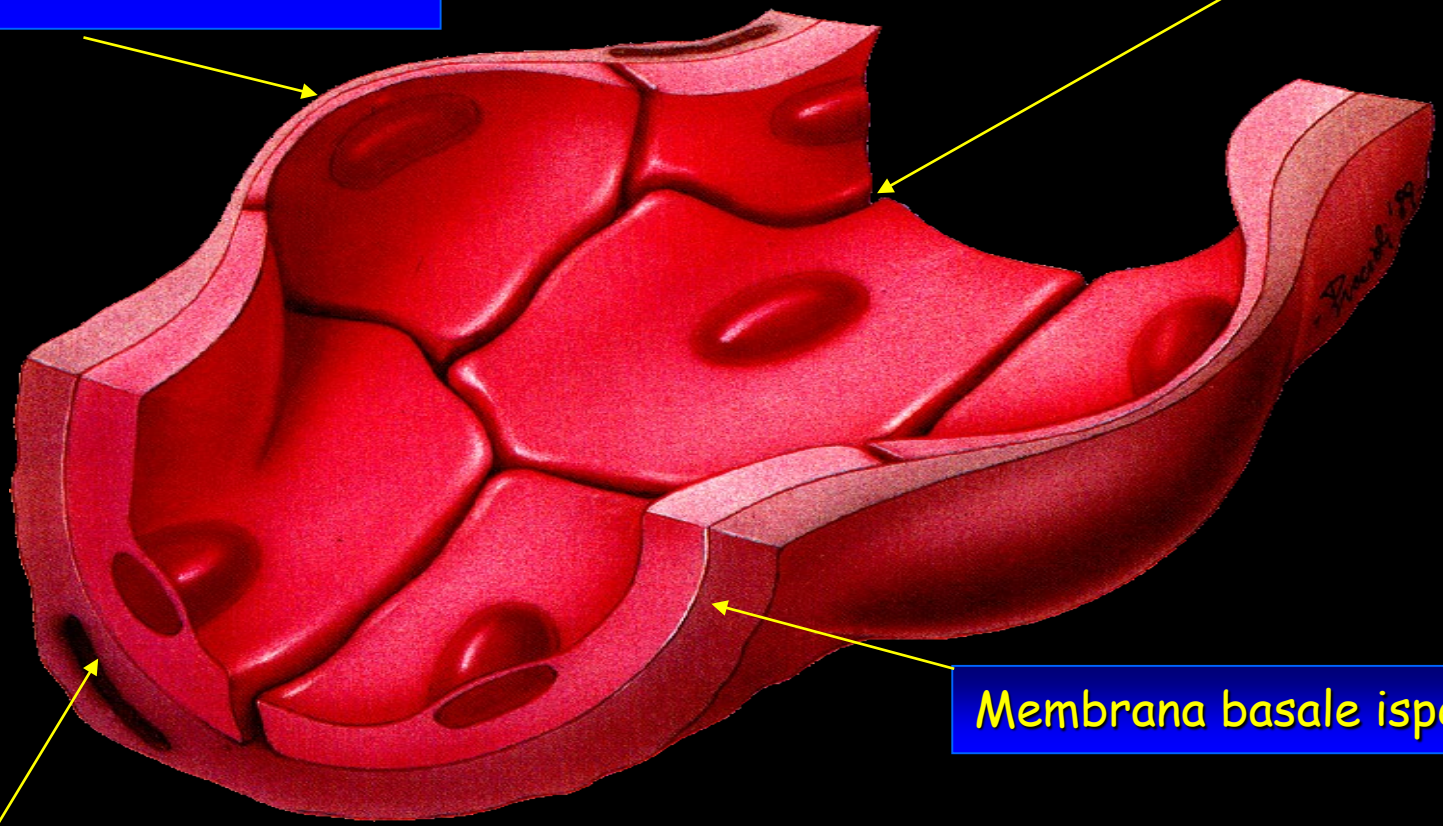
Capillare alterato



Capillare patologico

Sfiancamento delle pareti del capillare con formazione di microaneurismi

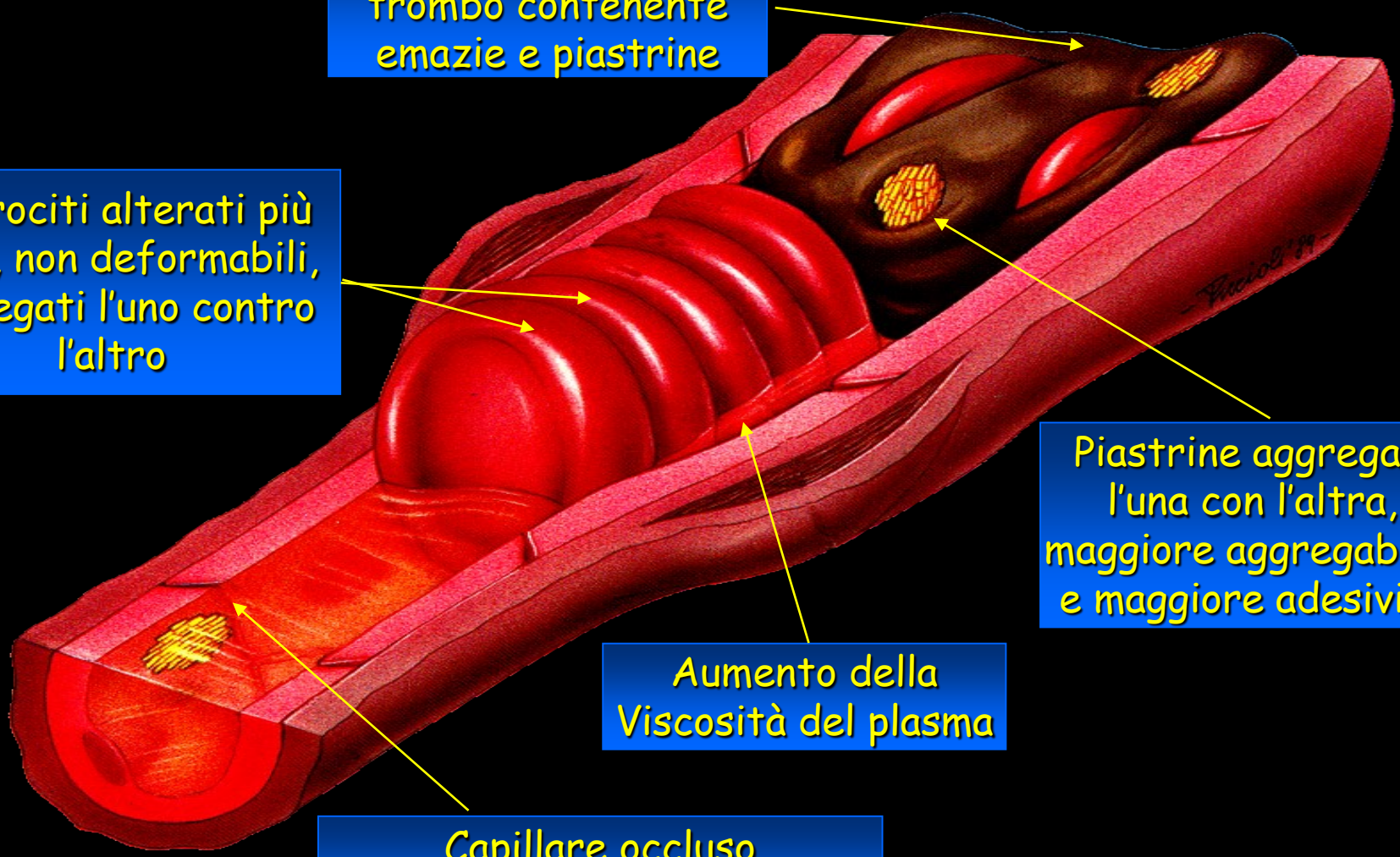
Alterazioni delle connessioni fra le cellule endoteliali con danni della barriera emato-retinica



Membrana basale ispessita

Nuclei alterati

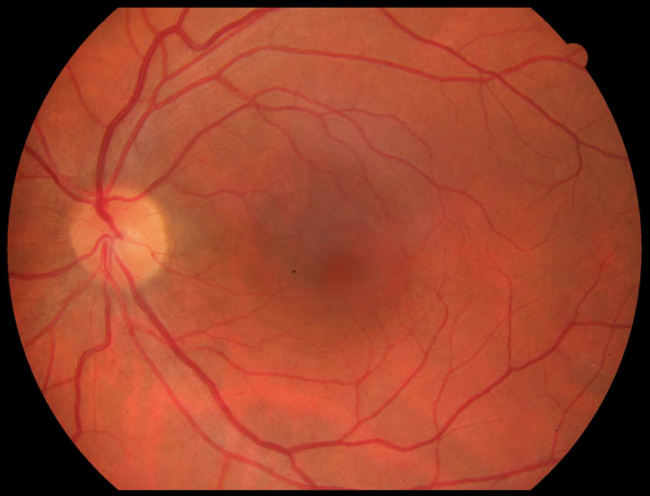
Occlusione capillare



Retinopatia diabetica

Alterazione dell'autoregolazione del flusso sanguigno (presente nei soggetti con DM anche senza RD)

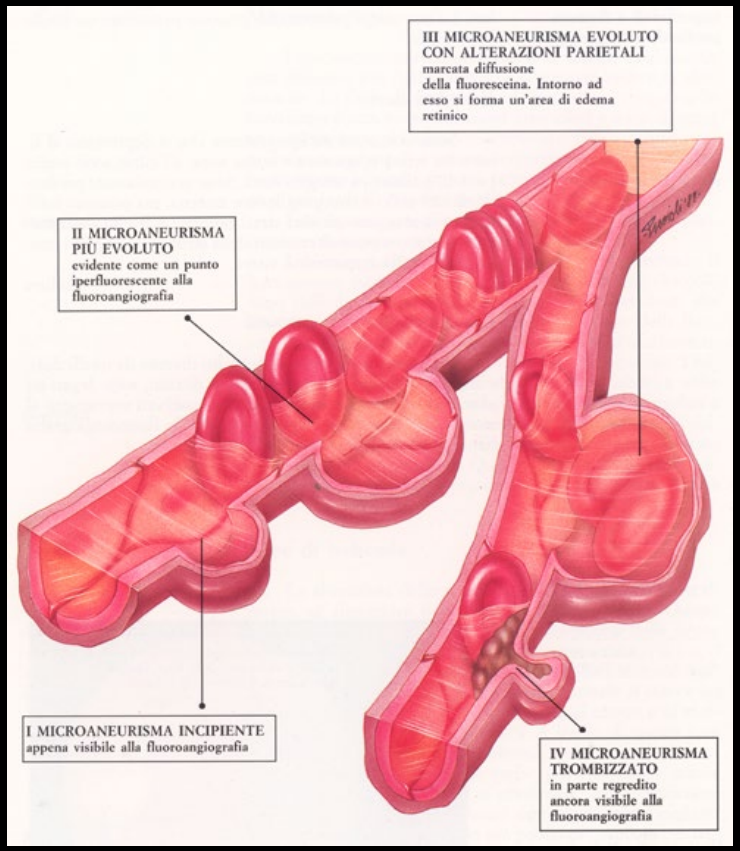
per perdita della funzionalità dei periciti.



Retinopatia diabetica

non proliferante

microaneurismi

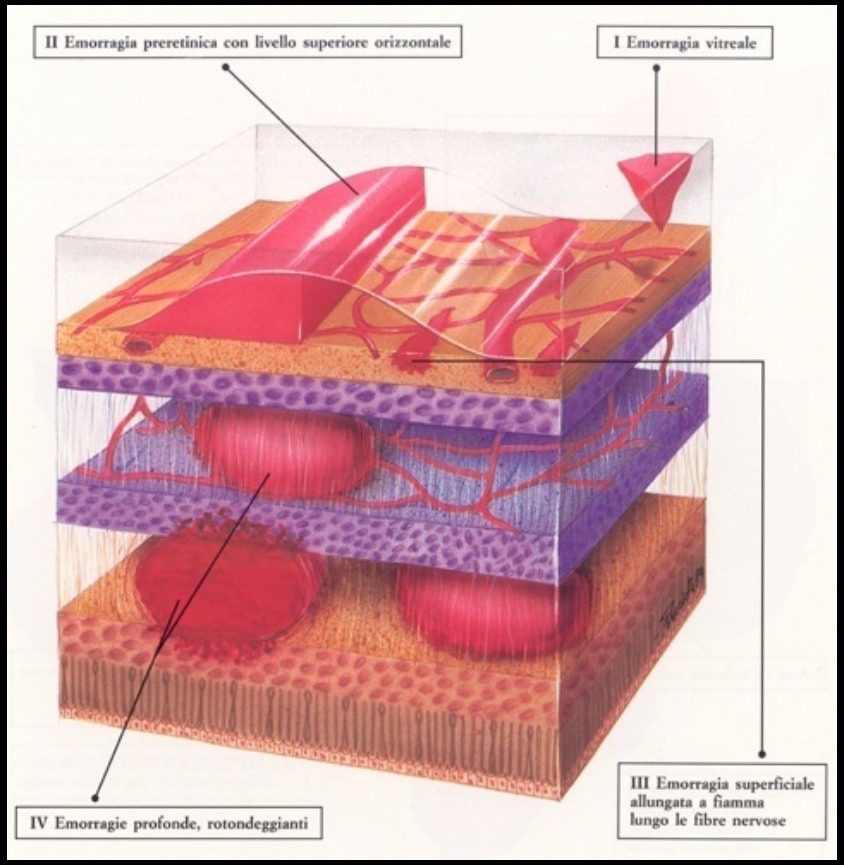


Retinopatia diabetica

non proliferante

microaneurismi

microemorragie



Retinopatia diabetica

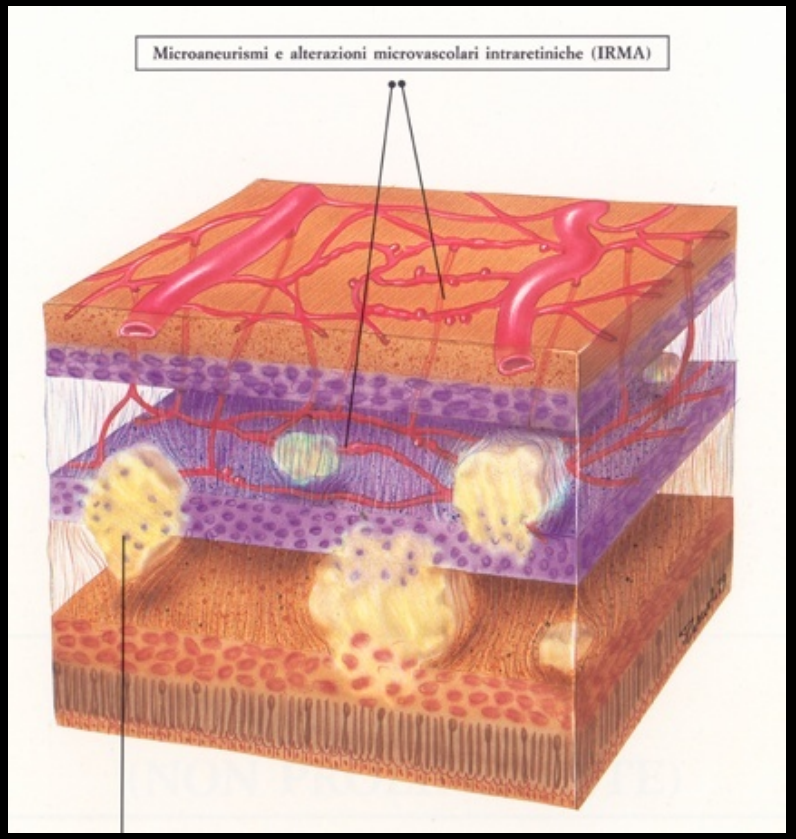
non proliferante

microaneurismi

microemorragie

essudati duri

IRMA



Retinopatia diabetica

non proliferante

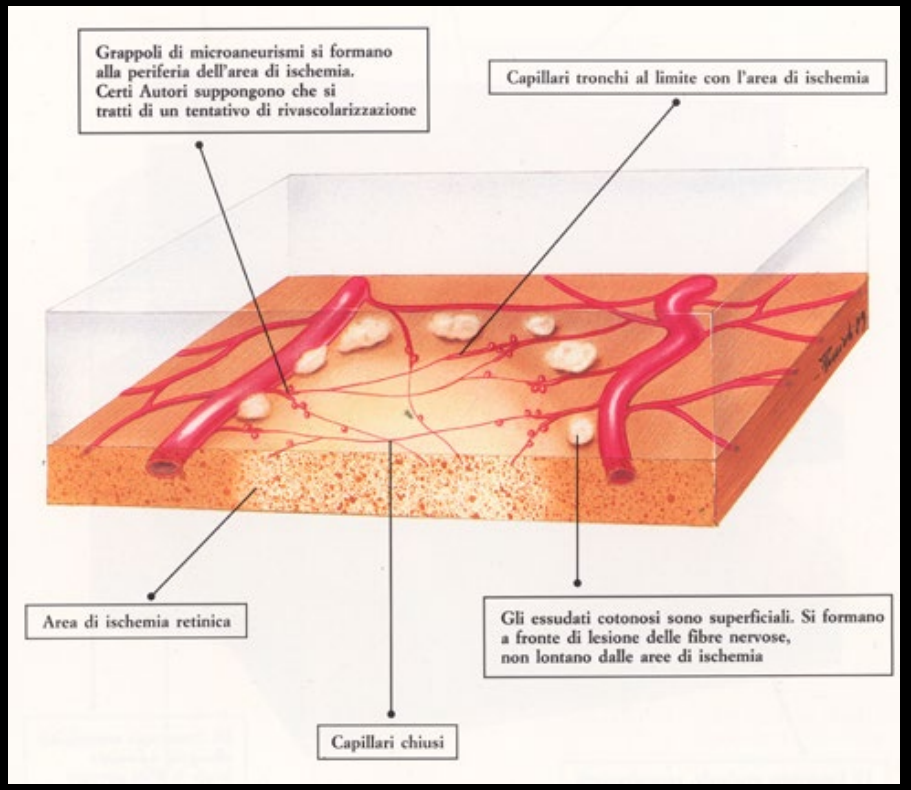
microaneurismi

microemorragie

essudati duri

IRMA

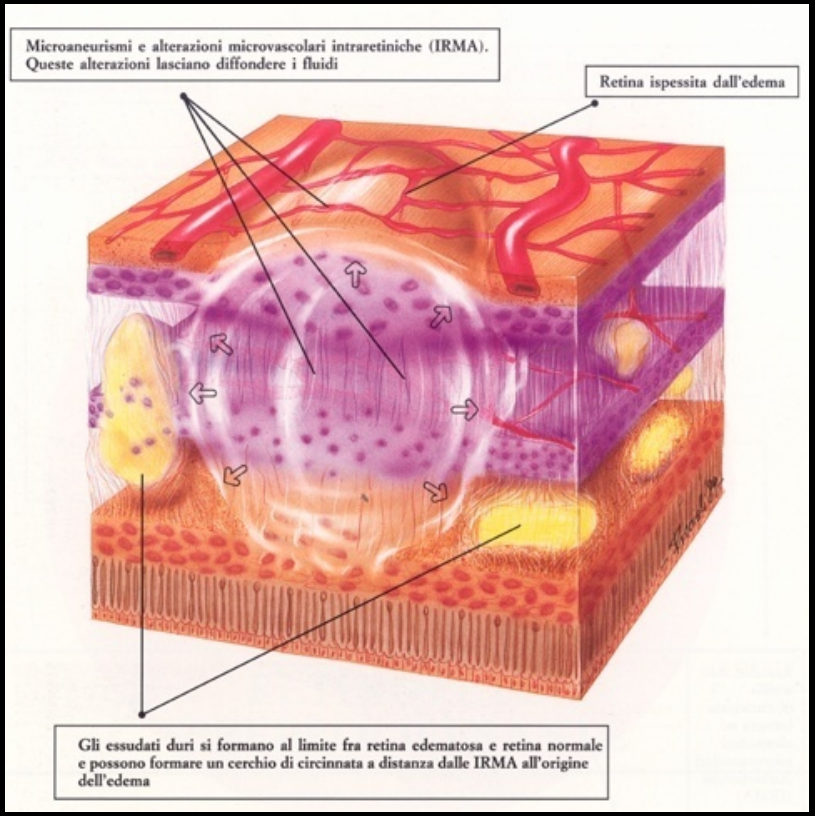
noduli cotonosi



Retinopatia diabetica

non proliferante

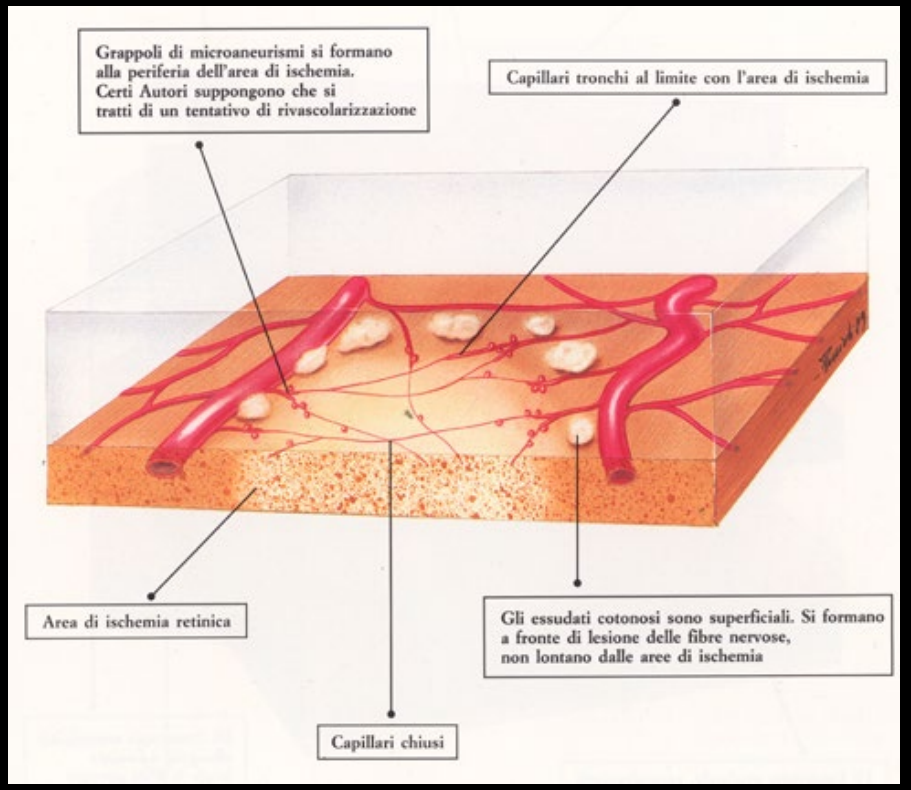
maculopatia edematosa



Retinopatia diabetica

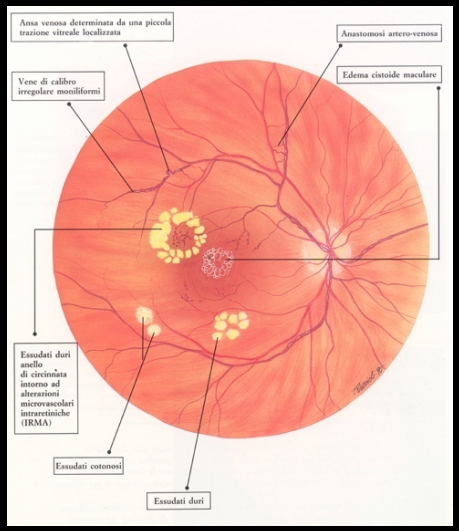
non proliferante

maculopatia ischemica



Retinopatia diabetica

non proliferante



i piccoli vasellini della retina diventano deboli, fragili, permeabili e tendono ad occludersi

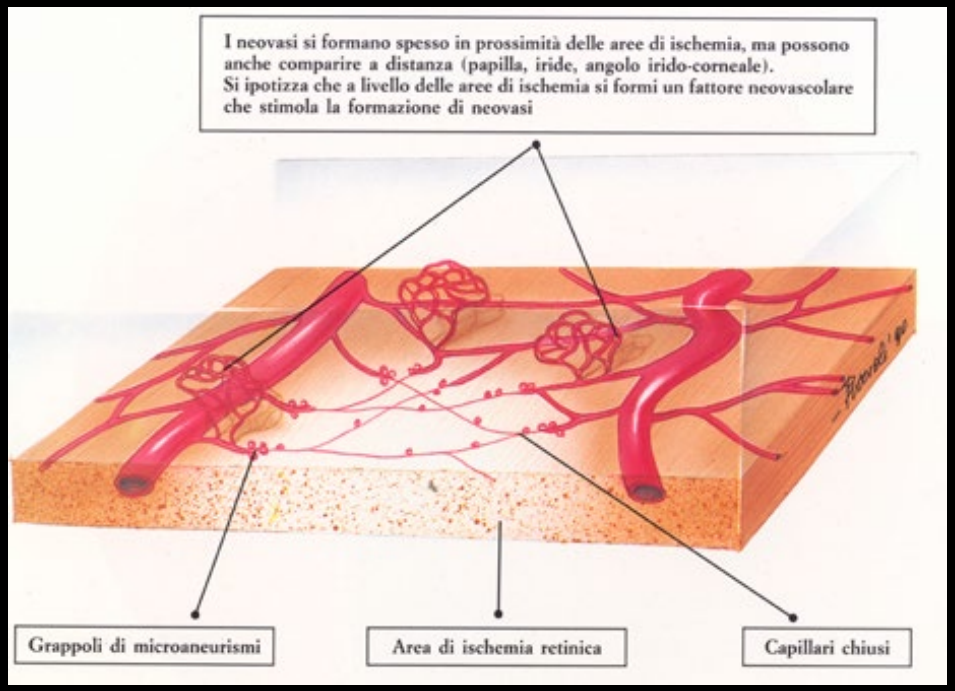
quando si occludono creano aree ischemiche cioè poco irrorate dal sangue e dall'ossigeno

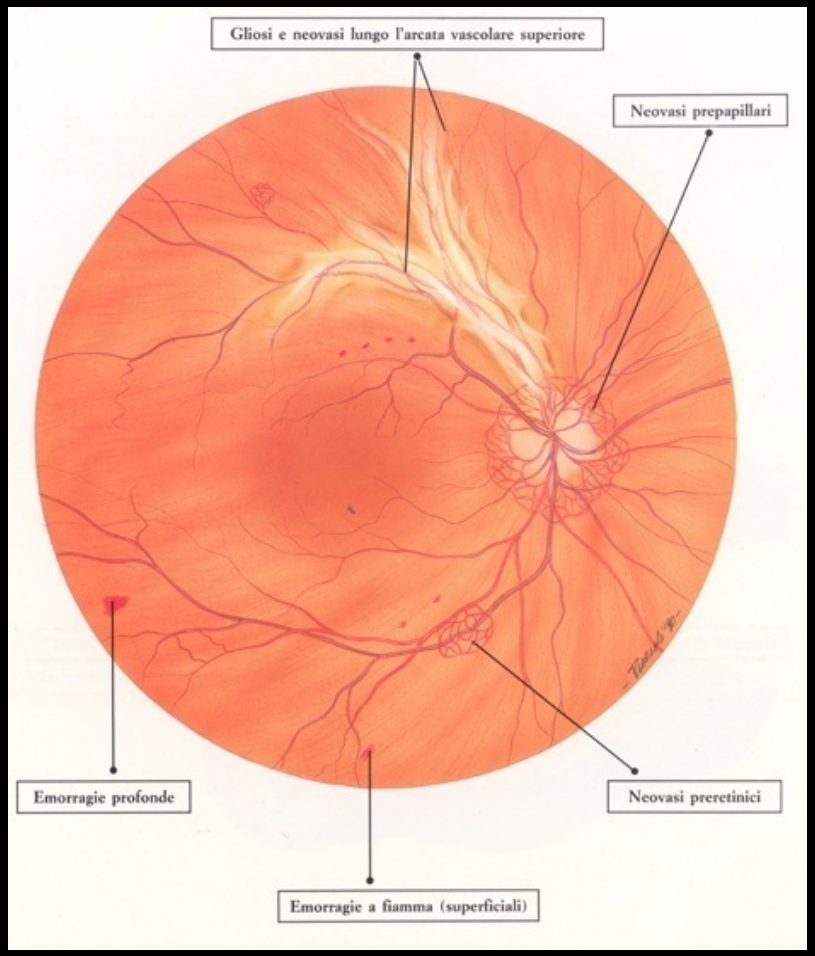
la retina quindi per mantenere la circolazione crea dei nuovi vasi passando al quadro di:

Retinopatia diabetica

proliferante

neovasi



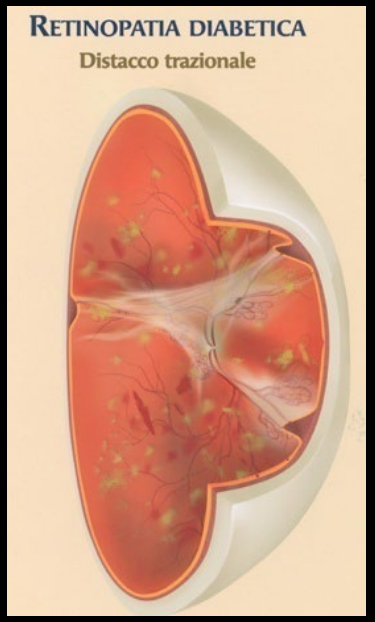


Retinopatia diabetica

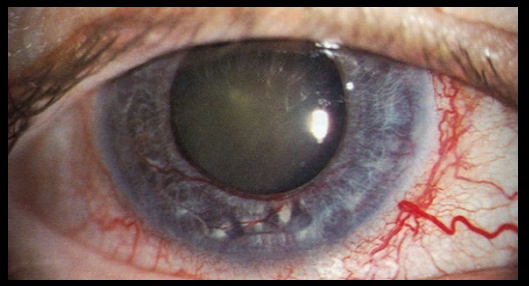
proliferante

i neo-vasi sono fragili e tendono a sanguinare (emovitreo)

possono “tirare” il tessuto retinico creando un distacco di retina



possono causare un glaucoma neovascolare



International Clinical Diabetic Retinopathy Disease Severity Scale

Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild nonproliferative diabetic retinopathy	Microaneurysms only
Moderate nonproliferative diabetic retinopathy	More than just microaneurysms but less than severe NPDR
Severe nonproliferative diabetic retinopathy	Any of the following: More than 20 intraretinal hemorrhages in each of four quadrants Definite venous beading in two or more quadrants Prominent IRMA in one or more quadrants and no signs of proliferative retinopathy.
Proliferative diabetic retinopathy	One or both of the following: Neovascularization Vitreous/preretinal hemorrhage

Proposed **international clinical diabetic retinopathy and diabetic macular edema disease severity scales**

Ophthalmology *Volume 110, Number 9, September 2003*

Classificazione della retinopatia diabetica (RD)

- Assenza di RD
- RD non proliferante
  - Lieve
  - Moderata
  - Avanzata (o grave o pre-proliferante)
- RD proliferante
- Oftalmopatia diabetica avanzata

Rubeosi dell'iride
Glaucoma neovascolare
Proliferazione neovasi nel vitreo

Maculopatia

- Edema maculare non clinicamente significativo
- Edema maculare clinicamente significativo
- Maculopatia ischemica

Adapted from Bandello F., L'Oculista Italiano

Diagnostica della retinopatia diabetica

Una volta individuati i pazienti che necessitano di approfondimento diagnostico oftalmologico (mediante uno screening mirato), si rende necessaria l'esecuzione di una visita oculistica completa e, qualora si vogliano documentare le lesioni iniziali che caratterizzano la retinopatia, è indicata l'esecuzione di fotografie a colori o in bianco e nero del fondo oculare (retinografia)

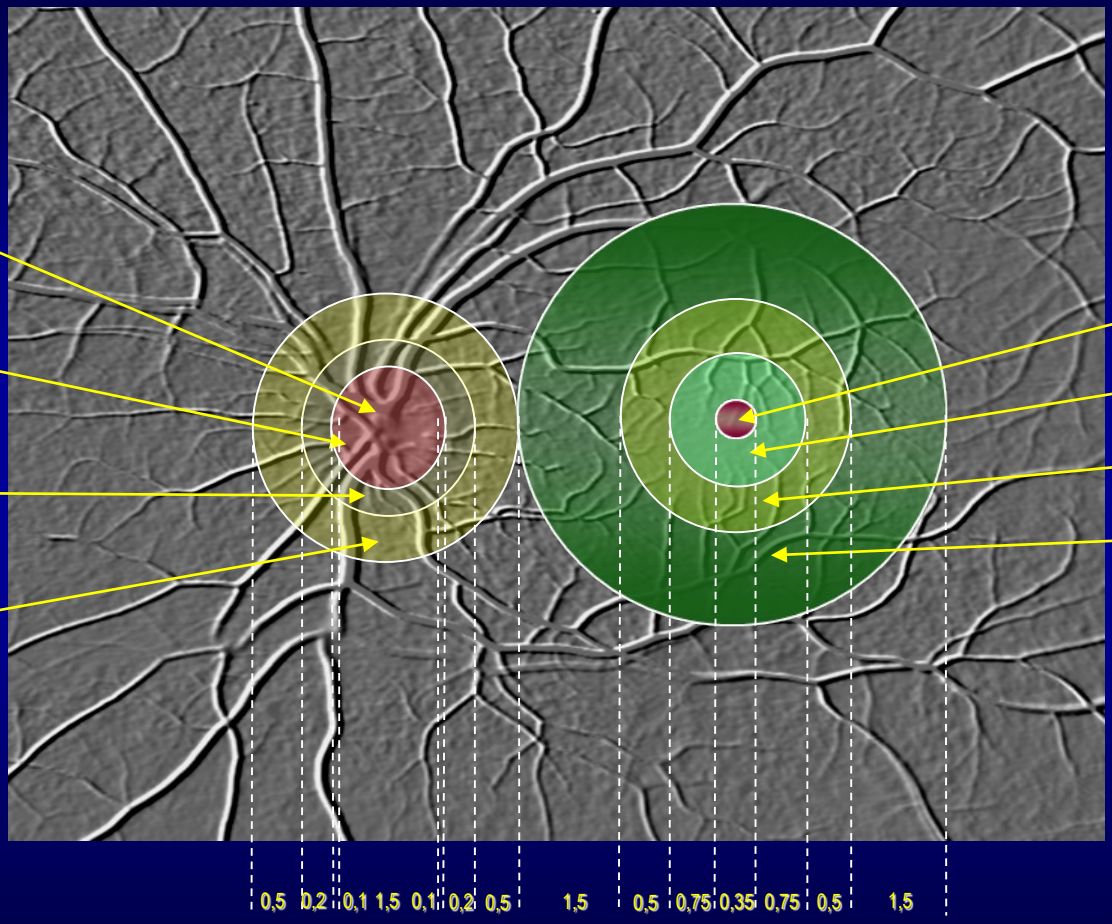

TOPCON
MARK II

Schema di fondo oculare normale

(valori numerici in micron)

Area papillare

1. Area discale
2. Area iuxtapapillare
3. Area parapapillare
4. Area peripapillare



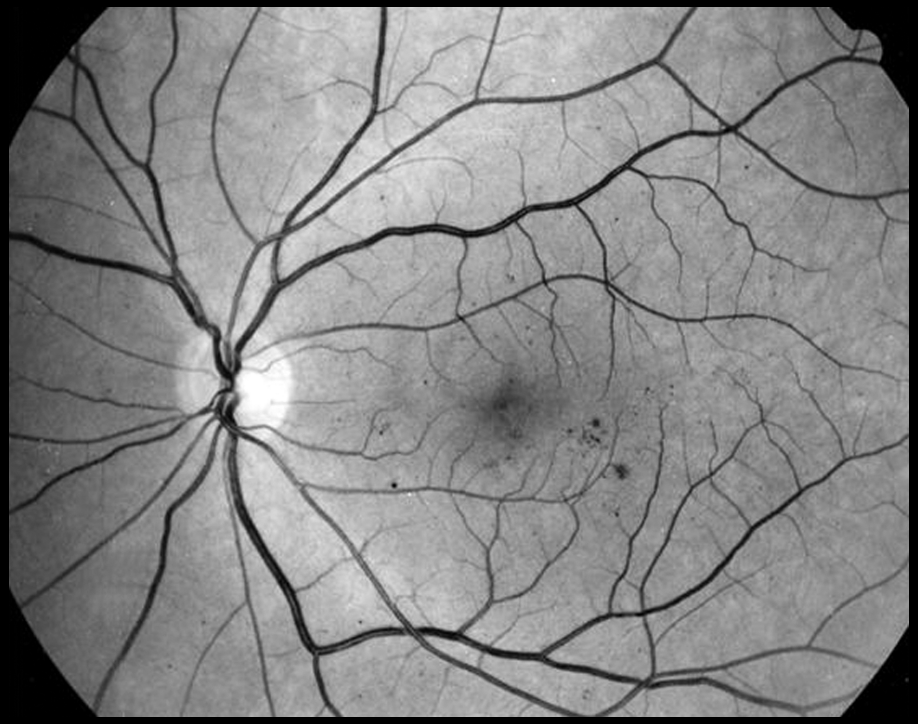
Area maculare

1. Foveola
2. Fovea
3. Parafovea
4. Perifovea

Fondo sano

Retinopatia diabetica lieve

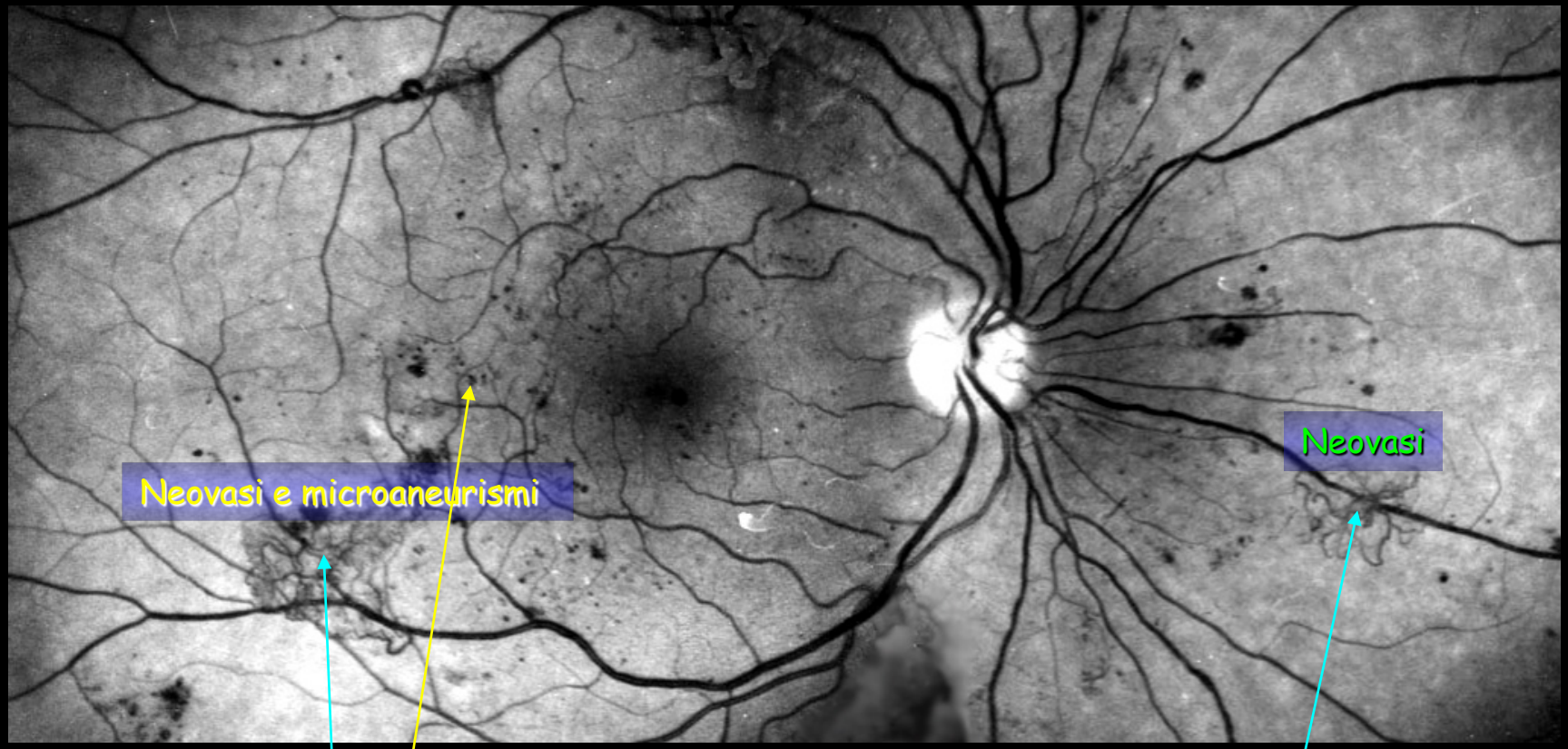
Microaneurismi

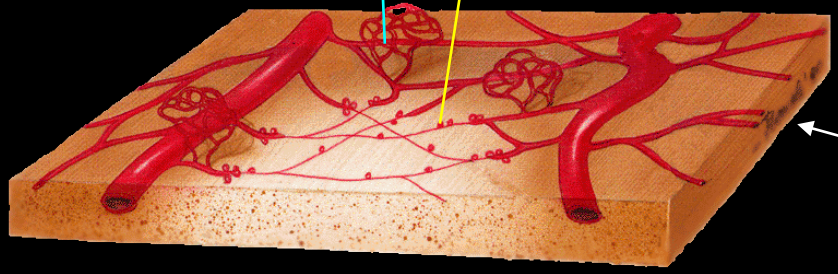


Retinopatia diabetica con maculopatia essudativa

Retinopatia diabetica proliferante

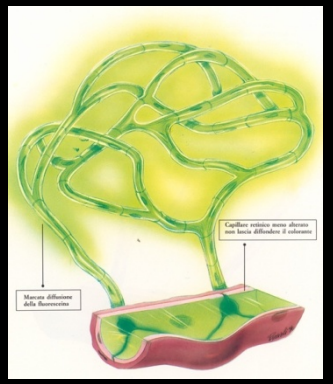
Retinografia di retinopatia diabetica proliferante





Adattato da: "Retinopatia Diabetica"
Del Prof. B. Lumbroso

Fluorangiografia (FAG)



Si inietta del colorante (fluoresceina) in vena e poi si scattano delle foto al fondo dell'occhio in modo da vedere alterazioni morfologiche e funzionali dei vasi retinici.

In particolare si vede se il liquido trasuda dai vasi e se ci sono delle aree non perfuse.

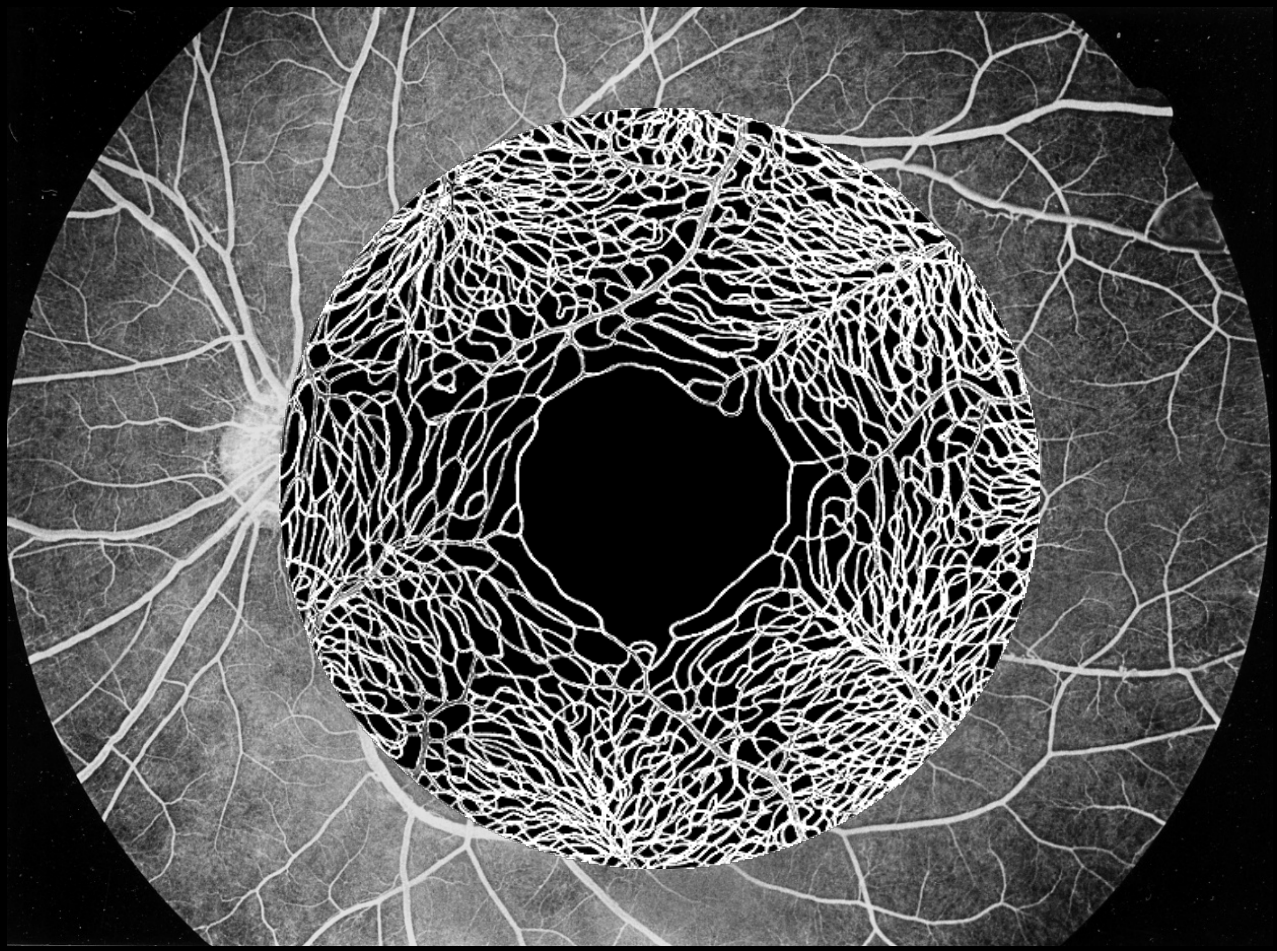
Apparecchiatura per angiografia a fluorescenza computerizzata

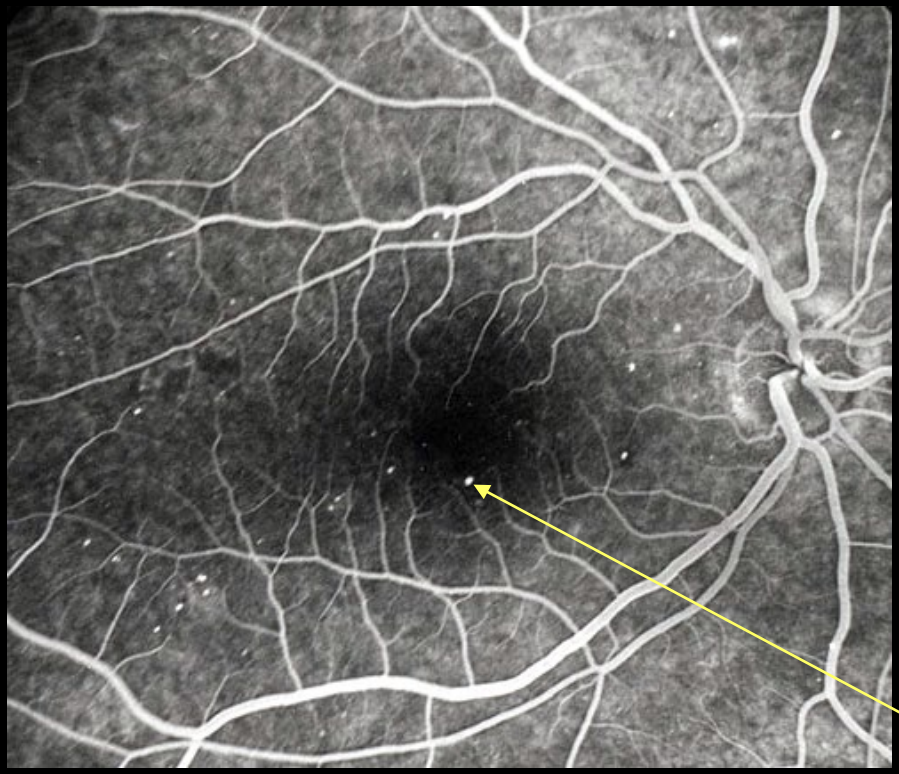
Gli scopi della fluorangiografia retinica sono i seguenti:

a) Interpretazione patogenetica dell'edema maculare
b) Individuazione di neovascolarizzazioni dubbie
c) Esatta definizione delle zone retiniche ischemiche
d) Studio della macula nei casi di perdita visiva non giustificata clinicamente

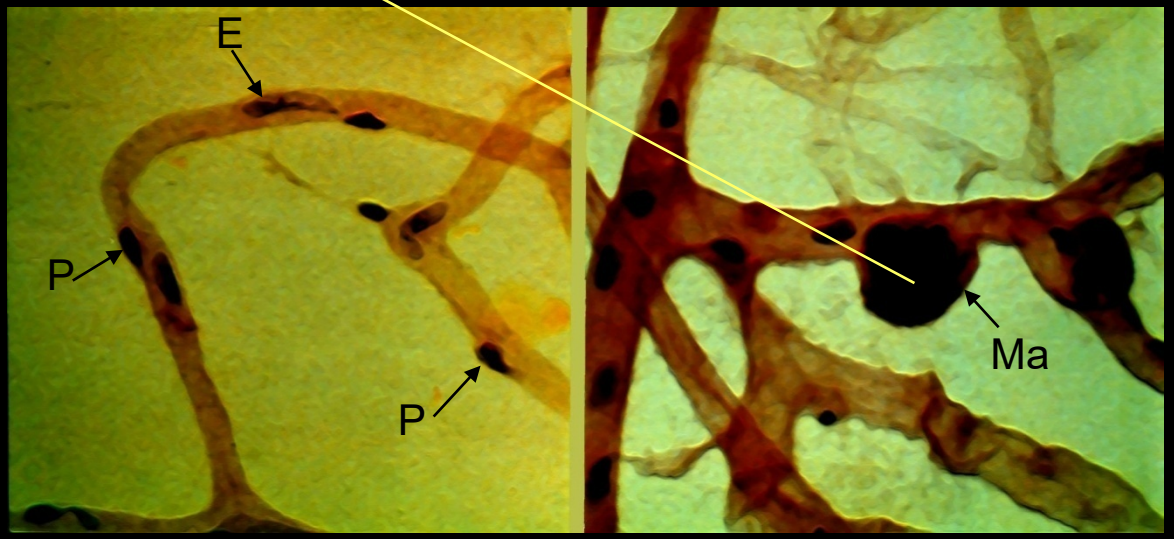
La fluorangiografia retinica non è indicata per lo screening e la diagnosi della retinopatia diabetica.

Fluorangiografia di un fondo sano





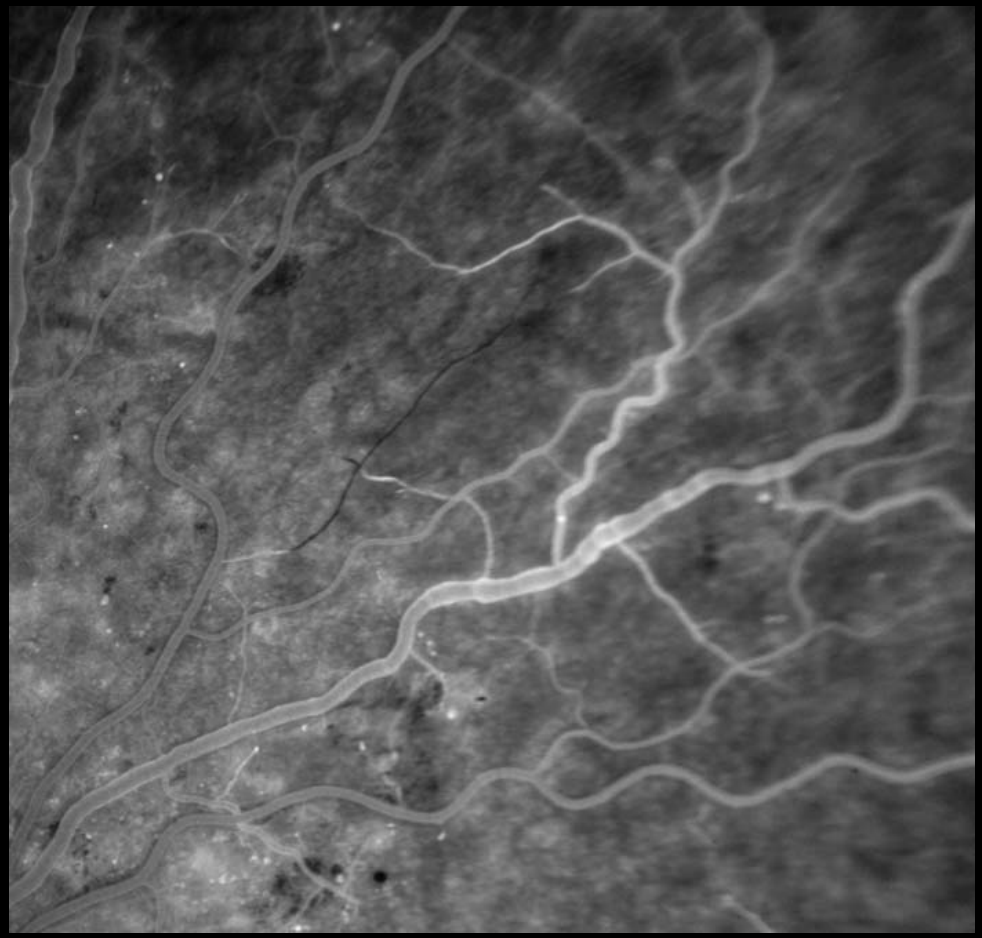
Fluorangiografia
di retinopatia
diabetica lieve
non proliferante



Fluorangiografia di retinopatia diabetica non proliferante con microaneurismi

Fluorangiografia di retinopatia diabetica non proliferante con IRMA

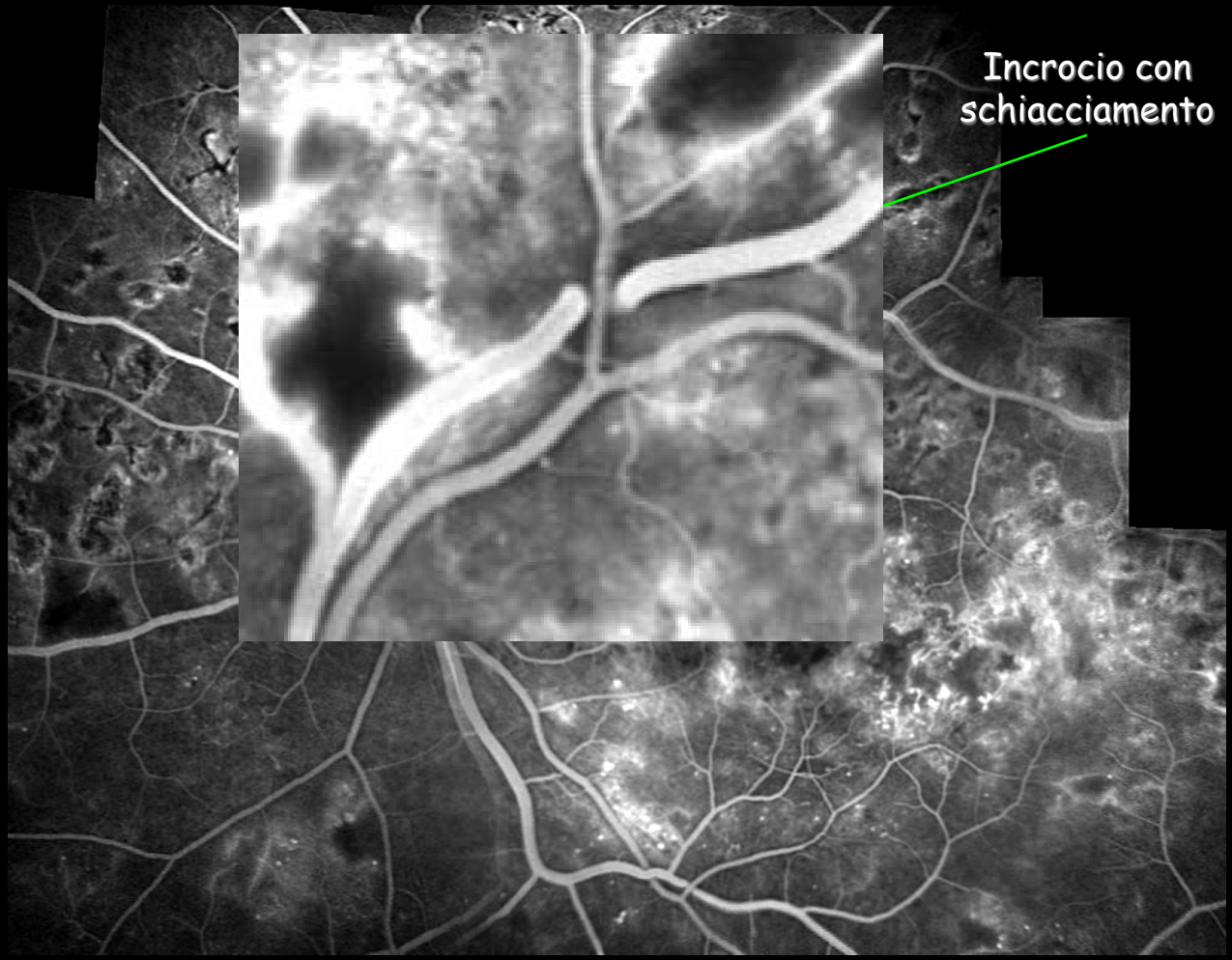
(Alterazioni Microvascolari IntraRetiniche)



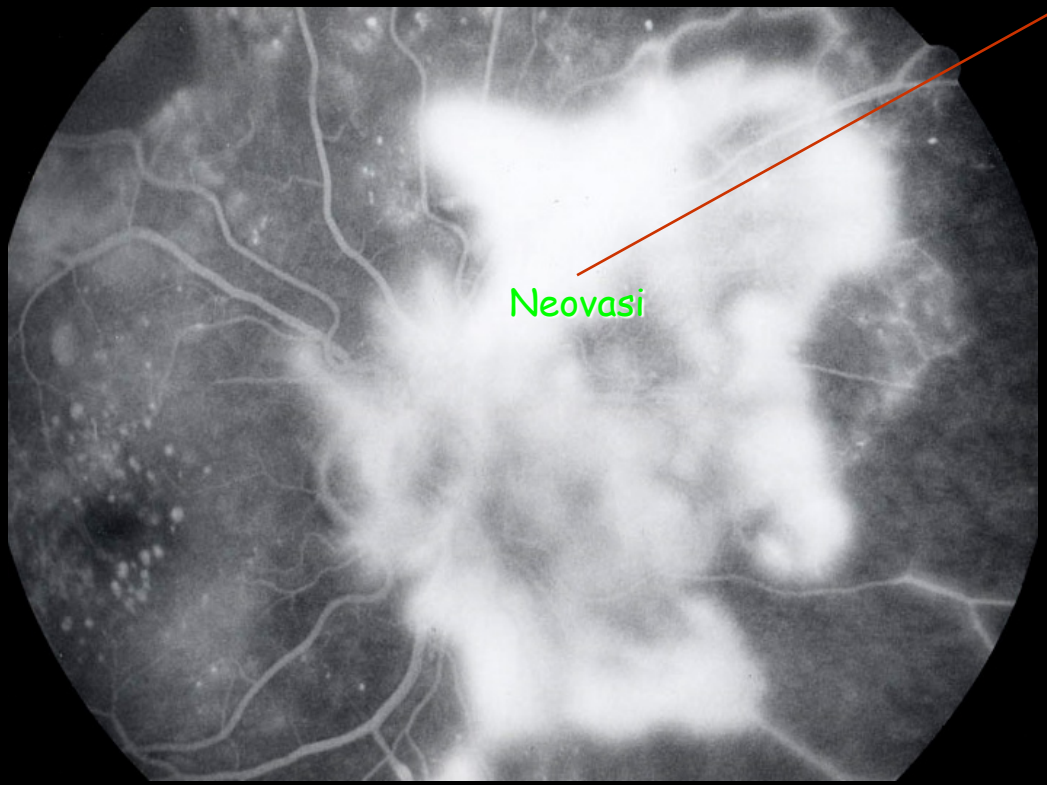
Fluorangiografia di retinopatia diabetica con

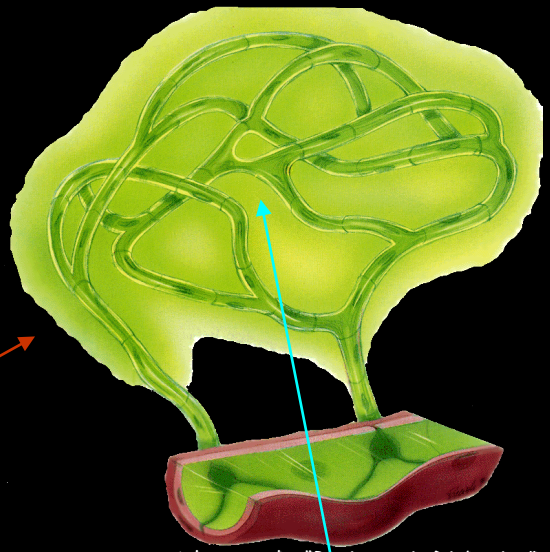
Alterazioni del calibro delle vene
(dilatazione, aspetto moniliforme, formazione di anse)
adiacenti ad aree di non perfusione

Fluorangiografia di retinopatia diabetica ischemica e trombosi venosa



Retinopatia diabetica proliferante
(fluorangiografia)

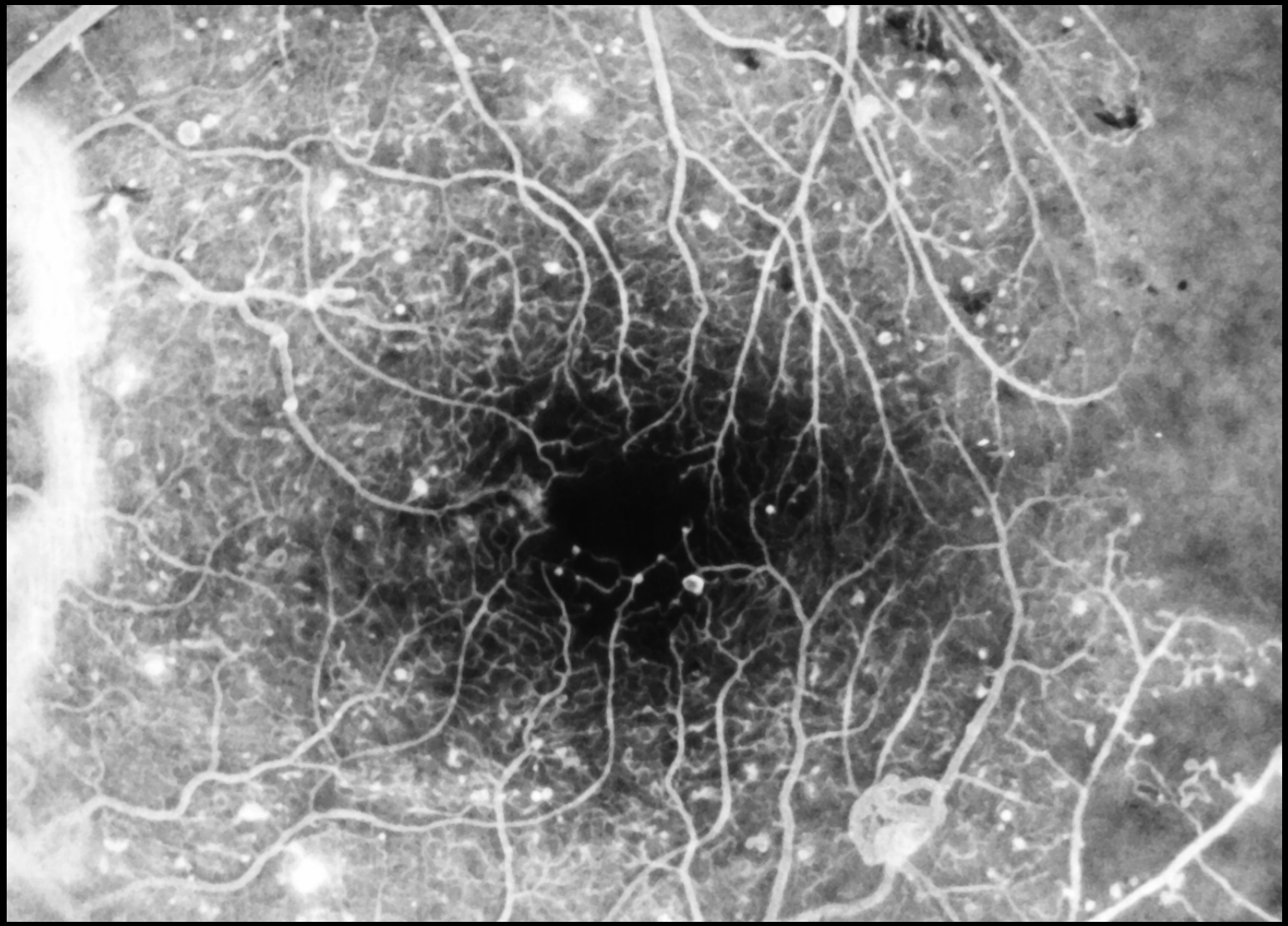




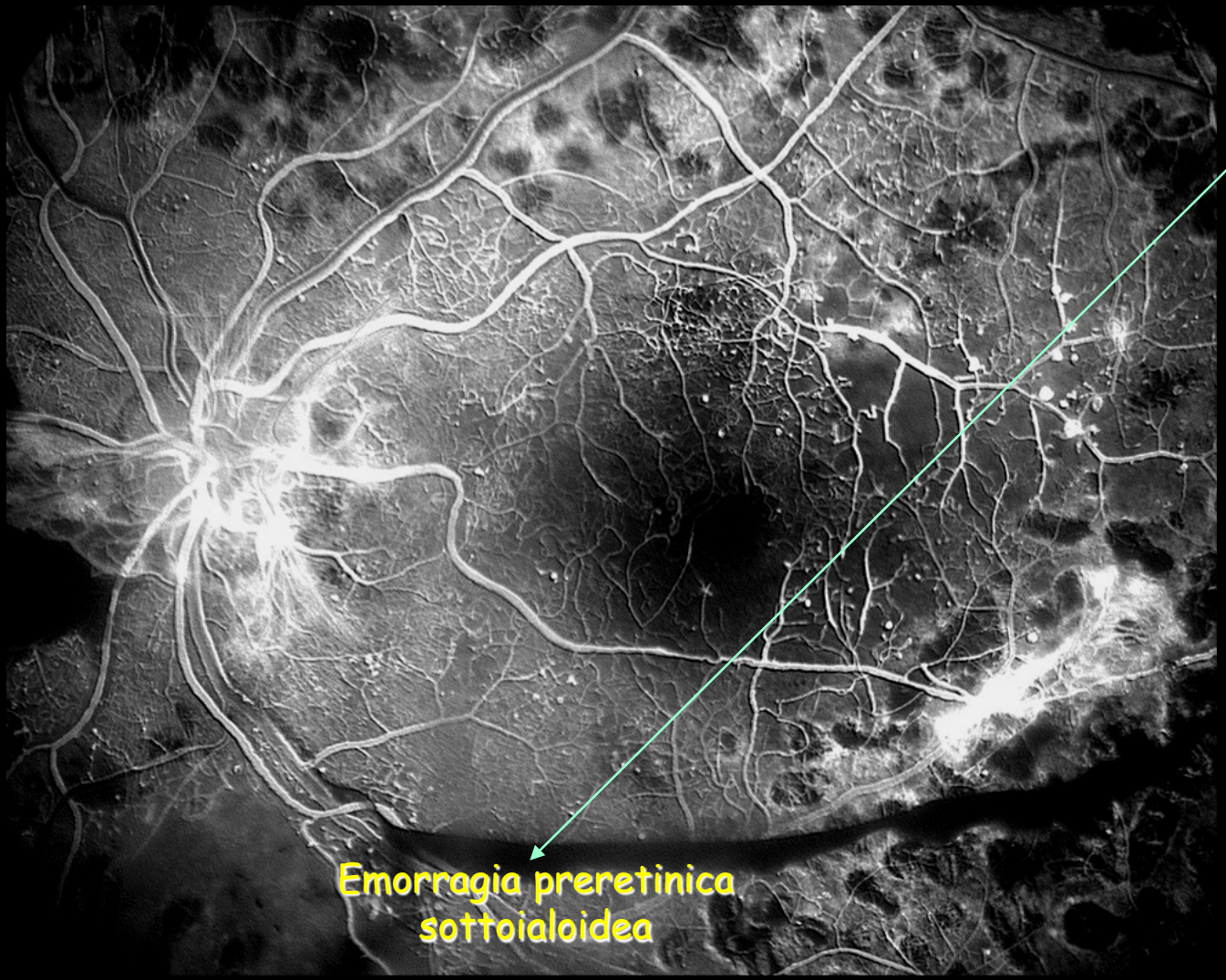
Adattato da: "Retinopatia Diabetica"
Del Prof. B. Lumbroso

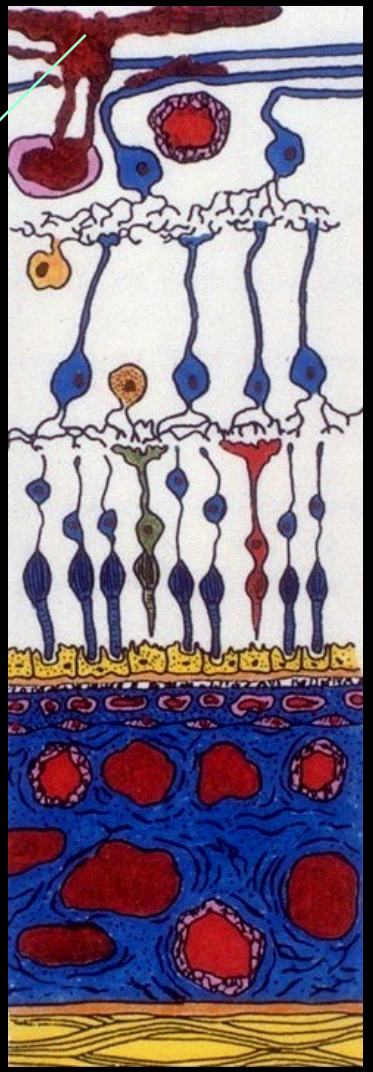
(In verde diffusione
di fluoresceina)

Fluorangiografia di retinopatia diabetica proliferante



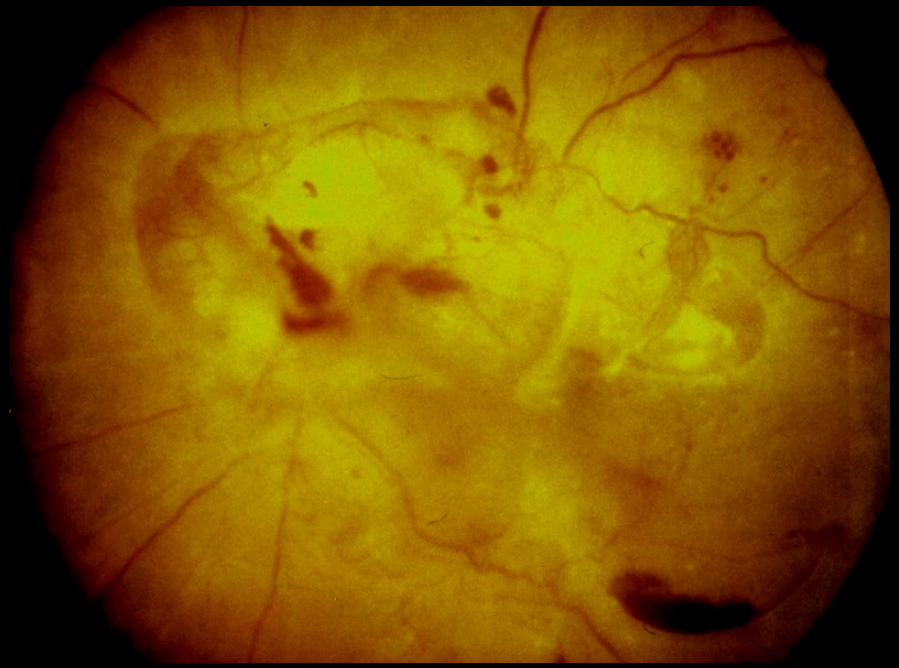
Fluorangiografia di retinopatia diabetica proliferante parzialmente laser trattata

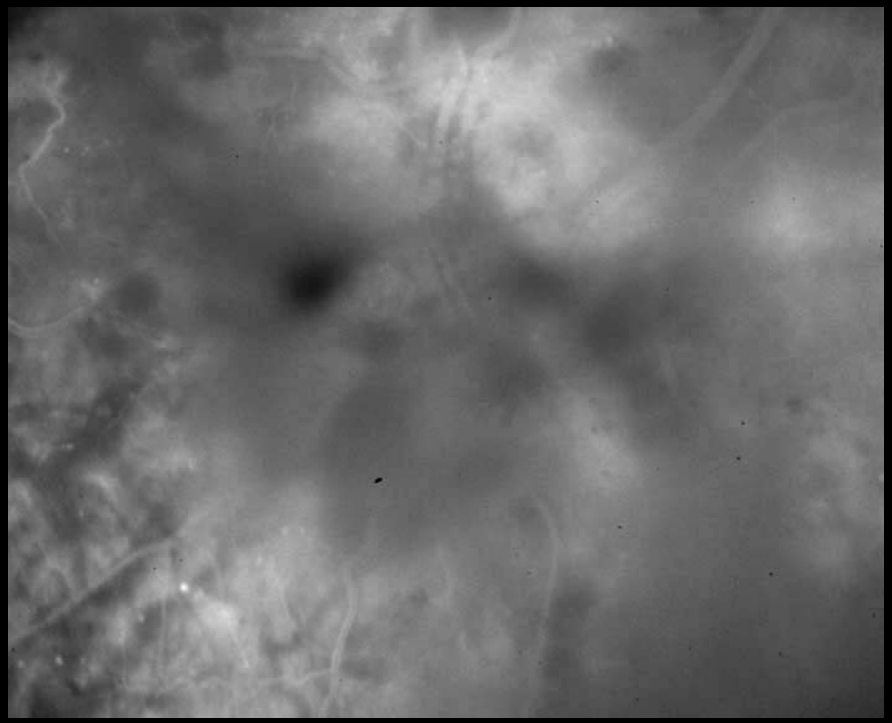




Fluorangiografia di retinopatia diabetica proliferante

I neovasi si propagano sulla superficie della retina e lungo i tralci vitreali, sono molto fragili e possono esitare in emorragie vitreali





In particolari situazioni cliniche, o per acquisire dati utili a fini prognostici e/o terapeutici, ci si può avvalere dei seguenti ulteriori esami:

- ecografia oculare
- iridografia
- tomografia ottica a luce coerente (OCT)

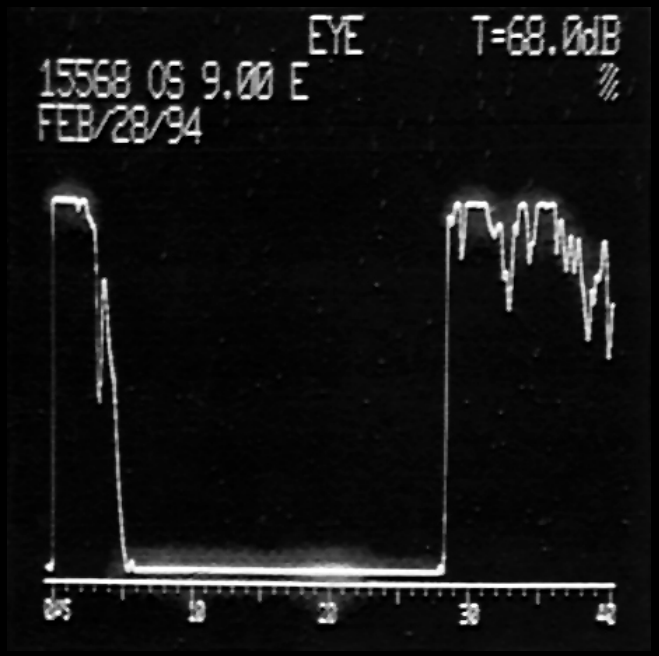
Ecografo A e B scan

L'ecografia oculare trova indicazione nei casi in cui la visualizzazione del fondo oculare sia resa difficile da opacità dei mezzi diottrici (cataratta, emorragia endovitreale) o per meglio definire i rapporti anatomici tra corpo vitreo e retina.

Ecografia B scan e A scan normale

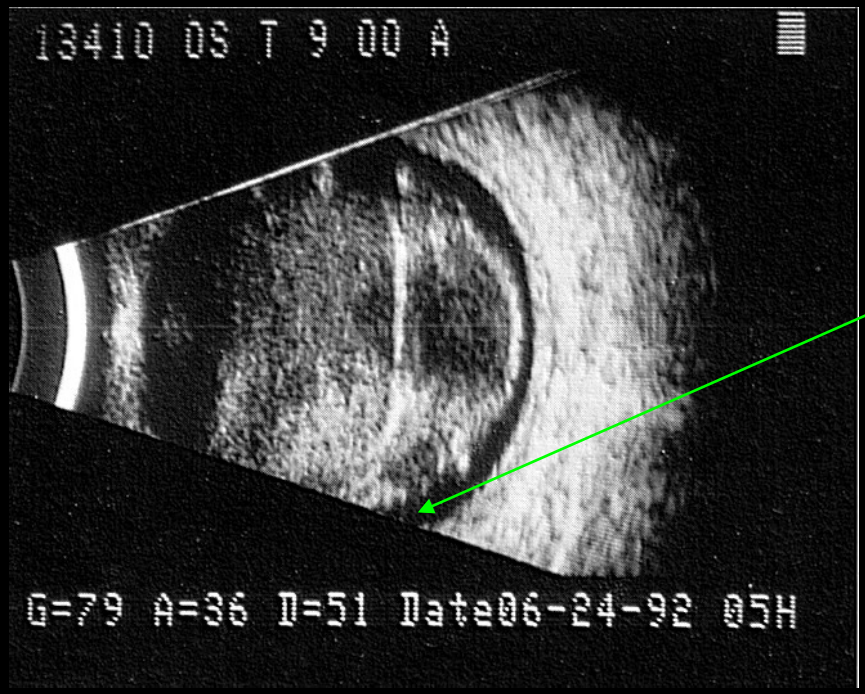
Tracciato ecografico del bulbo oculare ottenuto con la tecnica B scan a contatto in proiezione assiale verticale, che mette in evidenza il cristallino ed una zona acusticamente silente corrispondente al corpo vitreo, delimitato dalla parete del bulbo oculare.

Tracciato ecografico del bulbo oculare ottenuto con la tecnica A scan standardizzata, in cui si evidenzia una zona acusticamente vuota seguita da un picco ad alta reflettività a risalita rapida, corrispondente all'interfaccia vitreo retinica, seguita dai picchi provenienti dalle strutture orbitarie.

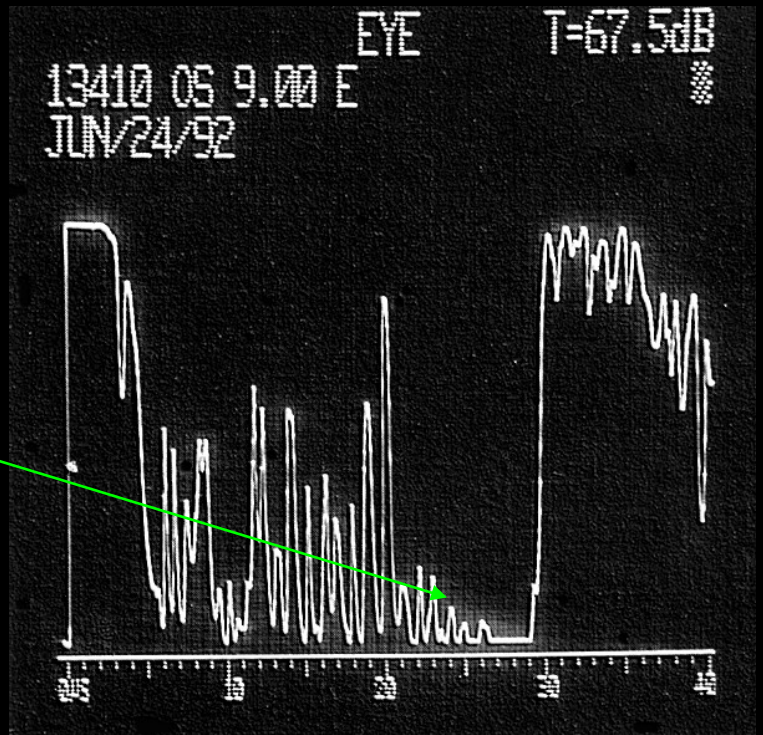


Per gentile concessione del Prof. N. Rosa

Ecografia B scan e A scan in diabetico con emovitreo



Tracciato ecografico del bulbo oculare ottenuto con tecnica B-scan a contatto. Presenza di emovitreo con enhancement della corticale vitreale e di una zona di silenzio acustico tra quest'ultima e la superficie retinica, corrispondente allo spazio retroialoideo apparentemente normale.



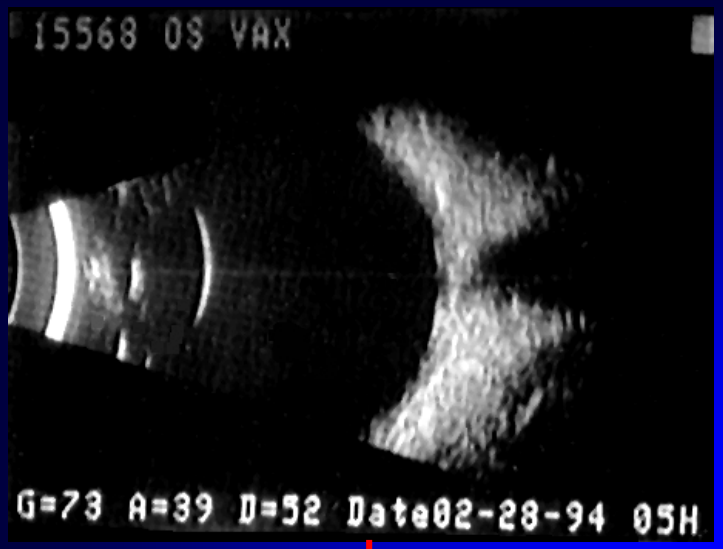
Tracciato ecografico del bulbo oculare ottenuto con tecnica A-scan a contatto. Presenza di emovitreo e una zona che mette meglio in evidenza dei picchi a bassa reflettività nello spazio retroialoideo, indice di un intorbidamento emorragico anche di quest'ultimo.

Per gentile concessione del Prof. N. Rosa

Ecografia normale

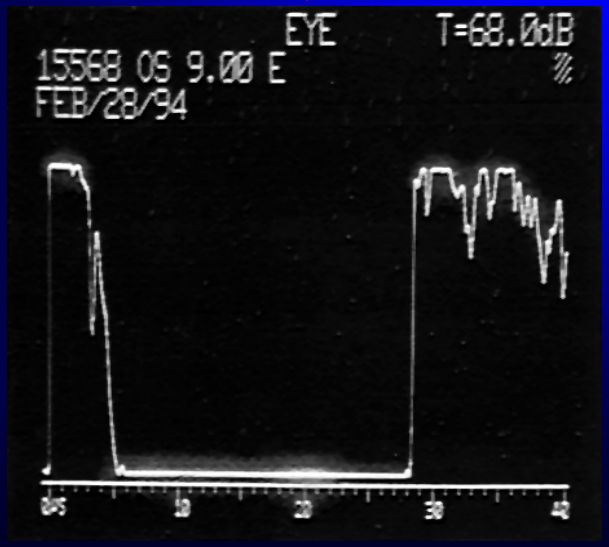
Ecografia diabetico con emovitreo

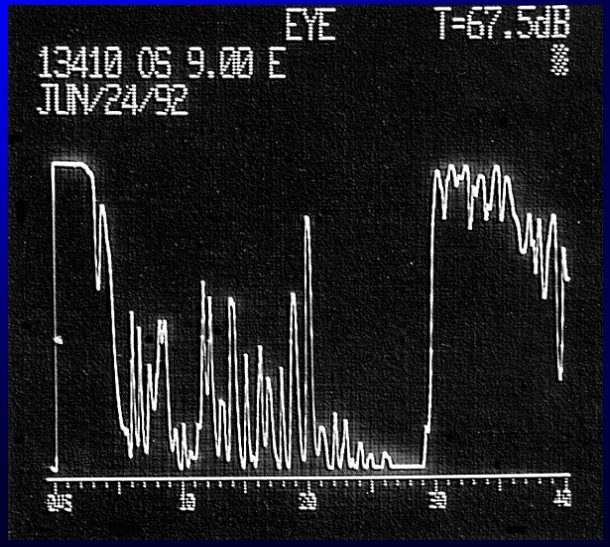
B scan



B scan

A scan





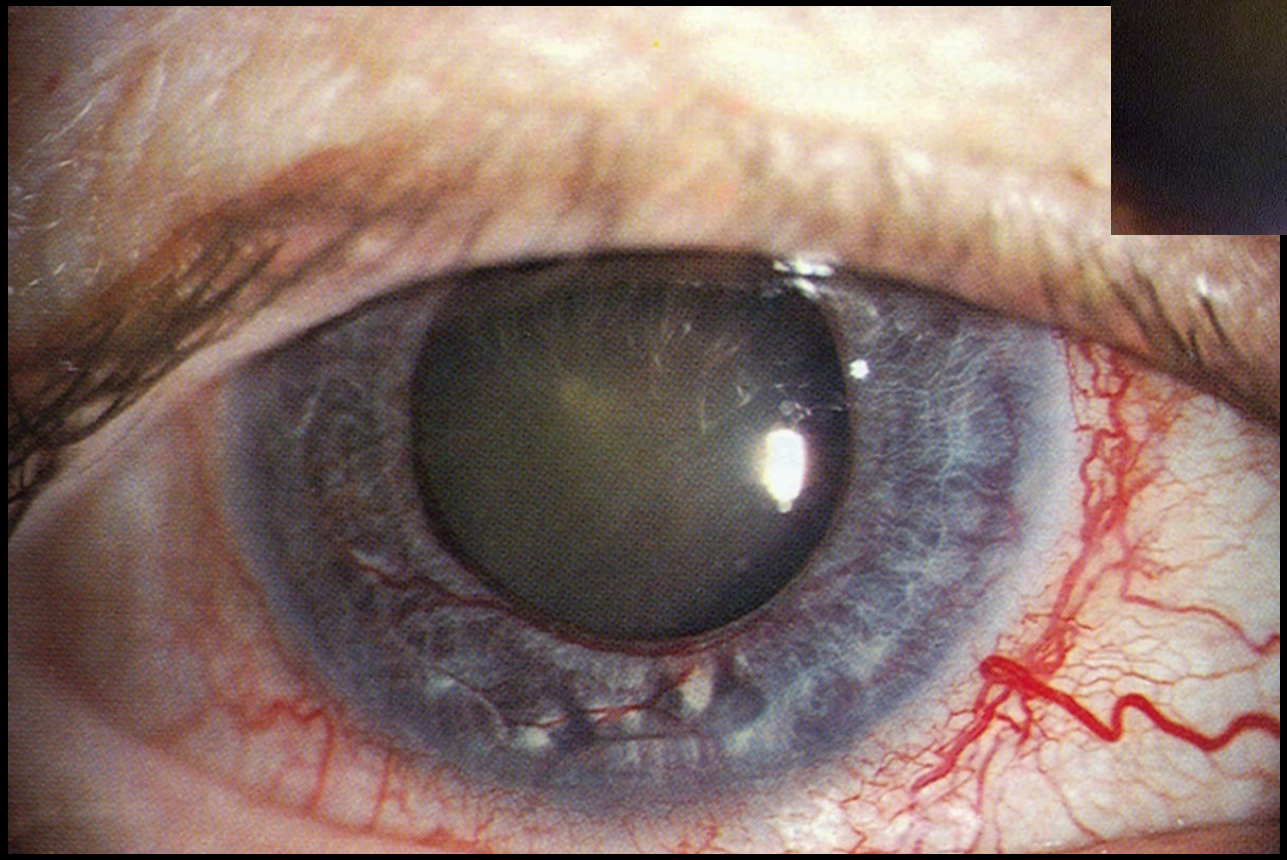
A scan

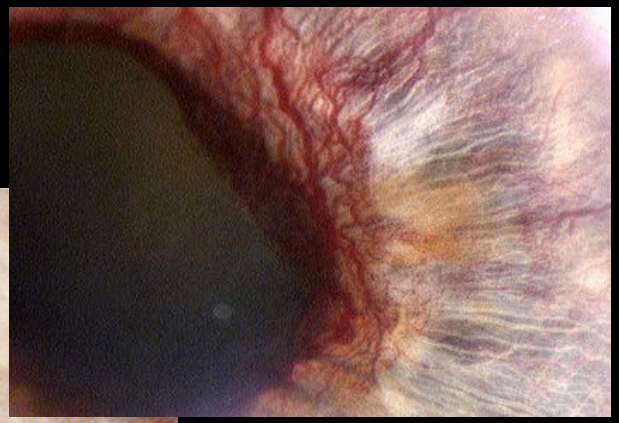
Per gentile concessione del Prof. N. Rosa

- ecografia oculare
- iridografia
- tomografia ottica a luce coerente (OCT)

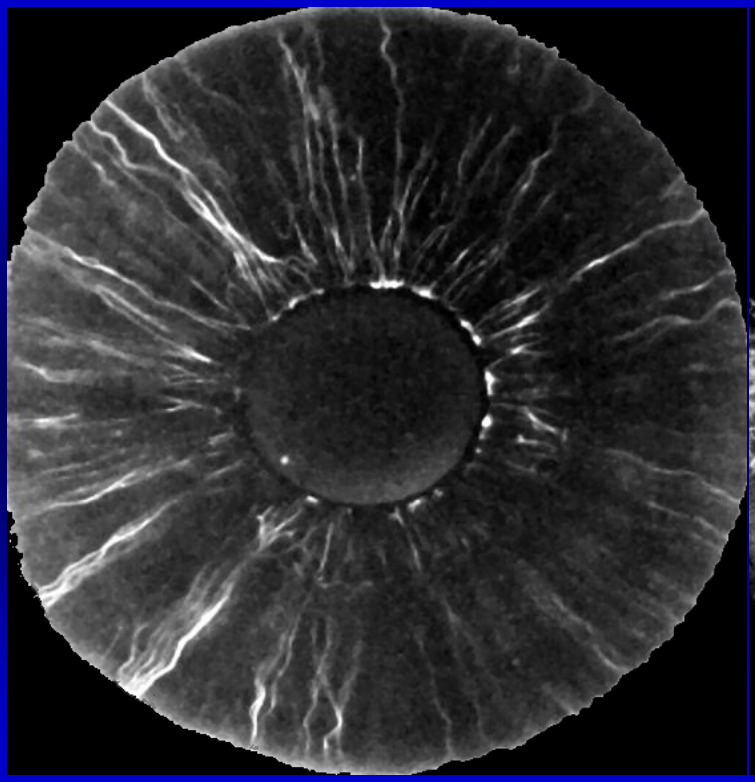
L'iridografia può essere utile per una precoce diagnosi di neovascolarizzazione dell'iride e per avere informazioni indirette sulla microangiopatia retinica se non accessibile ad un esame diretto.

Fluorangiografia Iridea

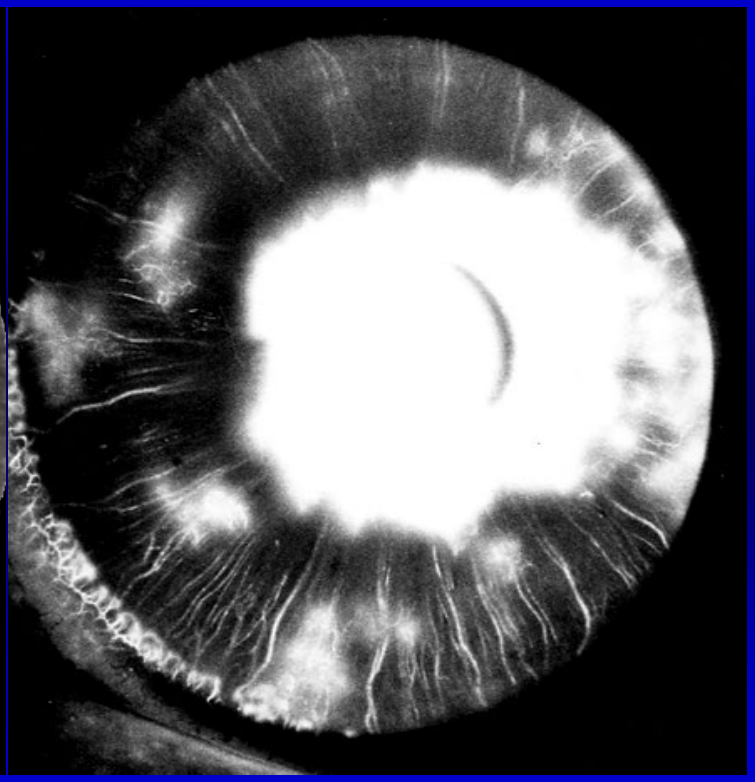




Fluorangiografia Iridea



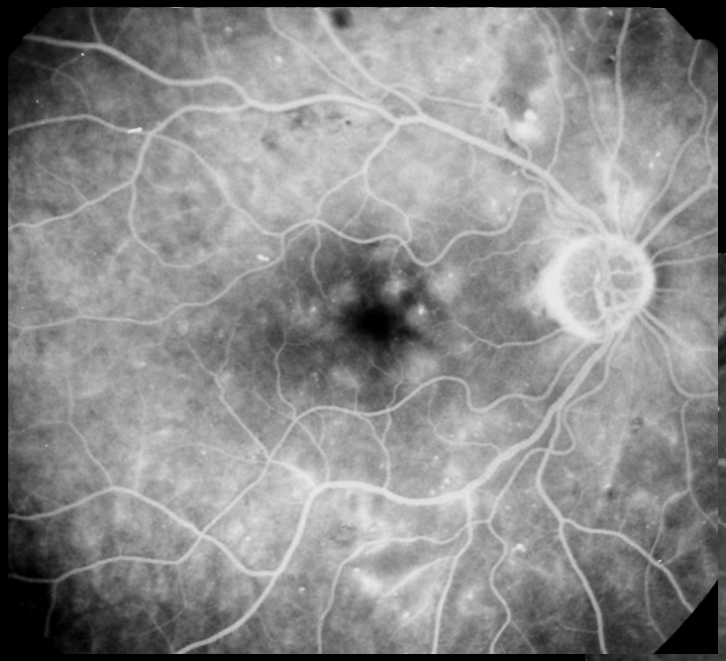
FAG iride normale



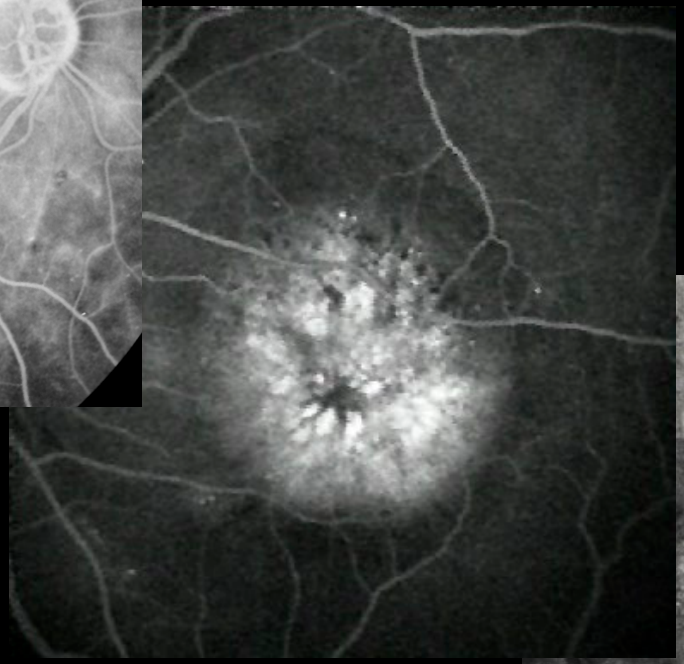
FAG iride retinopatia diabetica

(Rubeosis Iridea)

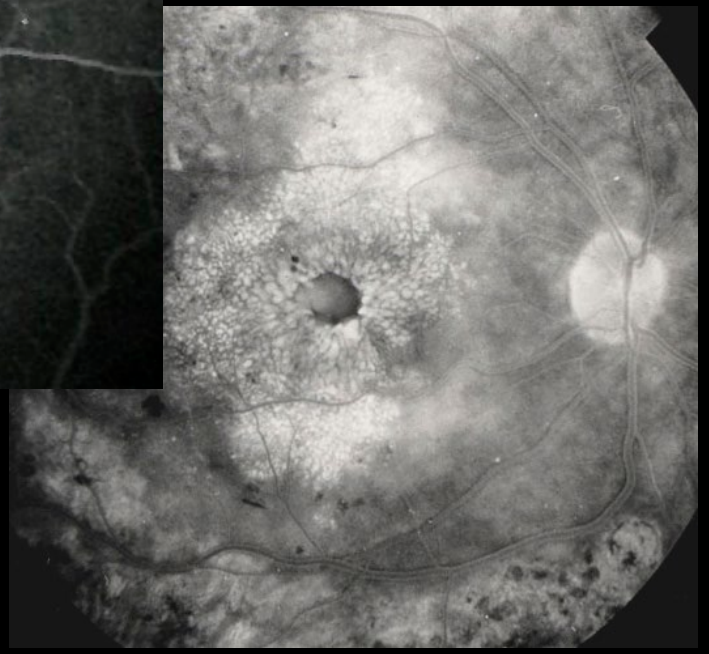
Fluorangiografia dell' edema maculare cistoide in via di strutturazione



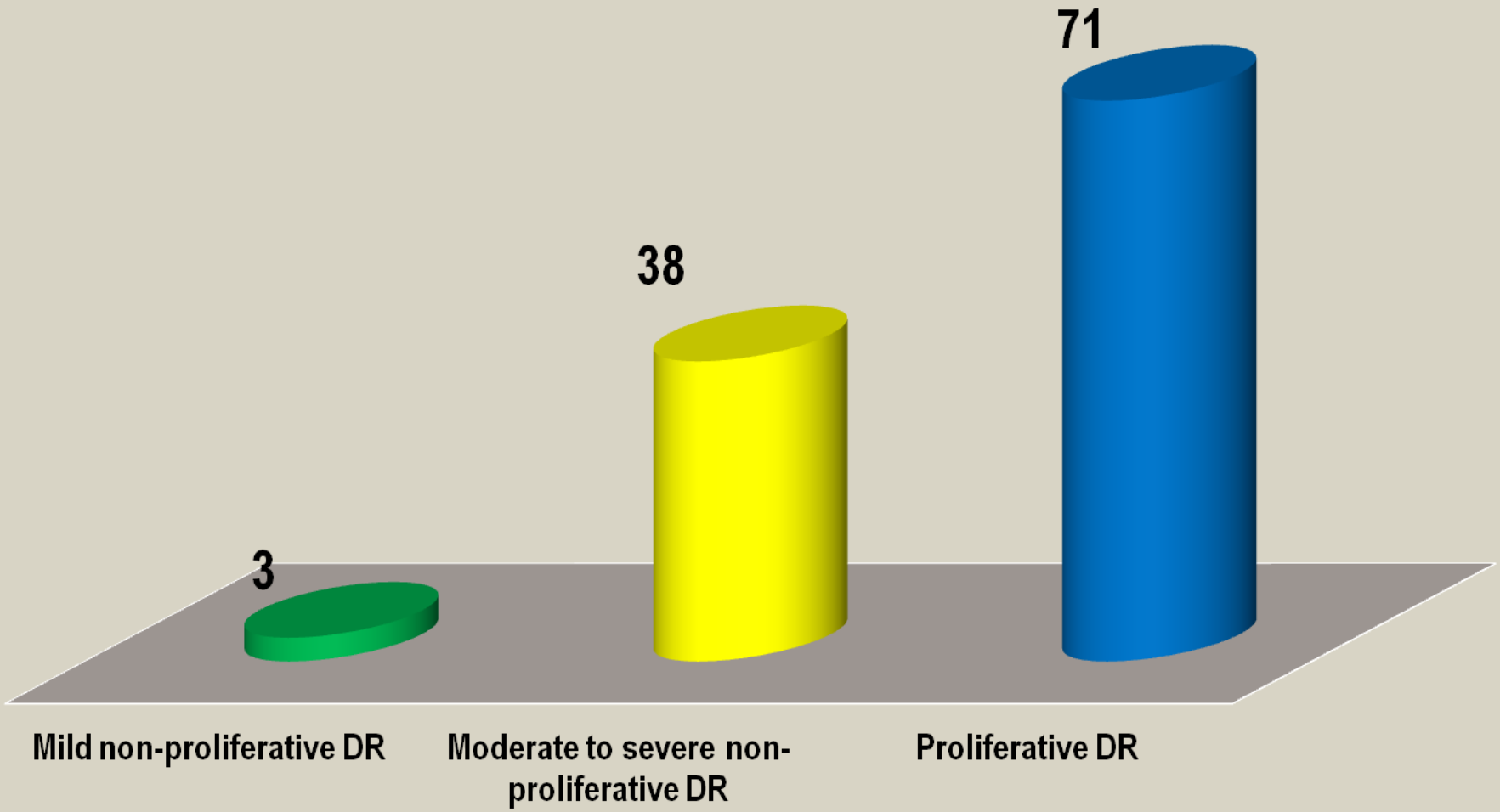
Fluorangiografia dell' edema maculare cistoide strutturato



Fluorangiografia di grave edema cistoide maculare con pseudoforo



Diabetic Macular Edema Prevalence



Meta analysis and review on the effect on bevacizumab id diabetic macular edema
Graefes Arch Clin Exp Ophthalmol(2011) 249:15-27

October, 2002

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The Eye M.D. Association

INTERNATIONAL CLINICAL DIABETIC MACULAR EDEMA DISEASE SEVERITY SCALE

2 major levels, with subcategories for diabetic macular edema

Proposed Disease Severity Level	Findings Observable Upon Dilated Ophthalmoscopy
Diabetic Macular Edema Absent	No retinal thickening or hard exudates in posterior pole
Diabetic Macular Edema Present	Some retinal thickening or hard exudates in posterior pole

If diabetic macular edema is present, it can be categorized as follows:

Proposed Disease Severity Level	Findings Observable Upon Dilated Ophthalmoscopy *
Diabetic Macular Edema Present	☐ Mild Diabetic Macular Edema Some retinal thickening or hard exudates in posterior pole but distant from the center of the macula
	☐ Moderate Diabetic Macular Edema Retinal thickening or hard exudates approaching the center of the macula but not involving the center
	☐ Severe Diabetic Macular Edema Retinal thickening or hard exudates involving the center of the macula

* Hard exudates are a sign of current or previous macular edema. Diabetic macular edema is defined as retinal thickening and this requires a 3-dimensional assessment that is best performed by a dilated examination using slit-lamp biomicroscopy and/or stereo fundus photography.
A more detailed table for the International Clinical DME Disease Severity Scale is available, with more explanation of the disease severity levels, definition of CSME, and management options. Please contact Flora Lum, M.D. at the AAO, 415 561-8500.

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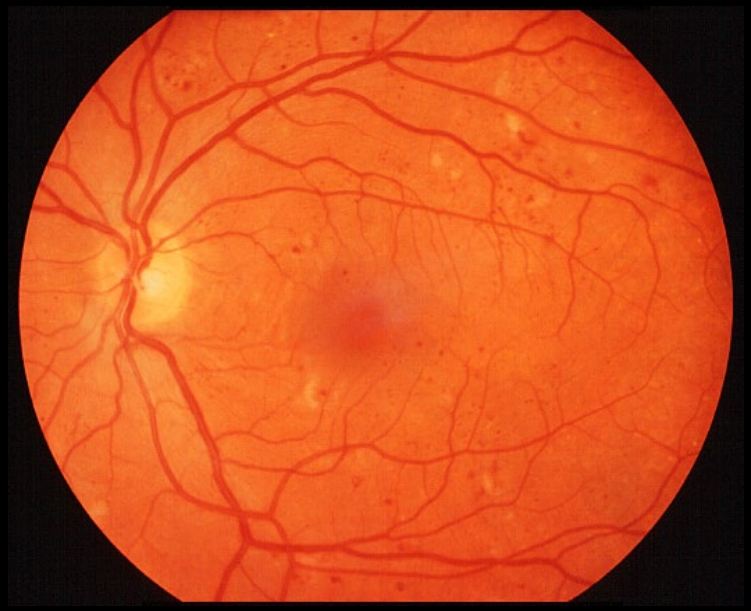

Diabetic Macular Edema Absent	No retinal thickening or hard exudates in posterior pole

Diabetic Macular Edema Present	Some retinal thickening or hard exudates in posterior pole

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☐ Mild Diabetic Macular Edema

Some retinal thickening or hard exudates in posterior pole but distant from the center of the macula

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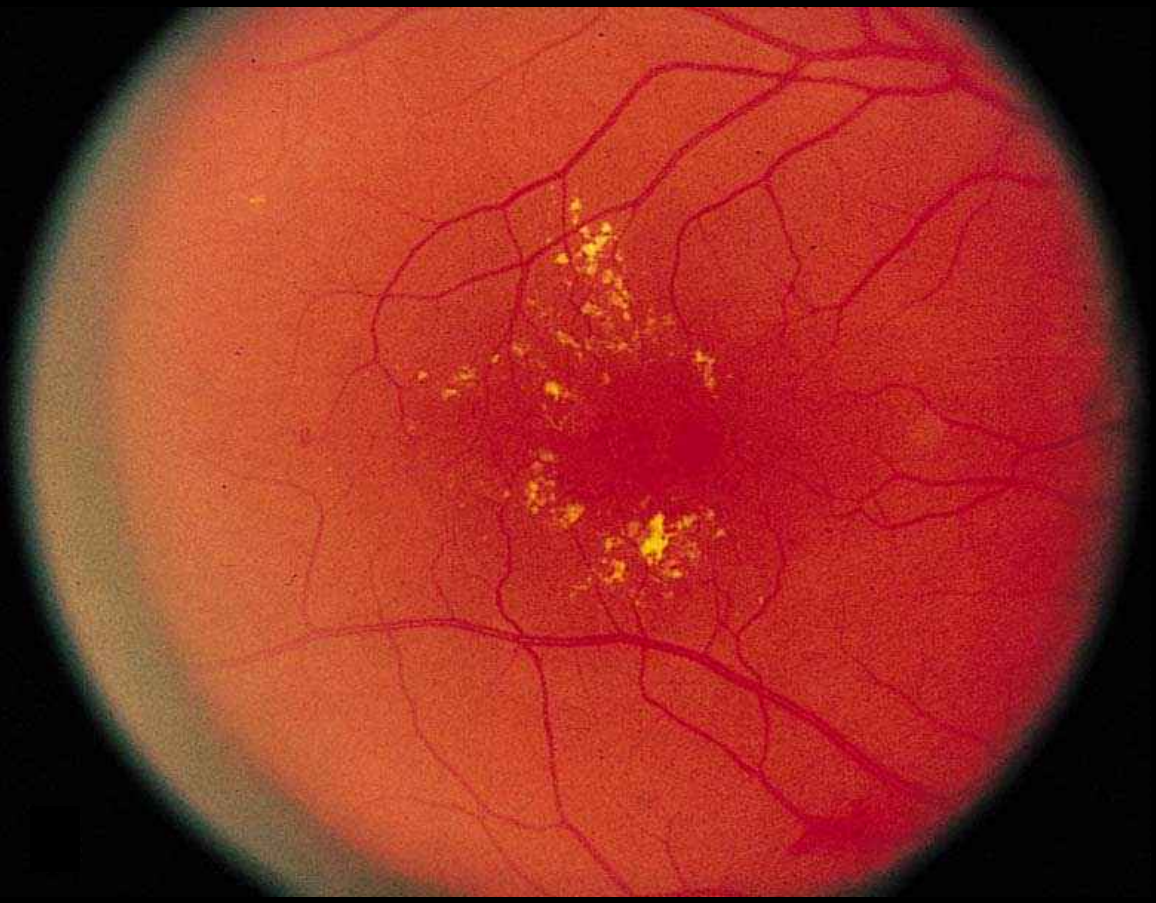
☐ Moderate Diabetic Macular Edema

Retinal thickening or hard exudates approaching the center of the macula but not involving the center



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The Eye M.D. Association

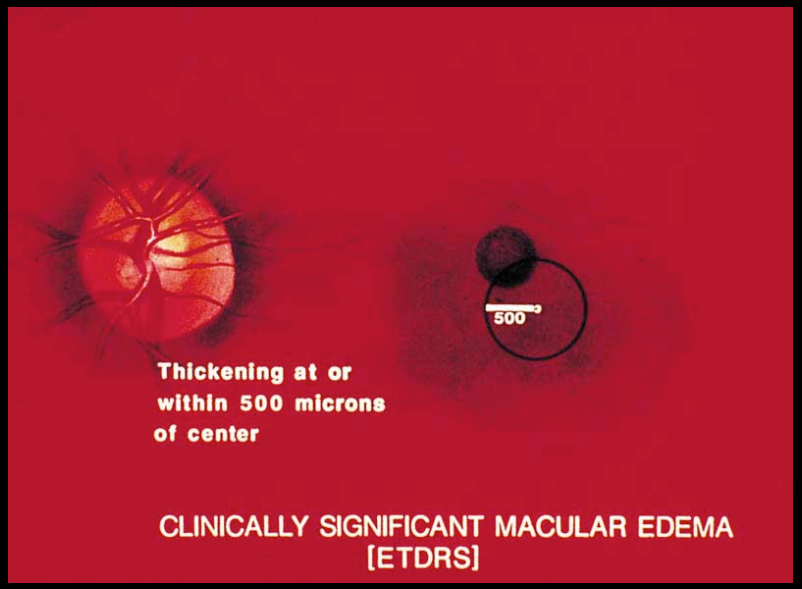
☐ Severe Diabetic Macular Edema

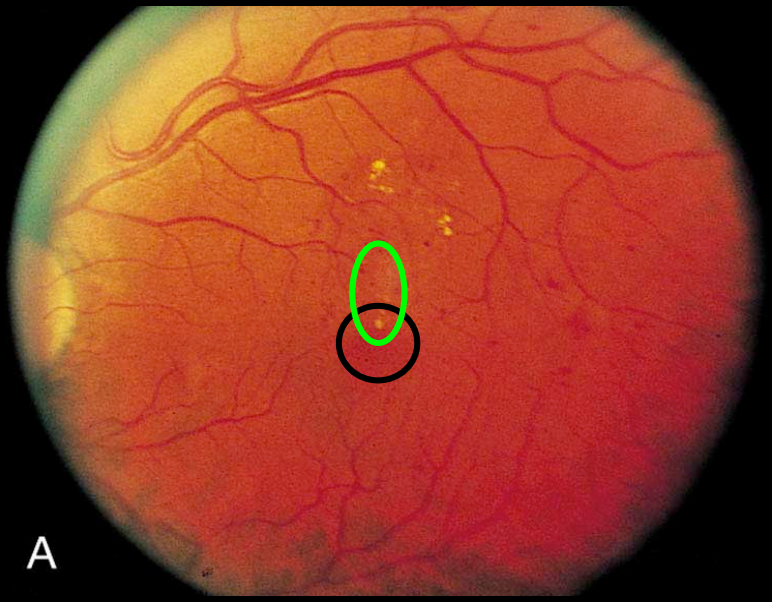
Retinal thickening or hard exudates involving the center of the macula

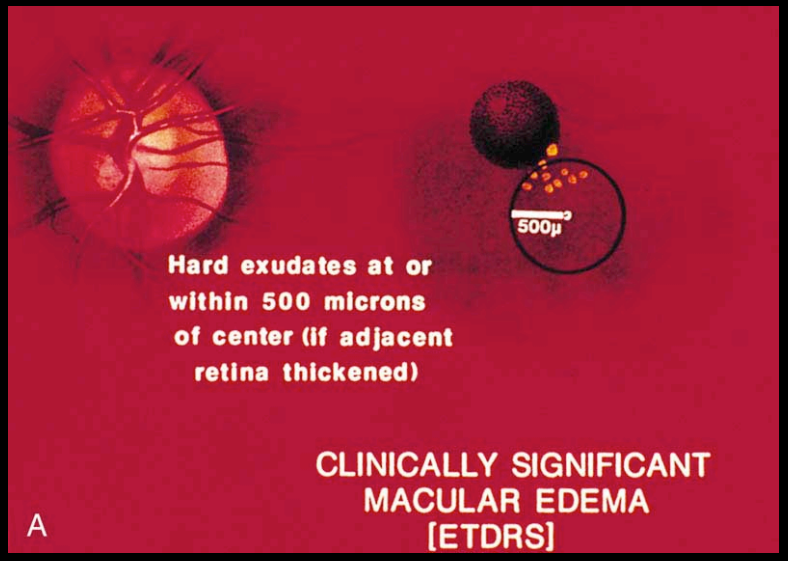
International Clinical Diabetic Macular Edema Disease Severity Scale

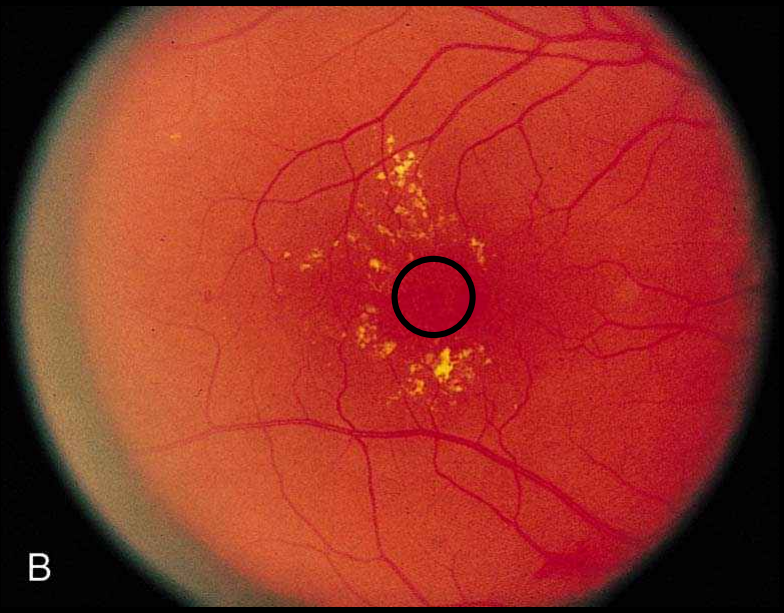
Proposed disease severity level	Findings observable upon dilated ophthalmoscopy
DME apparently absent	No apparent retinal thickening or hard exudates in posterior pole
DME apparently present	Some apparent retinal thickening or hard exudates in posterior pole
DME present	Mild DME (some retinal thickening or hard exudates in posterior pole but distant from the center of the macula)
	Moderate DME (retinal thickening or hard exudates approaching the center of the macula but not involving the center)
	Severe DME (retinal thickening or hard exudates involving the center of the macula)

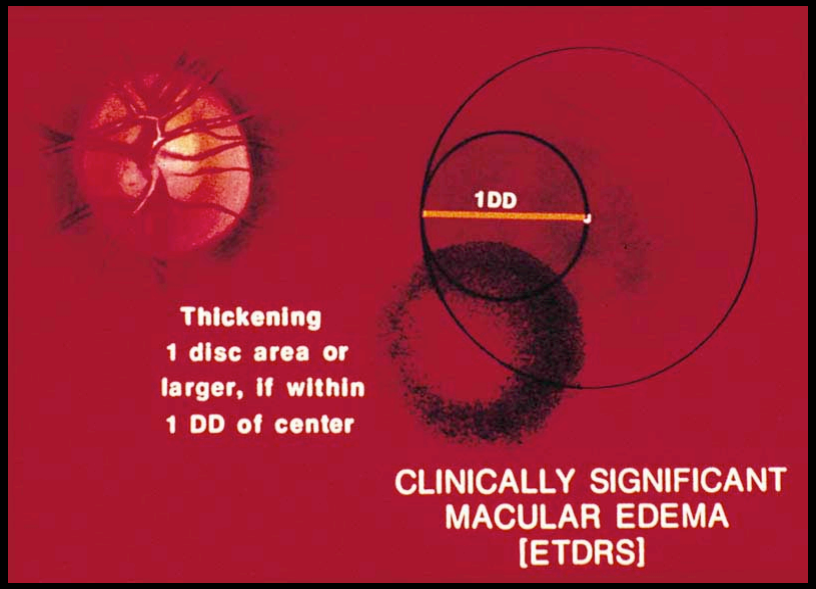
Proposed International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales
Ophthalmology *Volume 110, Number 9, September 2003*

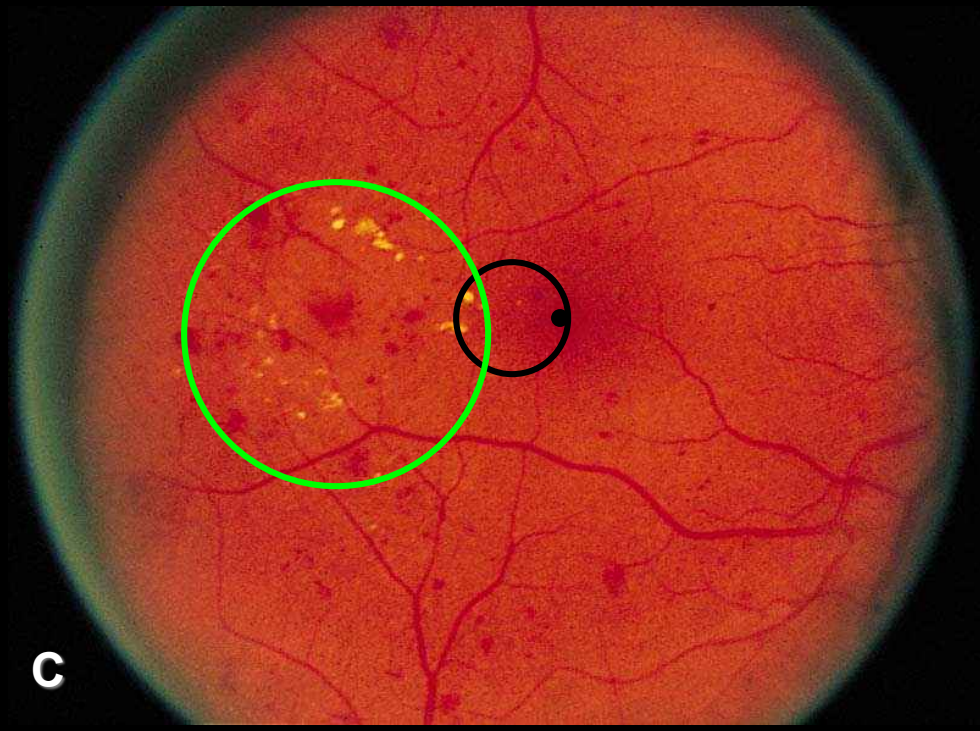

500
Thickening at or
within 500 microns
of center
CLINICALLY SIGNIFICANT MACULAR EDEMA
[ETDRS]


A


500μ
Hard exudates at or
within 500 microns
of center (if adjacent
retina thickened)
CLINICALLY SIGNIFICANT
MACULAR EDEMA
[ETDRS]
A

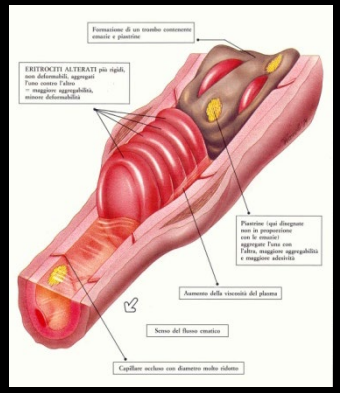

B

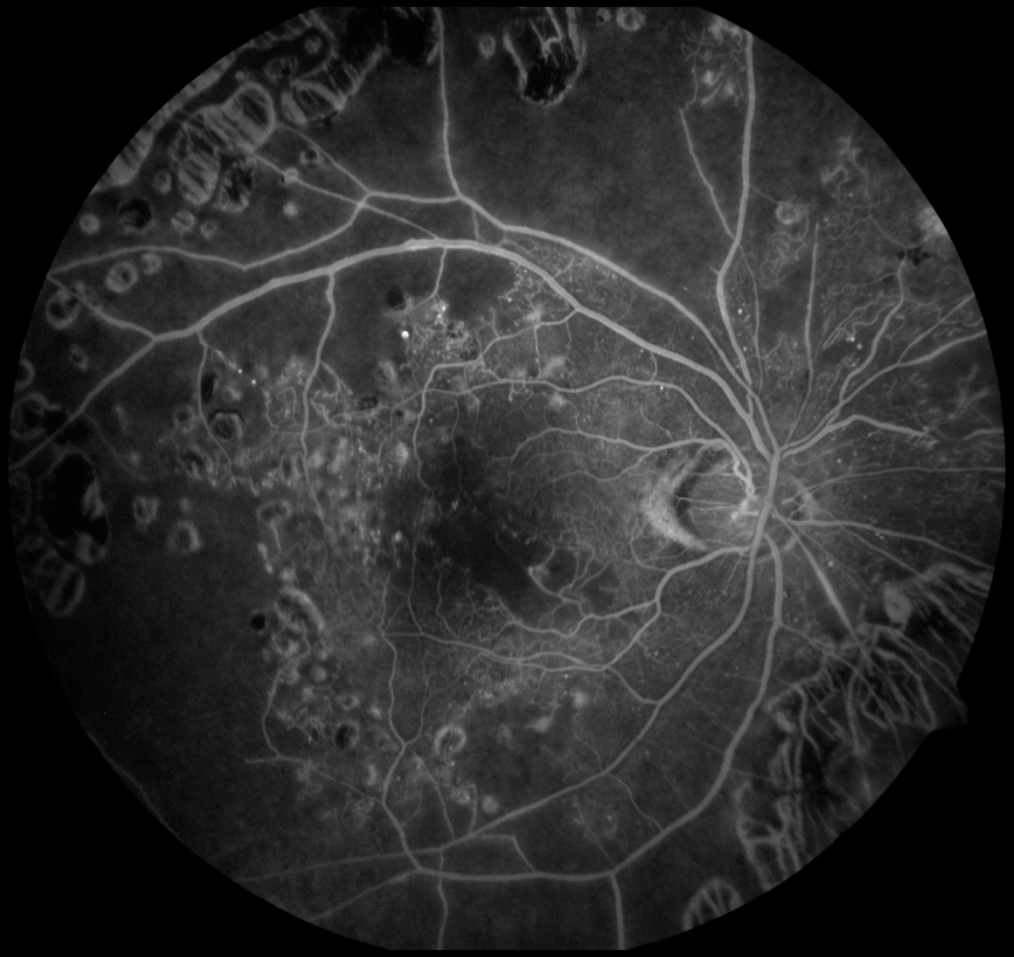

1DD
Thickening
1 disc area or
larger, if within
1 DD of center
CLINICALLY SIGNIFICANT
MACULAR EDEMA
[ETDRS]

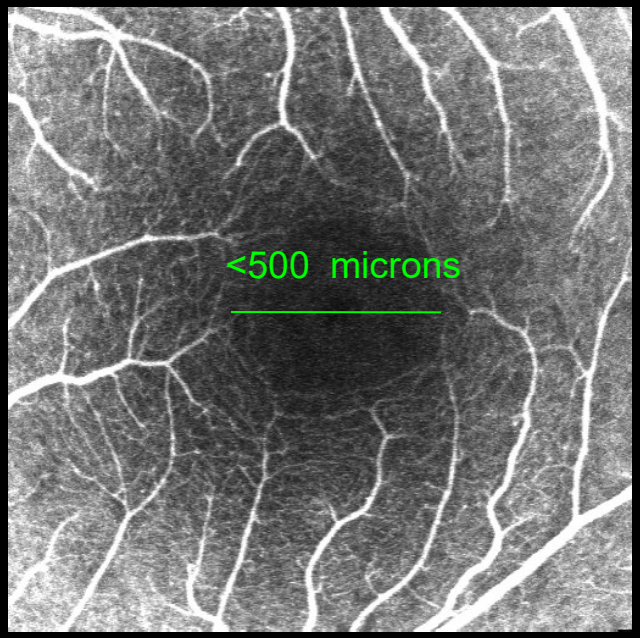

C

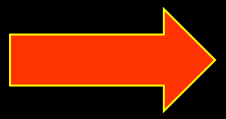
Maculopatia ischemica

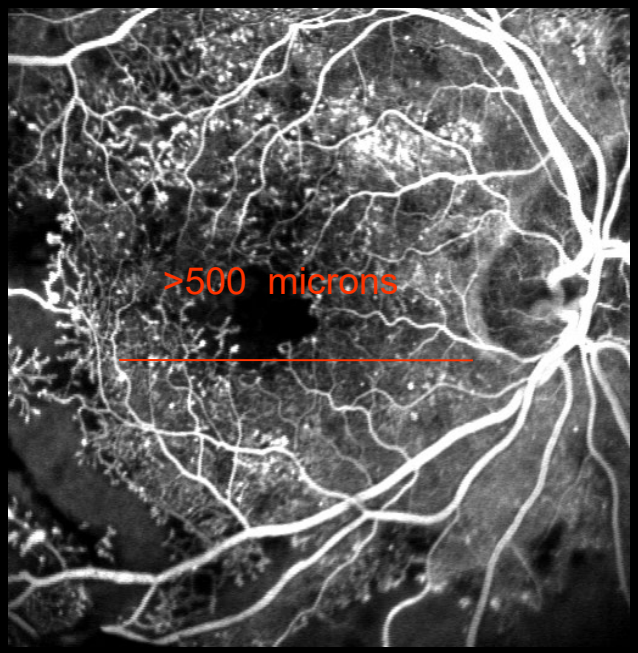
OCCLUSIONE CAPILLARE











ALLARGAMENTO DELLA ZONA AVASCOLARE FOVEALE

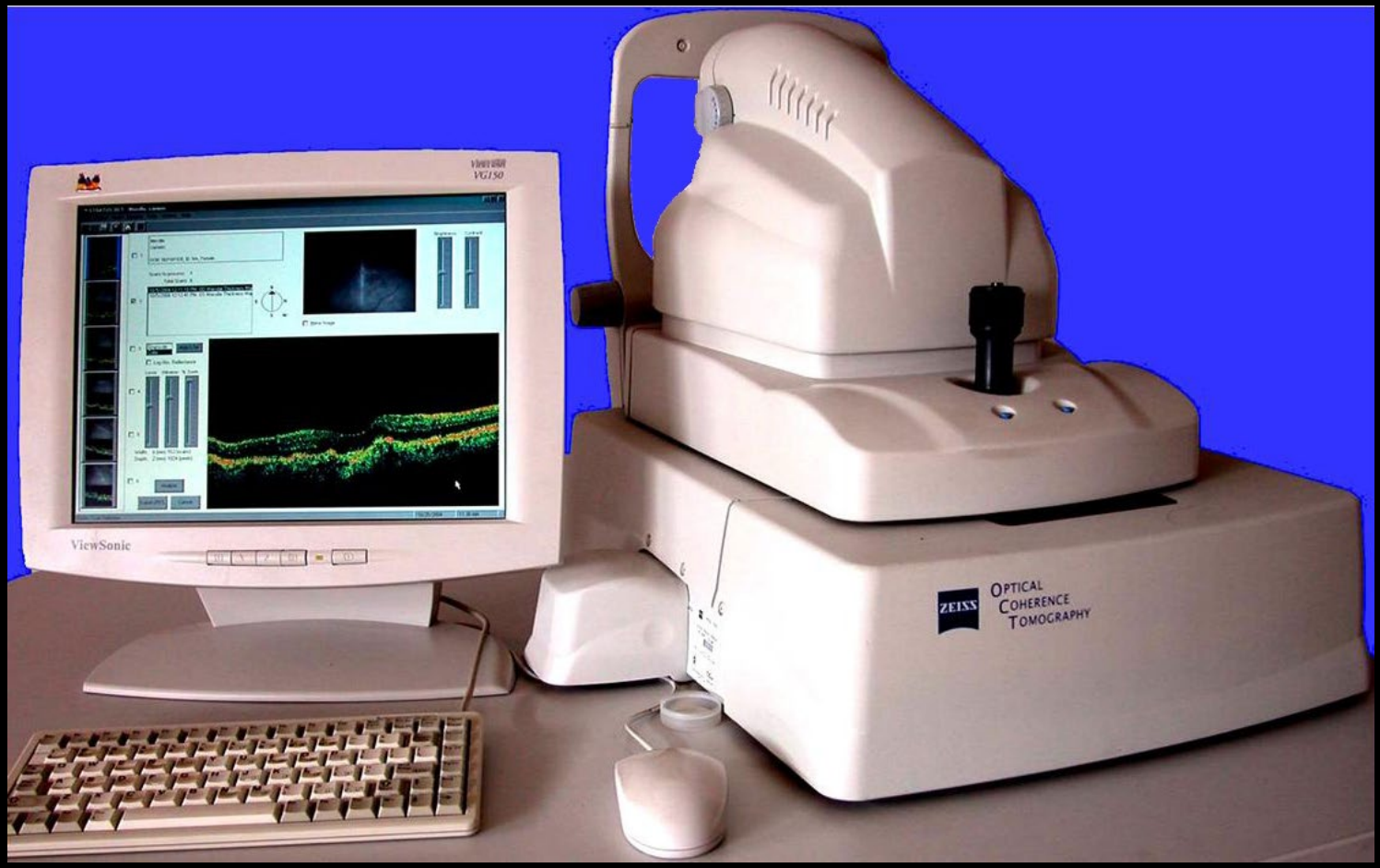
(se >1000 micron l'acuità visiva è fortemente compromessa)

- ecografia oculare
- iridografia
- tomografia ottica a luce coerente (OCT)

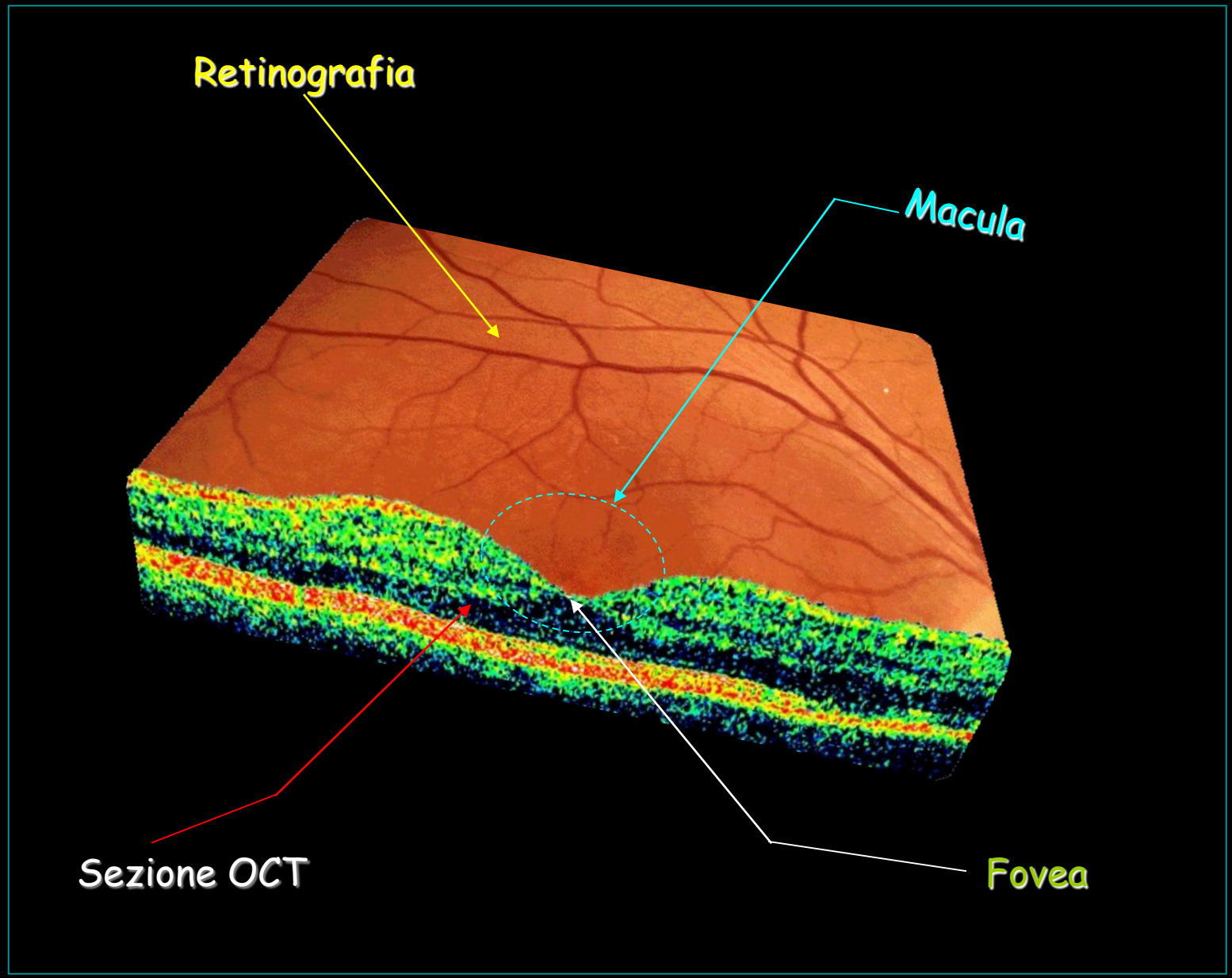
Tomografia ottica a luce coerente (OCT)

OCT al fine di quantificare e documentare lo spessore retinico a livello maculare e per meglio visualizzare le eventuali trazioni vitreo -retiniche.

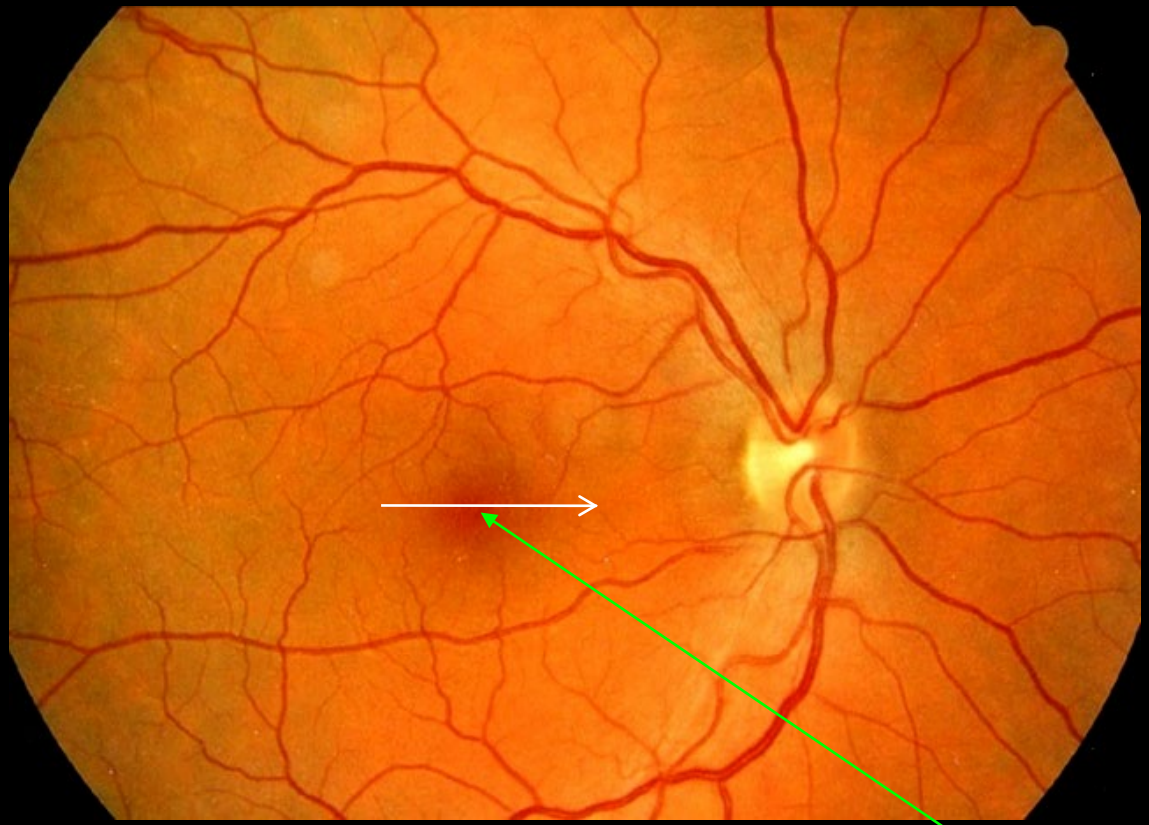
L' OCT (Optical Coherence Tomography)

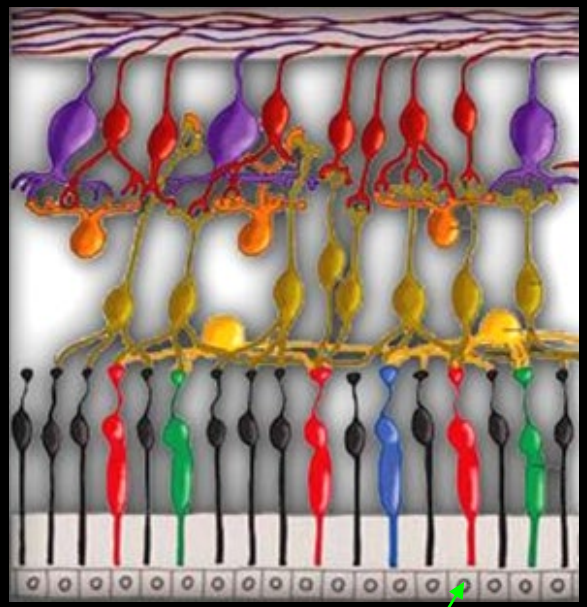


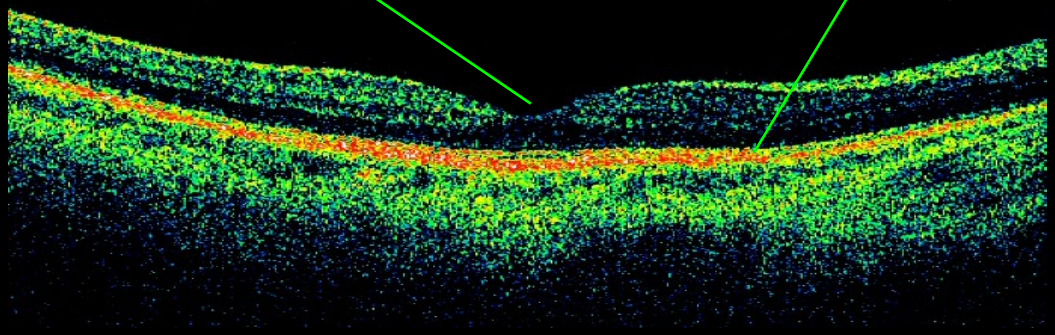
L' OCT (Optical Coherence Tomography) è una moderna tecnica diagnostica per immagini basata sull'analisi della riflessione di una radiazione semicoerente da parte del tessuto esaminato.


Retinografia
Macula
Sezione OCT
Fovea

Fondo sano

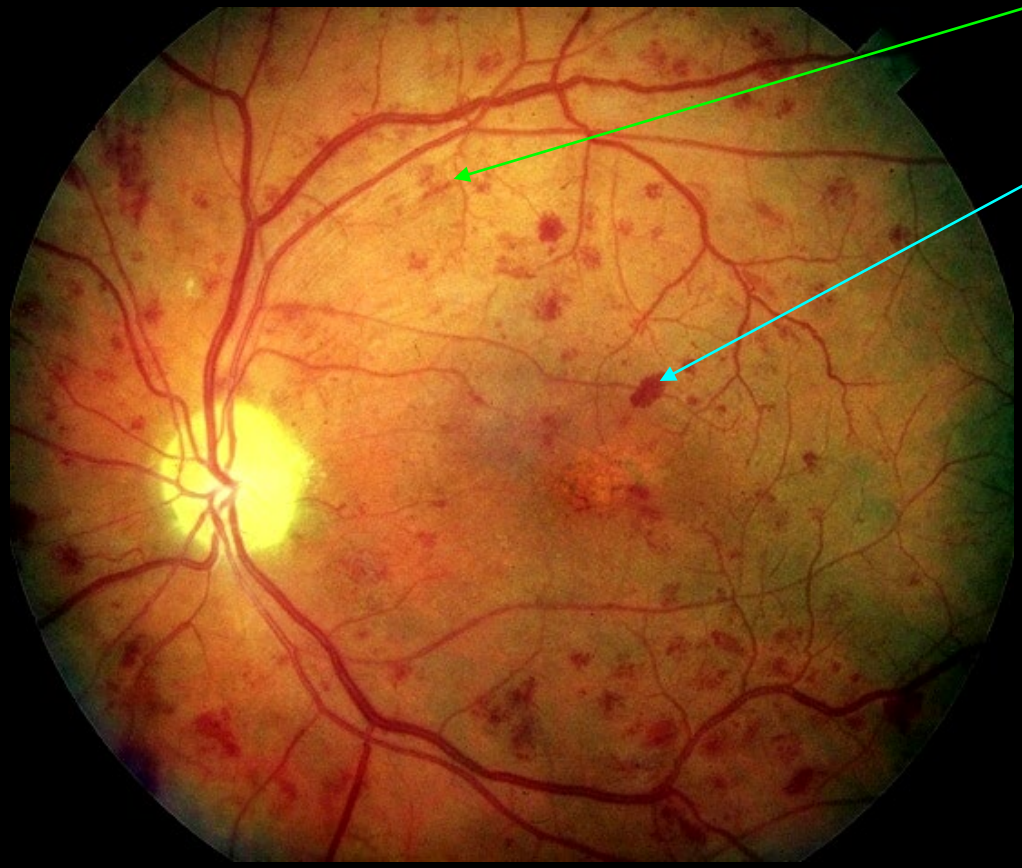


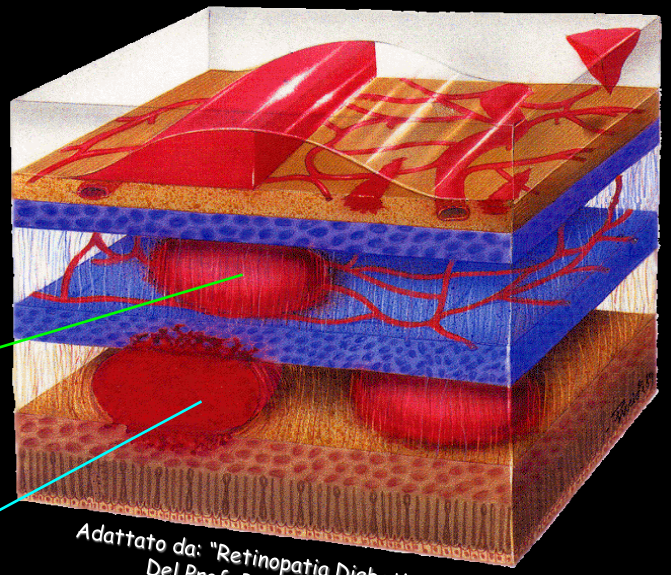




Sezione OCT normale

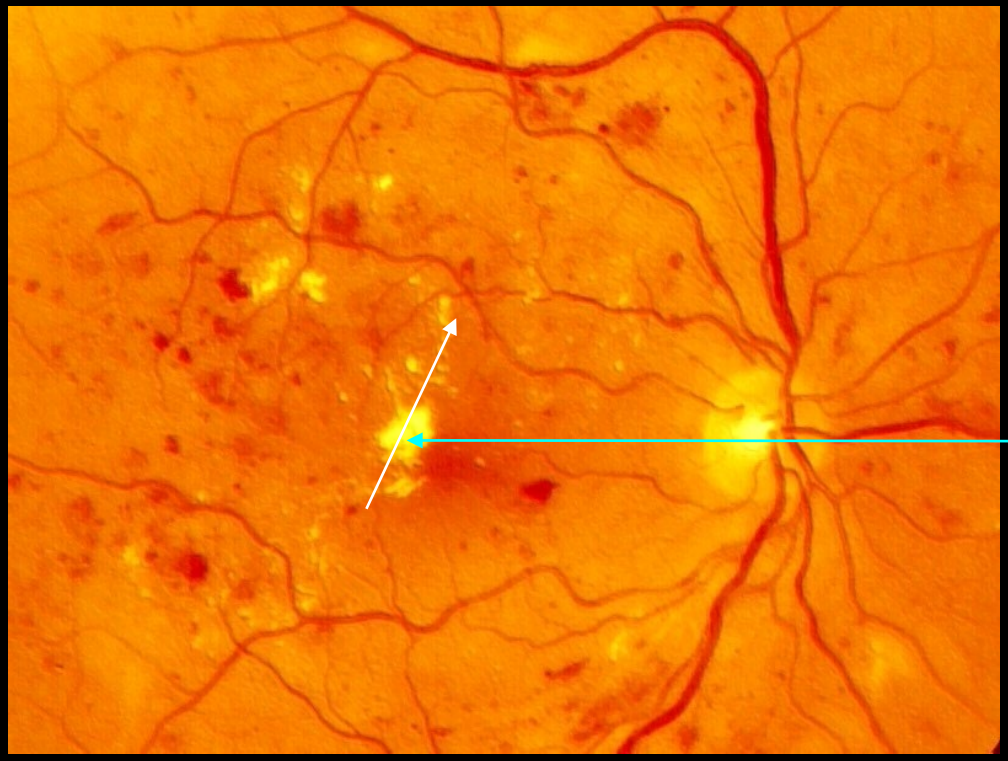
Emorragie retiniche

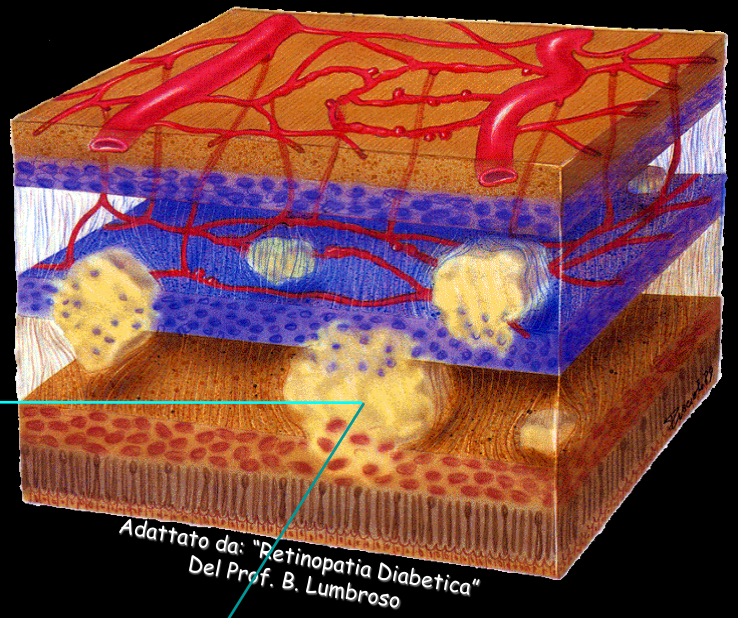




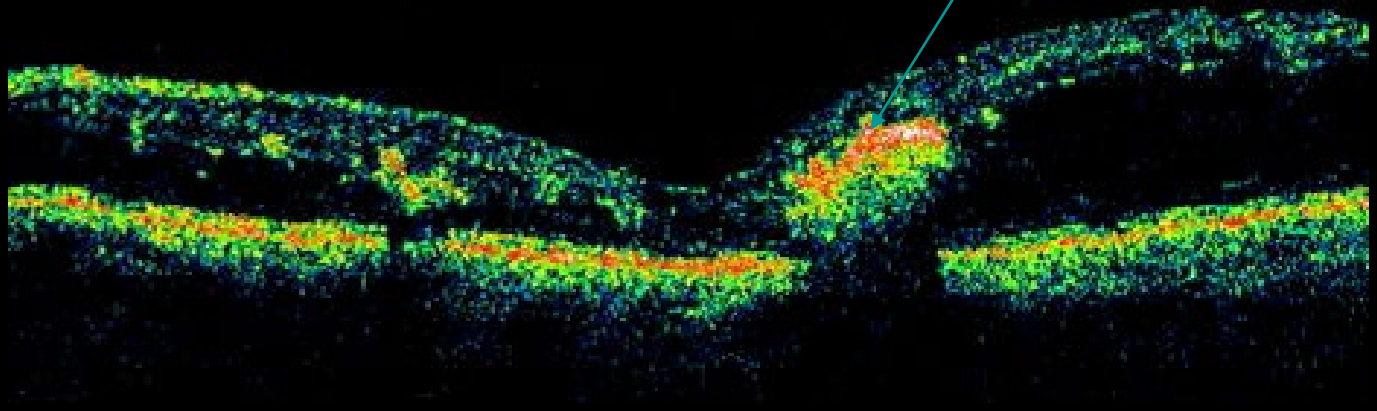
Adattato da: "Retinopatia Diabetica"
Del Prof. B. Lumbroso

Essudati duri

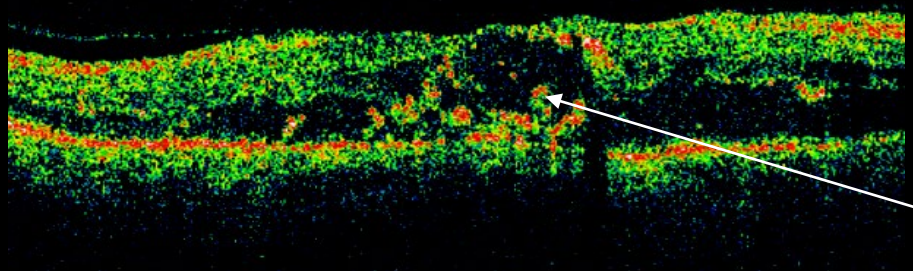


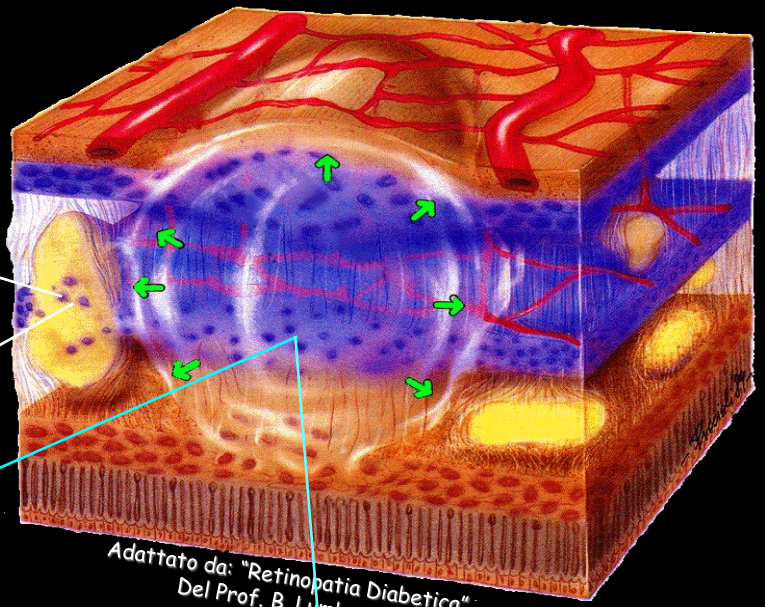


Adattato da: "Retinopatia Diabetica"
Del Prof. B. Lumbroso

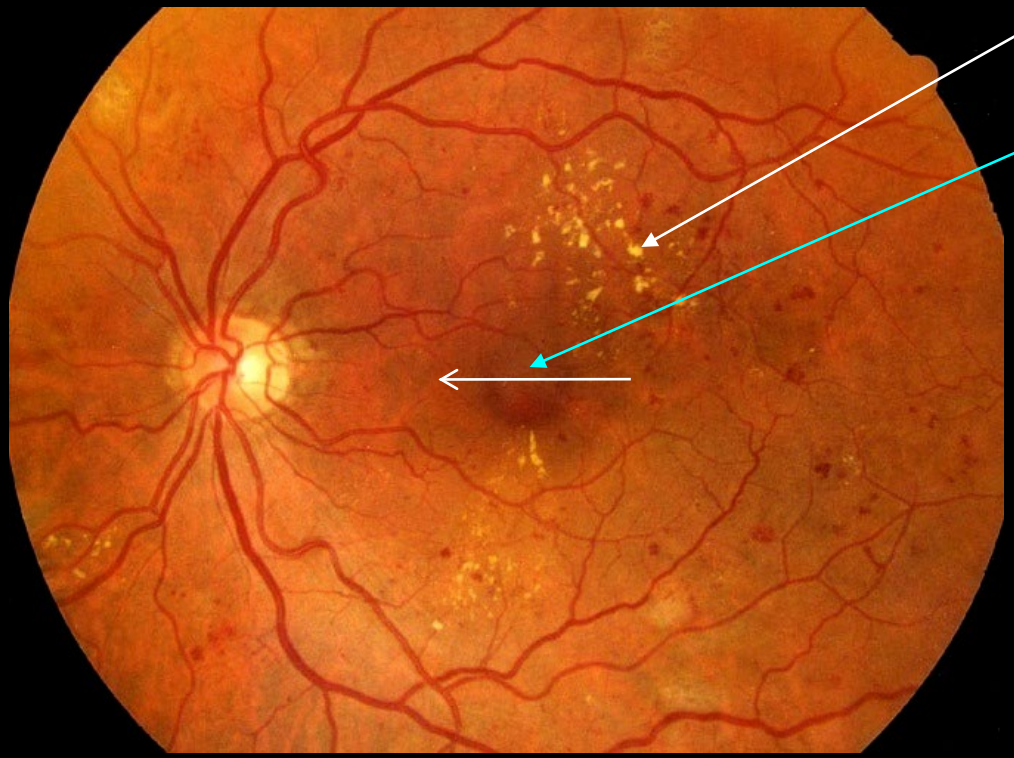


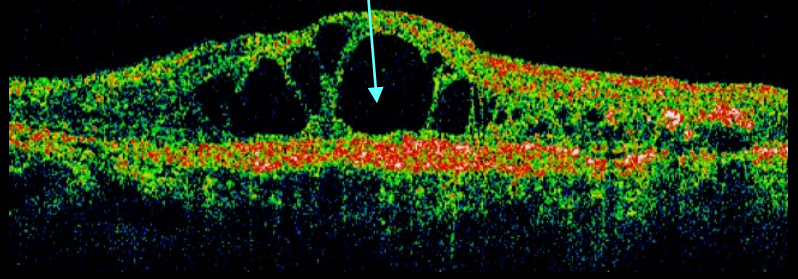
Edema maculare cistoide ed essudati



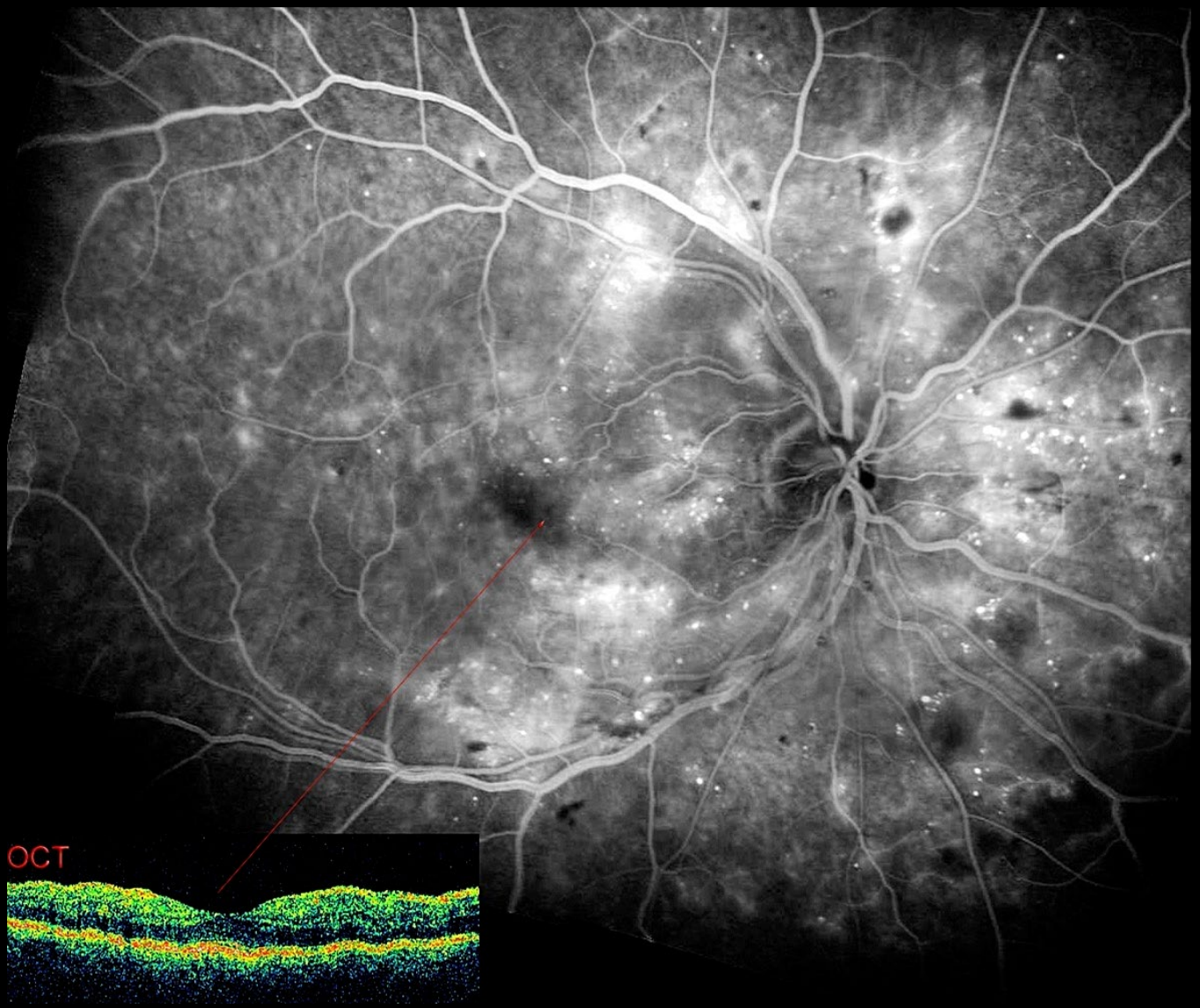


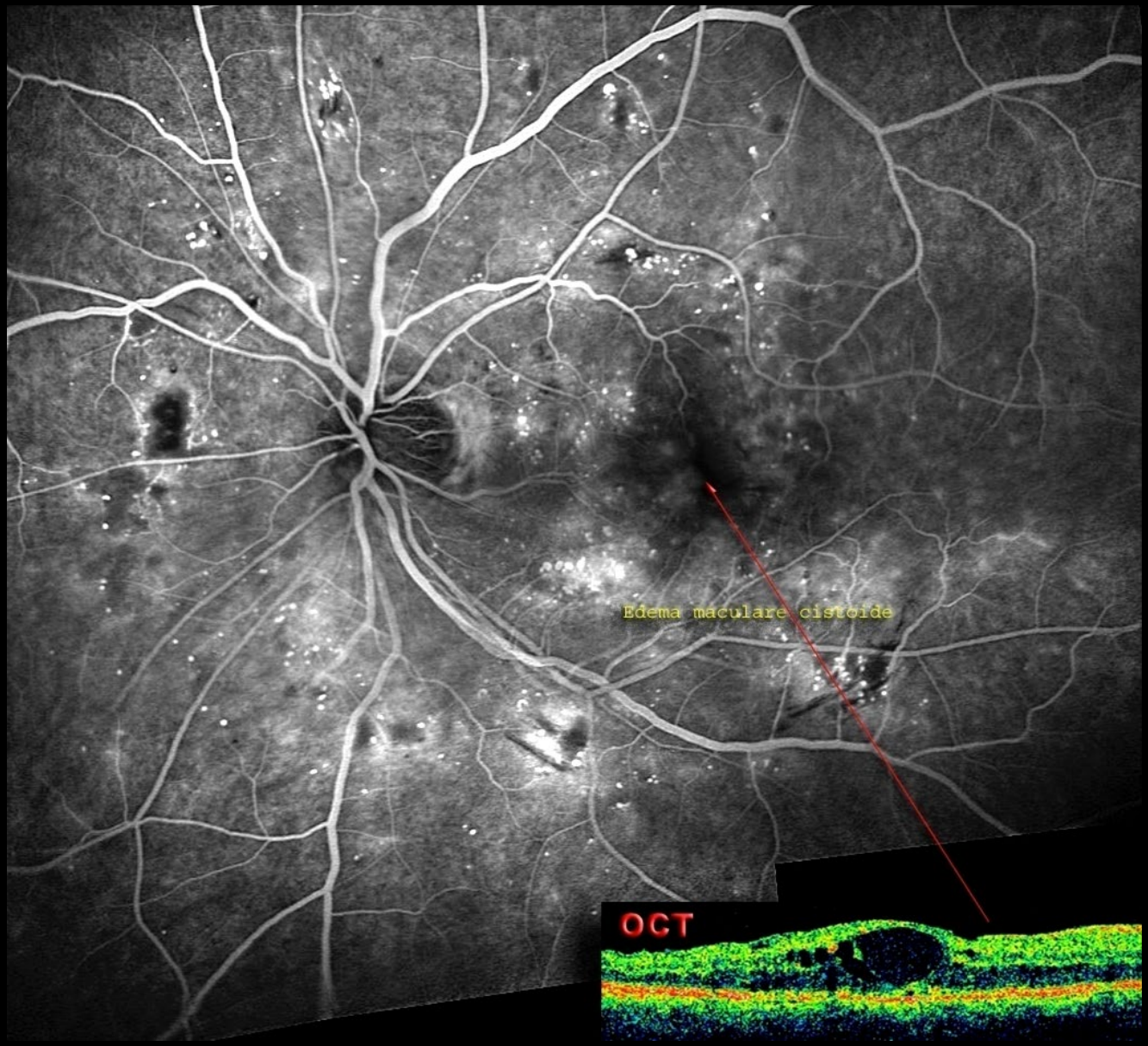
Adattato da: "Retinopatia Diabetica"
Del Prof. B. Lumbroso



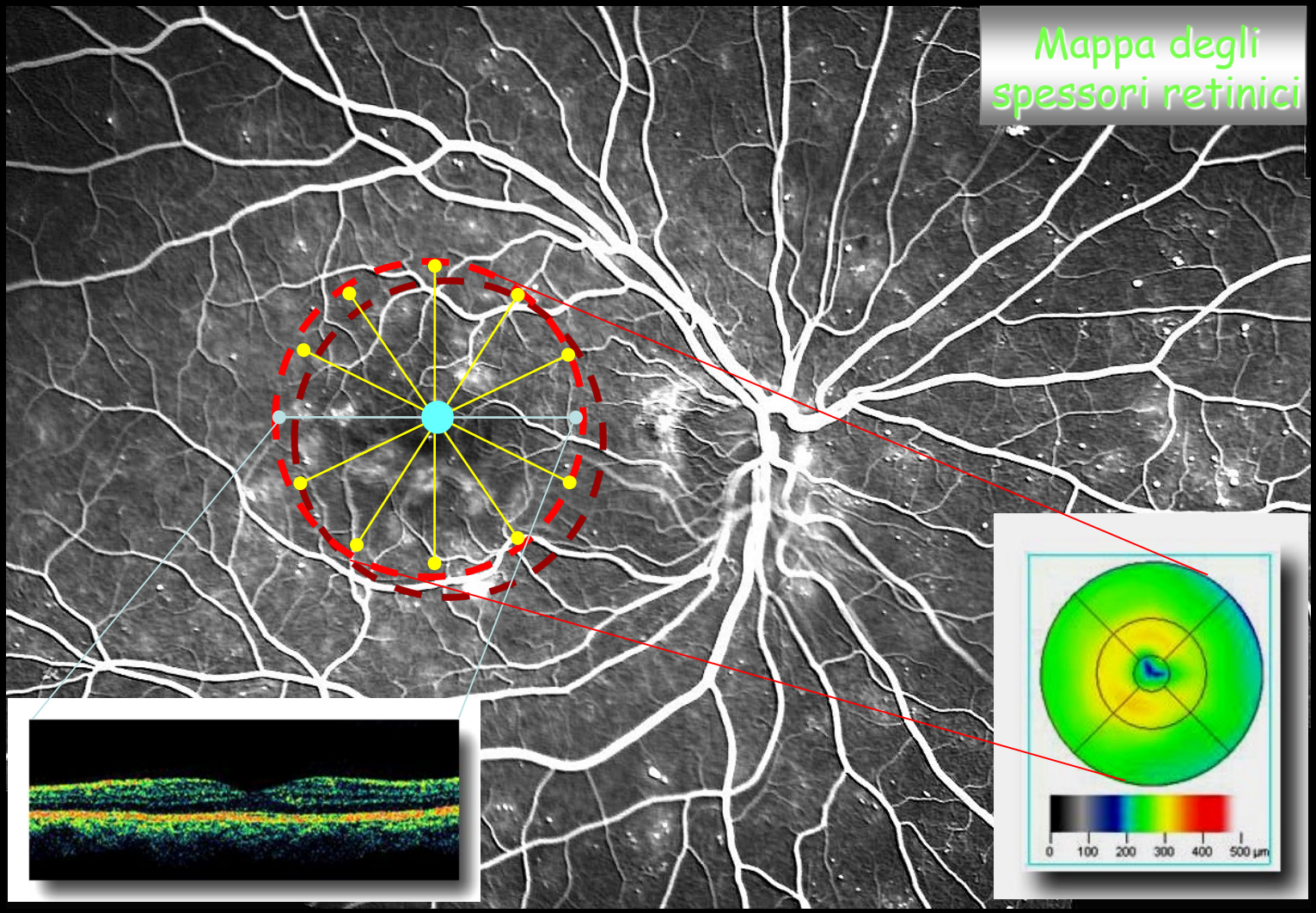


Edema maculare diffuso non cistoide



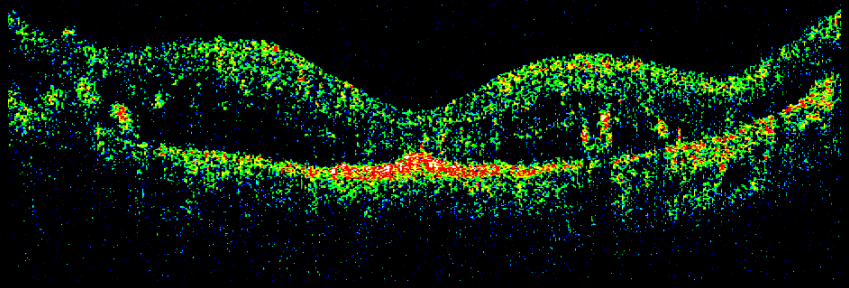

Edema maculare cistoide
OCT

Mappa degli spessori retinici

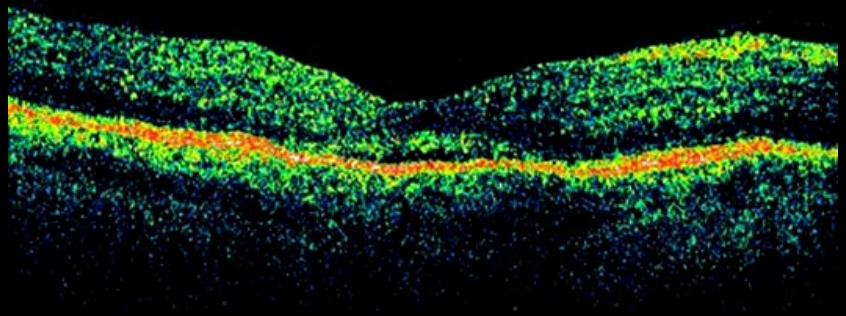


Forme di Edema Maculare

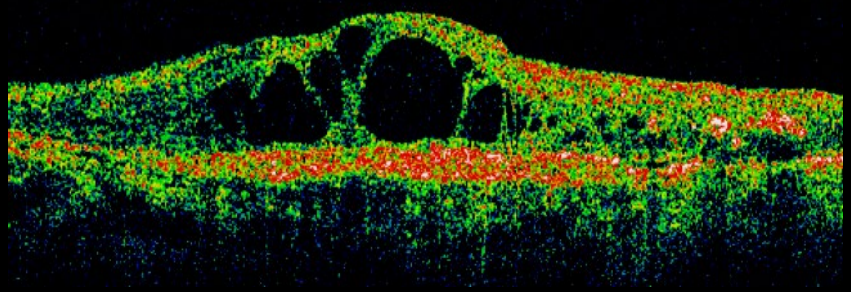
spugnoso (42% dei casi)



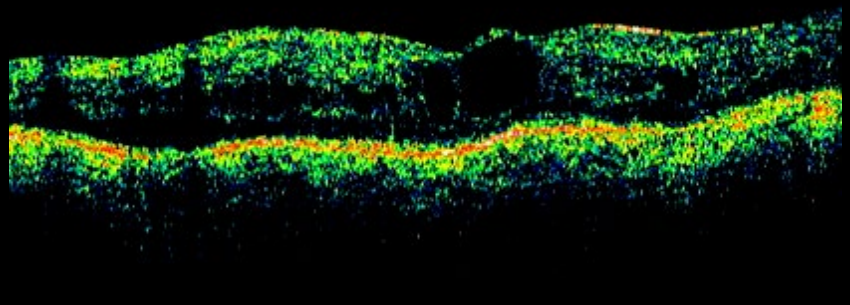
spugnoso e distacco sieroso (10% dei casi)



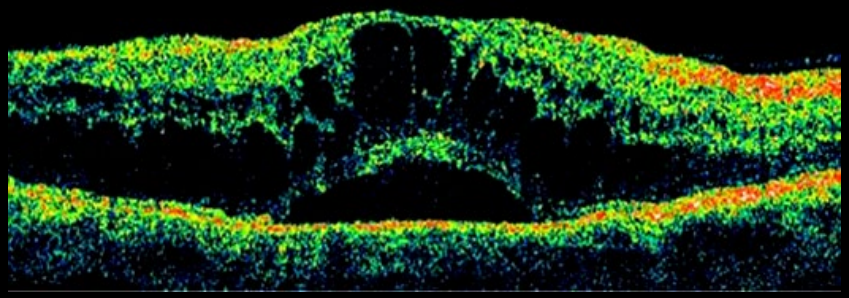
cistoide (12% dei casi)



spugnoso e cistoide (30% dei casi)



spugnoso, distacco sieroso e cistoide (5% dei casi)



Otani, Kishi and Maruyama

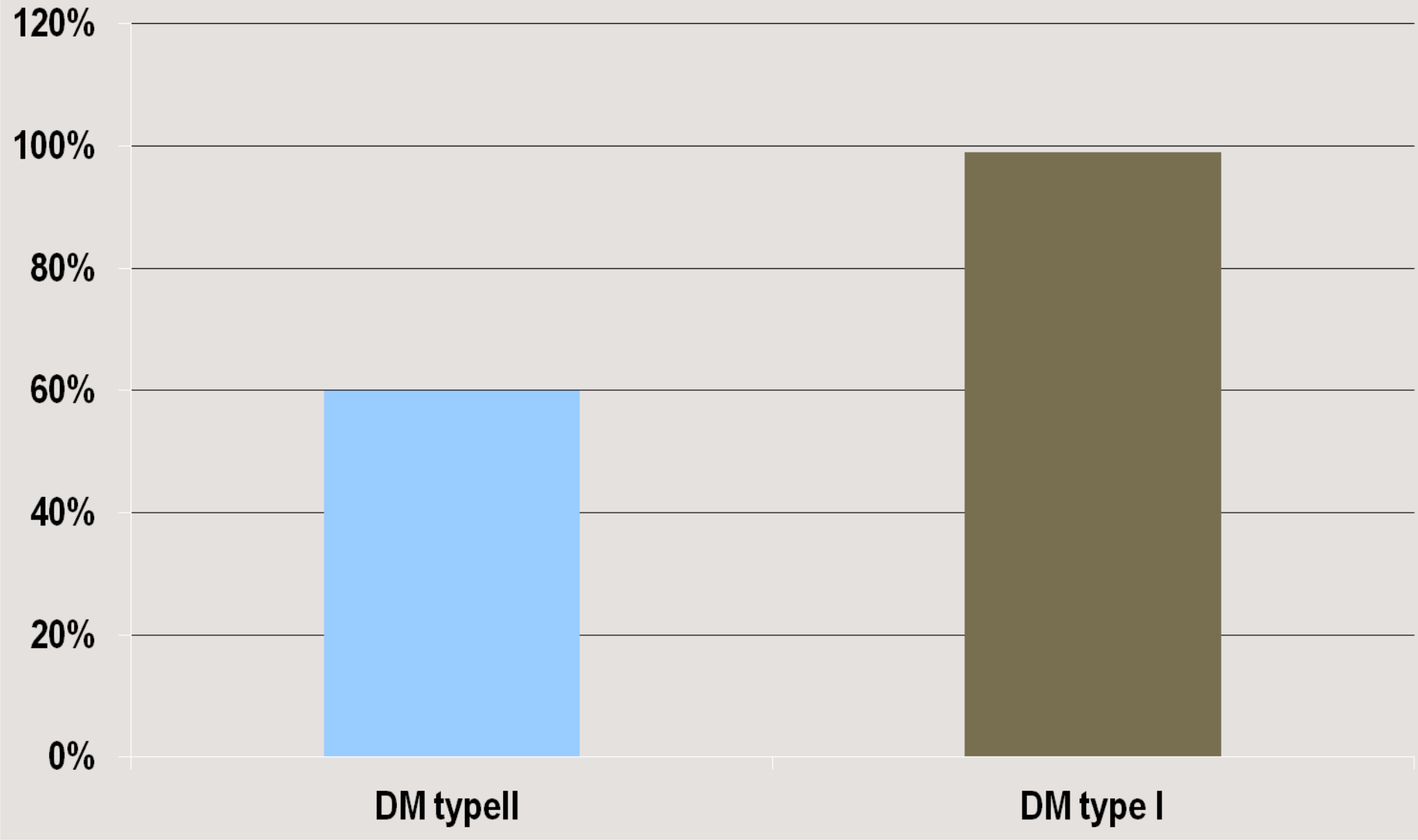
Am J Ophthalomol 1999; 1277:688-633

Cenni sulla prevenzione della Retinopatia diabetica

La durata della malattia è il maggiore fattore di rischio per l'evoluzione della retinopatia diabetica.

✓Dopo 5 anni	20%
✓Dopo 10 anni	45 – 55%
✓Dopo 15 anni	80%

Prevalence of diabetic retinopathy after 20 years of diagnosis



I principali fattori di rischio associati alla comparsa più precoce e ad una evoluzione più rapida della retinopatia sono:

- la durata del diabete
- lo scompenso glicemico
- l'eventuale ipertensione sistemica concomitante

Fattori di rischio

NON MODIFICABILI

- ✓età di insorgenza
- ✓durata della malattia
- ✓genetica

MODIFICABILI

- ✓iperglicemia
- ✓ipertensione arteriosa
- ✓microalbuminuria
- ✓colesterolo - trigliceridi
- ✓nefropatia
- ✓gravidanza
- ✓fumo

Sulla prevenzione della retinopatia diabetica

E' indispensabile stretto controllo
dell'iperglicemia e dell' ipertensione
per ridurre la comparsa e/o l'evoluzione
della retinopatia diabetica

La dislipidemia
rappresenta un fattore di rischio per la perdita del visus

La gravidanza
è un fattore di rischio per la progressione della retinopatia

Il fumo
è un fattore di rischio per malattie
cardiovascolari in tutti i pazienti con diabete

The Effect of Intensive Diabetes Treatment On the Progression of Diabetic Retinopathy In Insulin-Dependent Diabetes Mellitus

The Diabetes Control and Complications Trial

The Diabetes Control and Complications Trial Research Group

Intensive control reduced the risk of developing retinopathy by 76% and slowed progression of retinopathy by 54%; intensive control also reduced the risk of clinical neuropathy by 60% and albuminuria by 54%.

Arch Ophthalmol. 1995; 113:36-51

Primary prevention

Strict glycemic control

Blood pressure control

Secondary prevention

Screening RD

Tertiary prevention

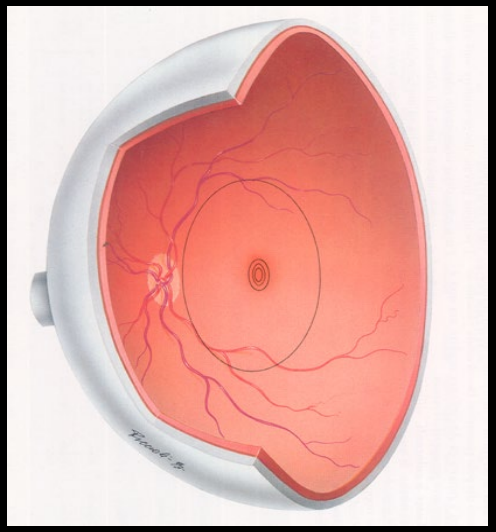
Retinal Laser photocoagulation

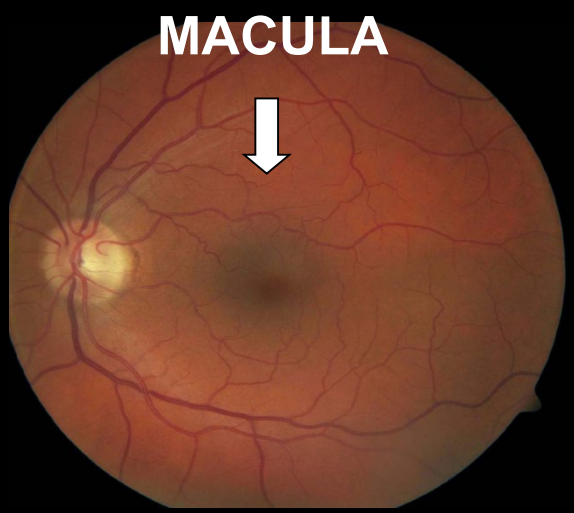
Vitrectomy

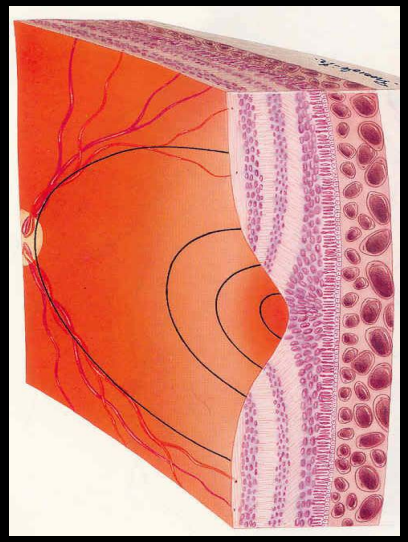
Sintomatologia

Le alterazioni della vista sono sempre tardive rispetto all'insorgere della malattia che può evolvere a lungo asintomatica

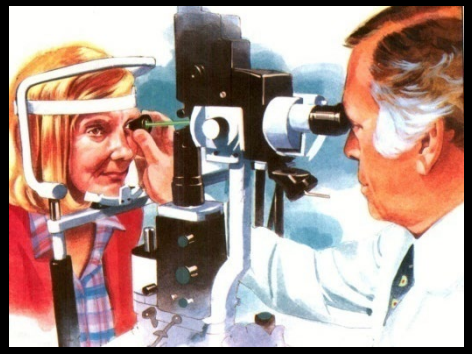
La diminuzione della vista si ha solo quando la malattia coinvolge la regione centrale della retina (macula)







Prevenzione



Prima visita oculistica in dilatazione:

Diabete tipo I : alla diagnosi, dopo 5 anni dalla diagnosi o alla pubertà

Diabete tipo II : alla diagnosi

Gravidanza : alla conferma della gravidanza, ogni tre mesi fino al parto

RECOMMENDED EYE EXAMINATION SCHEDULE

Diabetes Type	Recommended Time of First Examination	Recommended Follow-up*
Type 1	3-5 years after diagnosis	Yearly
Type 2	At time of diagnosis	Yearly
Prior to pregnancy (type 1 or type 2)	Prior to conception and early in the first trimester	No retinopathy to mild moderate NPDR every 3-12 months Severe NPDR or worse every 1-3 months.

*Abnormal findings may dictate more frequent follow-up examinations

h ttp://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=d0c853d3-219f-487b-a524-326ab3cecd9a

Primary prevention

Strict glycemic control

Blood pressure control

Secondary prevention

Screening RD

Tertiary prevention

Retinal Laser photocoagulation

Vitrectomy

Trattamento

FOTOCOAGULAZIONE LASER

to seal leaking blood vessels (focal laser)

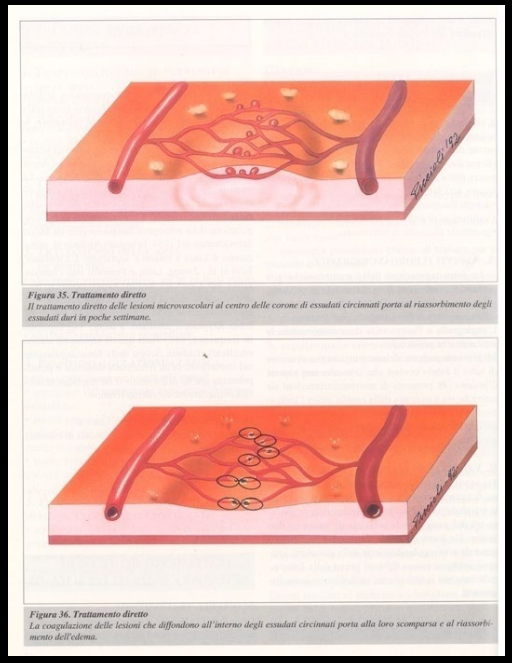
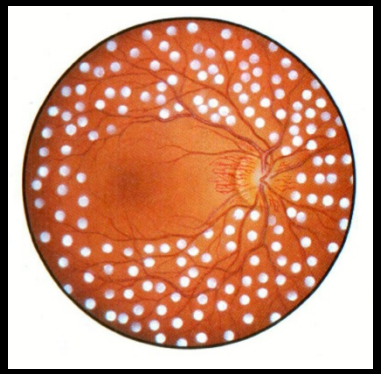


Figura 35. Trattamento diretto
Il trattamento diretto delle lesioni microvascolari al centro delle corone di essudati circinnati porta al riassorbimento degli essudati duri in poche settimane.

Figura 36. Trattamento diretto
La coagulazione delle lesioni che diffondono all'interno degli essudati circinnati porta alla loro scomparsa e al riassorbimento dell'edema.



Laser therapy to reduce retinal oxygen demand (scatter laser)

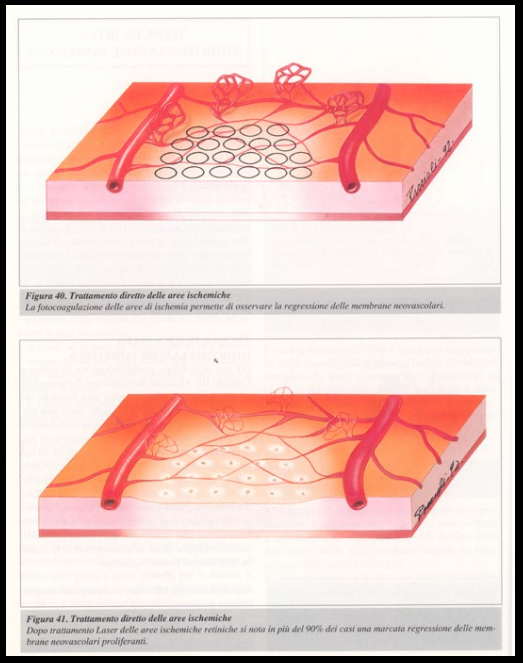
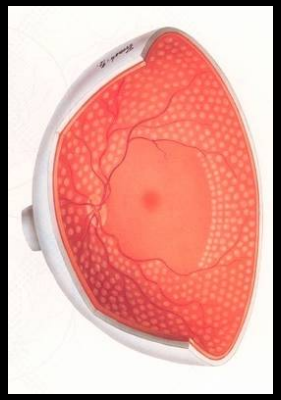
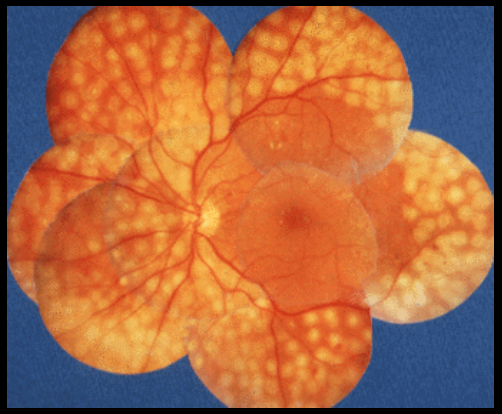


Figura 40. Trattamento diretto delle aree ischemiche
La fotocoagulazione delle aree di ischemia permette di osservare la regressione delle membrane neovascolari.

Figura 41. Trattamento diretto delle aree ischemiche
Dopo trattamento Laser delle aree ischemiche retiniche si nota in più del 90% dei casi una marcata regressione delle membrane neovascolari proliferanti.



Panfotocoagulazione laser (PFC)

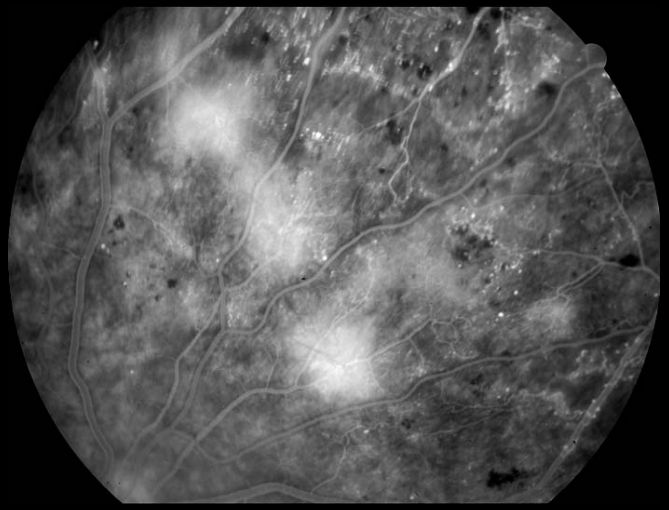


La PFC deve essere eseguita:

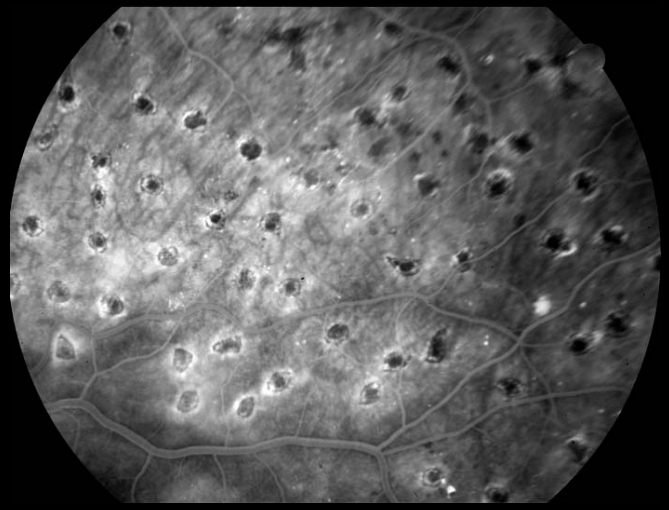
-RD proliferante ad alto rischio con neovascolarizzazioni papillari o retiniche associate a emorragie preretiniche o vitreali

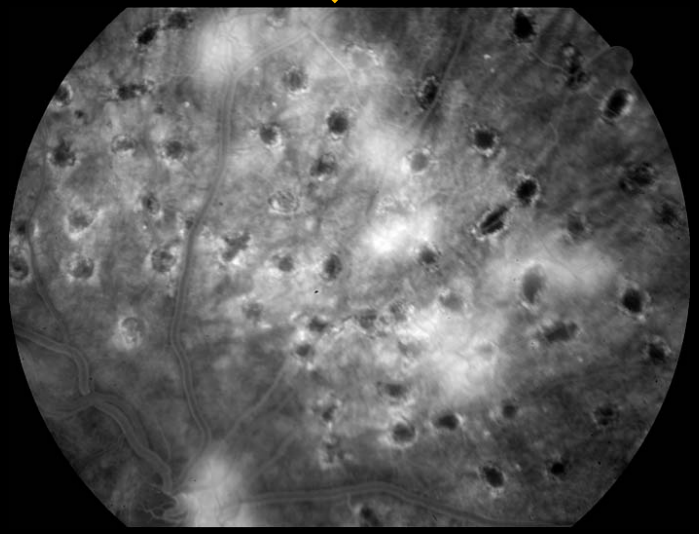
-RD proliferante non al alto rischio, RD non proliferante grave se il monitoraggio non è garantito

Trattamento



PFC



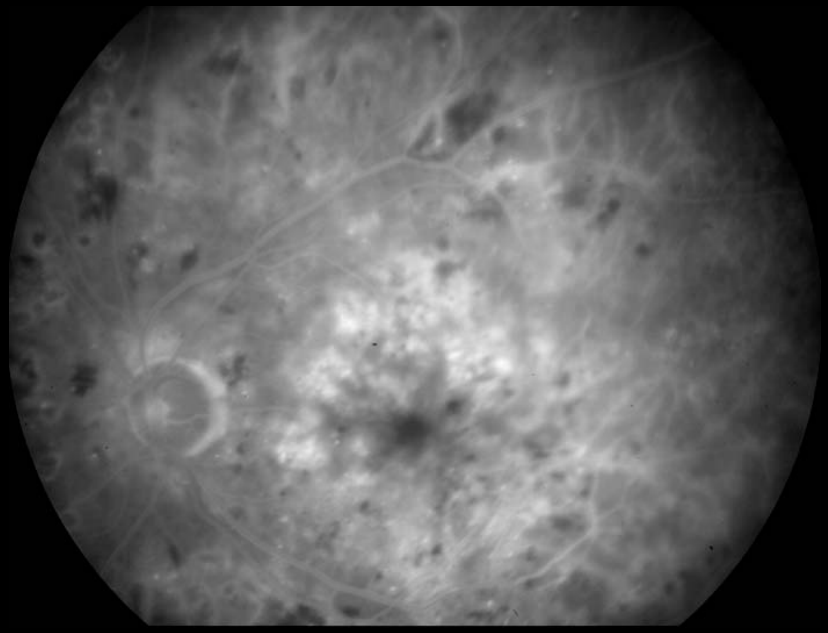


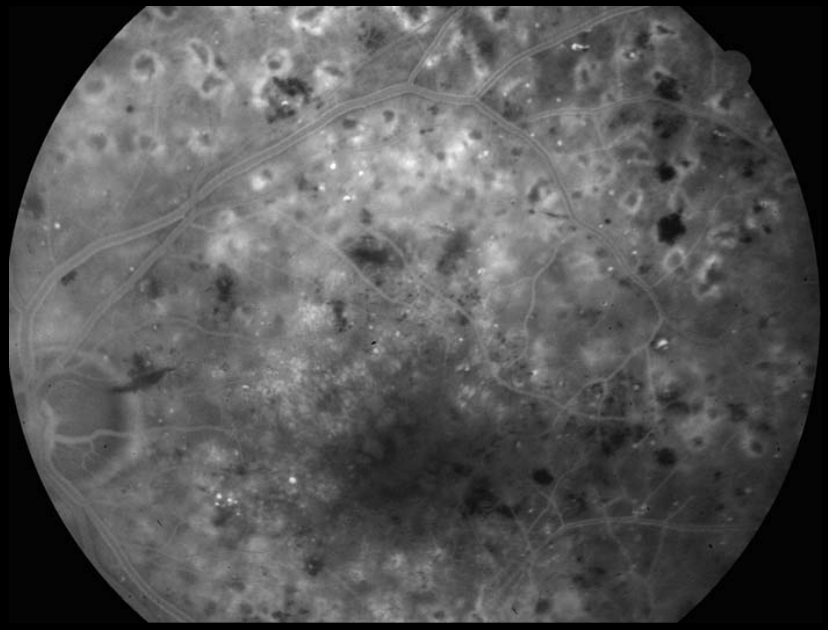
Controlli ogni 4 mesi
dopo il trattamento
Ritrattamento di lesioni
persistenti o recidivanti

Fotocoagulazione laser panretinica

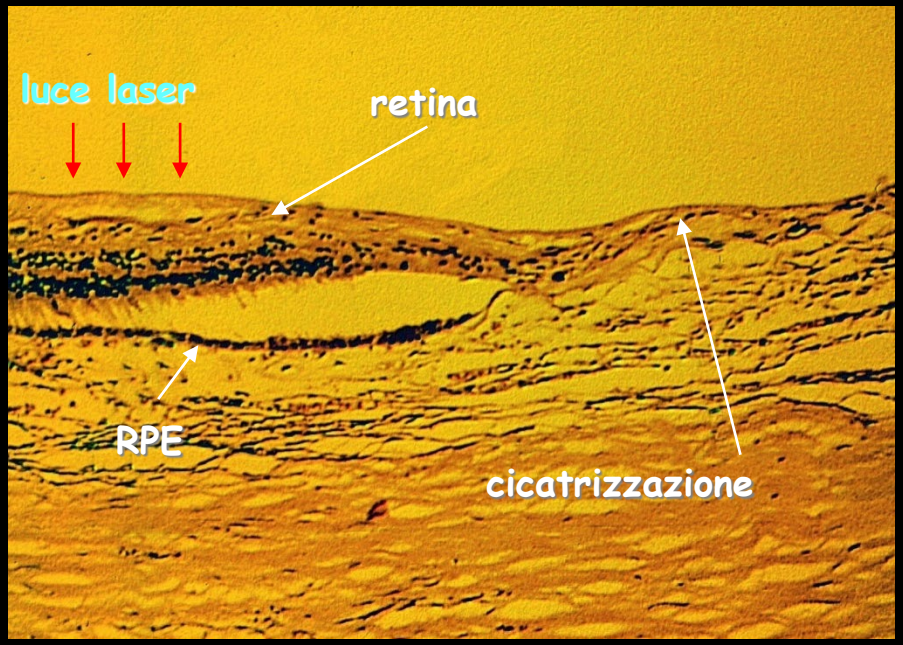
Trattamento

Trattamento focale dell'Edema Maculare
(prima della PFC, se programmata)

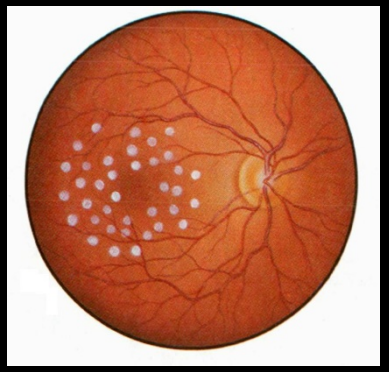


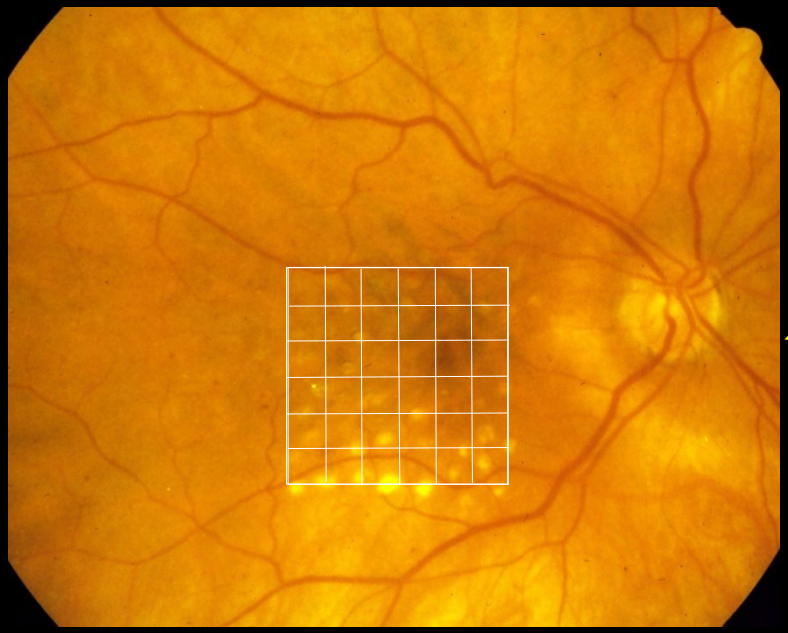


Trattamento laser focale

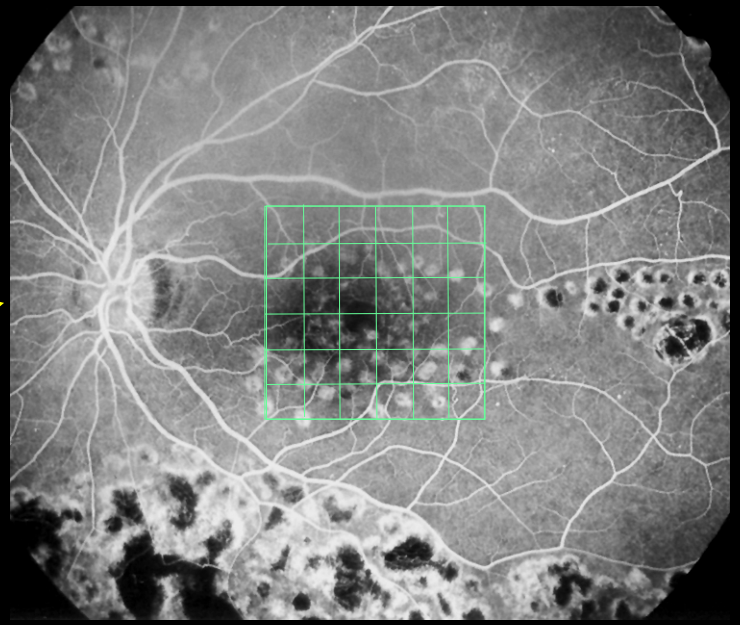


Trattamento laser a griglia





Retinografia a colore



Fluorangiografia

Trattamento laser dell'edema maculare

EM clinicamente significativo non centrale

EM che coinvolge il centro della macula con riduzione della AV e spessore OCT < 400 μm

Terapia antiangiogenica

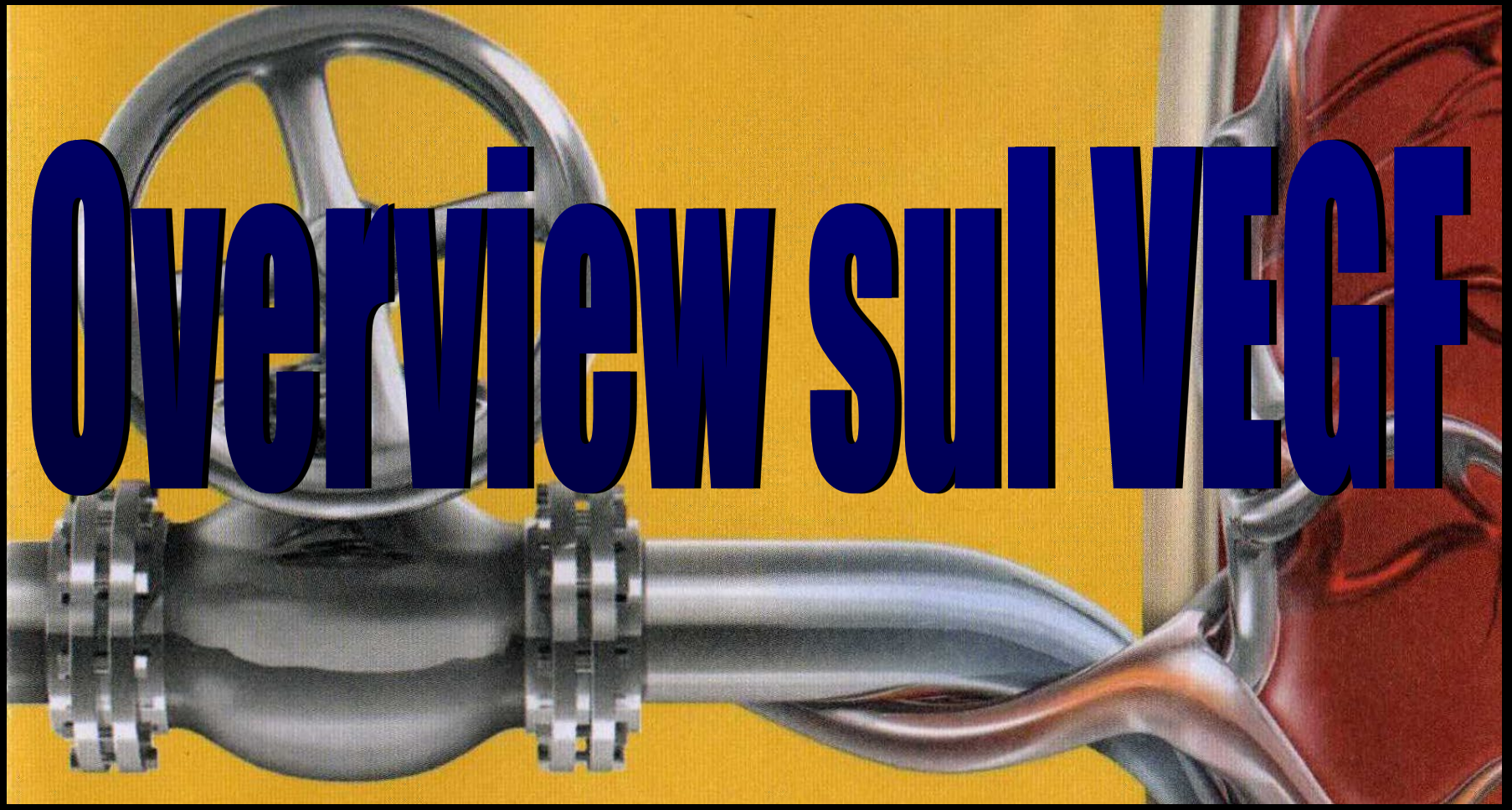
EM che coinvolge il centro della macula con riduzione della AV e spessore OCT > 400 μm

DIABETIC RETINOPATHY TREATMENT NEWER DEVELOPMENTS:

The use of anti-vascular endothelial growth factor antibodies has been shown to be useful in the treatment of DR

Anti-VEGF antibody treatment appears to be useful for both macular edema and proliferative retinopathy

Studies to determine the exact role of anti-VEGF treatment in relation to laser treatment in specific situations are underway.


Overview sul VEGF

Angiogenesi

FISIOLOGICA

- Embriogenesi
- Ciclo mestruale
- Riparazione ferite

PATOLOGICA

- Neoplasia
- Artrite
- Endometriosi
- Retinopatia diabetica
- DMLE essudativa
- Psoriasi
- Ulcere
- Ischemia
- Cardiovasculopatia

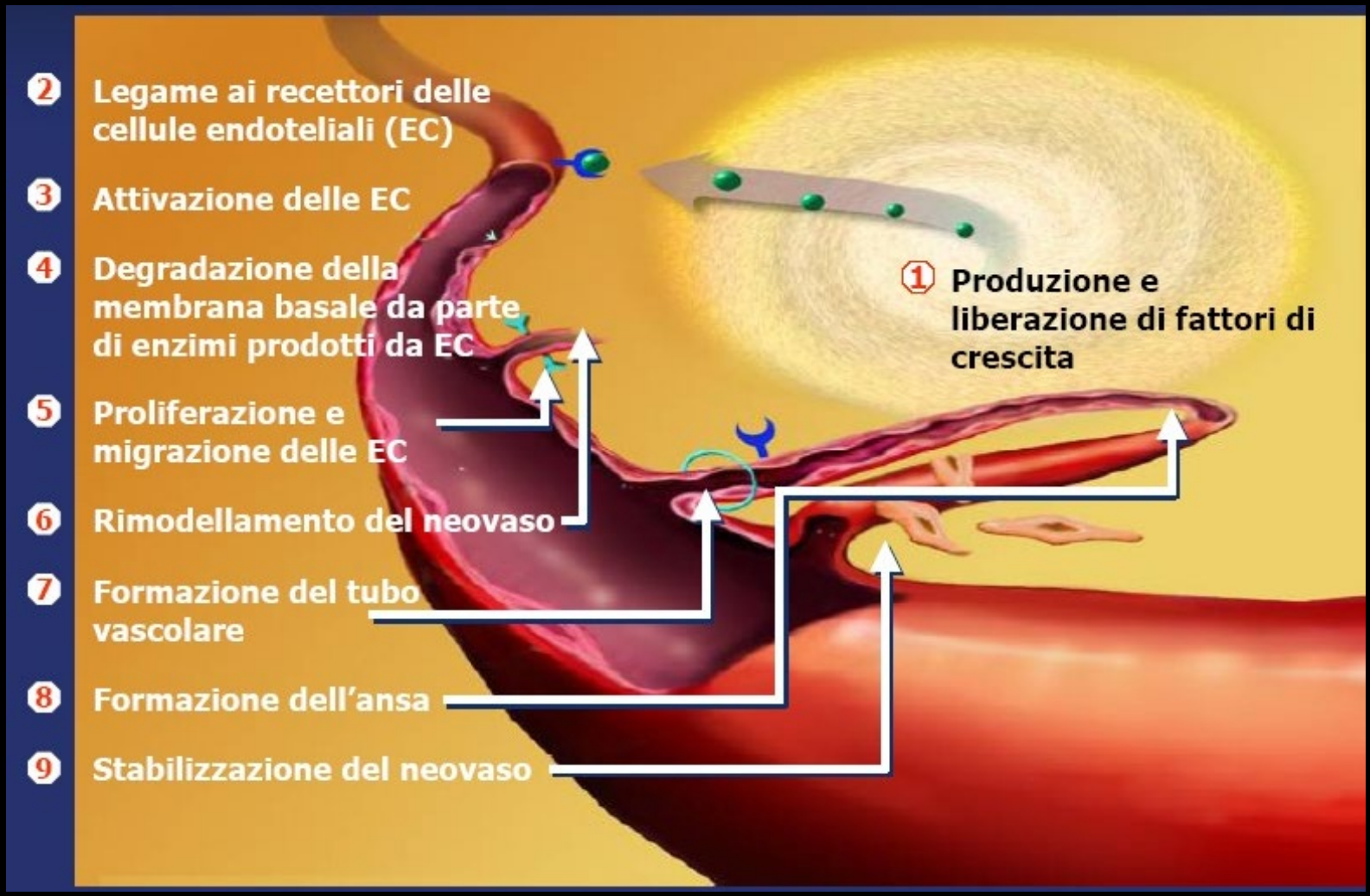
ECCESSIVA

ANGIOGENESI

INSUFFICIENTE

Angiogenesi

Una serie ordinata di eventi altamente regolata



Fattori di Crescita Angiogenici

- Angiogenin
- Angiopoietin-1
- Del-1
- Fibroblast growth factors: acidic (aFGF) and basic (bFGF)
- Follistatin
- Granulocyte colony-stimulating factor (G-CSF)
- Hepatocyte growth factor (HGF) /scatter factor (SF)
- Interleukin-8 (IL-8)
- Leptin
- Midkine
- Placental growth factor
- Platelet-derived endothelial cell growth factor (PD-ECGF)
- Platelet-derived growth factor-BB (PDGF-BB)
- Pleiotrophin (PTN)
- Progranulin
- Proliferin
- Transforming growth factor-alpha (TGF-alpha)
- Transforming growth factor-beta (TGF-beta)
- Tumor necrosis factor-alpha (TNF-alpha)
- Vascular endothelial growth factor (VEGF)/vascular permeability factor (VPF)

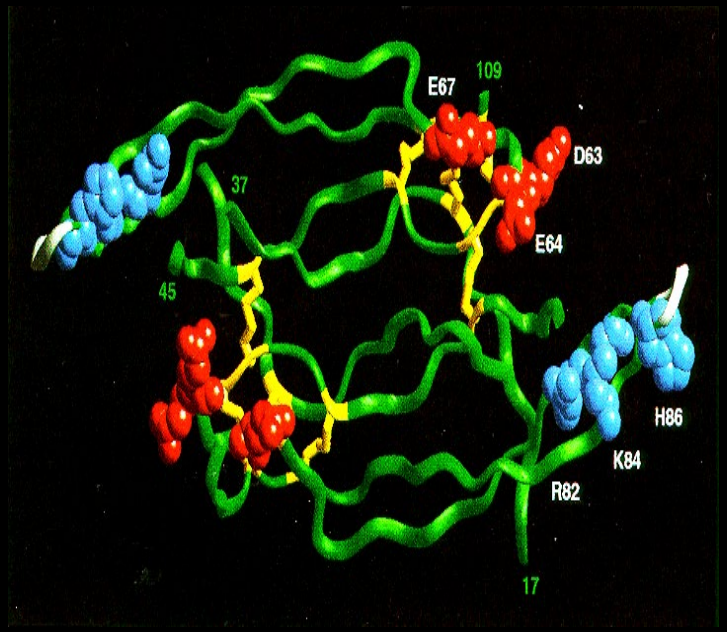
Fattori Inibenti l'Angiogenesi

- Angioarrestin
- Angiostatin (plasminogen fragment)
- Antiangiogenic antithrombin III
- Cartilage-derived inhibitor (CDI)
- CD59 complement fragment
- Endostatin (collagen XVIII fragment)
- Fibronectin fragment
- Gro-beta
- Heparinases
- Heparin hexasaccharide fragment
- Human chorionic gonadotropin (hCG)
- Interferon alpha/beta/gamma
- Interferon inducible protein (IP-10)
- Interleukin-12
- Kringle 5 (plasminogen fragment)
- Metalloproteinase inhibitors (TIMPs)
- 2-Methoxyestradiol
- Placental ribonuclease inhibitor
- Plasminogen activator inhibitor
- Platelet factor-4 (PF4)
- Prolactin 16kD fragment
- Proliferin-related protein (PRP)
- Retinoids
- Tetrahydrocortisol-S
- Thrombospondin-1 (TSP-1)
- Transforming growth factor-beta (TGF-b)
- Vasculostatin
- Vasostatin (calreticulin fragment)

Vascular Endothelial Growth Factor

- Glicoproteina omodimerica purificata e clonata nel 1989 da Ferrara[1]

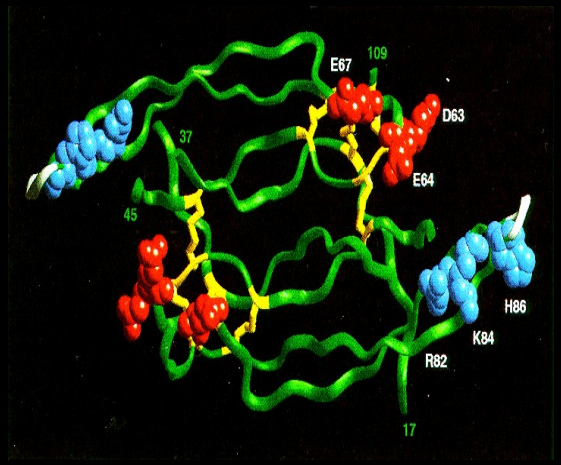
- Funzioni del VEGF
  - angiogenesi
  - permeabilita' vascolare
  - infiammazione
  - neuroprotezione

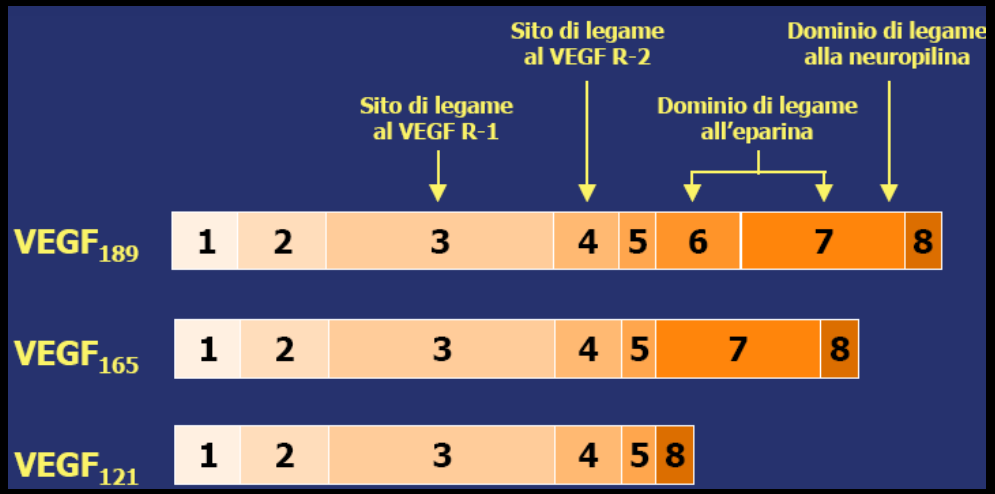


[1] *Ferrara et al. Biochem Biophys Res Commun. 1989;161:851*

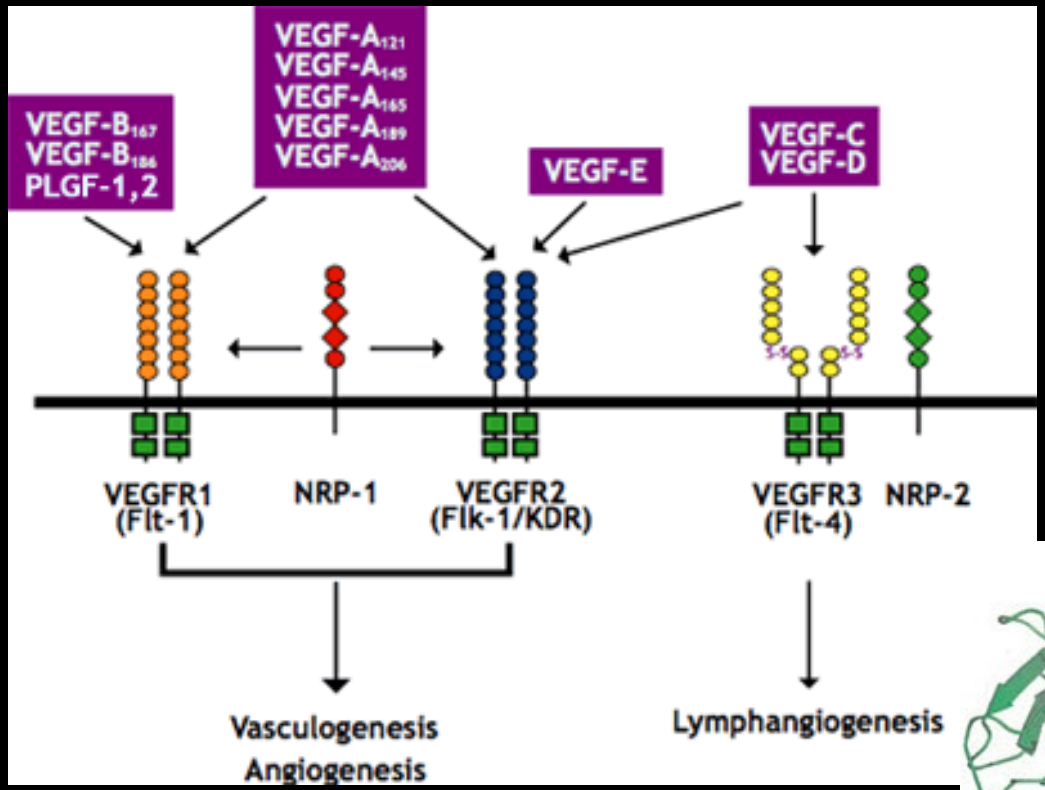
Vascular Endothelial Growth Factor

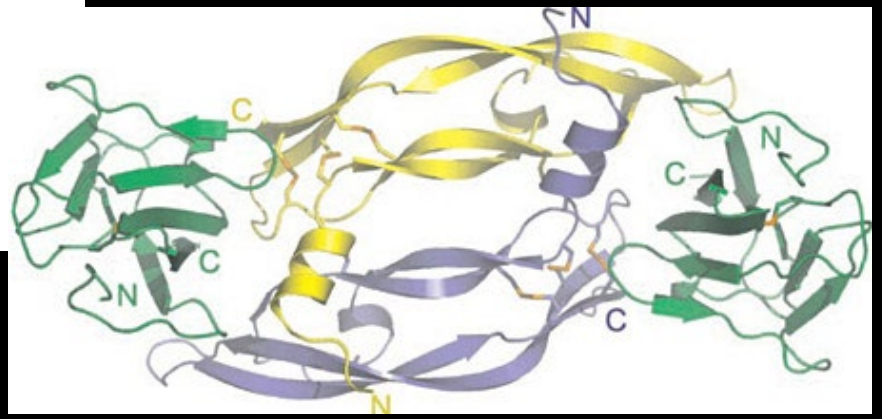
- Gene del VEGF sul cromosoma 6
  - Famiglia VEGF
    - VEGF-A
    - VEGF-B
    - VEGF-C
    - VEGF-D
    - VEGF-E
    - PIGF
  - Isoforme VEGF-A
    - $VEGF\text{-}A_{121}$
    - $VEGF\text{-}A_{165}$
    - $VEGF\text{-}A_{189}$
    - $VEGF\text{-}A_{206}$





Recettori del VEGF





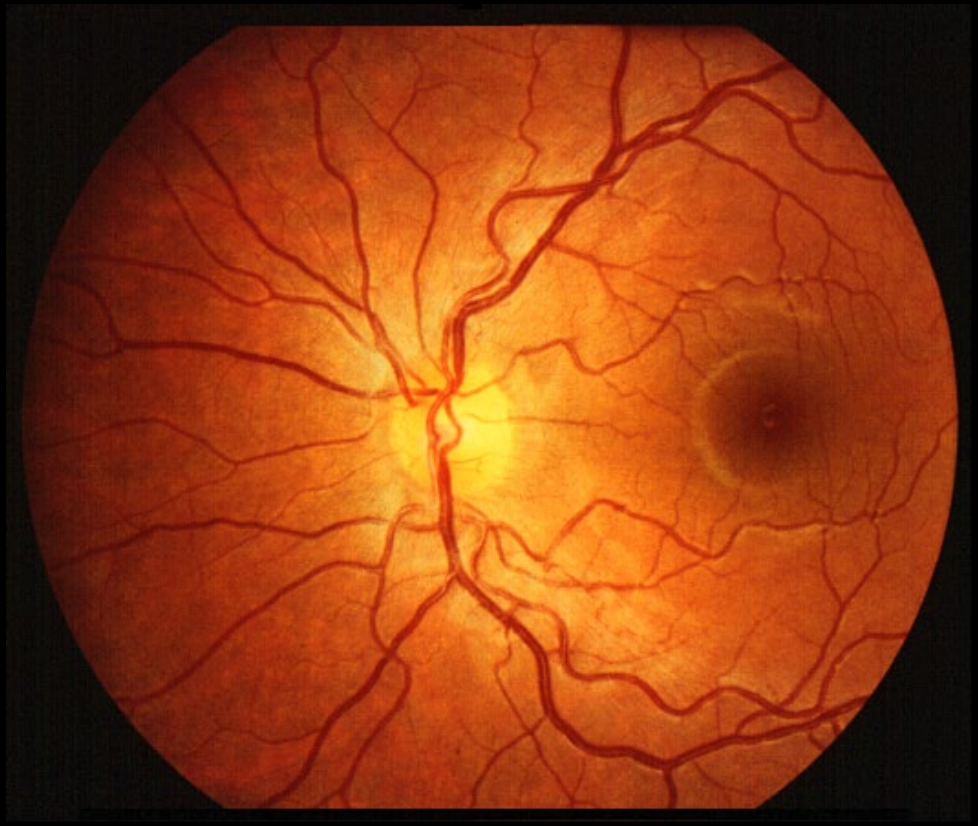
Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev. 2004; 25(4):581-611. © 2004 The Endocrine Society

Recettori del VEGF

VEGFR-1[1,2]	Cruciale per l'embriogenesi Non sembra fondamentale nella angiogenesi patologica
VEGFR-2[1,3]	Il più importante nell'angiogenesi tumorale Media la maggior parte degli effetti angiogenici del VEGF
VEGFR-3[1,4]	Presente solo nelle cellule endoteliali linfatiche Associato con metastasi linfonodali

[1]Hicklin DJ, Ellis LM. J Clin Oncol. 2005;23:1011-1027
[2]Olofsson B, Korpelainen E, Pepper MS, et al. Proc Natl Acad Sci USA. 1998;95:11709-11714
[3]Ogawa S, Oku A, Sawano A, et al. J Biol Chem. 1998;273:31273-31282
[4]Dumont DJ, Jussila L, Taipale J, et al. Science. 1998;282:946-989

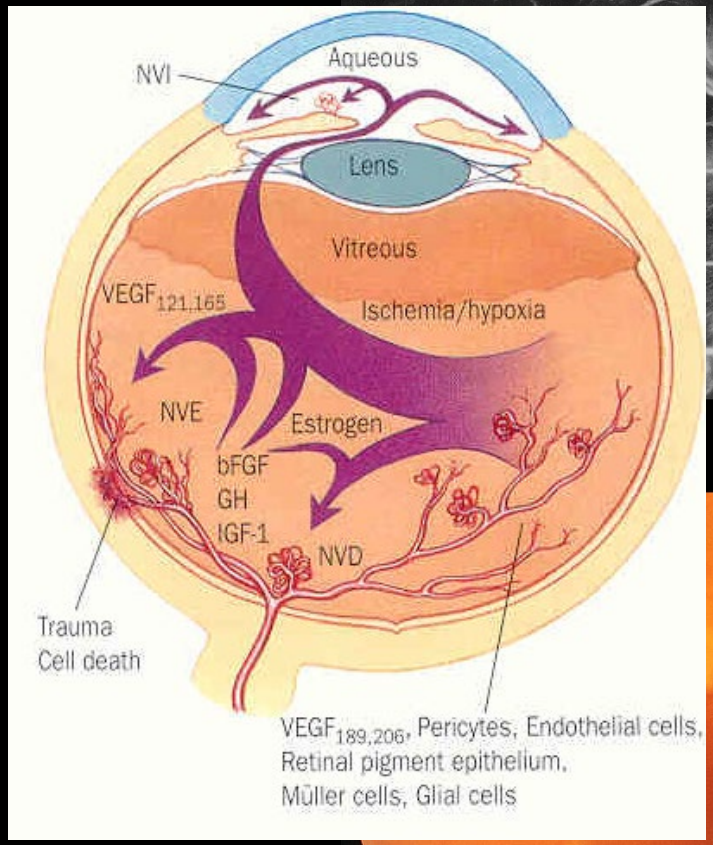
VEGF e occhio sano

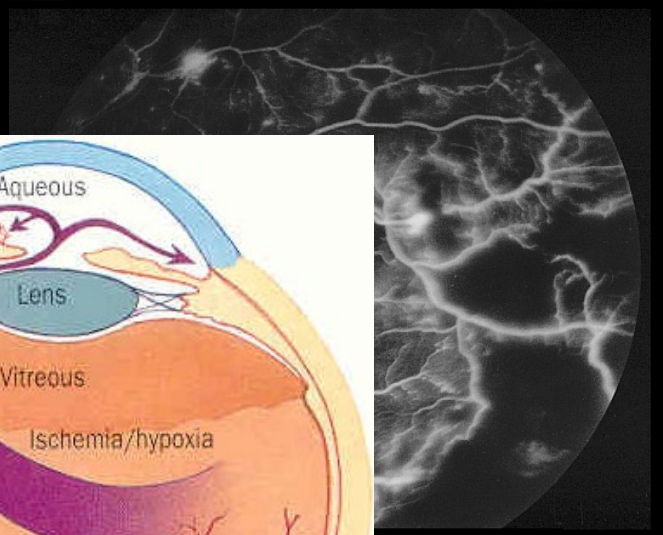


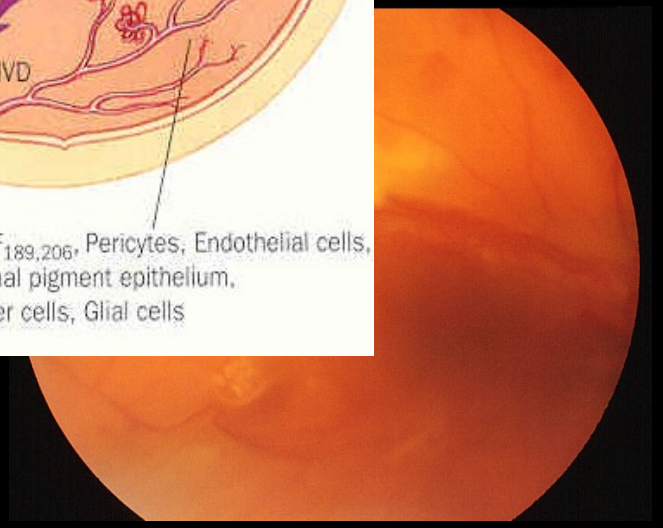
- Elevata concentrazione VEGF nelle cellule dell'EPR
- I recettori per il VEGF sono prevalentemente localizzati sulle cellule endoteliali vascolari
- Ruolo nel mantenimento di un adeguato flusso ematico retinico

VEGF e patologia oculare

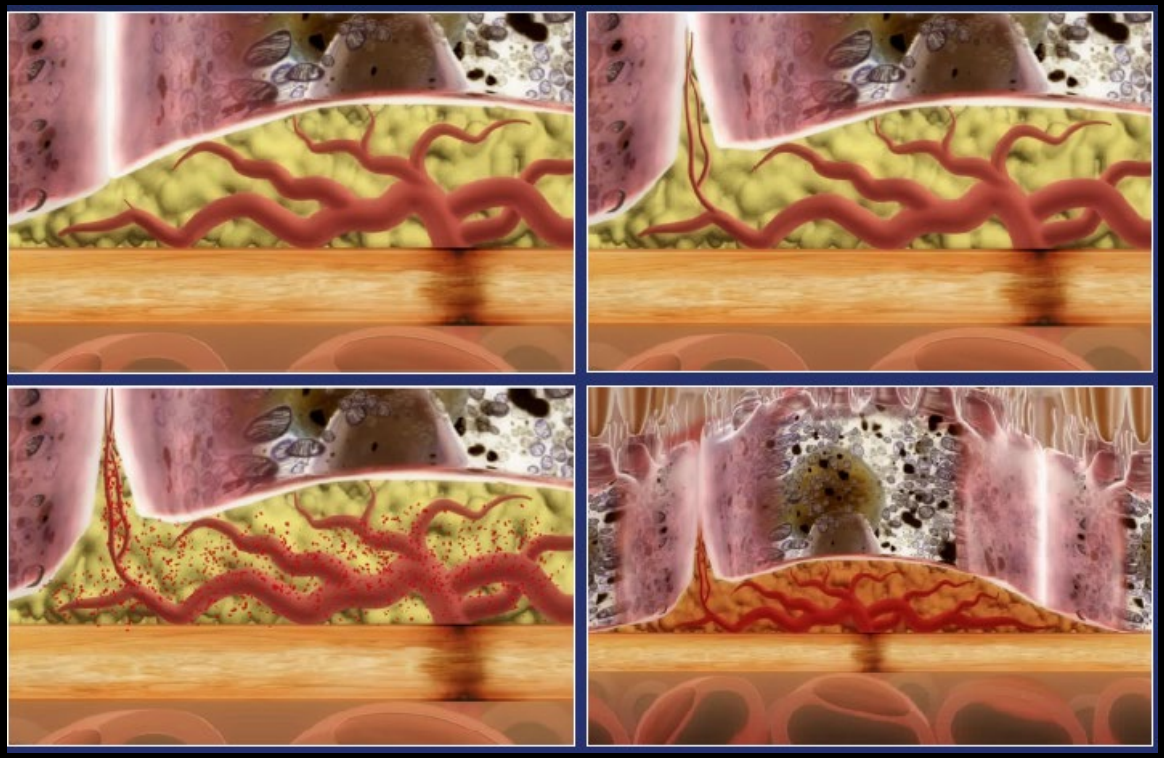
- DMLE neovascolare
- Retinopatia diabetica
- Occlusione venosa retinica
- ROP
- Neovascolarizzazione corneale ed iridea







VEGF e angiogenesi



- Attiva la degradazione della membrana basale delle cellule edoteliali
- Le cellule endoteliali:

✓ modificano la loro forma ed invadono lo stroma

✓ proliferano e migrano

✓ aderiscono l'una all'altra e formano nuovi vasi

VEGF e permeabilità vasale

- 50.000 volte più potente dell'istamina
- Leakage vasale:

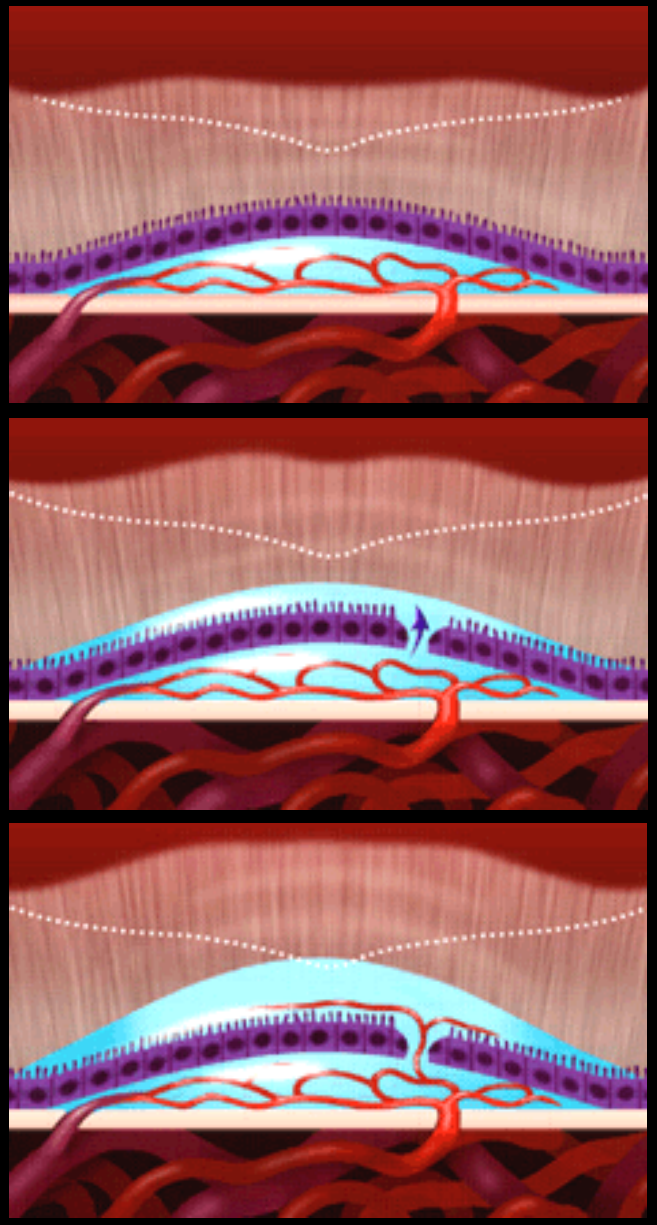
✓ danno delle cell. endoteliali mediato dai leucociti

✓ formazione fenestrature

✓ alterazioni giunzioni strette

Ruolo del VEGF nella CNV

- Fondamentale per l'angiogenesi
- Iperespressione VEGF nell'EPR induce CNV sperimentale
- Iperespressione VEGF nell'EPR dei pz affetti da AMD
- Presenza VEGF in qualsiasi sottotipo di CNV, soprattutto le più vascolarizzate



Spilsbury K et al. Overexpression of VEGF in RPE leads to the development of CNV. Am J Pathol,2000

Kliffen M et al. Increased expression of of angiogenic growth factors in ARM. Br J Ophthalmol, 1997

Kvanta A et al. Subfoveal fibrovascular membranes in ARM express VEGF. Invest Ophthalmol Vis Sci, 1996

Matsuoka M et al. Expression of pigment epithelium derived factor and VEGF in CNV and IPV. Br J Ophthalmol, 2004

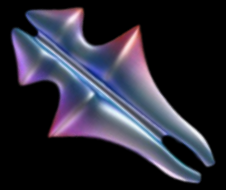
FARMACI ANTIANGIOGENICI IN OFTALMOLOGIA
PER USO INTRAVITREALE

Ranibizumab: Lucentis

Frammento (Fab) di un anticorpo monoclonale ricombinante anti VEGF-A (bevacizumab), umanizzato

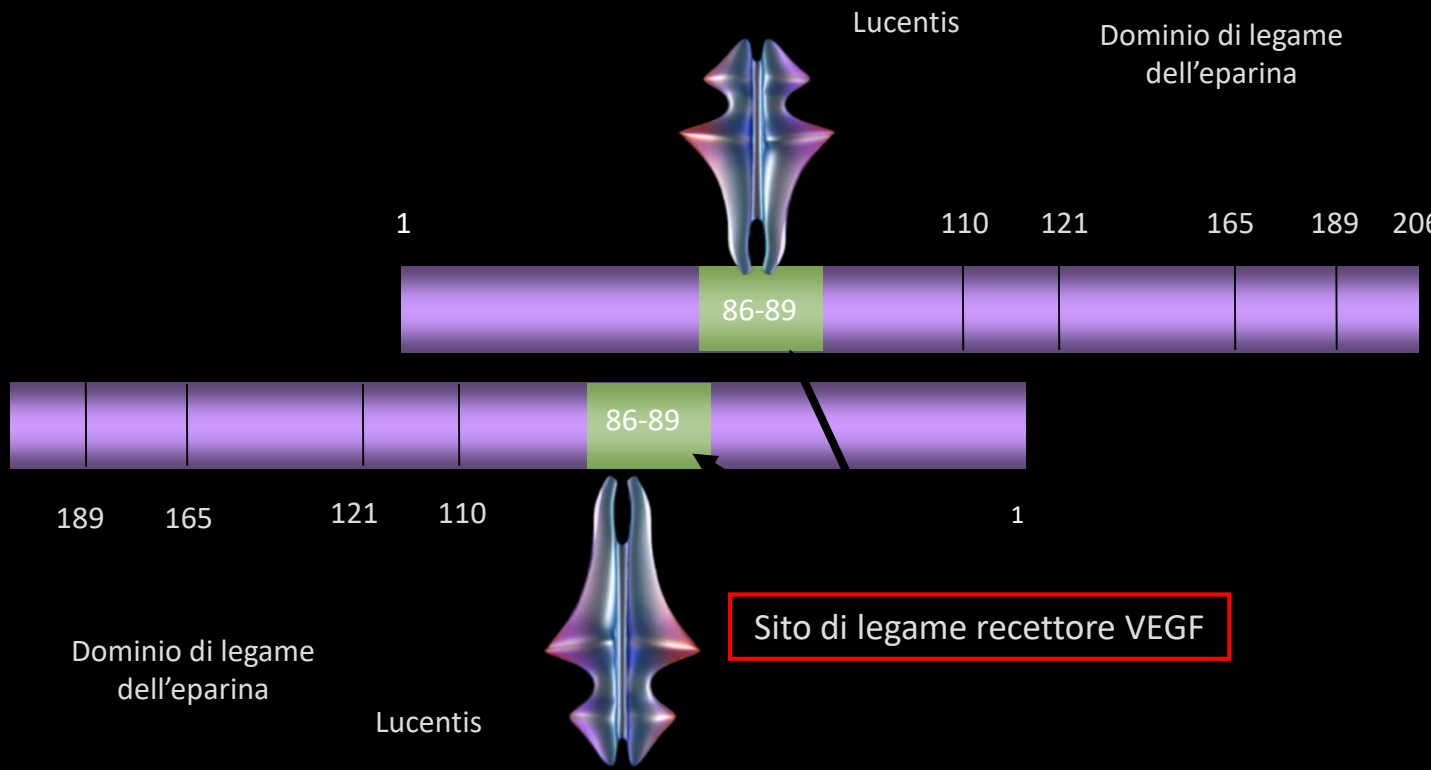
rhu Mab
150 Kdaltons

rhu Fab
48 Kdaltons



rhu Fab V2

alta affinita' per tutte le isoforme biologicamente attive del VEGF-A (VEGF-A189, VEGF-A165, VEGF-A121, VEGF-A110)




Grazie per l’attenzione