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Pathology GUS

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Pathology Lecture - 2

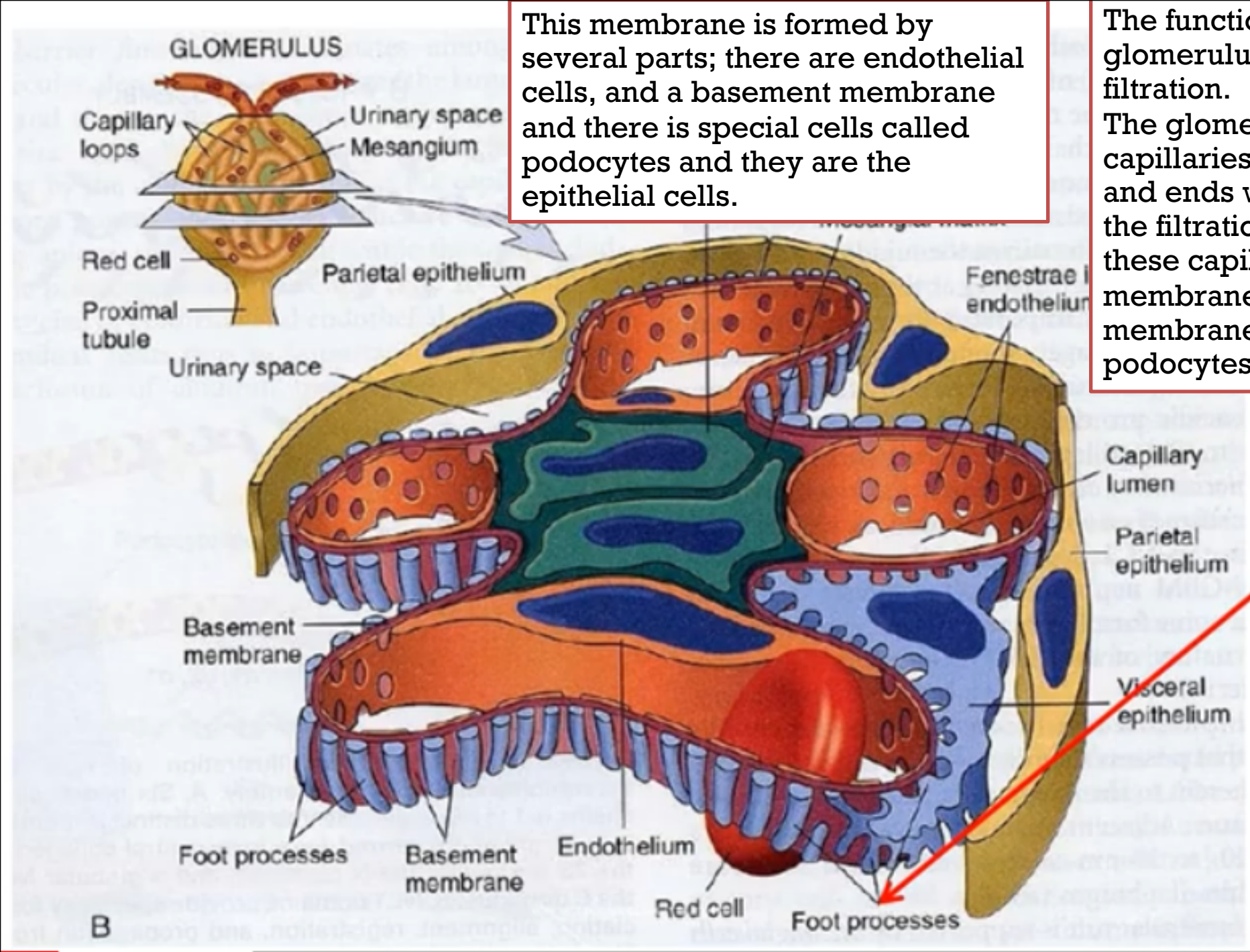
Nephrotic Syndrome

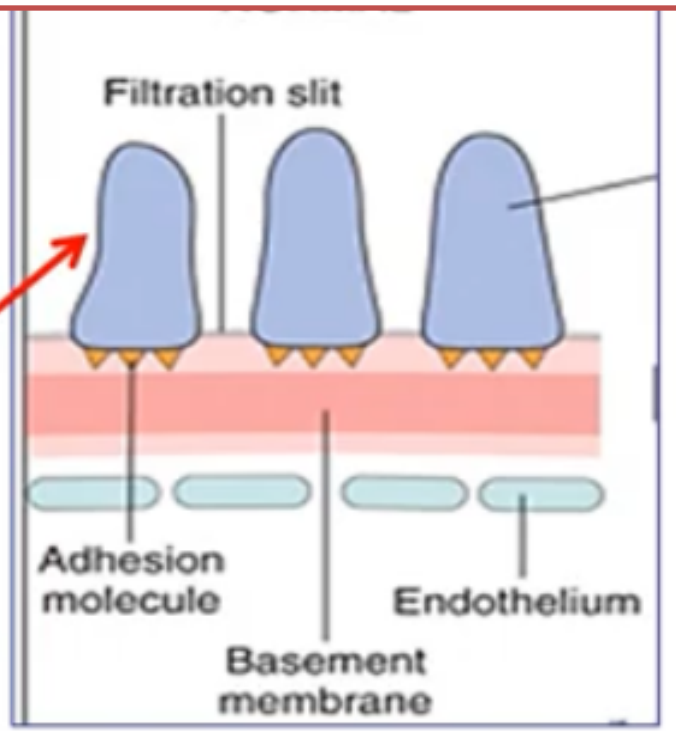
The function of the kidney is the filtration of the blood and the removal of waste products and toxins and return the clean blood back to the circulation.
This occurs continuously all throughout our life.

Dr. Nisreen Abu Shahin

This membrane is formed by several parts; there are endothelial cells, and a basement membrane and there is special cells called podocytes and they are the epithelial cells.

The functional part of the kidney is the glomerulus, and its function is the filtration.
The glomerulus is a network of capillaries, it starts with afferent arterioles and ends with an efferent arterioles and the filtration is through the membrane of these capillary networks; the filtration membrane, the glomerular basement membrane (GBM)and some of the podocytes above it.





The Nephrotic Syndrome

- a clinical complex resulting from glomerular disease & includes the following:
- (1) **massive proteinuria (**3.5 gm /day in adults).

The hallmark & the cause of the other manifestations

Big amounts of protein are lost in the urine. Normally proteins should not be able to pass through the filtration membrane and reach the urine. The damage that occurs in nephrotic syndrome damages the filtration membrane (podocytes) and allows them to pass through

- (2) **hypoalbuminemia (**≤ 3 gm/dL).

Decreased level of albumin in the blood

- (3) **generalized edema**

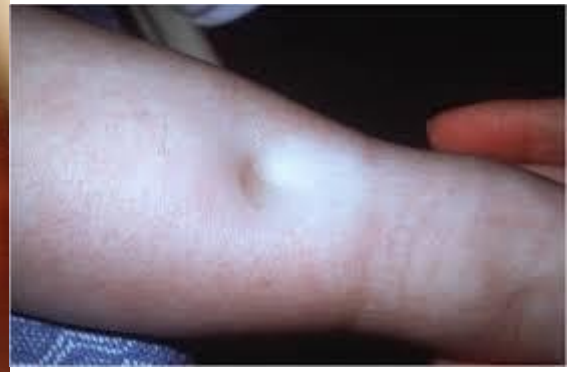
Proteinuria —> loss of proteins (including albumin) —> hypoalbuminemia —> decreased colloid press—> edema

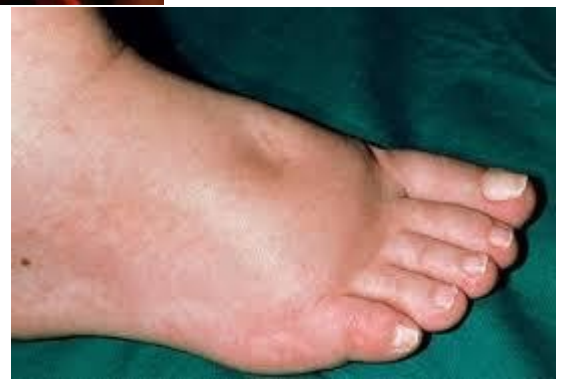
- (4) **hyperlipidemia and lipiduria**.

Increased levels of lipids in blood including triglycerides and LDL & the presence of lipids in urine

Normally lipids shouldn't be present in urine, one of the theories that explained it that there's increased synthesis and production of lipoproteins in liver because of shift of metabolic pathways.
--> Another theory : albumin which is a transporter or lipids, when its levels is decreased, lipids level is increased

- (5) little or no azotemia, hematuria, or hypertension.

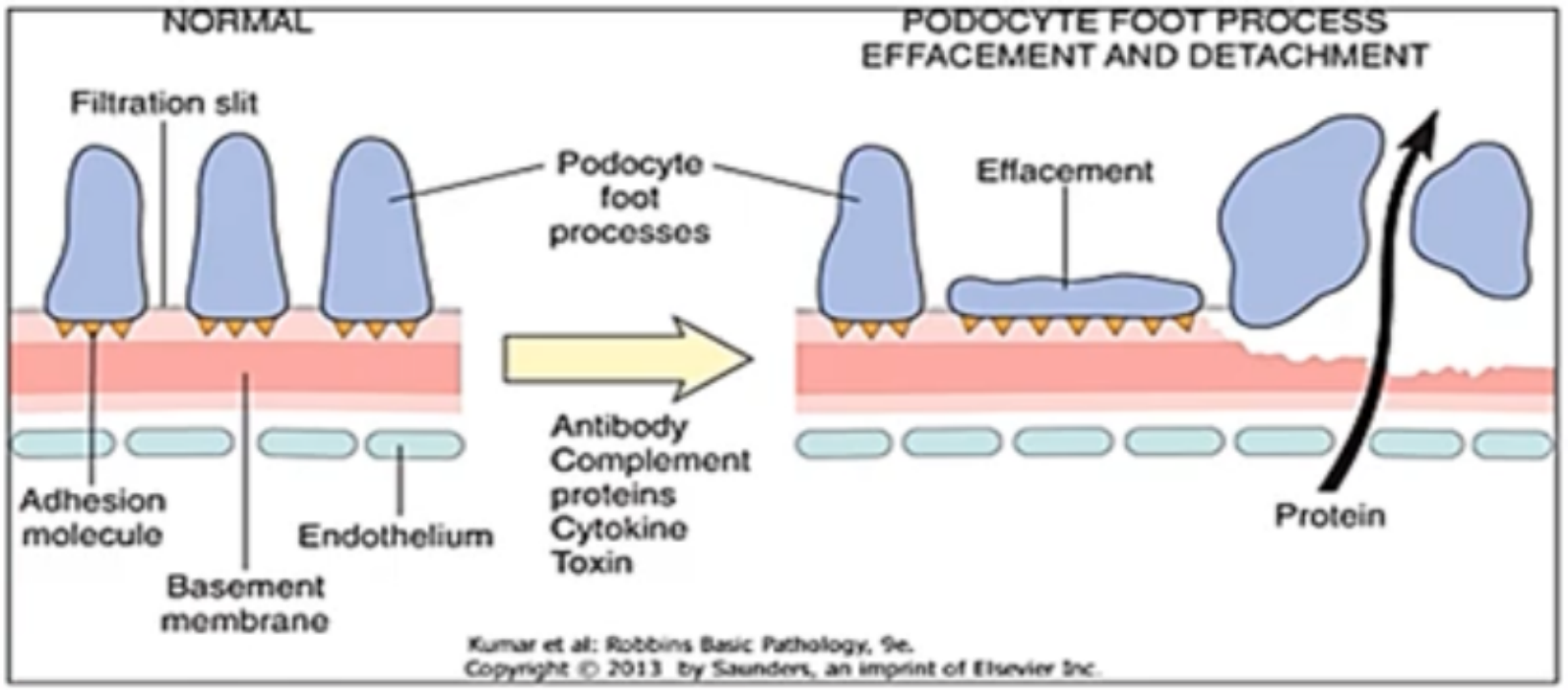




Generalized edema is the alarming symptom in nephrotic syndrome patients

Then the doctor starts looking for the other manifestations
Firstly, hypertension is investigated, blood pressure readings are done but the doctor will not find hypertension.
Then the doctor will do lab tests (kidney function test [creatinine & urea] and urine analysis), in urine analysis the doctor will find proteinuria [+3] , the kidney function test usually will be normal, leading the doctor to suspect nephrotic syndrome

Podocyte injury leads to proteinuria/nephrotic syndrome



There are many diseases cause nephrotic syndrome which is a group of manifestations

Pathogenesis:
Damage to filtration membrane either to the basement membrane or to the podocytes which have foot processes (finger-like projections that cover the capillary from the outside) and cover the capillary wall and they are important for the impermeability for proteins

Causes of Nephrotic Syndrome

- **1- Primary Glomerular Diseases**
- **2- Secondary (Systemic Diseases with Renal Manifestations)**

Primary Diseases that Present Mostly with Nephrotic Syndrome

1- Minimal-change disease

2- Focal segmental glomerulosclerosis (FSGS).

3- Membranous nephropathy

4- membranoproliferative GN type 1 (usually a combination of nephrotic/ nephritic syndrome)

Causes of Nephrotic Syndrome

1-primary glomerular diseases

Cause	Prevalence)%(Children	Prevalence (%) Adults
Primary Glomerular Disease		
Membranous GN	5	30
Minimal-change disease	65	10
Focal segmental glomerulosclerosis	10	35
Membranoproliferative GN	10	10
IgA nephropathy	10	15

65% of children who have nephrotic syndrome is found that they had minimal change disease

While 35 % of adults present with nephrotic syndrome are associated with focal segmental glomerulosclerosis

Causes of Nephrotic Syndrome

B-Systemic Diseases with Renal Manifestations:

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- **Diabetes mellitus:**
- **Amyloidosis**
- **Systemic lupus erythematosus**
- **Drugs (gold, penicillamine, "street heroin")**
- **Infections (malaria, syphilis, hepatitis B, HIV)**
- **Malignancy (carcinoma, melanoma)**
- **Miscellaneous (e.g. bee-sting allergy)**

1- Minimal-Change Disease (Lipoid Nephrosis(

- **benign disorder.**

Good prognosis, minimal change to the kidney

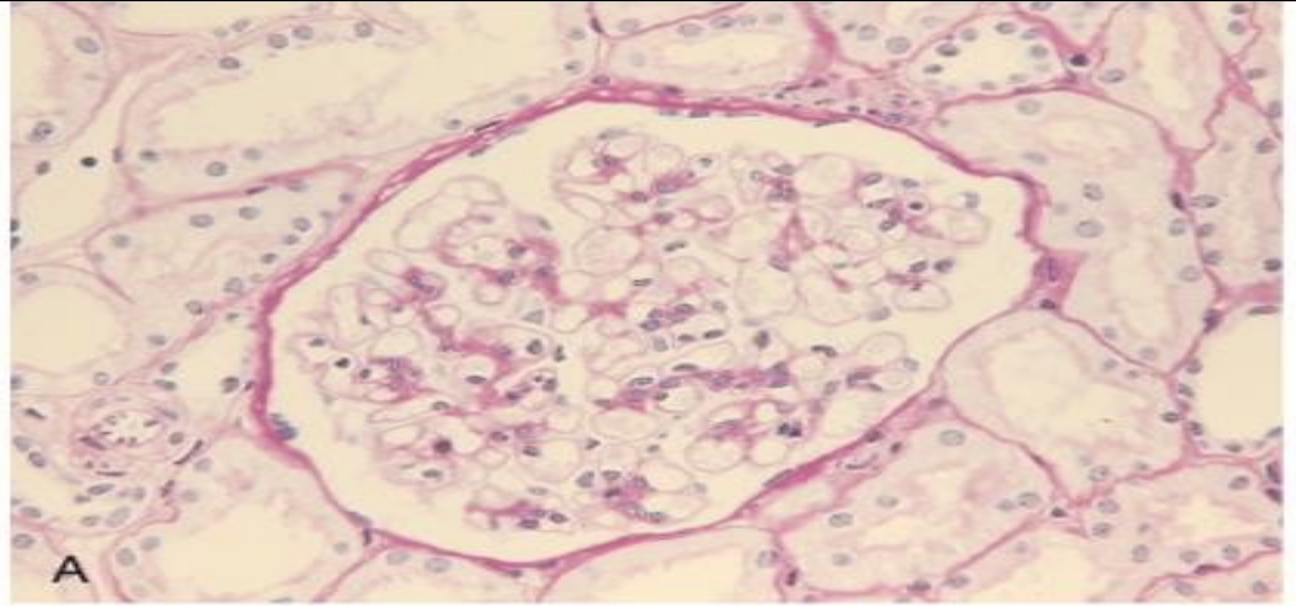
- **The most frequent cause of the nephrotic syndrome in children (ages 1-7 years).**

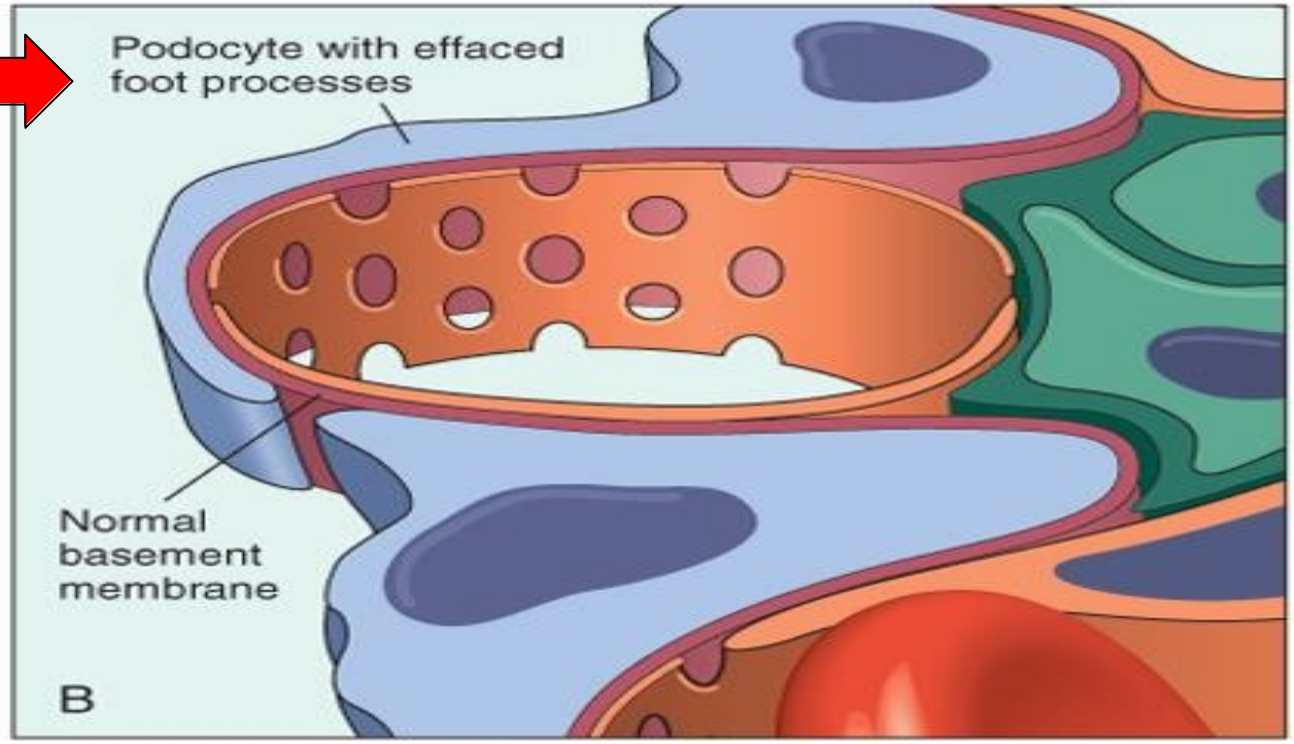
Most minimal change disease patient are children

- ***Pathogenesis:*** **still not clear.**

? T-cell derived factor that causes podocyte damage and effacement of foot processes.

This change can only be seen on EM, but it cannot be seen otherwise which is why it is named minimal change disease





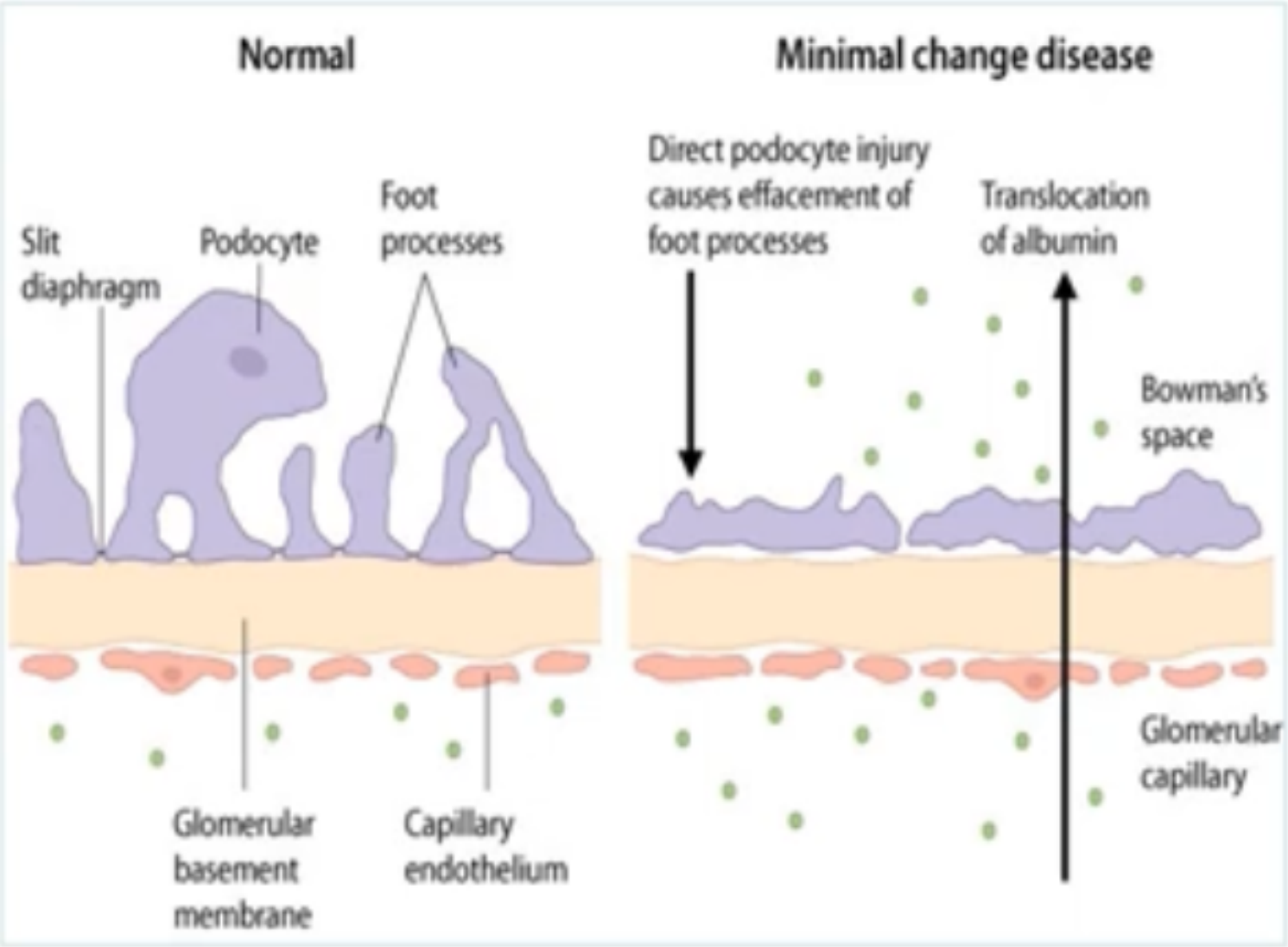
Minimal change disease.

A

glomerulus appears normal, with a delicate basement membrane

B

diffuse effacement of foot processes of podocytes with no immune deposits.



The evidence of podocytes damage is the effacement of foot processes
The change is seen only by electron microscope

Damage to podocytes, alteration to the function of the filtration membrane—>> loss of the filtration barrier and loss of large amounts of proteins in urine

Morphology

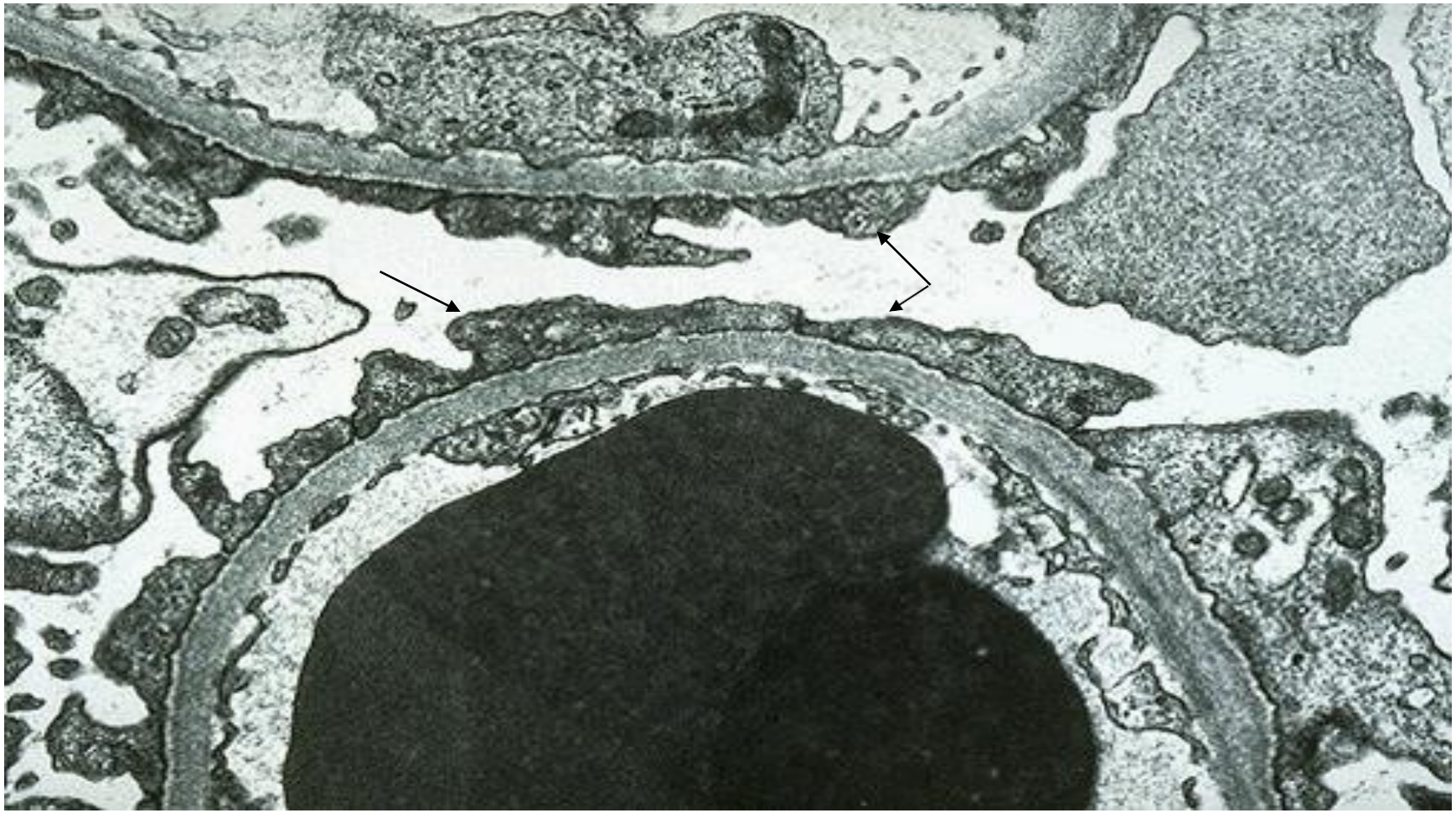
- **LM**
- the glomeruli appear normal.

- **IF**
- negative
- **EM**
- **uniform and diffuse effacement of the foot processes of the podocytes .**
- No immune deposits

MCD-EM

the capillary loop in the lower half contains two electron dense RBC's. Fenestrated endothelium is present and the BM is normal.

The overlying epithelial cell foot processes are fused (arrows).



MCD- Clinical Course

- **nephrotic syndrome in an otherwise healthy child.**
- **no hypertension.**
- **renal function preserved**
- **selective proteinuria (albumin)**
- **prognosis is good.**

Recovery of podocytes processes with treatment with corticosteroids

- **Treatment: corticosteroids (90% of cases respond)**
- **< 5% develop chronic renal failure after 25 years**
- **In Adults with minimal change disease the response is slower and relapses are more common.**

2- Focal and Segmental Glomerulosclerosis (FSGS)

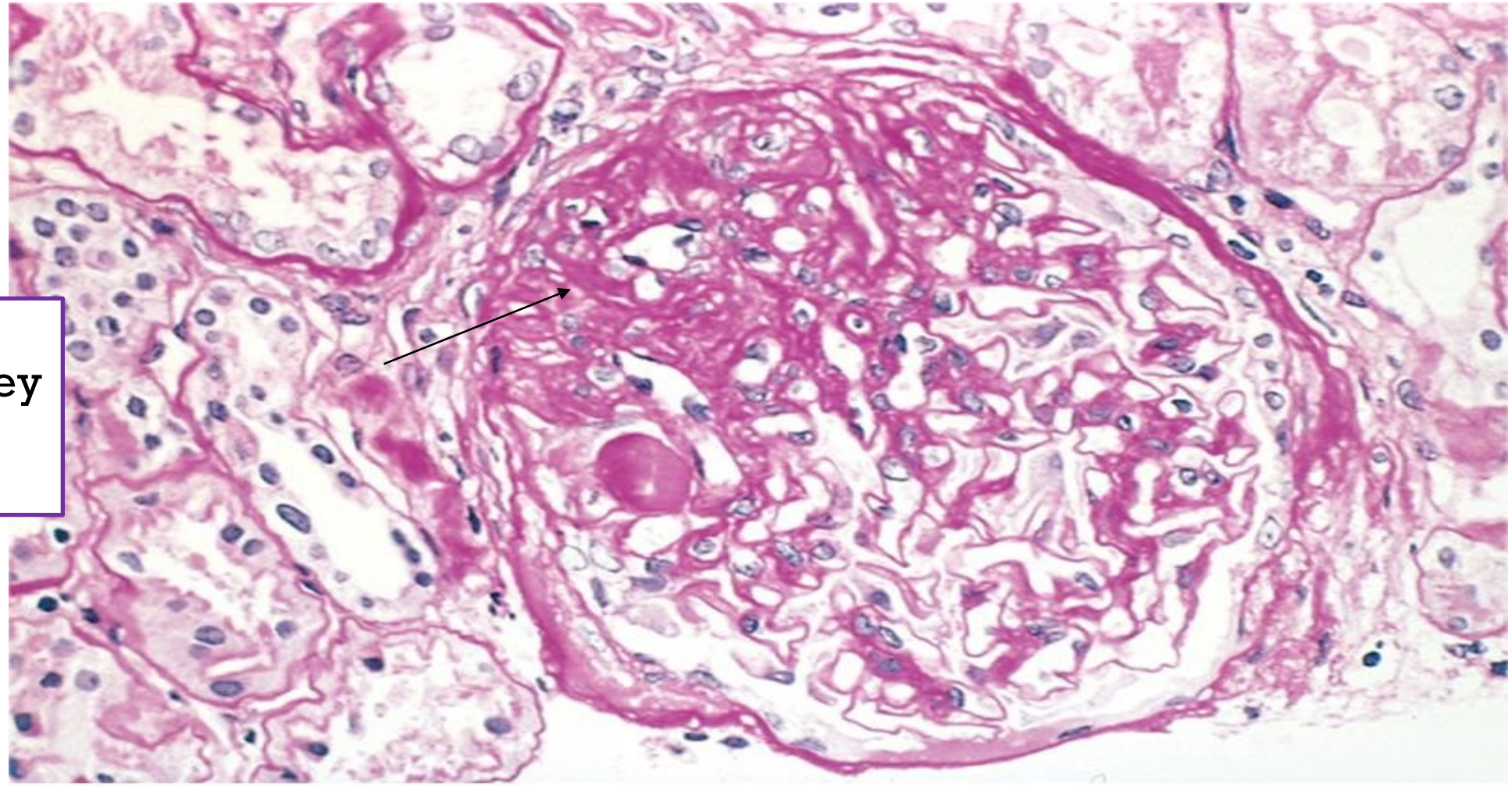
- **sclerosis (fibrosis) affecting some but not all glomeruli (focal involvement) and involving only segments of glomerulus.**
- **Usually nephrotic syndrome.**
- **It can occur :**
- **as a primary disease(20% to 30% of NS)**
- **Or: in association with AIDS; heroin abuse; nephron loss; inherited or congenital forms resulting from mutations affecting nephrin; etc….**

- Focal : Some of the glomeruli are affected
- Segmental : a segment of the single glomerulus is affected

Secondary

focal and segmental glomerulosclerosis (PAS stain).
a mass of scarred, obliterated capillary lumens with accumulations of matrix material

Fibrosis, more pinkey (fibrous tissue)



MCD versus FSGS

	MCD	FSGS
hematuria	-	+
hypertension	-	+
proteinuria	selective	nonselective
response to corticosteroid therapy	good	poor

- ***Pathogenesis***
- **unclear**
- ***injury to the podocytes* ? ↑ GFR ? Genetics ?**
- **entrapment of plasma proteins and lipids in foci of injury where sclerosis develops.**

sudden and severe elevation in GFR
Genetic mutation in the filtration membrane proteins (specifically nephrin)

- **Clinical Course**
- **about 50% of individuals suffer renal failure after 10 years**
- **Poor responses to corticosteroid therapy.**
- **Adults do worse than children**

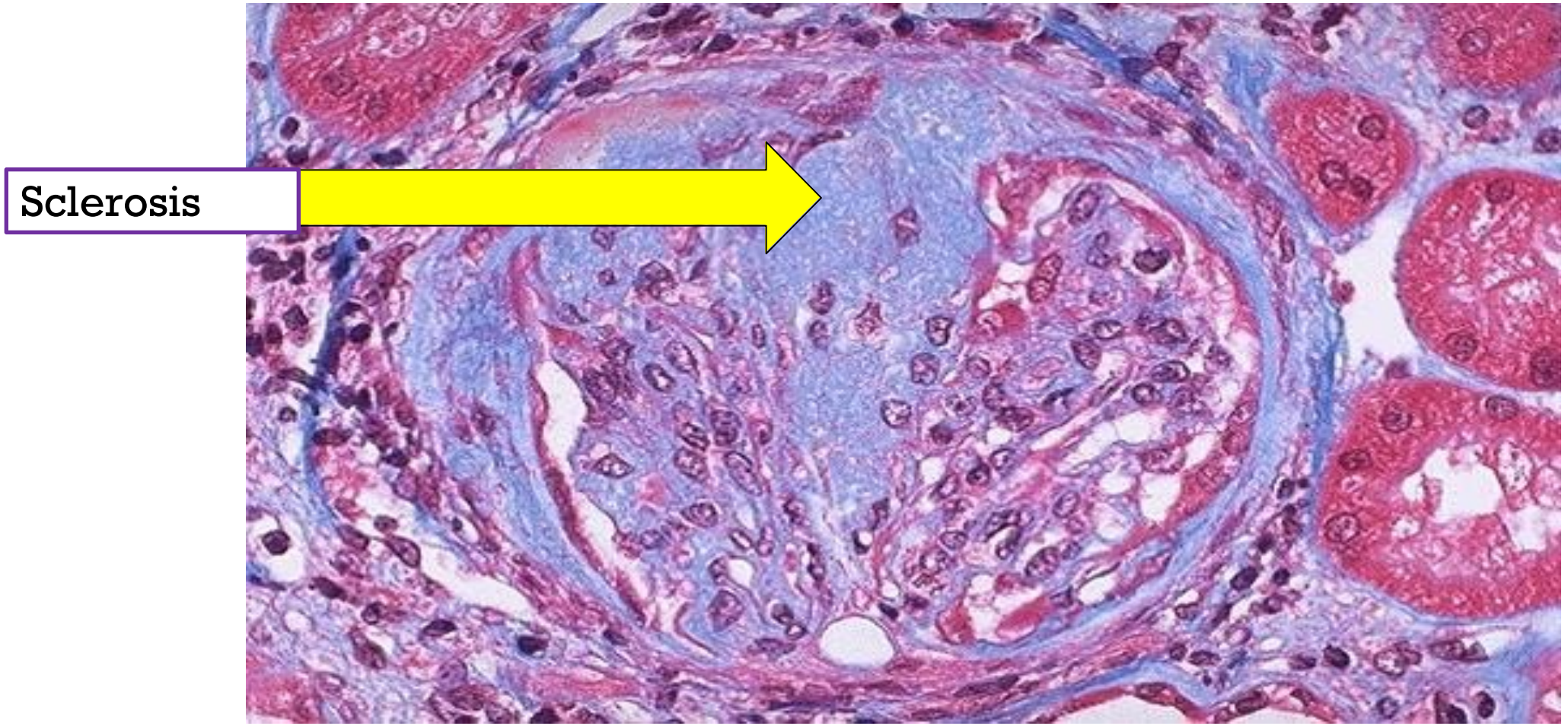
- **Morphology**
- **LM:**
- Sclerosis in some glomeruli not all of them; and in a segment not all of the affected glomerulus
- **IF microscopy**
- Negative

Normal

- **EM**
- **effacement of foot processes**

FSGS

blue = collagen deposition (MT stain).



Collapsing glomerulopathy

- a morphologic type of FSGS.
- poor prognosis.
- collapse of glomerular tuft and podocyte hyperplasia.
- It may be :
- 1-idiopathic .
- 2-associated with **HIV infection**.
- 3-drug-induced toxicities.

Remember this note only

3- Membranous nephropathy:

- **Immune complex deposition in glomerulus**

Antigen – antibody complex circulate in blood to reach the glomerulus and deposits there which leads to damage the structure of GBM (filtration membrane) >> loss of proteins in urine

- **Types of Membranous glomerulonephritis :**

1-Idiopathic (85% of cases): antibodies against

podocyte antigen phospholipase A2 receptor (PLA2R) antigen

2-Secondary

Secondary Membranous glomerulonephritis :

- (1) infections (HBV, syphilis, schistosomiasis, malaria).
- (2) malignant tumors (lung, colon and melanoma).
- (3) autoimmune diseases as SLE .
- (4) inorganic salts exposure (gold, mercury).
- (5) drugs (penicillamine, captopril,NSAID).

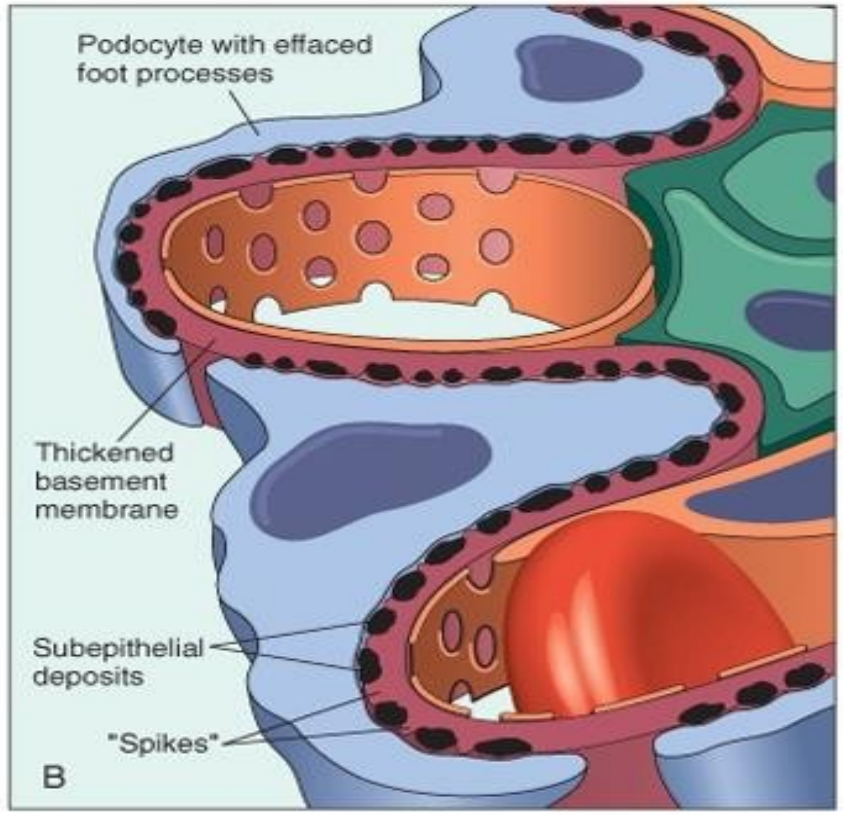
- **Morphology**
- **LM**
- **diffuse thickening of the GBM** .

Deposition of complexes extending the membrane

- **IF**
- **deposits** of immunoglobulins and complement along the GBM (IgG)

Because of immune complexes

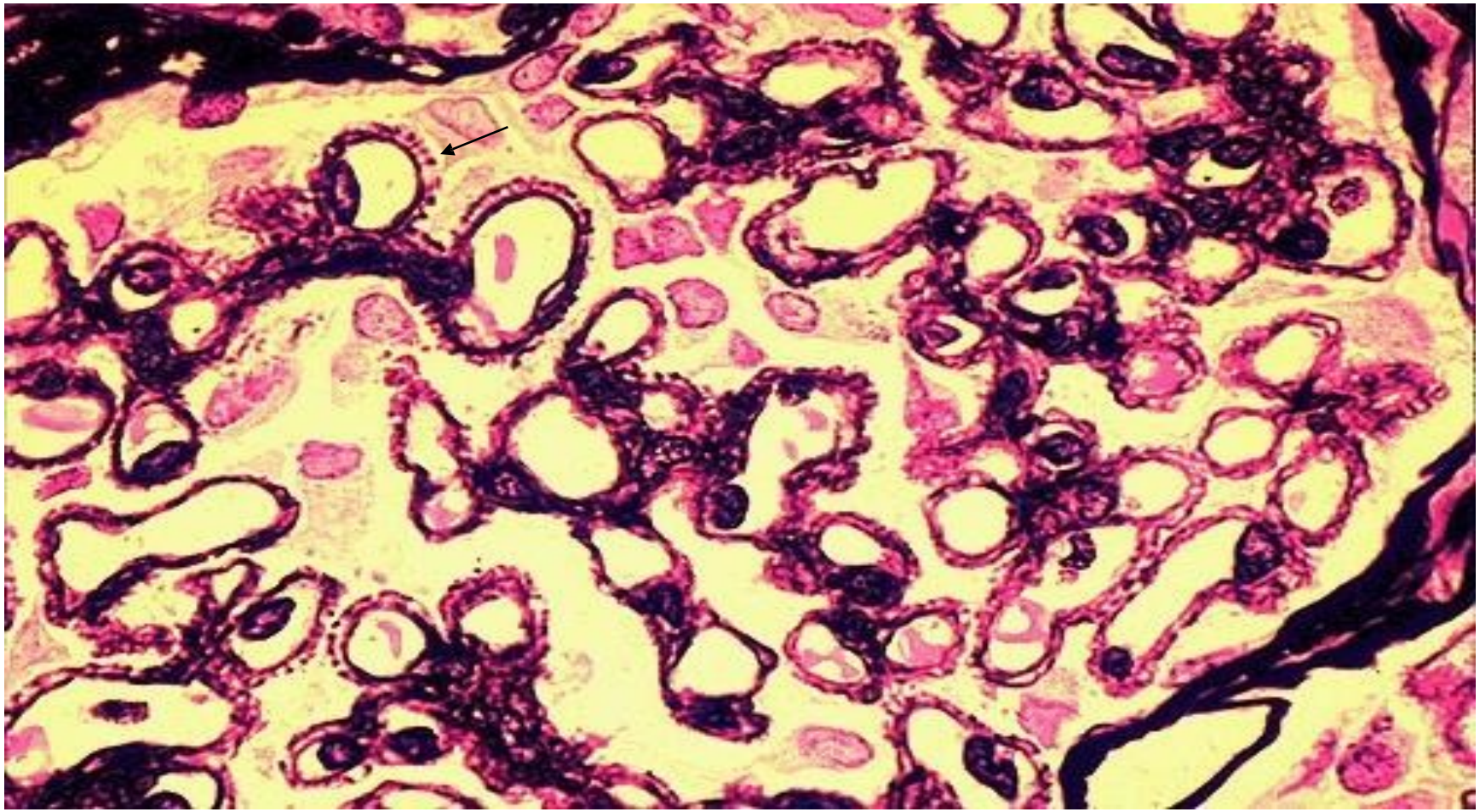
- **EM**
- **subepithelial deposits "spike and dome" pattern**.



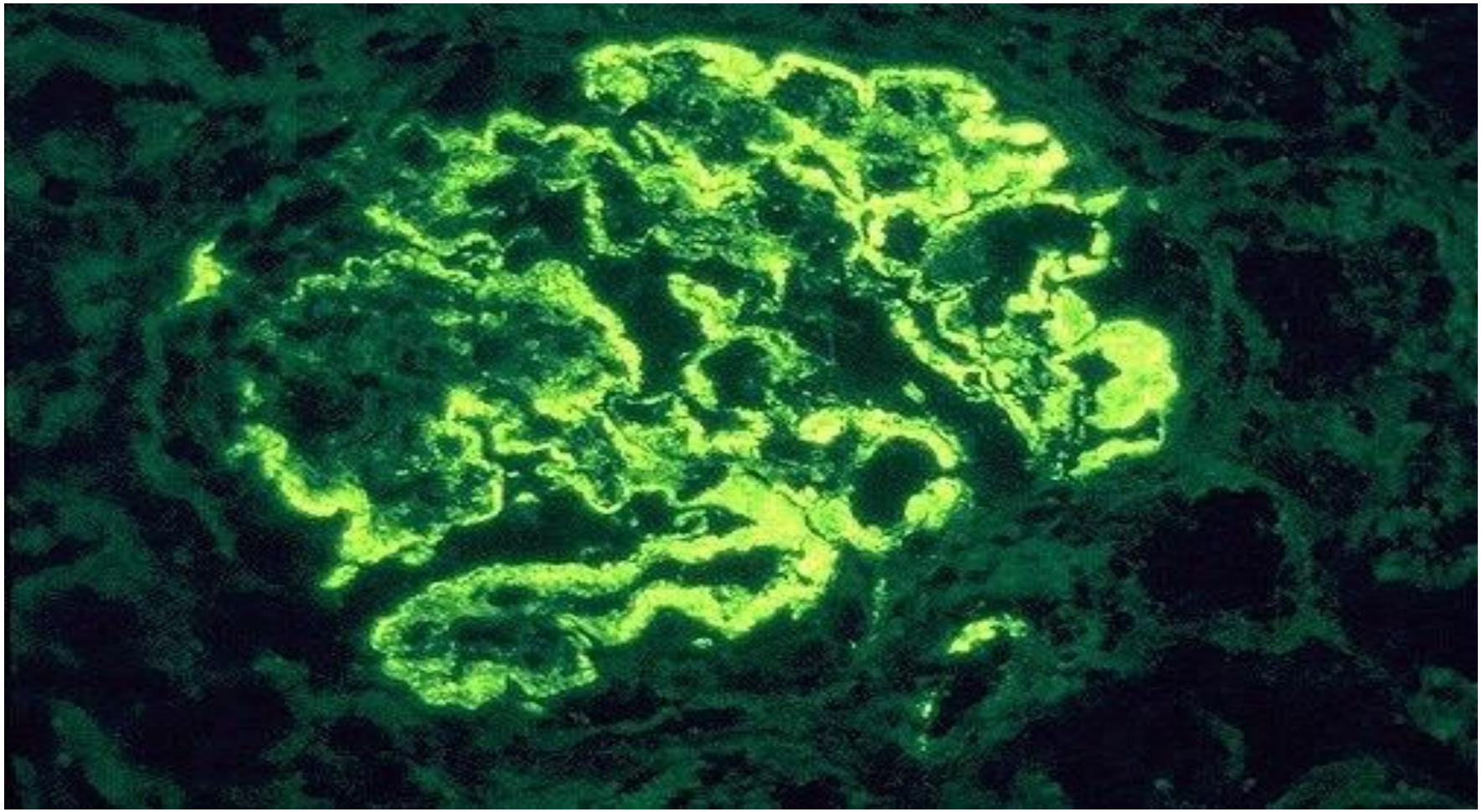
Membranous nephropathy.
subepithelial deposits and the presence of "spikes" of basement membrane material between the immune deposits .

Deposits Under the podocytes & above the GBM >> sub epithelial

A silver stain (black). Characteristic "spikes" seen with membranous glomerulonephritis as projections around the capillary loops.



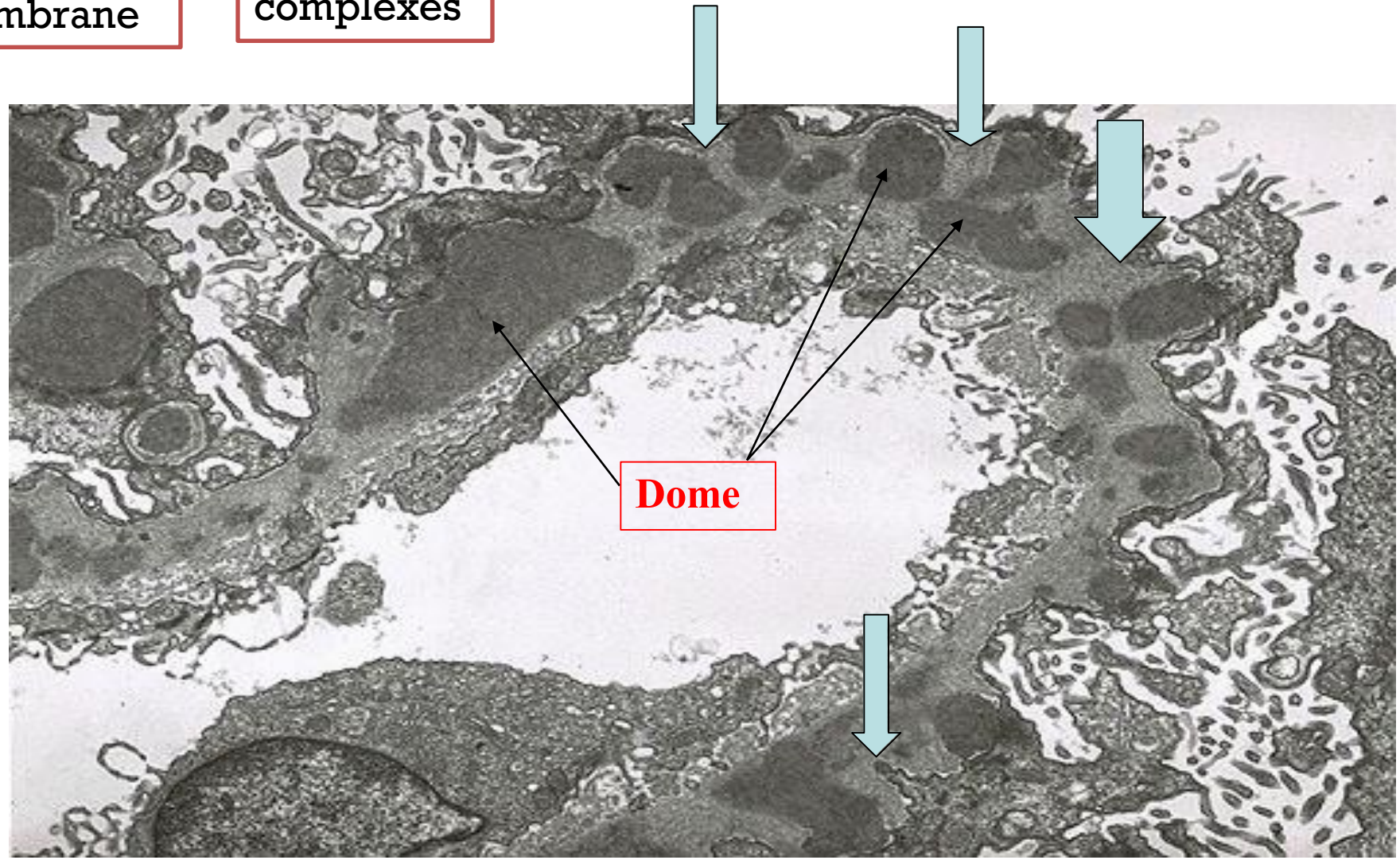
Membranous GN
IF: deposits of mainly IgG and complements



EM- ("spike and dome" pattern).

Basement membrane

Immune complexes



- **Clinical Course**
- **nephrotic syndrome**
- **poor response to corticosteroid therapy.**
- **60% of cases→ proteinuria persists**
- **~ 40%→ progressive disease and renal failure 2 to 20 yr.**
- **30% →partial / complete remission of proteinuria.**