Immuno-pathology of renal diseases

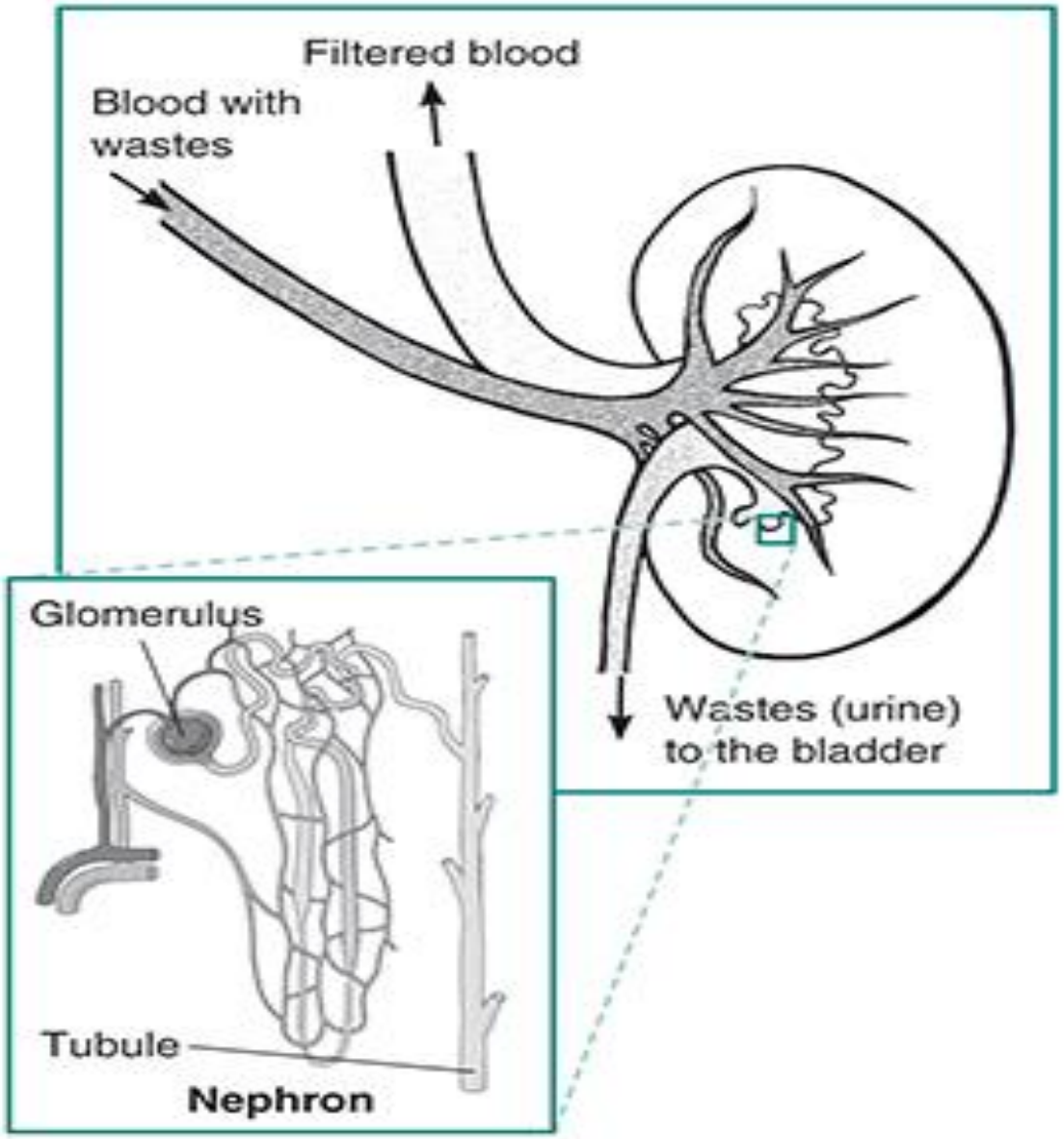
Dr. Nadisha Badanasinghe

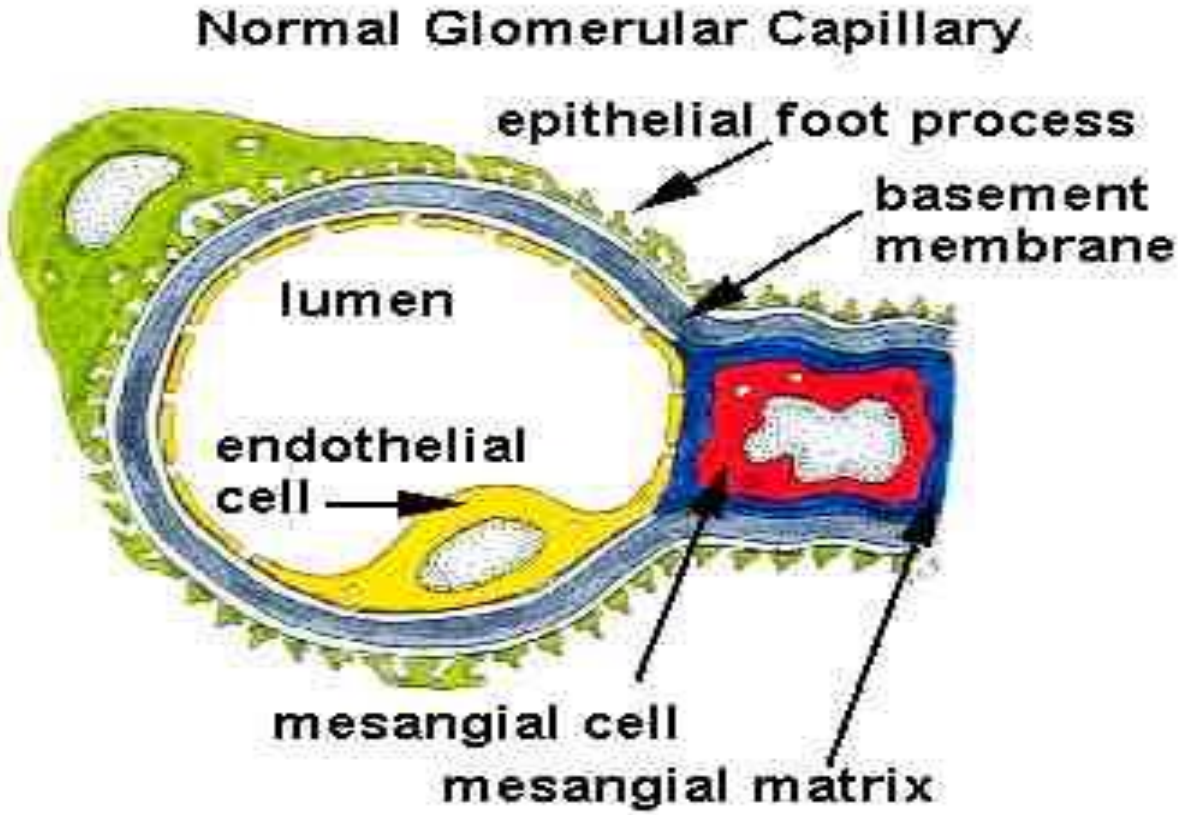
Senior Lecturer

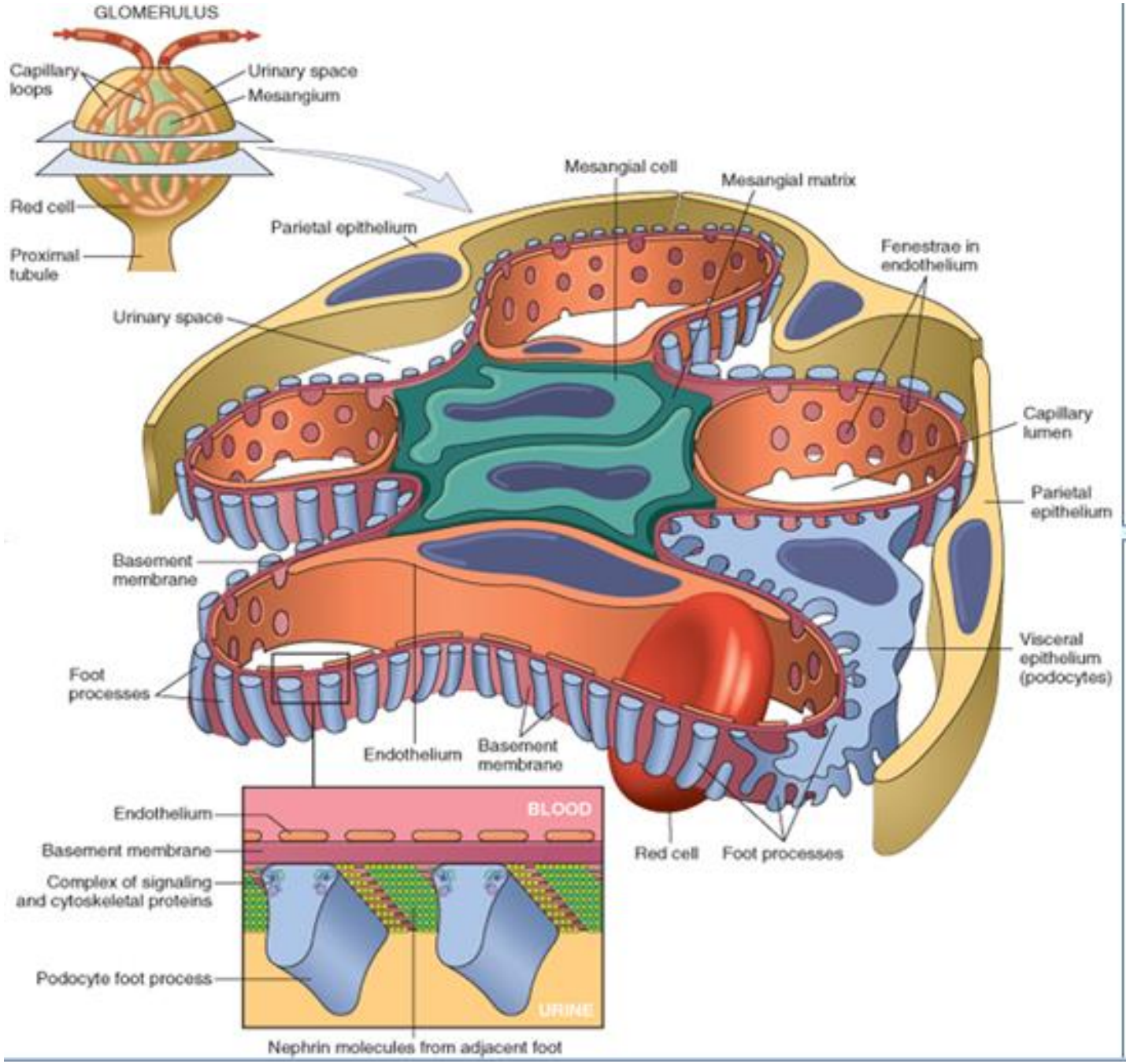
UNIVERSITY OF KELANIYA

Objectives

- Immunological mechanisms leading to renal diseases
- Immuno-pathogenesis of Glomerulonephritis
- Immunopathogenesis of nephrotic syndrome


Filtered blood
Blood with wastes
Wastes (urine) to the bladder
Glomerulus
Tubule
Nephron


Normal Glomerular Capillary
epithelial foot process
basement membrane
lumen
endothelial cell
mesangial cell
mesangial matrix


GLOMERULUS
Capillary loops
Urinary space
Mesangium
Red cell
Proximal tubule
Mesangial cell
Mesangial matrix
Parietal epithelium
Fenestrae in endothelium
Urinary space
Capillary lumen
Parietal epithelium
Basement membrane
Visceral epithelium (podocytes)
Foot processes
Endothelium
Basement membrane
Red cell
Foot processes
Endothelium
BLOOD
Basement membrane
Complex of signaling and cytoskeletal proteins
Podocyte foot process
URINE
Nephrin molecules from adjacent foot

Immune mediated renal diseases

- Diseases Presenting as Nephritic Syndrome – (Glomerulonephritis)
- Diseases Presenting as Nephrotic syndrome

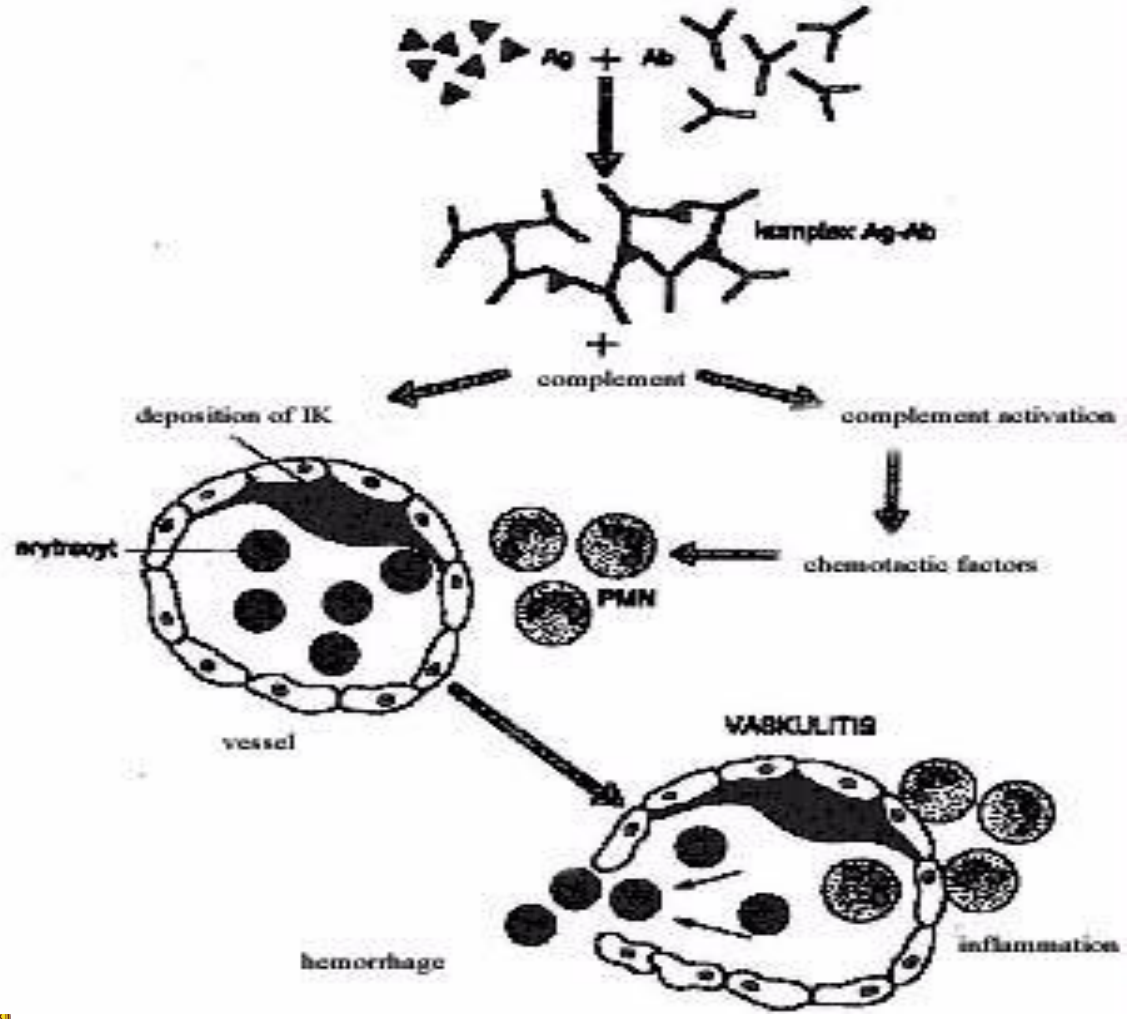
Immunological Effector Mechanisms

- Antibodies
  - Immune complexes (IC) – Type III HS
  - Cytotoxic antibodies – Type II HS
  - Autoimmune antibodies

- Cell mediated immune injury
  - Th1 → DTH – Type IV HS
  - Th17, Th2, CD8

- Damage by complement and other pro-inflammatory cytokines

Type III Hypersensitivity (Immune Complex Mediated)



- Soluble immune complex formation
- Deposition in various sites

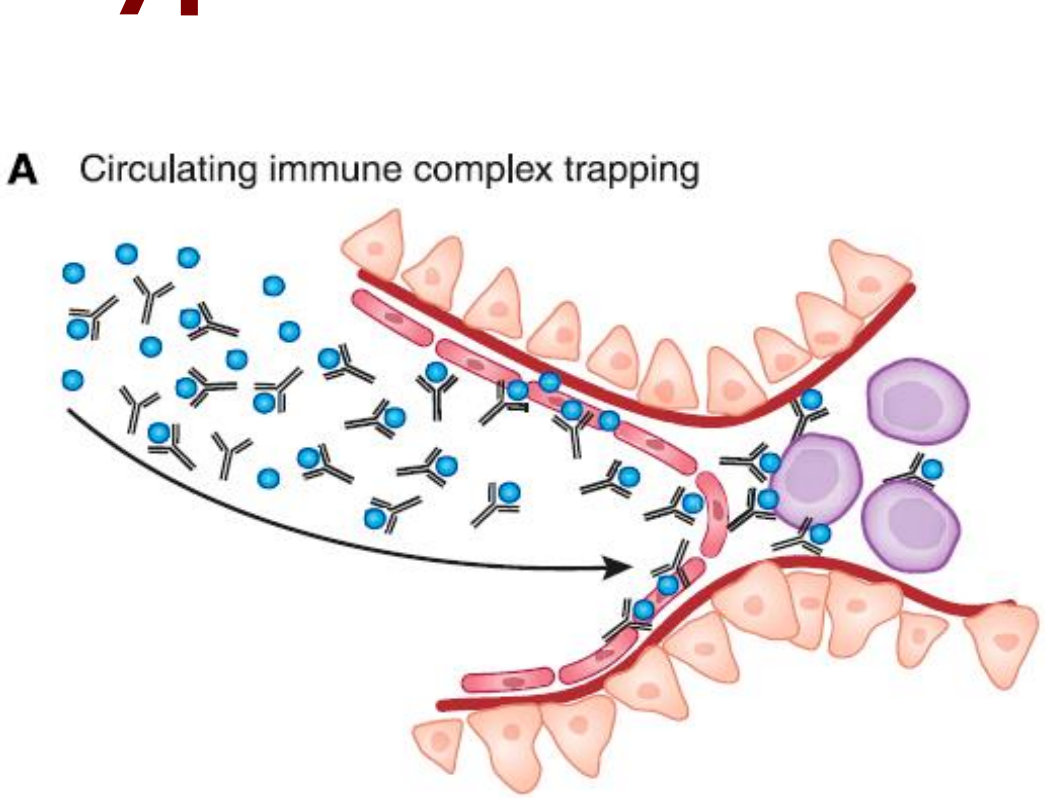
- Damage by
  - Activation of complement
  - Induce inflammation

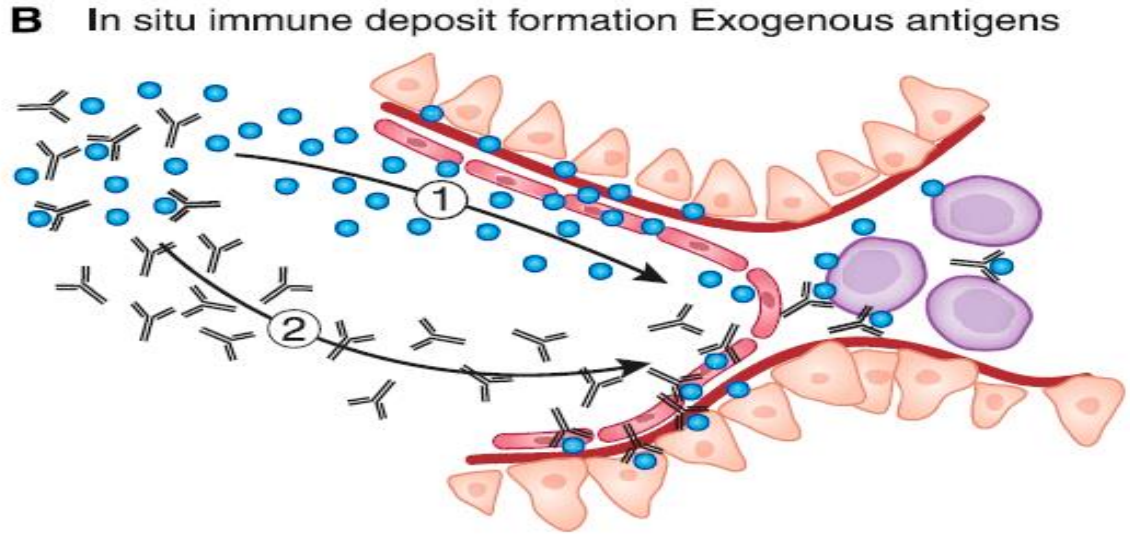
.

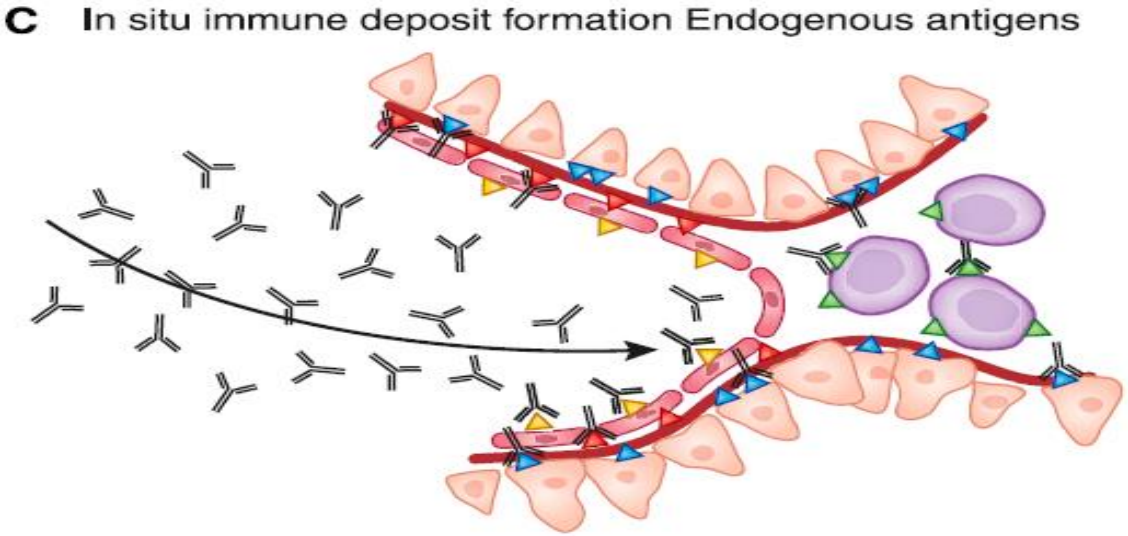
Type of antigens forming Immune complexes

- Fixed intrinsic tissue antigens
  - Goodpasture antigen (anti GBM antigen) – Linear deposits
  - Haymen antigen- podocyte (Membranous nephropathy)
  - Mesangial antigens
- Planted antigens
  - Exogenous (infectious antigens, drugs)
  - Endogenous (DNA, complement, IgA)
- Circulating immune complex deposition
  - Endogenous antigens (DNA, tumour antigens)
  - Exogenous antigens (Infectious products)

Types of Immune complexes

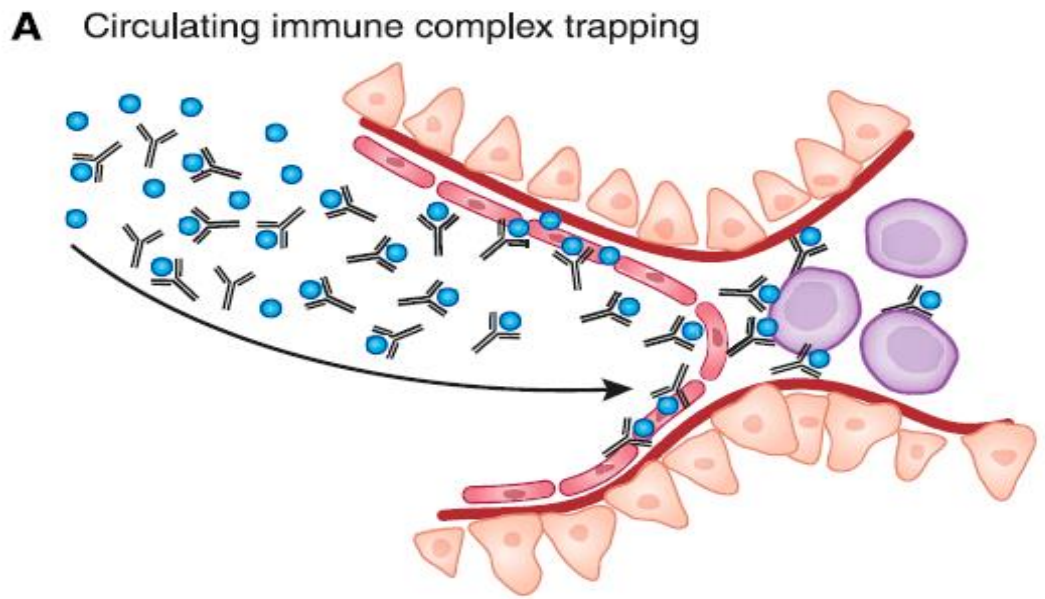






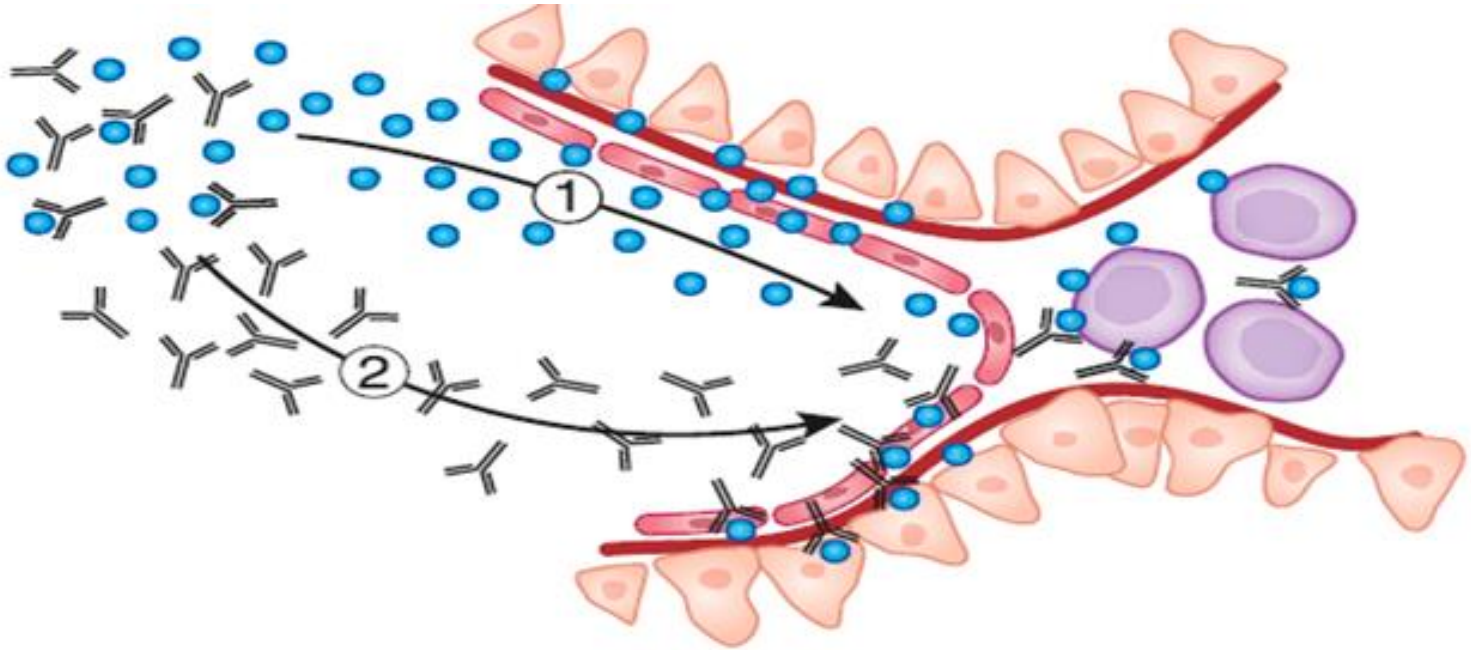
Circulating Immune Complexes

- Antigen-antibody complexes are forming in slight antigen excess
- Soluble immune complexes formed in the circulation are then passively trapped in subendothelial and mesangial areas of the glomerulus



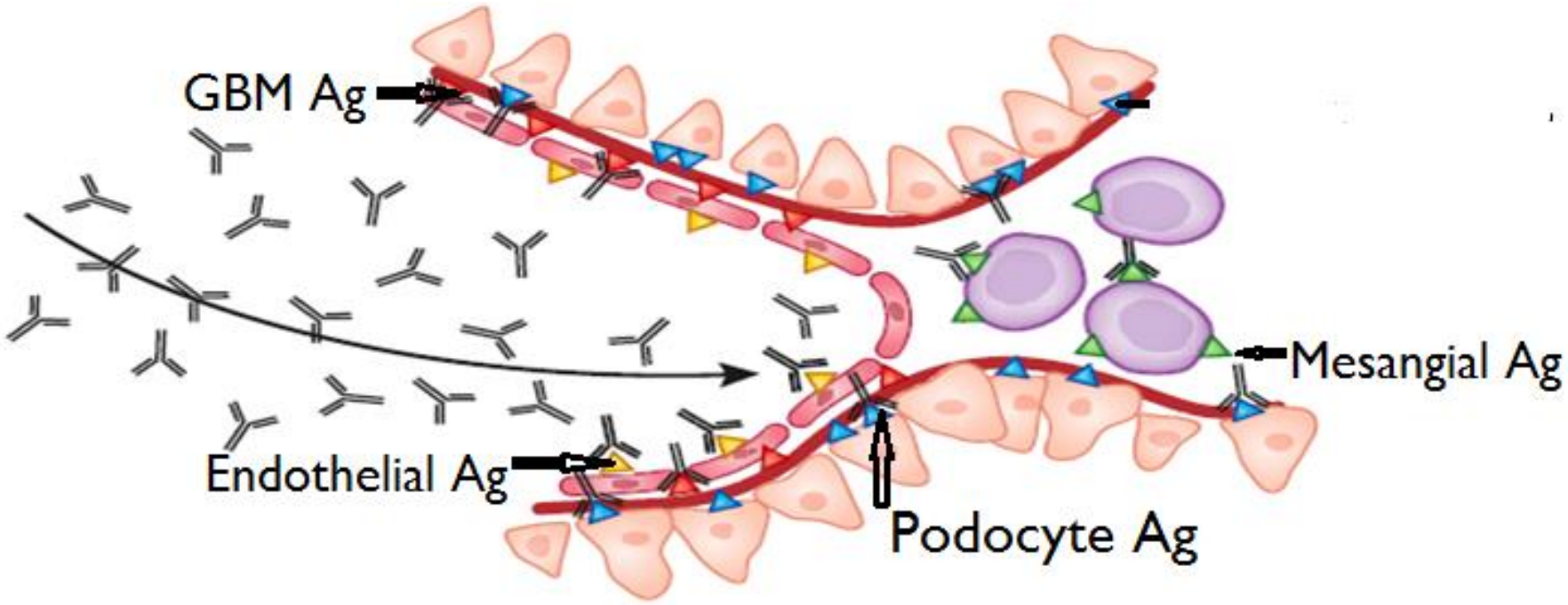
In situ formation of immune deposits with Exogenous antigens

- Antigens localize independently of antibody in subendothelial or mesangial sites (larger antigens) or beneath podocytes in the subepithelial space (smaller antigens).
- Free antibody binds to these planted antigens to form immune complexes in situ.

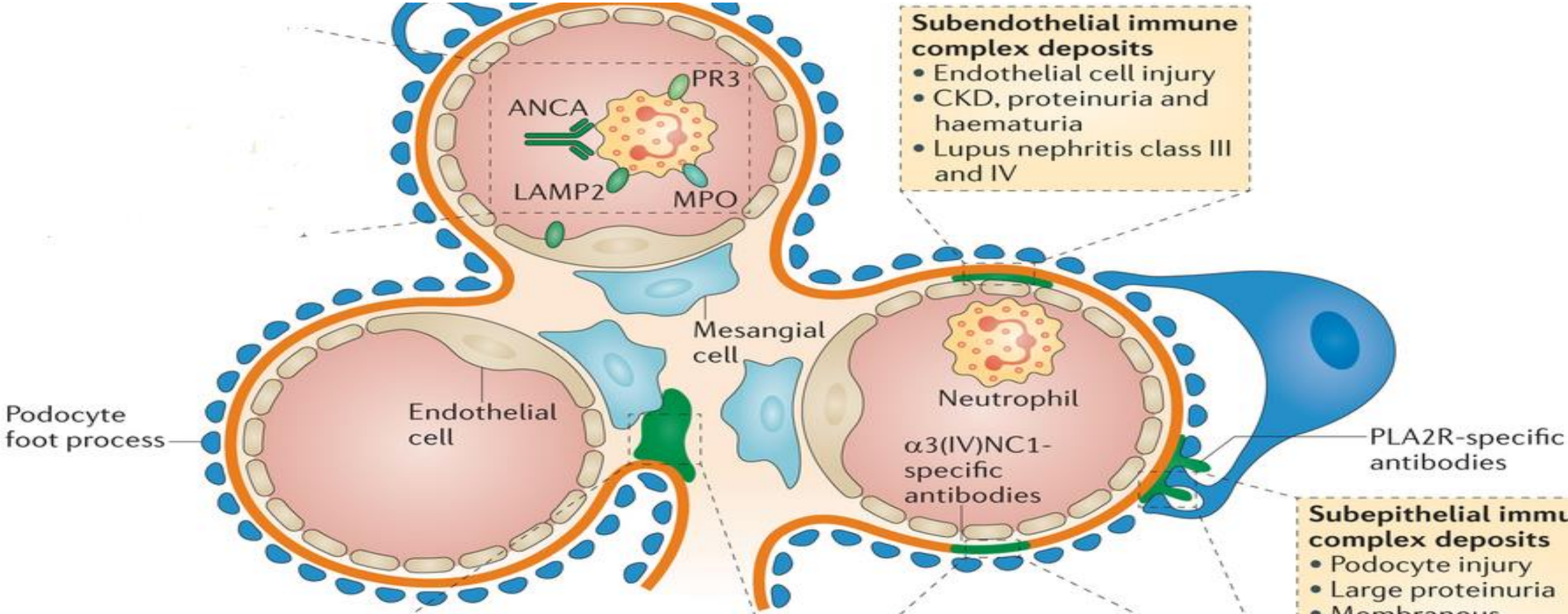


In situ formation of immune deposits with Endogenous antigens

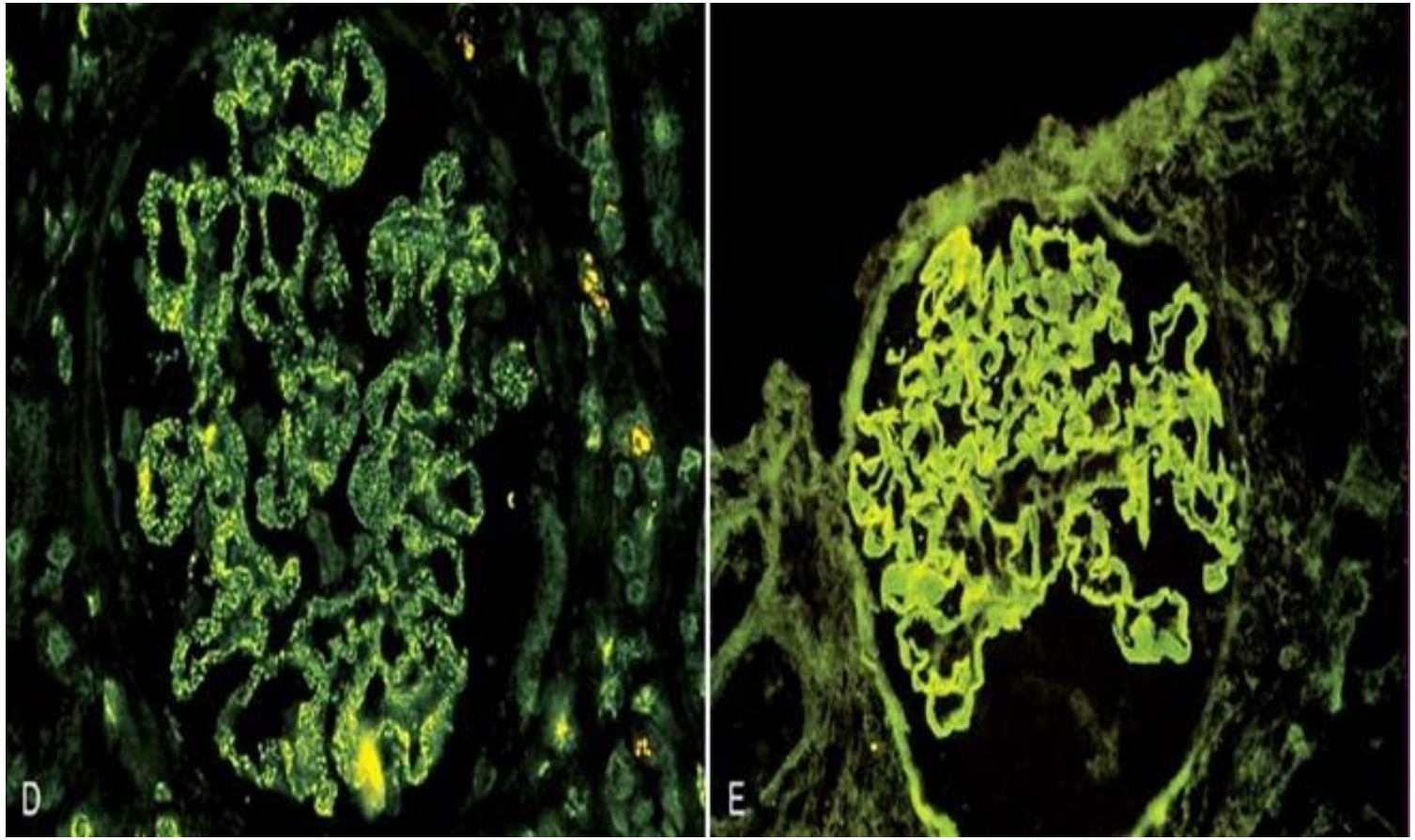
- Glomerular in situ immune deposit formation due to autoantibodies to normal glomerular constituents



Sites of Immune complex deposition


Subendothelial immune complex deposits
• Endothelial cell injury
• CKD, proteinuria and haematuria
• Lupus nephritis class III and IV
PR3
ANCA
LAMP2
MPO
Mesangial cell
Podocyte foot process
Endothelial cell
Neutrophil
α3(IV)NC1-specific antibodies
PLA2R-specific antibodies
Subepithelial immune complex deposits
• Podocyte injury
• Large proteinuria
• Membranous nephropathy
– Primary (PLA2R)
– Secondary (lupus nephritis class V)
Mesangial immune complex deposits
• Mesangial cell injury
• Asymptomatic proteinuria and microscopic haematuria
• IgA nephropathy and lupus nephritis class I and II
Linear immune complex deposits
• Endothelial cell and podocyte injury
• CKD, proteinuria and haematuria
• Anti-GBM disease

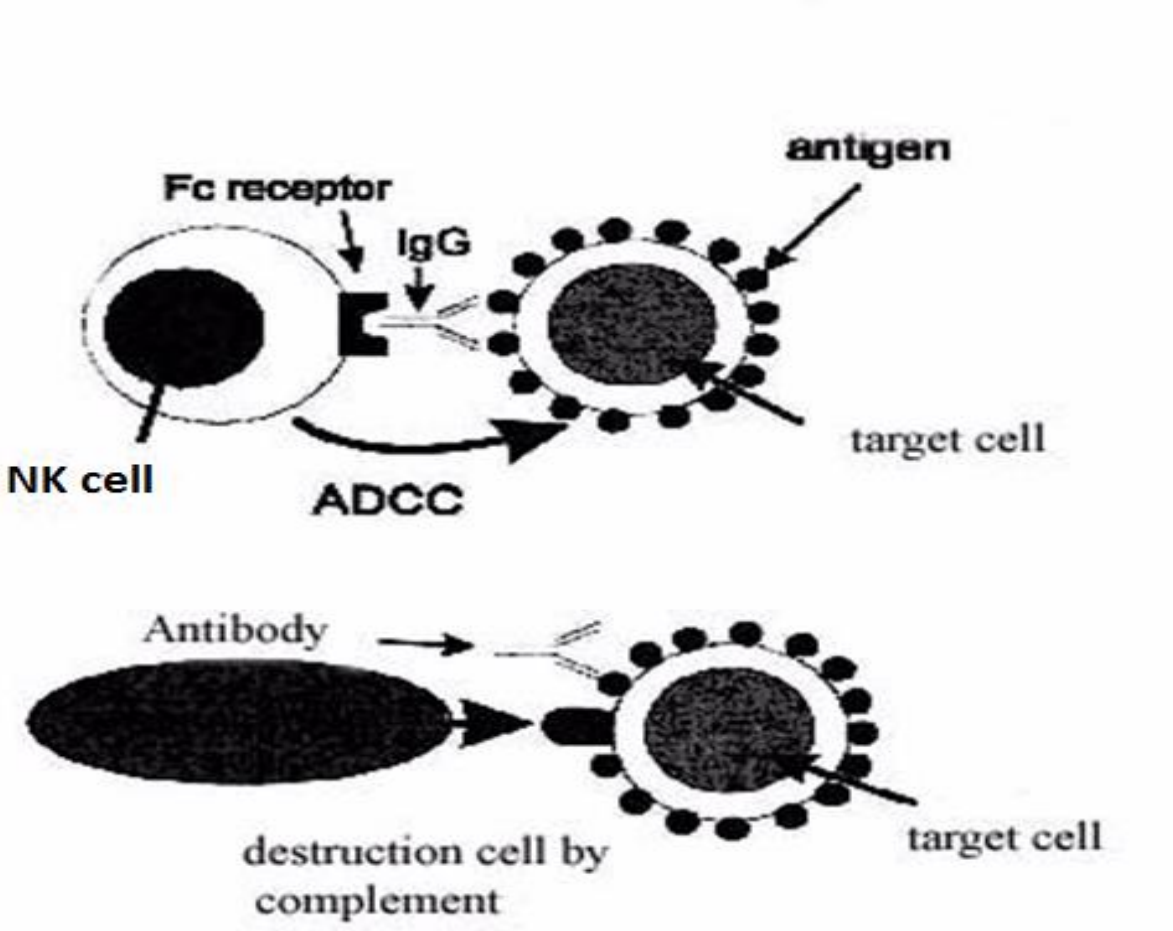
Immunofluorescence microscopy



Granular pattern
Circulating IC, Planted Ags

Linear smooth - anti-GBM disease

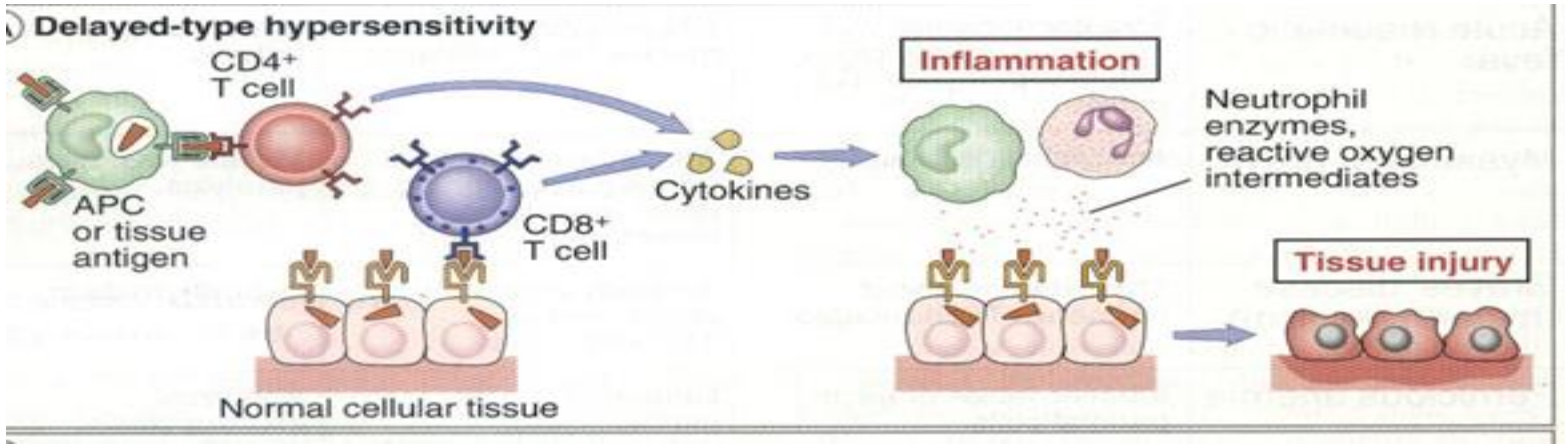
Type II hypersensitivity (antibody mediated Cytotoxicity)



- Antibodies are directed to cell surface antigens
- 2 mechanisms
  - ADCC
  - Complement mediated damage

Type IV Hypersensitivity

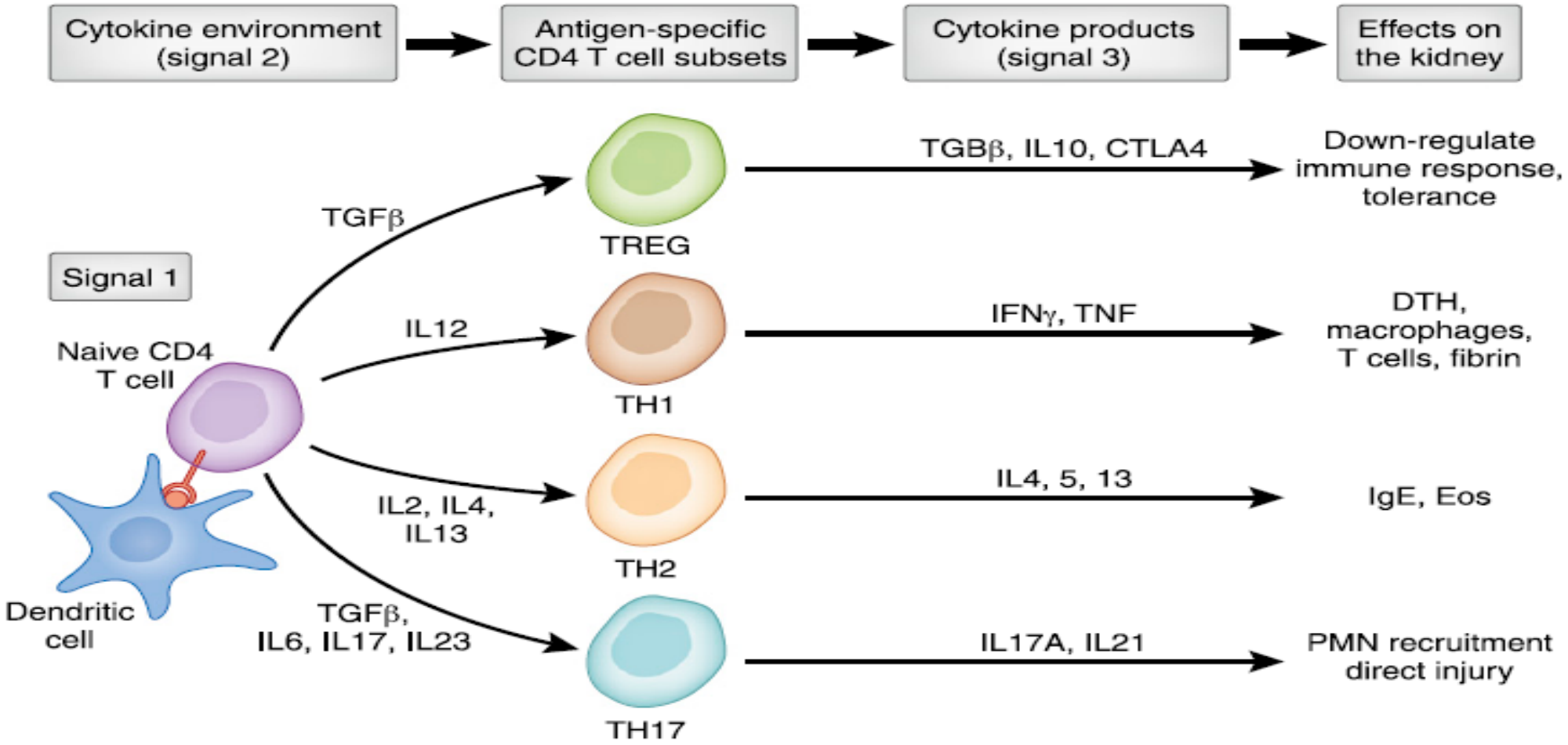
Continuous release of cytokines by Th1 cells lead to accumulation of macrophages which form in to epithelioid and giant cells-→ granuloma



T cell mediated injury

- Through regulation of B-cell differentiation and antibody production
- TH1 → Cytokines → macro
- TH2 → Cytokines → baso, eosino
- TH17 → IL-17 and pro-inflammatory cytokines → inflammation
- CD8 → cytotoxic

T cell mediated injury



Complement and cytokines

- ICs/Ig deposits → activate complement PWs → inflammation, C5b-9 (MAC)

- Cytokines secreted by T cells and Innate cells → activate cells → inflammation

Autoimmunity

- Auto-antibodies
  - antiendothelial antibodies, anti-DNA antibodies, and antineutrophil cytoplasmic antibodies, anti-GBM antibodies

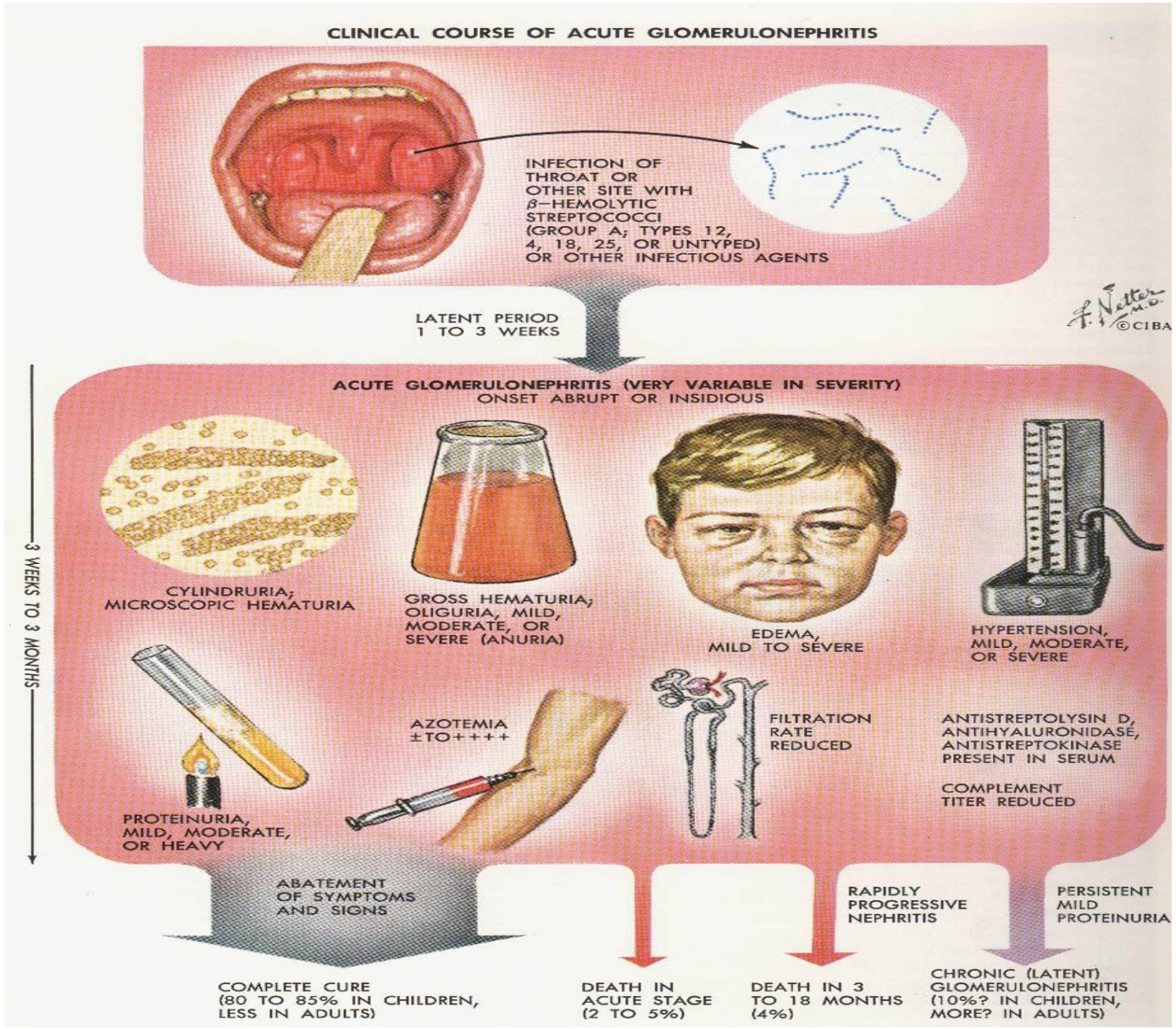
- Auto reactive T cells

Nephritic syndrome

Diseases Presenting as GN

- Postinfectious or Poststreptococcal GN
- IgA Nephropathy
- Anti-GBM Nephritis
- Lupus Nephritis
- Membranoproliferative GN
- Henoch-Schönlein purpura

Signs & Symptoms



Postinfectious or Poststreptococcal GN

- Occurs 10-14 days after nephritogenic group A Streptococcal infection → impetigo/ sore throat
- Form **circulating** immune complexes
- The antigen responsible
  - **Streptococcal pyogenic exotoxin B (SpeB)**
  - **nephritis-associated plasmin receptor (NAPlr)**
- Sub-epithelial IC deposition → complement activation → cell injury

PSGN

- Other auto- antibodies also present
  - IgM and IgG rheumatoid factors, antiendothelial antibodies, anti-DNA antibodies, and antineutrophil cytoplasmic antibodies (ANCA)

- Other infectious causes
  - Staphyloccocci, Pneumococci, Herpesvirus, EBV, Hep. B

Immunology profile

- Low C3
- Circulating IC
- Cryoglobulin
- Rheumatoid factor
- High IgG
- Past Strep infection – Anti-Dnase-B
  - Anti- Streptolysin-O

IgA nephropathy (IgAN)

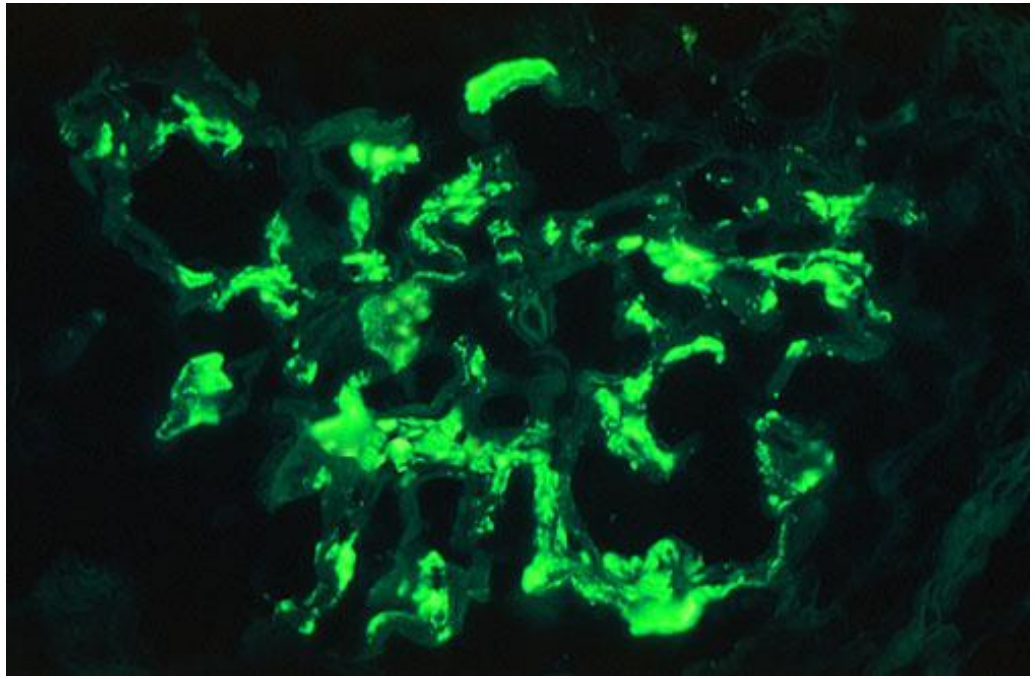
- Characterized by focal mesangial proliferation

- Caused by
  - aberrant glycosylation of IgA molecules (galactose-deficient IgA1)
    - Act as autoantigens → form IC complexes
  - Abnormal hepatic and mesangial clearance of IgA

- Leads to diffuse mesangial IgA immune complex deposition

Immunology profile

- High circulating polymeric IgA 1
- IgA containing immune complexes in serum
- Mesangial IgA staining immunofluorescence in renal biopsies



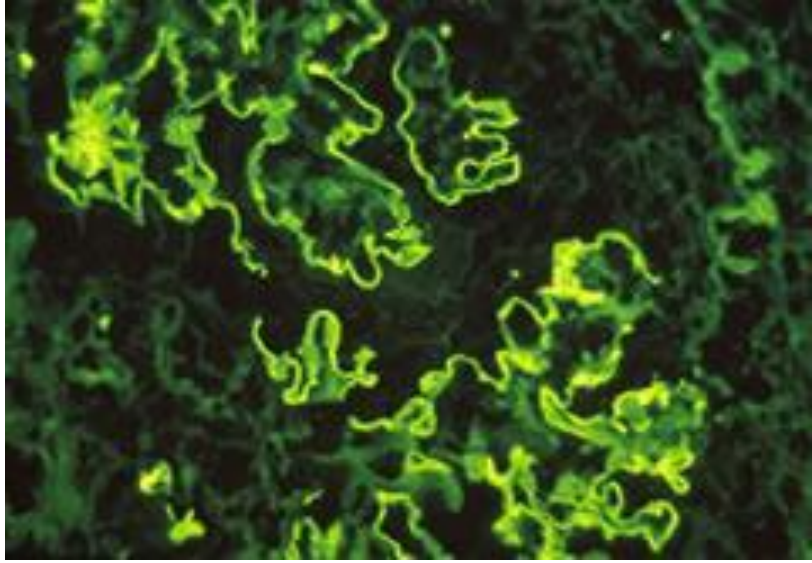
Henoch-Schönlein purpura

- Multisystem disorder characterized by the deposition of IgA ICs in affected organs
- Pathogenesis is similar to IgAN
- Typically affects children less than 10 years of age with a male predominance.
  - Often follows an upper respiratory tract infection

Anti-GBM disease

- Characterized by an acute, focal necrotizing GN
- Deposition of IgG and C3 along the GBM (linear pattern)
- Caused by
  - Deposition of IgG Anti-GBM antibodies directed against GBM Type IV collagen
  - Classical complement pathway activation
  - Activated T h17 cells → direct damage

Immunology profile



- Immunofluorescent studies
  - Linear staining of IgG along the GBM
- Diagnosis is confirmed by the detection of circulating antibodies directed against the type IV collagen (quantitative anti-GBM)
- Circulating antineutrophil cytoplasmic antibodies (ANCA) – in upto 1/3rd

Lupus nephritis

- Autoimmune response
  - anti-double-stranded DNA antibodies (anti-DNA) in serum and in glomerular deposits – most prominent feature
  - Other auto antibodies
    - lupus anticoagulant, anticardiolipin antiphospholipid, and anti-beta2 glycoprotein antibodies, rheumatoid factor

→ Form ICs → complement activation

- Antigen-specific T cell reactivity to nuclear antigens

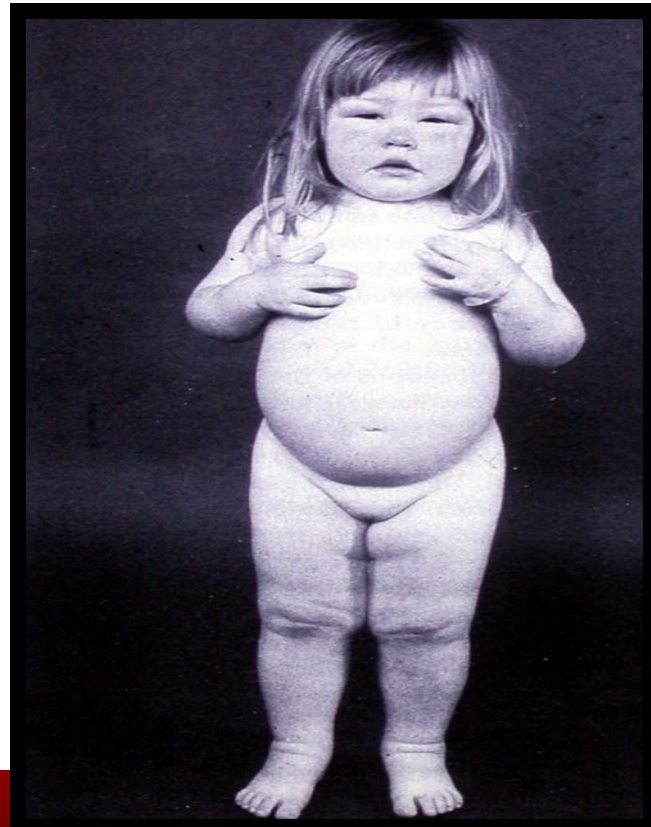
Nephrotic syndrome

Diseases Presenting as Nephrotic syndrome

- Minimal change nephrotic syndrome
- Membranous nephropathy
- Focal segmental glomerulosclerosis
- Amyloidosis

Clinical / Lab features

- Proteinuria (urine protein loss > 2 gm/day)
- Hypo-proteinemia (serum albumin < 2.5 gm/dL)
- Edema
- Hyperlipidemia
- Weight gain
- Ascites



Minimal change nephrotic syndrome

- Most common diagnosis associated with nephrotic syndrome in children – mainly idiopathic
- Triggered by infections, drugs, malignancies, autoimmune diseases etc

- Caused by
  - Primarily T cell mediated →cytokines, permeability factors
    - soluble podocyte urokinase receptor, TNF, IL-13, IL-8, Il-12
  - Defect in the podocyte which increases the permeability
    - Mutations in podocyte genes that regulate the slit diaphragm, cell membrae and cytoskeleton

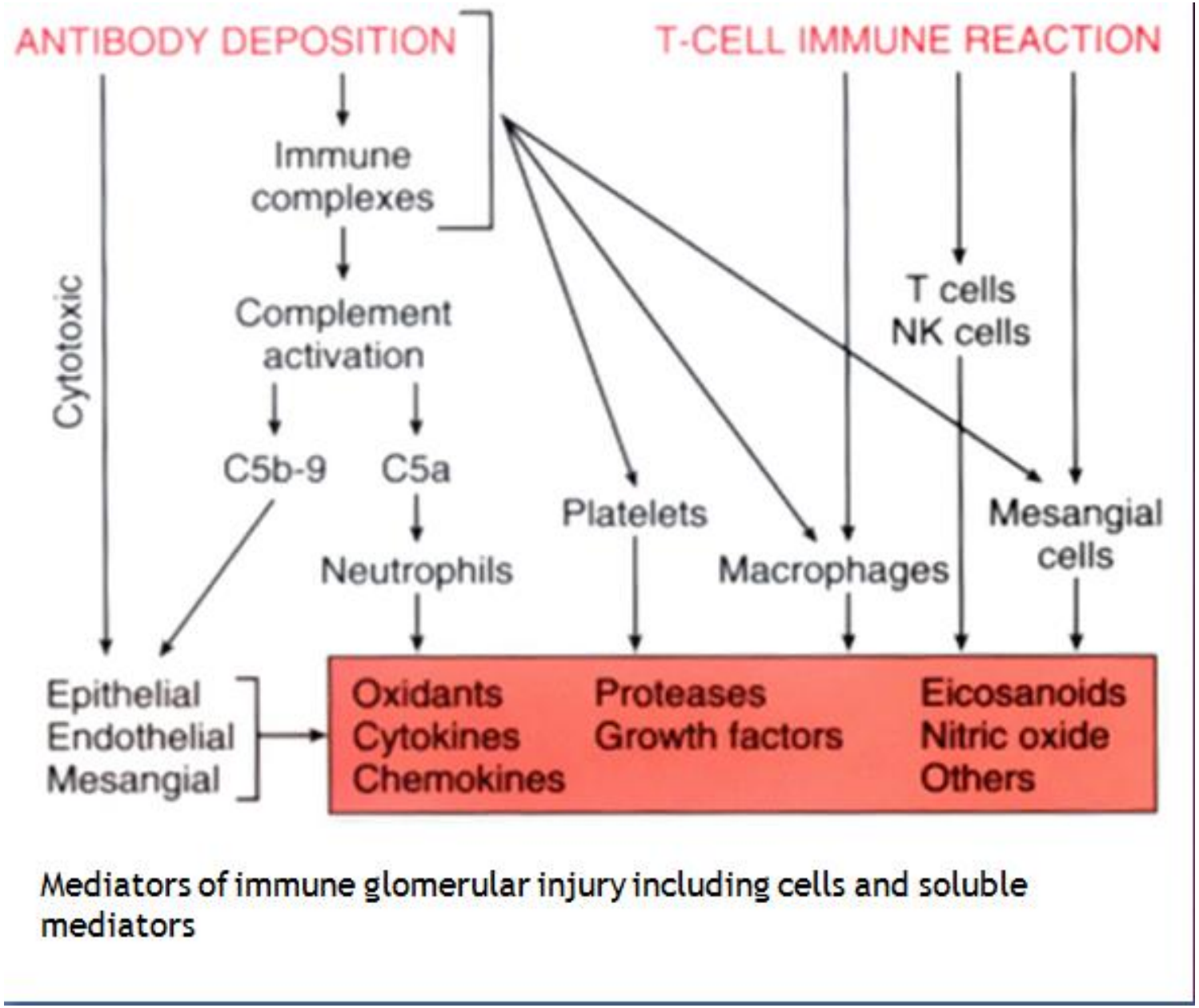
Membranous nephropathy

- Commonest cause of nephrotic syndrome in adults

- Caused by:
  - humoral - IgG antibodies form subepithelial immune deposits →binding to podocytes
  - activated complement cascade – activated C5b-9 alters the actin cytoskeleton, and podocyte DNA damage

Focal segmental glomerulosclerosis

- Final pathway of many glomerular diseases
- Immunopathogenesis = Minimal change disease



Mediators of immune glomerular injury including cells and soluble mediators

Summary

- Immunological mechanisms involved in renal diseases
  - Innate
  - Adaptive
  - Hypersensitivity reactions
  - Autoimmunity
- Mechanisms involved in nephritic diseases
- Mechanisms involved in nephrotic diseases