

Chronic glomerulopathies

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Clinical signs

- asymptomatic course
- accidental finding in urine
- nephrotic syndrome
- nephritic syndrome
- change in colour and volume of urine
- renal insufficiency
- hypertension
- oedema
- dyspnoea
- vision disorders
- skin purpura
- recurrent sinusitis
- haemoptysis
- severe peripheral neuropathy
- trophic defects in extremities
- arthralgias, butterfly exantema, polyserositis



Urinary syndromes in chronic glomerulonephritis

- **small isolated proteinuria - less than 1,5-2g/24h**
 - orthostatic proteinuria
 - benign nephroangiosclerosis in hypertensive patient
 - early stage of diabetic nephropathy
- **isolated (mild) erythrocyturia (proteinuria less than 0,3g/24h)**
 - glomerular hematuria - acanthocytes
 - IGA nephropathy
 - thin basal membrane nephropathy, Alport syndrome
 - vasculitis
- **massive isolated selective proteinuria (5-25g/24h)**
 - minimal change disease



Urinary syndromes in chronic glomerulonephritis

- **prevailing - massive - erythrocyturia (50mil/24h)**
 - IgA nephropathy
 - thin basal membrane nephropathy
- **prevailing nonselective proteinuria more than 5g/24h and erythrocyturia (less than 15mil/24h)**
 - focal segmental glomerulosclerosis
 - membranous glomerulonephritis
 - lupoid nephritis
- **balanced (proportional) proteinuria a erythrocyturia**
 - mesangioproliferative glomerulonephritis
 - membranoproliferative glomerulonephritis



Urinary syndromes in chronic glomerulonephritis

- **asymptomatic proteinuria of glomerular origin**

- FSGS
- mesangioproliferative GN
- diabetic nephropathy
- benign hypertonic nephroangiosclerosis

- **asymptomatic microhematuria of glomerular origin**

- thin basal membrane nephropathy
- IgA nephropathy
- mesangioproliferative GN



Classification of glomerulopathies

- **acute GN**
- **rapid progressive GN**
- **chronic GN**

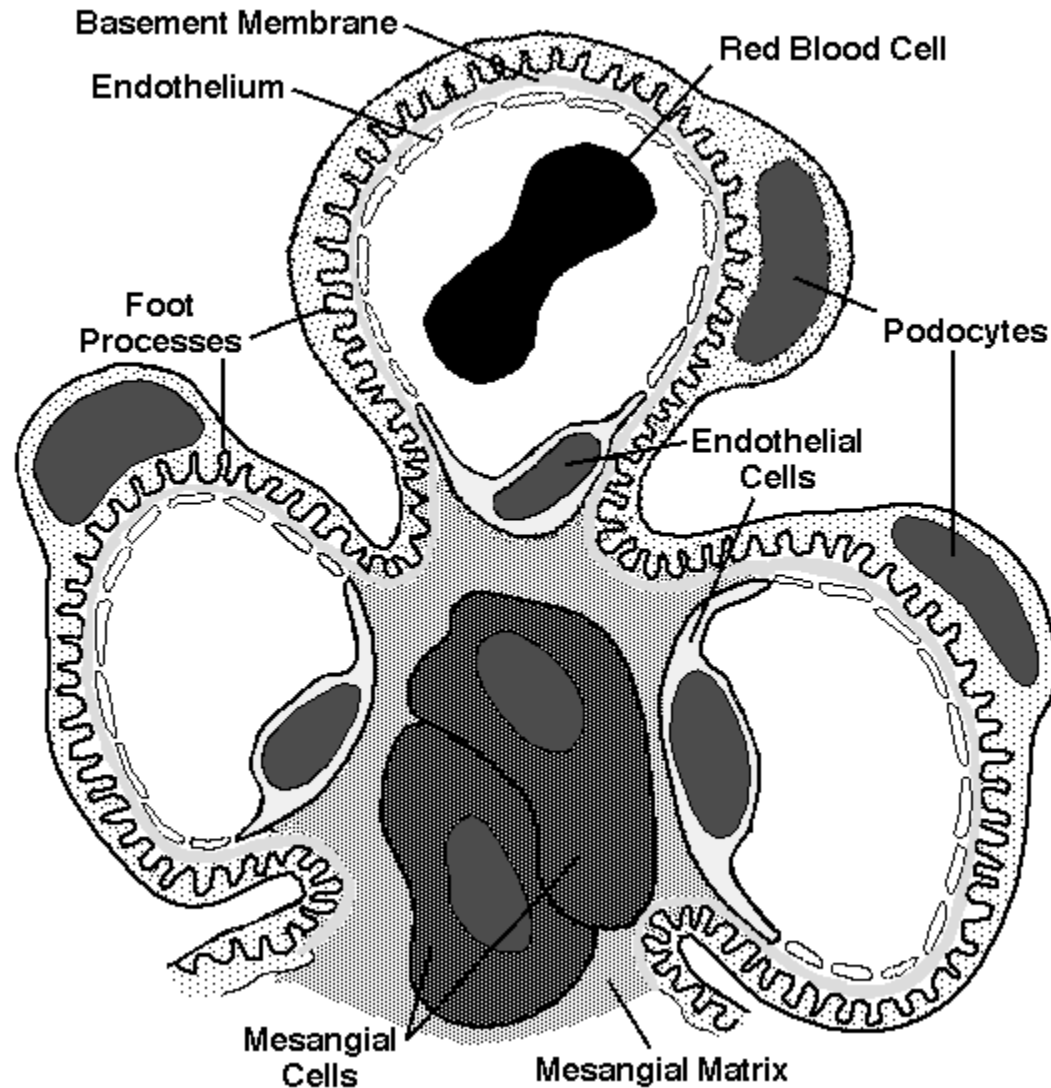


Classification of glomerulopathies

• **classification according to:**

- clinical picture
- type of glomerular pathology – diffuse or focal, global or segmental
- cellularity of glomerulus - proliferative, nonproliferative
- immunofluorescence type - immunocomplex, antirenal, pauciimmune
- localisation of immunocomplexes - mesangial, subendothelial, epimembranous, intramembranous
- etiology - primary, secondary (infectious, inflammatory disease, immunopathologic states, malignancy, toxic gas, organic solvent, medicaments, „idiopathic“ GN)
- pathogenetic mechanism: autoantibody (anti GBM, ANCA), complement, circulating inflammatory cells, macrophages, locally activated residential cells

Schematic description of the glomerular structure





Primary chronic glomerulopathy

- **A/ non proliferative CHGN**

- idiopathic nephrotic syndrome (minimal change disease, FSGS)
- membranous nephropathy
- lupoid nephritis type V

- **B/ proliferative CHGN**

- mesangioproliferative CHGN (IgA nephropathy, Hennoch-Schonlein purpura), lupoid nephritis type V
- membranoproliferative CHGN (type I,II,III, lupoid nephritis type III,IV)



Secondary glomerulopathy

- **systemic vasculitides with renal involvement**

- Wegener granulomatosis
- microscopic polyarteritis
- Churg-Strauss syndrome
- Henoch-Schonlein disease

- **systemic connective tissue disease**

- lupoid nephritis
- systemic sclerosis, Sjogren syndrome, Sharp syndrome
- essential mixed cryoglobulinemia



Prognosis of primary chronic glomerulopathies

- FSGS development of chronic renal failure during
10 years in 50%
- membranous GN
10 years in 20-33%
- IgA nephropathy
20 years in 33%
- membranoproliferative GN
10 years in 50%

- 30% of dialyzed patients without biopsy proven glomerulonephritis



Prognosis of primary chronic glomerulopathies

- **bad prognosis signs:**

male sex, higher age, proteinuria, hypertension, decrease of GF at time of diagnosis tubulointerstitial fibrosis, vascular sclerosis, crescents

- **renal failure development:**

glomerular wall lesion ... scarring of renal interstitium ... reduction of GF and renal insufficiency ... decrease of size of kidney in USG



Treatment of chronic glomerulopathies

steroids

Cyklosporine A or tacrolimus

cyklofosfamide, chlorambucil, azathioprine, mycofenolate, methotrexate

monoclonal antibodies (rituximab, belimumab...)

- **treatment of primary disease**

Hypertension - less than 125/75

ACE blockers, AT I blockers, statins,

Ca channel blockers, diuretics, betablockers, alpha blockers

vitamine D3, Calcium, NaHCO₃, erythropoetin



Minimal Change Disease /lipoid nephrosis, idiopathic primary nephrotic syndrome/

- the most frequent cause of nephrotic syndrome in childhood
- Unclear pathogenesis: certain cytokine leading to loss of sialic acid and heparansulfate in basal membrane and loss of electronegative charge of basal membrane resulting in selective proteinuria

Minimal Change Disease /lipoid nephrosis, idiopathic primary nephrotic syndrome/

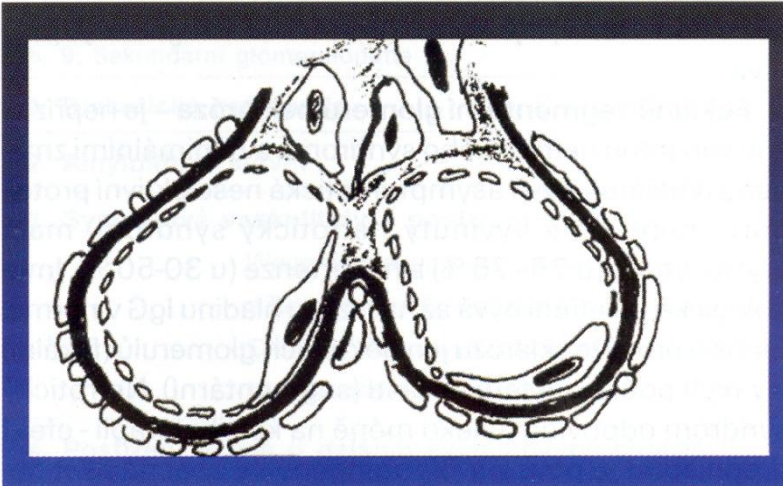
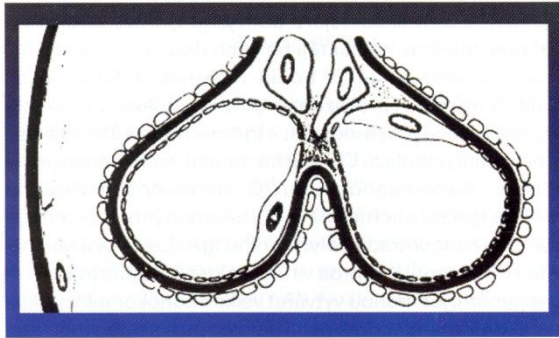
- **treatment**

prednisolone 20-40mg/sqm/day:

Corticosteroid sensitive – dependent - resistant
(Cyclophosphamide, CyA)

- **rather good prognosis**

complete remission in 80% adults after 6 month
steroidal treatment



rarely cytoplasmic intumescence of epithelial cells,
nuclear hyperchromasia, small mesangial proliferation

electron microscopy: pedicelial fusion



Focal Segmental Glomerulosclerosis (FSGS)

- **secondary to:**

- unilateral kidney agenesis, nephrectomy in childhood

- vesicoureteral reflux

- obesity

- congenital cyanotic heart defects

- HIV

- heroin nephropathy

- **typical laboratory findings**

- nonspecific proteinuria, small erythrocyturia, hypertension

- nefrotic syndrome

- low IgG in blood

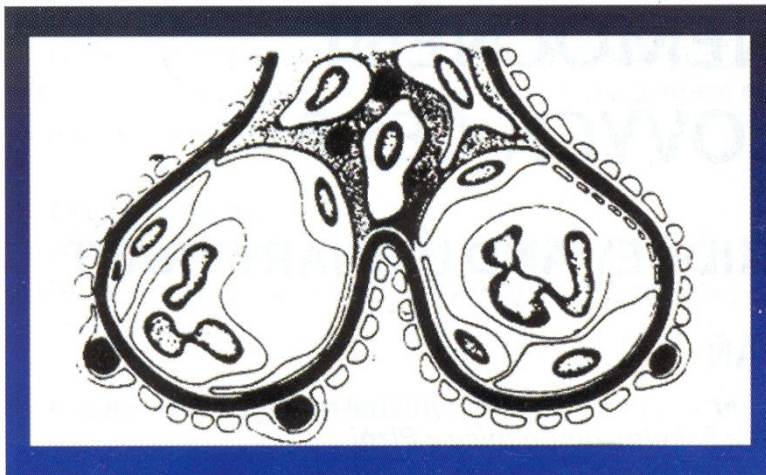
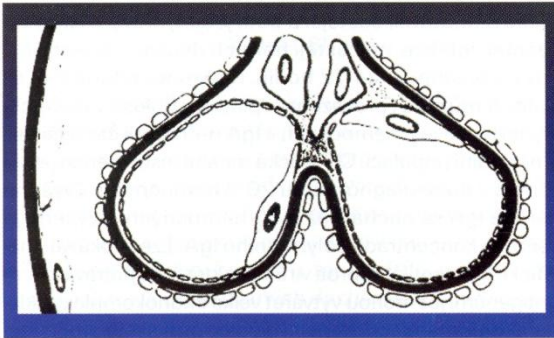
Focal Segmental Glomerulosclerosis (FSGS)

- **treatment:**

poor response to steroids -25%
frequent relapse ... cyclosporin dependency
CFA

- **prognosis:**

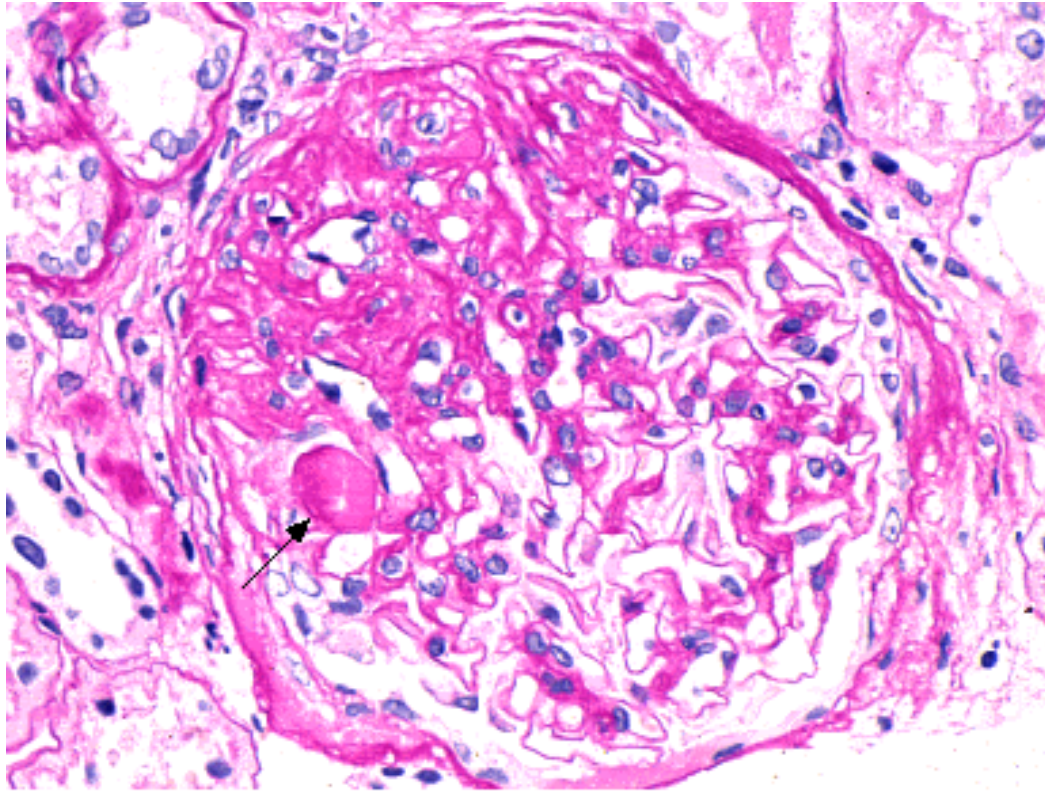
10 years survival without renal failure 50%



mesangial proliferation, endocapillar neutrophil infiltration,
rare sclerotic changes, necrosis of capillary loops, fibrine
deposition

lesion of some glomerules only (less than 50%) - focal
lesion of parts of these glomerules - segmental

Histological picture of FSGS



Moderate FGS Light micrograph in focal segmental glomerulosclerosis shows a moderately large segmental area of sclerosis with capillary collapse on the upper left side of the glomerular tuft; the lower right segment is relatively normal. Focal deposition of hyaline material (arrow) is also seen. Courtesy of Helmut Rennke, MD.



Membranous Nephropathy

- third most frequent cause of nephrotic syndrome in adults - 20-40%
- immunopathological disease with development of immunocomplexes
localised between epithelial cells and glomerular basal membrane
- clinical picture - nephrotic syndrome 80%, renal insufficiency 5-10%

secondary to:

cancer, SLE, sarcoidosis, pemphigoid, dermatitis herpetiformis, diabetes mellitus, penicilamin, gold, NSAIDs, captopril
HBV, HCV, malaria, lepra, syphilis

Membranous Nefropathy

- **prognosis:**

spontaneous remission 30%

persistent nephrotic syndrome with stabilized GF 20%

progression to renal insufficiency 25%

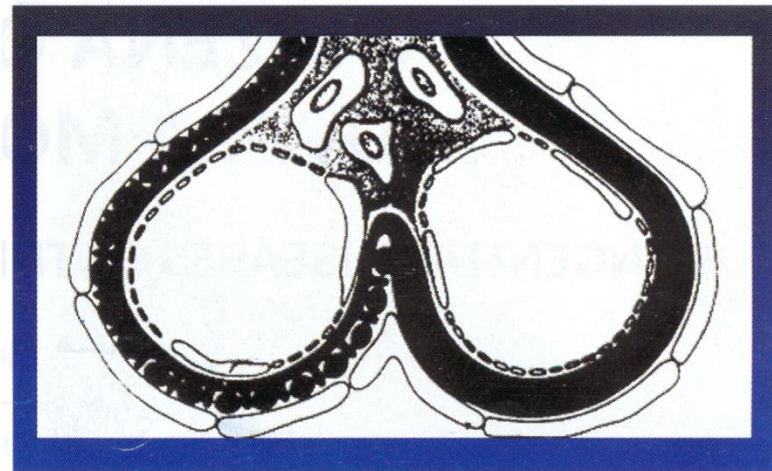
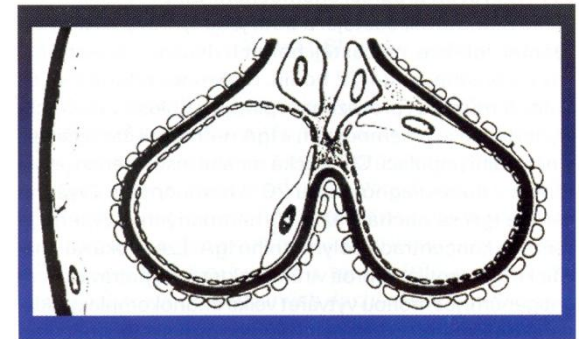
- **therapy:**

steroid and CyA or CFA (chlorambucil)

mycophenolate mophetil,

rituximab (anti CD 20),

belimumab (anti BLYS)



predominant infliction of peripheral loop of glomerular cappillary,
increased thickness of basal membrane with subsequent occlusion of
capillary. No proliferation.



Membranous Nefropathy

- **bad prognosis:**

male sex, proteinuria more than 10g/24h, hypertension, decrease of GF, tubulointerstitial fibrosis, stadium IV

- **4 stages:**

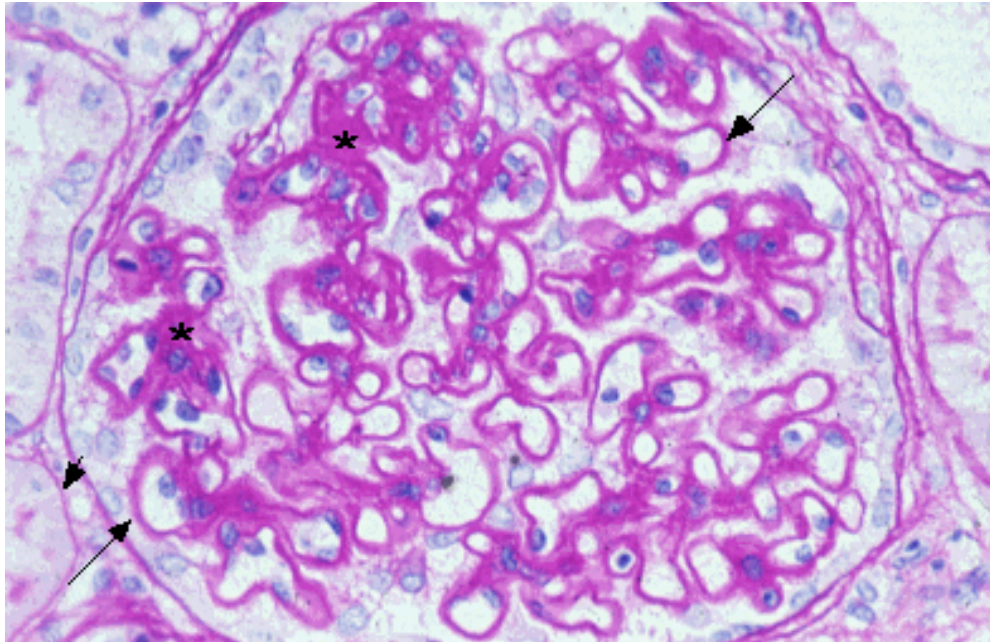
I evidence of subepitelial deposits

II spikes of basal membrane among deposits

III incorporation of deposits in thickened basal membrane

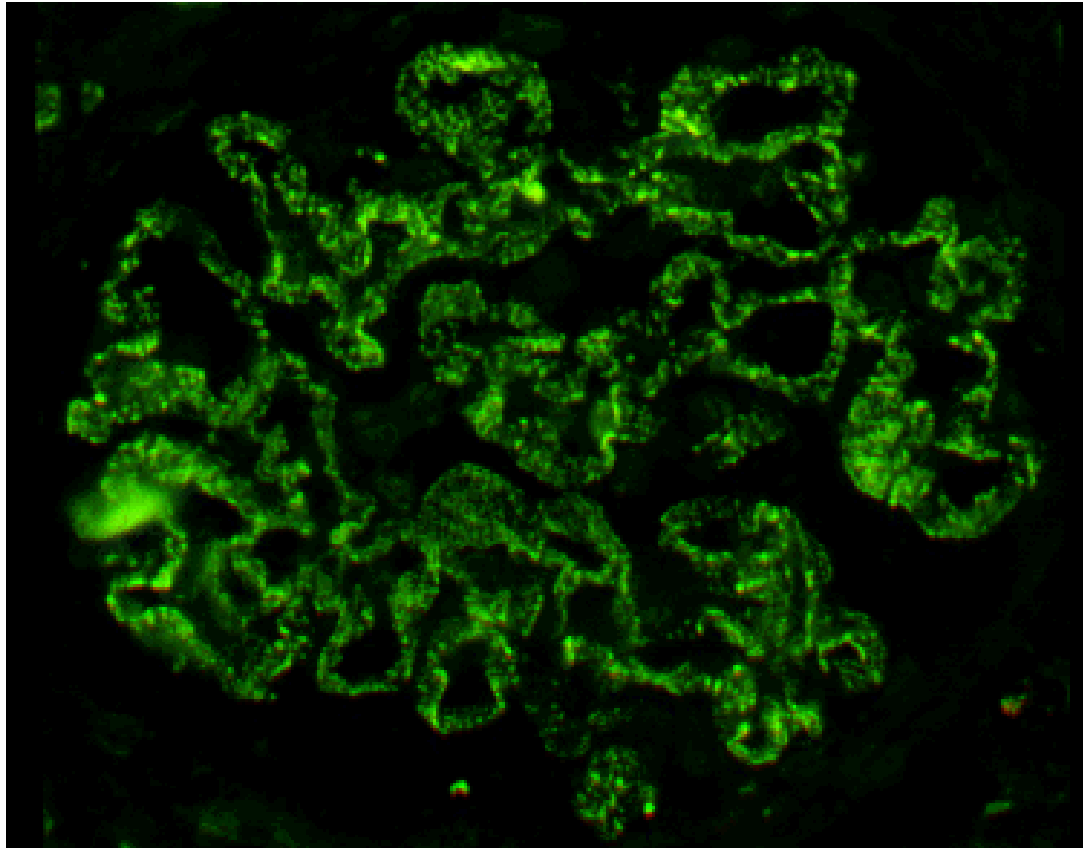
IV diminishing imunodeposits from irregularly thickened basal mambrane

Light microscopy in MN



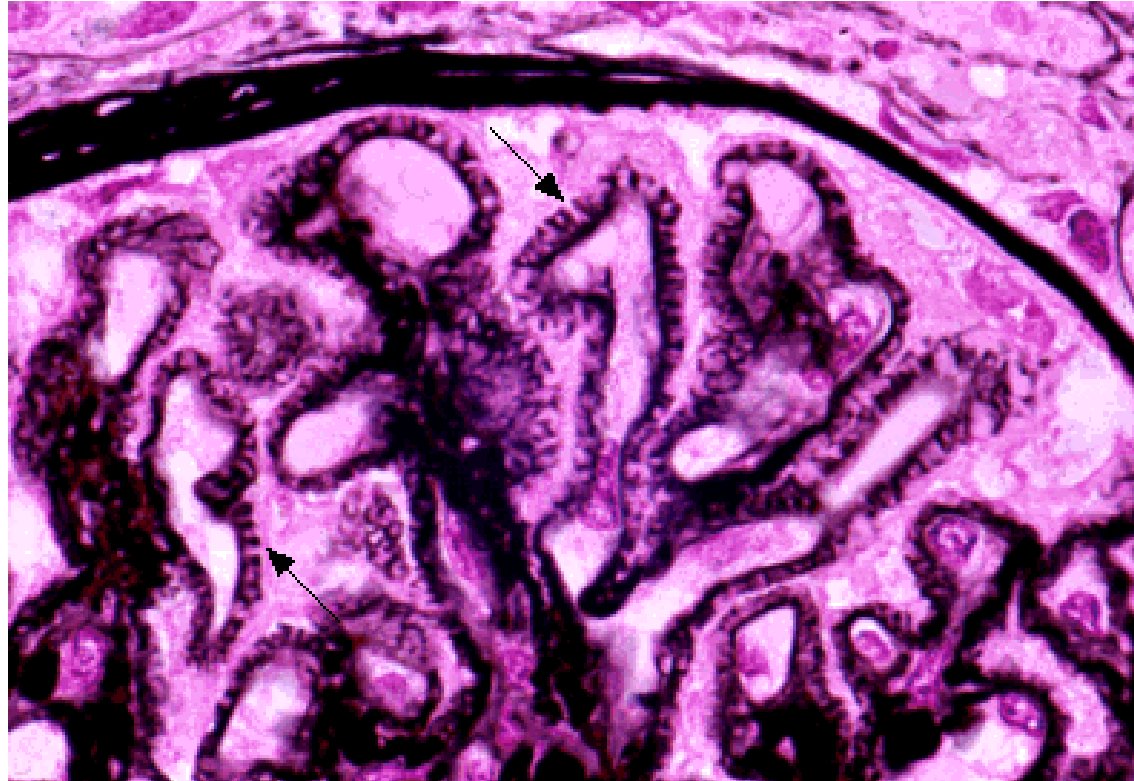
Membranous nephropathy Light micrograph of membranous nephropathy, showing diffuse thickening of the glomerular basement membrane (long arrows) with essentially normal cellularity. Note how the thickness of the glomerular capillary walls is much greater than that of the adjacent tubular basement membranes (short arrow). There are also areas of mesangial expansion (asterisks). Immunofluorescence microscopy (showing granular IgG deposition) and electron microscopy (showing subepithelial deposits) are generally required to confirm the diagnosis. Courtesy of Helmut Rennke, MD.

Immunofluorescence in MN



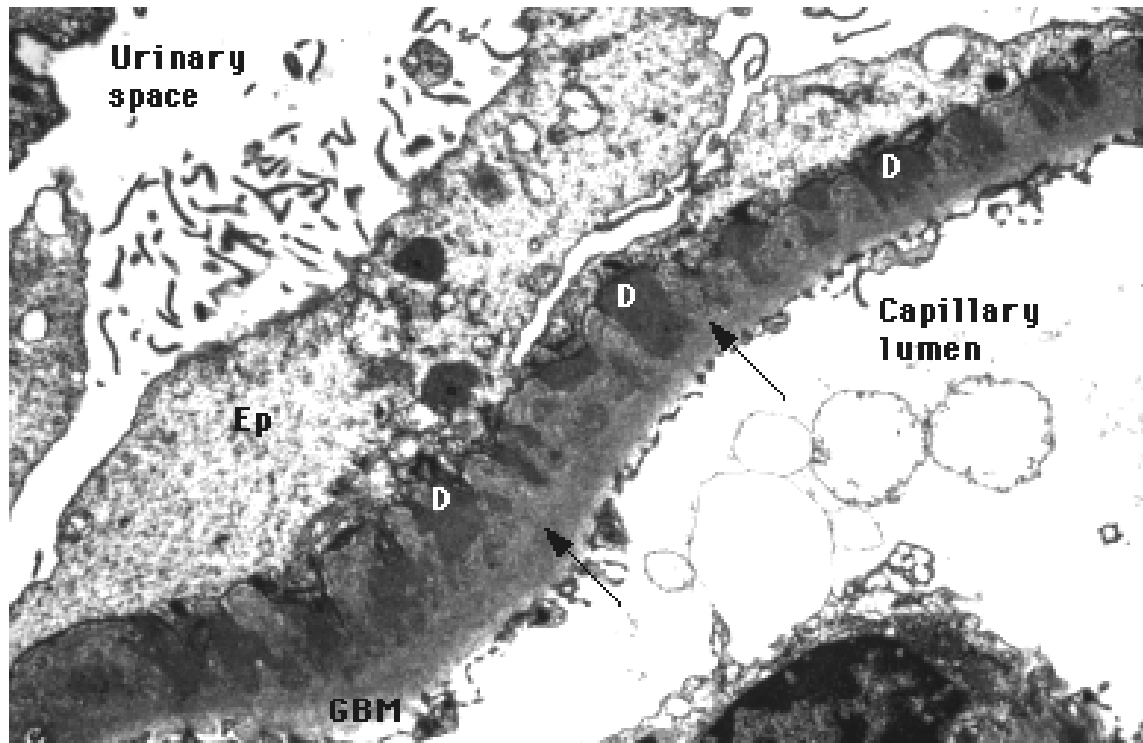
Membranous nephropathy Immunofluorescence microscopy in membranous nephropathy showing diffuse, granular IgG deposition along the capillary walls. Courtesy of Helmut Rennke, MD.

Spikes in membranous nephropathy



Silver stain in membranous nephropathy Light micrograph silver stain of membranous nephropathy shows a spike appearance (arrows). The spikes represent new basement membrane growing between the subepithelial immune deposits which are visible on electron microscopy, but not with this stain. Courtesy of Helmut Rennke, MD.

Electron microscopy in MN



Membranous nephropathy Electron micrographs shows stage II membranous nephropathy. Electron dense deposits (D) are present in the subepithelial space across the glomerular basement membrane (GBM) and under the epithelial cells (Ep). New basement membrane is growing between the deposits, leading to a spike appearance on silver stain. Courtesy of Helmut Rennke, MD.



Membranoproliferative glomerulonephritis

C3 nephritic factor-IgG antibody activates alternative pathway of complement through C3 activation

- **Typical clinical picture:**

- nonselective proteinuria and glomerular hematuria - nephritic syndrome

- nephrotic syndrome in 50% patients

- hypertension

- low level of C3 complement in blood, increased CIK

- increased aggregability of thrombocytes



Membranoproliferative glomerulonephritis

- **secondary to**

SLE, malignoma, sarcoidosis, Down syndrome, liver cirrhosis
lepra, malaria, filariasis, endocarditis, abdominal abscess, HCV, HBV

- **prognosis**

tendency toward renal insufficiency

more than 50% patients in renal failure after 10 yers

more than 90% patients in renal failure after 20 yers

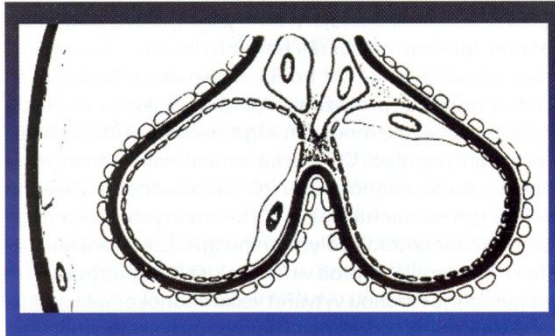
- **treatment**

prednisolone 60mg/sqm/day

CyA, CFA, azathioprine

antiaggregans, anticoagulants

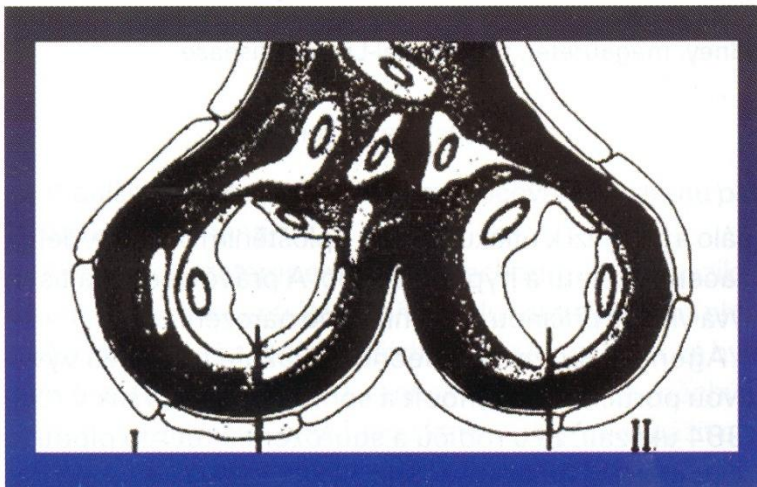
Membranoproliferative glomerulonephritis



Type I **mesangial and subendothelial immunodeposition**

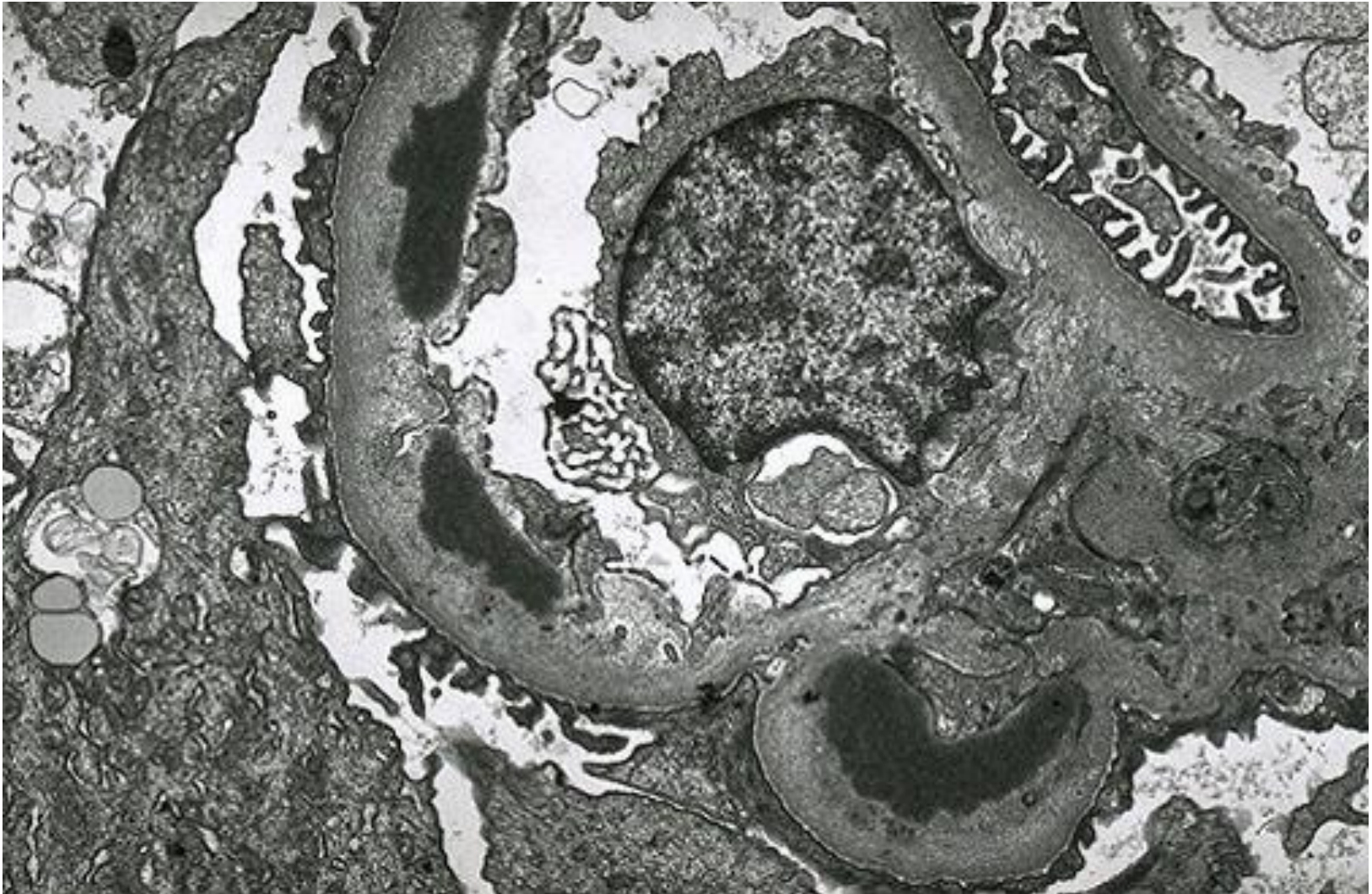
Type II deposition of **amorph electron-dense material into lamina densa** of basal membrane

Type III combination of type I and membranous GN



mesangial and endothelial proliferation
increased thickness of basal membranes of peripheral capillary loops by immunodeposition and
sometimes interposition of mesangium

Dense deposit disease





Mesangioproliferative GN

- IgA Nephropathy (Morbus Berger)

most frequent GN - almost 30%

activated Th lymphocytes stimulate B-lymphocytes to increased production of abnormal IgA1-pathologically glycosylated IgA

• **typical clinical picture**

intermittent macrohematuria following infection

persistent or intermittent asymptomatic microhematuria

isolated proteinuria

nephrotic syndrome

hypertension

renal insufficiency

• **secondary to**

chronic liver disease, psoriasis vulg., malignancies, Crohn dis., idiopathic proctocolitis, Bechterev dis., mycosis fung., dermatitis herpetiformis, HIV



Mesangioproliferative GN

- IgA Nephropathy (Morbus Berger)

very variable course - chronic renal failure in 50% in 20 years

- **bad prognosis signs**

male sex, higher age, hypertension

renal insufficiency at beginning of treatment, proteinuria more than 2g/24h interstitial fibrosis, vascular sclerosis, crescents

- **treatment**

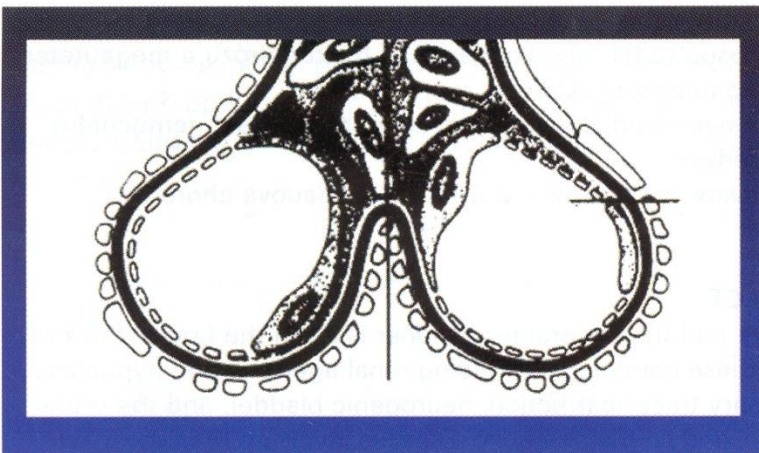
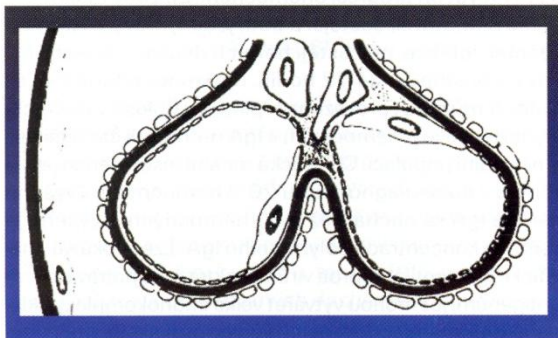
conservative

fish oil, olive oil

steroids, CFA, CyA

Mesangioproliferative GN

- IgA Nephropathy (Morbus Berger)



- **5 stages:**

- I** enlargement of mesangial **matrix**

- II** mesangial **cellular** proliferation,
rarely partial crescents

- III Focal segmental** glomerulonephritis

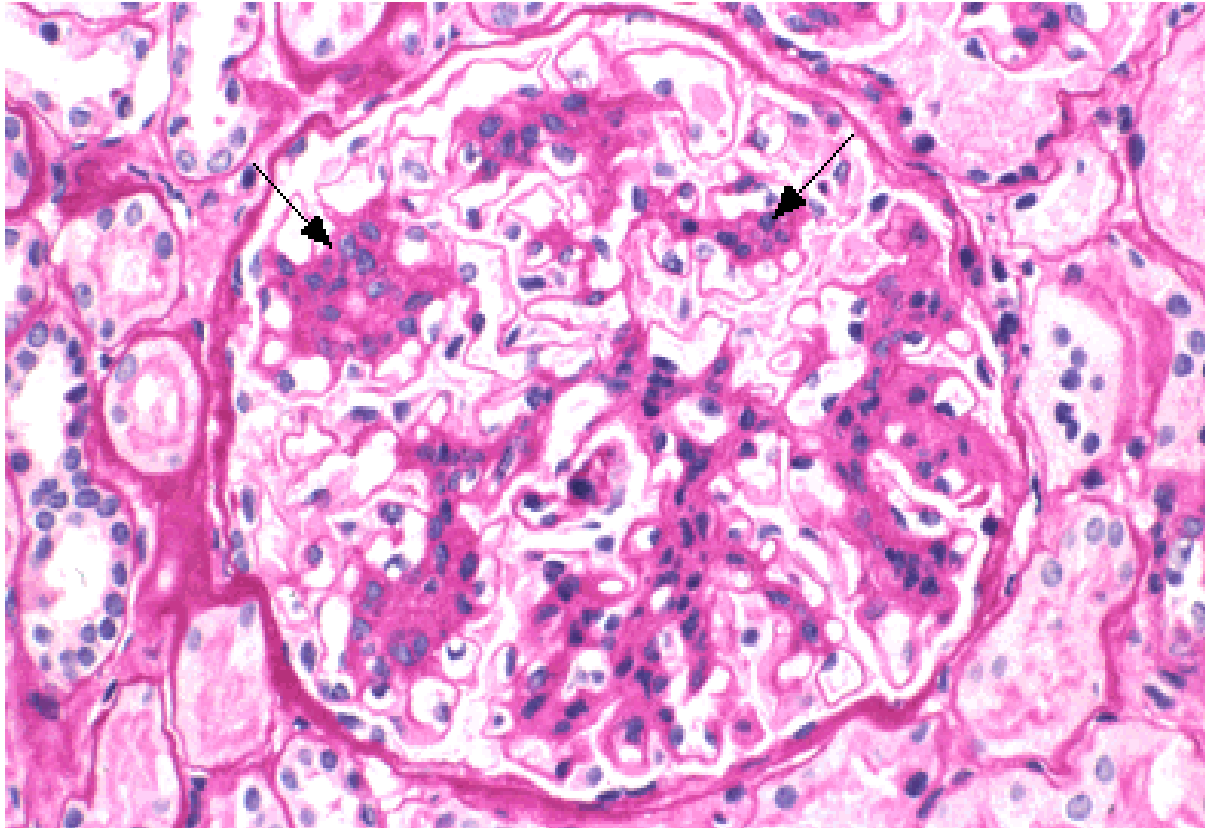
- IV diffuse** mesangioproliferative GN

- V** diffuse **sclerosing** GN

proliferation of mesangial cells, enlargement of mesangial matrix volume

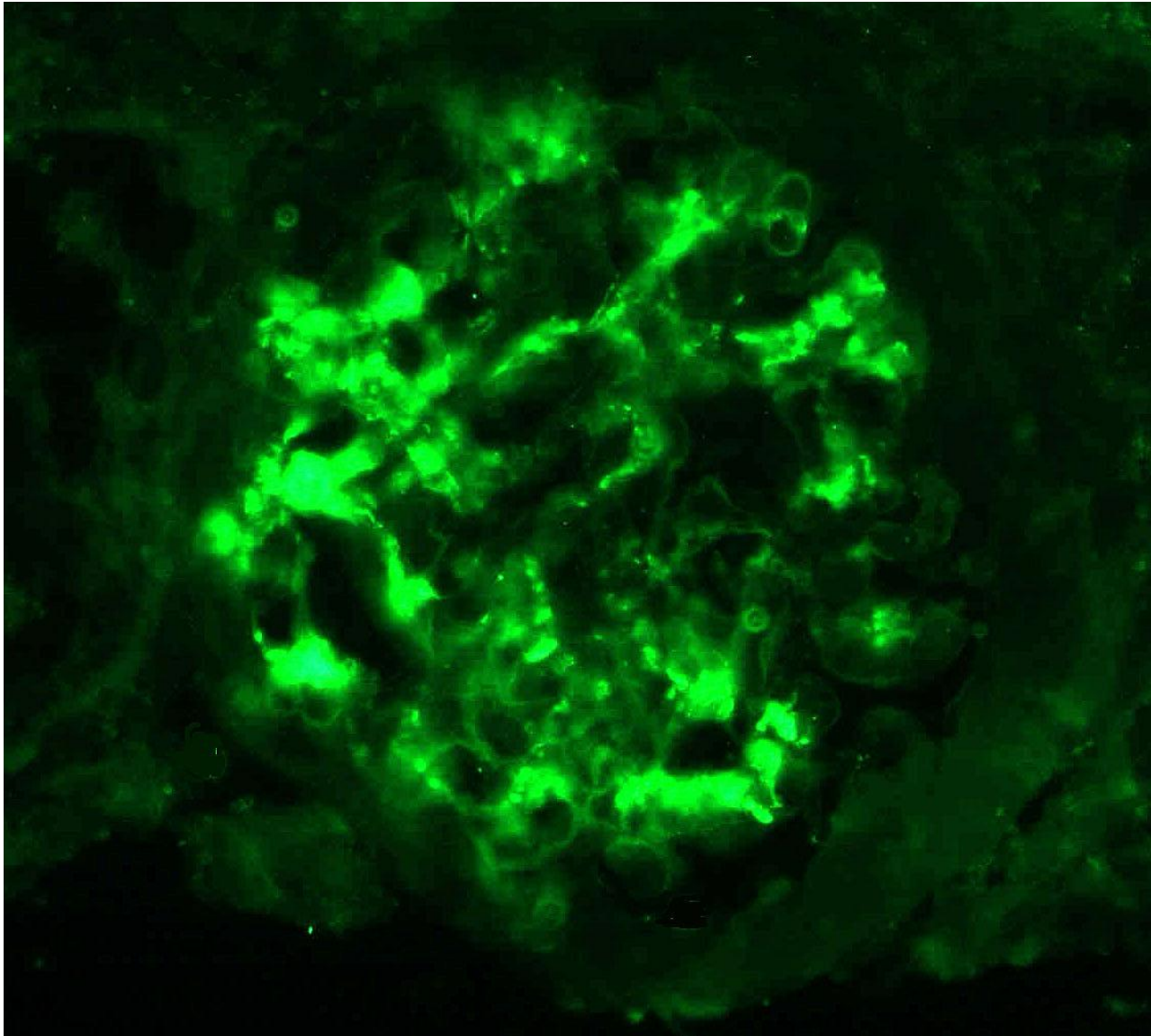
immunodeposition - predominantly IgA (C3, IgG, IgM) - in mesangium and in subendothelial space

Mesangial proliferative GN



Mesangial proliferative glomerulonephritis Light micrograph of a mesangial glomerulonephritis showing segmental areas of increased mesangial matrix and cellularity (arrows). This finding alone can be seen in many diseases, including IgA nephropathy and lupus nephritis. Courtesy of Helmut Rennke, MD.

Immunofluorescence in IgA nephropathy (400x)





Secondary glomerulopathy - Lupoid Nephritis

- **prognostic factor of SLE**
- **discrepancy between clinical and histological picture**
- **kidney biopsy is prognostic tool and important point for decision about aggressivity of treatment**



Secondary glomerulopathy - Lupoid Nephritis

- **ARA diagnostic criteria**

- dsDNA antibodies

- decreased level of complement

- increased CIK level

- **clinical picture**

- small proteinuria

- microhematuria

- nephrotic syndrome 40%

- acute renal failure

- renal tubular acidosis



Secondary glomerulopathy - Lupoid Nephritis

- **histological finding:**

- irregular hypercellularity of mesangium, proliferation of endothelial, mesangial and epithelial cells
- neutrophil, monocyte exudation
- necrosis, crescents
- hematoxylin corpuscles- pathognomonic but rare
- immunoglobulins (IgG, IgA, IgM) and complement (C3, C1q, C4) deposits - wire loop picture



Secondary glomerulopathy - Lupoid Nephritis

- **Classification of lupoid nephritis (WHO):**

- I normal finding** - ususally minimal IF deposits
- II mesangial GN** - asymptomatic proteinuria and microhematuria
- III focal proliferative GN** - proteinuria and microhematuria, 30% nephrotic syndrome
- IV diffuse proliferative GN** - usually nephrotic syndrome, hypertension, renal insufficiency
- V membranous GN** - nephrotic syndrome in 66%, microhematuria often, seldom renal insufficiency or hypertension, may precede clinical manifestation of SLE
- VI sclerosing GN** - terminal stage



Secondary glomerulopathy - Lupoid Nephritis

- **activity index**

- cellular proliferation
- fibrinoid necrosis
- epithelial crescents
- hyaline thrombosis, wire loops
- leucocytes, monocytes infiltration

- **chronicity index:**

- glomerular sclerosis
- connective tissue crescents
- interstitial fibrosis, atrophy



Secondary glomerulopathy - Lupoid Nephritis

- **Treatment:**

- st I, II - no specific therapy

- st III - depends on severity of clinical signs - if severe than as st IV

- st IV - steroids, CFA - pulse therapy, azathioprine, CyA

- st V - steroids and chlorambucil or CyA

- Plasmapheresis - no improvement in survival, symptomatic therapy only

- Kidney transplantation



Renal Amyloidosis

- Deposition of amyloid - polypeptide of fibrillar structure into kidneys and other organs and muscles
- **AA - amyloidosis**
protein of nonimmunoglobuline nature, synthesized in liver
complication of chronic inflammatory diseases
rheumatoid arthritis, recurrent pulmonary infection, Crohn disease, Bechterev disease, TBC, osteomyelitis, psoriasis
- **AL - amyloidosis** (amyloid light chain)
deposition of lambda light chain immunoglobuline produced by:
multiple myeloma, benign monoclonal gammopathy, macroglobulinemia, chronic lymphadenosis, orther lymphomas

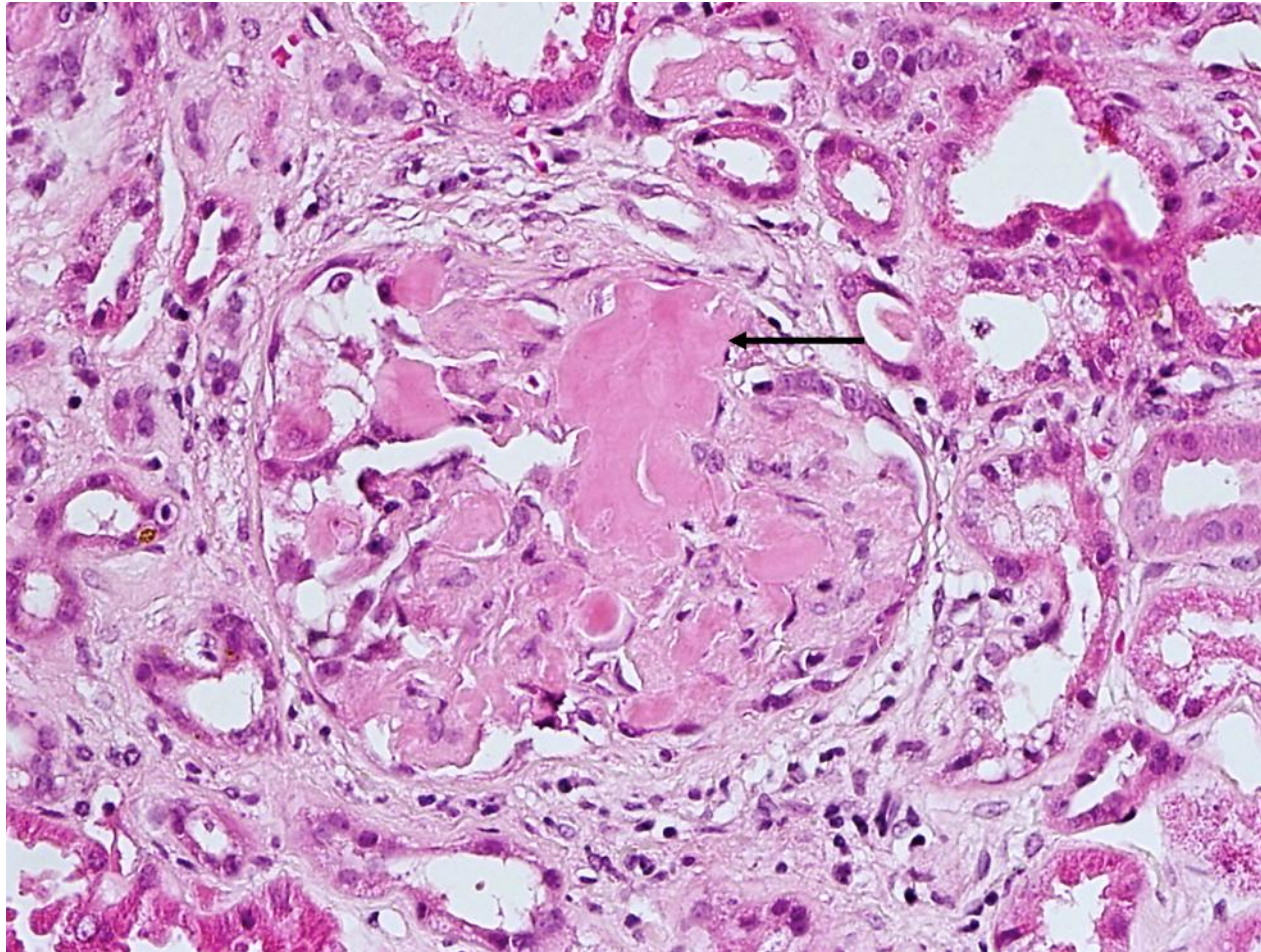
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FN Olomouc
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GAIN 60
COMP 80

A +	DIST	9.63 cm
B x	DIST	4.20 cm
C +	DIST	1.21 cm

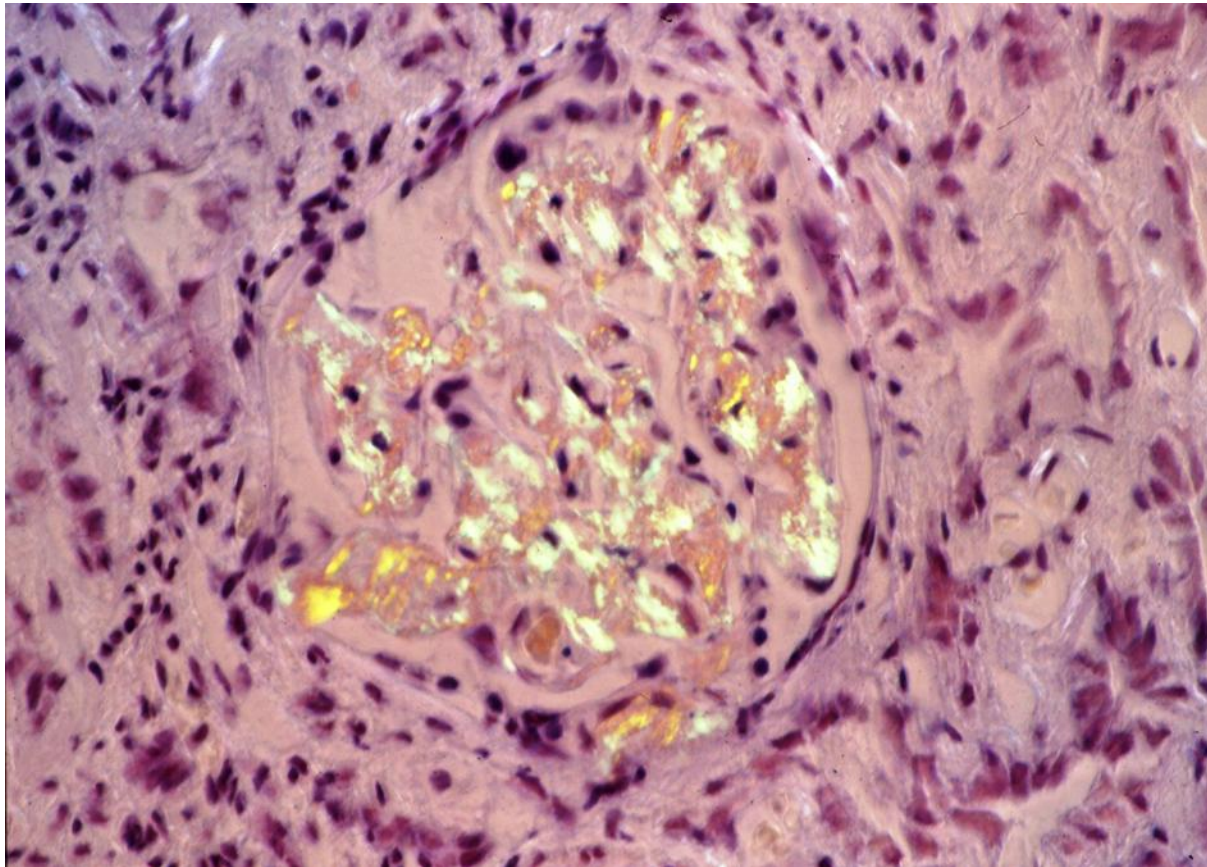
17CM
25HZ



Amorphous eosinophilic glomerular amyloid



Congo red staining of amyloid, dichroism viewed under polarized light





Renal Amyloidosis

- **Very various clinical picture:**

- primary disease
- oedemas
- arthralgia
- haemorrhagic diatesis
- hypotension /cardiac involvement/
- proteinuria, nephrotic syndrome in 35% of patients

- **Treatment:**

primary disease,

steroids,

bone marrow transplantation

mean survival time 12 month