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Why does a Serous Retinal Detachment occur ?

An introduction

Alain Gaudric

Service d'Ophtalmologie
Hôpital Lariboisière

CiL

Financial disclosure

NONE

Definition

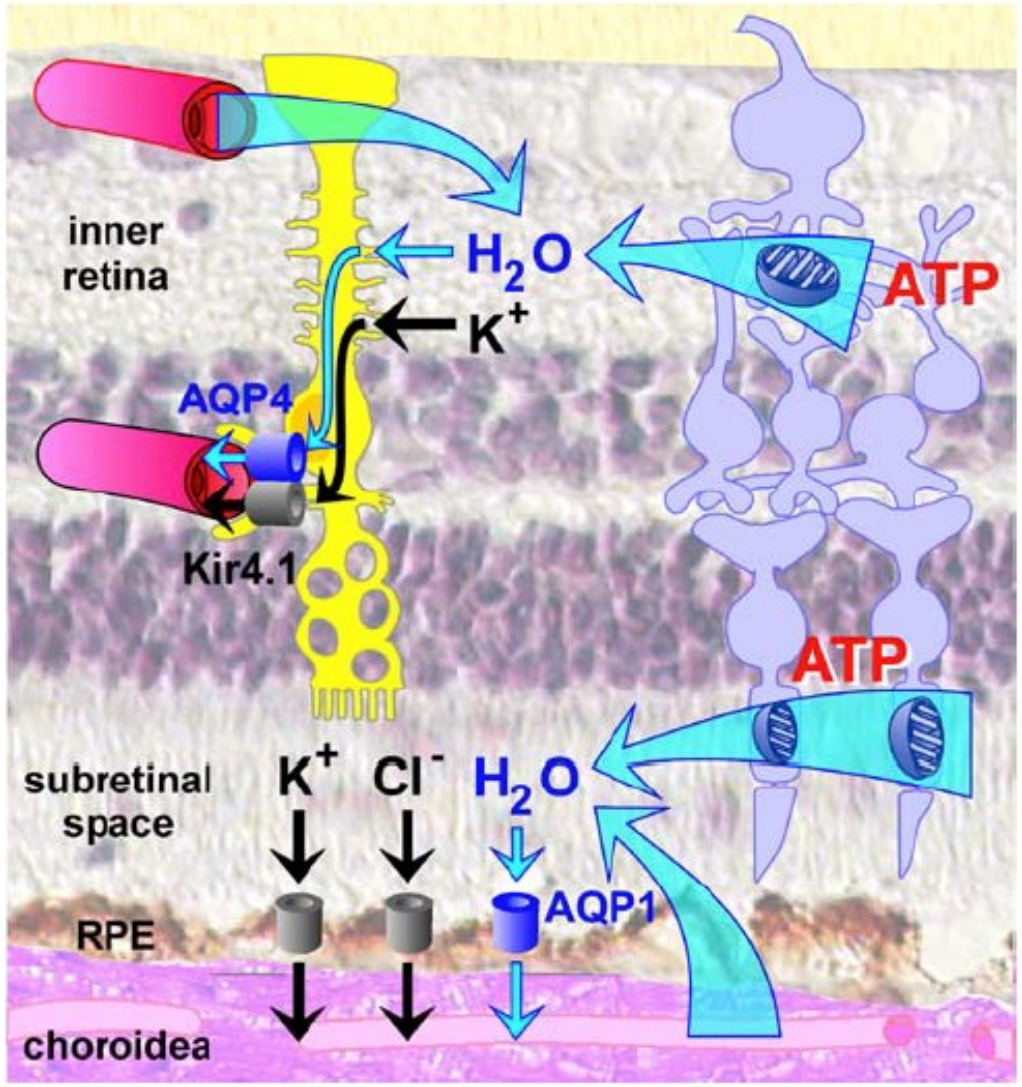
- *Wikipedia :* In physiology, the term "serous fluid" is any of various body fluids resembling serum.

- *Webster Dictionary:* "Serous fluid" means relating to or resembling serum: "a serous exudate"

- Synonymous :
  - Serous retinal detachment
  - Exudative retinal detachment
  - Sub retinal fluid

- The origin of fluid in a "serous" retinal detachment is thus supposed to be blood.

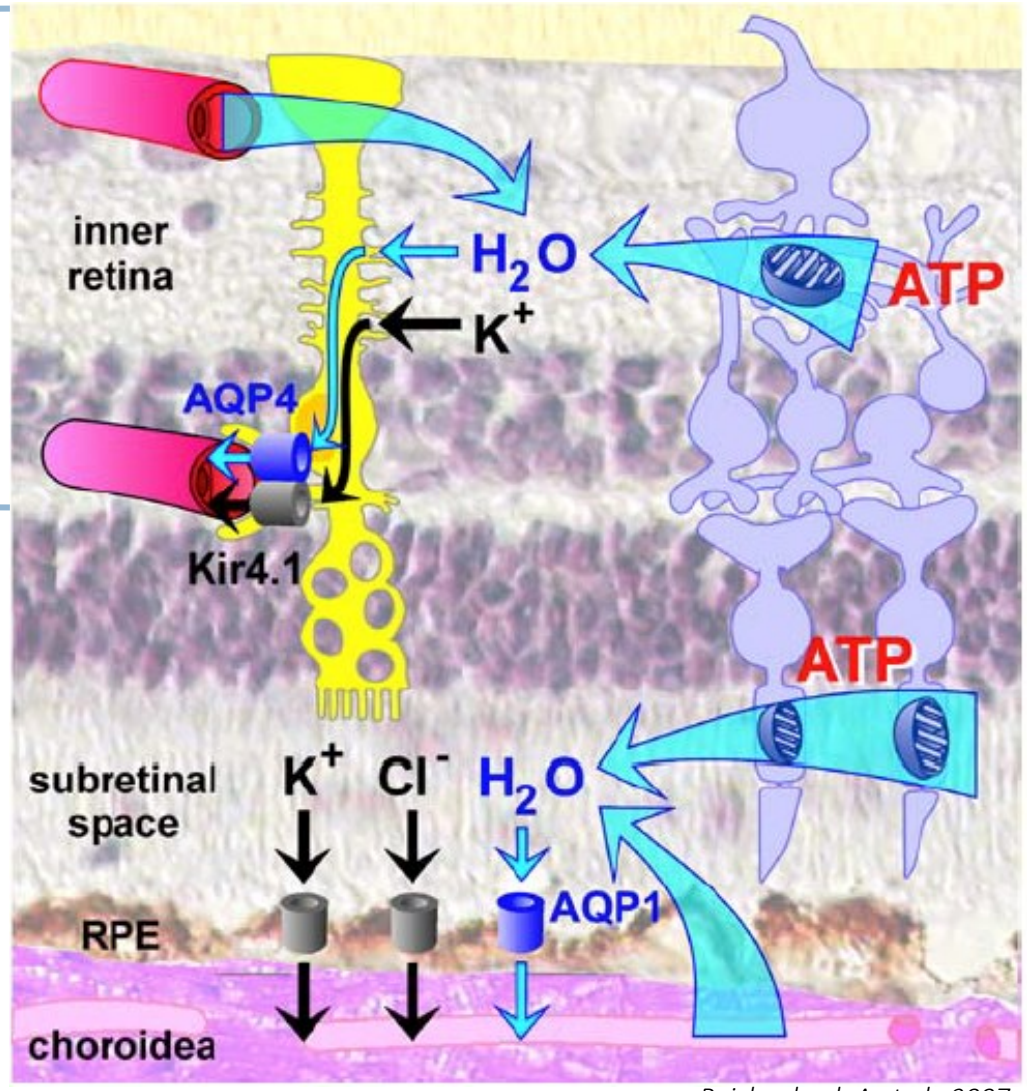
Sources of fluid in the retina



- Blood Retinal Barrier
  - maintains the cohesion and transparence of the retina
  - while providing and controlling nutrients transfer from the blood to neurons, photoreceptors and glia.

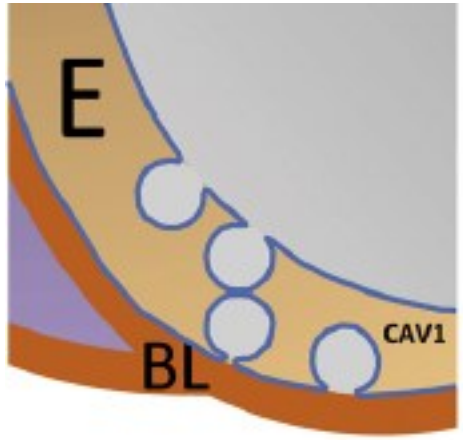
Reichenbach A et al . Müller cells as players in retinal degeneration and edema. Graefe's archive for clinical and experimental ophthalmology 2007;245(5):627-636.

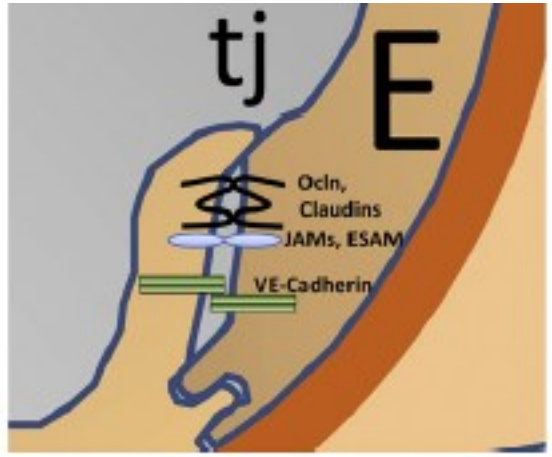
Sources of fluid in the retina



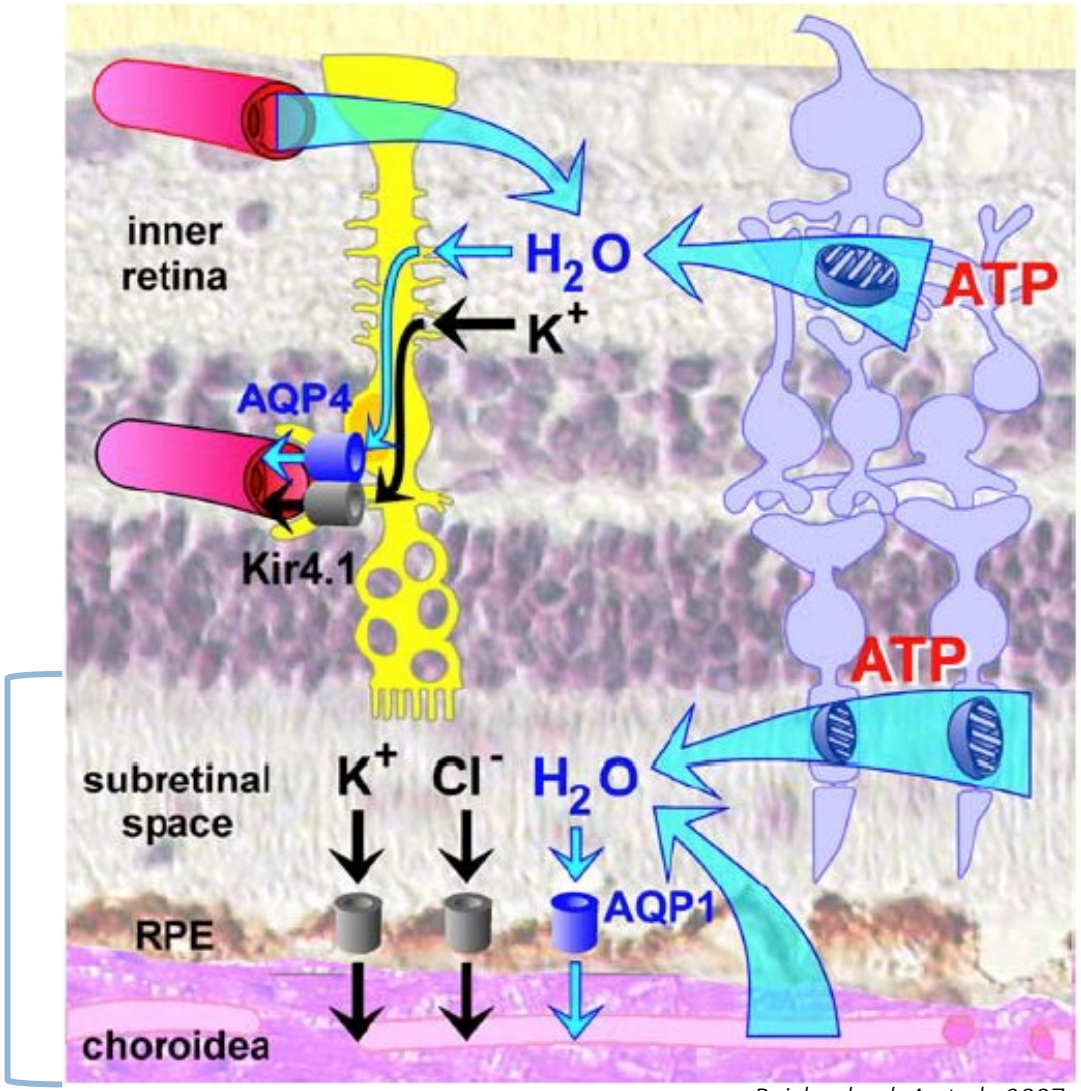
Reichenbach A et al . 2007

- Blood Retinal Barrier is composed of two systems :
  - the endothelial tight-junctions of the retinal capillaries



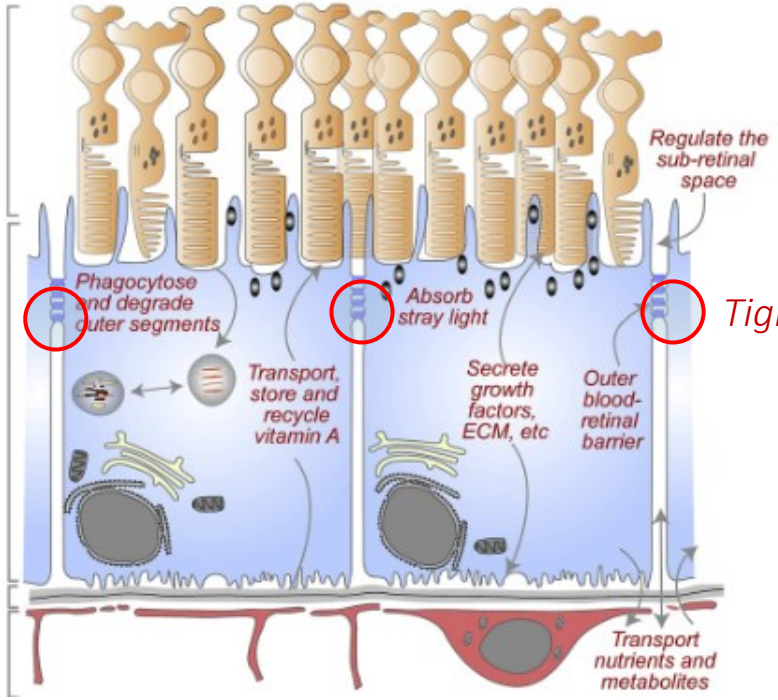


Sources of fluid in the retina



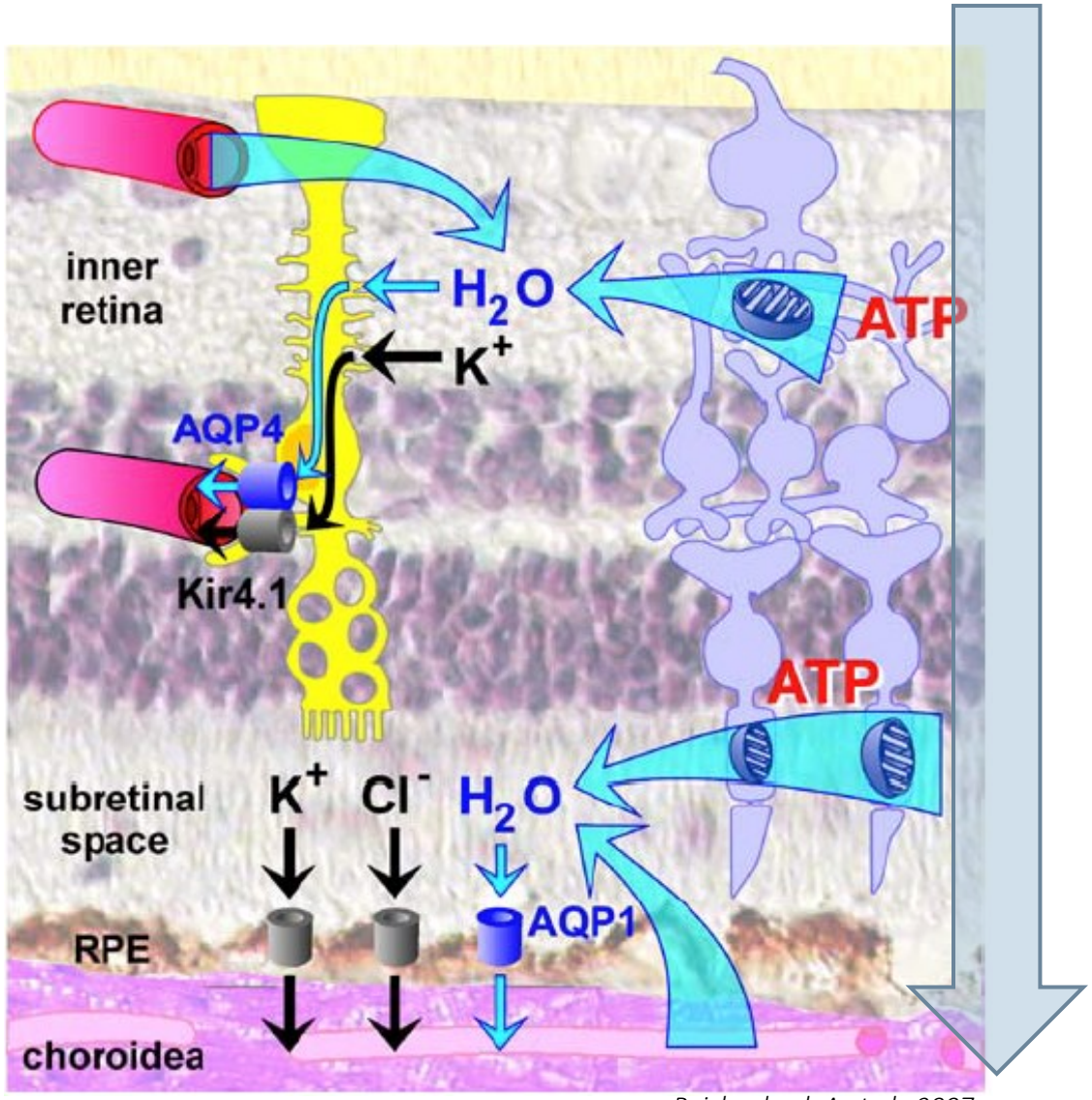
Reichenbach A et al . 2007

- Blood Retinal Barrier is composed of two systems :
  - the RPE tight-junctions



Lakkaraju A et al. Prog Retin Eye Res. 2020;78:100846.

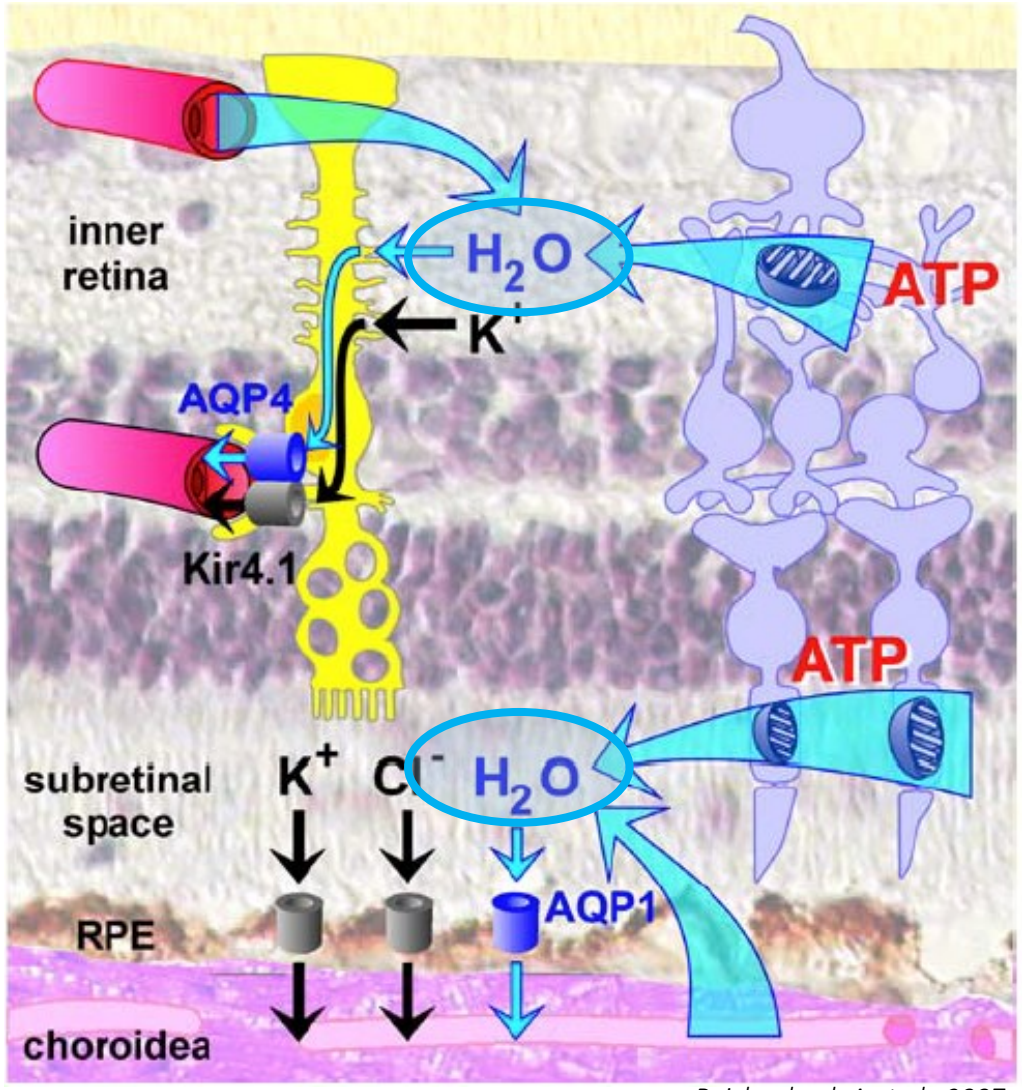
Sources of fluid in the retina



Reichenbach A et al . 2007

- Despite the BRB the retina is permanently crossed by a flow of water coming from the vitreous and reabsorbed by the choroid

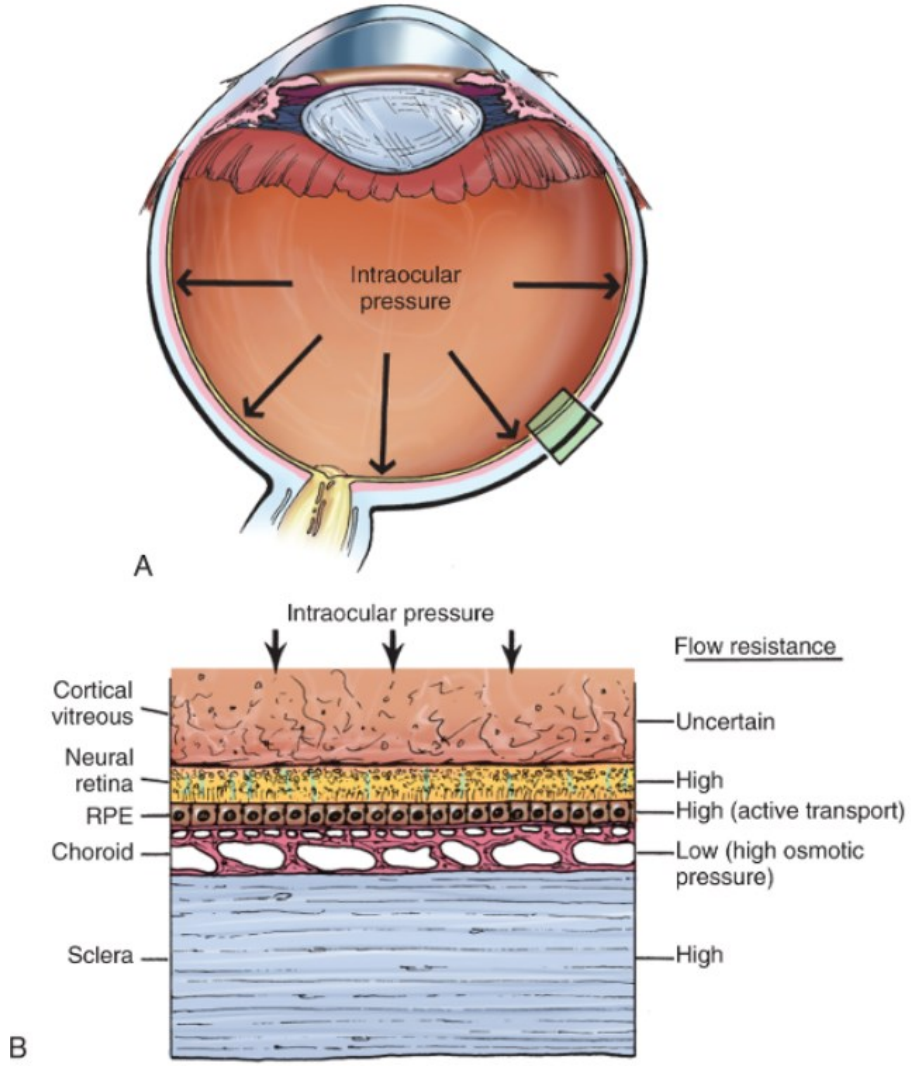
Sources of fluid in the retina



Reichenbach A et al . 2007

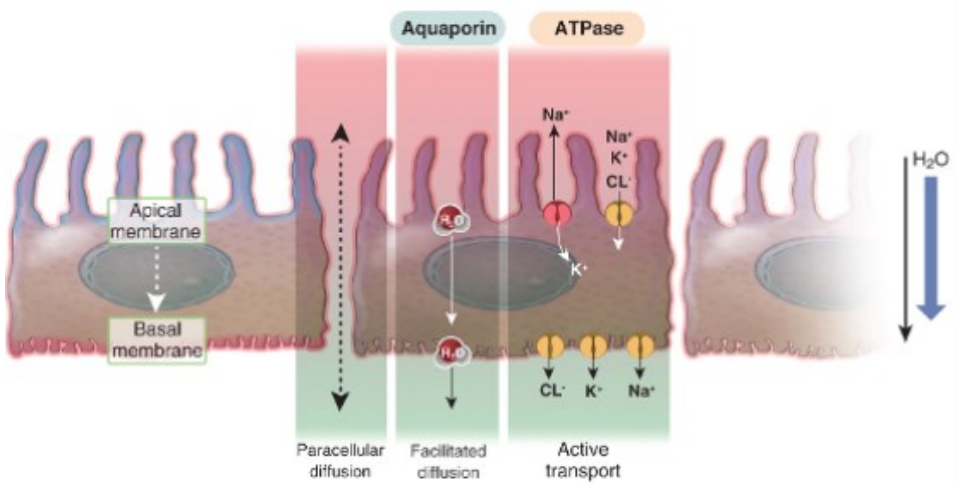
- Despite the BRB the retina is permanently crossed by a flux of water coming from the vitreous and reabsorbed by the choroid
- The neuronal metabolism also produces endogenous H_2O, which is resorbed by Müller cells and RPE .

Sources of fluid in the retina



Marmor M. Ryan's Retina vol 1 Ch 21

- The transit of H_2O from the vitreous side of the retina to the choroid is driven by 3 forces :
  - IOP
  - Choroidal osmotic pressure
  - RPE pumping function



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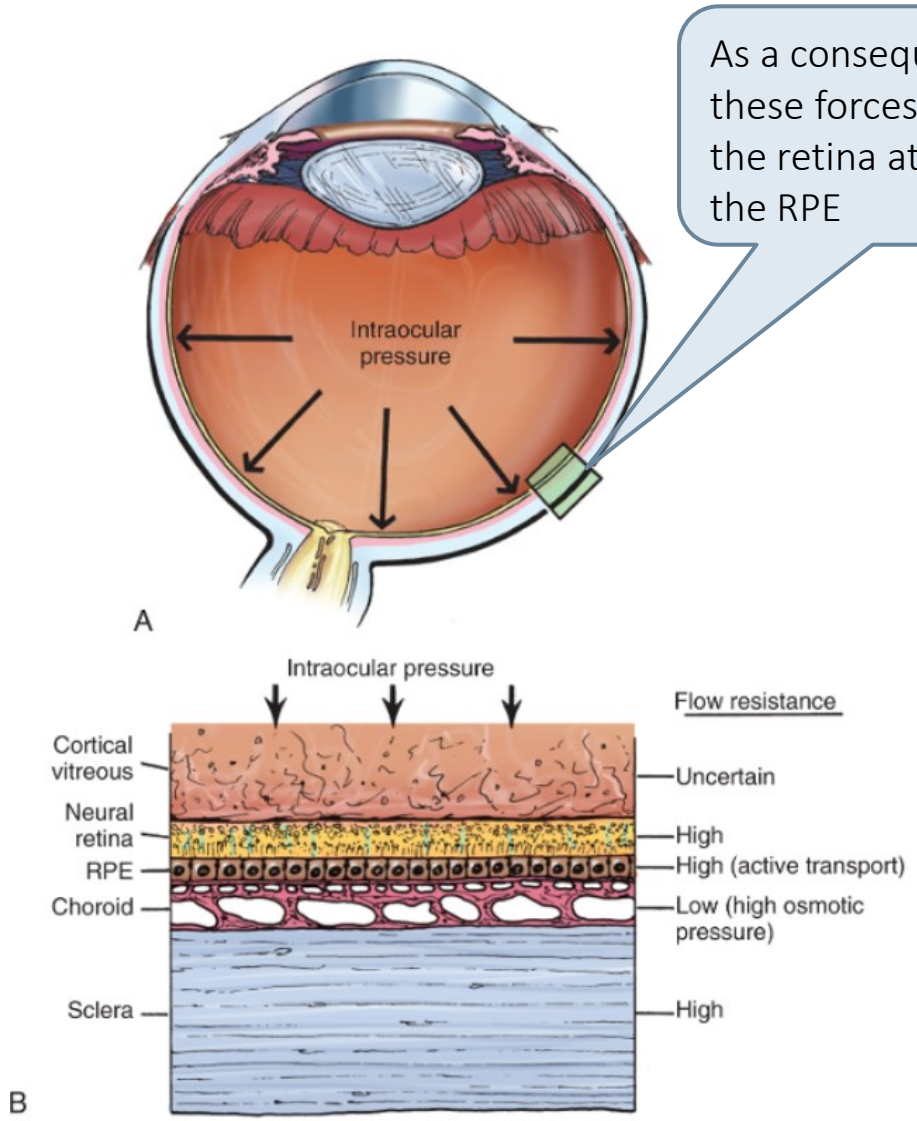
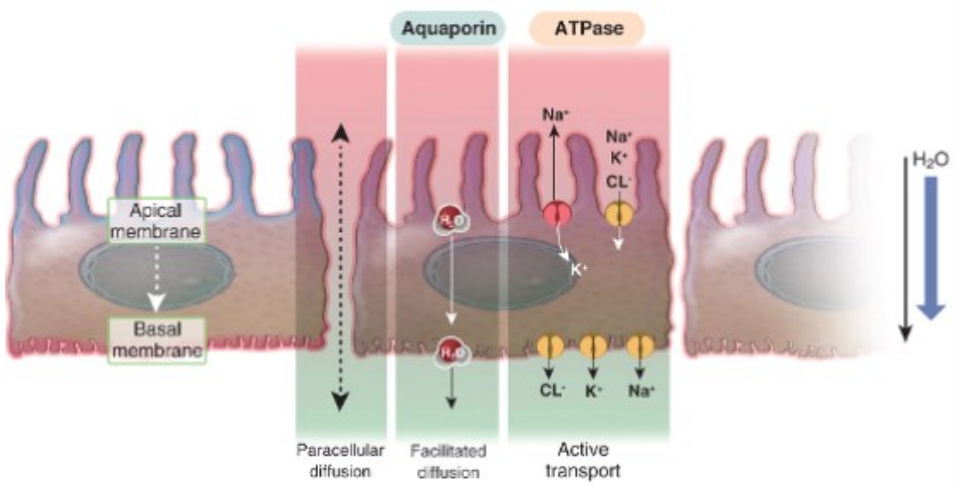
Sources of fluid in the retina



Marmor M. Ryan's Retina vol 1 Ch 21

- The RPE can drain 3.5ml of H_2O/d , in case of RD
- Much less in normal conditions
- Even in the absence of RPE, H_2O transfer continues from the retina to the choroid



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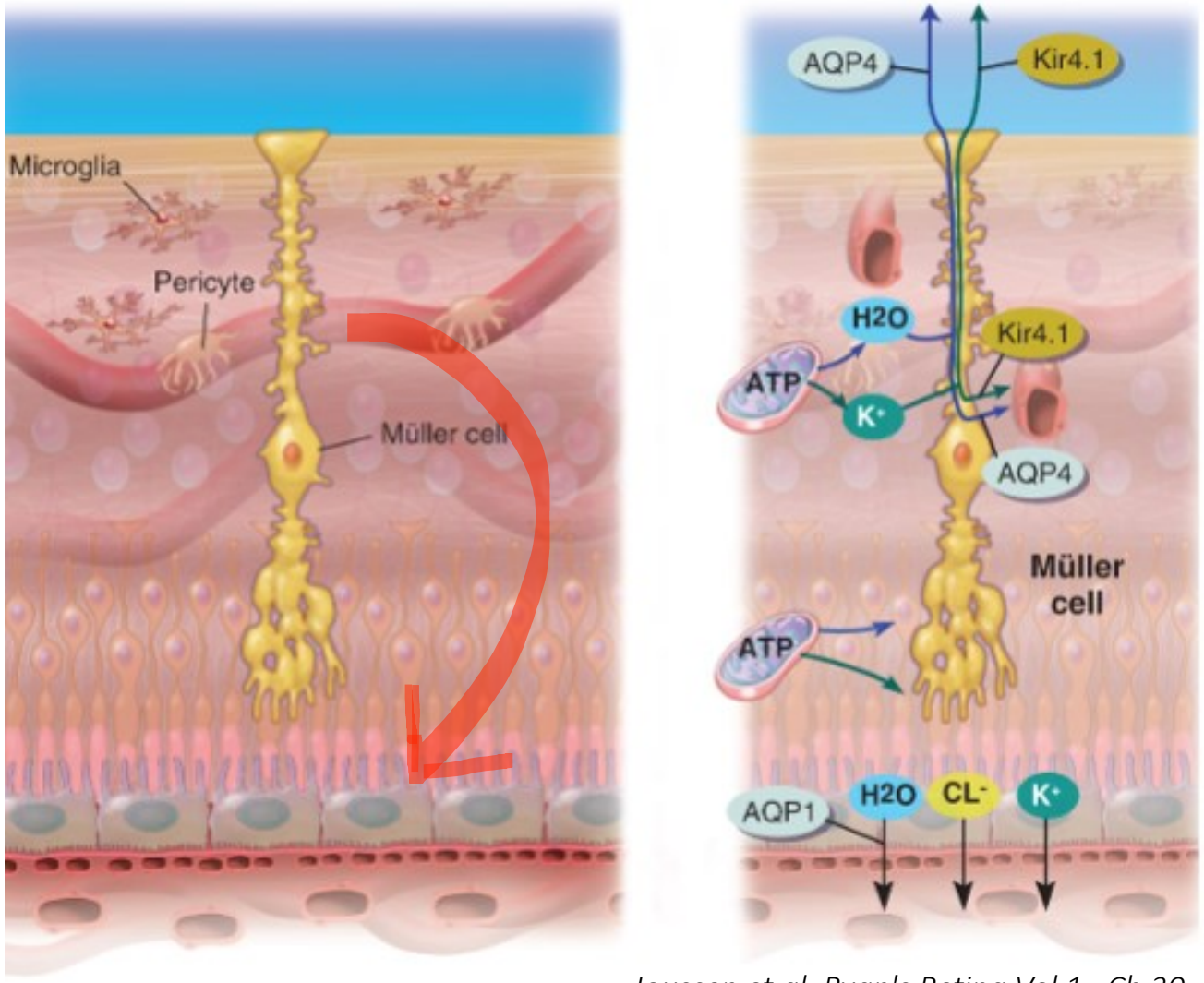
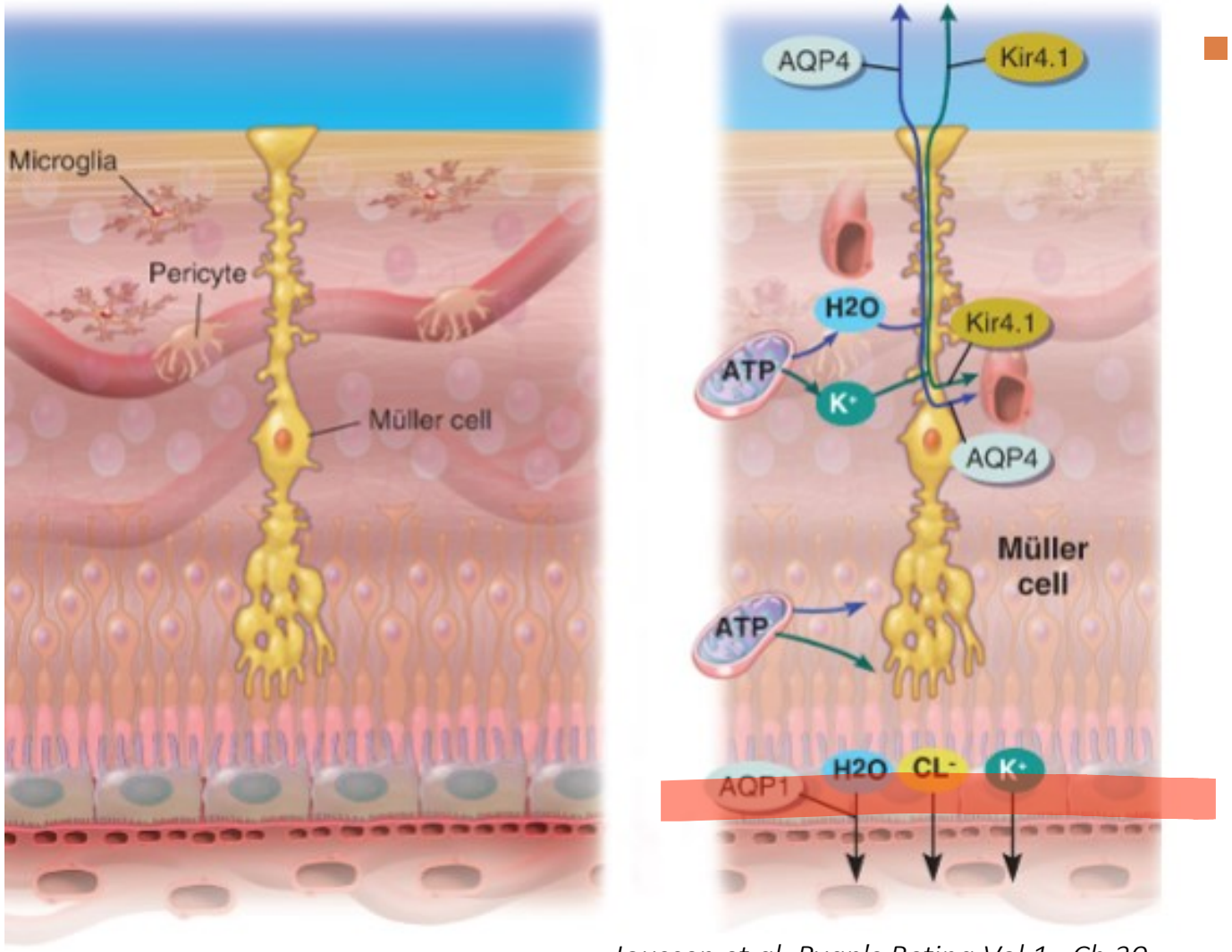
Sources of abnormal SRF



Joussen et al. Ryan's Retina Vol 1 , Ch 30

- There are then several potential sources of fluid which may accumulate under the retina .
  - Excess of fluid coming from the retinal capillaries

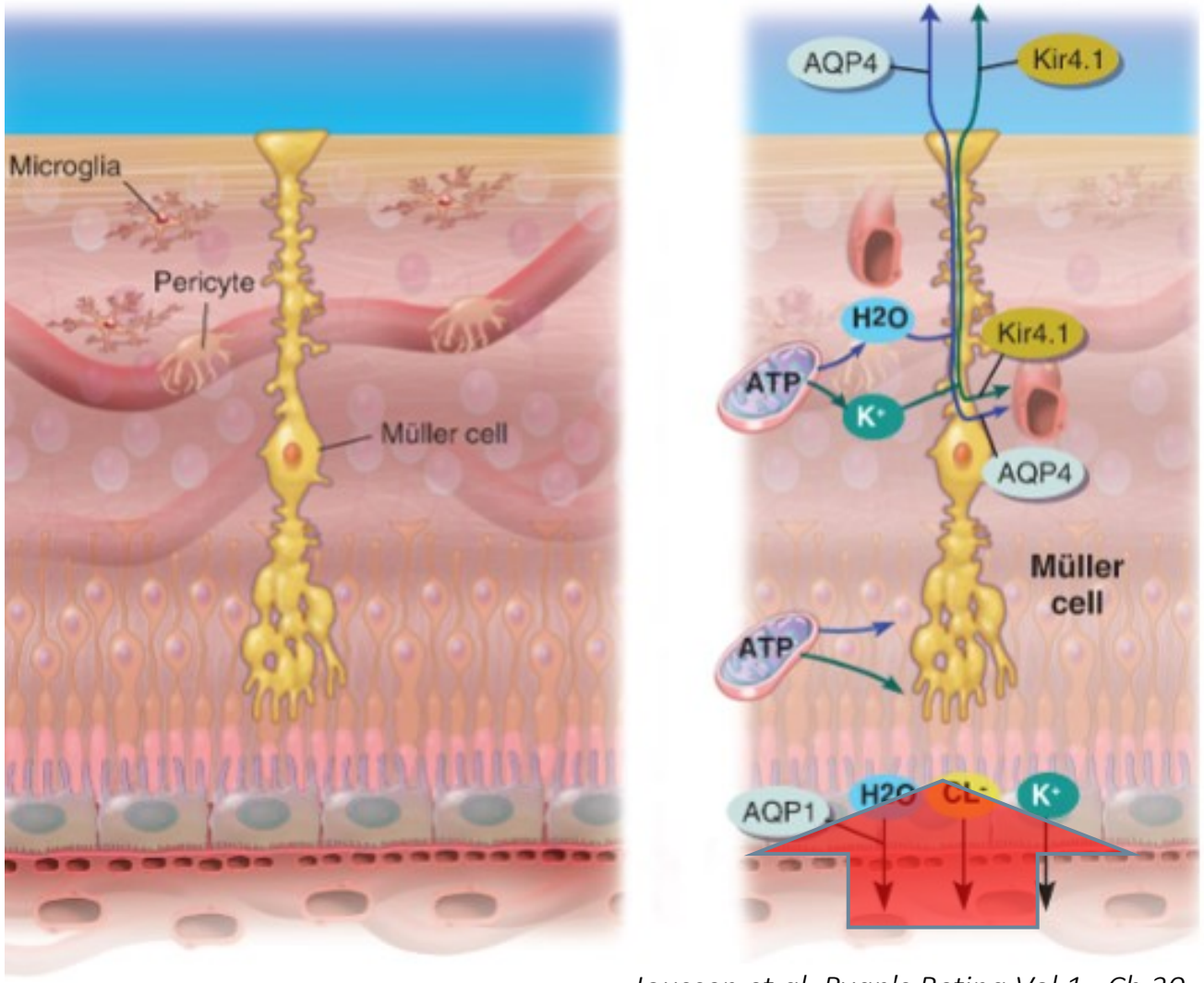
Sources of abnormal SRF



Joussen et al. Ryan's Retina Vol 1 , Ch 30

- There are then several potential sources of fluid which may accumulate under the retina .
  - Excess of fluid coming from the retinal capillaries
  - Failure of the RPE to resorb and transfer H_20

Sources of abnormal SRF



Joussen et al. Ryan's Retina Vol 1 , Ch 30

- There are then several potential sources of fluid which may accumulate under the retina .
  - Excess of fluid coming from the retinal capillaries
  - Failure of the RPE to resorb and transfer H_20
  - Abnormal passage of fluid through the RPE

Classification and differential diagnosis of SRD

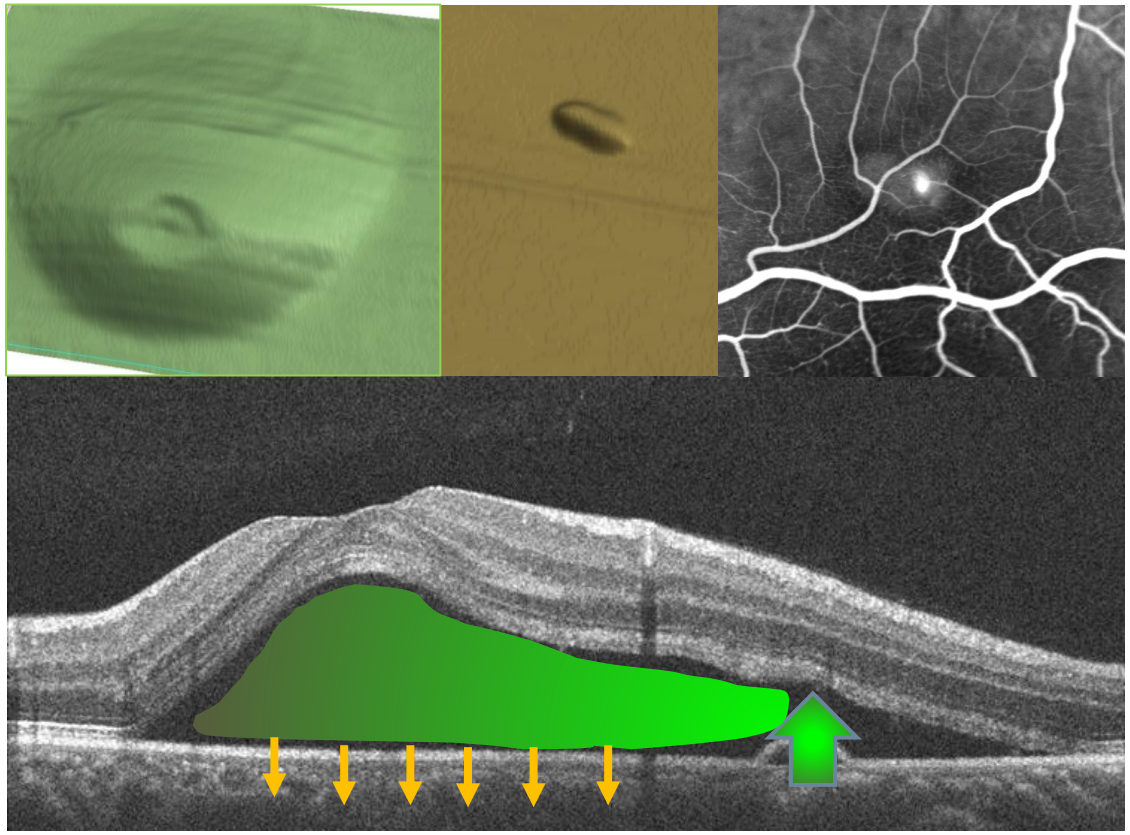
- Exudation coming from the choroid
  - CSCR
  - CNV
  - Inflammation
  - Choroidal ischemia
  - Tumors and infiltration
- Exudation coming from the retinal vessels
  - DR and RVO
  - Angiomatosis and telangiectasia
- Macular detachment without exudation
  - Retinal dystrophies
  - Cuticular drusen
  - Tractional maculopathies
  - Drug toxicity
  - Optic disc pit

SRD due to exudation from the choroid

- Primitive dysfunction of the RPE
  - CSCR
- RPE dysfunction due to inflammation/infection
  - Syphilis
- Macular new-vessels
- RPE dysfunction due to underlying choroidal tumors
  - Benign
  - Malignant
  - BDUMP paraneoplastic syndrome
- RPE dysfunction due to choriocapillaris hypoperfusion
  - Inflammatory context:
    - Harada's disease
    - AMPPE
    - AUIM
  - Hypercoagulability context
    - Toxemia of pregnancy
    - Anti phospholipid syndrome
    - Disseminated Intravascular Coagulation
    - Moskowitz disease
  - Tumoral infiltration
    - Choroidal tumoral infiltration
    - Leukemia, Lymphoma

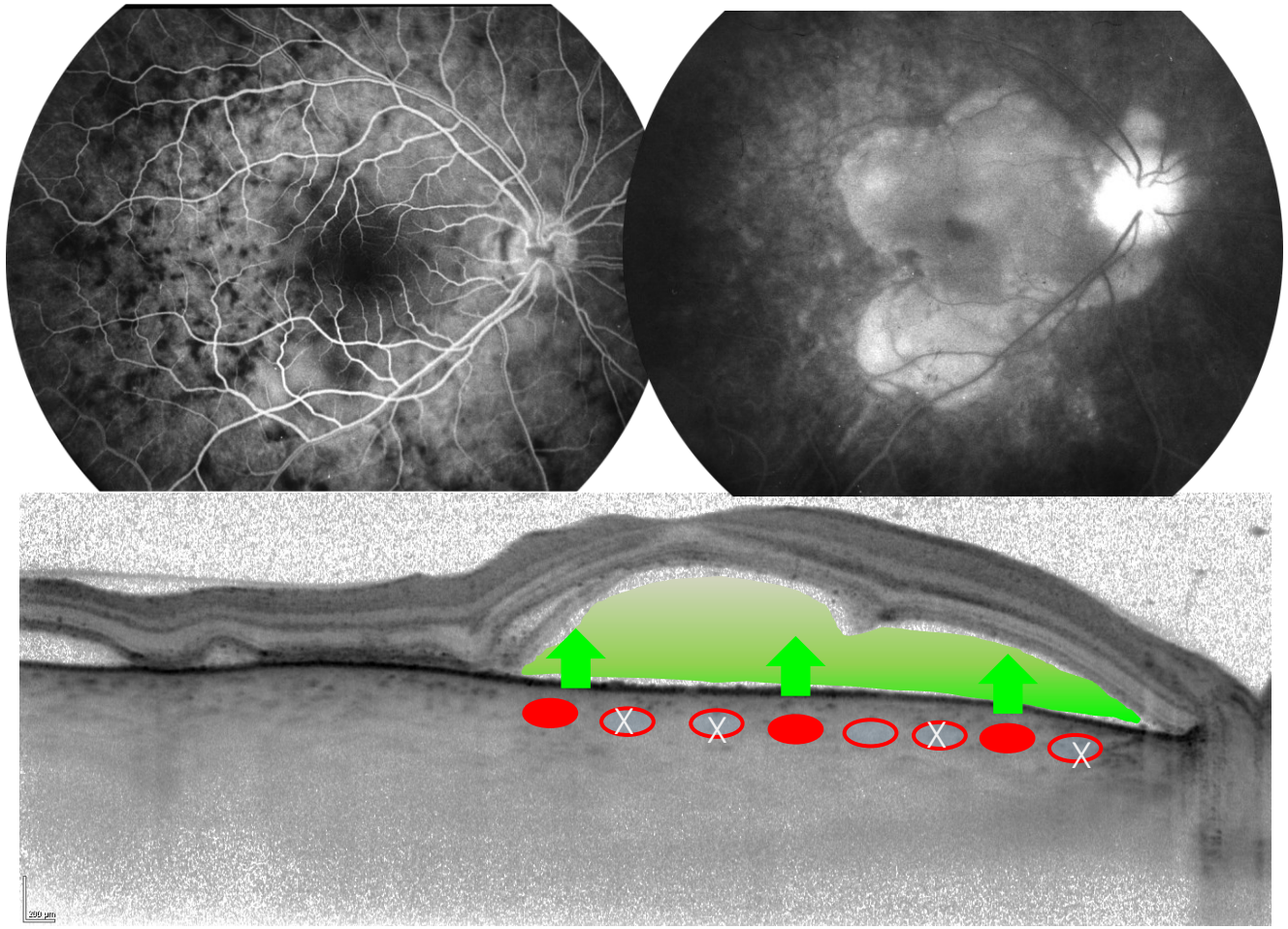
SRD due to exudation from the choroid

- Primary dysfunction of the RPE
  - CSCR
  - Choroidal fluid enters the subretinal space through a PED
  - But fluid reabsorption by the RPE is deficient and cannot remove this small amount of fluid as it goes.



SRD due to exudation from the choroid

- RPE dysfunction due to choriocapillaris hypoperfusion
  - Inflammatory context, Harada's disease
    - multifocal occlusion of the choriocapillaris
    - Ischemic RPE alteration
    - Leakage through a damaged RPE from residual choriocapillaris circulation



SRD due to exudation from the choroid

- RPE dysfunction due to choriocapillaris hypoperfusion
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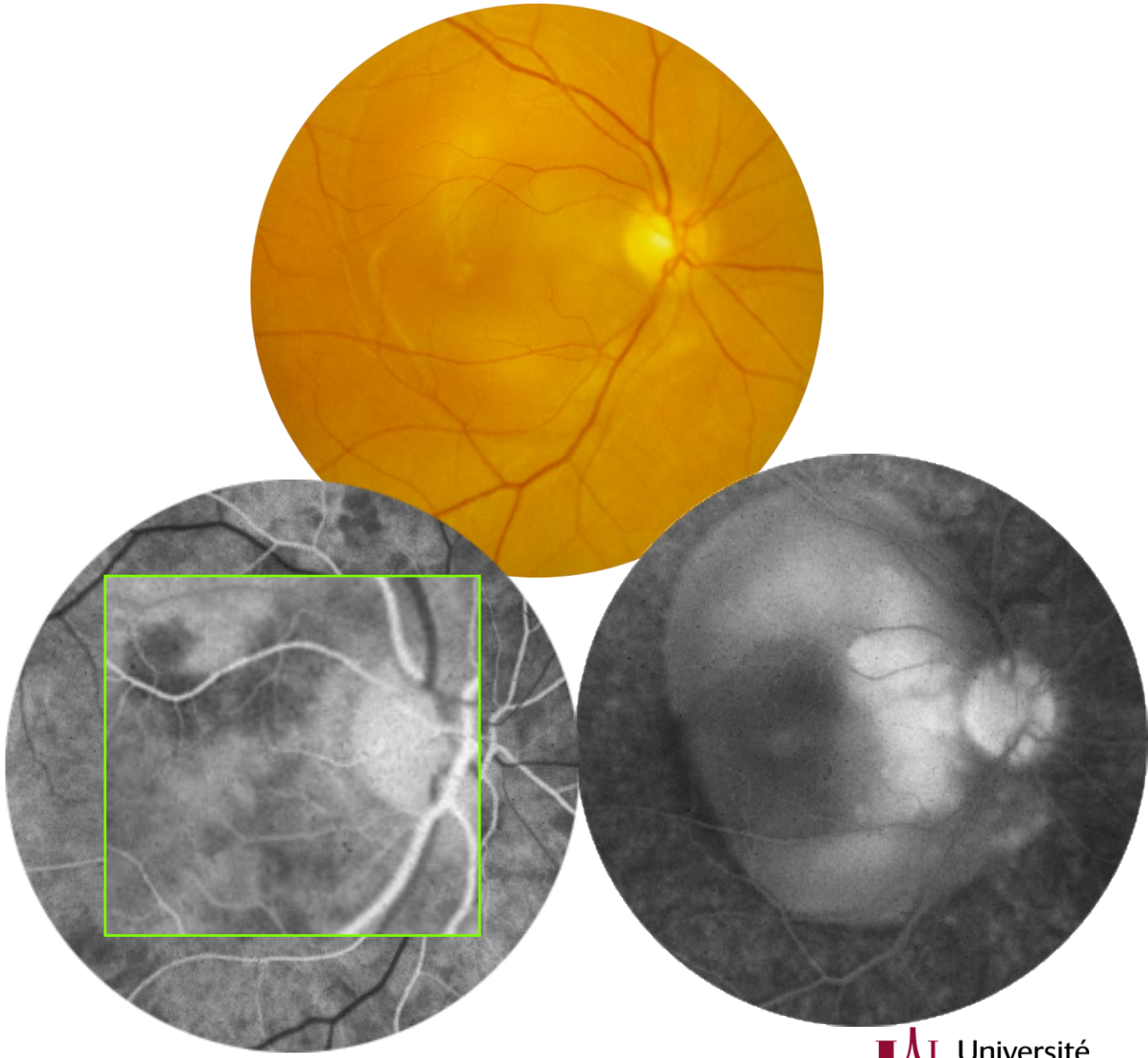
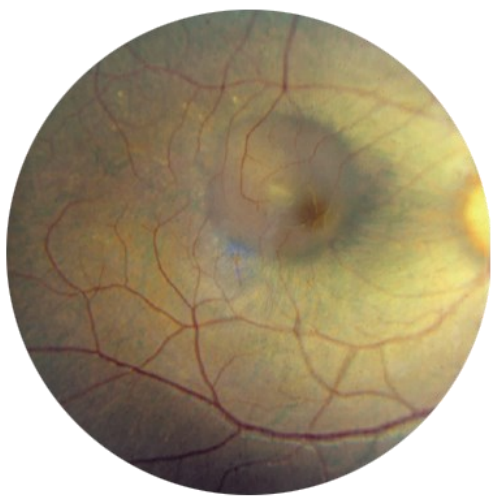
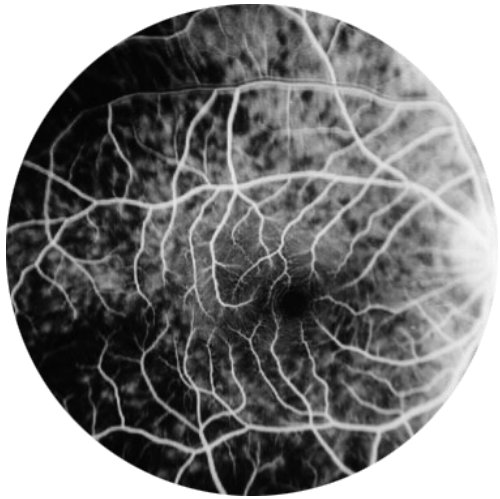
    - Choroidal tumoral infiltration



Experimental SRD by choriocapillaris embolization in monkey eyes.





Retinal Detachment After Choroidal Ischemia

Alain Gaudric, M.D., Margaret Sterkers, M.D., and Gabriel Coscas, M.D.

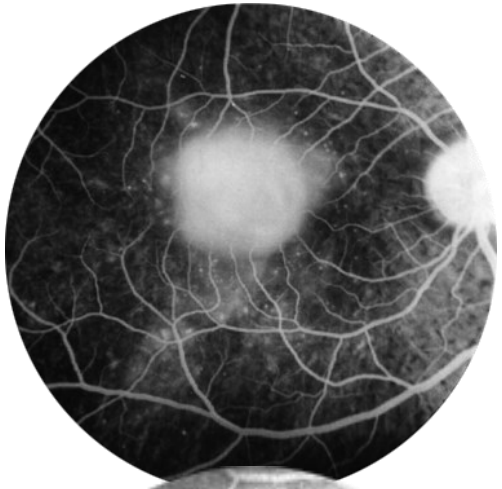
Am J Ophthalmol 1987

Injection of a 15-μm microsphere suspension through one or two vortex veins of nine monkey eyes caused various degrees of sectorial choroidal ischemia, which were documented by fluorescein angiography and electron microscopy. The severity of the lesions to the fundus depended on the volume of microspheres injected (0.4 to 1.6 ml of a suspension of 600,000 microspheres/ml). Three hours after embolization white patches appeared in the retinal pigment epithelium as well as a posterior pole serous retinal detachment in five eyes. Delayed choroidal filling was noted in the quadrant involved, but a few choriocapillaris units slowly perfused, leading to fluorescein leakage in the serous retinal detachments. Histologic examination showed various types of damage to the retinal pigment epithelium, including vacuolization and cell membrane rupture.

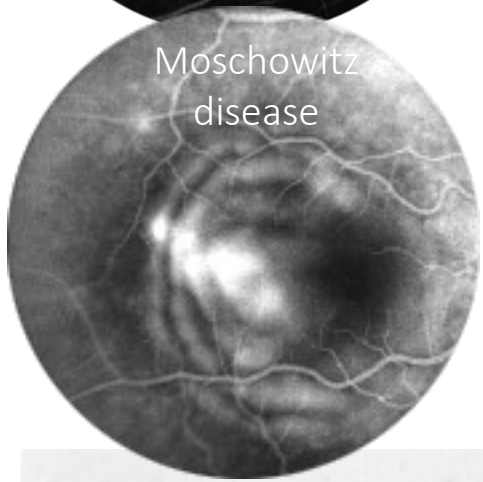
the retinal pigment epithelium were responsible for the serous retinal detachments in monkey eyes.

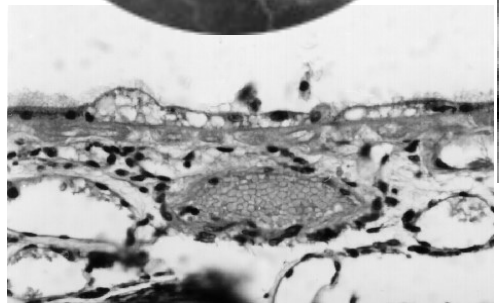
Material and Methods

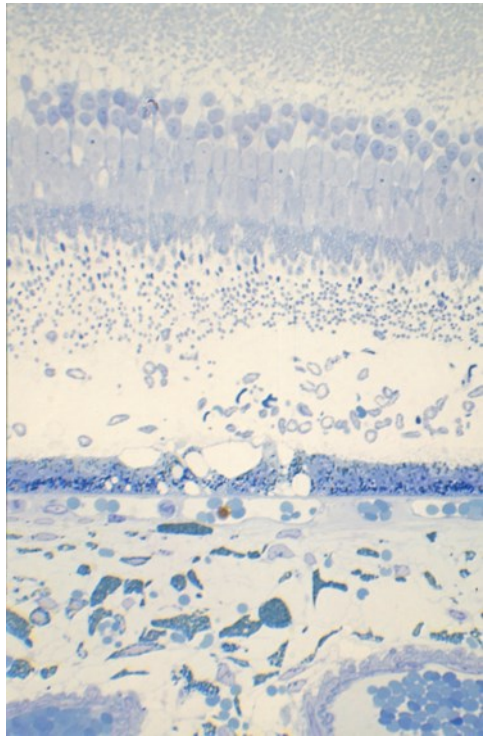
Five adult monkeys of the *Papio papio* and *Patas* species were tranquilized with intramuscular ketamine (10 mg/kg of body weight) and anesthetized with intravenous pentobarbital sodium. Systolic blood pressure did not rise above 140 mm Hg during anesthesia. After lateral orbitotomy, either the superotemporal or inferotemporal vortex vein was exposed and catheterized with a Teflon tube (outside diameter, 0.4 mm; inside diameter, 0.2 mm). The catheter had previously been filled with a saline suspension of polystyrene microspheres,

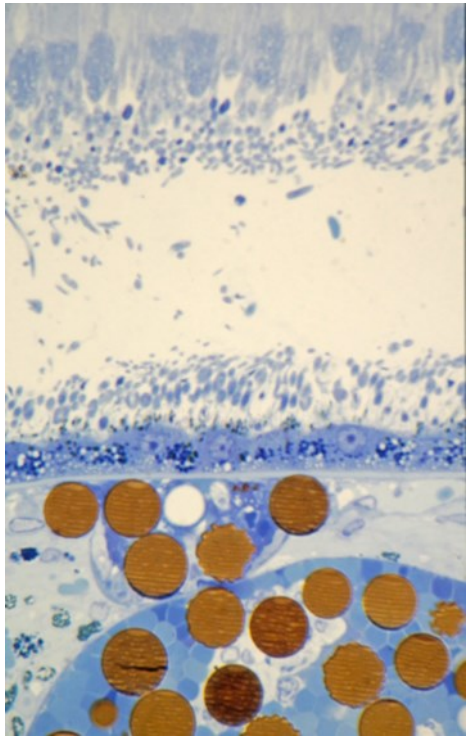


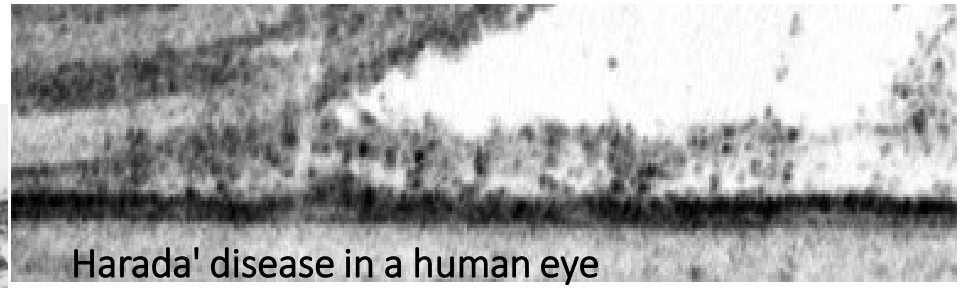
Moschowitz disease







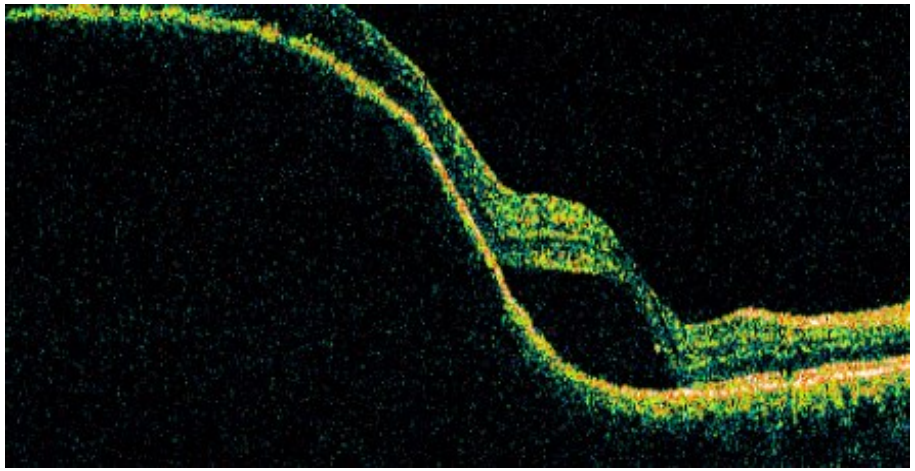


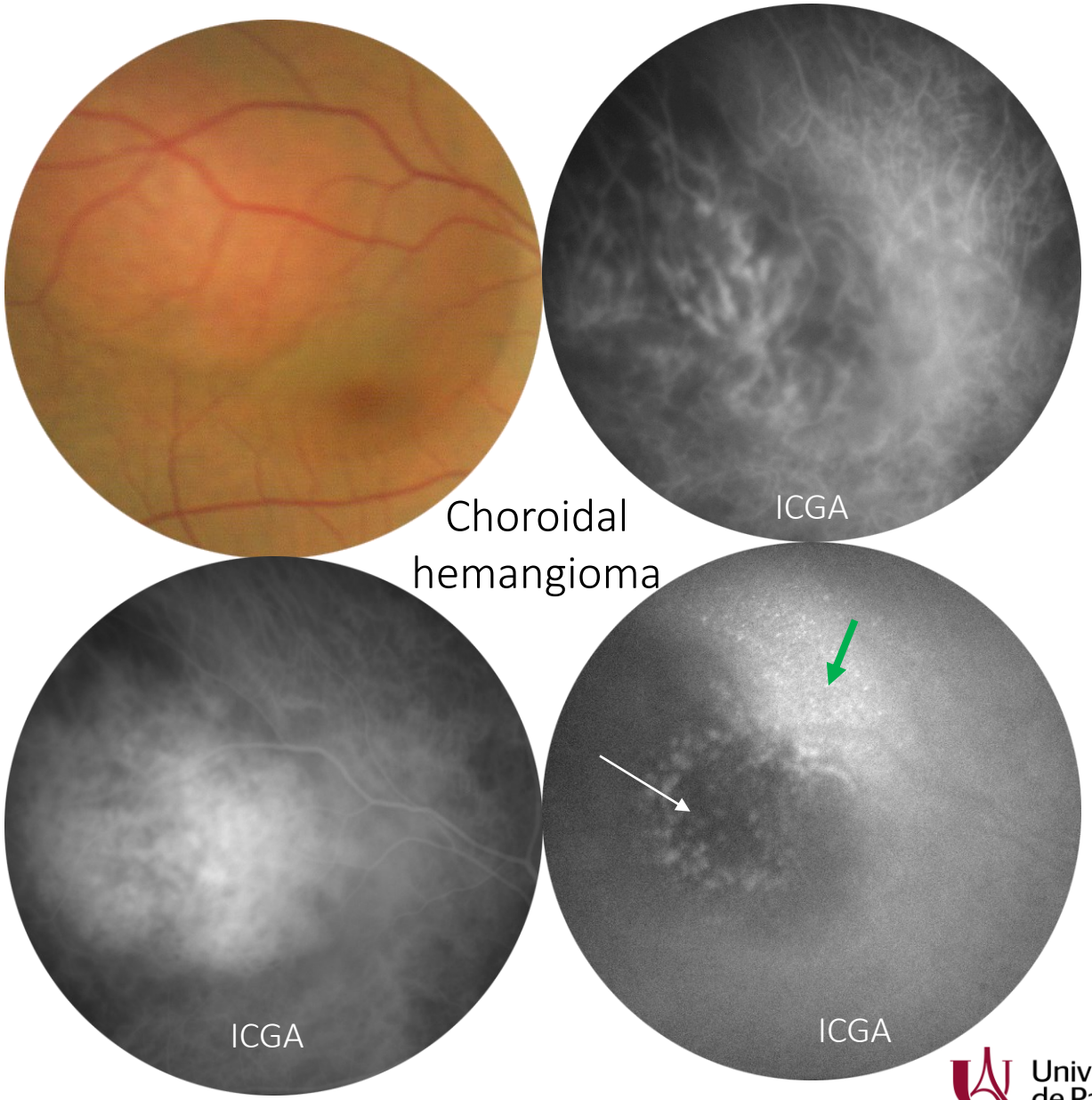


Harada' disease in a human eye

SRD due to exudation from the choroid

- RPE dysfunction due to choroidal tumor
  - Late phase of ICGA
    - hypofluorescence of the RPE
    - leakage of ICG in the subretinal space





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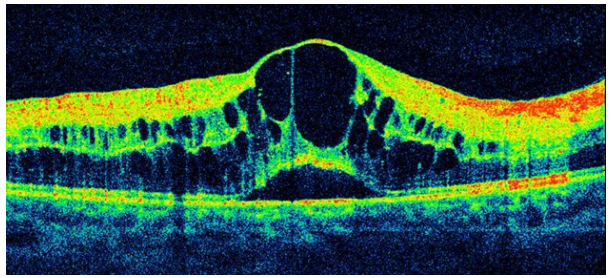
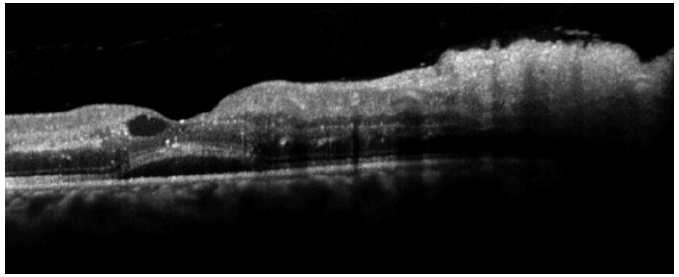
SRD due to exudation coming from retinal vessels

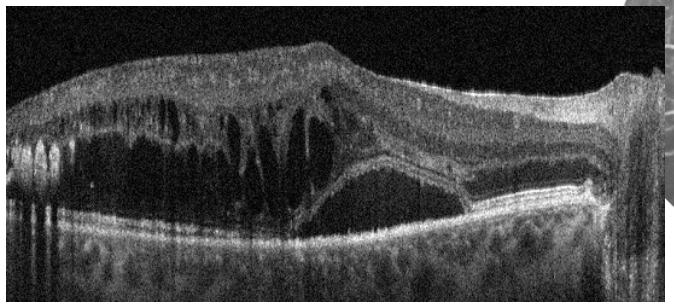
- Diabetic macular edema

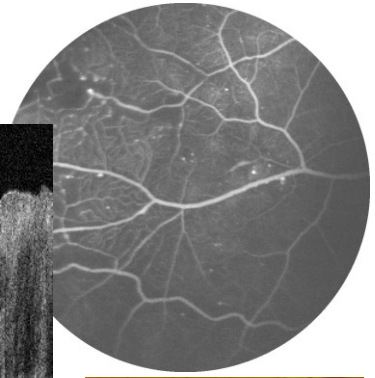


- Acute RVO

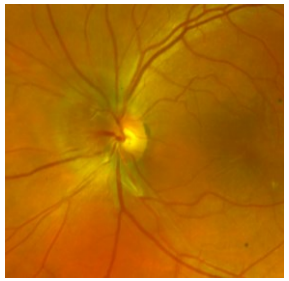


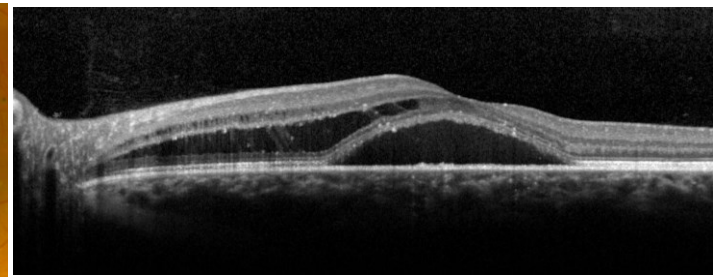
- Coats' disease





- VHL disease

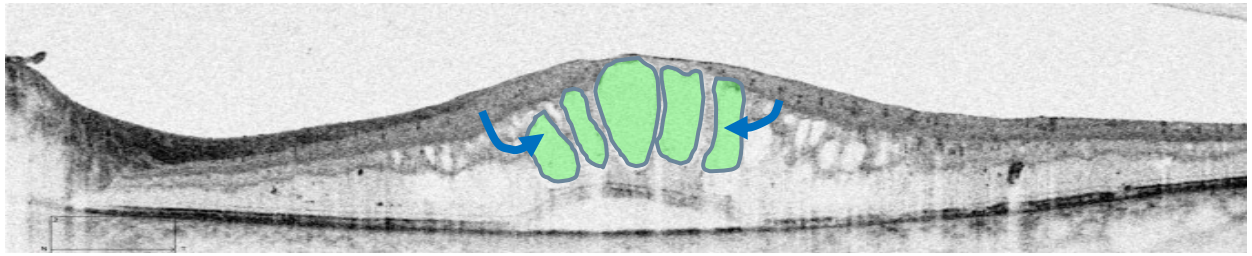


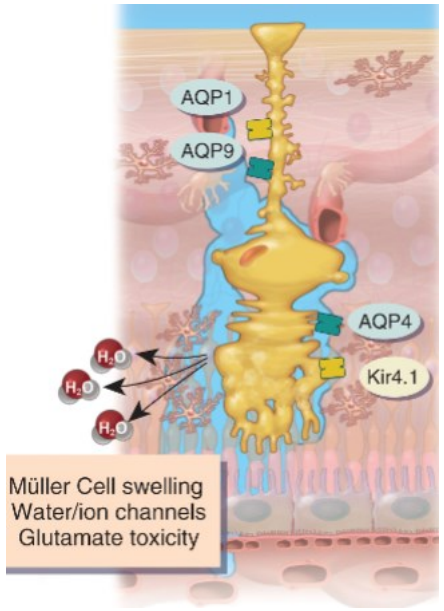


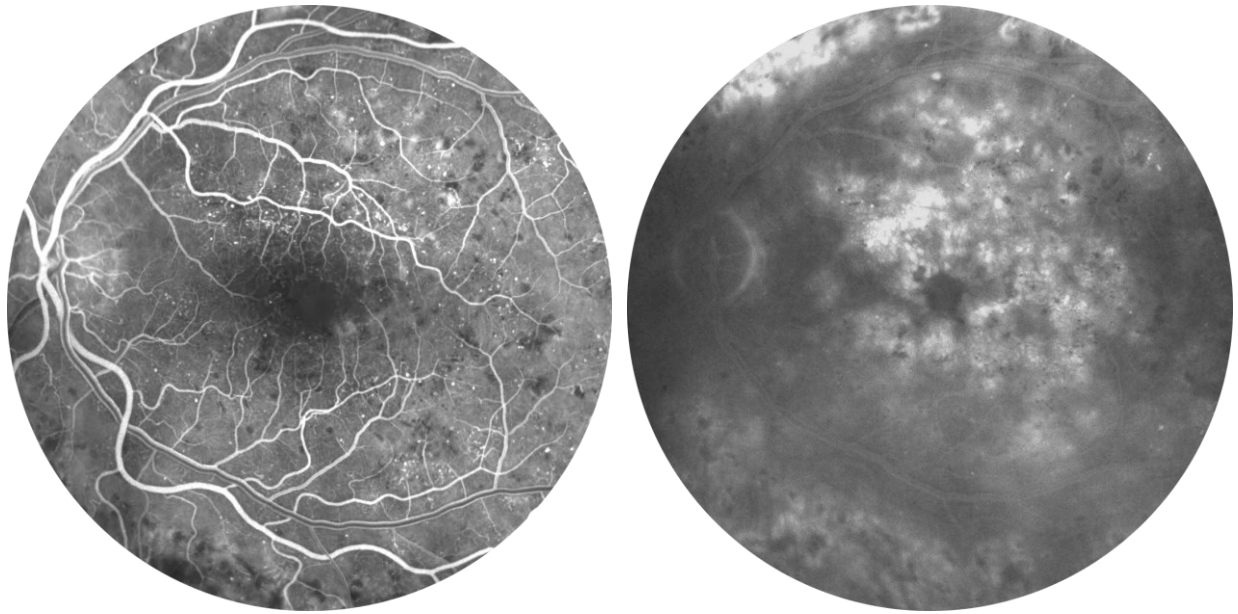
- Waldenström macroglobulinemia

SRD due to exudation coming from retinal vessels

- Diabetic macular edema
  - Intraretinal fluid comes from the retinal capillaries , by breakdown of the inner BRB
  - Saturation of the Müller cell function







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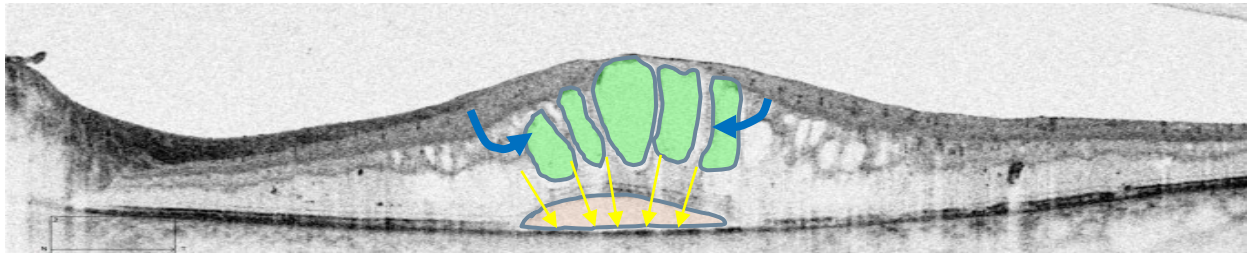
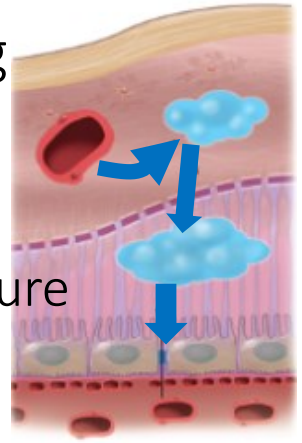
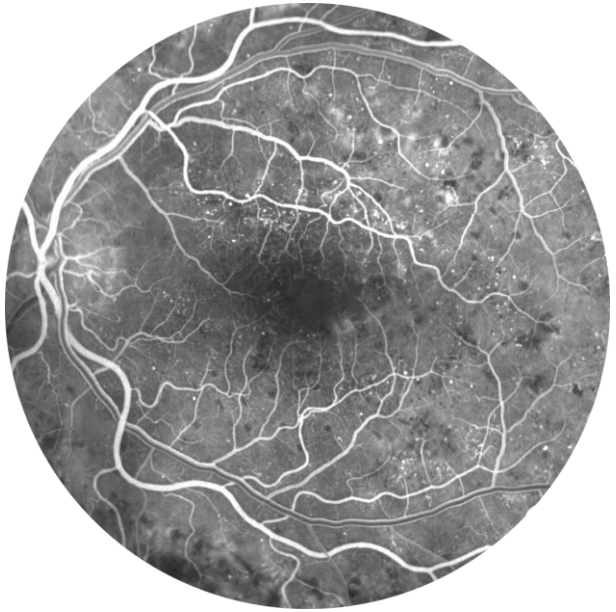
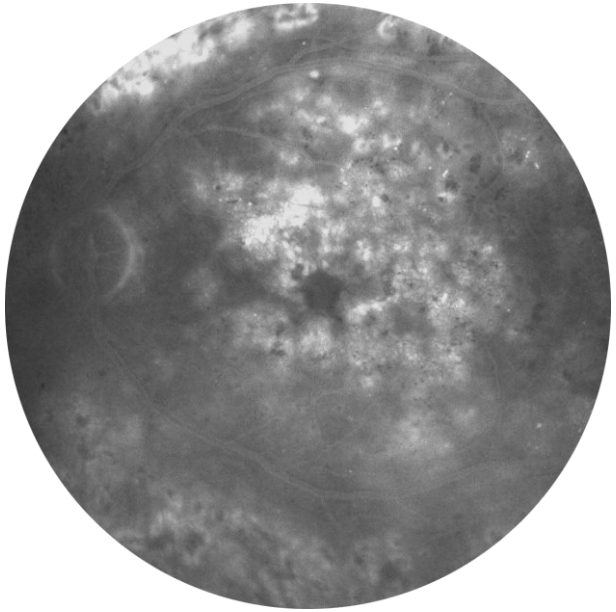
SRD due to exudation coming from retinal vessels

- Diabetic macular edema
  - Intraretinal fluid comes from the retinal capillaries , by breakdown of the inner BRB
  - Saturation of the Müller cell function
  - Insufficient H_2O pumping by the RPE
    - possibly due to the high sub-retinal osmotic pressure









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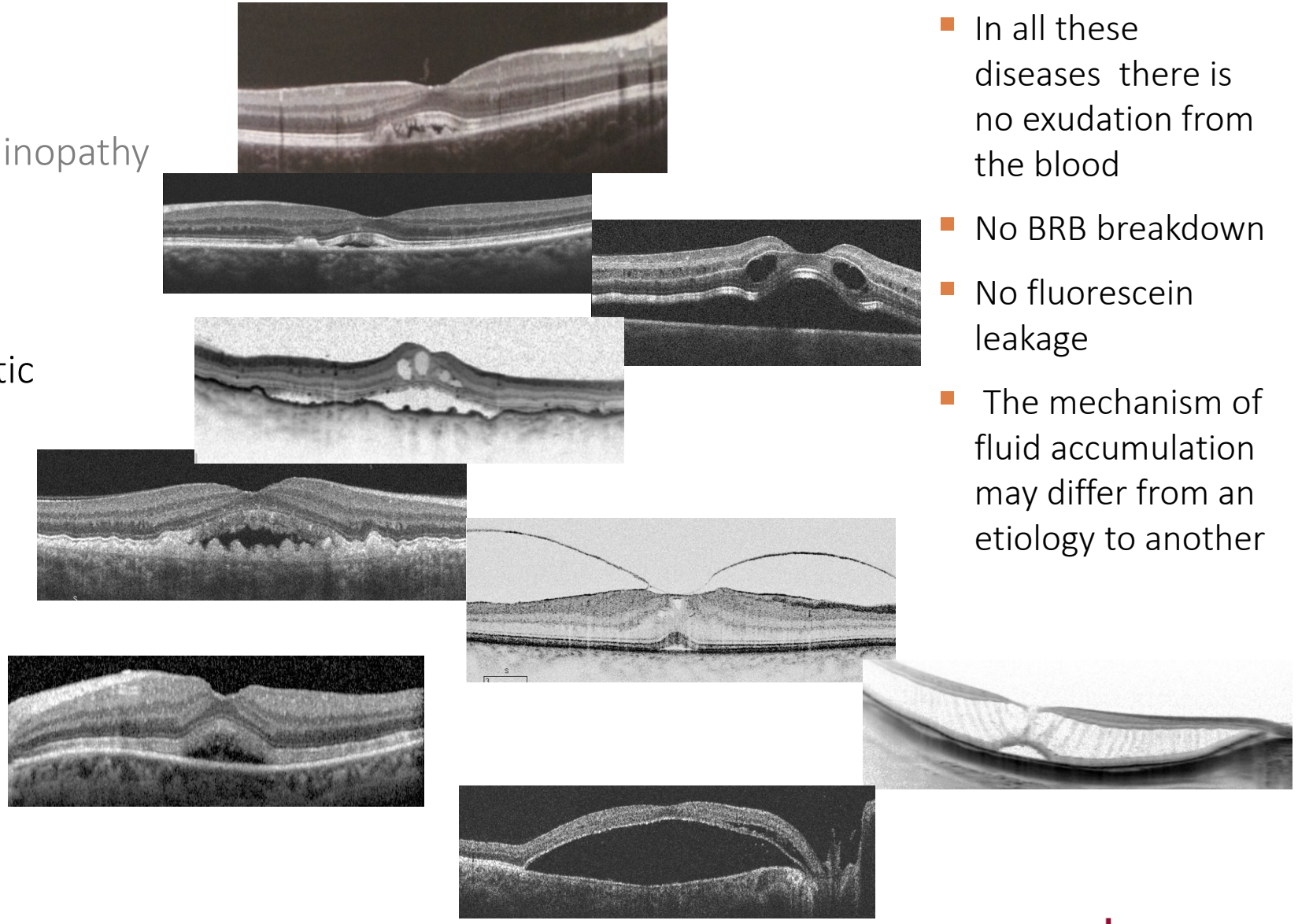
Macular detachment without exudation

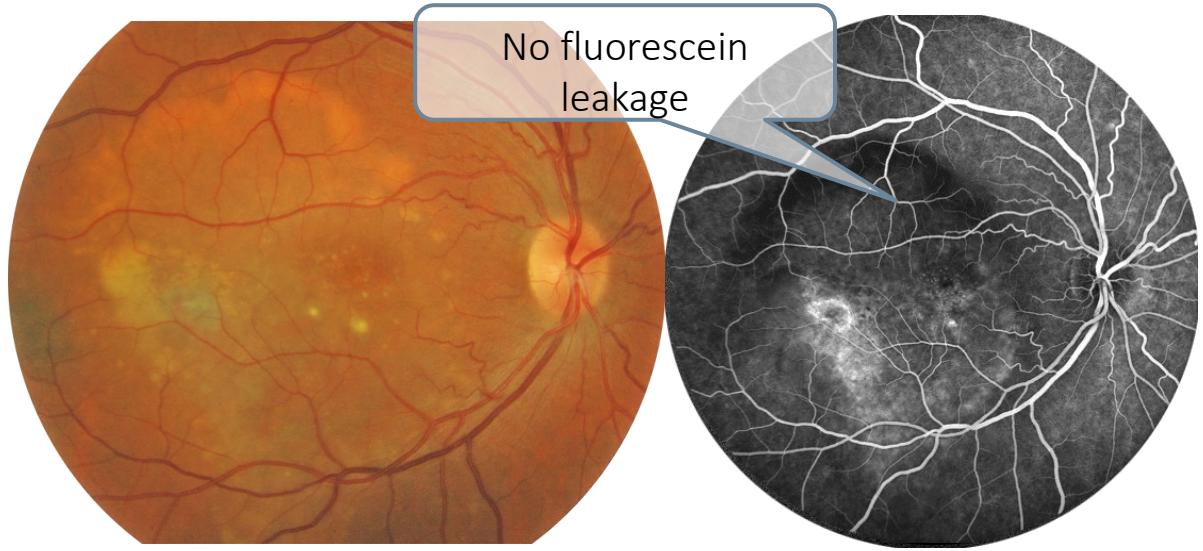
- Bestrophinopathies
  - Best's disease
  - Autosomal recessive Bestrophinopathy
- Pseudovitelliform dystrophy
- Acute exudative polymorphous vitelliform maculopathy
- Bilateral diffuse uveal melanocytic proliferation
- Cuticular drusen
- Tractional maculopathies
- Drug toxicity
  - MEKAR
  - Hair dyes
  - Deferoxamine
- Optic disc pit maculopathy

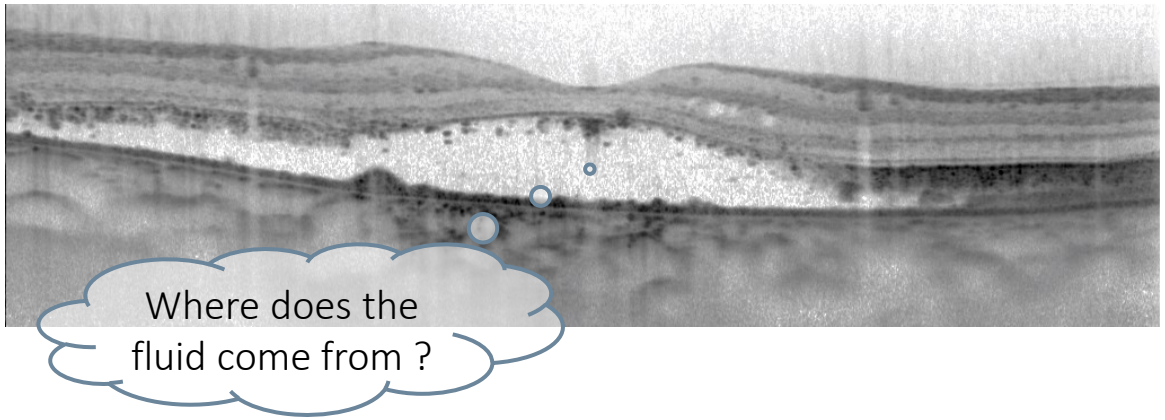


- In all these diseases there is no exudation from the blood
- No BRB breakdown
- No fluorescein leakage
- The mechanism of fluid accumulation may differ from an etiology to another

Macular detachment without exudation

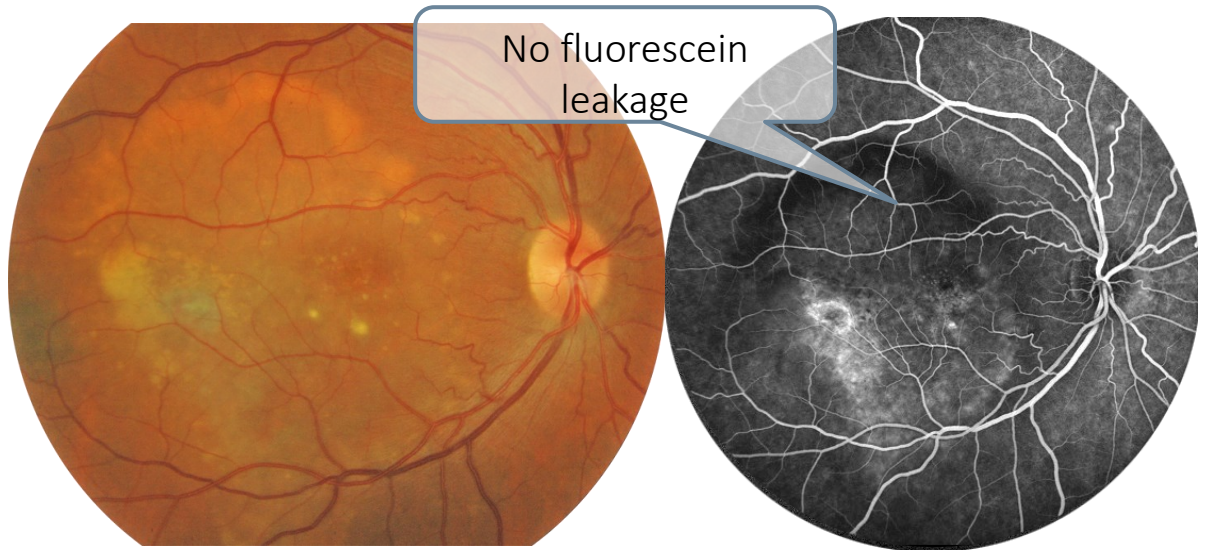
- Bestrophinopathies are due to mutations on BEST1 gene.
  - No fluorescein leakage

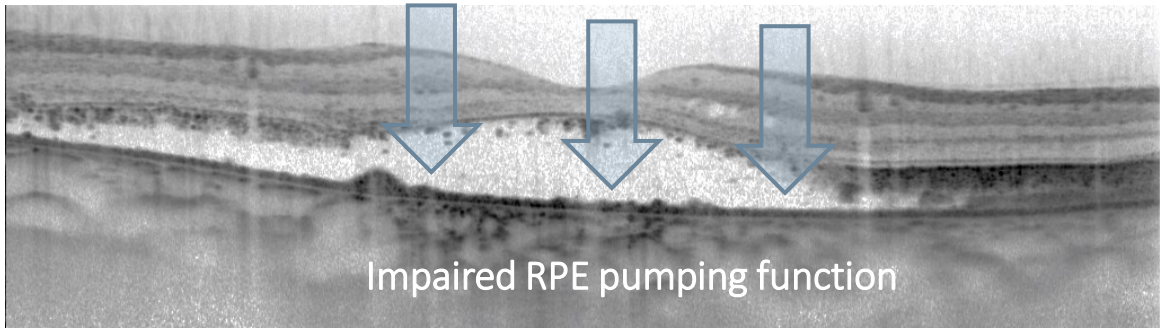


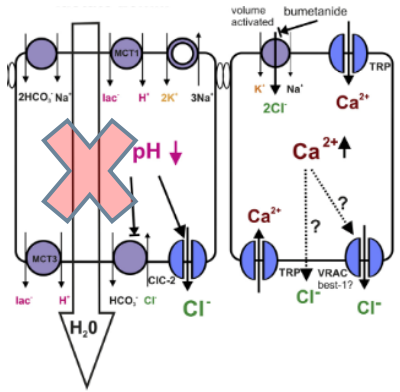


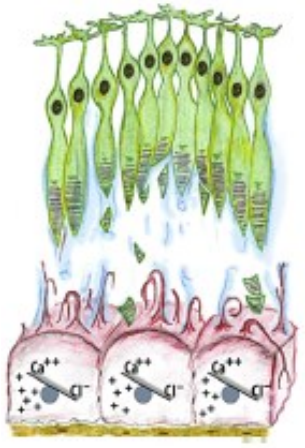
Macular detachment without exudation

- Bestrophinopathies are due to mutations on BEST1 gene.
  - No fluorescein leakage
  - The muted Best-1 protein is unable to regulate intracellular Ca2+ signalling and to maintain fluid transfer through the RPE
    - accumulation of SRF
    - loss of phagocytosis function









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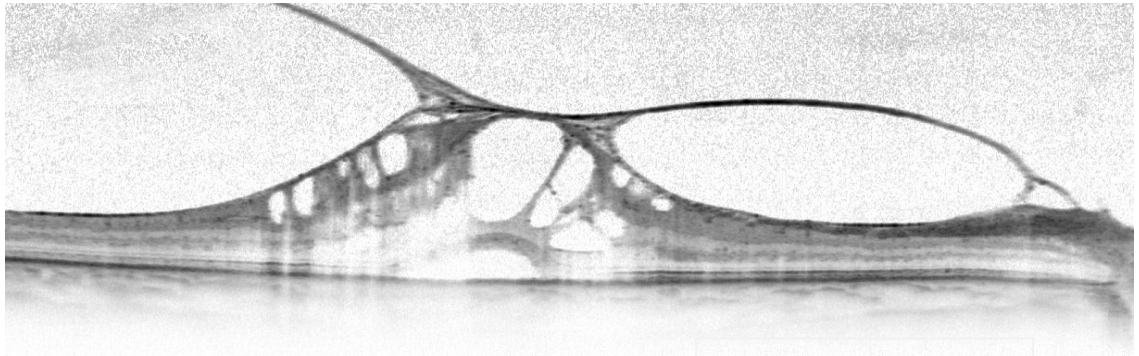
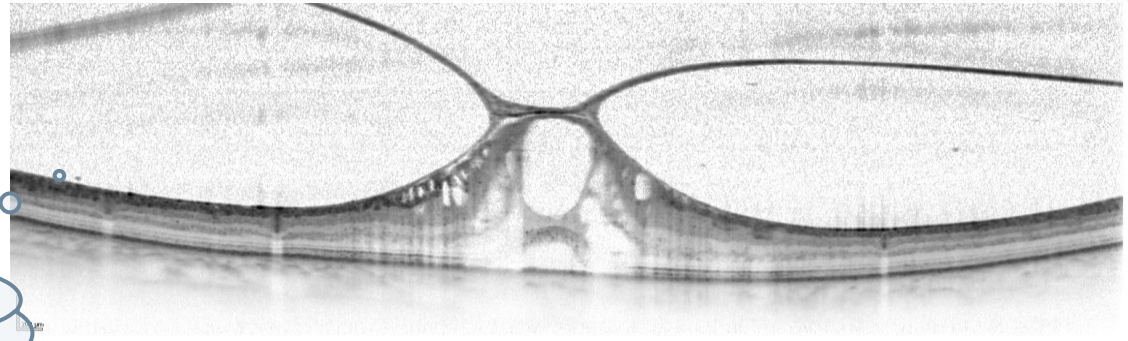
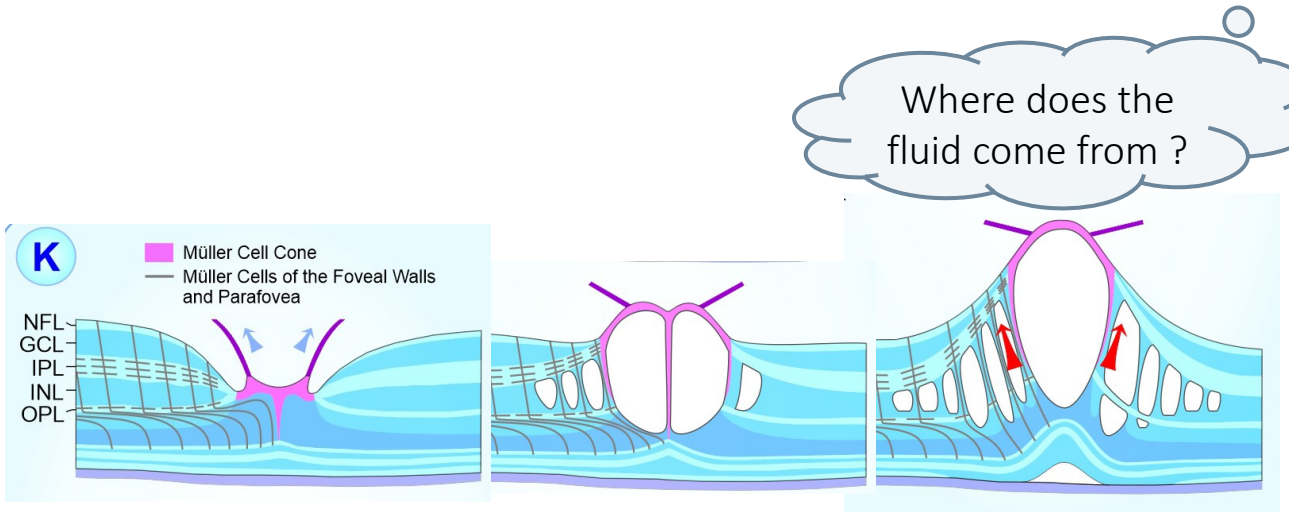
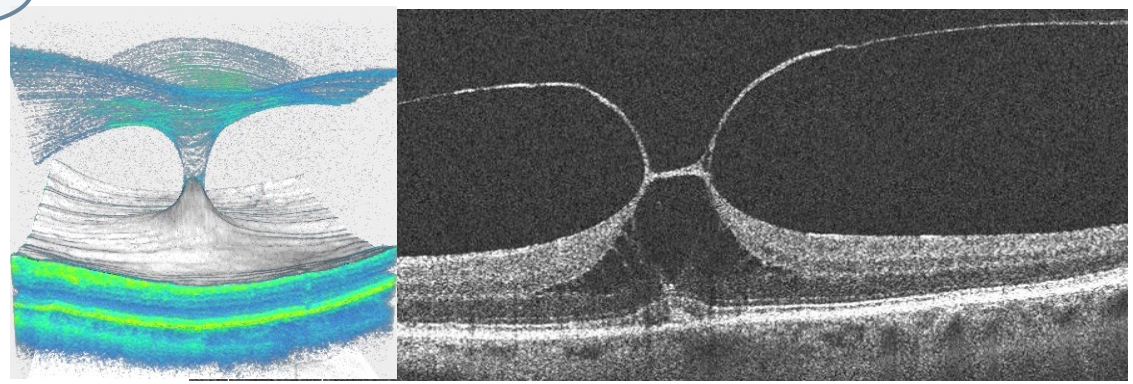
Macular detachment without exudation

- Tractional macular detachment
  - cystoid cavities often associated with foveal detachment
    - no fluorescein leakage









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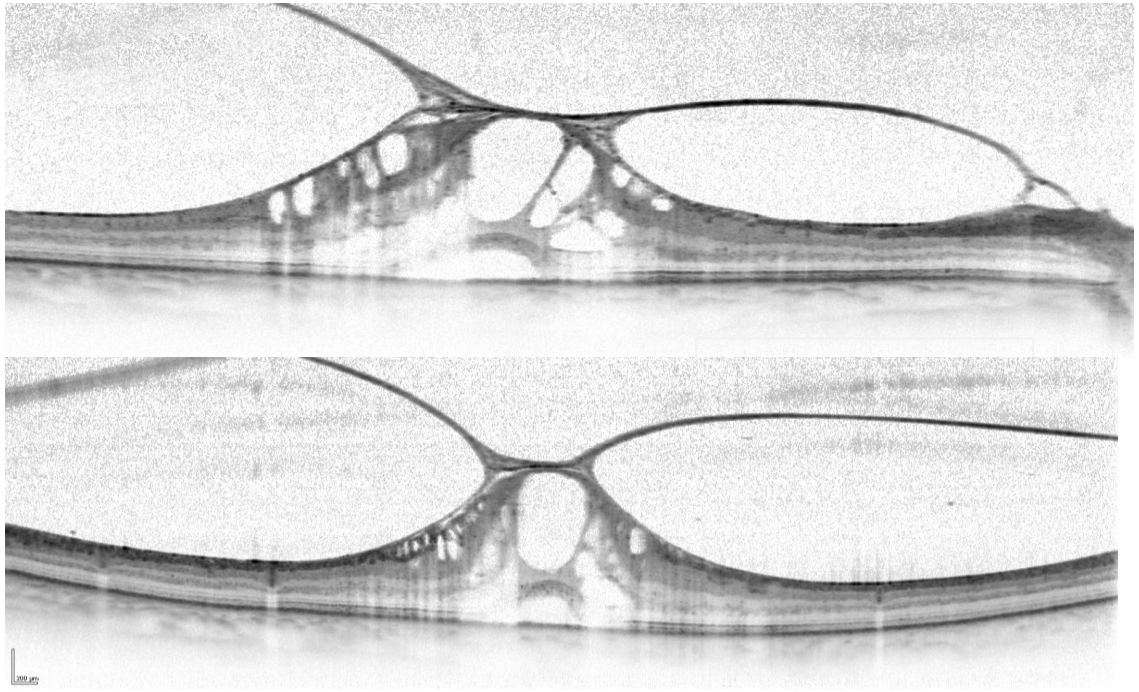
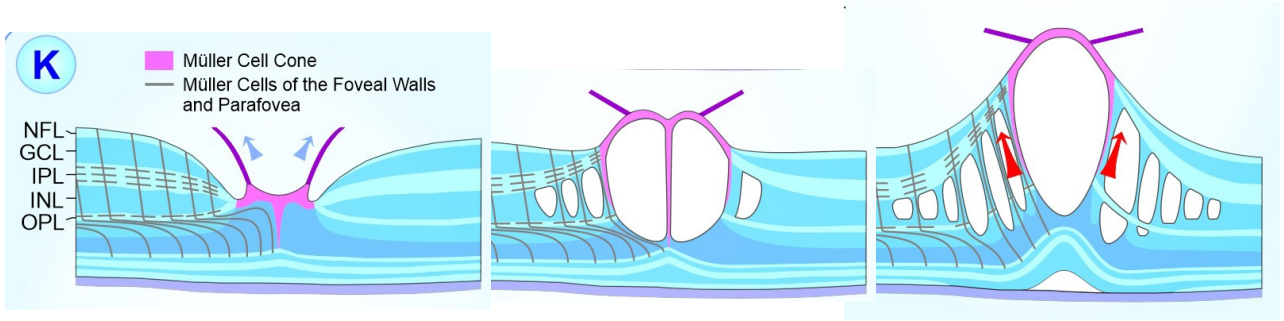
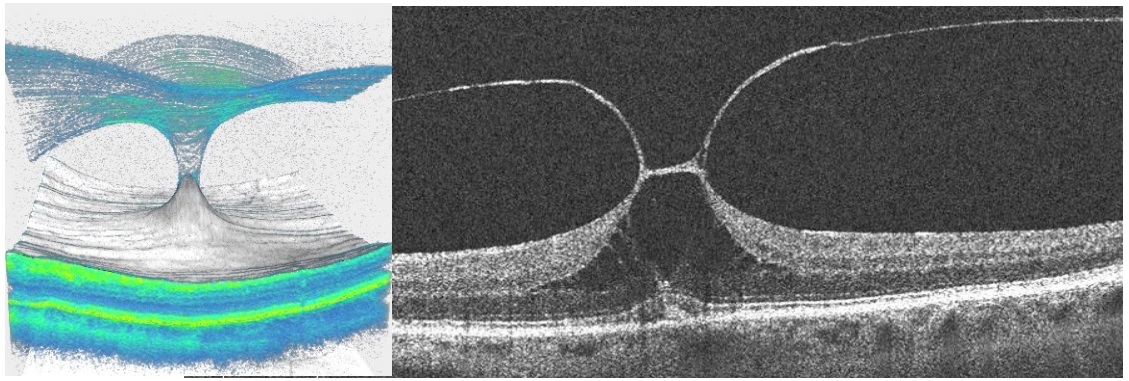
Macular detachment without exudation

- Tractional macular detachment
  - vitreous traction on central Müller cell cone
  - dissociation between the central Müller cells and the parafovea
  - *disturbed Müller cell function of H_2O recycling and drainage*



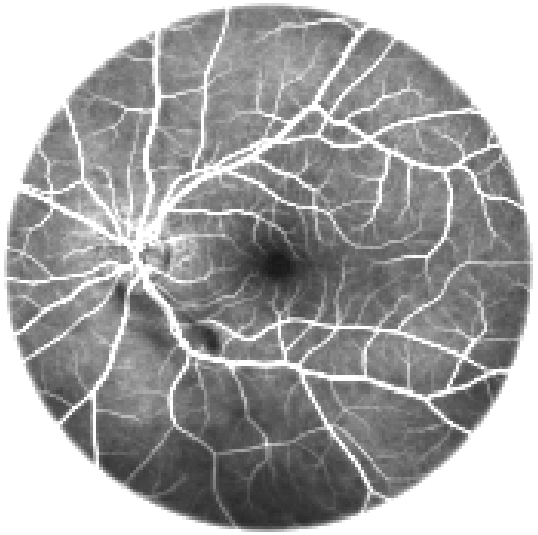


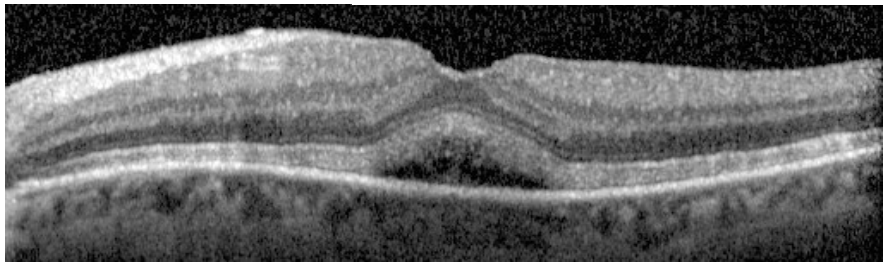


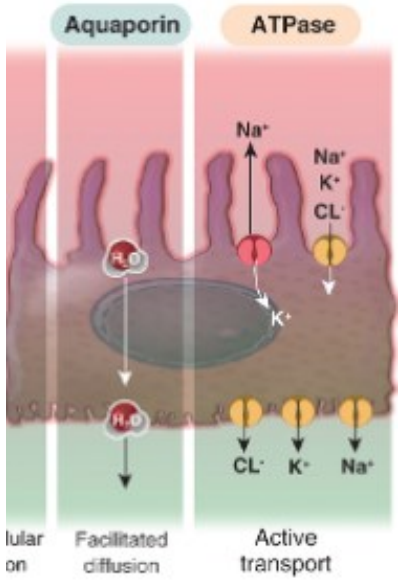
Bringmann A et al , Progr Ret Eye Res 2021

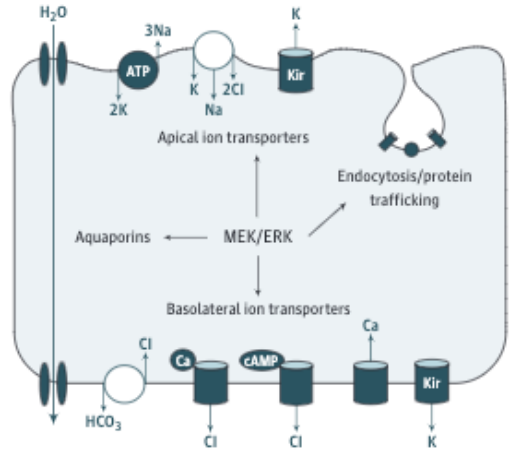
Macular detachment without exudation

- Drug toxicity :
  - MEK inhibitor Associated Retinopathy (MEKAR)
    - MEK inhibitors are commonly used in advanced melanoma , ovarian or thyroid carcinoma and others
  - are responsible for transient multiple SRD without any leakage
  - the MEK pathway regulates the density of AQ1 in the RPE cells
  - its inhibition results in
    an accumulation of fluid coming from the retina which cannot transit through the RPE towards the choroid.









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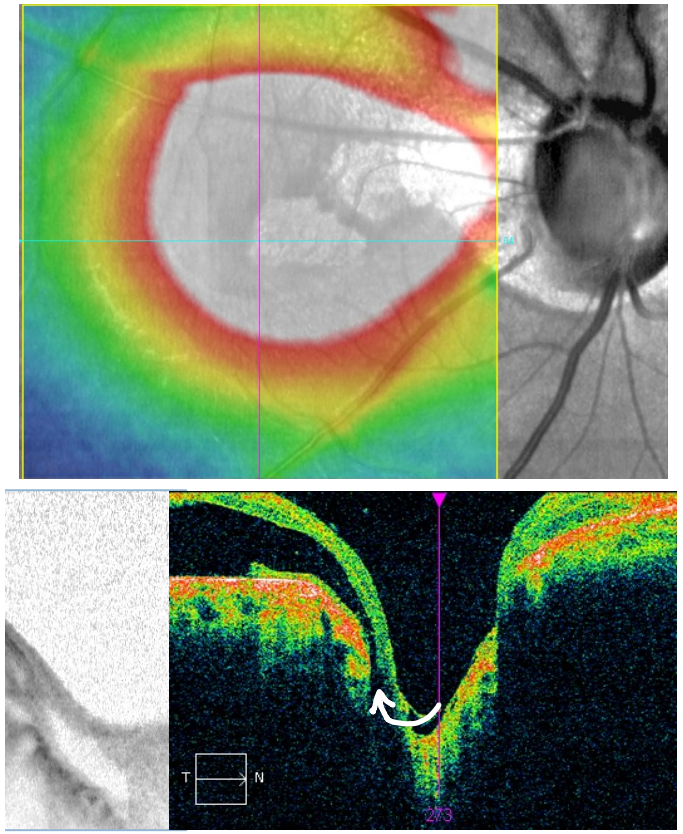
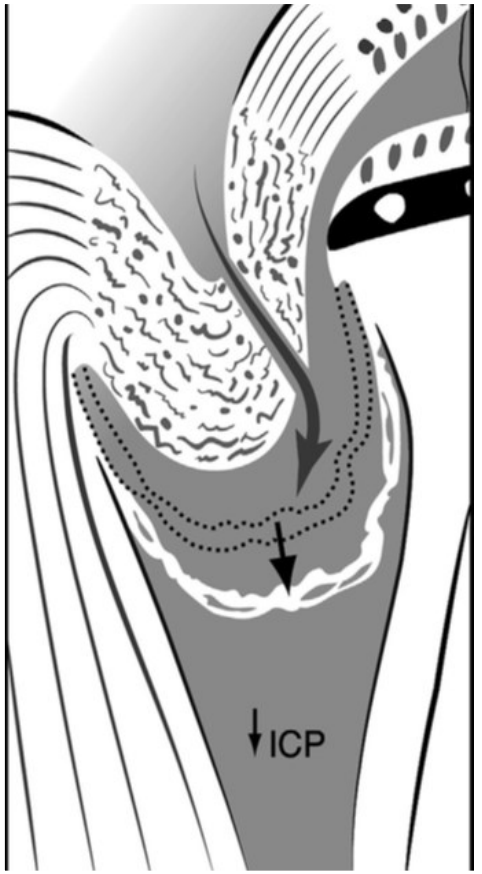
Macular detachment without exudation

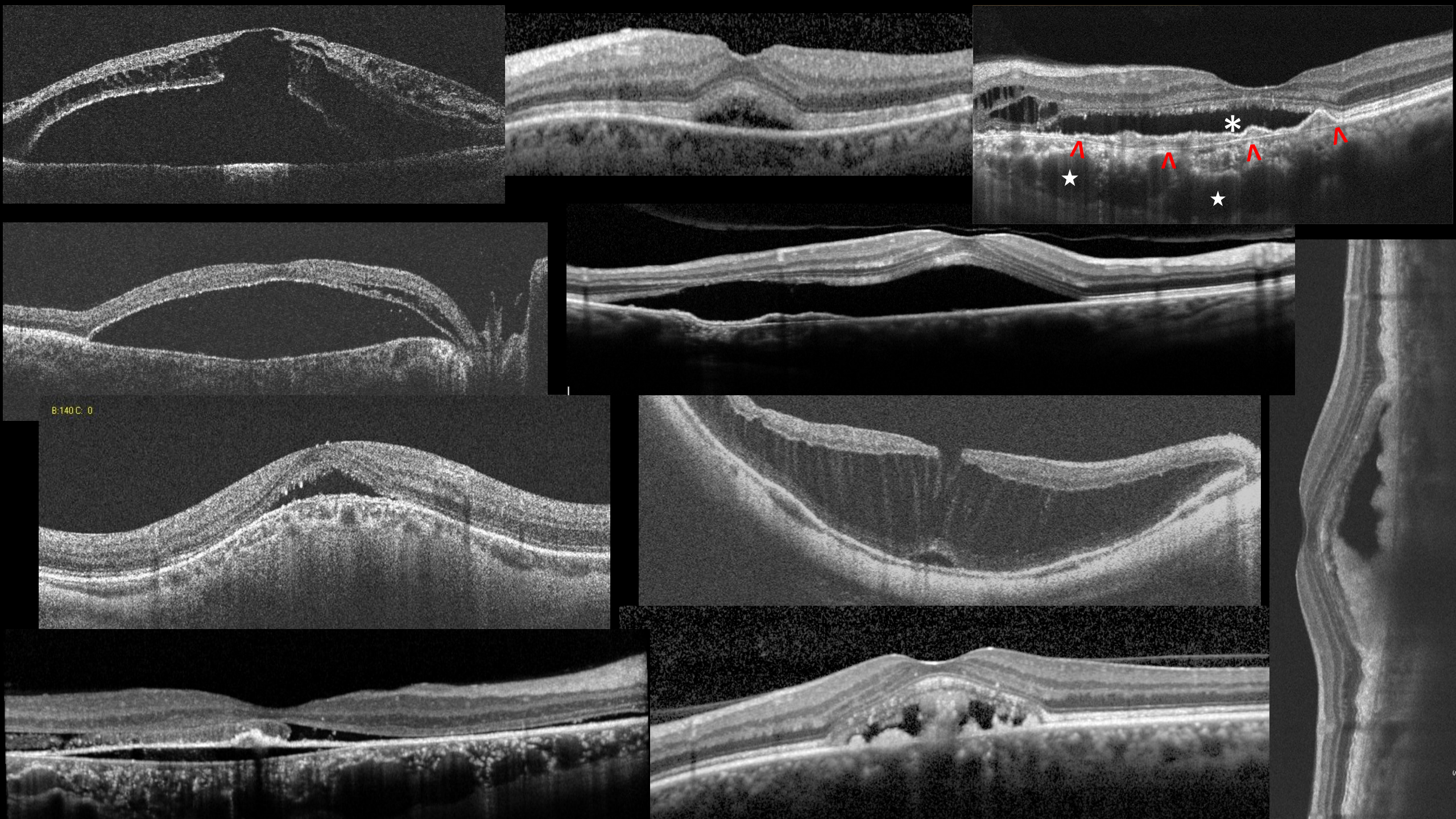
- Optic disc pit maculopathy
  - the subretinal fluid comes from the vitreous
  - not via a trans-retinal route
  - but through the optic disc pit anomaly.





Take home message

- Serous retinal detachments are due to various causes
  - Exudation due to a breakdown of the outer BRB
    - fluid comes from the choroid through a RPE altered by inflammation, ischemia, neovascularization or tumors
  - Exudation due to a breakdown of the inner BRB
    - fluid comes from retinal vessels through a capillary endothelium altered by inflammation, pericyte loss, venous stasis, abnormal capillary proliferation , most often mediated by VEGF over-expression
- Macular detachment without exudation
    - where the subretinal fluid comes from the vitreous and the retina metabolism but is insufficiently resorbed by an impaired RPE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Serous business: Delineating the broad spectrum of diseases with subretinal fluid in the macula

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ABSTRACT

A wide range of ocular diseases can present with serous subretinal fluid in the macula and therefore clinically mimic central serous chorioretinopathy (CSC). In this manuscript, we categorise the diseases and conditions that are part of the differential diagnosis into 12 main pathogenic subgroups: neovascular diseases, vitelliform lesions, inflammatory diseases, ocular tumours, haematological malignancies, paraneoplastic syndromes, genetic diseases, ocular developmental anomalies, medication-related conditions and toxicity-related diseases, rhegmatogenous retinal detachment and tractional retinal detachment, retinal vascular diseases, and miscellaneous diseases. In addition, we describe 2 new clinical pictures associated with macular subretinal fluid accumulation, namely serous maculopathy with absence of retinal pigment epithelium (SMARPE) and serous maculopathy due to aspecific choroidopathy (SMACH). Differentiating between these various diseases and CSC can be challenging, and obtaining the correct diagnosis can have immediate therapeutic and prognostic consequences. Here, we describe the key differential diagnostic features of each disease within this clinical spectrum, including representative case examples. Moreover, we discuss the pathogenesis of each disease in order to facilitate the differentiation from typical CSC.

1. Introduction

Central serous chorioretinopathy (CSC) is a relatively common chorioretinal disease that typically presents with a sudden disruption of central vision. This vision loss is caused by a detachment of the neurosensory retina due to an accumulation of serous subretinal fluid (SRF) in the macula. However, abnormalities may extend well beyond the posterior pole, possibly leading to only mild visual complaints. Middle-aged men are most commonly affected, despite the fact that an older age does not rule out a first-time presentation of CSC, especially in women. Both corticosteroid use and endogenous hypercortisolism, as well as several genetic factors, have been found to increase the risk of developing CSC (Brinks et al., 2021; Daruich et al., 2015; de Jong et al., 2015; Kaye et al., 2020; van Dijk et al., 2016a, 2017b; van Rijssen et al., 2019b).

A wide variety of other diseases and conditions can also present with serous SRF in the macula and can therefore clinically mimic CSC (Table 1). Since the differentiation between these diseases and CSC can be challenging, we discuss the extensive differential diagnosis of CSC. Moreover, we describe the pathogenic mechanisms specific to the various diseases that contribute to this differential diagnosis. These diseases can be broadly categorised into the following 12 main pathogenic subgroups:

1. Neovascular diseases
2. Vitelliform lesions
3. Inflammatory diseases
4. Ocular tumours
5. Haematological malignancies
6. Paraneoplastic syndromes
7. Genetic diseases
8. Ocular developmental anomalies
9. Medication-related conditions and toxicity-related diseases
10. Rhegmatogenous retinal detachment and tractional retinal detachment
11. Retinal vascular diseases
12. Miscellaneous diseases

A thorough medical history, including medical conditions, medication use, and familial eye diseases, as well as the nature and pattern of

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Merci de votre attention

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