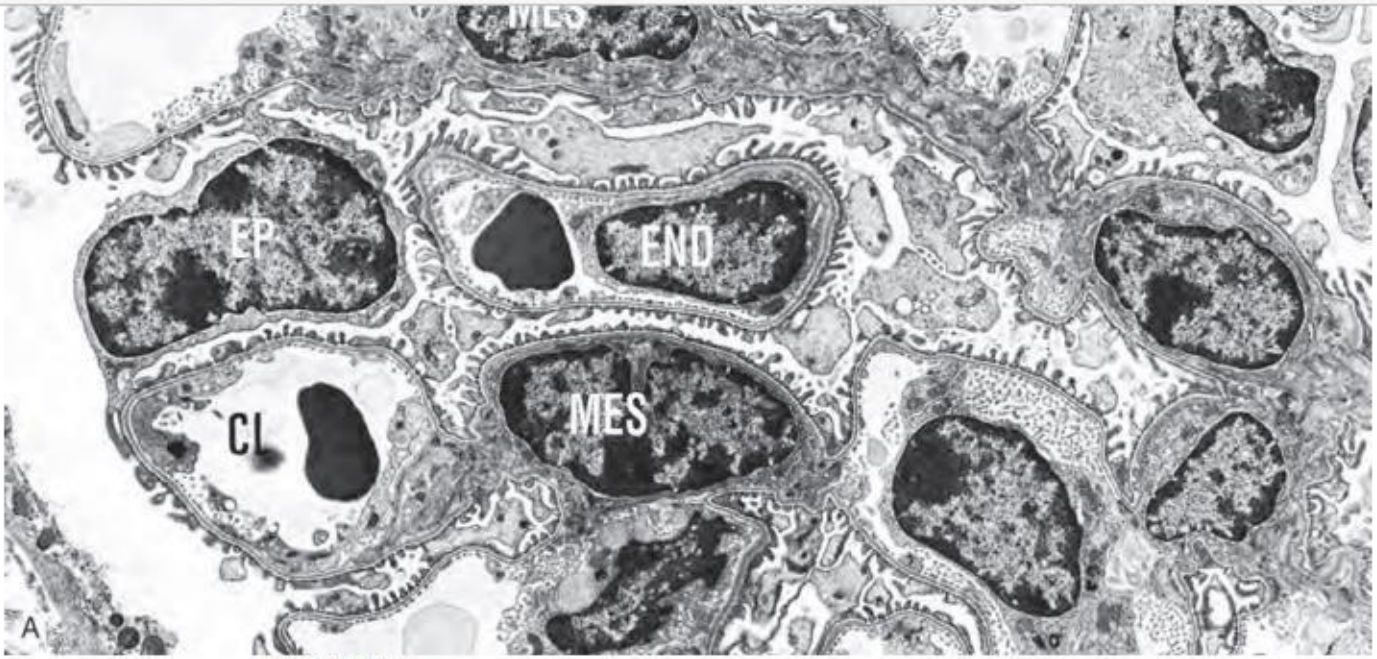
NEPHROTIC SYNDROME

Pathogenesis of Renal diseases

- **Glomerular disease** ---- Most often immunologically mediated
- **Tubular disease** ---- Toxins / infections
- **Interstitial disease** --- Toxins / infections
- **Vascular disease** --- Hypertension / Ischaemia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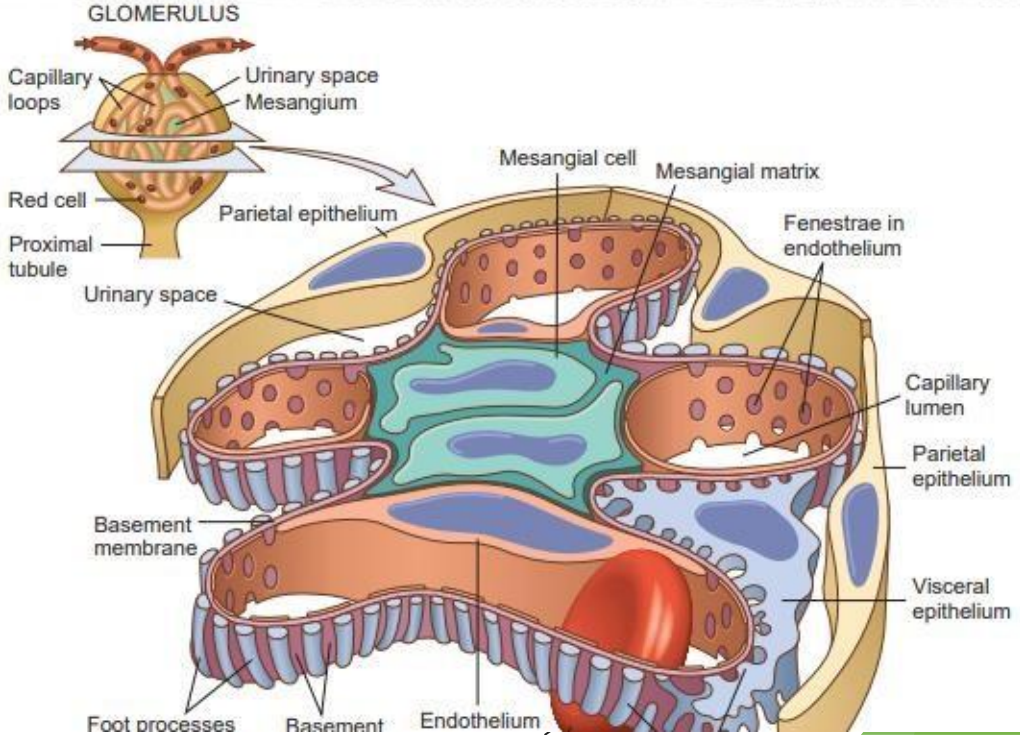
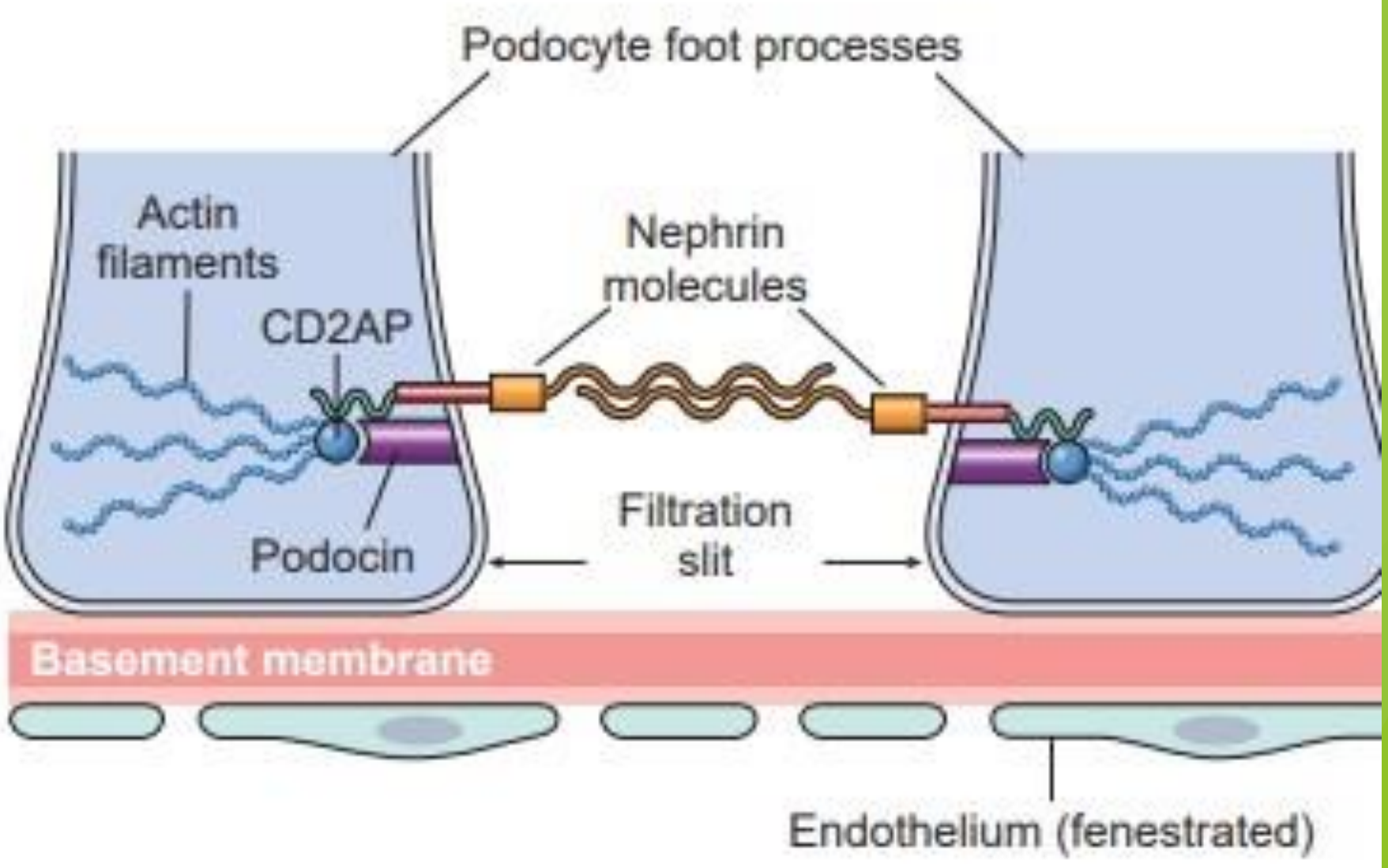
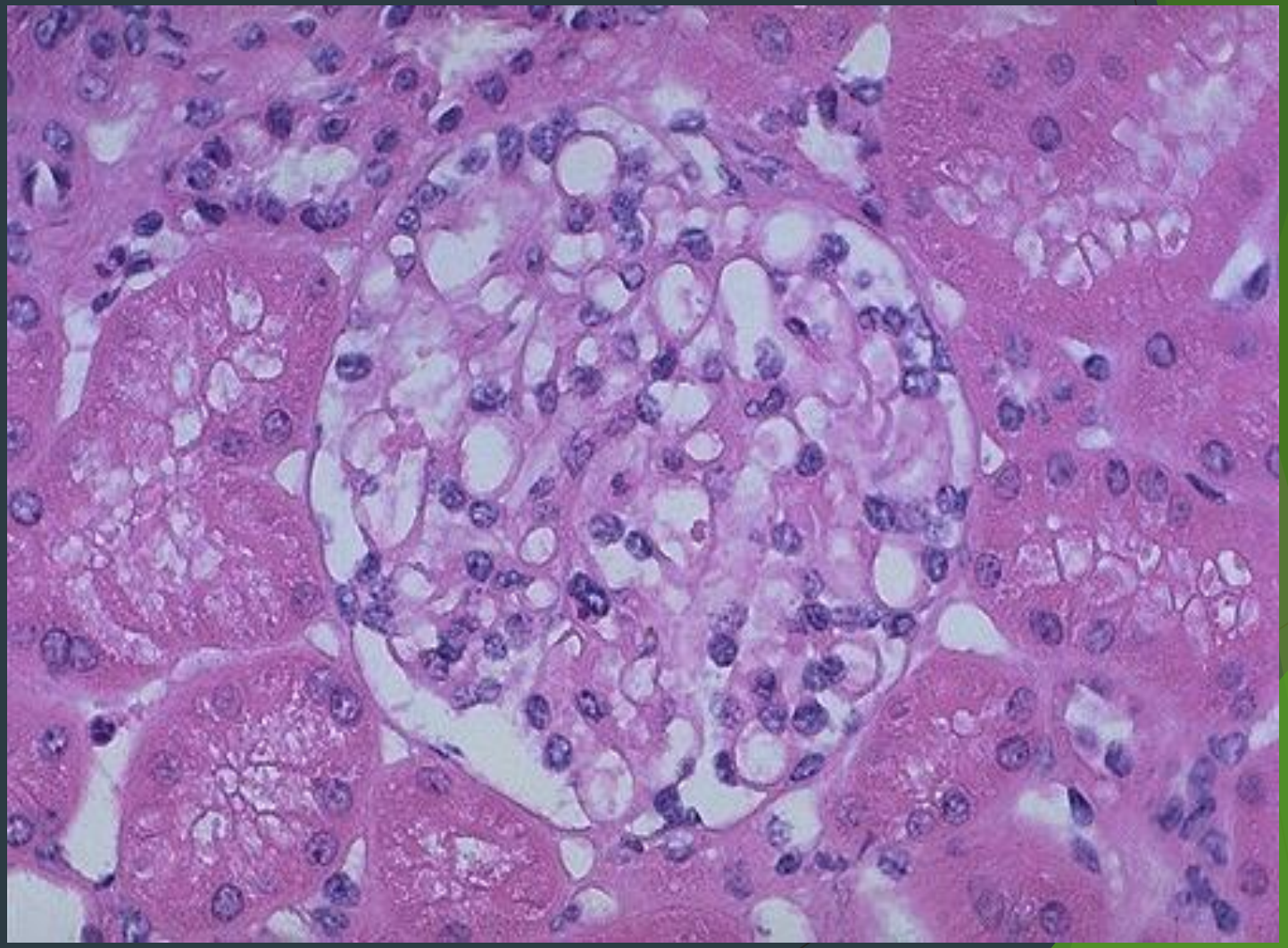

GLOMERULUS
Capillary loops
Urinary space
Mesangium
Red cell
Proximal tubule
Parietal epithelium
Mesangial cell
Mesangial matrix
Fenestrae in endothelium
Urinary space
Capillary lumen
Parietal epithelium
Basement membrane
Visceral epithelium
Foot processes
Basement
Endothelium


Podocyte foot processes
Actin filaments
CD2AP
Nephrin molecules
Podocin
Filtration slit
Basement membrane
Endothelium (fenestrated)

Normal Glomerulus



Normal Glomerulus

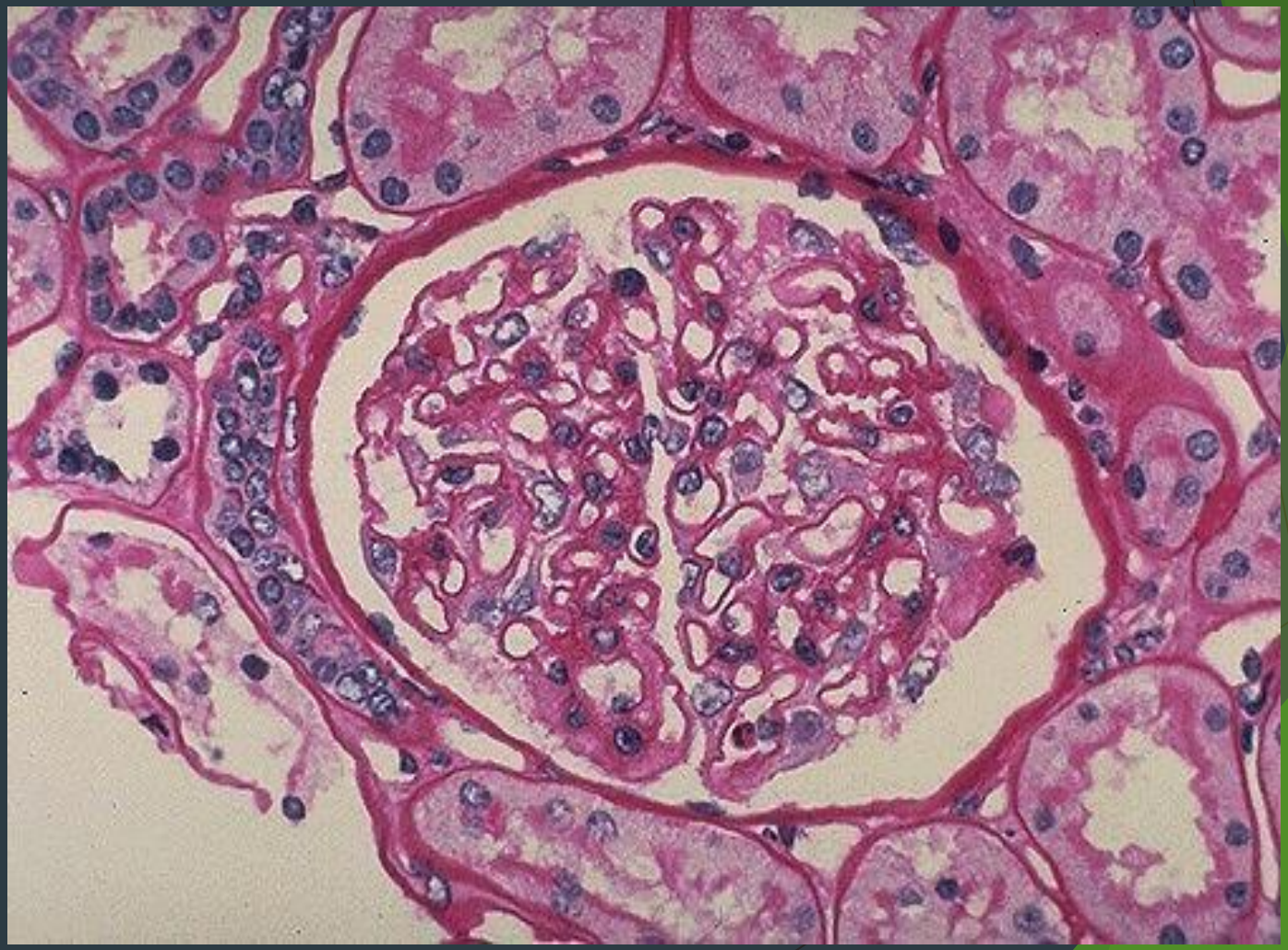


Table 20-3 Glomerular Syndromes

Syndrome	Manifestations
Nephritic syndrome	Hematuria, azotemia, variable proteinuria, oliguria, edema, and hypertension
Rapidly progressive glomerulonephritis	Acute nephritis, proteinuria, and acute renal failure
Nephrotic syndrome	>3.5 gm/day proteinuria, hypoalbuminemia, hyperlipidemia, lipiduria
Chronic renal failure	Azotemia → uremia progressing for months to years
Isolated urinary abnormalities	Glomerular hematuria and/or subnephrotic proteinuria

NEPHROTIC SYNDROME

- Massive Proteinuria - 3.5 gm or more
- Hypoalbuminaemia - albumin < 3 gm/ dl
- Edema
- Hyperlipidaemia and Lipiduria;

PATHOPHYSIOLOGY

- Nephrotic syndrome is caused by a derangement in glomerular capillary walls resulting in increased permeability to plasma protein
- The glomerular capillary wall, with its endothelium, GBM, and visceral epithelial cells, acts as a size and charge barrier through which the plasma filtrate passes.
- Increased permeability resulting

Proteinuria

- **Selective -** Low molecular weight proteins

  Albumin - 70 kDa

  Transferrin – 76 kDa,

- **Poorly selective** - High molecular weight globulins

Hyperlipidaemia

Increase in cholesterol , LDL , VLDL , Lipoprotein , apoprotein

Decrease in HDL

CAUSES:

- Increased synthesis of lipoproteins in liver
- abnormal transport of lipids
- decreased catabolism

Lipiduria

- Leakage across glomerular capillary wall
- Oval fat bodies

Susceptibility to infection

- Loss of immunoglobins
- Loss of low molecular weight complement components in urine

Thrombotic & Thromboembolic complications

Loss of - Antithrombin III

- Antiplasmin activity

Renal vein Thrombosis

CAUSES OF NEPHROTIC SYNDROME

Table 20-7 Cause of Nephrotic Syndrome

Causes	Approximate Prevalence (%)*	
	Children	Adults
Primary Glomerular Disease		
Membranous nephropathy	3	30
Minimal-change disease	75	8
Focal segmental glomerulosclerosis	10	35
Membranoproliferative glomerulonephritis and dense deposit disease†	10	10
Other proliferative glomerulonephritides (focal, "pure mesangial," IgA nephropathy)†	2	17
Systemic Diseases		
Diabetes mellitus		
Amyloidosis		
Systemic lupus erythematosus		
Drugs (nonsteroidal anti-inflammatory, penicillamine, heroin)		
Infections (malaria, syphilis, hepatitis B and C, HIV)		
Malignant disease (carcinoma, lymphoma)		
Miscellaneous (bee-sting allergy, hereditary nephritis)		

*Approximate prevalence of primary disease = 95% of nephrotic syndrome in children, 60% in adults. Approximate prevalence of systemic disease = 5% in children, 40% in adults.
†Membranoproliferative and other proliferative glomerulonephritides may result in mixed nephrotic/nephritic syndromes.

MINIMAL CHANGE DISEASE

(Lipoid Nephrosis)

Lipoid Nephrosis
Minimal change Glomerulonephritis

- Most frequent cause of NS in children,
- Peak incidence in children = 2 - 6 yrs
- Sometimes follows respiratory infection / immunisation
- **characteristic feature : responds to corticosteroid therapy**

Minimal change disease – Etiology & Pathogenesis:

IMMUNOLOGIC BASIS:

1. Association with respiratory infections and immunisations,
2. Response to steroids,
3. Association with other atopic disorders,
4. Prevalence of certain HLA haplotypes

Etiology & Pathogenesis

Immune dysfunction of T cells

↓

cytokine like circulating substance

↓

affects visceral epithelial cells & increases glomerular permeability

Pathogenesis

- Immune dysfunction that results in the elaboration of factors that damage visceral epithelial cells and cause proteinuria.
- Candidate pathogenic factors such as angiopoietin-like-4, circulating permeability factor

Morphology

- *Light microscopy* : Glomeruli - Normal,
  - … Cells of PCT laden with lipid
- *Electron Microscopy* :
  - … Basement Membrane - Normal ,
  - … No electron dense deposits

  Visceral epithelial cells - effacement of foot processes
- *Immunofluorescense*: No immune / complement deposits;

Minimal change Disease-Normal BM, Absence of proliferation

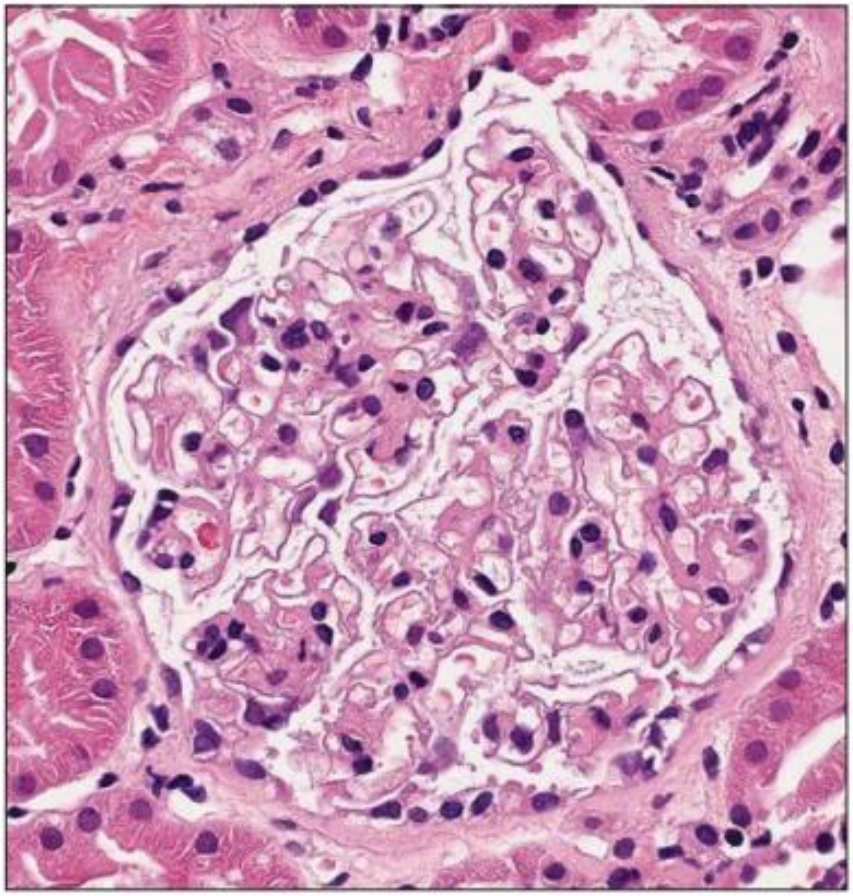
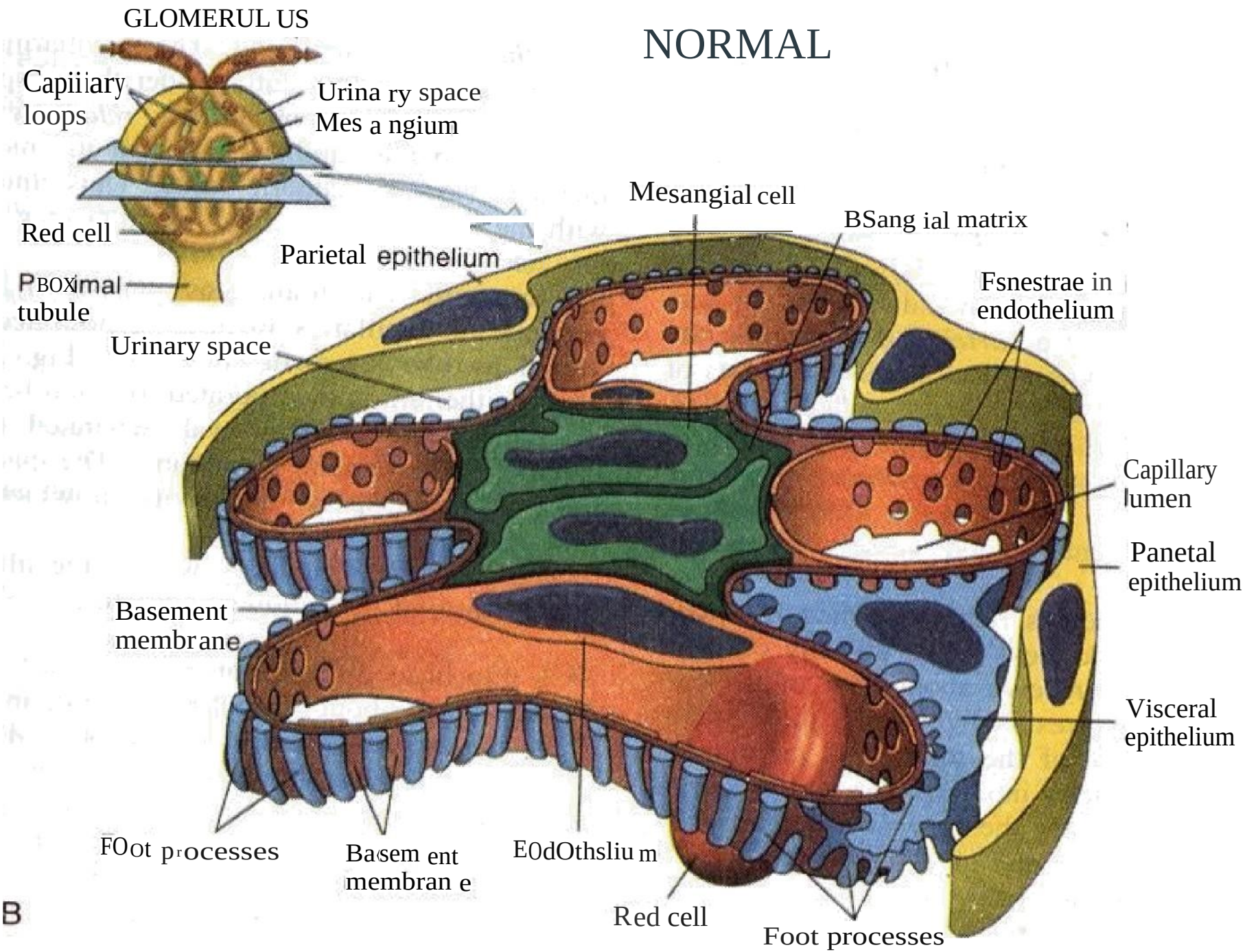
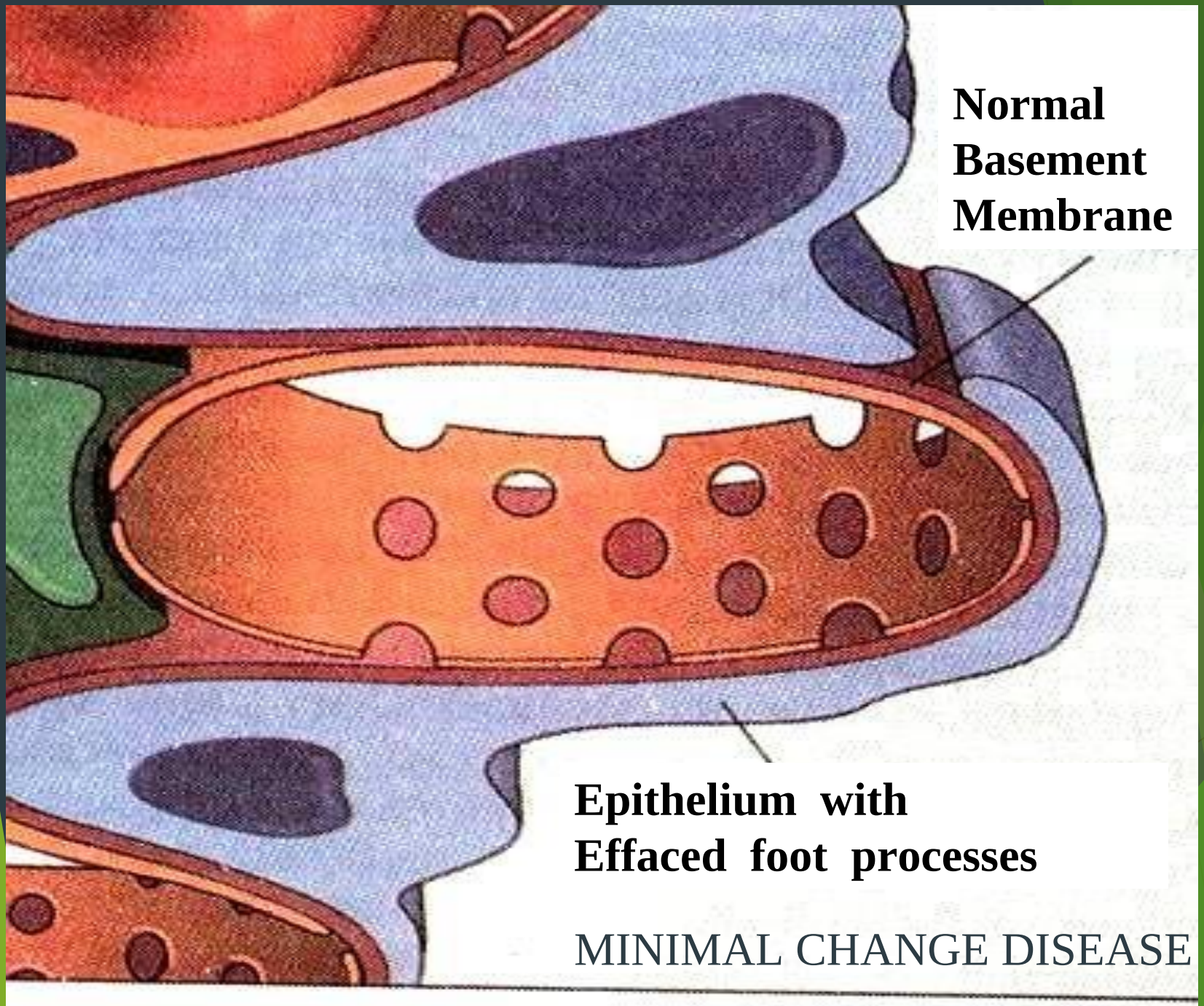


FIGURE 5.4 Light micrograph of glomerulus from a child showing no glomerular changes. (H&E, ×370.)

NORMAL


GLOMERUL US
Capiiiary loops
Urina ry space
Mes a ngium
Red cell
PBOXimal tubule
Parietal epithelium
Urinary space
Mesangial cell
BSang ial matrix
Fsnestrae in endothelium
Capillary lumen
Panetal epithelium
Basement membrane
Visceral epithelium
FOot processes
Basem ent membran e
E0dOthsliu m
Red cell
Foot processes
B



MINIMAL CHANGE DISEASE

Minimal change disease … Clinical Course

- Despite massive proteinuria renal function remains good,
- Proteinuria - highly selective,
- > 90 % children respond to corticosteroid therapy,
- Adults: - slower to respond,
  - long term prognosis excellent;

MEMBRANOUS GLOMERULONEPHRITIS

Membranous Glomerulonephritis

- Most common cause of NEPHROTIC SYNDROME in adults
- Characterised by
  - diffuse thickening of the glomerular capillary wall
  - electron dense immunoglobin deposits along subepithelial side of BM

Membranous Glomerulonephritis … Types

- Idiopathic/primary - 85%- PLA2R, THSDR2A
- Secondary
  - Drugs : captopril , penicillamine , gold , NSAID,
  - Tumors : lung , colon , melanoma
  - SLE
  - Infections : Hepatitis B,C, Malaria
  - Other autoimmune- Thyroiditis

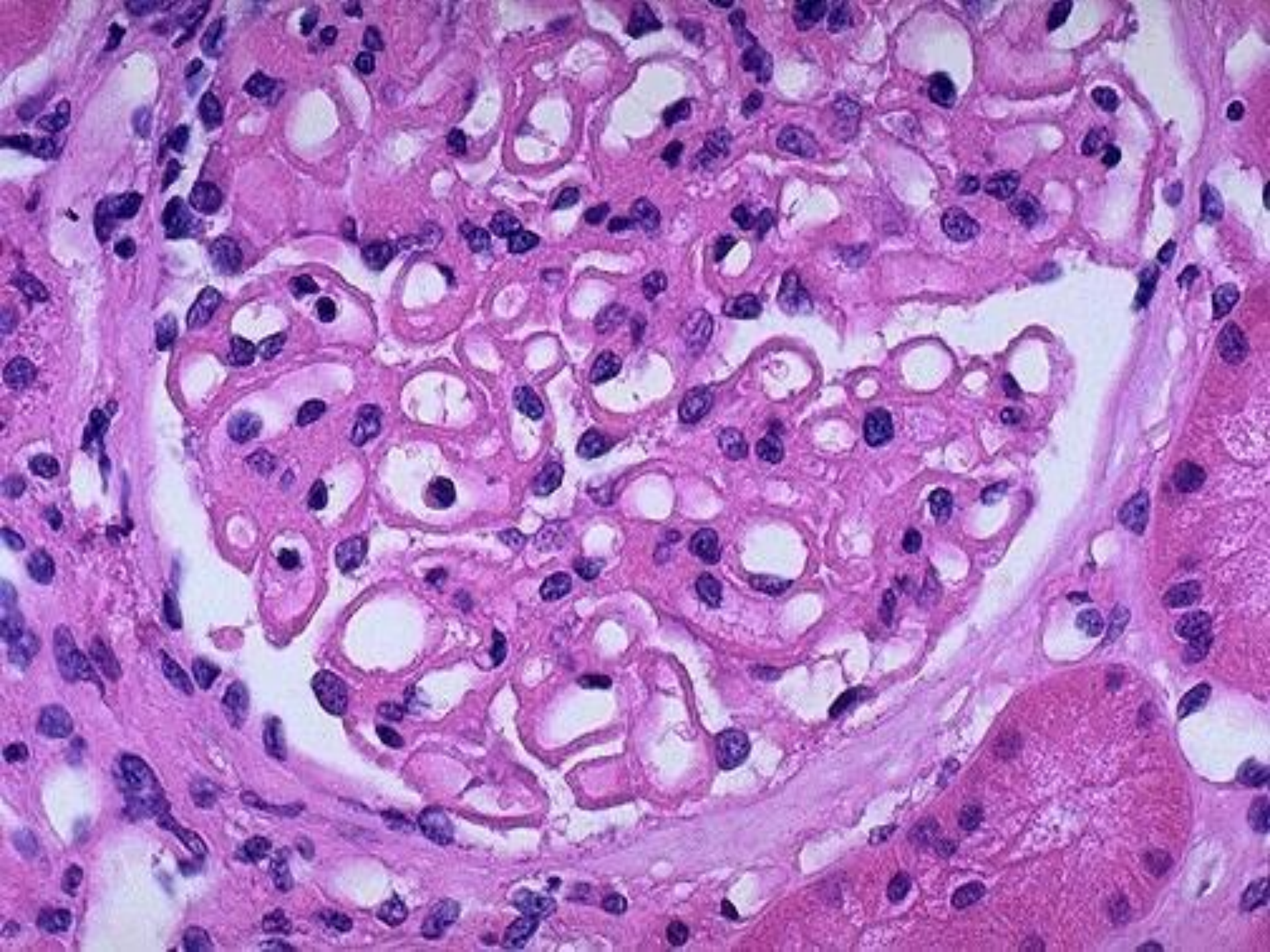
Membranous Glomerulonephritis -- Etiology & Pathogenesis

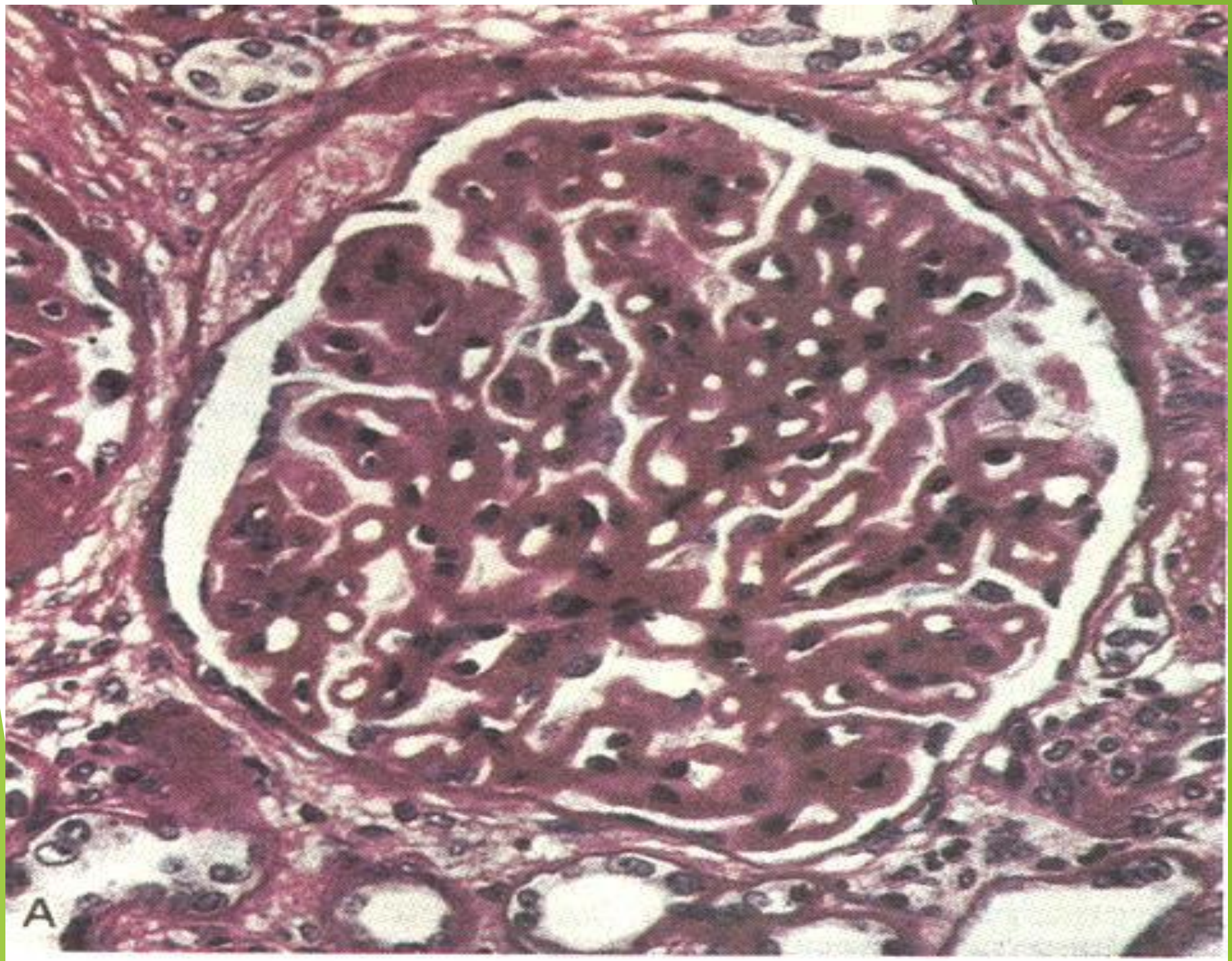
- Chronic immune complex-mediated disease,
- Autoimmune
- Direct damage to glomerulus by C5b - C9
- C5b- C9 induce epithelial & mesangial cells to secrete proteases & oxidants

Membranous Glomerulonephritis -- Morphology

Light Microscopy

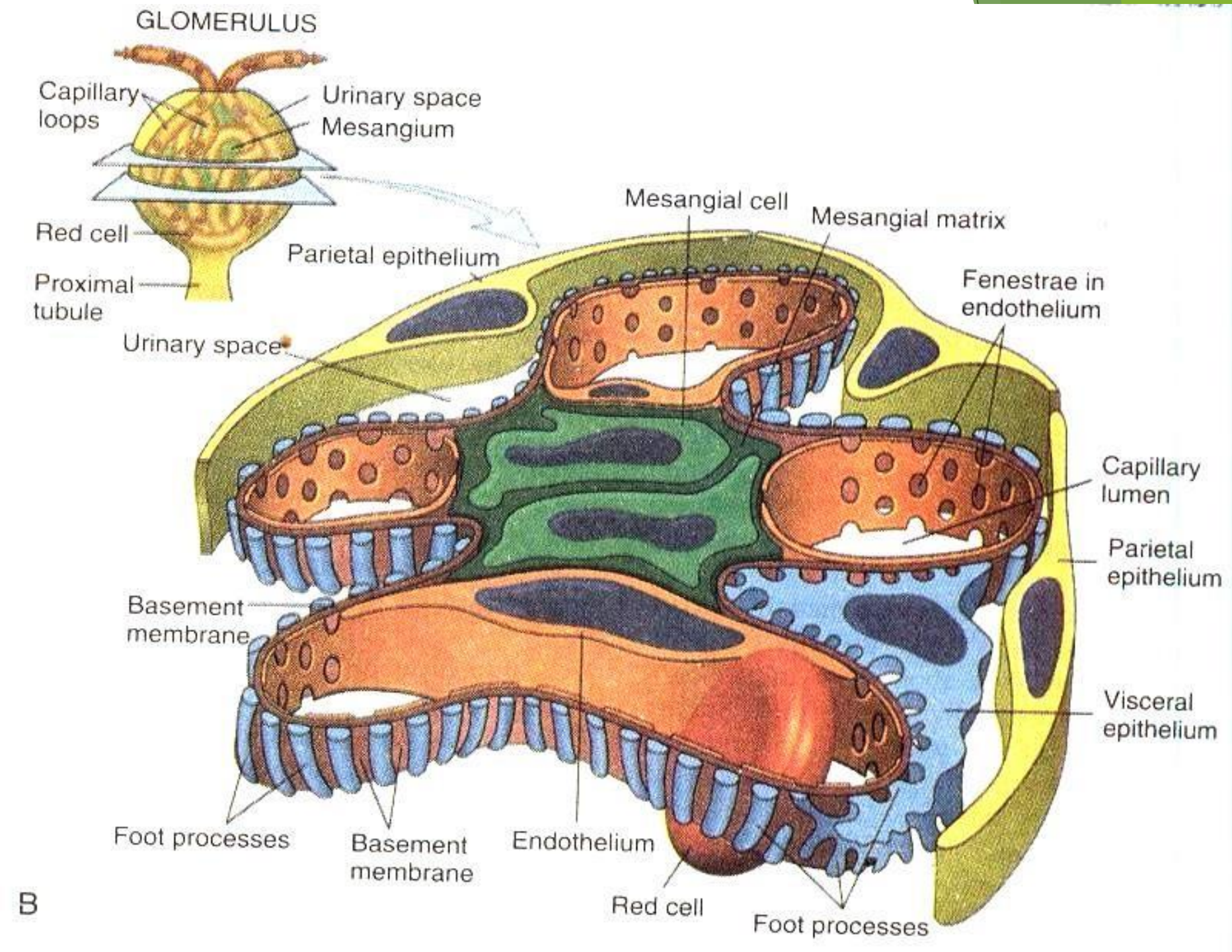
Uniform , diffuse thickening of glomerular capillary wall

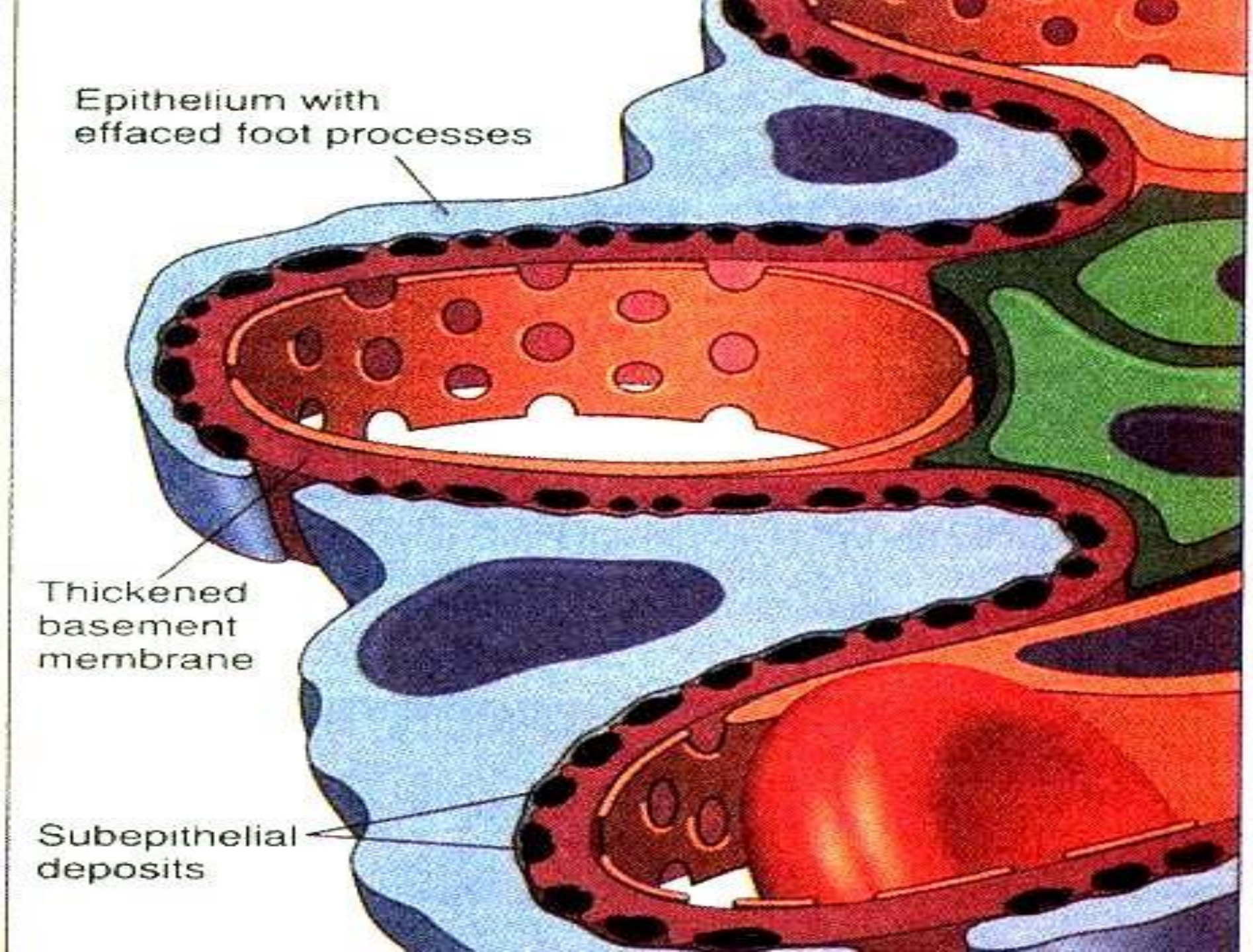



A

Electron Microscopy

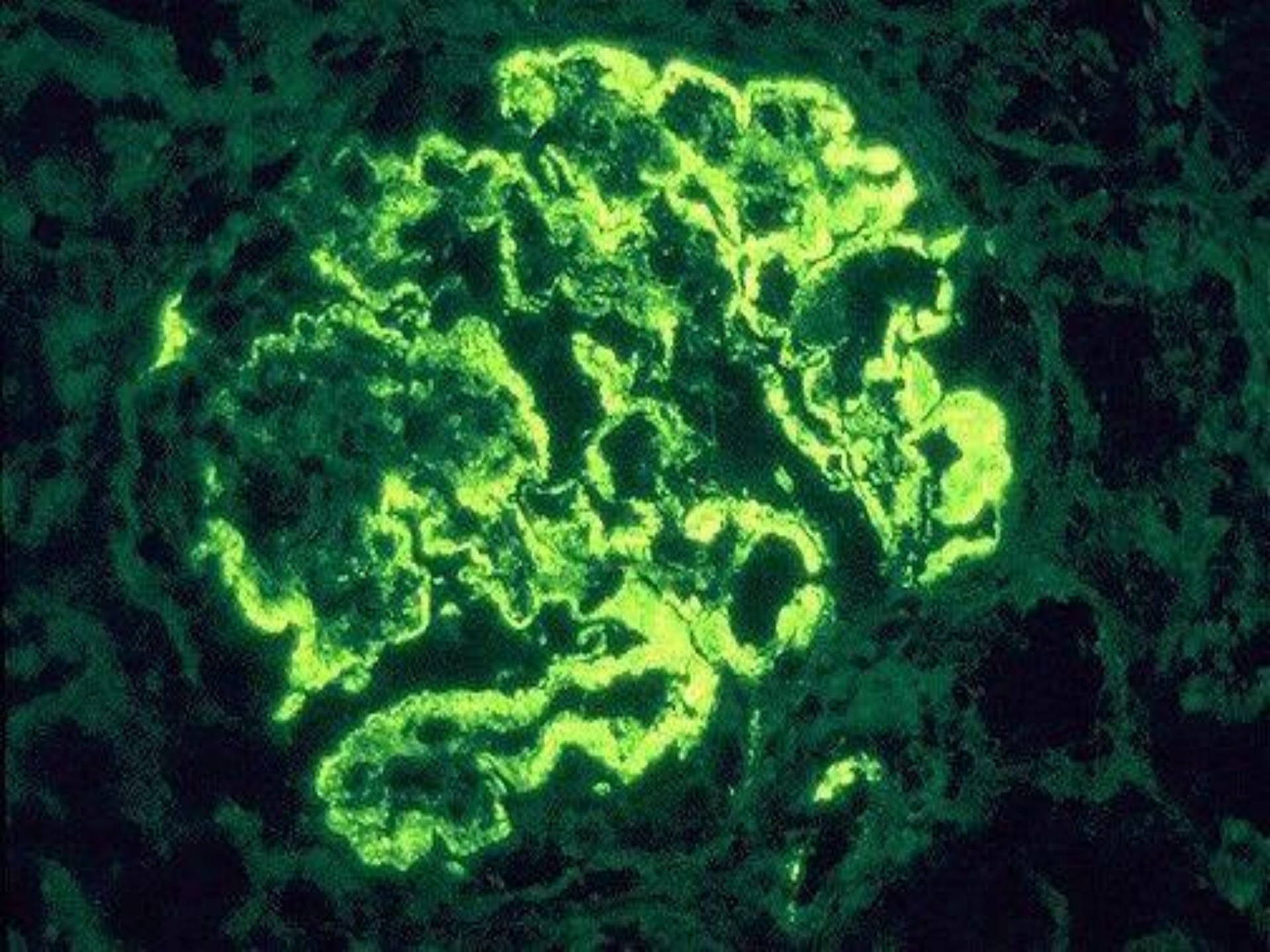
- Subepithelial Irregular electron dense deposits between Basement Membrane & overlying epithelial cells.
- Basement Membrane laid down between deposits -SPIKES

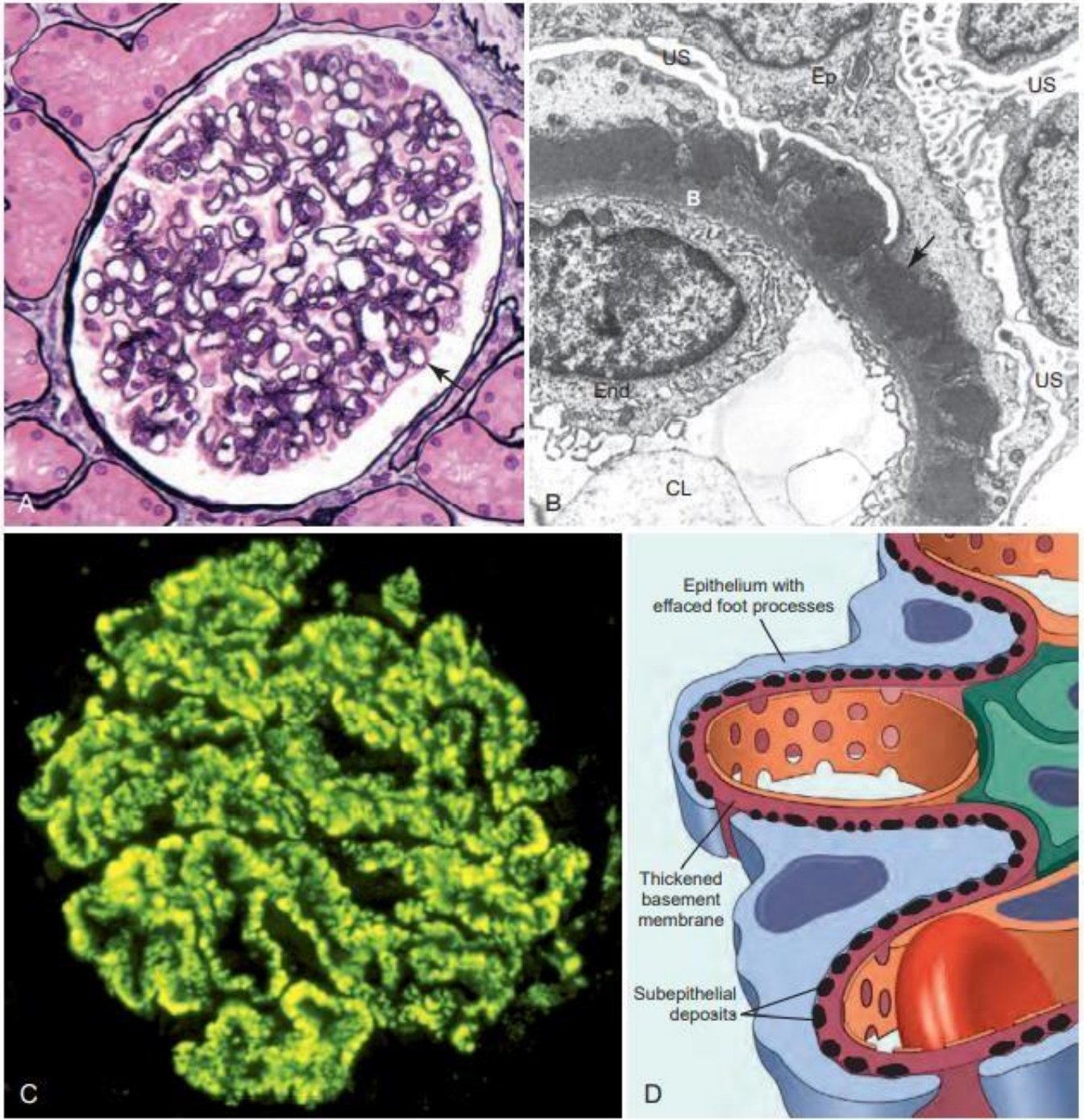

GLOMERULUS
Capillary loops
Urinary space
Mesangium
Red cell
Proximal tubule
Parietal epithelium
Urinary space
Mesangial cell
Mesangial matrix
Fenestrae in endothelium
Capillary lumen
Parietal epithelium
Basement membrane
Visceral epithelium
Foot processes
Basement membrane
Endothelium
Red cell
Foot processes
B


Epithelium with
effaced foot processes
Thickened
basement
membrane
Subepithelial
deposits

Immunofluorescence

The granular deposits contain both immunoglobulins & complement




A
US
Ep
US
B
End
US
CL
B
C
Epithelium with
effaced foot processes
Thickened
basement
membrane
Subepithelial
deposits
D

Clinical Features

- Nephrotic Syndrome
- Non-nephrotic Proteinuria - 15 %

  Proteinuria is non-selective & non- responsive to corticosteroids

Clinical Course

- Course irregular but indolent,
- Although proteinuria persists in > 60% , only 10% die / progress to Renal failure in 10 years
- Spontaneous remissions & benign outcome in women & non-nephrotic range proteinuria

Membranoproliferative Glomerulonephritis

(Mesangiocapillary Glomerulonephritis)

MPGN is best considered a pattern of immune-mediated injury rather than a specific disease

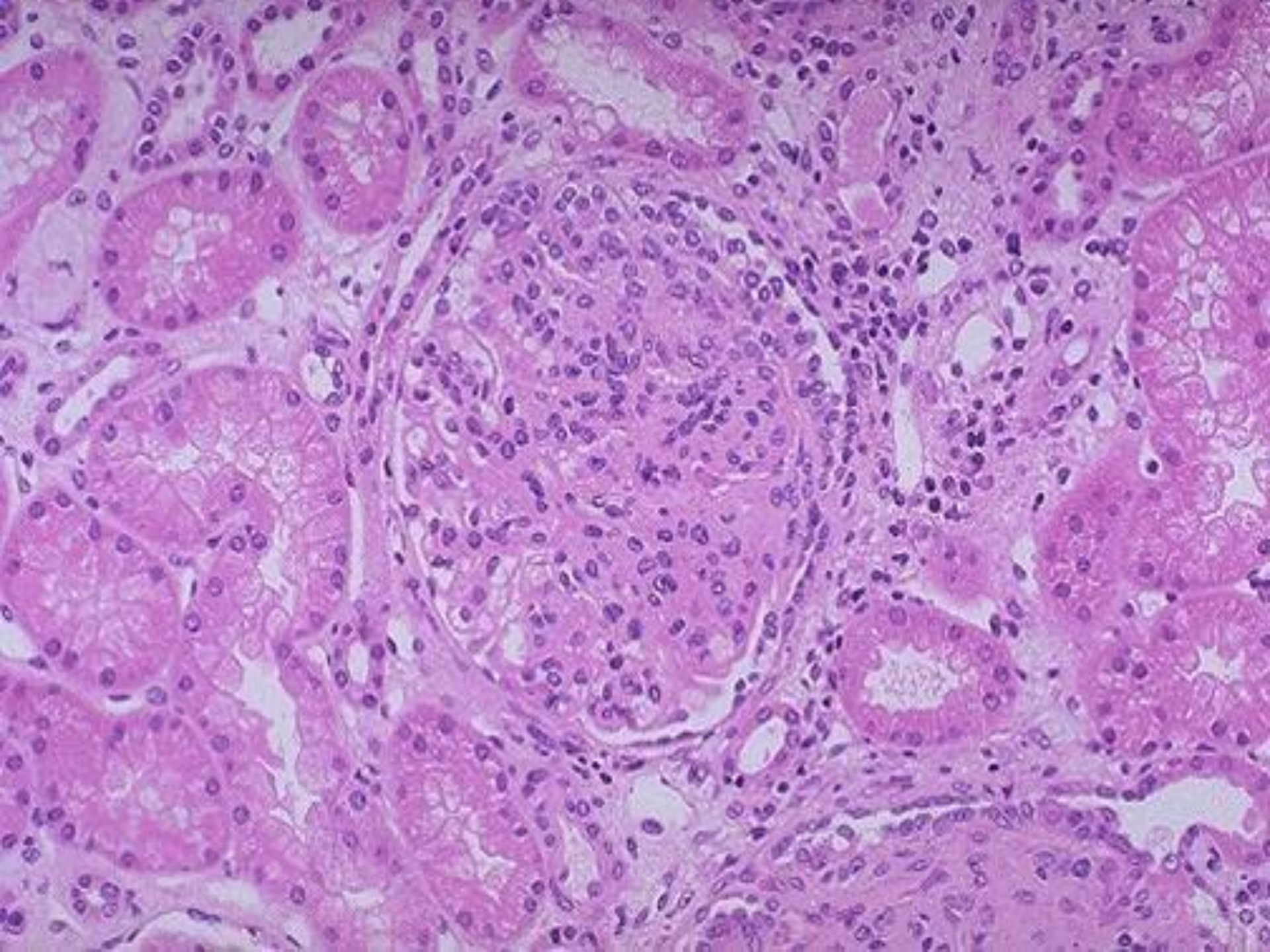
Classification

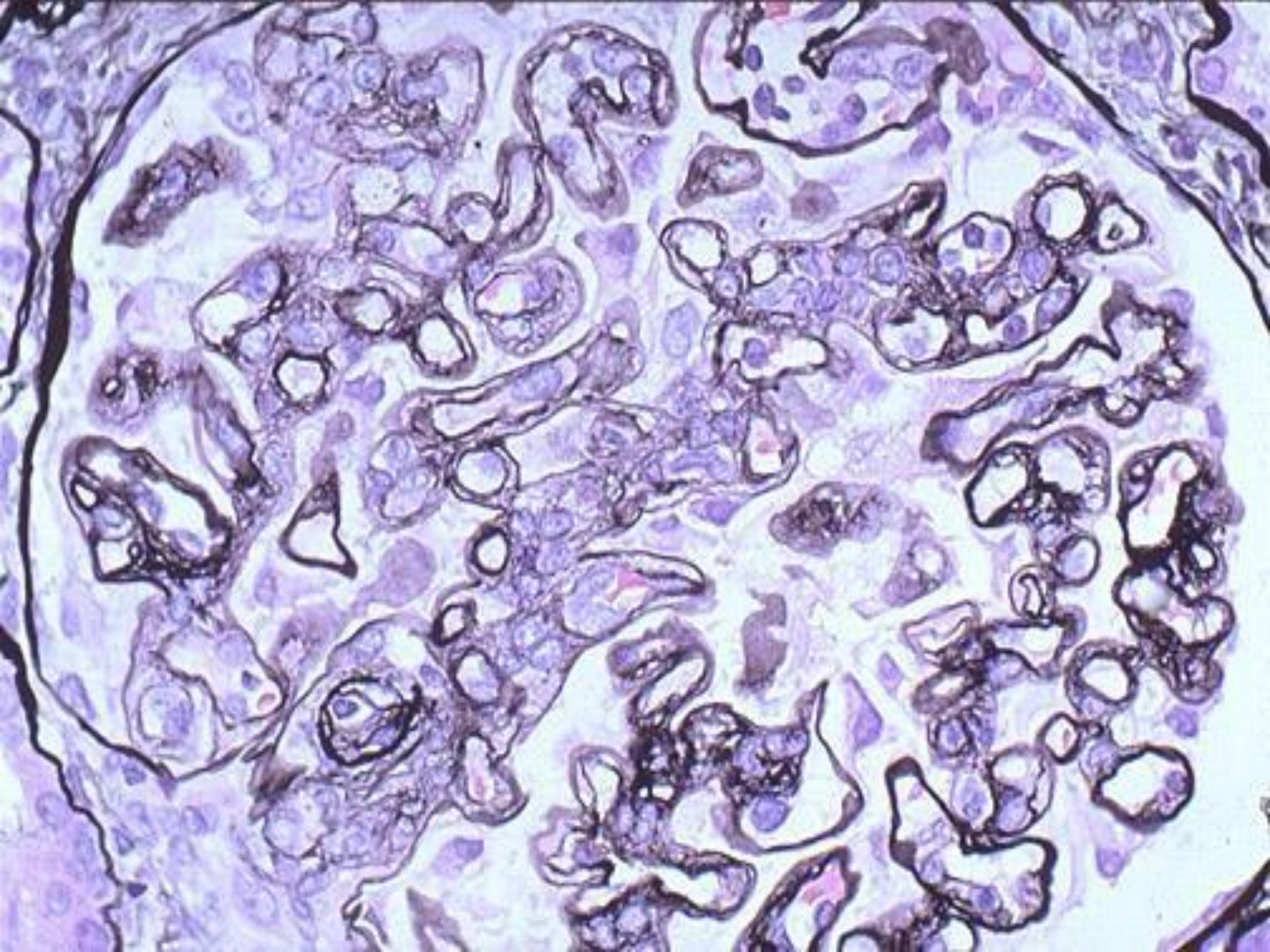
- Primary
- Type - I MPGN
- Type - II MPGN (DDD- C3 Glomerulopathy)
- Secondary
- Chronic immune complex disorders, such as SLE; hepatitis B infection; hepatitis C infection, usually with cryoglobulinemia; endocarditis; infected ventriculoatrial shunts; chronic visceral abscesses; HIV infection; and schistosomiasis
- • α1-Antitrypsin deficiency •
- Malignant diseases, particularly lymphoid tumors such as chronic lymphocytic leukemia, which are commonly complicated by development of autoantibodies

Light Microscopy

- Glomeruli large & hypercellular
  - Proliferation of cells in mesangium
  - infiltrating leukocytes

  Parietal epithelial crescents
- Glomeruli - lobular appearance
- Capillary wall - double contour / tram track appearance





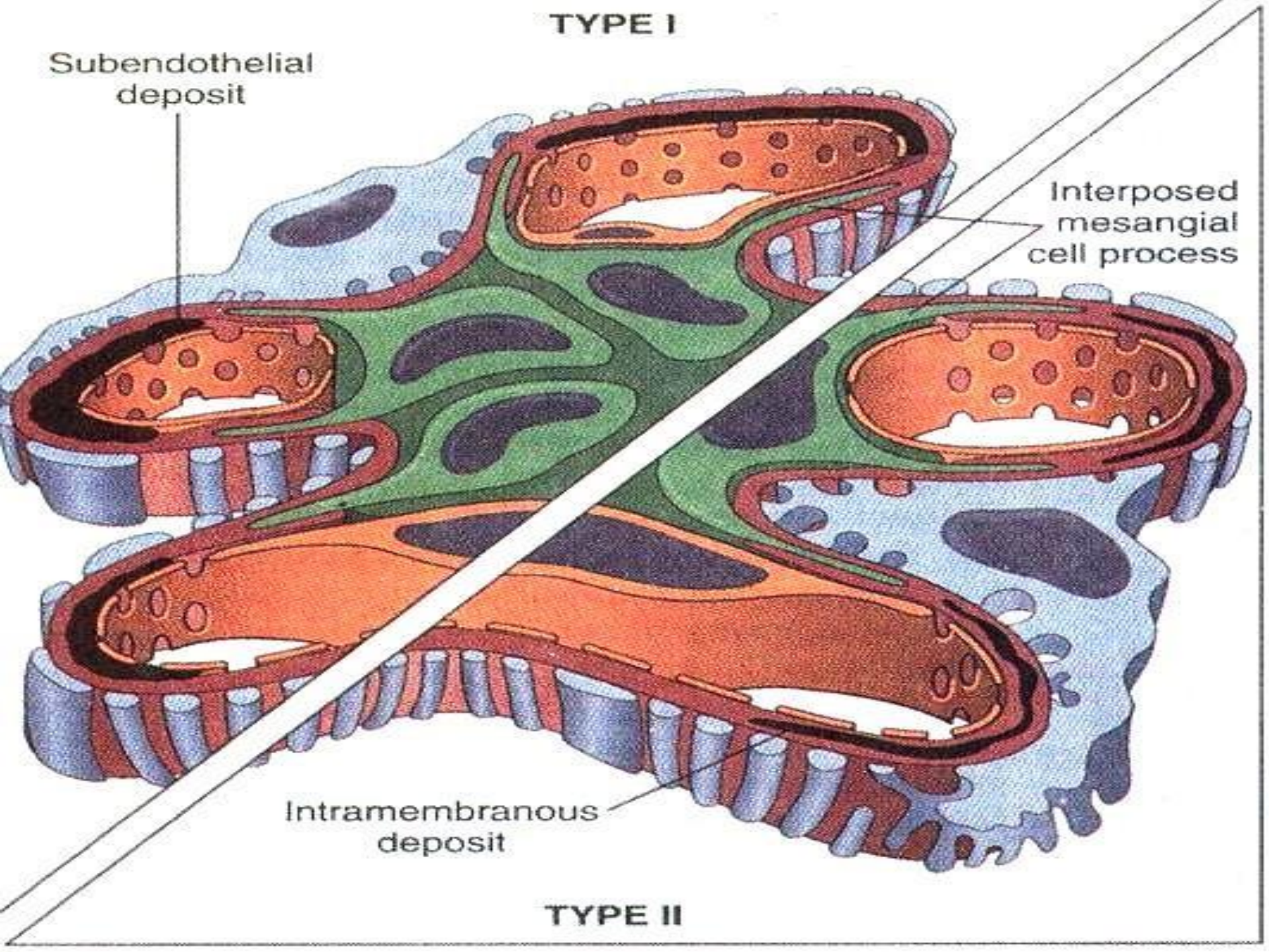
Electron Microscopy & IF

- **Type - I** : sub endothelial deposits

  IF - C3 , early complement components (C1q -C4) , IgG in granular pattern

- **Type - II : (Dense deposit disease)**

  GBM contains electron dense material in a ribbon like fashion(intra membranous deposit). C3 is present but no early complement components


TYPE I
Subendothelial deposit
Interposed mesangial cell process
Intramembranous deposit
TYPE II

PATHOGENESIS

- **Type I** : immune complexes

- **Type II** : Activation of alternate pathway

  C_3 nephritic factor present in serum

Clinical Course

- 50 % develop chronic renal failure in 10 years
- High recurrence rate in transplant patients especially in Type II disease

Focal Segmental Glomerulosclerosis (FSGS)

- Characterized by sclerosis of some, but not all, glomeruli (thus, it is focal); and in the affected glomeruli, only a portion of the capillary tuft is involved (thus, it is segmental)

Focal Segmental Glomerulosclerosis

Pathogenesis

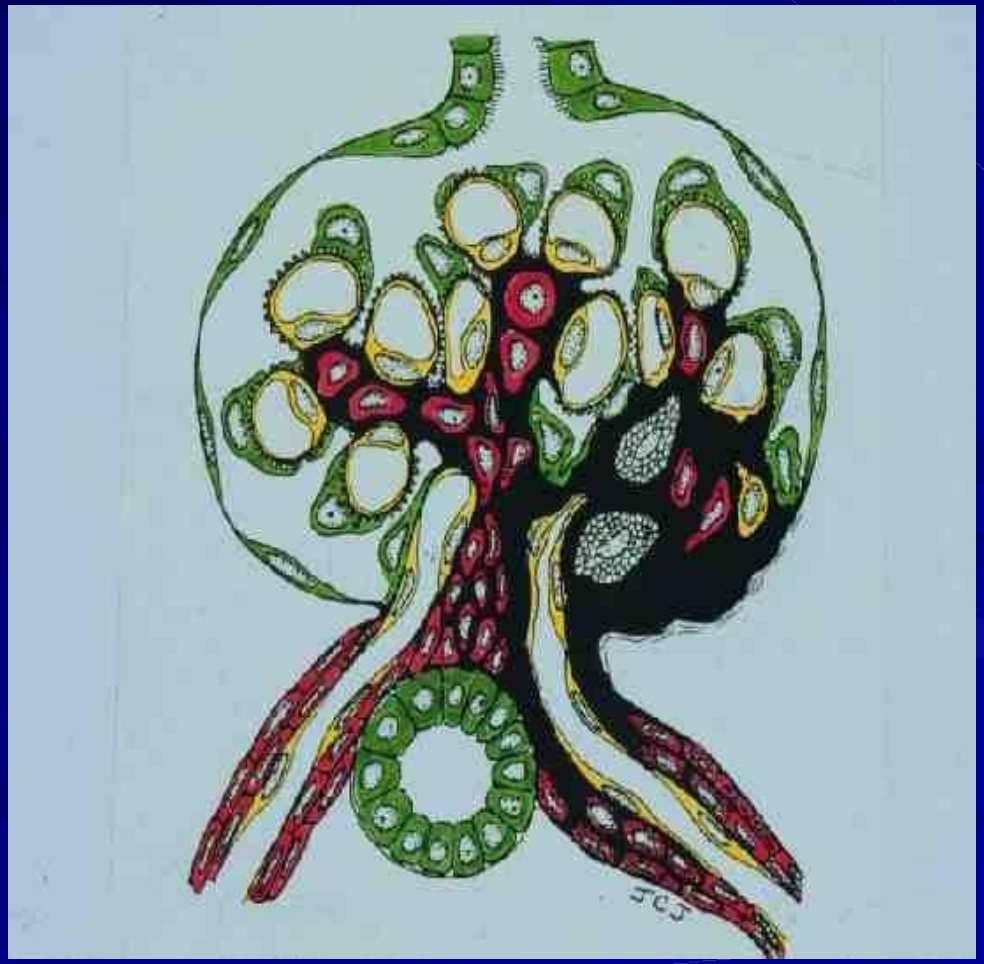
Injury to visceral epithelial cell – Hallmark of FSG

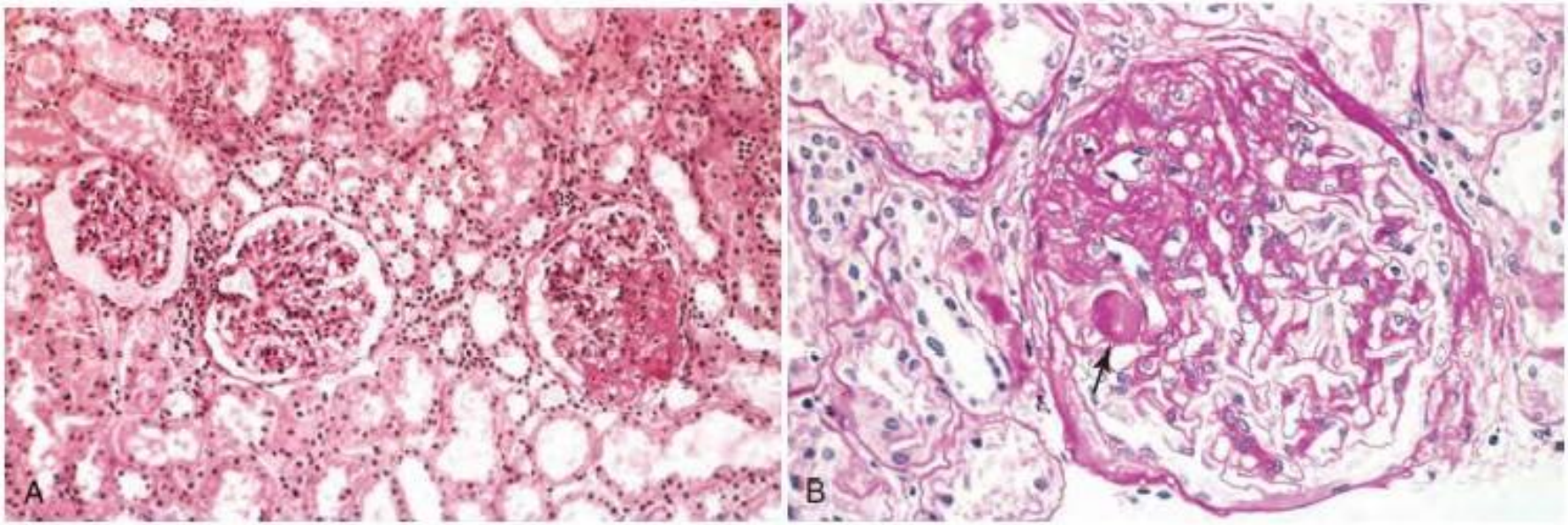
- Presence of permeability increasing factor in circulation
- Hyalinosis / sclerosis – entrapment of plasma protein & lipid in mesangium

FSGS - Classification

- PRIMARY DISEASE (idiopathic focal segmental glomerulosclerosis)
- SECONDARY
- In association with other known conditions, such as HIV infection (HIV-associated nephropathy), heroin addiction (heroin nephropathy), sickle-cell disease, and massive obesity

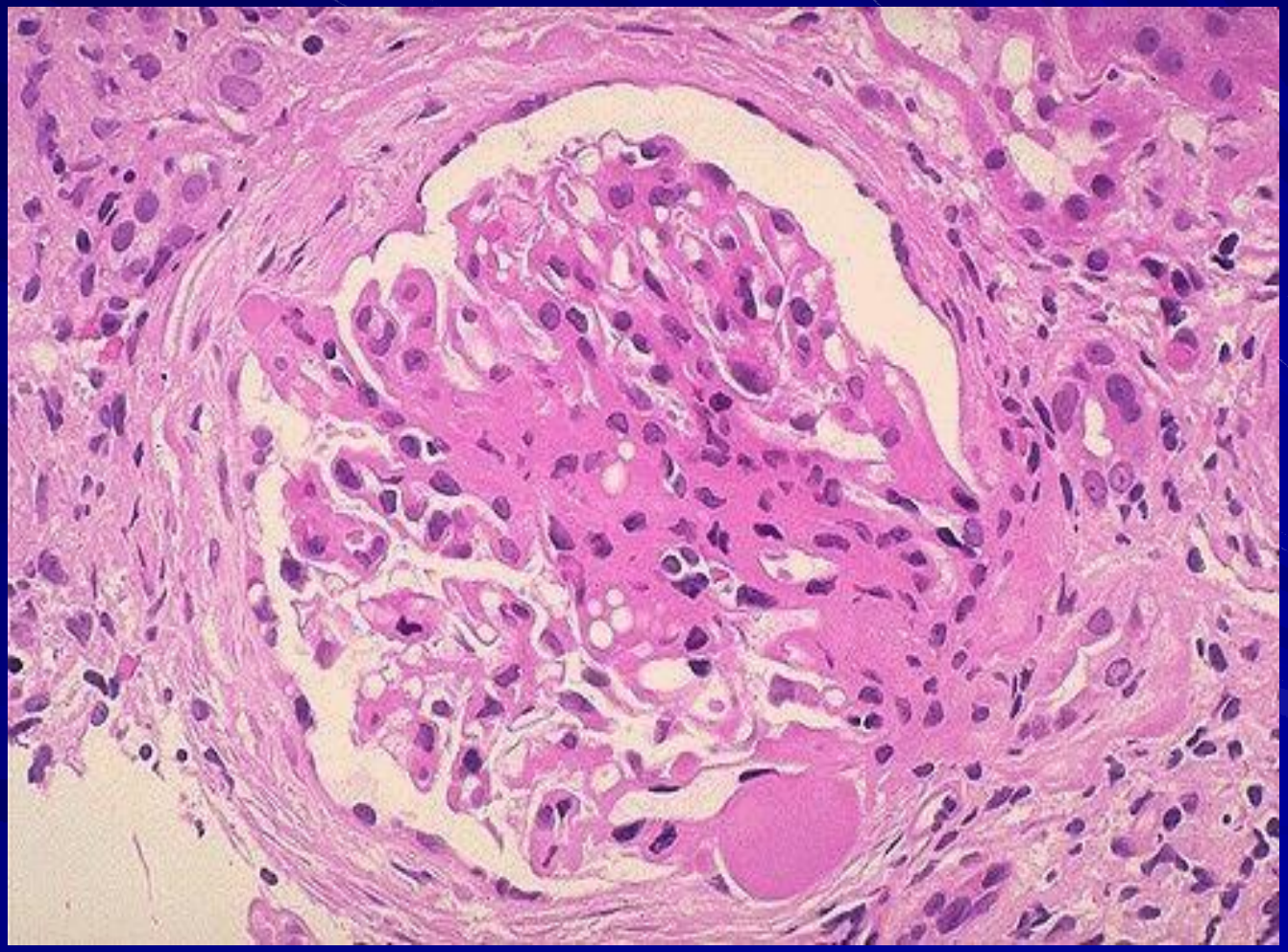
Focal Segmental Glomerulosclerosis



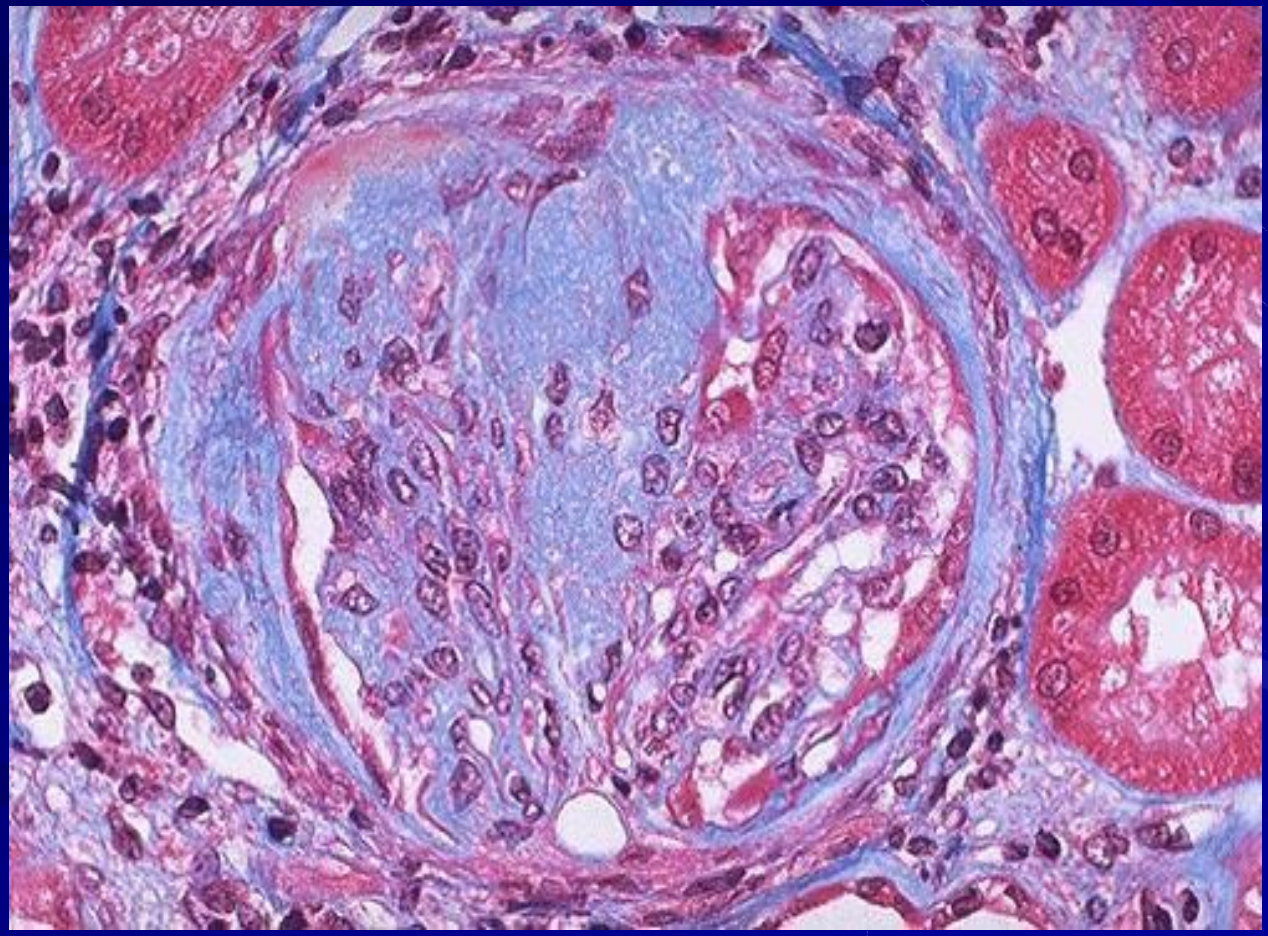


igure 20-14 Focal segmental glomerulosclerosis, PAS stain. **A,** Low-power view showing segmental sclerosis in one of three glomeruli (at 3 o'clock). **B,** High-power view showing hyaline insudation *(arrow)* and lipid (small vacuoles) in sclerotic area.

FSGS



FSGS - Trichrome



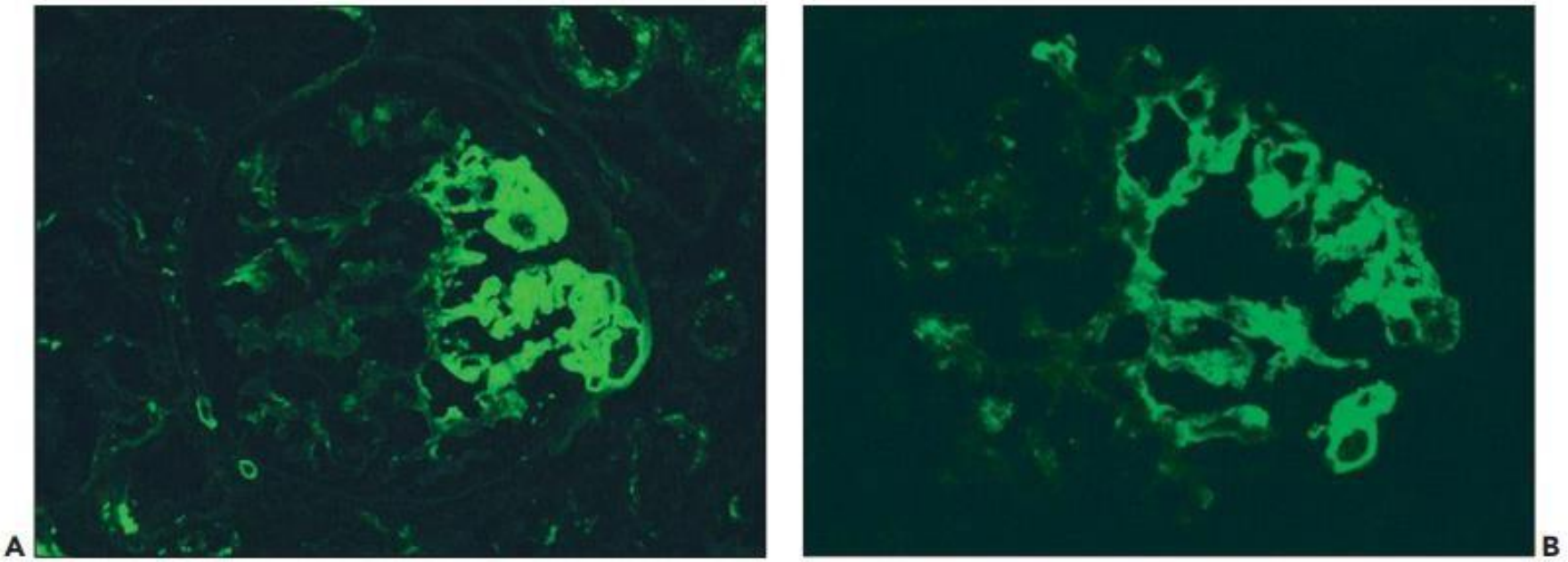


FIGURE 6.20 Immunofluorescence microscopy shows segmental glomerular tuft staining for IgM **(A)** and C3 **(B)**. (FITC anti-human IgM **[A]** and FITC anti-human C3 [B], ×330.)

Treatment and outcome

- There is poor response to corticosteroid therapy
- There is progression to chronic kidney disease, with at least 50% developing ESRD within 10 years


Thank you