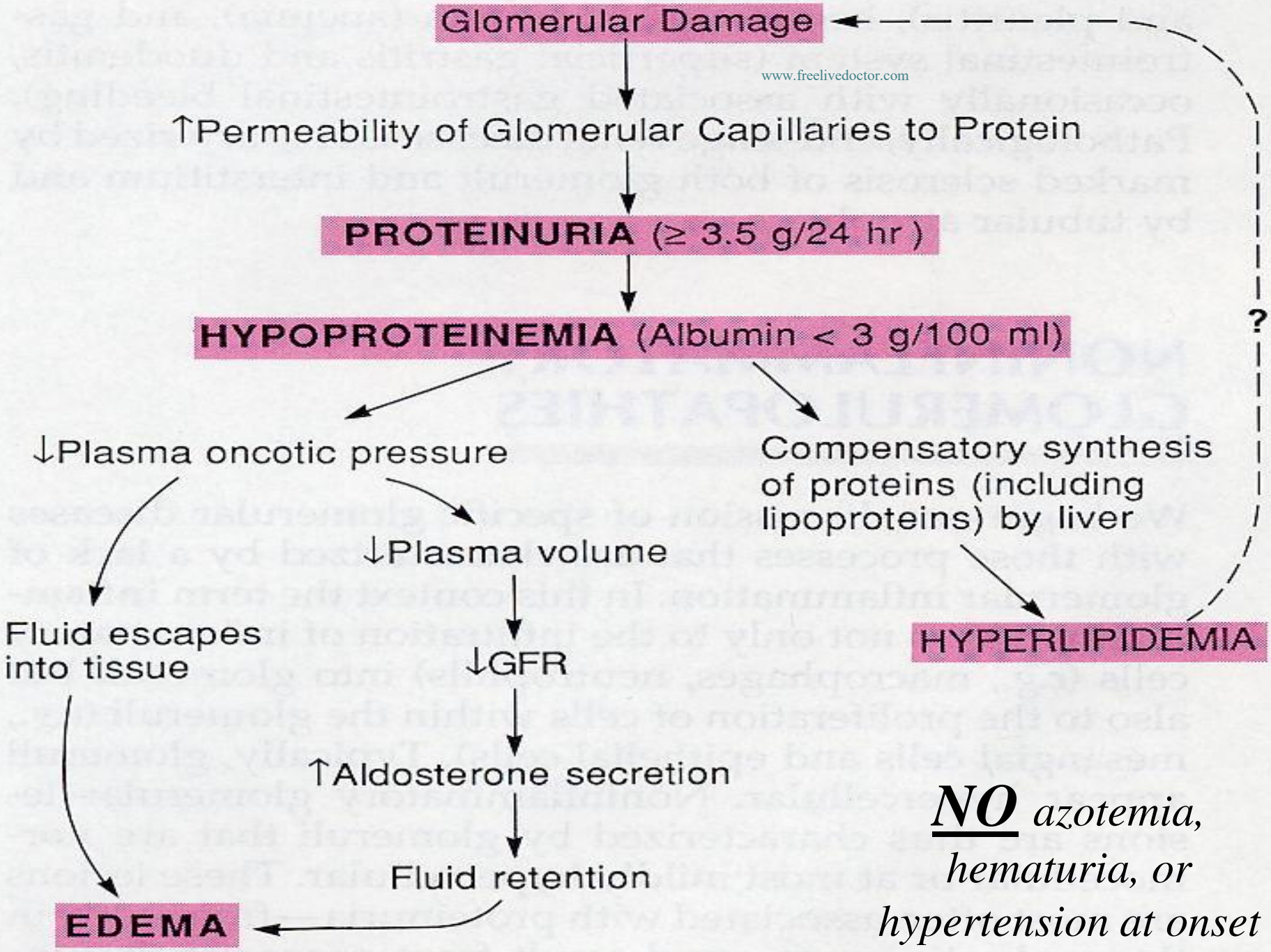
Nephrotic syndrome

Nephrotic Syndrome (NS):

- A glomerular syndrome characterized by insidious onset of:
  - Massive proteinuria (>3.5 gm / 24 hr).
  - Hypoproteinemia (plasma albumin < 3 gm / dL).
  - Generalized edema.
  - Hyperlipidemia + Lipiduria.
- Pts have ↑ risk of *infection* & *hypercoagulation*.
- Different forms of primary and secondary GN.
  - In **children** are most frequently caused by primary renal diseases (most common is MCD).
  - In **adults** are often caused by secondary renal diseases.


Glomerular Damage
www.freelivedoctor.com
↑Permeability of Glomerular Capillaries to Protein
PROTEINURIA (≥ 3.5 g/24 hr)
HYPOPROTEINEMIA (Albumin < 3 g/100 ml)
?
↓Plasma oncotic pressure
Compensatory synthesis of proteins (including lipoproteins) by liver
↓Plasma volume
Fluid escapes into tissue
HYPERLIPIDEMIA
↓GFR
↑Aldosterone secretion
Fluid retention
EDEMA
NO azotemia, hematuria, or hypertension at onset

Causes of Nephrotic syndrome	Prevalence (%)	
Cause	Children	Adults
Primary Glomerular Disease		
Membranous GN (MGN)	5	30
Minimal-change disease (MCD)	65	10
Focal segmental glomerulosclerosis (FSGS)	10	~35
Membranoproliferative GN (MPGN)	10	10
IgA nephropathy	10	15
Systemic Diseases with Renal Manifestations		
Diabetes mellitus		
Amyloidosis		
Systemic lupus erythematosus		
Ingestion of drugs (gold, penicillamine, heroin)		
Infections (malaria, syphilis, hepatitis B, HIV)		
Malignancy (carcinoma, melanoma)		
Miscellaneous (bee-sting allergy, hereditary nephritis)		

1. Minimal change disease (MCD):

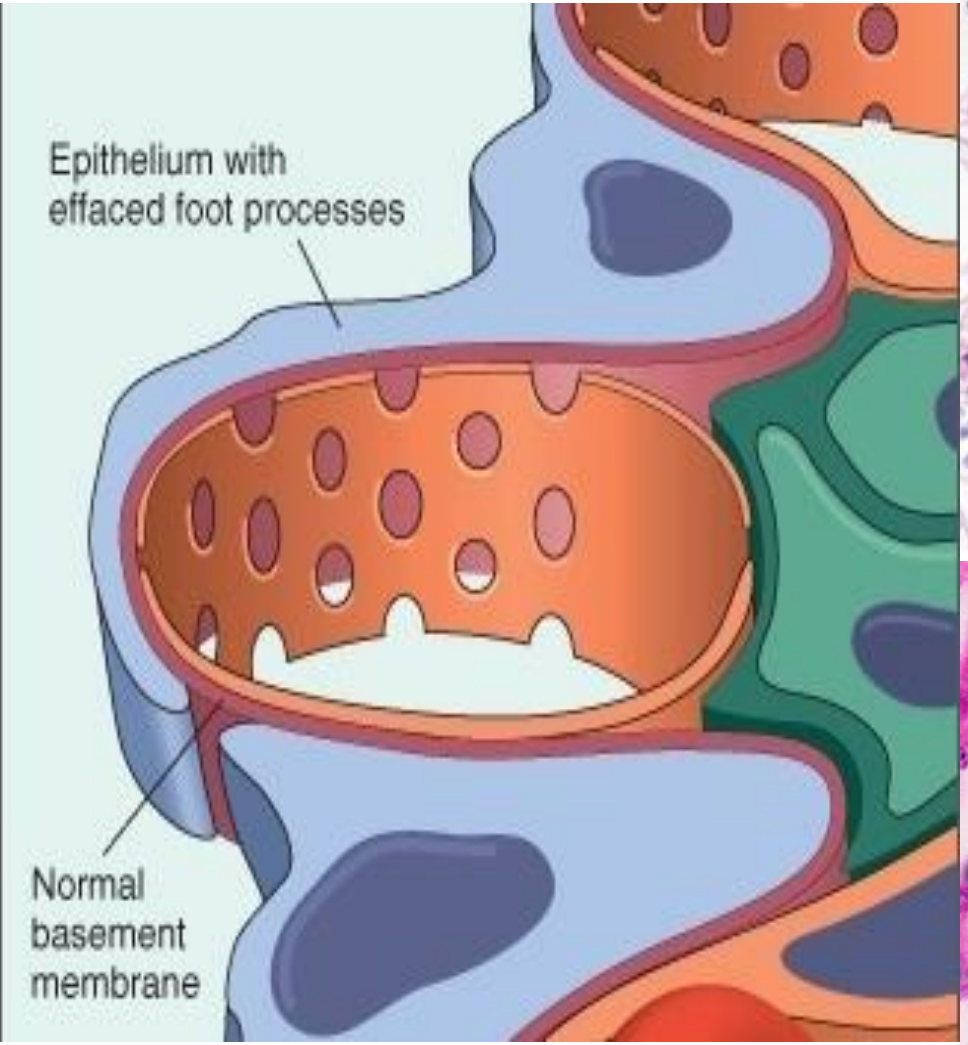
(Lipoid nephrosis , nil change disease)

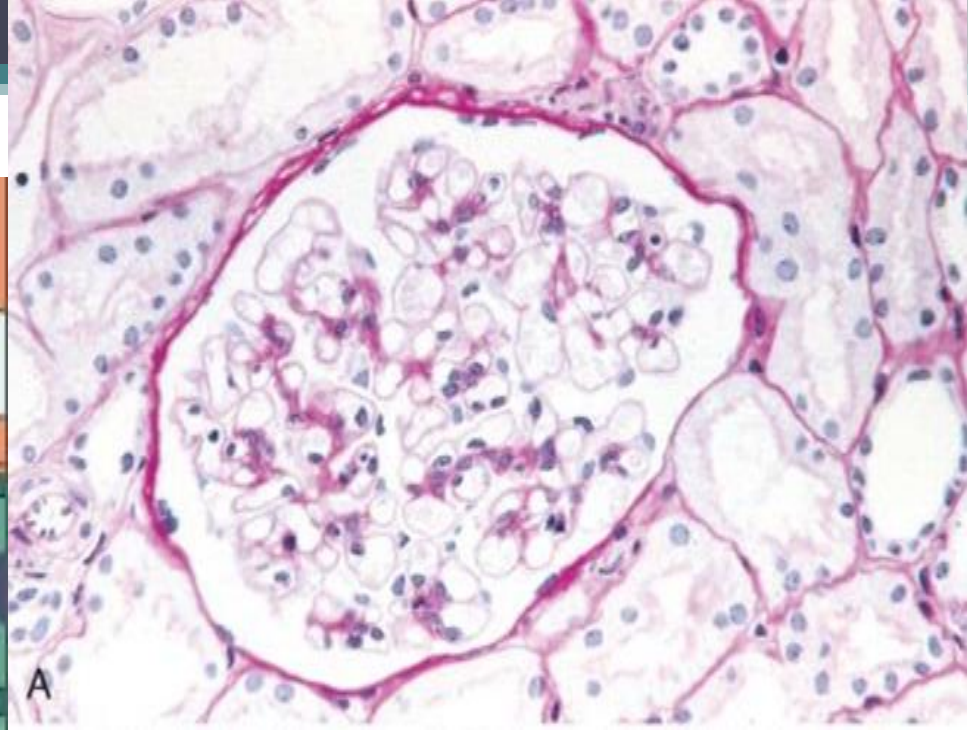
- The most frequent cause of the nephrotic syndrome in children (esp. 2-6 yrs).

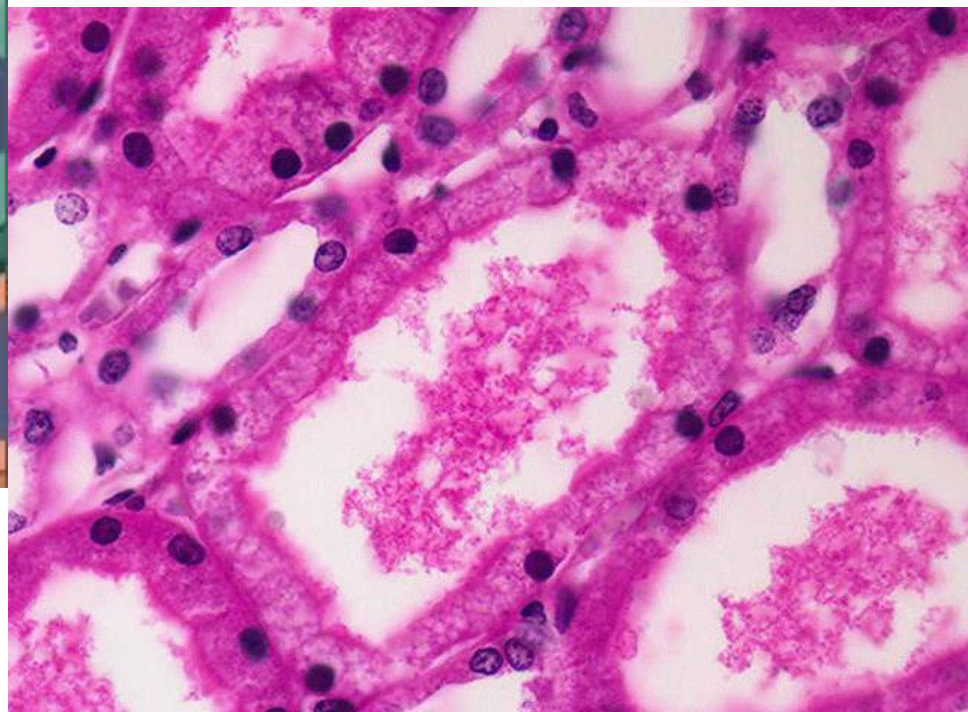
- **Pathogenesis:**
  - Podocyte damage and effacement of foot processes.
  - ? Dysfunction of T-cell function.
- **Morphology:**

LM	IF	EM
Nil	Nil	fusion of foot processes

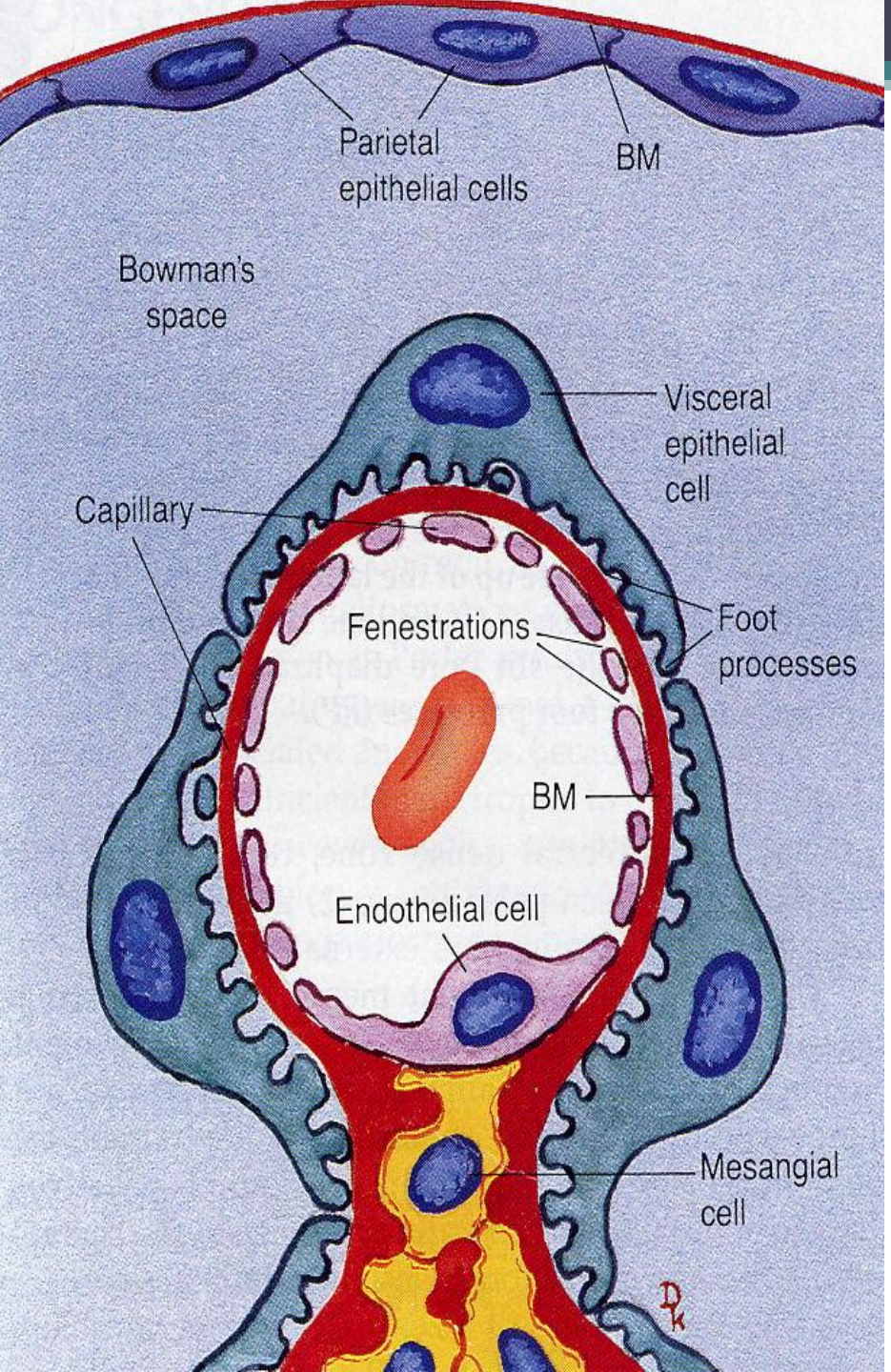
PCT are laden with
protein & lipids (lipoid nephrosis)

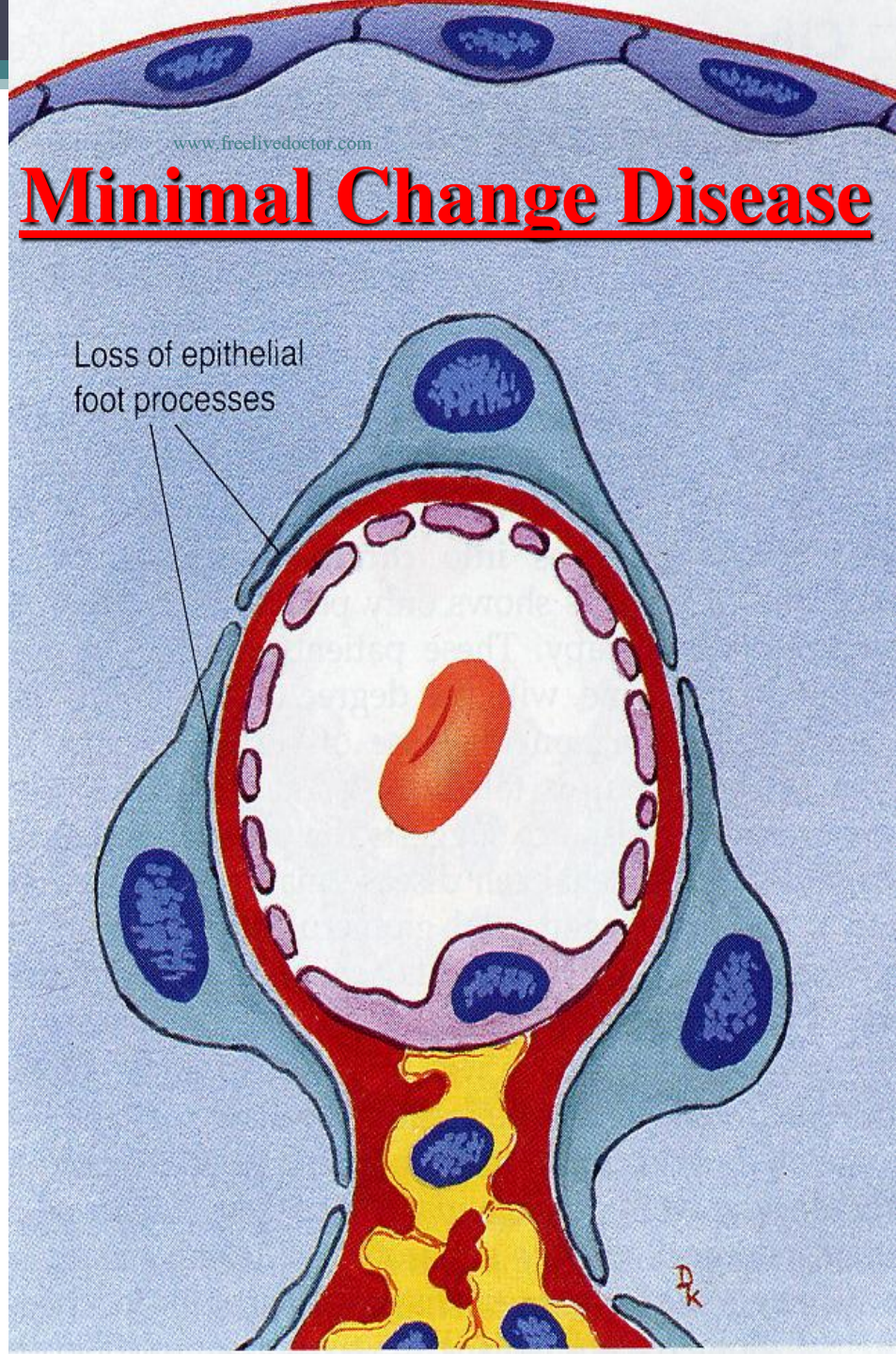

Epithelium with
effaced foot processes
Normal
basement
membrane


A

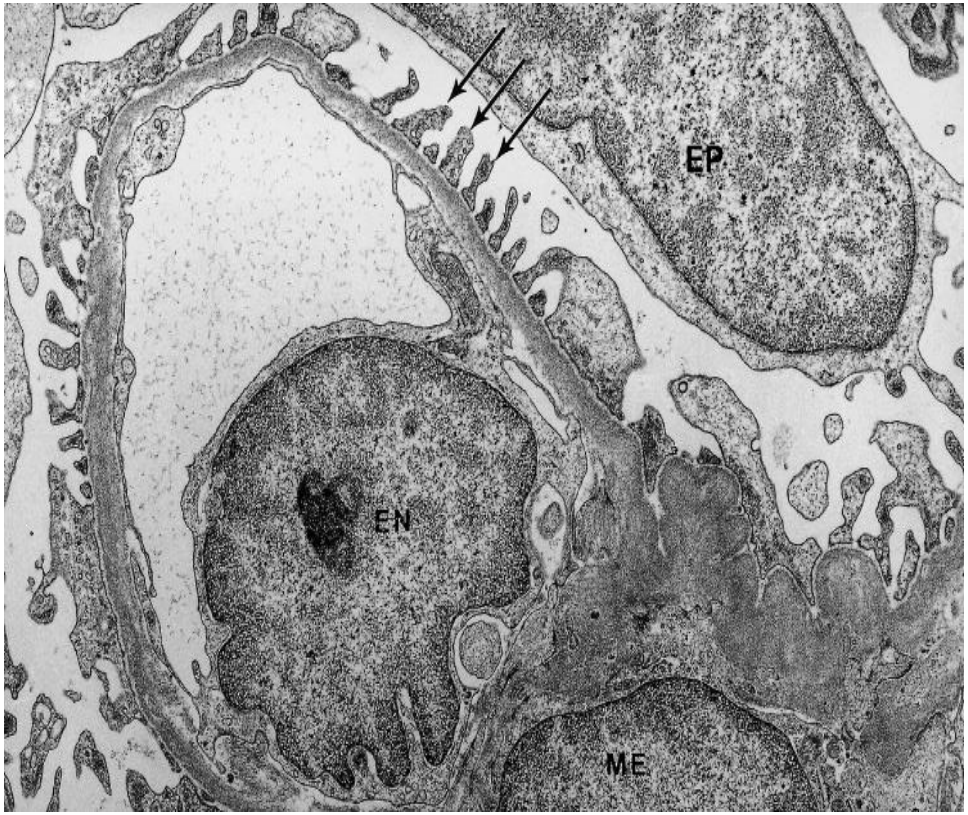


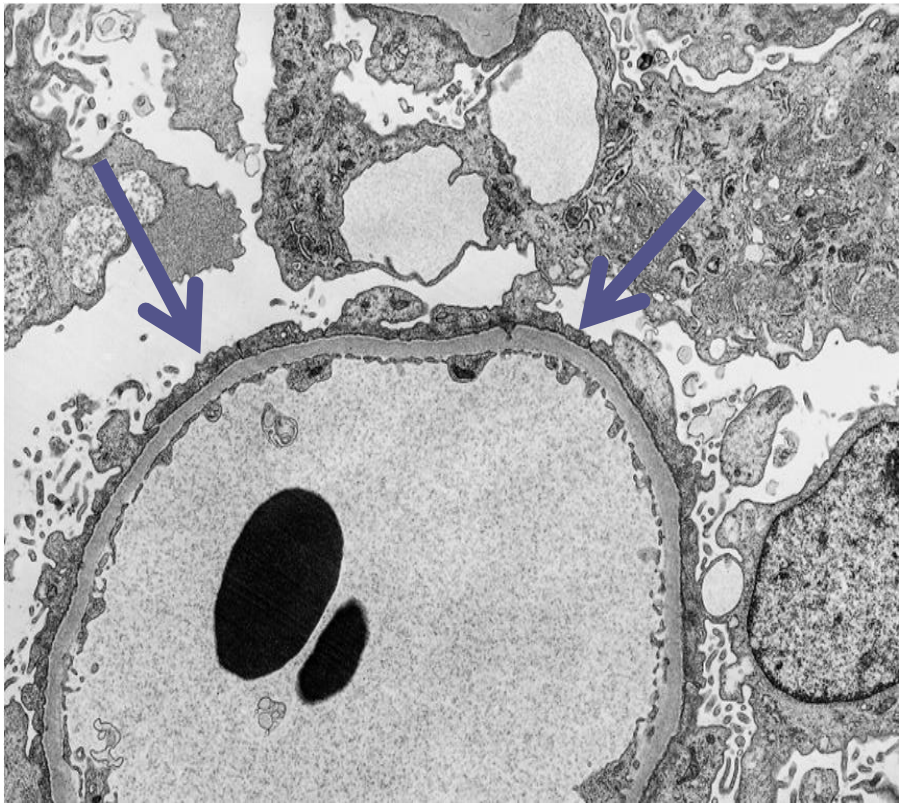
Minimal Change Disease





EM





Clinical features:

- Insidious onset of the **nephrotic syndrome:**
  - Highly selective proteinuria (mainly albumin).
  - May follow URTI or immunization.
  - > 90% of respond to a short course of CS therapy.
- **Prognosis in children →** Excellent
  - Proteinuria may recur, and some patients may become steroid dependent or steroid resistant .
  - < 5% develop CRF after 25 years.
- **Prognosis in adults →** Good*
  - Slower response to steroids.
  - More common relapses.

2. Focal segmental glomerulosclerosis (FSGS)

- The most common cause of NS in adults.

CAUSES	
Secondary FSGS	
-In association with other known conditions	HIV, Heroin abuse, Sickle cell dis., Morbid obesity
-A secondary event in other forms of GN	IgA nephropathy
-Adaptive response to nephron loss	Reflux nephropathy Hypertensive nephropathy Unilateral renal agenesis
-Inherited forms of NS*	Mutaions in nephrin
Primary disease	Idiopathic FSGS 10-35%

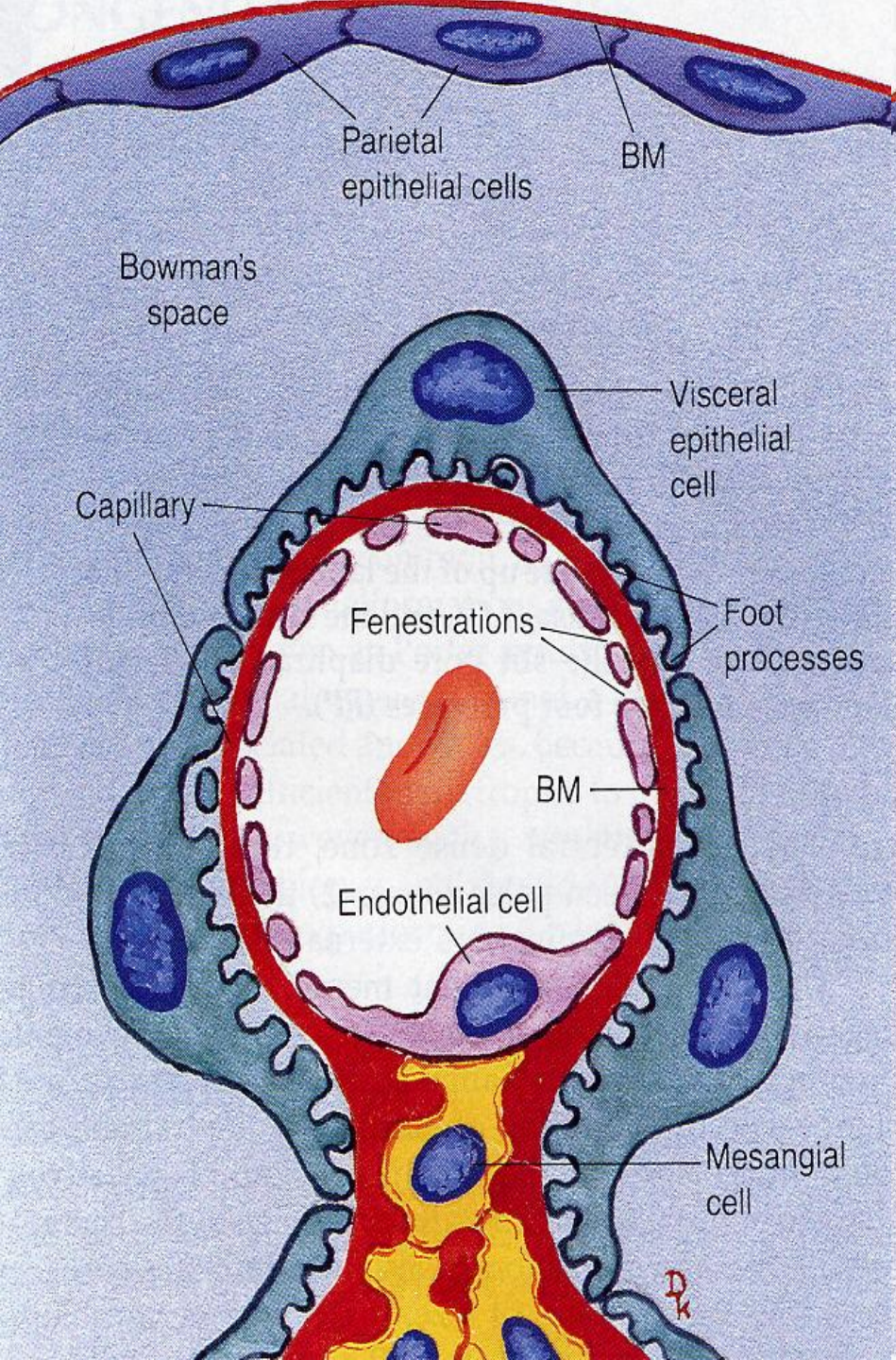
Morphology of FSGS

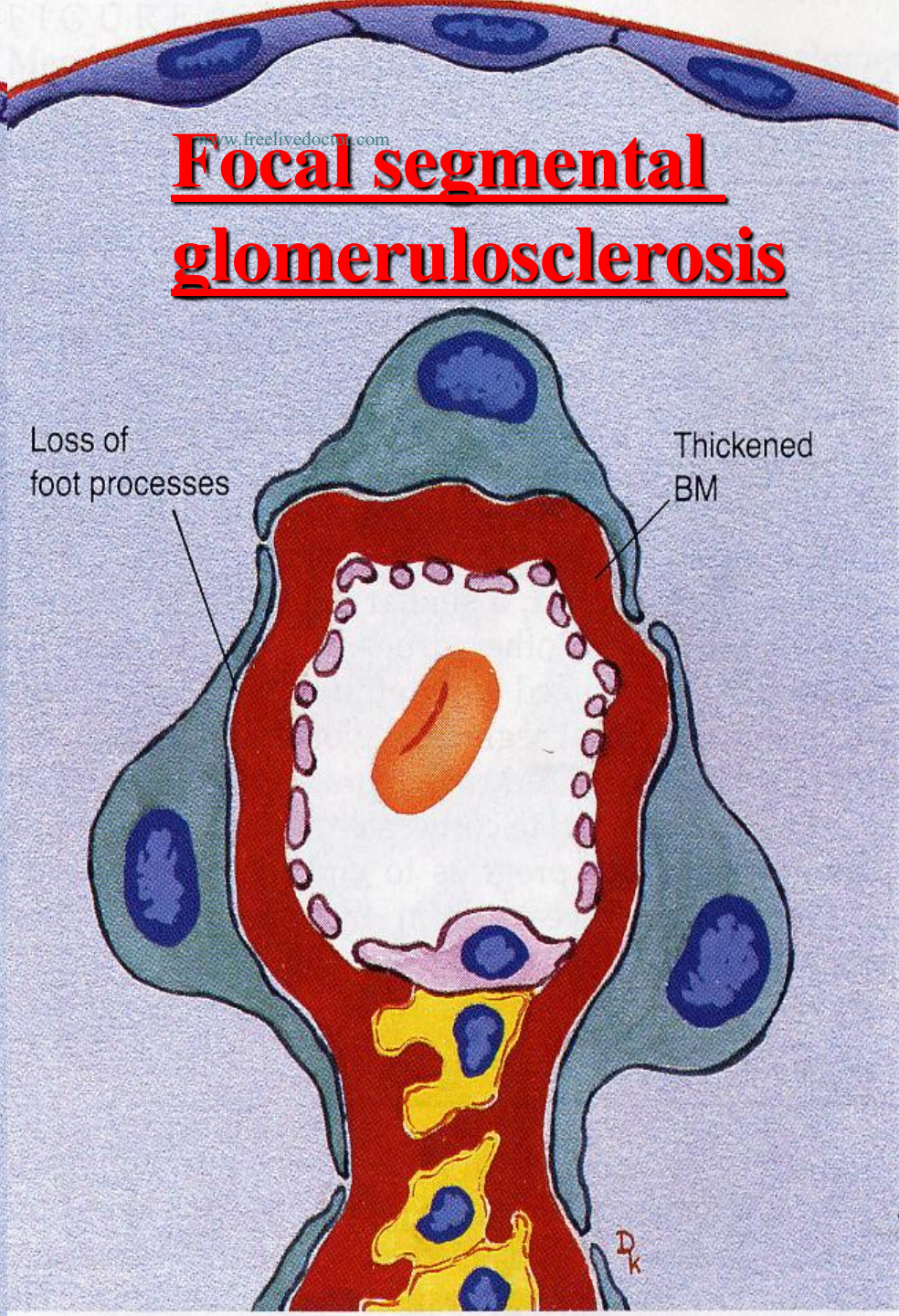
- **LM:** *FOCAL* & SEGMENTAL*
  - Sclerosis (with collapse of BM).
  - Increased mesangial matrix.
  - Hyalinosis.

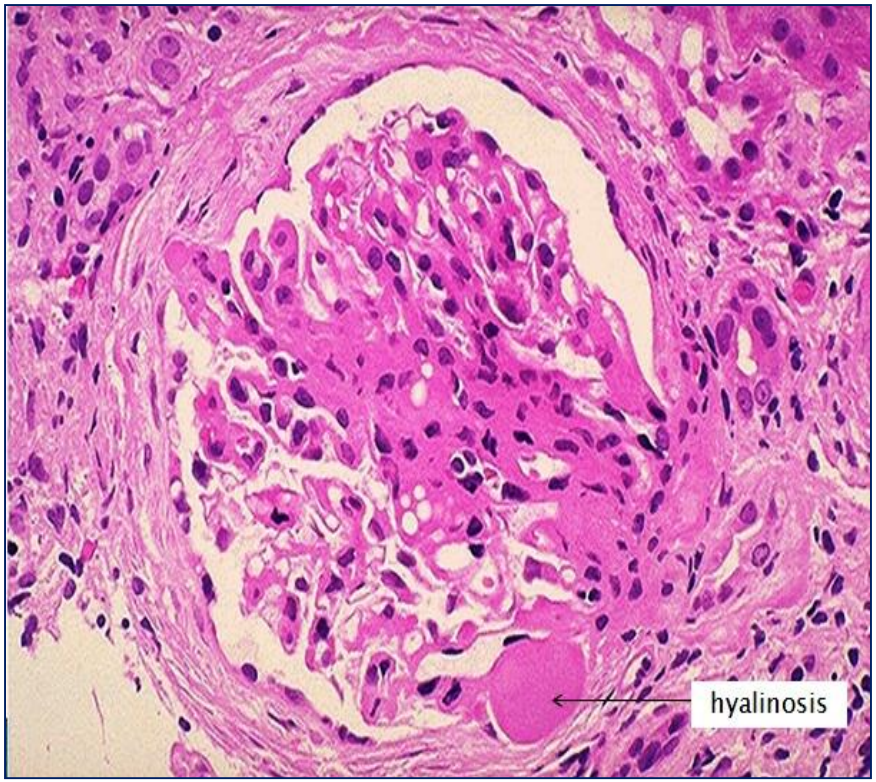
- **EM:**
  - Non -sclerotic segments show effacement of foot processes with focal disruption of BM**.

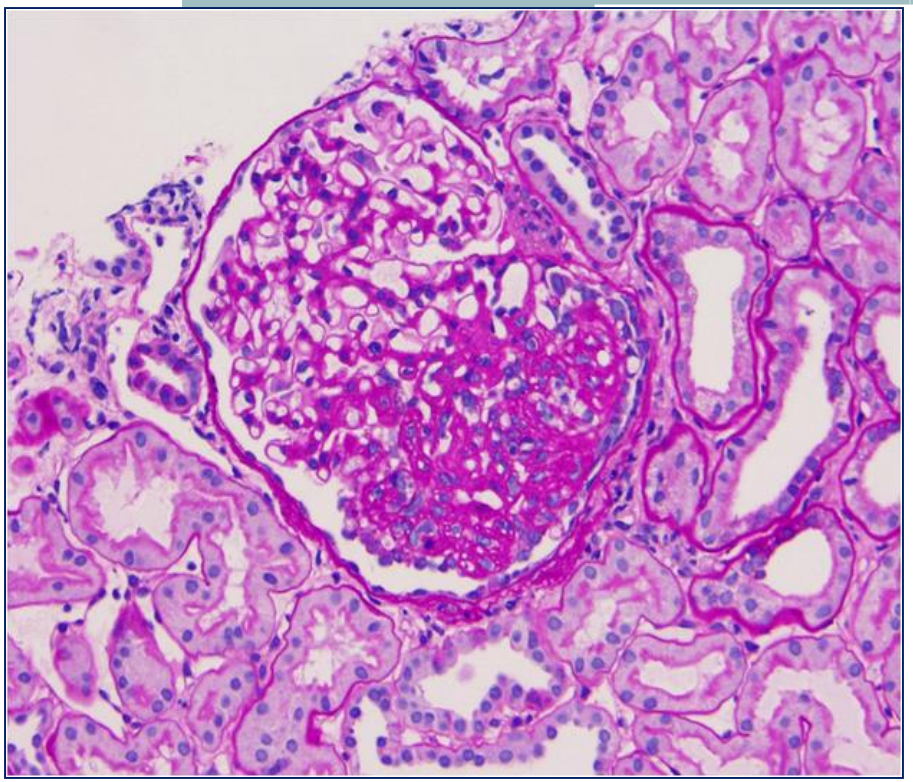
- **IF:**
  - Non-specific **IgM & C3** in sclerotic segments.

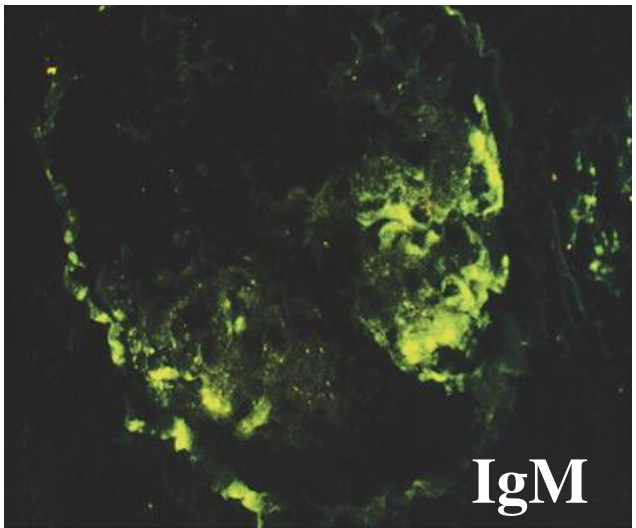
Focal segmental glomerulosclerosis

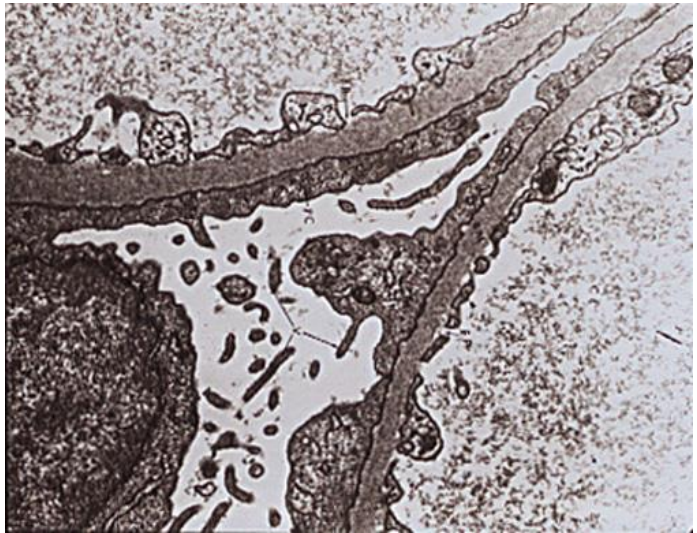





hyalinosis




IgM



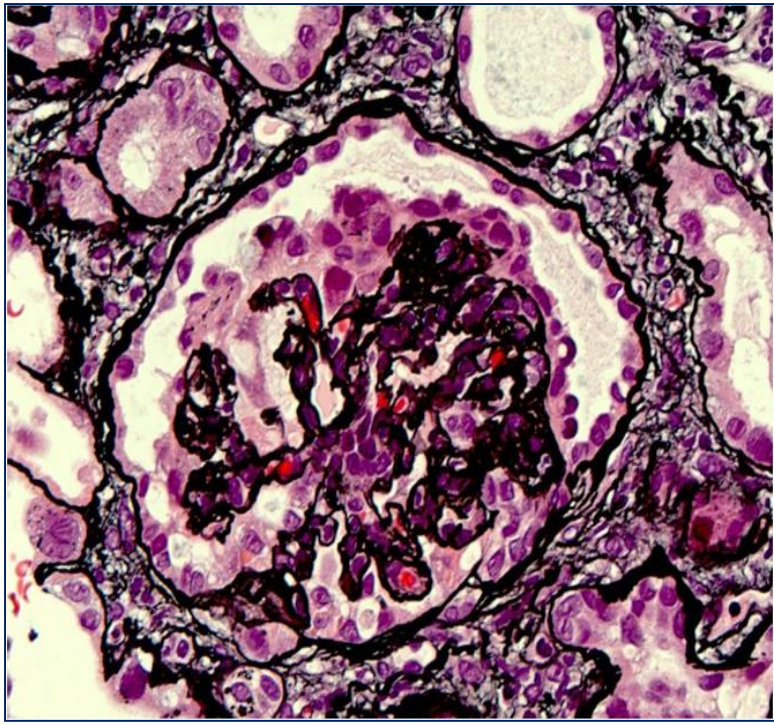
Clinical features:

- Insidious onset of **nephrotic syndrome:**
  - Non-selective proteinuria
  - Higher incidence of hematuria & HT (cuz of ↓ GFR).
  - Poor response to steroids.

- **Prognosis:**
  - 50% will develop end-stage renal failure in 10 yrs.

Collapsing glomerulopathy

- A morphologic variant of FSGS
- Commonly seen in **AIDS.**
- It is characterized by:
  - Collapse of the entire glomerular tuft.
  - Podocytes hyperplasia.
- It carries poor prognosis.



3. Membranous GN

- Slowly progressive disease affecting adults>children (30-50 yrs).

CAUSES

Idiopathic in **85%** of cases* → Podocyte phospholipase A2 receptor auto-Ab is common

Secondary MGN:

- Infections (**chronic hepatitis B**, hepatitis C, syphilis, schistosomiasis, malaria)
- Malignant tumors (carcinoma of the lung and colon, melanoma and NHL
- SLE
- Inorganic salts (gold, mercury)
- Drugs (penicillamine, captopril, NSAIDs)

Pathogenesis of MGN

- **Chronic immune complex (in situ) glomerulonephritis** mainly affecting the podocytes on the epithelial aspect of the GBM.

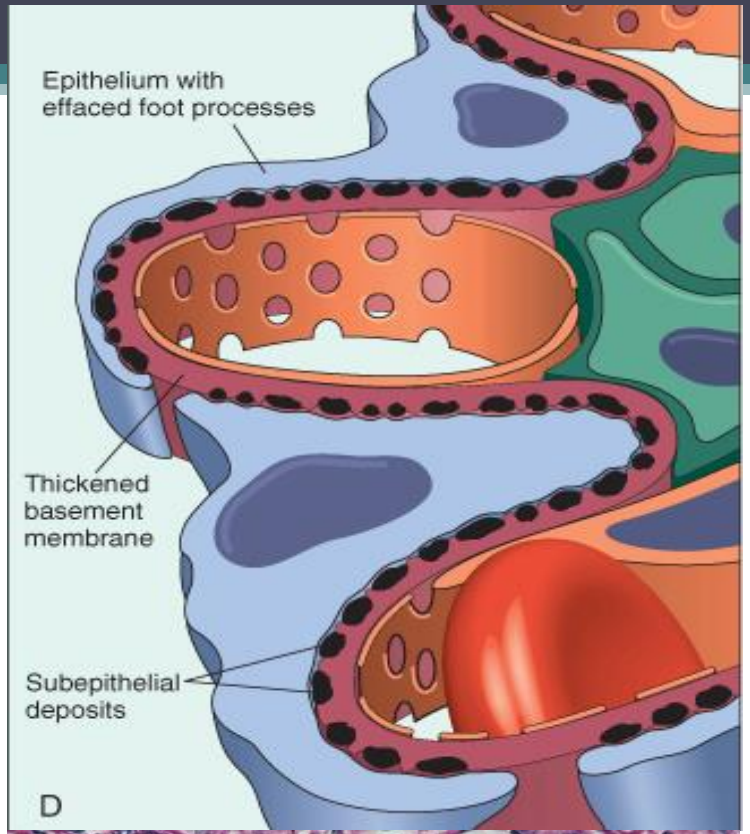
- Followed by complement activation & formation of membrane attack complex (MAC).

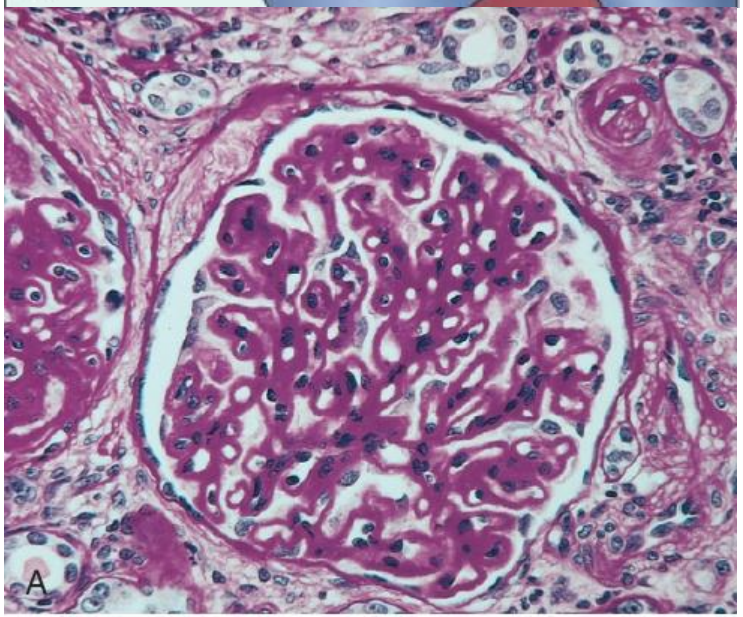
Morphology of MGN

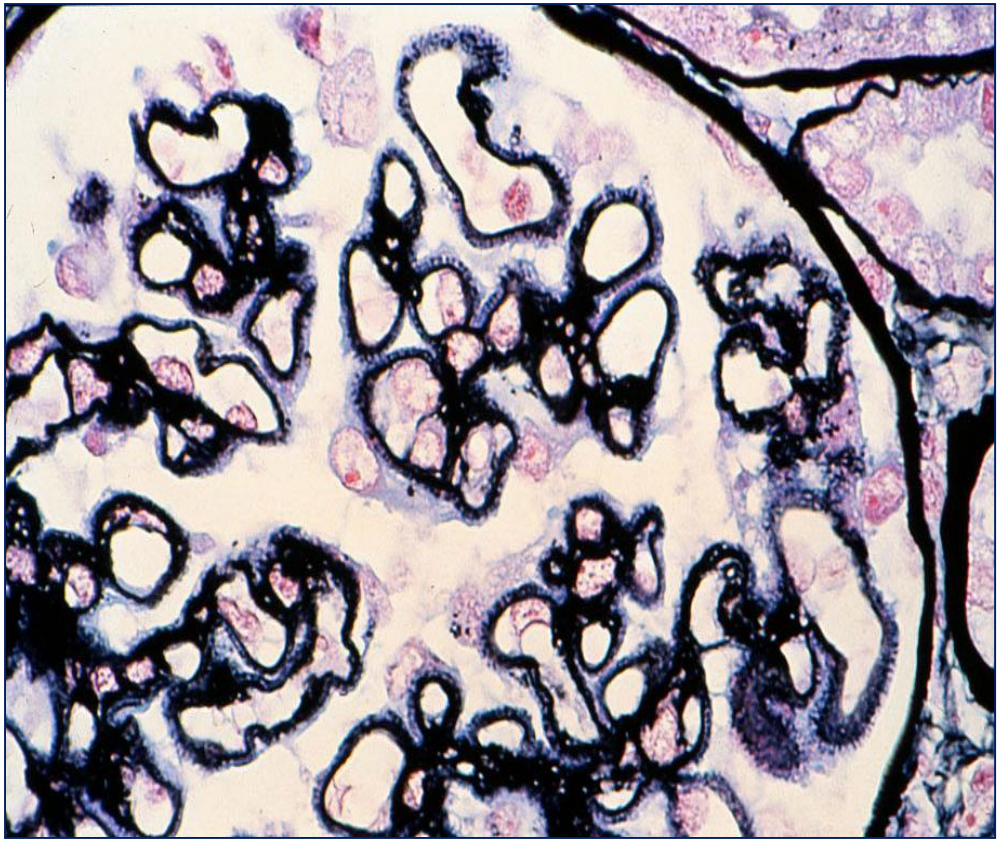
- **LM:**
  - Normal early.
  - *Diffuse thickening of capillary wall*, without proliferation of cells.
  - "*Spikes* " seen on silver stain

- **EM:**
  - Diffuse *subepithelial* deposits ± fusion of foot processes.

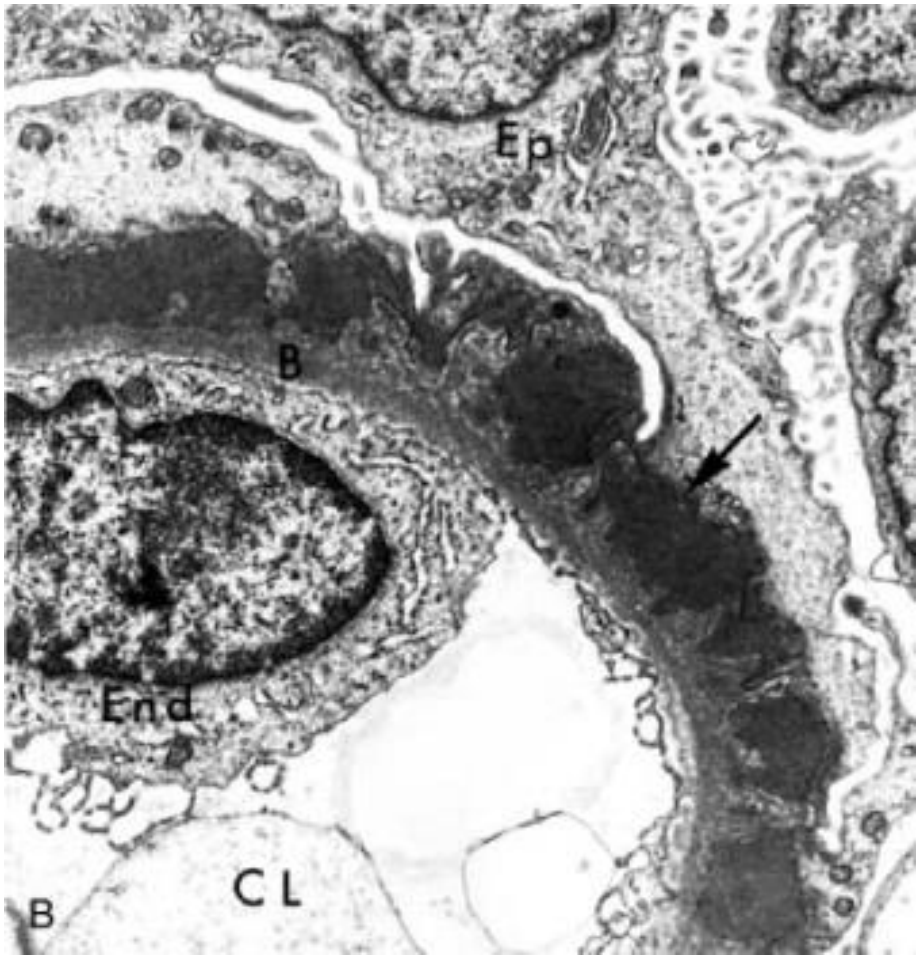
- **IF:**
  - *Granular IgG &C3** along the GBM.

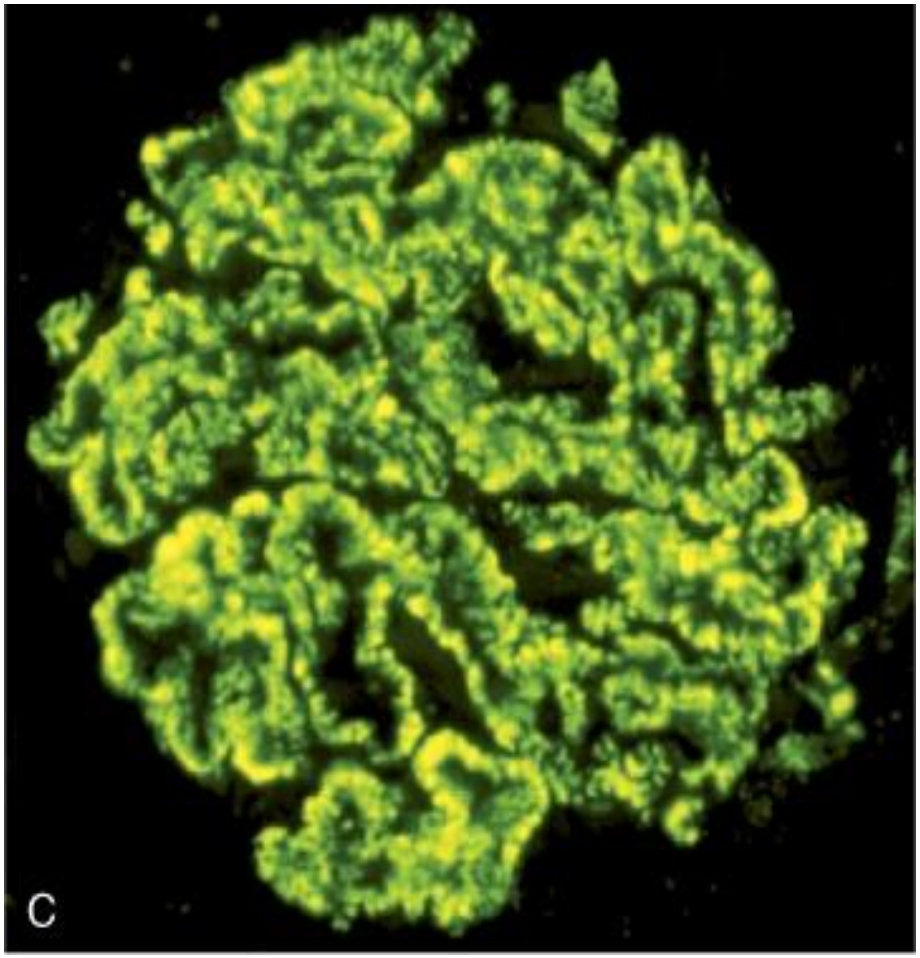






Silver stain


Ep
B
End
CL
B


C

Clinical features:

- Insidious onset of **nephrotic syndrome:**
  - Non-selective proteinuria .
  - Does not respond well to corticosteroid

- **Prognosis:**
  - Spontaneous remission in ~ 1/3.
  - Proteinuria persists in ~2/3:
    - 10-30% are stable.
    - 40% progress to CRF & ESRD.

4. Membranoproliferative (mesangiocapillary) GN:

- Accounts for ~ 10% of cases of idiopathic NS in children and adults (young).

- Clinically can present with:
  - Nephrotic synd. (~ 50%*), nephritic synd., proteinuria ± hematuria OR compined nephrotic/nephritic.

Classification of MPGN

- **Type-I MPGN (80%):**
  - Mostly present with *nephrotic* syndrome.
  - Idiopathic or secondary MPGN.
- **Dense deposit disease DDD (Type-II MPGN):**
  - Mostly *nephritic* syndrome.

- Both types have the *same LM morphology* **BUT** differ in their *pathogenesis, EM & IF findings*.

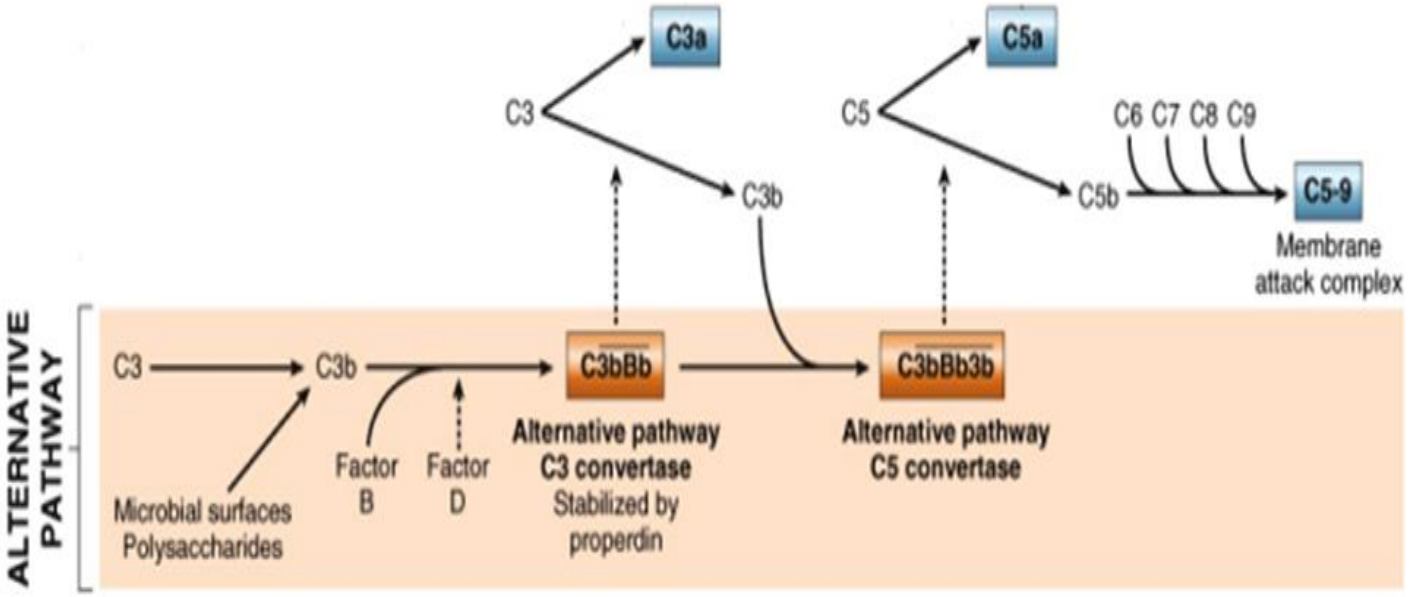
Pathogenesis of type-I MPGN

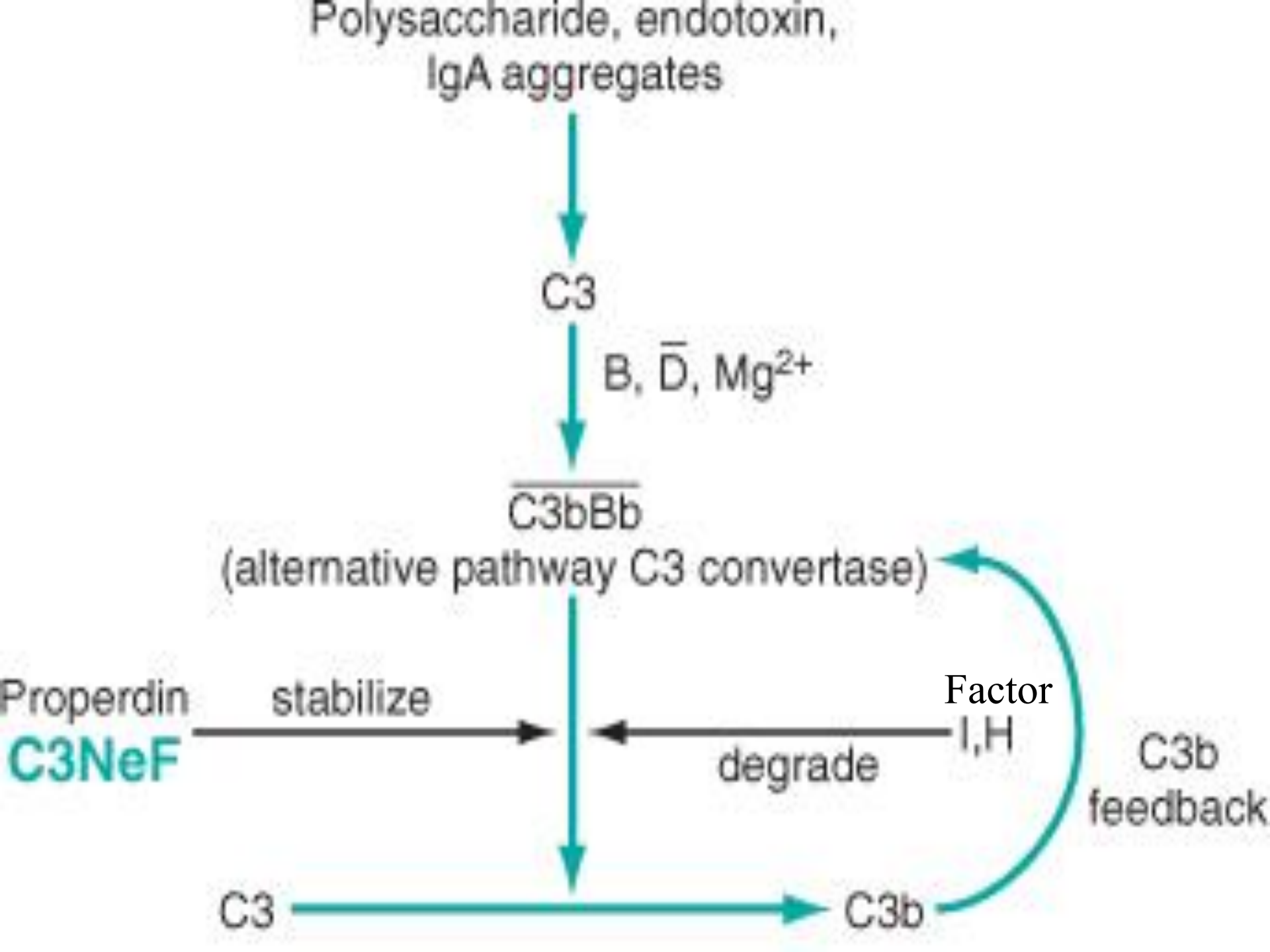
- Deposition of circulating immune complexes

Causes of MPGN type I	
Autoimmune	**SLE**
Infections	**Chronic HBV** **HCV with cryoglobulinemia** Infected atrioventricular shunts Infective endocarditis Chronic visceral abscesses
Malignancy	CLL
Hereditary	Deficiency of complement regulatory proteins
Idiopathic MPGN type I*	

Pathogenesis of DDD (type II MPGN)

- ?? Patients have abnormality that lead to *activation of alternative complement pathway* → they have persistent *low C3 , normal C1 & C4, low factor B & properdin*.
  - >70% have **C3 nephritic factor**, an autoAb that <u>stabilizes</u> C3 convertase leading to persistence of C3 degradation & hypocomplementemia.
  - Impairment of complement regulatory protein **Factor H** due to mutation or autoAbs.

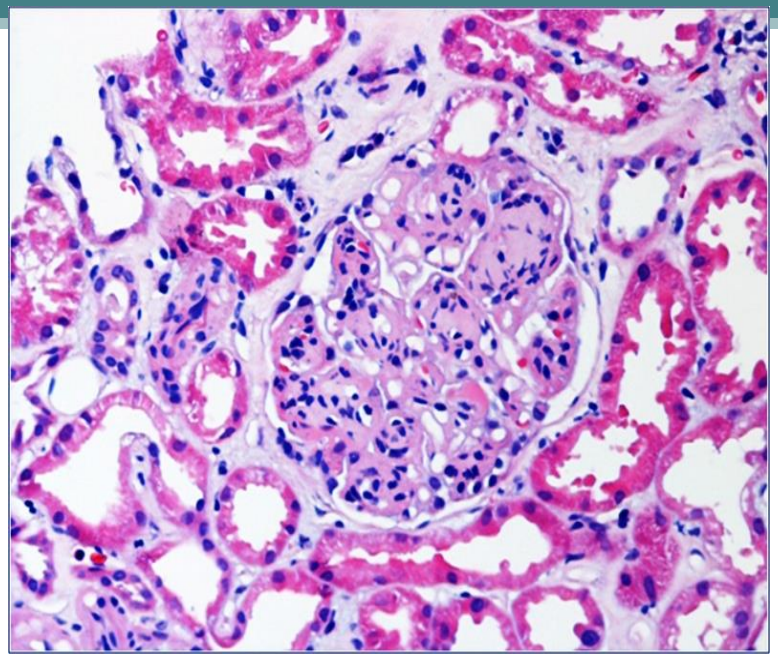


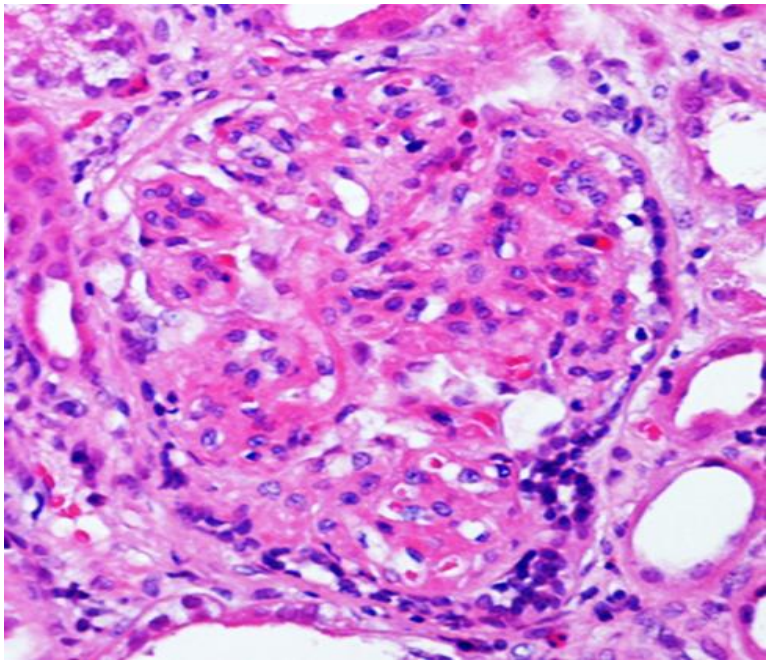

Polysaccharide, endotoxin,
IgA aggregates
C3
B, D̄, Mg2+
C3bBb
(alternative pathway C3 convertase)
Properdin
C3NeF
stabilize
Factor
I,H
degrade
C3b
feedback
C3
C3b

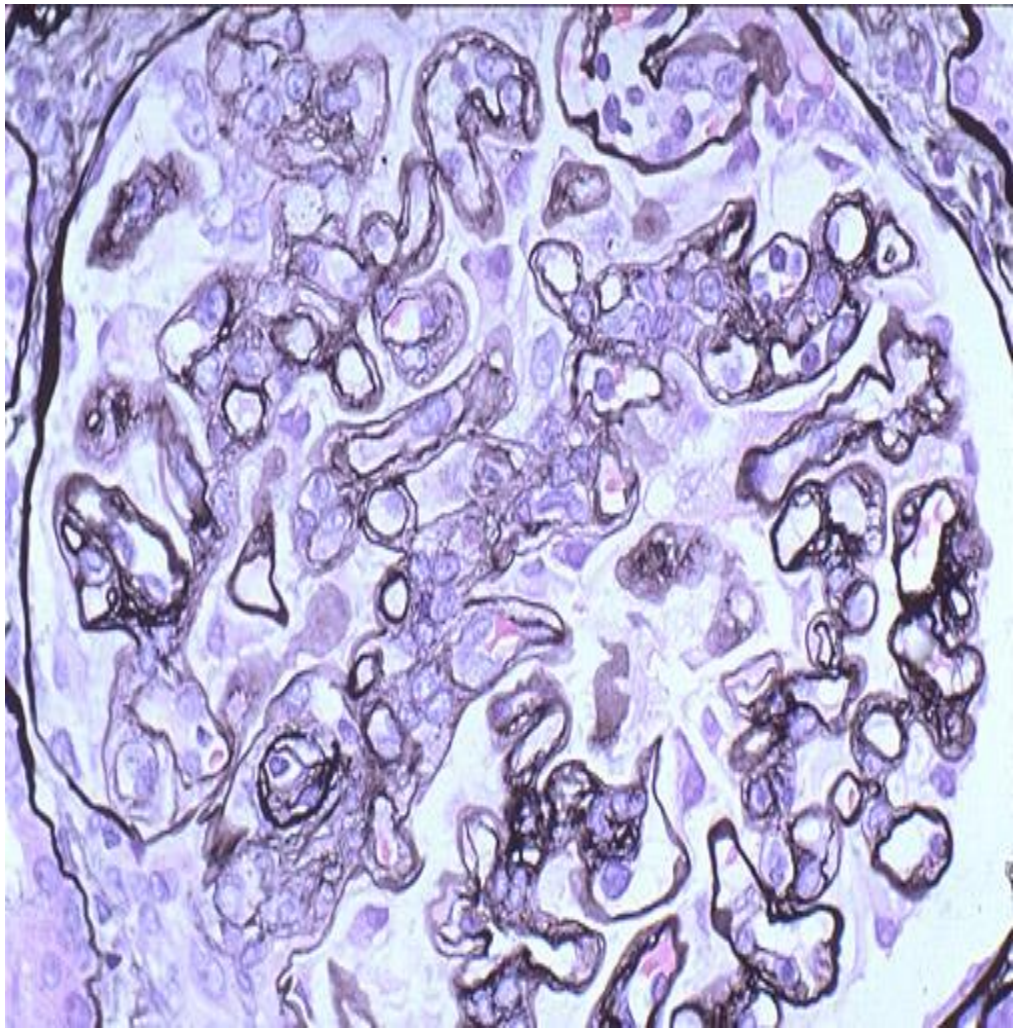
Morphology of MPGN by LM

Same for both types (I+II)

- Glomeruli:
  - Large, hypercellular (with *accentuated lobular arrangement*) due to:
    - Proliferation of endothelial cells → leading to thickening or splitting of GBM (on silver stain appears as "**double contour***" or "**tram-track**").
    - Proliferation of mesangial cells & ↑mesangial matrix.
    - Infiltration of leukocytes.
  - Crescents may be seen.



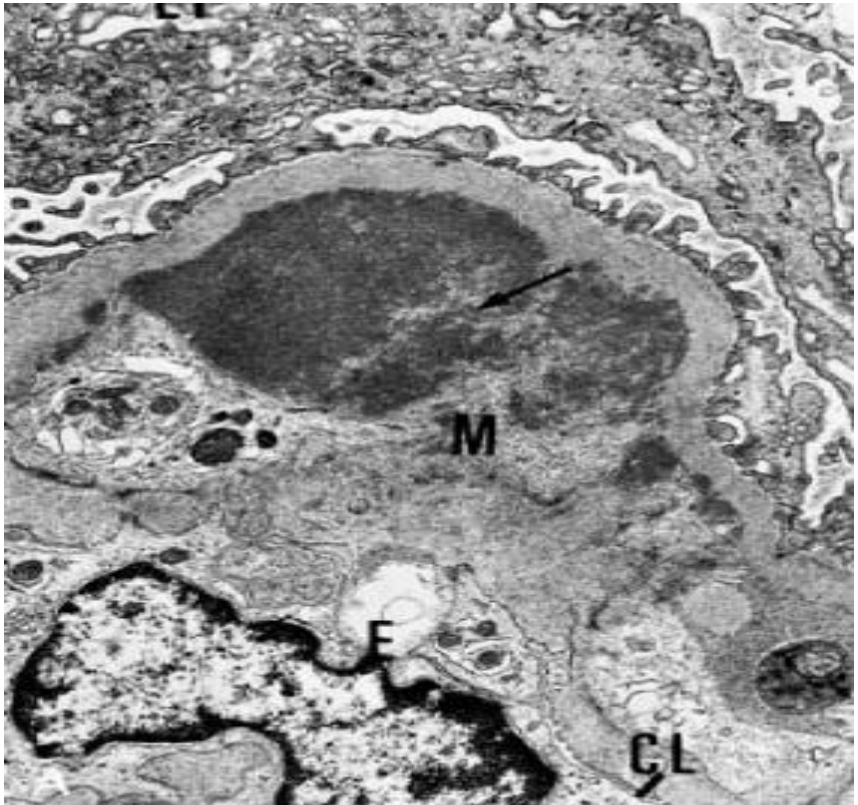


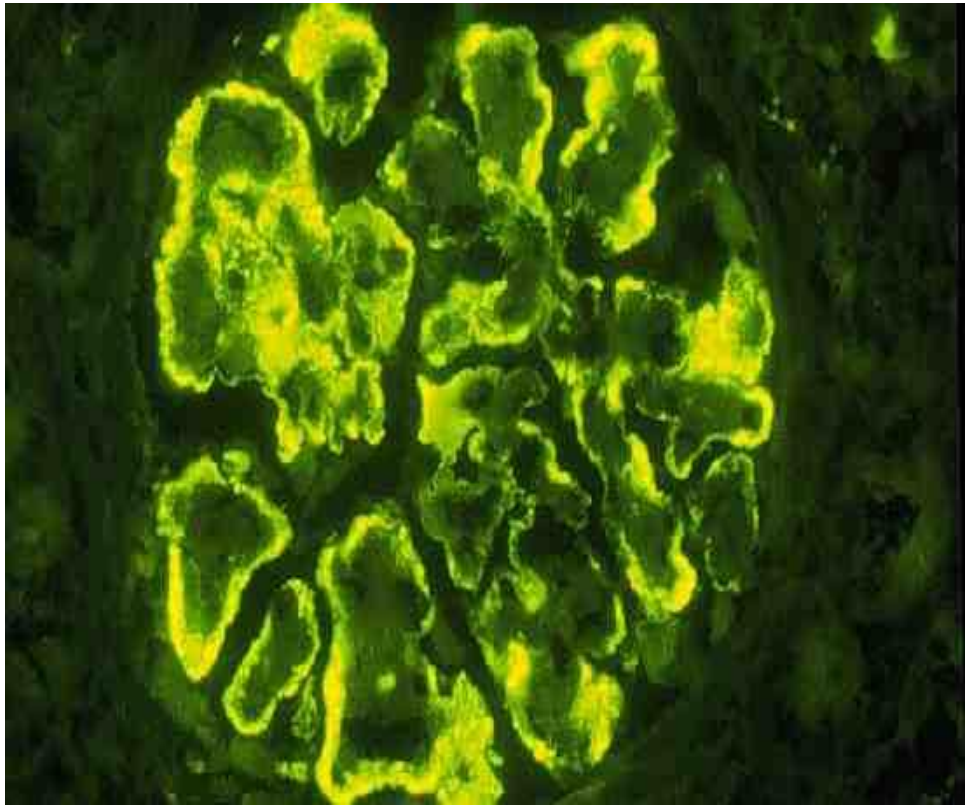


Silver stain

MPGN type I

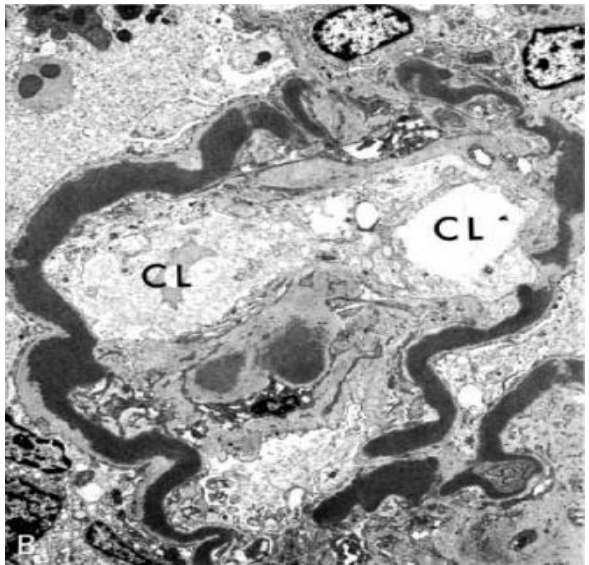
- **EM:** Subendothelial deposits*.
- **IF:** Granular deposition of IgG, C3, C1 & C4**.

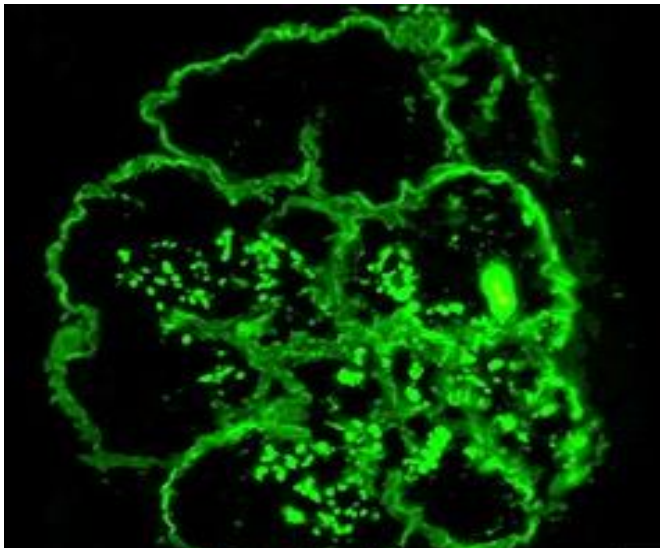




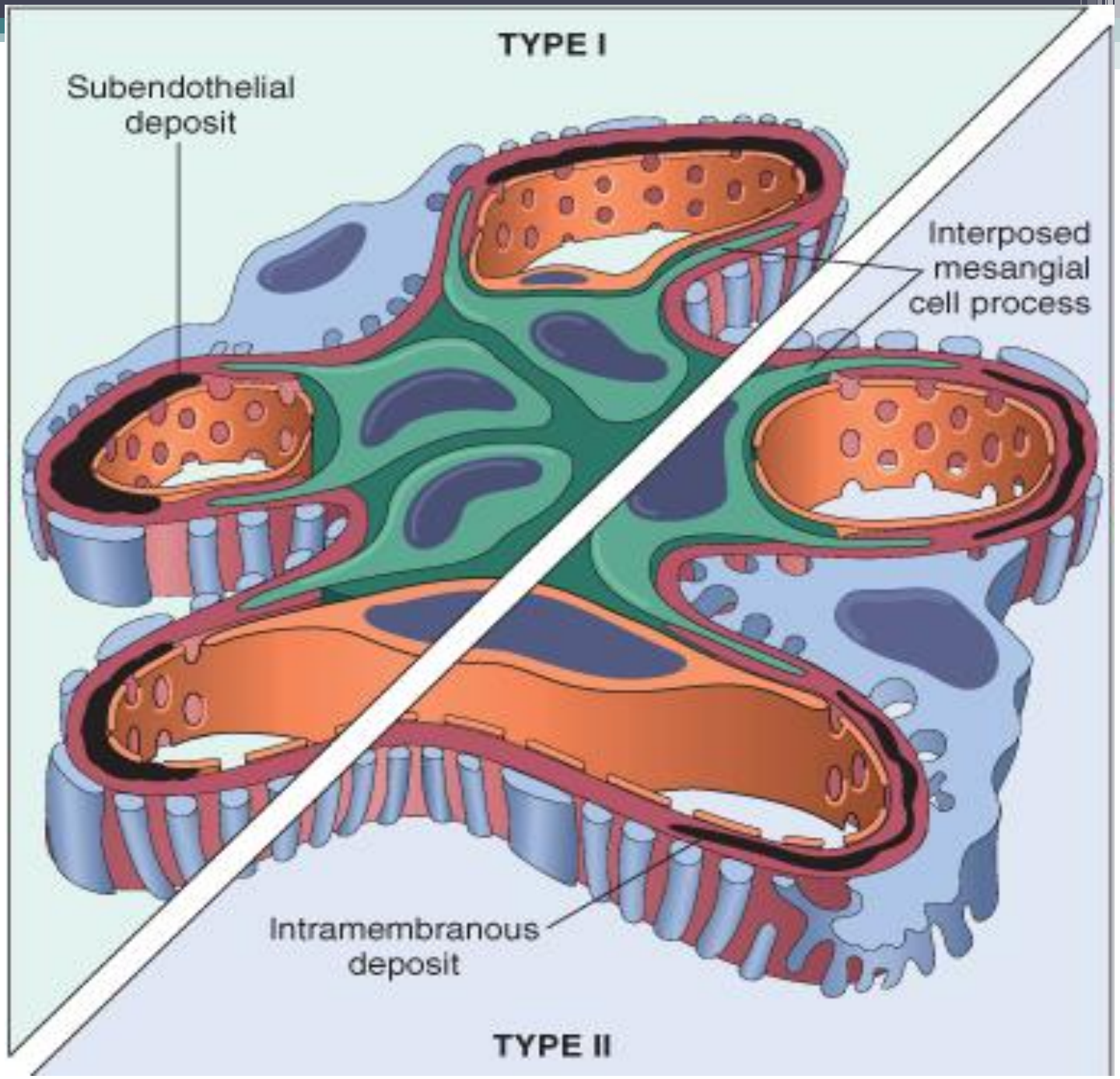
DDD (MPGN type II)

- **EM:** Lamina densa transformation into an irregular , **ribbon - like** ,extremely electron dense structure* (Dense Deposit Disease – DDD).
- **IF:** Granular **C3** staining is present in irregular chunky and segmental** linear foci in the BM & in the mesangium **(mesangial rings).** IgG, C1q and C4 are usually **absent**.

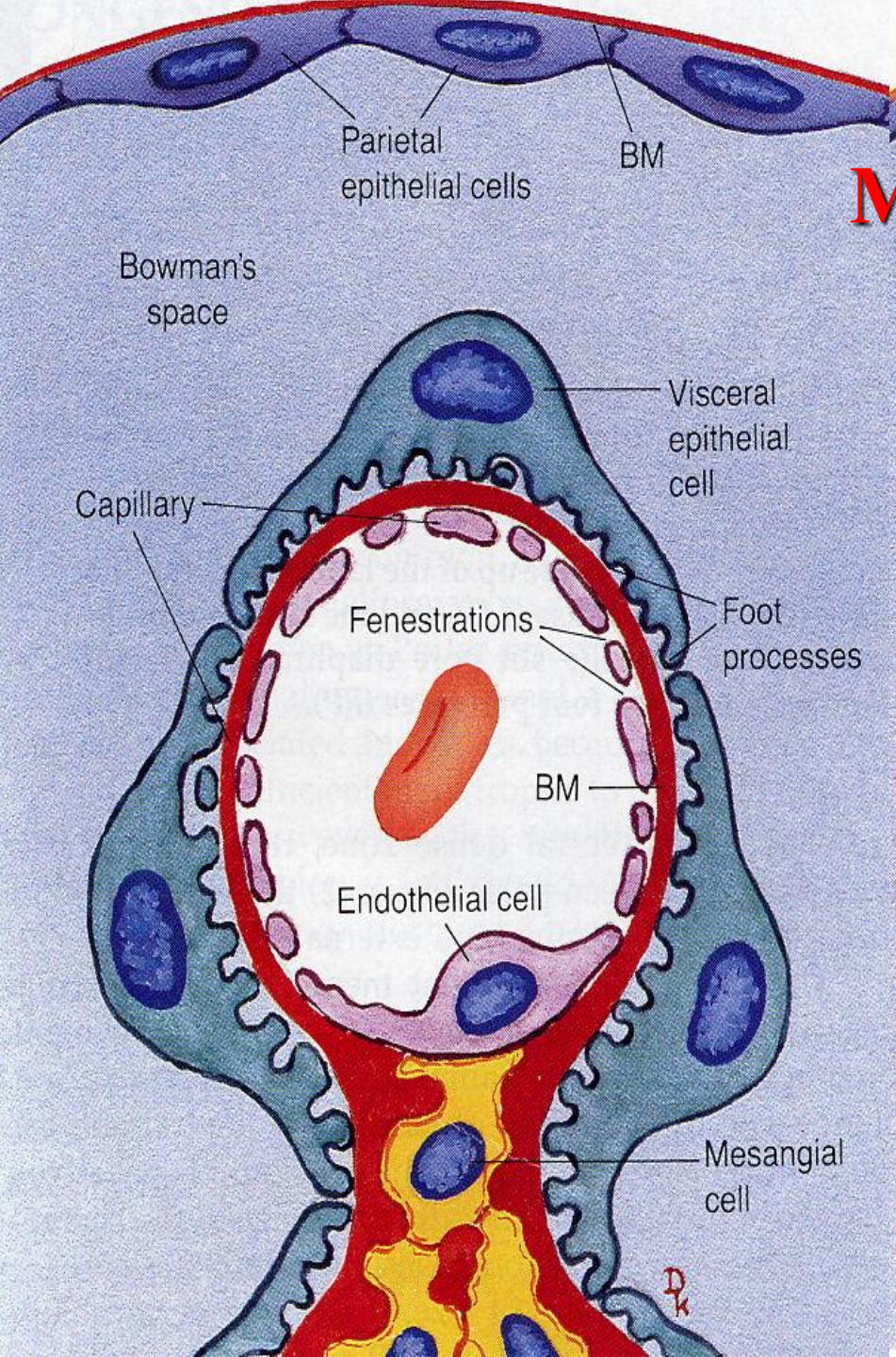


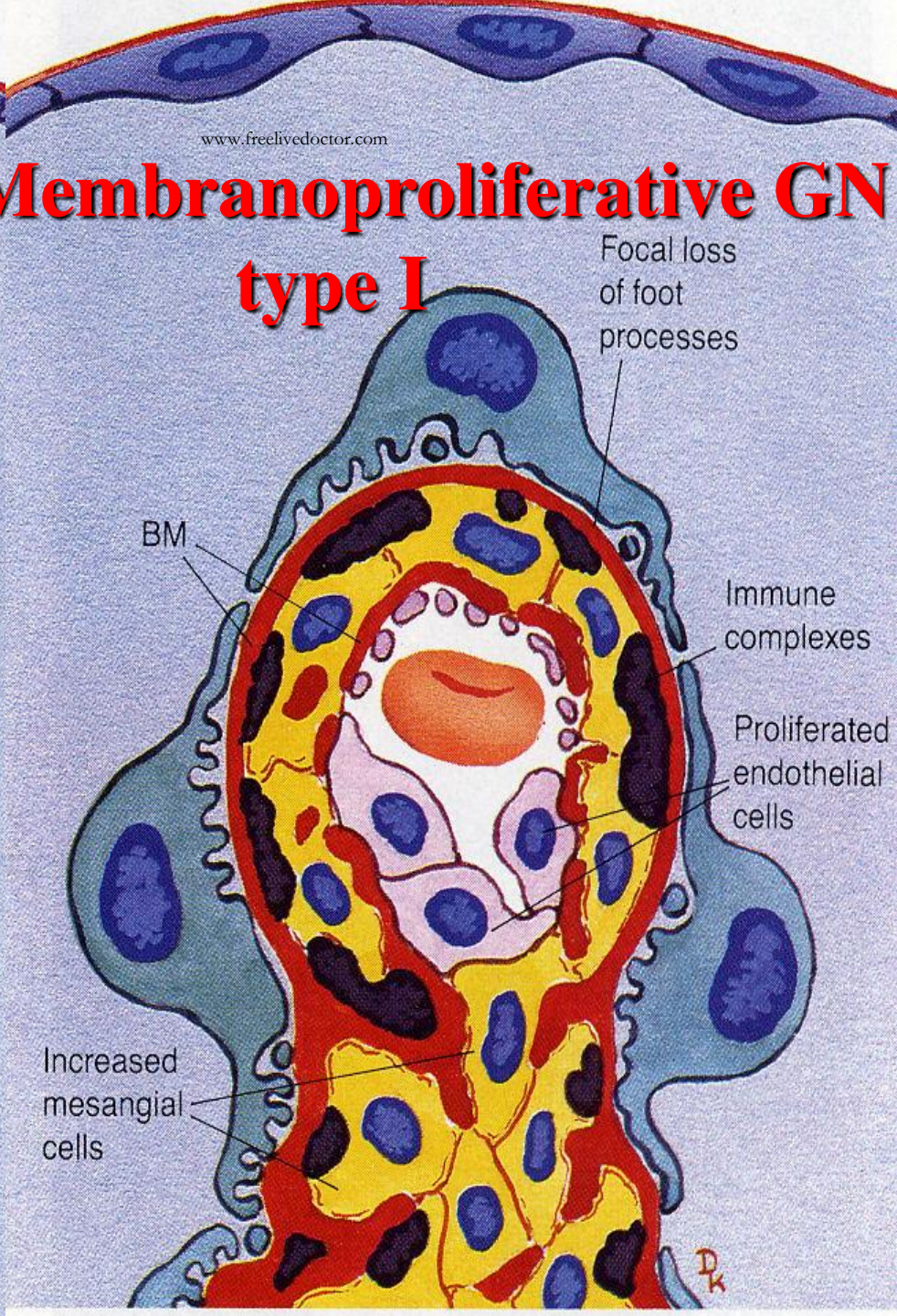


MPGN


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

Membranoproliferative GN type I





Prognosis of MPGN

- Slowly progressive unremitting disease with **poor** long term prognosis:
  - 40% develop CRF within 10 years.
  - 30% had variable degrees of renal insufficiency.
  - 30% had persistent nephrotic syndrome without RF.

- Dense-deposit disease has a **worse prognosis**, and it tends to recur in renal transplant recipients*.

Disease	Pathogenesis	L/M	IF	E/M
MCD	Podocyte injury	Normal Lipid in tubules	Negative	Effacement of foot processes
MGN	In-situ immune complexes	Thick GBM Spikes	Granular IgG & C3	Subepithelial deposits
FSGS	Podocyte injury Nephrin mutation Ablation theory	Focal & segmental hyalinosis & sclerosis Foam cells	IgM & C3	Effacement of foot processes Focal disruption of BM
MPGN type I *Mostly nephrotic*	Immune complexes	Lobular & cellular glomerulus Thick BM Tram track	Granular IgG, C3, C1q, c4	Subendothelial deposits
MPGN type II *Mostly nephritic*	C3NeF Alternative complement pathway		C3 in BM & mesangial rings	Dense deposits in BM