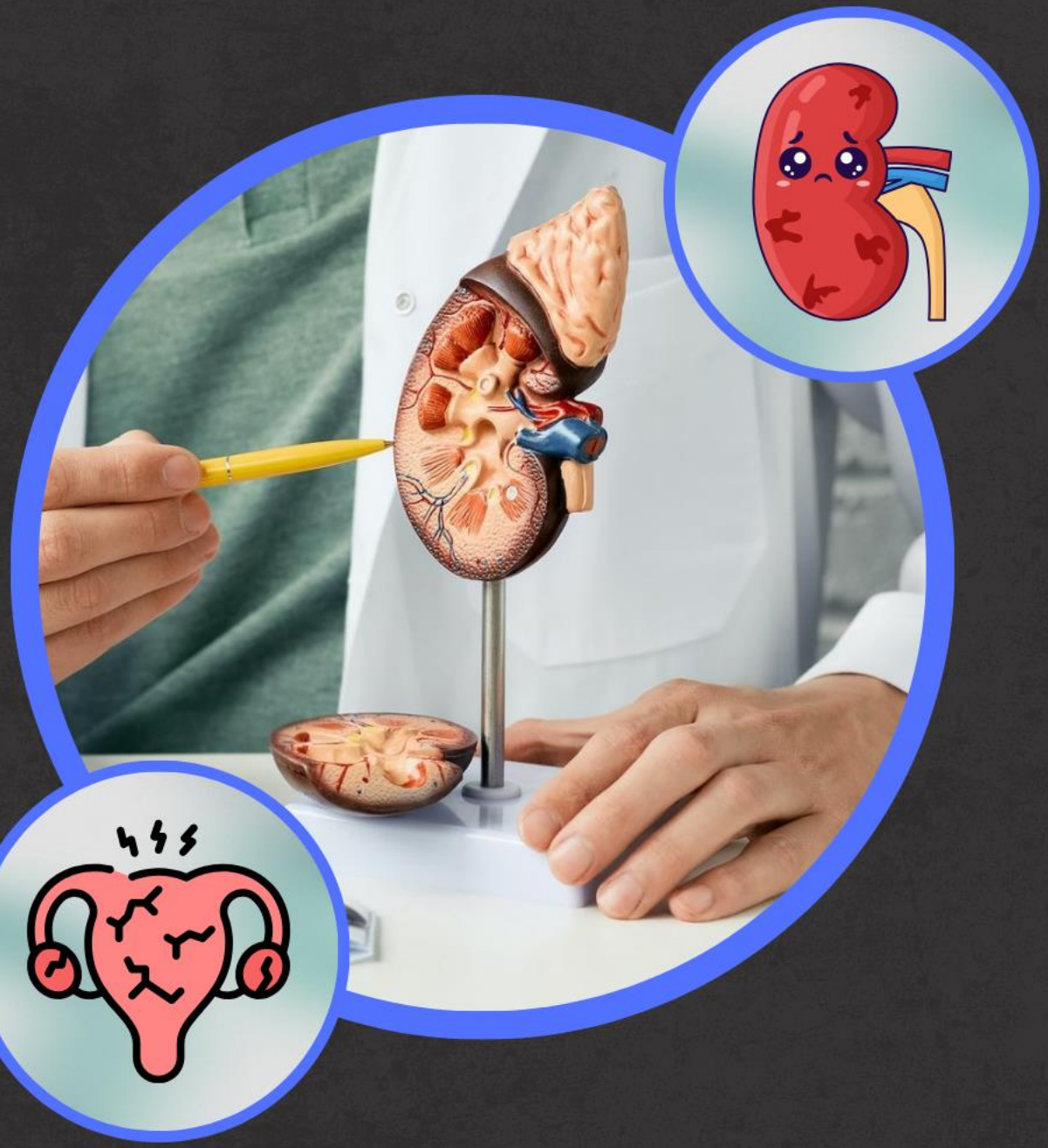

# PATHO

## MODIFIED NO. 2


الكُتّاب: شهد الأحمد و إسماعيل العارضة

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# Pathology Lecture
# Nephrotic Syndrome

| Color code |
| --- |
| Slides |
| Doctor |
| Additional info |
| Important |


Dr. Nisreen Abu Shahin

## Introduction to Kidney Function

•The kidney's primary role is the **filtration of blood**.
•This includes:
- Removal of **waste products** and **toxins**
- Returning **clean blood** to the circulation

•This process occurs **continuously**, 24 hours a day, 7 days a week, for the entire lifespan.

## Overview of Kidney Structure

•The kidney performs **multiple functions**.
•One key functional unit or compartment is called the **glomerulus**.
•The **glomerulus** is responsible for the kidney's filtration role.
•It is essentially the "**filtration cup**" of the kidney.

## What is the Glomerulus?

•The **glomerulus** is a **network of capillaries**.
•It is **tiny** but **long**, coiled to form a dome-like structure.
•It starts with an **afferent arteriole** and ends with an **efferent arteriole**.
•Filtration occurs through the **membrane of the capillary network**

The filtration membrane consists of:

- **Endothelial cells**
- The **basement membrane**
- Special cells called **podocytes** (also known as **epithelial cells**)

Together, these form the **filtration barrier** within the glomerulus.

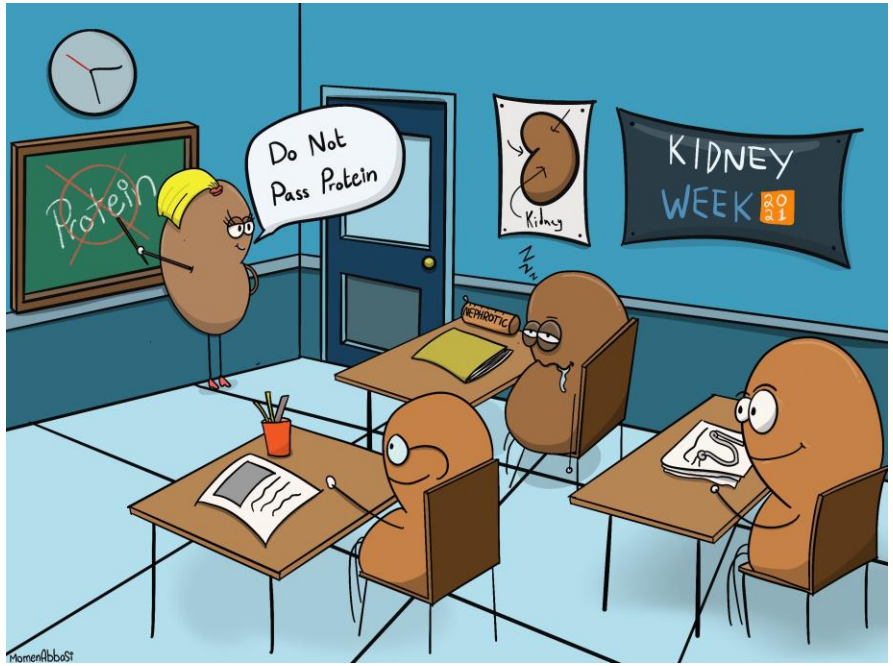
The **glomerular basement membrane (GBM)** is the central part of the filtration membrane.

From this point onward, **GBM** will be used as an abbreviation.
The **filtration membrane** includes:

- The **endothelial layer** above
- The **GBM** in the middle
- The **podocytes (epithelial cells)** below

⚠ **Vulnerability to Disease:**

•Like any structure in the body, the **capillaries** in the glomerulus are vulnerable to **problems and diseases**.



# The Nephrotic Syndrome

**syndrome** means **constellation of symptoms** or **clinical manifestations** that appear together in the patient.
It is a **clinical complex** that results from a renal disease and typically includes several features).

- a clinical complex resulting from glomerular disease & includes the following signs and symptoms:
- (1) **massive proteinuria (**3.5 gm /day in adults). **Proteinuria** is the **hallmark** of nephrotic syndrome.
- (2) **hypoalbuminemia (**≤ 3 gm/dL).
- (3) **generalized edema**
- (4) **hyperlipidemia and lipiduria**.
- (5) little or no azotemia, hematuria, or hypertension.

**NephrOtic" and "prOteinuria"** both contain the letter **O**.
Other students link it with:
**"Nephrotic" → PodOcyte** (podocyte damage is common in nephrotic syndrome :)

(1) **massive proteinuria : The most important and defining feature** of nephrotic syndrome is **massive proteinuria**.

•This refers to **heavy protein loss** in the urine (proteinuria = presence of excess proteins in urine).

Large amounts of protein being lost through the urine is **abnormal**

🚫 **What Normally Passes Through the Filtration?**

•Under normal circumstances, the kidney filters:

- **Toxins , Waste products**
- **Salts, Water**

•**Proteins** and **large molecules** are **not** supposed to pass through the filtration membrane.

**The filtration membrane is composed of:**

•Endothelial cells, The glomerular basement membrane (GBM), Podocytes (epithelial cells)

- These structures work together to prevent protein leakage. In nephrotic syndrome, there is damage to one or more parts of the filtration membrane.

•This damage allows proteins to escape into the urine, leading to massive proteinuria.

😷 (2) **hypoalbuminemia**

Definition: **Decreased levels of albumin** in the blood.

•Cause: Direct result of **proteinuria**.

•Why albumin?

- Albumin is one of the **most important plasma proteins**.
- It is found in the **highest concentration** in the plasma.
- So when there's protein loss, **most of it is albumin**.

• ➡ Therefore, **massive proteinuria → hypoalbuminemia**.

💧 (3) **generalized edema**

•Also caused by massive proteinuria.

Mechanism:

- Due to hypoalbuminemia, there is a decrease in plasma colloidal (osmotic) pressure.
- Albumin is the main molecule responsible for maintaining this pressure.
- Reduced osmotic pressure leads to fluid leakage into interstitial spaces → edema.

Reminder: This concept was covered in the cardiovascular system lectures when discussing edema mechanisms.

🧈 (4) **hyperlipidemia and lipiduria**

•Hyperlipidemia: Increased levels of lipids in the blood.

•Lipiduria: Presence of lipids in the urine.

•These also appear as consequences of nephrotic syndrome, commonly associated with massive proteinuria.

## Hyperlipidemia and Lipiduria

- **Hyperlipidemia** refers to increased levels of **lipids in the blood**.
- These include:
  - **Triglycerides**, **Low-density lipoproteins (LDL)**
- ❌ It is **not normal** to have lipids in the urine.
- Under normal conditions, **lipids should not pass through the filtration membrane**

## Theories Behind Hyperlipidemia in Nephrotic Syndrome

### Theory 1:

**Increased Lipoprotein Synthesis**

- The **liver increases the synthesis of lipoproteins**.
- Why?
  - Due to a **shift in metabolic pathways**.
  - When there's a **problem in protein production**, especially **albumin**, the system redirects to produce **lipoproteins** instead.

These **lipoproteins are released into circulation** in large amounts.

Damaged **GBM** allows **lipoproteins to leak into urine**, contributing to **lipiduria**

### Theory 2:

**Loss of Albumin Transport Function**

- **Albumin** functions as a **transporter of lipids** in the bloodstream.
- When **albumin levels drop**, due to **proteinuria**, it can no longer transport lipids.
- Result: Lipids appear **unbound** in tests → **elevated free lipoproteins** in circulation.

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

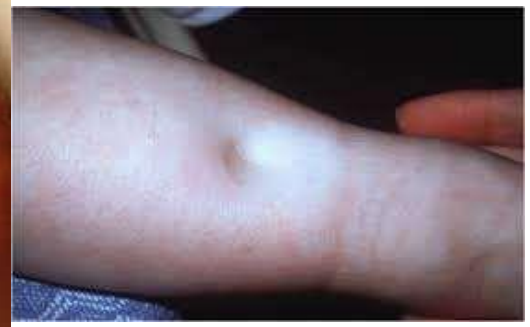
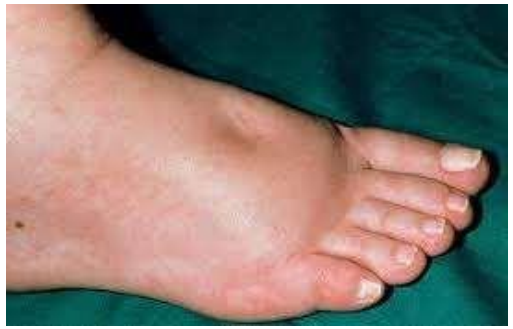
📖 **What is Azotemia?**

•**Azotemia** is defined as **high levels of blood urea nitrogen (BUN) and creatinine**.
•This indicates **impaired renal function**.

🧍 **How Do Patients Present?**

•For sure, Patients **will not come to ur clinic and say they have nephrotic syndrome**.
•Instead, what draws their attention?

- The **edema**. ↴
- This is usually the **primary symptom** that prompts medical consultation.

•**Edema** is usually what grabs the patient's attention.
•Patients do **not notice proteinuria** on their own.
•The **visible swelling**: face, eyes, lips, abdomen, is the alarming symptom.
•This is the **most common presentation**, in both children and adults.

**Clinical Approach**

•The **doctor begins evaluation** by:
- Observing the **edema**
- **Examining the patient**
- **Checking blood pressure** (often normal in nephrotic syndrome)

## 🧪 Lab Investigations

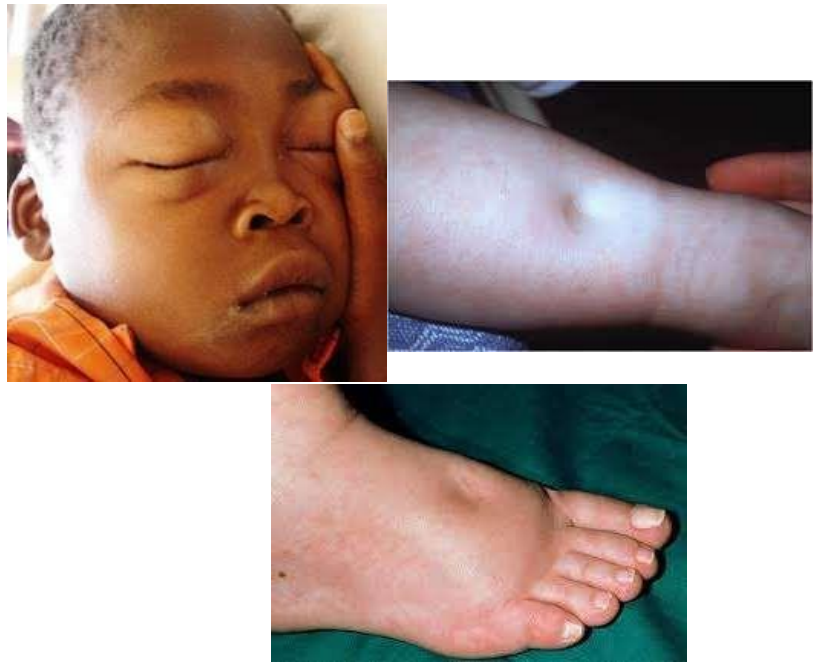
- **Urinalysis**:
  - Used to detect **protein levels**
  - Results shown as: +1, +2, +3, etc.
- **Kidney Function Tests:**
  - Focus on **creatinine** and **urea**
  - These are the **main markers** for assessing kidney function
- Most patients with nephrotic syndrome have:
  - **Normal creatinine and urea**

**Abnormal protein in urine** as the key finding

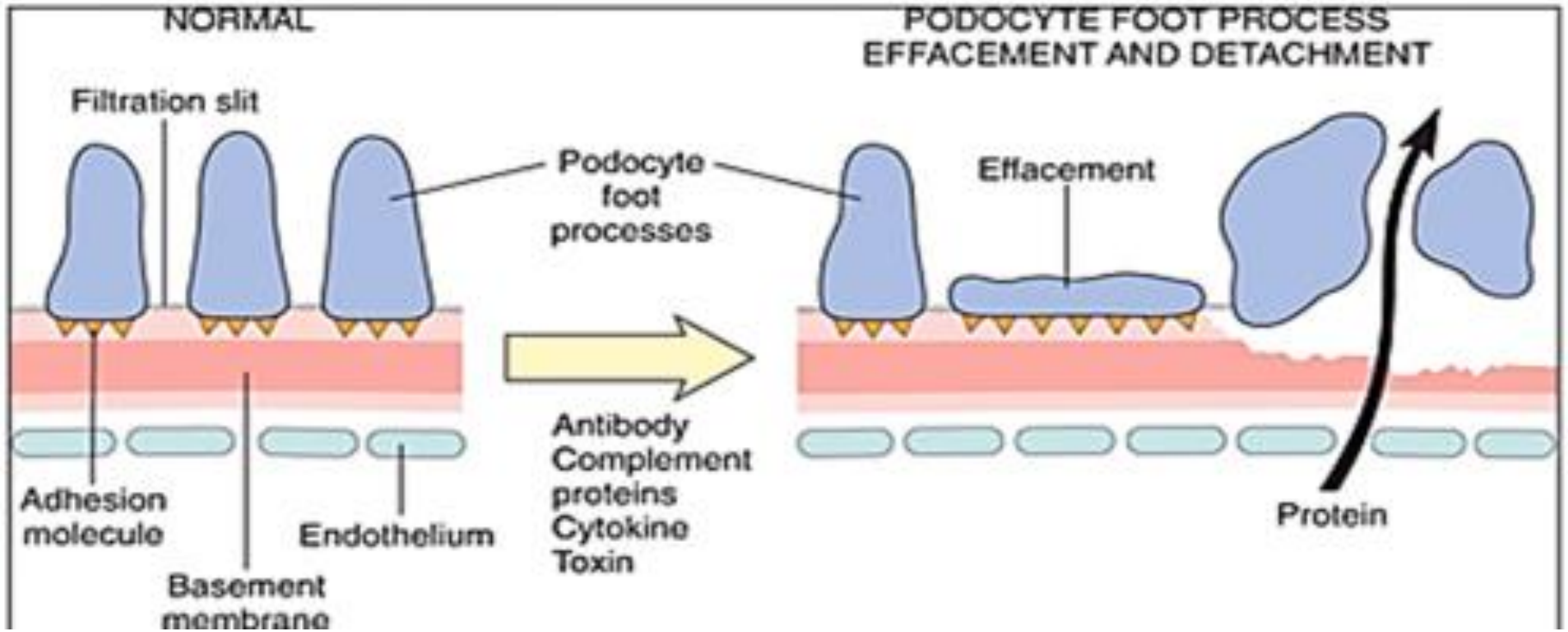
## 🔬 Forming a Diagnosis

- The pattern of:
  - **Edema**
  - **Normal kidney function**
  - **Significant proteinuria**

    → Suggests **nephrotic syndrome**
- At this stage, the doctor may **suspect** the diagnosis and begin to explore the cause



# Podocyte injury leads to proteinuria/nephrotic syndrome




🔬 **Multiple Diseases, One Syndrome**

Nephrotic syndrome is a **group of manifestations** that can result from **different diseases**. All of them cause damage to the **filtration membrane**, leading to **proteinuria**.

Damage may occur in:

- The **glomerular basement membrane (GBM)**
- The **podocyte** (epithelial cell) , These structures are critical for **protein impermeability**.

# Causes of Nephrotic Syndrome

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

⚖️ **Types of Diseases**

- **Primary glomerular diseases** → arise **within the kidney** itself.
- **Secondary diseases** → result from **systemic or underlying conditions**.

# 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)

**Dr read the slide**

# Causes of Nephrotic Syndrome

## 1-primary glomerular diseases

**Prevalence by Age**

**Dr only mentioned the following:**

- **Children with primary nephrotic syndrome**:
  - ~65% have **minimal change disease**
- **Adults with primary nephrotic syndrome**: 35%
  - Most common cause is **focal segmental glomerulosclerosis**

| 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 |

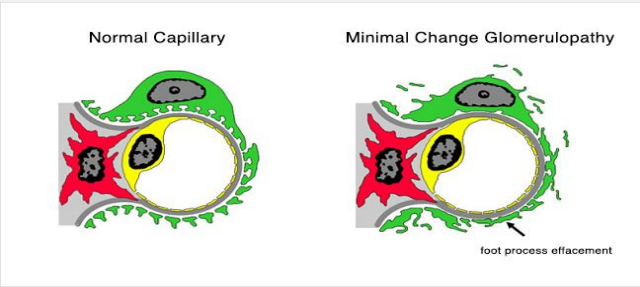
## Prevalence by Age: شرح اضافي للفهم فقط

### In Children:

- Around **65%** of kids with nephrotic syndrome have a condition called **Minimal Change Disease (MCD)**.
- It's called “minimal change” because when doctors look at the kidney under a regular microscope, it looks **normal**.
- But under an **electron microscope**, there are changes in the **podocytes** (those leggy cells we talked about).
- MCD is usually **mild**, responds well to **steroids**, and has a **good prognosis**

### In Adults:

- The **most common cause** of nephrotic syndrome in adults is **Focal Segmental Glomerulosclerosis (FSGS)**.
- “Focal” means it affects **some** of the glomeruli.
- “Segmental” means it affects **part of each glomerulus**.
- FSGS causes **scarring** in the kidney filters and is usually **more serious** than MCD.
- It may not respond well to treatment and can lead to **chronic kidney disease**



# ملخص للسلايدات السابقة :))

| Topic | Details |
|---|---|
| **Kidney Function** | **Filters blood, removes waste/toxins, returns clean blood to circulation – 24/7 function :))** |
| **Glomerulus** | **Functional unit of kidney, capillary network, site of filtration.** |
| **Filtration Membrane** | **Made of: Endothelial cells, GBM (Glomerular Basement Membrane), Podocytes (epithelial cells).** |
| **Vulnerability** | Capillaries in glomerulus are susceptible to damage and disease. |
| **Nephrotic Syndrome Definition** | Clinical complex from renal disease, includes 5 features: proteinuria, hypoalbuminemia, edema, hyperlipidemia/lipiduria, minimal/no azotemia/hematuria/hypertension. |
| **Main Feature: Proteinuria** | Heavy protein loss in urine; hallmark of nephrotic syndrome. |
| **Normal Filtration** | Filters: toxins, waste, salts, water. Proteins should NOT pass. |
| **Proteinuria Mechanism** | Damage to filtration membrane allows protein leakage. |
| **Hypoalbuminemia** | Low albumin due to protein loss. Albumin is major plasma protein. |
| **Edema** | Result of hypoalbuminemia → low oncotic pressure → fluid leaks → swelling. |
| **Hyperlipidemia & Lipiduria** | ↑ Lipids in blood & urine. Associated with protein loss. |
| **Lipid Types** | Triglycerides, LDL. Normally shouldn't be in urine. |
| **Hyperlipidemia Theory 1** | Liver shifts to make more lipoproteins due to low albumin → lipid spillover. |
| **Hyperlipidemia Theory 2** | Albumin transports lipids; low albumin → unbound lipids in circulation. |
| **No Azotemia/Hematuria/HTN** | Usually absent in primary nephrotic syndrome. |
| **Azotemia** | ↑ BUN & creatinine = sign of impaired kidney function. Not seen here. |
| **Typical Presentation** | Patients –for sure- don’t report "nephrotic syndrome"; they notice **edema** first. |
| **Most Common Symptom** | Generalized edema: face, eyes, lips, abdomen – main reason for clinic visit. |
| **Clinical Evaluation** | Doctor checks: edema, BP (often normal), general exam. |
| **Labs: Urinalysis** | Shows protein levels (+1, +2, +3…). finding: proteinuria. |
| **Labs: Kidney Function** | Tests: Creatinine, Urea → usually normal in nephrotic syndrome. |
| **Diagnosis Suspicion** | Based on: edema + proteinuria + normal kidney function. |
| **Cause = Membrane Damage** | Could affect GBM, podocytes, or both. All lead to proteinuria. |
| **Types of Causes** | 1. Primary glomerular diseases. 2. Secondary systemic diseases. |
| **Primary Diseases** | MCD, FSGS, Membranous nephropathy, Membranoproliferative GN (Type 1). |
| **Prevalence by Age** | Children → ~65% MCD. Adults → most common is FSGS. |

# Causes of Nephrotic Syndrome

## B-Systemic Diseases with Renal Manifestations:

- We will focus on the primary causes of nephrotic syndrome.

- **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.**

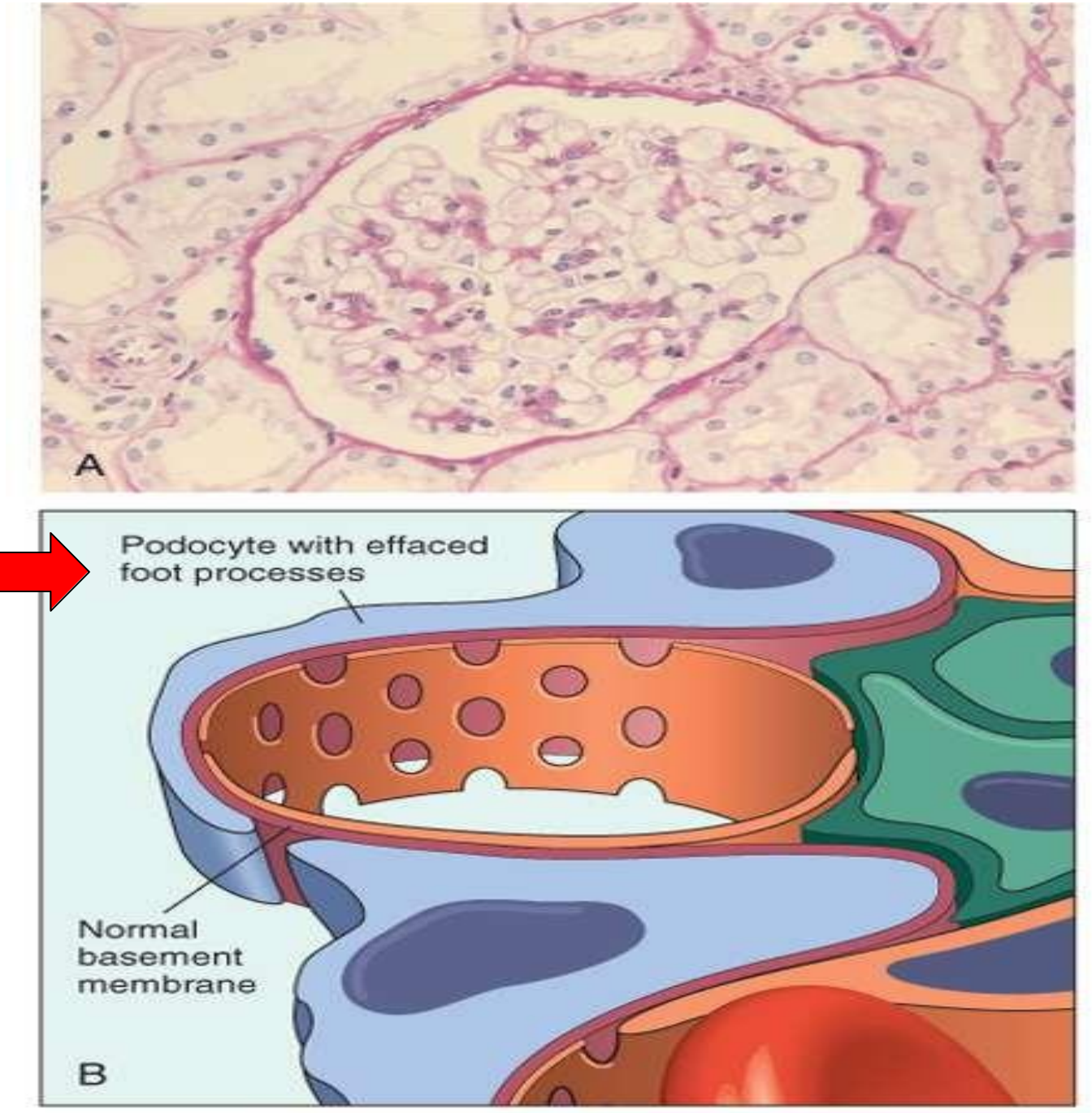
- When we see the kidney with this disease, we wouldn't notice any change in it.

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

- ***<u>Pathogenesis</u>*: still not clear.**

**? One of the theories said that it is a T-cell derived factor that causes podocyte damage and effacement of foot processes.**

- When the podocyte damaged, the working of filtration membrane will change and altered which will make loss of the filtration barrier exist and loss of large amounts of proteins in urine.





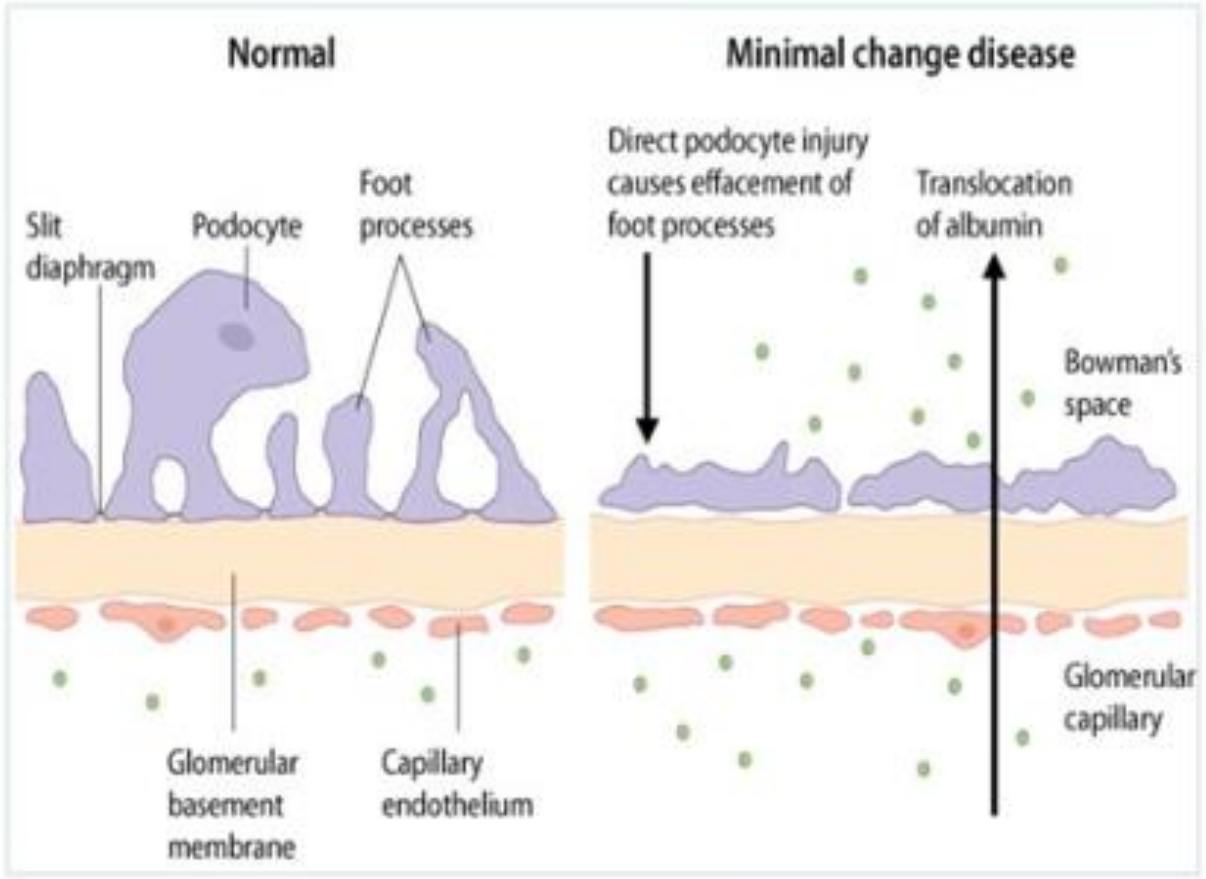

**Minimal change disease.**

**A**

glomerulus appears normal, with a delicate basement membrane

**B**

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




- The evidence of podocyte damage is effacement (طمس) of foot processes like villi atrophy in small intestines.
- We can see it only in electron microscope.

# Morphology

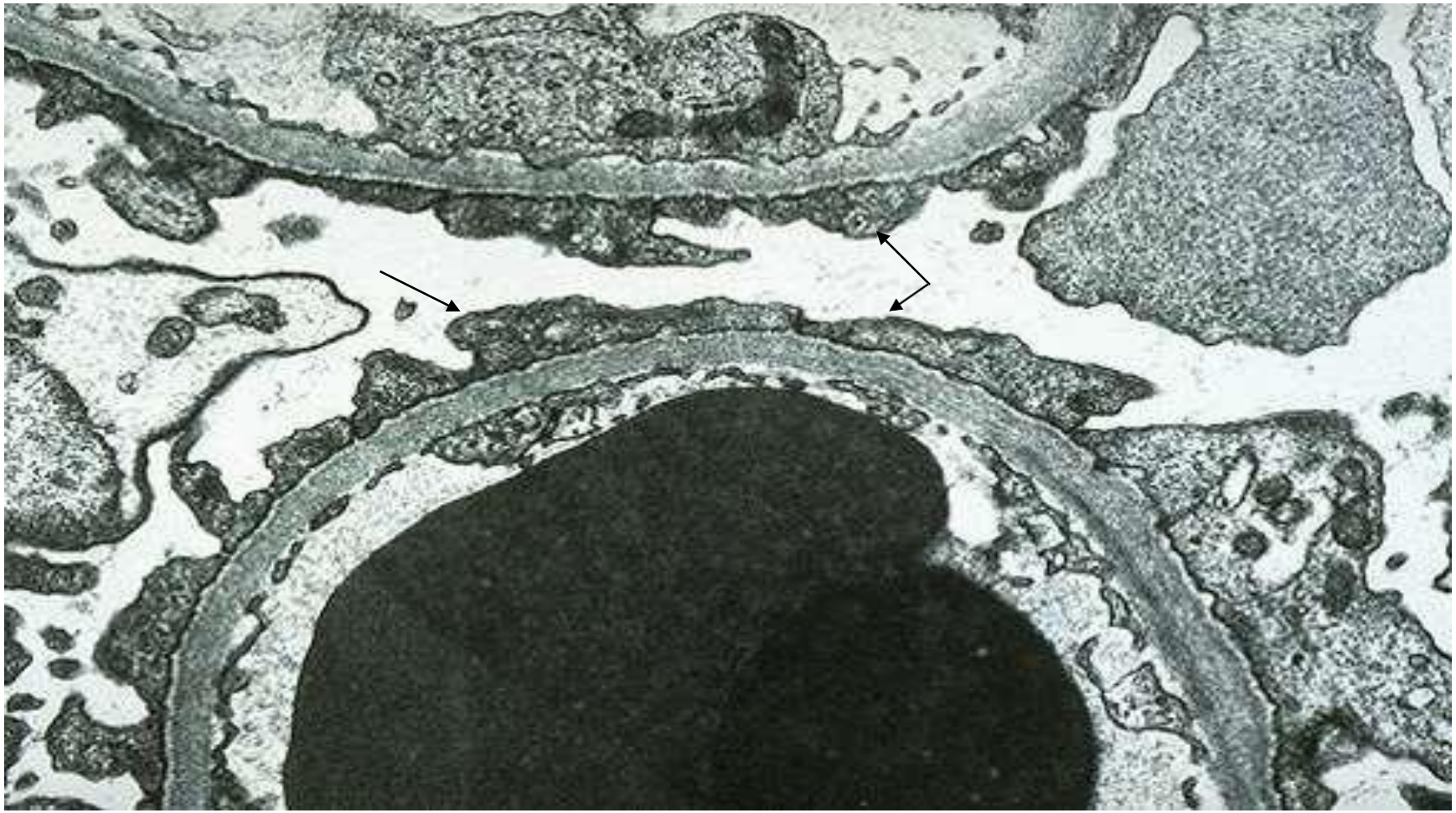
- **LM** (light microscope)
- the glomeruli appear normal.

- **IF** (immunofluresense)
- negative
- **EM** (electron microscope)
- **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.** (Due to recovery of the podocyte foot processings)

- This condition makes nephrotic syndrome appears in the children, a child come to the emergency with his parents and he has a generalized edema ,so we make tests like measure the blood pressure and find the disease that make the problem and labeling of the patient as nephrotic syndrome.

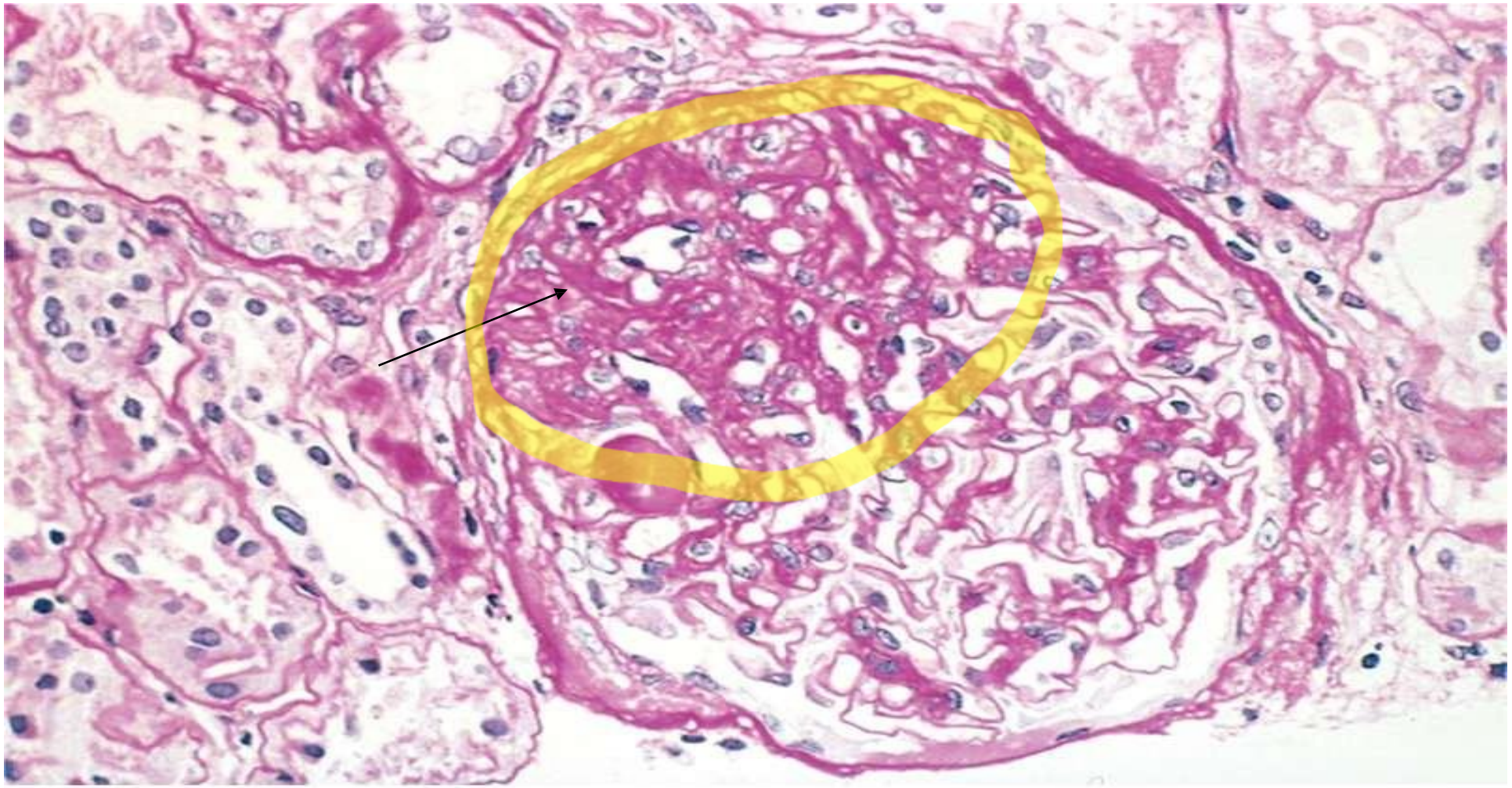
- **Treatment: corticosteroids (90% of cases respond)**
- **< 5% develop chronic renal failure after 25 years**
- **In Adults with minimal change disease the response is slower and relapses are more common.**

# 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):**
- **e.g. inherited or congenital forms resulting from mutations affecting nephrin**
- **Or: in association with underlying condition:**
- **e.g.; AIDS; heroin abuse; nephron loss; inherited or congenital forms resulting from mutations affecting etc….**

- Focal means that some of the glomeruli have the disease and the other glomeruli are normal.
- Segmental means that part of the glomerulus has the disease ,not all glomerulus.

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





- The area highlighted in more pink than other areas due to presence of connective or fibrous tissues.
- I take apart glomerulus called a segment and seen on most of glumerulus ,but not all glomeruli

# MCD versus FSGS

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

- ***Pathogenesis***

> - The details of the pathogenesis isn't required.

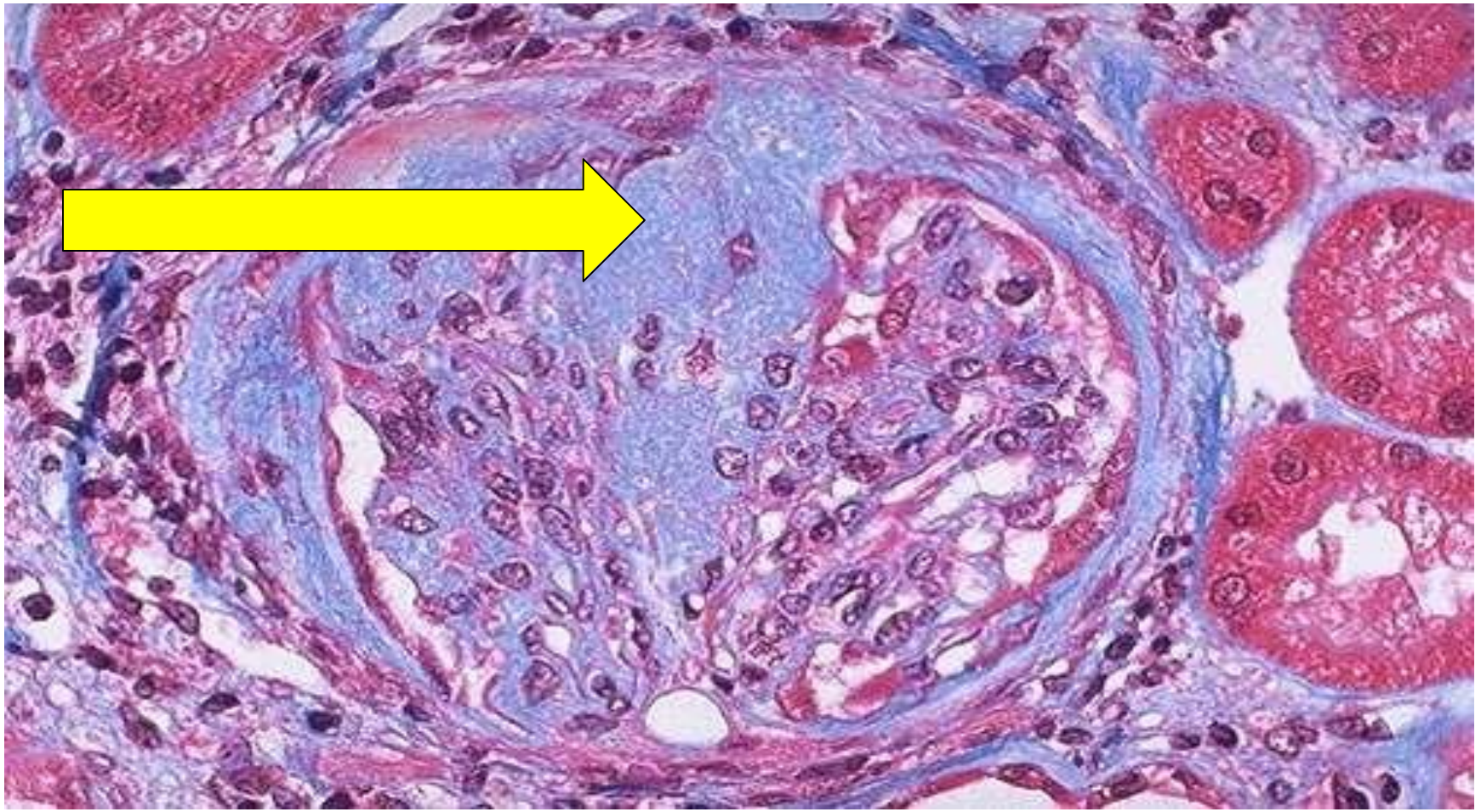
- **unclear**
- ***injury to the podocytes*** **? ↑ GFR at first? Genetics?**
- **entrapment of plasma proteins and lipids in foci of injury where sclerosis develops.**

- **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 podocyte foot processes**

# FSGS

## blue = collagen deposition (MT stain).



- Trichrome Staining that make the connective tissues seen in blue color.
- There is a deposition of a blue material which made of collagen or connective tissues (sclerosis).

# 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.** (Just know this info. About this disease)

3-drug-induced toxicities.

# *3- Membranous nephropathy:*

- Immune complex (antigen+antibody) deposition in glomerulus which make a imbalance in the architecture of GBM.

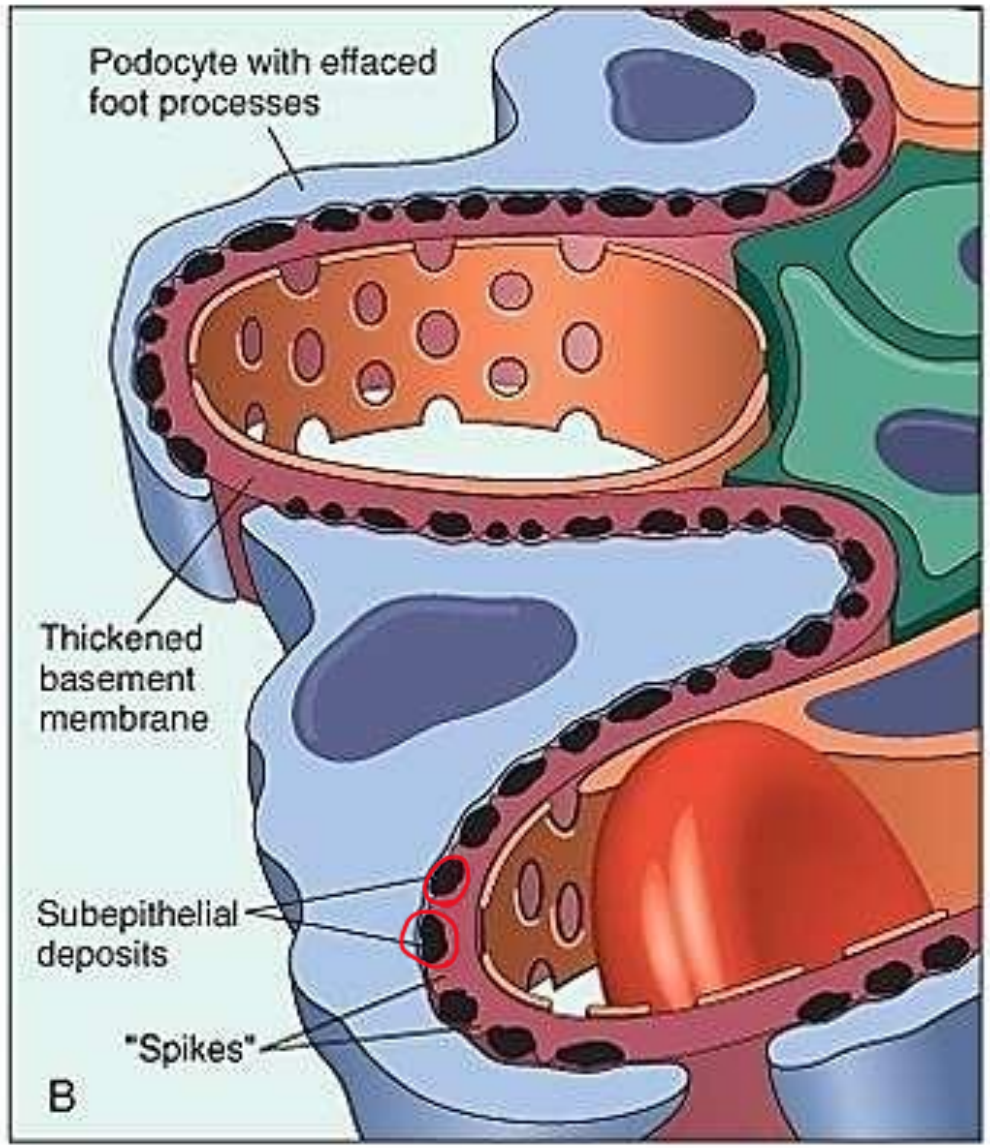
- Types of Membranous glomerulonephritis :

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

## 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) (positive)
- **EM**
- **subepithelial deposits "spike and dome" pattern.**



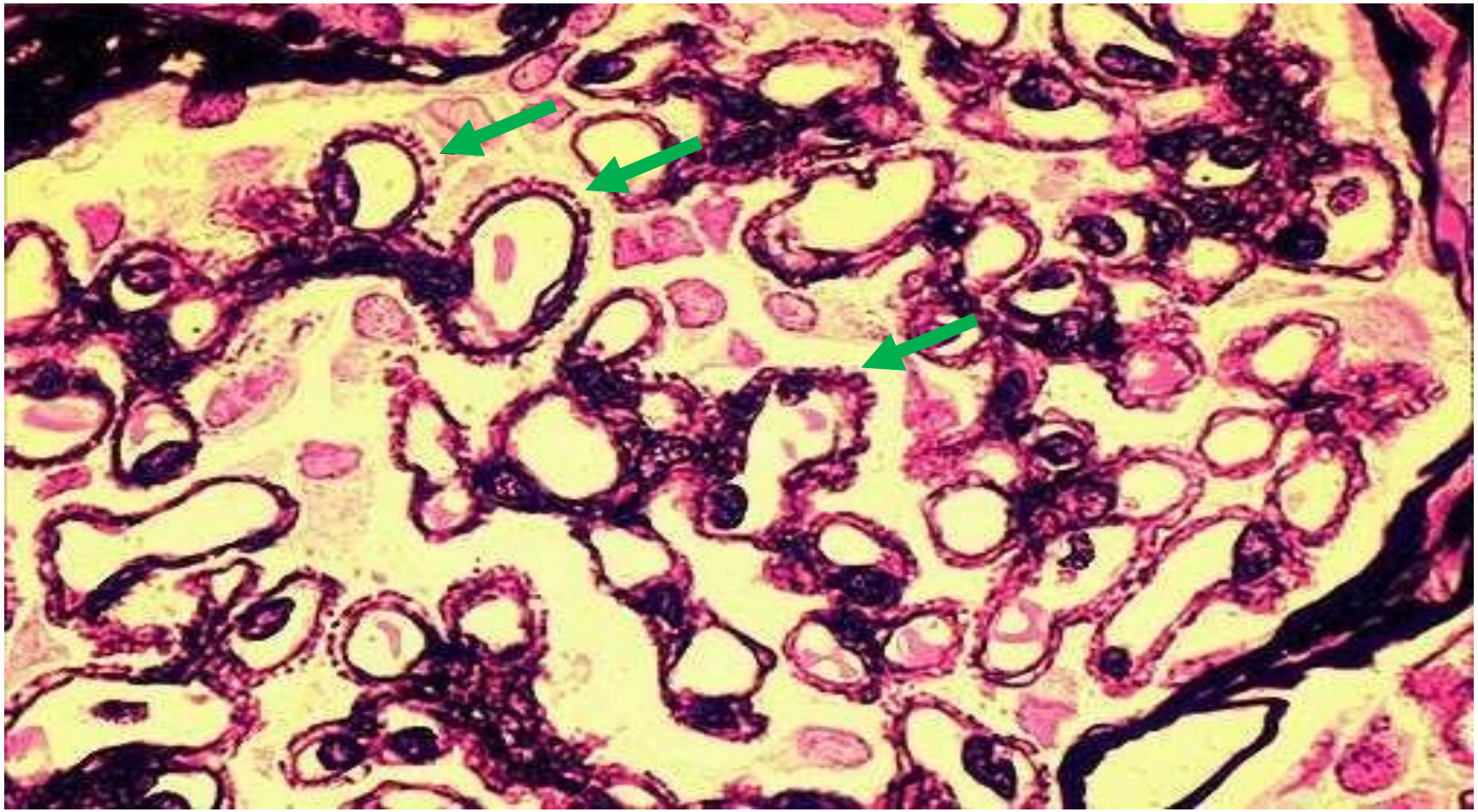



Membranous nephropathy.

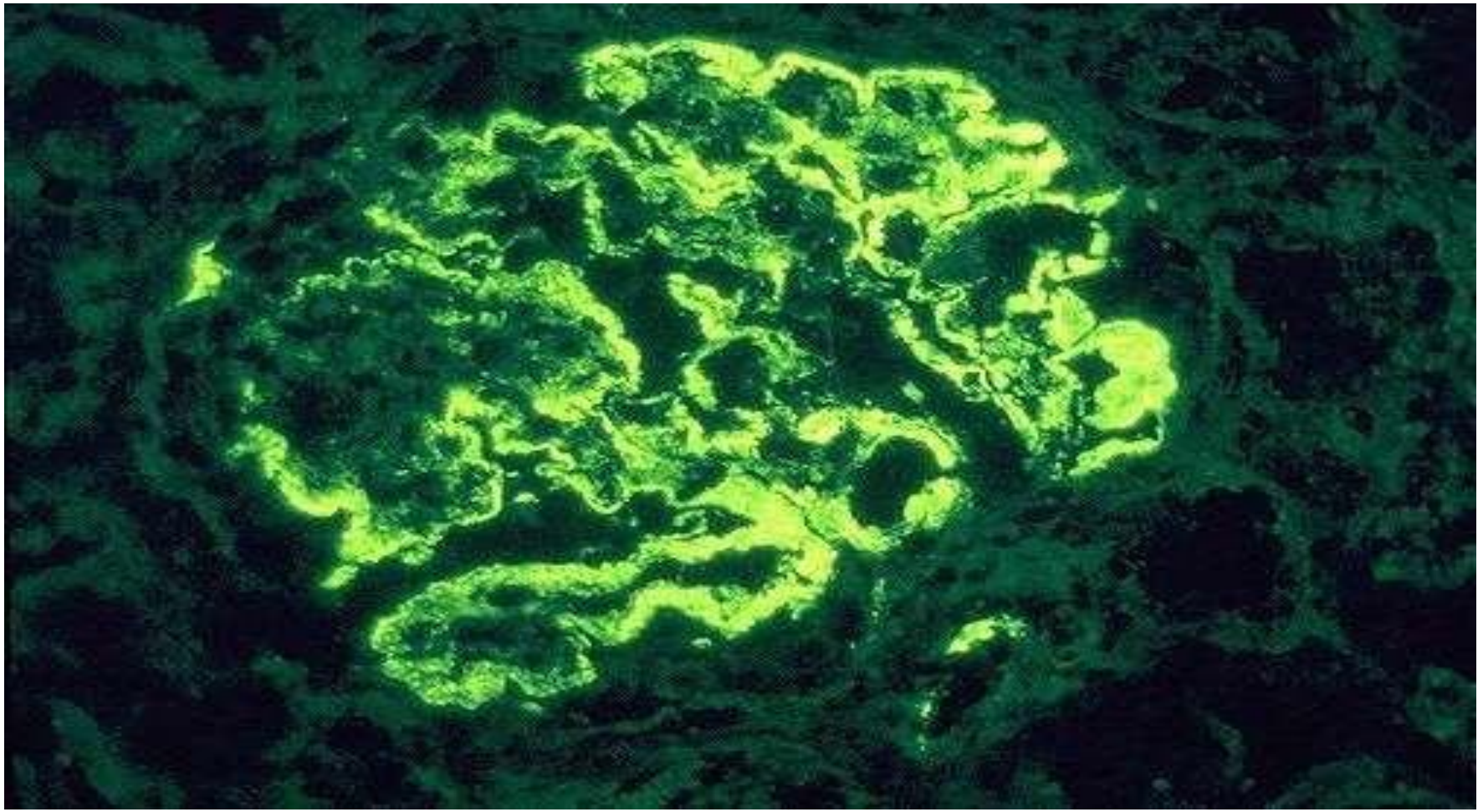
subepithelial deposits and the presence of "spikes" of basement membrane material between the immune deposits.

- The immune complexes prefer a certain location inside filtration membrane which is under the podocyte and above of GBM ,so it called subepithelial.
- This deposition will disrupt filtration membrane which make loss of a large amount of proteins into urine ,so there is proteinuria and nephrotic syndrome.

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

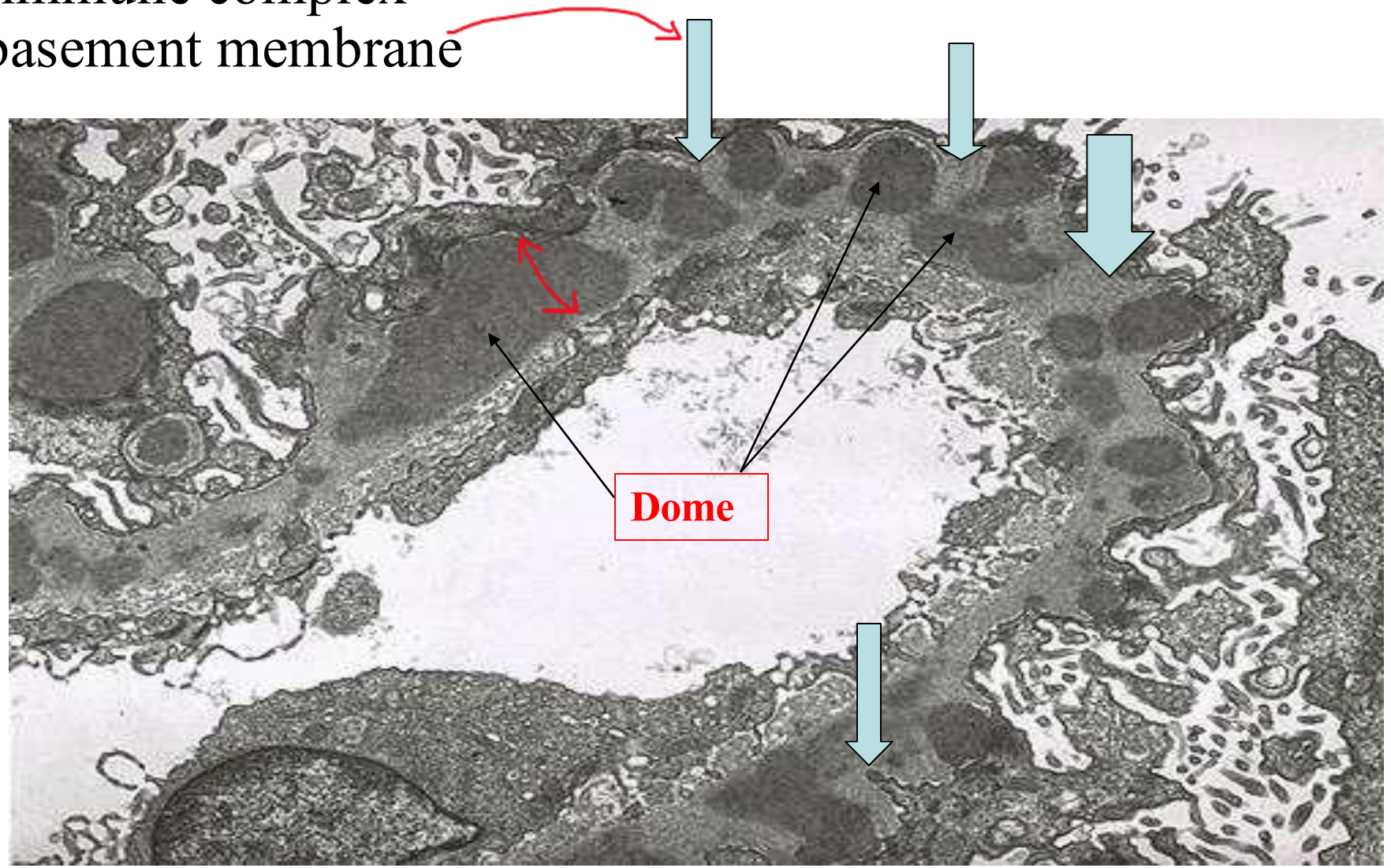


**Membranous GN**
**IF: granular deposits of IgG and complements along the capillary walls**



# EM: "spike and dome" pattern is characteristic

Dome= immune complex
spike= basement membrane



- **Clinical Course**
- **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.**

قال النبي صلى الله عليه وسلم يومًا لأصحابه: إن الله كريم يحب الكرم، ويحب معالي الأخلاق، ويكره سفاسفها!
اجعل لك هدفًا ساميًا كأن تحفظ القرآن، ووجهة حلوة كأن تحصل على الدكتوراه في تخصصك، تابع سلسلة مفيدة، وشاهد برامج نافعة، عش حياتك انت، ولا تعش في حياة الناس، من الناس من همه صغائر الأمور، حياة فارغة، واهتمامات تافهة.
ألهذا الشي خُلقنا؟ ولهذه الغاية نحن في هذه الأرض؟
ابنوا القبور التي ستسكنونها طويلاً لأنكم ستكونون فيها وحدكم.

## Additional sources

1. Book pages
2. Youtube videos
3. Webpages...etc

| VERSIONS | SLIDE # | BEFORE CORRECTION | AFTER CORRECTION |
|---|---|---|---|
| V1→ V2 | | | |
| V2→V3 | | | |

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!