GLOMERULAR DISEASES

MED 341

November 2018

Objectives

1- To understand the pathophysiology of Glomerular Diseases.

2- To be able to correlate between the clinical presentation & the underlying Glomerular pathology.

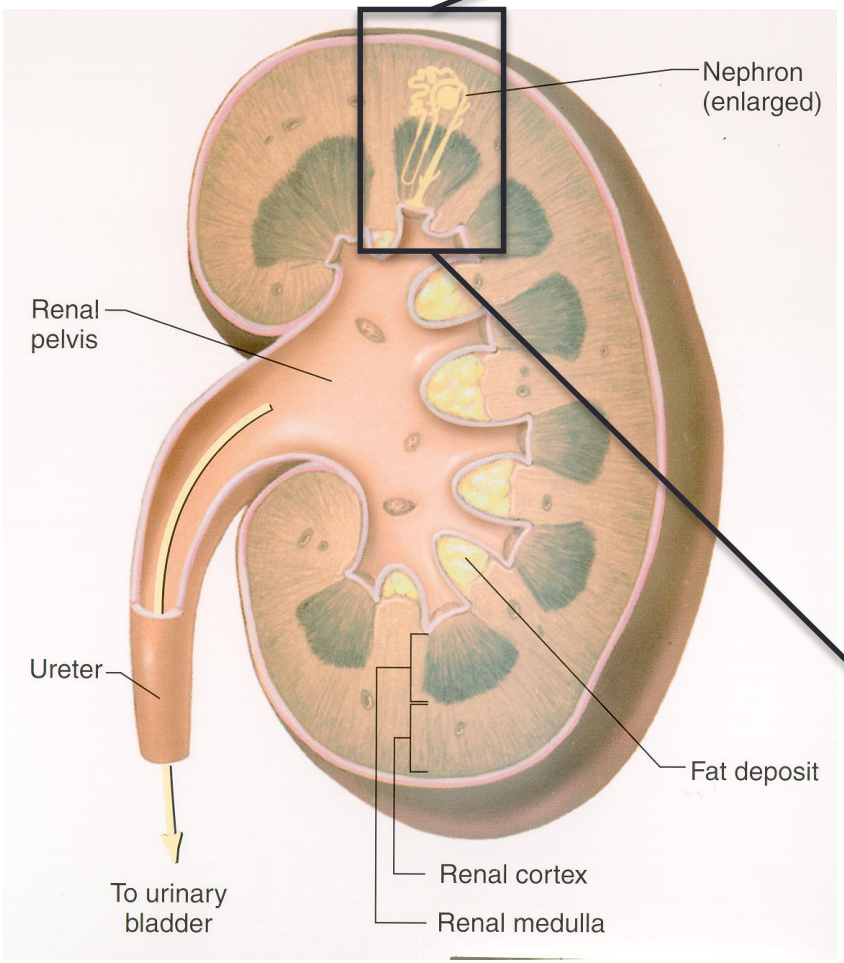
3- To recognize the differences between Nephritic & Nephrotic Glomerular diseases.

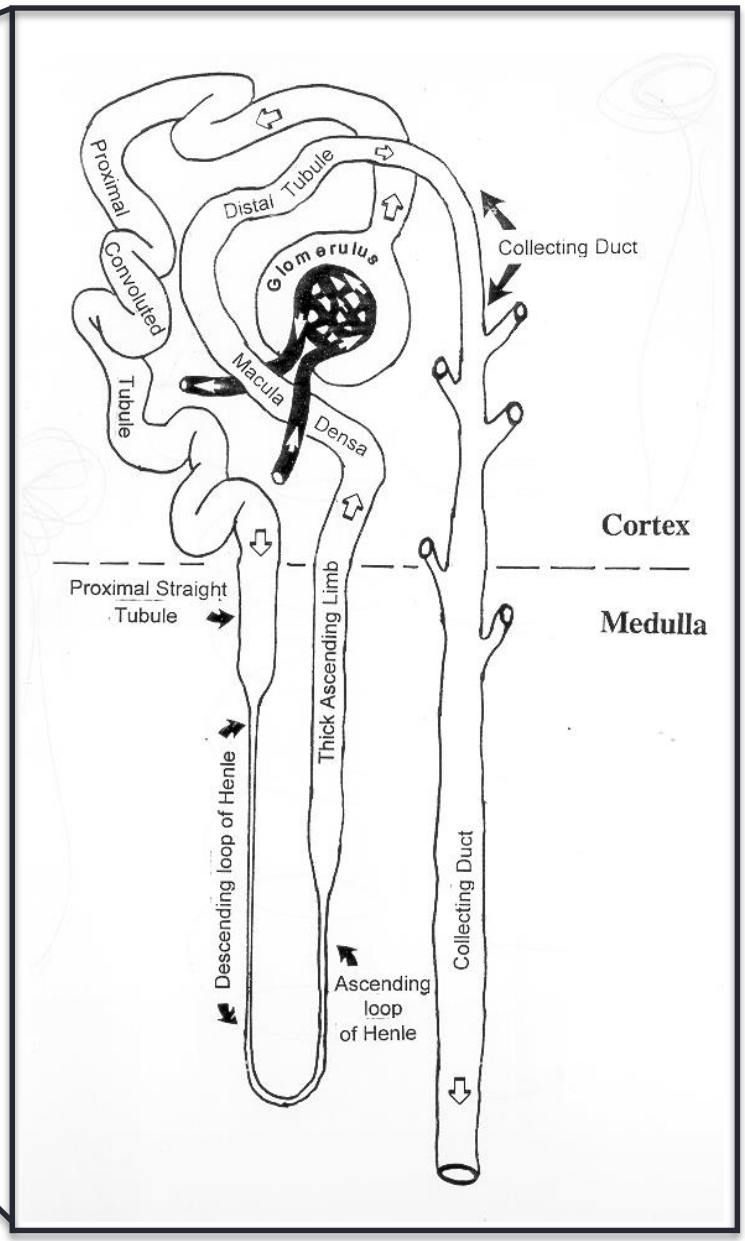
4- To recognize the important features of Nephritic & Nephrotic renal diseases.

5- To be able to recognize the early features of Glomerular diseases before it is too late!

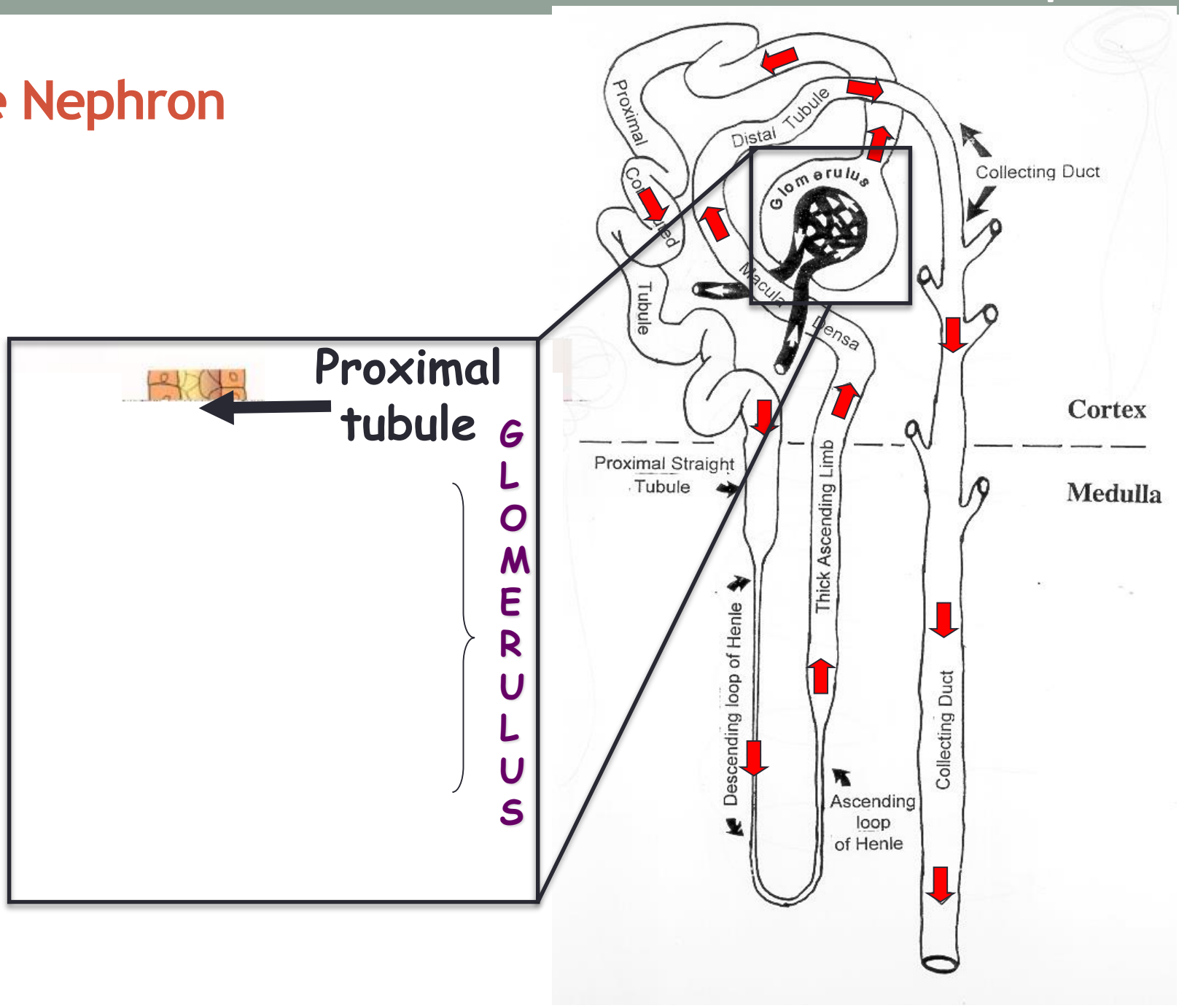
6- To learn the common causes of Nephrotic & Nephritic renal diseases.

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

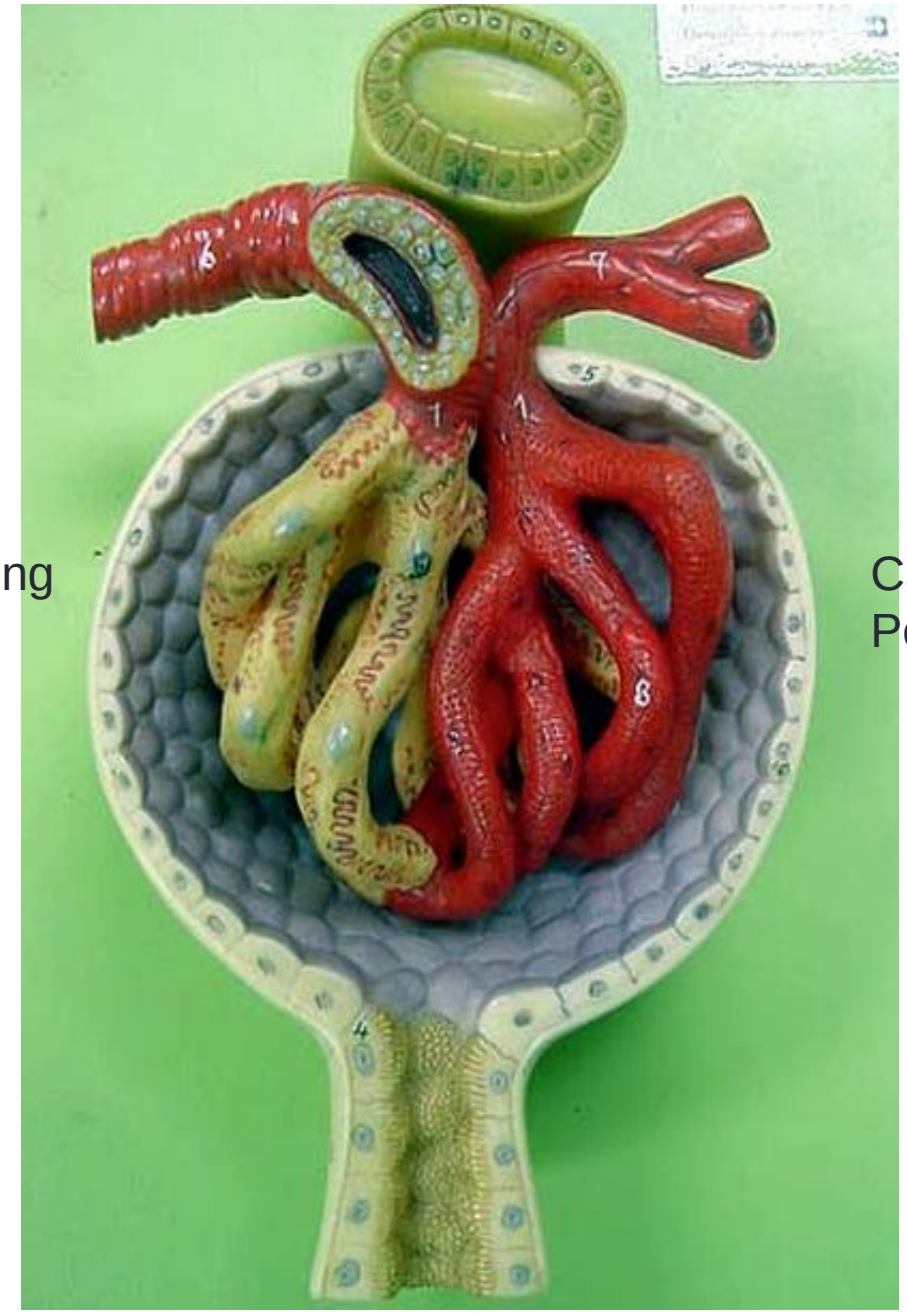




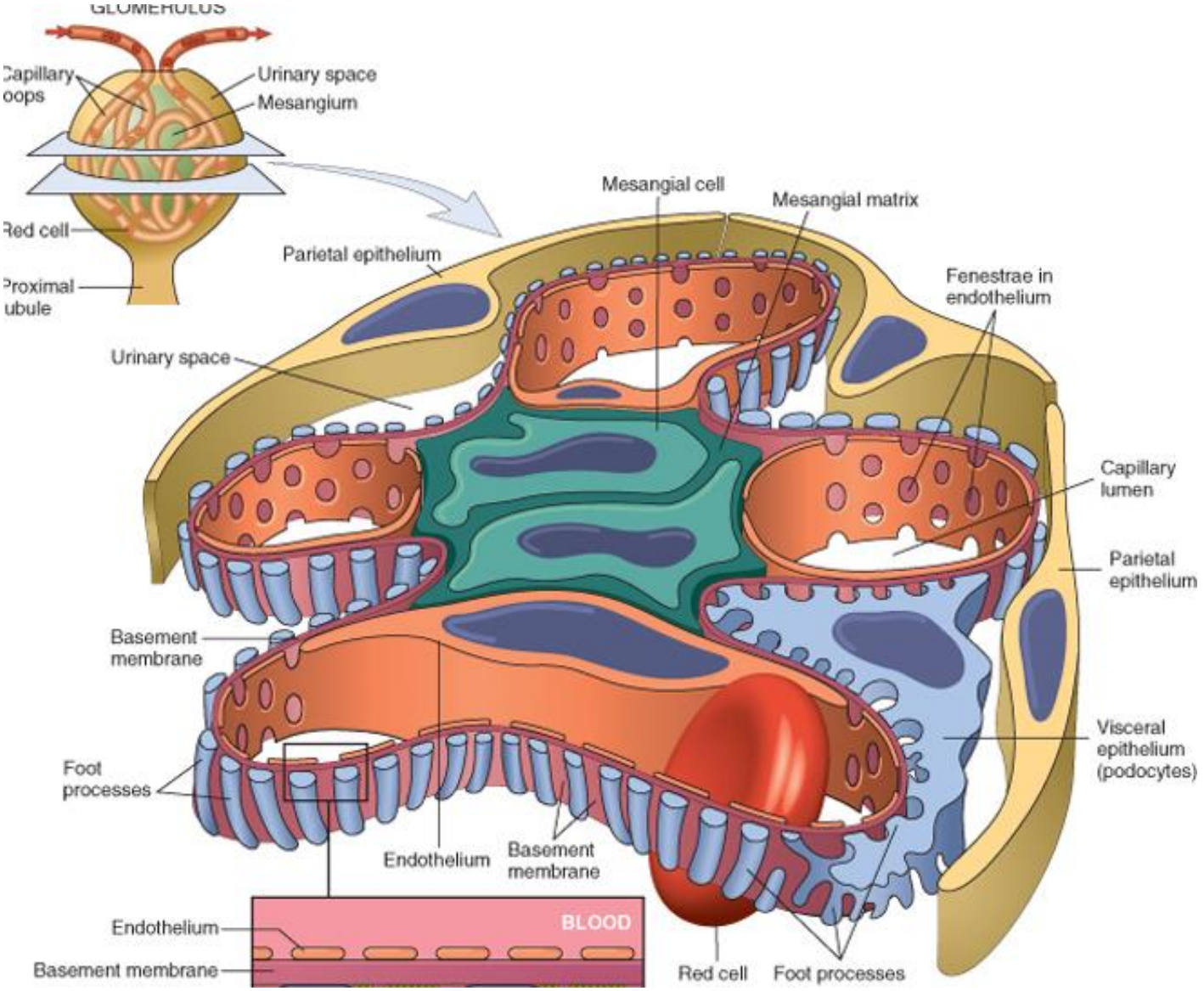
The Nephron


Proximal tubule
GLOMERULUS
Proximal Convoluted Tubule
Distal Tubule
Glomerulus
Macula Densa
Collecting Duct
Cortex
Medulla
Proximal Straight Tubule
Thick Ascending Limb
Descending loop of Henle
Ascending loop of Henle
Collecting Duct

Podocytes covering Capillary wall



Cappilary wall without Podocytes

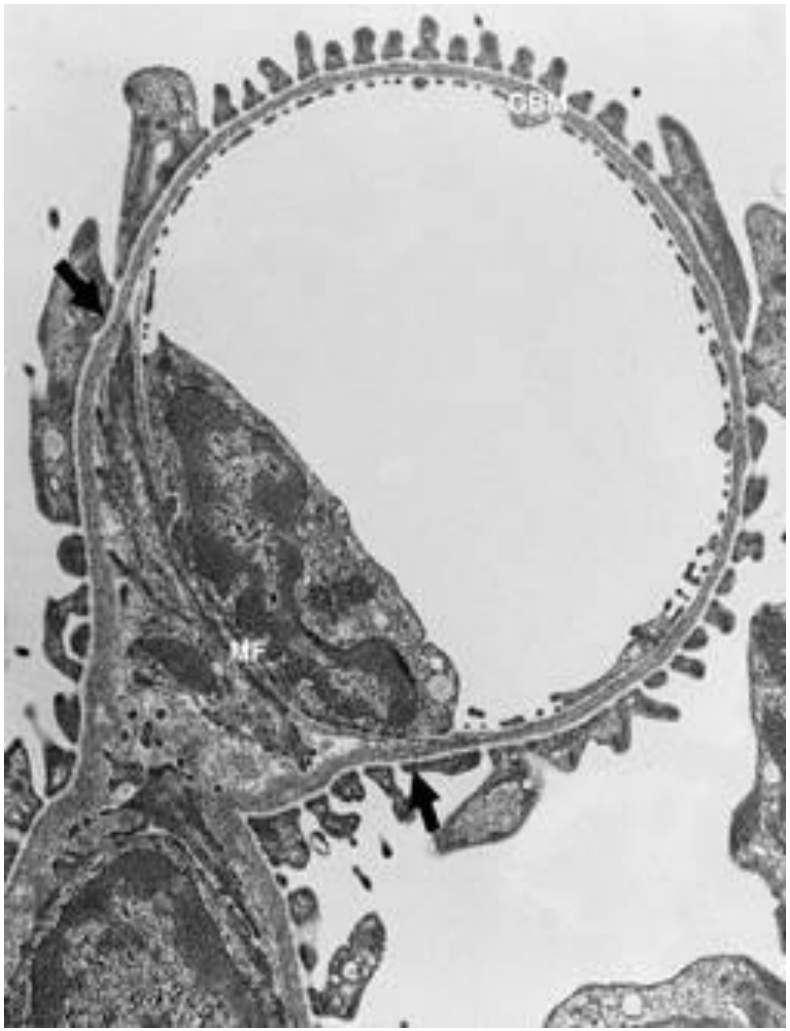

GLOMERULUS
Capillary loops
Urinary space
Mesangium
Red cell
Proximal tubule
Mesangial cell
Mesangial matrix
Parietal epithelium
Fenestrae in endothelium
Urinary space
Capillary lumen
Parietal epithelium
Basement membrane
Visceral epithelium (podocytes)
Foot processes
Endothelium
Basement membrane
BLOOD
Endothelium
Basement membrane
Red cell
Foot processes

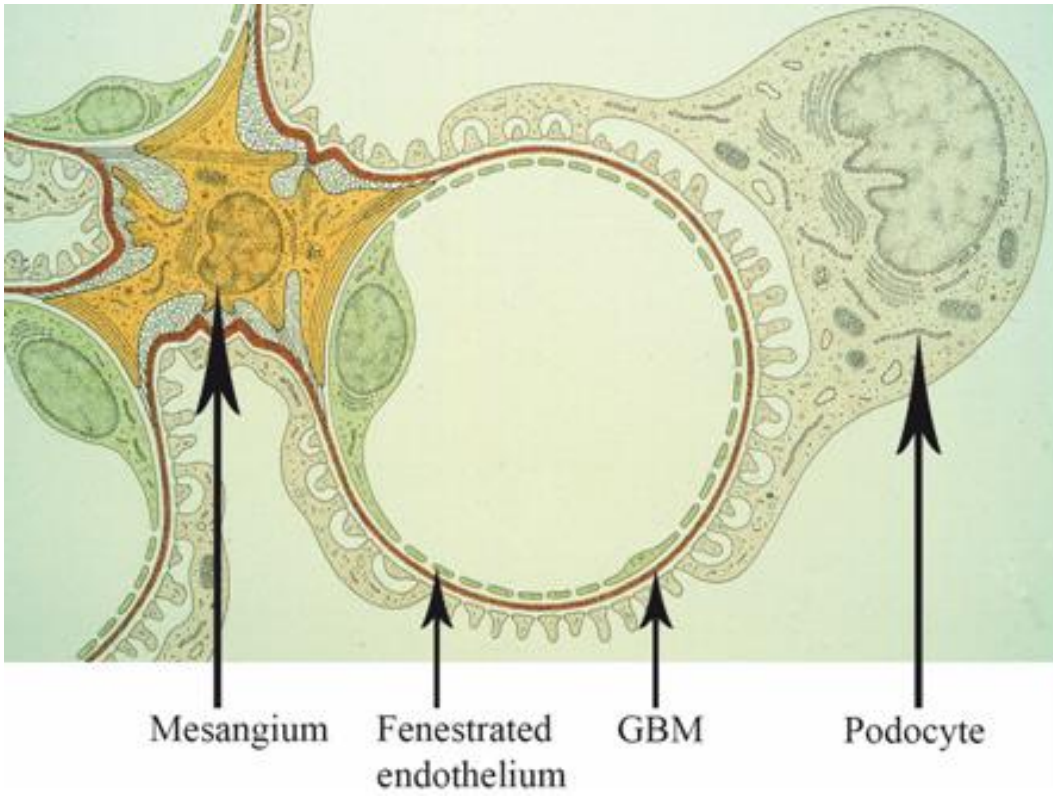
Microscopy

Light Microscope 2000x

EM 10,000,000

Normal Capillary Loop / wall (Electron Microscopy)





Normal Glomerular structure:

- Keeps 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.

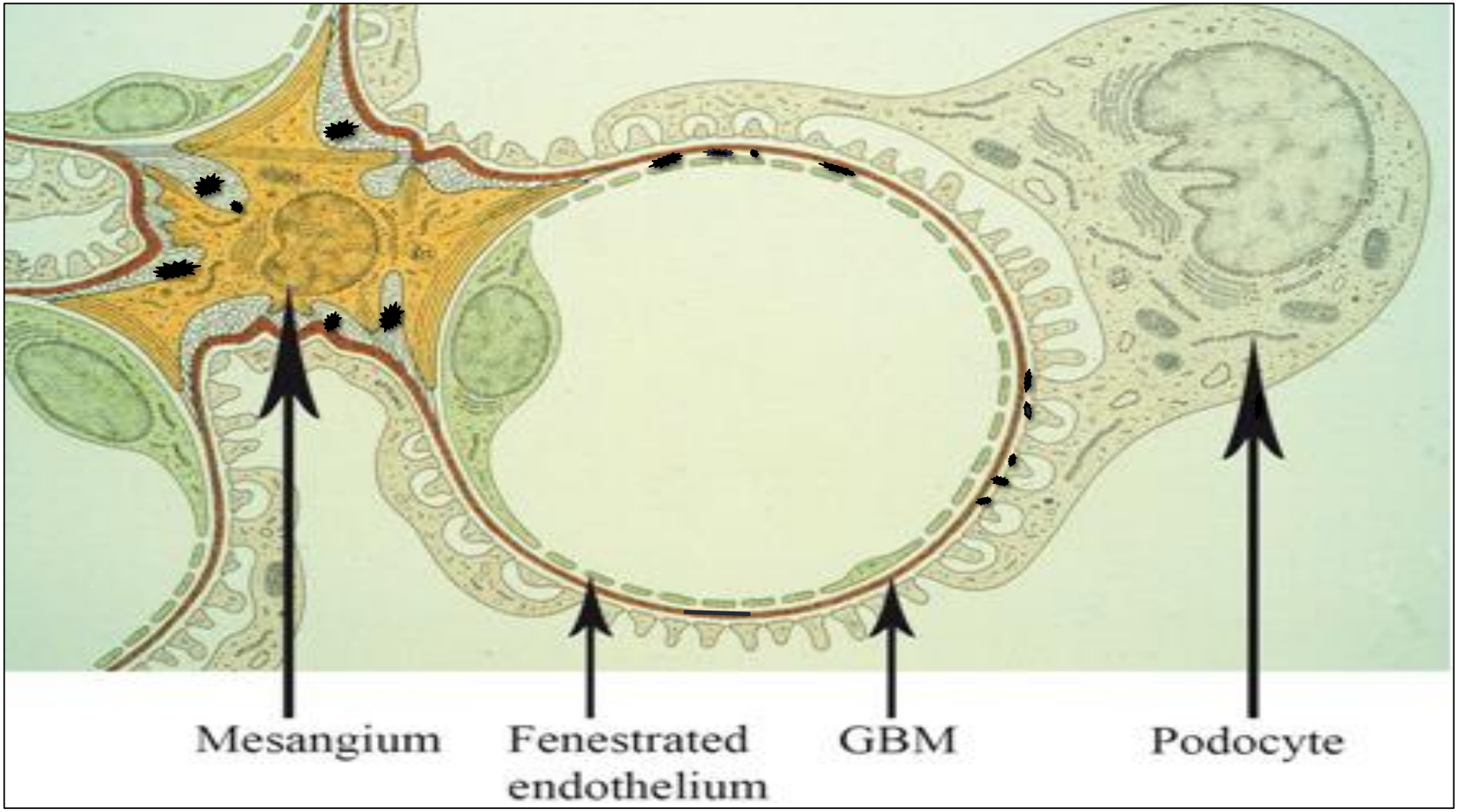
So, if Glomerular structure is **intact** the urine will show:

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

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.


Mesangium
Fenestrated endothelium
GBM
Podocyte

How glomerular diseases start?

Most important to recognize:

- *The manifestations of a glomerular disease are usually indicative of which components of glomerulus structure was affected mainly by the disease process:*

if ***Podocytes*** were the main target of the disease process this leads mainly to ***proteinuria*** (at large amount) ***due to foot process effacement***; thus **Nephrotic Syndrome** will be the main finding.

if ***endothelial cells*** **or Mesangial cells or GBM or all of them together** were targeted; then Glom Capillary wall will be damaged by inflammation so blood components will leak to the urine space causing: ***hematuria, proteinuria and abnormal renal function***; thus **Nephritic** pattern of renal disease will be present **(Clinically called: Glomerulonephritis or GN)**

Another important things to remember;

>> Glomerular diseases are named based on their histo-pathological 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 causing foot process effacement)

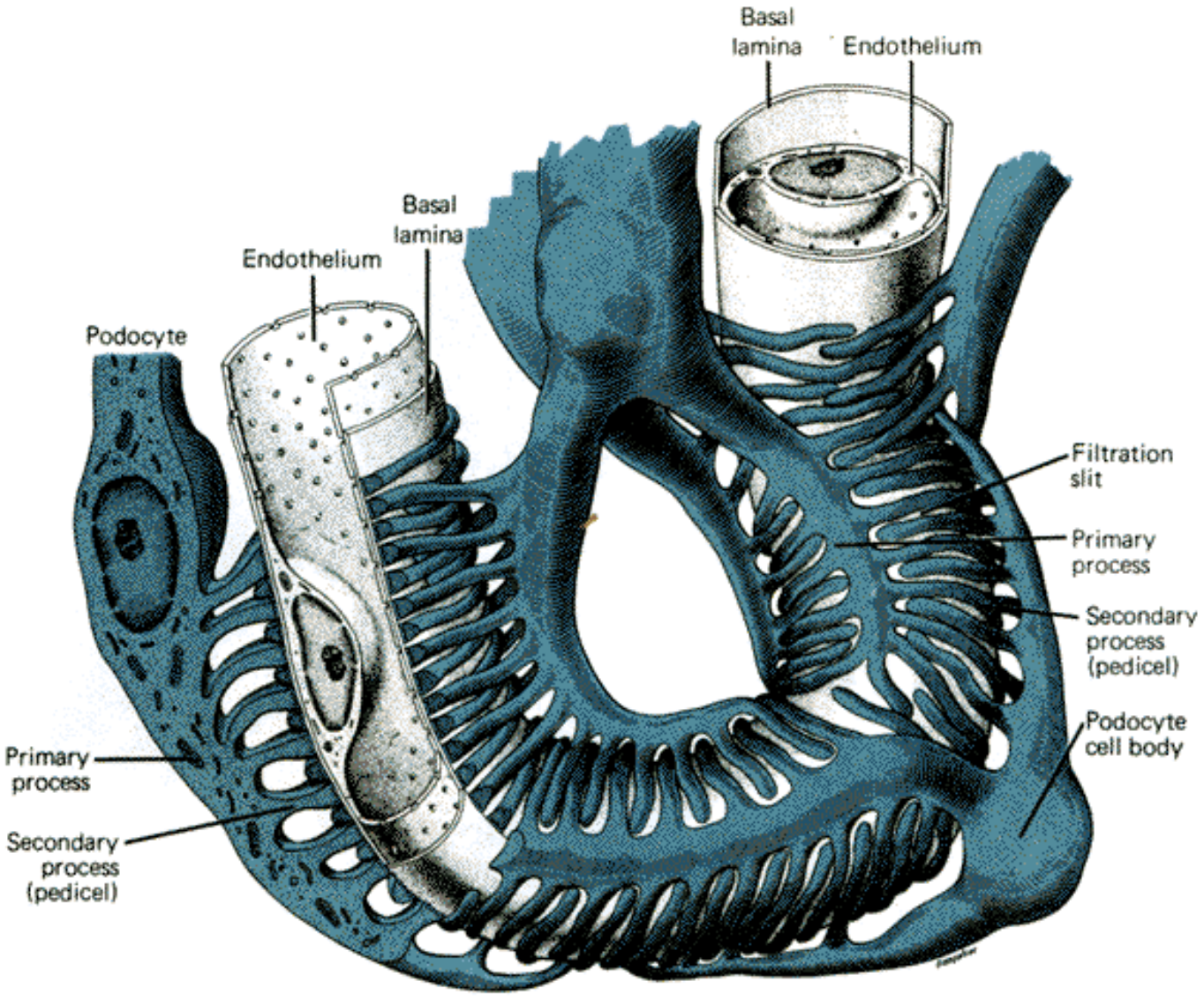
>>> **Nephritic** = **Glomerulonephritis** or **GN** (due to glomerular mesangial cells; endothelial cells proliferation & glomerular capillary wall inflammation

Nephrotic Syndrome (NS):

- Podocytes abnormality (pathology) is the primary finding in NS.

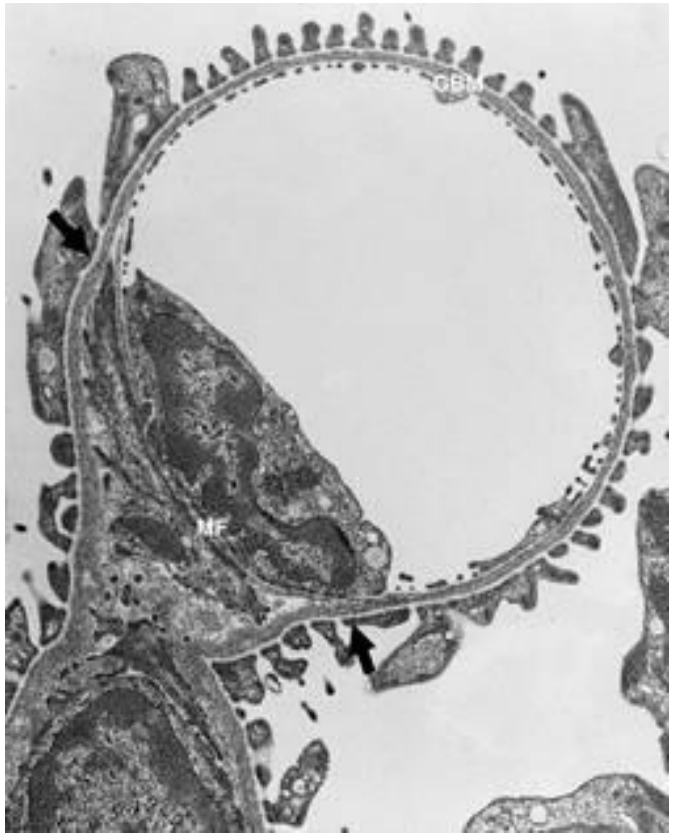
- Podocytes will sustain a structural dysfunction; making them lose their Foot-processes (called: Foot process effacement) while their cells' bodies remain intact; this pathology makes Glom capillary wall becomes permeable to Albumin.

- This will lead to significant amount of protein appearing in the urine (Proteinuria).

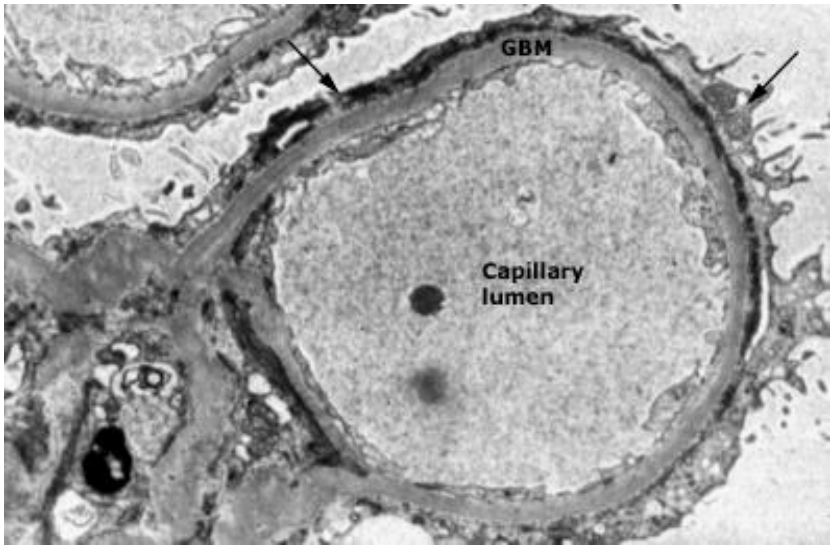

Basal lamina
Endothelium
Basal lamina
Endothelium
Podocyte
Filtration slit
Primary process
Secondary process (pedicel)
Podocyte cell body
Primary process
Secondary process (pedicel)

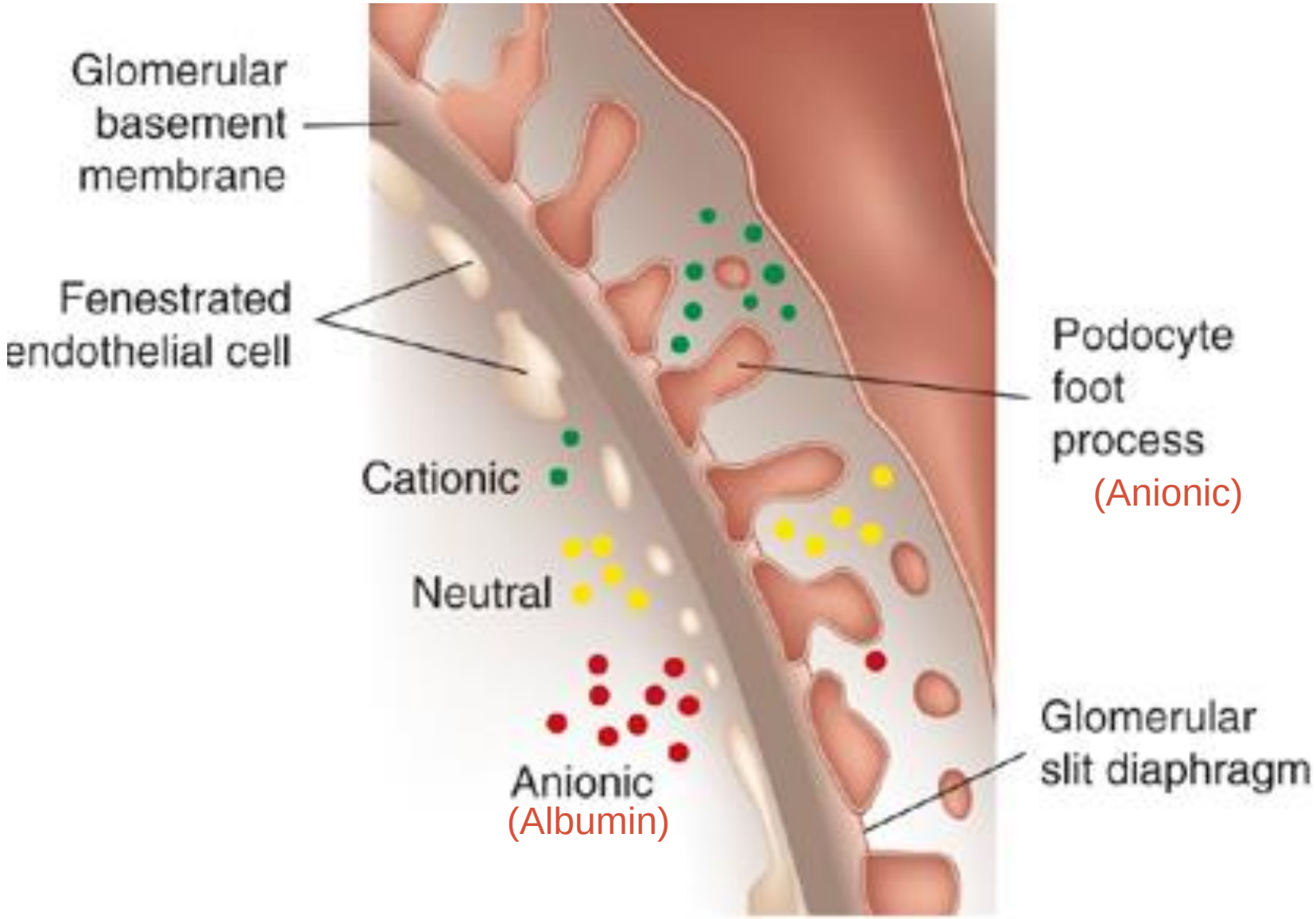
Podocytes pathology in NS

Normal Foot Processes



Diffuse Foot Processes Effacement




Glomerular basement membrane
Fenestrated endothelial cell
Cationic
Neutral
Anionic (Albumin)
Podocyte foot process (Anionic)
Glomerular slit diaphragm

Nephrotic Syndrome

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

- **Hypoalbuminemia (serum Albumin <30 g/L),** the Normal serum Albumin level : 35-55g/L
- **proteinuria (secretion of > 3.5 g** (> 3500 mg) **of Protein in the urine per day).** detect by 24h urine collection;
- **Peripheral or generalized edema**
- **Hyperlipidemia**

Large amount of proteinuria = is called Heavy proteinuria

Complications of Nephrotic Syndrome

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

Important definitions about Proteinuria:

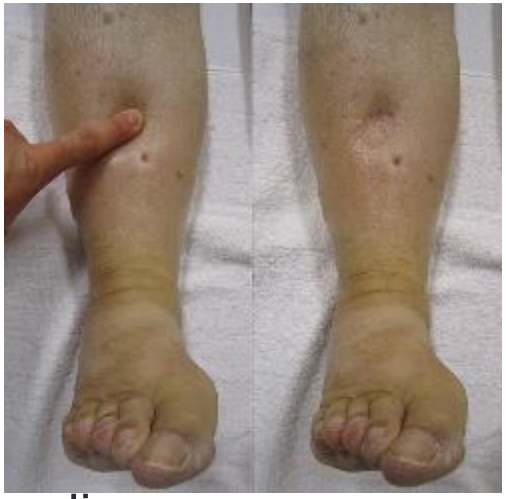
How many milligrams of proteins are normally secreted in the urine per-day?

- **< 150 mg/day of all kinds of proteins**. (albumin & non-albumin proteins), on average; 4-7 **mg**/day out the 150mg/Day is Albumin, the remaining is Non Albumin proteins.
- Proteinuria > 150 mg/day is a pathological indicator.
- If Proteinuria >150 & ≤300 mg is called Microalbuminuria
- > 300 mg/ Day : overt proteinuria
- > 3500 mg/ Day : Nephrotic range Proteinuria Or Heavy Proteinuria

Urine Analysis in Nephrotic Syndrome will show:

- **A lot of protein is secreted in the urine per day**
- Must be (>3.5 g/24h urine) ; called ***Nephrotic range proteinuria***
- No RBCs (some times few RBCs are occasionally seen)
- No RBCs casts
- **Fat in the urine (Lipiduria)** : Fatty casts, oval fat bodies & fat droplets)
- No WBCs (few may be seen)

Clinical Presentation:

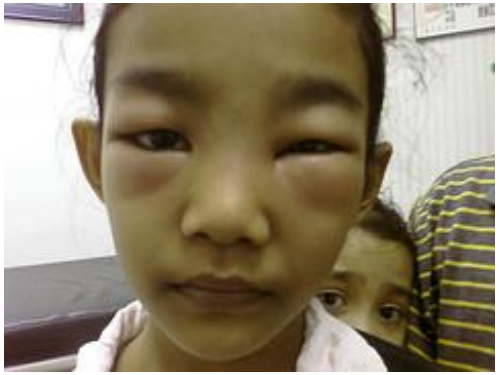


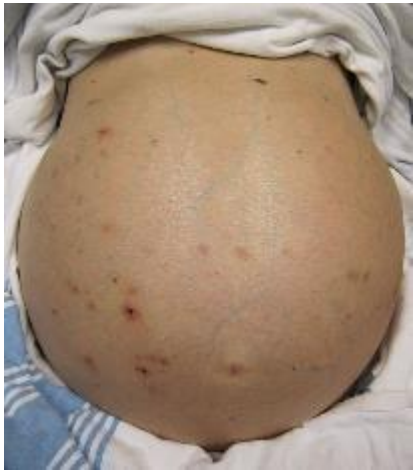
Edema due to:

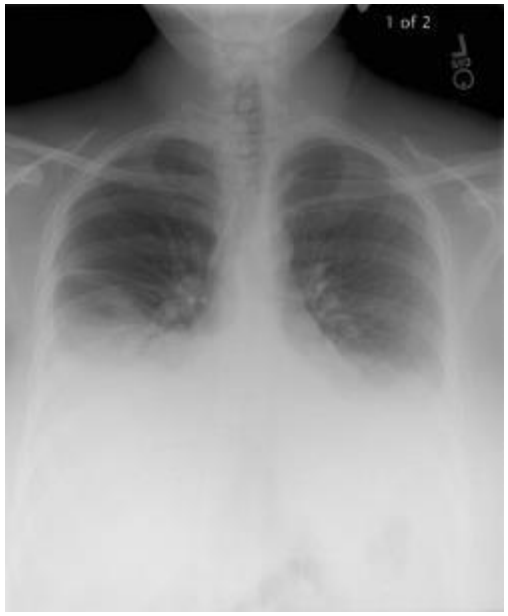
1- Low serum Albumin (Low oncotic pressure)

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 due to bowel edema
- Weight gain due to fluid retention
- Shortness of breath if having pleural effusion
- May be signs & symptoms of DVT, PE as complications

Glomerular Diseases that may present as Nephrotic Syndrome

1-**Focal Segmental GlomeruloSclerosis (FSGS)**

2- **Minimal Change Disease (MCD)**

3- **Membranous Nephropathy** (MN)

Focal Segmental GlomeruloSclerosis (FSGS)

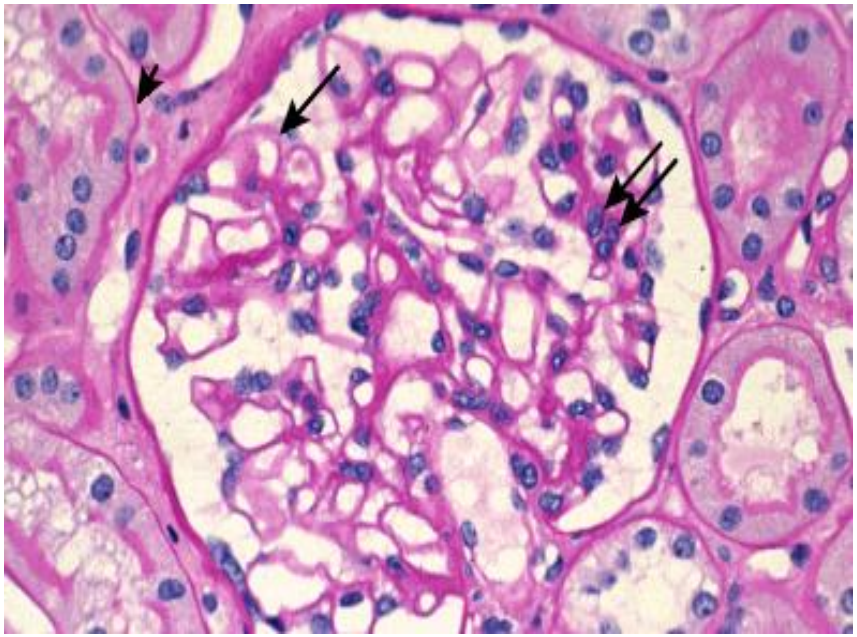
Could be Primary Or Secondary Or Genetic

- ***Focal mean***: some glomeruli are affected by sclerosis (the rest of them look normal)
- ***Segmental means***: sclerosis only involves a segment of each glomerulus that is affected by the disease.

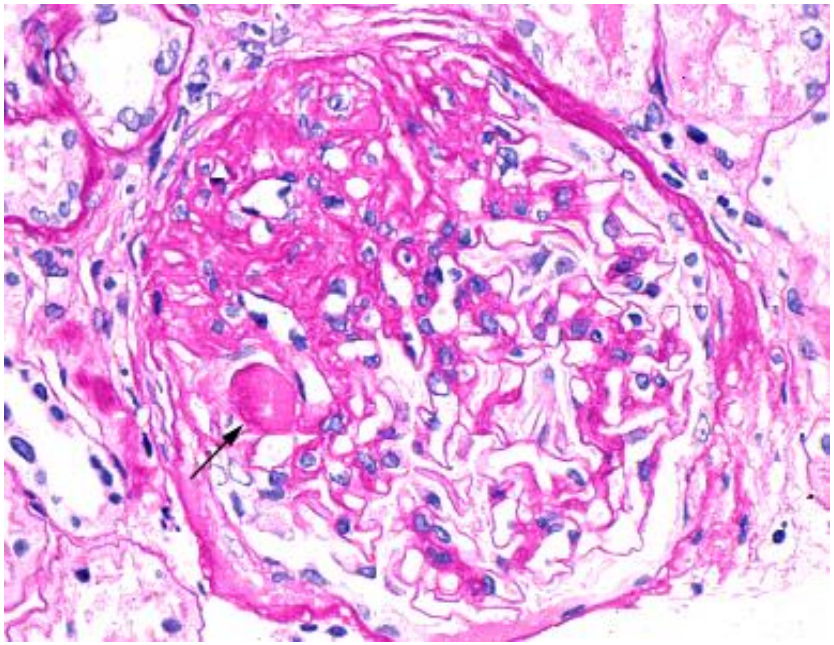
- But most importantly; in The **primary type :** all glomeruli (the ones that are affected by sclerosis and the ones that are not affected) **ALL** of them will have a **diffuse foot processes effacement** (thus Nephrotic syndrome appears as the clinical presentation).

Focal Segmental GlomeruloSclerosis (FSGS)

Normal

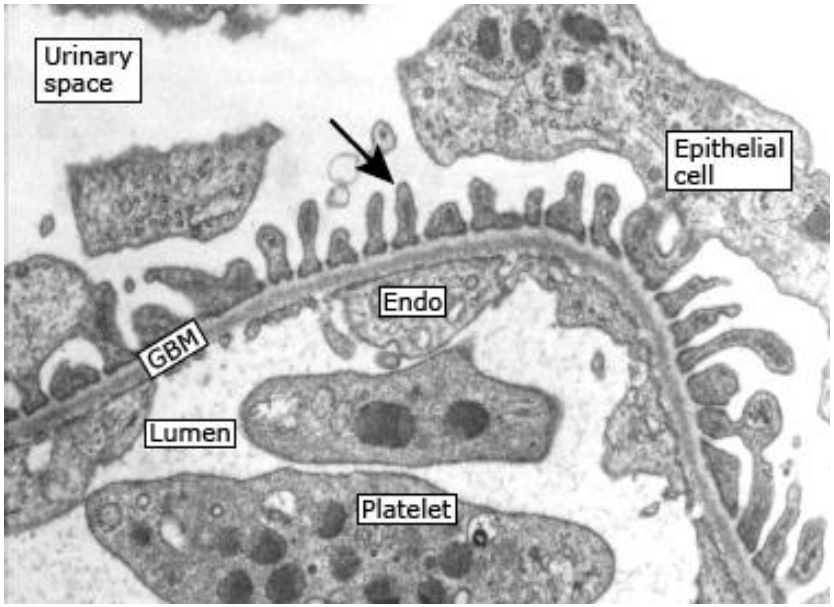


FSGS

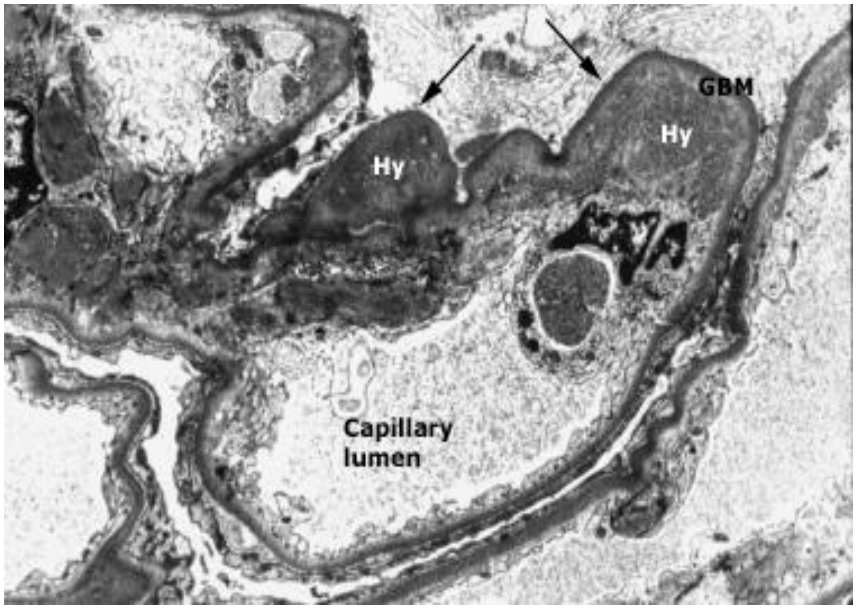


Focal Segmental GlomeruloSclerosis (FSGS)

Normal



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



Focal Segmental GlomeruloSclerosis (FSGS)

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

Focal Segmental GlomeruloSclerosis (FSGS)

Can be:

Primary FSGS:

- Has sudden onset of heavy proteinuria and other manifestations of nephrotic syndrome.
- ? Circulating Factor (like autoantibodies) targets podocytes and causes effacement
- Usually treated with corticosteroids and other immunosuppressing medications like CNI

Focal Segmental GlomeruloSclerosis (FSGS)

Or can be

Secondary FSGS:

-Proteinuria is less heavy than other causes of nephrotic syndrome, even less < 3.5 gm/Day

-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:

- Severe obesity
- Nephron loss (> 75% of renal mass) e.g renal agenesis
- Reflux nephropathy
- DM
- Sickle Cell Anemia
- Healing of prior GN (example IgA)
- Anabolic steroid
- Severe preeclampsia
- Drugs: Interferon, Bisphosphonates (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 (CNIs)

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 also called: nil disease. (nil = nothing)

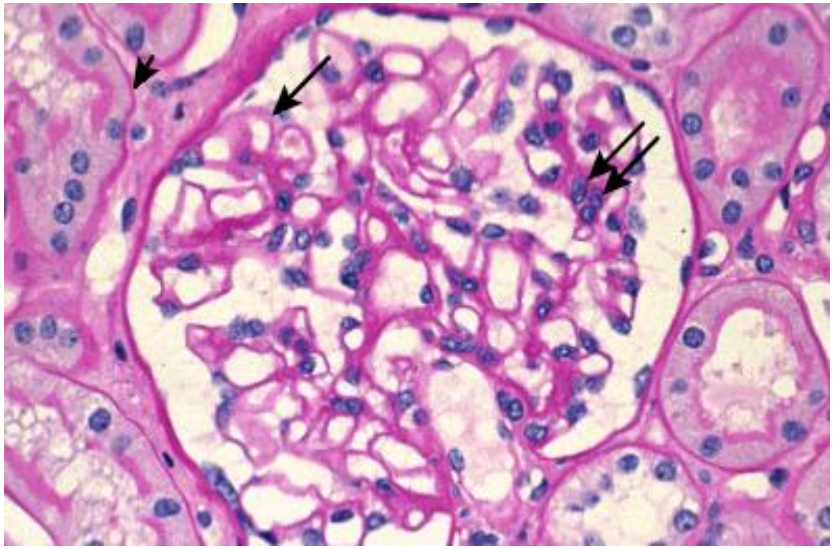
  BUT:

- electron microscopy: shows *diffuse effacement of the epithelial cells' foot processes only. No other abnormality is seen.*

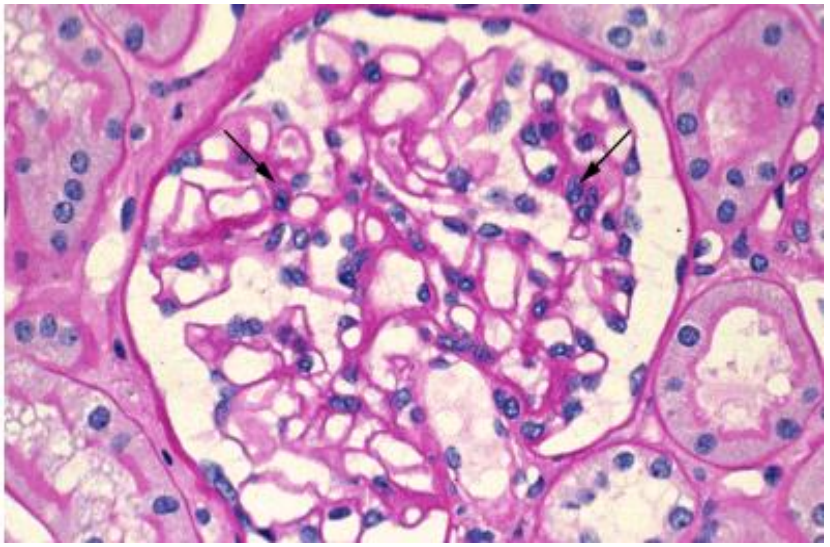
- *So the most important difference between MCD and Primary FSGS is the presence of glomerular sclerosis in FSGS*
- *there is no sclerosis in MCD.*

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

Normal Glomerulus

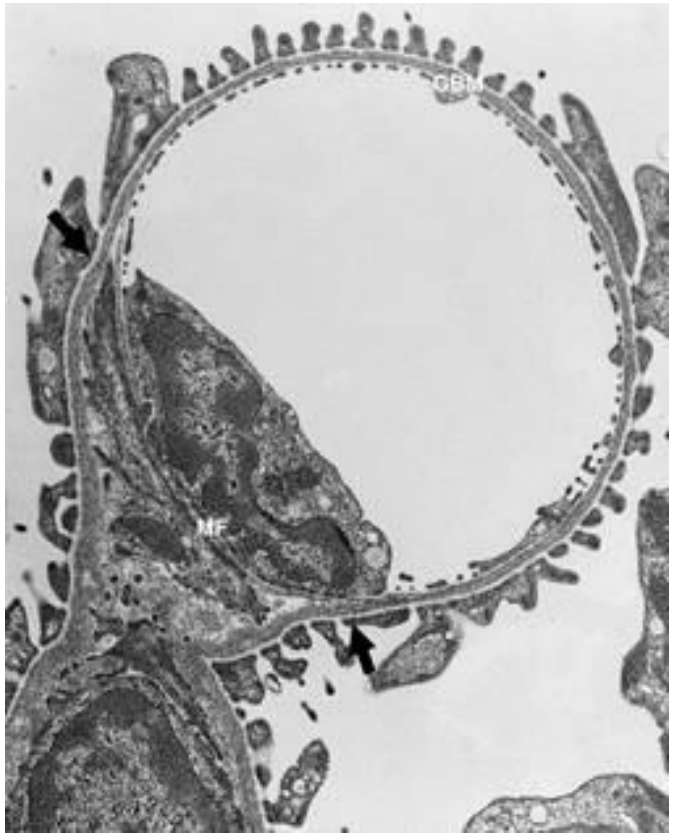


MCD, basically no abnormality is seen on light microscopy

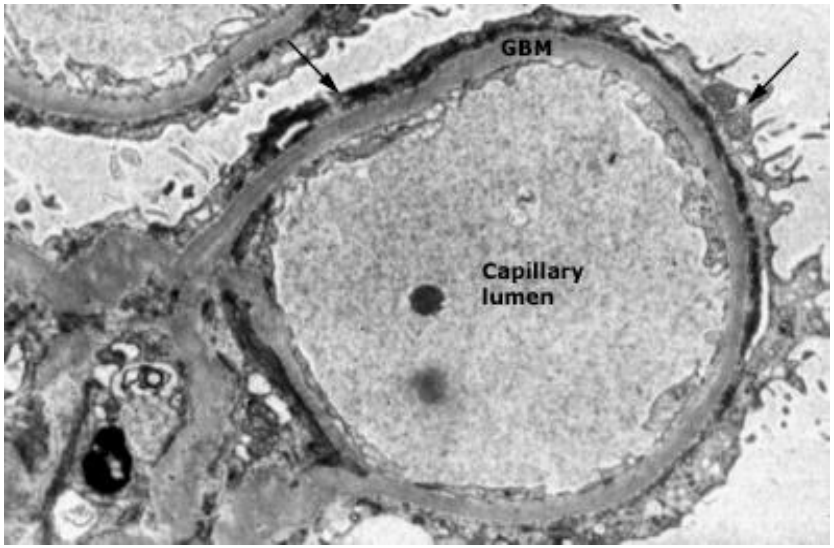


Cont. **Minimal Change Disease (MCD)**

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:

- Causes 90 % of NS 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 (few days)
- BP may be normal or slightly elevated
- Heavy proteinuria (Nephrotic range)
- Lipiduria
- Hypoalbuminmia (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 will show Diffuse effacement of foot process ONLY.

Treatment:

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

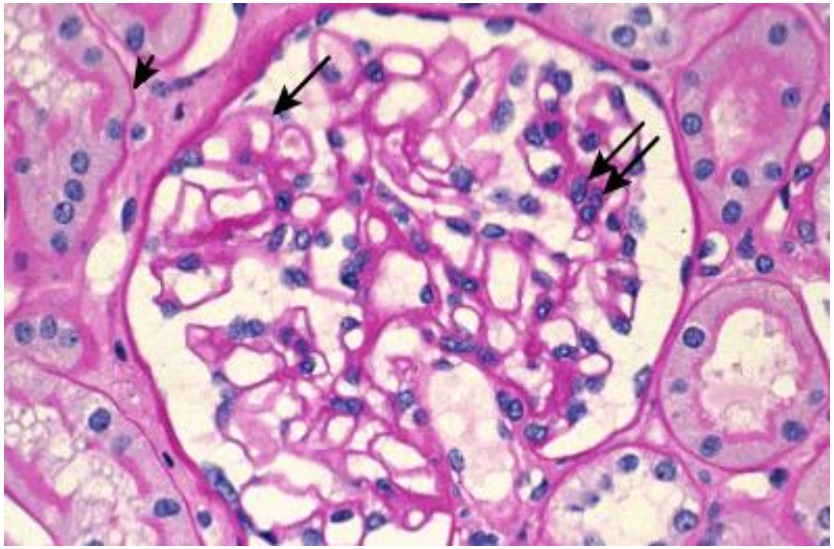
Second line: oral Cyclophosphamide, Cyclosporin

Membranous Nephropathy (MN)

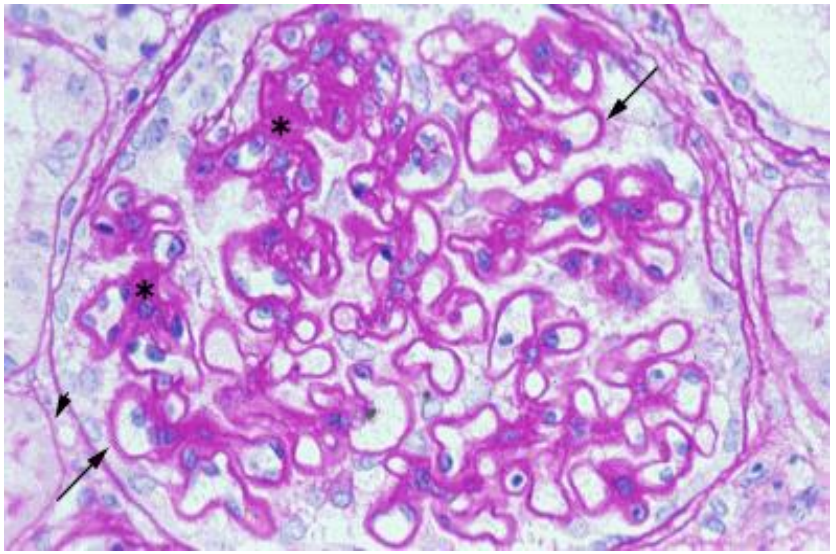
- **Most common cause of Primary nephrotic syndrome in adults** (15% and 33%)
- Mostly secondary in children (hepatitis B antigenemia)
- Presentation: slowly developing nephrotic syndrome (few weeks)

Membranous Nephropathy (MN)

Normal



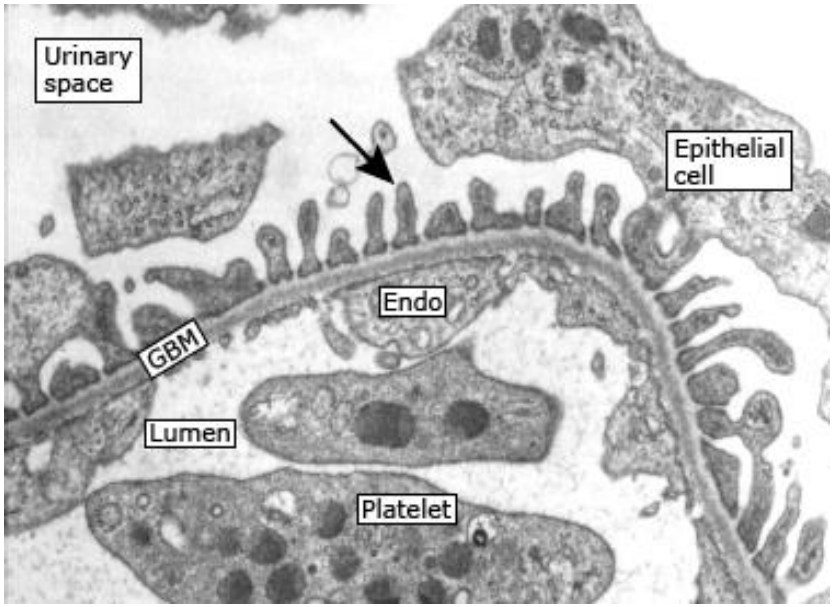
MN



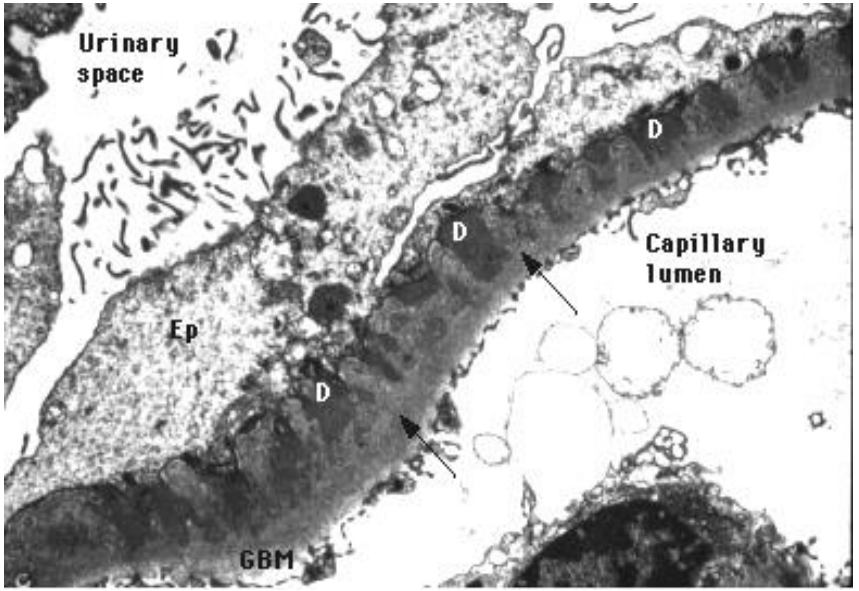
Diffuse thickening of the glomerular capillary wall throughout all glomeruli (IgG and C3 deposition)

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** like 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

How glomerular diseases start?

Most important to recognize:

- *The manifestations of a glomerular disease are usually indicative of which components of glomerulus structure was affected mainly by the disease process:*

if ***Podocytes*** were the main target of the disease process this leads mainly to ***proteinuria*** (at large amount) ***due to foot process effacement***; thus **Nephrotic Syndrome** will be the main finding.

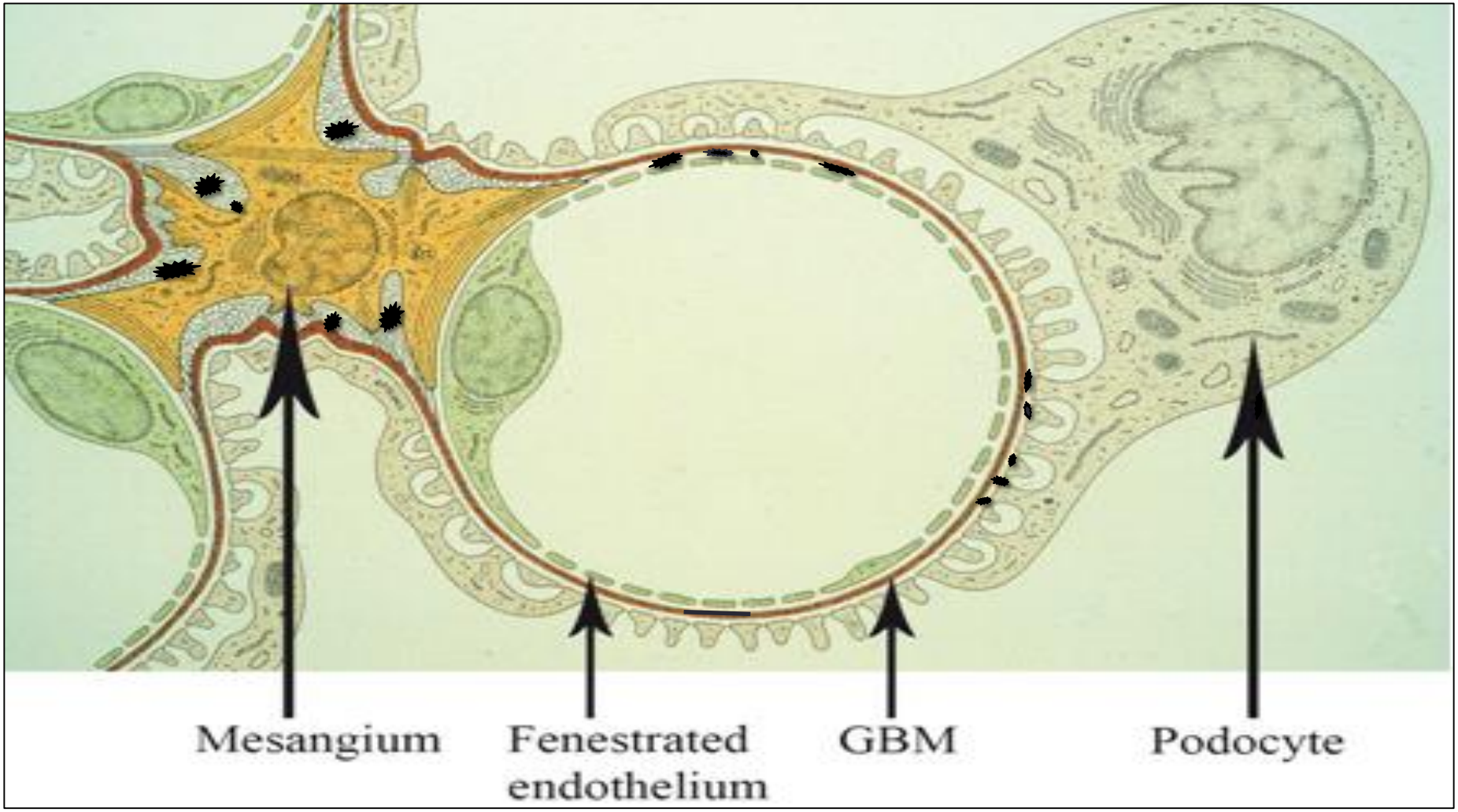
if ***endothelial cells*** **or Mesangial cells or GBM or all of them together** were targeted; then Glom Capillary wall will be damaged by inflammation so blood components will leak to the urine space causing: ***hematuria, proteinuria and abnormal renal function***; thus **Nephritic** pattern of renal disease will be present **(Clinically called: Glomerulonephritis or GN)**

Nephritic Glomerular diseases - GN

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


Mesangium
Fenestrated endothelium
GBM
Podocyte

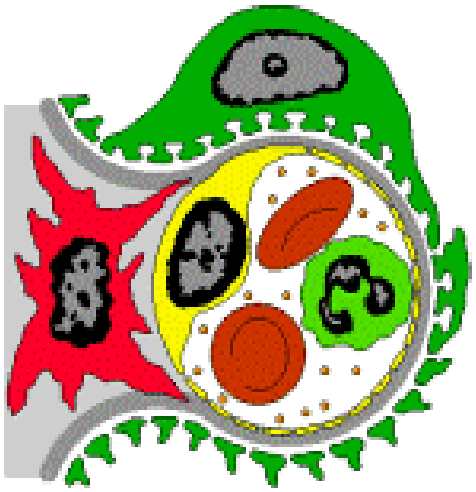
Nephritic urine will show:

- Red Blood Cells (RBCs)
- RBCs casts, or cellular casts
- Dysmorphic RBCs (RBCs lose their smooth surface while passing through the cracks in inflamed glomerular capillary wall)
- Proteinuria (at variable amount from subnephrotic to nephrotic range)

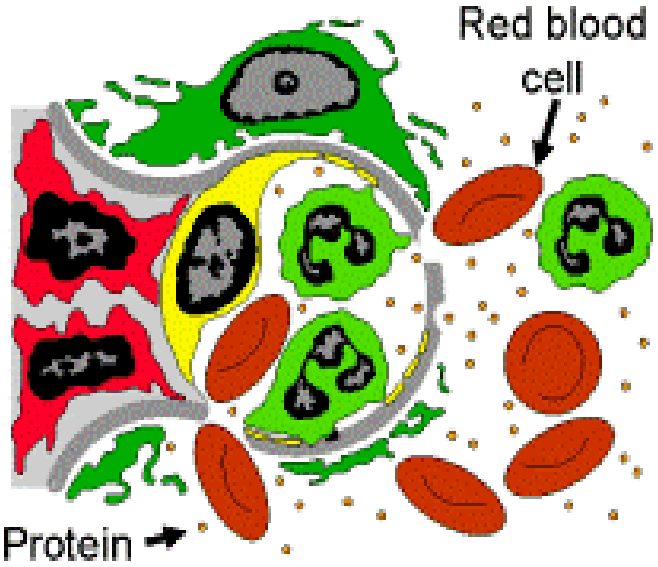
Dysmorphic RBCs & RBC casts are called **Active Urinary Sediments** when seen under microscope in urine sample

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

Proteinuria and Hematuria

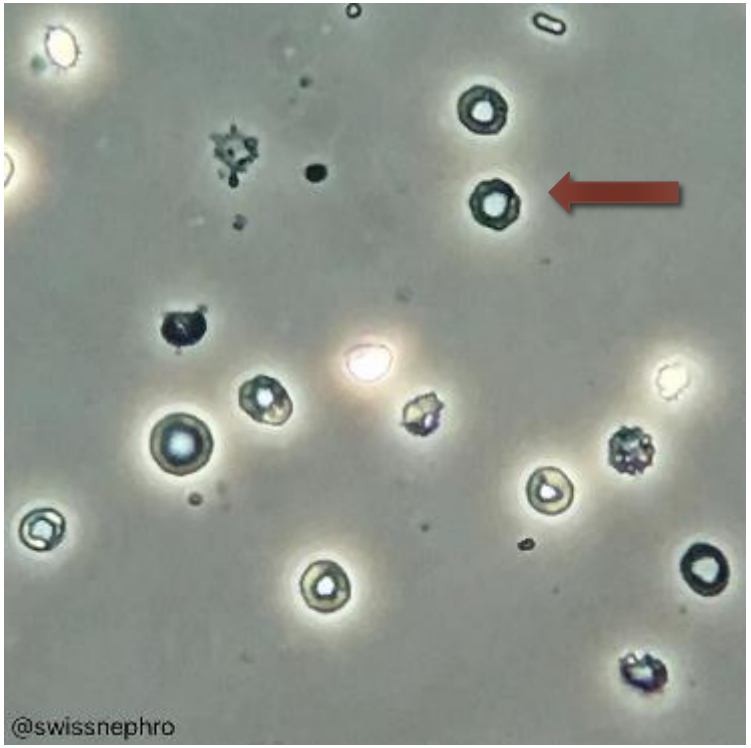


A normal capillary in a glomerulus keeps red blood cells, white blood cells and most proteins in the blood and only lets watery fluid into the urine.

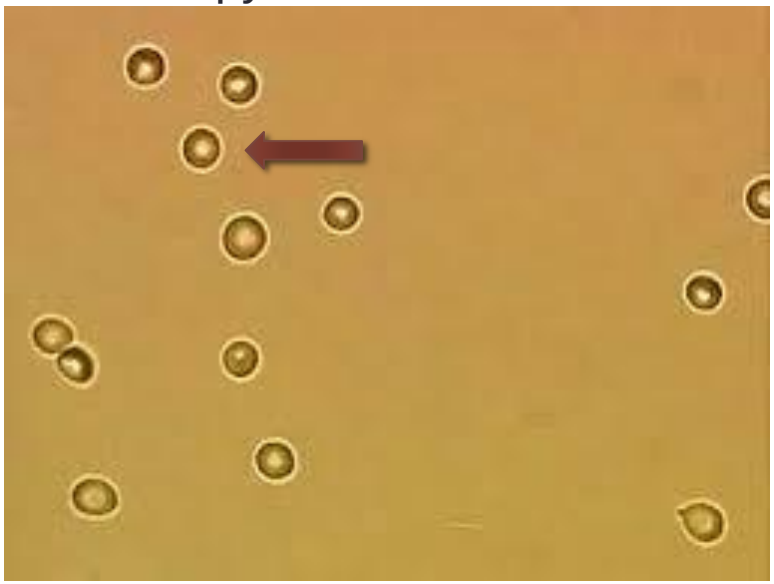


A capillary in a diseased glomerulus lets protein into the urine (proteinuria) and red blood cells into the urine (hematuria).

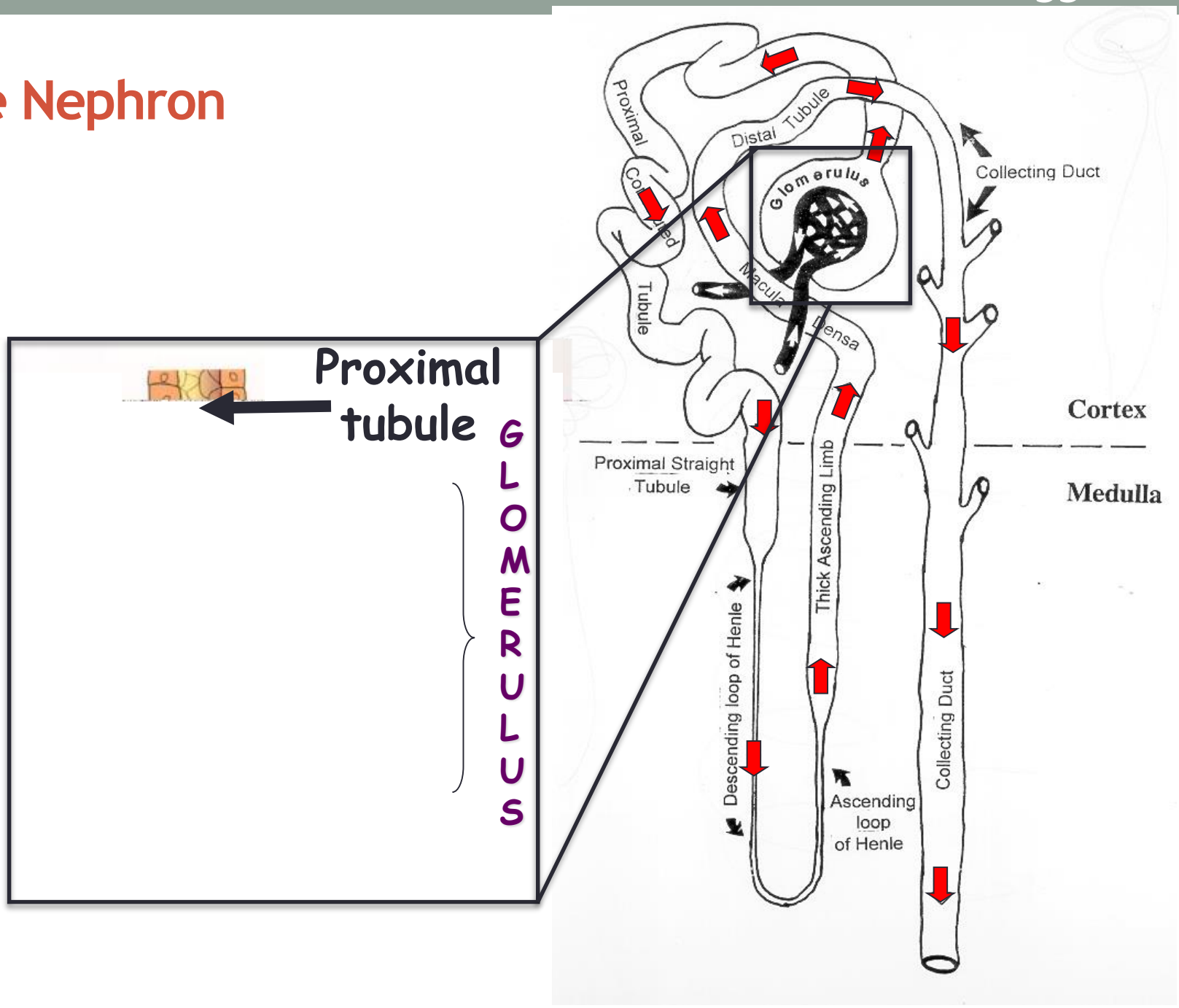
Dysmorphic RBCs in urine microscopy



Normal looking RBCs in microscopy

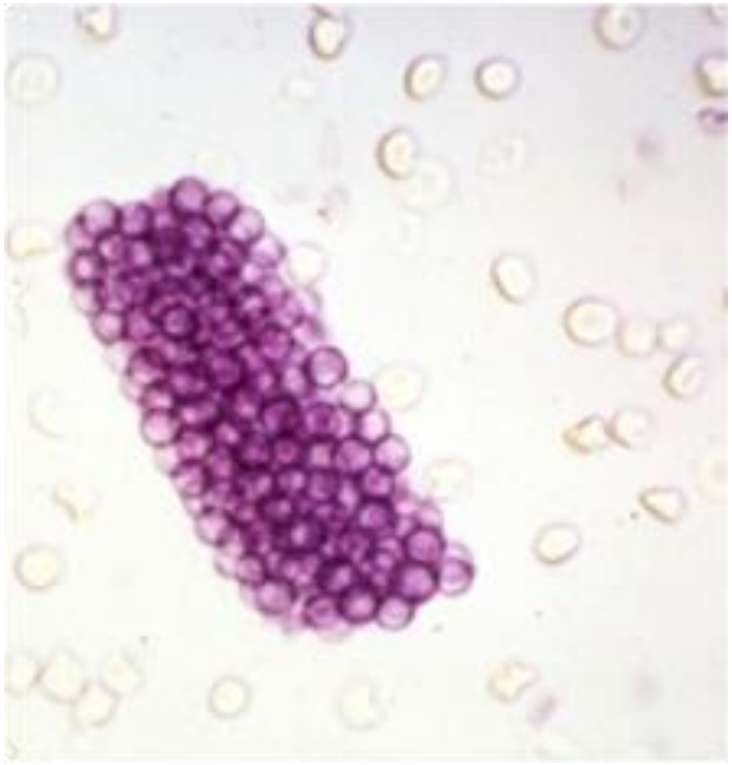


The Nephron


Proximal tubule
GLOMERULUS
Proximal Convoluted Tubule
Distal Tubule
Glomerulus
Collecting Duct
Macula Densa
Cortex
Medulla
Proximal Straight Tubule
Thick Ascending Limb
Descending loop of Henle
Ascending loop of Henle
Collecting Duct

RBCs cast

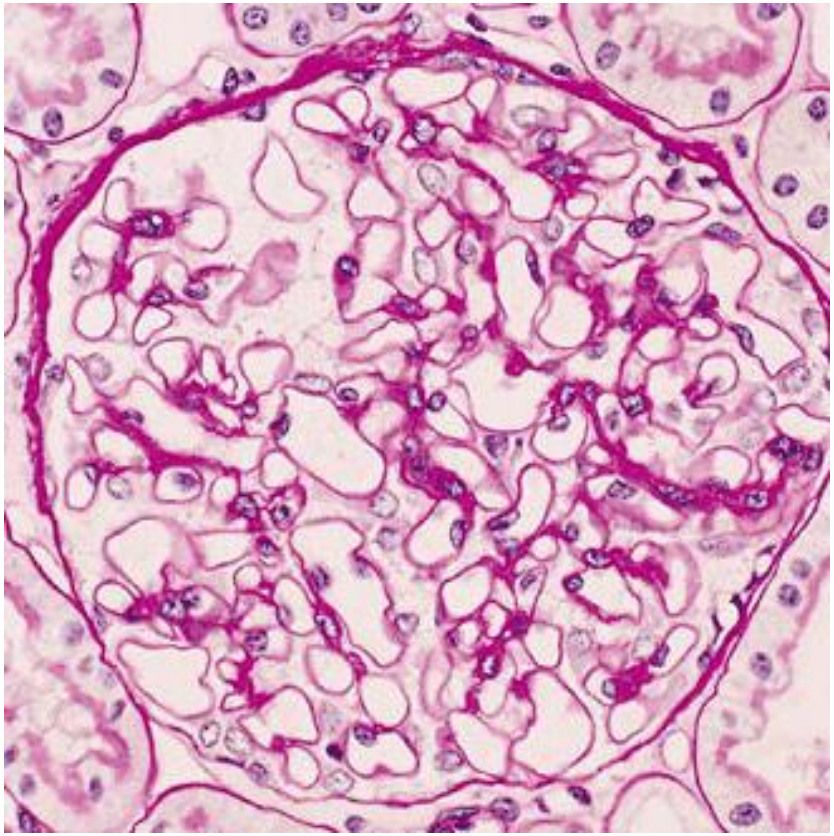
formed by naturally occurring *Tamm-Horsfall mucoprotein in the distal tubules & collecting ducts when they become loaded with RBCs coming from the inflamed Glomerulus (due to GN)*



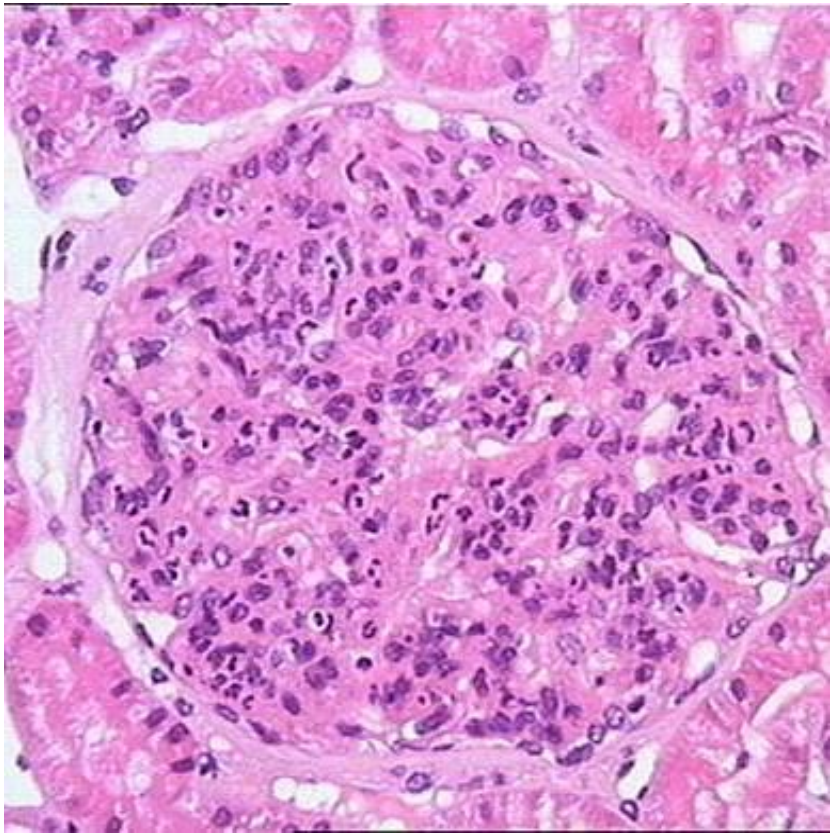
Nephritic clinical manifestations:

- **AKI** (Acute Kidney Injury) =Acute Renal impairment or Failure= elevated Creatinine) & electrolytes imbalance.
- **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 of GN)

Normal Glom.

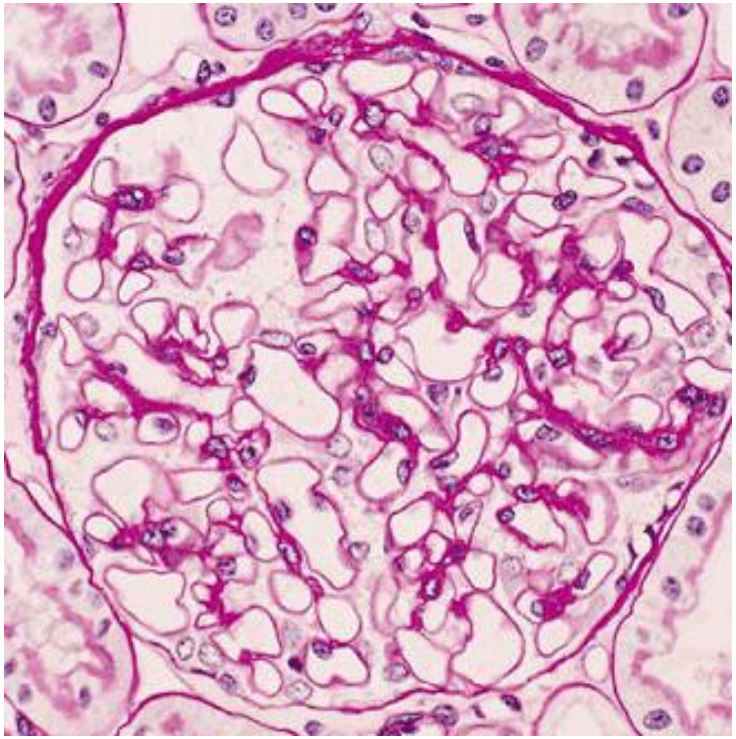


Glom. with proliferative (inflammatory) GN

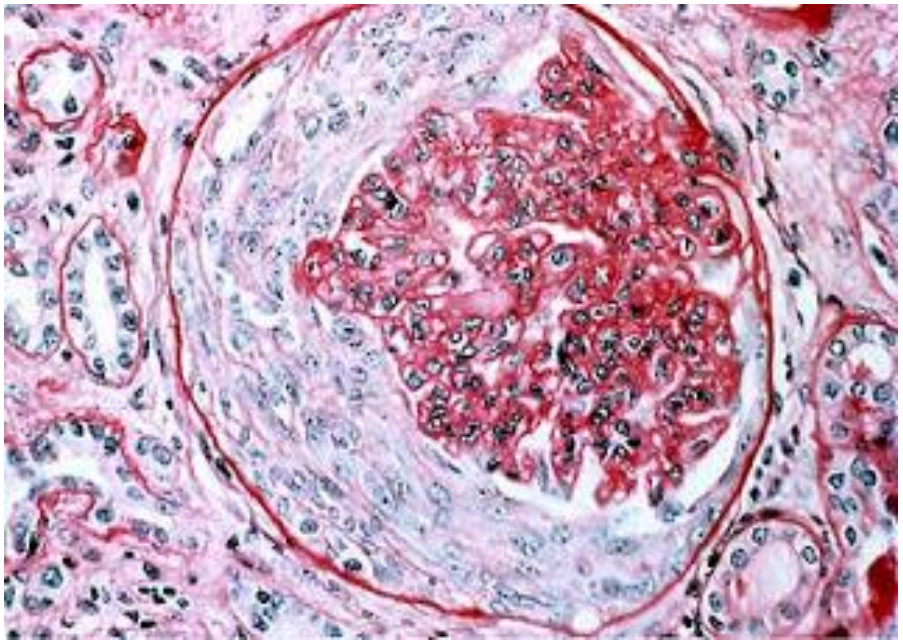


Crescentic GN; is a very bad GN!!!!

- Normal Glom.



- Glom. with Crescent



Indicates severe inflammation & worse outcome if not treated in a short time from presentation

Nephritic Glomerular diseases or **Glomerulonephritis or GN**

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

- IgA Nephropathy / HSP (Henoch-Schönlein purpura)
- Post streptococcal glomerulonephritis (PSGN)
- Lupus Nephritis
- Anti-GBM (Goodasture'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)**
- Commonly picked up **incidentally** by finding abnormal urine analysis (Hematuria+/- Proteinuria) done for other reasons with no symptoms; e.g. pre-employment investigations.
- It has a chronic course that may or may not worsen.
- Needs kidney biopsy to reach the diagnosis.

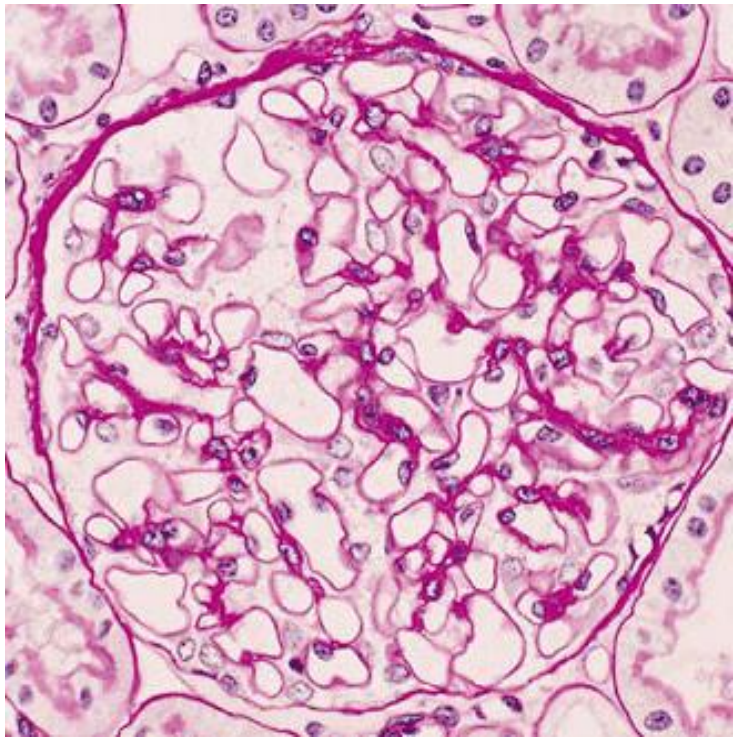
- The diagnosis is made by finding abnormal deposition of Ig A immunoglobulin in the Glomeruli, it elicit a local inflammatory response in the Glom mesangium (causing mesangial expansion)

- 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 , with ACEi or ARB.

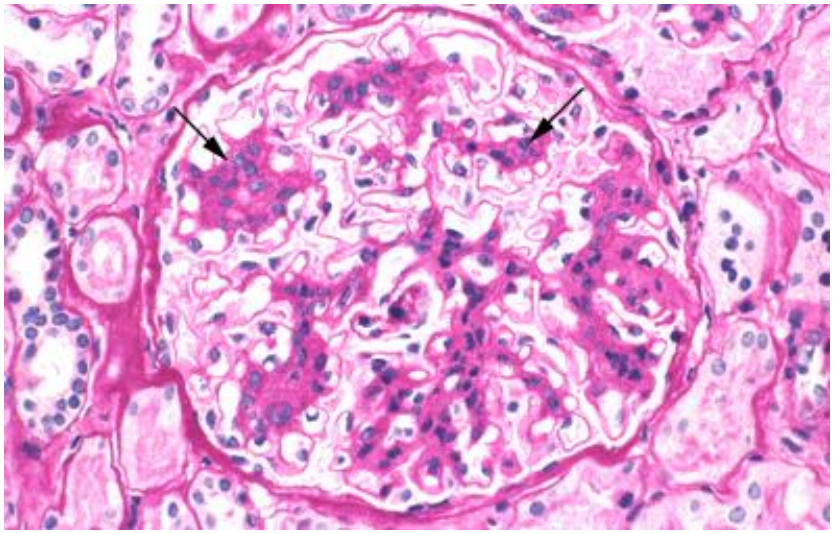
- HSP (Henoch-Schönlein purpura) is a systemic vasculitis caused by immune deposition of IgA in different organs; typically skin capillaries, bowel and kidneys.

IgA

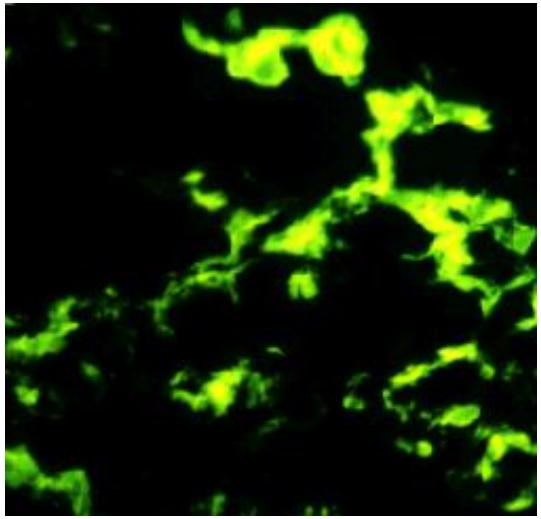
Normal Glomerulus



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 (ANA, Anti DNA), 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

This molecule establishes vascuilitis cascade

<u>Two types of ANCA:</u>

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

Angiitis in this disease: 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.
- Kidney pathology will show sever Glomerulonephritis; maybe RPGN; but all stating with immunofluorescence for immunoglobulins is NEGATIVE; hence the name **Pauci-Immune vasulitis or GN (Pauci = little or non)**
- 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:

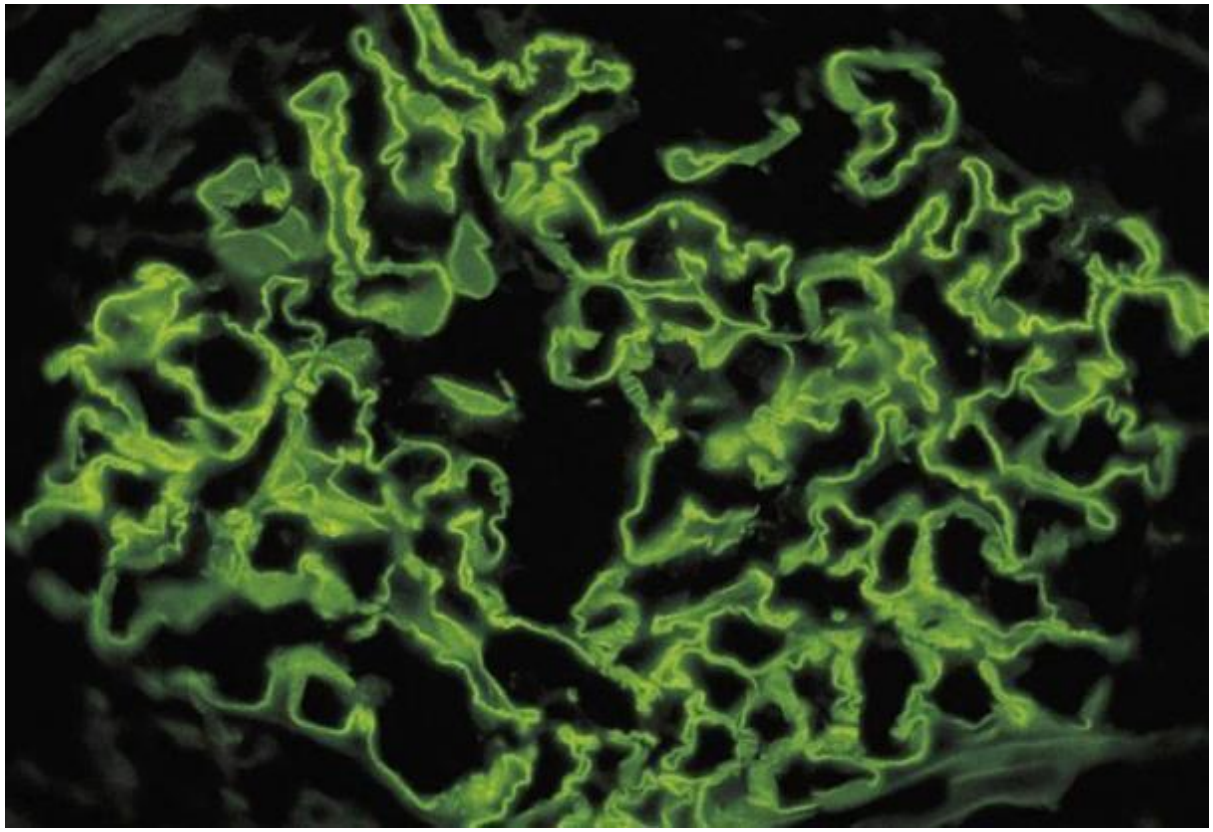
1- GN (can be the only presenting finding) &

2- Pulmonary hemorrhage (disease is called *Goodpasture's disease if Lung vasculitis + GN*)

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 in the Glomerulus 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

	NS	Nephritic (GN)
Pathology	Mainly a Podocytes disease present with foot process effacement +++ Usually No Glom inflammation	Is an inflammatory disease involves any or all of Glom elements: Base Membrane, Endothelium or mesangium. Foot Proce effacement ++
Proteinuria	> 3.5 g/Day	Variable amount from few 100s mg to grams / day
Urine microscopy	No hematuria + Lipids (Lipiduria)	+ RBCs, + dysmorphic RBCs, + RBC casts (active sediments)
Labs	Low serum Alb < 30 gm/L High Cholesterol	Low GFR (Renal impair) Electrolytes imbalance
Clinical	Edema ++++ BP maybe high	Edema ++ High BP ++ Symptoms & signs of renal impairment or vasculitis
Complications Acute	Thrombosis Infection	RPGN AKI
Complications chronic	Atherosclerosis Tubular atrophy & Fibrosis then CKD	Glom sclerosis then CKD (chronic Kidney disease) to ESRD