Pathology lecture .1

Topics : some concepts of renal diseases and introduction to glomerulonephritis.

Anything added is written in italic

The doctor discusses the topics totally in a different way in each section so I will just stick with section 3 recording after this lecture

CLINICAL MANIFESTATIONS OF RENAL DISEASES

(robbins) : The clinical manifestations of renal disease can be grouped into reasonably well-defined syndromes. Some are peculiar to glomerular diseases and others are shared by several renal disorders. Before we list the syndromes, a few terms must be defined :

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

Known by doing blood tests, so these are just blood tests reading

- **II-uremia**
- **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**

So besides having increased BUN and creatinine, the patient might have clinical symptoms (1-5)

- **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).**

The major renal syndromes

So as said, the clinical manifestation of renal diseases (i.e. the presentation of renal diseases) can be grouped into either acute nephritic or nephrotic syndromes :

So knowing each renal disease presents as which one of these syndromes help us in diagnosing and management.

- **1-Acute nephritic syndrome:**
- **it is a glomerular syndrome characterized by:**
- **1- acute onset .**
- **2- gross hematuria.**
- **3- mild to moderate proteinuria (< 3.5 gm of protein/day in adults)**
- **4- azotemia.**
- **5- edema.**
- **6- hypertension.**

Nephritic syndrome is related to inflammation, so here we have inflammation inside the glomerulus with WBCs infiltration and proliferation

This is the one of the most important characteristics that help us to distinguish between nephritic and nephrotic syndromes

2-NephrOtic syndrome

In nephrOtic syndrome we have heavy prOteinuria

- **it is a glomerular syndrome characterized by:**

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

- **2- hypoalbuminemia** → *Related to the heavy proteinuria, but why albumin in particular ? Because it's the major plasma protein*
- **3- severe edema** → *Related to decreased plasma proteins and consequently decreased colloid oncotic pressure*
- **4- hyperlipidemia** → *Related to decreased albumin in the blood because albumin is one of the major carrier proteins of the insoluble lipids*
- **5- lipiduria (lipid in the urine).**

Microscopic hematuria means that blood cant be seen using bare eyes

3-Asymptomatic hematuria or proteinuria

- *So accidently, we might find that the patient has mild/microscopic hematuria or mild proteinuria, and these are* **usually a manifestation of mild glomerular abnormalities.**

4-Rapidly progressive glomerulonephritis

- **It results in acute loss of renal function in a short period of time (few days or weeks)**
- **It is manifested by :**
- **1-microscopic hematuria.**
- **2-dysmorphic red blood cells and red blood cell casts in the urine sediment.**
- **3-mild-moderate proteinuria**

5-Acute renal failure

This case is an emergency and needs rapid management,

Oligouria :is when the urine execration is less than 400ml in 24hours
Anuria : there is no urine execration

- **is dominated by oliguria or anuria (no urine flow).**
- **recent onset of azotemia.**
- **It can result from *anything that affects the 4 functional compartments of the kidney* :**
- **1-glomerular injury (such as crescentic glomerulonephritis).**
- **2-interstitial injury.**
- **3-vascular injury (such as thrombotic microangiopathy).**
- **4-acute tubular necrosis.**

So failure in any of the 4 functional compartments might lead to acute renal failure

• 6- Chronic renal failure

- **It is characterized by prolonged symptoms and signs of uremia *(for months to years)*.**
- **It is the end result of all chronic renal diseases .**

• 7- Urinary tract infection

- **It is characterized by bacteriuria and pyuria (bacteria and leukocytes *(pus)* in the urine).**
- **The infection may be symptomatic or asymptomatic.**
- **Types *(depending on the site of infection)*:**
- **1- pyelonephritis (kidney).**
- **2- cystitis (bladder).**

There is a certain number of bacterial colonies that if reached we can call bacteria in the urine bacteriuria

Pyelonephritis is abbreviated from the renal pelvis which is the proximal part of the ureter

8-Nephrolithiasis

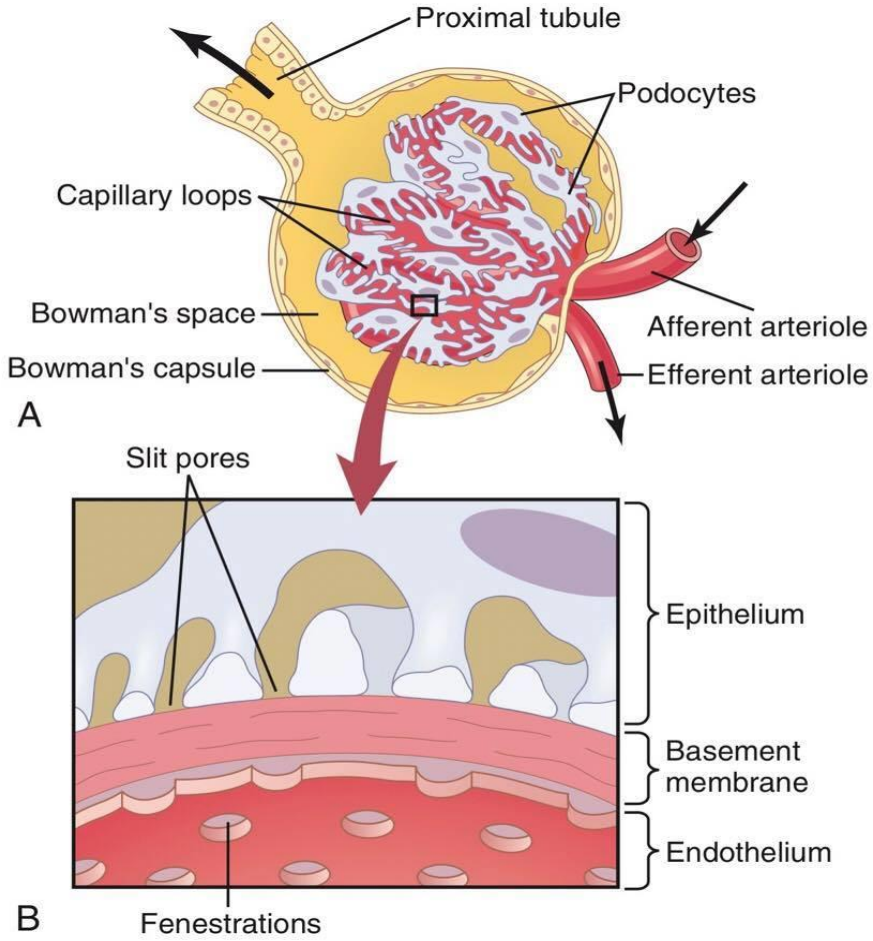
- **Means Renal stones.**
- **It is manifested by:**
- **1-renal colic.**
- **2-hematuria.**
- **3-recurrent stone formation.**

Glomerular diseases-1

- **concepts**

GLOMERULAR DISEASES

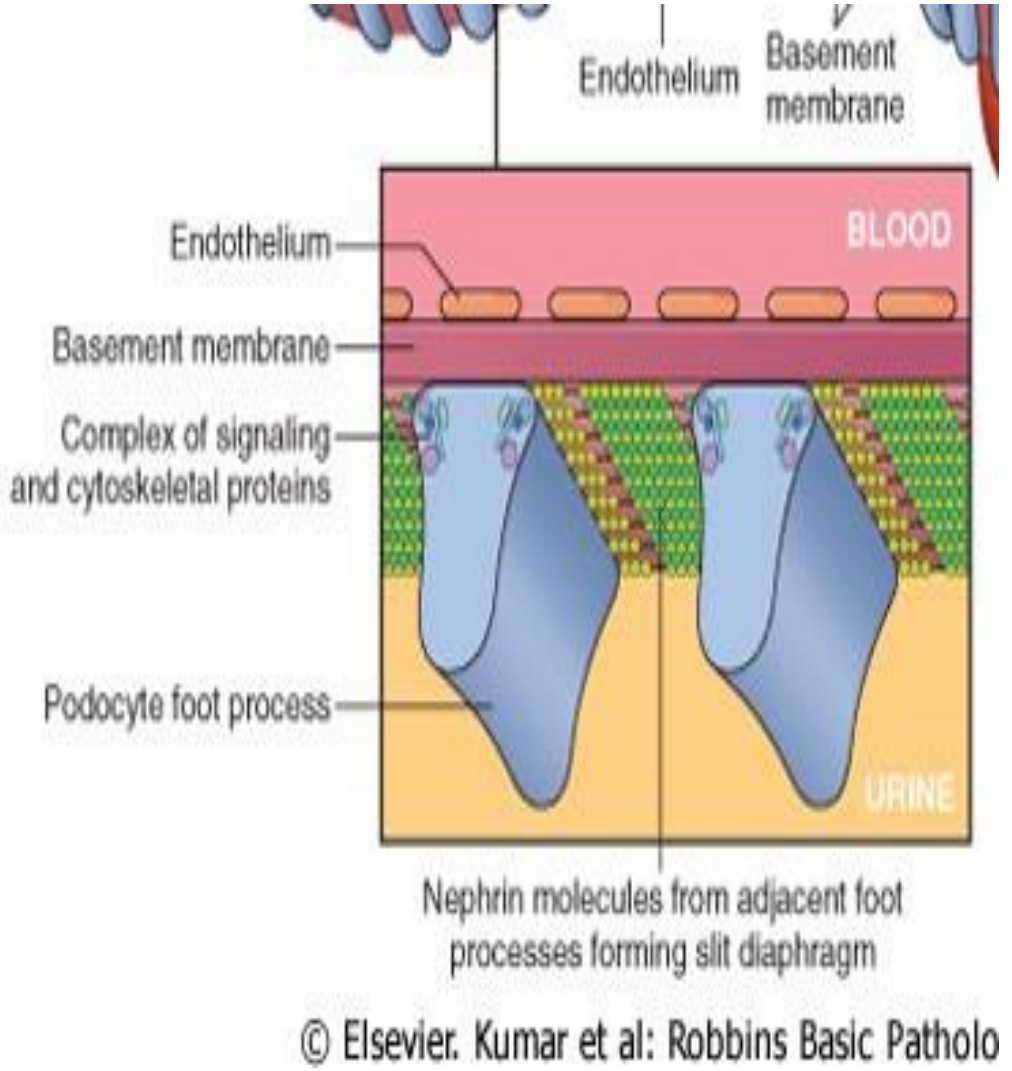
- one of the most common causes of chronic kidney disease in humans.
- **the glomerulus** =anastomosing network of capillaries invested by two layers of epithelium: podocytes and parietal epithelium
- Bowman space (urinary space)= the cavity in which plasma ultrafiltrate first collects.
- **The glomerular capillary wall is the filtration unit *(filtration membrane)* and consists of *(The cells that contribute to the filtration process – slide 13 illustrates this-)* :**
- **1-A thin layer of fenestrated endothelial cells**
- **2- glomerular basement membrane (GBM)**
- **3- foot processes of podocytes ,** *the foot processes are separated by a space called slit diaphragm .*
- **4-Supportive cells (mesangial cells) lying between the capillaries**

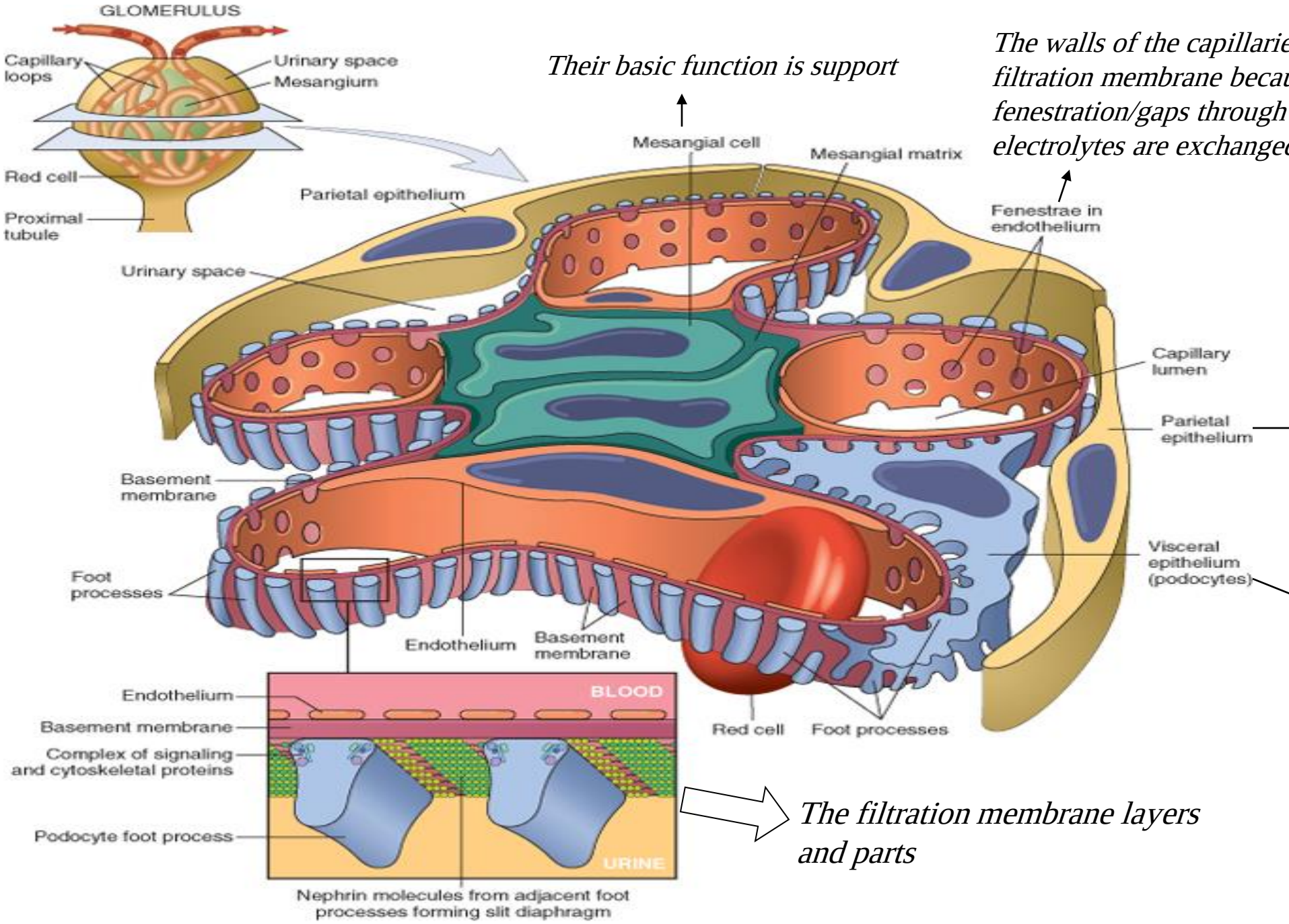


The glomerulus function is to filtrate the plasma in order to get rid of urea, other byproducts, extra water (and electrolytes) and toxins, and its impermeable to plasma proteins and cells

The capillary basement membrane

- **consists of <u>collagen (type IV)</u>, 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 and covered by a large part of <u>nephrin</u>.**





Their basic function is support

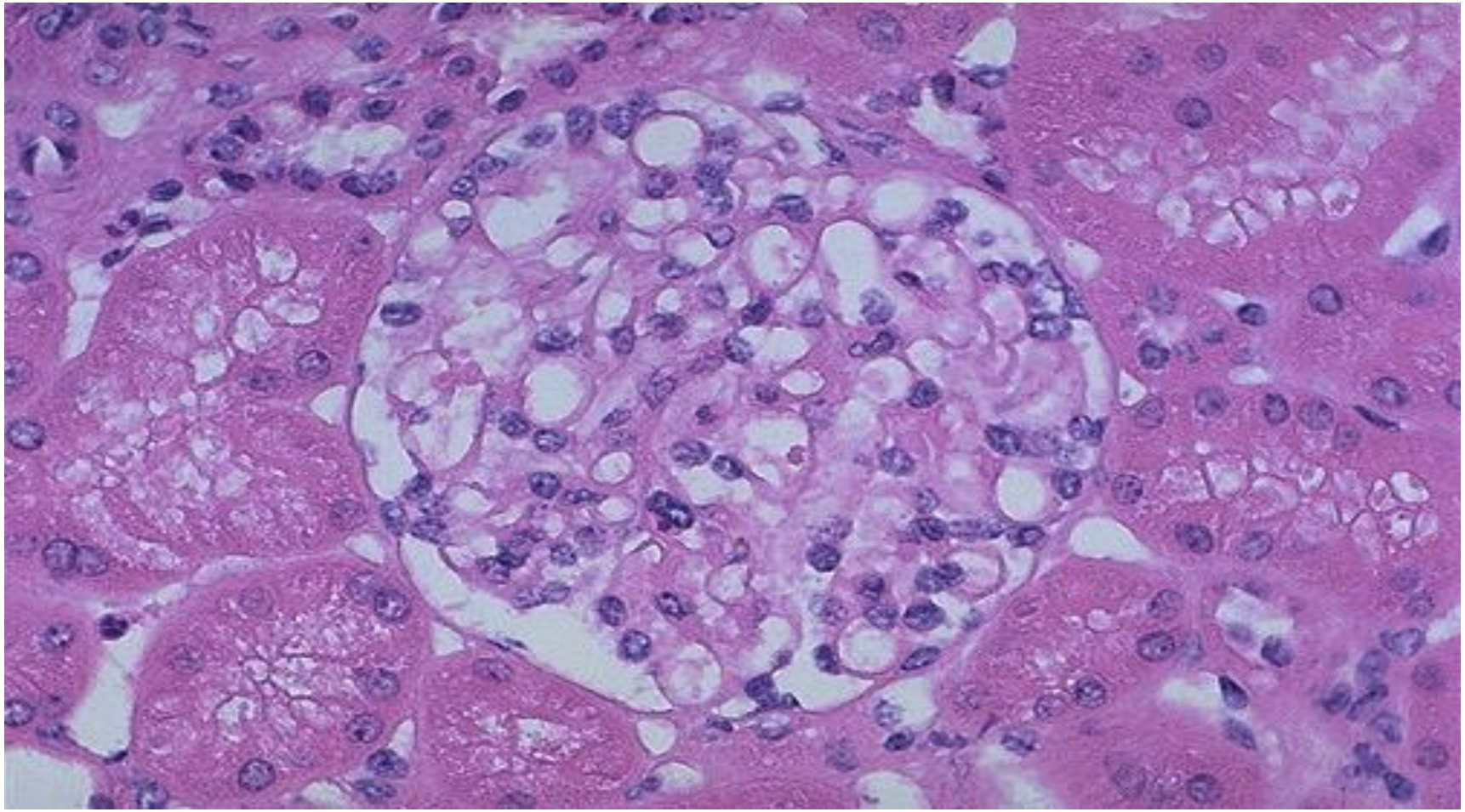
The walls of the capillaries are a part of the filtration membrane because they have fenestration/gaps through which water and electrolytes are exchanged

These are the ones that form bowman's capsule

Named Podocytes because they have finger-like projections, they form a part/layer of the filtration membrane

The filtration membrane layers and parts

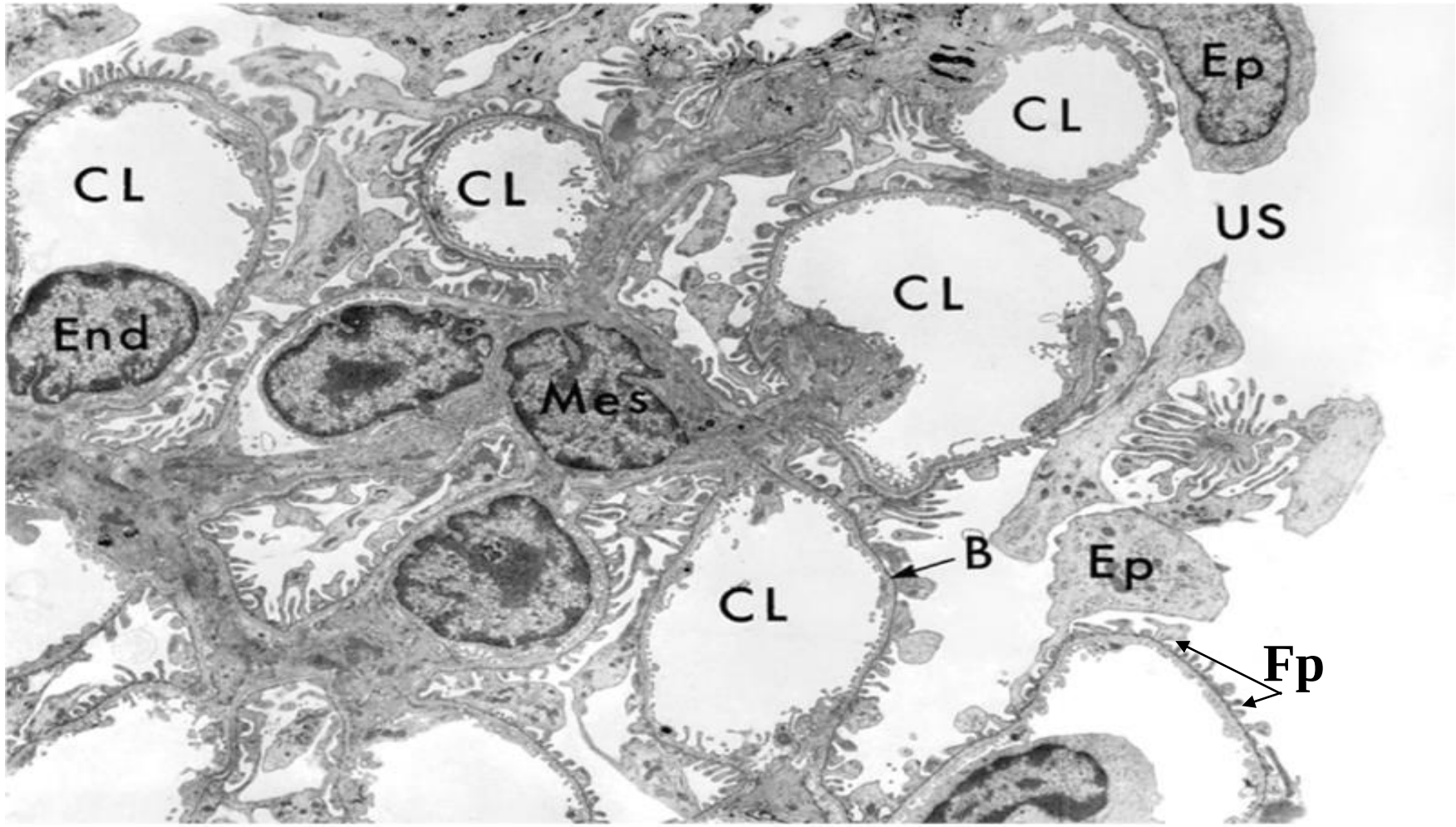
Normal glomerulus by Light Microscope (LM).
The glomerular capillary loops are thin and delicate.
Endothelial and mesangial cells are normal in number. The surrounding tubules are normal.



Electron Microscope (EM)-GLOMERULUS

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

We distinguish between EM and LM by the color
EM→ black and white



Low-power electron micrograph of rat glomerulus. B, basement membrane; CL, capillary lumen; End, endothelium; Ep, visceral epithelial cells (podocytes) with foot processes; Mes, mesangium; US, urinary space.

The major characteristics of glomerular filtration

- **1- an extraordinarily high permeability to water and small solutes**
- **2- an almost complete impermeability to molecules of the size and molecular charge of albumin (size: 3.6 nm radius; 70,000 kD).**
- **The selective permeability discriminates among protein molecules depending on:**
- **1- their size (the larger the less permeable),**
- **2- their charge (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.**

Pathogenesis of Glomerular Diseases

The injury caused by AB complexes is due to inflammation

- **Antibody-associated**

Types of Antibody-associated injury :

- **(1) injury resulting from deposition of soluble circulating Ag-Ab complexes in the glomerulus.**
- **(2) injury by Abs reacting in situ within the glomerulus *(The immune complexes are formed in the glomeruli)* .**
- **)3) Abs directed against glomerular cell components.**

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

1-in the mesangium.

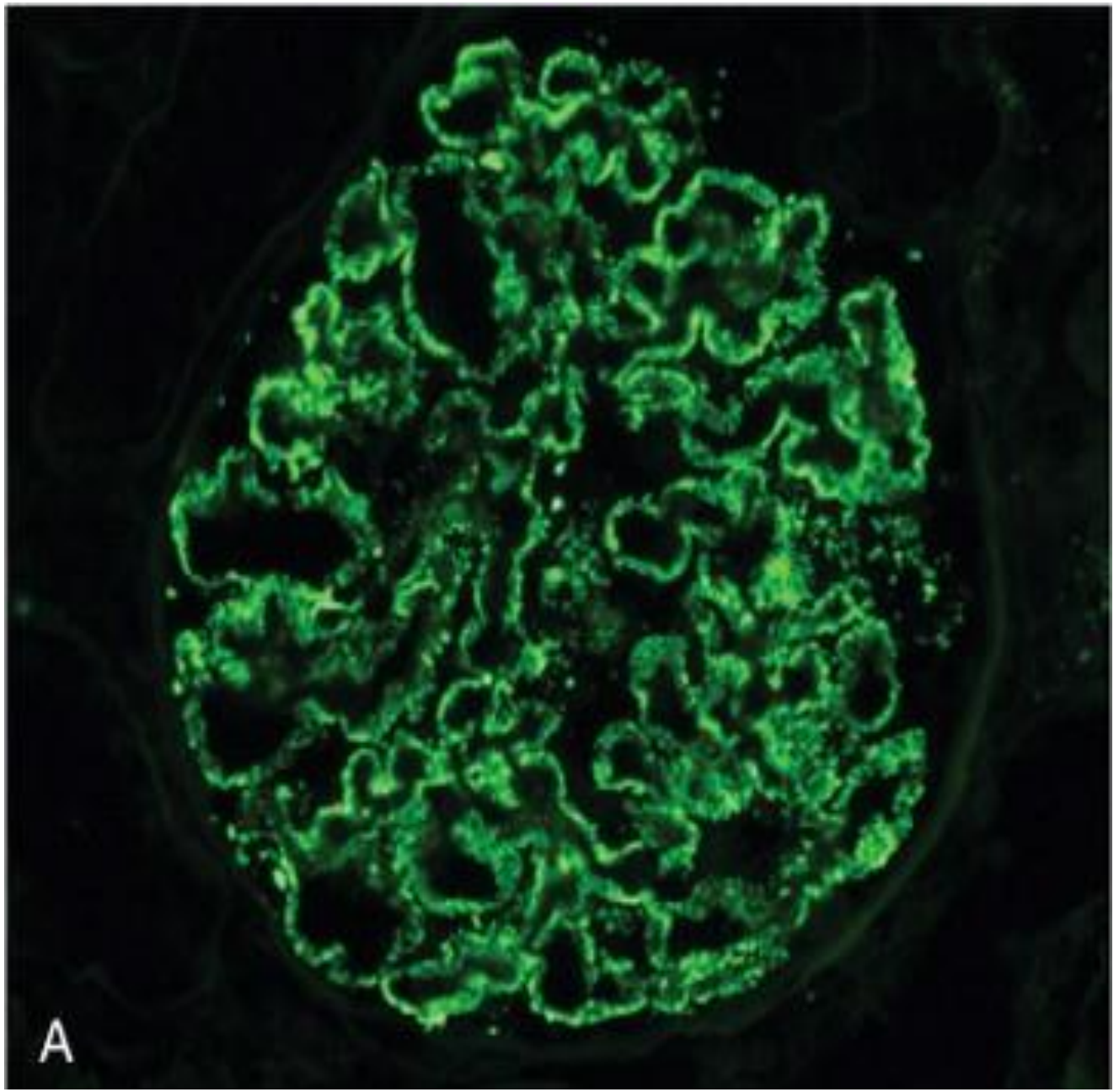
2-between the endothelial cells and the GBM (subendothelial deposits).

3-between the outer surface of the GBM and the podocytes /foot processes(subepithelial deposits).

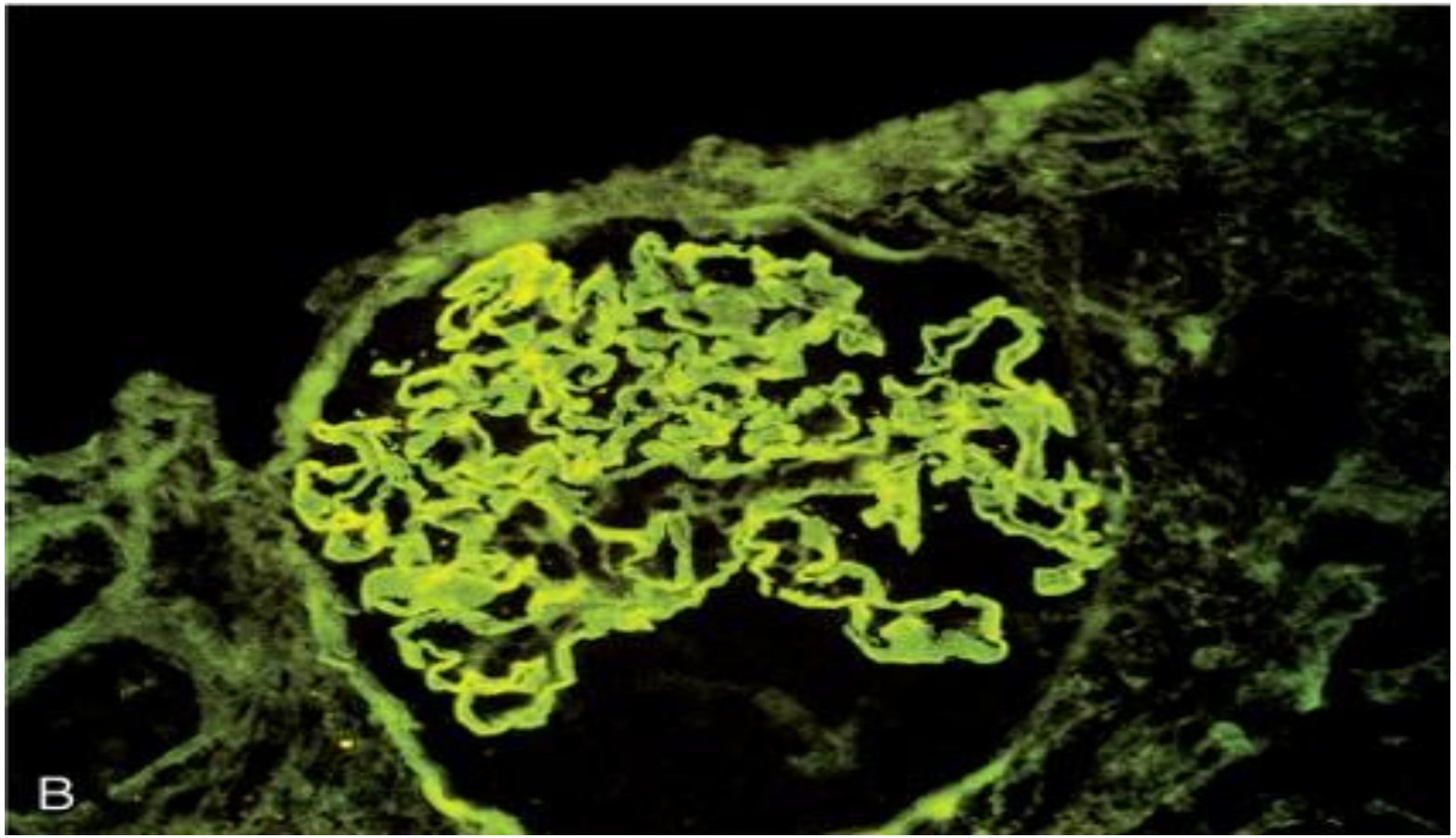
- **The pattern of immune complex deposition is helpful in distinguishing various types of GN**

Immunofluorescence microscopy

How does it work ?
-As u can see there is a black background., and a fluorescent color inside the glomerulus, this color is produced by a secondary Anti-body that reacts with the anti-body we are looking for so color production means the result is positive and the Antibody we are looking for is there.



immunofluorescence linear deposition of immune complexes



We need to know what syndrome or clinical manifestation every disease follows

Glomerular diseases-1

- **Most of glomerular diseases lead to nephrotic syndrome**

The Nephrotic Syndrome

- The nephrotic syndrome refers to a clinical complex that includes the following:
- (1) **massive proteinuria** with daily protein loss in the urine of 3.5 gm or more in adults.
- (2) **hypoalbuminemia** with plasma albumin levels less than 3 gm/dL.
- (3) **generalized edema**
- (4) **hyperlipidemia and lipiduria**.
- (5) little or no azotemia, hematuria, or hypertension.

Causes of Nephrotic Syndrome

nephortic syndrome can be due to primary glomerular disease or systemic disease with renal manifestations

A-primary glomerular diseases

The doctor didn't read the numbers

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

B-Systemic Diseases with Renal Manifestations:

or secondary causes of nehprotic syndrome

Here the patient doesn't have a problem in the kidneys but as a result of other disease, renal damage occurs and sometimes these secondary renal manifestations are the reason of patient presentation to a doctor.

- **Diabetes mellitus**
- **Amyloidosis** ***(autoimmune disease leads to accumulation of amyloid deposits)***
- **Systemic lupus erythematosus** ***(autoimmune disease)***
- **drugs (gold, penicillamine, "street heroin*/contaminated heroin*")**
- **Infections (malaria, syphilis, hepatitis B, HIV)**
- **Malignancy (carcinoma, melanoma)**
- **Miscellaneous (e.g bee-sting allergy)**

Minimal-Change Disease (Lipoid Nephrosis)

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

Named minimal change disease Because of the normal appearance in LM (minimal change occurred)

- ***Pathogenesis:* still not clear.**
- **?T-cell derived factor that causes podocyte damage and effacement of foot processes.**

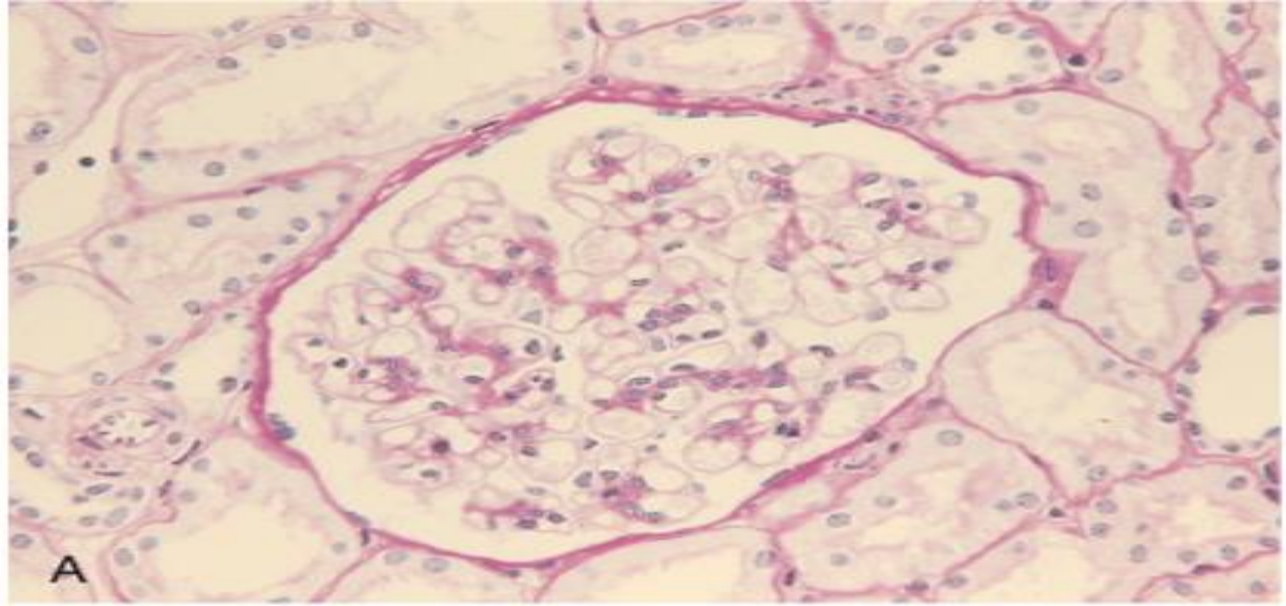
So filtration will be affected because foot processes are part of the filtration membrane that prevents large and charged proteins to pass, so proteinuria occurs.

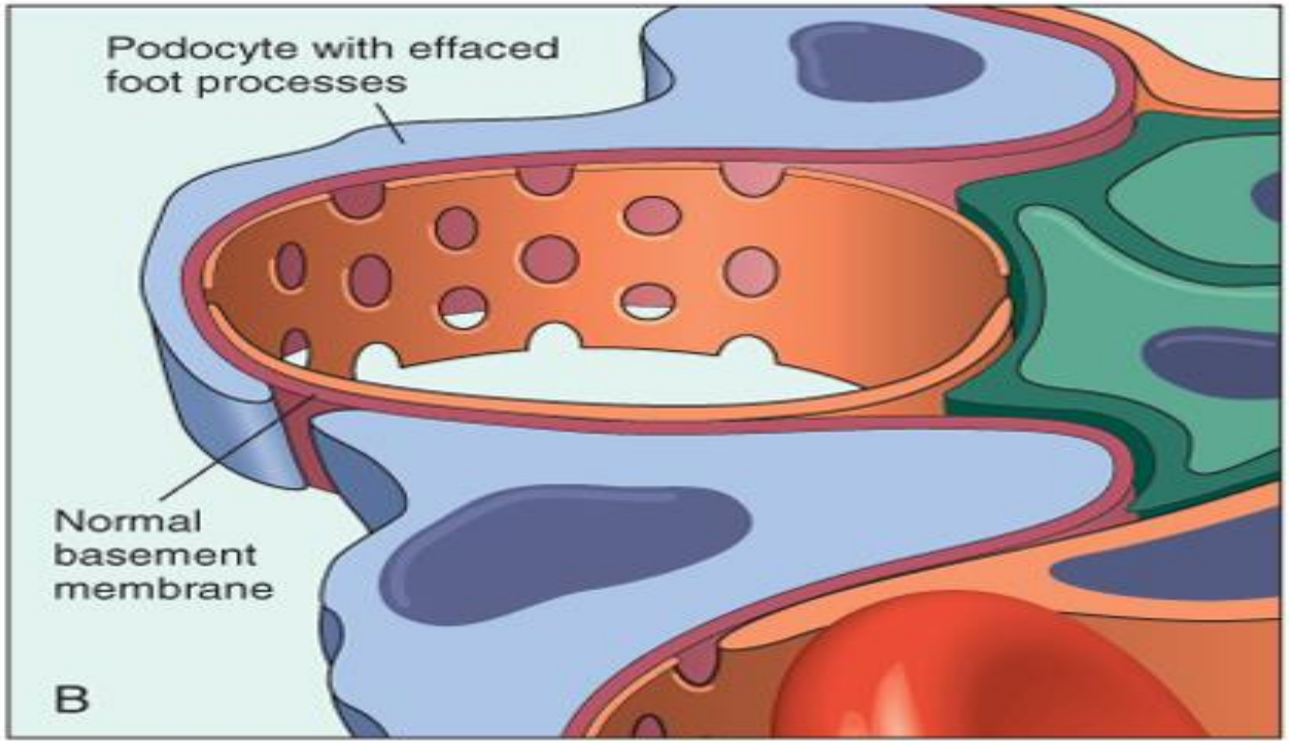
(mentioned after a student question)
-Not only the foot processes will be affected, but also the slit diaphragm (especially the nephrin component) and its thought that the clinical manifestations are mainly caused by a problem in nephrin.
-The basement membrane is intact and there is no inflammation.

Morphology

- **LM**
- the glomeruli appear normal.
- IF
- Negative, meaning the problem has nothing to do with immune-complexes
- **EM** ***(the only evidence that there is a problem)***
- **uniform and diffuse effacement of the foot processes of the podocytes, *so it shows the pathogenesis of the disease*** .
- No immune deposits

Effacement: means to make something fade or disappear, and it means here that the foot processes disappear and will not appear finger-like structures in EM





Minimal change disease.

A

glomerulus appears normal, with a delicate basement membrane

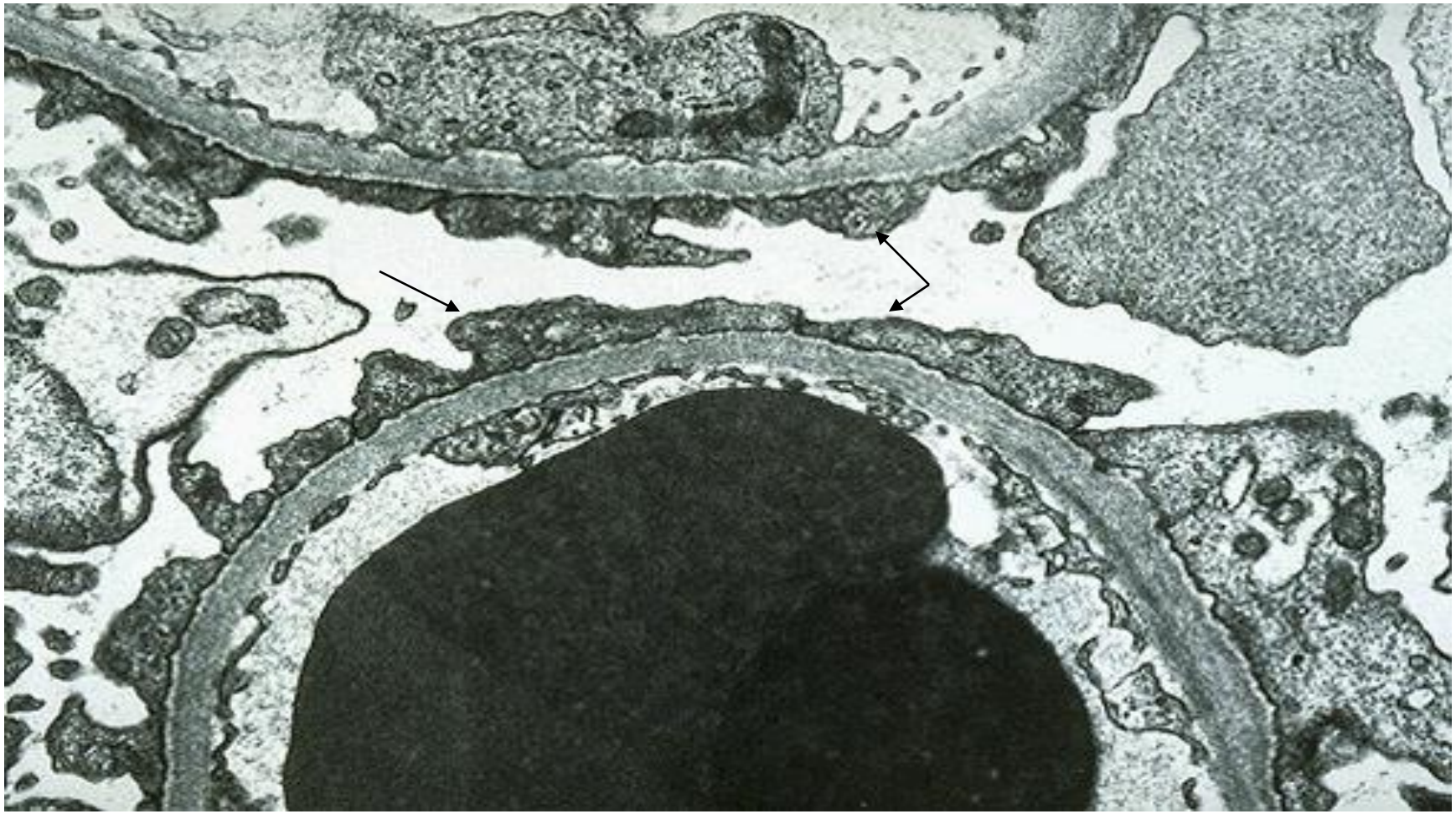
B

diffuse effacement of foot processes of podocytes with 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.

<u>The overlying epithelial cell foot processes are fused</u> (arrows).



Clinical Course

- **insidious development of the nephrotic syndrome in an otherwise healthy child.**
- **There is no hypertension.**
- **renal function is preserved in most individuals.**
- **selective proteinuria (the protein loss is usually confined to albumin)**
- **The prognosis is good.**
- **When the changes in the podocytes reverse (e.g., in response to corticosteroids) the proteinuria remits**
- **Treatment : More than 90% of cases respond to corticosteroid therapy *so the disease has good prognosis.***
- **< 5% develop chronic renal failure after 25 years.**
- **Adults with minimal change disease also respond to steroid therapy but the response is slower and relapses are more common.**

Focal and Segmental Glomerulosclerosis (FSGS)

We have 2 million glomeruli in both kidneys, when we say that this disease is a focal disease it means that not all 2 million glomeruli are affected, and segmental means that if we take a look at one of the affected glomeruli, a part of the glomeruli has the problem and the others are normal, and in this disease we have both focal and segmental.sclerosis

- ***The most common cause of nephrotic syndrome in adults***
- **characterized histologically by sclerosis *(fibrosis/collagen deposition)* affecting some but not all glomeruli (focal involvement) and involving only segments of each affected glomerulus (segmental involvement).**
- **This histologic picture is often associated with the nephrotic syndrome.**
- **It can occur :**
- **Primary disease (20% to 30% of NS)**
- ***Secondary* :in association with other known conditions as AIDS or heroin abuse, inherited or congenital forms resulting from mutations affecting nephrin, etc.**

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

- **Pathogenesis**
- **unknown .**
- **injury to the podocytes ?**
- **entrapment of plasma proteins and lipids in foci of injury where sclerosis develops.**
- **Clinical Course**
- **Poor responses to corticosteroid therapy *, so poor prgnosis.***
- **about 50% of individuals suffer renal failure after 10 years.**