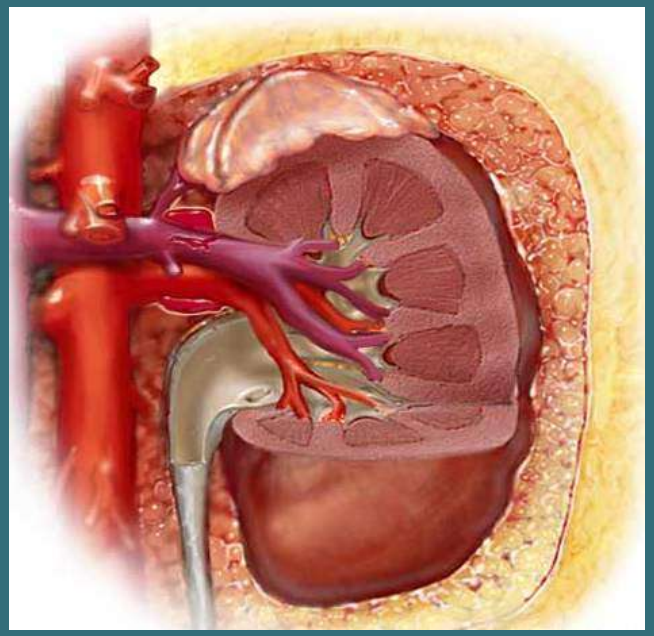
Acute and chronic glomerulonephritis in children



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Glomerulonephritis (GN)

Heterogeneous group of disorders with an initial renal glomerular lesion (later in the disease process may involve other renal structures - tubules, vessels, interstition), having different etiology, pathogenesis, clinical and morphological manifestations, course and outcome.

Glomerulonephritis (GN)

Primary (idiopathyc) **– the actual primary glomerular disease**

Secondary **(developing in a number of systemic connective tissue diseases - systemic lupus erythematosus, systemic vasculities, etc.).**

Glomerulonephritis (GN)

Although at present the morphological differentiation of GN is considered the most correct than clinical classification, it's still widely used in everyday clinical pediatric practice – Vinniza classification of GN 1976 y.

Despite the fact that there is overlap between the clinical and histological variants GN ***only morphological verification allows correct the diagnosis and hold the most appropriate therapy and monitoring the disease***.

Glomerulonephritis (GN)

Clinical classification:

- ***Acute***
- ***Chronic***
- ***Rapidly progressive (RPGN)***

Classification, Vinniza 1976

Form of GN	Activity	Kidney function
Acute GN with • nephritic syndrome • nephrotic syndrome • urinary syndrome • mixt – nephrotic syndrome+ hematuria+AG	• manifestation • recovery • transformation in chronic	• normal • with kidney impairment • Acute renal failure (kidney injury)

Classification, Vinniza 1976

Form	Activity	Kidney function
Chronic GN : • nephrotic form • hematiric • mixt	• relapse • partial remission • complete clinical and laboratory remission	• without kidney impairment • with kidney impairment • CRF (CKD)

Classification, Vinniza 1976

Form	Activity	Kidney function
Rapidly progressive, RPGN GN		with renal impairment Chronic renal failure (kidney disease)

Glomerulopathies / nephritis

Non-immune

- Minimal changes;
- Membranous nephropathy;
- Focal segmental glomerulosclerosis FSGS (hyalinosis);
- Thin membranes
- Diabetic nephropathy;
- Amyloid nephropathy;
- Ischemic nephropathy;

Immune

- Acute poststreptococcal / post infectious GN
- Chronic GN:

❖ proloferative:

- with «crescents»
- mesangioproliferative
- Membranoproliferative

❖ Fibroplastic (sclerosic):

- focal
- diffuse

Main mechanisms of glomerular injury

1. No-immune

The changes are degenerative /or dysplastic nature and often reversible

2. Immune

Manifested classic signs of inflammation:

- infiltratio;

- proliferatio;

- exudatio;

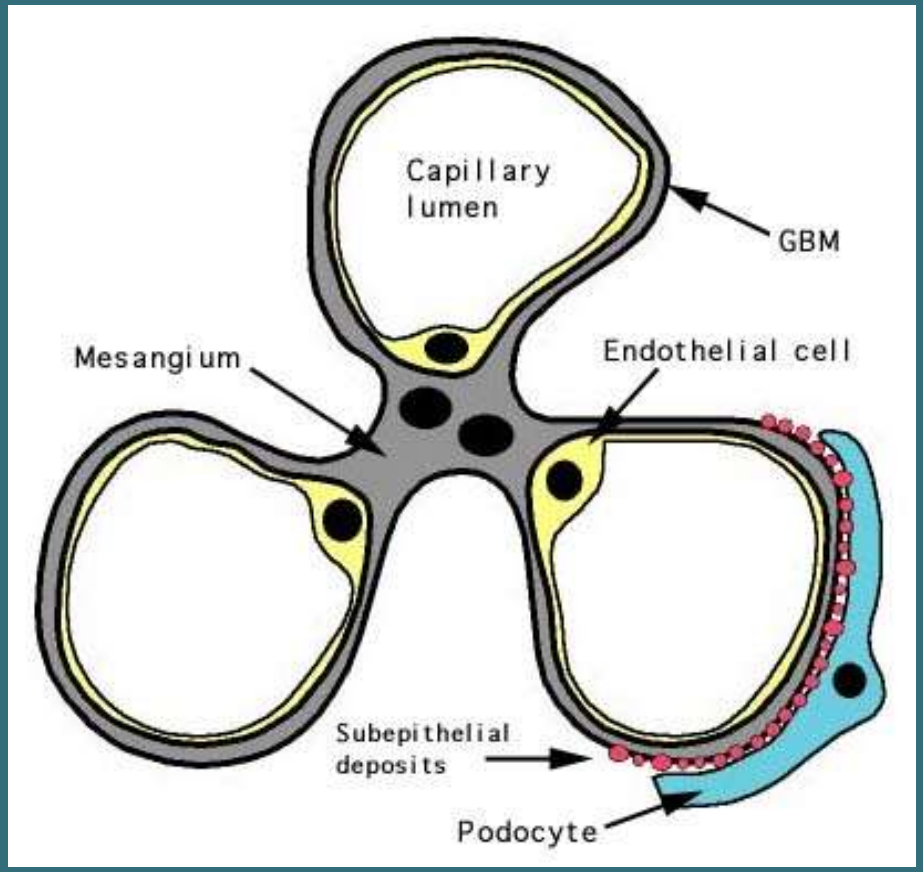
- alteratio.

Glomerulonephritis (GN)

Non-inflammatory (glomerulopathies)

The principal target of the immune attack are visceral epithelial cells of the glomeruli=

podocytopathies

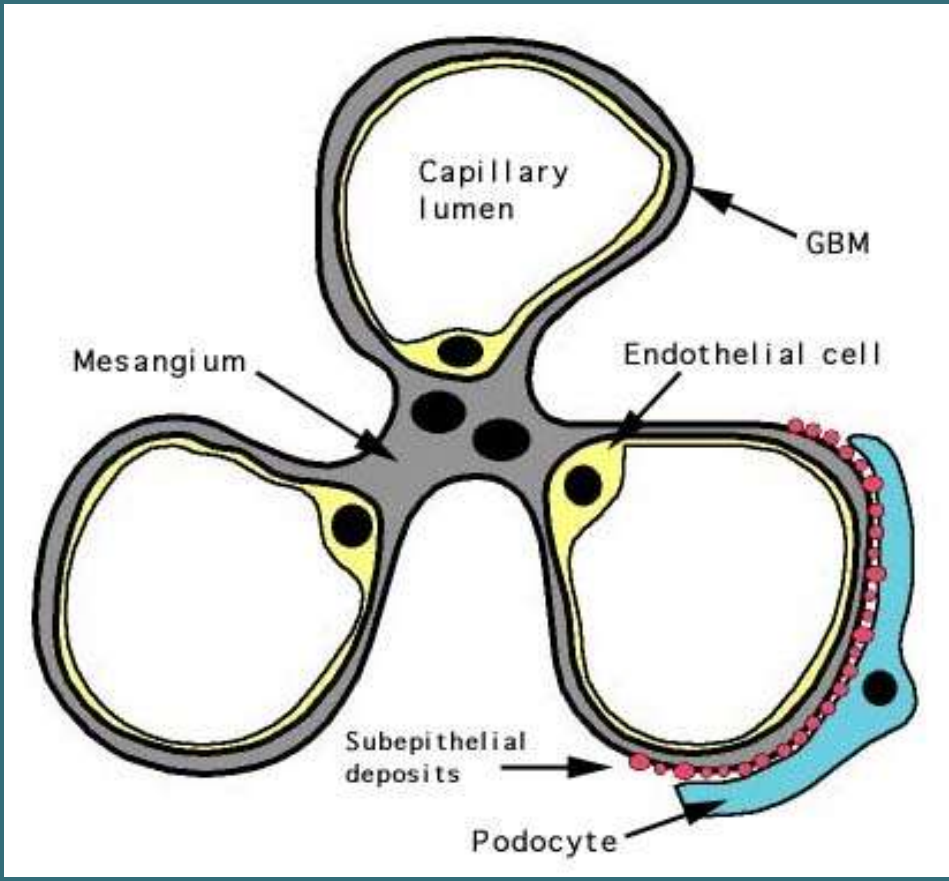


Glomerulonephritis (GN)

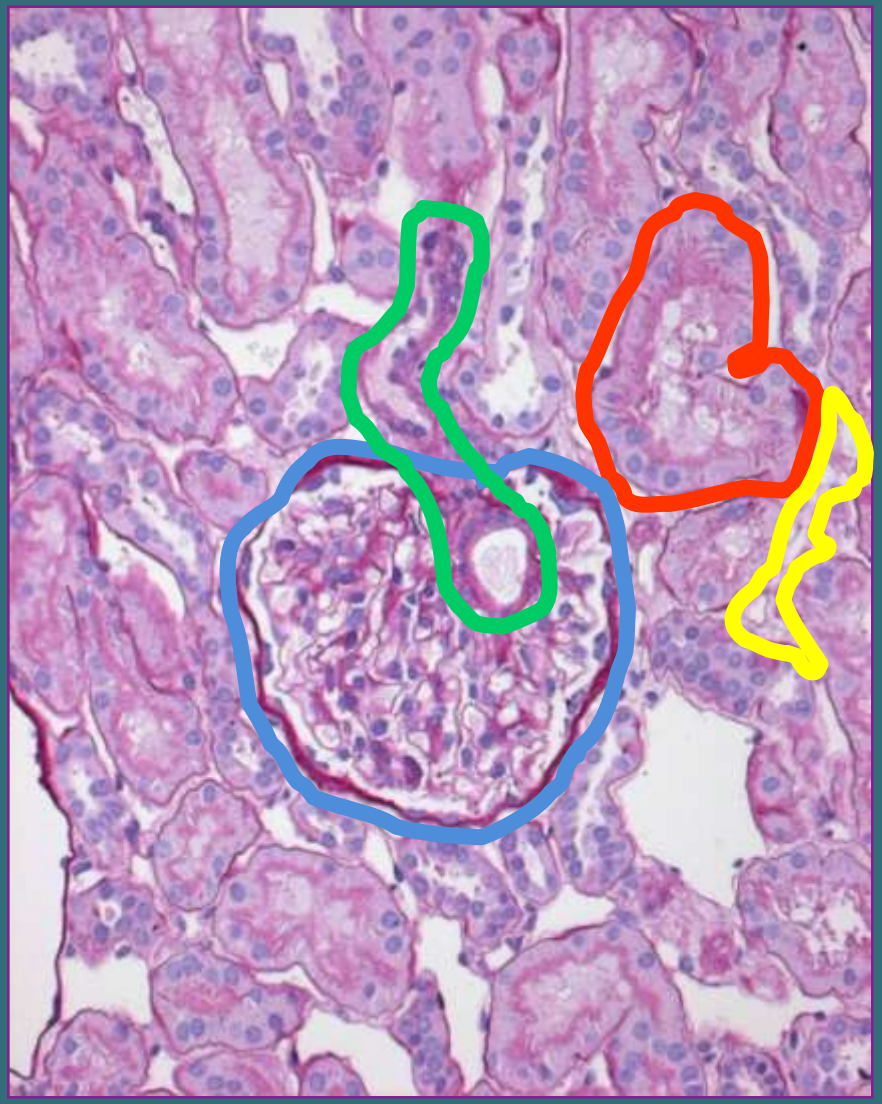
Inflammatory (immune GN)

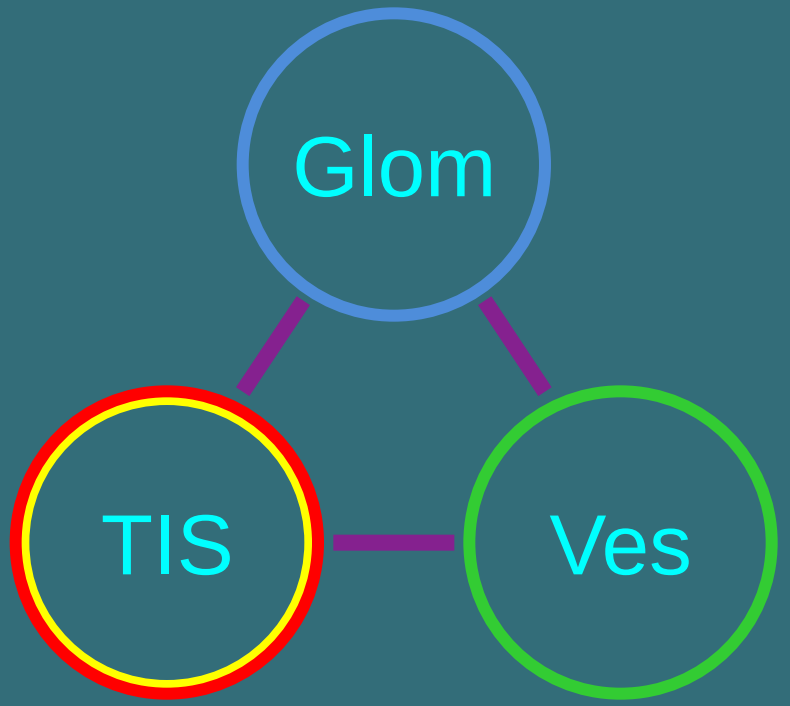
The principal target of the immune attack are endothelium, mesangium, epi-peri-, intramembranouse structures=

Real nephritis

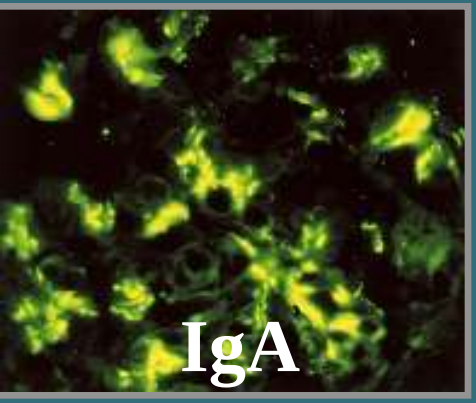
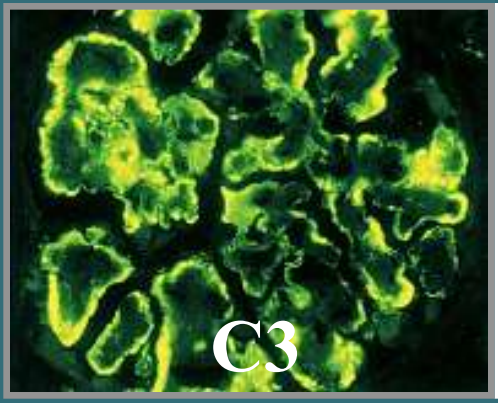
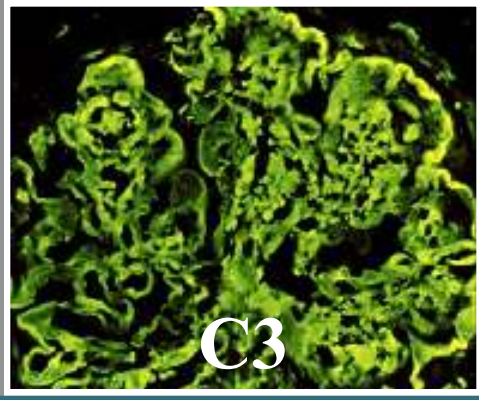
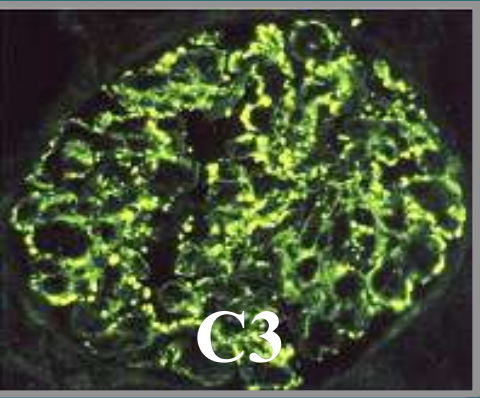
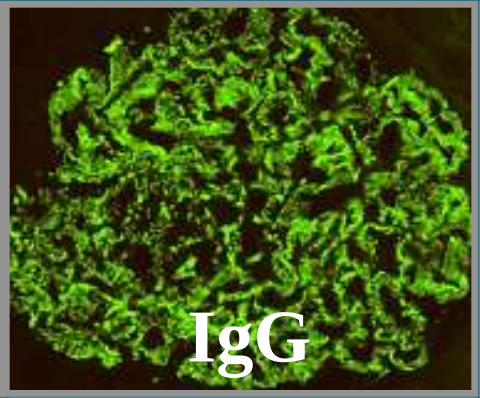
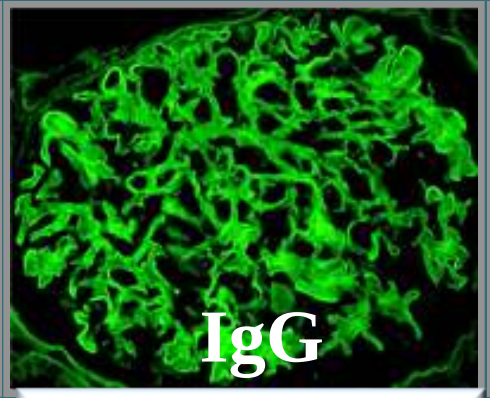
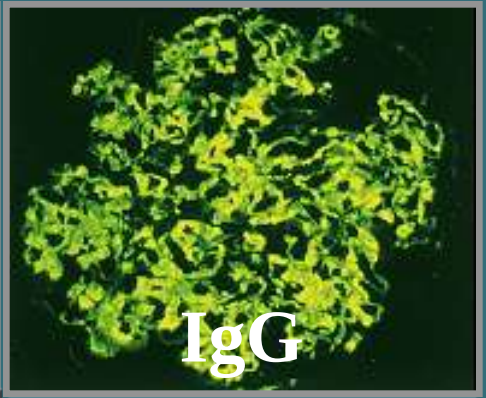


Light microscopy

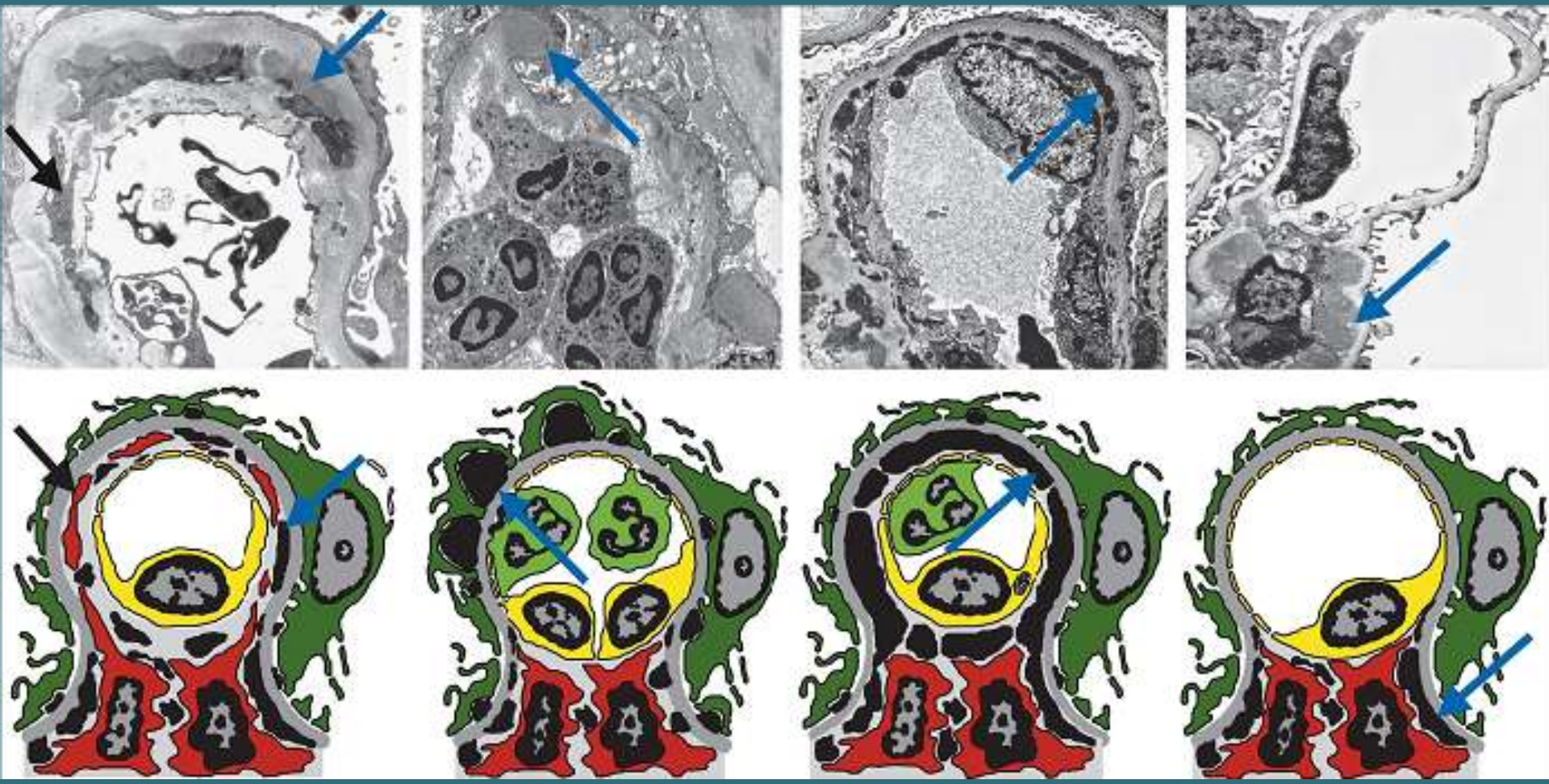


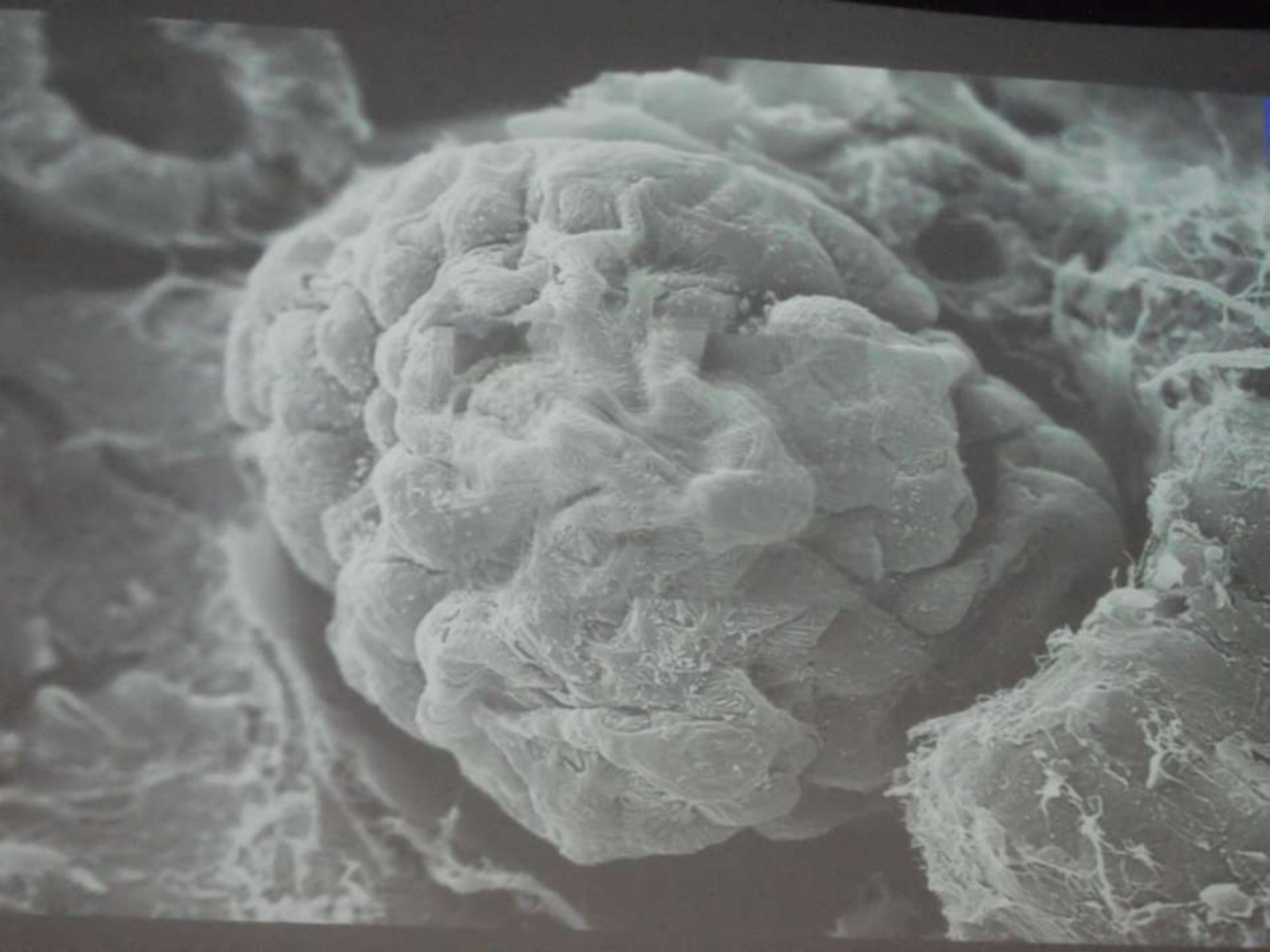


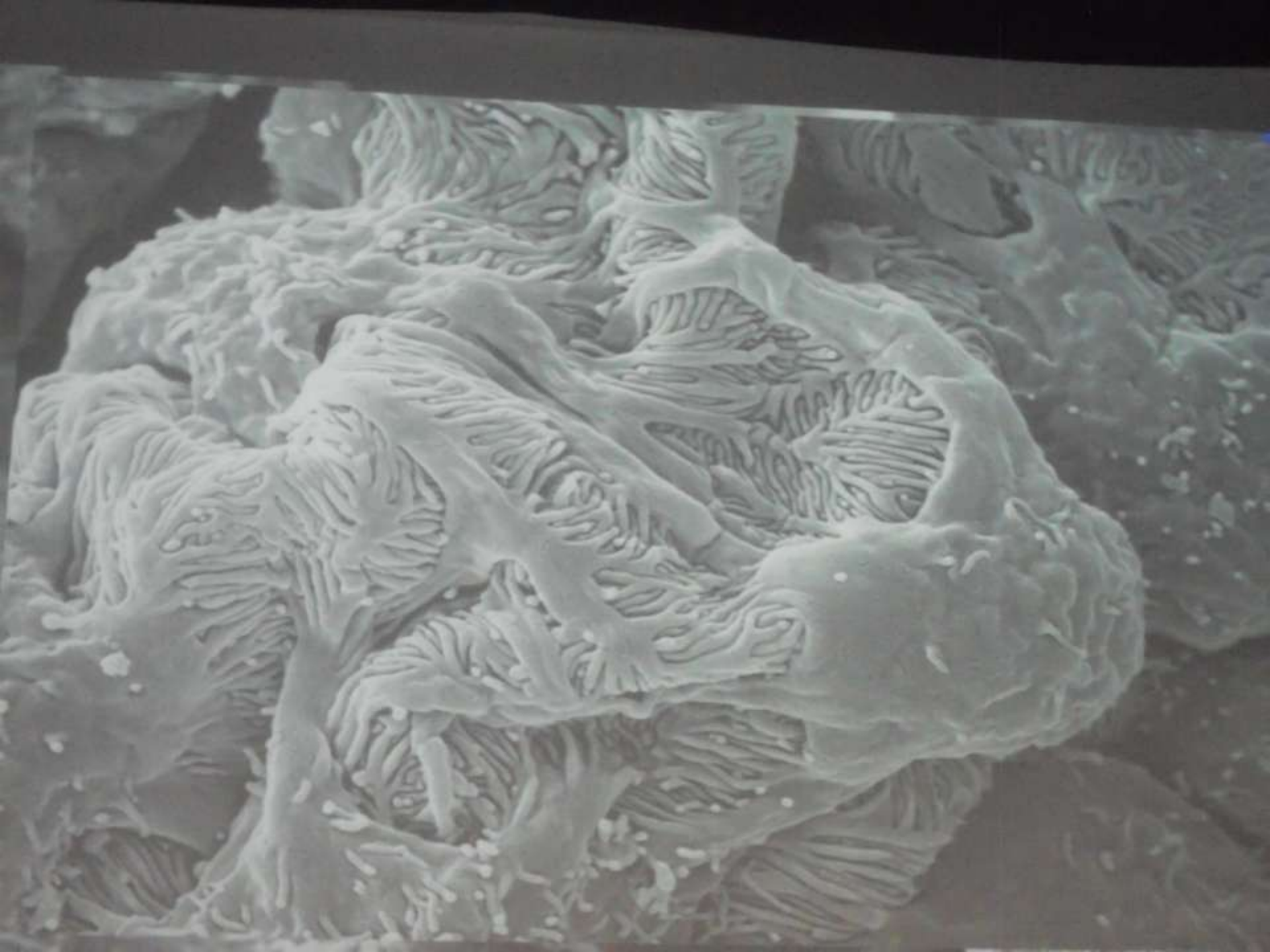
Immunohistochemistry

MesPrGN	Prolif GN	Memr Pr GN type I	Membr Pr GN type II
			
IgA	IgG	C3	C3
			
C3	IgG	IgG	IgG
Acute GN	Membranose GP	Anti-GBM GN	Phybrill GN

Electron microsopy







Acute GN

Acute diffuse immune-inflammatory (mediated) kidney disease, mainly affecting the glomeruli, in which there are changes in the glomeruli with exudative-proliferative component.

Prevalence - 0.1 - 0.2%.

More common at the age – 5 -12 years.

Etiology

- Streptococci ("nephritogenic" strains, β-hemolytic group A, type 1, 2, 4, 12, 49, 55 et al.)

Infection of the throat or skin - flu, fever, streptodermia, impetigo etc .;

- Other infections: influenza, viruses etc .;
- Vaccination (often R2, R1);
- Season (February-March, October-November in Belarus).

Predisposing factors

- *Hereditary predisposition;*
- *Increased familial susceptibility to streptococcal infection;*
- *Chronic foci of infection, hypovitaminosis;*
- *Hypothermia.*

Pathogenesis

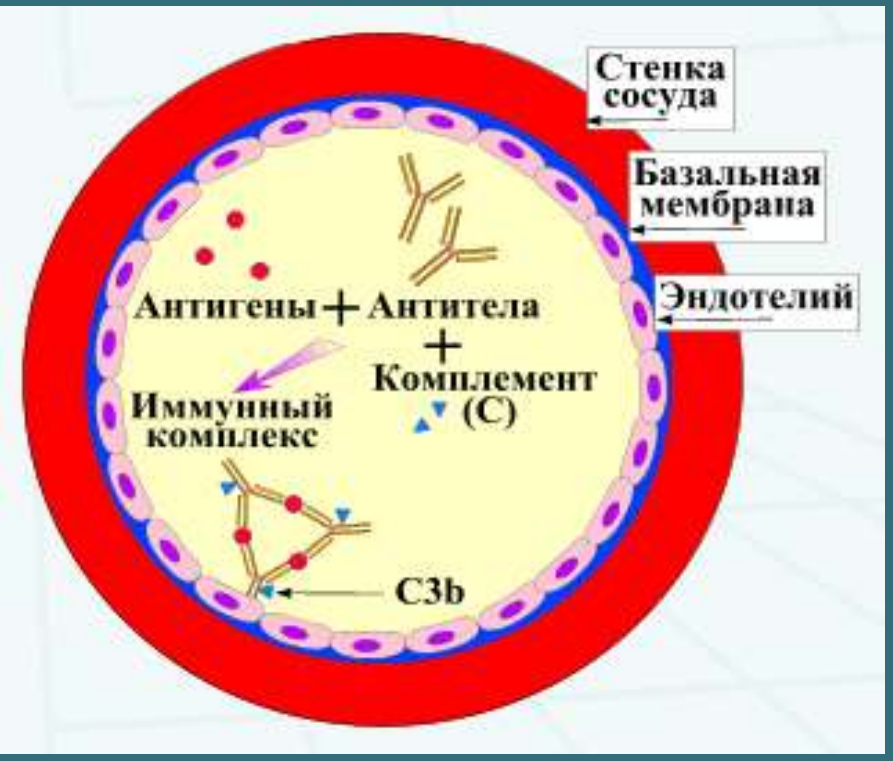
- Immune –complex disease.
- The streptococcus produces toxins and enzymes (streptolysin, Hyaluronidase, streptokinase, and others.) That initiate the production of specific antibodies with the subsequent formation of the immune complexes (IC)
- IC deposited on the glomerular capillary wall, activate complement with further production of proinflammatory mediators of glomerular cells

Pathogenesis

As a result of these processes capillary endothelial lesion occurs with increasing their permeability to blood components such as red blood cells and protein.

An important role play a cross-reaction between streptococcal and glomerular antigens ("antigenic mimicry"), especially the individual features of immune response

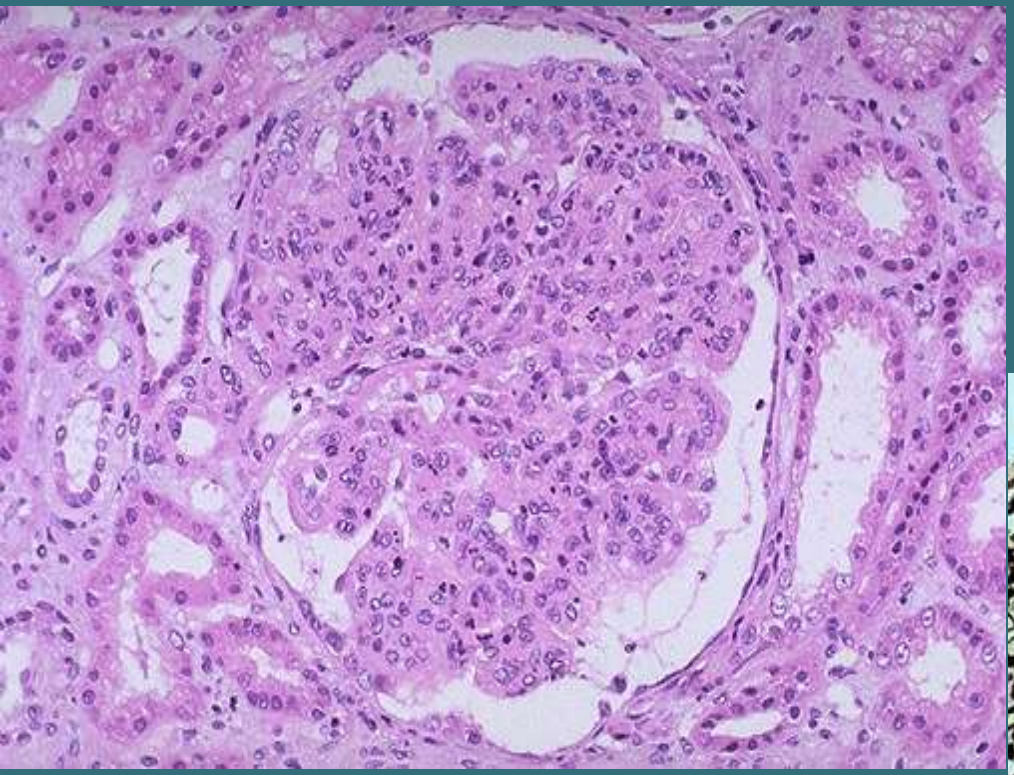
IIId– immune-complex type of immune-pathological reactions

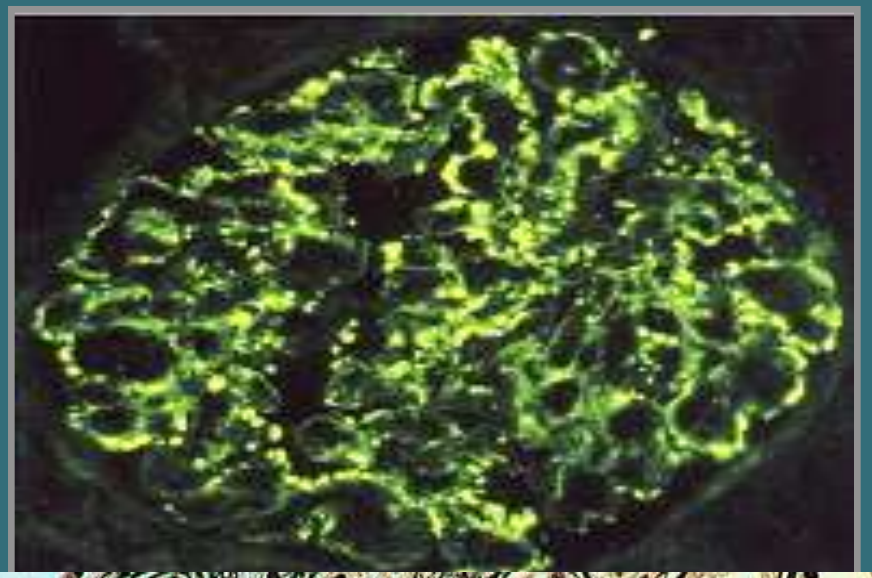


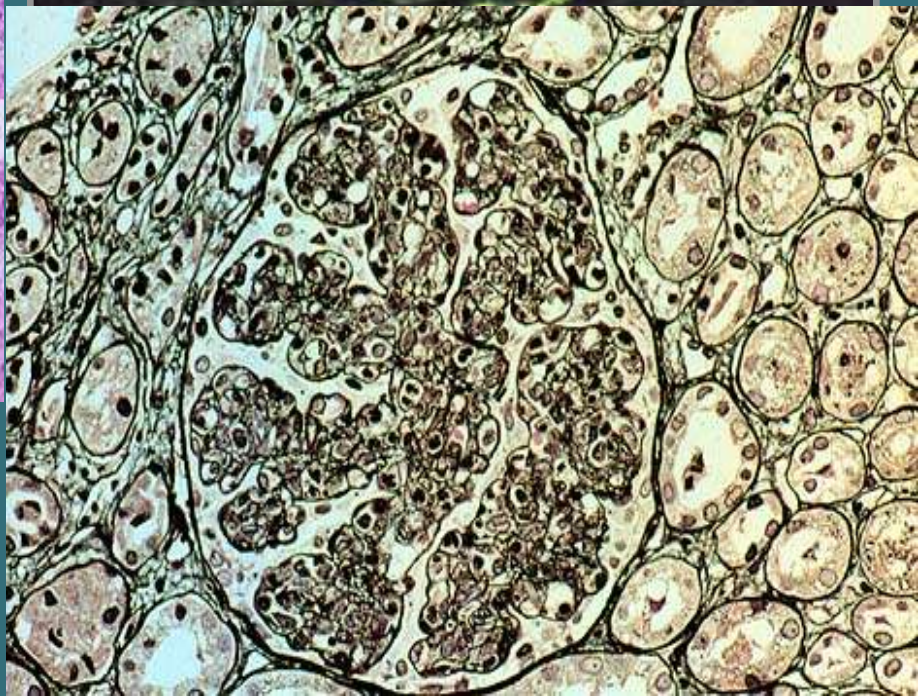
Pathogenesis

- Intravascular damage – edema → reduced GFR → renin-AT-aldosteron → retention of sodium and water → hyperhydration = edema, blood pressure increased
- Urinary and blood changes
- Light microscopy- exudative-proliferative changes in glomeruli .
- EM, IF –IgG or M, C3-complement deposts;
- 6 months duration of changes.

LM, IF, silver







Clinic of acute PSGN

- Acute onset of the disease after 1-3 weeks after preceding of streptococcal infection.
- Typical acute nephritic syndrome:
- Mild proteinuria (1 - 2 g / l);
- Hematuria from the micro to the macrohematuria ("meat slops", "Coca-Cola" or "beer");
- Cellular casts (hyaline and erythrocyte);
- oliguria;
- Moderate edema of the eyelids, face, at least - shins;
- Hypertension.
- The prognosis is favorable (recovery up to 95% of patients)

Clinic

Extrarenal manifestations.

- moderate edema ;
- ↑ BP, tachy- or bradycardia;

- Acute manifestation: headache;
- nausea, vomiting;
- deterioration of general condition;
- decreased appetite;
- change in urine color (brown, the color of beer, cola)
- lower back pain;
- brain syndrome - convulsions, insomnia, autonomic dysfunction.

Labs

Blood.

- anemia
- Lei↑
- neutrophils ↑
- ESR ↑

Serology:

- ↑ASLO

Immunology

- C3-complement ↓ - especially during follow-up

Indications for kidney biopsy

- Clinically, a classic manifestation of AGN is nephritic syndrome, although not an exception are other clinical syndromes - nephrotic (NS), NS with hematuria and hypertension, isolated urinary syndrome.
- In typical cases of AGN biopsy is not required.

- ***Morphological examination is necessary in atypical manifestations and / or long-term preservation of symptoms.***

Indications for kidney biopsy

- Suspected RPGN (severe proteinuria, hematuria, the rapid growth of creatinine, blood urea, oliguria)
- Suspected kidney disease in the frame of systemic diseases (SLE, systemic vasculites etc.)
- Low C3-complement over 2-3 months
- Persistent proteinuria of more than 6 months
- Hematuria +proteinuria persistant

Treatment

Basic therapy:

- regimen- bed at the time of edema;
- diet (salt restriction, fluid and spice restriction);
- antibacterial - penicillin or cephalosporins of I-th generation, or macrolides for 10-14 days;
- syndromal therapy

Treatment

Syndromic therapy:

- **Antihypertensive - Nifedipine 0.25-0.5 mg / kg / day, amlodipine and 0.06 mg / kg / day, β-blockers, α, β-Blockers**
- **NB! Carefully ACE inhibitors - captopril, enalapril – high potassium!**
- **Diuretics - furosemide 1-2 mg / kg**
- **Antiplatelet agents - dipyridamole, curantil, Trental**

Rapidly progressive GN with «crescents» - malignant

Etiology

Idiopathic, postinfectious, in systemic diseases.

Pathogenesis:

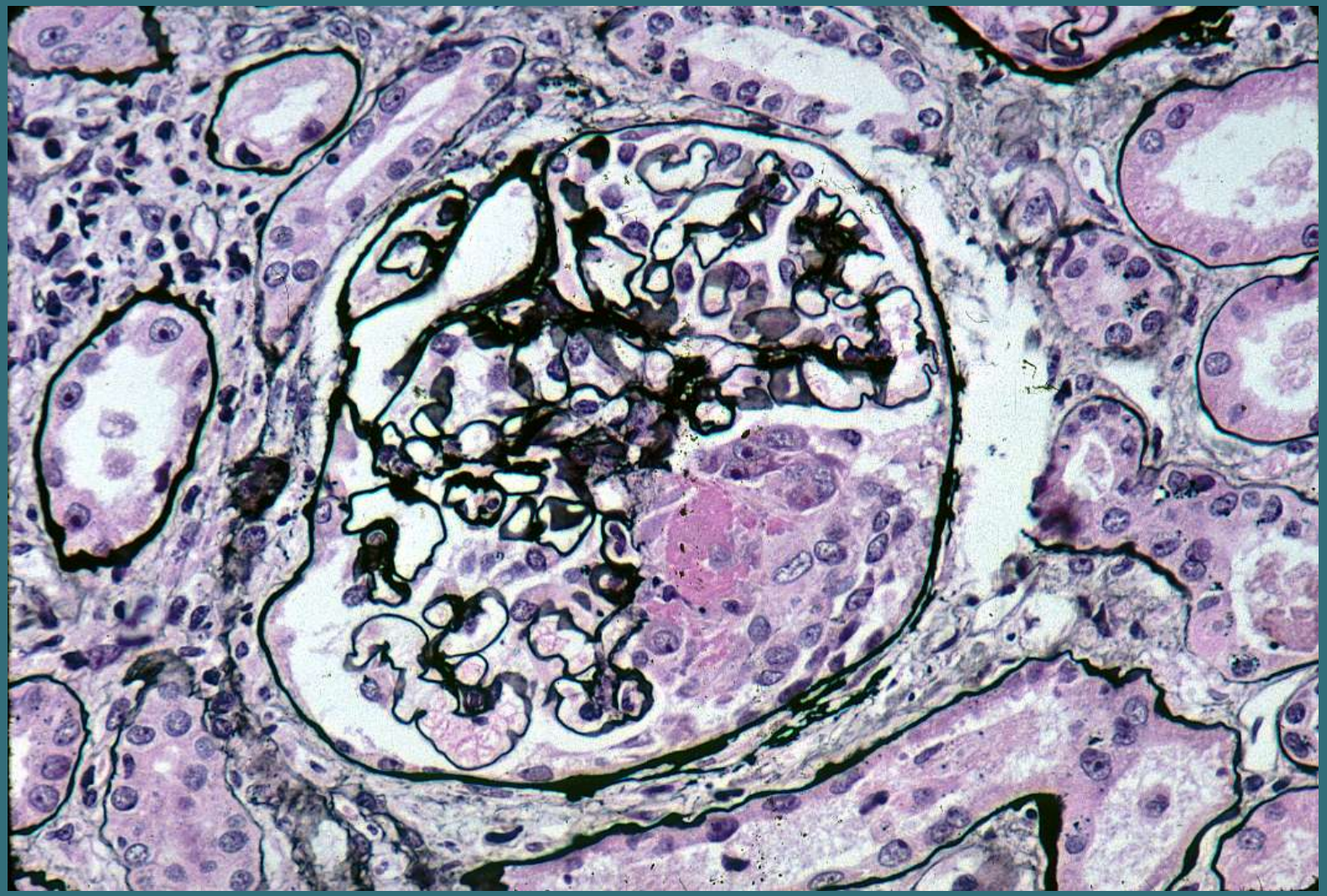
Immune-complex, antibody mediated.

Morphology:

Proliferation of the epithelium of the out-layer of the capsule Shymlansky-Bowman with the formation of crescents in more than 50% of the glomeruli.

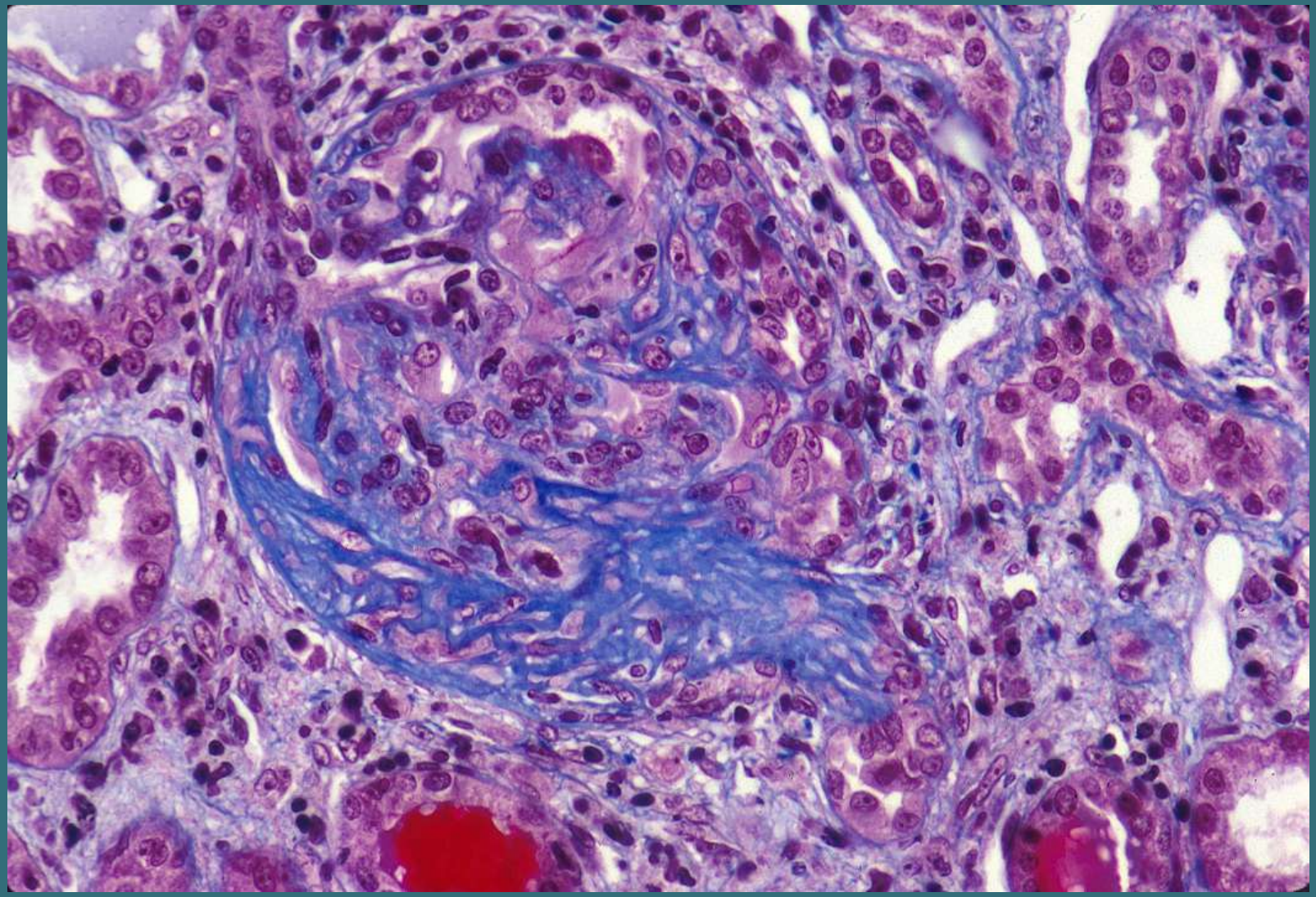
RPGN

Cellular crescents



RPGN

Fibrous crescents



Clinic

- Severe with extremely high activity;
- Rapid increase in renal failure (often irreversible), with the development of end-stage renal failure within a few weeks or months.
- Biopsy shown at the first suspicion of rapidly progressive glomerulonephritis.

- Outcome: Unfavorable.

Treatment

Immediate prescription of aggressive immunosuppressive therapy!

Pulse therapy with methylprednisolone (30 mg / kg per day to 1000 mg per administration) or cyclophosphamide (500-750 mg / m2 per administration) - 3-5 sessions performed in synchronization with plasmapheresis:

- **Day – medication prescription, next day - removal of plasma (source of pro-inflammatory immune mediators, cytokines, antibodies, etc.).**
- **Red blood returned to the patient, the plasma is removed**

Treatment

prescription of aggressive immunosuppressive therapy!

- **After pulse therapy with plasmapheresis - immunosuppressive therapy is administered orally (prednisolon 2 mg / kg / day + cytostatic) in combination with anticoagulants (heparin, Fragmin, aspirin, etc.), And antiplatelets.**
- **In severe cases may require dialysis (hemodialysis, hemodiafiltration, and so on.).**

Chronic GN

Chronic GN (GN) **– a group of chronic glomerulopathies, most immune-mediated, mainly affecting the glomerulus, with different clinical and morphological picture, course and outcome.**

ORIGIN:

A consequence of acute glomerulonephritis (rare!)

More often - the so-called primary chronic form).

Morphological classification of GN

Non-proliferative (non-inflammatory):

- **Minimal change nephropathy;**
- **Membranous nephropathy;**
- **Focal segmental glomerulosclerosis.**

Proliferative(inflammatory):

- **Mesangioproliferative glomerulonephritis;**
- **Membranoproliferative glomerulonephritis;**
- **Fibroplastic glomerulonephritis.**

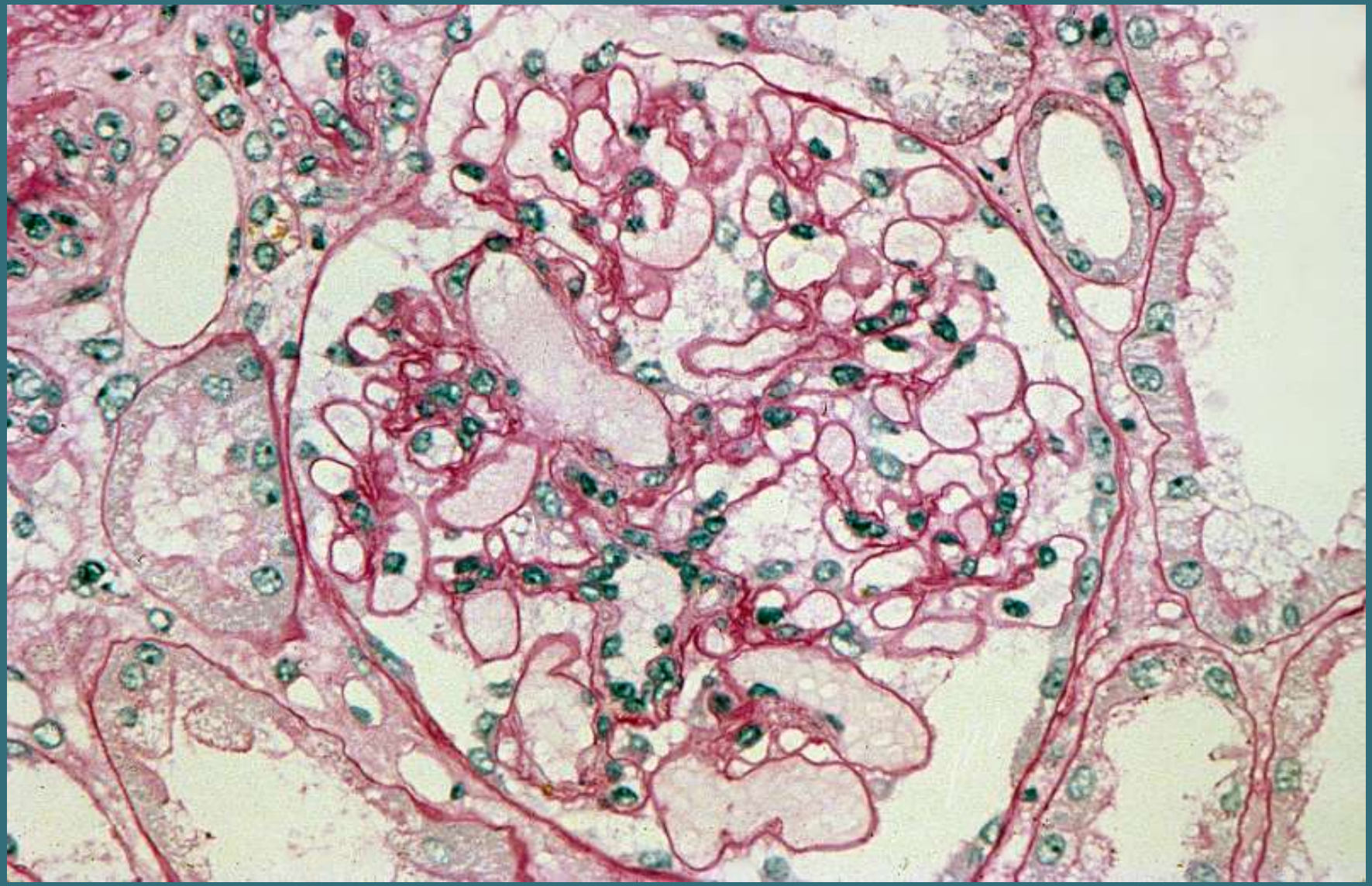
Minimal change disease (nephropathy)

Light microscopy:
Without changes.

IF / IGH:
negative.

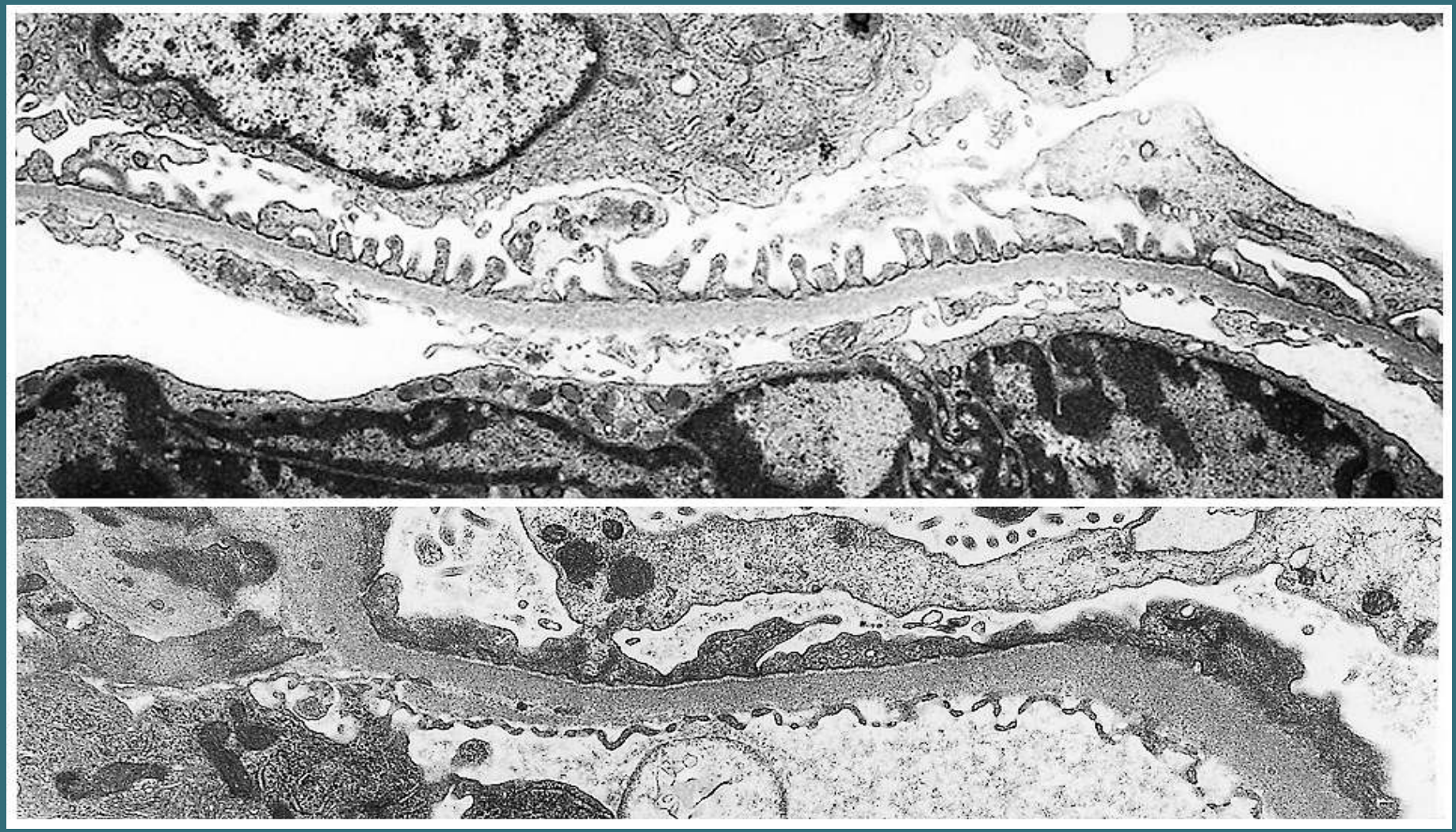
Electron microscopy:
absent of small feet podocyte processes (fusion) or merge them.

Minimal change disease
Light microscopy



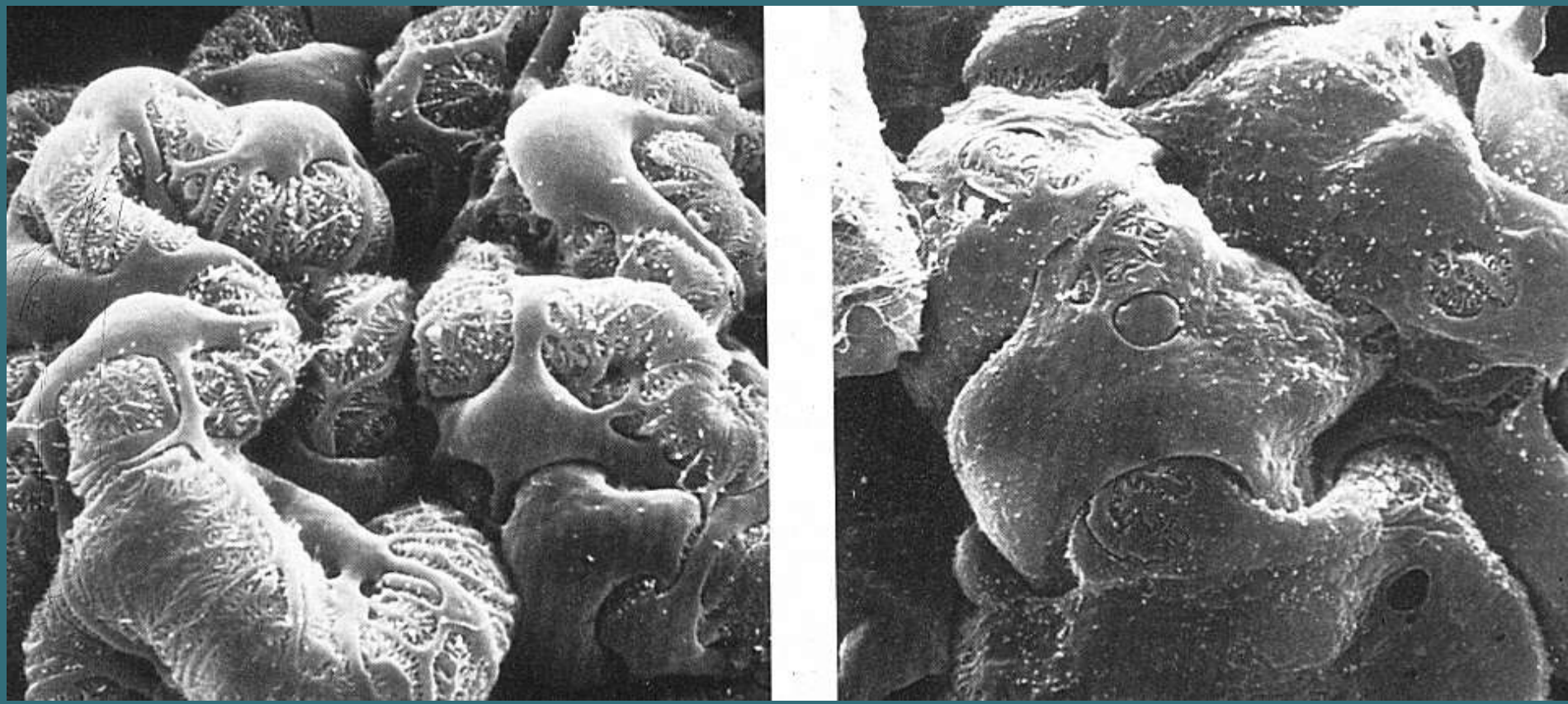
Minimal change disease

Electron microscopy



Minimal change disease

Electron microscopy



Minimal change disease

Clinic:

- Nephrotic syndrome (75-80% of the nephrotic syndrome in children).
- Mostly in infants and preschool children (2-7 years) with a history or allergy.
- More common in boys (2: 1).
- High sensitivity to corticosteroids.

Outcome:

In most cases favorable.

Nephrotic syndrome
4 signs

1. Massive proteinuria (> 3g / L or > 50 mg / kg per day, or ↑ 40 mg / m2 x h or protein-to-creatinine ratio in morning urine > 0.2 mg / mmol)

2. Low total protein <60 g / l in combination with low albumin<30g / l (characterized by increased α2-globulins and decreased gamma globulins).

3. Hyperlipidemia (Cholesterol> 5,2mmol / l)

4. Severe peripheral and abdominal swelling (ascites, hydropericardium, hydrothorax) till anasarca.

Nephrotic syndrome

Morphological changes in nephrotic syndrome in children

- **Glomerulonephritis with minimal changes.**
- **FSGS (focal segmental glomerulosclerosis)**
- **Membranous glomerulonephritis.**
- **membranoproliferative GN**

NS - treatment

prednisolone

60 mg / m2 (2mg / kg, but not more than 80 mg per day) during 4 weeks (duration may be up to 6 weeks)

Then alternating regimen:

60 mg / m2 every other day - 8 weeks;

45mg / m2 every other day - 2 weeks;

30 mg / m2 every other day - 2 weeks;

15 mg / m2 every other day - 2 weeks.

The total duration of treatment is 4-5 months.

Nephrotic syndrome - options for response to treatment GCS

1.Steroid-sensitive- complete remission with prednisolone at a standard dose achieved in 4-6 weeks.

1.1 Steroid-dependent - NS relapse during treatment with prednisolone or within 2 weeks after its cancellation.

1.2 Frequently relapsing - 2 or more relapses within 6 months or 3 or more relapses within a year.

Nephrotic syndrome - options for response to treatment GCS

2. Steroid-resistant **– lack of complete clinical and laboratory remission with prednisolone at a standard dose within 4 - 6 weeks (renal biopsy?) or after pulse therapy with methylprednisolone at a dose of 30 mg / kg per administration for 3 consecutive days**

Treatment of steroid-dependent NS

Chlorambucil (leykeran) - 0.2 mg / kg per day 8-12 weeks - today rarely used !;

Cyclophosphamide - 2 mg / kg per day to 8 weeks;
Cyclosporin A - 4 - 6 mg / kg per day in 2 divided doses (doses under the control serum concentration - 80 - 150 ng / ml)

in combination with prednisone 1 mg / kg / every other day

Treatment of steroid-resistant NS

Cyclosporin A (4-6 mg / kg / day in combination with prednisone 1 mg / kg / 48 hours), then to 18-24 months monotherapy

Mycophenolate mofetil (MMF)

Tacrolimus;

Alkylating agents (chlorambucil, cyclophosphamide);

Protocol MENDOZA;

ACE inhibitors or

Angiotensin receptor antagonists

Treatment of steroid-resistant NS

ACE inhibitors *(enalapril 0.05 to 0.5 mg / kg) administered in nephrology in order to reduce the damaging effect of the proteinuria on renal tubule epithelium, decrease GFR and thus proteinuria = nephroprotective effect;*

OR angiotensin receptor antagonists *(losartan 100 mg / day, irbersartan 75-150 mg / day).*

You can not assign at the same time both of them because of the risk of increasing potassium!

MENDOZA Protocol

Weeks	*IV Methylprednisolone*	*Prednisolone orally*
1-2	30 mg/kg/daily alternate day	—
3-10	30 mg/kg 1 time per week	2 mg/kg alternate day
11-18	30 mg/kg через неделю	2 mg/kg alternate day
19-52	30 mg/kg в месяц	2 mg/kg alternate day
53-78	30 mg/kg alternate day	2 mg/kg alternate day

Indications for biopsy in NS

- Steroid-resistant NS
- Steroid-dependent and often recurrent NS (3-rd relapse).
- NS with hematuria and hypertension.
- The patient's age up to 1 year (genetic research?) And older than 12 years.
- Cyclosporin A treatment for more than 6 months (with an increase in creatinine, decreased density of urine = cyclosporin nephrotoxicity?)

Indications for biopsy in NS

- **The patient's age up to 1 year - mostly genetic causes (Congenital NS can not be treated with CS and cytostatics - treatment more harmful than goodness!)**
- **Over 12 years - a suspicion of secondary damage of the kidneys through a systemic process - therapy should be more aggressive!**

NS with hypertension and hematuria

Combines the clinical manifestations of nephrotic and nephritic disease variants, but:

swelling less pronounced, but more resistant;

increased blood pressure;

hematuria;

anemia;

increase in γ - globulins.

NS - Treatment

Together with corticosteroids prescribed

- **Proton pump inhibitors - omeprazole, children up to 5 years – Gefal**
- **For the prevention of osteoporosis – calcium + vitamin D**
- **Limited salt, liquid account**
- **Control of blood pressure, blood glucose**
- **eye exam**

NS - Complications

- Hypovolemia - albumin intravenously when serum levels lower than 20 g / l and / or abdominal ascites
- Hyper coagulation (thrombosis) - heparin, aspirin
- Infection - intravenous immunoglobulin
- Hyperlipidemia - diet
- Protein-energy malnutrition
- Prolonged therapy with corticosteroids….

Steroid side-effects

- Erosive and ulcerative lesions of the gastrointestinal tract
- Sodium and fluid retention
- Hypertension
- Hyperglycemia, steroid diabetes
- Cushing's syndrome
- Violation of mineral metabolism
- Physical, sexual development delay
- immunodeficiency
- cataract….

Focal-segmental glomerulosclerosis/ hyalinosis FSGS

Clinically:

more often steroid-resistant nephrotic syndrome

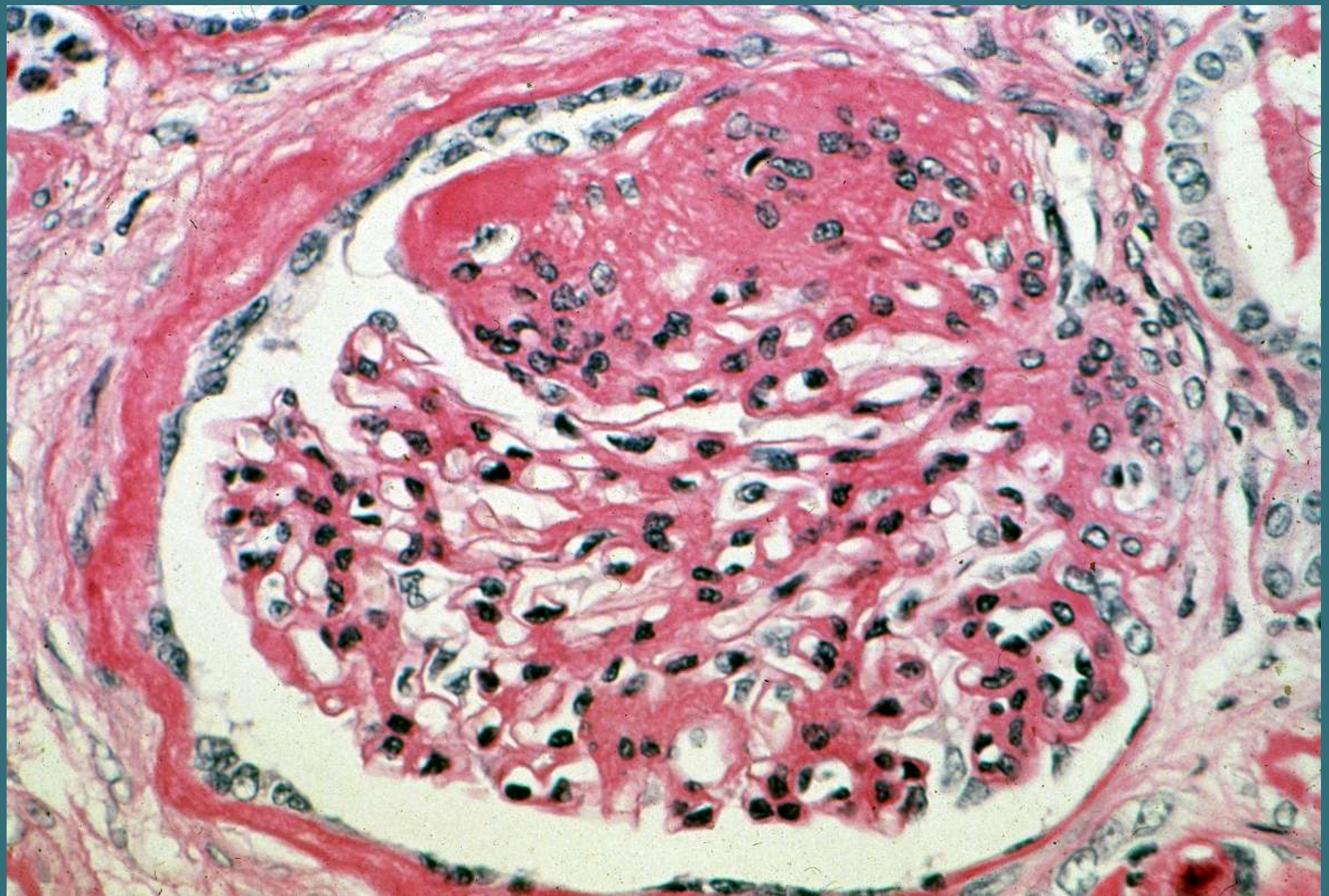
FSGS

LM: focal (some glomeruli) and segmental (part of glomerular capillary loops) glomerulosclerosis and / or hyalinosis.

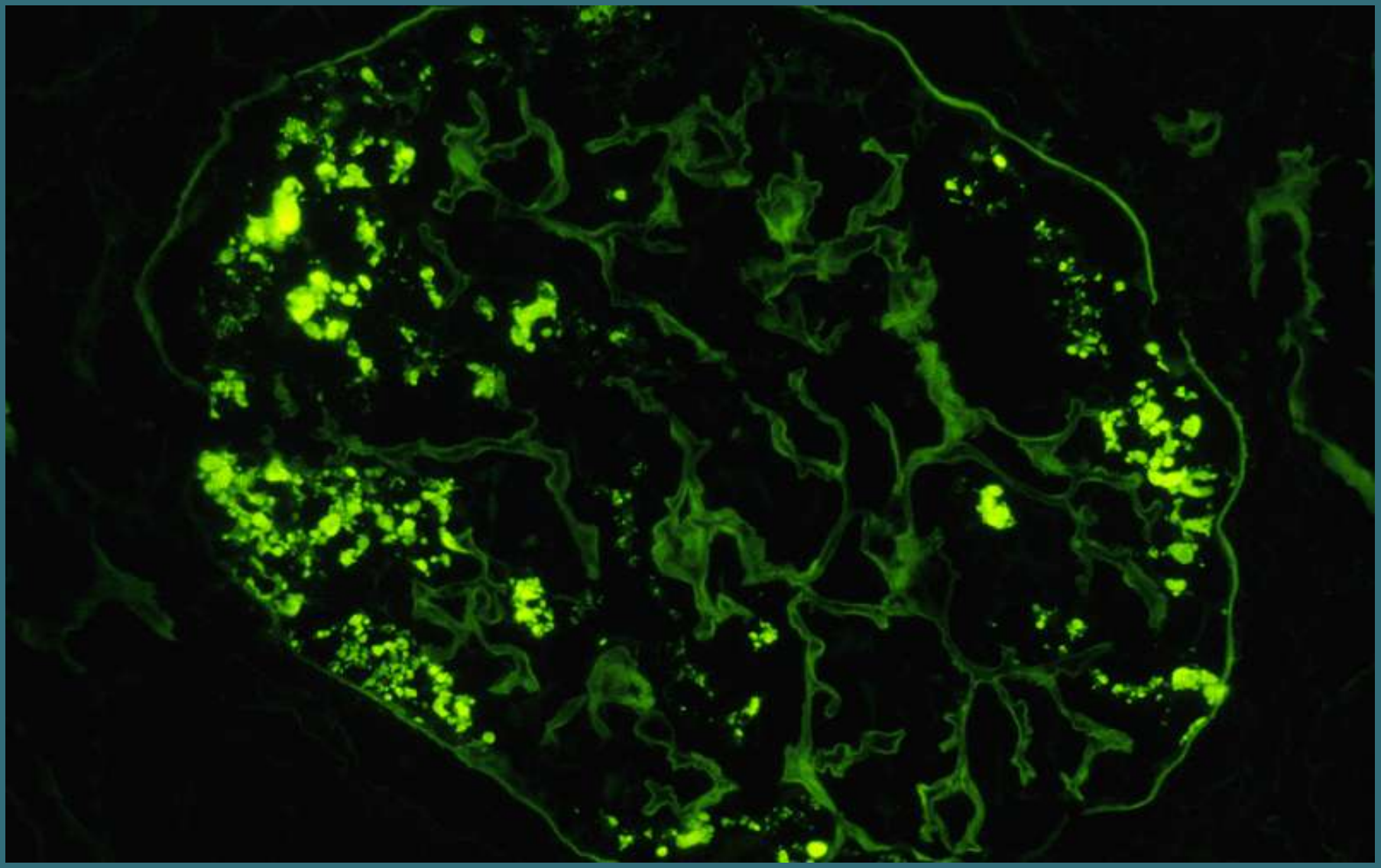
EM: in sclerosed segments - collapse of capillary loops, obliteration of the lumen (insudative changes); in other glomeruli – fusion of small processes podocytes.

IF: in sclerosed segments - IgM, C3; in unchanged glomeruli – negative.

FSGS



FSGS



FSGS - Treatment

Cyclosporin A - 4 - 7 mg / kg per day in combination with prednisone 1 mg / kg every other day for at least 18 months (25-40% remission, but there has been rapid relapse of nephrotic syndrome after discontinuation of treatment);

Protocol MENDOZA.

Recurrence in the graft - a special protocol for management of the recipient after kidney Tx!

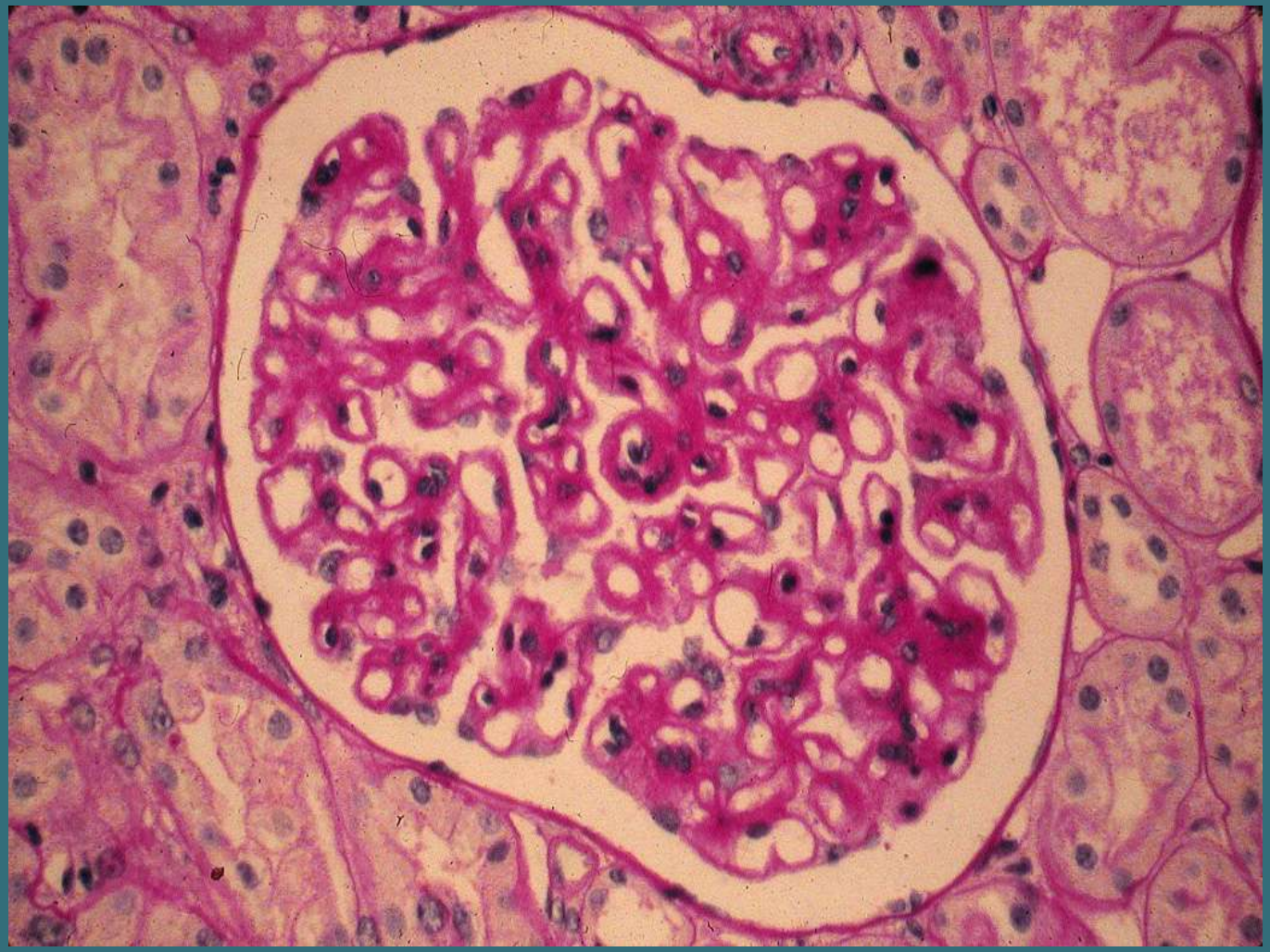
Membranous nephropathy

LM: diffuse thickening of the glomerular capillaries of BM. When silvered BM uneven contours with the emergence of numerous spines (diagnostic feature).

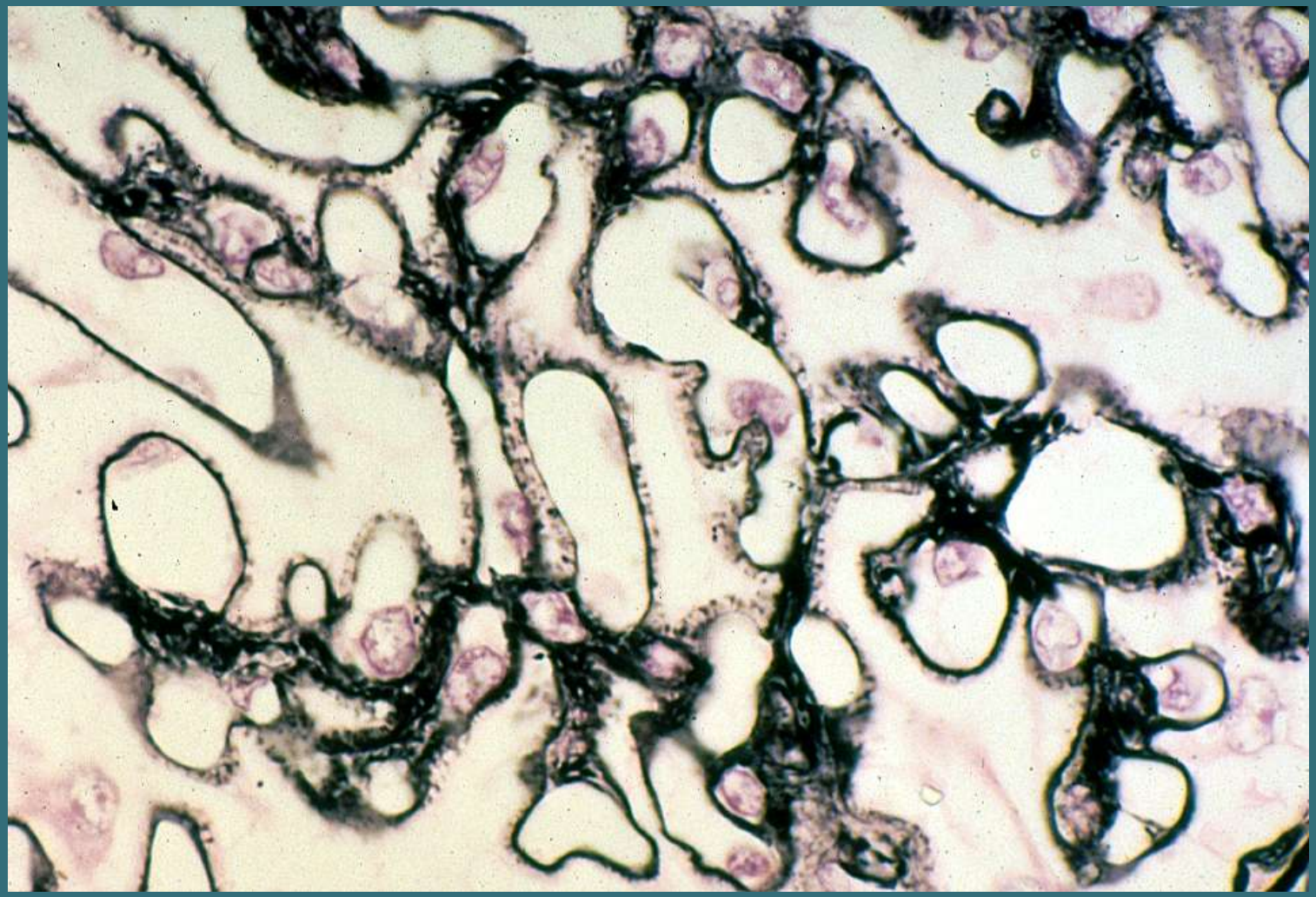
EM: subepithelial deposits, which are walled up in membranouse-dense substance produced by podocytes - "membranous transformation".

IF: peripheral granular deposits of IgG and C3, rarely IgM, rarely IgA.

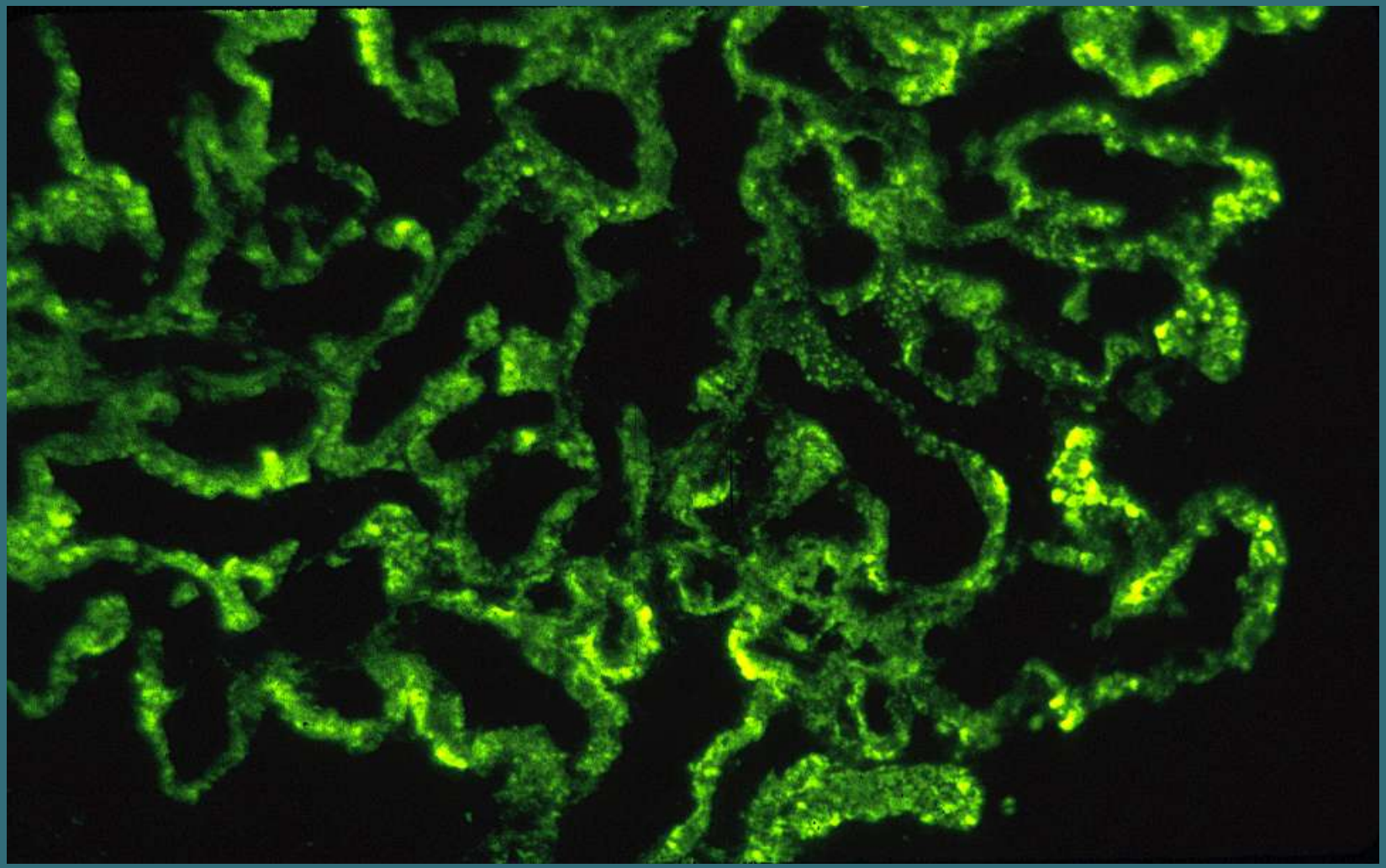
Membranous nephropathy
Light microscopy



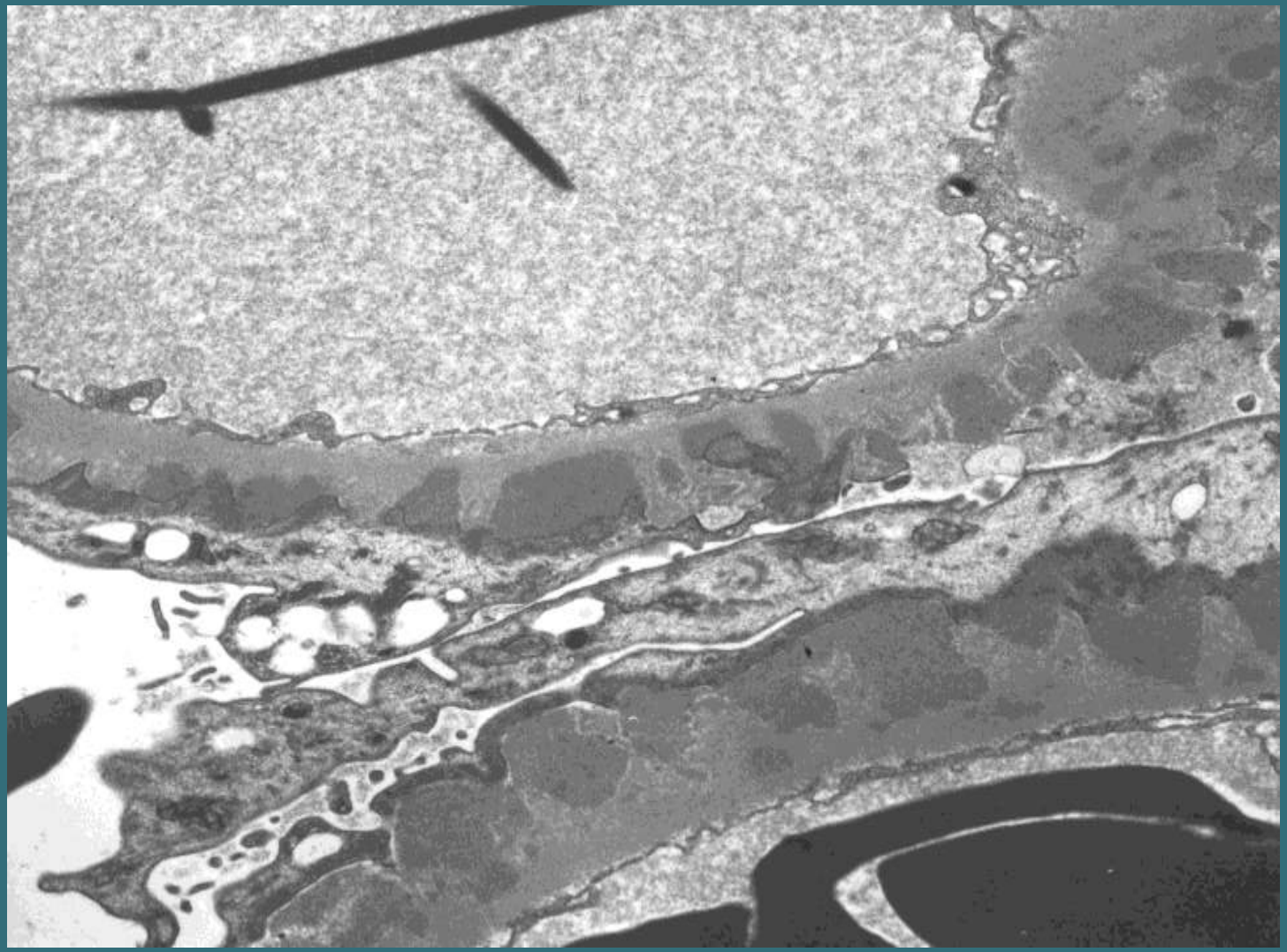
Membranous nephropathy
Light microscopy - Silver



Membranous nephropathy IF microscopy



Membranous nephropathy Electron microscopy



Membranous nephropathy

Etiology:

Idiopathic - 50%;

Secondary - 50% (hepatitis B, malaria, syphilis, tumors, captopril).

Pathogenesis: Immine-complexe.

Clinic:

7% of the children glomerulopathies;

More common in school age children;

Isolated proteinuria, hematuria+ proteinuria or nephrotic syndrome + hematuria;

Steroid-resistant

Outcome:

The high frequency of spontaneous remissions;

Rare progression to ESRD (for 5 years - 5%).

Membranous nephropathy

- No controlled studies in children for the treatment;
- In isolated proteinuria - ACE inhibitors, observation;
- With the development of nephrotic syndrome and progression:
- Long-term use of corticosteroid therapy alternating scheme (years);
- Chlorambucil, cyclophosphamide, cyclosporin A, ACE inhibitors; monoclonal antibodies (rituximab)
- Treatment of the underlying disease, against which there was nephropathy (hepatitis B, etc.).

Mesangioproliferative GN

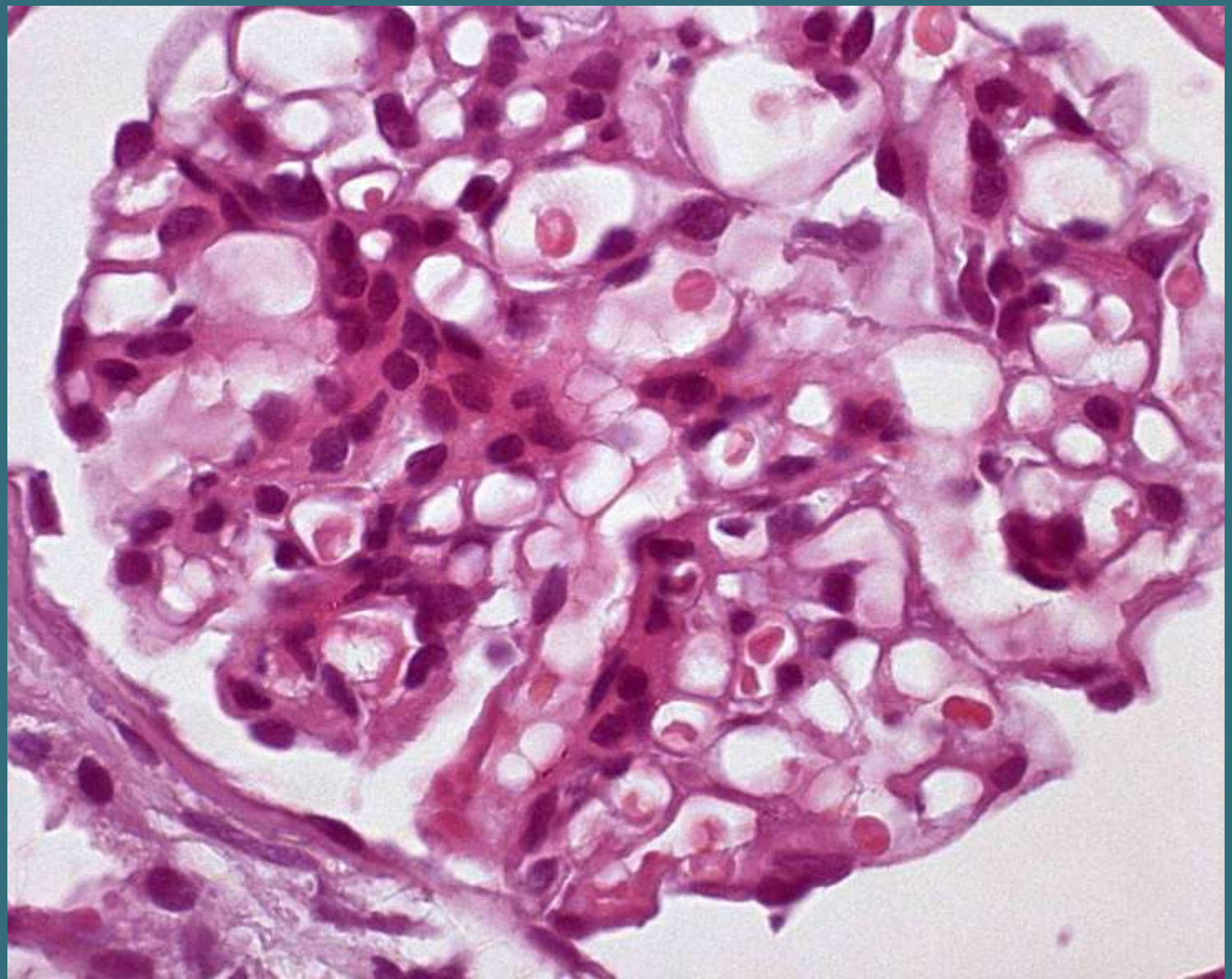
LM: *mesangial expansion due to the proliferation of mesangial cells.*

EM: *an increase in mesangial matrix, mesangial deposits.*

IF: granular diffuse of mesangial deposits of IgG, M, A, C3 -complement.

Clinically - hematuric or nephrotic form

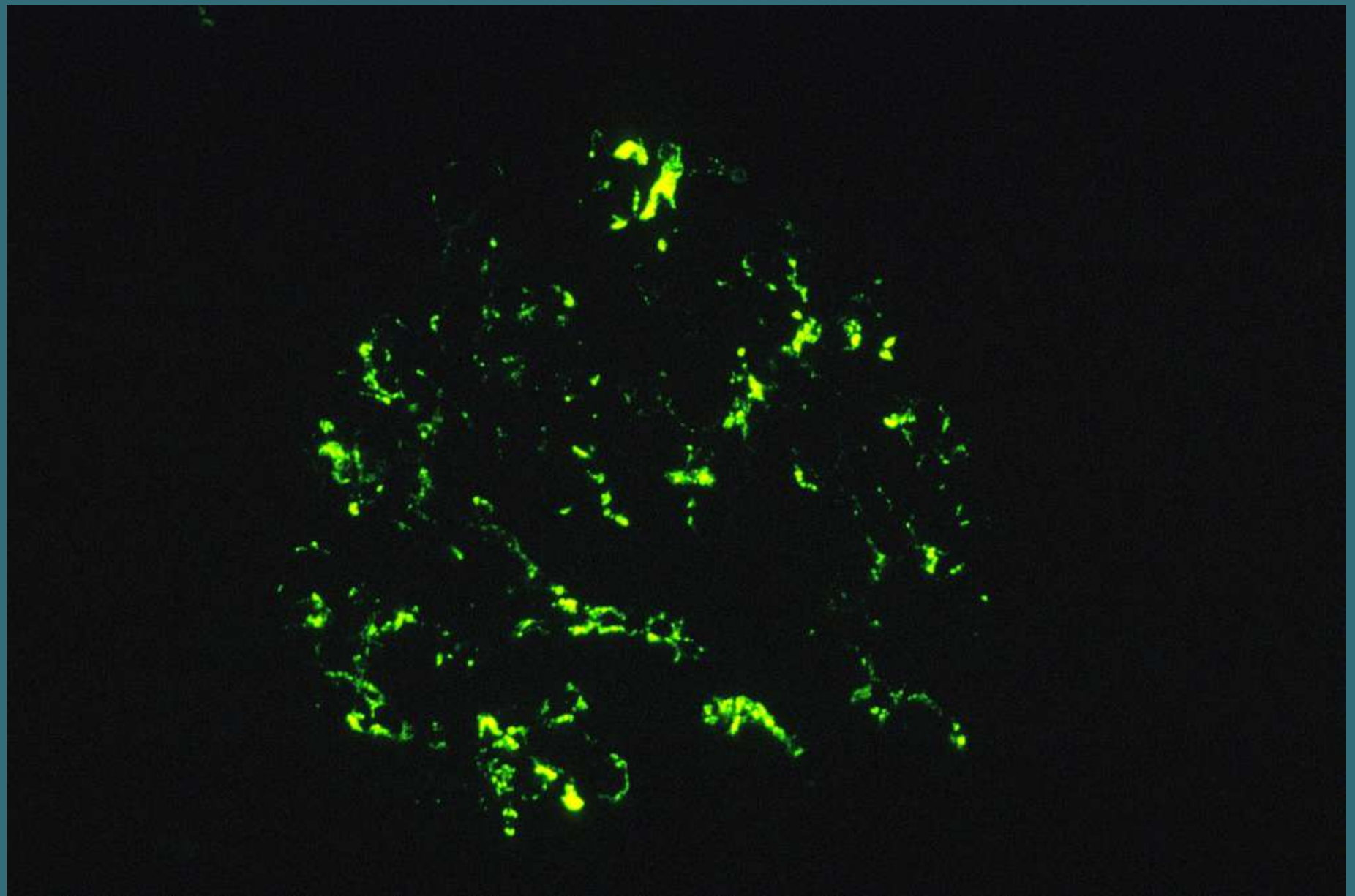
Mesangial proliferation



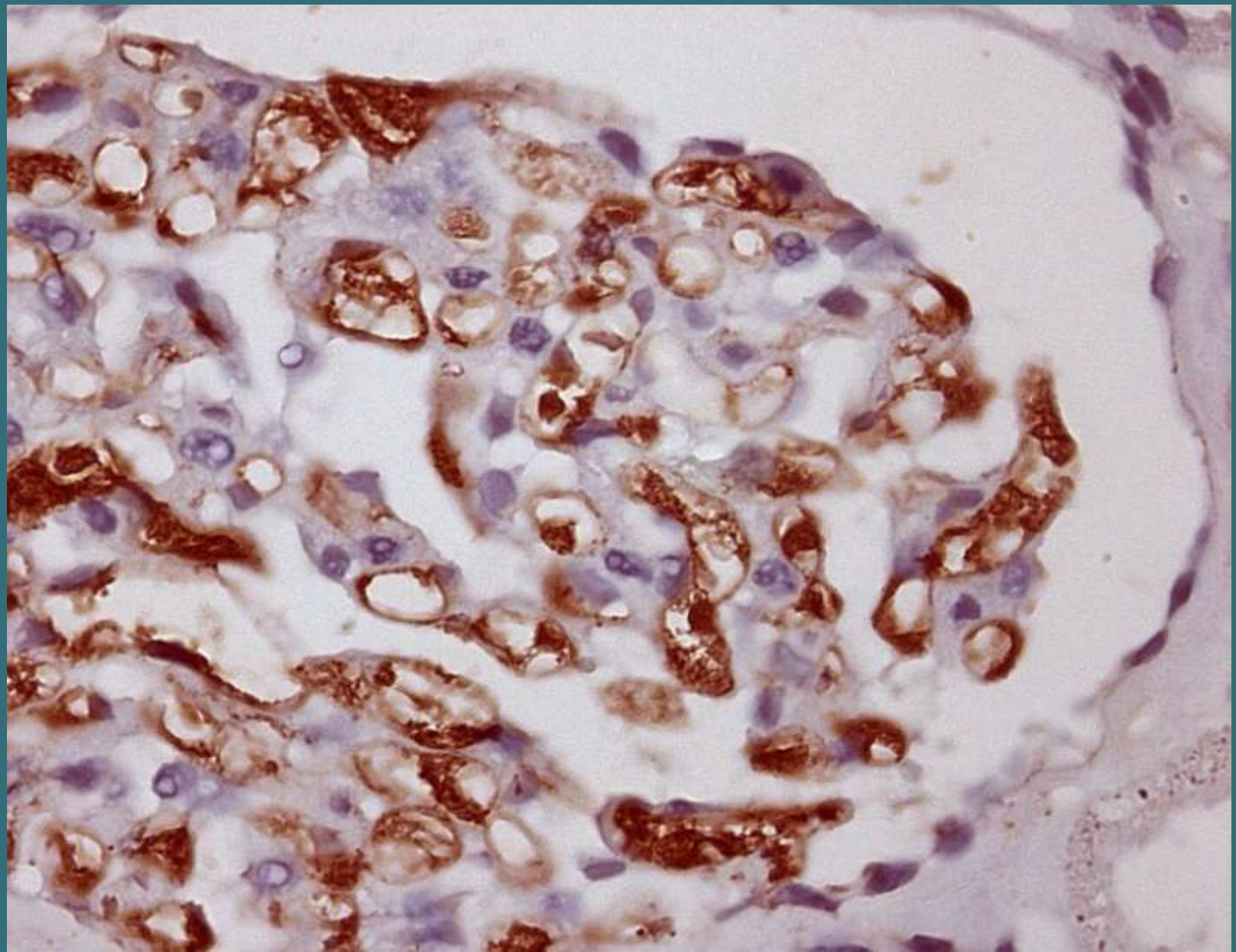
IgA-nephropathy

It's mesangio-proliferative GN with prevailing deposits of IgA (IgA-nephropathy)

IgA-nephropathy



IgA-nephropathy



IgA-nephropathy

Etiology:

In children often idiopathic;

Less common secondary – SHP vasculitis, bowel disease and so on.

Clinic:

In typical cases, recurrent gross (macro) hematuria, often provoked by ART infection. Between the previous infection and recurrent gross hematuria is usually no more than 1-2 days.

Less commonly nephrotic syndrome.

IgA-nephropathy

Outcome:

Previously it was thought that the disease is benign, but according to adults nephrologists data in 30-35% of patients the progression to ESRD is happened between 20-30 years.

IgA-nephropathy

With isolated hematuria only observation;

In Nephrotic syndrome:

steroids (60-30-15mg / m2 for 3-5 years)

Omega -3 fatty acids (fish oil 4 g for 2 years)

ACE inhibitors for long-time

Mesangiocapillary GN

LM: *diffuse thickening and splitting of GBM with expression of mesangial cells / proliferation.*

EM: *splitting of GBM, increased mesangial matrix and cellularity.*

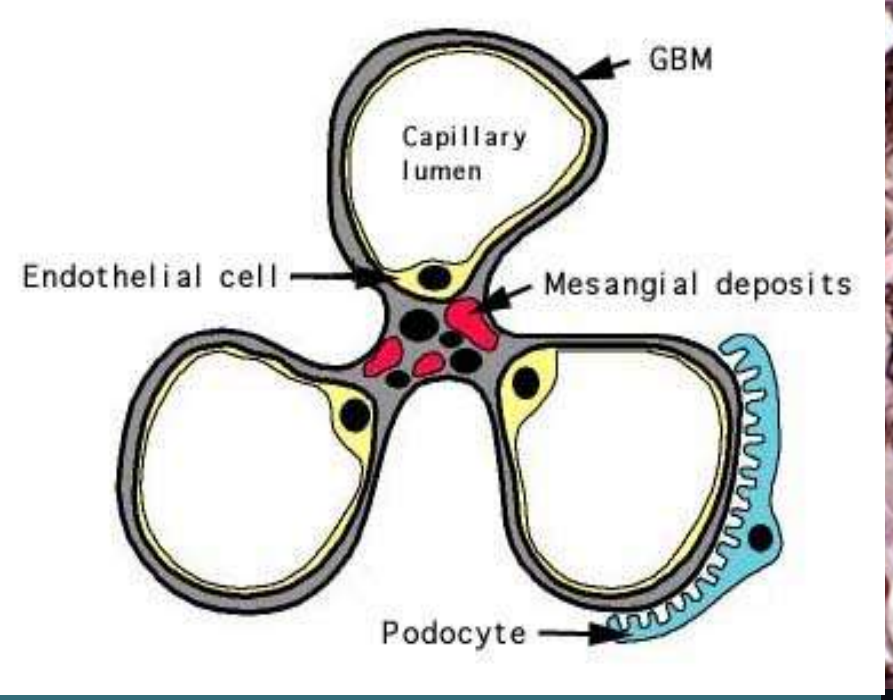
IF: *peripheral, large, confluent deposits of C3, rarely IgG, IgA, C4, fibrin.*

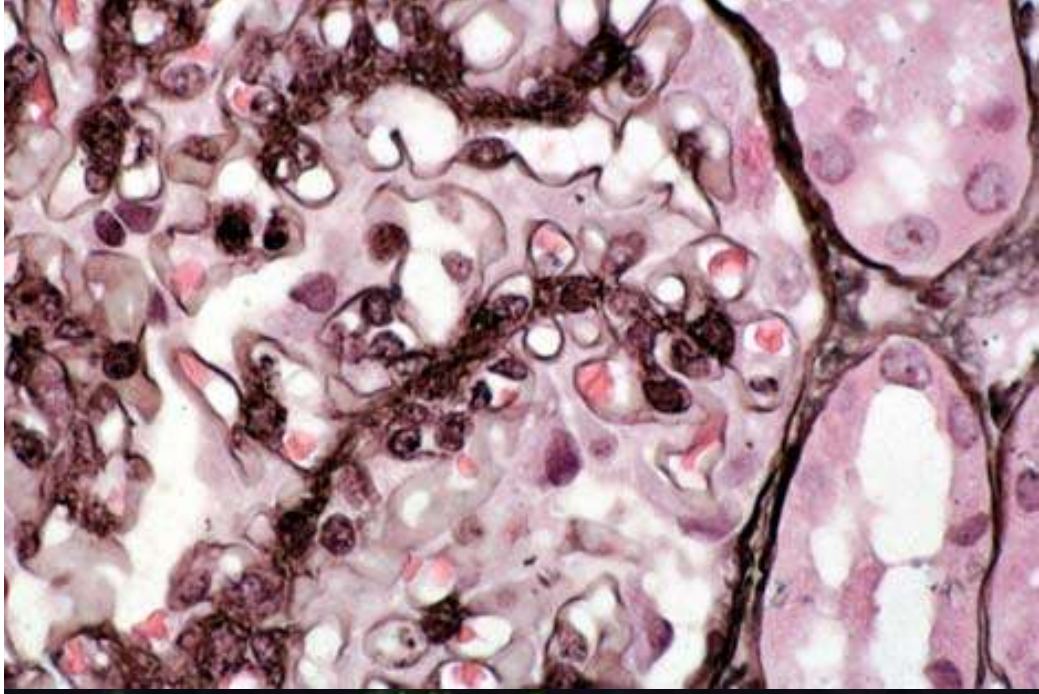
Mesangiocapillary GN

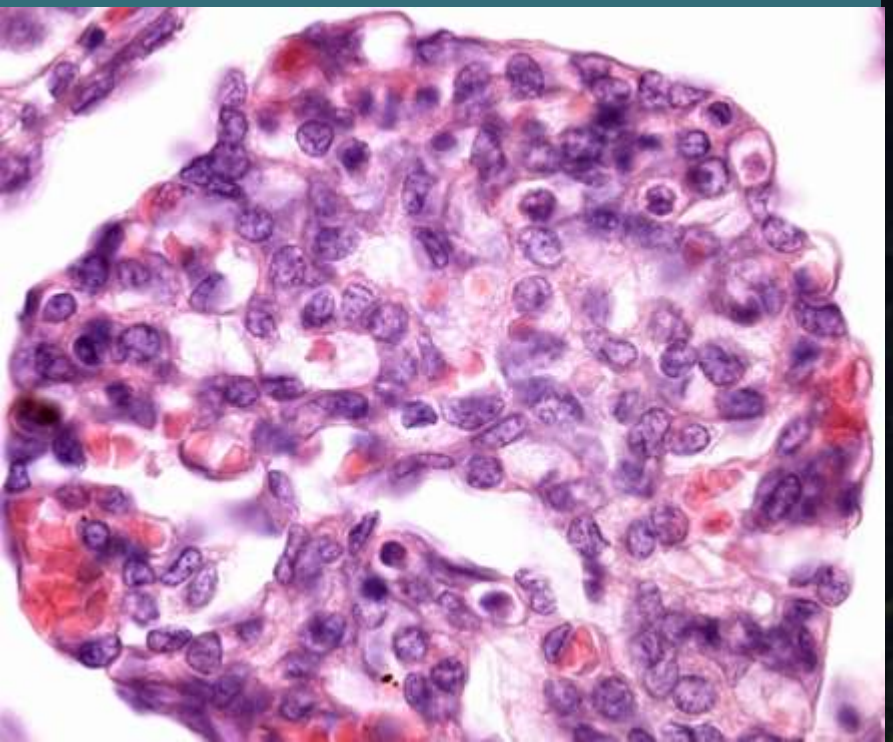
- 3 types on morphology:

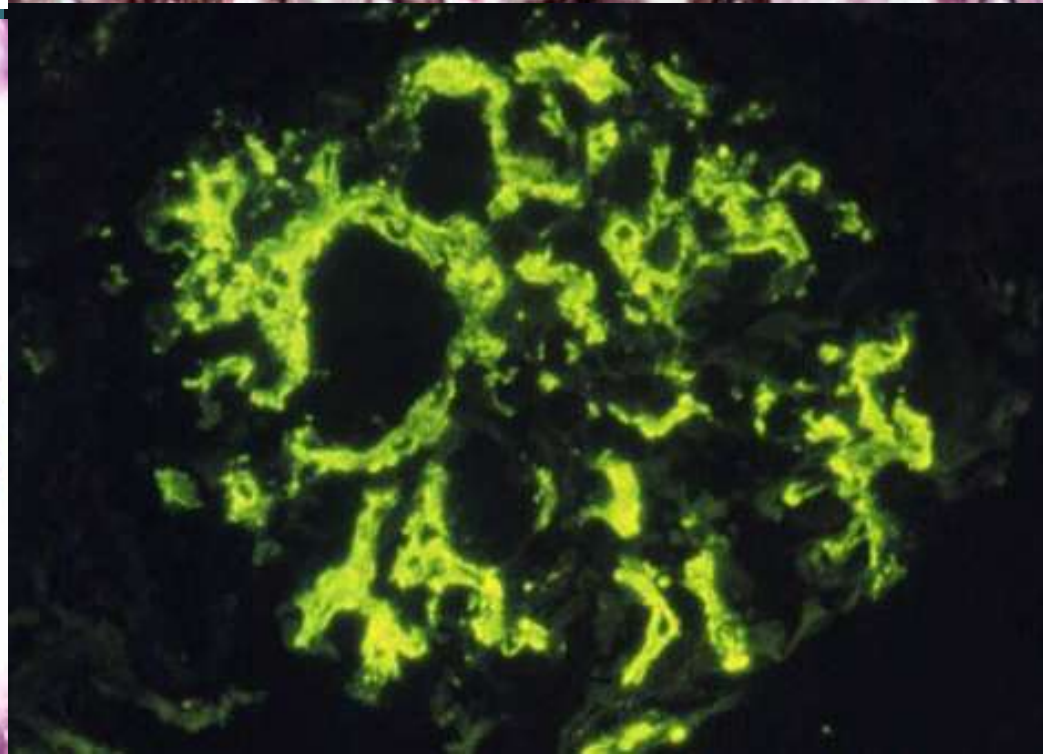
- Type I – sub-endothelial deposits
- Type II - "dense" deposits disease (at present - isolated in a separate disease)
- Type III - transmembrane deposits

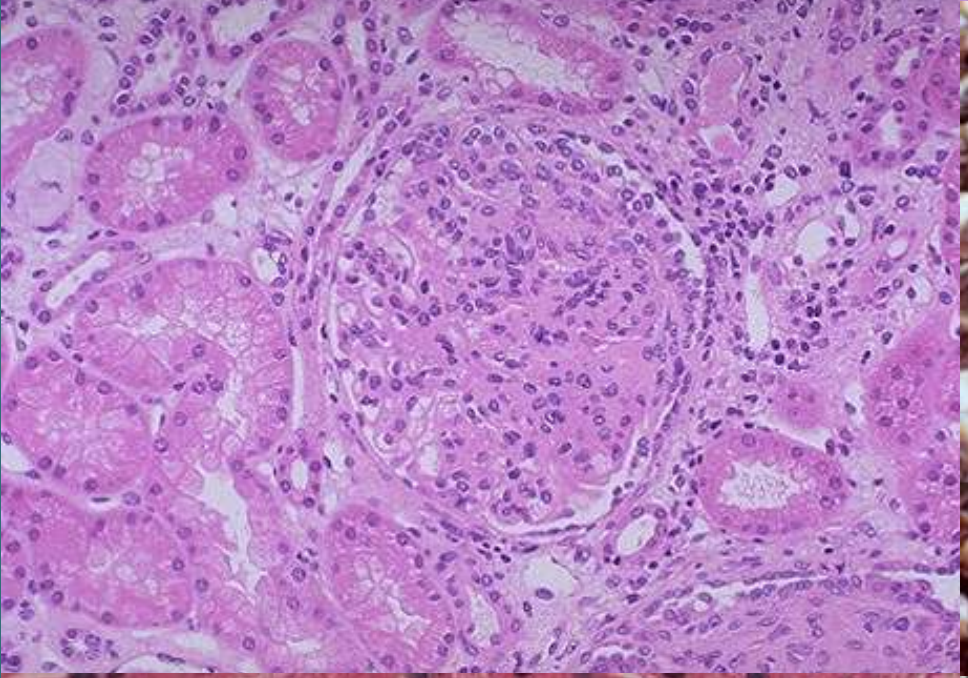
- Clinical differences between the three types is not detected: edema in conjunction with hematuria and / or hypertension, hematuria, isolated urinary syndrome, or mixed NS).

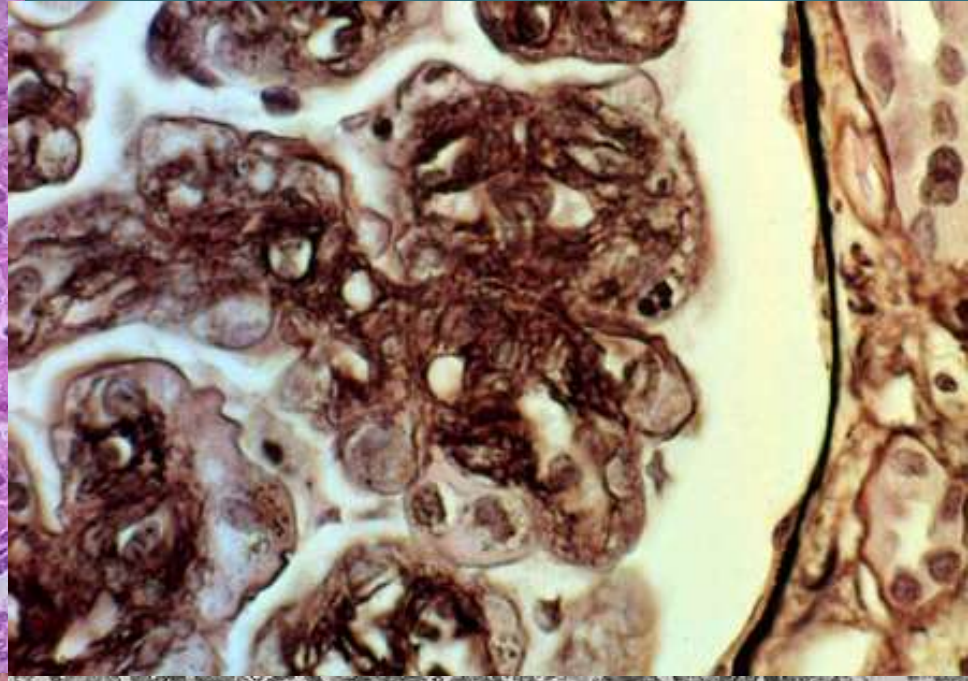

GBM
Capillary lumen
Endothelial cell
Mesangial deposits
Podocyte

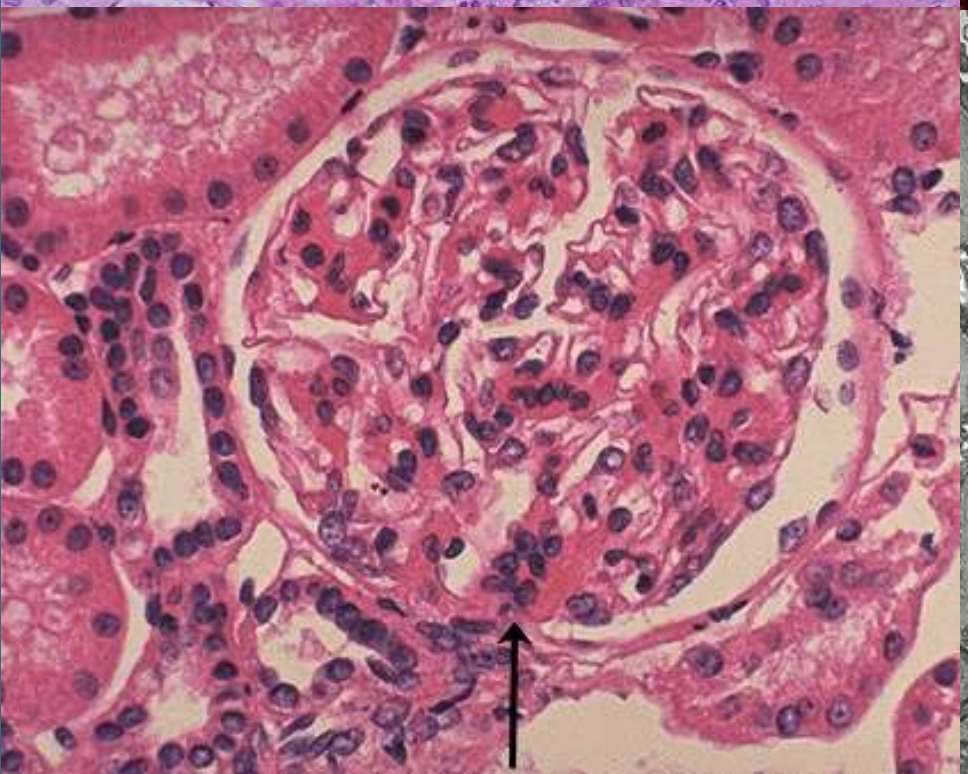


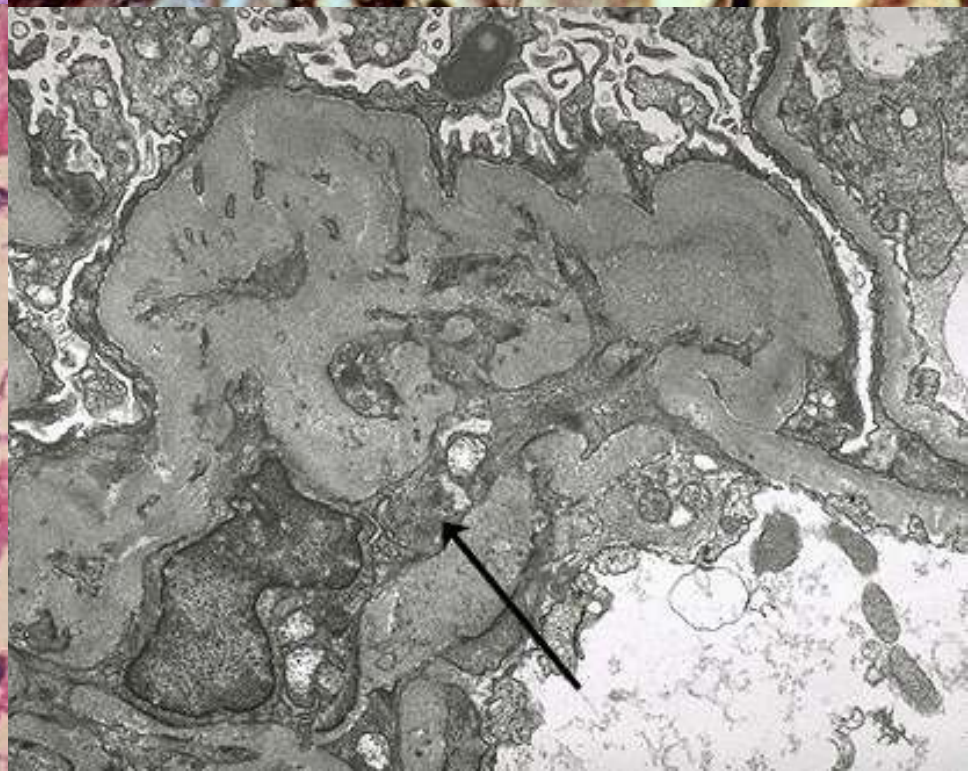












Mesangiocapillary GN

Etiology: *almost always idiopathic*

Clinic: high*ly variable (differential diagnosis - acute nephritic syndrome)*

C3 - hypo-complementemic GN

Suffer more school-age children, boys: girls = 1: 1

The lack of effect on the standard therapy of GCS

Outcome:

Progressive course with the development of ESRD (10-year survival rate of 32%)

High risk of recurrence in the graft!

Mesangiocapillary GN

1. No standard treatment;

2. When an isolated hematuria - just an observation;

3. In NS- long steroids therapy - within 1-5 years, possibly after pulse therapy with corticosteroids

4. Cyclosporine A

7. ACE inhibitors with antiproteinuric and renoprotective purpose for long-time

Thank you for your attention!