Uveitis
Clinician/ Academic View

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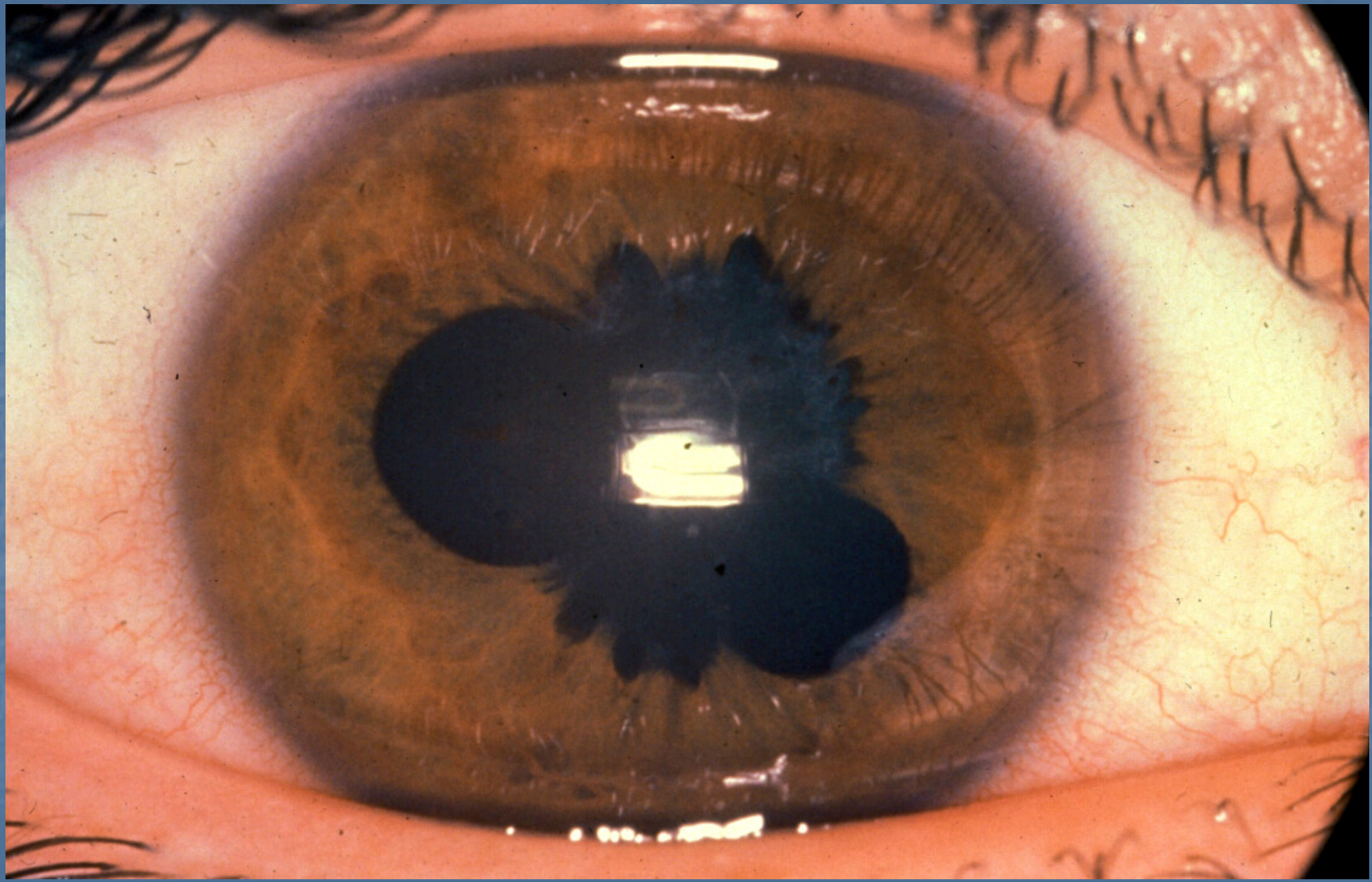
Definition „Uveitis“

- Inflammation of tissue inside the eye: Uvea, Retina

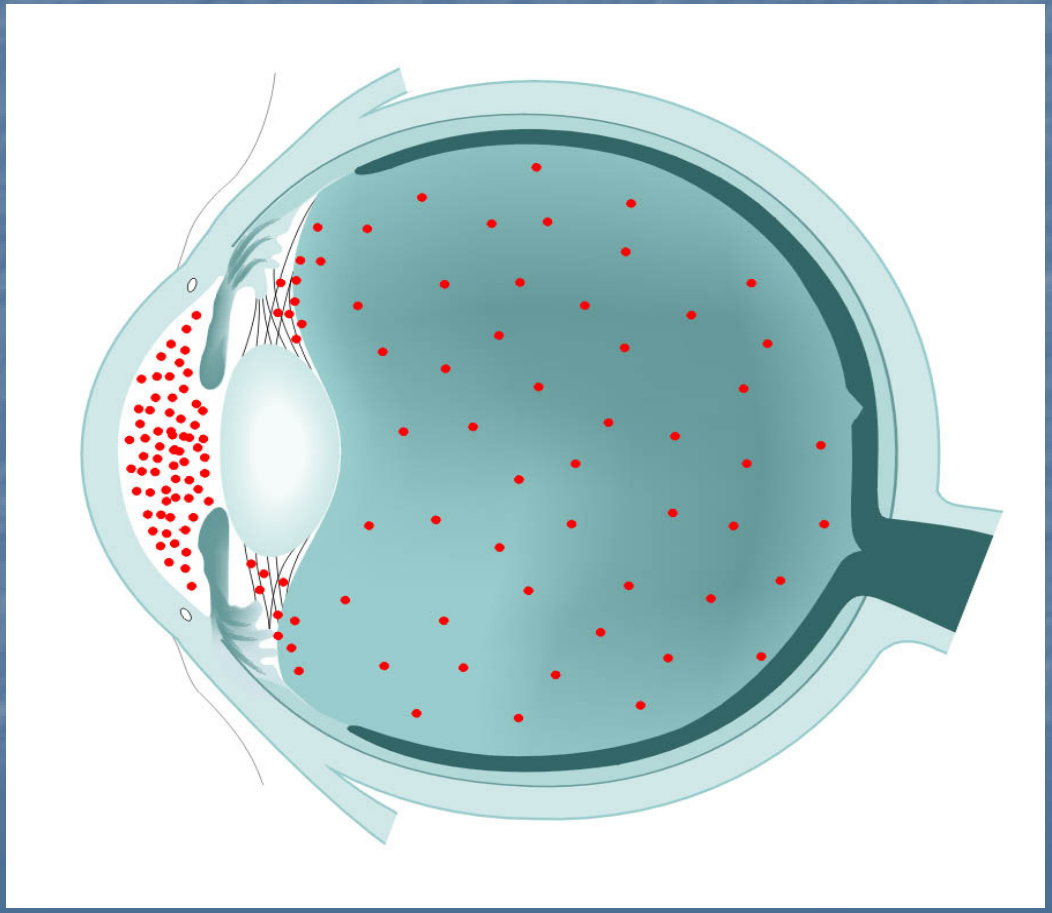


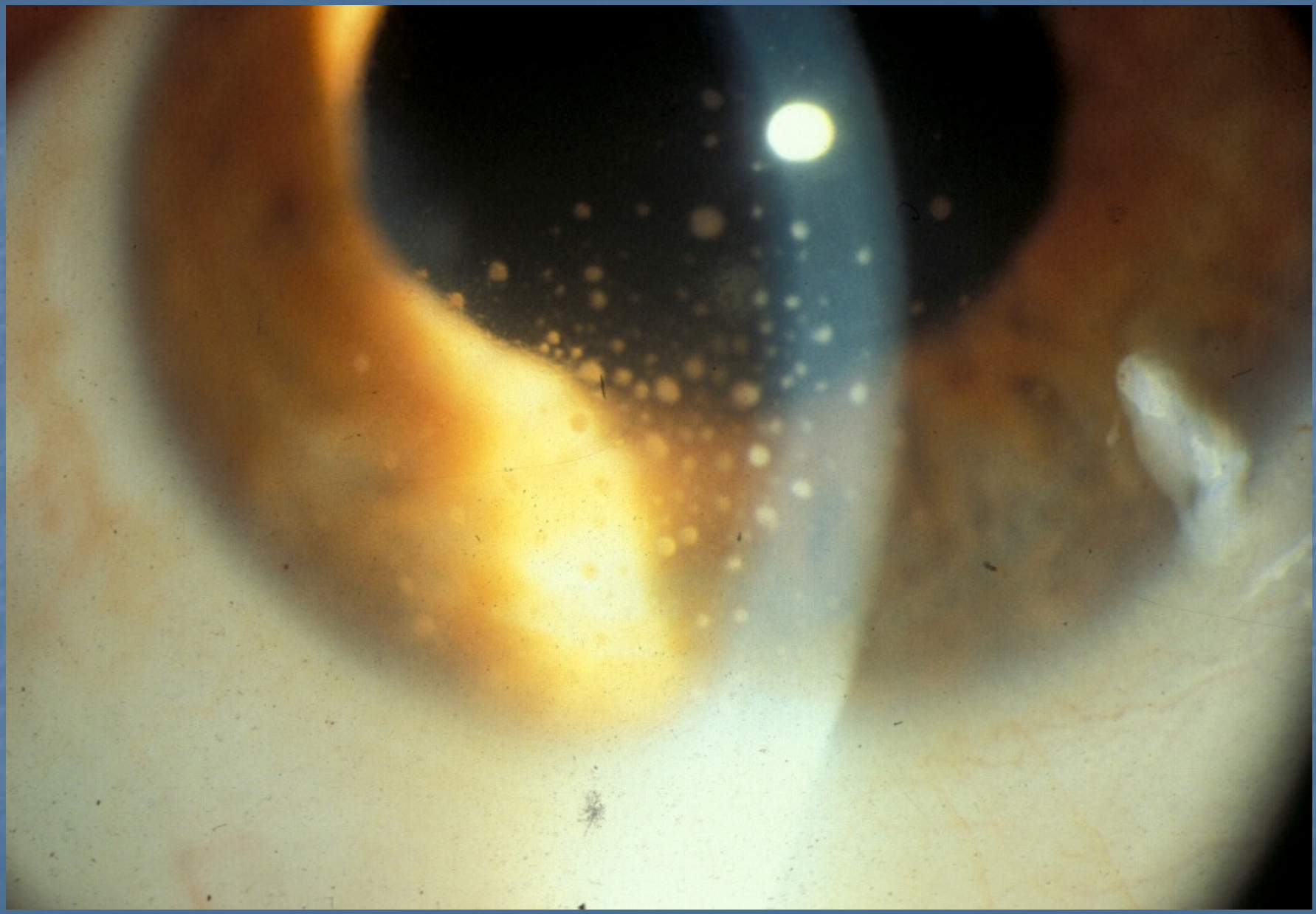
Classifications of Uveitis

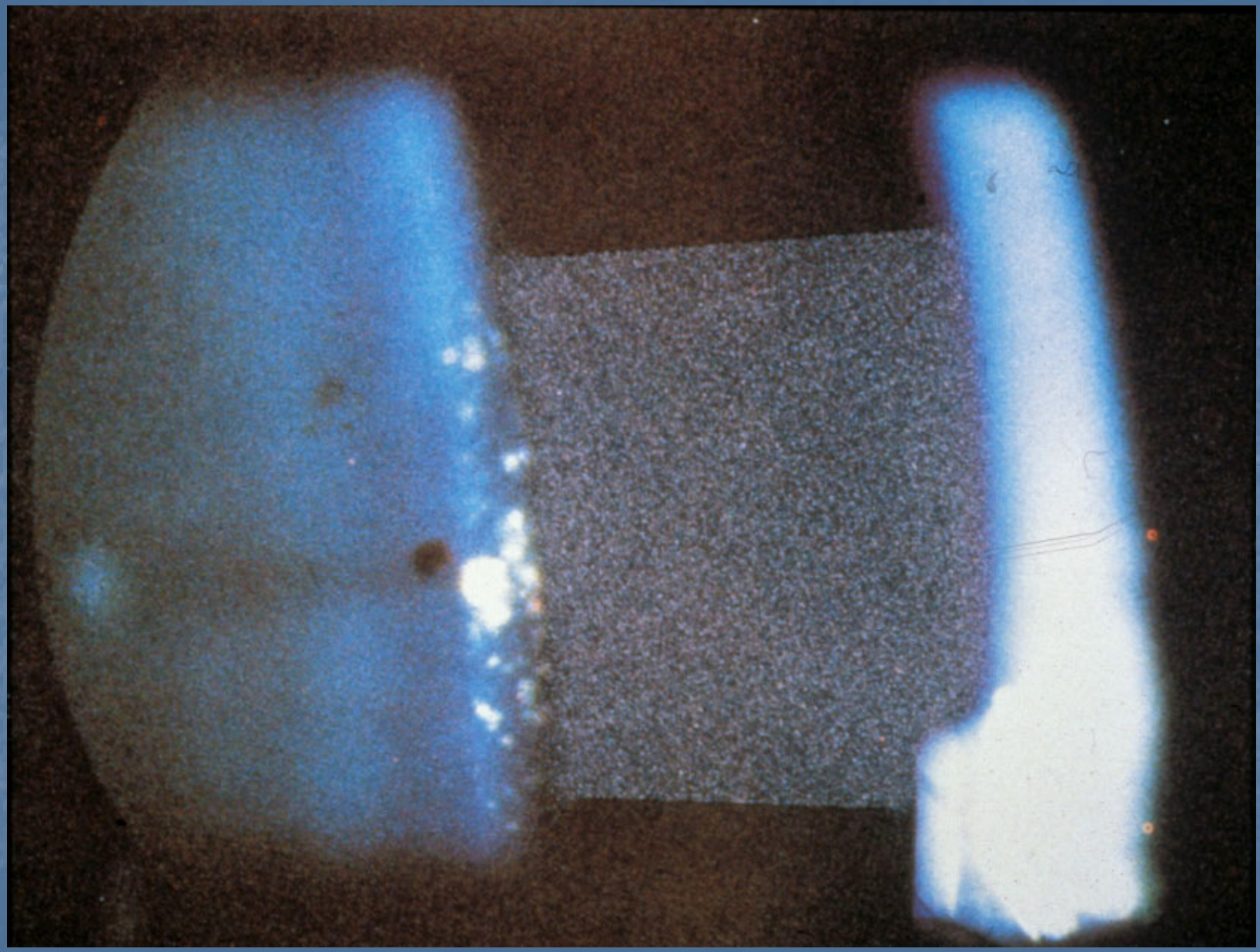
- Localisation
- Morphology
- Etiology
- Course

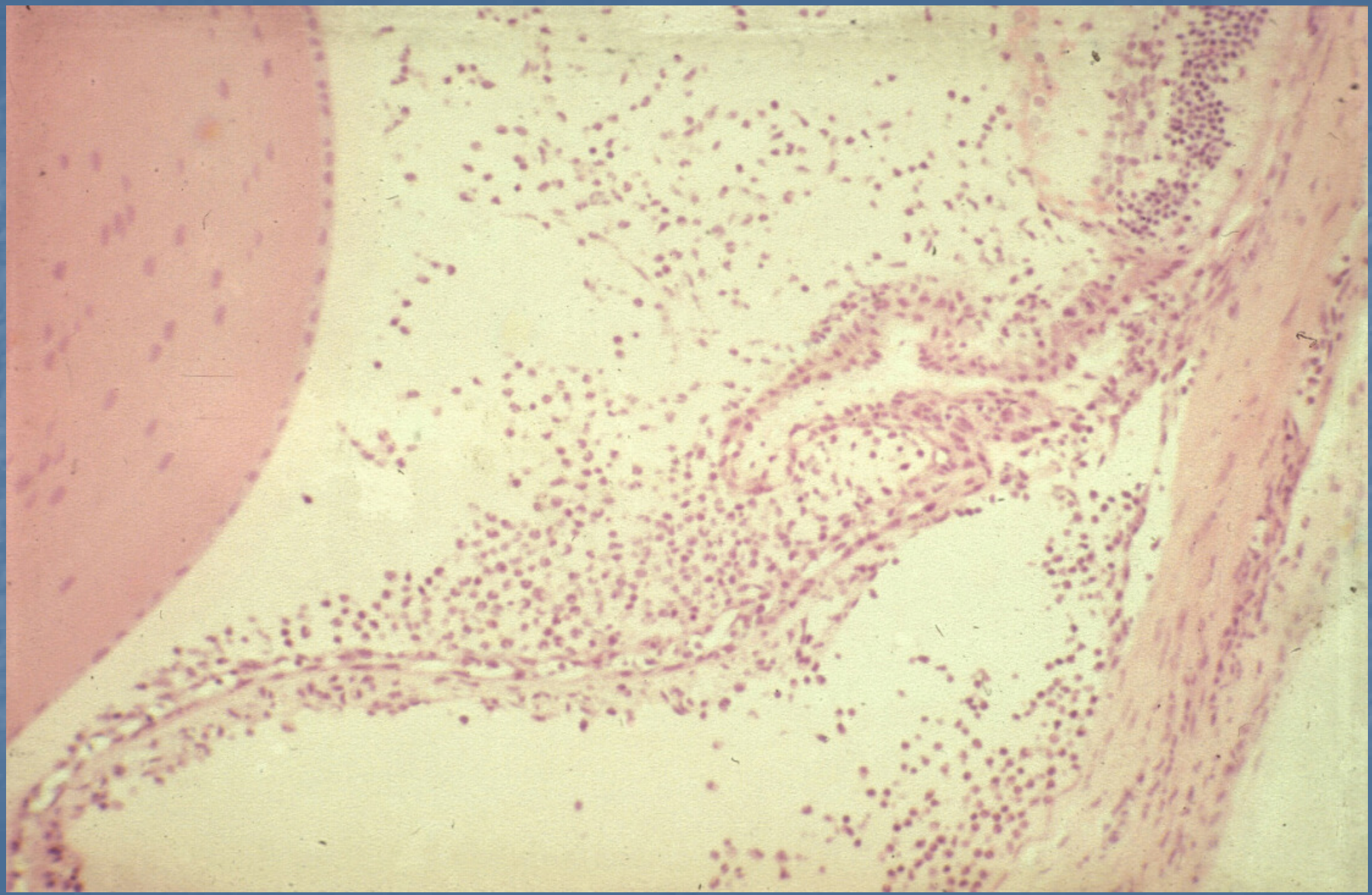
Localisation

- Anterior Uveitis
  - Iritis
  - Iridocyclitis



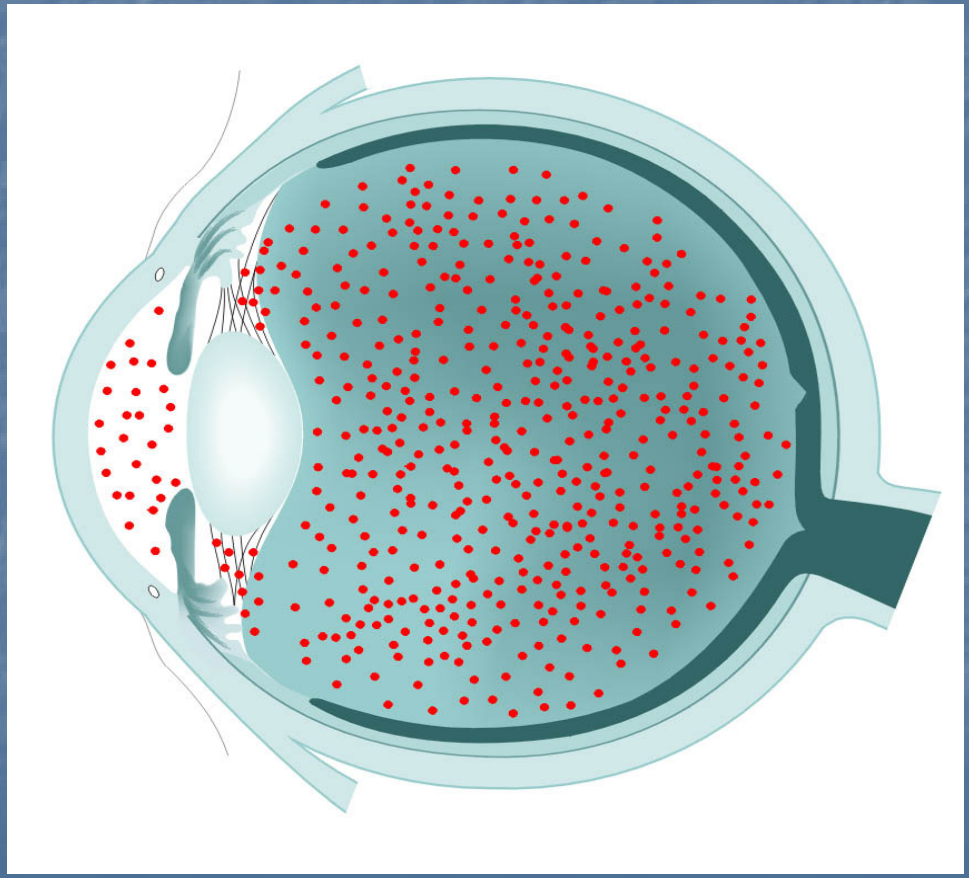


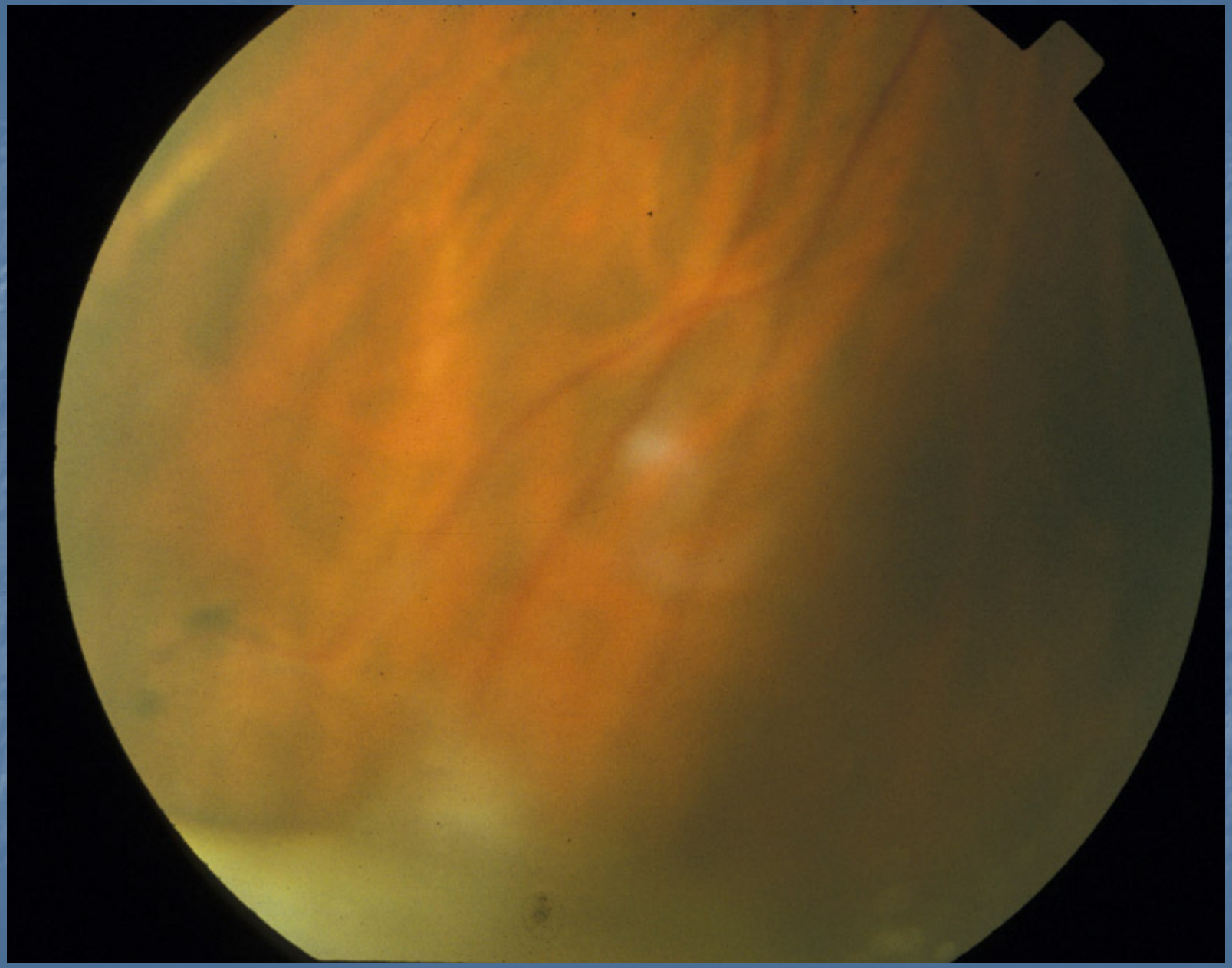




Localisation

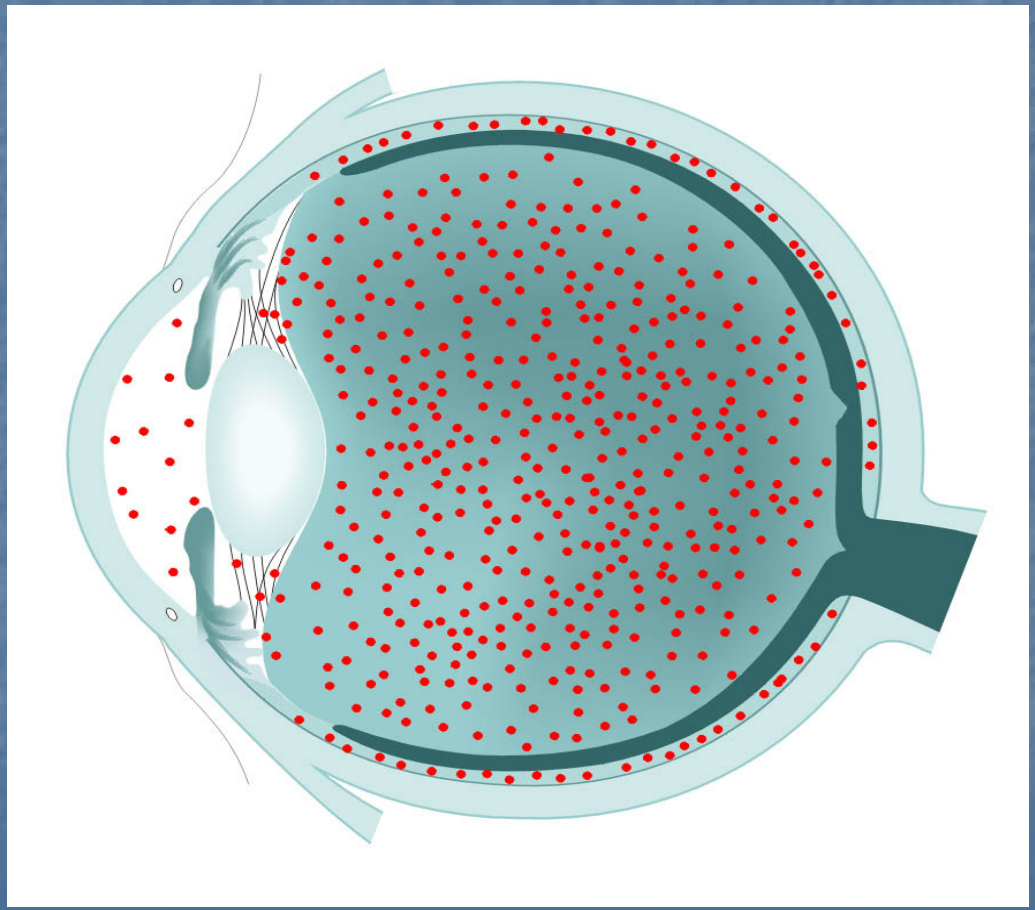
- Anterior Uveitis
  - Iritis
  - Iridocyclitis
- Intermediate Uveitis
  - Vitr.- and AC-cells

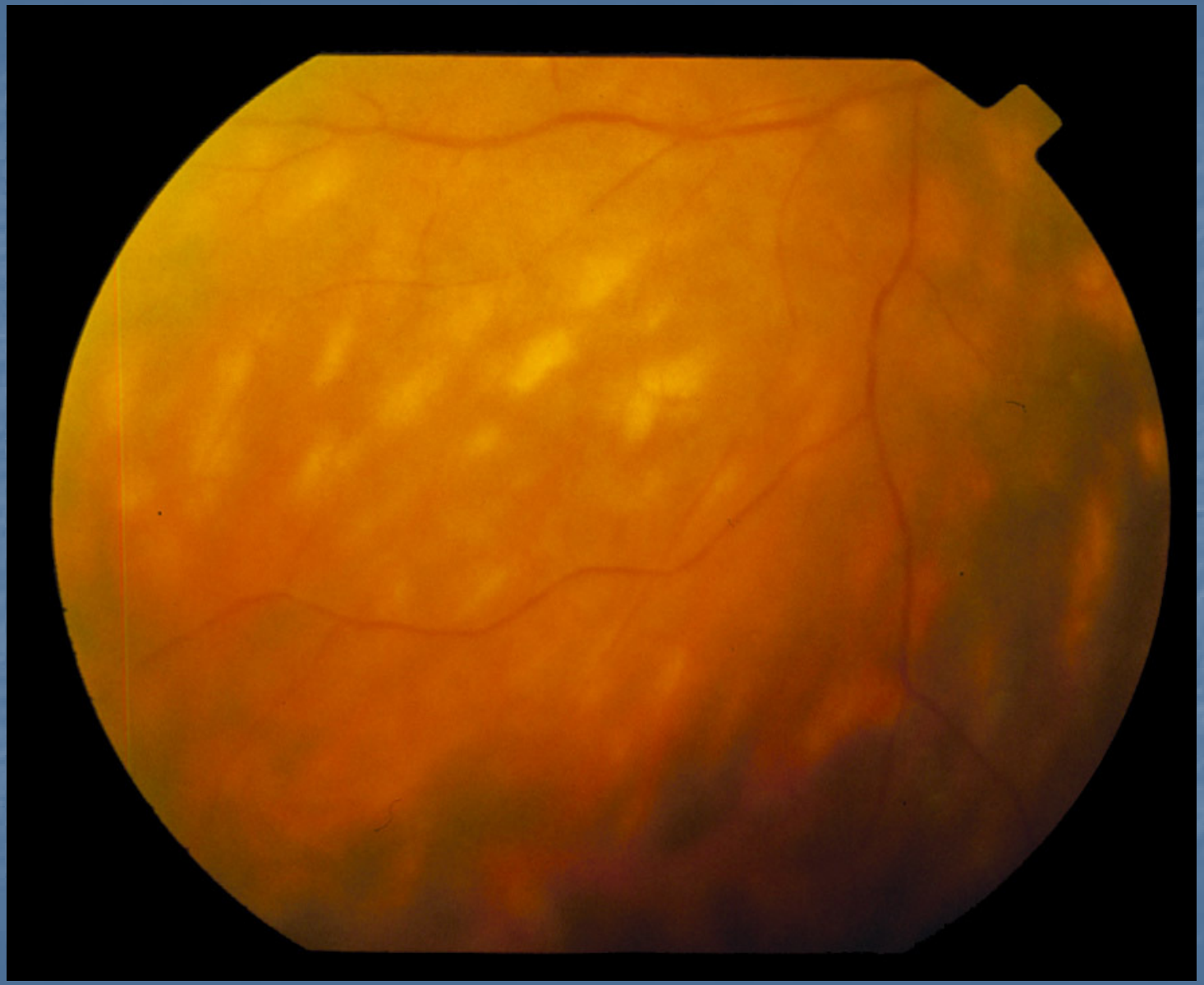




Localisation

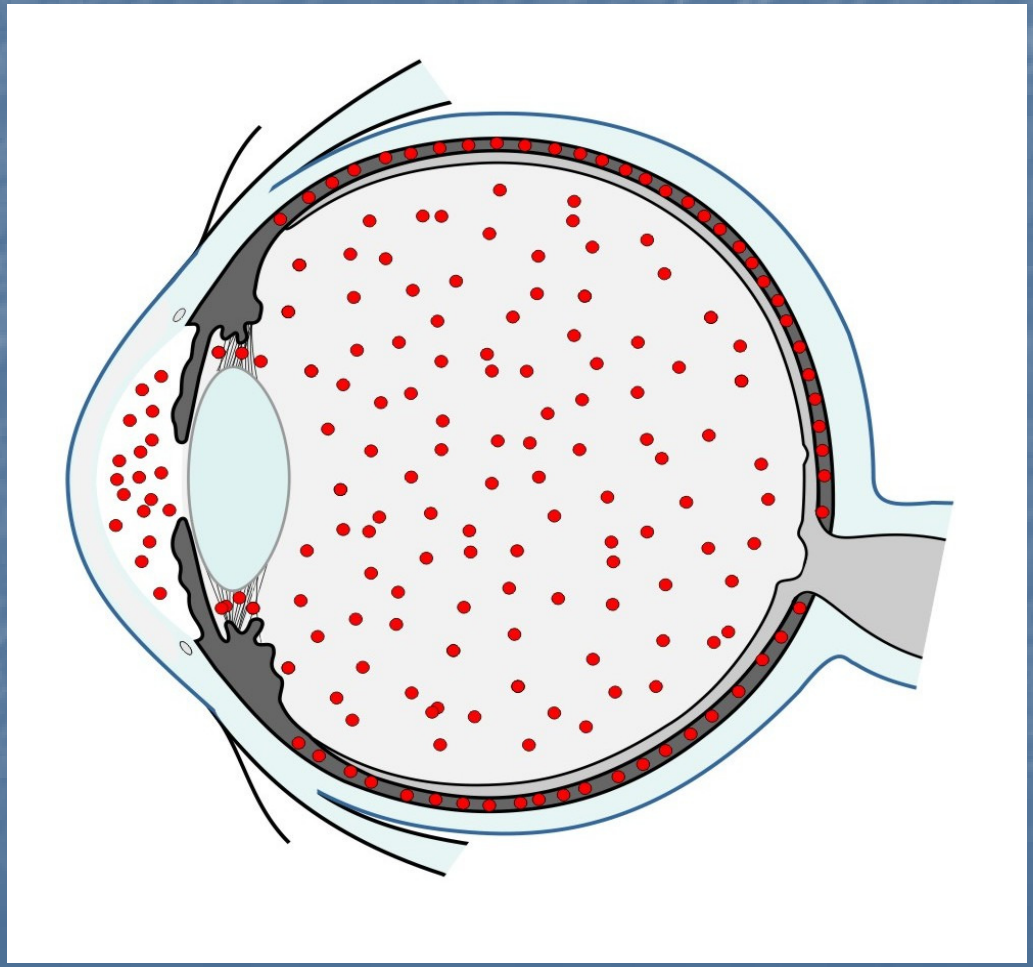
- Anterior Uveitis
  - Iritis
  - Iridocyclitis
- Intermediate Uveitis
  - Vitr. and AC-cells
- Posterior Uveitis
  - Chorioretinitis,
  - Retinochoroiditis





Localisation

- Anterior Uveitis
  - Iritis
  - Iridocyclitis
- Intermediate Uveitis
  - Vitr. and AC-cells
- Posterior Uveitis
  - Chorioretinitis,
  - Retinochoroiditis
- Panuveitis
  - AC cells
  - posterior uveitis



Etiology and Laterality

unilateral

Herpes simplex/Zoster

Fuchs' Heterochromic cyclitis

postsurgical

foreign body

bilateral

juv. Idiopathic Arthritis

HLA-B27-associated

Sarcoidosis

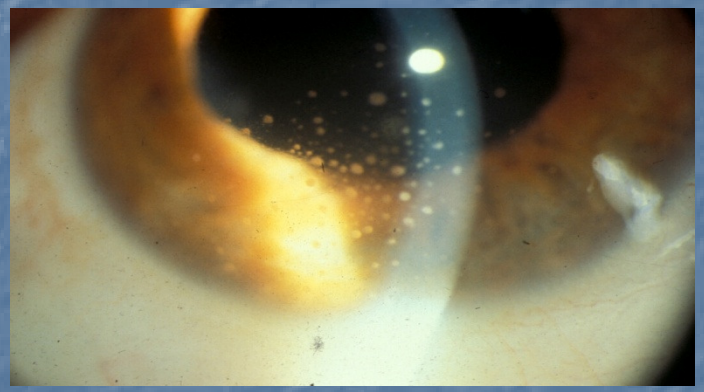
Multiple Sclerosis

APMPPE

Morphological Classification

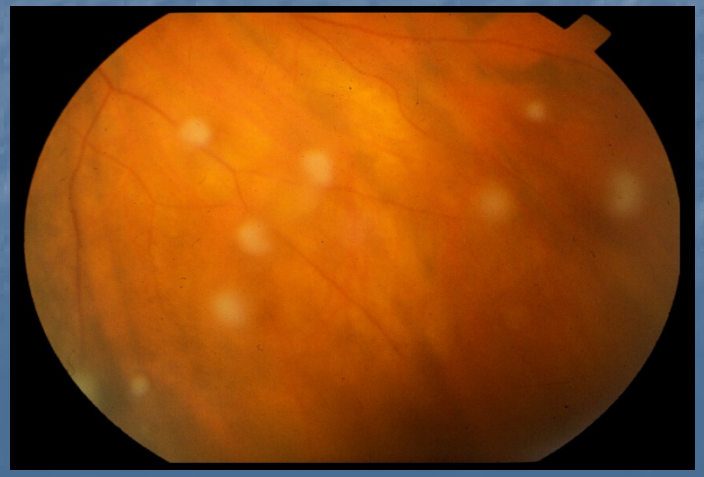
granulomatous vs non-granulomatous

speckled precipitates



Koeppe-nodules

Snowballs



Choroidal Granuloma

Classification based on Morphology

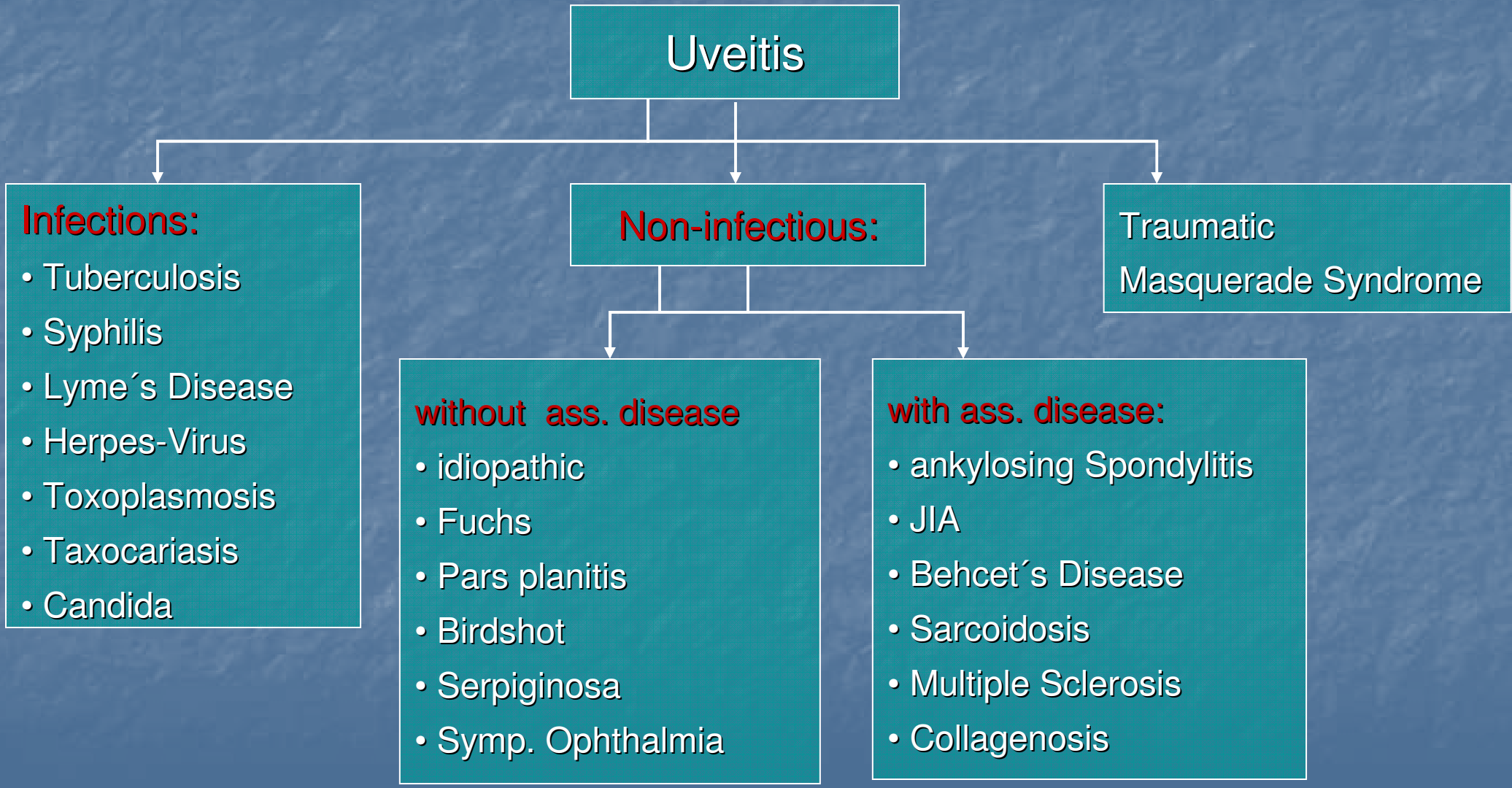
granulomatous

Sarcoidosis
Multiple Sclerosis
Sympathetic Ophthalmia
VKH
Infection: Syphilis
Tuberculosis
Herpes
Candida

non-granulomatous

JIA
HLA-B27- associated
Behcet´s Disease
ARN
CMV Retinitis
Birdshot Choroidopathy

Classification following Etiology



SUN Criteria

- Onset
  - sudden
  - insidious
- Duration
  - limited: up to 3 months
  - persistent: longer than 3 months

SUN Criteria

- Course
  - acute: sudden onset with limited duration
  - recurrent: multiple episodes, in between intervals without inflammation without therapy, at least 3 months
  - chronic: persistent uveitis with recurrences with less than 3 months free of recurrences after stop of therapy

Epidemiology of Uveitis Incidence

- Uveitis total: 35-50/100.000 inhabitants
- Anterior Uveitis: app. 50 %
- Intermediate Uveitis: app. 30 %
- Posterior Uveitis: app. 20 %

Epidemiology of Uveitis Prevalence

- Uveitis total: 100/100.000 inhabitants
- subgroups are unknown

Uveitis in Childhood
Epidemiology

- 5-10 % of all uveitis patients

Evaluating Signs and Symptoms Goal

- To identify etiology and ass. disorders
- Best for an effective treatment
- But: adequate diagnostics!

How to evaluate Symptoms

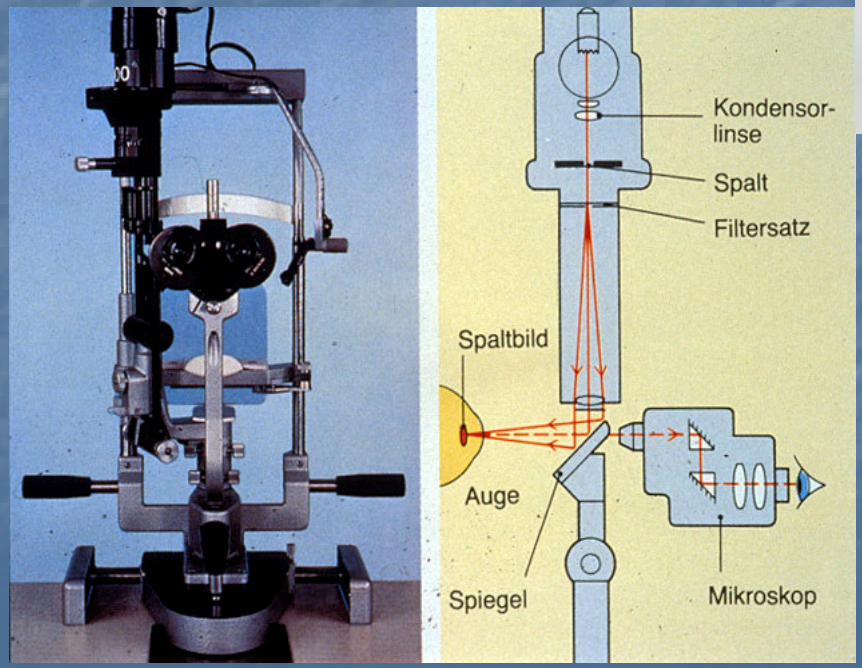
- History, eg. by questionnaire (symptoms)
- Quality of Life (NEI VFQ-25)
- no optimal uveitis „Evaluation of Symptoms“ questionnaire

How to evaluate Signs

- clinical investigation
- prob. new targeted history
  - add. investigations
  - FLA, ICG, OCT, Visual fields, ERG, CT, MRI
  - targeted (lab-) diagnostics

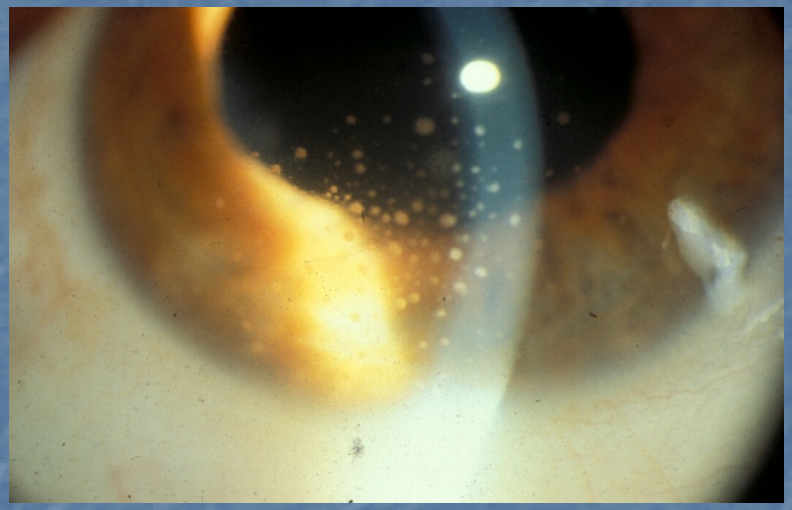
Clinical Investigation

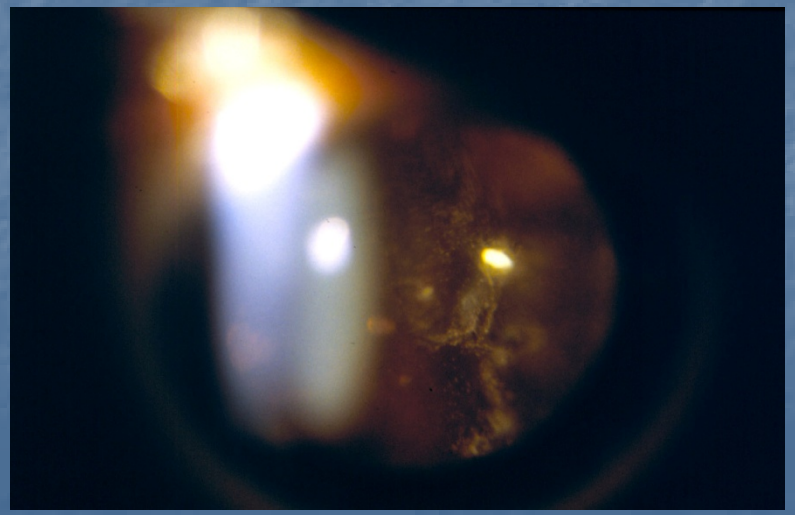
- visual acuity
- slip lamp, intraocular presssure
- funduscopy



Slit Lamp

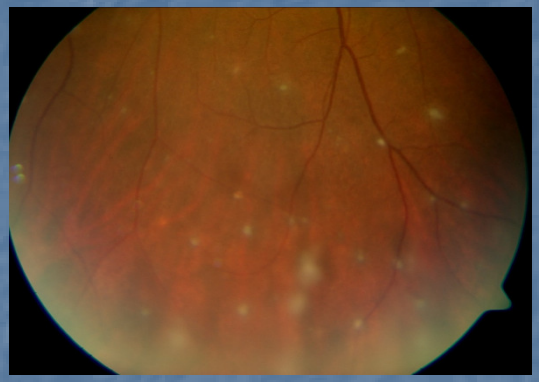
- conjunctiva
- sclera
- cornea
  - endothelial precipitates
- anterior chamber
  - Tyndall, cells
- lens
  - cataract
- anterior vitreous
  - cells, haze

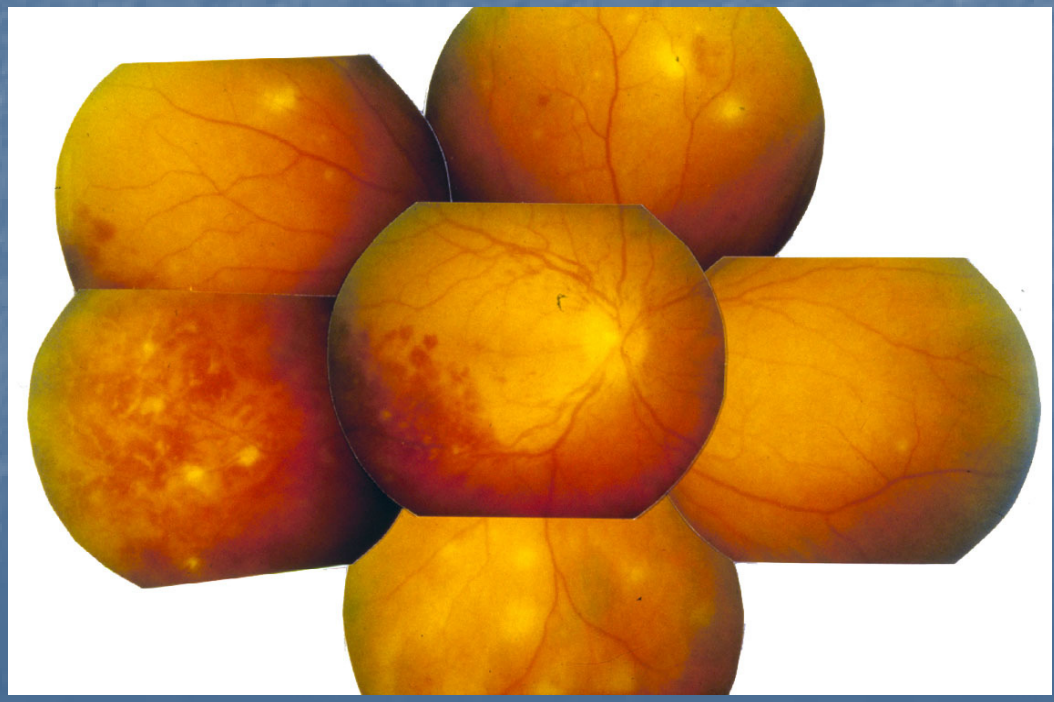




Funduscopy

- vitreous
  - snowballs, cells
- retina and choroid
  - infiltrates, granuloma
- macula
  - edema, gliosis
- optic disc
  - edema, excavation
- retinal vessels
  - hemorrhages, sheething,
  - neovascularisation



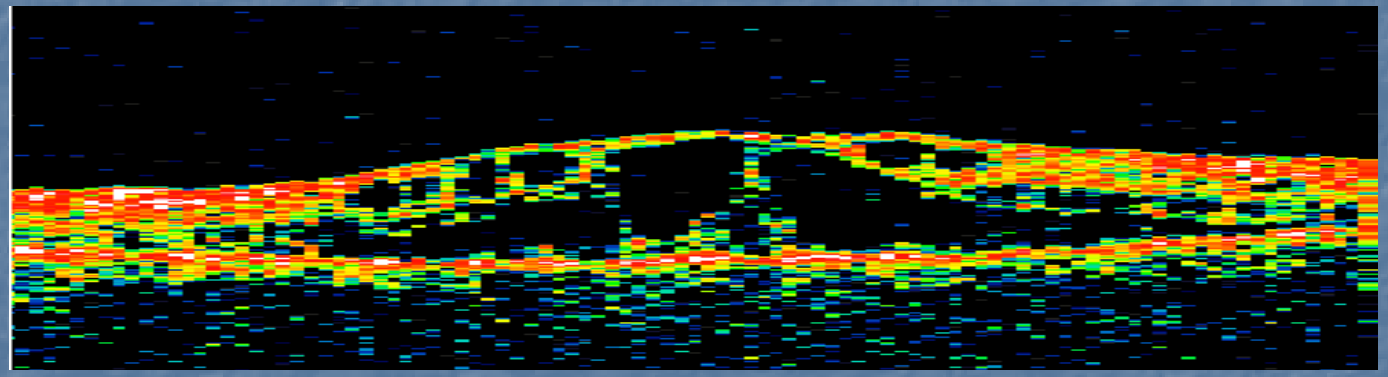


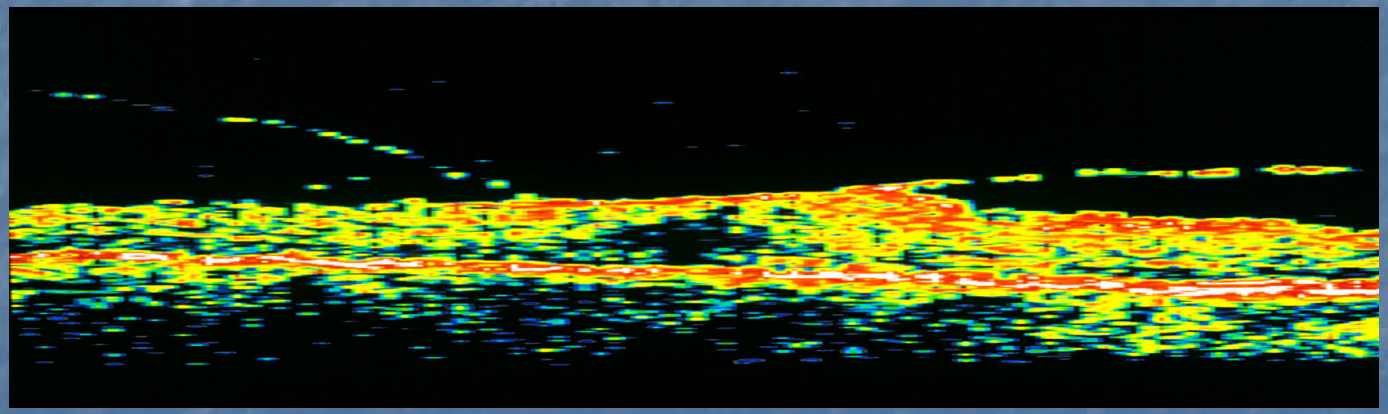
Additional Investigations

- Depending on clinical findings
  - Laser Flare Photometry (LFP)
  - Optical Coherence tomography (OCT)
  - Fluorescein angiography
  - Indocyanin-Green-angiography
  - Perimetry
  - Ultrasound
  - Electrophysiology

Optical Coherence Tomography (OCT)

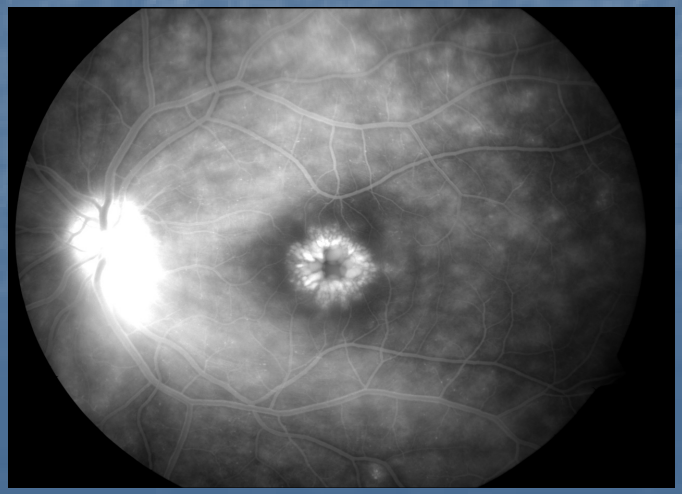
- Macula
  - Edema
  - Gliosis
  - Traction





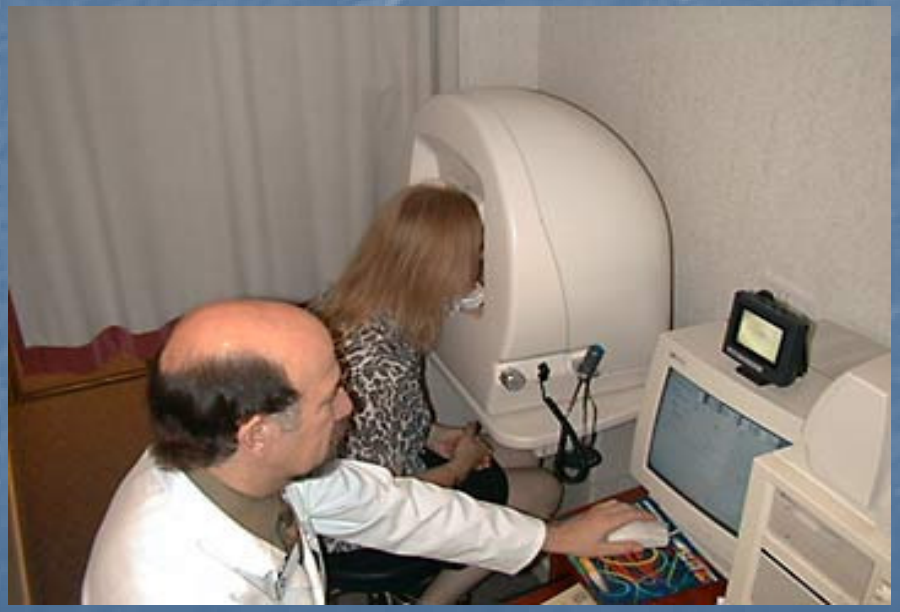
Fluorescein Angiography

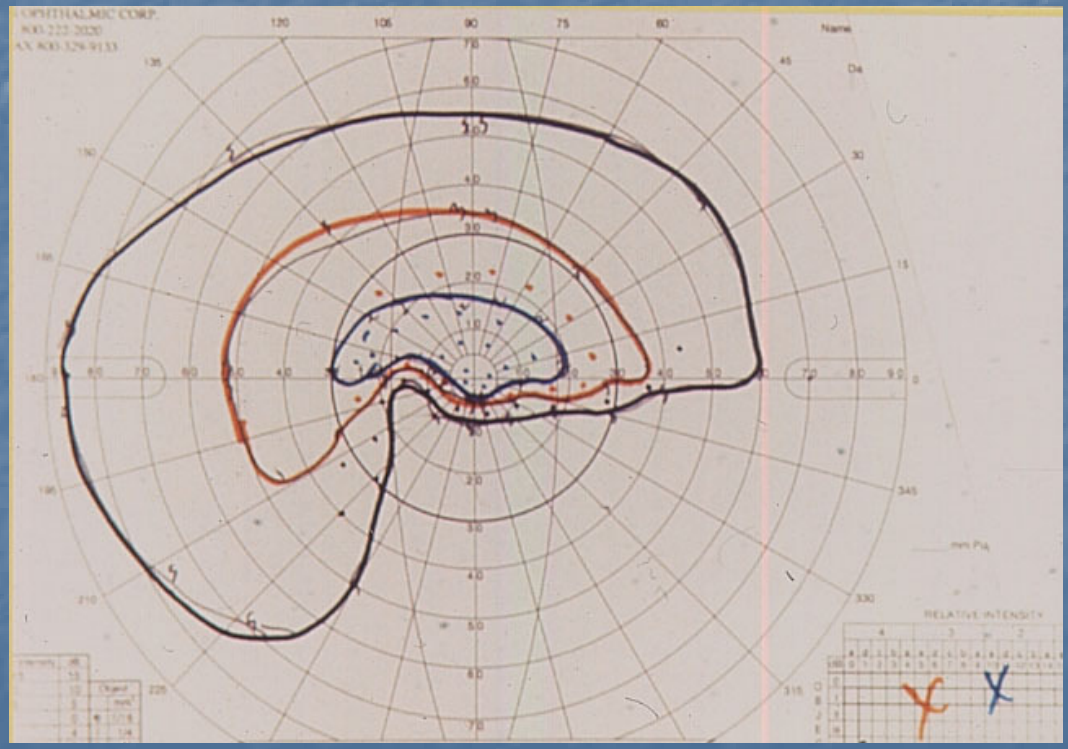
- Retinal vessels
  - vasculitis
  - obliterations
  - neovascularisation
  - non-perfusion-areas
- Macula
  - edema
- RPE-changes



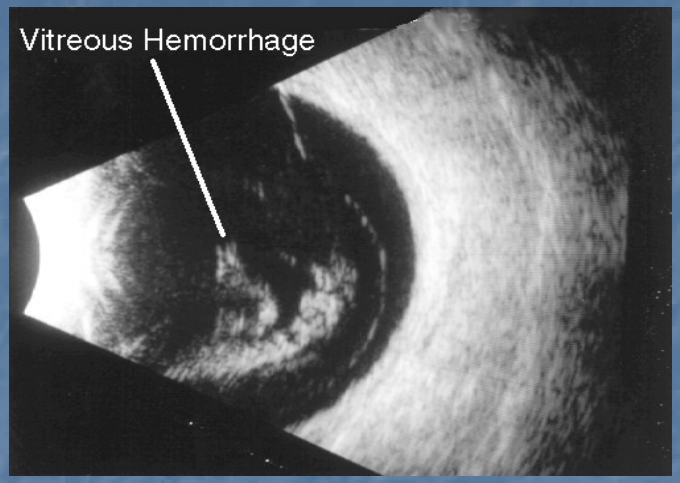
Perimetry

- unclear reduction of the visual acuity
- secondary glaucoma

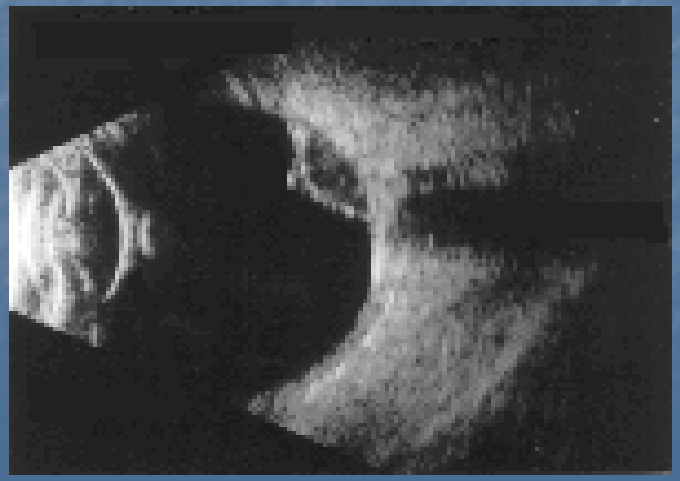




Ultrasound

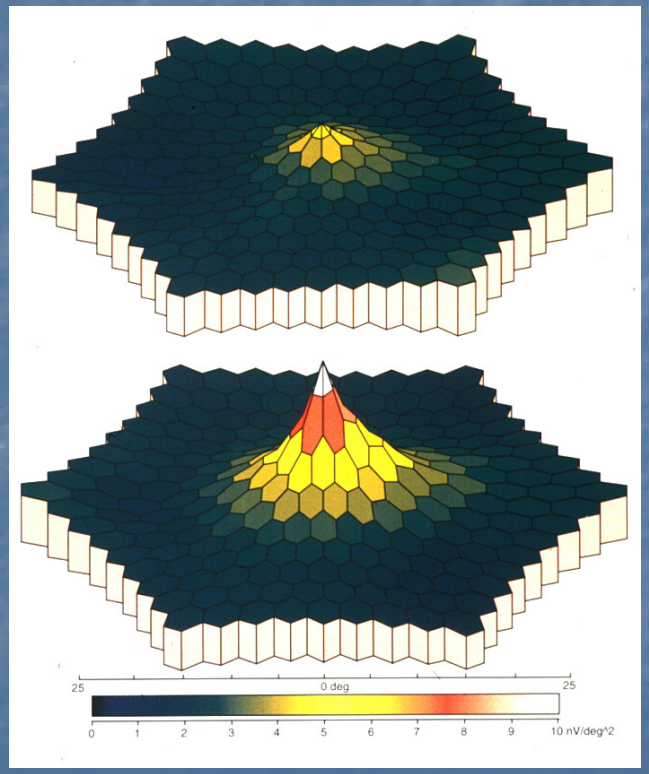


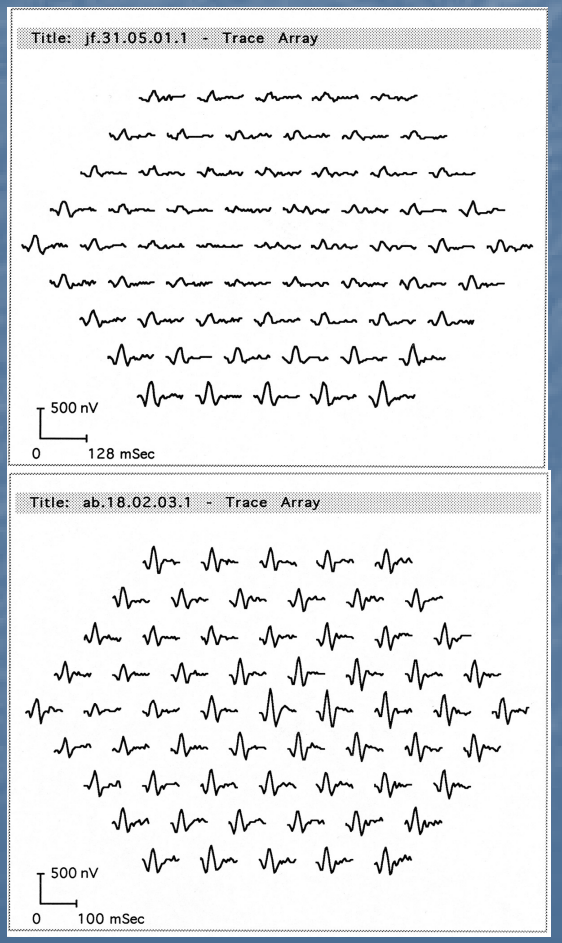
- sclera
  - posterior scleritis
- vitreous
  - bleeding, infiltrations, adhesions
- retina
  - detachment
- choroid
  - tumor, granuloma



Electrophysiology

- Retinal Function

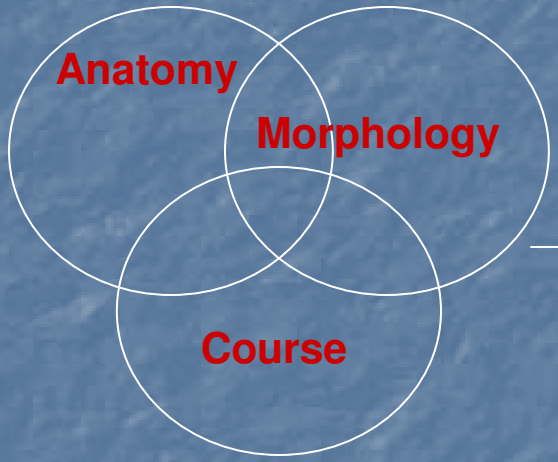




How to reach a Diagnosis

History

Findings

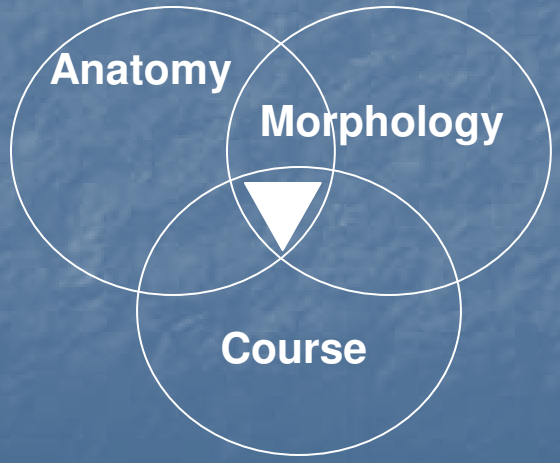


Working diagnosis (name it)

Differential-diagnosis

Differential-diagnosis

Add. Invest.



Diagnosis

Diagnostic Criteria

- Behcet´s Disease (Int. Study Group for BD 1990)
- Acute retinal necrosis (Holland et al. 1994)
- Vogt-Koyanagi-Harada Syndrome (Read et al. 2001)
- Birdshot chorioretinopathy (Levinson et al. 2006)
- Sarcoidosis (Herbort et. al 2009)(validation ongoing)
- Vasculitis (International Uveitis Study Group, ongoing)
- Tuberculosis (Indian Uveitis Society, ongoing)

Diagnostic Criteria

- SUN-Project
- purpose: development of a structured terminology for classification
- to standardize terms and criteria
- 28 entities
- worldwide project
- Douglas Jabs, NYC, and the SUN-Working Group

Grading Systems

- SUN - various parameters
- AC cells – IUSG, SUN
- AC flare – Laser-flare-photometry (not validated)
- vitreous haze
  - NIH grading scale
  - Janet Davis photographically
- macular edema – OCT (not evaluated)
- Disease activity Scores
  - Behcet´s Disease (Ben Ezra et al)

Treatment Options

- Corticosteroids
  - topical (anterior uveitis, AC cells)
  - subconjunctival (massive anterior uveitis)
  - parabulbar (all uveitis, macular edema)
  - intravitreal (mostly intermediate/posterior uveitis)
  - systemic (all uveitis, macular edema)

Treatment Options

- Immunosuppressives (systemic) (most off label)
  - Cyclosporine A
  - Methotrexate
  - Azathioprine
  - Mycophenolate mofetil, Mycophenolic acid
  - various others (Tacrolimus, Cyclophosphamide)

Treatment Options

- Biologicals (often off label)
  - anti-TNF-alpha (Etanercept, Infliximab, Adalimumab)
  - Rituximab (anti-CD 20)
  - Daclizumab (anti-IL2-receptor, anti-CD25)
  - Canalimumab and Anakinra (anti-IL-1, autoinflamm., JIA)
  - Interferons
    - alpha-interferon 2a (esp. Behcet´s Disease, CME)
    - beta-interferon (intermediate uveitis, MS ass.)

Problems of current Medication

- very few on label (steroids, CsA, Osurdex)
- Side effects
  - corticosteroids (but: intravitreal appl., receptor-specific)
  - immunosuppressives
- costs
- not well established for children

Unmet medical Needs

- no optimal treatment against macular edema
- better outcome measures
  - more specific for the uveitis entity
  - lab parameters (regulatory T-cells, interleukin levels?)
- is more specific (targeted) treatment really effective?
- more immunosuppressives on label
- steroid alternative for anterior uveitis
  - topical monoclonal ab´s (?)

Endpoints (EP) for Uveitis Studies

When is suppression of inflammation judged clinically meaningful?

- anterior uveitis
  - reduction of 2 steps (e.g. 3+ to 1, 2+ to 0.5)
- intermediate and posterior uveitis
  - vitreous haze: 2 steps reduction
- macular edema
  - reduction (amount not defined, complete resolution optimal)
- all types of uveitis
  - visual acuity: improvement for 2-3 lines (15 letters)
  - sparing of steroids (10 mg of prednisolone or less)

EPs for anterior Uveitis

- primary EP
  - active: AC-cells (3 months)
  - inactive: recurrence rate (optimal 1 year!)
- secondary EP
  - visual acuity
  - AC-cells (6 months), AC-flare (Laser-Flare-Photometry)
  - sparing of steroids
  - macular edema (OCT, FLA)
  - Quality of Life (NEI VFQ-25)

EPs for intermediate/posterior Uveitis

- primary EP
  - active: vitreous haze (3 months)
  - inactive: recurrence rate (6 months, optimal 1 year!)
- secondary EP
  - visual acuity
  - sparing of steroids
  - macular edema (OCT, FLA)
  - AC-cells (3, 6 months),
  - Quality of Life (NEI VFQ-25)

Conclusion

- „Uveitis“ is a heterogenous group of diseases
- features, treatment and prognosis depend on the etiology
- treatment primarily based on steroids or off label immunosuppressives (side effects)
- better definition of entities and endpoints
- more randomized controlled trials
- growing interest in uveitis studies

Our Wishes for Studies

- Well defined uveitis entities for inclusion
- so probably specific endpoints dep. on etiology
- longer follow up studies (recurrences: 1 year)
- children should also be involved in studies
- EP: OCT, Laser-Flare-Photometer (validation needed)
- Study reembursement should reflect the work we do

Our Message

- Damage tends to develop with inflammatory activity
- Control of this is the most important goal of our treatment
- Endpoints should reflect activity of inflammation
- Visual acuity is not always a good EP

Thanks to

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