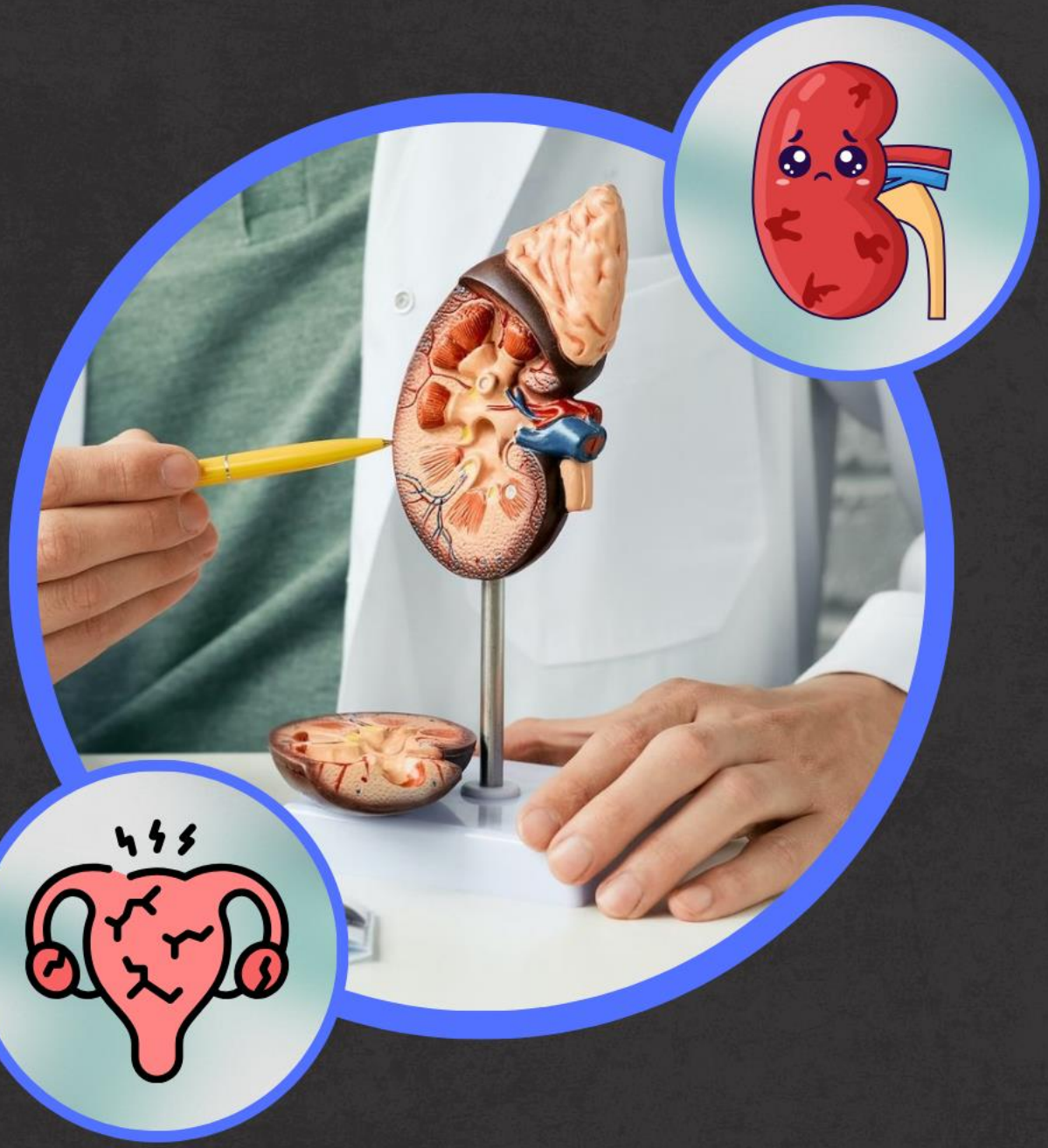

PATHO

MODIFIED NO.1

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Renal Pathology- Lecture 1

Contents:

1 Concepts of renal pathology

2 Introduction to glomerulus pathology

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Professor of Pathology

Color code

Slides
Doctor
Additional info
Important

CLINICAL MANIFESTATIONS OF RENAL DISEASES

1-Azotemia

- refers to an elevation of blood urea nitrogen(BUN) and creatinine levels
- It is largely related to a decreased glomerular filtration rate (GFR).

- Reduction in GFR means an impairment of the renal excretory function and this will be translated in the patient's blood test as elevation in the blood urea nitrogen and criatinine levels.

2-uremia (Urea in the blood)

- when azotemia progresses to clinical manifestations and systemic biochemical abnormalities.

➡ Uremia is characterized by:

1) failure of renal excretory function
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)

- All together, we call this condition: uremia

The major renal syndromes

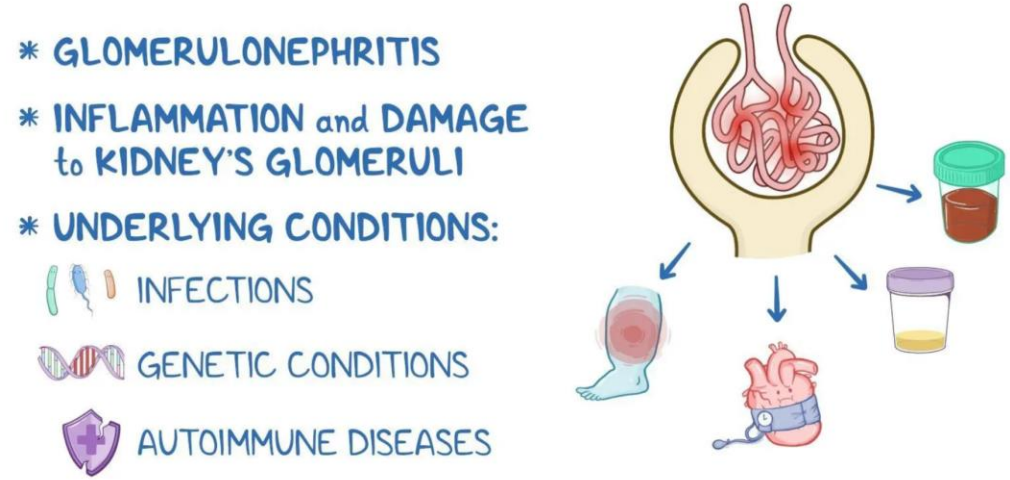
- During the upcoming 2 lectures, we will recognise two major renal syndromes that with a result from glomerular disease.

1-Nephritic syndrome:

- a glomerular syndrome characterized by:
- acute onset
- Gross (macroscopic) hematuria
- mild to moderate proteinuria
  (< 3.5 gm of protein/day in adults)
- azotemia
- edema
- hypertension

- It is usually a result of glomerular inflammation, so the problem here is inside the glomerulus.

- Extra



Nephritic Syndrome: Presentation

- **PHAROH**
- ***P**roteinuria*
  - *<3.5g/1.73m2/day*
- ***H**ematuria*
  - *Abrupt onset*
- ***A**zotemia*
  - *Increased creatinine and urea*
- ***R**BC Casts*
- ***O**liguria*
- ***H**TN*

Peripheral Edema/Puffy Eyes

- RBC in the urine

- Hypertension

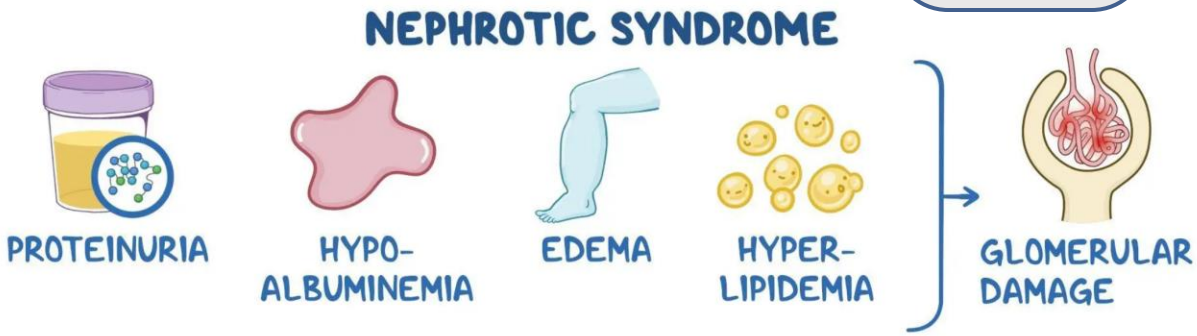
Urine”

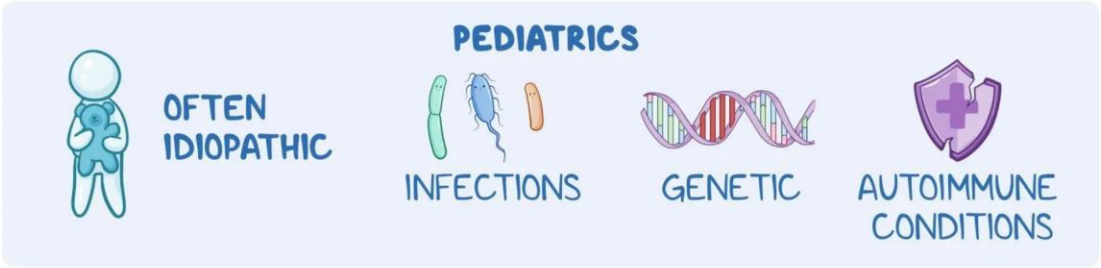
- Proteinuria: A proteins in the urine.
- Hematuria: RBC in urine.
- RBC casts: a microscopic finding that you find in the urine analysis test. Microscopic examination of the urine will show us those dysmorphic RBC that are packed together forming cast. It's a good indicator for glomerular inflammation.
- Oliguria: reduction in the urine output.

2-Nephrotic syndrome

- a glomerular syndrome characterized by:
- heavy proteinuria (excretion of >3.5 gm of protein/day in adults (it differs in children))
- hypoalbuminemia
- severe edema
- hyperlipidemia
- lipiduria (lipid in the urine).

• Extra





- The most important characteristic and the one that starts the whole cascade of findings is the massive proteinuria.
- Hypoalbuminemia: Reduction of albumin in the blood due to loss of proteins in the urine.
- Severe edema: The reduction in albumin will lead to decrease in osmotic pressure and consequently the patient will develop edema due to increased filtration of plasma to tissues.
- Hyperlipidemia: elevation of lipid in the blood, mainly triglycerides, how? 1- albumin is a major carrier for those molecules 2- the process of lipogenesis will be increased in the liver and decrease the metabolism and clearance of those lipid from circulation.
- Lipiduria: happens because we have something abnormal going on in the glomerular basement (filtration) membrane, so we have a proteins lose and with this proteins some of lipid molecules will also escape.

Nephrotic syndrome

- Puffy eyes/periorbital swelling

- General edema and pitting edema

- Extra

NEPHRITIC vs NEPHROTIC SYNDROME

	NEPHRITIC SYNDROME	NEPHROTIC SYNDROME
ONSET	Abrupt	Insidious
PATHOPHYSIOLOGY	Disruption of glomerular basement membrane due to inflammation	Damage to podocyte foot processes
GFR	Decreased	Normal or decreased
BLOOD	Azotemia	Low serum albumin Hyperlipidemia
URINE	Proteinuria < 3.5 Hematuria Pyuria RBC casts	Proteinuria > 3.5 Fatty casts or none
MANIFESTATIONS	Hypertension Oliguria Edema	Hypotension Edema Risk of thromboembolism or infection
DISEASES	Rapidly progressive glomerulonephritis Alport syndrome Poststreptococcal glomerulonephritis IgA nephropathy (Berger disease) Diffuse proliferative glomerulonephritis Membranoproliferative glomerulonephritis	Focal segmental glomerulosclerosis Membranous nephropathy Minimal change disease Amyloidosis Diabetic glomerulonephropathy

- ***3-Asymptomatic hematuria or proteinuria:***
- A manifestation of mild glomerular abnormalities.

- We discover it accidentally during urine analysis.
- The next approach we make a test to rule out your suspicion whether it is a mild or an early form of glomerular disease.

- ***4-Rapidly progressive glomerulonephritis (crescentic GN)***
- loss of renal function in a few days or weeks
- It is manifested by :
- microscopic hematuria.
- dysmorphic RBC and RBC casts in urine sediment.
- mild-moderate proteinuria

- If it lefts untreated, rapidly progressive glomerulomephritis can lead to a permanent renal failure.

5-Acute renal failure

- **oliguria (<400 ml/day) or anuria (no urine flow).**
- **recent onset of azotemia.**

  - This is a translation of acute deterioration of the renal excretory function.

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

6- *Chronic renal failure*

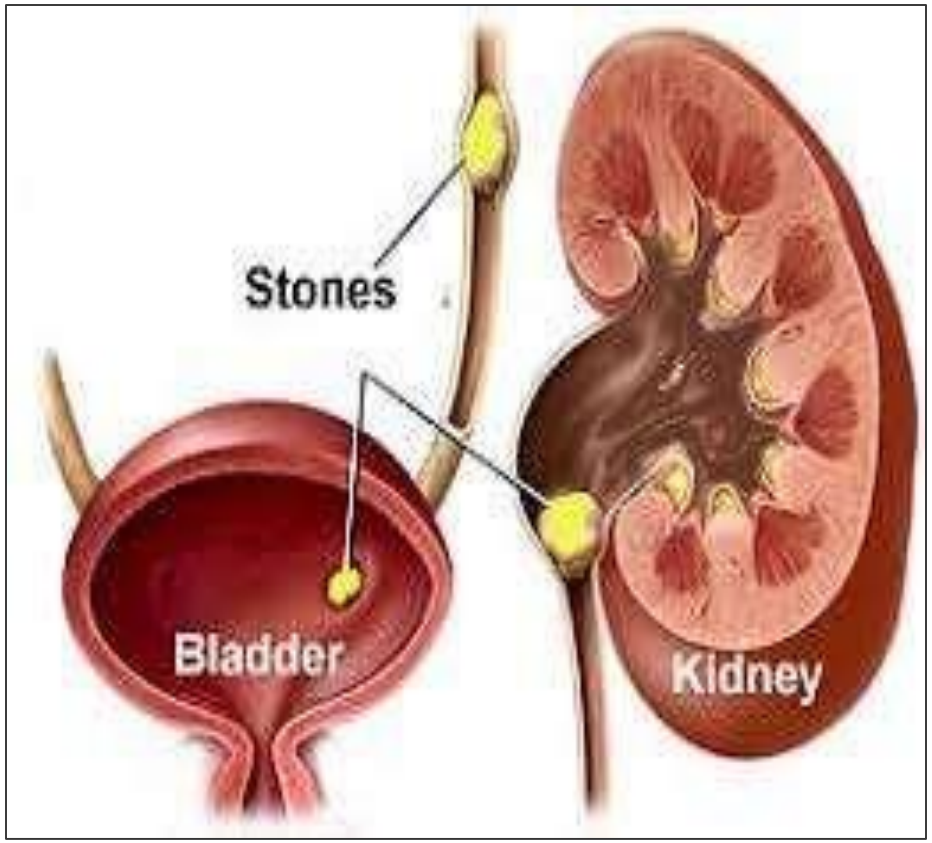
- prolonged symptoms and signs of uremia.
- the end result of all chronic renal diseases .

7- *Urinary tract infection*

- bacteriuria and pyuria (bacteria and WBCs in urine).
- symptomatic or asymptomatic.
- Types :
- 1- *pyelonephritis (*kidney).
- 2- *cystitis* (bladder).

- This topic is required in microbiology and we will not be asked about it here in pathology.

8-Nephrolithiasis



- = Renal stones
- manifested by:

1-renal colic (pain)

2-hematuria

3-possible recurrent stone formation

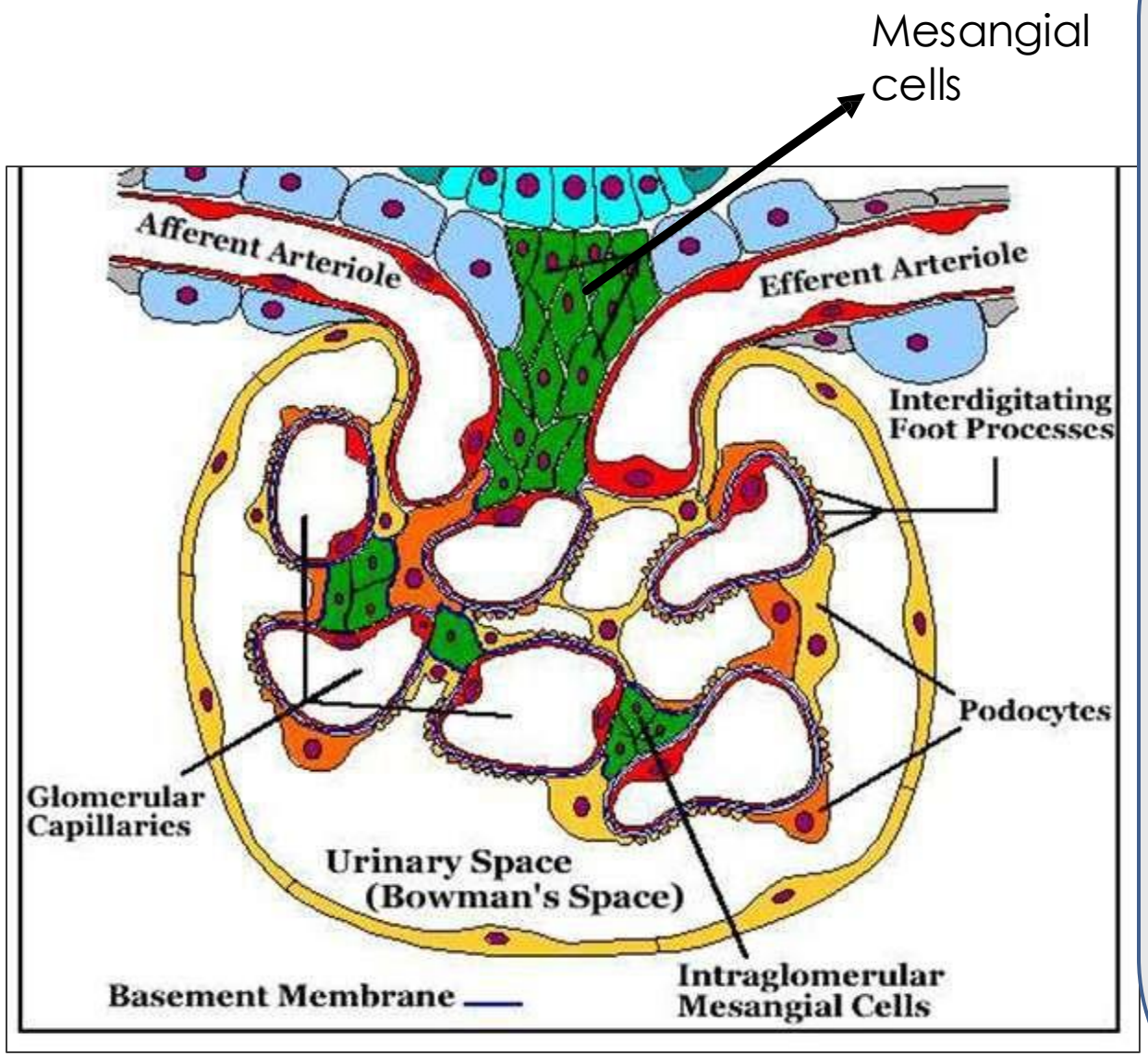
Glomerular diseases

- As we know from histology, we have a different structures in the kidney: glomerulus, renal tubules, blood vessels and interstitium and we will focus in this lecture and the next two lectures about glomerular diseases.

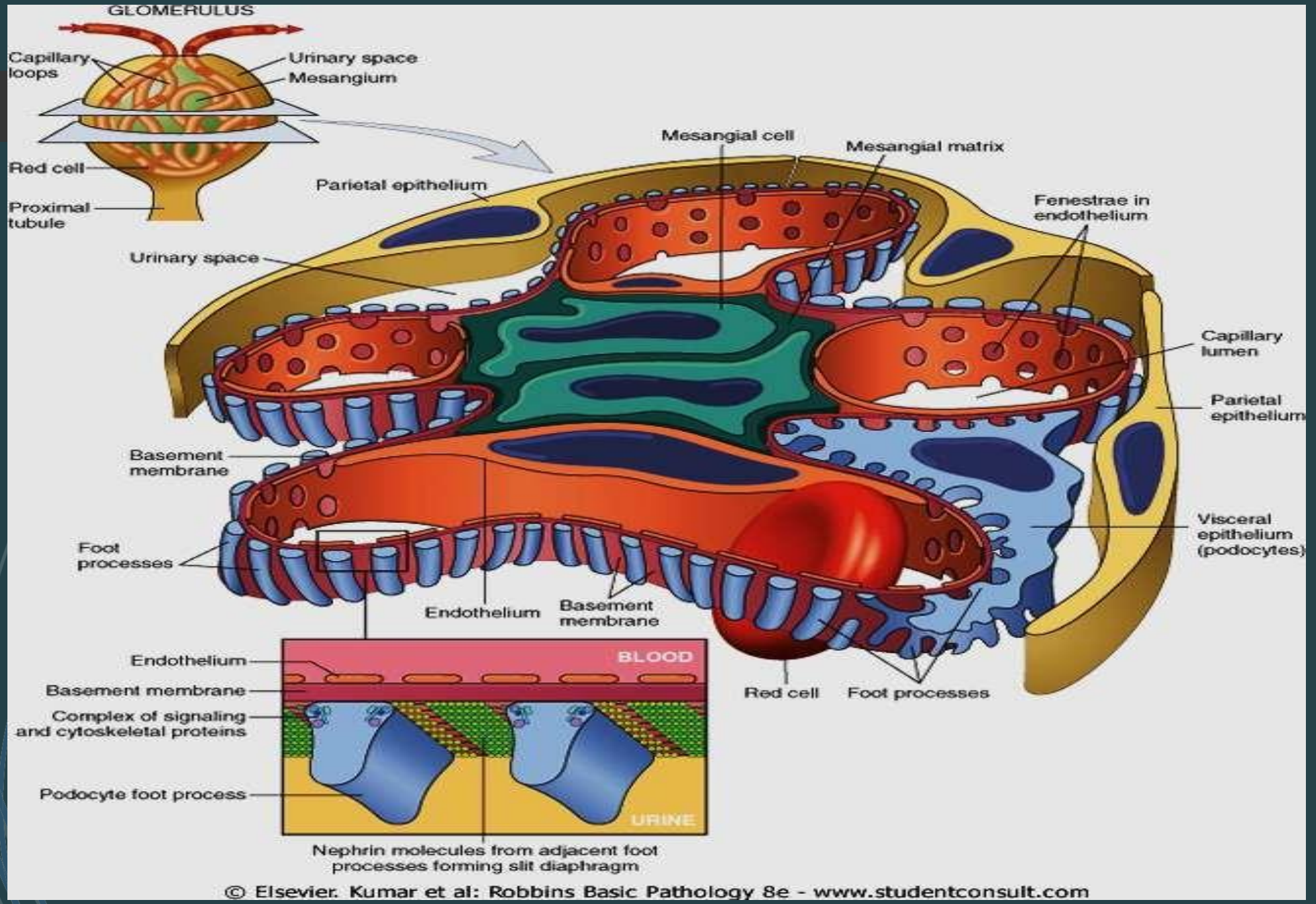
GLOMERULAR DISEASES

- 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.

Normal glomerulus



- The glomerulus (كبيبة الكلى) is a network of blood vessels that make filtration for the blood.
- It an anastomosing network of capillaries that start with an afferent arteriole and end with an efferent arteriole and those coiled capillary lobes are encased within a capsule called bowman's capsule.
- The coiled capillaries function in increasing the capillary length inside the glomerulus to make filtration more efficient with the lowest volume used.
- Like a capillary, we have fenestrated endothelial cells, and underlying the epithelial cells we have a basement membrane called glomerular basement membrane (GBM).
- Around those capillary loops, we have several types of cells. We have podocytes (orange cells) which ensheathe the capillary loops from outside and they are called podocytes because they have pedicles (foot processes) and they perform a very important function within filtration membrane unit.
- We have also mesangial cells (green cells) that give the support to the capillary and perform an immunological function.


GLOMERULUS
Capillary loops
Urinary space
Mesangium
Red cell
Proximal tubule
Mesangial cell
Mesangial matrix
Parietal epithelium
Fenestrae in endothelium
Urinary space
Capillary lumen
Parietal epithelium
Basement membrane
Visceral epithelium (podocytes)
Foot processes
Endothelium
Basement membrane
Red cell
Foot processes
Endothelium
Basement membrane
Complex of signaling and cytoskeletal proteins
Podocyte foot process
BLOOD
URINE
Nephrin molecules from adjacent foot processes forming slit diaphragm
© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com

- Here we have more details of the glomerular structures, we can see the foot processes of the podocytes. If we take a section under high magnification of the structure of the capillary wall, we can identify the endothelial cells with their pores, the GBM and the foot processes of the podocytes. Between those foot processes of the podocytes, we have a slit (a gap) and this slit is covered by a network of proteins that connects the podocytes processes together and they perform a very important function in filtration. These are called a slit diaphragm.
- The glomerular filtration membrane with an intact form will guarantee having normal physiological control over filtration.
- Some molecules in the blood are important, so we don't need to excrete them such as large molecules (proteins, cells, RBC, WBC and platelets), but we send some molecules to the glomerulus to be excreted outside the body like urea, excess solutes, drug metabolites and toxic substances.
- A problem in any component of the glomerular membrane will lead to a problem in the filtration.

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

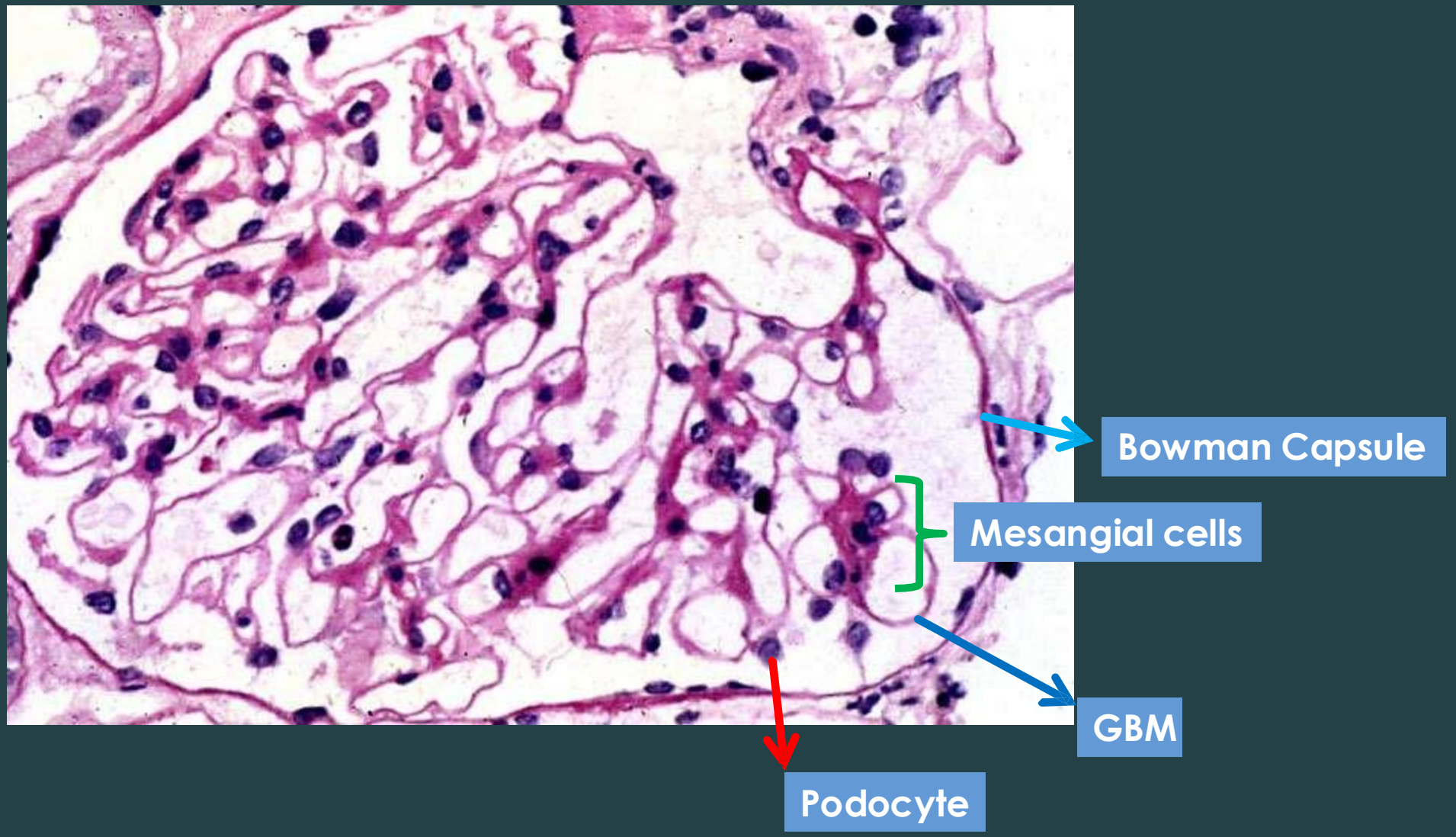
1 **Light microscopy (LM)**

2 **Immunofluorescence microscopy (IF)**

3 **Electron microscopy (EM) (usually Transmission electron microscope)**

- The nephrologist will take the history from the patient, ask about symptoms, see the signs, make blood test and urine analysis as well as looking for underlying renal problems.
- Some patients need further evaluation to reach a specific diagnosis and initiate treatment, so those patients will have a somewhat invasive procedure (a biopsy) which is a needle insertion into the kidney and taking a small piece of renal tissue (maybe 1cm or less than half).
- We take this biopsy to make a histopathological evaluation of the renal disease and once the biopsy is done, it is sent to the lab and some tests are performed, like light microscopic test, immunoflurecense microscope, and electron microscope (rarely used)

Normal glomerulus- light microscopy



- 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

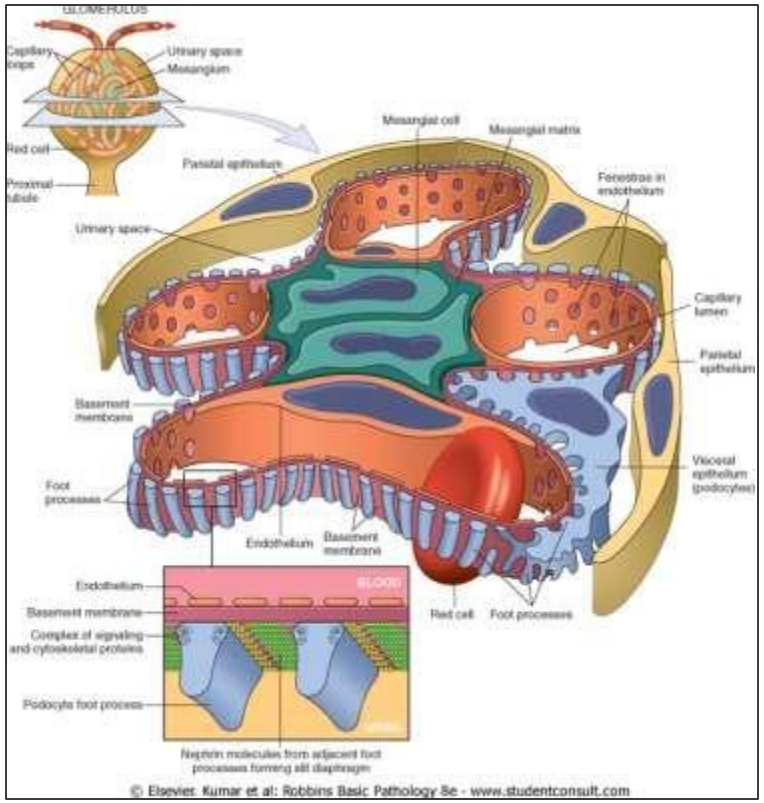
4 Supportive cells (*mesangial cells*) lying between the capillaries

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

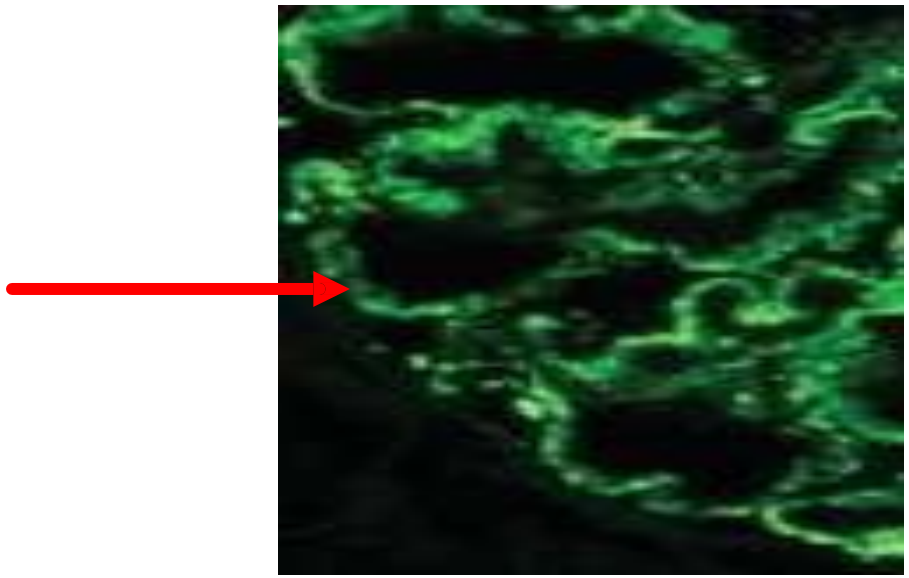
2 the more cationic the more permeable.

➨ Nephrin and its associated proteins, including podocin, have a crucial role in maintaining the selective permeability of the glomerular filtration barrier.

Immunofluorescence microscopy

- 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**

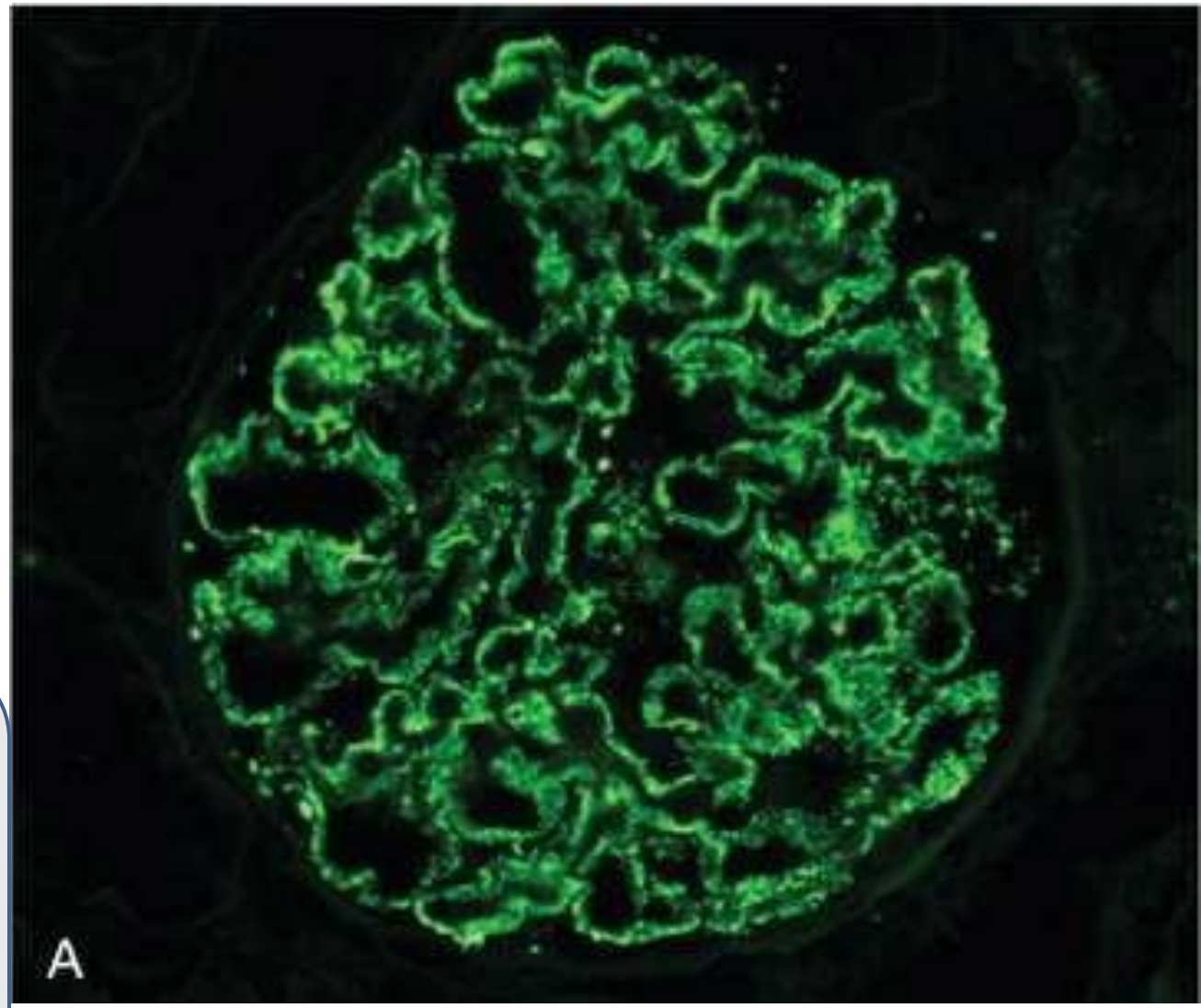


- If we perform the test for a specific antibody and the visual field stays black, this means that the test is negative, but if the test shows like this picture it is positive for the antibody used.

https://en.wikipedia.org/wiki/Immunofluorescence#/media/File:Immunofluorescence.jpg

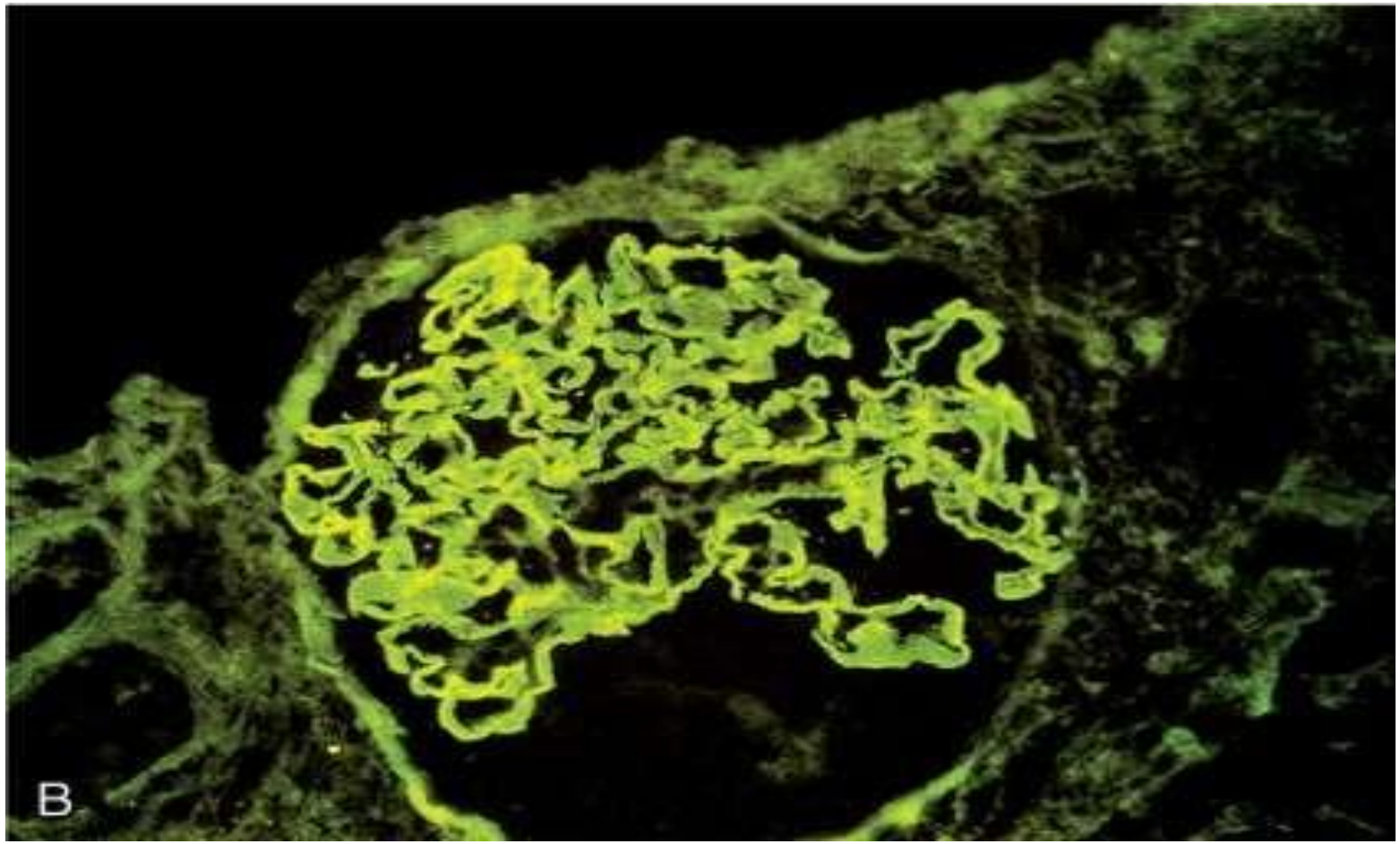
Immunofluorescence microscopy

granular pattern of deposition

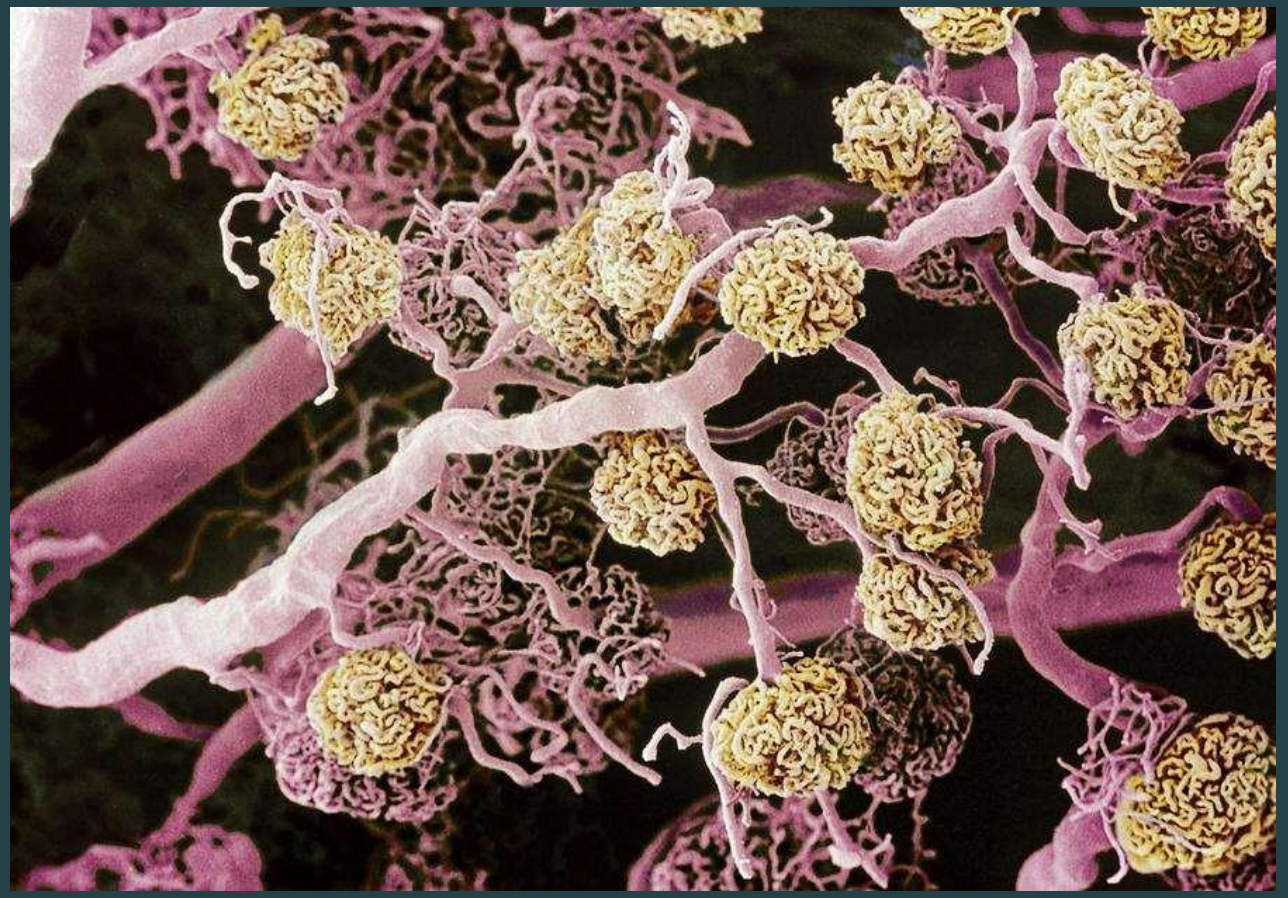


- Here we have a deposition for a fluorescence labelel antibody over the capillary wall and it was IgG.
- We should know from this picture:
  1. If the test is positive,
  2. determine which substance is positive
  3. The location and pattern of staining

immunofluorescence linear deposition of immune complexes over capillary walls

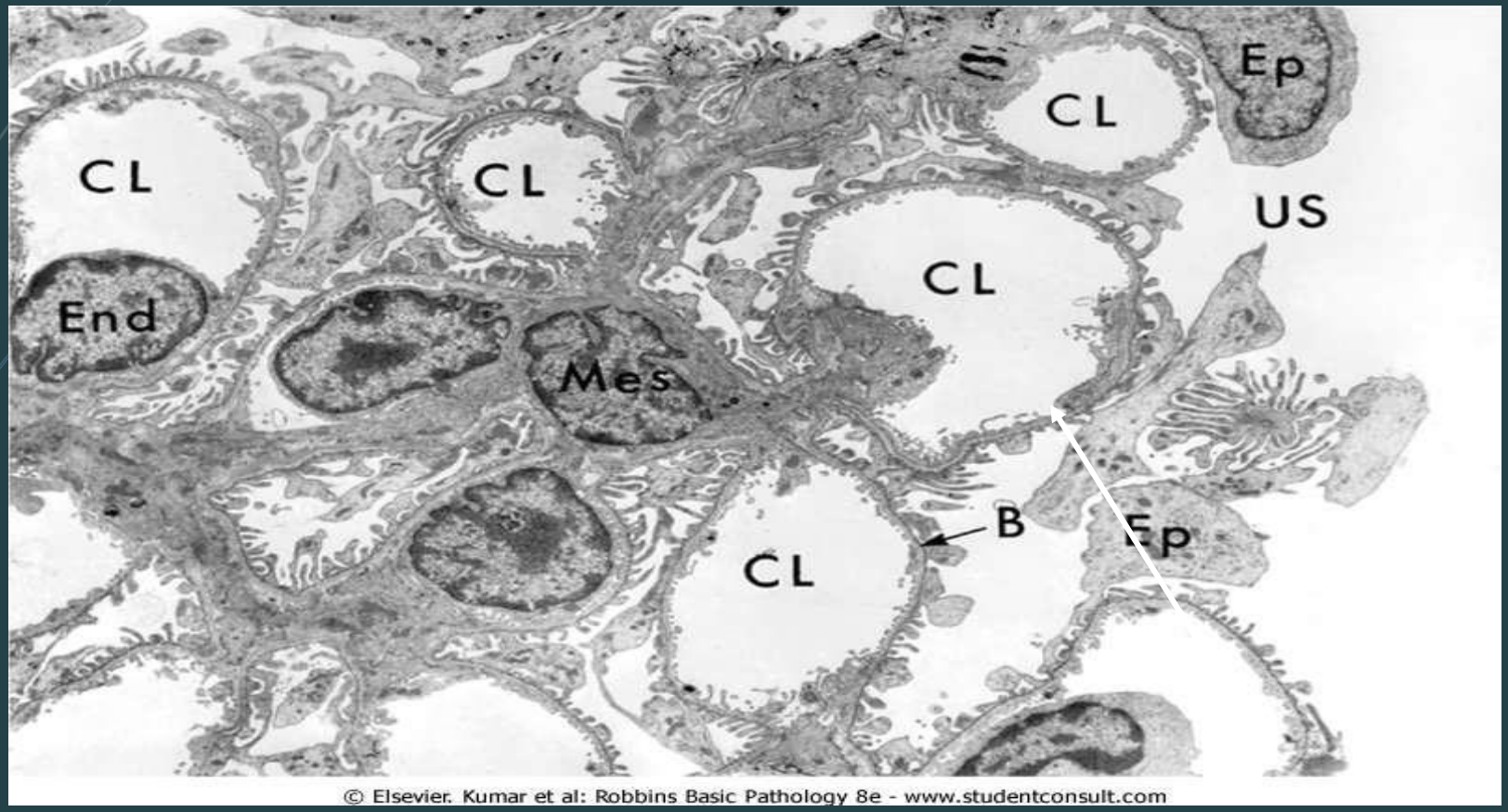


Electron Microscopy



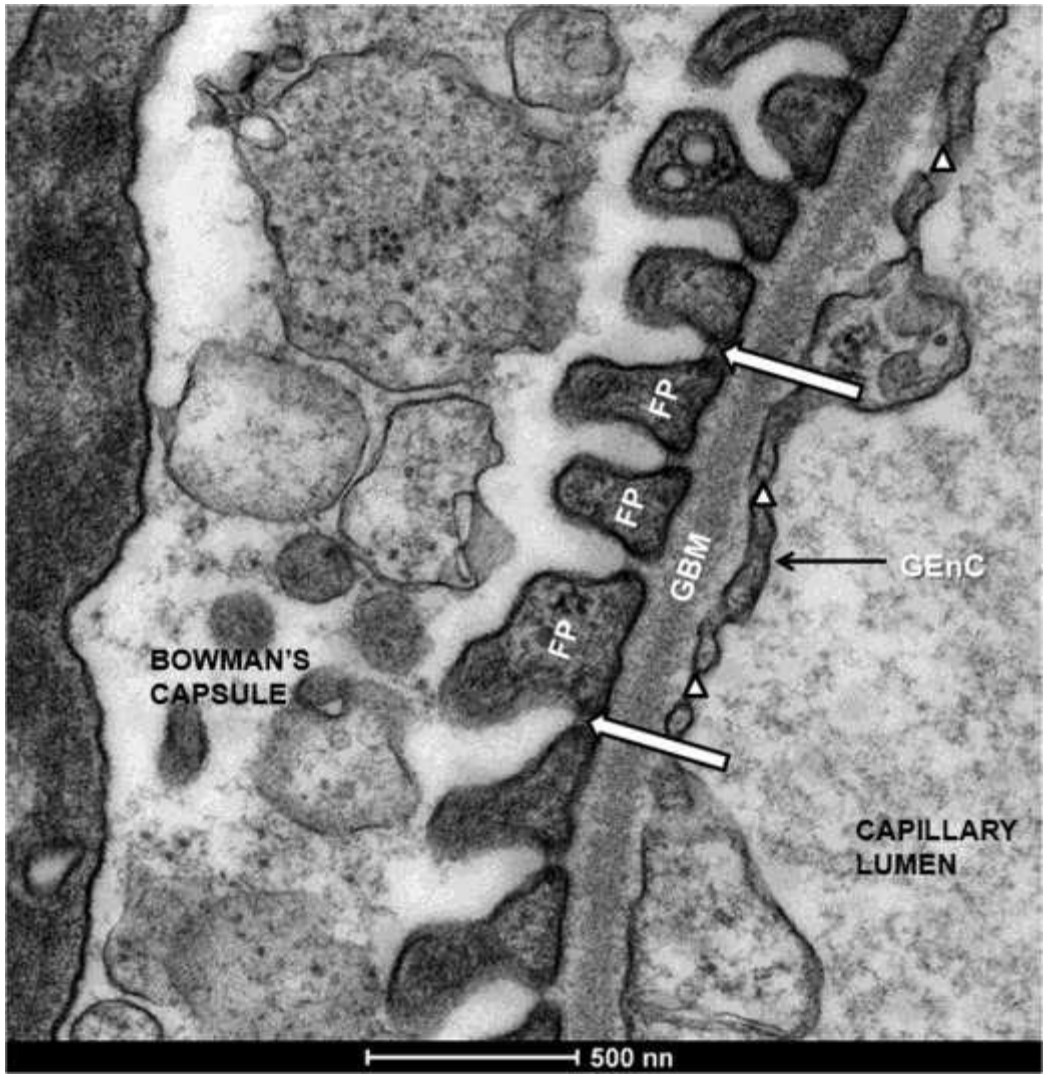
EM- normal GLOMERULUS

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



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

Normal GBM by EM

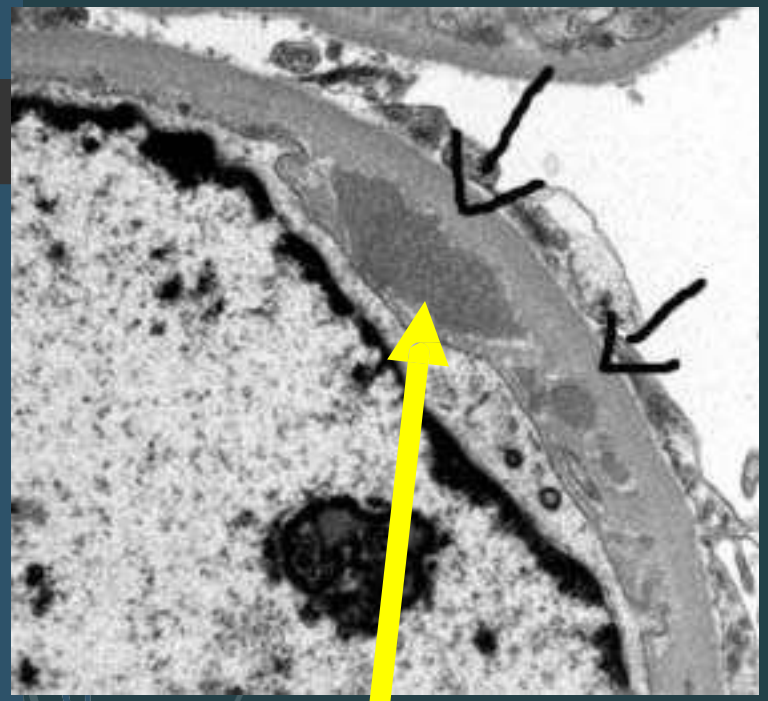


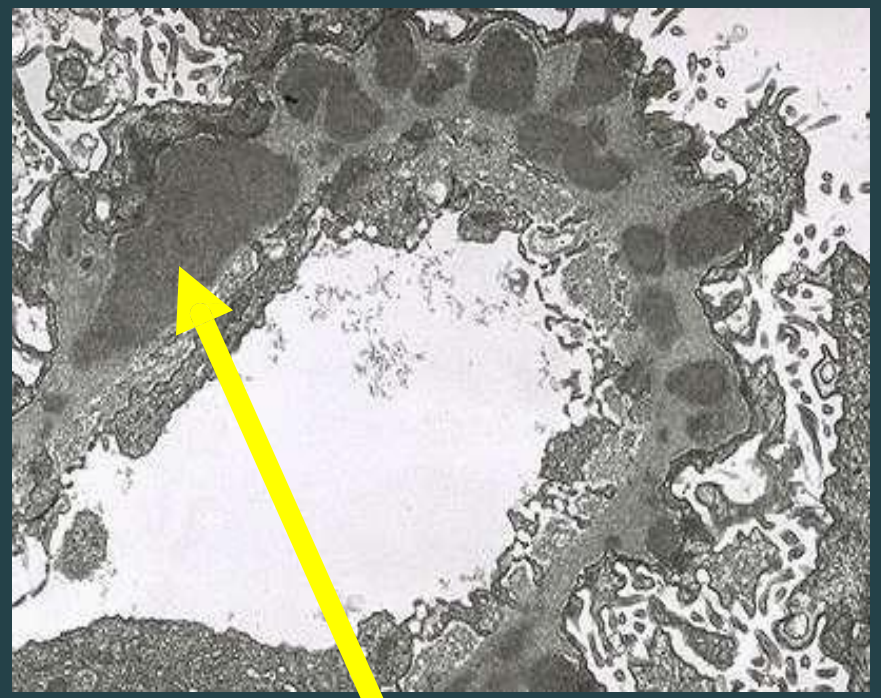
- In electron microscope, the background is white and the colors are mainly gray and black.
- Electron microscope shows more clear images for very small structures because it uses a high magnification ,so we can see structure like foot processes of the podocytes, the thickness of the glomerular basement membrane, endothelial cells and the cells inside bowman's capsule.

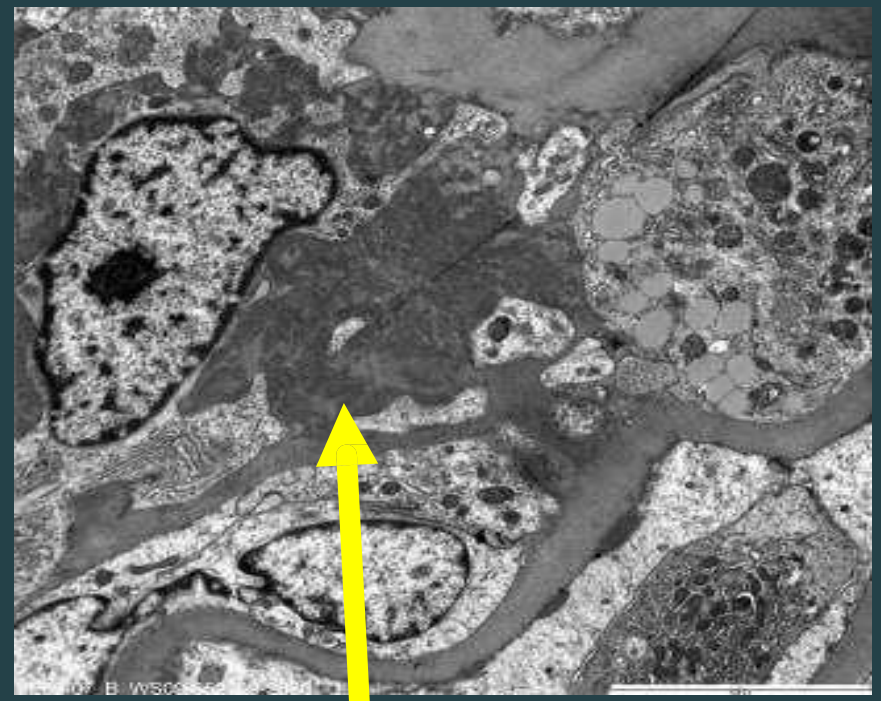
- Electron Microscopy:
- reveals the immune complexes as **electron-dense deposits** or clumps that lie at one of three sites:

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**).

- The pattern of immune complex deposition is helpful in distinguishing various types of GN







Subendothelial

- The dark color is an aggregate of immune complexes deposited in subendothelial zone
- Subendothelial means between endothelial cells and GBM.

Subepithelial

- Subepithelial means between glomerular basement membrane and podocytes.

Mesangial

Pathogenesis of Glomerular Diseases

1 Immune Mechanisms of Glomerular Injury

Antibody-associated → detected by immunoflourescence microscopy

Complements-associated

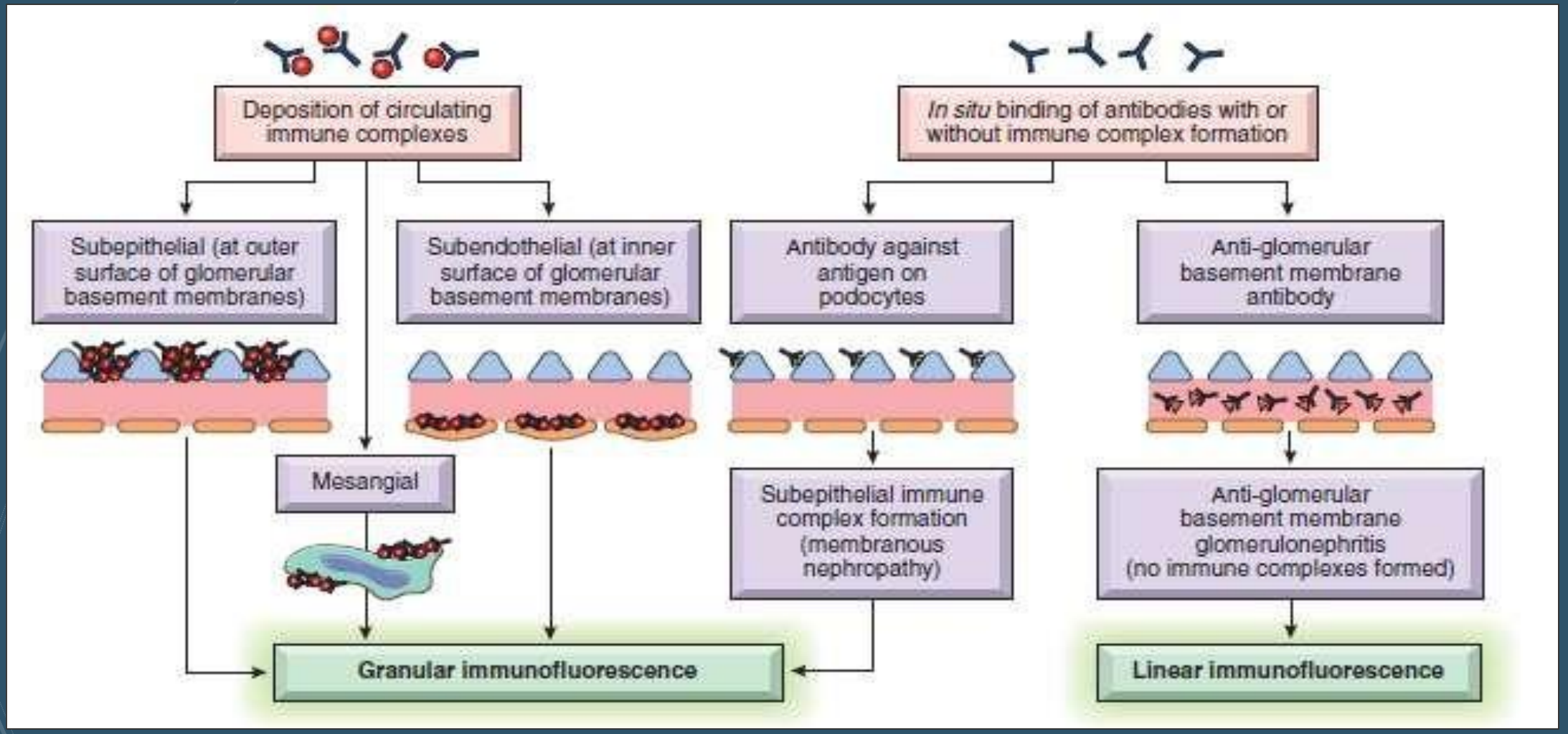
Sources of the Abs (antibodies):

(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.

Antibody- mediated glomerular injury



Pathogenesis of Glomerular Diseases

- 2- Non-immune Mechanisms of Glomerular Injury
- 1) Podocyte Injury:
  - ➡ Causes: toxins; cytokines; or poorly characterized circulating factors; mutations (inherited)
  - ➡ effacement (طمس/محي) of foot processes, results in the development of proteinuria (loss of normal slit diaphragms)

Pathogenesis of Glomerular Diseases

- 2- Non-immune Mechanisms of Glomerular Injury
- 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.

  - A nephron is the functional unit of the kidney that is composed of glomerulus and the connected tubules. We have about 2 million nephrons (one million in each kidney). We need to lose 30% of our nephrons to have this mechanism of progressive glomerulosclerosis ending with progressive renal impairment.

كانت عائشة تحسب ان أصعب يوم مر على النبي صلى الله عليه وسلم هو يوم أحد، فقد قتلوا عمه وشجوا رأسه، واسالوا دمه الشريف، وكسروا مقدمة أسنانه!
فقالت له تساله: هل أتى عليك يوم أشد من يوم أحد؟ فحدثها عن يوم رجمه في الطائف، ثم قال: فانطلقت وانا مهموم على وجهي ولم أستفق الا وانا في قرن الثعالب! كان من الحزن يمشي ولا يدري أين تأخذه قدماه!
تفهموا أن الحياة تضيق أحيانا بالناس، وأننا نضعف لا من قلة الإيمان ولكن من قسوة الأيام، قد ينزل الغم بكثير الضحك فيجعله عابسًا، وقد تقيدنا الهموم في غرفة، الهموم أغلال وان كانت لا تُرى!
فقدروا ظروف الناس، ولا تكونوا والدنيا عليهم، تمر بالإنسان لحظات لا يطيق فيها أن يسمع أو يقول كلمة!

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

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!