Acute Glomerulonephritis

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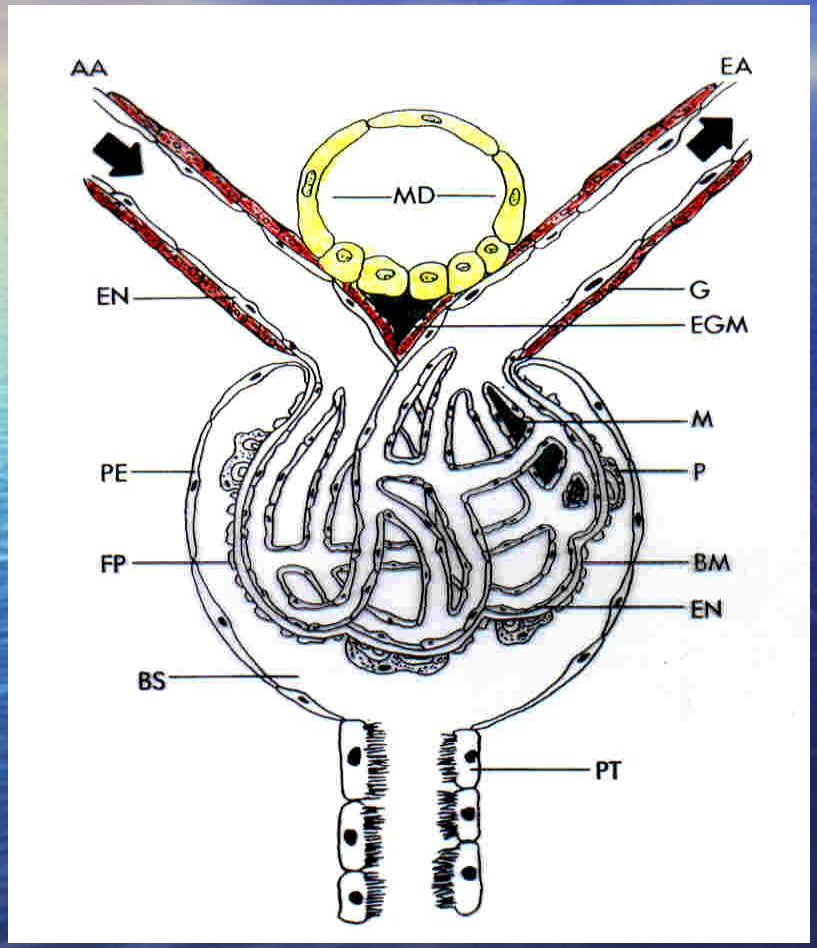
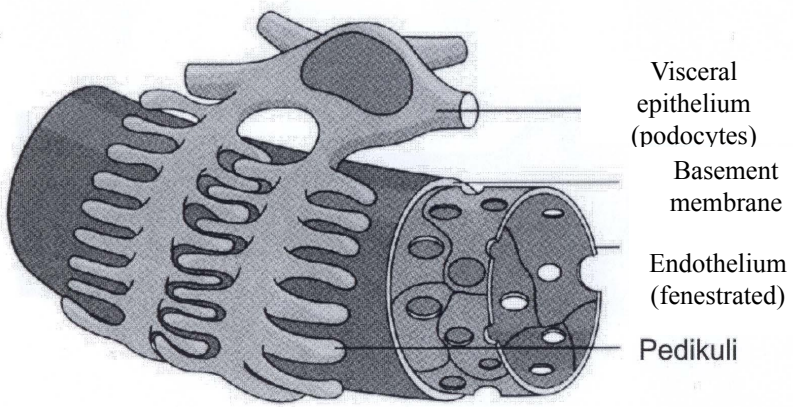
Anatomy of the glomerulus and the juxtaglomerular apparatus



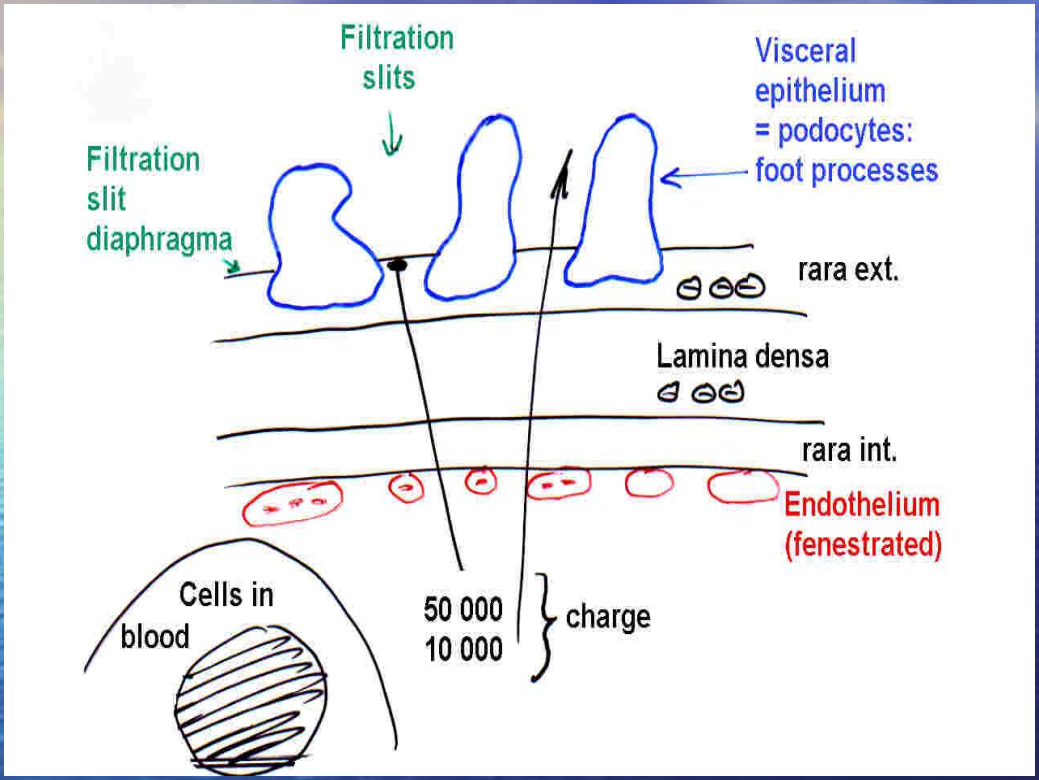
Glomerular basement membrane (GBM)

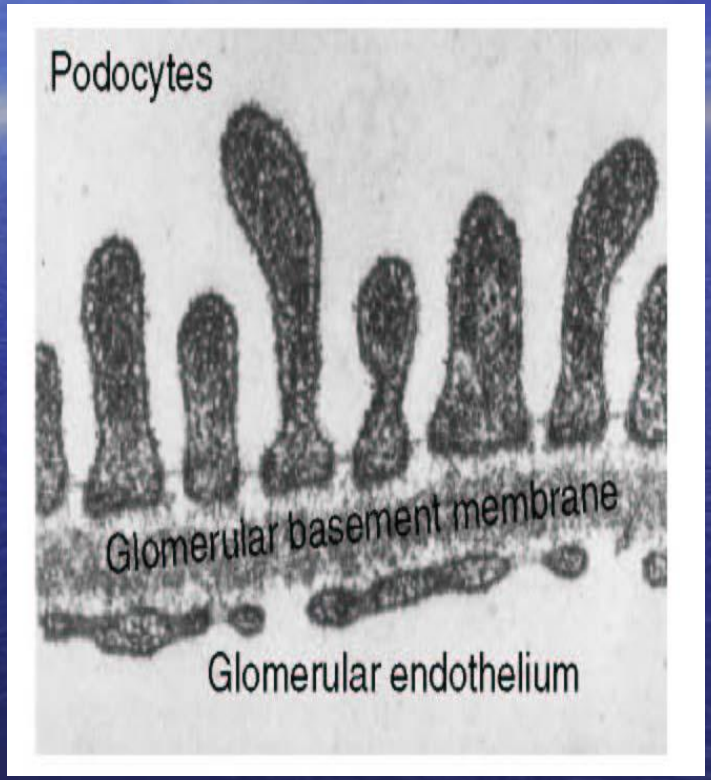


All three layers (endothelium, glomerular basement membrane, slit pores between podocytes)
are negatively charged

Mesangium is contractable

Fig. Glomerular basement membrane (GBM)





Glomerular diseases (glomerulopathy)

⇒ heterogeneous group of diseases

Dividing:

a) **Primary glomerulopathy**

b) **Secondary glomerulopathy**

c) – *can be manifestation of systemic diseases, vascular, metabolic or genetic disorders affecting also other organs*

d) The mechanisms for glomerular injury are complex

e) ⇓

f) more often are iniciated by an **immune response**

Immunopathologic mechanisms

Damage of kidney depend on:

- **mechanism and intensity of immune reaction**
- **collocation of antigens (Ag)**

Mechanisms:

- **Damage by immunocomplexes**
- **Damage by cytotoxic antibodies (Ab)**
- **Cell-mediated immune injury = delayed-type hypersensitivity**
- **Damage by complement and proinflammatory mediators**

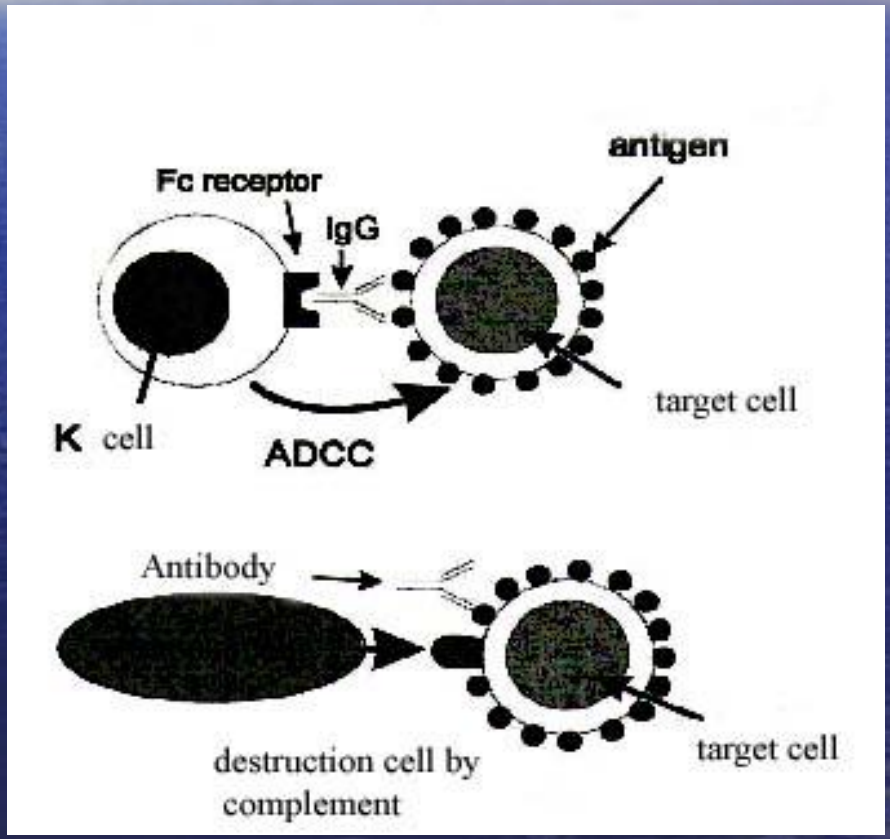
Cytotoxic (Type II) reaction – antibody mediated cytotoxicity (ADCC)

These occur when antibodies interact with antigens found on cell surface

2 mechanisms of cytotoxicity:

1. Ab mediate cell destruction via mechanism ADCC (cell cytotoxicity dependent on Ab)

2. Ab directed against cell-surface antigens mediate cell destruction via complement activation



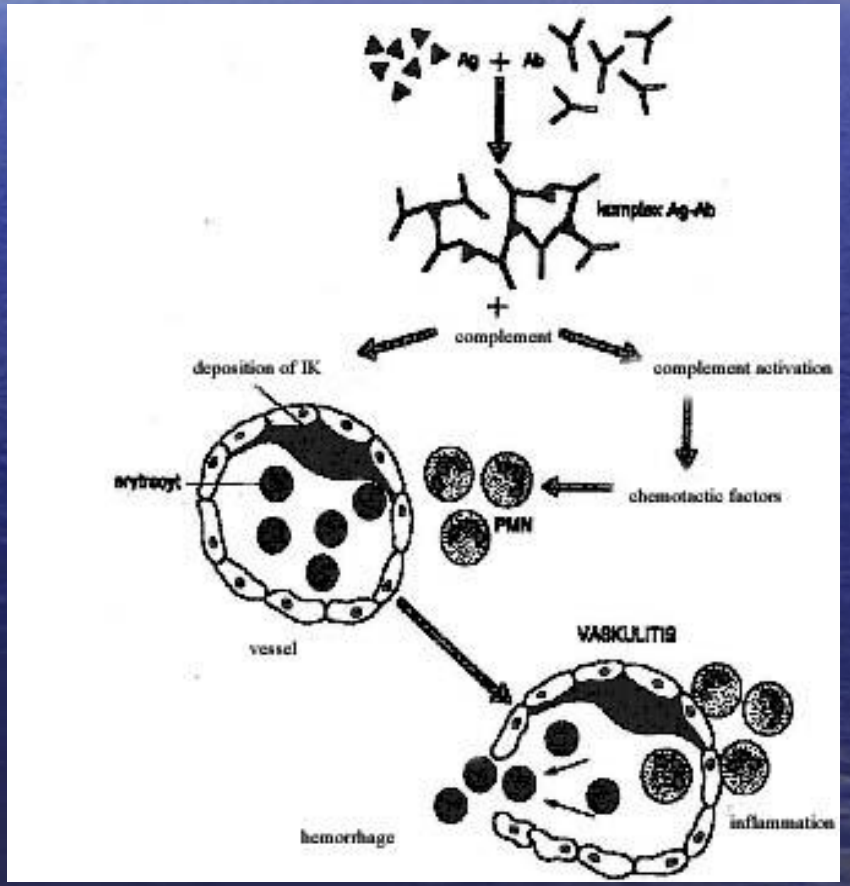
Type III reaction – immune complex-mediated hypersensitivity

- The reaction of antibody with antigen generates immune complexes. In some cases, large amounts of immune complexes can lead to tissue damage

  They deposited in various tissues

  ⇓

  induce complement activation and ensuing inflammatory response

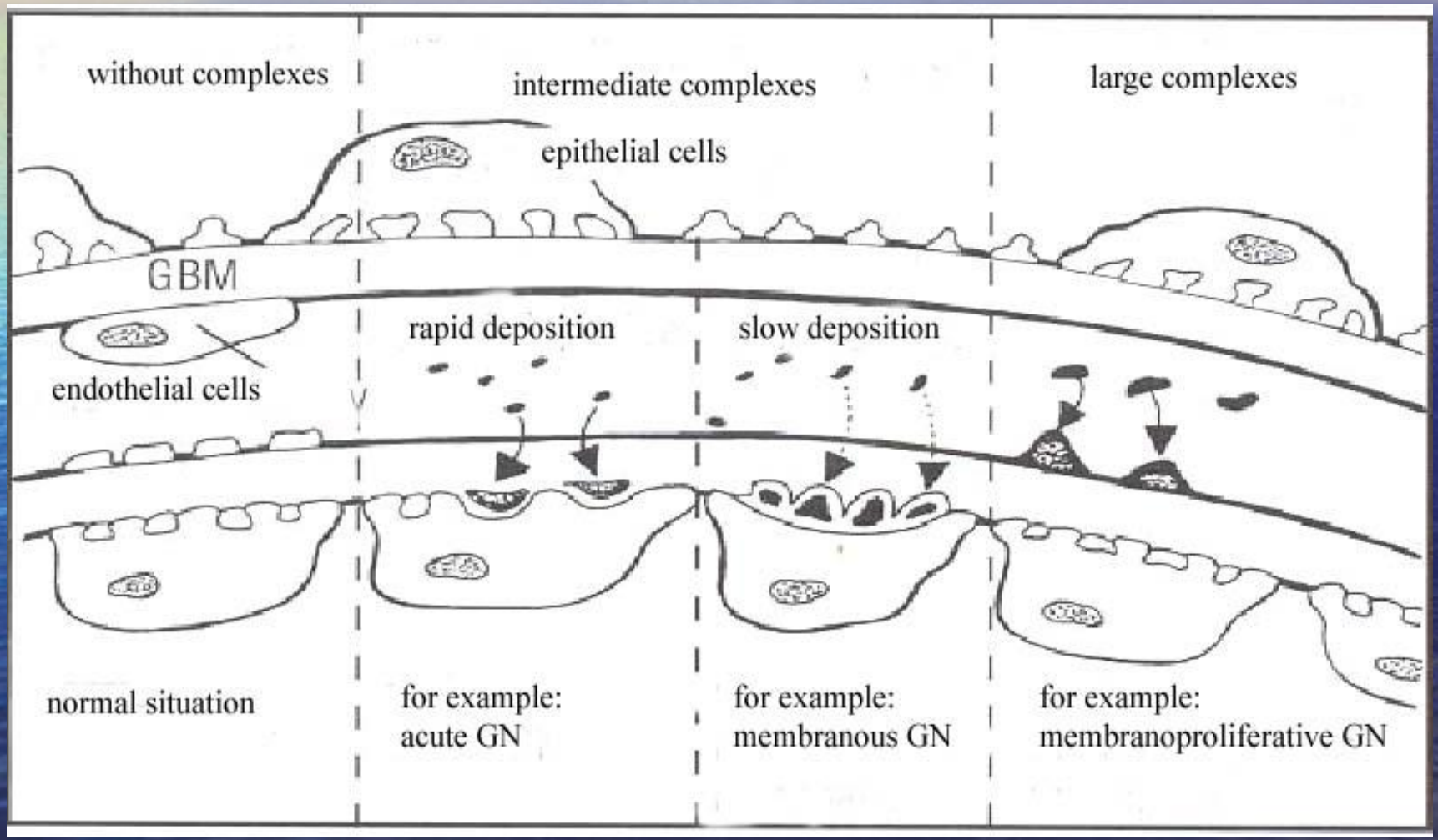


Antigens can be:

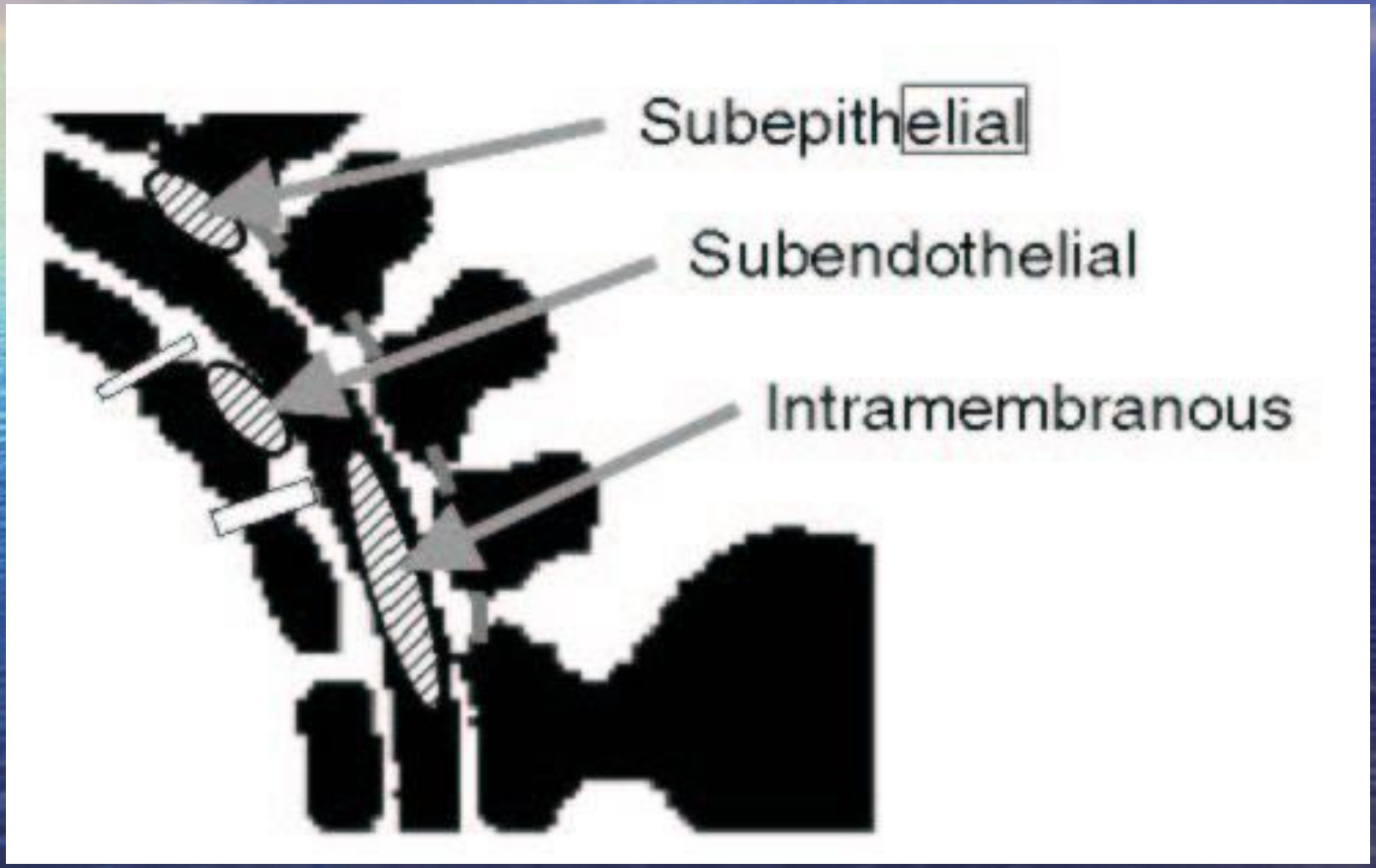
a) Endogenous – for example DNA in SLE

b) Exogenous – bacteria, viral, parasitical Ag

The magnitude of the reaction depends on the quantitity of immune complexes as well as distribution within the wall of glomerular capillary



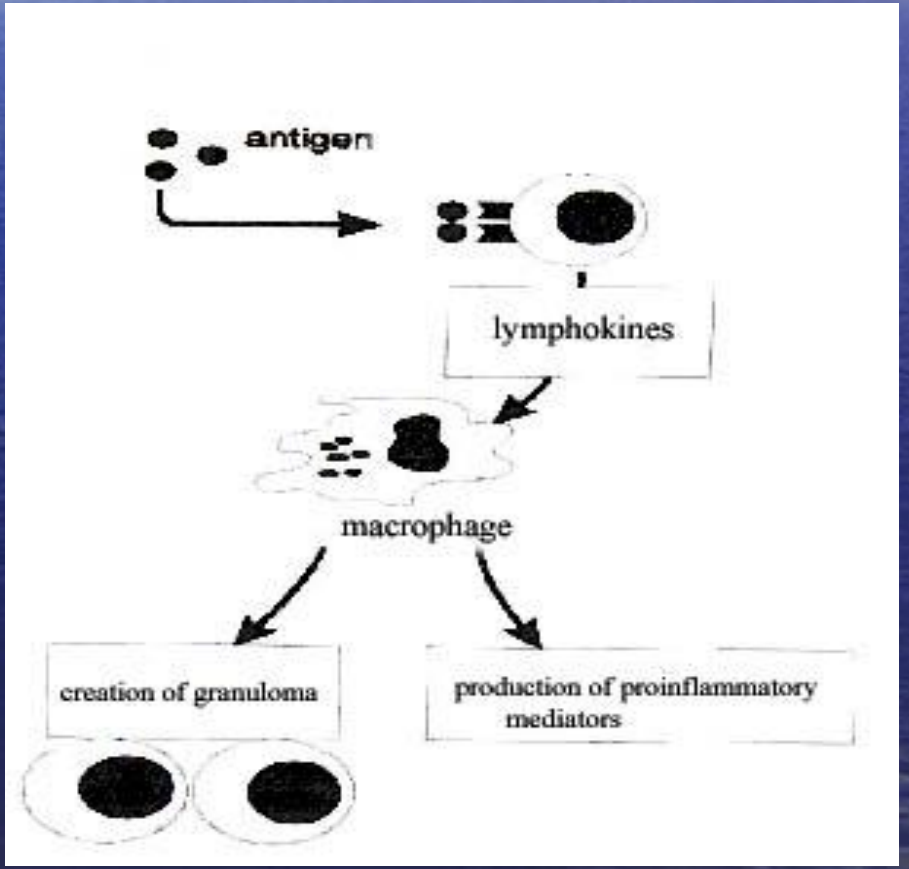
Location of immune deposits in the glomerular capillary wall



Delayed – type hypersensitivity (Type IV)

T lymphocytes may also recognize antigen

When they do, a mononuclear cell infiltrate may accumulate at the site of Ag concentration and lead to the elaboration of toxic products and tissue injury



Four major pathogenetic forms of glomerular injury

In non-proliferative glomerulopathy:

- Damage by antibodies
- Damage mediate by complement

In proliferative glomerulopathy:

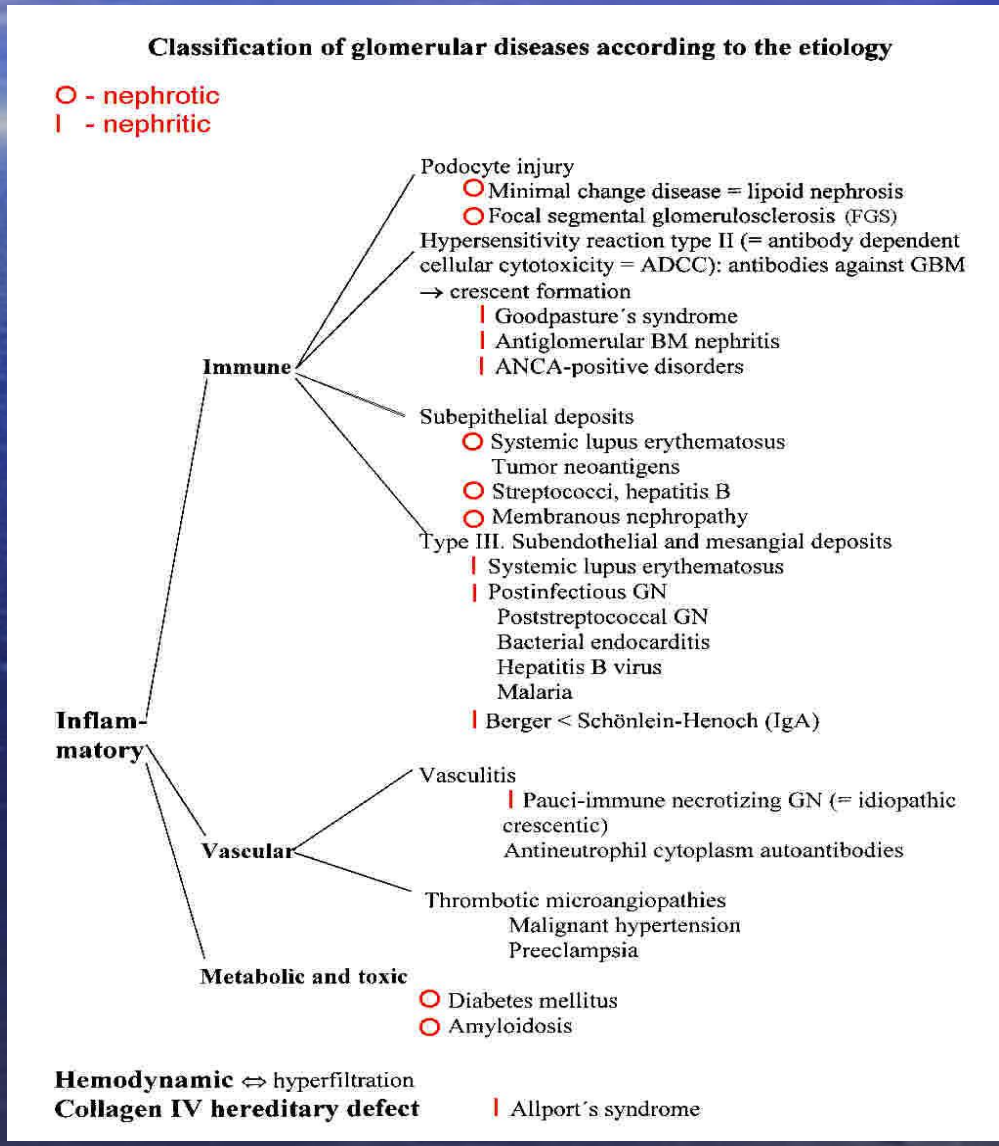
- Damage by circulating proinflammatory cells (especially neutrophils and macrophages)
- Damage by localy activating rezident cells (for example mesangial cells)

Classification of glomerulopathies

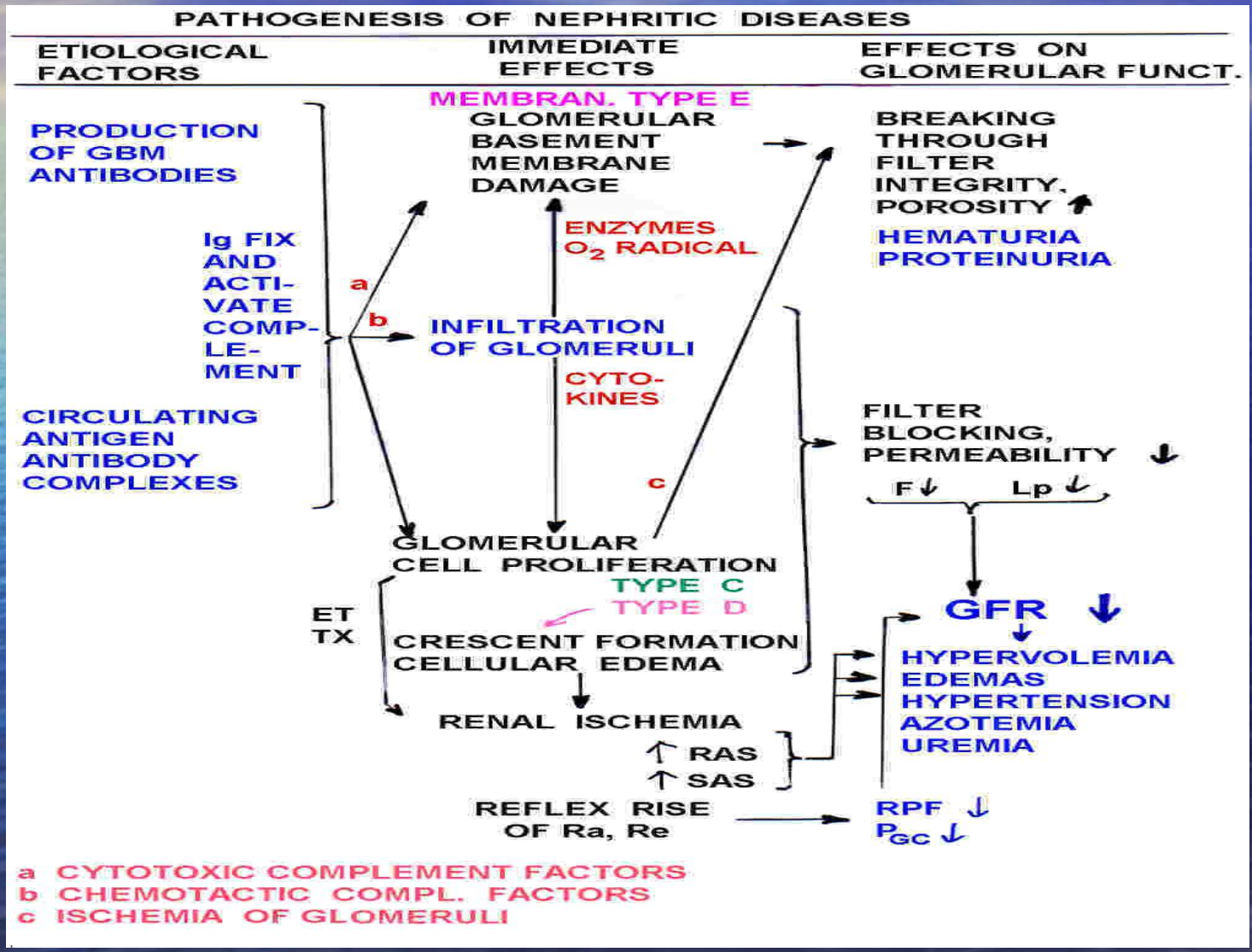
- **Clinical:** primary x secondary
- According **time period:** acute x subacute x chronic
- According **renal biopsy**: focal x segmental x diffuse
- According number of **cells**: non-proliferative x proliferative
- According **imunofluorescence**:

Pathogenic mechanisms of glomerular diseases

- NEPHRITIC
- NEPHROTIC
- Chronic glomerulonephritis

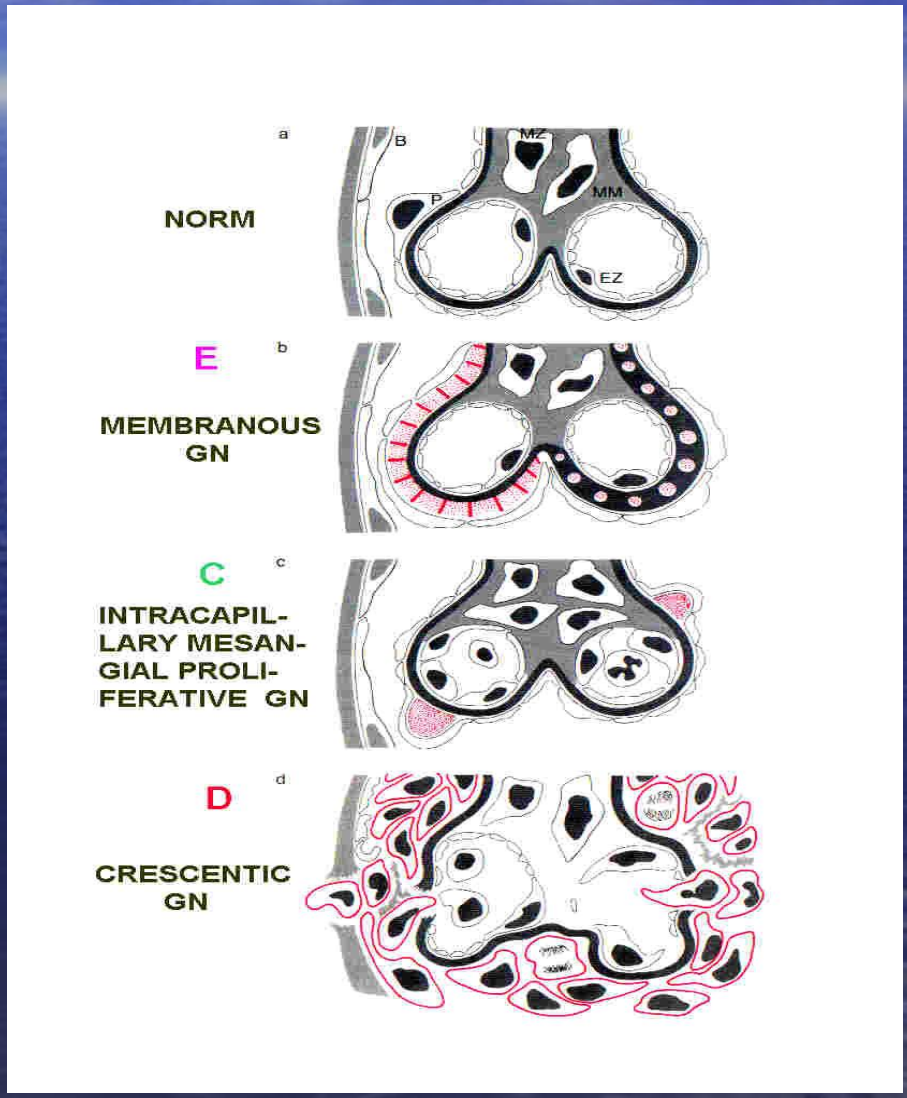


Pathogenesis of nephritic diseases



Histologic pattern

- May not correlate with the clinical presentation
- Various histological types of glomerulonephritis



B: "**Minimal changes" GN** = lipoid nephrosis: some mesangial proliferation, edematous podocytes, fusion ("loss") of their foot processes

C: **Intracapillary mesangial proliferative GN**: proliferation of endothelia and mesangium, peeling off of enthelial cells from the GBM, duplication of GBM, "humps" formed by immunocomplexes

D: **Crescentic GN**: proliferation of all components (aggressive white cells, endo- and epithelia, mesangium, epitheloid and giant cells), leakage of fibrin. Hypersensitivity reaction type II or IV

E: **Membranous GN**: Precipitation of immunoglobulins on the outer surface of the GBM ("spikes" → complete incorporation of Ig into the membrane)

F: **Proliferative sclerotizing GN**: advanced mesangial proliferation → narrowing and destruction of capillaries

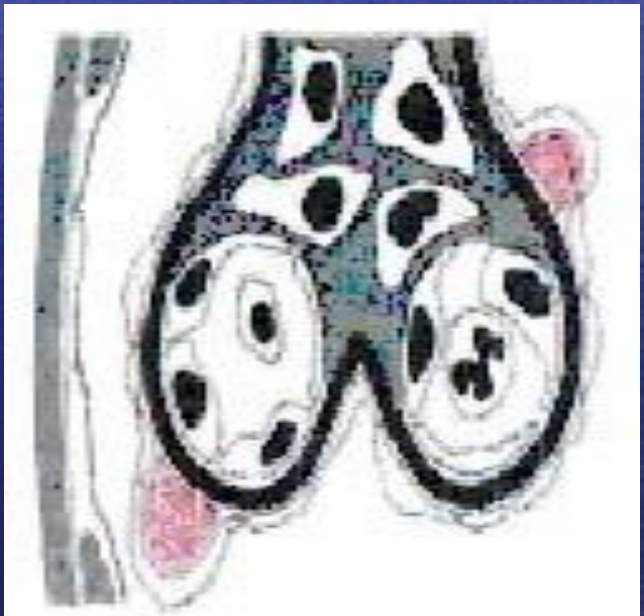
Acute glomerulonephritis (poststreptococcal GN)

- Is commonly caused by infection by certain strains of group A beta-hemolytic Streptococci (pharyngitis, pyoderma)

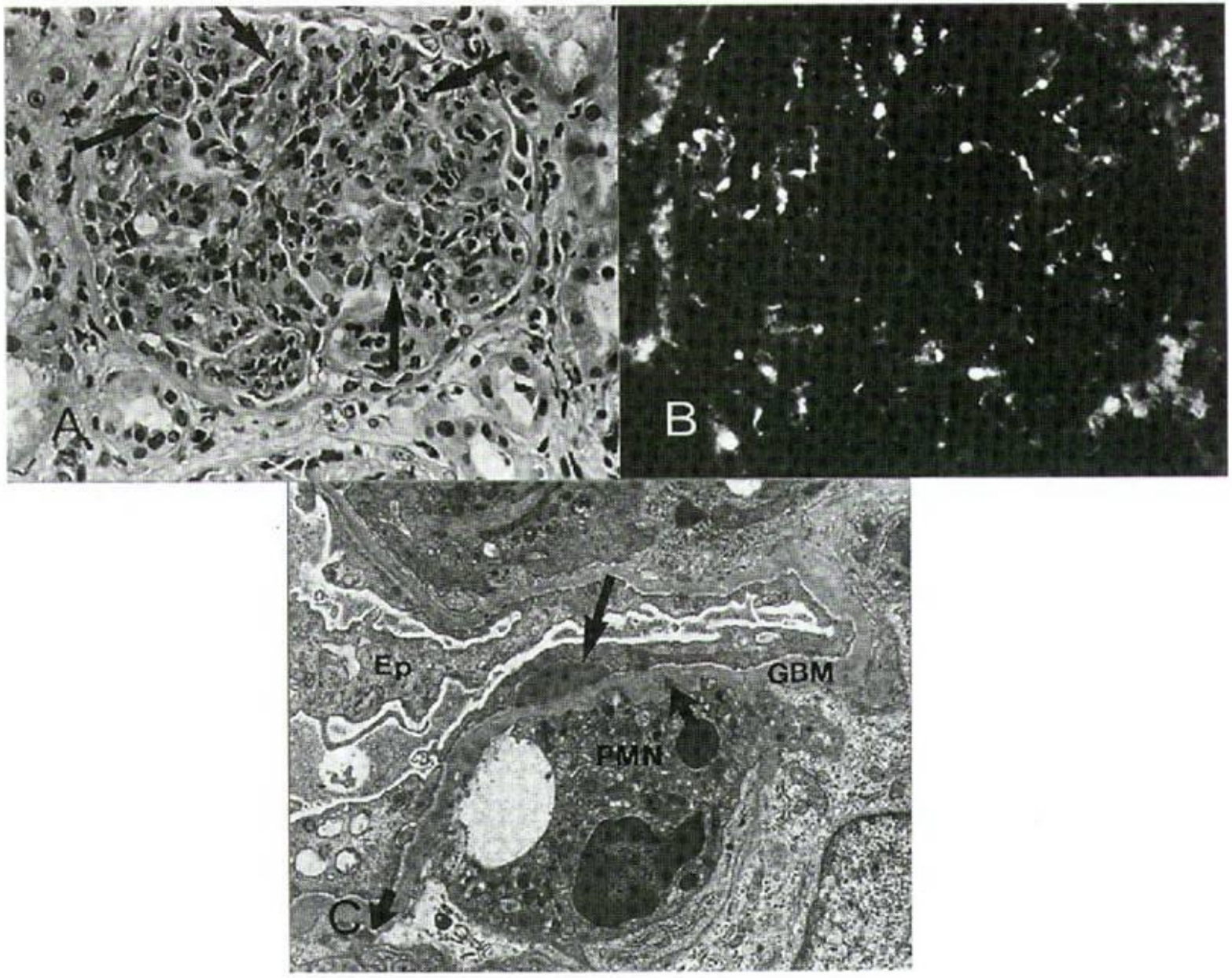
⇓

Ab against streptococci react with vimentin ⇒ imunokomplexes

- nephritis develop after a latent period of about 2-3 weeks
- Clinical syndrome: nephritic syndrom
- Histologic pattern: intracapillary proliferation of mesangial and endothelial cells with subepithelial („humps“) and subendothelial deposits (C3, or IgG)



Acute diffuse proliferative GN


A
B
Ep
GBM
PMN
C

Postinfectional non-streptococcus glomerulonephritis

- Acute glomerulonephritis can develope also in the course of other infections:
  - stafylococci
  - pneumococci
  - Klebsiella pneumonie
  - herpes virus
  - EBV
  - virus hepatitis B

- GN in infection endocarditis

- GN in visceral abscessus (especially lung)

Histologic pattern and clinical syndrome – similar one as in poststreptococcal GN

Focal proliferative glomerulonephritis

- different etiology:

- IgA nefropathy
- Nephritis in systemic lupus erythematodes (SLE)
- Nephritis in bacterial endocarditis
- Henoch-Schölein purpura

Rapidly progressive glomerulonephritis (RPGN)

- Heterogeneous group of diseases, it is characterised by intense proliferation of glomerular/capsular epithelial cells in the form of a crescent.

- crescemt = accumulation and proliferation of extracapillary cells.

  - The glomerular capillaries collapse and are bloodless, and fibrin can be identified within the capsule

    ⇓

    it can stimulate proliferation of parietal epithelial cells

    ⇓

    deposits of fibrin compress the glomerula capillaries tuft

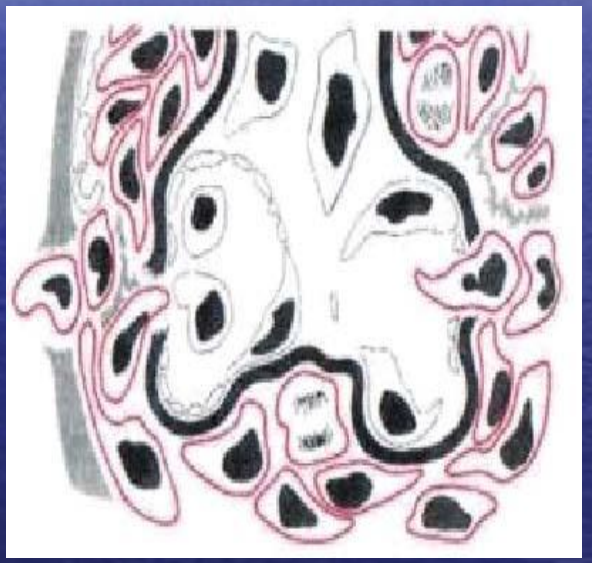
    (↓ GFR and destruction of glomerulus)

Three forms of RPGN

- **GN with creation of antiobdies (IgG, IgA) agains GBM (anti-GBM)**
  - **linear deposits of Ig**
  - **(+ alveolocapillary BM) ➙ Goodpastures´ syndrome**

- **GN with granular deposits of Ig and complemen**
  - **formation of crescent is complication less serious intracapillary proliferative GN (IgA nefropathy, SLE, acute GN e.g.)**

- **GN with ANCA antibodies**
  - **ANCA ab (Ab agains cytoplasma of neutrophiles)**
  - **2 forms – systemic disorders (Wegener granulomatosis)**
  - **only renal disease**



Crescent GN

Goodpastures´ syndrome

- It is charecterised antibodies against basal membrane of glomeruli (alveolocapillary membrane)

- **Etiology:** combination of exogenous factors (smoking, infection, toxines) with genetic predisposition (HLA B7, DR2)
- **Pathogenesis:** GBM is composed by collagen IV with proteins (laminine, entaktine, tenascine) and proteoglycans

Goodpastures antigen
(localised in C-terminal non-collagen globular domain (NC1) of the molecule α3 chain of collagen IV
⇓
formation of Ab (IgG1 – can activate complement)
⇓
damage of BM

- **Clinical manifestation:** typically presents with crescentic glomerulonephritis + pulmonary hemorrhage

Slowly progressive glomerulonephritis

- Group of GN called membrane-proliferative GN
- 2 forms:

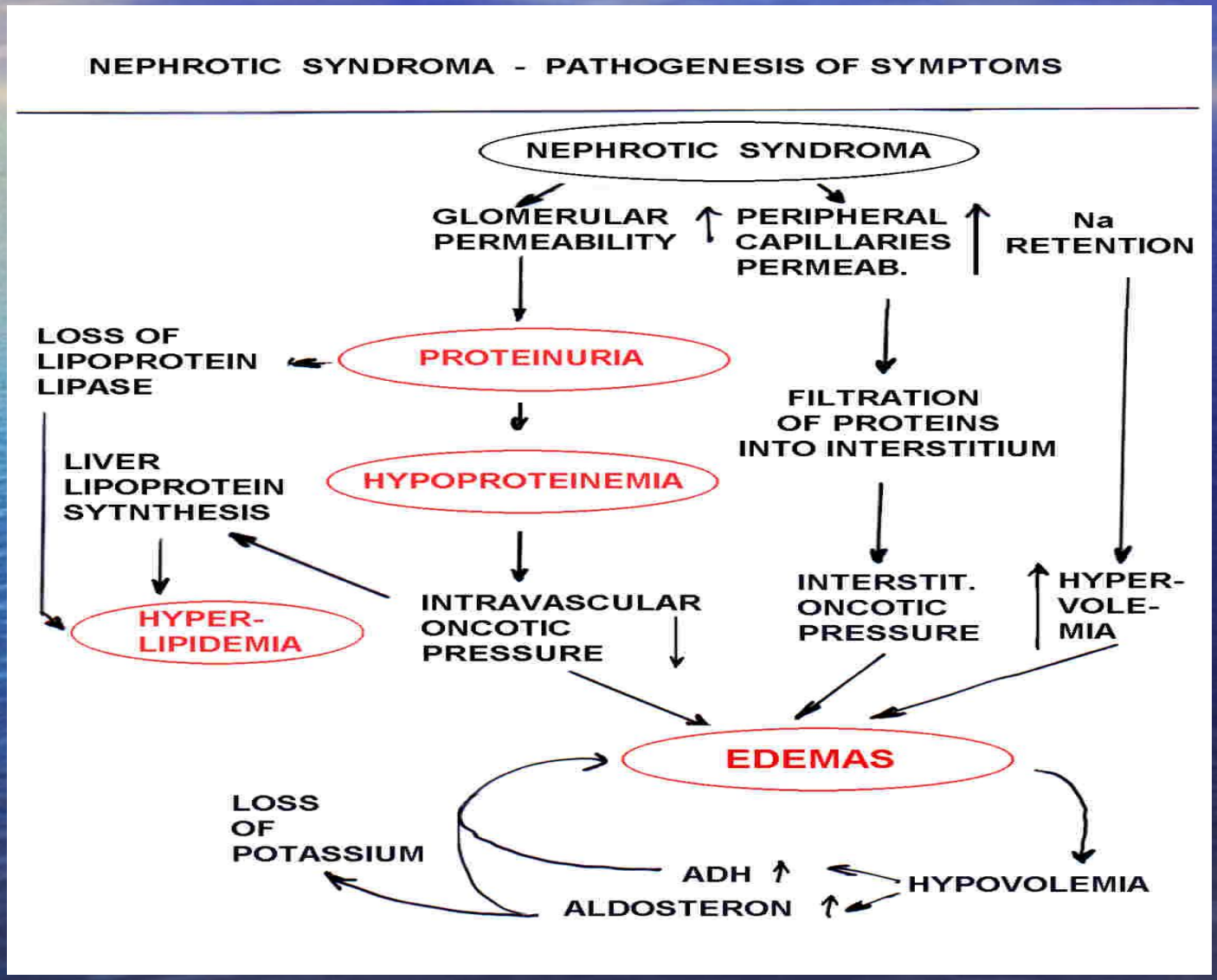
in 1 form : - ↓ levels of complements in plasma
- subendothelial and mesangial deposits are present

findings: proteinuria or picture of nephrotic syndrom

in 2 form: - activation of complement is due to nephritic factor C3
- intramembranous deposits are present

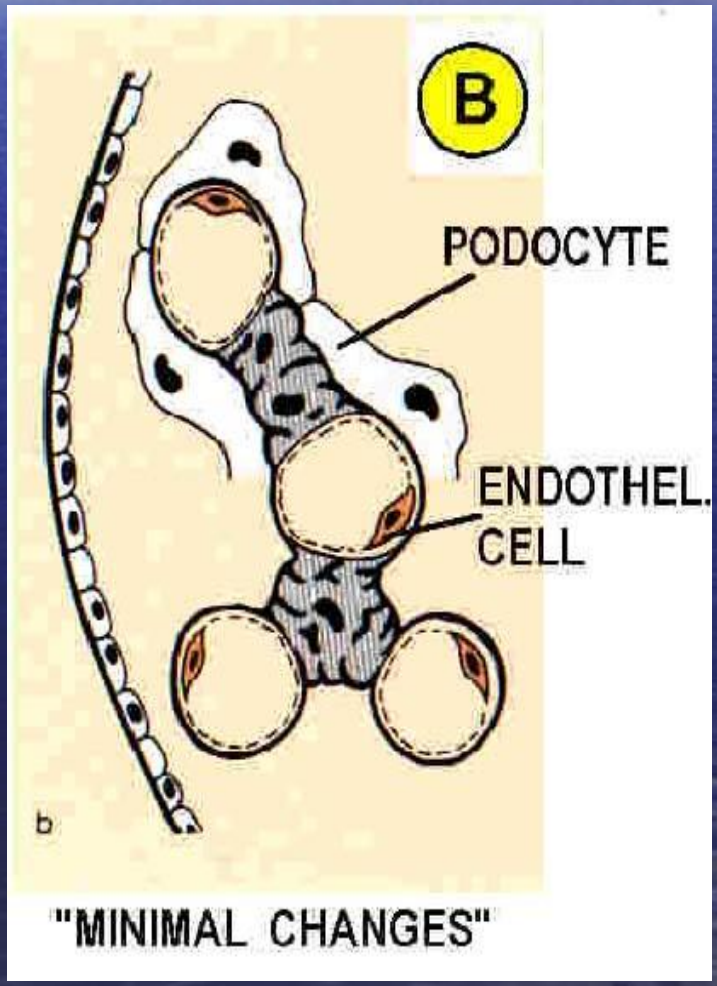
findings: proteinuria or picture of nephritic syndrom (similary as in RPGN)

Pathogenesis of nephrotic diseases



„Minimal changes“ GN (lipoid nephrosis)

- Especially in children
- Pathogenesis ambiguous – connection with viral infections, vaccination, atopy, application some drugs (antiphlogistics etc.), Association with several HLA antigens (DRw7, B8, B12 …)
- Finding: loss of negative charge (↑ permeability for some proteins – albumins)
- Histologic pattern: fusion („loss“) of foot processes of podocytes (pedicules), edematous podocytes, some mesangial proliferation
- Therapy: corticoids



Normal podocytes

Minimal change

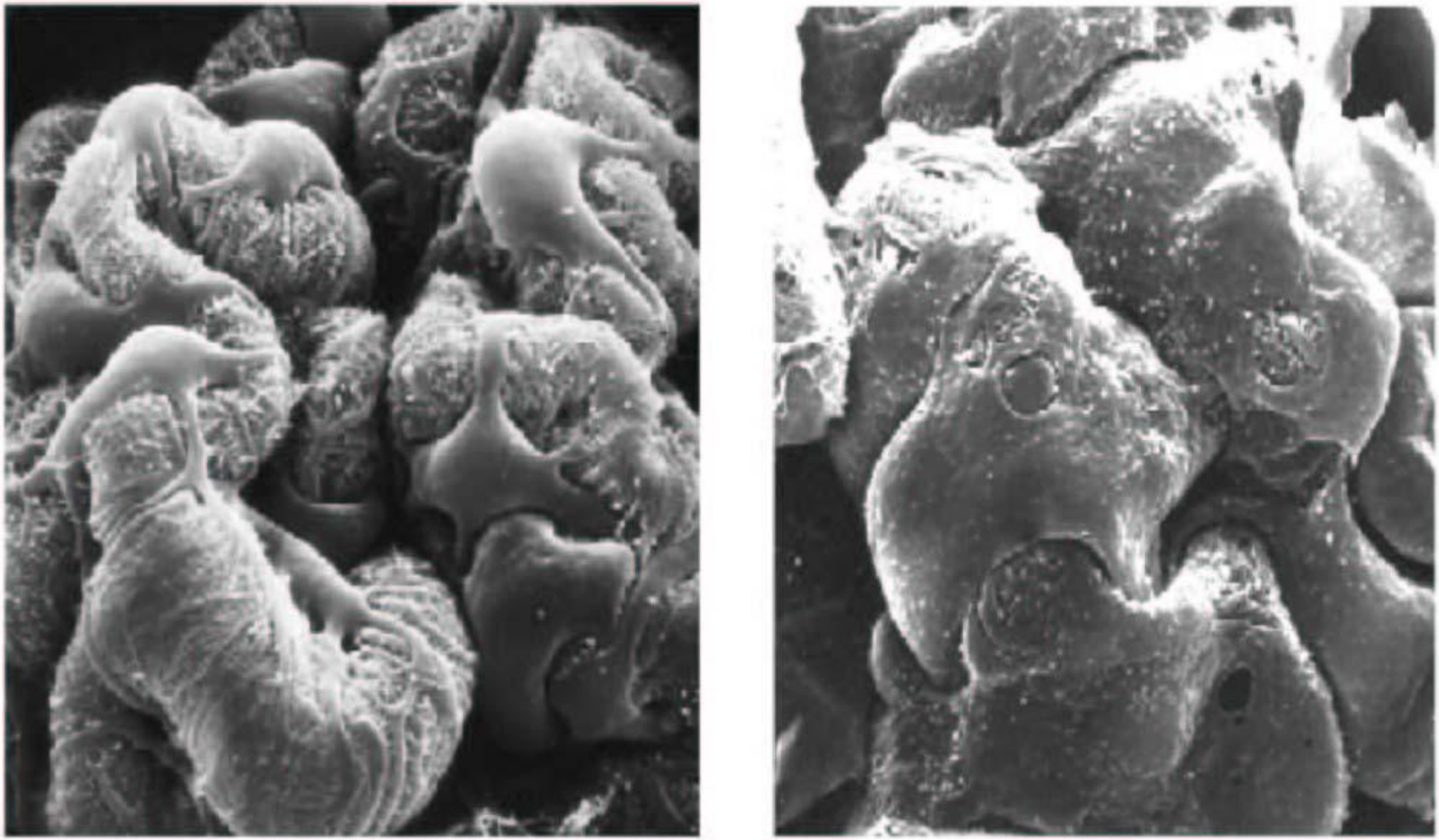


Fig. 2. Scanning electron microscopy of luminal aspect of human glomerulus: normal (left panel) and minimal change (right panel) nephropathy.

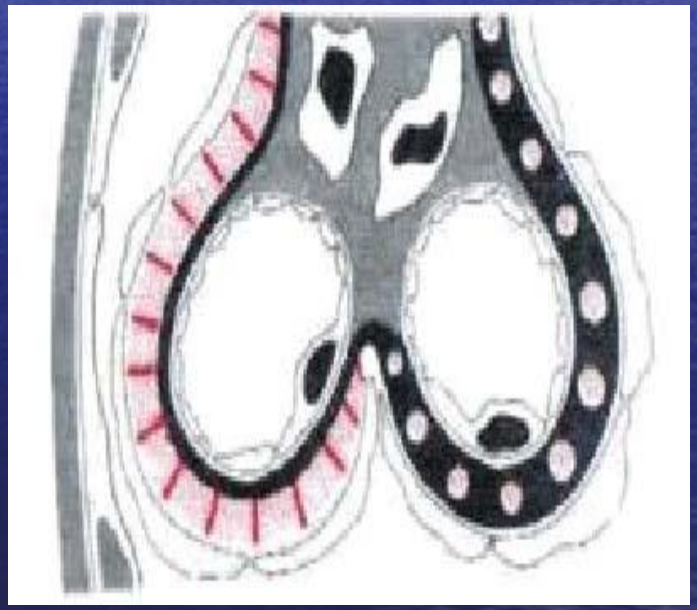
Focal (segmental) glomerulosclerosis

- More serious degree

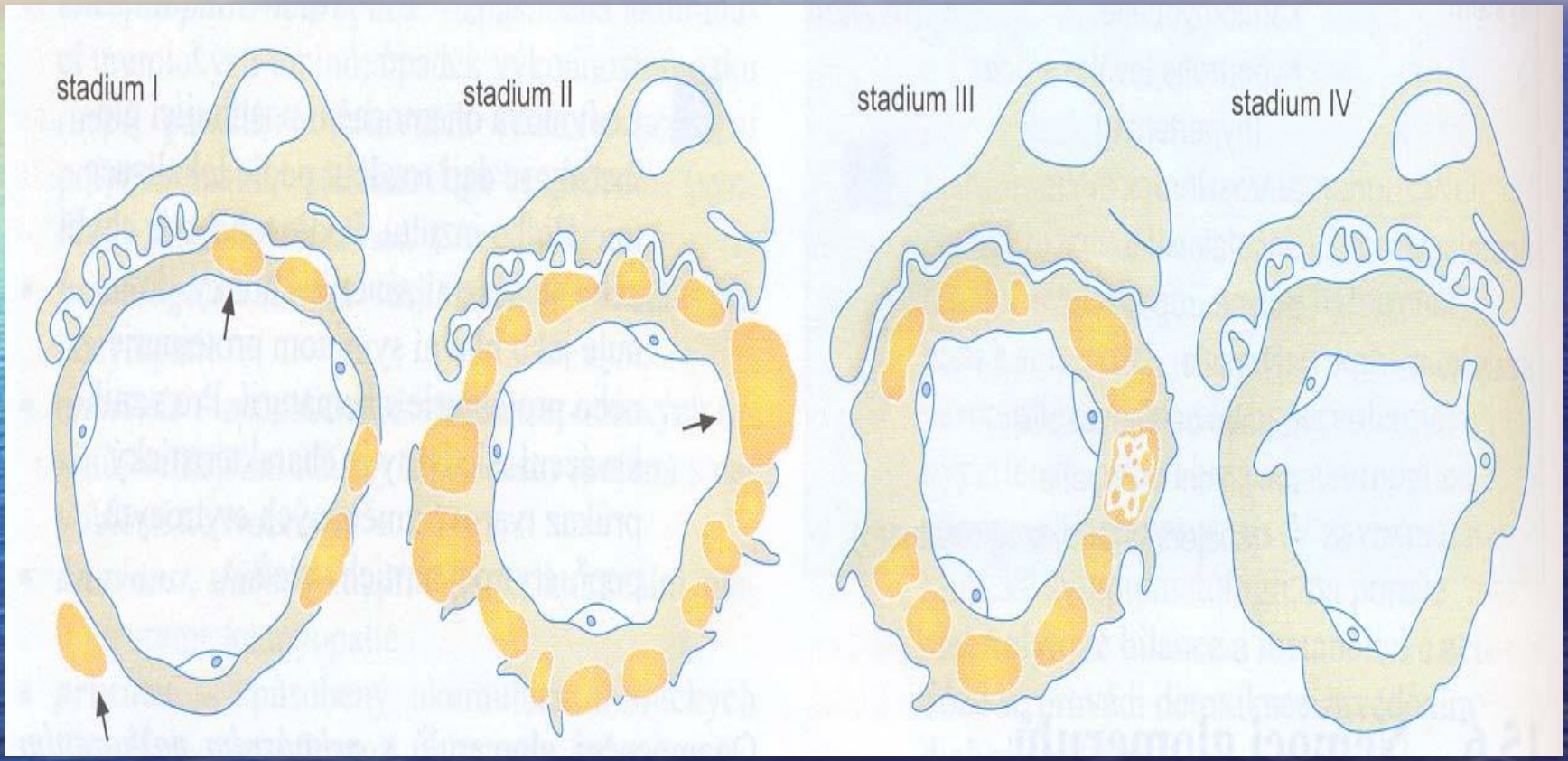
- focal: < 50% glomeruli are affected
- diffuse: > 50% glomerulů are affected
- segmental: only a part of the glomerular tuft is involved
- glomerulosclerosis: obliteration of capillary lumens

Membranous GN

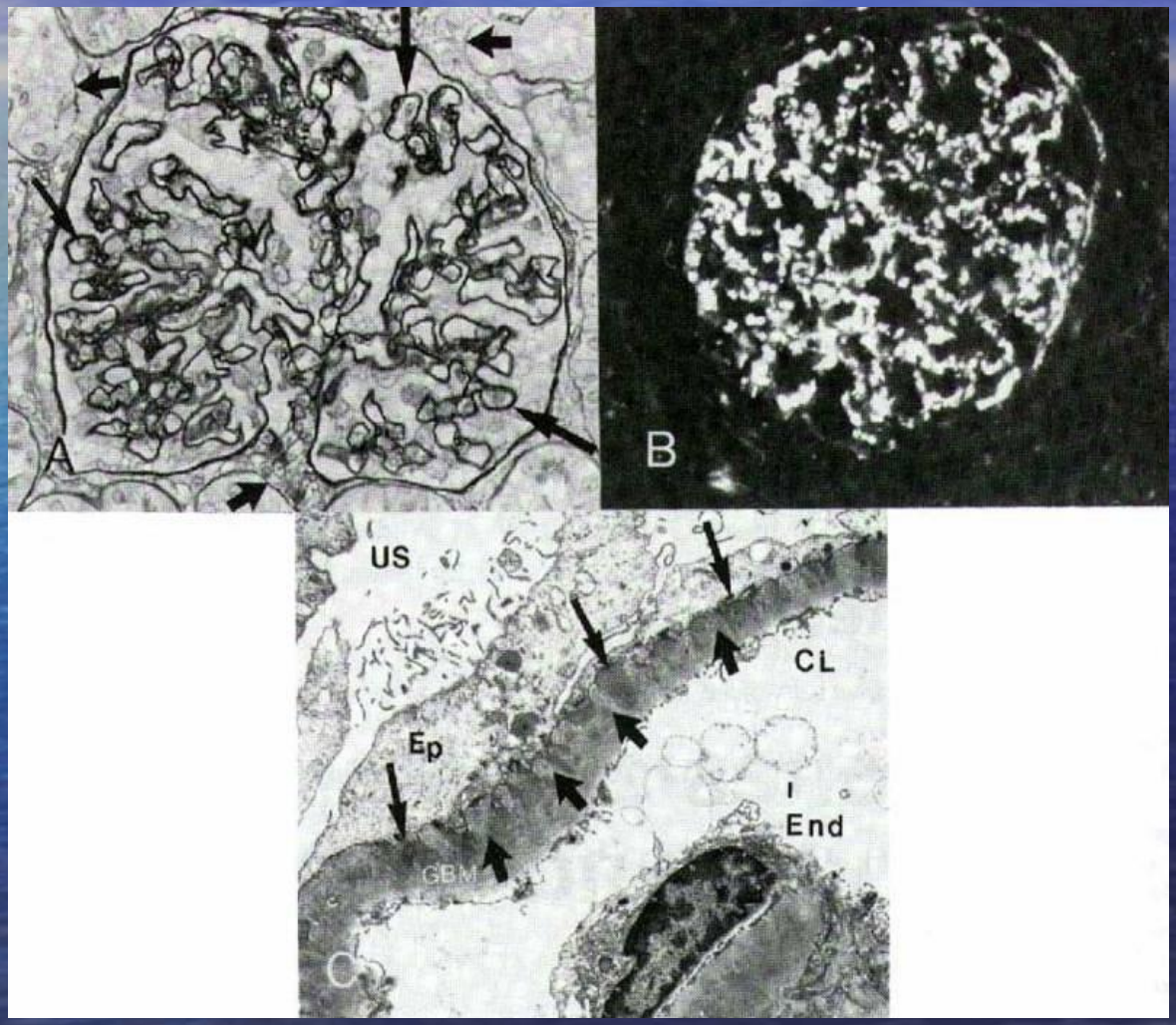
- Diffuse thickness of GBM due to deposition of IK in basement membrane
- Strong association with HLA (B8, DR3) and genes of alternative way of activation of complements (Bf)
- Often secondary etiology:
  - drugs (Au, penicilamin…)
  - tumors (especially ca GIT)
  - infection (hepatitis B)
- Clinical manifestation: nephrotic syndrome with mikroscopic hematuria and sometimes hypertension
- Therapy: according etiology



Stages of membranous GN



Idiopatic membranous glomerulopathy



Membranoproliferative (mesangiocapillary) glomerulopathy

- Is characterised by hypercellularity of the glomerular cells and basement membrane thickening
- 2 forms: classical form – proliferation of mesangial matrix with expansion to capillary walls between endothelium and BM
  disease of dension deposits – non-linear accumulation of material in lamina densa of the basal membrane

- etiopathogenesis: ??? - association with infection (endocarditis, abscessus….)
  - genetic faktors (HLA B8, DR3…)

- Clinical syndrome: nephrotic proteinuria with microhematuria, hypertension, anemia and decreased levels of the complements (↓C3)

IgA nephropathy (Berger´s disease)

- Mesangioproliferative GN with deposits of IgA, event. C3
- Etiology: - unknown, clinical manifestation is associated with infection – with latent period 2-3 days
  - association with HLA (DQ, DP)

  T-lymphocytes produce ↑ levels of IL-2 (+ ↑ IR-2R) and they are constantly stimulate

  ⇓

  ↑ production of IgA by B-lymphocytes

- Clinical manifestations: asymptomatic hematuria - nephrotic syndrome

Chronic glomerulonephritis

- Common terminal result of many glomerular diseases

  („end stage kidney“)
- It is charecterised by different degrees of sclerotization and proliferation

Pathogenesis: damage (loss) of nephrons

⇓

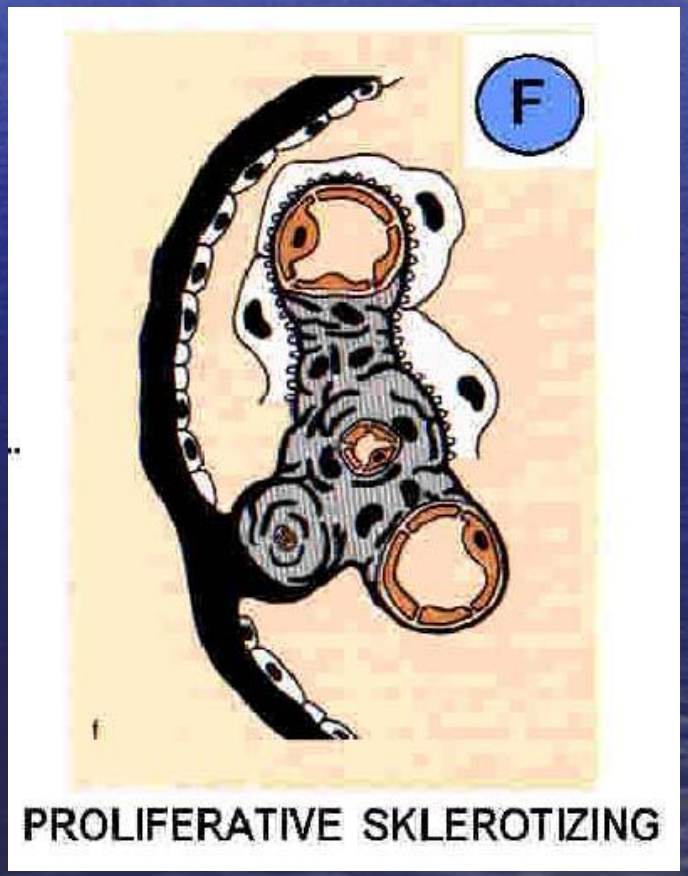
hyperperfusion

⇓

hyperfiltration

⇓

sclerosis of glomeruli



Glomerulopathy in connective tissue disorders

Systemic lupus erythematosis

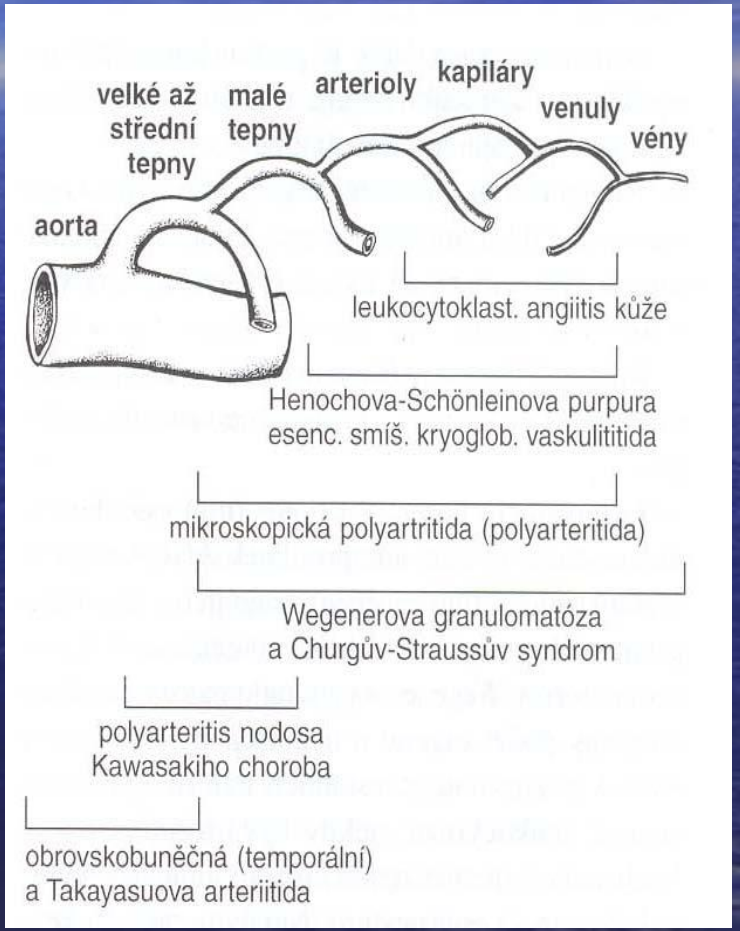
- SLE predominantly affects women, who account for 90% cases
- The age of onset is usually between 20 and 40 years
- Many different tissues and organs may be involved (the body produces antibody against its own DNA), but renal involvement is the most significant in terms of outcome

- **Histologic pattern:**

  WHO classification – normal glomerules (typ I)
  - mezangial GN (typ II)
  - focal proliferative GN (typ III)
  - diffuse proliferative GF (typ IV)
  - membranous GN (typ V)
  - glomerular sclerosis (typ VI)

Vasculitis

- Heterogenous group of diseases characterised by necrotizing inflammation of vessels
- Etiology: primary x secondary
- Pathogenesis:
  - damage by immunocomplexes
  - ANCA (pauciimmune form)
  - damage by cells (IV. typ)



Henoch-Schönlein purpura

- systemic vasculitis affecting medium-sized vessels

- especially in children and younger people
- It is frequently develops post-infections
- Clinical manifestation: - non-trombocytopenic purpura
  - affect joints, serose membrane, GIT and glomeruli

⇓

alterations are similar to finding in IgA nephropathy

Polyarteritis nodosa

- is an inflammatory and necrotizing disease involving the medium-sized and small arteries throughout the body.
- Men are more commonly affected than women

- **Etiopathogenesis:** usually unknown

- **Clinical manifestation**: variable – general symptoms + specific symptoms (skin, kidney, GIT, heart…)

- **Histologic pattern**: focal glomerular sclerosis, crescents

Pauci-immune necrotizing GN

Wegener´s granulomatosis

- is a vasculitis leading to sinus, pulmonary and renal disease

glomerulonephritis

⇓

90% of such patients have a positive ANCA

ANCA – react with neutrophils

⇓

respiratory burst of phagocytic cells

⇓

release of free radicals

⇓

degranulation

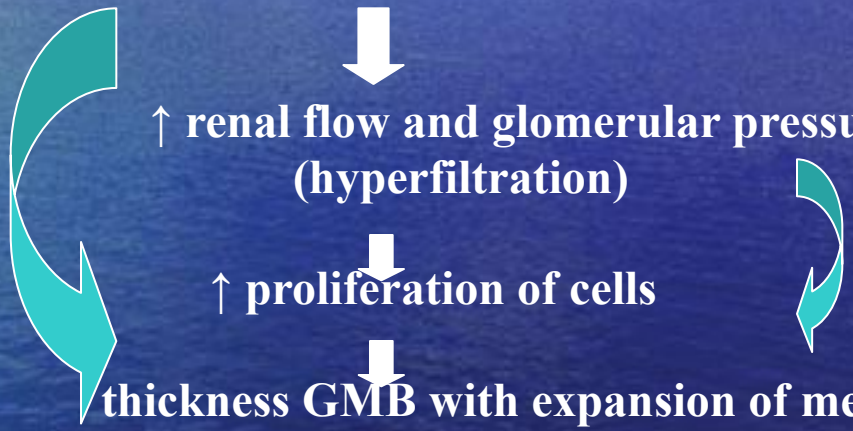
⇓

injury to endothelial cells

Diabetic nephropathy

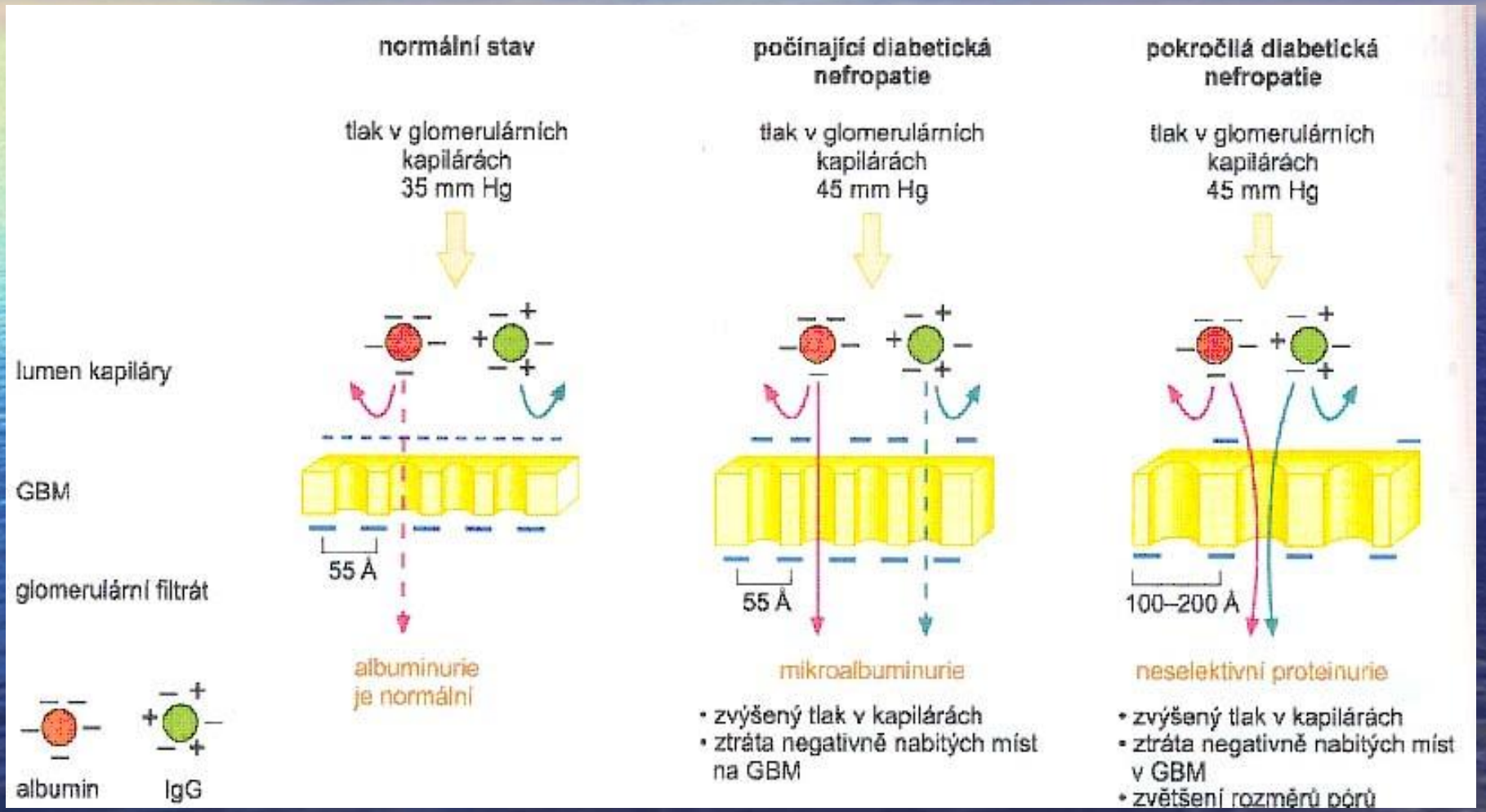
= diabetic intracapillary glomerulosclerosis (sy Kimmelstielův-Wilsonův)

Etiopathogenesis: hyperglycemia affects conformation BM and mesangial matrix



Clinical manifestation: latent stage - asymptomatic
incipient stage
manifest stage of diabetic nepropathy
chronic renal failure

Schematic demonstration of running diabetic nephropathy



Amyloidosis

Kidney belong to organs most frequently affected by amyloidosis

AL amyloidosis – is a complication of myeloproliferative diseases (myelom, makroglobulinémie)
(primary)

AA amyloidosis – is a complication of chronic inflammatory diseases (RA, TBC, Crohn´s disease e.g.)
(secondary)

Clinical manifestation: nephrotic syndrom, subsequently renal failure develops

Hereditary nephropaties

Alport syndrom

- Hereditar nephritis with deafness (X chromosome)
- Pathogenesis: congenital defect of collag synthesis

↓

GMB very slight or with more layers

GN focal (diffuse) proliferation with segmental sclerosis

⇒ hematuria, proteinuria or renal failure (males)

Congenital nephotic syndrom

- AR heredity
- Pathogenesis: defect of syntesis of basal membrane
  - pronounced and non-selective proteinuria

⇒ Nephrotic syndrom from first weeks of the life --- renal failure