Glomerulonephritis

Normal glomerulus

- The glomerulus is a specialized net work of **capillaries** with an arteriole at each end.
- It has a central connective tissue material known as **mesangium** containing cells known as mesangial cells.
- The glomerular capillaries are lined by **fenestrated endothelium** lying on a **basement membrane** , which is covered by specialized **epithelial cells.**

Epithelial cells

- **Two types:**

  A. Parietal:

  - Line Bowman's capsule

  B. Visceral (*podocytes*):

  - Rest on GBM.
  - They have cytoplasmic projections known as **foot processes** that surround the GBM.
  - Between the processes there are the **filtration slits** → podocytes are the *major glomerular filter barrier*.

Mesangium

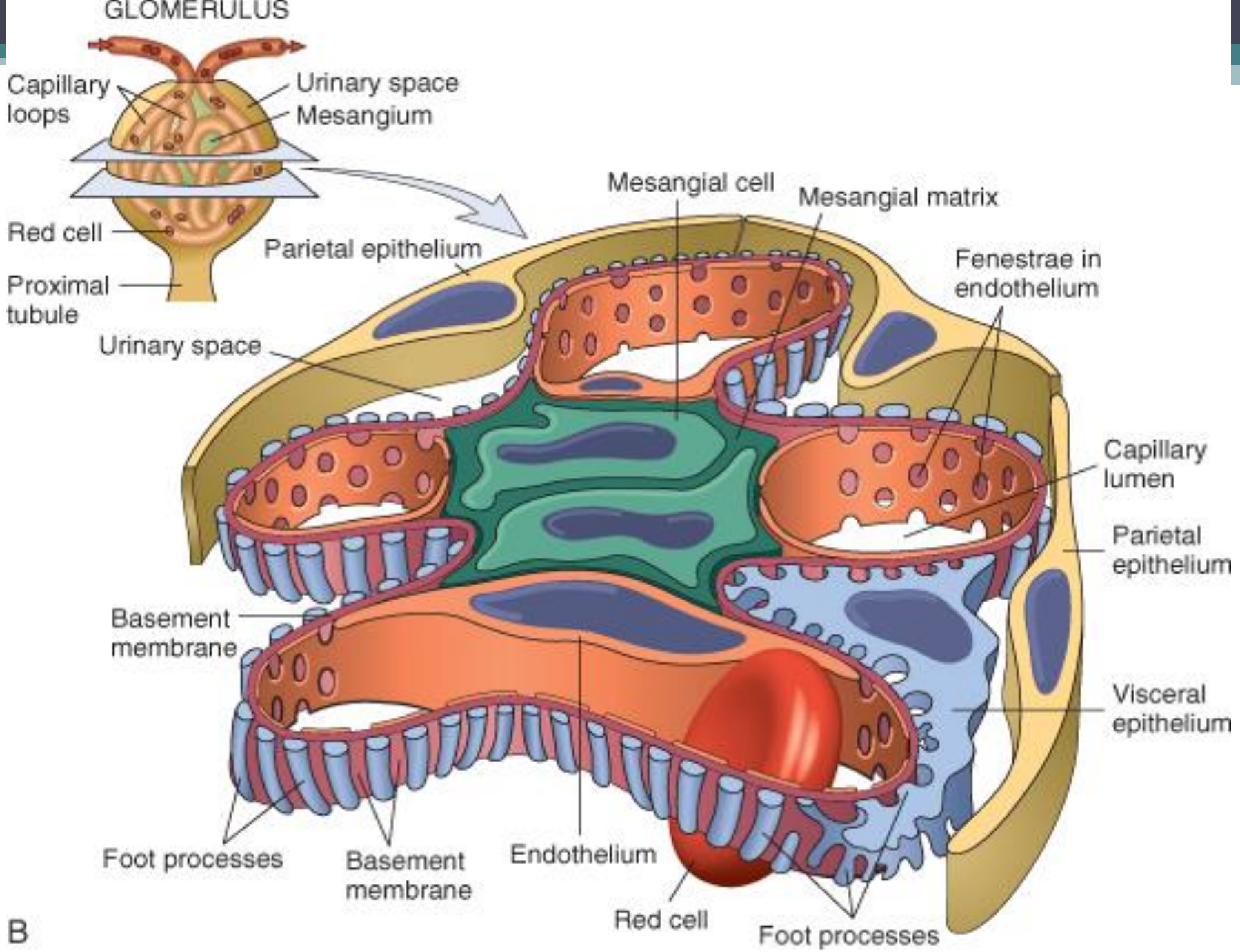
- Acellular **mesangial matrix + mesangial cells** (which has similarities to smooth muscle cells) in the center of glomerulus between capillaries.

- Mechanical support, modulation of glom. filtration, generation of active mediators.

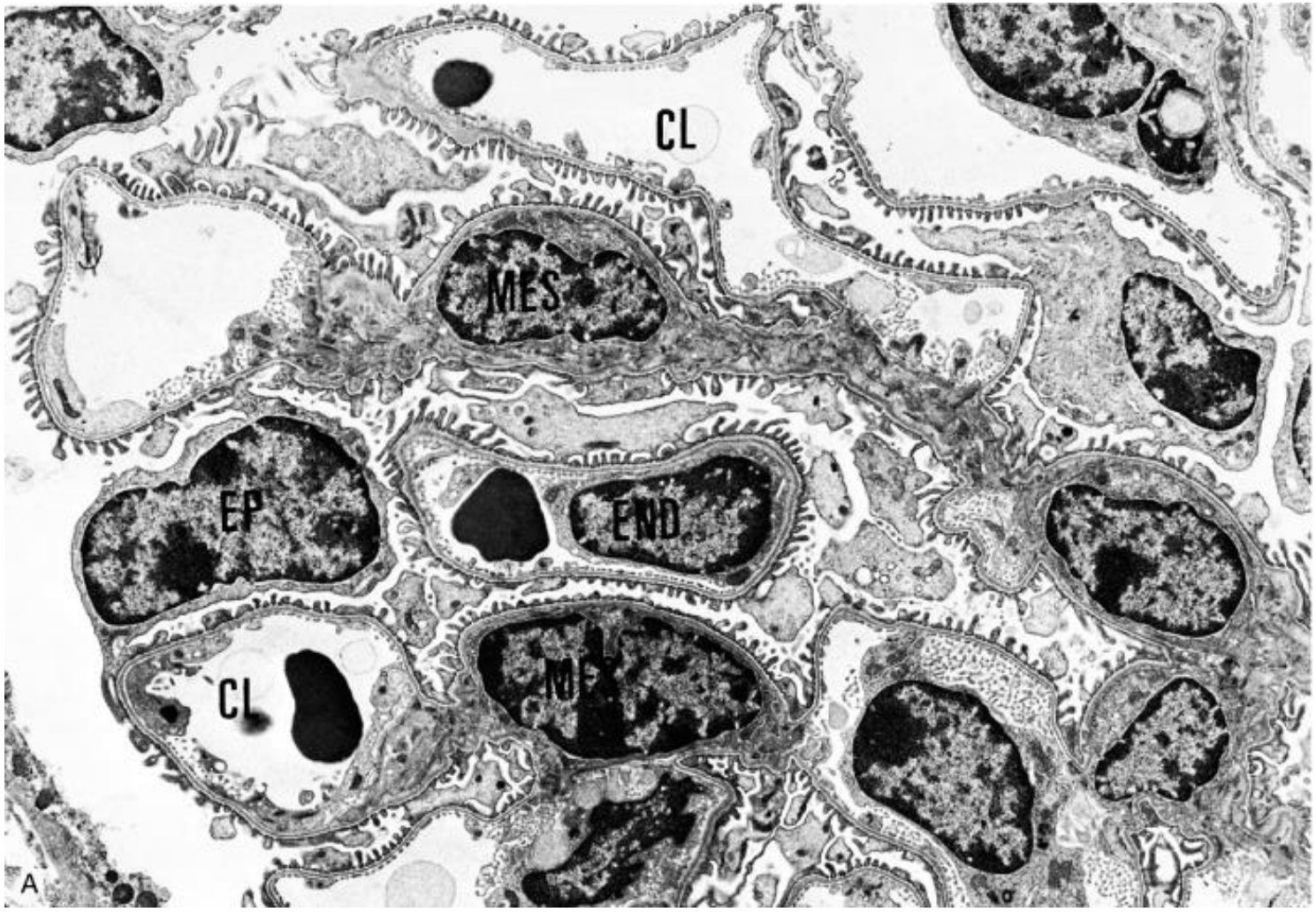
- Important players in many forms of human glomerulonephritis (GN).

Glomerular basement membrane (GBM)

- Main component is **type IV collagen.**
- Consists of 3 layers:
  - Lamina densa
  - Lamina rara interna
  - Lamina rara externa
- Has a strong *negative* charge.
- It has a size and charge selective permeability.

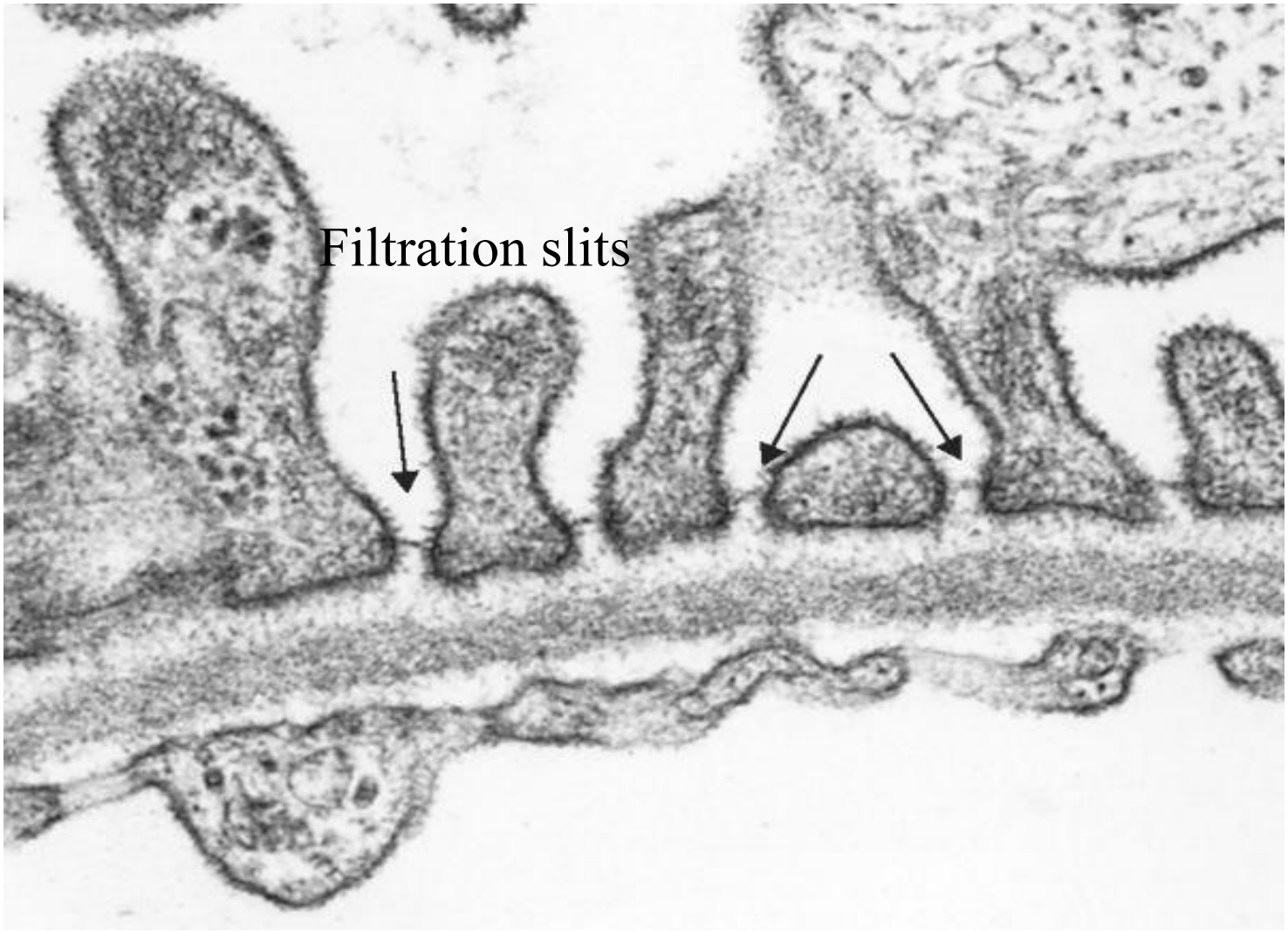


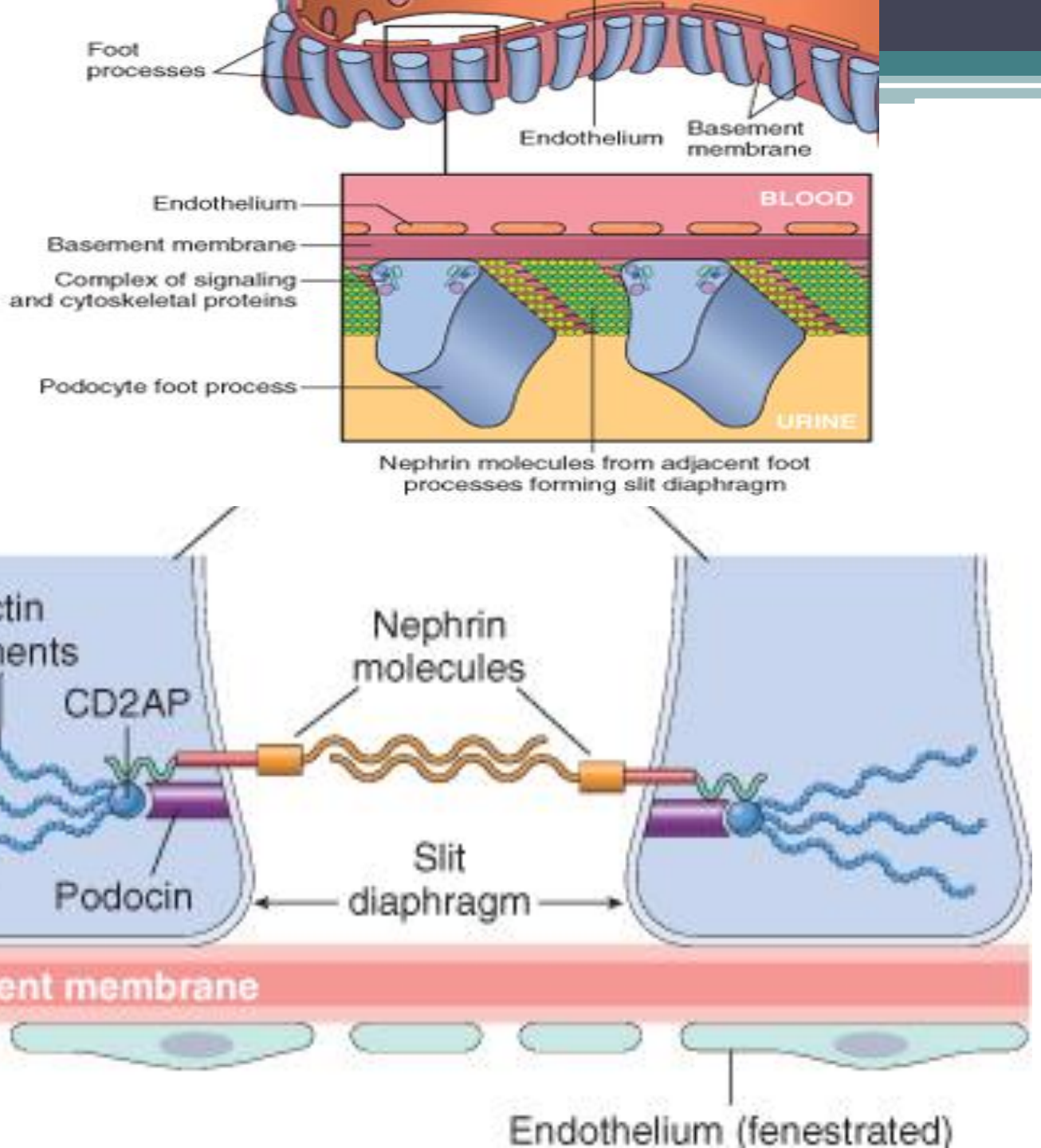
Glomerulus by E/M



CL, capillary lumen; EP, visceral epithelial cells with foot processes; END, endothelium; MES, mesangium

Glomerular capillary wall




Foot processes
Endothelium
Basement membrane
Endothelium
Basement membrane
Complex of signaling and cytoskeletal proteins
Podocyte foot process
BLOOD
URINE
Nephrin molecules from adjacent foot processes forming slit diaphragm
Actin filaments
CD2AP
Nephrin molecules
Podocin
Slit diaphragm
Basement membrane
Endothelium (fenestrated)

Glomerulonephritis (GN)

- A heterogeneous group of renal diseases in which the *primarily affecting the glomeruli.*
- Lesion is bilateral and symmetrical.
- Acute and chronic types.
- Primary and secondary types.

What causes glomerular disease?

Most are of immunologic origin, and caused by immune complexes !

Pathogenesis of glomerular injury

1- **IMMUNOLOGICAL** mechanisms*:

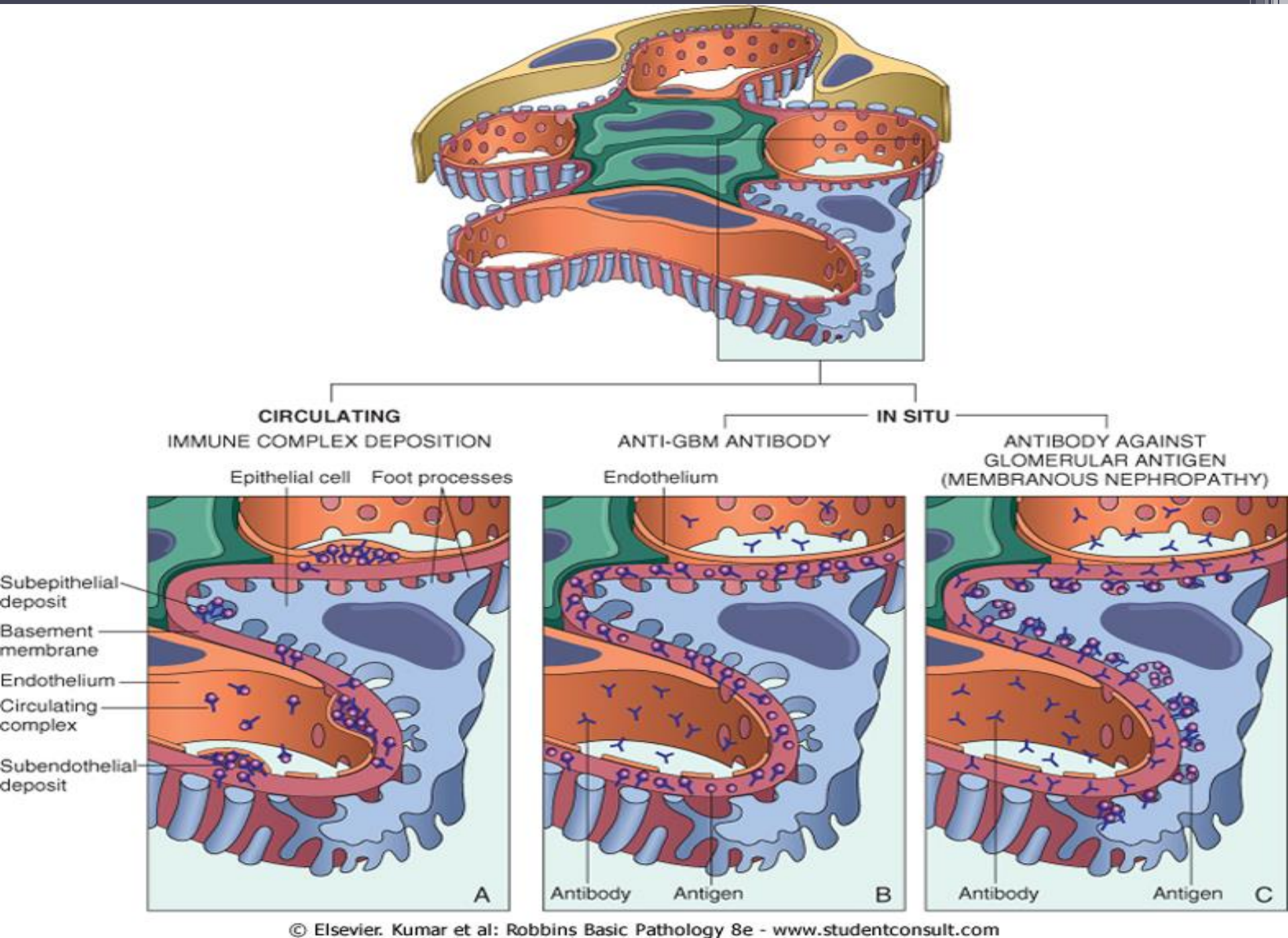
- **Antibody mediated**
- Others less frequent
  - Cell mediated
  - Activation of alternative pathway of complement

2- **NON- IMMUNOLOGICAL** mechanisms:

- Podocyte injury
- Nephron loss (Renal ablation glomerulopathy).

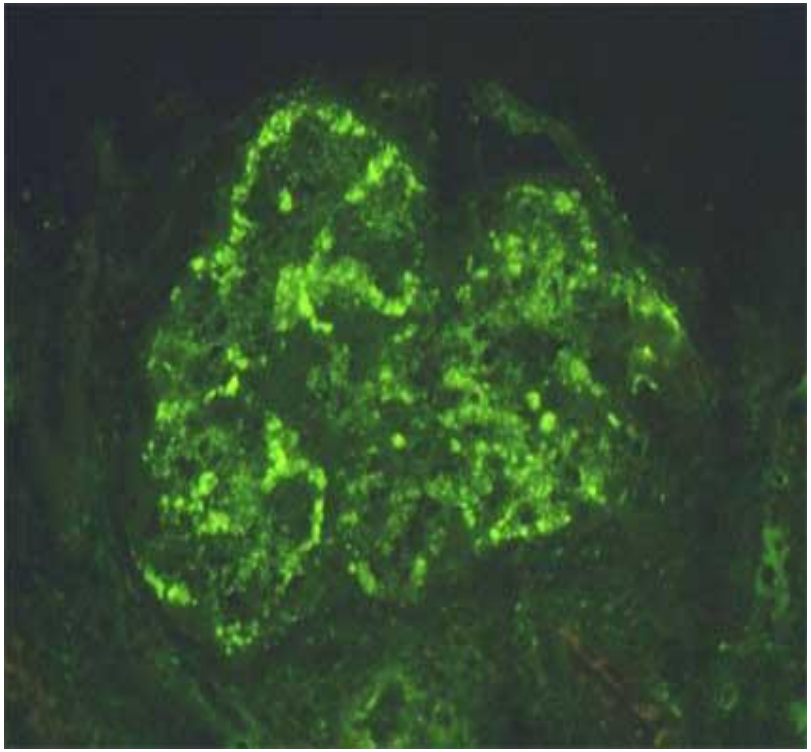
Immune complex mediated glomerular injury

- ***Circulating Immune Complex Deposition*:***
  - Endogenous antigens (e.g., DNA, nuclear proteins, tumor antigens).
  - Exogenous antigens (e.g., infectious products, drugs ….).
- ***In Situ Immune Complex Deposition:***
  - Fixed intrinsic tissue antigens
    - ❖NC1 domain of the α3 chain of collagen type IV antigen (anti-GBM nephritis)
    - ❖Heymann antigen (Membranous glomerulopathy).
    - ❖Mesangial antigens.
  - Planted antigens:
    - ❖Exogenous (infectious agents, drugs …).
    - ❖Endogenous (DNA, nuclear proteins, immunoglobulins, immune complexes, IgA).

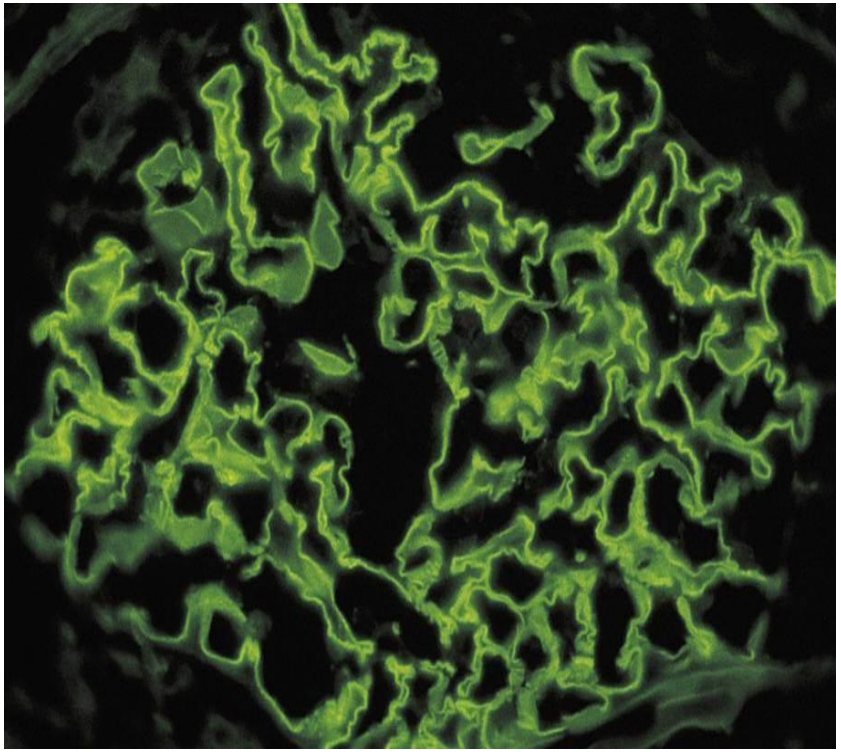


Immunoflurescence microscopy

The pattern, location & type of immune complex deposition are helpful in distinguishing among various types of GN.



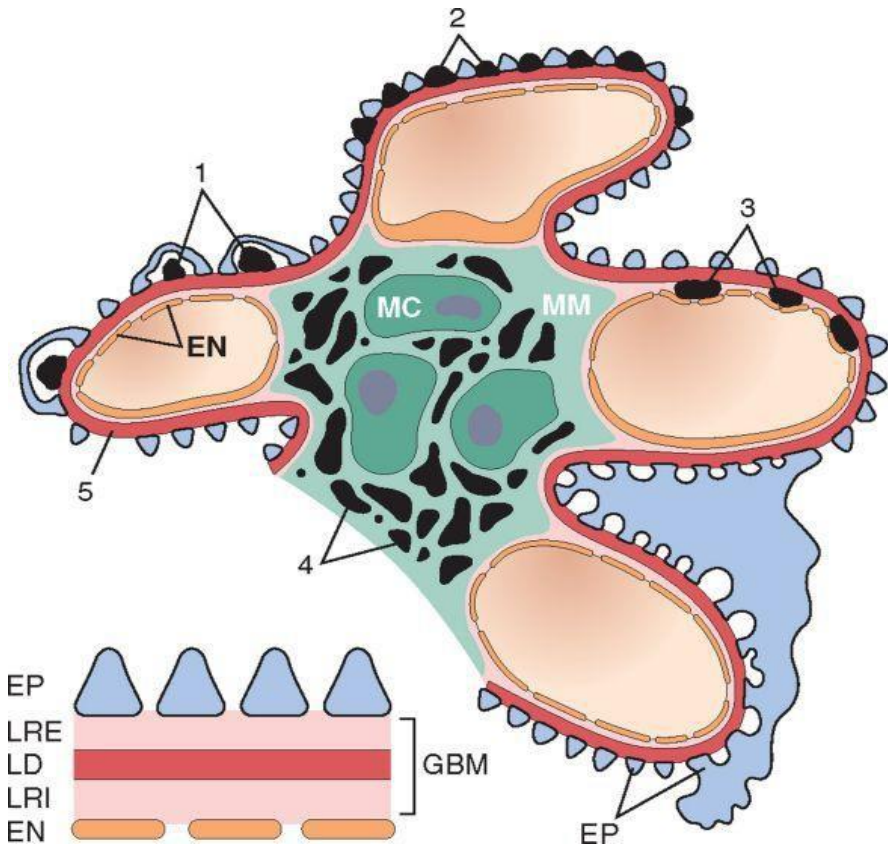
Granular pattern
(majority of GN; e.g. PSGN)



Linear pattern
(anti-GBM Ab GN)

Localization of immune complexes in the glomerulus

1. Subepithelial humps, as in PSGN.
2. Epimembranous (subepithelial) deposits, as in MGN.
3. Subendothelial deposits, as in lupus nephritis & MPGN.
4. Mesangial deposits, as in IgA nephropathy;
5. Basement membrane deposits; as in anti-GBM

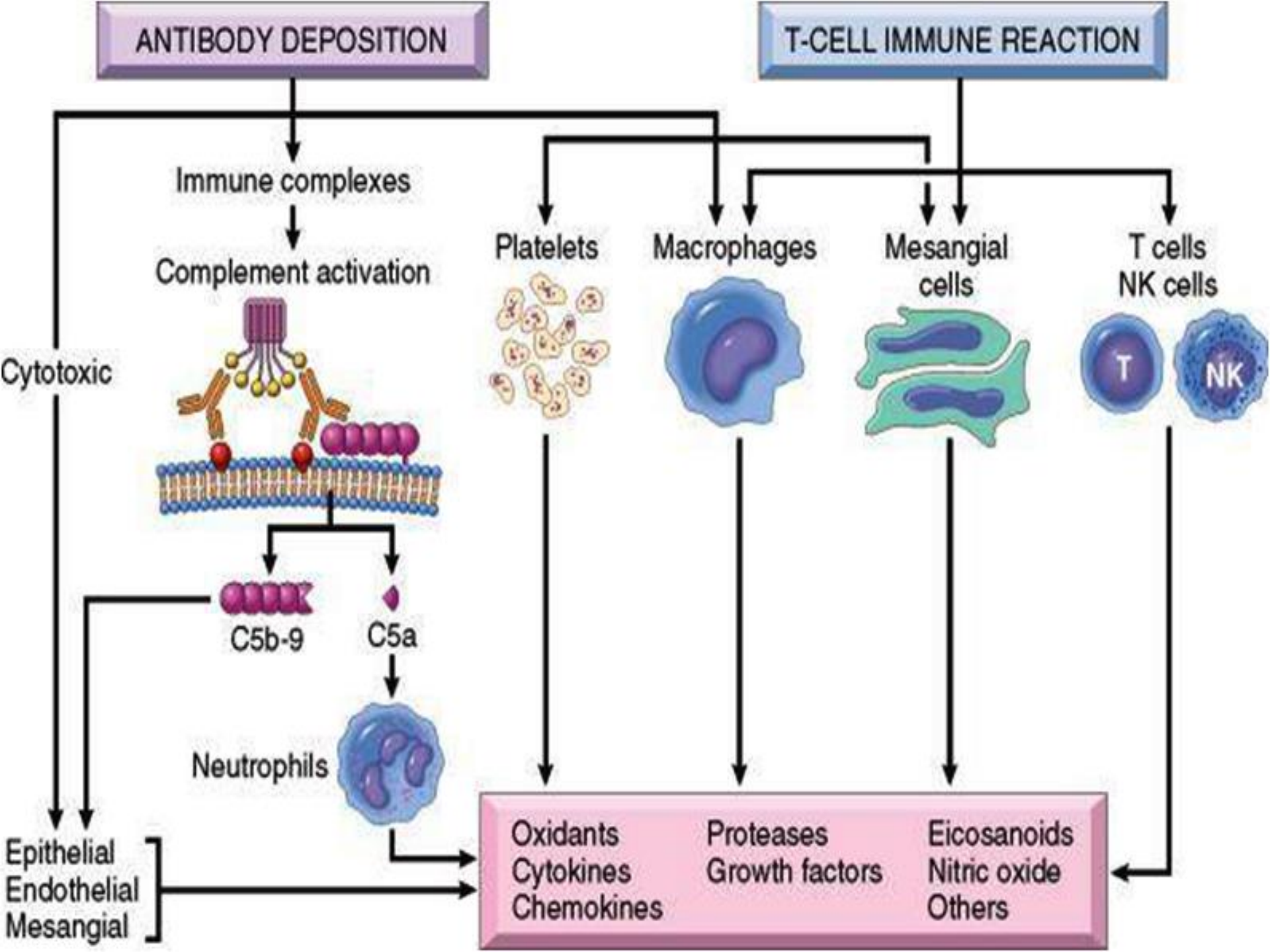


Mediators of immune injury

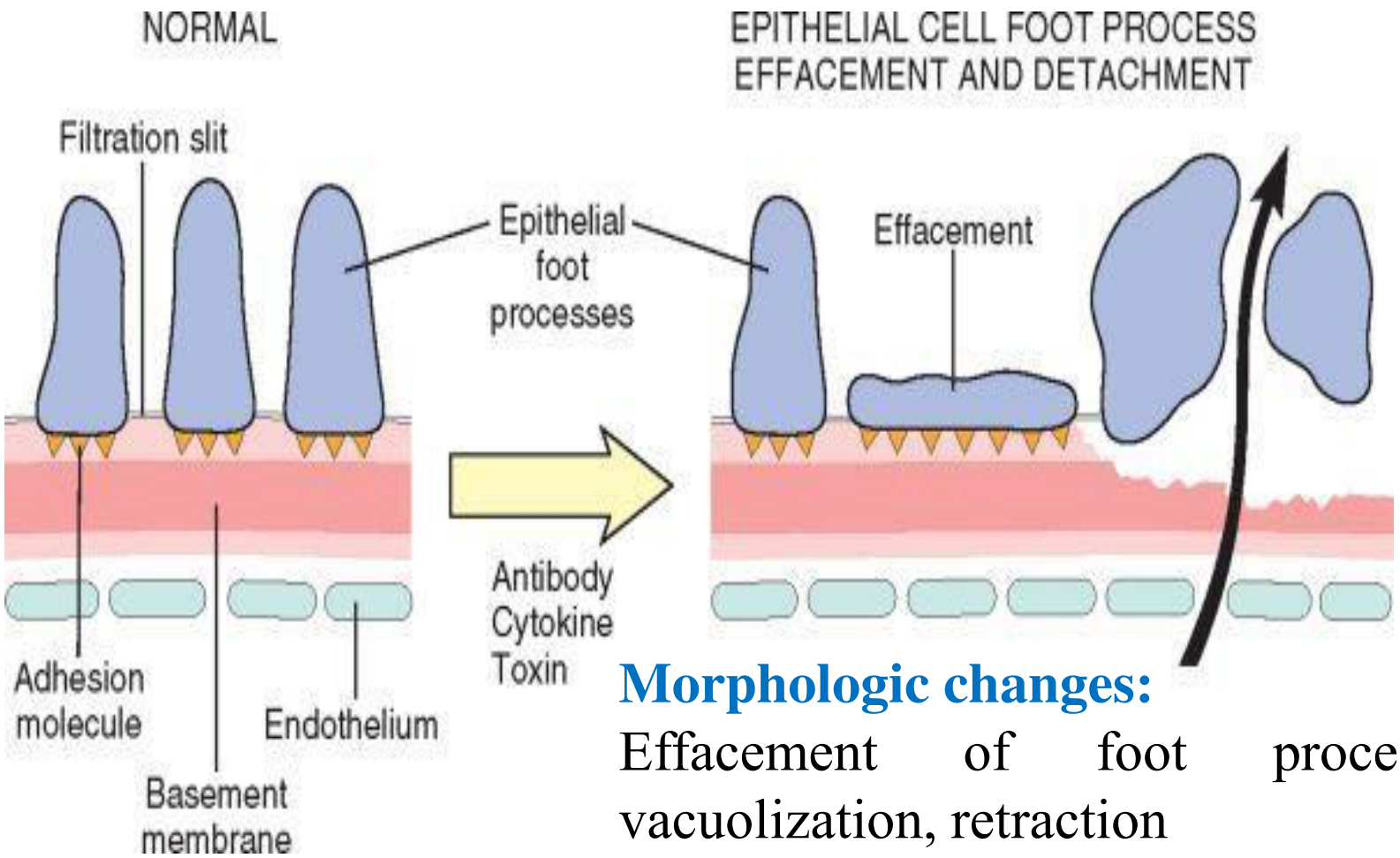
- Neutrophils
  - Protreases
  - Oxygen metabolites
  - Arachidonic acid metabolites
- Complement activation
  - C5a
  - C5 -C 9
- Monocytes
  - Monokinase
- Platelets & coagulation system.
- Resident glomerular cell.
- Thrombinwhich causes leukocyte infiltration, and glomerular cell proliferation.

Other mechanisms of injury

- Cell mediated injury
  - Presence of T - lymphocytes & macrophages in some GN.
- Activation of alternative complement pathway
  - As in membranoproliferative GN.
- Direct epithelial cell (podocytes) injury:
  - By antibodies ,toxins ,cytokines ,? Unknown factors.
- Nephron loss.


ANTIBODY DEPOSITION
T-CELL IMMUNE REACTION
Immune complexes
Complement activation
Cytotoxic
Platelets
Macrophages
Mesangial cells
T cells
NK cells
T
NK
C5b-9
C5a
Neutrophils
Epithelial
Endothelial
Mesangial
Oxidants
Cytokines
Chemokines
Proteases
Growth factors
Eicosanoids
Nitric oxide
Others

Podocyte injury

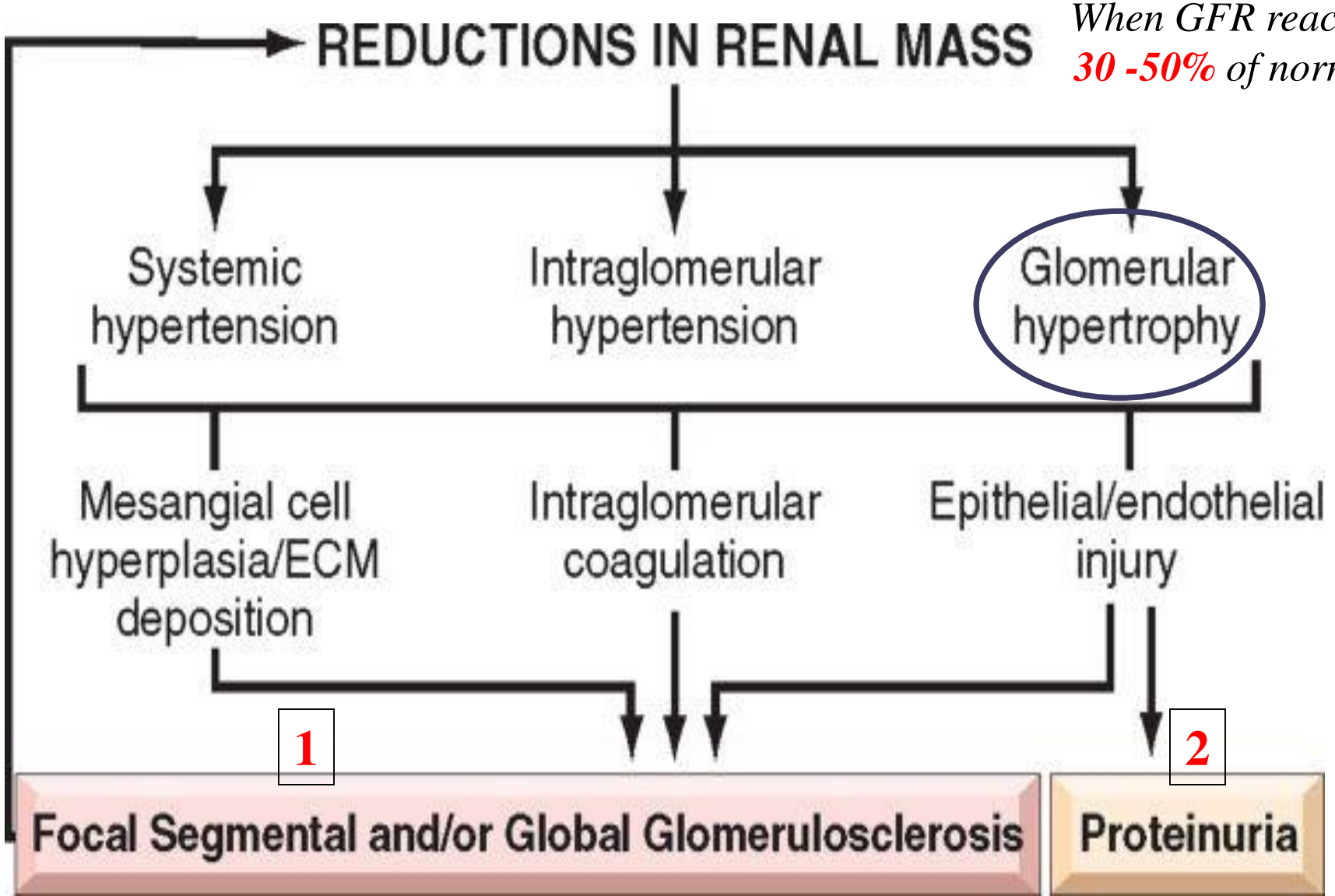


Morphologic changes:

Effacement of foot processes, vacuolization, retraction & detachment of cells from the GBM.

Clinically manifests with ***proteinuria***

Nephron loss

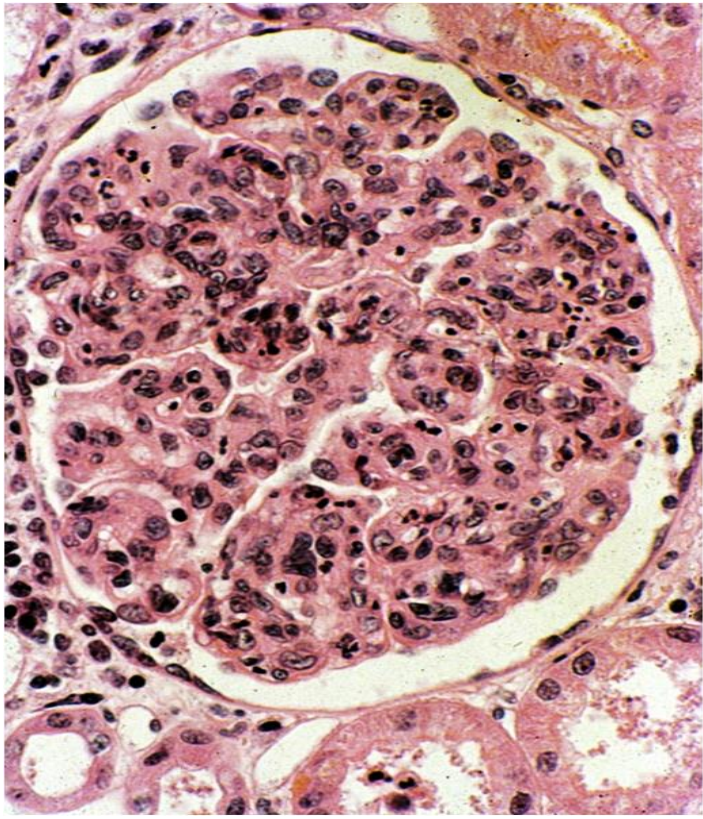


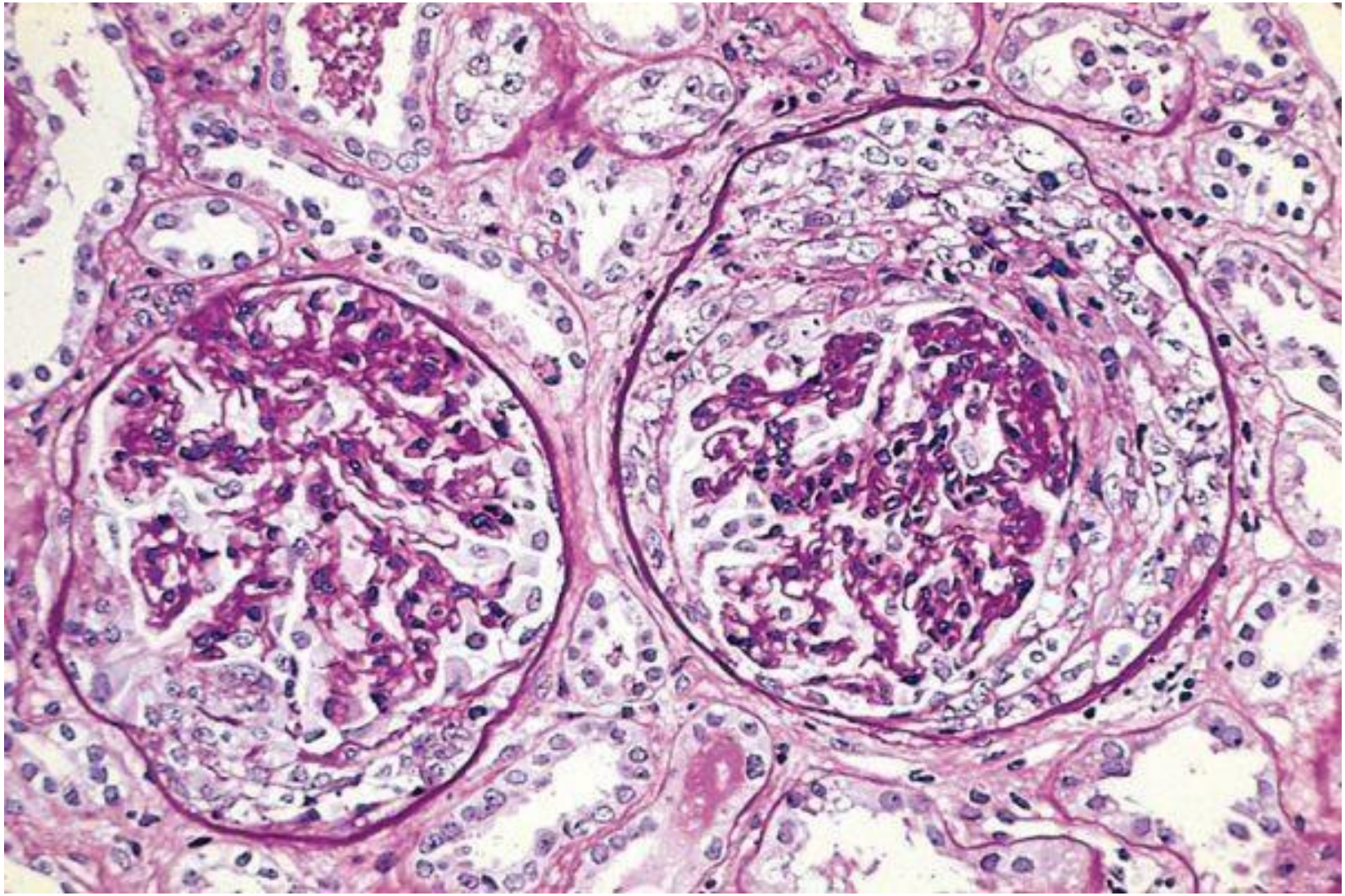
Histologic manifestations of glomerular diseases

- **Basic tissue reactions:**
  - Hypercellularity.
  - Thickening of GBM.
  - Hyalinization (hyalinosis).
  - Sclerosis (collagnosis).
  - Others (necrosis & thrombi).

Hypercellularity

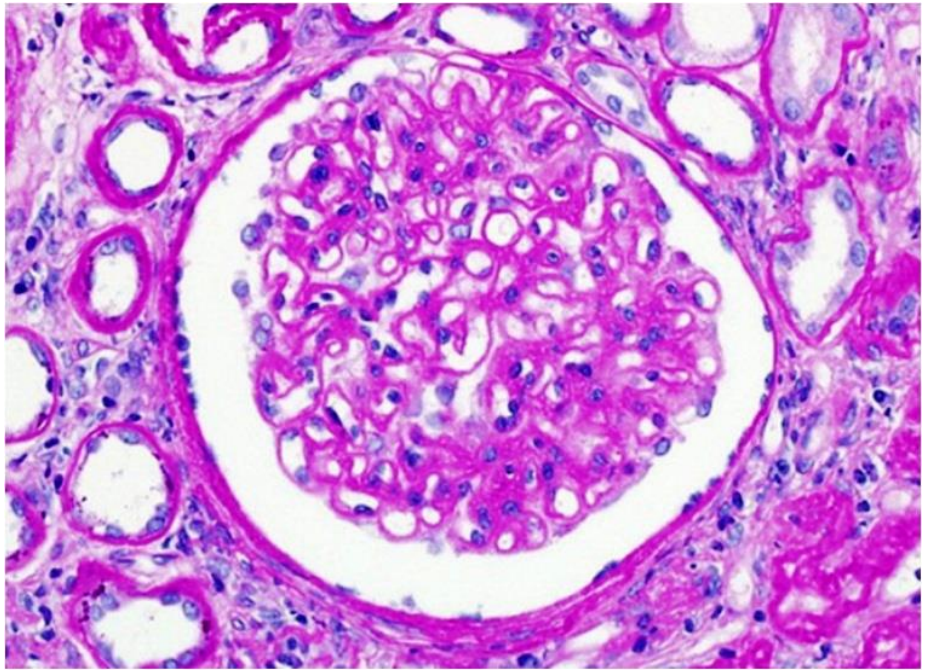
- Seen in some inflammatory GNs due to:
  - Proliferation of mesangeal, endothelial or epithelial cells.
  - Leucocyte infiltration*.
- May be associated with CRESCENT** formation → proliferating parietal cells and infiltrating leucocytes occluding **>1/3** of glomerulus in response to ***fibrin*** leakage to urinary space.

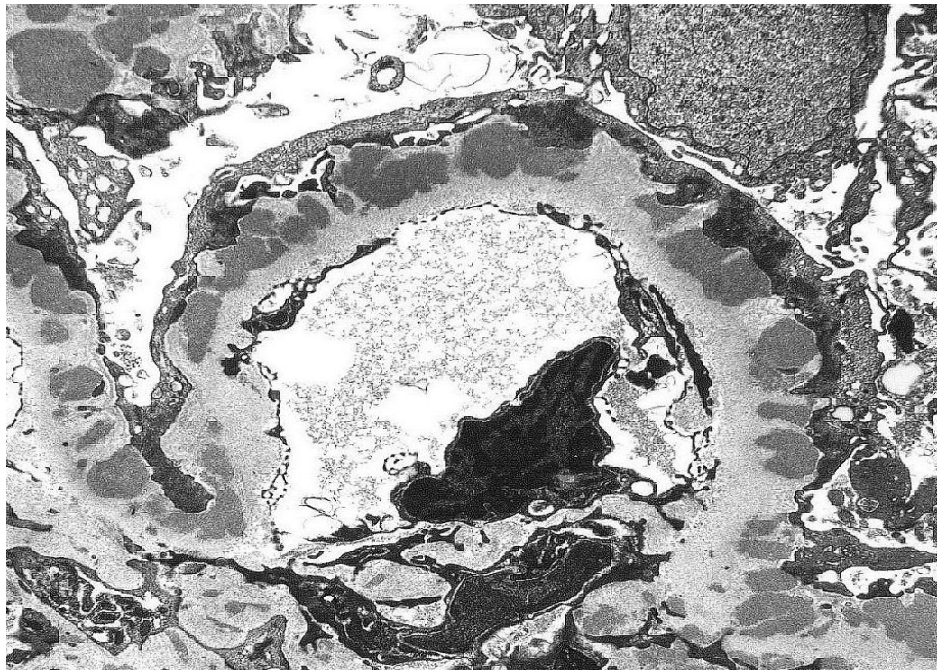




Thickening of GBM

- **Due to:** Deposition of immune complexes (as membranous GN), increased synthesis of its protein components (as in diabetic glomerulosclerosis) or interposition of mesangial cells.
- By light microscopy → best seen with (**PAS stain**).



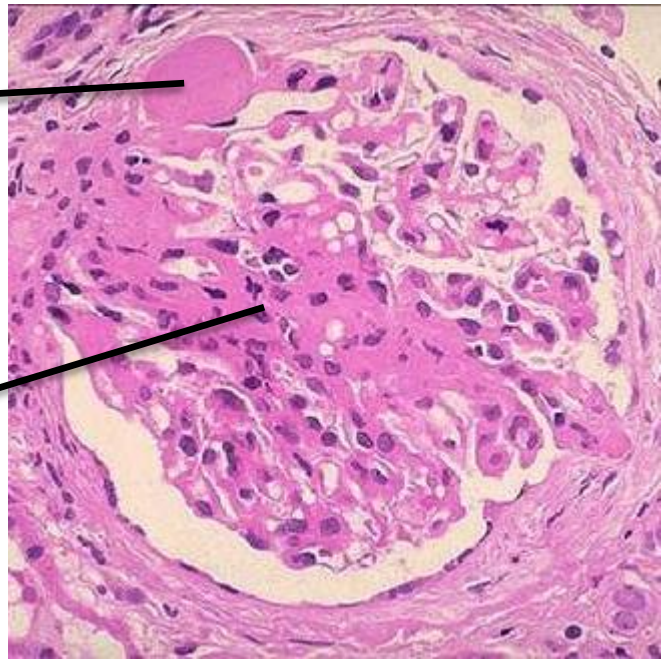


Hyalinosis & Sclerosis:

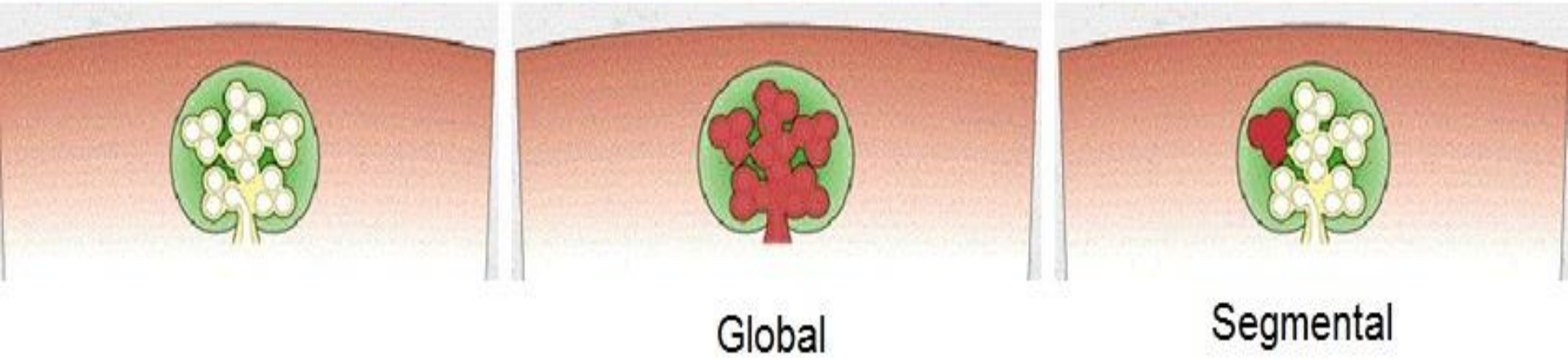
- **Hyalinosis*:**
  - Deposistion of homogeneous & eosinophilic material; caused by capillary injury & leak of plasma proteins.

- **Sclerosis:**
  - Accumulations of extracellular collagenous matrix in chronic diseases → may lead to obliteration of some or all of the capillary lumens.

- Some can differentiate between both (as *silver, trichrome, or PAS stains …*).



Patterns of glomerular involvement



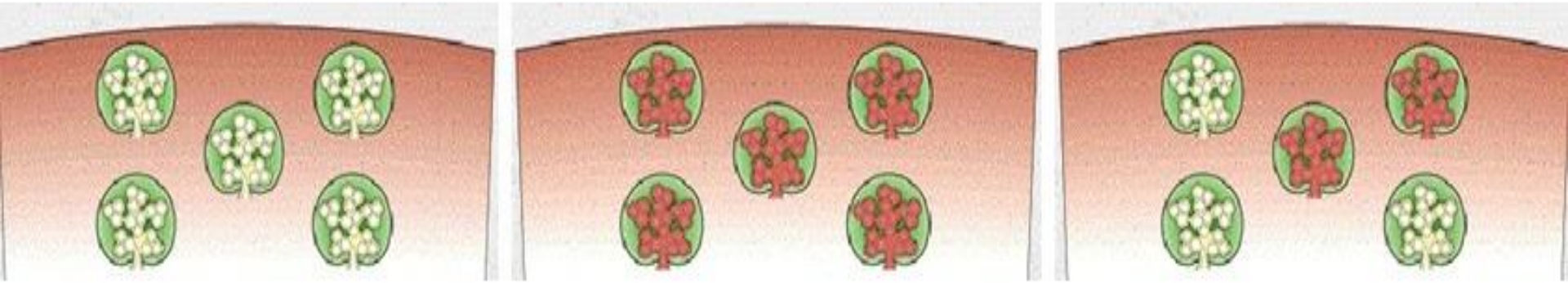


Table 20-2 Glomerular Diseases

Primary Glomerulopathies
Acute proliferative glomerulonephritis
Postinfectious
Other
Rapidly progressive (crescentic) glomerulonephritis
Membranous nephropathy
Minimal-change disease
Focal segmental glomerulosclerosis
Membranoproliferative glomerulonephritis
Dense deposit disease
IgA nephropathy
Chronic glomerulonephritis
Systemic Diseases with Glomerular Involvement
Systemic lupus erythematosus
Diabetes mellitus
Amyloidosis
Goodpasture syndrome
Microscopic polyarteritis/polyangiitis
Wegener granulomatosis
Henoch-Schönlein purpura
Bacterial endocarditis
Hereditary Disorders
Alport syndrome
Thin basement membrane disease
Fabry disease

How are renal diseases diagnosed?

Usually by history, physical findings, urinalysis and other laboratory data. Occasionally a renal biopsy must be performed!