

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



Urinary System Pathology

MID | Lecture 1

Written by:

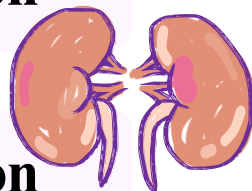
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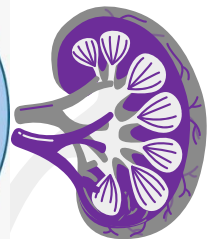
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﴿قُلْ بِفَضْلِ اللَّهِ وَبِرَحْمَتِهِ فَبِذَلِكَ فَلْيَفْرَحُوا هُوَ خَيْرٌ مِمَّا يَجْمَعُونَ﴾



"اللَّهُمَّ إِنِّي أَسْأَلُكَ فَهَمَ النَّبِيِّينَ، وَحِفْظَ الْمُرْسَلِينَ، وَالْهَامَ الْمَلَائِكَةِ الْمُقَرَّبِينَ، بِرَحْمَتِكَ يَا أَرْحَمَ الرَّاحِمِينَ"

Renal Pathology- Lecture 1

Contents:

- 1 Concepts of renal pathology**
- 2 Introduction to glomerulus pathology**

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Professor of Pathology

CLINICAL MANIFESTATIONS OF RENAL DISEASES

1- Azotemia: It is a sign that can be detected by blood tests (kidney function tests)

- **refers to an elevation of blood urea nitrogen (BUN) and creatinine levels.**
 - ✓ Because these molecules are excreted by the kidneys, they serve as reliable indicators of renal function.
- **It is largely related to a decreased glomerular filtration rate (GFR).**
 - ✓ This represents an indicator of **impaired renal function**.

2- Uremia

- **when azotemia progresses to **clinical** manifestations and systemic biochemical abnormalities.**
 - ✓ It's related to the toxic effect of urea and the accumulation of other toxic substances in the circulation.

❖ Uremia is characterized by:

1. failure of renal excretory function (reduction in the urinary output; either oliguria or anuria)
2. metabolic and endocrine alterations
3. 2ry gastrointestinal manifestations (e.g., uremic gastroenteritis)
4. 2ry neuromuscular manifestations (e.g., peripheral neuropathy)
5. 2ry cardiovascular manifestations (e.g., uremic fibrinous pericarditis)

} 2ry
systematic
abnormalities

The major renal syndromes

- **Syndrome:** a constellation of related signs and symptoms that occur together and are associated with a specific pathogenetic mechanism.

1-Nephritic syndrome:

✓ a glomerular syndrome characterized by:

acute onset

Gross (macroscopic) hematuria (blood in urine) → symptom

mild to moderate proteinuria (< 3.5 gm of protein/day in adults)

- The presence of proteins in urine is **abnormal** because the glomerular filtration barrier normally prevents proteins from being lost in the urine.

azotemia

Edema

- Occurs due to **decreased oncotic pressure** resulting from protein loss in the urine, along with reduced renal excretory function.

hypertension

○ When the blood in urine is not visible and only detected on laboratory testing (microscopic hematuria) It is considered a **sign**.

Nephritic Syndrome: Presentation

- Changes in urine **color and consistency** may occur, including frothy urine, which is suggestive of proteinuria. Urine may also become turbid or discolored, appearing brownish, reddish, or smoky.

- **PHAROH**

- ***Proteinuria***

- $<3.5\text{g}/1.73\text{m}^2/\text{day}$

- ***Hematuria***

- *Abrupt onset*

- ***Azotemia***

- *Increased creatinine and urea*

- ***RBC Casts***



- Microscopic urinalysis demonstrates red blood cells aggregated within casts, indicating renal damage or inflammation.

- ***Oliguria***

- ***HTN***

- ✓ Decreased urine output indicating impaired renal excretory function.



Peripheral Edema/Puffy Eyes
Periorbital edema



Urine”

2-Nephrotic syndrome:

✓ a glomerular syndrome characterized by:

✓ In children, calculations are weight-based (per kg).

☐ heavy proteinuria (excretion of >3.5 gm of protein/day in adults)

○ Heavy proteinuria is **severe** and clinically **significant**, and it leads to other associated manifestations.

☐ **Hypoalbuminemia**

☐ **severe edema**

☐ **Hyperlipidemia**

☐ **lipiduria (lipid in the urine)**

○ All the manifestations are interconnected.

✓ Heavy proteinuria results from loss of integrity of the glomerular filtration membrane, leading to loss of large amounts of proteins such as albumin. This causes **hypoalbuminemia**.

○ Hypoalbuminemia reduces plasma oncotic pressure, which results in generalized and **severe edema**.

○ In addition, the liver responds to hypoalbuminemia by increasing synthesis of proteins, including lipoproteins, which leads to **hyperlipidemia** (increased LDL and triglycerides).

○ The increased circulating lipoproteins, together with altered glomerular permeability, may also lead to **lipiduria**

Nephrotic syndrome

Severe generalized edema



Puffy eyes



Pitting edema



3-Asymptomatic microscopic hematuria or mild proteinuria:

- ✓ **A manifestation of mild glomerular abnormalities.**
- It is often an incidental finding on urinalysis. We should not alarm the patient, as these are mild changes that are not necessarily associated with renal failure. However, they should not be ignored, as they may represent an early manifestation of an underlying glomerular disease; therefore, further evaluation is required.

4-Rapidly progressive (severe) glomerulonephritis (crescentic GN)

- ✓ **loss of renal function in a few days or weeks leading to renal failure**

It is manifested by :

- microscopic hematuria.**
- dysmorphic RBC and RBC casts in urine sediment.**
- mild-moderate proteinuria**
- It is termed **crescentic** due to the formation of crescent-shaped inflammatory lesions within Bowman's space in the glomerulus.

5- Acute renal failure

- ❑ **oliguria (<400 ml/day) or anuria (no urine flow).** Which indicates an acute loss of renal function.
- ❑ **recent onset of azotemia.** Over a short period of time.

- ✓ **It can result from :**
 1. **glomerular injury**
 2. **interstitial injury**
 3. **vascular injury (thrombotic microangiopathy)**
 4. **acute tubular necrosis**

6- Chronic renal failure

Irreversible

- ✓ **prolonged symptoms and signs of uremia. Over a long period of time.**
- **the end and the most feared result of all chronic renal diseases**

7- Urinary tract infection

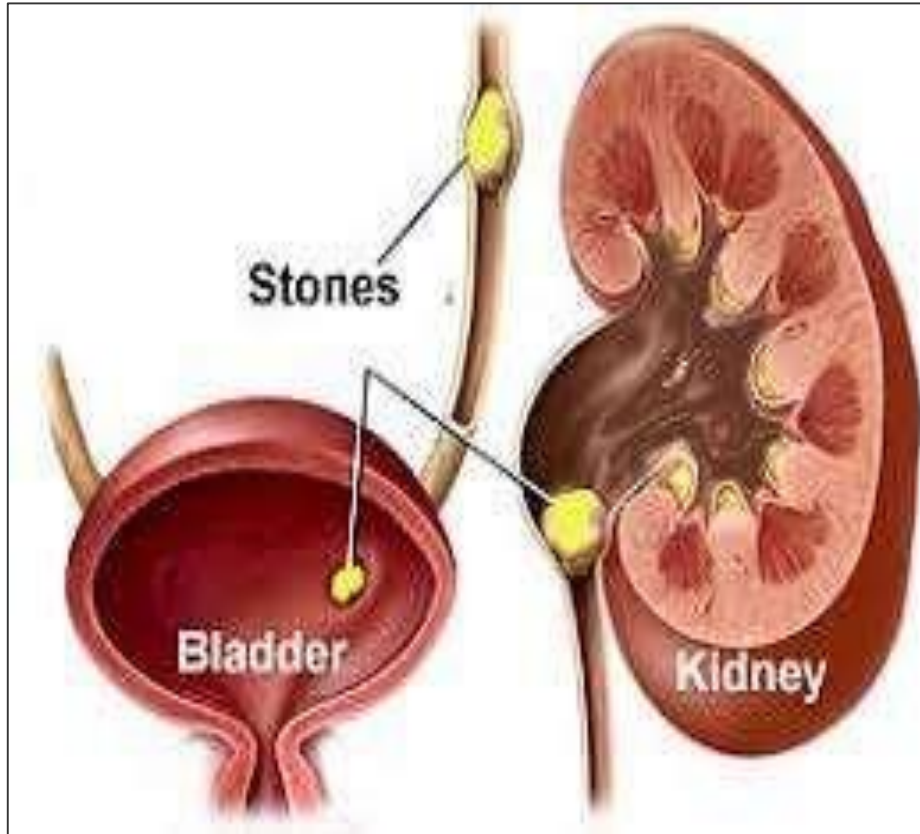
- ✓ **bacteriuria and pyuria (bacteria and WBCs in urine).**
- **symptomatic or asymptomatic.**

Types :

1- pyelonephritis (kidney).

2- cystitis (bladder).

8-Nephrolithiasis



✓ Renal stones

○ manifested by:

1-renal colic (pain) severe

2-hematuria because of the traumatic injury of the mucosa.

3-possible recurrent stone formation

- Renal stones can be found anywhere along the urinary system, including the renal calyces, renal pelvis, ureter, urinary bladder, and urethra. Their clinical effects vary depending on their location.

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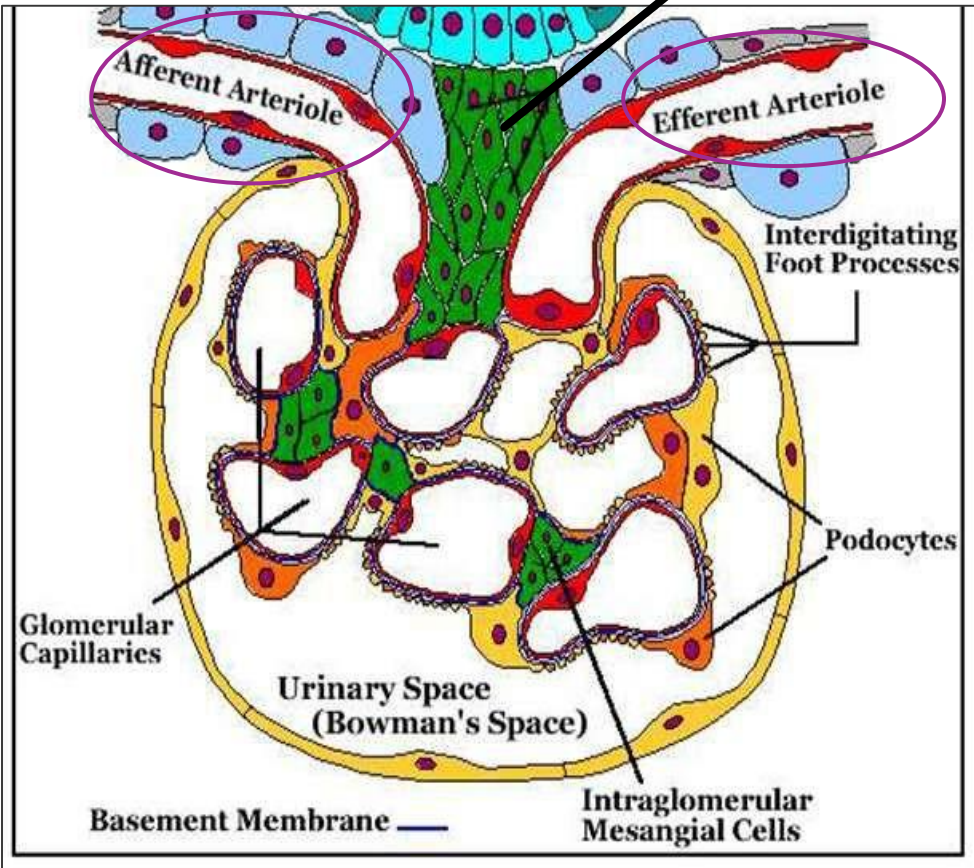
Glomerular diseases

Glomerulus: Structure and Function

الكبيبة الكلوية

Normal glomerulus

Mesangial cells



➤ Definition

- The glomerulus is a specialized capillary structure located within the kidney.
- It is not a simple vessel, but rather a complex network of capillaries responsible for filtration of blood.
- Blood enters the glomerulus through the afferent arteriole and exits through the efferent arteriole.

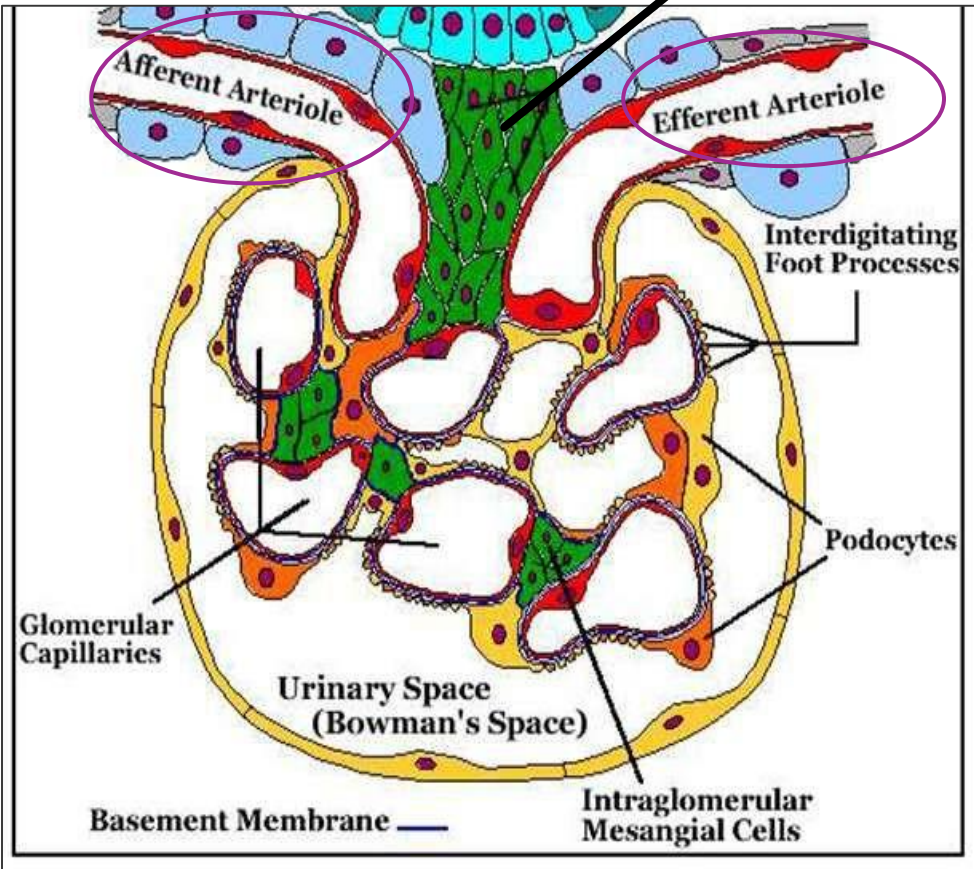
➤ Structure

- The glomerulus consists of a single, long capillary that is highly coiled and folded.
- Arranged in a compact, circular (tuft-like) structure
- This coiling allows: Maximum surface area & Efficient filtration in a small space.

Glomerulus: Structure and Function

Normal glomerulus

Mesangial cells



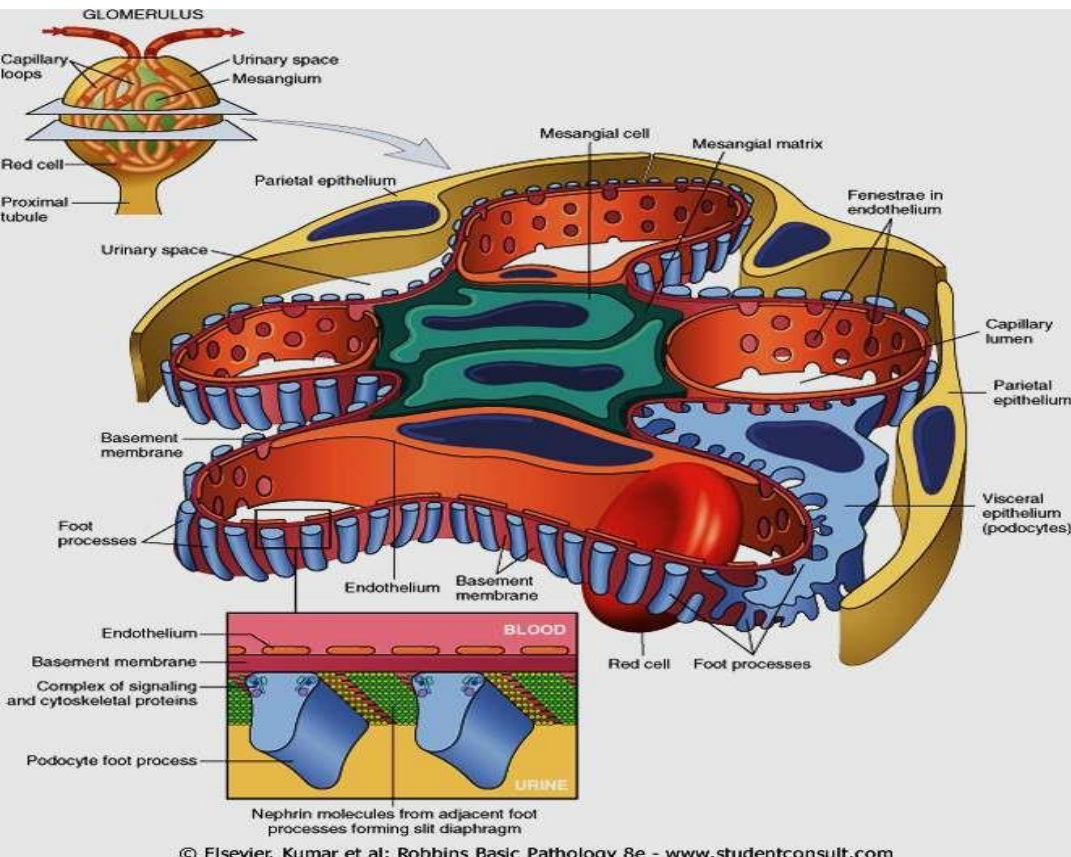
➤ Function

- ✓ The main function of the glomerulus is filtration of blood over a relatively long pathway, this process ensures the removal of waste products, toxins, and excess substances from the circulation.
- ✓ At the same time, filtration must be selective. It **should not allow the loss of important components** such as red blood cells, white blood cells, platelets, serum proteins (especially albumin), lipids, and other large or charged molecules. These components must remain in the blood.
- ✓ In contrast, small molecules can pass through the filtration barrier. Some of these filtered substances may later be reabsorbed in other parts of the nephron, maintaining the balance of essential substances in the body.

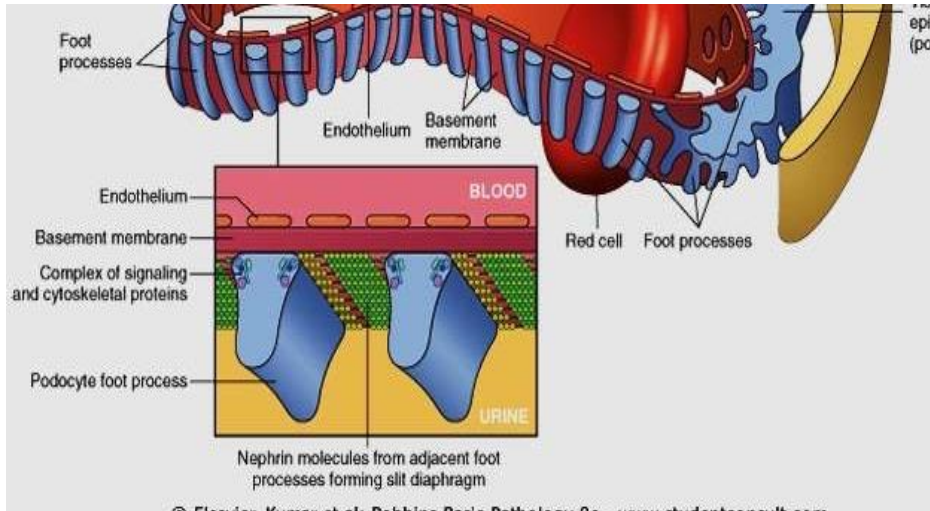
Glomerular Filtration Barrier

➤ The structure that ensures proper filtration in the glomerulus is the glomerular filtration barrier, which is composed of three main layers working together to control what passes from blood into the filtrate.

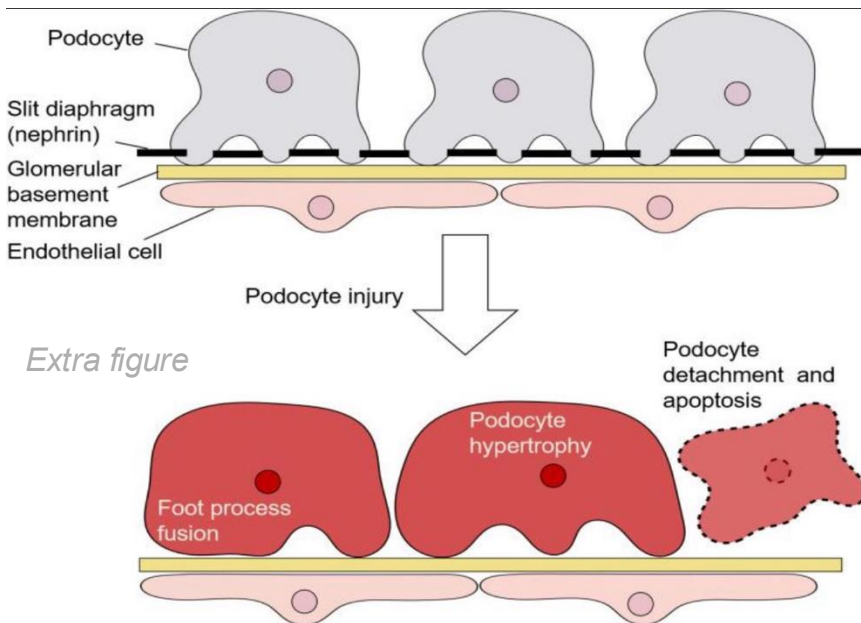
- First, the inner surface of the capillary is lined by **endothelial cells**, these cells form the inner layer and cover the capillary lumen.
- Surrounding the endothelium is the **glomerular basement membrane (GBM)**, this layer provides structural support and plays an important role in filtration.
- Outside the basement membrane are specialized cells called **podocytes (visceral epithelial cells)**. These are also known as “foot cells” because they have foot processes that extend and wrap around the capillaries. These processes support the capillaries and participate directly in forming the filtration barrier.



Glomerular Filtration Barrier



- Between the foot processes of podocytes, there are narrow gaps called **filtration slits**, these slits are not open spaces; they are bridged by a network of **proteins** forming slit diaphragms, which act as an additional filtration layer.
- Together, these structures (endothelium, GBM, and podocyte foot processes with slit diaphragms) provide precise control over membrane permeability. If any of these components are damaged, this control is lost or reduced, leading to abnormal filtration. As a result, important substances such as proteins or blood cells may pass into the urine, causing conditions like **proteinuria** and **hematuria**.



GLOMERULAR DISEASES

- ❑ one of the most common causes of chronic kidney disease.**
- ❑ The glomerulus =anastomosing network of capillaries invested by two layers of epithelium: podocytes and parietal epithelium**
- ❑ Bowman space (urinary space)= the cavity in which plasma ultra-filtrate first collects.**

Related to CLINICAL:

- **When a patient presents with gross hematuria or significant proteinuria, an appropriate clinical approach is required.**
- The initial step is to assess and manage **blood pressure**, basic investigations are then performed, including: **Kidney function tests & Urinalysis**, these tests help evaluate the severity of the condition and provide initial diagnostic information, At this stage, **additional blood tests** may be performed to better understand the cause.
- If the patient meets specific criteria indicating the need for definitive diagnosis, a more invasive investigation is considered. This involves performing a **renal biopsy (kidney biopsy)**. خزعة الكلى

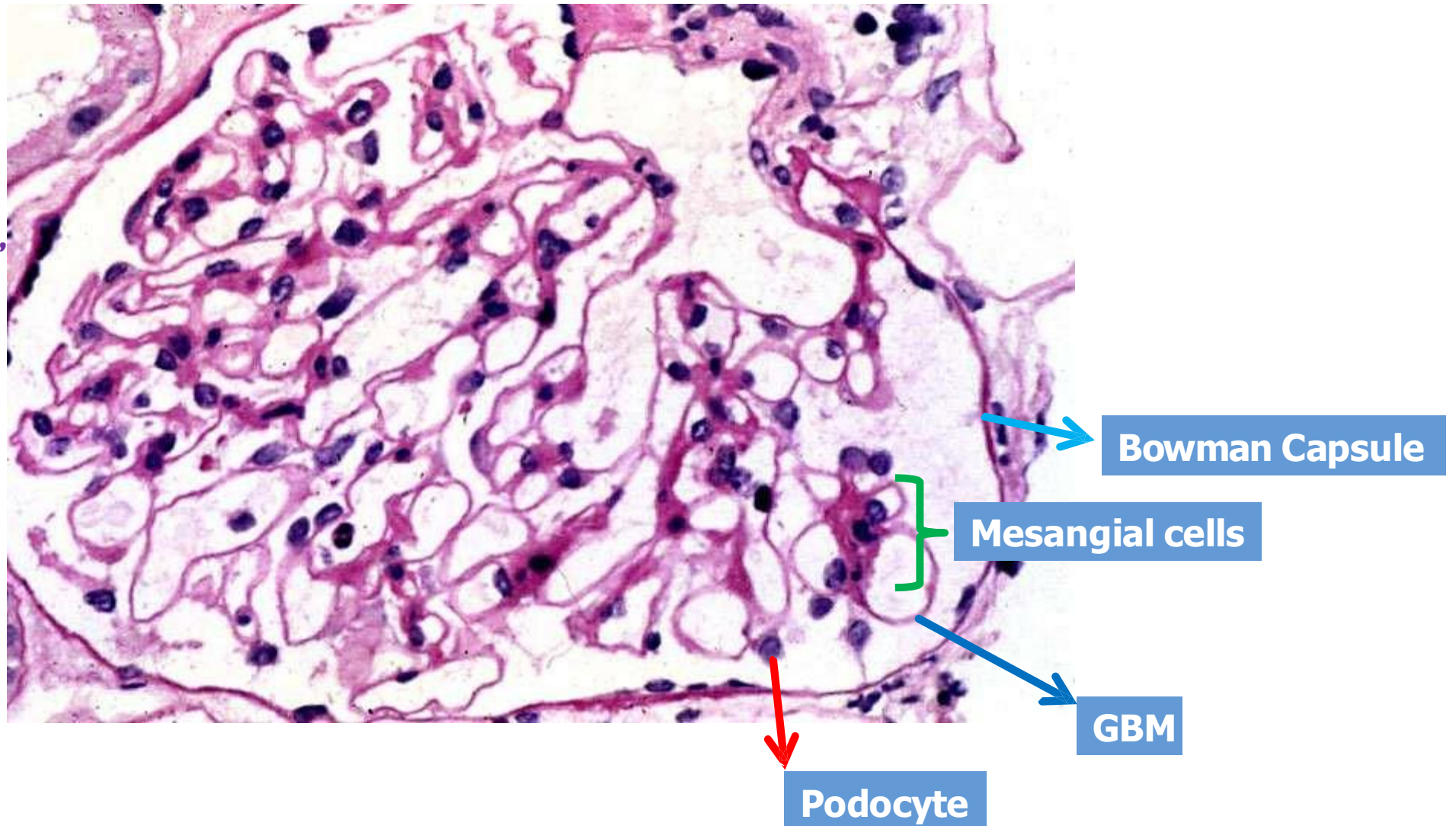
- ✓ **A renal biopsy** is performed under sedation or anesthesia and with radiological guidance, Imaging is used to accurately guide the insertion of a needle into the kidney to obtain a small tissue sample.
- ✓ The obtained tissue is then sent to the pathology laboratory for examination to identify any structural abnormalities in the kidney that may explain the disease.

Pathological tests used in the evaluation for renal medical diseases (renal biopsy):

- 1. Light microscopy (LM)**
 - 2. Immunofluorescence microscopy (IF)**
 - 3. Electron microscopy (EM) (usually Transmission electron microscope)**
may also be used, but its availability is limited. It is performed only in centers where the technique is available.
- } **The main methods of analysis**

Normal glomerulus- light microscopy

✓ Light microscopy is used to examine the structure of the kidney, particularly the glomerulus. It allows visualization of the tissue architecture and helps determine whether structural abnormalities are present or absent.

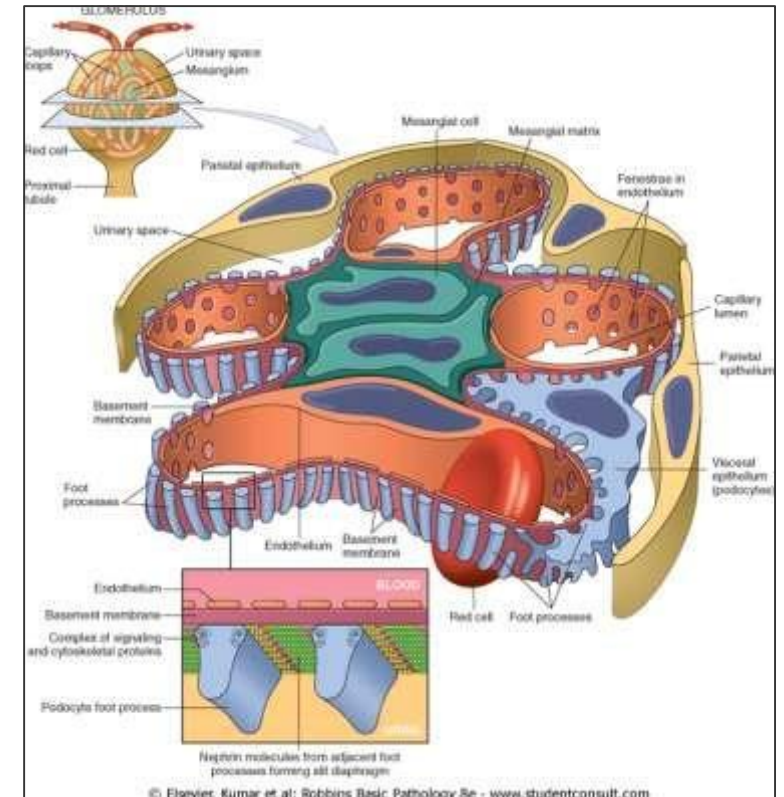


The glomerular capillary wall is the filtration unit and consists of :

1. A thin layer of fenestrated endothelial cells
2. glomerular basement membrane (GBM)
3. foot processes of podocytes
4. Supportive cells (mesangial cells) lying between the capillaries

Glomerular filtration membrane/ unit

- consists of collagen (type IV), laminin, polyanionic proteoglycans, fibronectin, and glycoproteins.
- interdigitating foot processes of The *visceral epithelial cells* (**podocytes**), embedded in and adherent to GBM
- *foot processes* are separated by *filtration slits* which are bridged by a thin slit diaphragm composed mainly of **Nephrin**.



The major characteristics of glomerular filtration

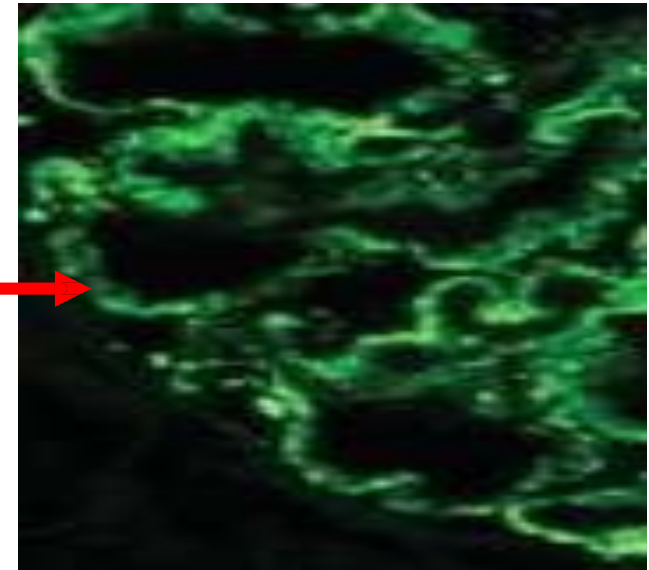
- 1 high permeability to water and small solutes**
- 2 complete impermeability to molecules of large size and molecular charge (e.g. albumin)**
 - **So:**
 - 1 the larger the less permeable**
 - 2 the more cationic the more permeable.**
 - **Nephrin** and its associated proteins, including **podocin**, have a crucial role in maintaining the selective permeability of the glomerular filtration barrier.

Immunofluorescence microscopy

- is a technique used to detect immune-related abnormalities in the kidney, the term “immune” refers to the immune system, while “fluorescence” refers to the use of fluorescent labels to identify specific structures in the tissue so this method is used to identify **immune-mediated renal diseases**. In these conditions, the immune system forms immune complexes, which can deposit within the kidney, particularly in the glomerulus, these deposits are responsible for causing glomerular disease.
- ✓ In immunofluorescence microscopy, small sections of renal tissue are taken and stained using specific antibodies that target different antigens, these antibodies are labeled with fluorescent markers (fluorescein).
- ✓ When the antibody binds to its corresponding antigen, a fluorescent signal is produced. The background appears dark (black), while positive areas show bright fluorescence.
- ✓ The renal tissue is divided into multiple slides, and each slide is stained with a different antibody. For example: Antibodies against IgG, IgA, IgM / Complement components such as C3 and C4 / Light chains such as kappa and lambda. Each marker is tested separately to identify the pattern of deposition

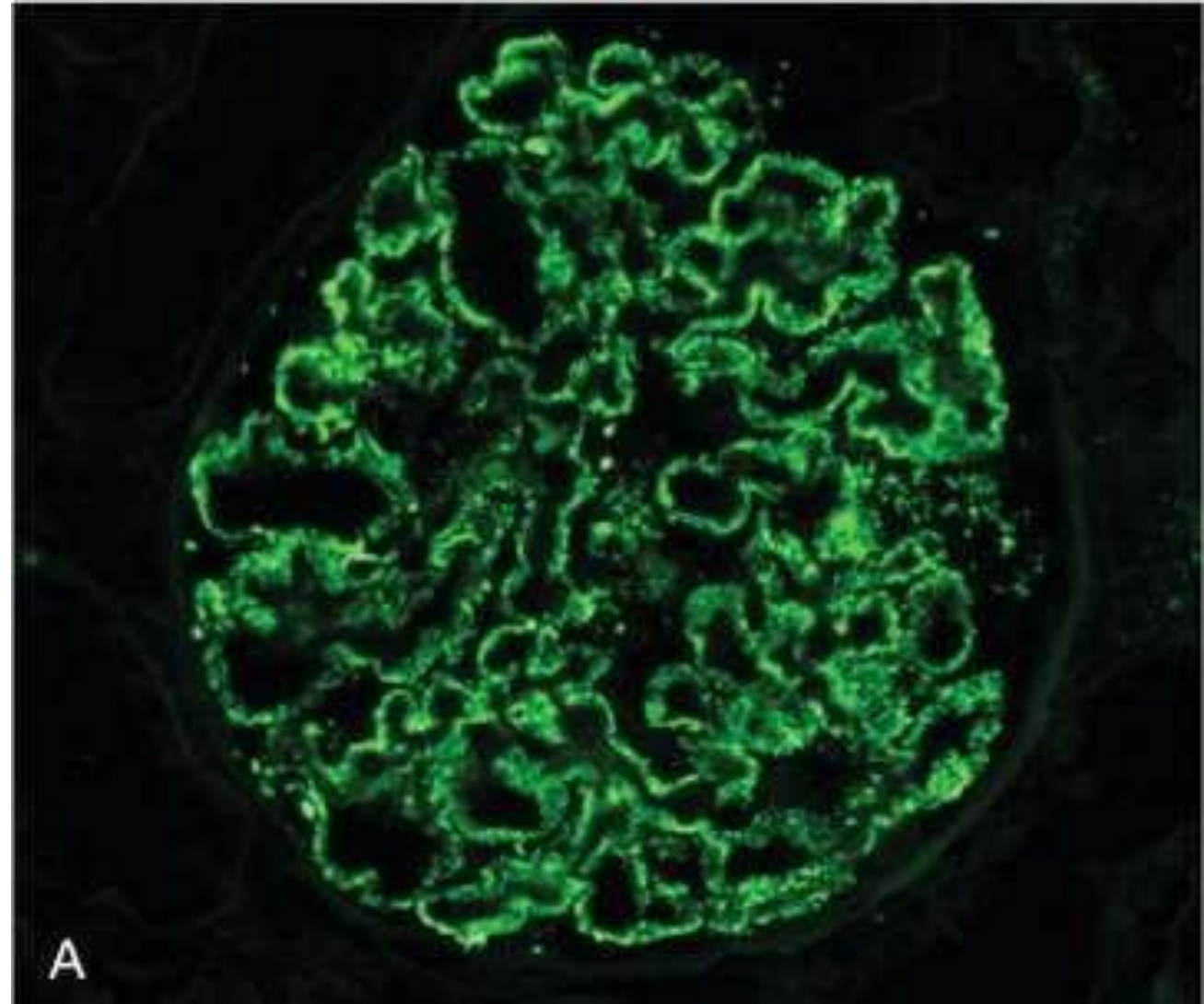
Immunofluorescence microscopy

- **Fluorescein-labeled antibodies used for the antigens that should be routinely examined include immunoglobulins (primarily IgG, IgM, and IgA), complement components (primarily C3, C1q, and C4), fibrin, and kappa and lambda light chains.**
 - **Important in detecting immune complex-mediated glomerular disorders**
 - **The pattern and location of immune complex deposition is helpful in distinguishing various types of GN**
-
- **If, for example, IgA is positive, this indicates that IgA immune complexes are present in the kidney tissue. This supports the diagnosis of an immune complex-mediated renal disease, where immune deposits in the kidney are responsible for the pathology.**
 - **If all immunofluorescence stains are negative, it means there are NO detectable immune complex deposits in the kidney tissue.**

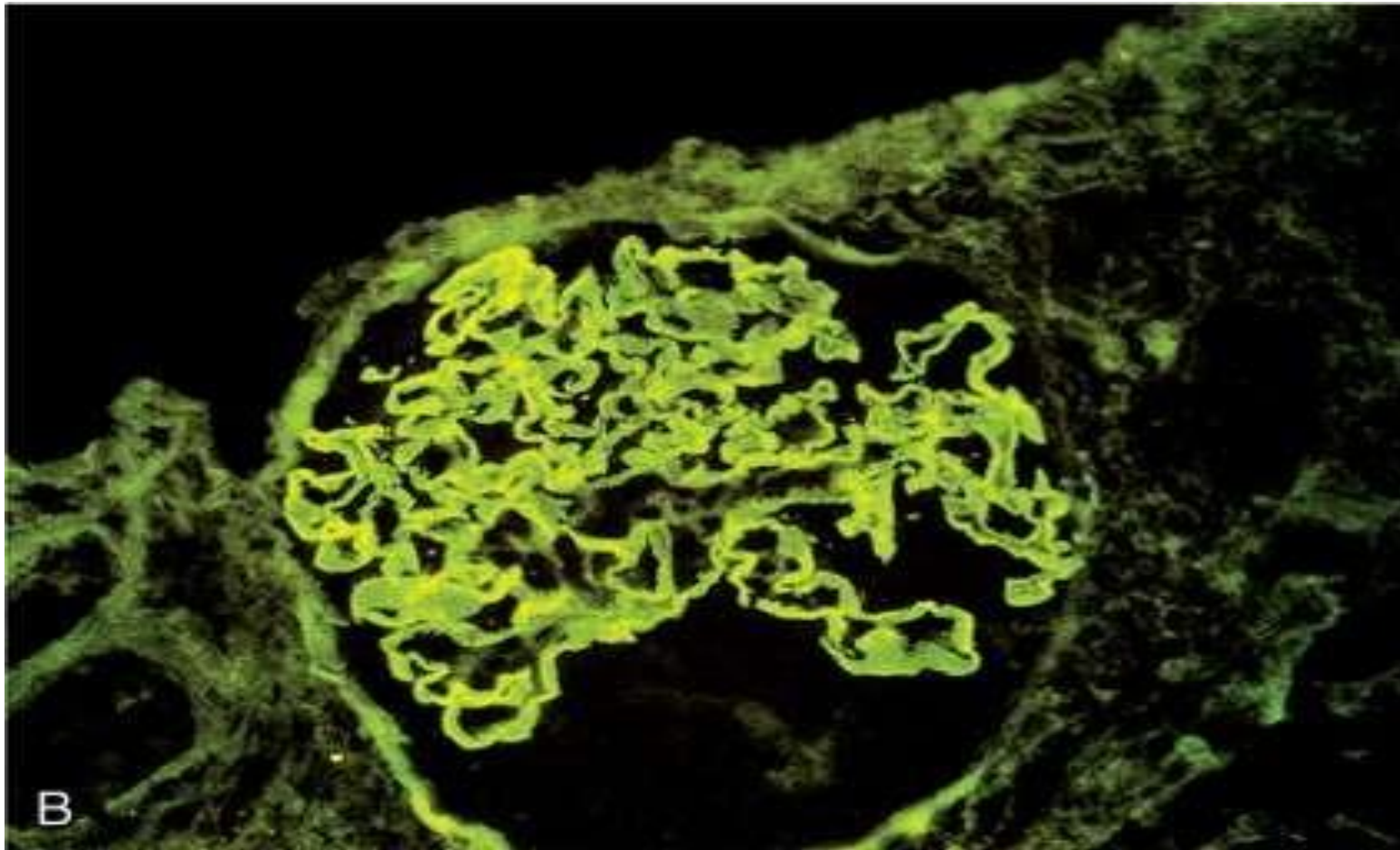


**Immunofluorescence
microscopy**

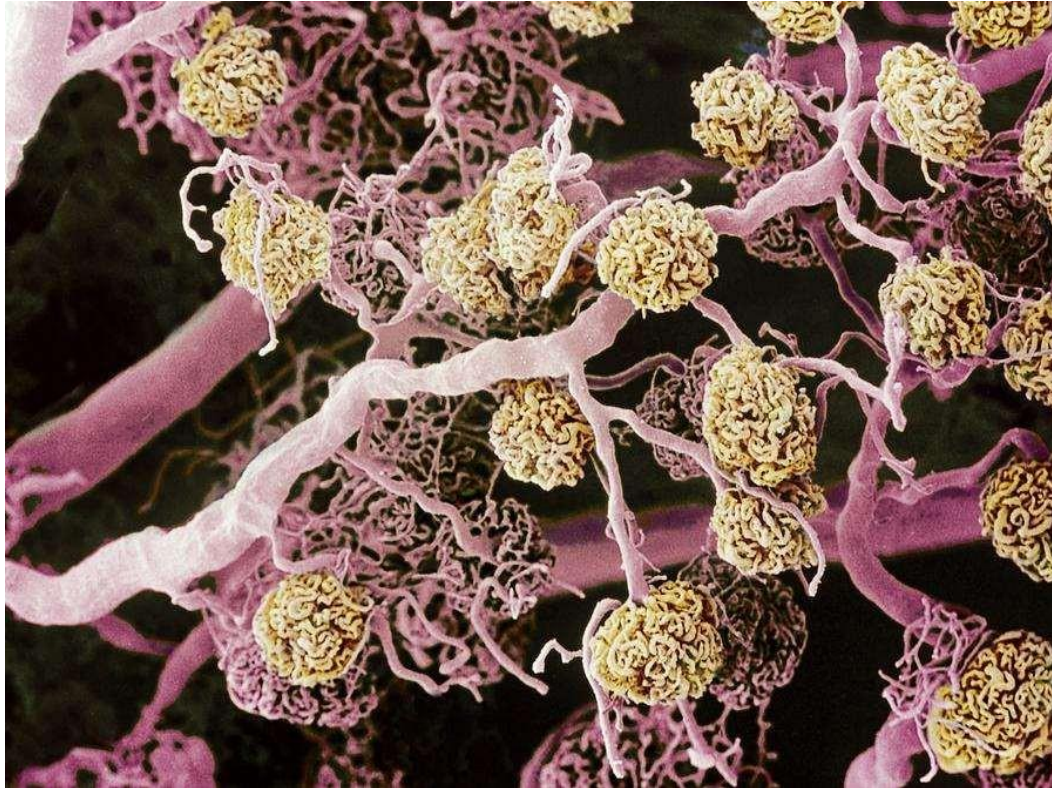
**granular pattern of
deposition**



immunofluorescence linear deposition of immune complexes



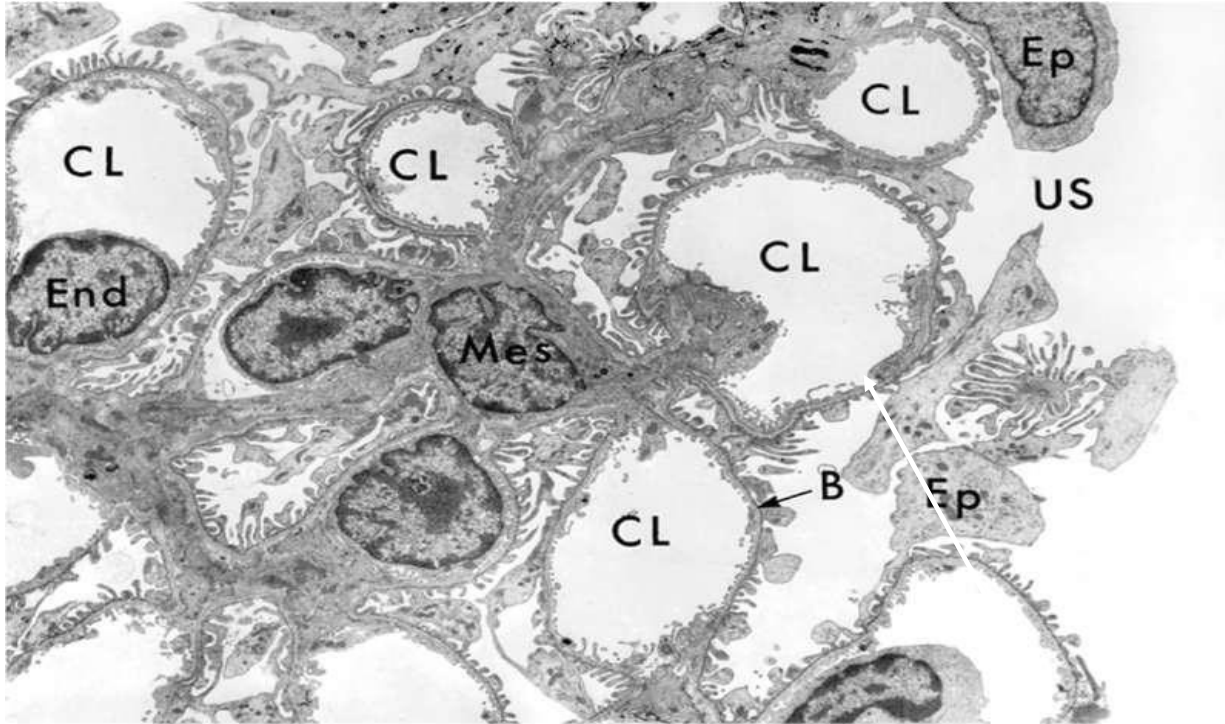
Electron Microscopy



- ✓ Scanning electron microscopy (SEM) is mainly used for research purposes.

EM- normal GLOMERULUS

CL- capillary lumen, End-endothelium, US-urinary space, B-basement membrane, Ep-epithelial cell, Mes-mesangial cell, Fp-foot process.

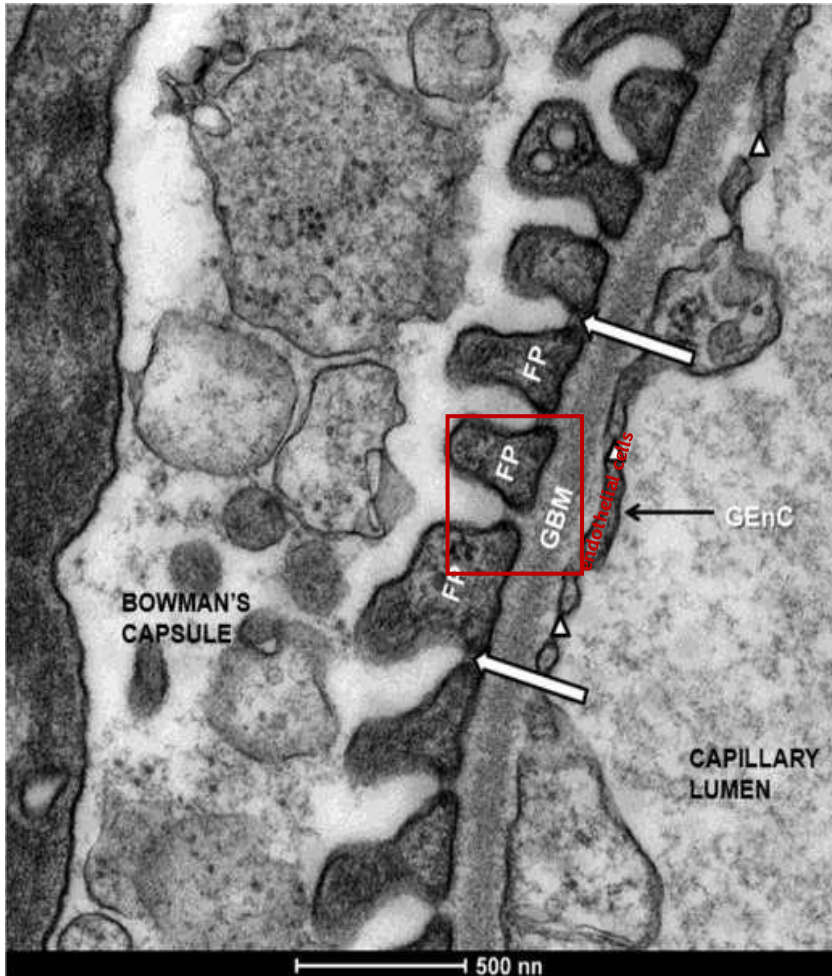


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- ✓ Transmission electron microscopy (TEM) is used for diagnostic purposes, The image appears in black, white, and gray shades.

https://en.wikipedia.org/wiki/Transmission_electron_microscopy

Normal GBM by EM



- provides a very high magnification view of a section of the glomerulus.

Electron Microscopy:

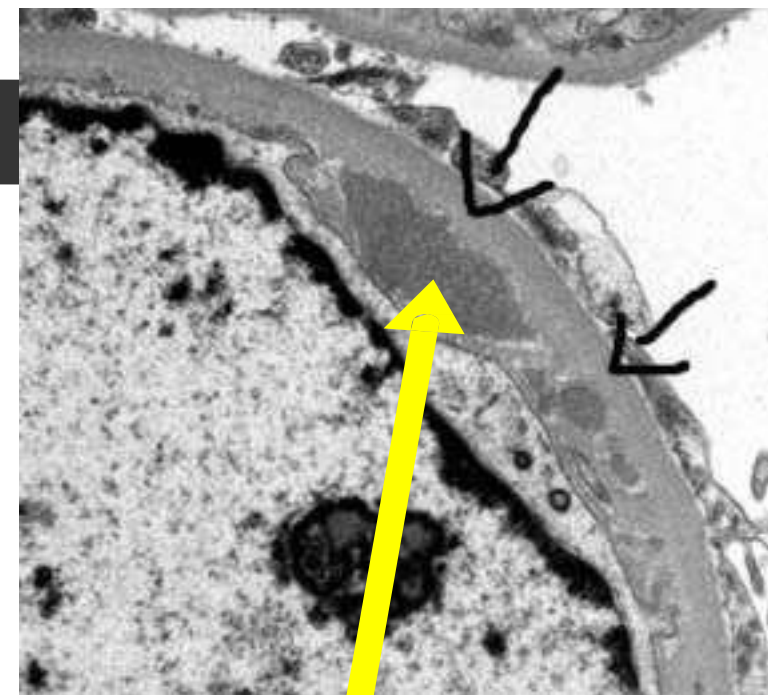
❑ reveals the immune complexes as **electron-dense deposits** or clumps that lie at one of three sites:

- 1 in the **mesangium**.
- 2 between the endothelial cells and the GBM (**subendothelial deposits**).
- 3 between the outer surface of the GBM and the podocytes (**subepithelial deposits**).

- When antibodies bind to antigens, they form immune complexes. These complexes can accumulate and become deposited in the kidney, especially in the glomerulus.
- This deposition affects both the structure and function of the kidney. The immune complexes attach to local cells and activate an inflammatory response. This leads to the release of cytokines and other inflammatory mediators, which in turn recruit white blood cells to the affected area.
- As inflammation progresses, there is increasing cellular activity and further damage, which contributes to the development and worsening of glomerular disease.

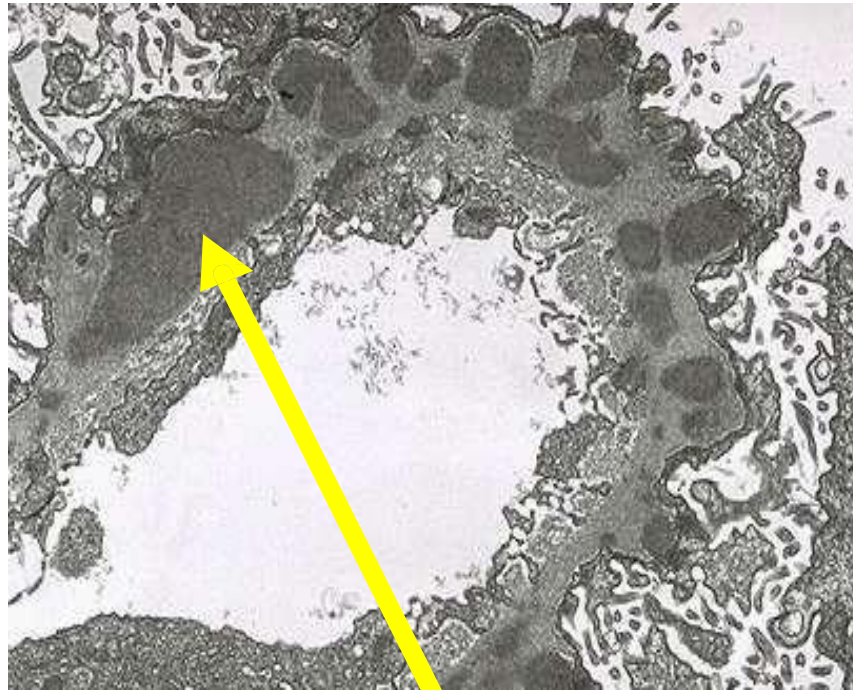
❑ The pattern of immune complex deposition is helpful in distinguishing several types of GN

Location of Immune Complex Deposition in the Glomerulus



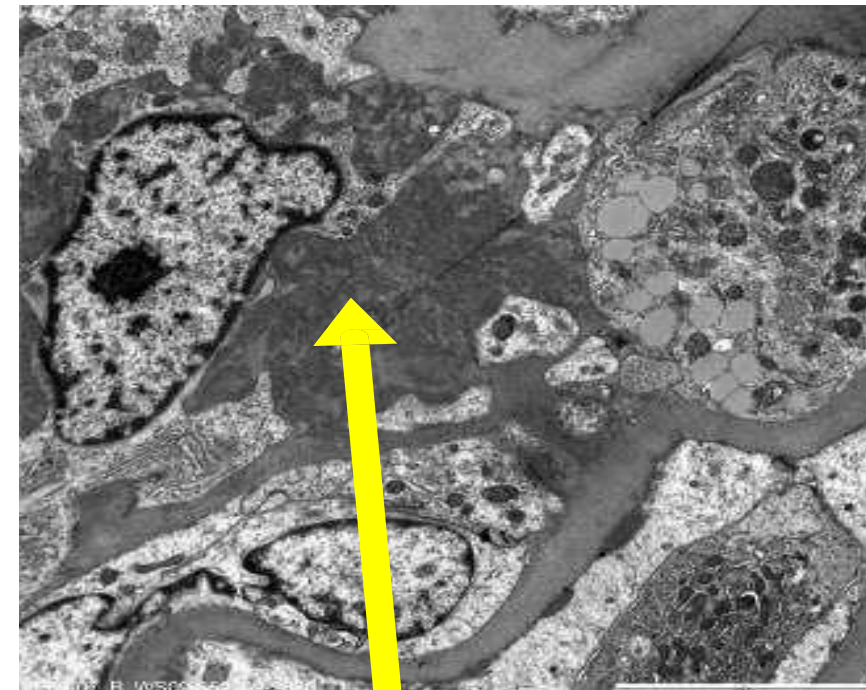
Subendothelial

- between the endothelial cells and the glomerular basement membrane.



Subepithelial

- between the podocytes (visceral epithelial cells) and the basement membrane.



Mesangial

- within the mesangial area, which is related to the mesangial cells in the glomerulus.

Pathogenesis of Glomerular Diseases

1 Immune Mechanisms of Glomerular Injury

- The immune system may react abnormally to certain factors, leading to the formation of immune complexes, such as antigen-antibody complexes, autoimmune antibody-related complexes, or complement-associated complexes.

Antibody-associated detected by immunofluorescence microscopy

Complements-associated

➤ Sources of the Abs:

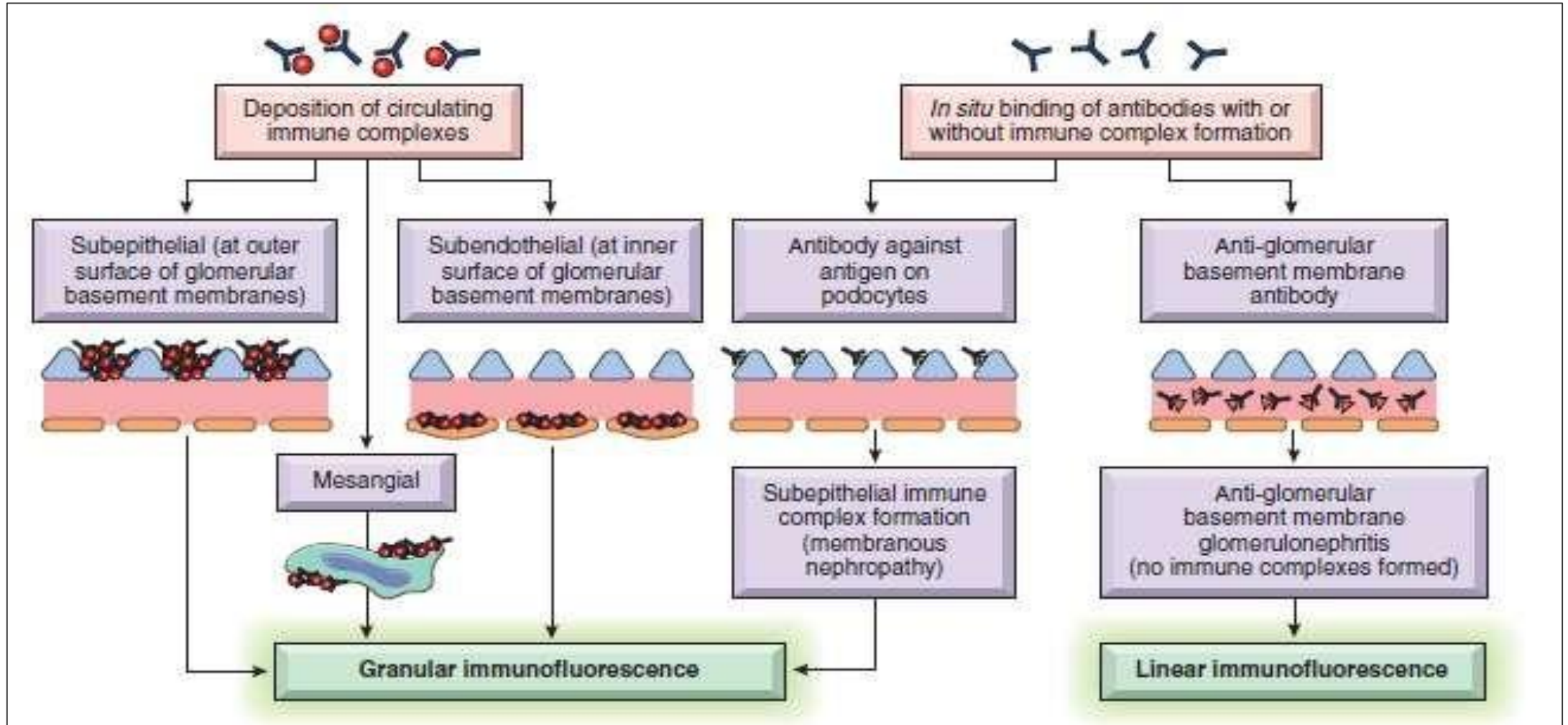
(1) deposition of soluble circulating Ag-Ab complexes in glomerulus.

(2) Abs reacting in situ within the glomerulus.

(3) Abs directed against glomerular cell components **as proteins**

- ✓ In all these cases, there may be immune complex deposition in the kidney lead to glomerular disease which may present as either nephritic syndrome or nephrotic syndrome

Antibody-mediated glomerular injury



2- Non-immune Mechanisms of Glomerular Injury

1) Podocyte Injury:

- In this type of injury, there is direct damage to podocytes and the glomerular structure even in the absence of immune complexes.

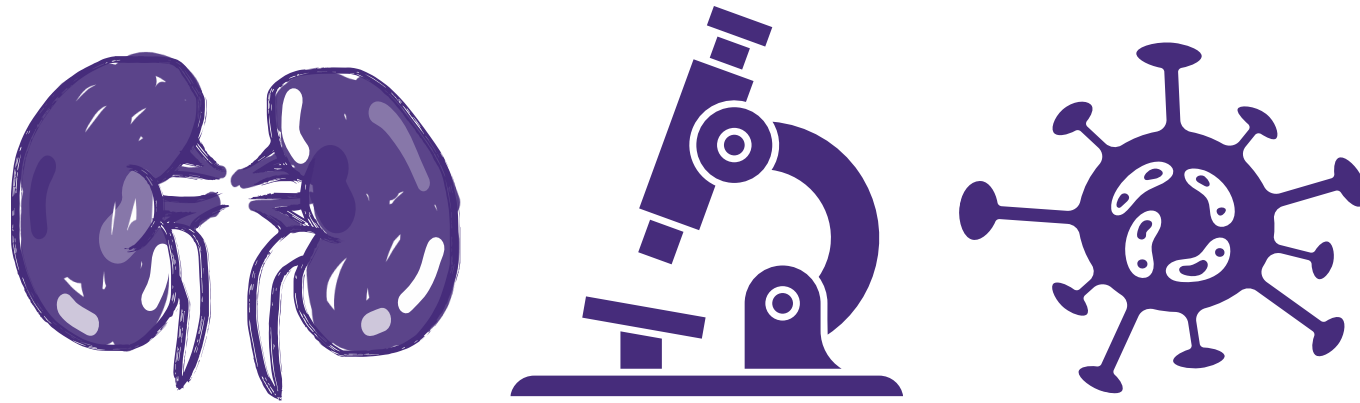
Causes:

- toxins; **poisons, certain drugs**, cytokines; or poorly characterized circulating factors; **In addition, hereditary (genetic) factors such as mutations**
- Effacement (مسح أو طمس) of foot processes affects the **glomerular filtration membrane**, leading to loss of its normal selective function so the ability of the filtration barrier to control protein passage is reduced results in the development of proteinuria (loss of normal slit diaphragms)

- The **nephron** is the structural and functional unit of the kidney, each kidney contains about 1 million nephrons, so both kidneys together have approximately 2 million. When we say nephron loss, we do not mean one nephron only; we mean a **significant number of nephrons are lost**, and this is clinically important.

2) Nephron Loss:

- Many different mechanisms that eventually leads to segmental or global (complete) sclerosis of glomeruli → further reduction of nephron mass, initiating a vicious cycle of progressive glomerulosclerosis.



**PATHOLOGY
QUIZ
LECTURE 1**

رسالة من الفريق العلمي

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقه من فتنة القبر وعذاب النار،
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اللهم إني أسألك صبراً جميلاً وفرحاً قريباً وقولاً صادقاً وأجرًا
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