GLOMERULAR DISEASES

MED 341

November 2022

Objectives

1- Understand the physiology / pathophysiology of Glomerular structure.

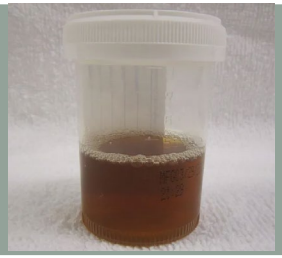
2- Recognize Normal & abnormal urine analysis in making diagnosis of Glomerular Disease vs Non-Glomerular disease

3- Recognize the differences between Nephritic & Nephrotic Glomerular diseases.

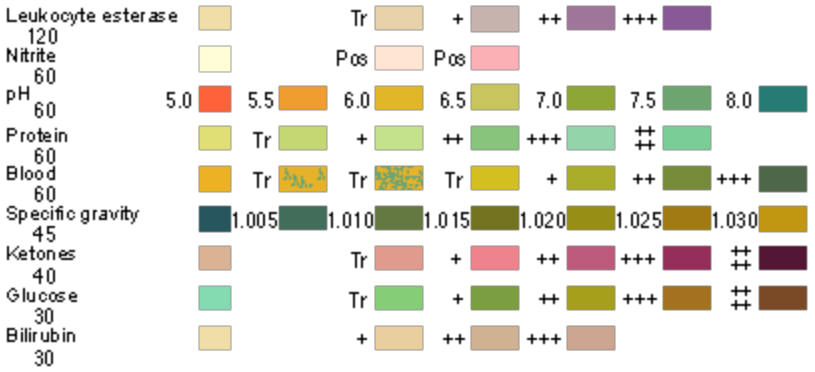
5- To recognize the early features of Glomerular diseases before it is too late! Early Dx & Rx makes a huge difference

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

Which one is a Normal urine sample?



Urine dipstick :



Rapid Semiquantitative test for urine: Specific gravity, pH, heme, leukocyte esterase, nitrite, **Albumine**, Glucose, ketones
Semiquantitative means : values from Nil , trace, 1+, 2+, 3+ and 4+ (0- ++++)

Urine Microscopy

- Urine sample is centrifuged to form sediments at the bottom of urine sampler
- The sediments will be examined under light microscope
- Looking for : Red blood cells, white blood cells , cats, cysts , lipid droplets

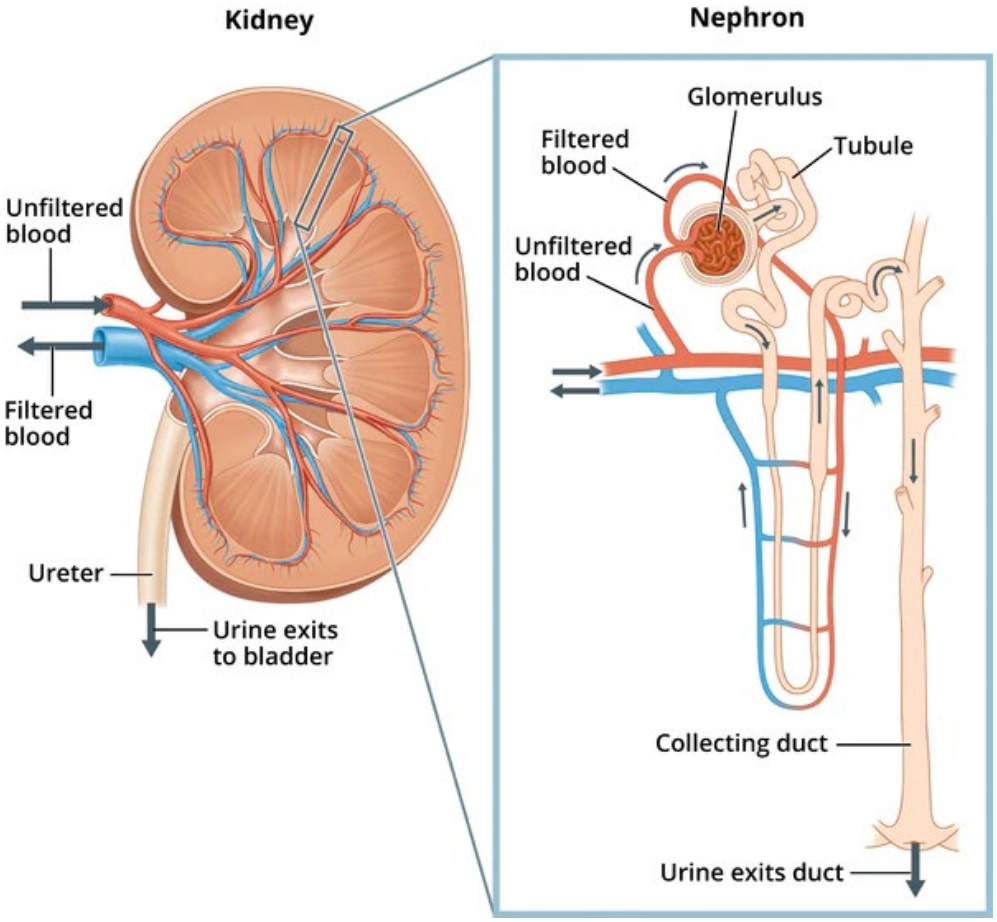
RBCs count : 0 – ### & shape
WBCs count : 0- ###
Casts : type and number
Bacteria:

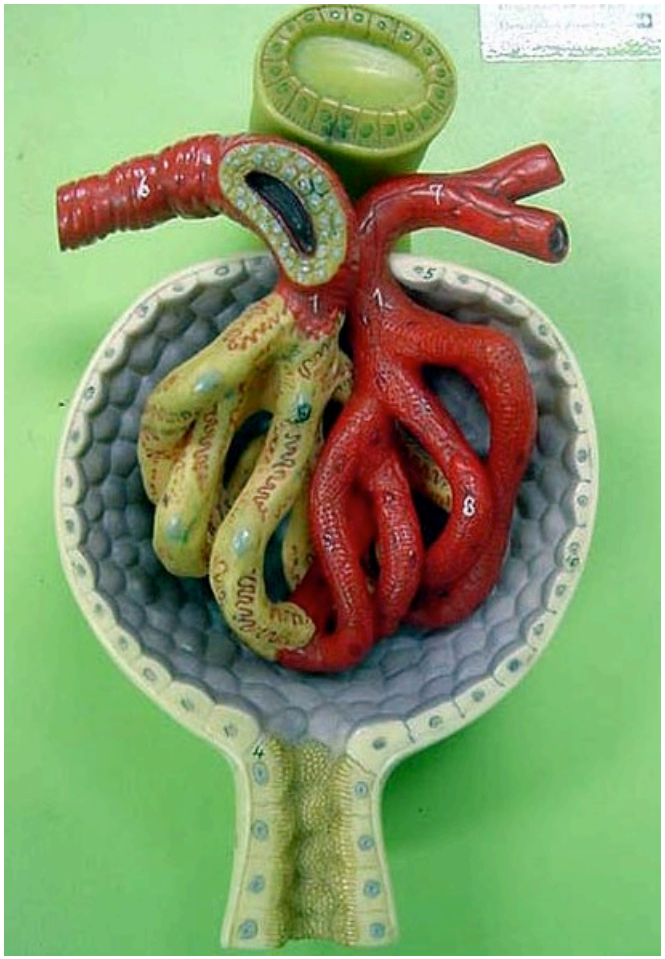
Modern days urine analyzer

Automated urine analyzer
It does dipstick and microscopy at the same time

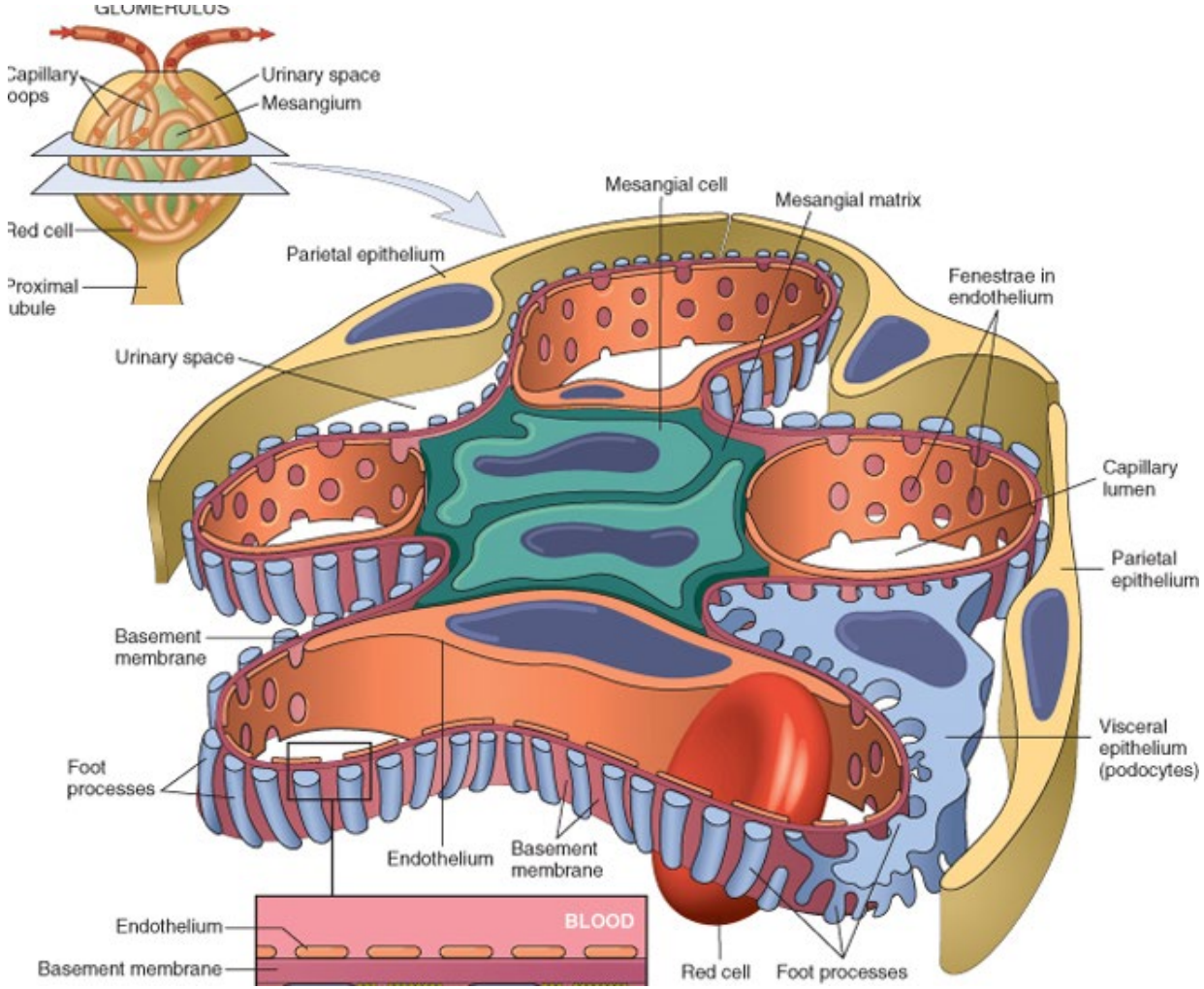
Test Name	In Range	Out Of Range	Reference Range
Urinalysis w Micro rflx Culc			
Color	YELLOW		YELLOW
** Please note change in unit of measure and reference range(s). **			
Appearance		CLOUDY	CLEAR
Specific Gravity	1.010		1.001-1.035
pH	6.0		5.0-8.0
Glucose	NEGATIVE		NEGATIVE
Bilirubin	NEGATIVE		NEGATIVE
Ketone	NEGATIVE		NEGATIVE
Occult Blood		2+	NEGATIVE
Protein		3+	NEGATIVE
Nitrite	NEGATIVE		NEGATIVE
Leukocyte Esterase		1+	NEGATIVE
WBC		20-40	<=5 WBC/HPF
RBC		10-20	<=2 RBC/HPF
Squamous Epithelial		6-10	<=5 HPF
Bacteria		MANY	NONE SEEN HPF
Crystals	NONE SEEN		NONE SEEN HPF
Casts	NONE SEEN		NONE SEEN LPF
Yeast	NONE SEEN		NONE SEEN HPF

Nephron : the Kidney's functioning unit (located in the Renal cortex)

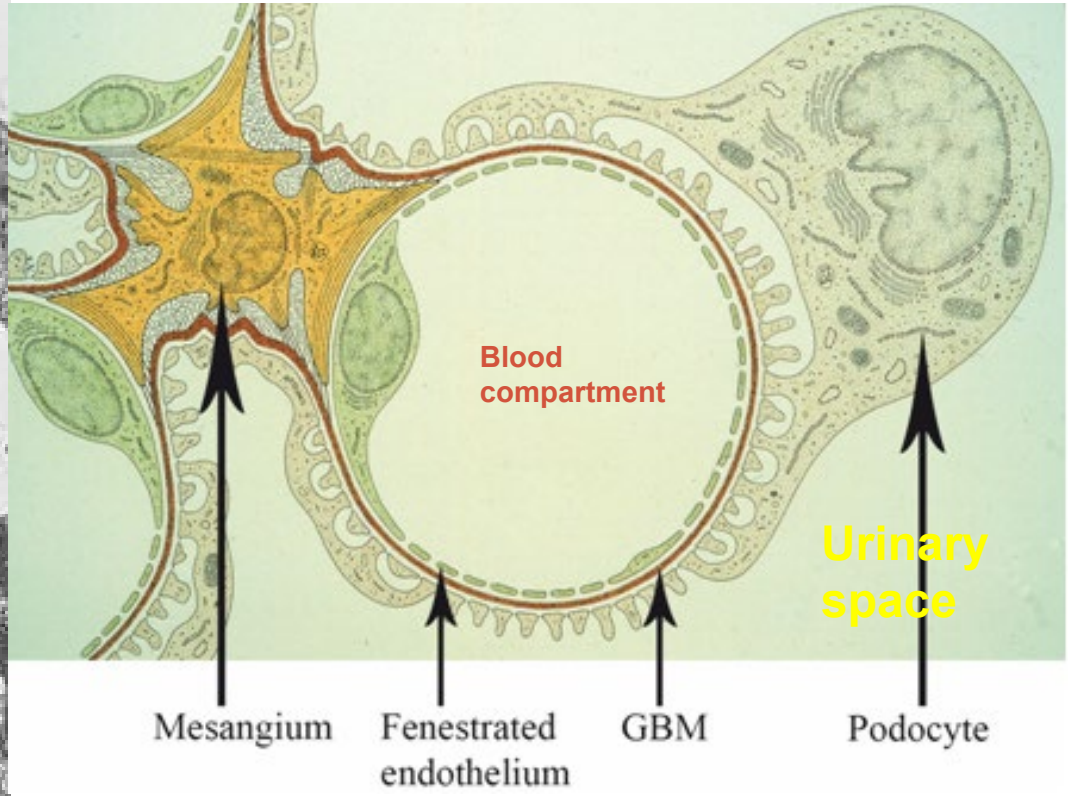




Transection of a normal Glomerulus



Normal Capillary Loop / wall (Electron Microscopy)



Normal Glomerular structure:

1- Keeps the glomerular filtration normal, thus maintains normal kidney function.

2- keeps the urine volume maintained; so preventing fluid retention in the body which causes edema and high blood pressure.

3- Prevents the blood components (cells & proteins) from leaving the blood stream and appearing in the urine, this means intact Glom filtration membrane will lead to Normal urine analysis, and damaged Glom filtration membrane will lead to abnormal urine analysis

So, if Glomerular structure is **intact (Normal)** the urine analysis test should have:

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

(Non of the blood cells or proteins will be detected in the urine in a Normal renal/Glomerular / tubular functions)

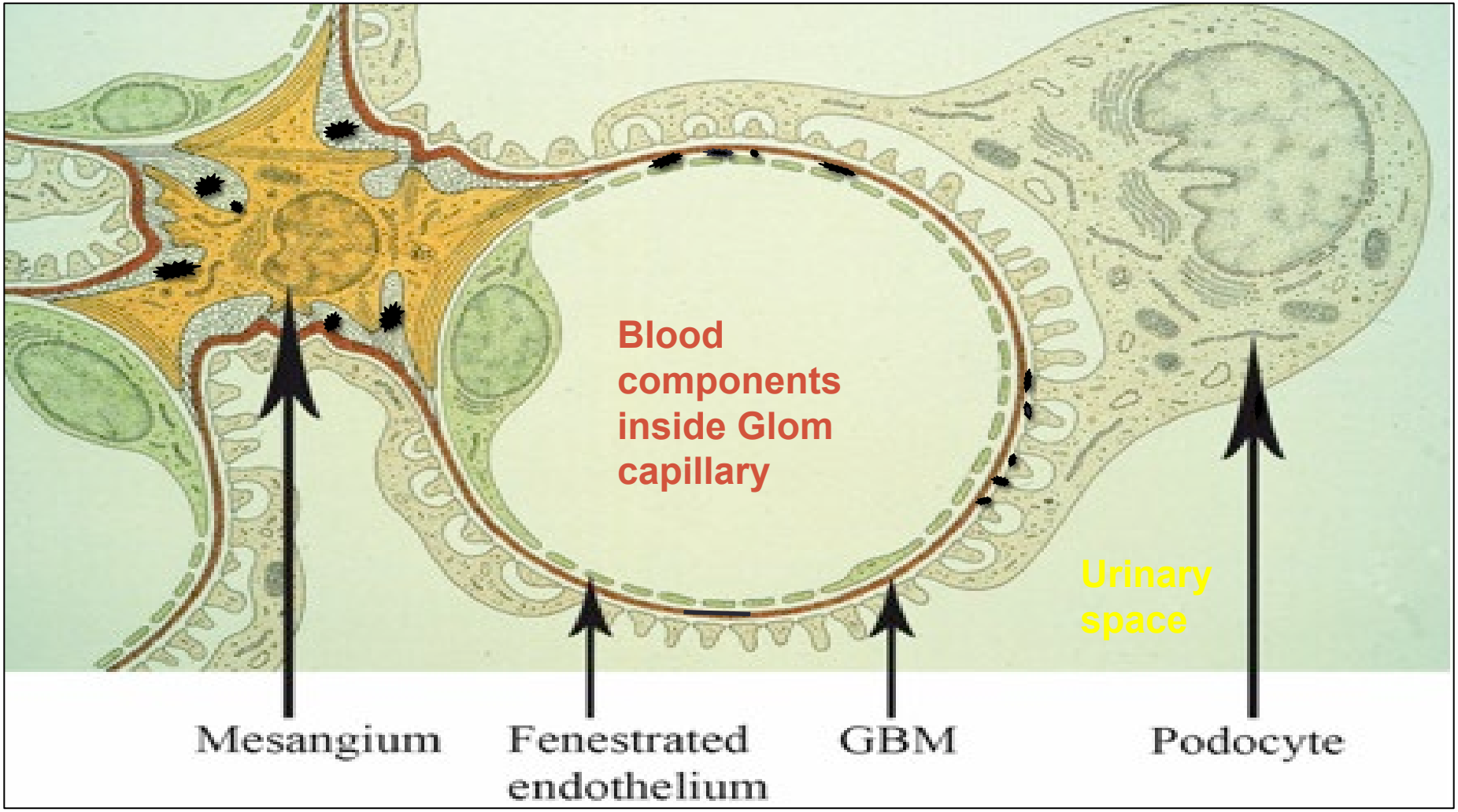
How glomerular diseases start?

- Here we are talking about primary glomerular diseases that are mostly caused by immune system abnormality.

Immune system abnormality causes formation of Auto-antibodies that are either :

- targeting glomerular structure (autoantibodies) or
- causing immune-complexes (antigen-antibody) in the circulation depositing in Glom and cause inflammation or direct damage to Glom.

The Auto antibodies or immuncomplexes can affect any component in the Glom



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 processes 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 into the urine space causing: ***hematuria + proteinuria + 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, when the clinician identifies an abnormal urine analysis that is either suspicious or indicative of an underlying 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)

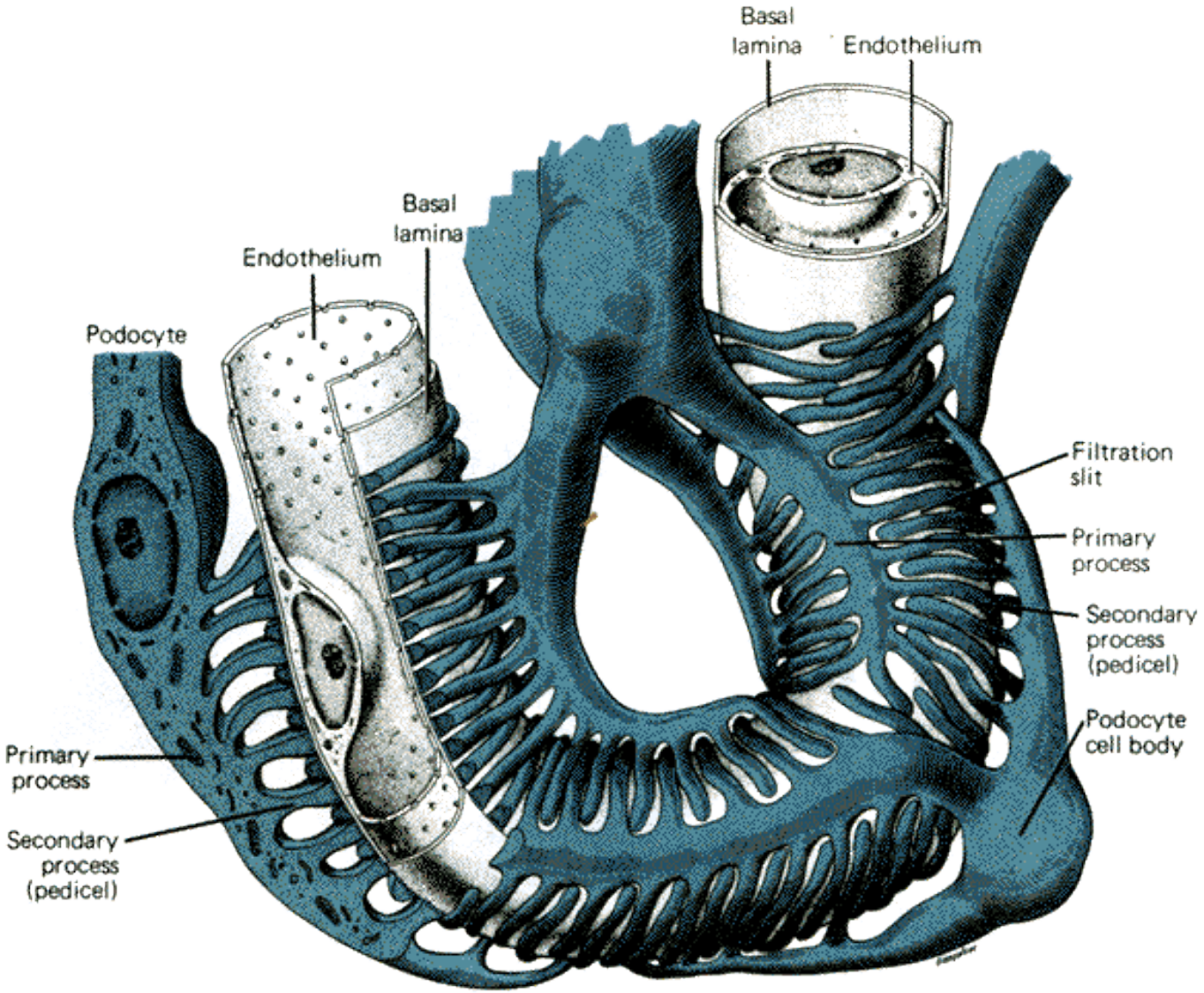
>>> **Nephrotic** (due to Podocytes dysfunction causing foot process effacement)

>>> **Nephritic** = **Glomerulonephritis** or **GN** (due to glomerular mesangial cells; endothelial cells proliferation & glomerular capillary wall inflammation and then disruption of Glom filtration barrier

Nephrotic Syndrome (NS):

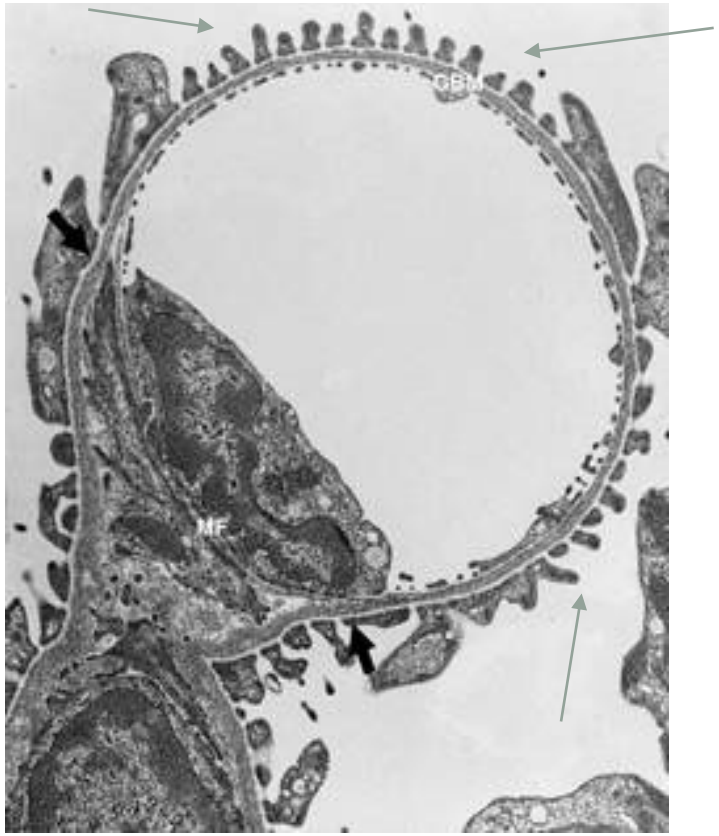
- The main pathology in NS: is **Podocytes problem**.

- When Podocytes sustain a structural dysfunction; it makes 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 (called: **Nephrotic range Proteinuria**).
- Foot process effacement is reversible pathology with Rx

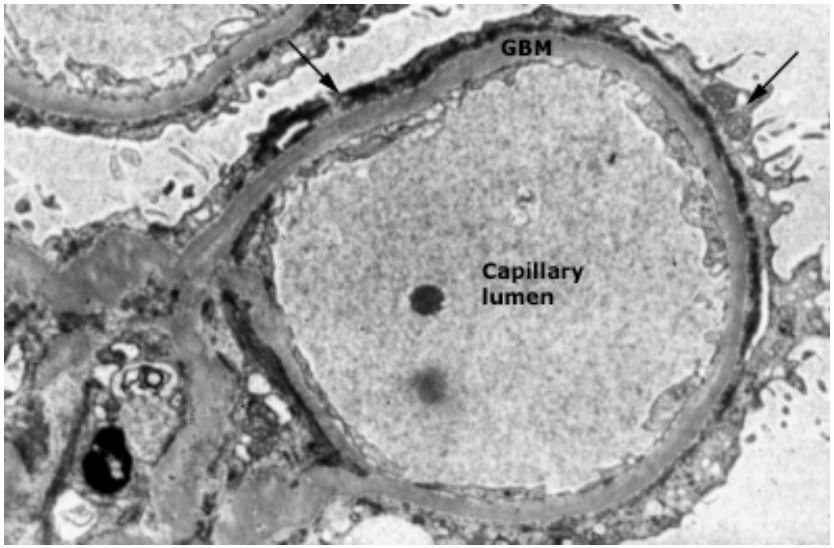

Basal lamina
Endothelium
Basal lamina
Endothelium
Podocyte
Filtration slit
Primary process
Secondary process (pedicel)
Podocyte cell body
Primary process
Secondary process (pedicel)

Podocytes pathology in NS

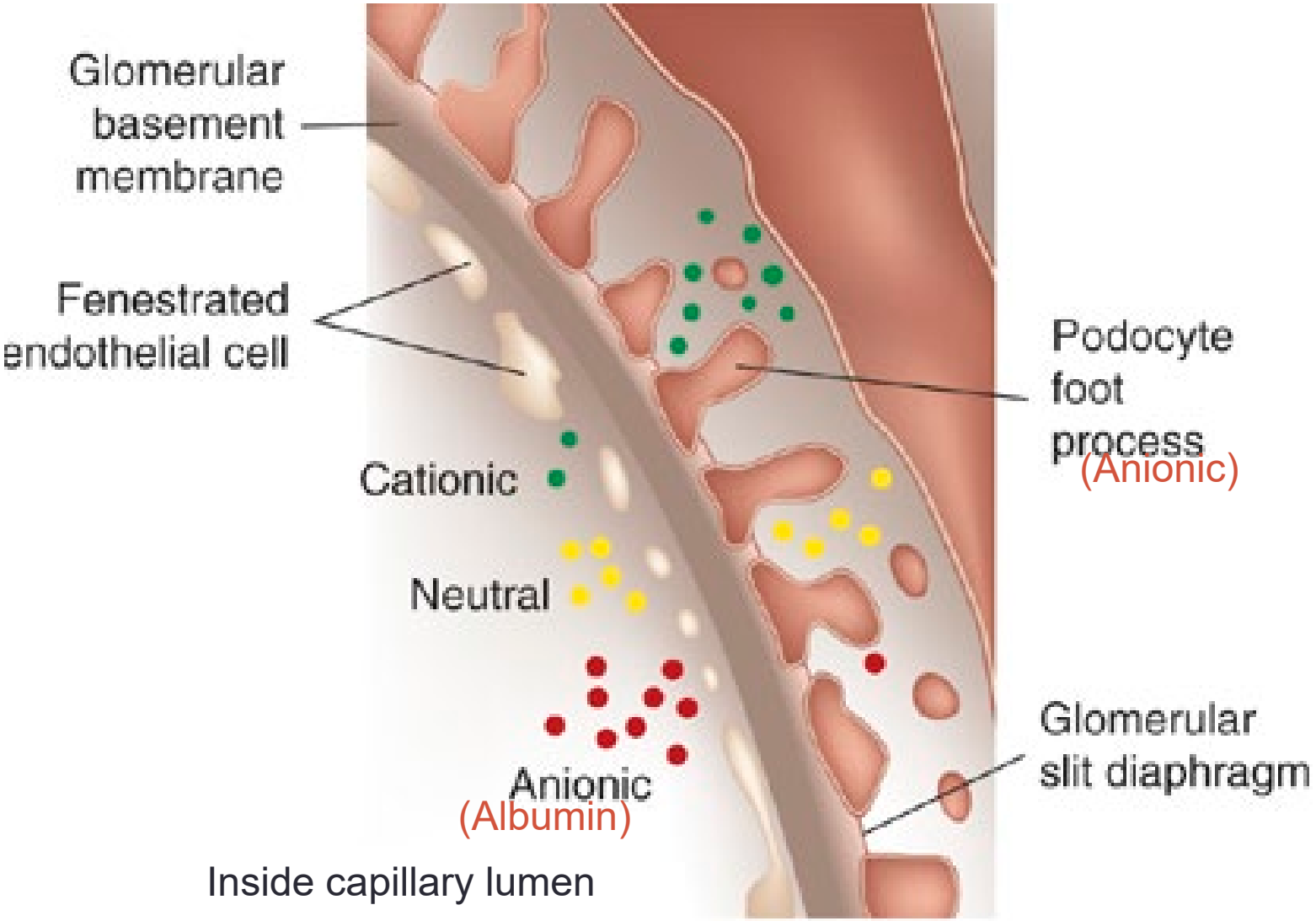
Normal Foot Processes



Diffuse Foot Processes Effacement



What keeps Albumin inside the capillary lumen in the Glom?



Nephrotic Syndrome

It refers to a constellation of clinical and laboratory features of a renal disease that has the following:

- **Hypoalbuminemia** (serum Albumin drops to <30 g/L ; because it is wasted in the urine), the Normal serum Albumin level : 35-55g/L
- **Nephrotic range Proteinuria** (urine secretion of > 3.5 g (> 3500 mg) of Albumin in the urine per day), estimated by doing 24h urine collection.
- **Peripheral or generalized edema**
- **Hyperlipidemia**

Complications of Nephrotic Syndrome

- Infections & sepsis (loss of Immunoglobulins)
- Thrombosis (loss of antithrombotic in the urine)
- Acute kidney injury.
- ESRD if heavy proteinuria does not resolve for a long period of time.
- Hyperlipdemia

Important definitions about Proteinuria:

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

- **< 150 mg/day of all kinds of proteins**. (albumin & non-albumin proteins), 4-7 **mg**/day out of the 150mg/Day is made of Albumin, the remaining is Non Albumin proteins.
- Urinary Secretion of > 150 mg/day of protein is a pathological indicator of underlying kidney disease and is usually made of Albumin in Glomerular diseases, if Not all Albumin then most likely Paraproteins (Immunoglobulin light chains) secreted by abnormal Plasma B cells clones, Note: Urine Dipstick does not detect immunoglobulins, it only detects Albumin.

Pathological Albumin urinary secretion :

- **30-300 mg/day** is called Microalbuminuria (Moderately increased Albuminuria (indicates early stages renal disease) will Not be detected by Dipstick, but detected by ACR (Albumin / creatinine ratio) analysis.
- **> 300 to < 3500** mg/ Day : overt proteinuria (Severely increased Albuminuria) , usually detected by Dipstick
- **> 3500 mg/ Day** : Nephrotic range Proteinuria Or Heavy Proteinuria

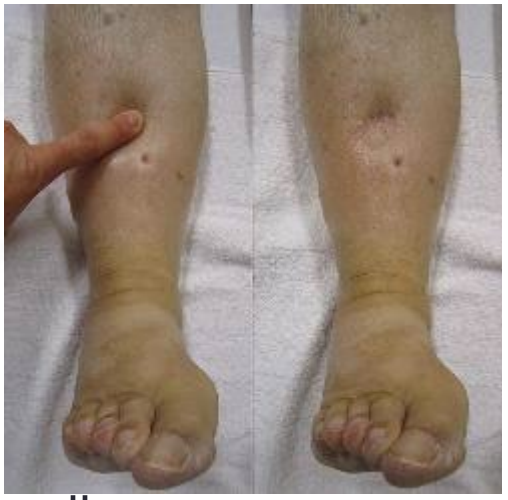
Urine Analysis in Nephrotic Syndrome will show:

- **Lots of protein (Albumin) is secreted in the urine per day**

& must be (>3.5 g/24h urine) ; soo called ***Nephrotic range proteinuria***

- No RBCs (some times few RBCs are occasionally seen)
- No RBCs casts
- **Presence of Fat in the urine (Lipiduria)** : Fatty casts, oval fat bodies & fat droplets)
- No WBCs (very few may be seen)

Clinical Presentation of Nephrotic Syndrome :

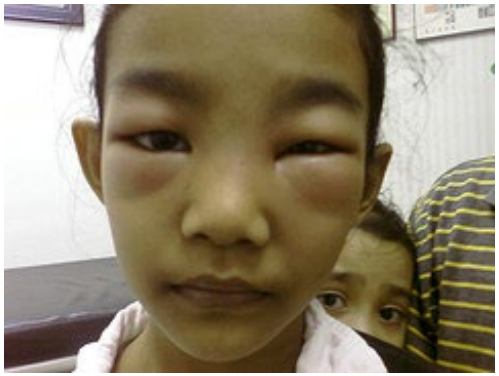


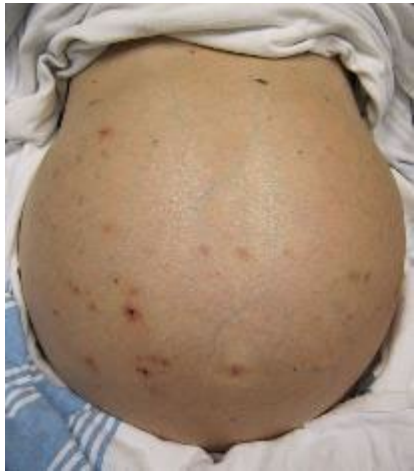
Edema due to:

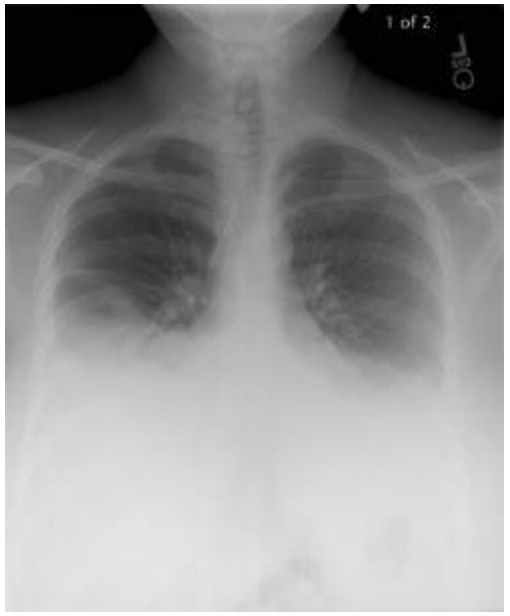
1- Low serum Albumin (Low oncotic pressure)

2- Increase Renal sodium retention

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







Symptoms of Nephrotic Syndrome:

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

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

3- **Membranous Nephropathy** (MN)

Focal Segmental GlomeruloSclerosis (FSGS)

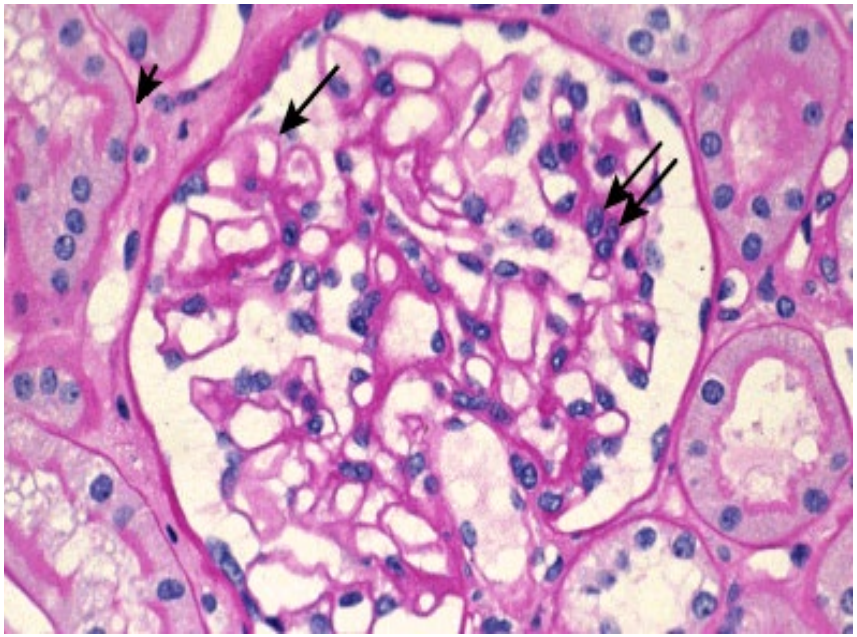
Could be **Primary** Or Secondary Or Genetic

- *Sclerosis :* means hardening of glom structure with fibrosis
- ***Focal mean***: some glomeruli are affected by sclerosis & others are not (the remaining Gloms look normal)
- ***Segmental means***: the process of sclerosis only involves a segment of each glomerulus that is affected by the disease.

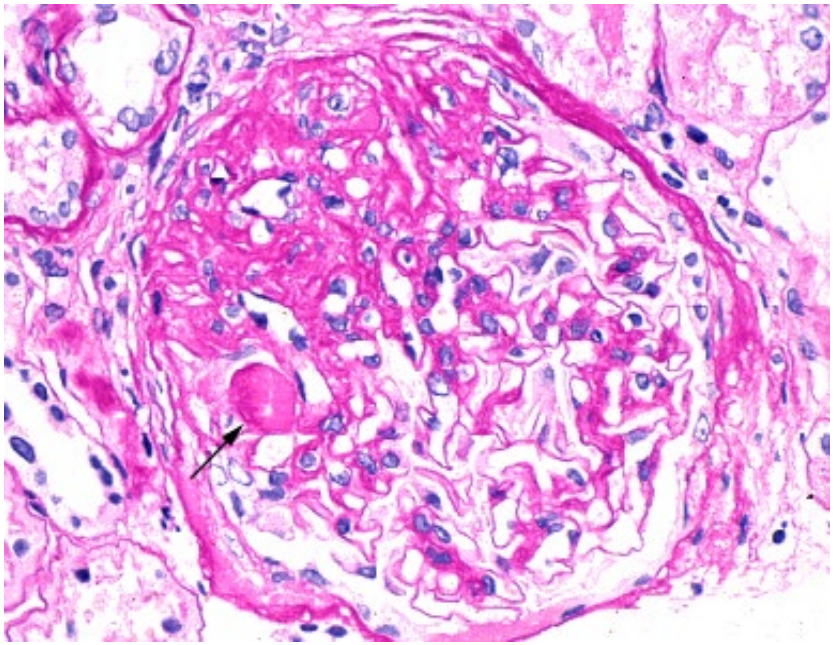
- But most importantly; in The **primary type :** all glomeruli (the ones that are affected by sclerosis and the ones that are not showing sclerosis) **ALL** of them will have a **diffuse foot processes effacement** (thus Nephrotic syndrome appears as the clinical presentation).

Focal Segmental GlomeruloSclerosis (FSGS)

Normal

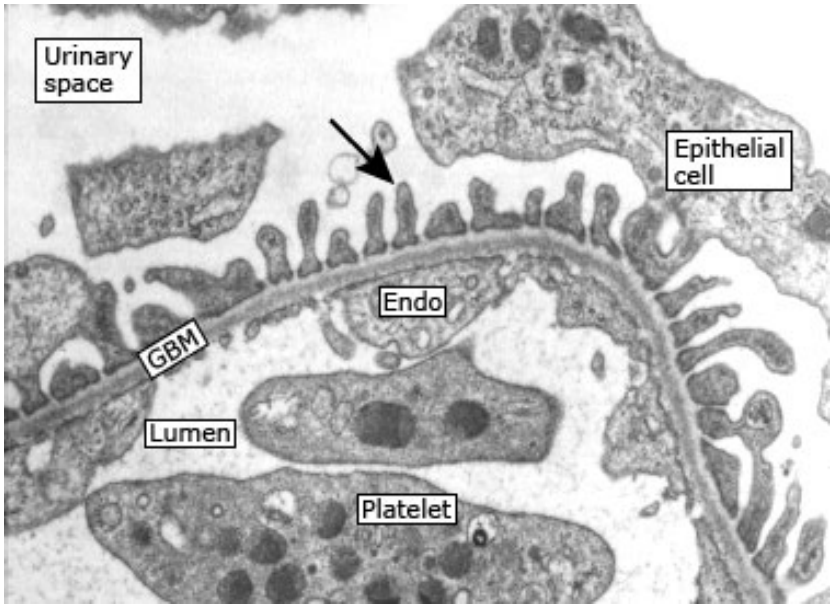


FSGS

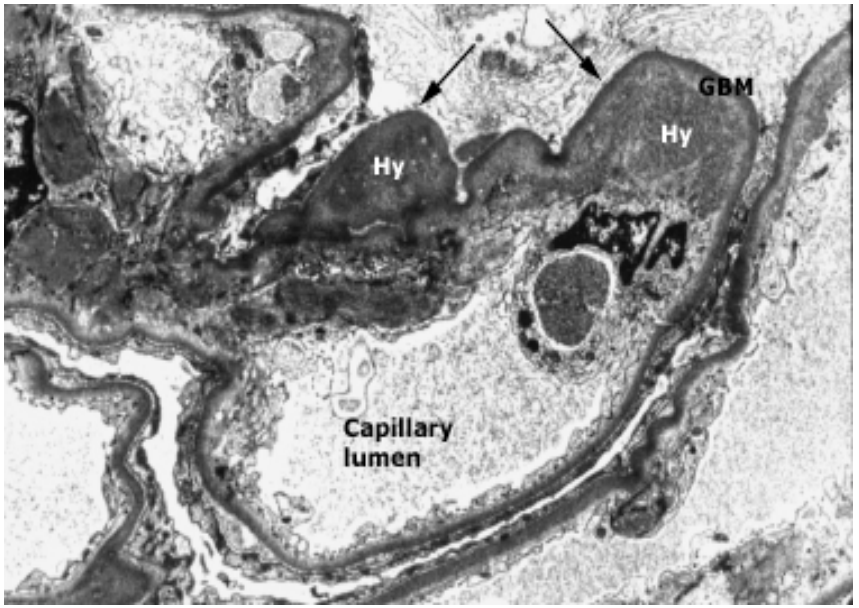


Focal Segmental GlomeruloSclerosis (FSGS)

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.
- Maybe related to presence of Circulating Factor (like autoantibodies) that targets podocytes and causes effacement of foot processes

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

- First line: corticosteroids
- Second line: cyclosporine or tacrolimus (CNIs)
- Diuretics and ACEi

Focal Segmental GlomeruloSclerosis (FSGS)

Or can be

Secondary FSGS:

-Proteinuria is less heavy than other causes of nephrotic syndrome, even < 3.5 gm/Day (Not nephrotic range)

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

-**Renal impairment is commonly seen with the secondary FSGS at time of diagnosis and this is not a good prognostic sign**

Focal Segmental GlomeruloSclerosis (FSGS)

Possible causes of Secondary FSGS:

- Morbid Obesity
- Nephron loss (> 75% of renal mass) e.g renal agenesis (born with one functioning kidney only)
- 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)

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

(they also have Antiproteinuric effect) which is protective for the kidneys from long term effect of proteinuria

Long term proteinuria that is > 0.5 gram /day by itself can cause permeant damage of renal tubules (this causes Chronic Kidney Disease (CKD) then maybe ESRD)

Minimal Change Disease (MCD)

Called **Minimal** because:

- light microscopy: *is typically showing normal glomeruli*

  So also called: nil disease. (nil = nothing)

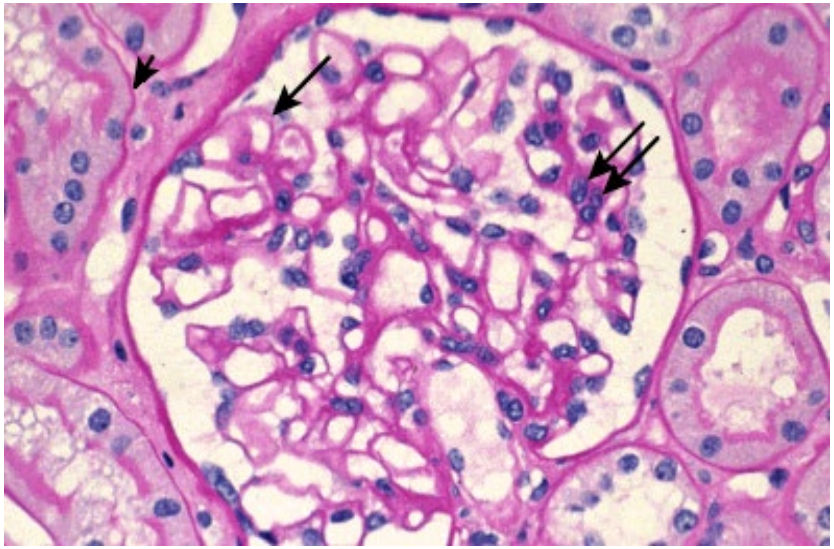
  BUT:

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

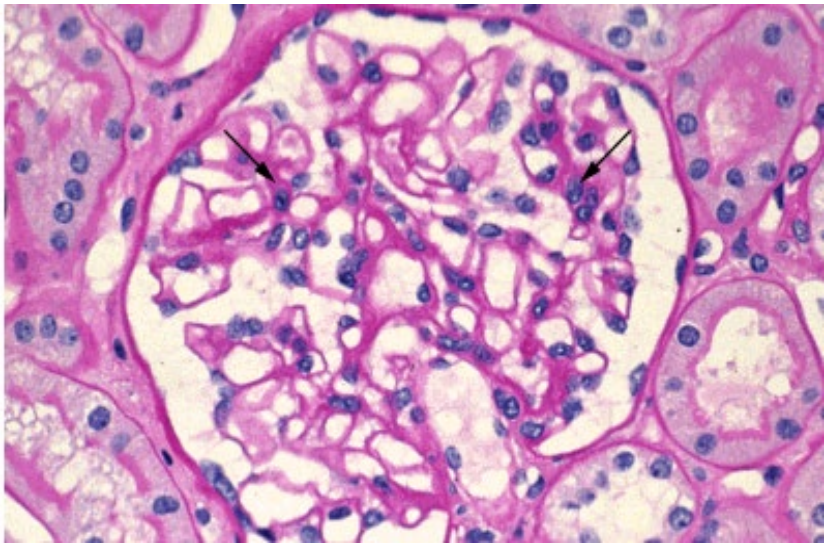
- So the most important difference between MCD and Primary FSGS is the presence of glomerular sclerosis in FSGS
- *there is no sclerosis in MCD.*

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

Normal Glomerulus

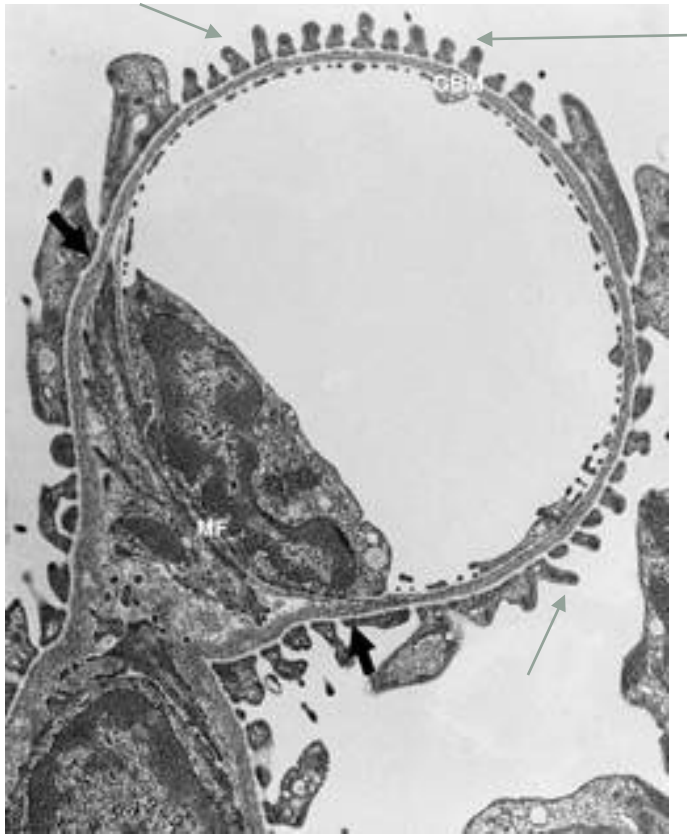


MCD, basically no abnormality is seen on light microscopy

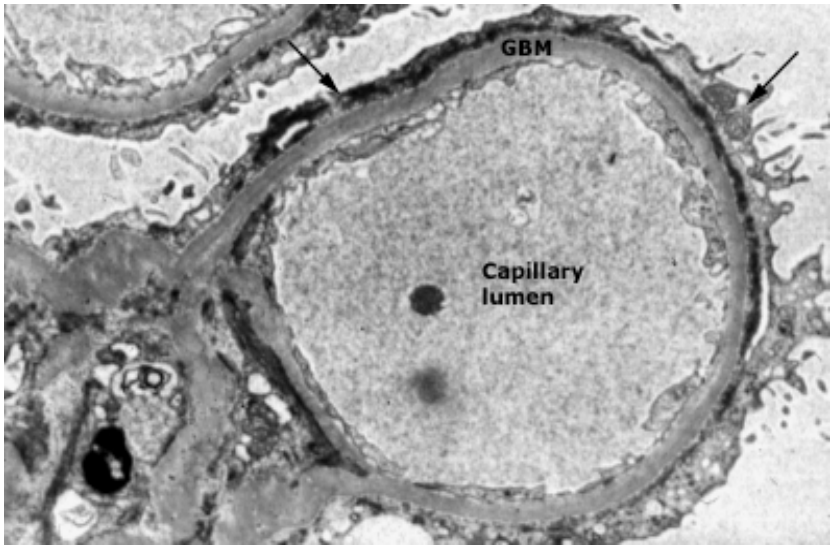


Cont. **Minimal Change Disease (MCD)**

Normal Glomerulus (arrows : normal foot processes)



MCD, EM shows the diffuse foot process effacement (arrows)



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 (less common e age)
- typically is corticosteroid responsive in > 90% in children, thus kidney biopsy is commonly not done on first presentation in this age group, and treatment is given empirically for such cases. *So, usually nephrotic syndrome in a child < 10 years old is due to 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 (rapid onset)
- BP may be normal or slightly elevated
- Heavy proteinuria (Nephrotic range > 3.5 g/d)
- 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 compared to children

It will show **Diffuse effacement of foot process ONLY**.

Treatment: immunosuppression with

First line: Corticosteroids

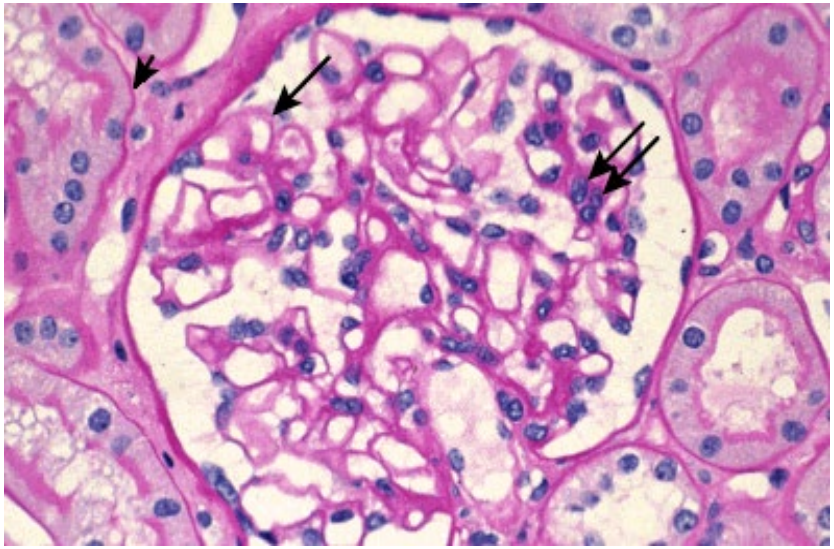
Second line: oral Cyclophosphamide, Cyclosporin

Membranous Nephropathy (MN)

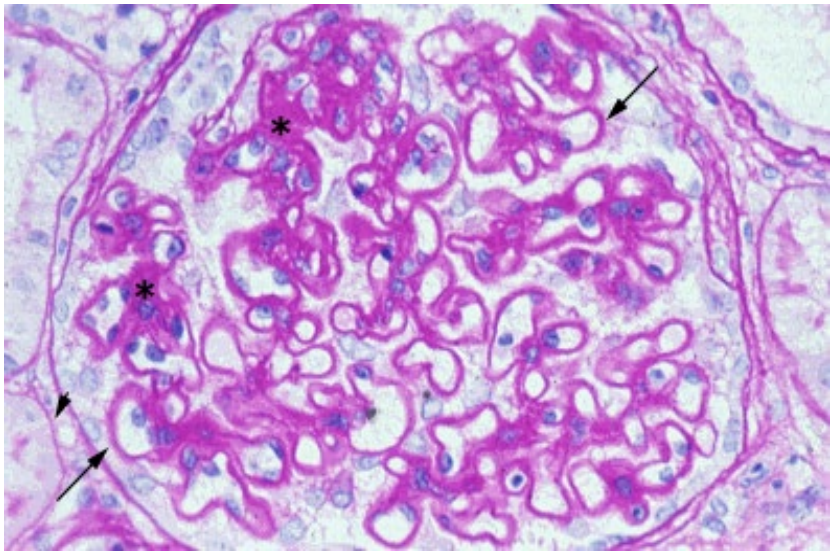
- **Most common cause of Primary nephrotic syndrome in adults** (15% and 33%)
- in children usually secondary due to (hepatitis B antigenemia)
- Presentation: slowly developing nephrotic syndrome (over few weeks)

Membranous Nephropathy (MN)

Normal



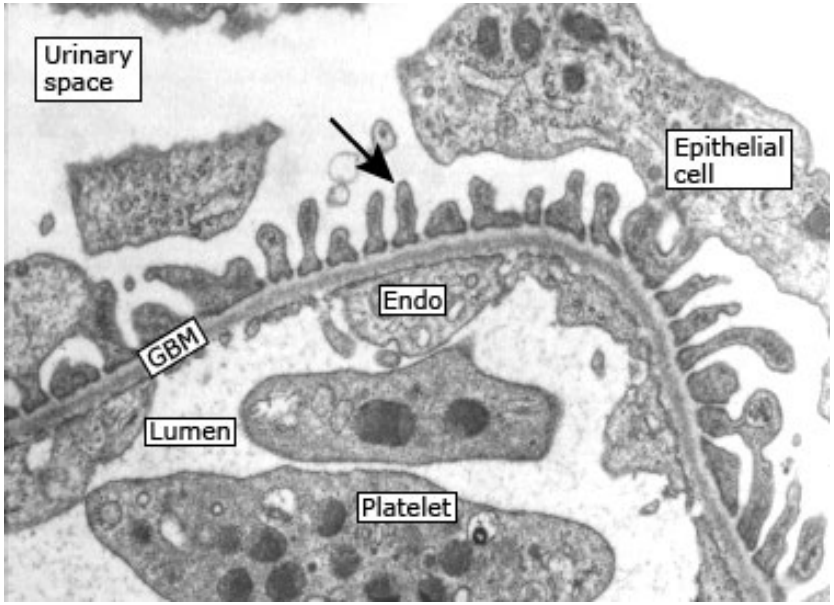
MN



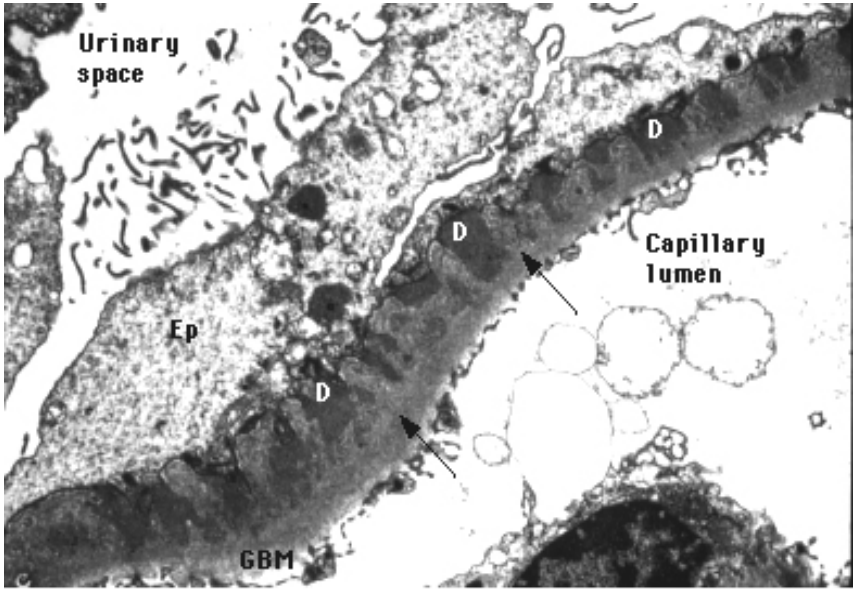
Diffuse thickening of the glomerular capillary wall throughout all glomeruli (IgG and C3 deposition)

Membranous Nephropathy (MN)

Normal (no deposits and foot process intact



MN (arrows show subepithelial immunoglobulin deposits, foot process effacement)



Membranous Nephropathy (MN)

Etiology:

- Primary (Idiopathic)

  In approximately 75% of cases in adults

Anti PLA2 R antibodies can be detected in 80% of primary MN cases , very useful test .

Membranous Nephropathy (MN)

Secondary: causes of MN in Adults:

- **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 (this why we must do age appropriate screening for cancer for adults presenting with MN)

Membranous **N**ephropathy (MN)

Treatment of Primary MN

- Corticosteroids **plus**
- Cyclophosphamide or cyclosporine
- Rituximab

Secondary MN

- Mainly treat the primary disease that caused MN, and treat the Nephrotic syndrome manifestations like with diuretics, ACEi and statins.

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

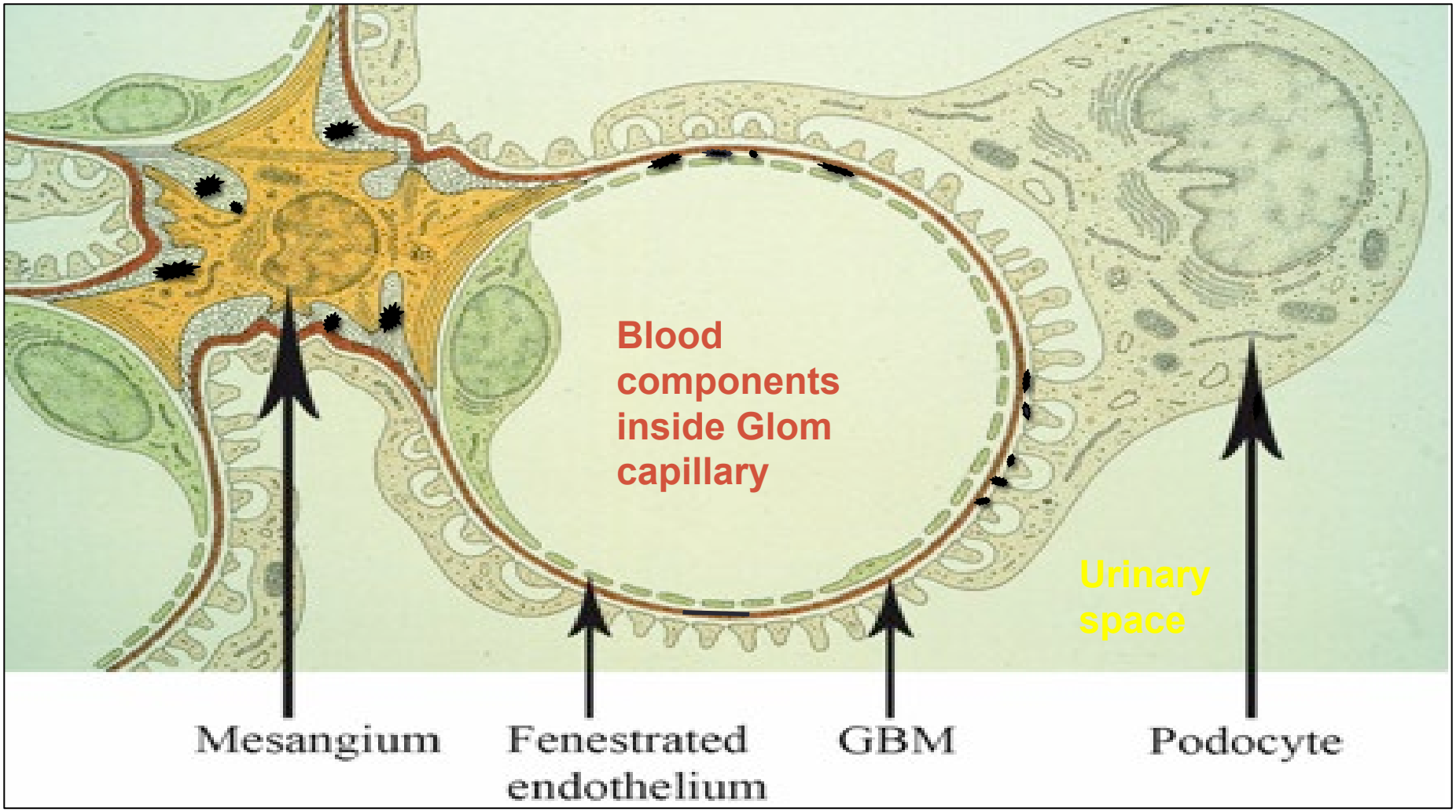
- **Diabetes Mellitus** (the commonest cause of secondary NS in adults)
- **Amyloid**
- IgA Nephropathy
- MPGN

Nephritic Glomerular diseases - GN

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

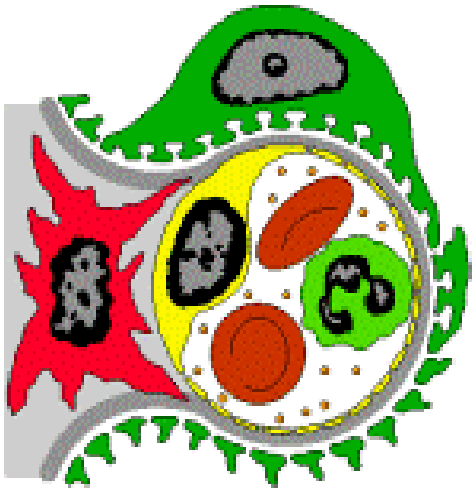
The **Nephritic** pattern is always indicative of underlying **inflammatory process in the glomeruli**; it involves inflammatory modulators attraction, inflammatory cellular proliferation and eventually glomerular permanent damage if left untreated.

The Glomerular Mesangial cells, endothelial cells and GBM are the targeted structures because of their proximity to blood circulation.

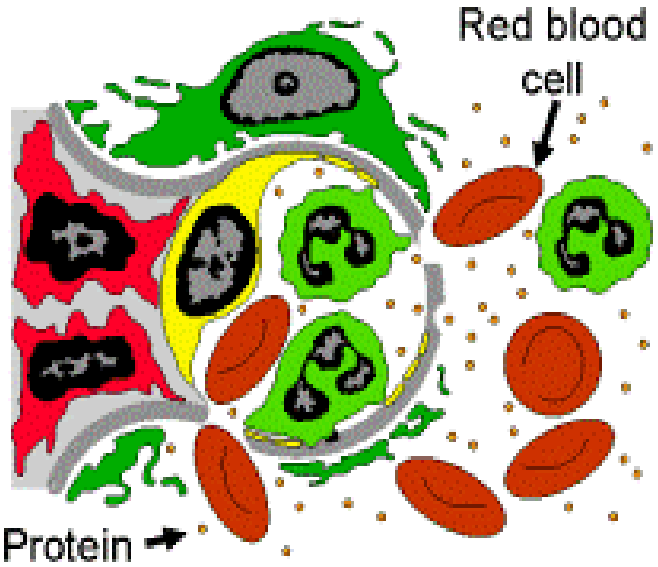

Blood components inside Glom capillary
Urinary space
Mesangium
Fenestrated endothelium
GBM
Podocyte

Nephritic

Proteinuria and Hematuria

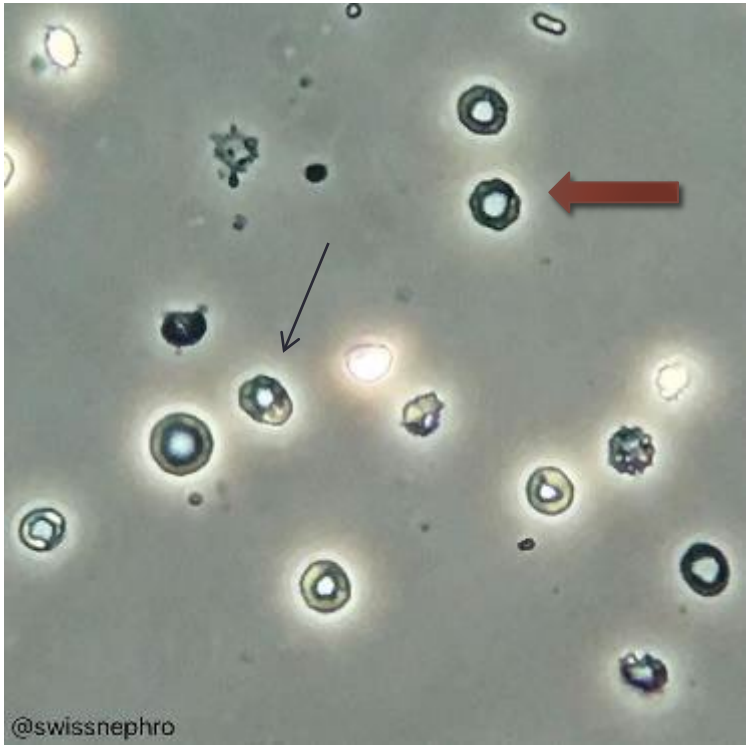


A normal capillary in a glomerulus keeps red blood cells, white blood cells and most proteins in the blood and only lets watery fluid into the urine.

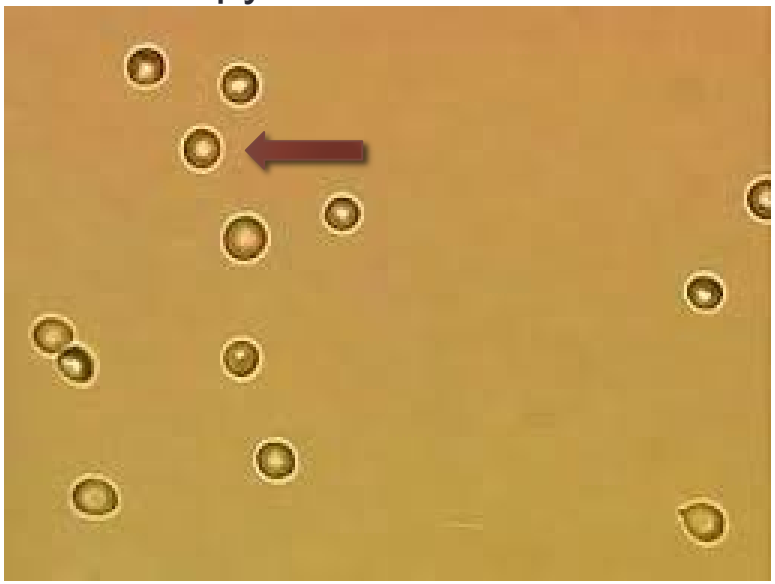


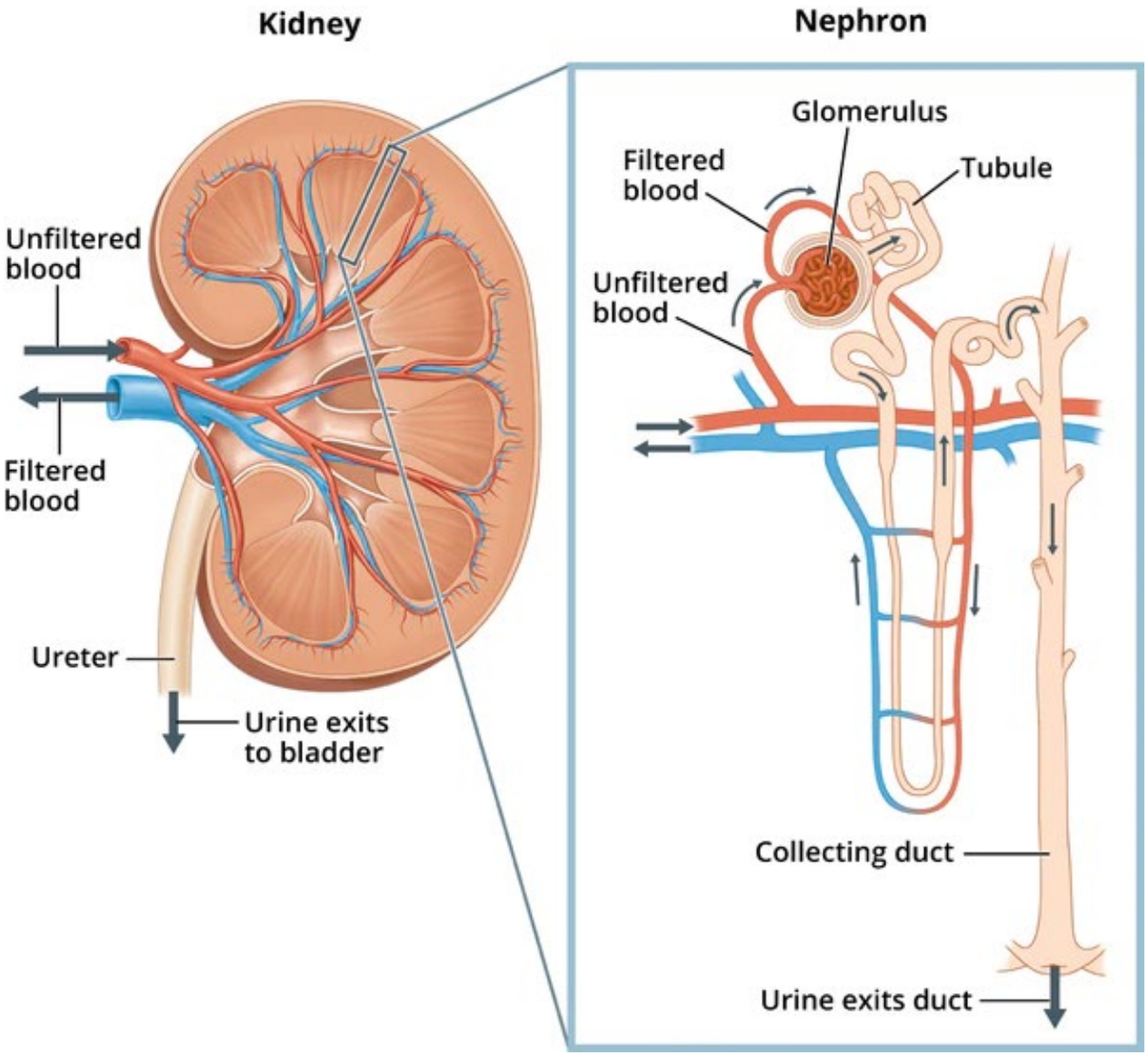
A capillary in a diseased glomerulus lets protein into the urine (proteinuria) and red blood cells into the urine (hematuria).

Dysmorphic RBCs in urine microscopy



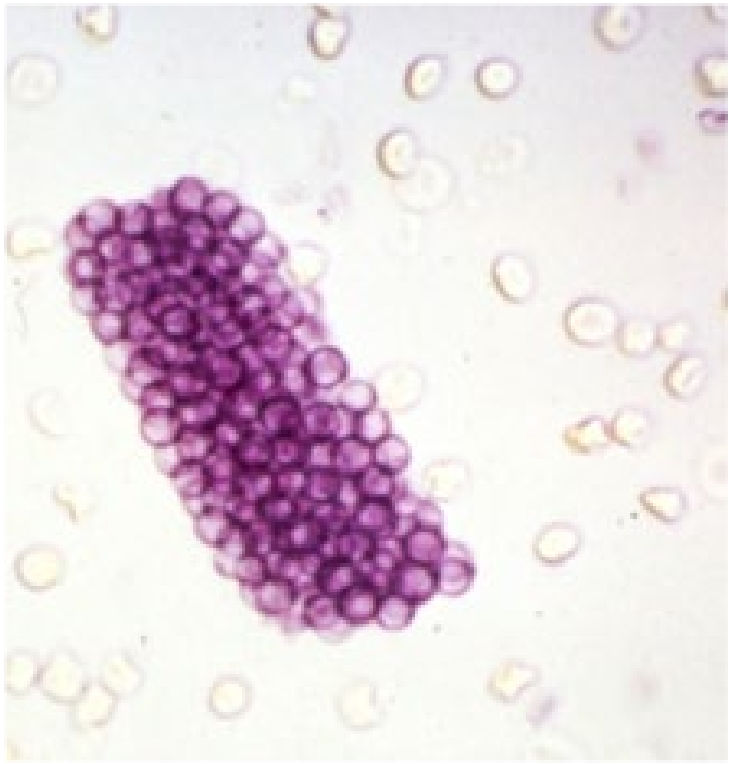
Normal looking RBCs in urine microscopy




Kidney
Nephron
Unfiltered blood
Filtered blood
Ureter
Urine exits to bladder
Glomerulus
Filtered blood
Tubule
Unfiltered blood
Collecting duct
Urine exits 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 urine analysis will show:

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

Dysmorphic RBCs & **RBC casts** are called:

Active Urinary Sediments when seen under microscope in urine sample

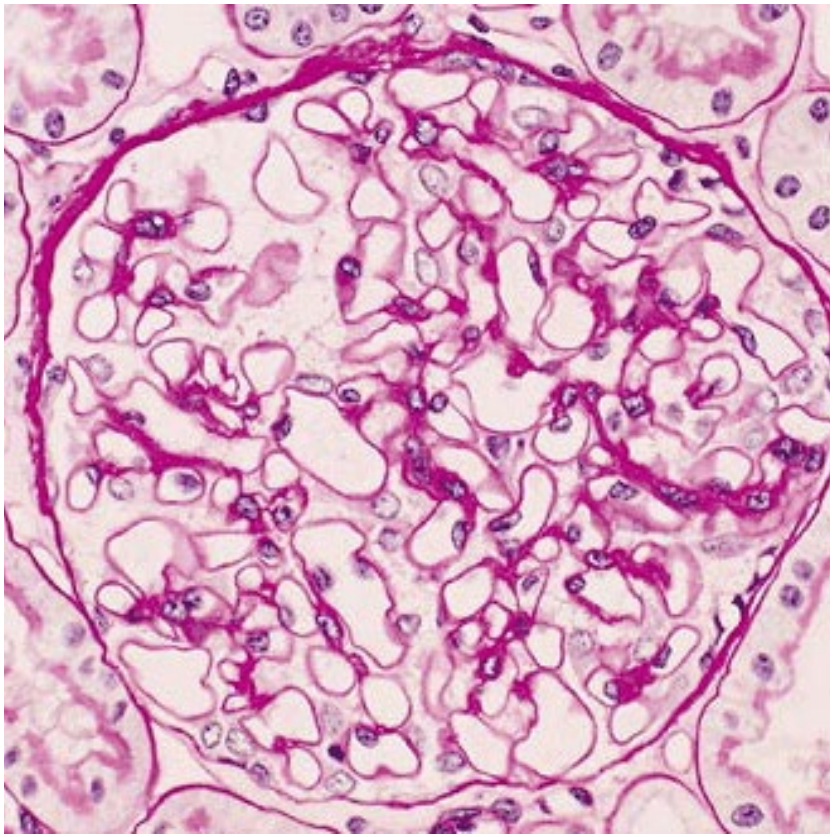
(Active = indicative of an underlying active glomerular inflammatory process; requiring **urgent medical attention**)

Nephritic clinical manifestations:

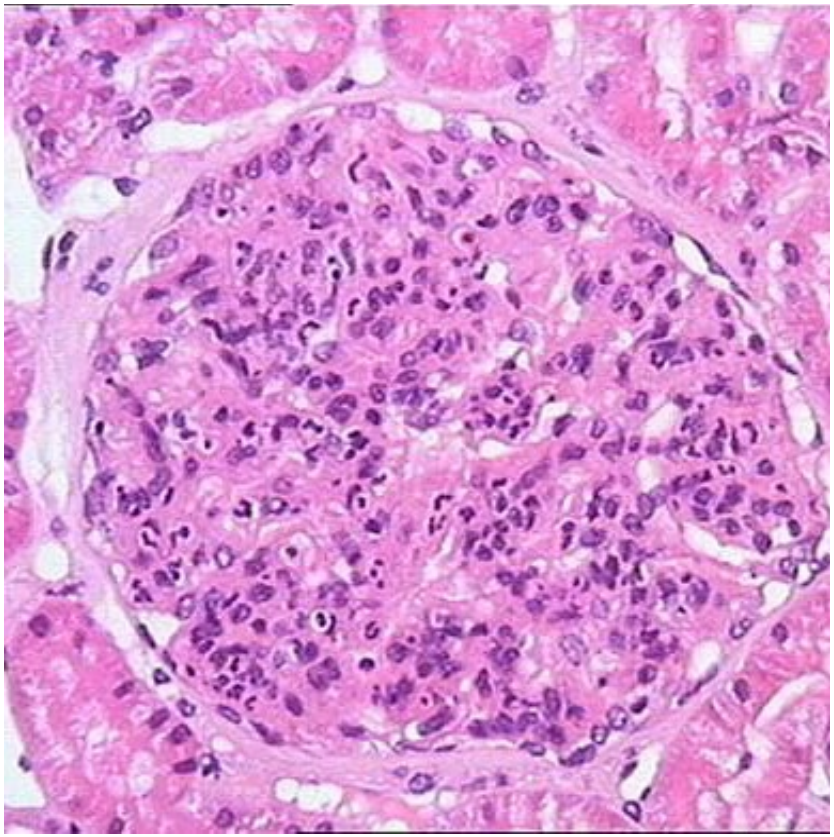
- **AKI** (Acute Kidney Injury) =Acute Renal impairment or Failure= elevated Creatinine) & electrolytes imbalance.
- **Decreased Urine output**
- **Edema**
- **High Blood Pressure**
- May have other manifestations of systemic vasculitis since some GN types are actually vasculitis (e.g. skin rash, pulmonary hemorrhage, etc) or symptoms and signs of an underlying connective tissue disease like SLE
- Positive immune markers: ANA, Anti-DNA, low complements, +ve ANCA or anti GBM (depends on the cause of GN or the underlying primary autoimmune disease)

Nephritic Glom

Normal Glom.

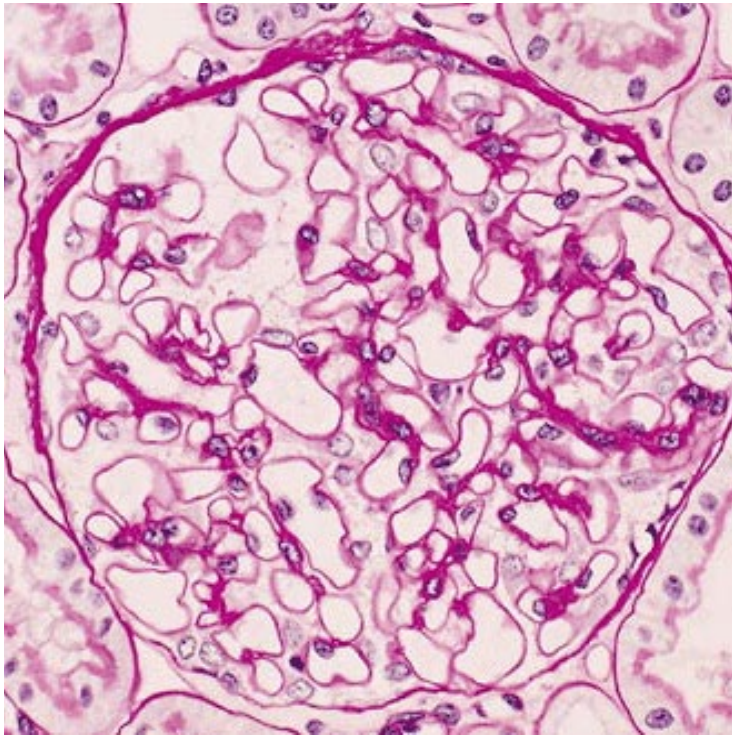


Glom. with proliferative (inflammatory= Nephritic) GN

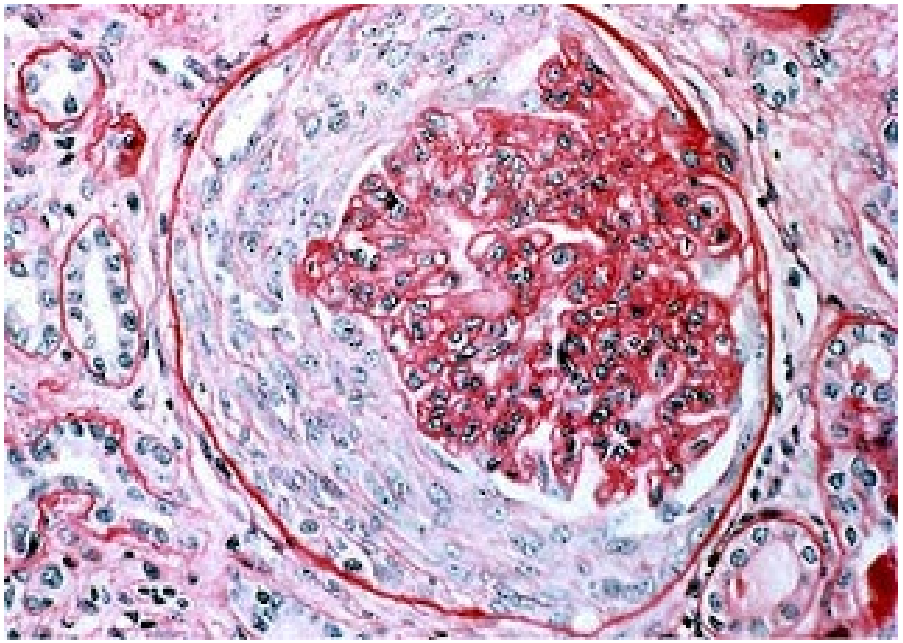


Crescentic GN; is a very bad GN!!!! It means very sever form of GN

- Normal Glom.



- Glom. with Crescent formation



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)**
- **SLE with Lupus Nephritis (class III & IV)**
- **Anti-GBM** anti Glomerular basement membrane (called Goodpasture's disease if there is lungs involvement)
- **ANCA associated vasculitis** (e.g. Wegner's Granulomatosis)
- Membranoproliferative GN (MPGN) like Cryoglobulinemia

IgA Nephropathy

- **Most common type of Primary GN in developed countries**
- Typical presentation: as dark red urine (**hematuria**) **1-3 days** after upper respiratory tract infection **(< one week of since the start of URT infection symptoms)**
- But 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 (progress from CKD to ESRD)
- Needs kidney biopsy to make 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 and cellualr proliferation hence Nephritic GN)

Urine color 3 days after upper respiratory tract infection in IgA (the typical)

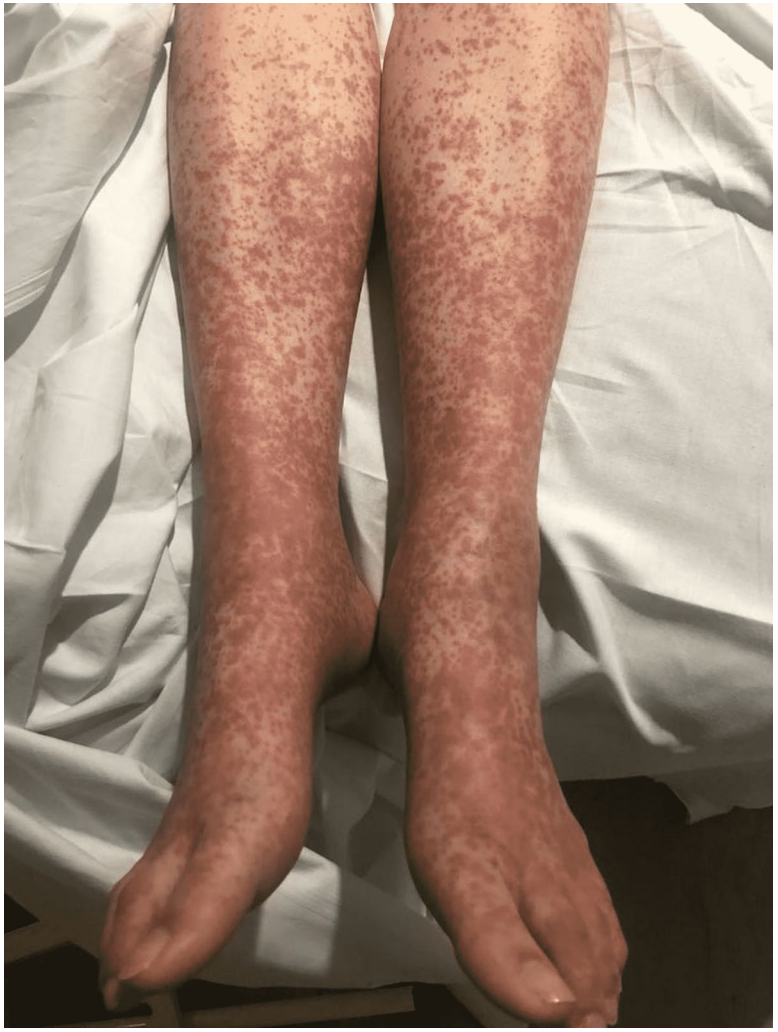
Cont IgA

- It is thought to be secondary to altered mucosal immunity that leads to excessive production of structurally altered IgA , followed by deposition in the gloms.
- There is really no effective immunosuppressing therapy except in severe cases where it can be tried. Maybe corticosteroids in certain cases.
- 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 (causes purpuric rash), bowel (abd pain) and kidneys (hematuria and proteinuria)

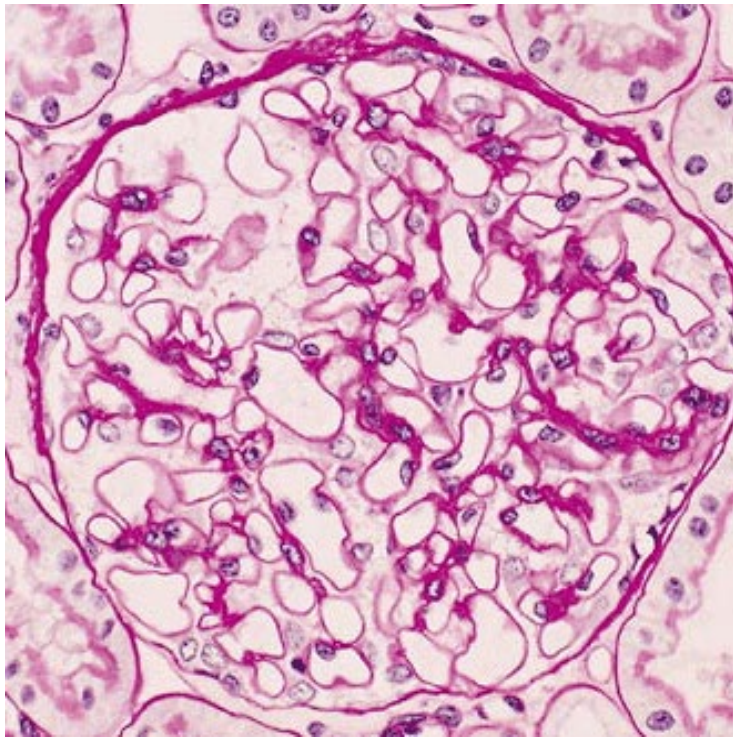
HSP (Henoch-Schönlein purpura)

Urine:
++ Protein
++ Active sediments (RBC casts & dysmorphic RBCs)

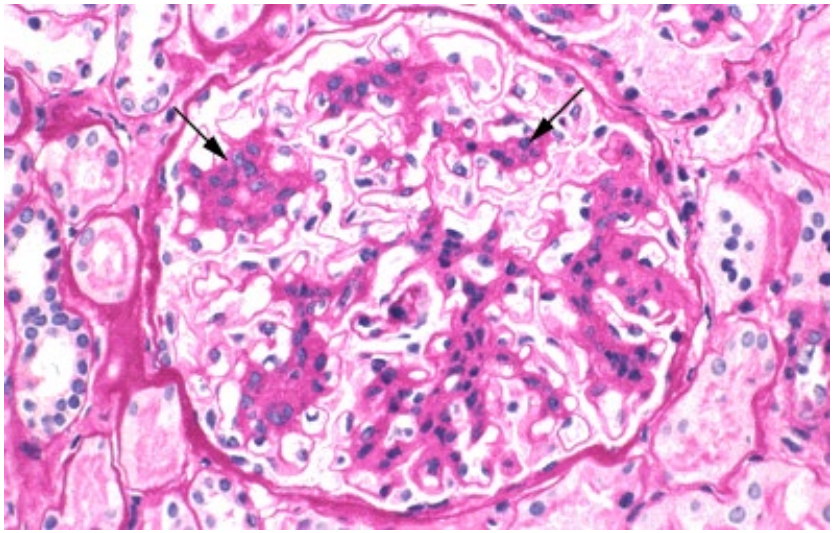


IgA

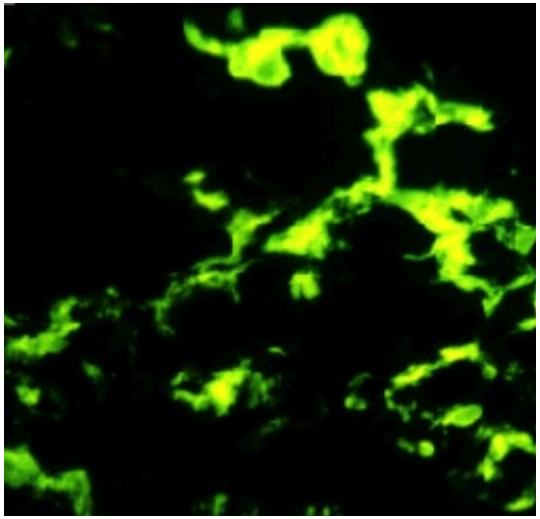
Normal Glomerulus



IgA Nephropathy (IgA deposits in mesangium)



IgA IF
Immunoflorecent



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 (Post infectious GN)
- Bacterial Antigen cross react with Glom antigens, or may be an immune-complex (Antigen-antibody) response that is responsible for glomerular capillary injury.
- Patients present with **hematuria** (Cola colored urine) usually **after 1 - 3 weeks from the start of infection symptoms**.
- **Blood Serum will show positive Antistreptolysin (ASO) titer.**
- **Low C3 complement**, Normal or slightly low C4 in the serum.
- May have positive throat culture or may not at time of presentation.
- Children have better and faster recovery than adults (self limited)
- Treatment is usually supportive= wait and see, some times they need dialysis until kidneys recover from inflammation.

Cola colored urine in Post Strep Glomerulonephritis (usually one week or more after the infection has started)

Lupus Nephritis

- **Lupus (SLE : Systemic Lupus Erythromatosis)**: *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 a very severe one causing ESRD in few months or few weeks.
- Most important in dealing with these cases is having a high level of suspicion of its presence (i.e renal involvement) and to start immediate workup & referral for diagnosis and treatment.

Lupus Nephritis

- Kidney biopsy is mandatory to make the diagnosis.
- abnormal urine analysis (+ve RBCs OR +ve Protein) , +/- abnormal renal function should make you think of its presence. Also SLE markers: ANA, Anti DNA , Low C3, Low C4 will be seen in this case.

- Lupus Nephritis treatment depends on the findings in kidney biopsy (6 classes of histological involvement)
- It usually involves high degree of immunosuppressing medications from steroids, Mycophenolic Acid Mofytil, and Cyclophosphamide

ANCA associated vasculitis

- Autoimmune diseases that involves the presence of Neutrophils adhesion enhancing molecule called:

ANCA=Anti-neutrophil cytoplasmic antibody

This molecule establishes SMALL vessels vasculitis cascade

<u>There are two types of ANCA molecules:</u>

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

Newer lab test: PR3-ANCA for C-ANCA

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

Newer lab test : MPO- ANCA for P-ANCA

ANCA vasculitis

- Upper airways and lung involvement is common in C-ANCA 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 (PR3 or MPO)
- Kidney pathology will show sever Glomerulonephritis; maybe RPGN; but all staining with immunofluorescence for immunoglobulins is NEGATIVE; hence the name **Pauci-Immune vasculitis or Pauci- immune GN (Pauci = little or non means no deposition of immunoglobulins that caused GN so most likely diagnosis is ANCA)**
- 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)

- Autoantibody against (alpha-3 chain) of type IV Collagen that is found in **Glomerular basement membrane** & **lungs alveolar basement membrane.**

- So the manifestations will be vasculitis in kidneys and lungs:

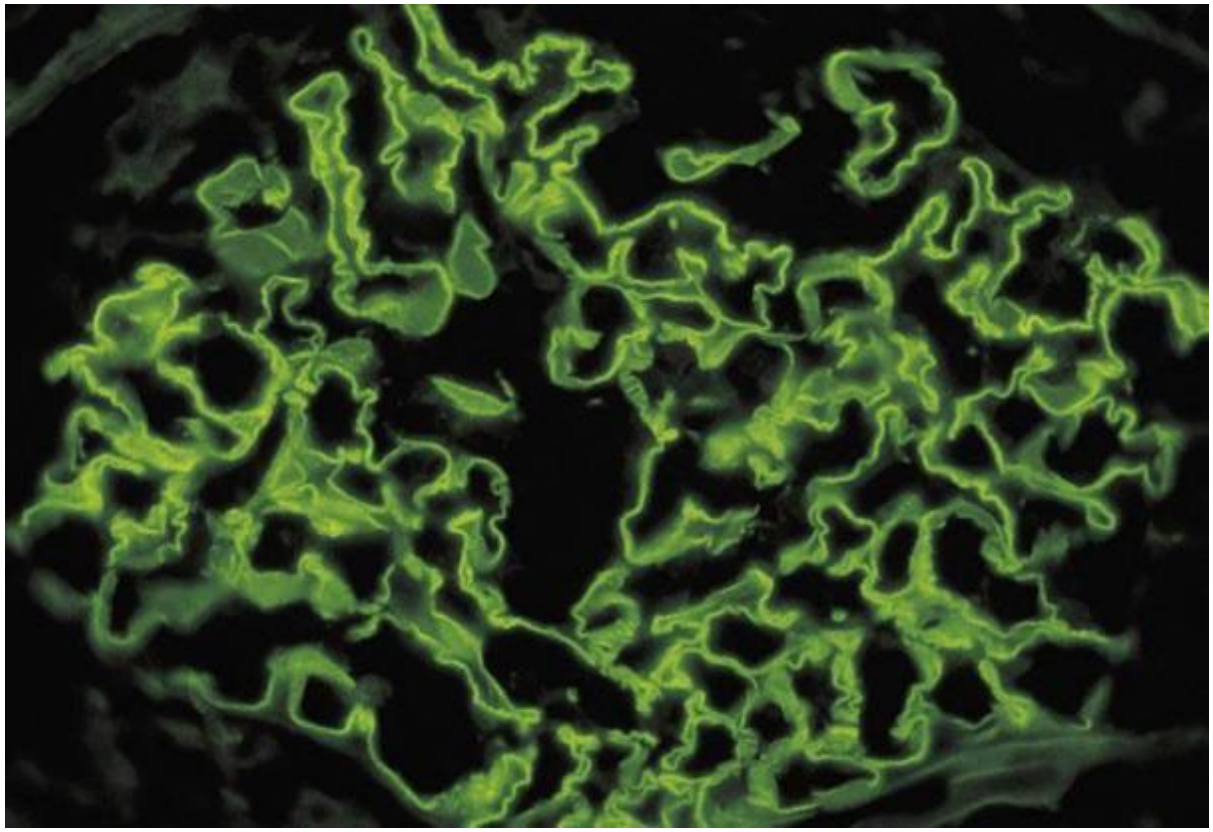
1- Glomerulonephritis (can be the only presenting finding) &

2- Pulmonary hemorrhage (disease is called *Goodpasture's syndrome if has : 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 (the anti GBM) and C3

Linear Anti-GBM staining in the Glomerulus by Immunofluorescence
is a *Diagnostic test (staining the auto antibodies at their site of deposition in the targeted antigen)*



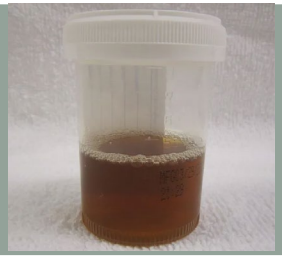
Anti-GBM

- 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.

Urine analysis comparison for Glom diseases

Urine analysis test	Normal urine	Nephrotic	Nephritic
Albumin	Nil	+++/ ++++	From + to +++
RBCs	Nil (<2)	Nil	+ to +++
Fat	Nil	++	Nil
Cellular casts	Nil	Nil	+++
Dysmorphic RBCs	Nil	Nil	+++
Color	Clear yellow	Frothy	If subclinical normal color Or blood color or cola colored

Which one is Normal urine sample?

				
Normal color	Normal color	Bright Red (frank hematuria)	Cola color	Turbid yellow with foam (frothy)
No RBCs No Protein Normal Creatinine	+ RBCs + RBCs casts + +Protein Slight high Crt	++++ RBCs **NO casts** ++ Protein (because of RBCs) Normal Creatinine	++ RBCs +++ Casts +++ Protein High Creatinine	No RBCs NO Casts **++++ Protein** Normal Crt
Normal Healthy kidneys	**Chronic IgA**	Bladder / kidney **cancer or stone** or prostate **(Not GN)**	Post Infectious **GN , or RPGN** or severe IgA (	**Nephrotic syndrome** : MCD FSGS MN

	Nephrotic Syndrome	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 Process effacement ++
Proteinuria	> 3.5 g/Day	Variable amount from few 100s mg to multiple grams / day
Urine microscopy	No hematuria + Lipids (Lipiduria)	+ RBCs, + dysmorphic RBCs, + RBC casts (active sediments)
Labs	Low serum Alb < 30 gm/L High serum Cholesterol	Low GFR=Renal impairment Electrolytes imbalance
Clinical	Edema ++++ BP maybe high	Edema ++ depends on severity High BP +++ Symptoms & signs of renal impairment or systemic vasculitis
Complications Acute	Thrombosis Infection , AKI	RPGN (crescentic GN) AKI (Acute kidney injury)
Complications chronic (untreated)	Vascular Atherosclerosis, Renal Tubular atrophy & Fibrosis >>> CKD then ESRD	Glom sclerosis then CKD (chronic Kidney disease) >>>> ESRD