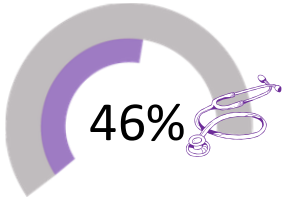


بسم الله الرحمن الرحيم

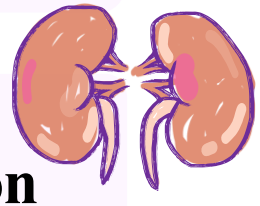
Nephrotic Syndrome

MID | Lecture 3

﴿قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾

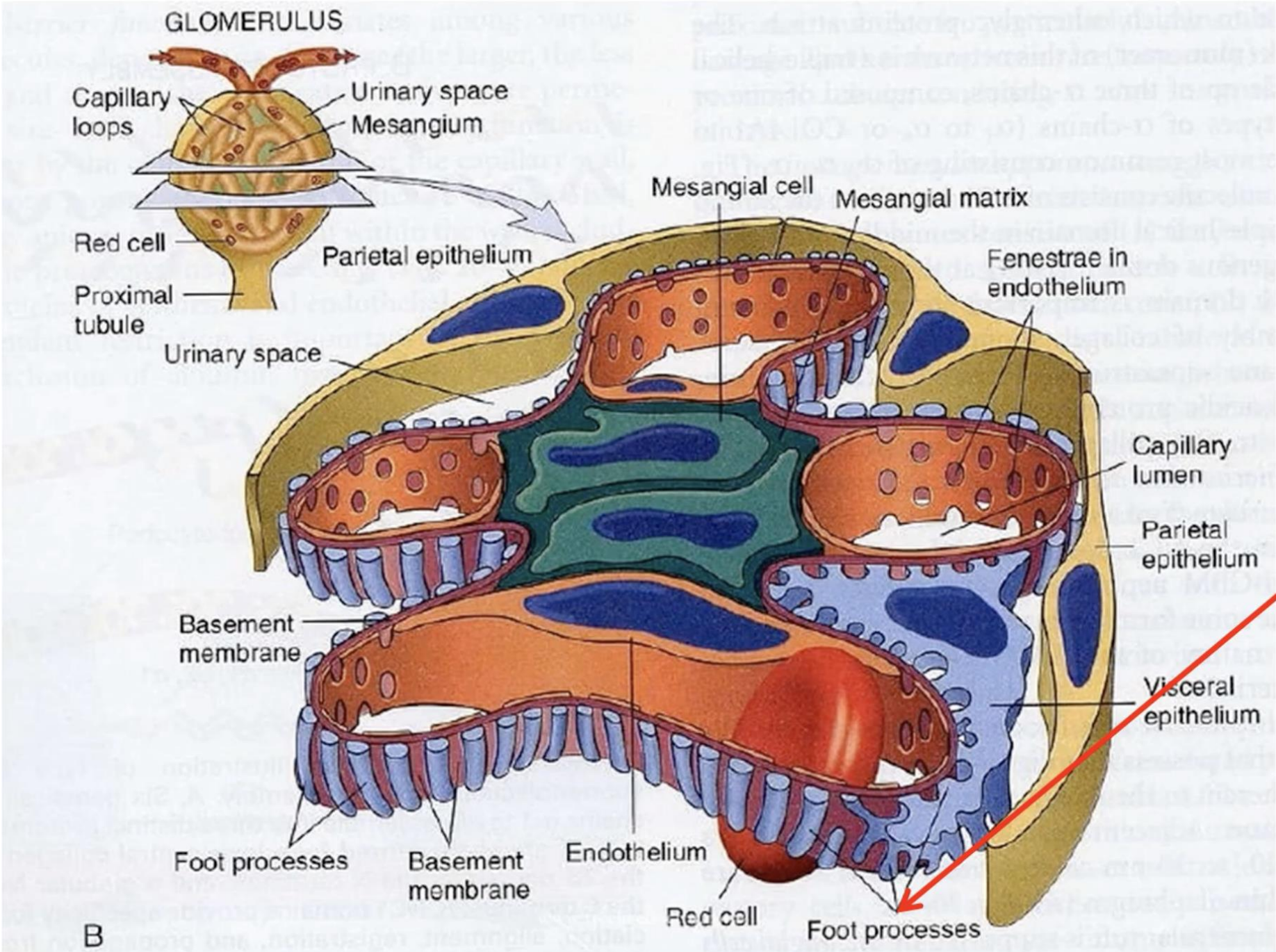
Written by: Layan Fawarseh
Aya Ghalayini

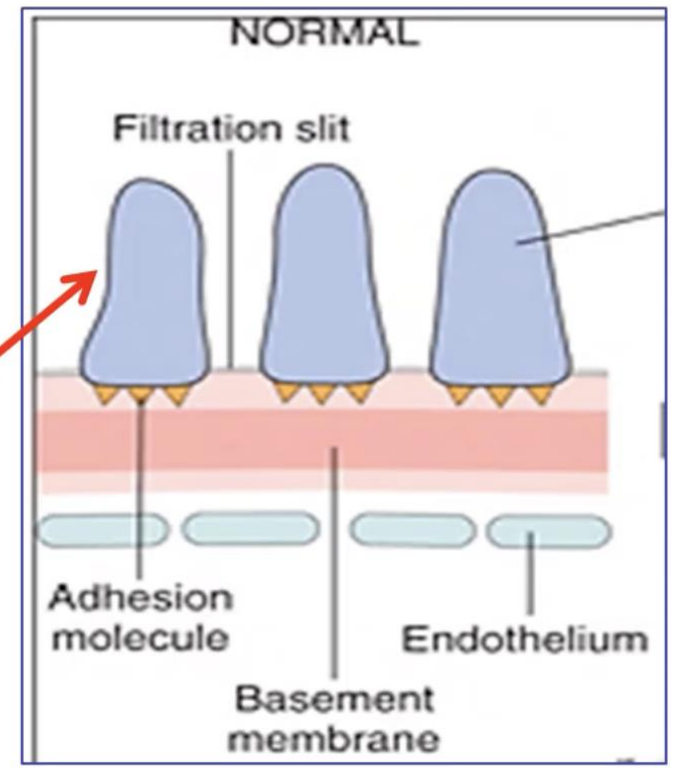
Reviewed by: Leen Mamoon



بسم الله الرحمن الرحيم

Before starting, please make sure that you study and got the key concepts in the first lecture , as many of the information in this lecture is repeated from it.


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 membrane
Endothelium
Red cell
Foot processes
B

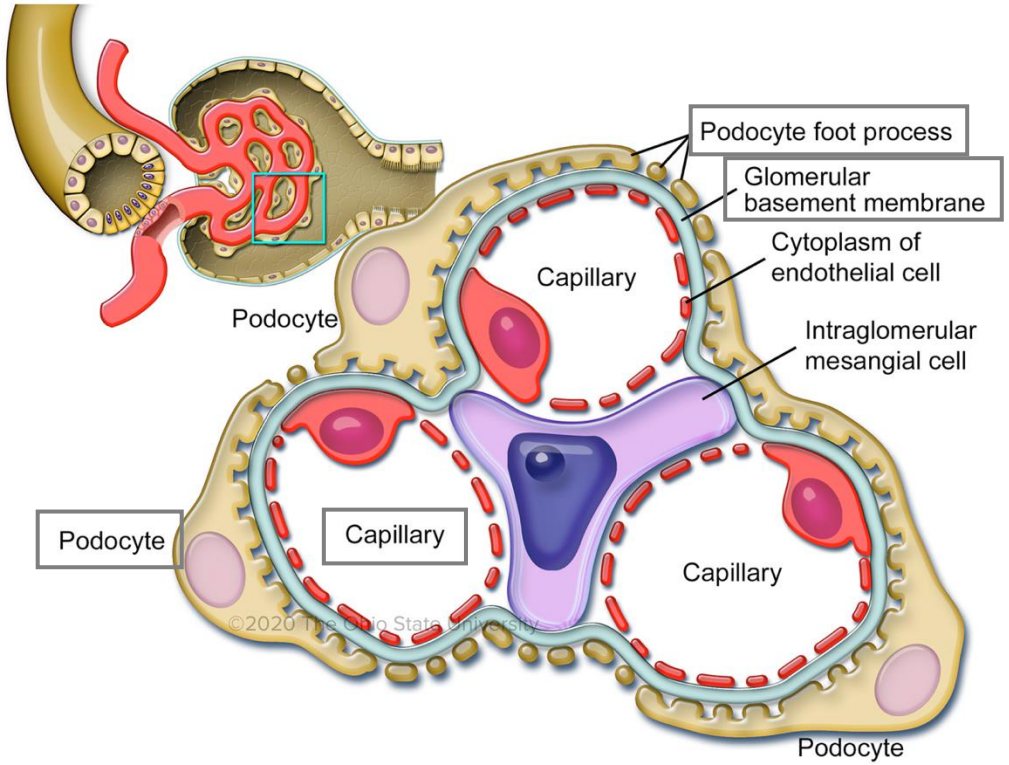

NORMAL
Filtration slit
Adhesion molecule
Endothelium
Basement membrane

Function of the Kidneys

- **Glomerulus** (كُبيبة الكلى): the functional compartment of the kidney, where filtration of blood takes place. It is a network of long capillary that start from an *afferent arteriole* then coils in a net-like structure forming the shape of glomerulus and finally ends up with *efferent arteriole*. Filtration occurs across the membrane of the capillary network.

- The **Capillary** consist of: epithelial cells, basement membrane, and Podocytes epithelial cells (Podocytes are highly specialized, terminally differentiated visceral epithelial cells in the kidney glomerulus that play a critical role in blood filtration-see slide 10).

- **Filtration membrane** is the specific region in the glomerulus where exactly filtration of blood takes place, consist of Glomerular Basement Membrane (GBM) + In-covering Epithelial cells + Out-covering podocytes epithelial cells.

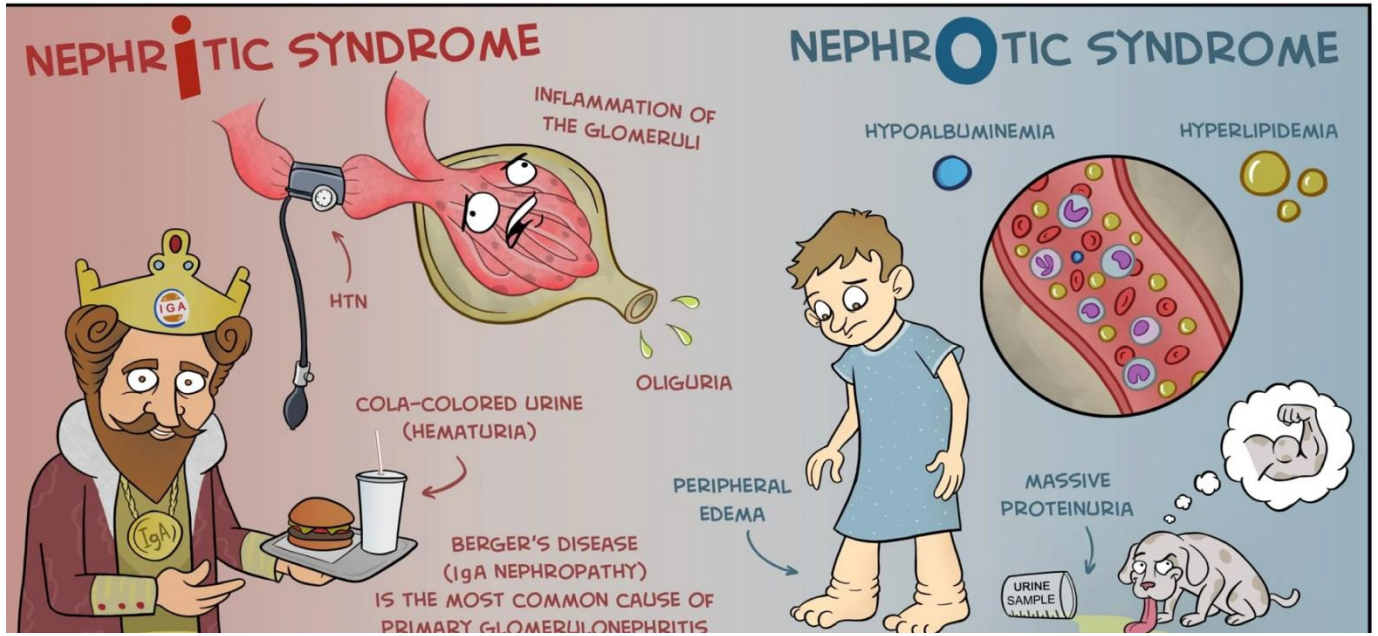


Extra Image

Pathology Lecture
Nephrotic Syndrome

Dr. Nisreen Abu Shahin

"اللَّهُمَّ إِنِّي أَسْأَلُكَ فَهْمَ النَّبِيِّينَ، وَحِفْظَ الْمُرْسَلِينَ، وَإِلْهَامَ الْمَلَائِكَةِ الْمُقَرَّبِينَ، بِرَحْمَتِكَ يَا أَرْحَمَ الرَّاحِمِينَ"



Extra Image

The Nephrotic Syndrome

- a clinical complex resulting from glomerular disease & includes the following signs and symptoms:

  (1) Most IMPORTANT feature and the hallmark is **massive proteinuria** (3.5 gm /day in adults) and is responsible for all other manifestations:

  (2) **hypoalbuminemia** (≤ 3 gm/dL).occurs because albumin is one of the main plasma proteins and is normally present in large amounts in the plasma. Therefore, when there is a large loss of protein in the urine, albumin is also lost.

  (3) **generalized edema,** occurs due to several mechanisms. One of the main mechanisms is a decrease in osmotic (colloid) pressure. The main osmotic molecule responsible for maintaining this pressure is albumin.

(4) **hyperlipidemia and lipiduria**.

- Normally, urine consist of toxins, waste products, salts, and water. Large components (e.i; proteins and lipids) can't pass the filtration membrane unless there is an injury in the filtration membrane (FM) mostly within podocytes.

- Hyperlipidemia could be illustrated via two mechanisms (theories):

a. Shifting in the metabolic pathways to lipoproteins in the liver → transport to the circulation → escape through the damaged FM into urine.
b. The function of Albumin -that involves transporting lipoproteins- will be affected via the decrease of Albumin serum level, causing an elevation in free lipoproteins serum levels.

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

- ✓ Recall Azotemia refers to elevated levels of blood urea nitrogen (BUN) and creatinine, which indicate impaired renal function.

Symptoms of Nephrotic Syndrome

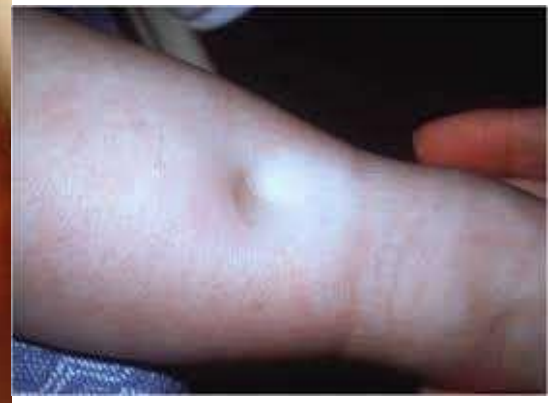
- **Edema** can occur anywhere in the body (Generalized: There is puffiness in the feet, eyes, and lips, and it can affect the whole body, including the upper and lower limbs) and it's an alarming symptom that is observed by the patient.

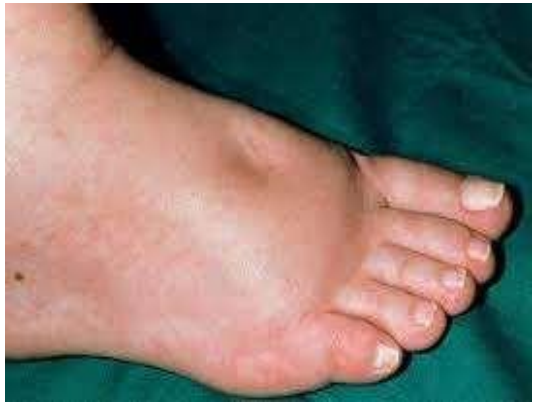
- Patient usually come suffering from ***edema*** which requires further investigation from the physician. First step is to take pressure readings, while the edema is highly linked to Cardio-Vascular or Renal problems, usually the physician will obtain ***normal BP***.
- Further lab-tests should be done, e.i; Kidney Function Test, and urine analysis.

a) ***Proteins*** results in urine analysis will be (***+3***).

b) ***Kidney Function Test*** (BUN and creatinine) will be ***normal***.

- These findings spot the light on Nephrotic Syndrome.



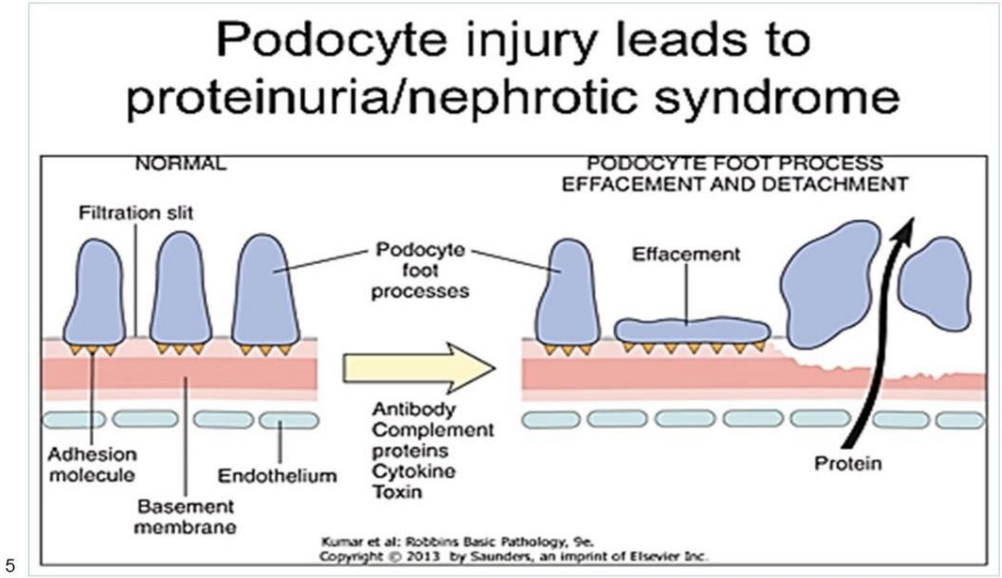


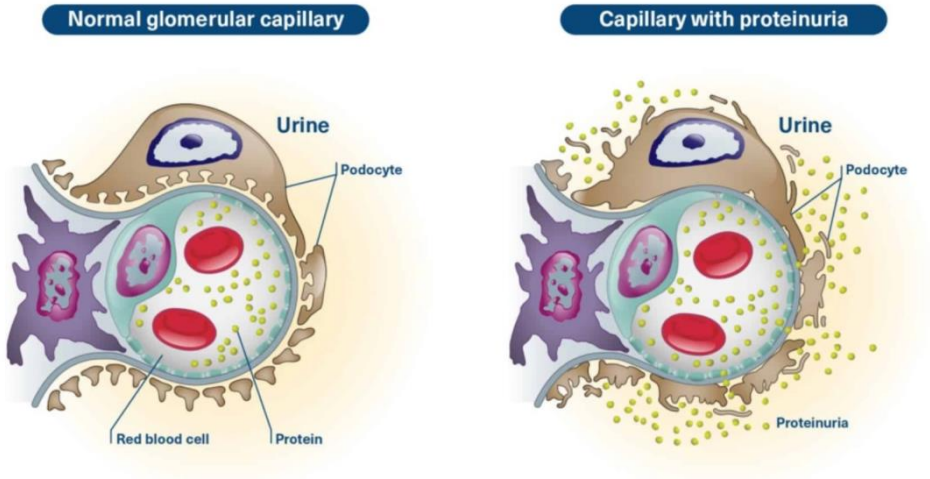
Pathogenesis of Nephrotic Syndrome

- As previously discussed, it is caused by a damage of any part of the FM:

a. Glomerular Basement Membrane (GBM)
b. Epithelial cells
c. Podocytes epithelial cells

- Podocyte have finger-like projections that cover the capillary from outside, it contributes to the impermeability of proteins.





Extra Image

Causes of Nephrotic Syndrome

- **There is no single disease that causes nephrotic syndrome; rather, many different diseases can lead to it.**

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

  - ✓ Primary causes refer to cases where the patient has nephrotic syndrome without any identifiable underlying cause, and the condition exists as the main disease.

  - ✓ Secondary causes refer to cases where nephrotic syndrome occurs as a result of another underlying disease.

Primary Diseases that Present Mostly with Nephrotic Syndrome

1. Minimal-change disease
2. Focal segmental glomerulosclerosis (FSGS).
3. Membranous nephropathy
4. membranoproliferative GN (Glomuronephritis) 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

- The prevalence of nephrotic syndrome varies among different age groups, such as children and adults, depending on the underlying diseases.
- In **adults**, focal segmental glomerulosclerosis (FSGS) is commonly associated with nephrotic syndromeIn **children**, minimal change disease is the most common cause.

- In children, approximately 65% of cases are associated with minimal change disease.

B-Systemic Diseases with Renal Manifestations:

- **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)**

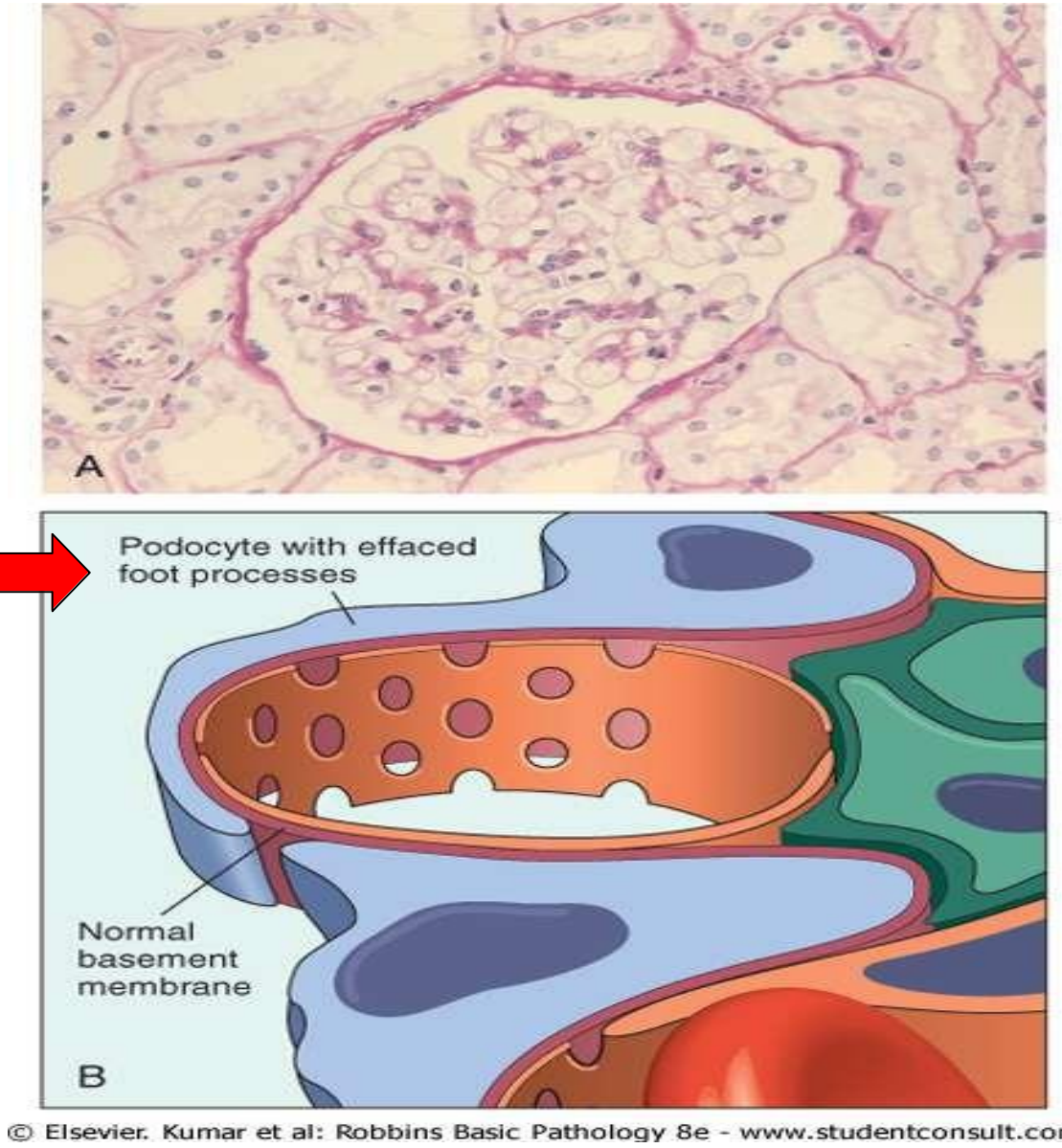
1- Minimal-Change Disease (Lipoid Nephrosis) /primary disease

- **benign disorder** (minimal change disease)

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

- ***Pathogenesis:*** **still not clear.**
- The exact cause (pathogenesis) of minimal change disease is still not completely understood. However, multiple theories have been suggested to explain how the disease develops, and on of them is:

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



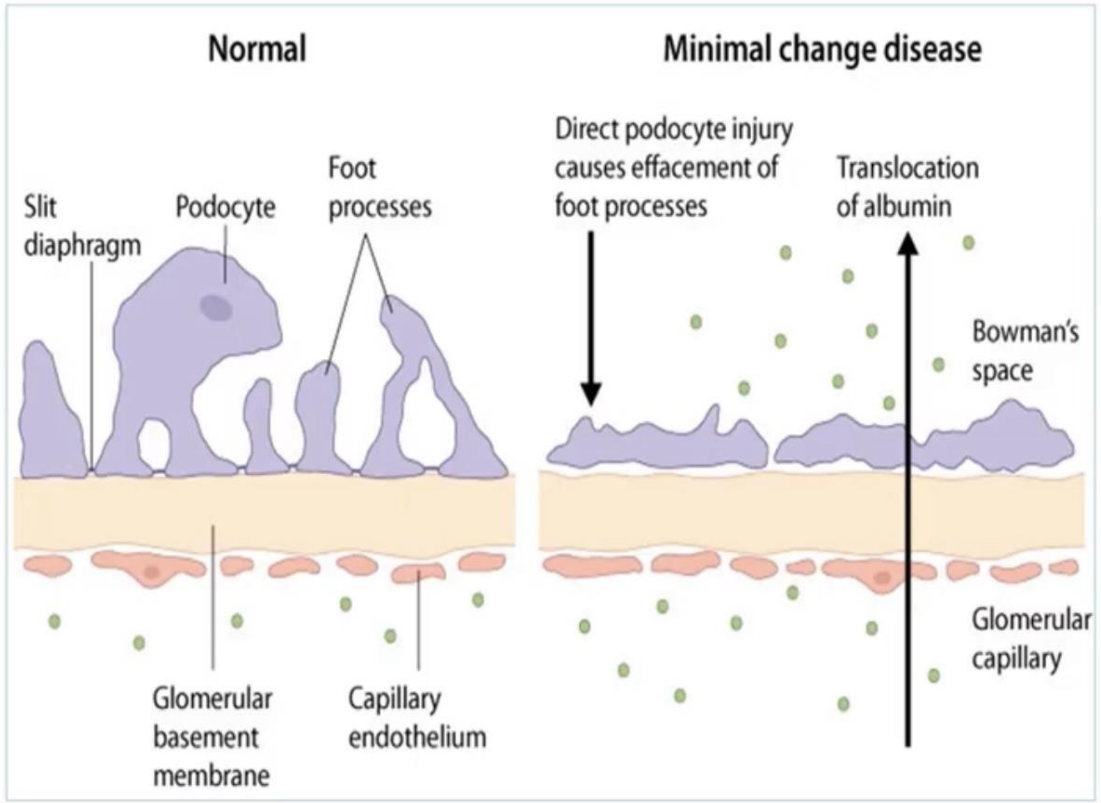
Minimal change disease.

A

glomerulus appears normal, with a delicate basement membrane

B

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



- ✓ In minimal change disease, the hallmark of this condition is **effacement of the podocyte foot processes**. Normally, these foot processes are interdigitating and form an essential part of the glomerular filtration barrier that prevents protein loss.
- ✓ When podocyte damage occurs, the foot processes become flattened and lose their distinct structure, forming a smooth surface instead. This alteration disrupts the filtration barrier and leads to the loss of large amounts of protein in the urine, resulting in nephrotic syndrome. Importantly, **these changes are not visible under light microscopy and can only be detected using an electron microscope.**

Morphology

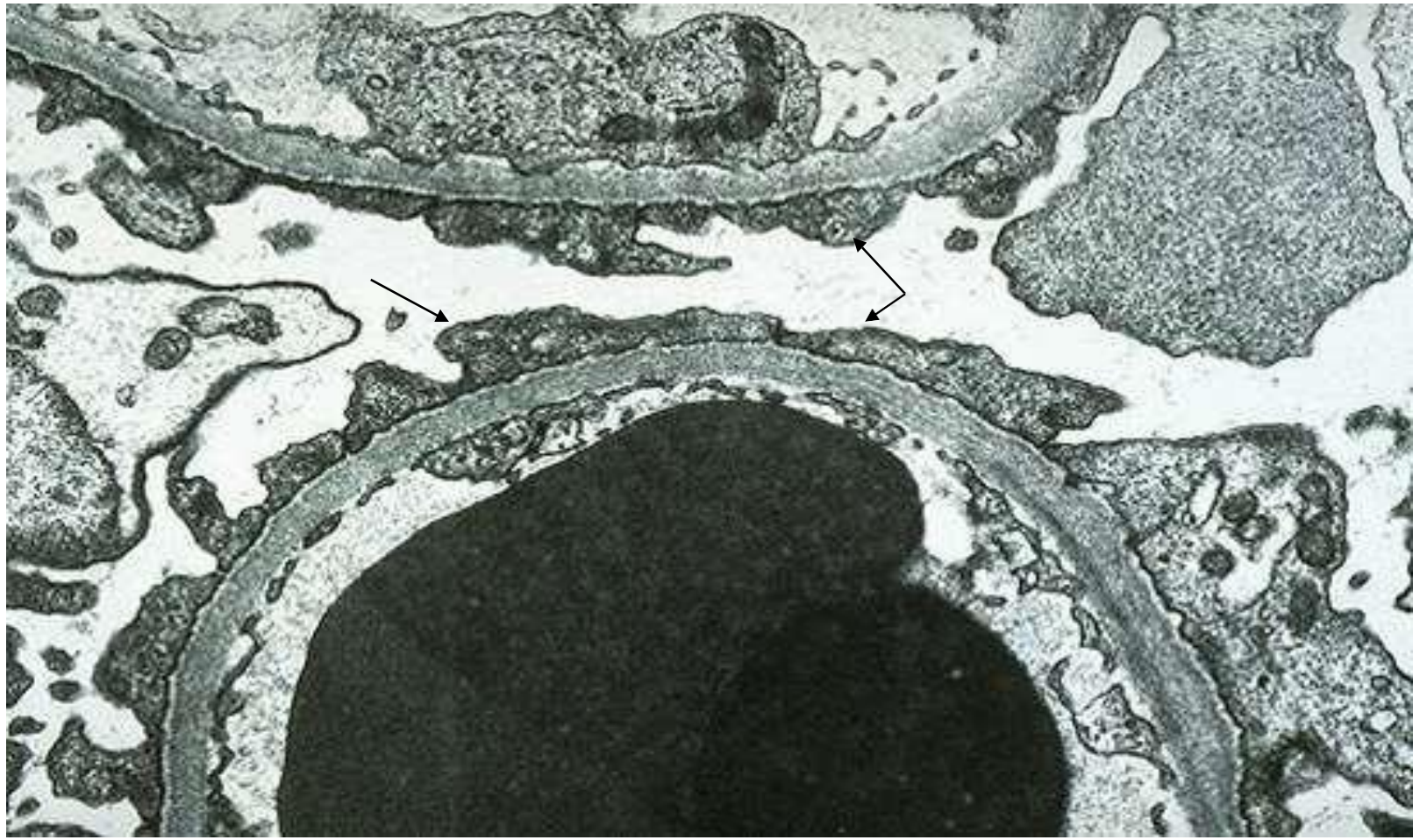
- **LM**
- the glomeruli appear normal.

- **IF**
- Negative which means normal
- **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).



- ✓ **Electron microscopy shows the characteristic changes in podocytes.**
- ✓ **Check elearning lecture to compare between the normal appearance of interdigitating foot processes and the abnormal effaced (flattened) foot processes seen in this disease**

MCD- Clinical Course

In minimal change disease, children often present with sudden generalized edema, noticed when they wake up in the morning. This alarming swelling usually leads to emergency admission, and the patient is diagnosed with **nephrotic syndrome.**

Despite the dramatic presentation, the prognosis is generally good because the disease is reversible. Most patients respond well to corticosteroids, which promote recovery of podocyte function and reversal of foot process effacement. As a result, proteinuria and other symptoms resolve. This occurs in more than 95% of cases, especially in children.

In adults, the response may be slower, and relapses are more common, so the prognosis is relatively less favorable.

MCD- Clinical Course

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

- **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.**

- That's why it is called **focal and segmental**: focal means only some glomeruli are affected while others are normal, and segmental means only part of each affected glomerulus is involved, not the whole structure.
- Clinically, it usually presents with **nephrotic syndrome** and may be either primary or secondary, associated with various underlying conditions.

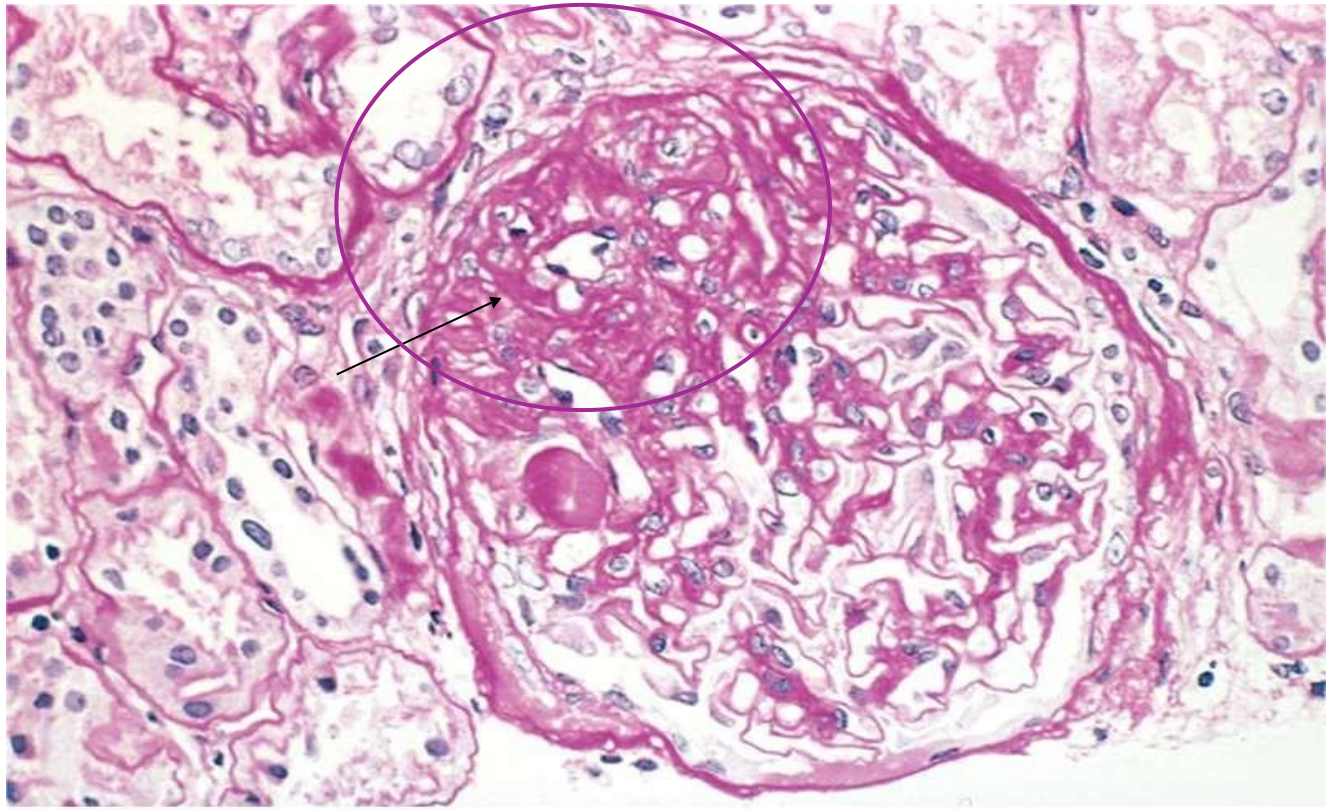
1 as a primary disease(20% to 30% of NS):

- **e.g. inherited or congenital forms resulting from mutations affecting nephrin**

2- Or: in association with endless underlying conditions:

- **e.g.; AIDS; heroin abuse; nephron loss; etc….**

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



- ✓ In the **glomerulus**, you see an area that looks different from the normal structure, **with a pink-staining region representing fibrotic connective tissue**. This area shows loss of part of the glomerular structure, so only a segment of the glomerulus is affected, not the whole thing.

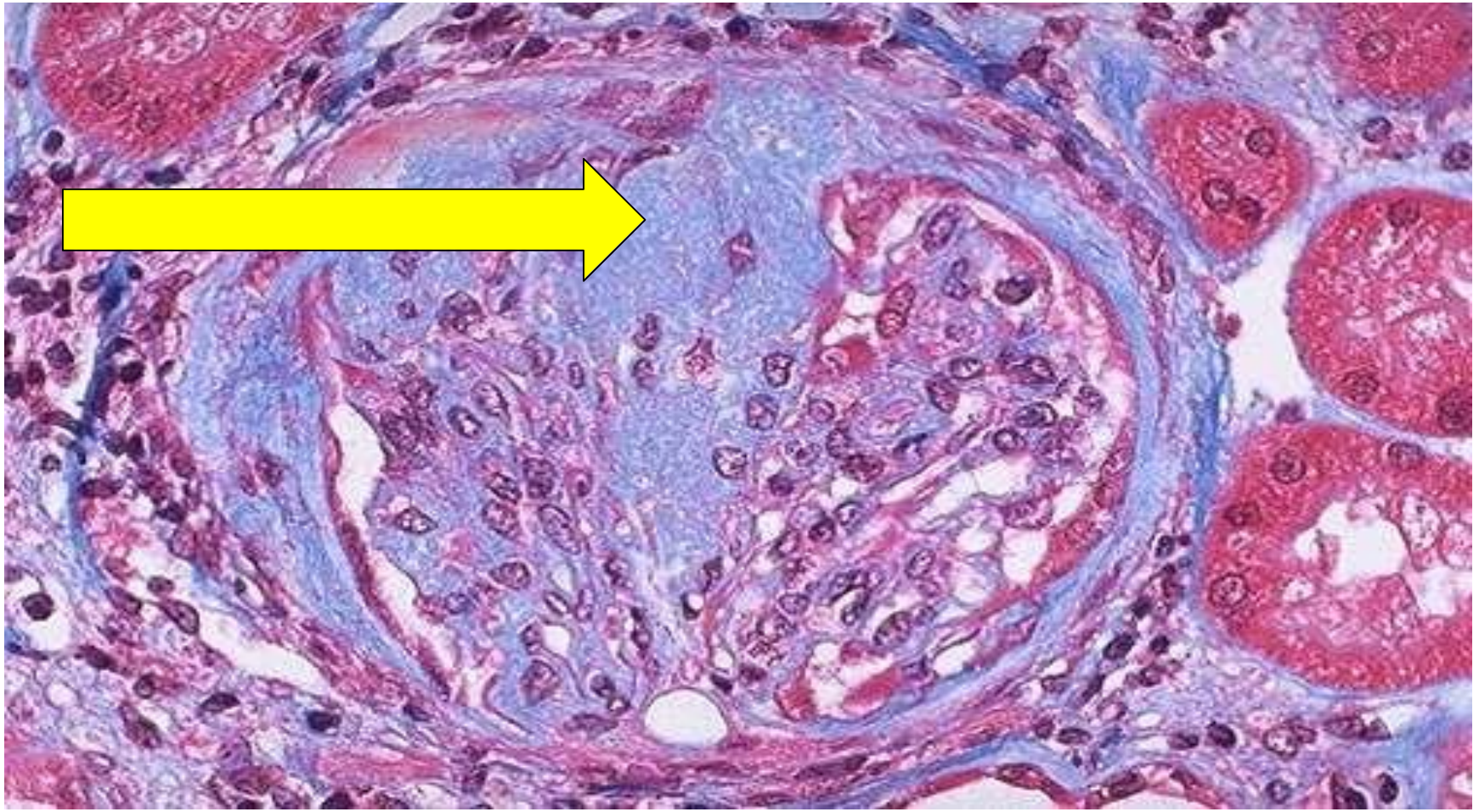
- ***Pathogenesis***
- **unclear**
- ***injury to the podocytes*** **? ↑ GFR at first. IMPORTANT!**
- **? Genetics,** especially those involving proteins like nephrin.
- **entrapment of plasma proteins and lipids in foci of injury where sclerosis develops.**
- Regardless of the cause, there's injury and damage of the filtration barrier resulting in loss of plasma proteins. Some of these proteins, together with lipids, become trapped at the sites of injury. These foci of damage later progress to sclerosis within the glomerulus.
- This condition leads to significant protein loss and has a **poor prognosis, with about 50% of patients eventually developing chronic renal failure. It also shows a poor response to corticosteroid therapy, and adults generally have a worse outcome than children.**
- **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 which means normal
- **EM**
- **effacement of podocyte foot processes**

FSGS

blue = collagen deposition

(MT stain),used to observe connective tissue



MCD versus FSGS

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

Collapsing glomerulopathy

- **Collapsing glomerulopathy is a severe variant of focal segmental glomerulosclerosis seen in HIV patients.**

- 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.

3- Membranous nephropathy:

- Immune complex deposition in glomerulus

✓ **This disease is an immune complex deposition disease, meaning antigen-antibody complexes form together. These immune complexes travel and deposit in the glomerulus, where they cause damage to the filtration membrane and disrupt the normal architecture of the glomerular basement membrane (GBM).**

- Types of Membranous glomerulonephritis : 1-Primary (85% of cases): antibodies against
- podocyte antigen phospholipase A2 receptor (PLA2R) antigen
- 2-Secondary to another condition or disease

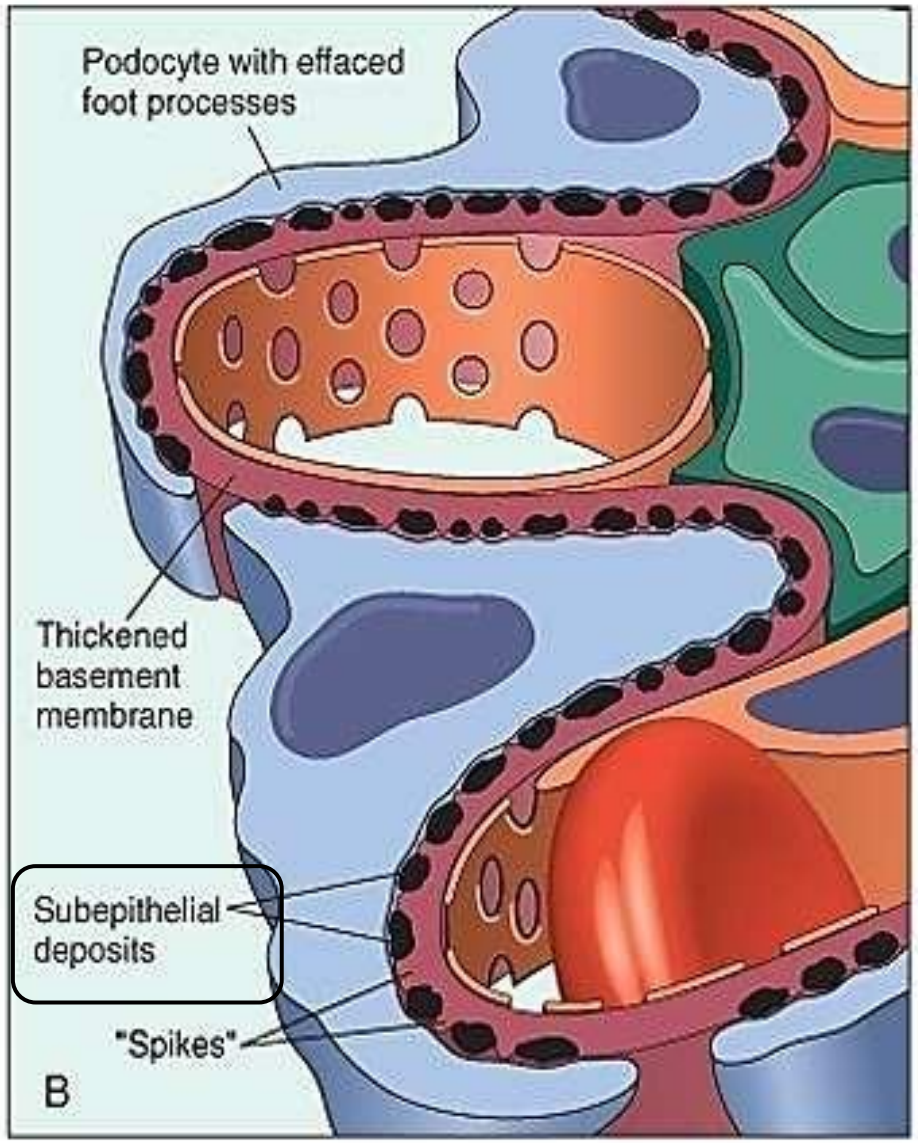
This slide wasn't explained by the doctor

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 .**
- **IF**
- **deposits** of immunoglobulins and complement along the GBM (mainly IgG)
- **EM**
- **subepithelial deposits "spike and dome" pattern.**

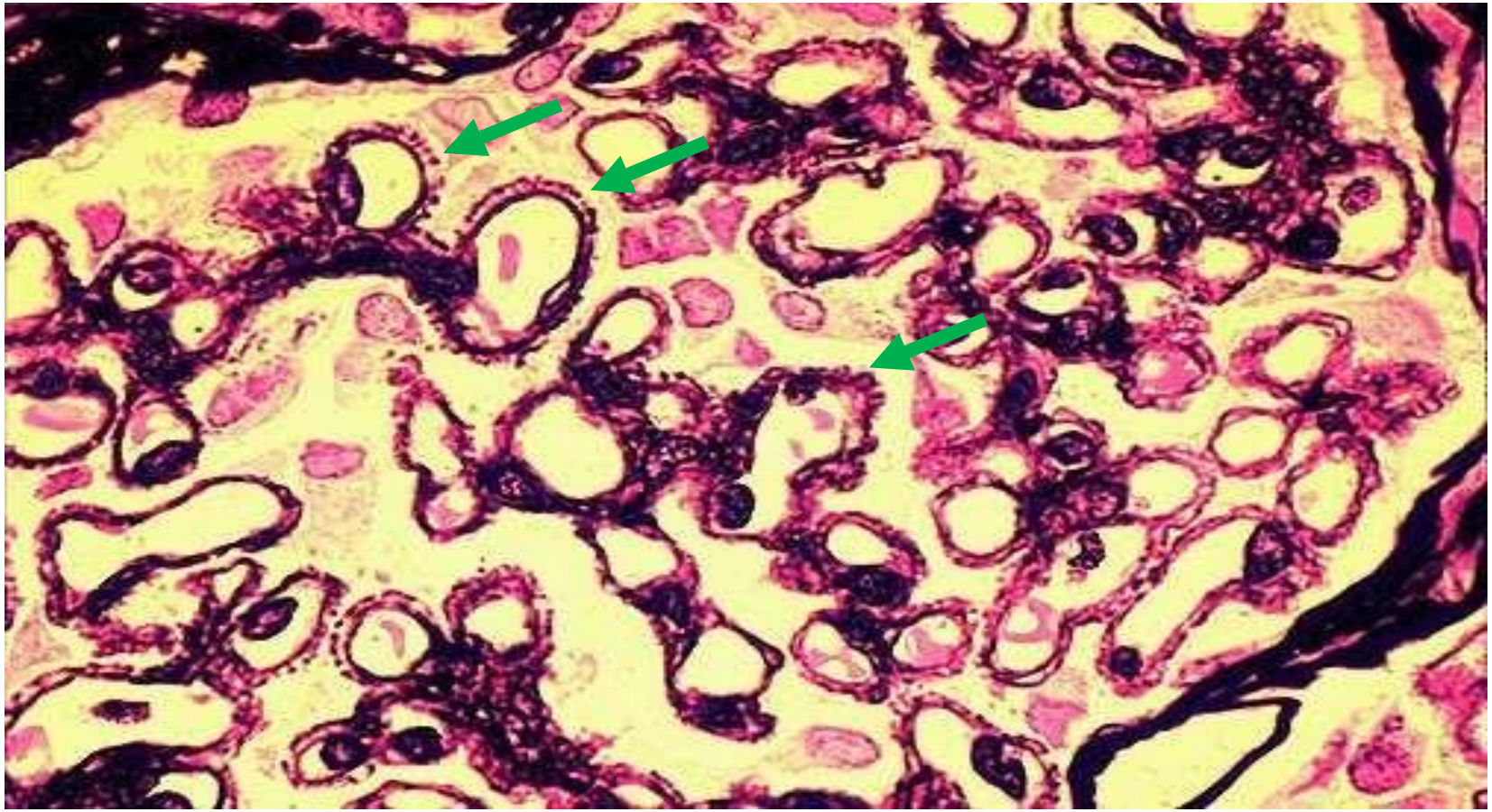
✓ **On electron microscopy, the characteristic finding is the “spike and dome” pattern, where electron-dense deposits (“domes”) are seen on the subepithelial side of the GBM, with intervening GBM projections forming the “spikes,” reflecting irregular thickening of the membrane.**



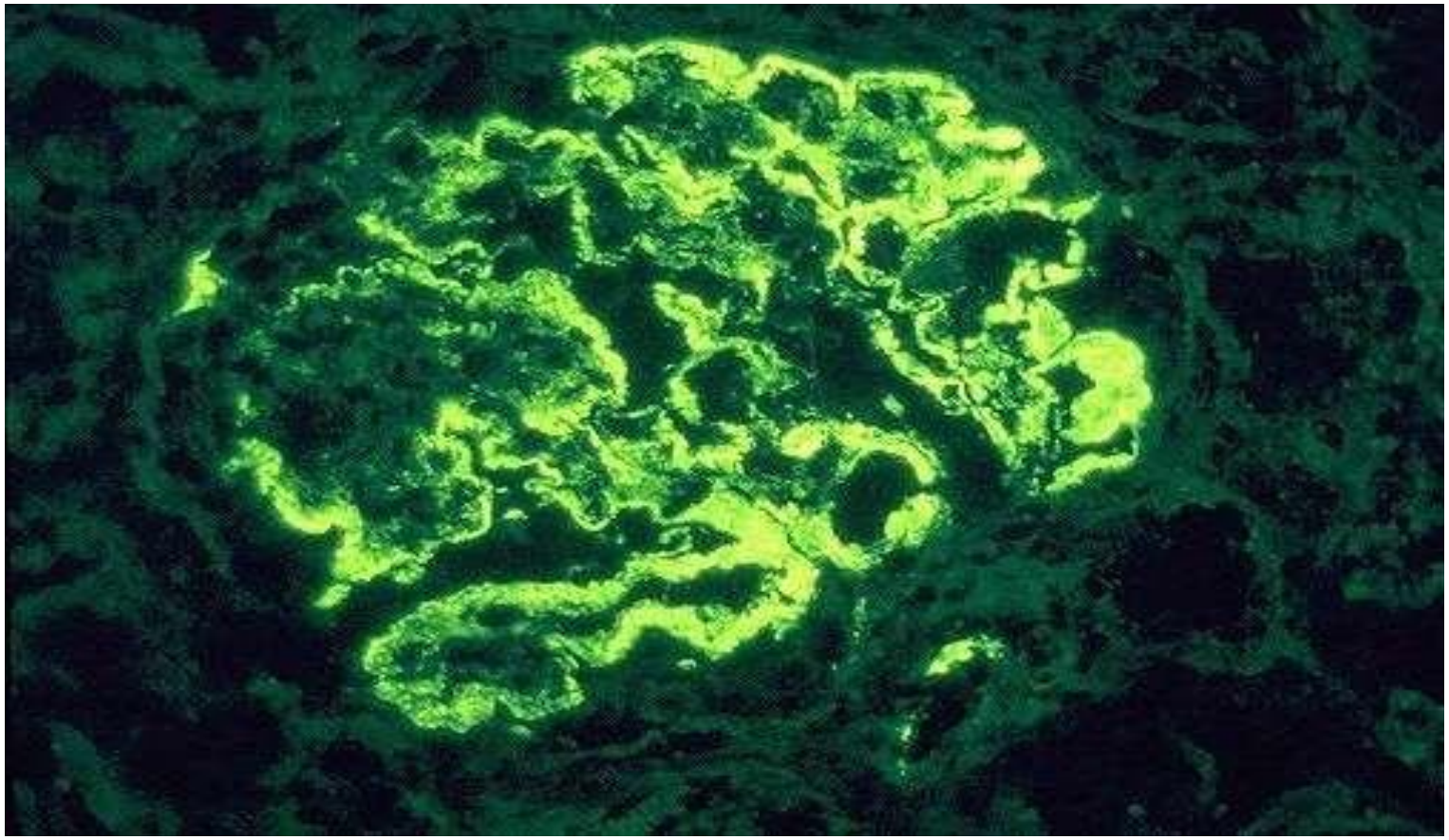
Membranous nephropathy. subepithelial deposits and the presence of "spikes" of basement membrane material between the immune deposits .

- ✓ The deposits tend to localize in a specific area of the filtration barrier, beneath the podocytes and above the GBM, which is why this pattern is called **subepithelial deposition**. This immune complex deposition interferes with the function of the filtration barrier, leading to significant loss of proteins in the urine, resulting in proteinuria and nephrotic syndrome.

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



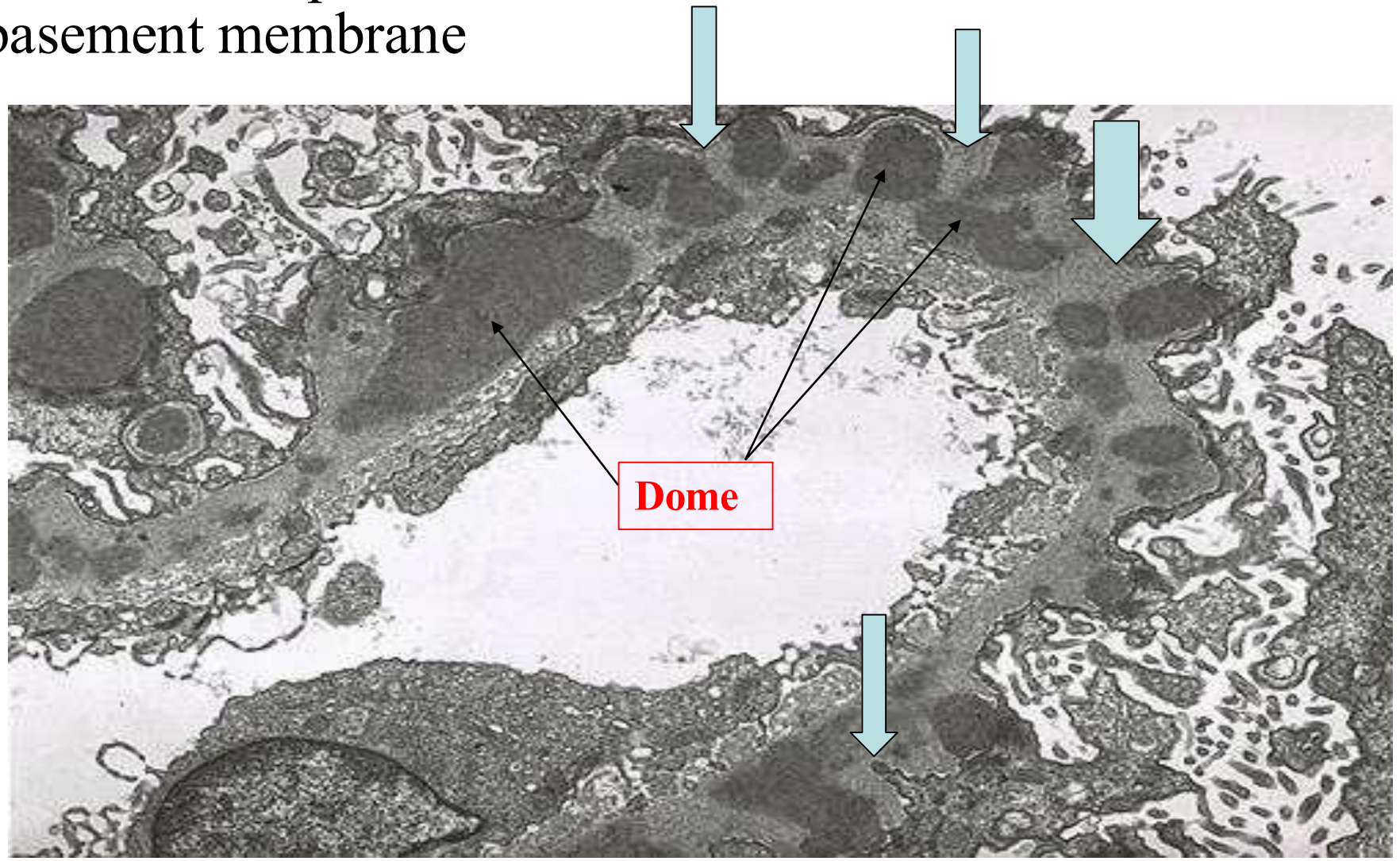
Membranous GN
IF: granular deposits of IgG and complements along the capillary walls



- ✓ **immunofluorescence is positive because it is an immune complex disease, showing deposition of immunoglobulins and complement** (especially IgG and C3) **along the glomerular basement membrane (GBM).**

EM: "spike and dome" pattern is characteristic

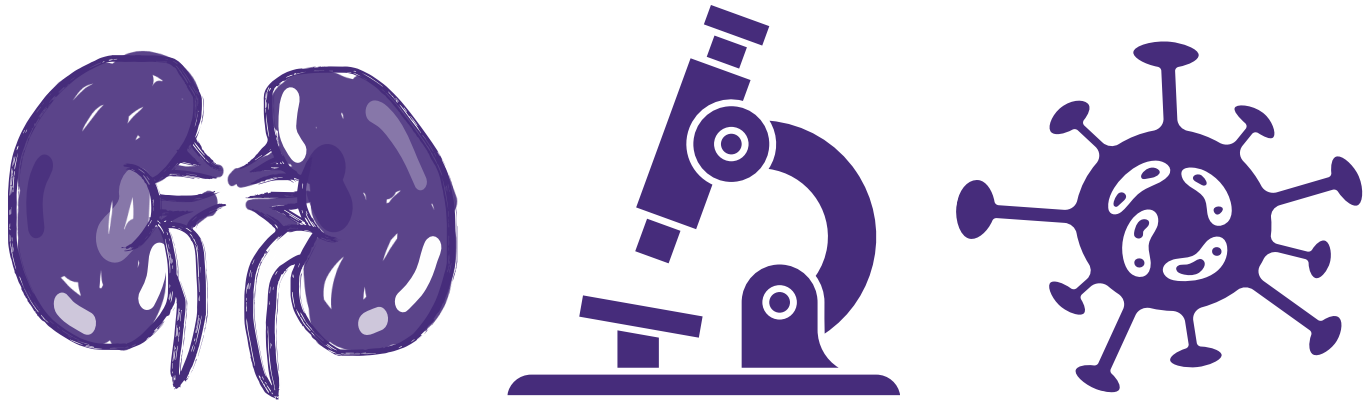
Dome= immune complex
spike= basement membrane



Clinical Course

✓ The clinical course is nephrotic syndrome with a poor response to steroids. Some patients have persistent proteinuria, and many eventually progress to chronic renal failure.

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



PATHOLOGY
QUIZ
LECTURE 3

External Resources

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