

GLOMERULAR DISEASES

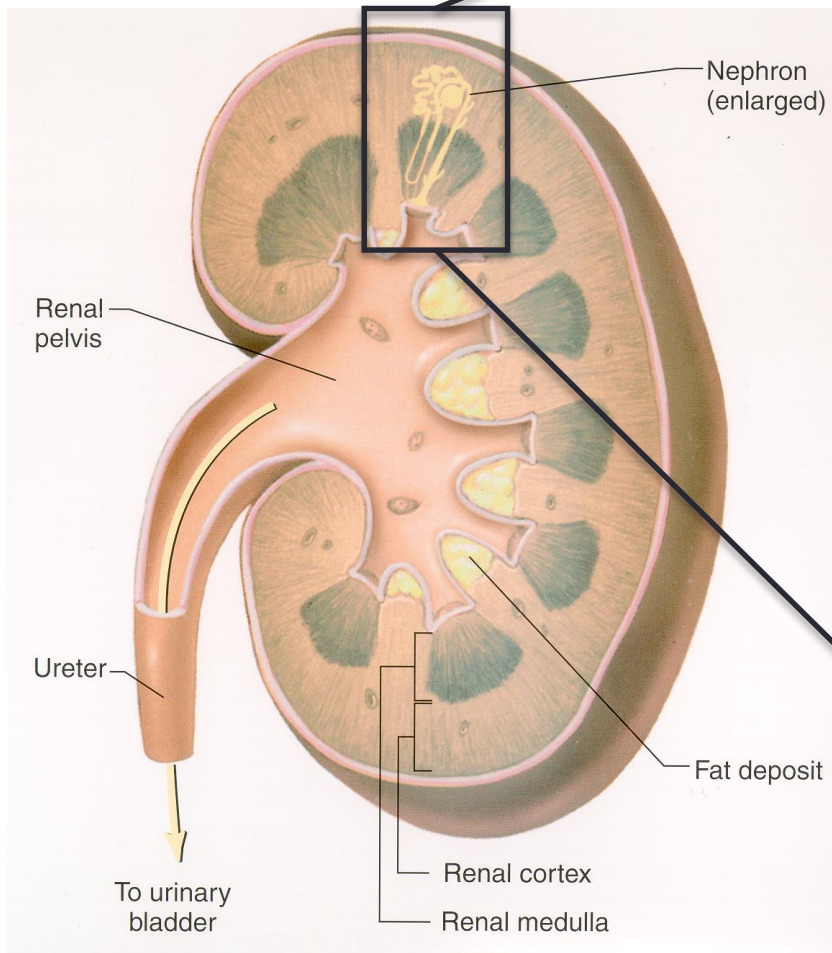
MED 341

Nov 2, 2015

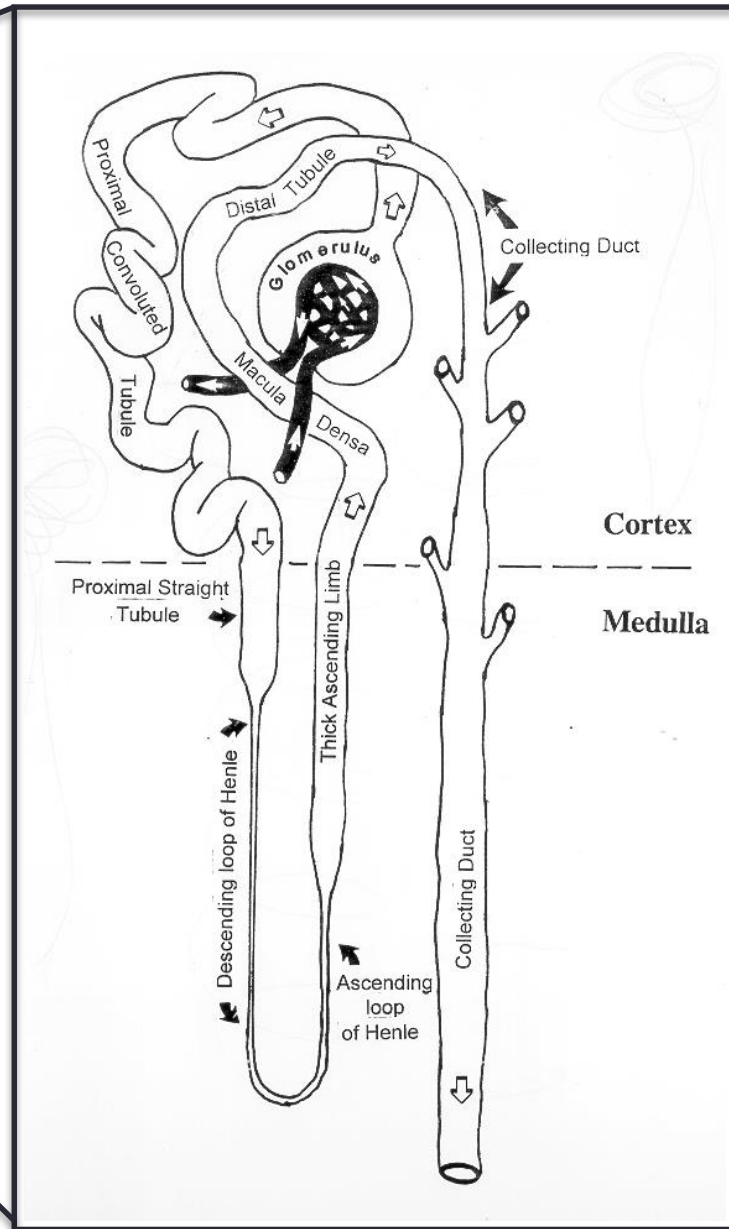
Objectives

- 1- To understand the pathophysiology of Glomerular Diseases.
- 2- To correlate the clinical findings with the underlying renal pathology.
- 3- To recognize the important features of Nephrotic syndrome.
- 4- Learn the most common causes of NS in adults.
- 5- To recognize the most important Glomerular diseases that cause Nephritic pattern (Glomerulonephritis).

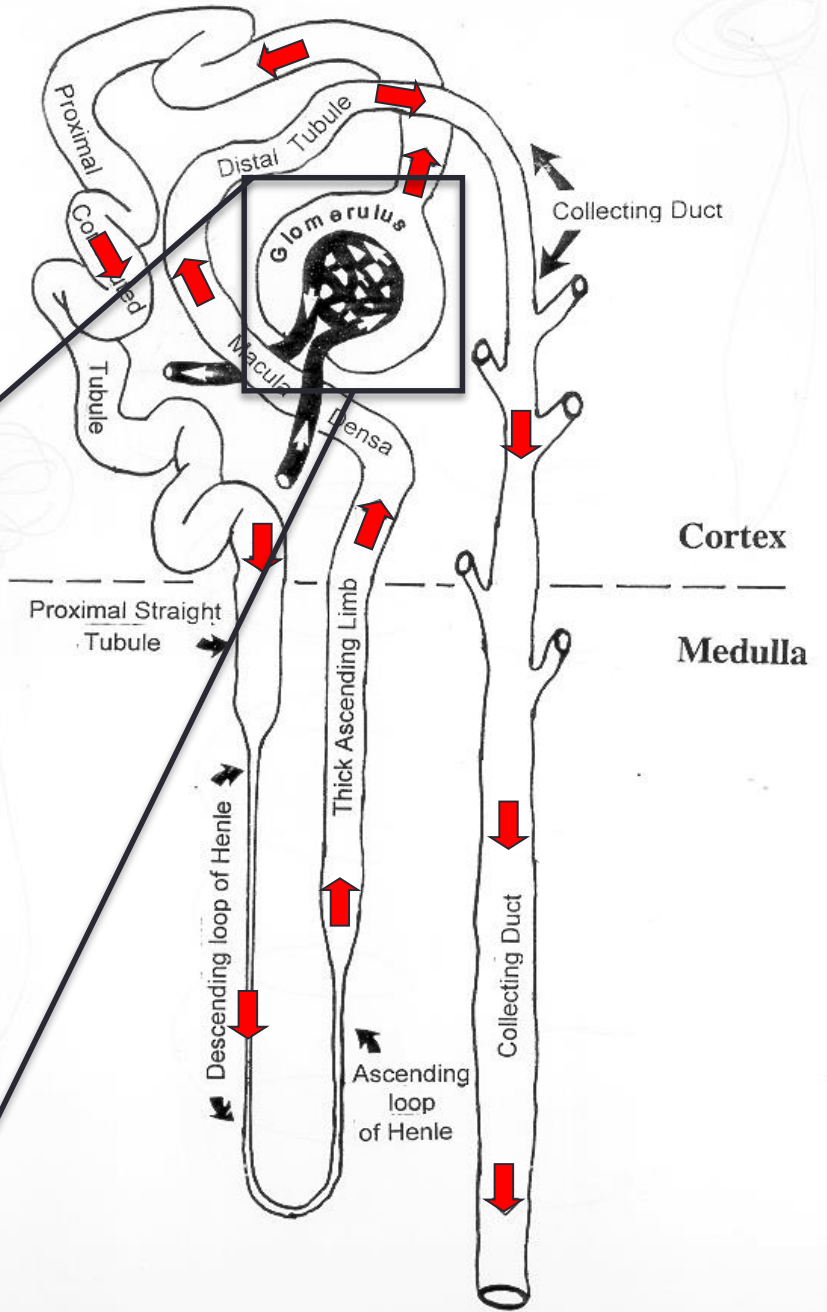
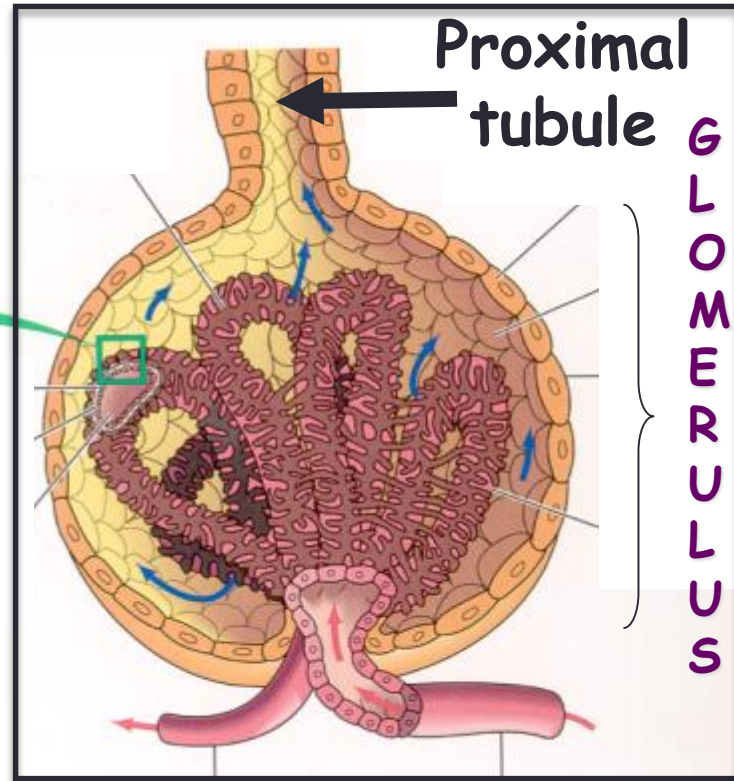
Renal cortex is the most important functional part of the kidney, because it has the Glomeruli

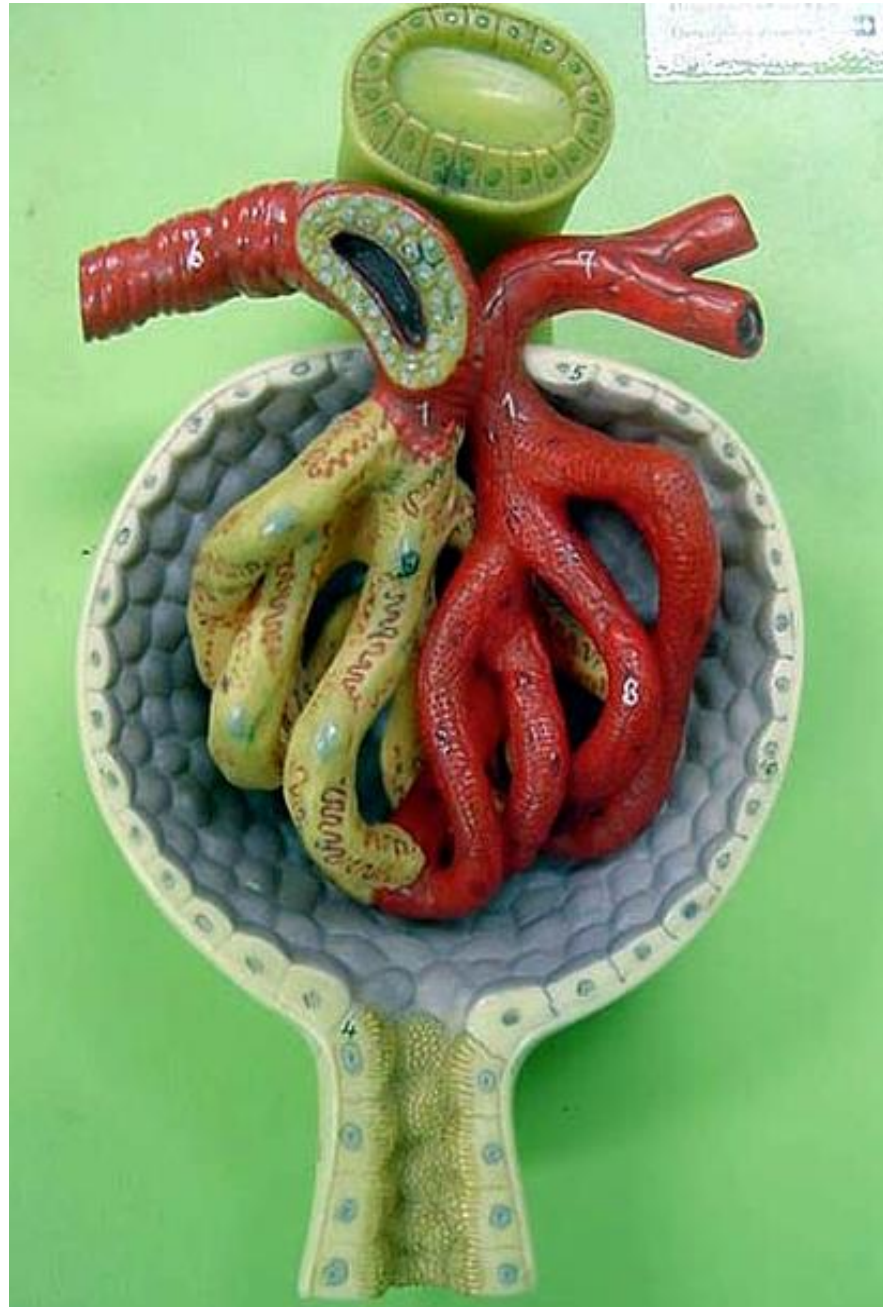


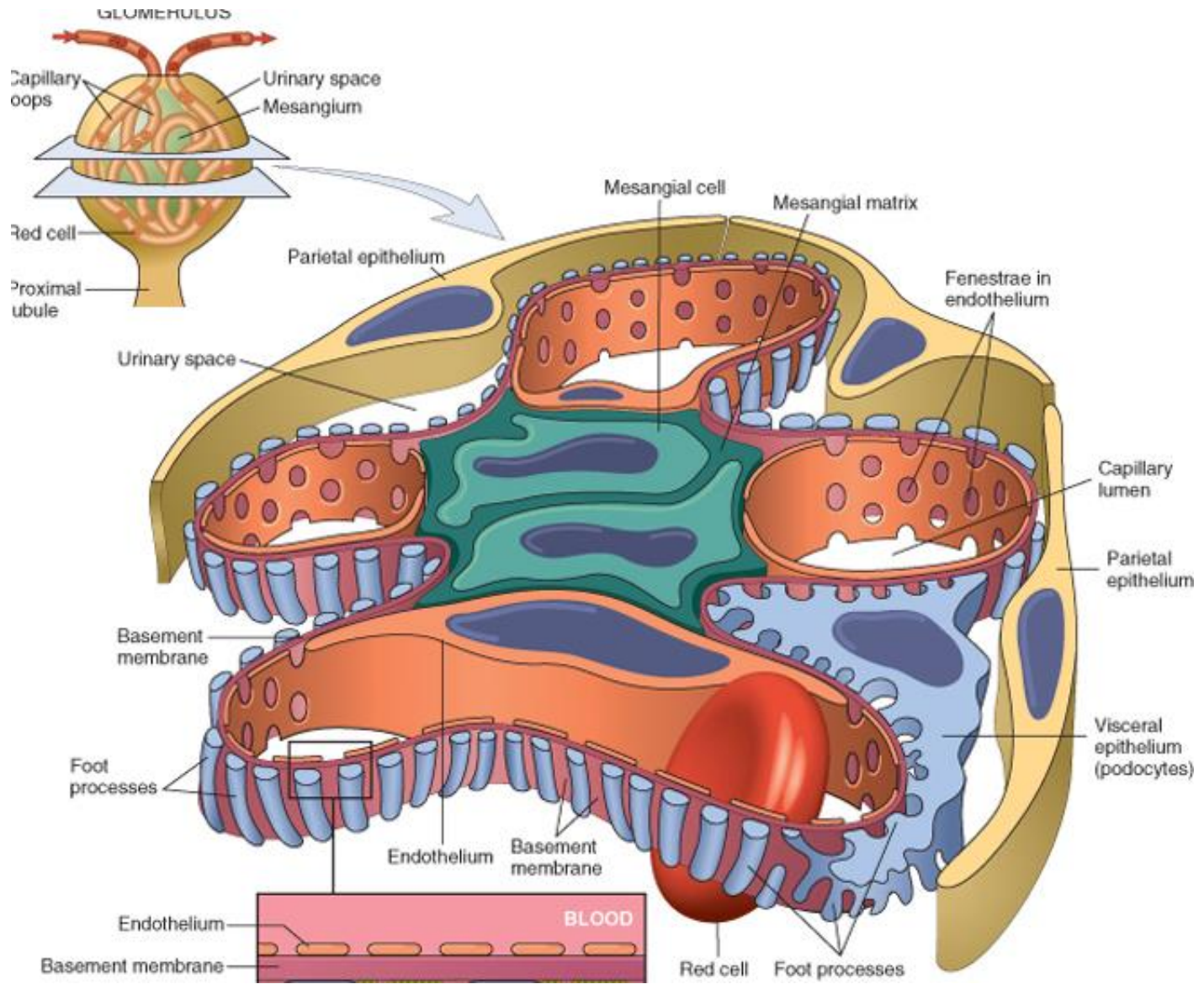
Nephron (zoom)



The Nephron







Microscopy

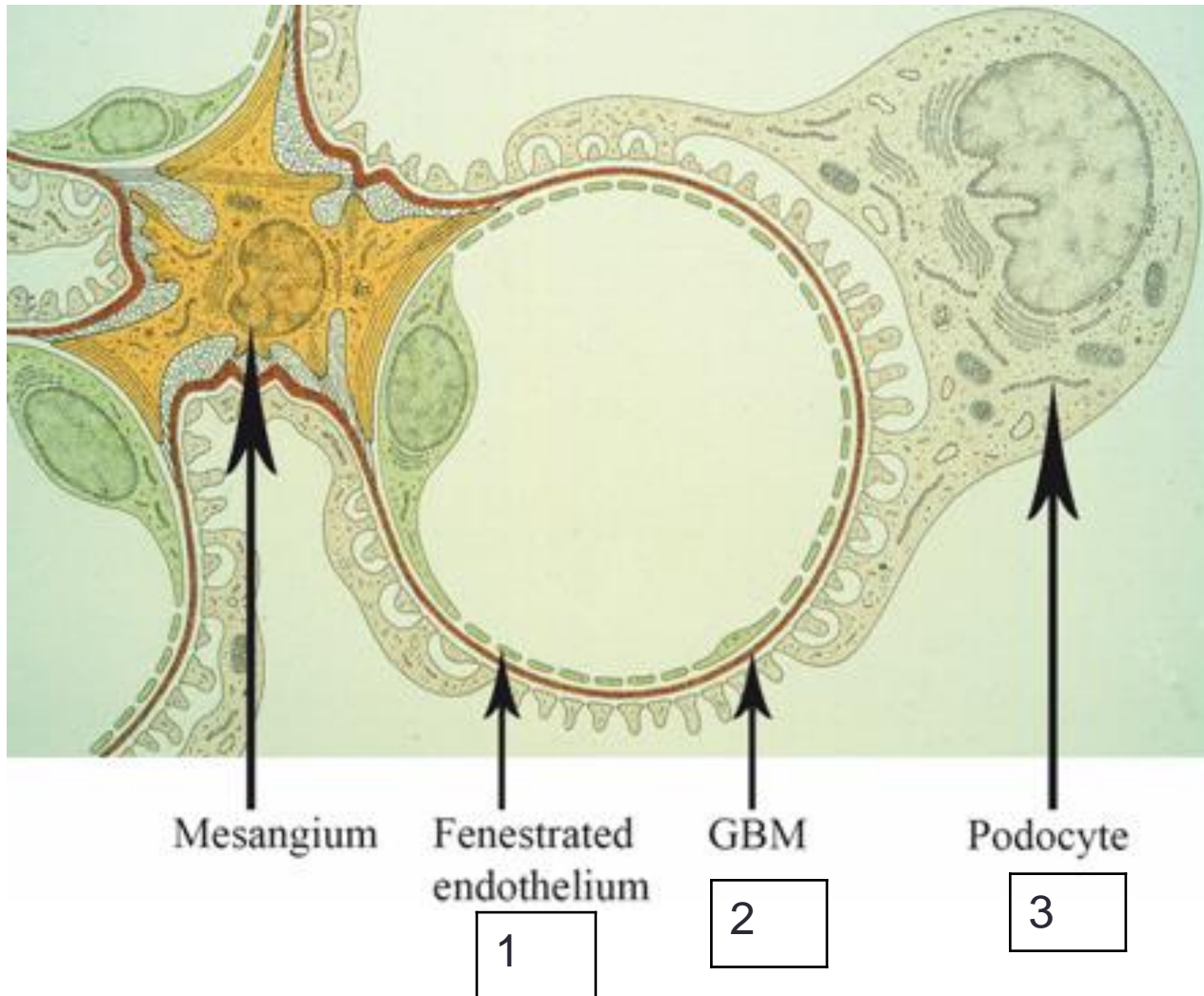
Light Microscope 2000x



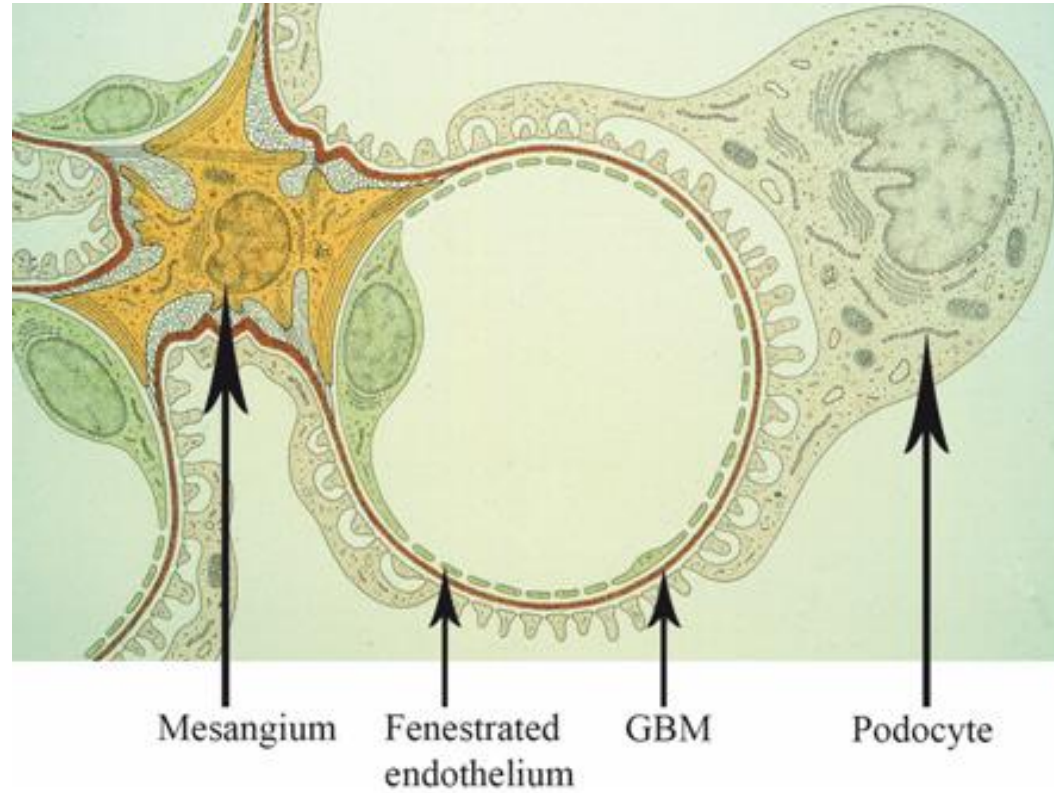
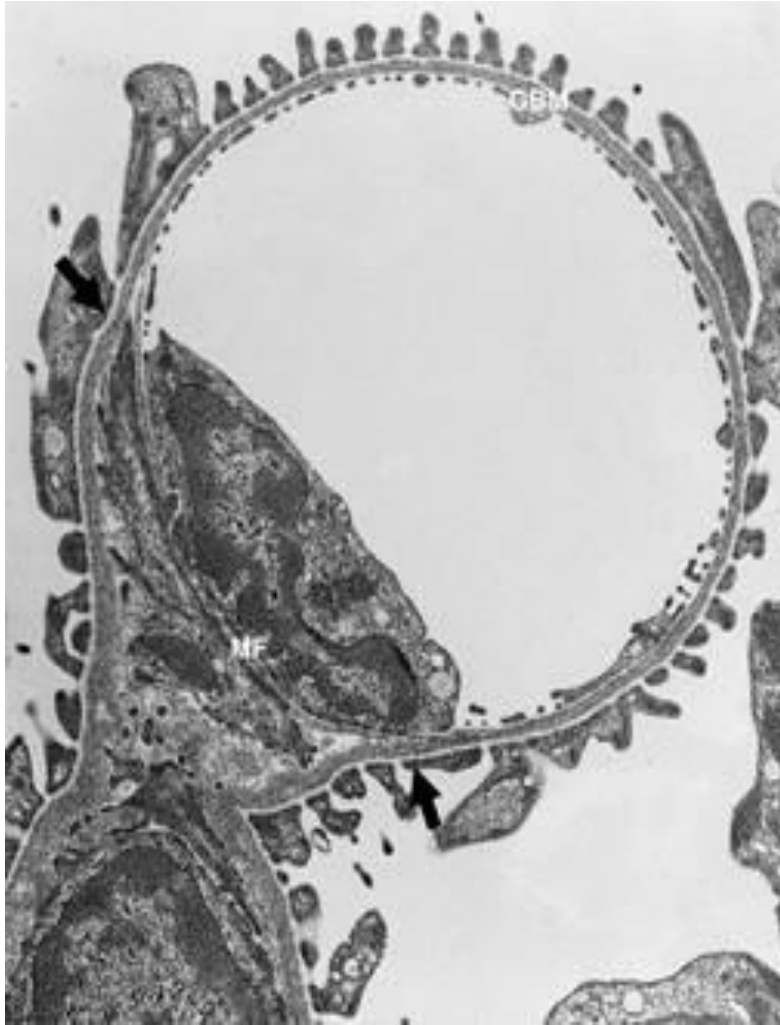
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The Glomerular Capillary wall has 3 layers, through which filtration occurs



Normal Capillary Loop (Electron Microscopy)



Normal Glomerular structure is needed to:

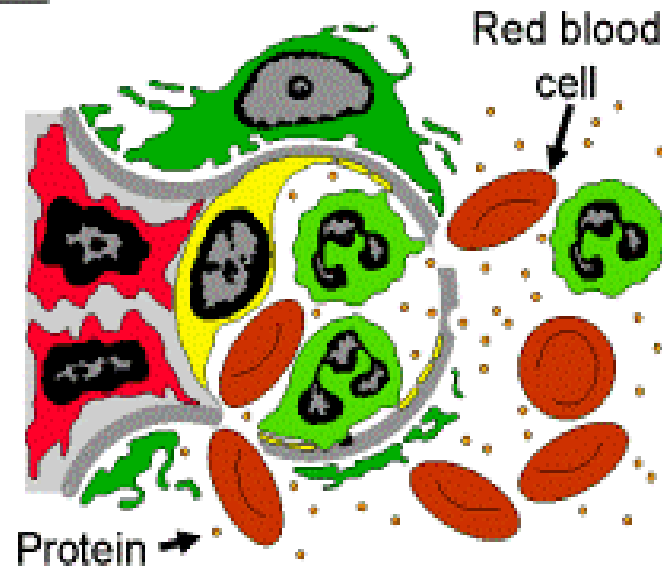
- Keep the glomerular filtration normal, thus maintains normal kidney function.
- keeps the urine volume maintained; so preventing fluid retention in the body which causes edema and high blood pressure.
- Prevents the blood components (cells, proteins) from leaving the blood stream and appearing in the urine.

Normal versus disrupted G. capillary wall

Proteinuria and Hematuria



A normal capillary in a glomerulus keeps red blood cells, white blood cells and most proteins in the blood and only lets watery fluid into the urine.



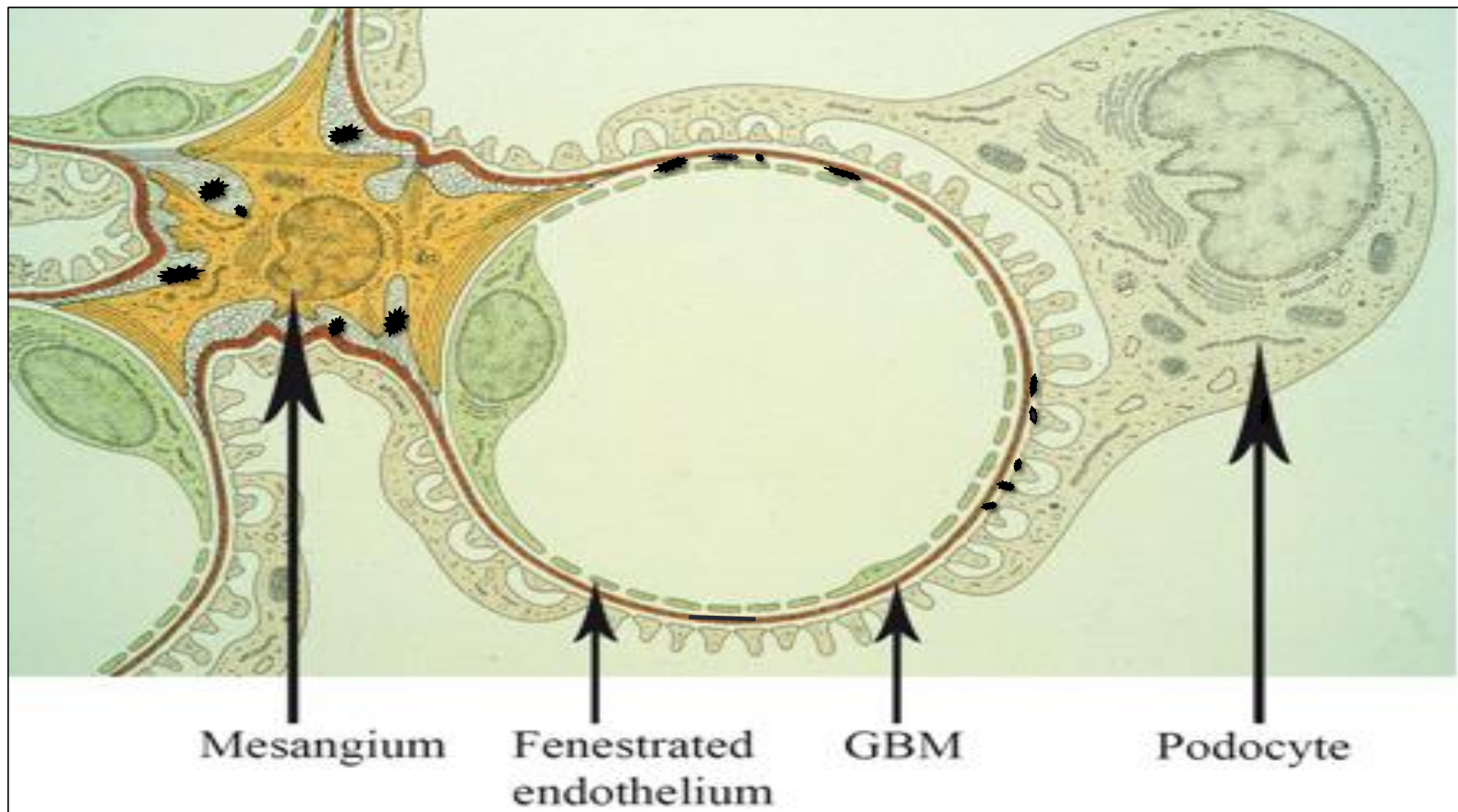
A capillary in a diseased glomerulus lets protein into the urine (proteinuria) and red blood cells into the urine (hematuria).

So normal urine will have:

- NO PROTEIN.
- NO RED BLOOD CELLS (Accept: <2 RBCs/High power field)
- NO HEME.
- NO CELLULAR CASTS.
- No fat
- No sugar

How glomerular diseases start?

- Here we are talking about primary glomerular diseases that are mostly caused by immune system dysfunction.
- Auto-antibodies targeting glomerular structure or immune-complexes (antigen-antibody) depositing and traumatizing the glomerular components.



How glomerular diseases start?

Most important to recognize:

- The manifestations of a glomerular disease are usually indicative of which components of glomerular capillary wall was affected at the most.

if **Podocytes** are the main target of the disease process
>>>> mainly ***proteinuria*** (at large amount) will manifest; thus Nephrotic Syndrome will be the main finding.

if **endothelial cells, Mesangial cells or GBM** are affected>>>>
mainly ***hematuria and abnormal renal function*** will manifest because of disruption in glomerular filtration wall; thus Nephritic pattern of renal disease will manifest.

Proteinuria is always present in this kind of Glom injury as well.

Another important things to remember;

>> Glomerular diseases are named based on their histopathological characteristics seen under the microscope

>> So, almost always a kidney biopsy is needed to diagnose any suspected primary glomerular disease

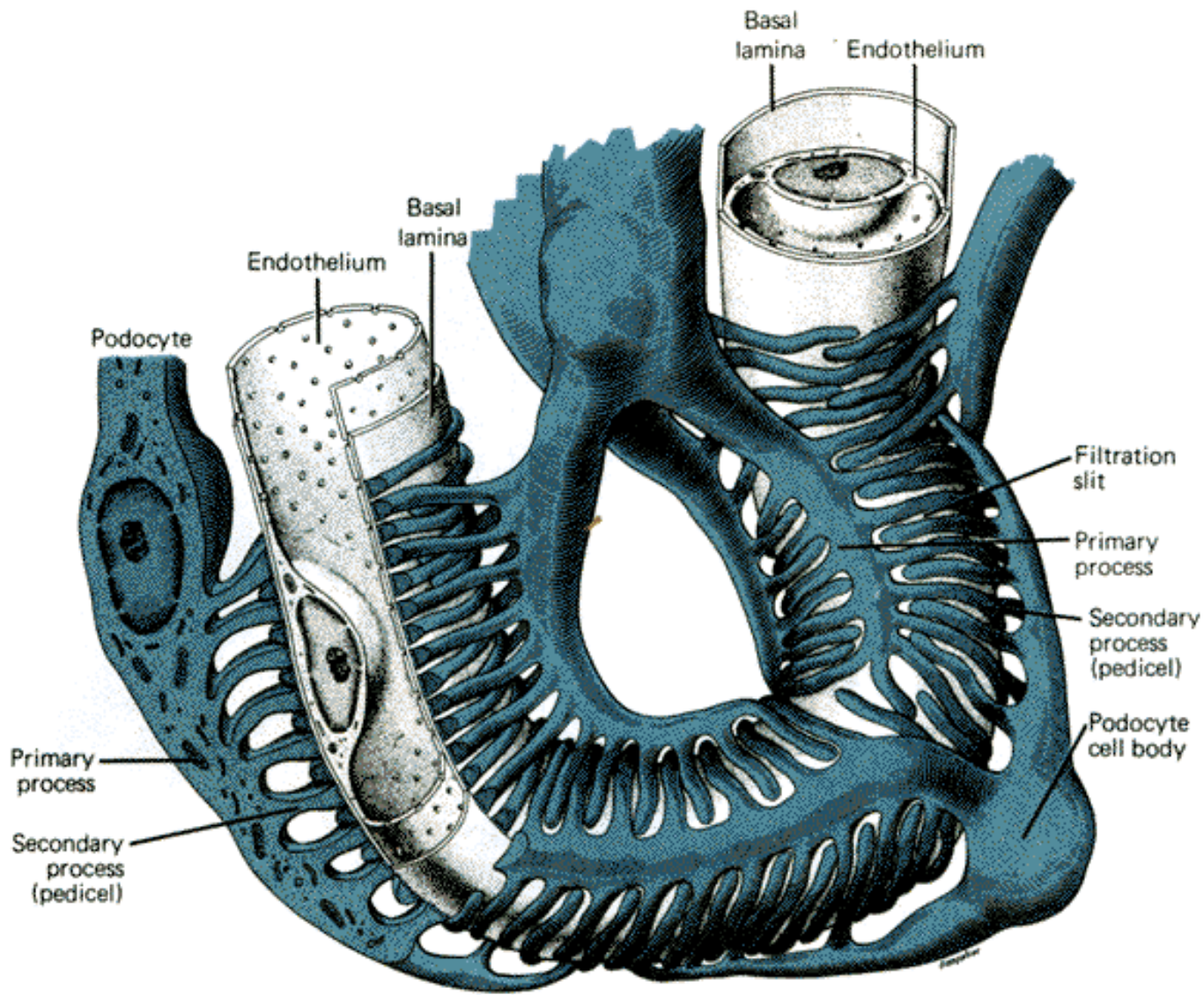
- But to make things easier, we can put Glomerular diseases in **two main clinical categories** (clinical i.e. the symptoms, signs and laboratory abnormalities)

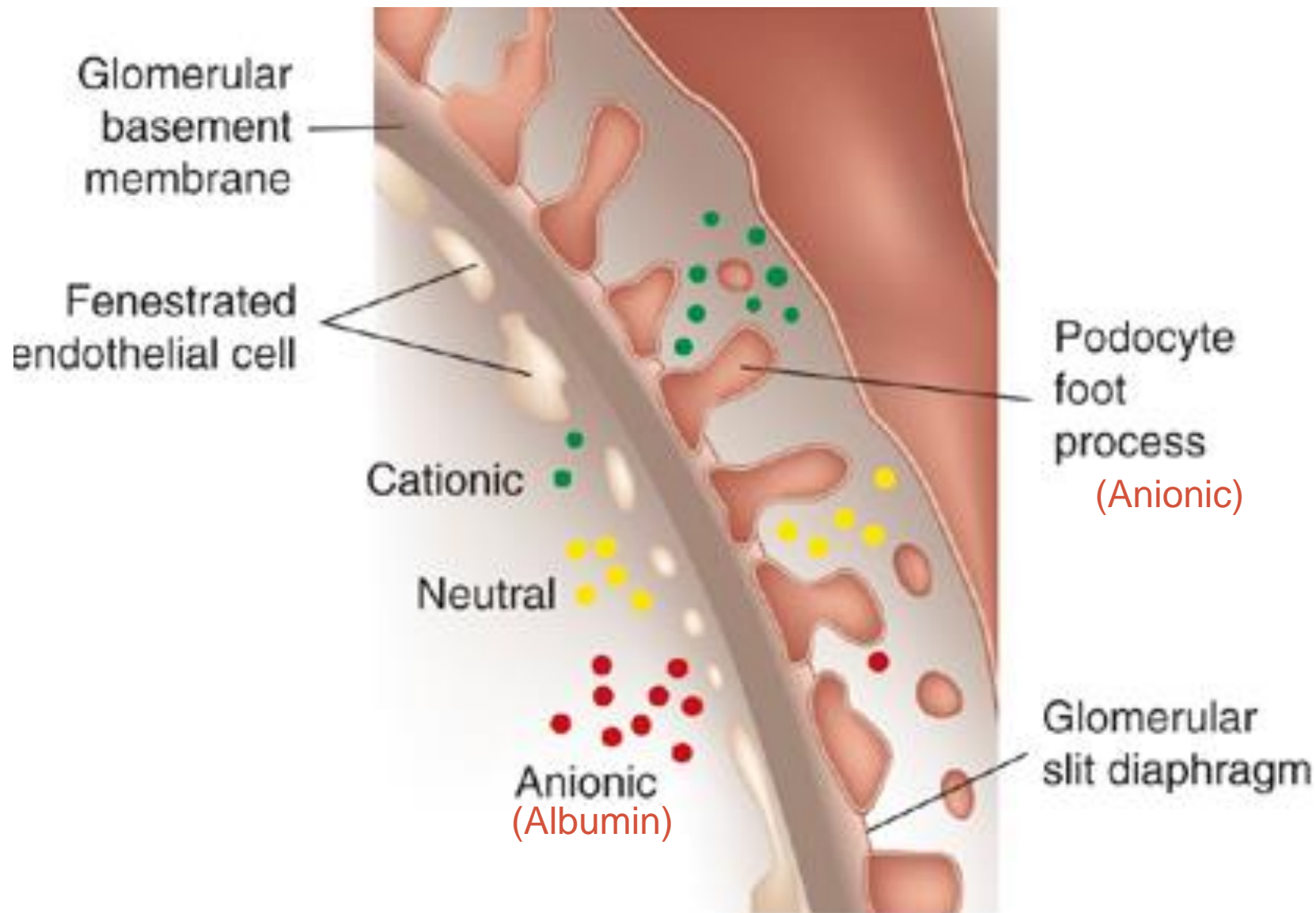
>>> **Nephrotic** (due to Podocytes dysfunction, so heavy proteinuria will be present)

>>> **Nephritic** (due to glomerular mesangial cells proliferation glomerular capillaries inflammation; so hematuria, impaired renal function and variable amount of proteinuria will be present)

Nephrotic Syndrome (NS)

- Podocytes abnormality is the primary finding in NS.
- Podocytes will sustain a structural dysfunction; making them lose their Foot-processes, but the cells bodies are intact.
- This will lead to significant amount of protein appearing in the urine (Proteinuria).





Nephrotic Syndrome

It refers to a constellation of clinical and laboratory features of renal disease:

- **Hypoalbuminemia (serum Albumin <30 g/L)** Normal serum Alb: 35-55g/L
- **Heavy proteinuria (> 3.5 g/24 hours of urine collection)**
- **Peripheral or generalized edema**
- **Hyperlipidemia**

Complications of Nephrotic Syndrome

- Infections & sepsis.
- Thrombosis.
- Acute kidney injury.
- ESRD if heavy proteinuria does not resolve.

Proteinuria

How many milligrams of proteins are normally secreted in the urine per-day?

- **< 150 mg/day of all kinds of proteins.**
- Including on average 4-7 mg/day of Albumin that are secreted in the urine normally.

Urine Analysis in Nephrotic Syndrome will show:

- Lots of protein (Proteinuria) or called Nephrotic range proteinuria (>3.5 g/24h urine)
- No RBCs (some times few are occasionally seen)
- No RBCs casts
- Fat (Lipiduria)(Fatty casts, oval fat bodies & fat droplets)
- No WBCs (few may be seen)

Clinical Presentation:

Edema due to:

1- Low serum Albumin (Low oncotic pressure)

2- Increase Renal sodium retention

Because of uncontrolled activation of the epithelial sodium channels (ENaC channels in the renal tubules)



Clinical Presentation

Patients also get:

- Fatigue
- Frothy urine (froth persists for long time after voiding)
- Anorexia
- Nausea & vomiting
- Abdominal pain
- Weight gain due to fluid retention
- Shortness of breath if having pleural effusion
- Signs & symptoms of DVT, PE

Glomerular Diseases that present as Nephrotic Syndrome

- 1- **Focal Segmental Glomerulosclerosis (FSGS)**
- 2- **Minimal Change Disease (MCD)**
- 3- **Membranous Nephropathy (MN)**

Focal Segmental Glomerulosclerosis (FSGS)

The **primary type** seen on light microscopy as:

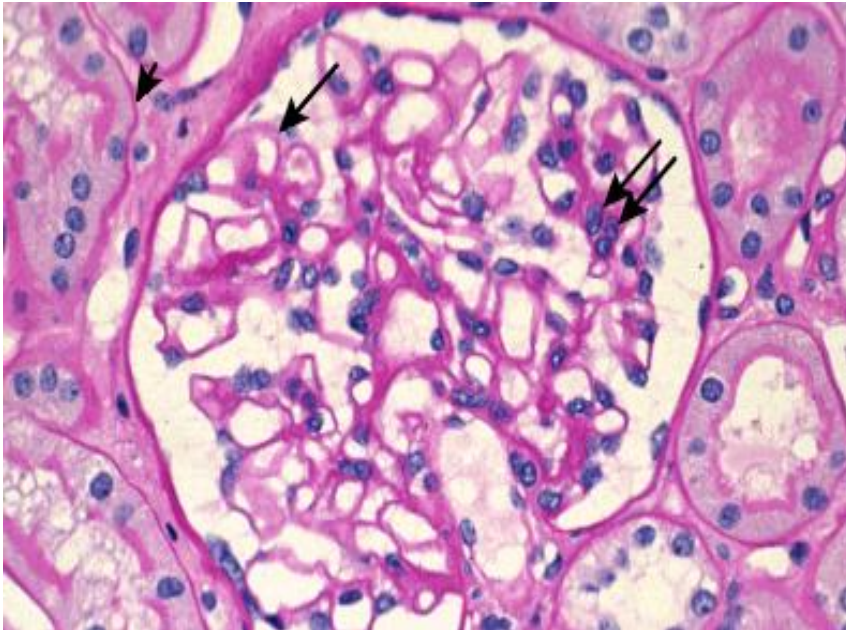
- Focal: some glomeruli are affected by sclerosis (the rest of them look normal)
- Segmental: sclerosis only involves a segment of each glomerulus that is affected.
- But most important; all glomeruli (the ones affected by sclerosis and the ones that are not affected) will have a diffuse foot processes effacement (thus Nephrotic syndrome appears)

Focal Segmental Glomerulosclerosis (FSGS)

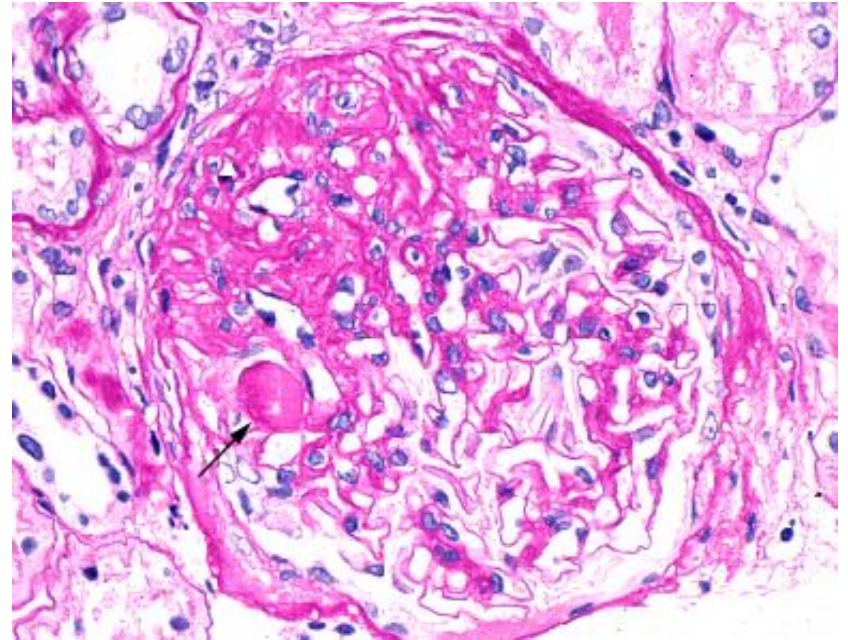
- A common cause of Nephrotic syndrome in adults.
- Causes 12 – 35 % of the cases in adults.

Focal Segmental Glomerulosclerosis (FSGS)

Normal

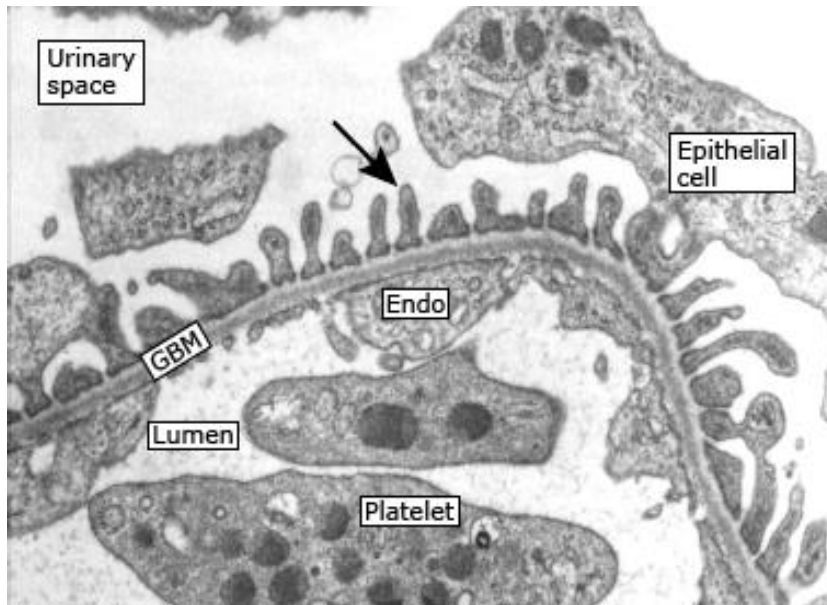


FSGS

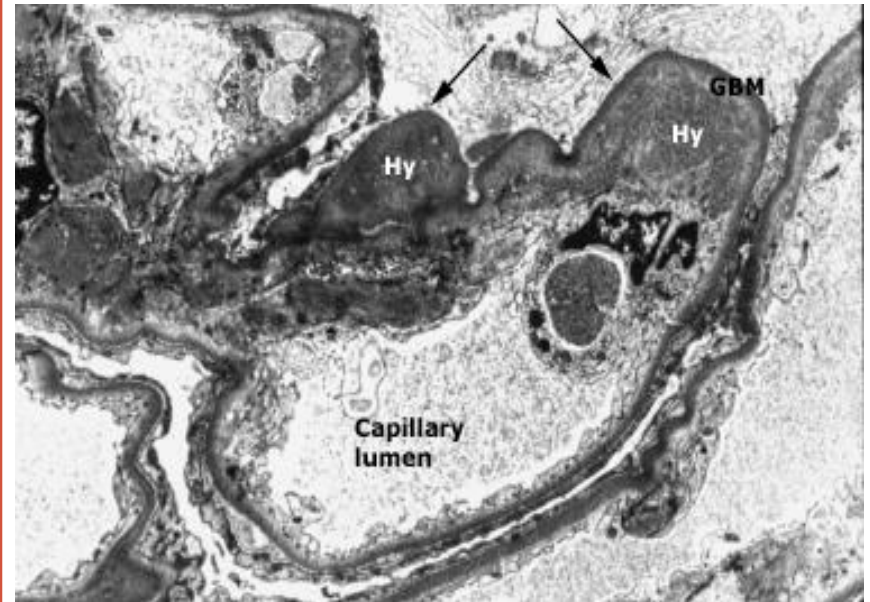


Focal Segmental Glomerulosclerosis (FSGS)

Normal



FSGS, like minimal change disease, diffuse foot process effacement but with segmental sclerosis



Focal Segmental Glomerulosclerosis (FSGS)

Can be:

Primary FSGS:

- Has sudden onset of heavy proteinuria and other manifestations of nephrotic syndrome.
- Usually treated with corticosteroids and other immunosuppressing medications.

Focal Segmental Glomerulosclerosis (FSGS)

Or can be

Secondary FSGS:

-Proteinuria is less heavy than other causes of nephrotic syndrome.

-Serum Albumin is not very low like the primary type.

-Renal impairment is commonly seen with the secondary FSGS and this is not a good prognostic sign

Focal Segmental Glomerulosclerosis (FSGS)

Possible causes of Secondary FSGS:

- Obesity
- Nephron loss (> 75% of renal mass) e.g renal agenesis
- Reflux nephropathy
- Healing of prior GN (example IgA)
- Anabolic steroid abuse
- Severe preeclampsia
- Drugs: Interferon, Pamidronate, Heroin
- Infections: HIV

Focal Segmental GlomeruloSclerosis (FSGS)

Immunosuppressive therapy is indicated in most patients with **primary FSGS**

- First line: corticosteroids
- Second line: cyclosporine or tacrolimus

Secondary FSGS: not typically treated with Immunosuppression, treat the primary cause and add supportive measures to protect the kidneys, e.g. keeping blood pressure well controlled with ACEi.

Minimal Change Disease (MCD)

Called **minimal** because:

- light microscopy: *is typically showing normal glomeruli*

So called: nil disease.

BUT:

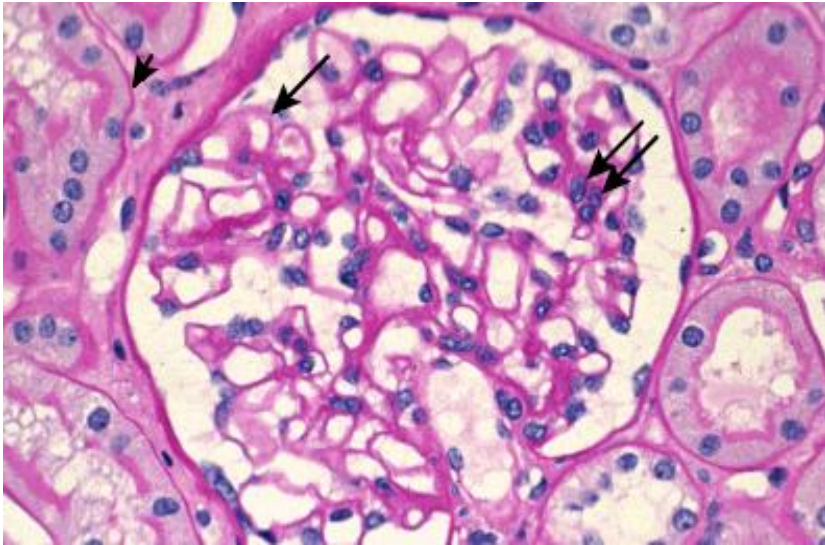
- electron microscopy: *shows diffuse effacement of the epithelial cells' foot processes only.*

- *So the most important difference between MCD and the FSGS is the presence of glomerular sclerosis in FSGS*

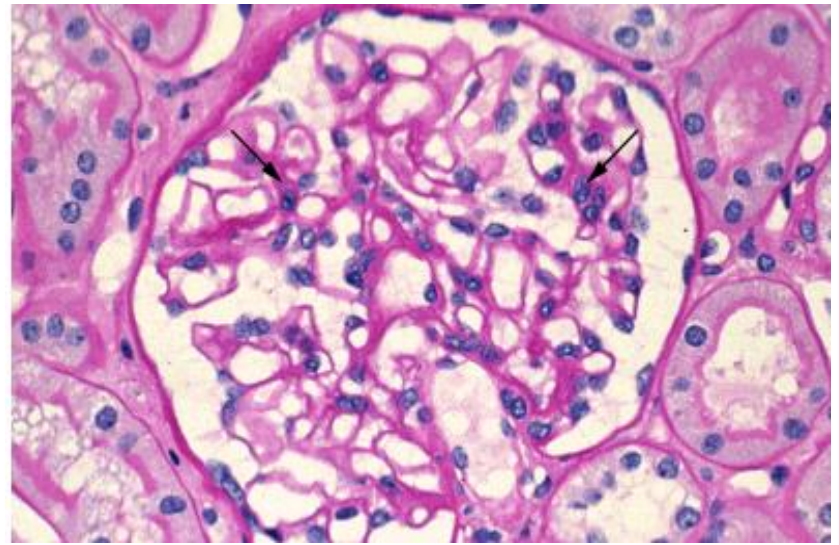
- *Here there is no sclerosis i.e. in MCD.*

Cont. **Minimal Change Disease (MCD)**

Normal Glomerulus

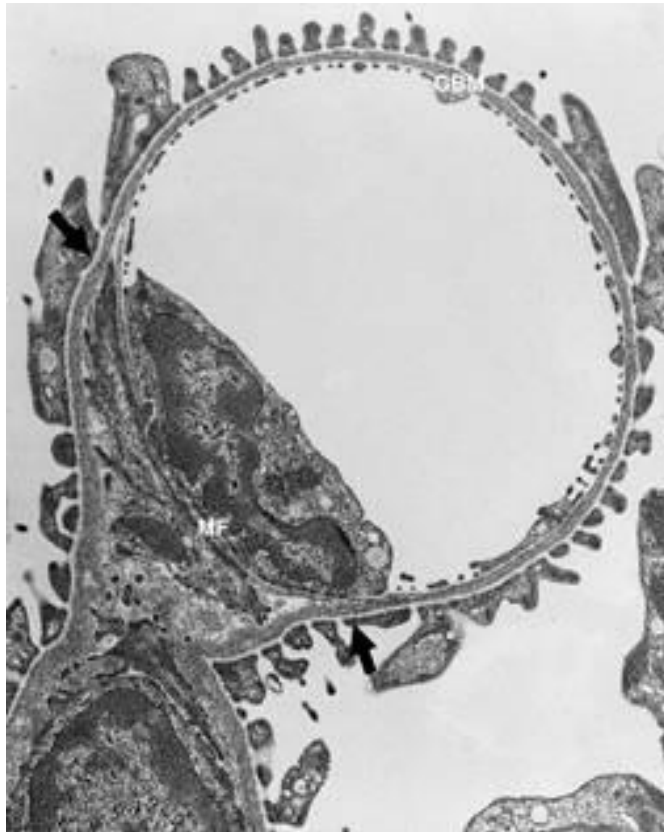


MCD, basically no abnormality is seen on light microscopy

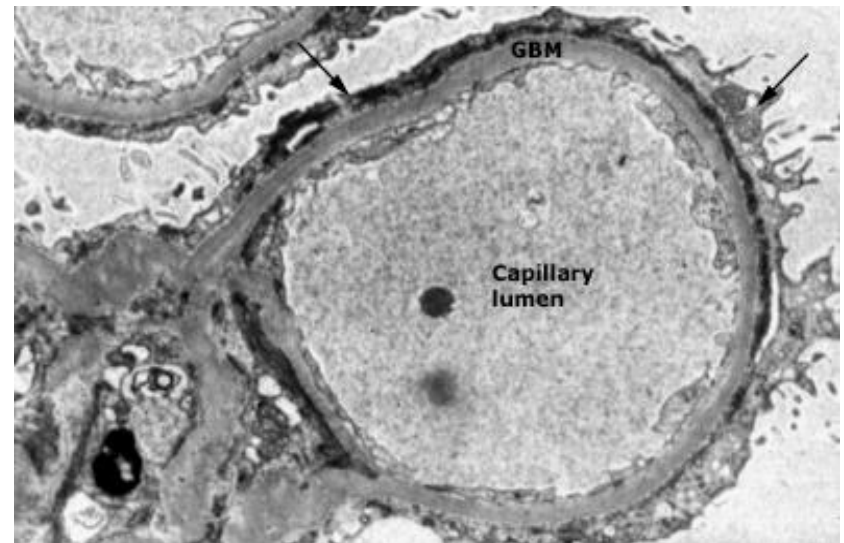


Cont. Minimal Change Disease (MCD)

Normal Glomerulus



MCD, EM shows the diffuse foot process effacement



Cont. Minimal Change Disease (MCD)

It is the main cause of Nephrotic syndrome in children:

- The cause in 90 % of cases in children < 10 years old.
- > 50 % of cases in older children

In children; typically is corticosteroid responsive in > 90%, thus kidney biopsy is commonly not done and treatment is given empirically for such cases. So, usually nephrotic syndrome in a child < 10 years old is MCD until proven otherwise.

- **It causes 10-25 % of Nephrotic syndrome cases in adults**

Cont. **Minimal Change Disease (MCD)**

Can be :

Primary (Idiopathic)

or

Secondary (much less common):

- *Drugs* (**NSAIDs**, Lithium, Sulfasalazine, Pamidronate, D-penicillamine, some antibiotics)
- *Neoplasm* (**Hodgkin Lymphoma**, non-Hodgkin lymphoma, and leukemia)
- *Infections* (TB, syphilis)
- Allergy

Cont. **Minimal Change Disease (MCD)**

Clinical presentation:

- Typically has a sudden onset Edema
- BP may be normal or slightly elevated
- Heavy proteinuria (Nephrotic range)
- Lipiduria
- Hypoalbuminemia (usually very low serum Albumin)
- Hyperlipidemia
- Creatinine is always within the normal range or slightly elevated and normalizes with remission

Cont. Minimal Change Disease (MCD)

Diagnosis:

Must do kidney biopsy in adult patients with this presentation,
It shows Diffuse effacement of foot process.

Treatment:

First line: Corticosteroids, given x 3-4 months then taper over 6 months

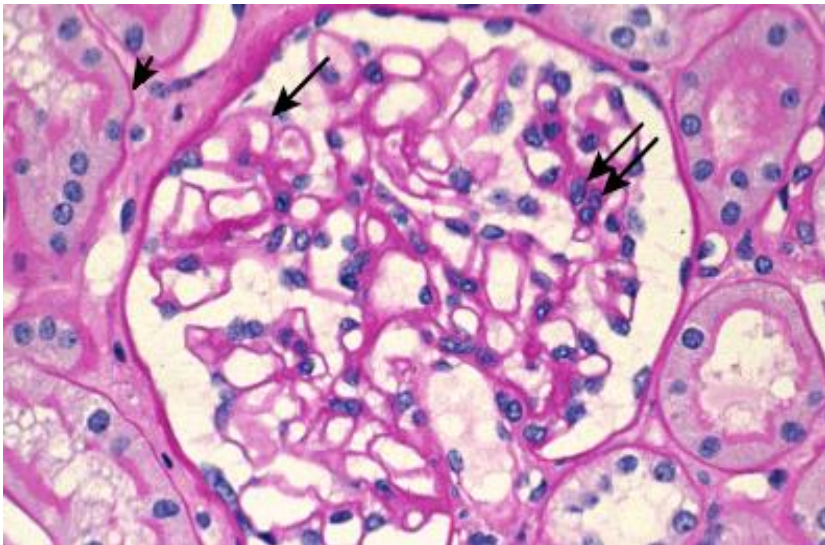
Second line: oral Cyclophosphamide, Cyclosporin

Membranous Nephropathy (MN)

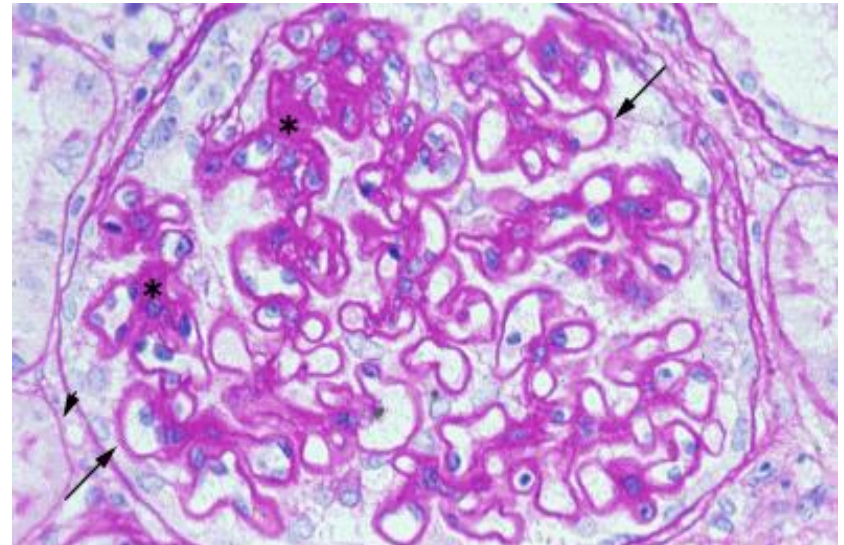
- Most common cause of Primary nephrotic syndrome in adults (15% and 33%)
- Mostly secondary in children (hepatitis B antigenemia)
- Presentation: slowly developing nephrotic syndrome

Membranous Nephropathy (MN)

Normal



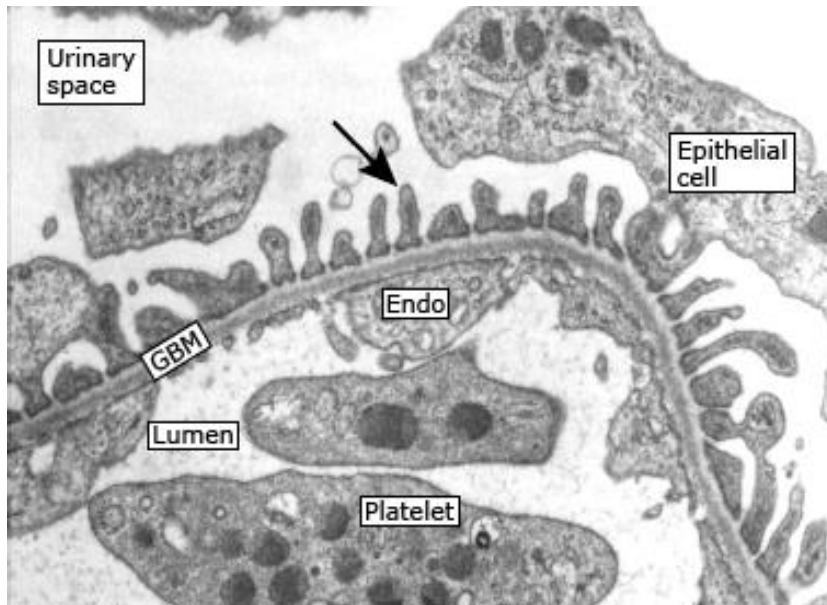
MN



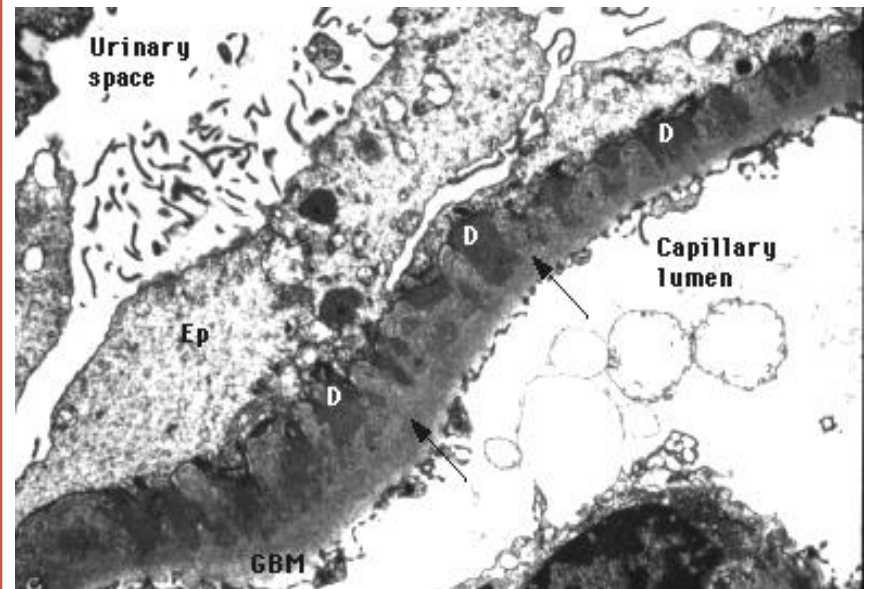
Diffuse thickening of the glomerular capillary wall throughout all glomeruli (IgG and C3 deposition)

Membranous Nephropathy (MN)

Normal



MN



Membranous Nephropathy (MN)

Etiology:

➤ Primary (Idiopathic)

In approximately 75% of cases in adults.

Membranous Nephropathy (MN)

Secondary: causes of MN:

➤ **Systemic lupus erythematosus (SLE)**

Class V Lupus Nephritis (10-20%)

- Drugs: penicillamine, IV gold salts, high dose Captopril, and NSAIDs, Anti-TNF.
- Infections: Hepatitis B, Hepatitis C, syphilis
- **Malignancy: solid tumors** prostate, lung, or GI track

Membranous Nephropathy (MN)

Treatment of Primary MN

- Corticosteroids plus
- Cyclophosphamide or cyclosporine
- May be Rituximab

Secondary MN

- Mainly target the primary disease that caused MN, and treat the Nephrotic syndrome manifestations.

Other **important secondary causes** of Nephrotic syndrome in adults:

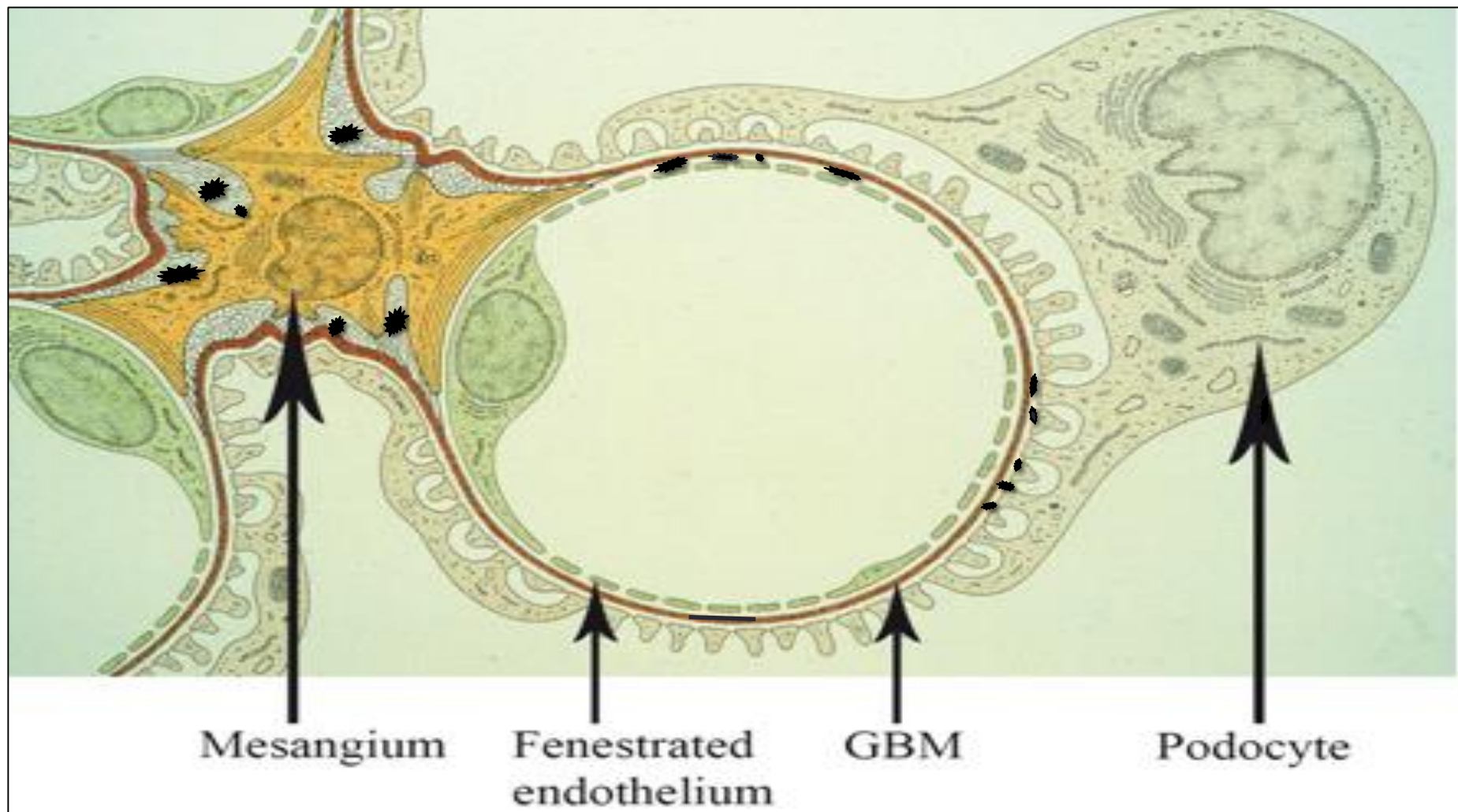
- **Diabetes Mellitus**
- **Amyloidosis**
- IgA Nephropathy
- MPGN

Nephritic Glomerular diseases

When we say **Nephritic**; it means a clinical pattern of presentation for a group of GNs, and not a syndrome like what we saw in Nephrotic causes.

The **Nephritic** pattern is always indicative of underlying **inflammatory process in the glomeruli**; causing inflammatory modulators attraction, cellular proliferation and eventually glomerular permanent dysfunction if left untreated.

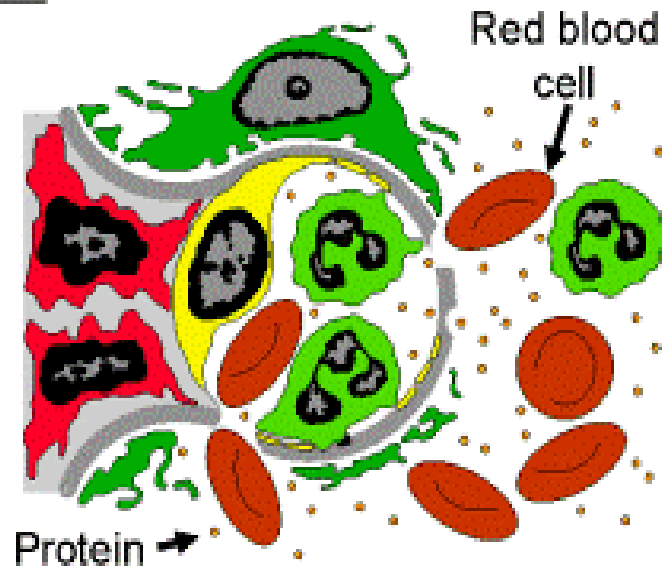
The Glomerular mesangium, endothelium and GBM components of the Glomerulus are likely going to be targeted because of their proximity to blood circulation.



Proteinuria and Hematuria



A normal capillary in a glomerulus keeps red blood cells, white blood cells and most proteins in the blood and only lets watery fluid into the urine.



A capillary in a diseased glomerulus lets protein into the urine (proteinuria) and red blood cells into the urine (hematuria).

Nephritic urine analysis shows:

- Red Blood Cells (RBCs)
- RBCs casts, or cellular casts
- Dysmorphic RBCs (RBCs lose their smooth surface passing through the cracks in inflamed glomerular basement membrane)
- Protein (at variable amount from mgs to grams per day)

Those are called **Active Urinary Sediments**

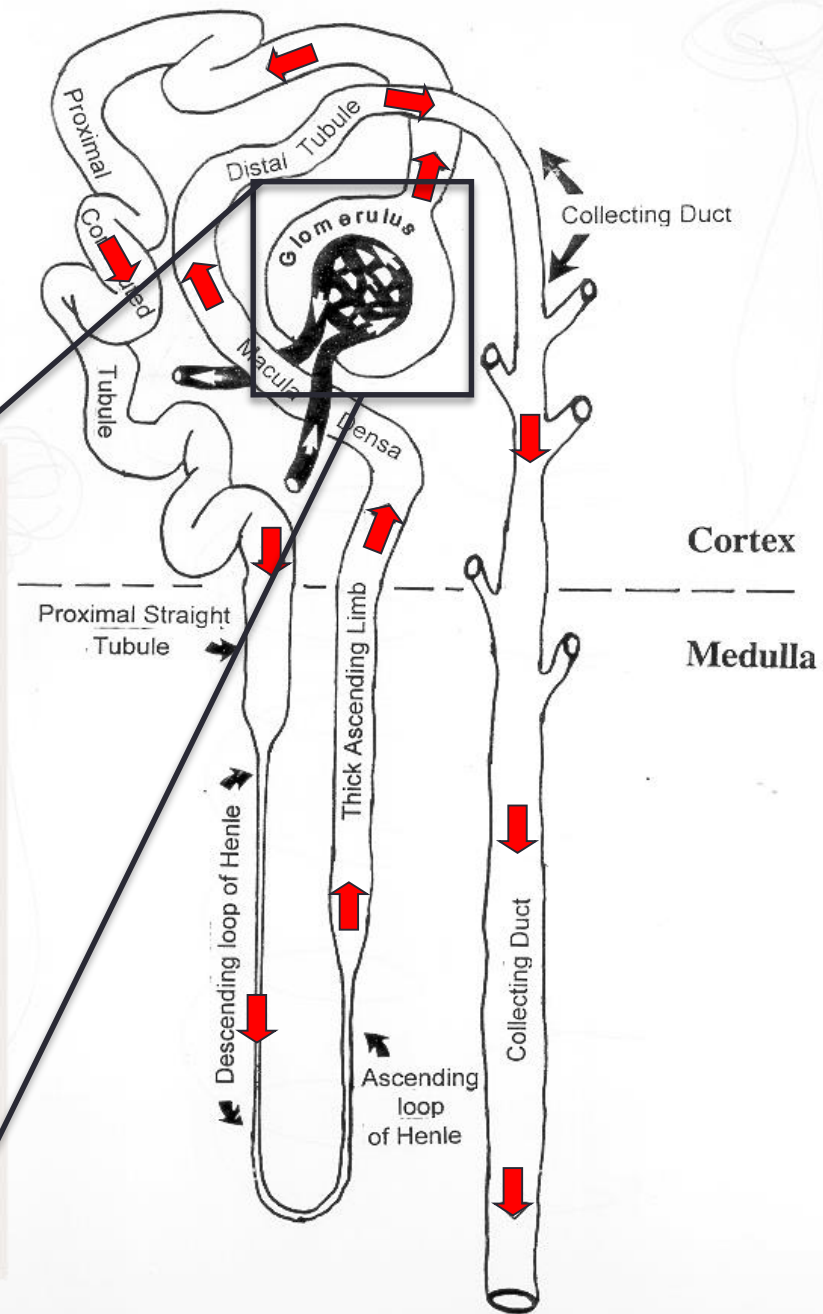
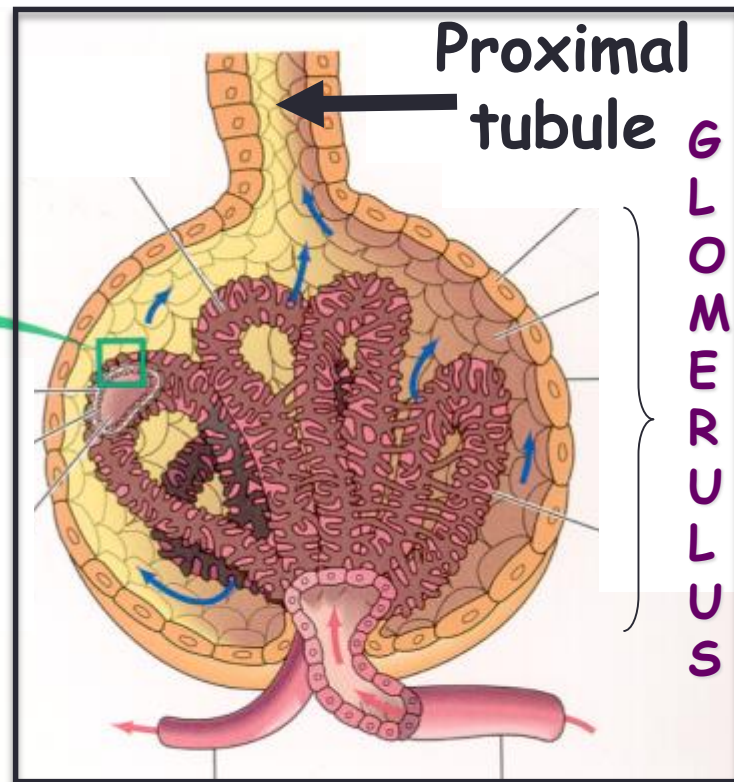
(Active = is indicative of underlying glomerular inflammatory process; requiring urgent medical attention)

RBCs cast

formed by naturally occurring *Tamm-Horsfall mucoprotein* in the distal tubules & collecting ducts when they become loaded with RBCs coming from the inflamed Glomerulus (due to GN)



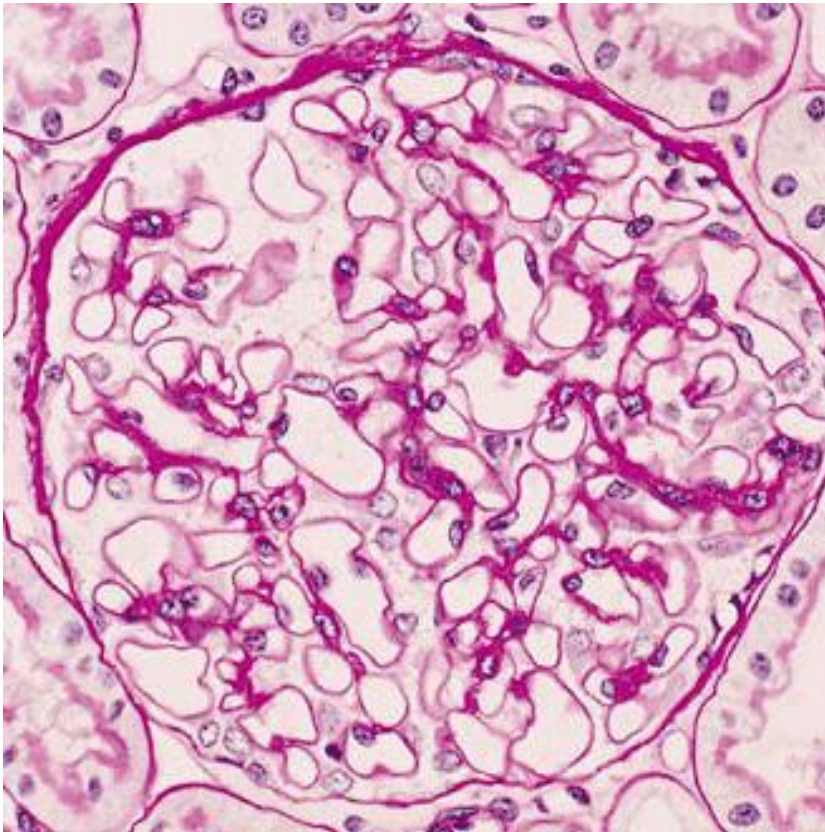
The Nephron



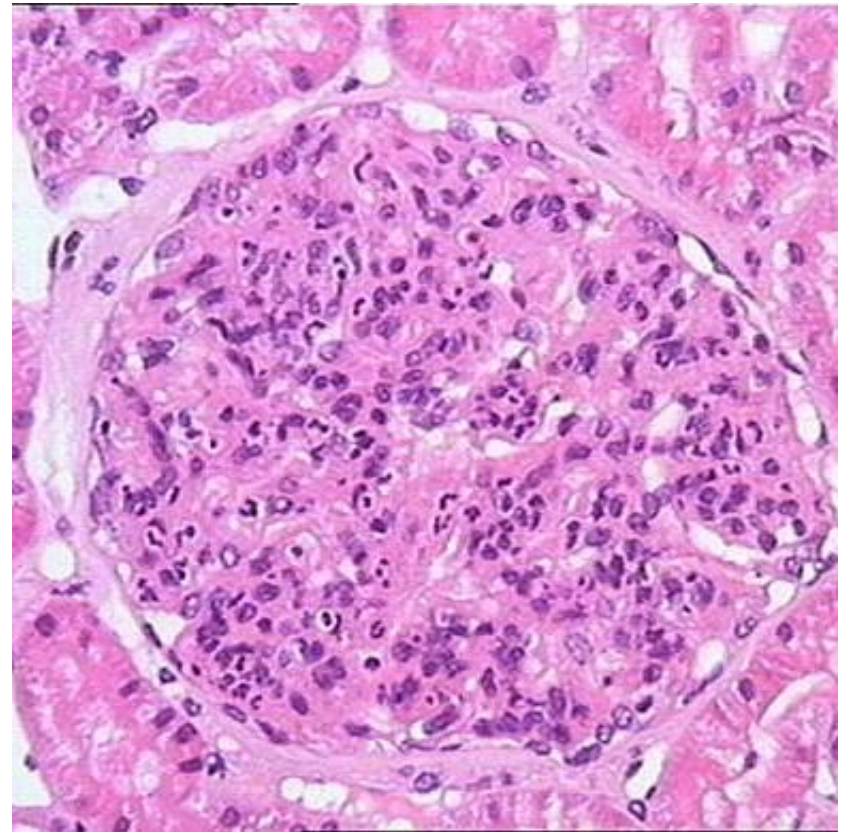
Nephritic clinical manifestations:

- **AKI** (Acute Kidney Injury) =Acute Renal impairment or Failure= elevated Creatinine)
- **Decreased Urine output**
- **Edema**
- **High Blood Pressure**
- May have other manifestations of systemic vasculitis since some GN types are actually vasculitis (e.g. skin rash, pulmonary hemorrhage, etc)
- Positive immune markers: ANA, Anti-DNA, low complements, +ve ANCA (depends on the cause)

Normal Glom.

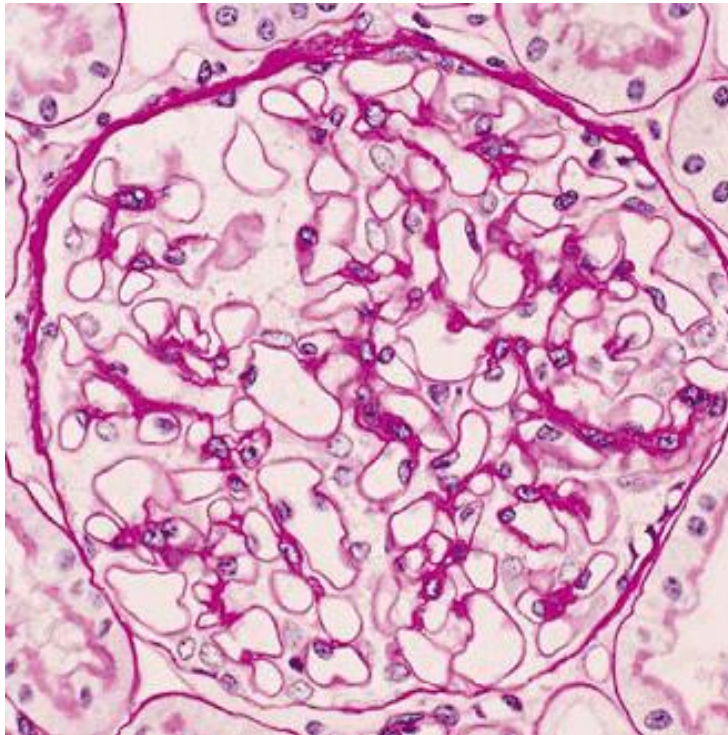


Glom. with proliferative
(inflammatory) GN

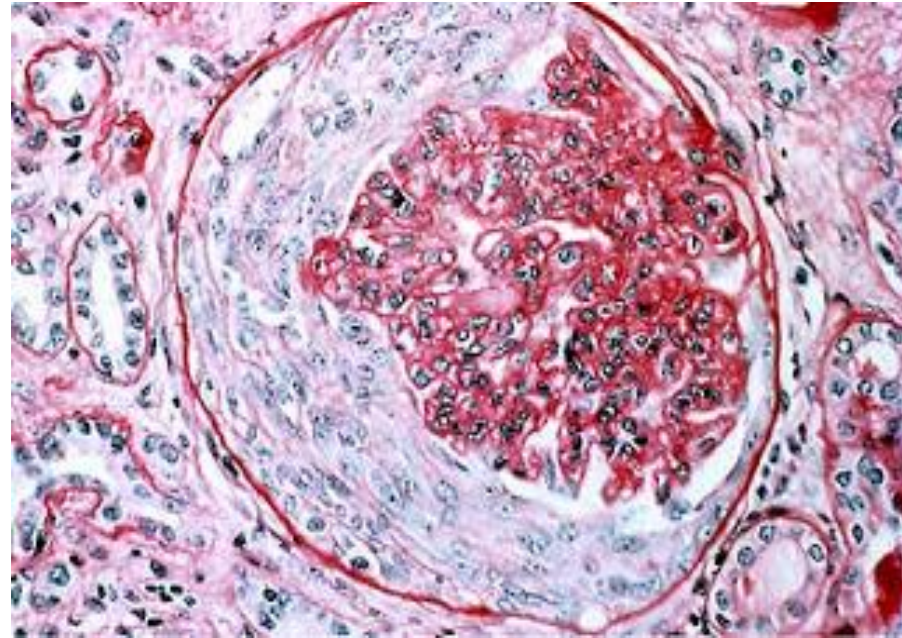


Crescentic GN; is a very bad GN!!!!

- Normal Glom.



- Glom. with Crescent



Indicates severe inflammation & worse outcome if not treated rapidly

Nephritic Glomerular diseases

Here; they are called **GN=Glomerulonephritis**

Renal Diseases that can present with **Nephritic** picture:

- IgA Nephropathy / HSP (Henoch-Schönlein purpura)
- Post streptococcal glomerulonephritis (PSGN)
- Lupus Nephritis
- Anti-GBM (Goodpasture's disease)
- ANCA vasculitis (e.g. Wegner's Granulomatosis)
- Membranoproliferative GN (MPGN)

IgA Nephropathy

- Most common type of Primary GN in developed countries
- Can present as dark urine (hematuria) **1-3 days** after upper respiratory tract infection. (< one week of URT infection)
- A lot of times it gets picked up **incidentally** by finding abnormal urine analysis (Hematuria+/- Proteinuria) done for other reasons with no symptoms.
- It has a chronic course that can progress to ESRD.
- Needs kidney biopsy to reach the diagnosis.

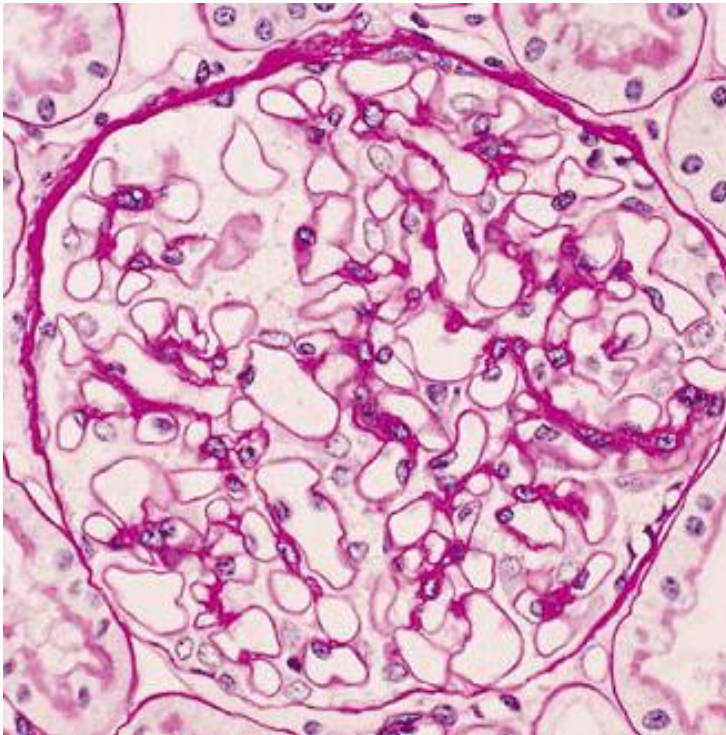
- The diagnosis is made by finding abnormal deposition of Ig A immunoglobulin in the Glomeruli, it elicit a local inflammatory response in the Glom mesangium (mesangial expansion)

- It is thought to be secondary to altered mucosal immunity that leads to excessive IgA synthesis followed by deposition in the gloms.
- There is really no effective immunosuppressing therapy except in severe cases where it can be tried.
- Most important treatment is to control the blood pressure which also decreases the proteinuria.

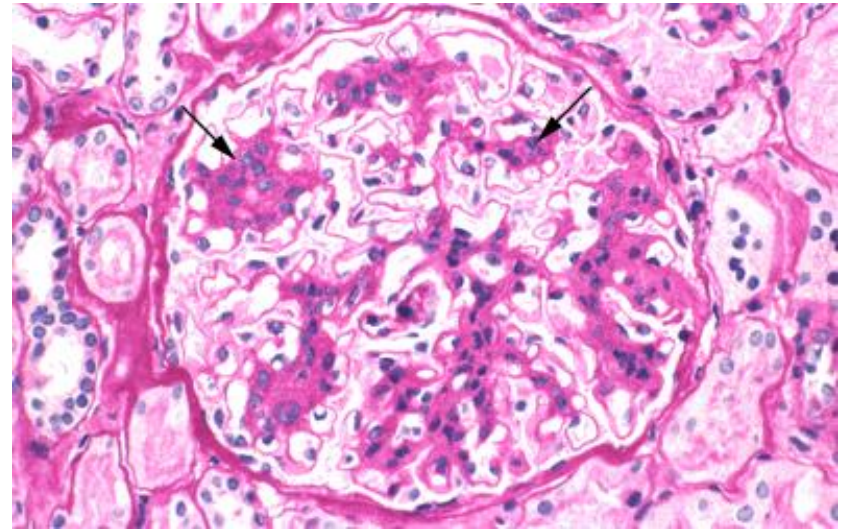
- HSP (Henoch-Schönlein purpura) is a systemic vasculitis caused by immune deposition of IgA in different organs; typically skin, bowel and kidneys.

IgA

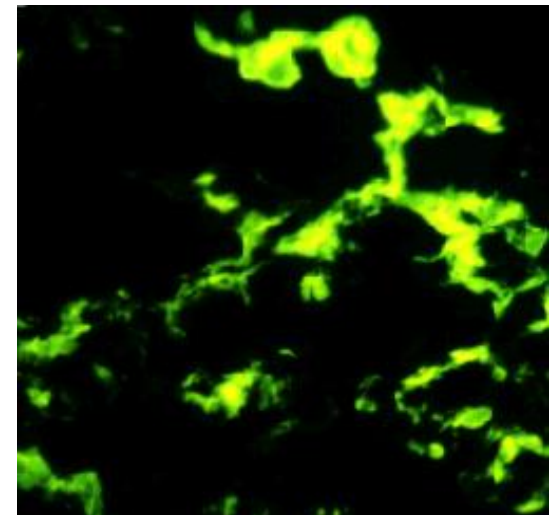
Normal Glomerulus



IgA Nephropathy



IgA IF



Post streptococcal glomerulonephritis (PSGN)

- Typically caused by throat infection with Gram positive cocci (Group A beta-hemolytic **Streptococcus** (GAS)).
- But also can be caused by Staphylococcus soft tissue or bone infection in adults.
- Bacterial Antigen cross react with Glom antigens, or may be an immune-complex (Antigen-antibody) response that is responsible.
- Patients present with frank hematuria usually **after one week** and up to 3 weeks from the start of infection.
- Serum will show positive Antistreptolysin (ASO) titer.
- Low C3, Normal or slightly low C4 in the serum.
- May have positive throat culture.
- Children have better and faster recovery than adults.
- Treatment is usually supportive= wait and see.

Lupus Nephritis

- **Lupus (SLE):** *The Disease with a Thousand Faces*
- Kidneys can be affected by SLE like other organs.
- The degree of involvement can be from mild (or even not visible to the physician) to a very severe one causing ESRD in few months.
- Most important in dealing with these cases is having high suspicion of its presence and to start immediate workup & referral for diagnosis and treatment.

Lupus Nephritis

- Kidney biopsy is mandatory to make the diagnosis.
- Low complements (C3, C4) level along with the positive Lupus markers, abnormal urine analysis & abnormal renal function should make you think of its presence.
- Lupus Nephritis treatment depends on the findings in renal biopsy.
- It usually involves high degree of immunosuppressing medications.

ANCA vasculitis

- Autoimmune disease that involves the presence of Neutrophils adhesion enhancing molecule called **ANCA=Anti-neutrophil cytoplasmic antibody**

Two types of ANCA:

1- C-ANCA= **C**ytoplasmic type, more commonly causing Granulomatous Polyangiitis = old name *Wegner's Granulomatosis* (so a **granuloma forming disease**)

Angiitis: means small vessels vasculitis

2- P-ANCA= **P**erinuclear type, more commonly associated with Microscopic Polyangiitis & Churg-Strauss syndrome

ANCA vasculitis

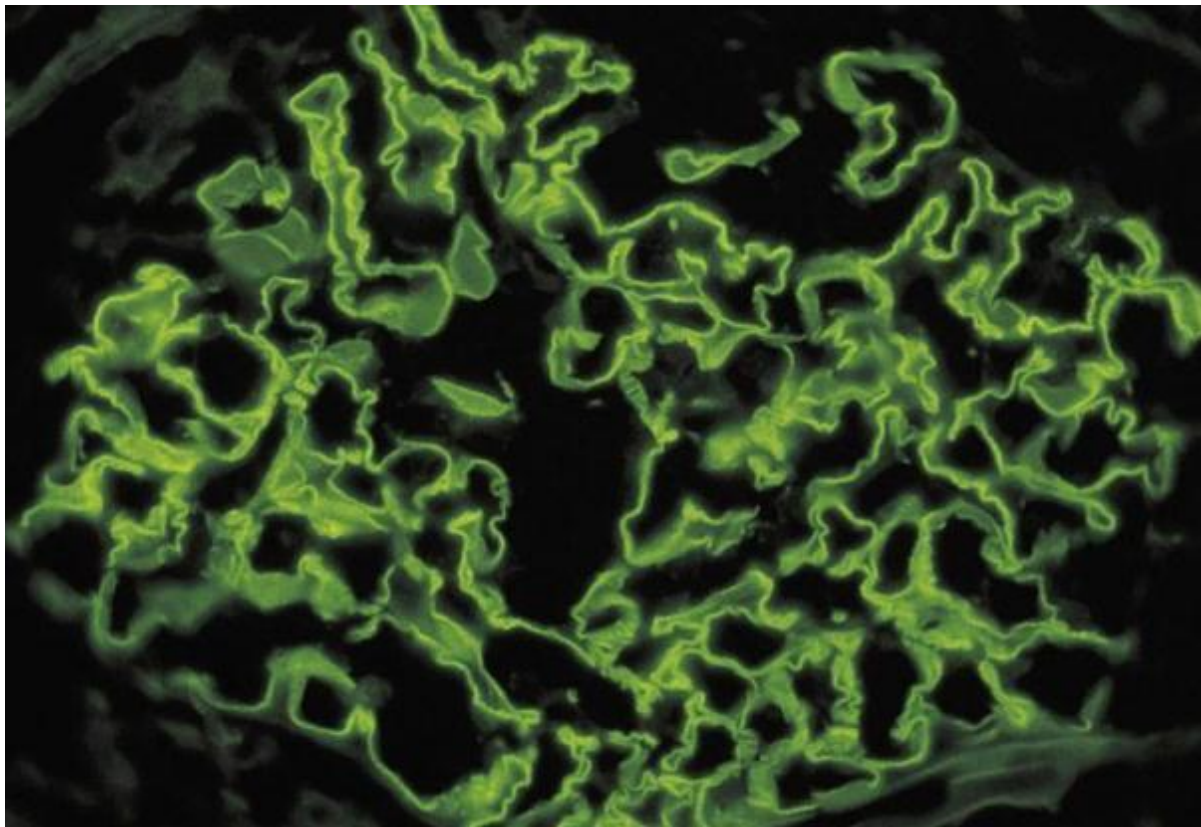
- Upper airways and lung involvement is common and patients can present with renal and pulmonary manifestations (GN + Pulmonary hemorrhage: hemoptysis)
- Diagnosis is made by kidney biopsy and positive ANCA titer in the serum.
- It is usually an aggressive disease that should be treated with potent immunosuppressing medications. (high dose corticosteroids & cyclophosphamide).

Anti-GBM antibody disease

(Anti Glom Basement Membrane)

- Due to autoantibody against (alpha-3 chain) of type IV Collagen that is found in Glomerular & alveolar (lungs) basement membrane.
- So the manifestations will be:
 - 1- GN (can be the only presenting finding) &
 - 2- Pulmonary hemorrhage (if with GN; is called Goodpasture's disease = Lungs + renal involvement.
 - 3- positive test for Anti-GBM antibodies in the serum
 - 4- Kidney biopsy shows the diagnostic Immunofluorescence pattern : Linear stain of IgG and C3

Linear Anti-GBM staining by Immunofluorescence
is a *Diagnostic test*



Anti-GBM

- Treatment is always started immediately to remove the antibodies by **Plasmapheresis** and preventing further antibodies production by giving heavy immunosuppression that includes corticosteroids and cyclophosphamide.

Membranoproliferative GN (MPGN)

It is a pathological description & has multiple causes.

It may present with Nephritic picture or Nephrotic syndrome

The primary (idiopathic) MPGN is mainly seen in children.

The secondary type is seen in adults due to:

- Hepatitis B and C
- Endocarditis
- Lupus and Sjogren's syndrome
- Cancer
- Complement deficiency