Approach to Hematuria & Proteinuria

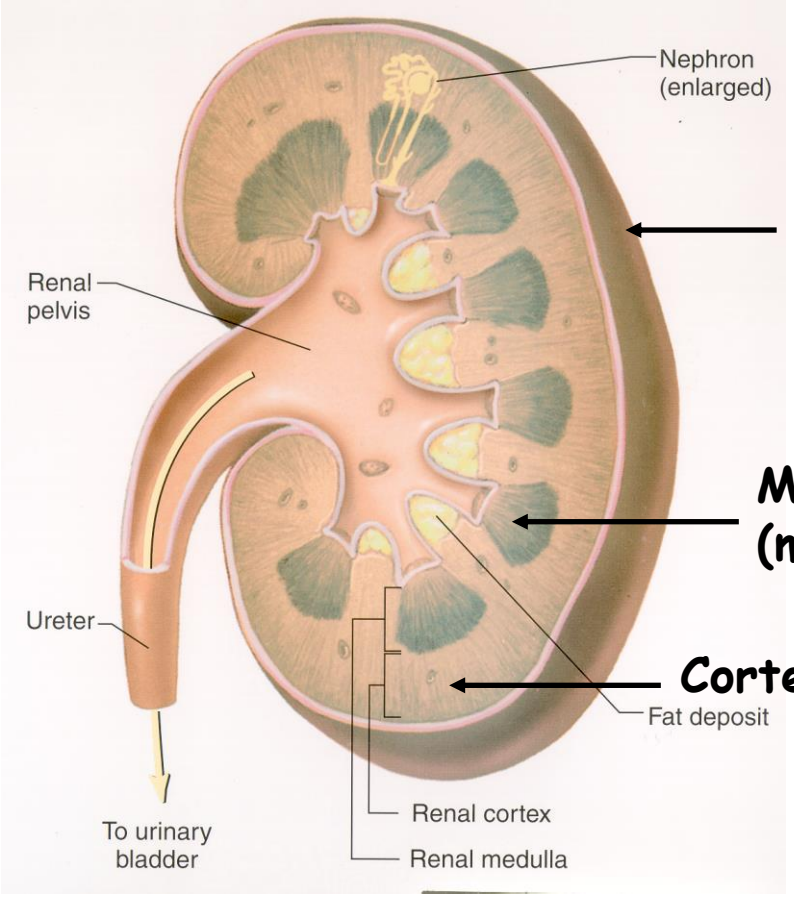
Med 441

1434 / 2013

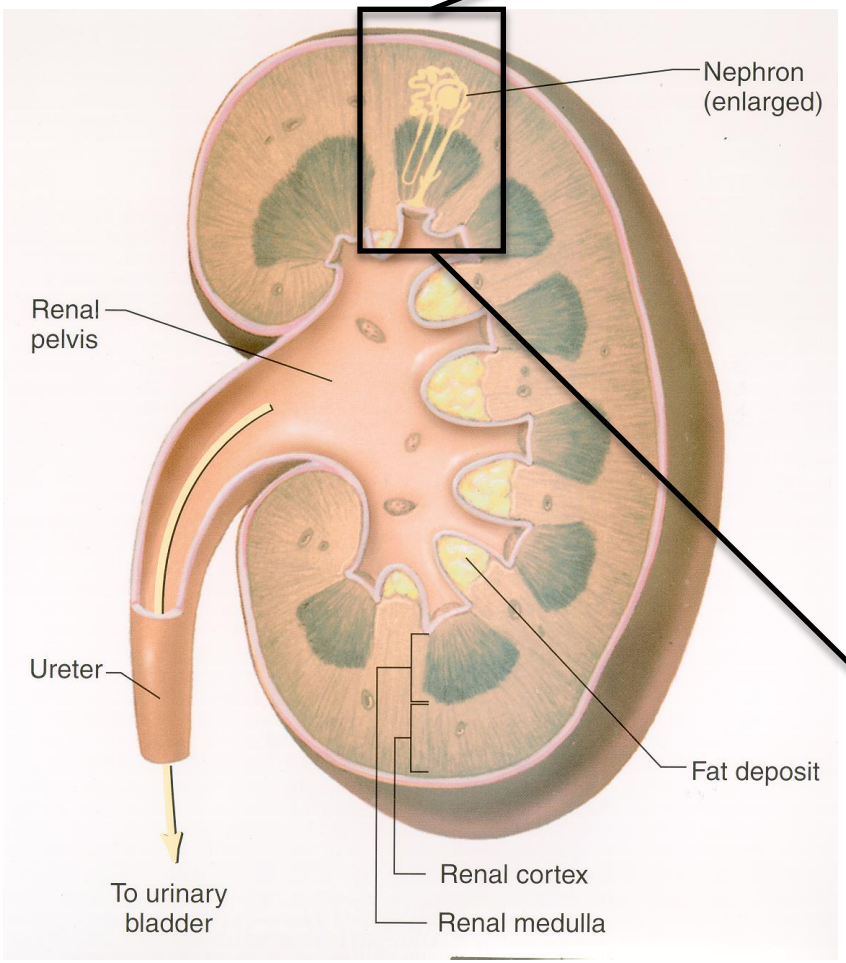
Objectives

- To review the basic structure of the Glomerulus.
- To understand the pathophysiology of glomerular immune mediated injury.
- To be capable of recognizing the underlying diseases by careful interpretation of simple tests' results.
- To recognize the differences between Glom. Vs. Non-glom. Hematuria.
- To recognize the different grades of Proteinuria and their clinical importance.

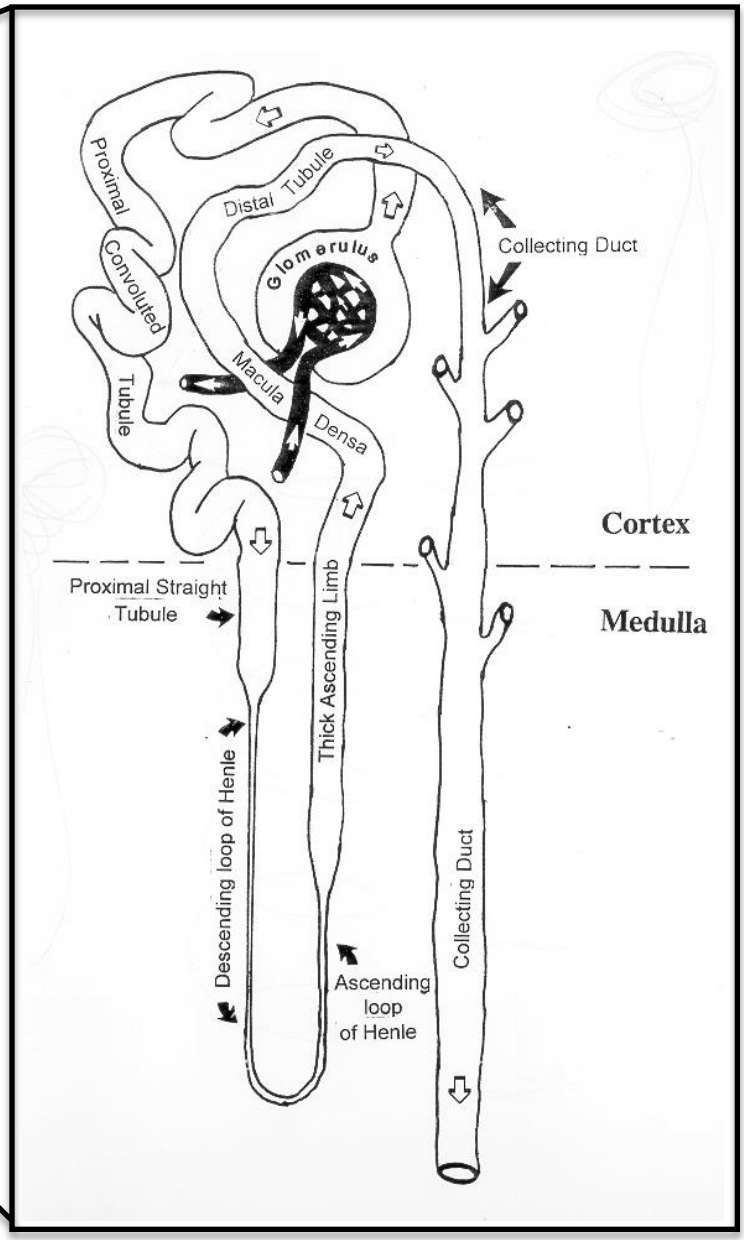
Gross Kidney Anatomy



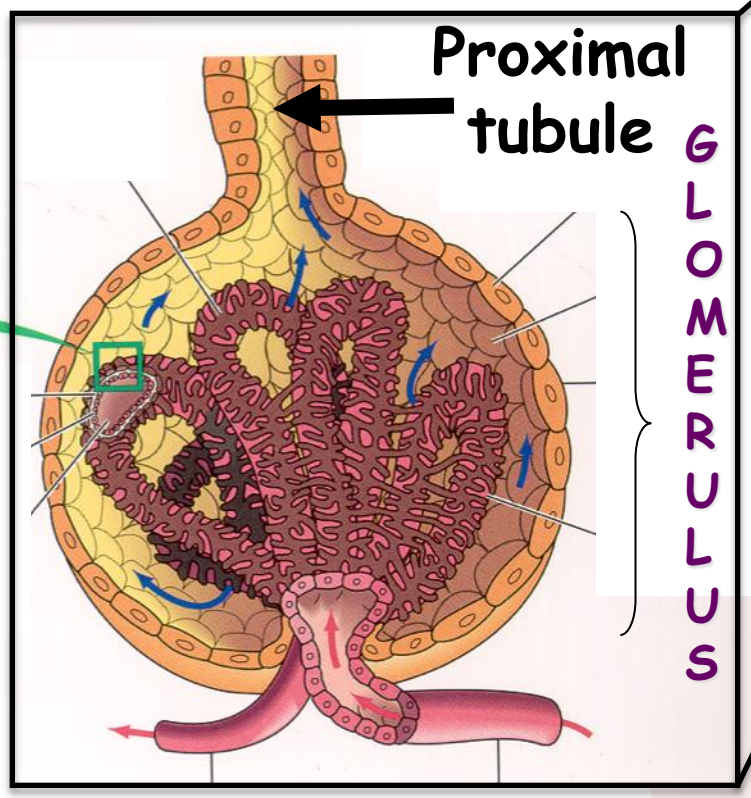
The Nephron

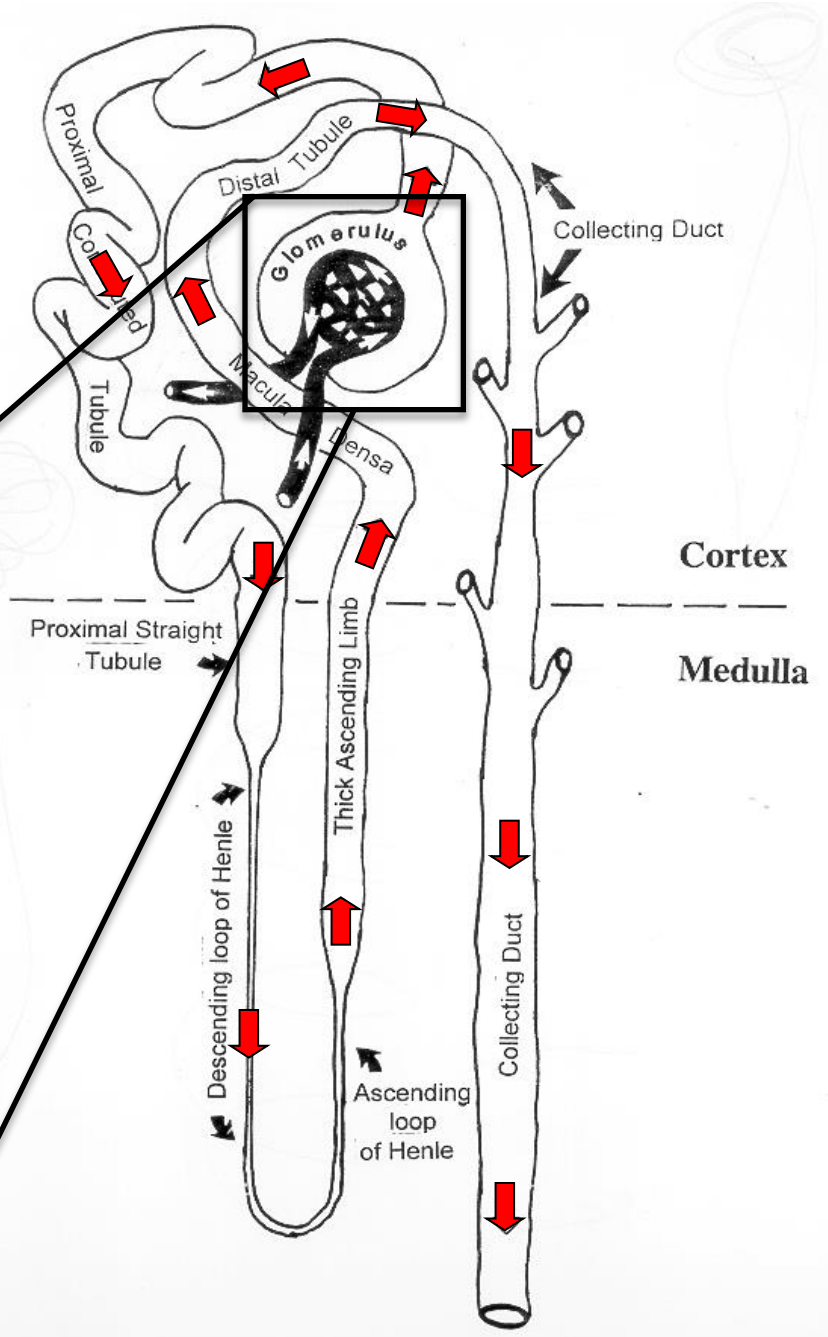


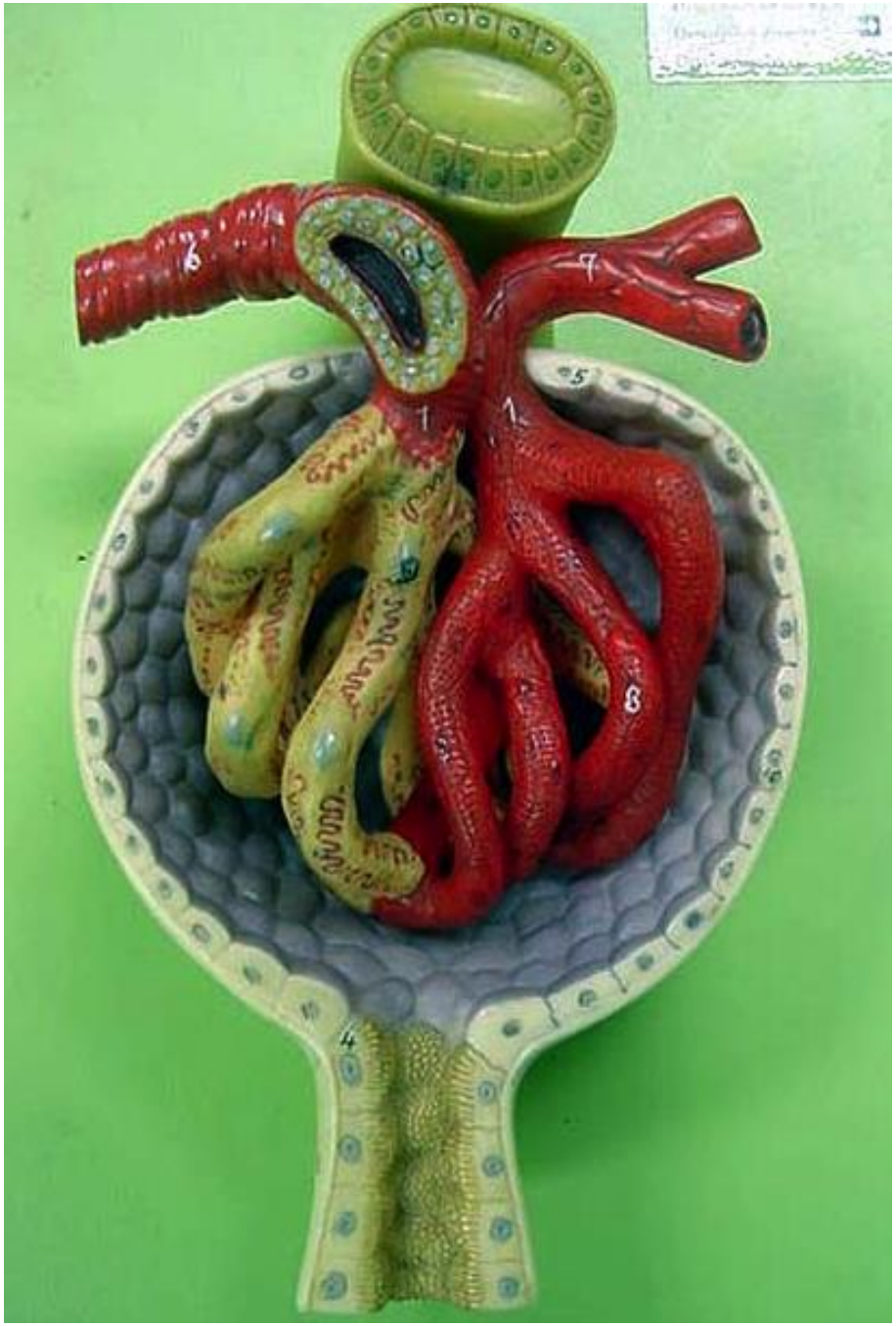
Nephron (zoom)



The Nephron


Proximal tubule
GLOMERULUS


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


6
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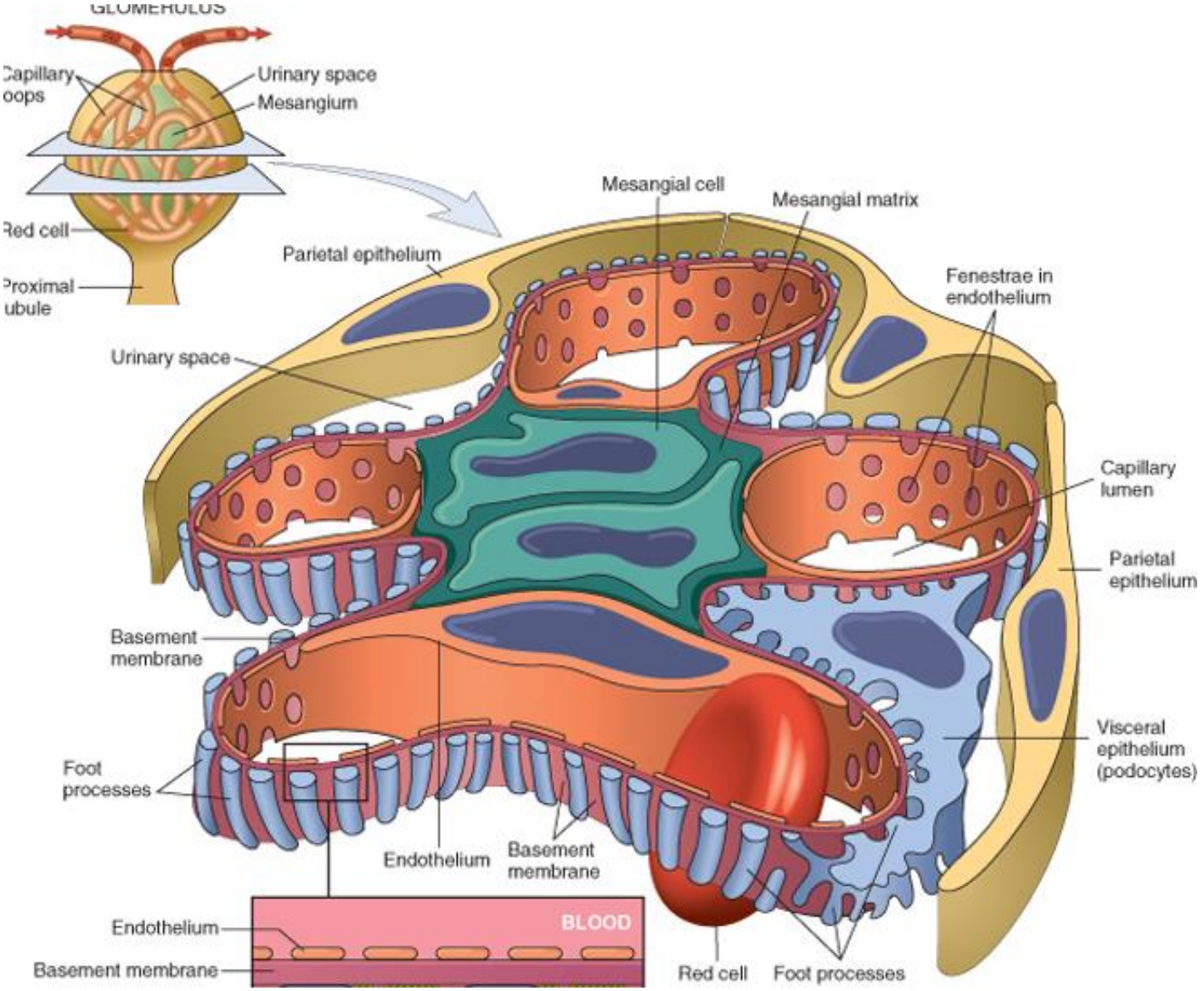
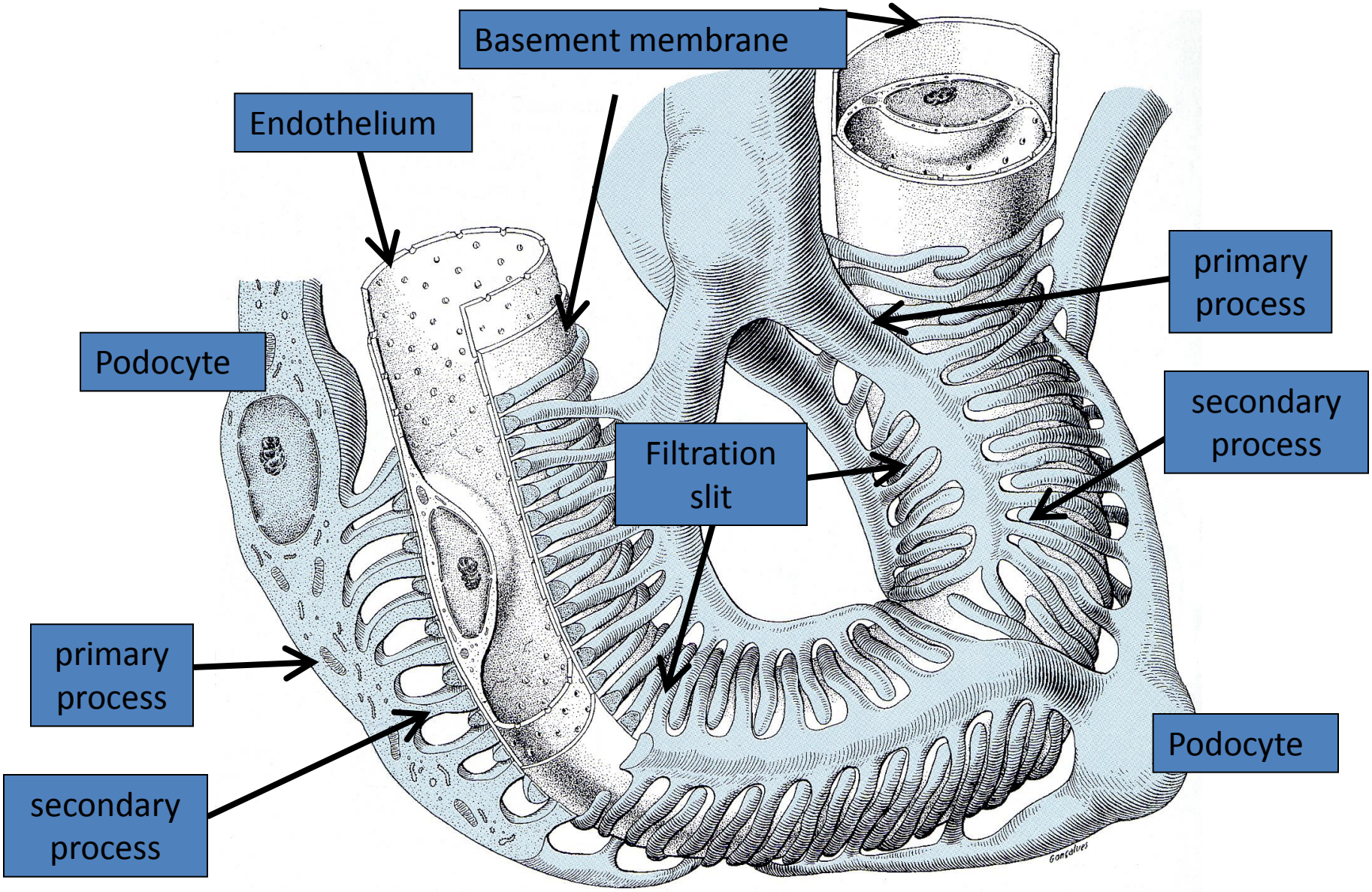
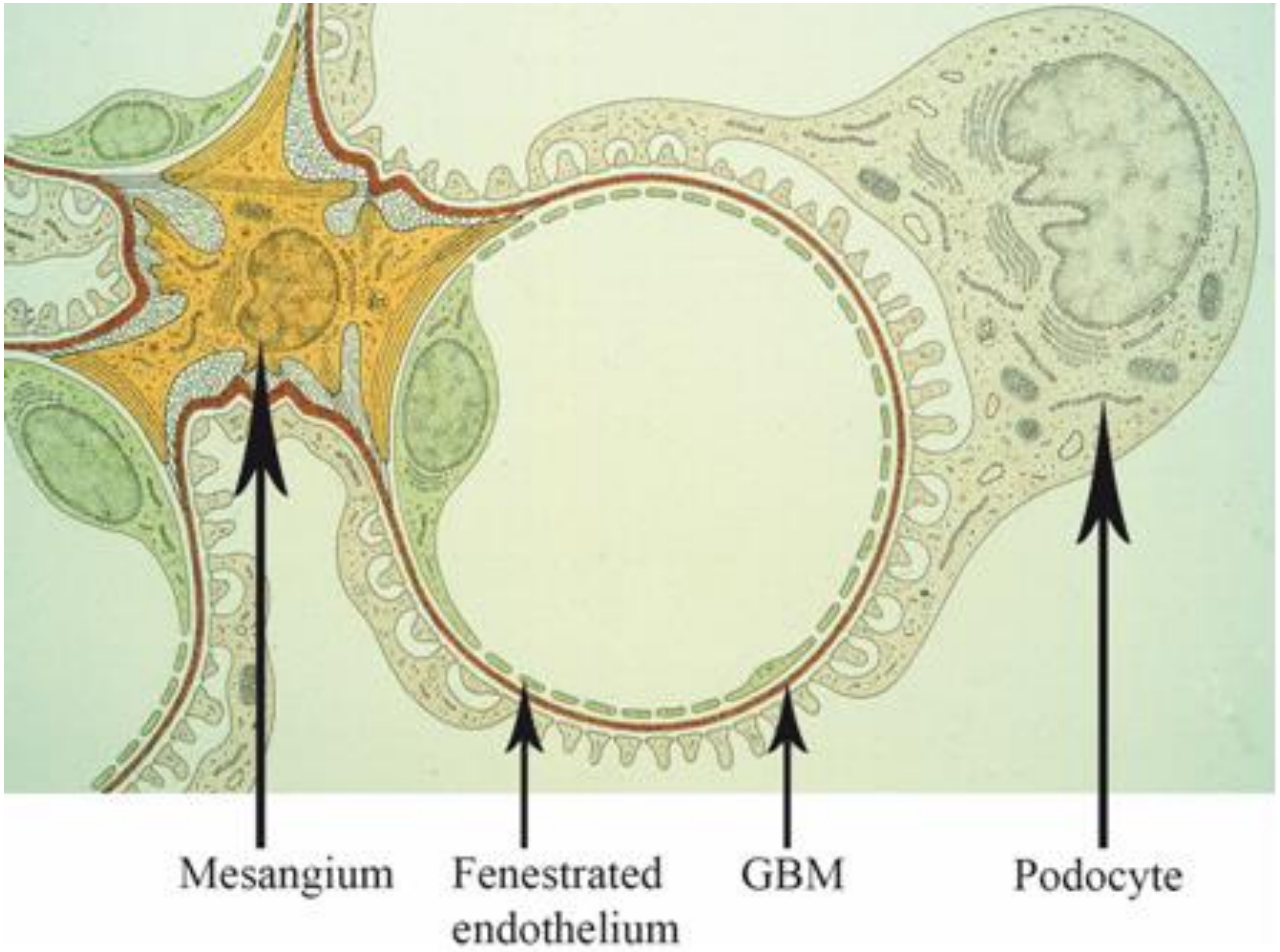
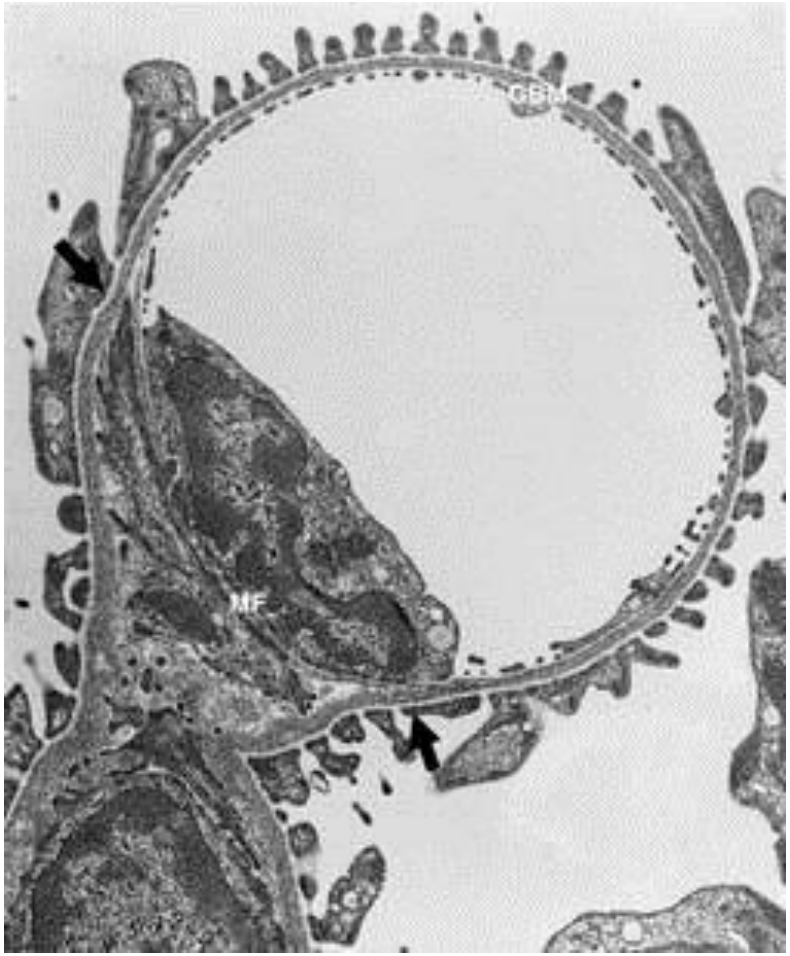

GLOMERULUS
Capillary loops
Urinary space
Mesangium
Red cell
Proximal tubule
Mesangial cell
Mesangial matrix
Parietal epithelium
Fenestrae in endothelium
Urinary space
Capillary lumen
Parietal epithelium
Basement membrane
Visceral epithelium (podocytes)
Foot processes
Endothelium
Basement membrane
BLOOD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


Basement membrane
Endothelium
primary process
Podocyte
secondary process
Filtration slit
primary process
Podocyte
secondary process

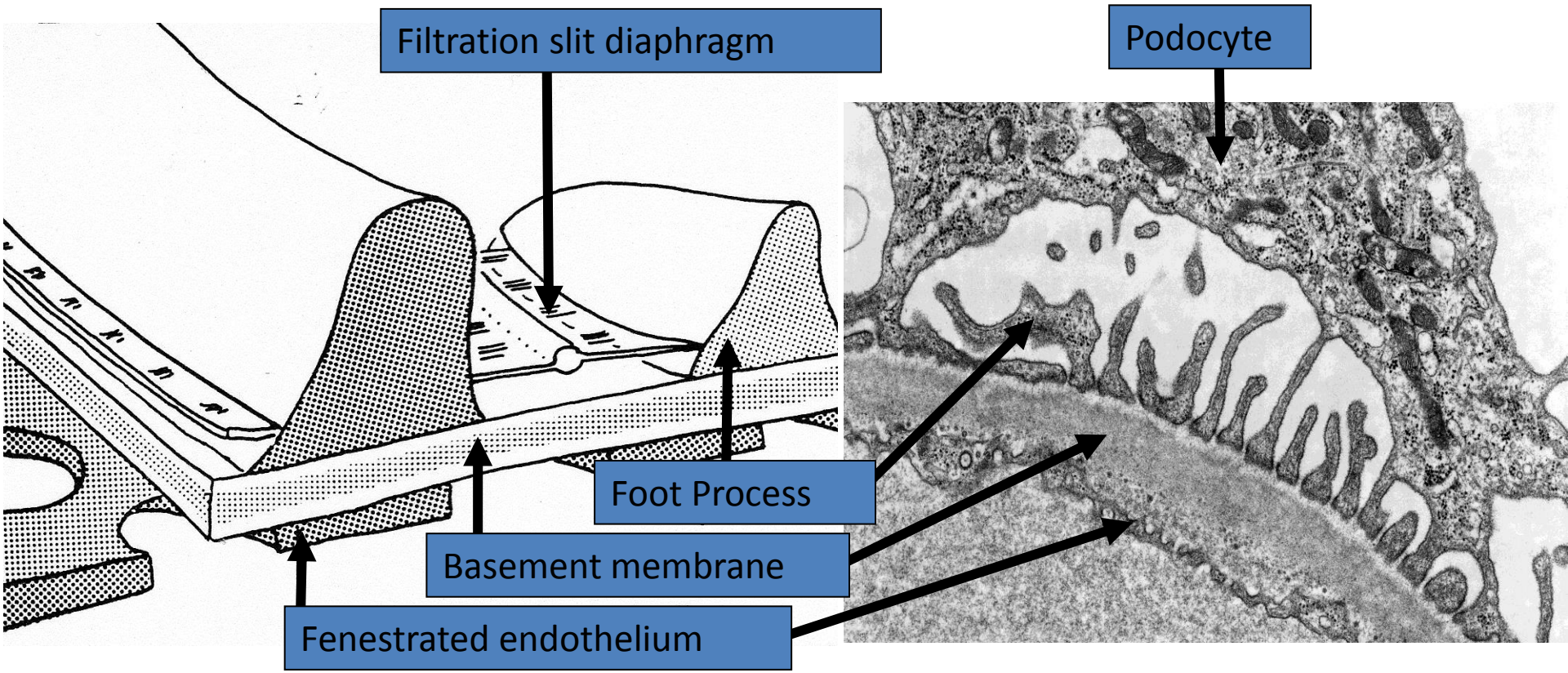
Capillary loop 3 layers wall:
1- Endothelial layer, 2- GBM, 3- Podocytes



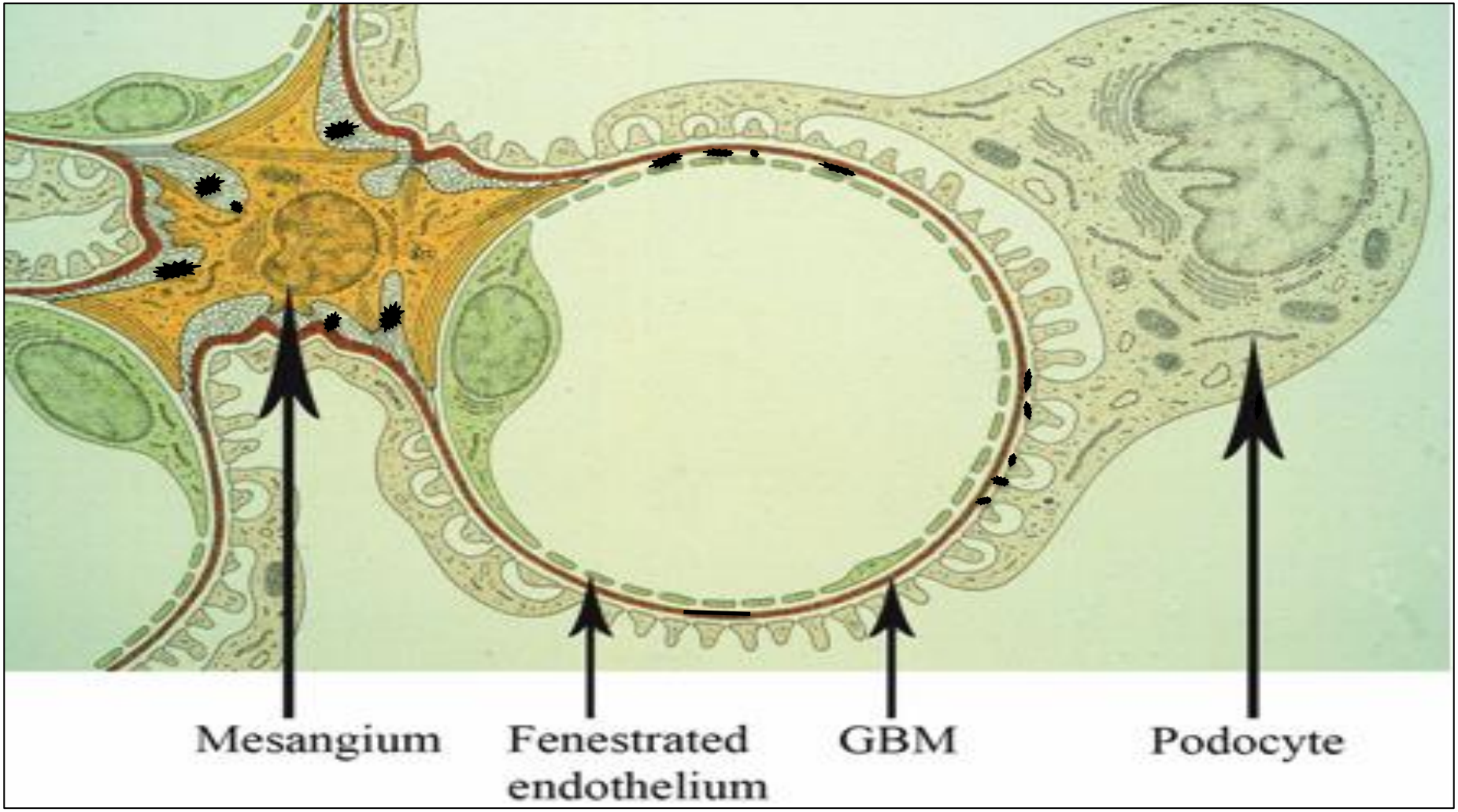
Normal Capillary Loop (Electron Microscopy)



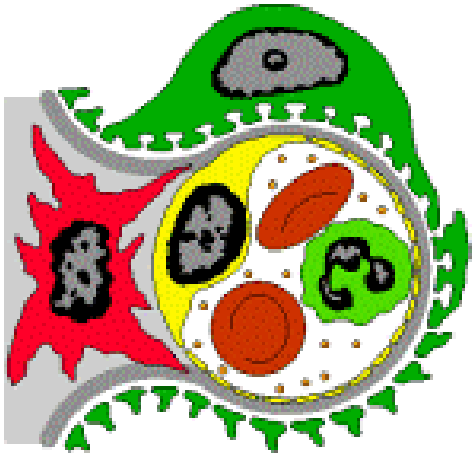
The podocyte and its associated endothelial cell is the site of ultrafiltration



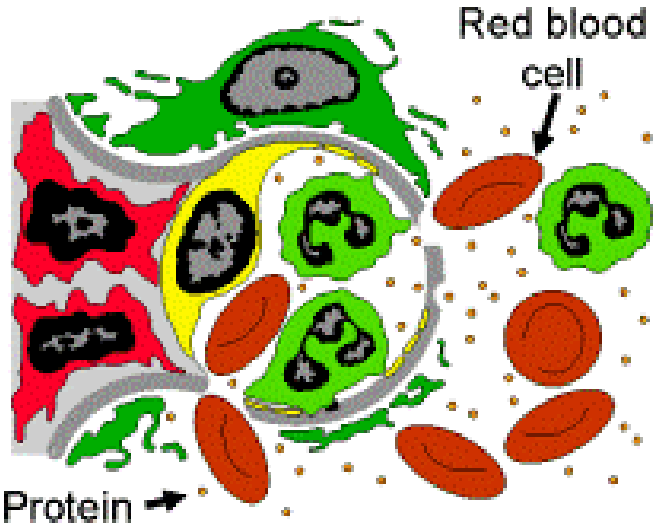
The targeted site of the immune mediated injury will likely determine the clinical manifestations of glomerular diseases



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.

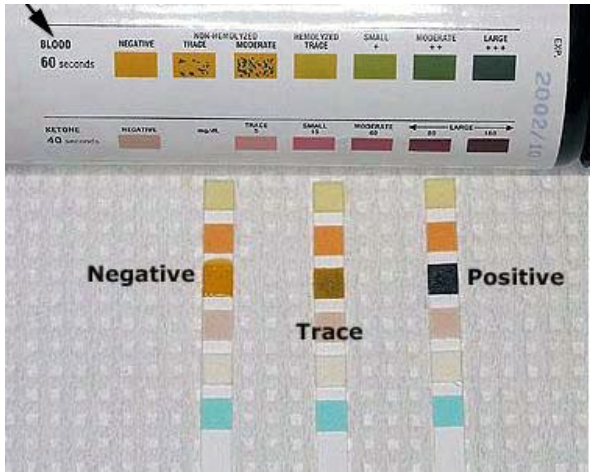


A capillary in a diseased glomerulus lets protein into the urine (proteinuria) and red blood cells into the urine (hematuria).

Normal urine analysis

- NO RED BLOOD CELLS (Accept: 1-2 RBCs/HPF)
  (< 8000 RBCs/ml in centrifuged urine)
- NO HEME.
- NO CELLULAR CASTS.
- NO PROTEIN.

URINE TESTING:



SIMPLE URINE DIPSTICK:

- Very sensitive for blood *(**NO FALSE NEGATIVE**)*
- Detects Heme coming from as low as (1-2 RBCs/ high power field).
- But may be false positive for Heme by detecting e.g. Myoglobin (Rhabdomyolysis)

URINE TESTING:

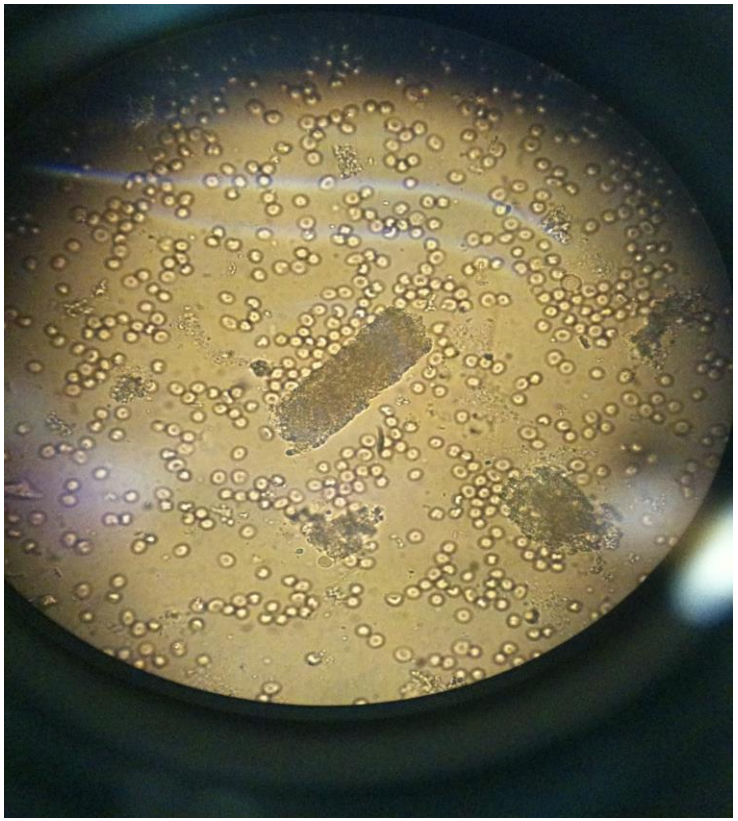
SIMPLE URINE DIP STICK:

- Of all kinds of proteins in the urine; it only dtects Albumin, but has to be > 300mg/day (early DM-Neph)
- Non Albumin proteins will not be detected

  (e.g MM. Light chains; Bence Jones Proteins)
- Semiquantitative for Albuminuria (Nil, Trace,1+, 2+, 3+,4+), and that can be affected by urine concentration.
- False +ve Albumin: PH>8, or after Radiocontrast.

URINE TESTING:

HPF



<u>URINE MICROSCOPY</u>:

LOOKING FOR:

- Red Blood Cells (RBCs)
- White Blood Cells (WBCs)
- CASTS (Red or whites cells)
- CRYSTALS
- BACTERIA
- ABNORMAL CELLS (e.g. malignant cells)

Hematuria

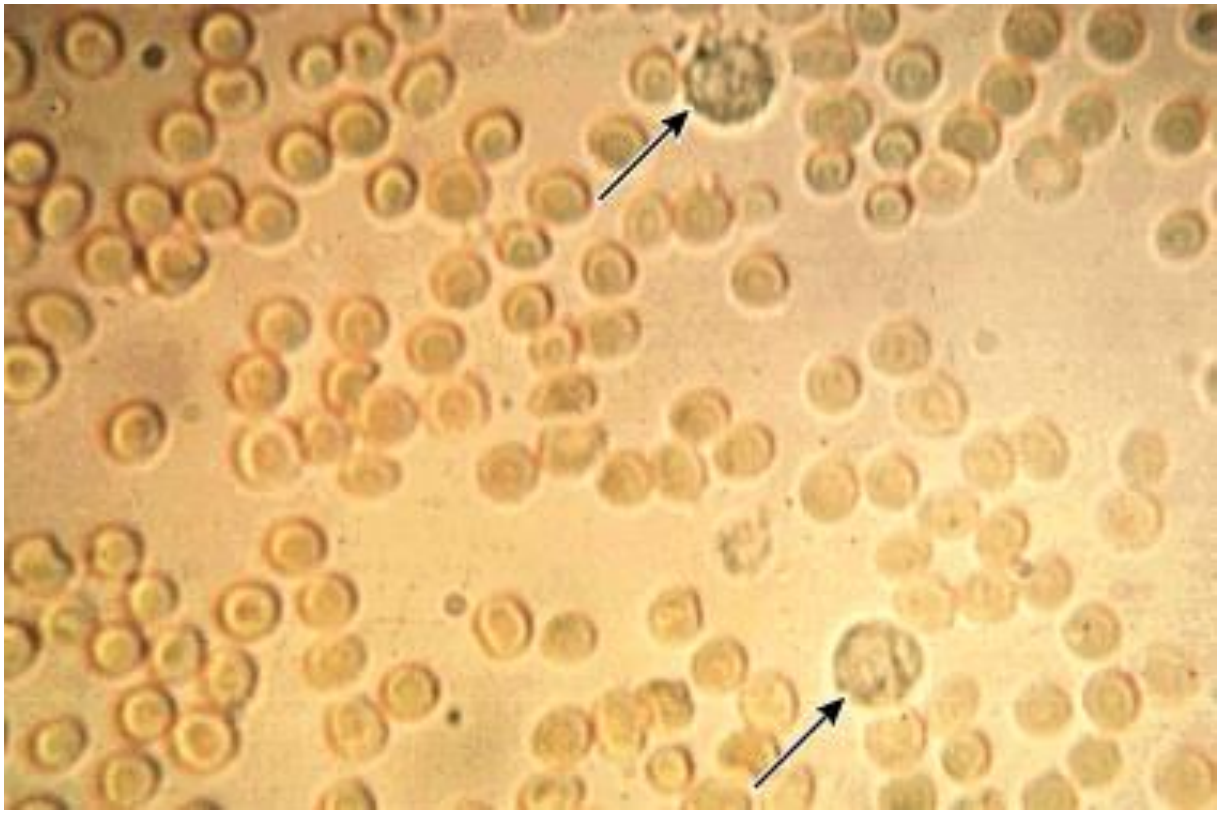
Definition: **> 3 RBC/hpf** on 2 separate **(persistent)** urinalyses without recent exercise, menses, Infection, sexual activity or instrumentation.

HPF= microscope high power field

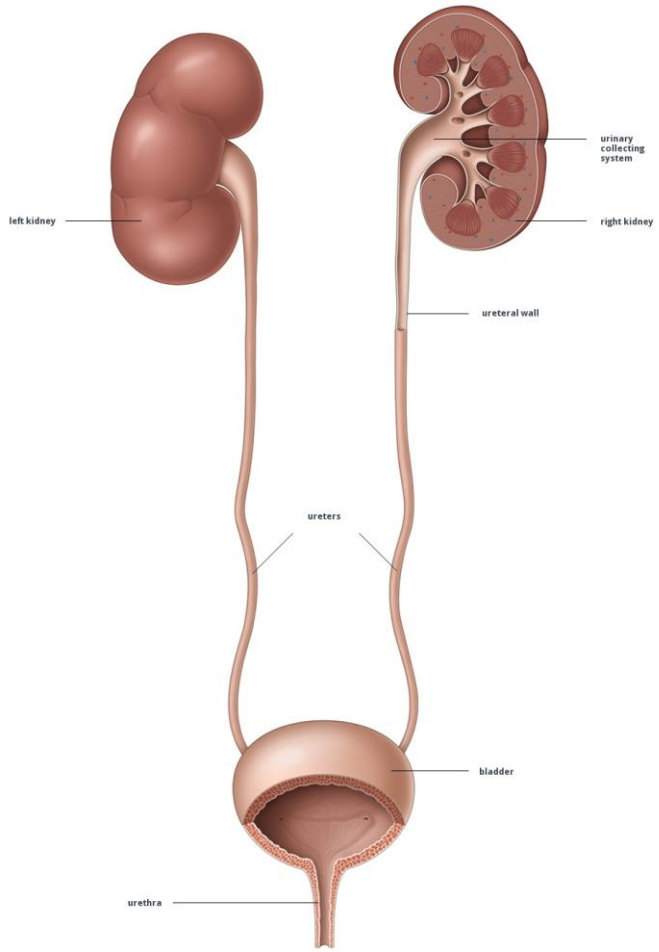
Transient hematuria is benign in young patients, specially if no other GN suspicious signs.

Transient hematuria in patients > 35 y ; warrants further workup.

RBCs in a spun urine (in case of hematuria)



Source of Hematuria



Hematuria: is very likely to be Glomerular in origin if you see any of the following in urine microscopy

- **Dysmorphic OR Fragmented RBCs**
- RBCs Acanthocytes
- **RBCs Casts**
- WBCs Casts

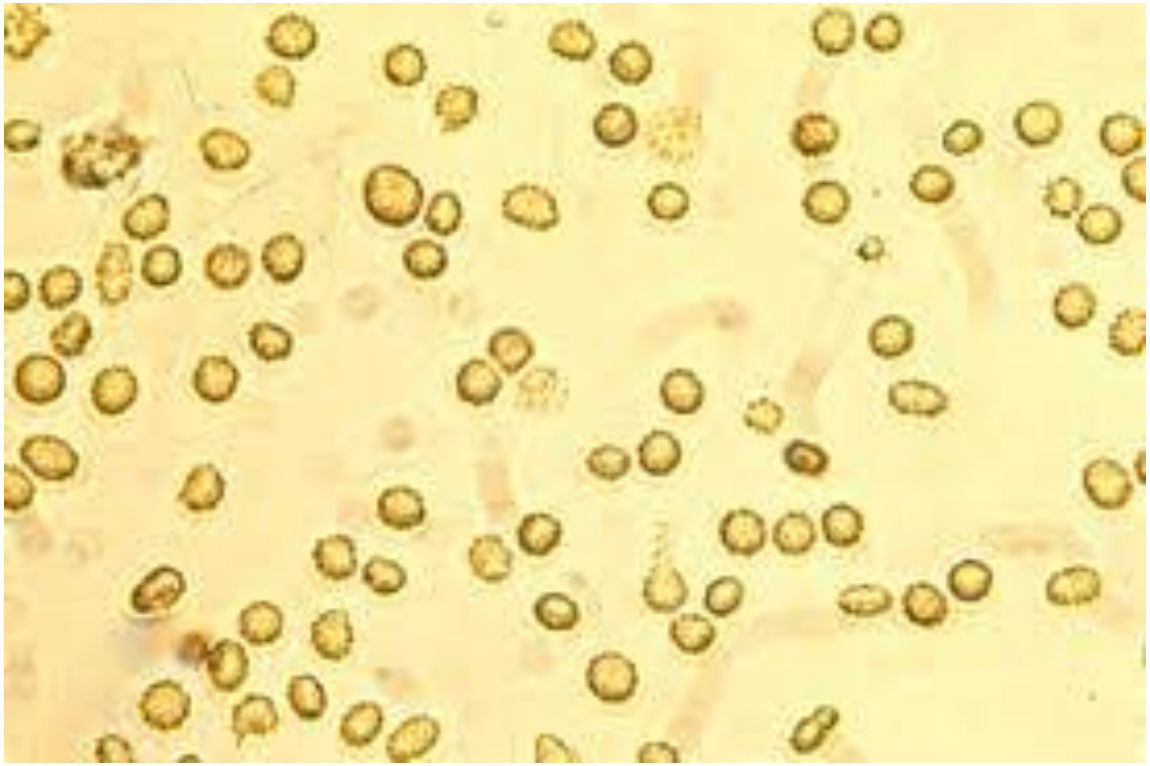
In Nephrology they are called:

Active Urine Sediments , because indicative of GN.

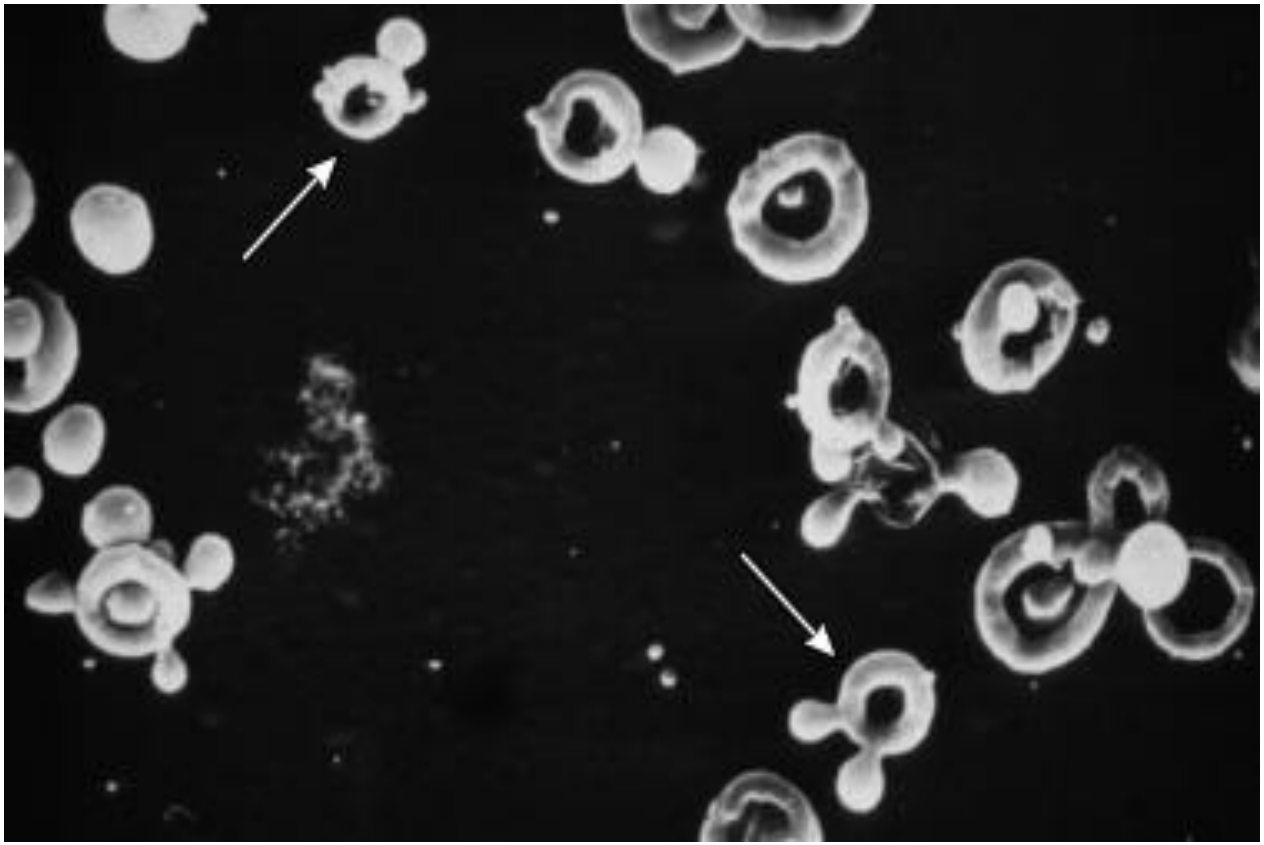
And If associated with Cola colored urine, Low GFR and Proteinuria--> most likely Glom. In origin

GN= Glomerulonephritis

Dysmorphic RBCs

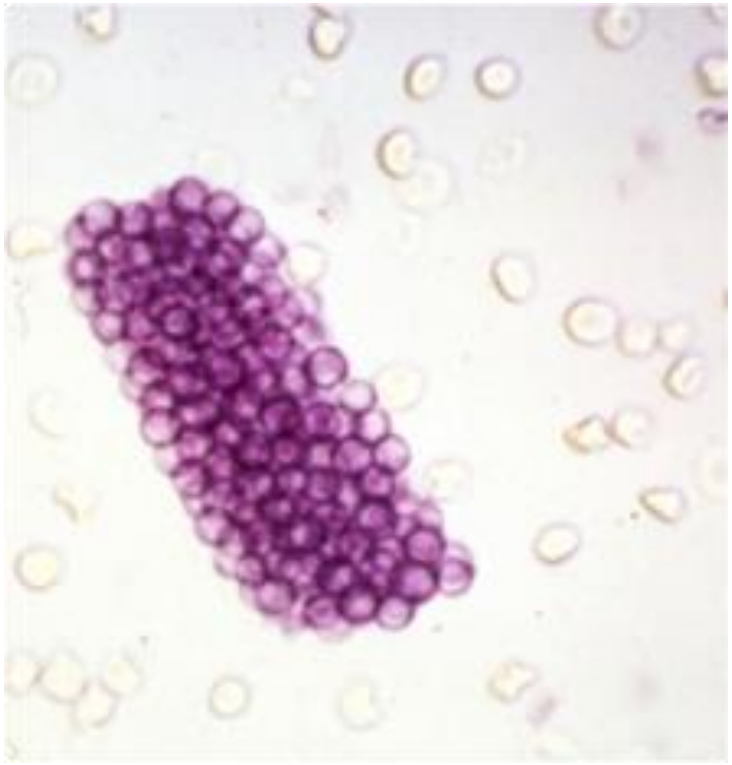


RBCs *Acanthocytes >= 5%*

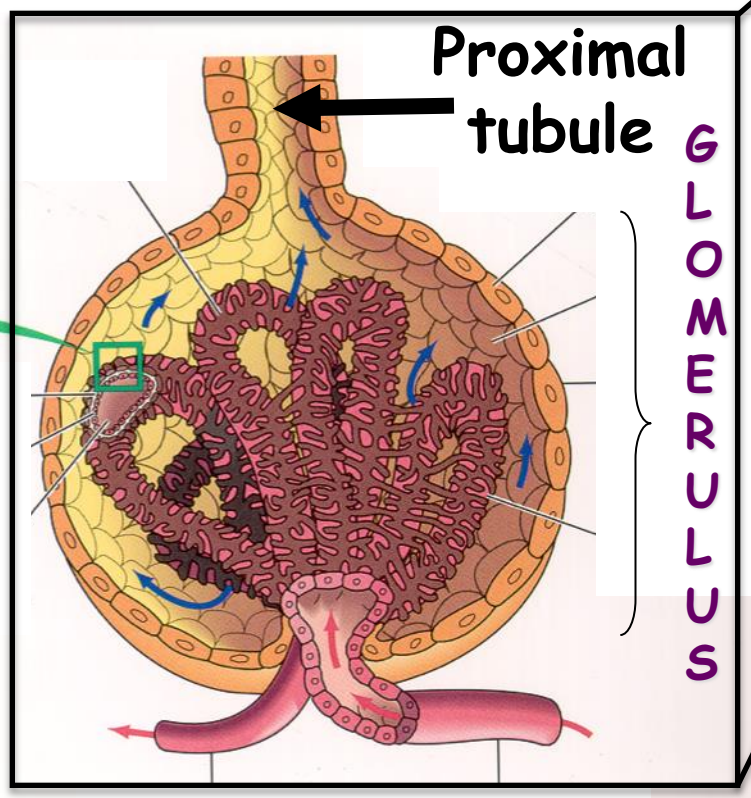


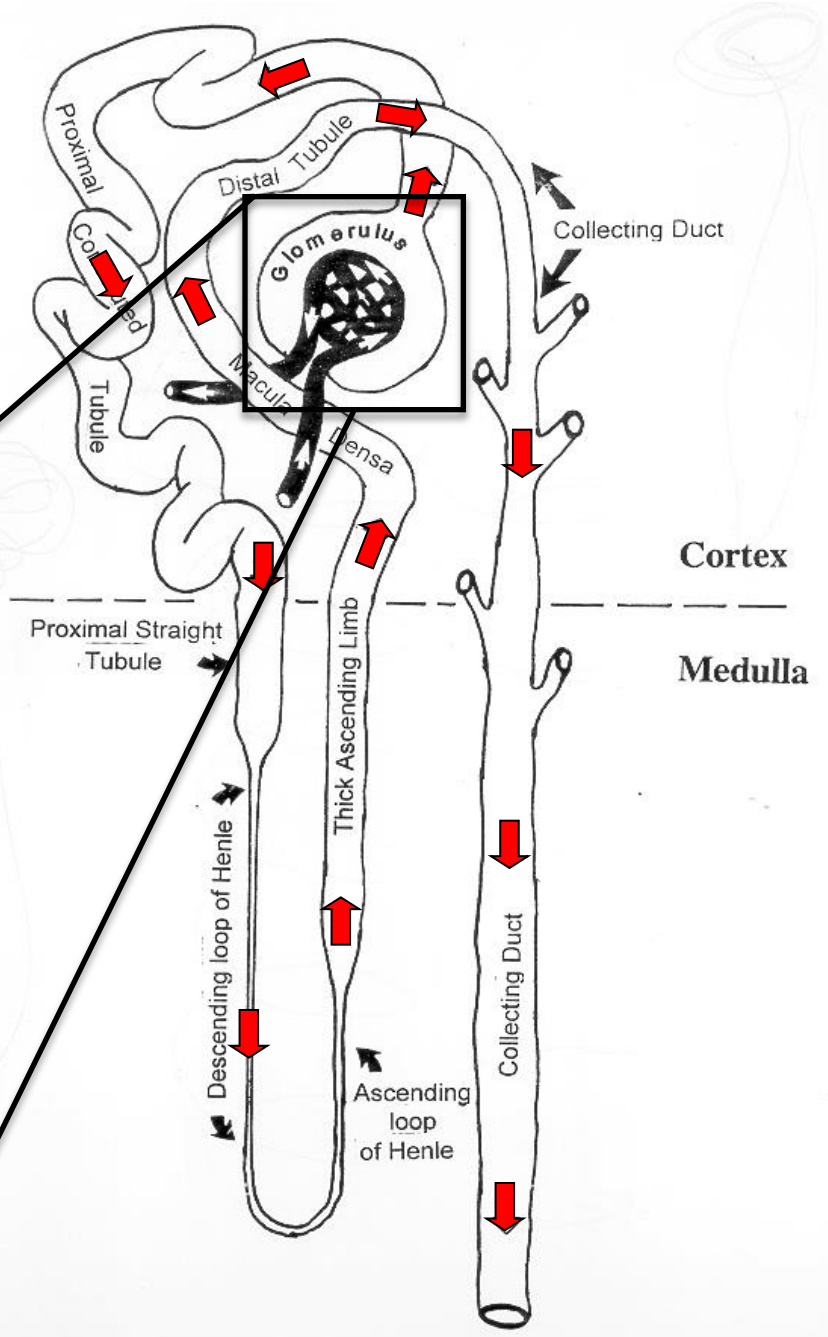
RBCs cast

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

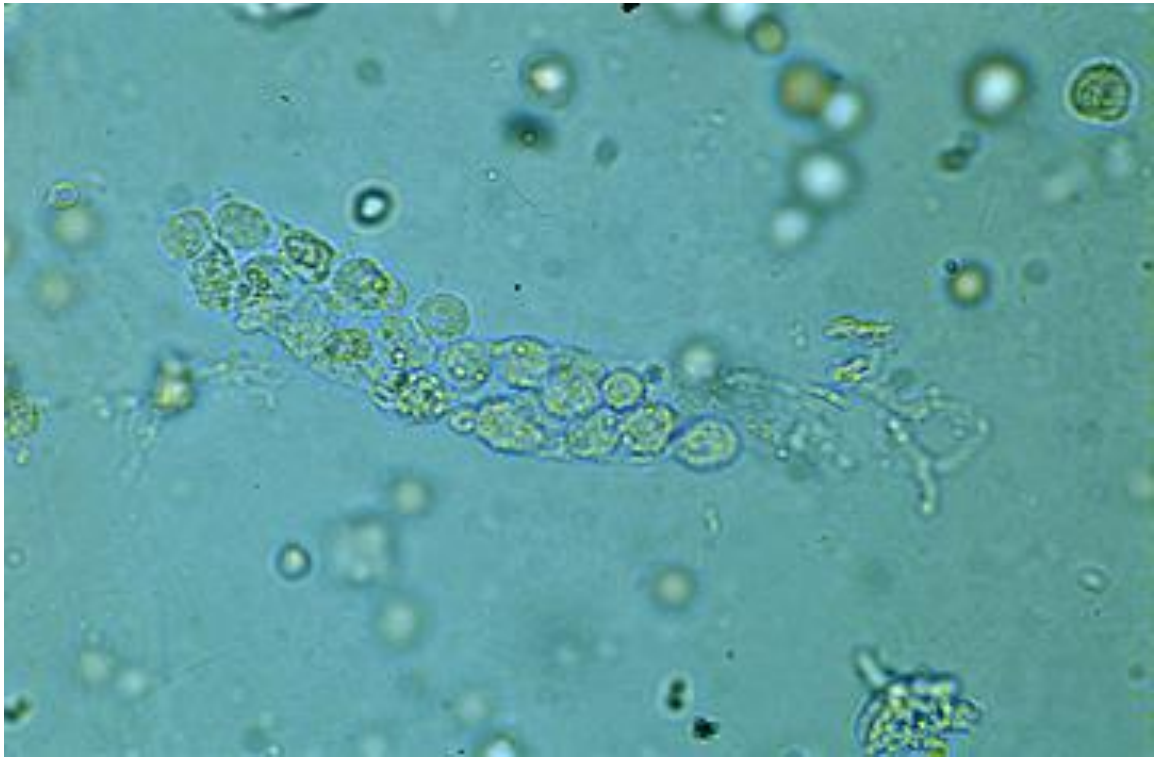


The Nephron


Proximal tubule
GLOMERULUS


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

White Blood Cells cast



- If urine dipstick is positive for Heme--> then you have to search for **Active Urine Sediments** by doing urine MICROSCOPY. Basically looking for RBCs and their casts.

- *Those Glomerular diseases causing*

  Active Urine Sediments are generally:

  > Inflammatory in nature (Glom inflammation)

  > And may be Crescentic GN (Rapidly Progressive GN)

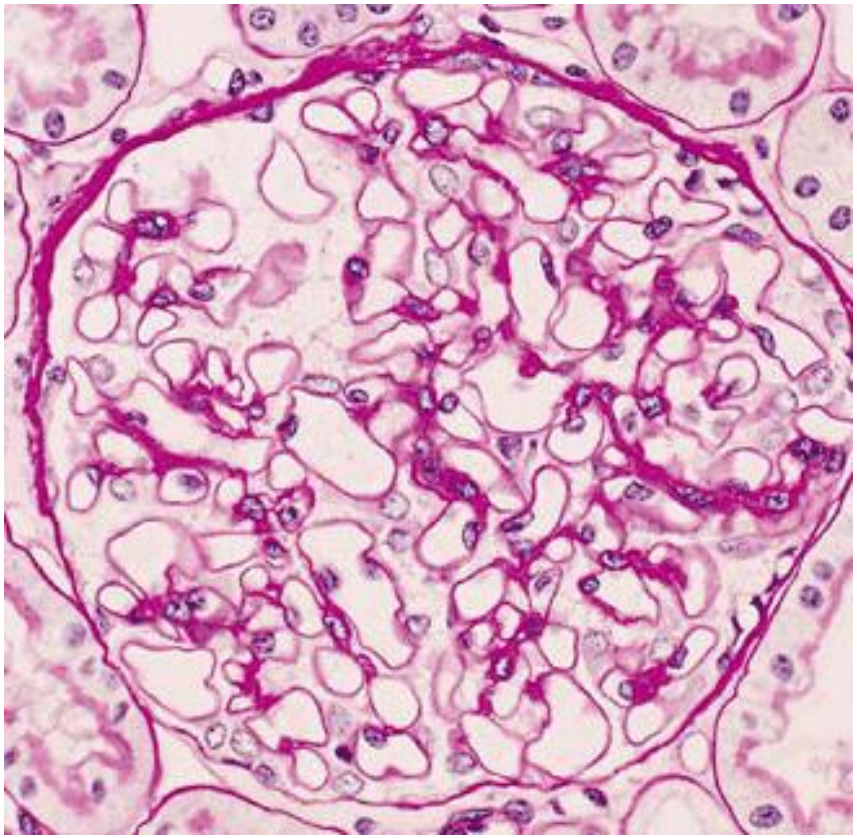
Crescentic GN means it causes glomerular crescents formation

Crescents are indicative of severe disease that can cause ESRD in weeks to few months

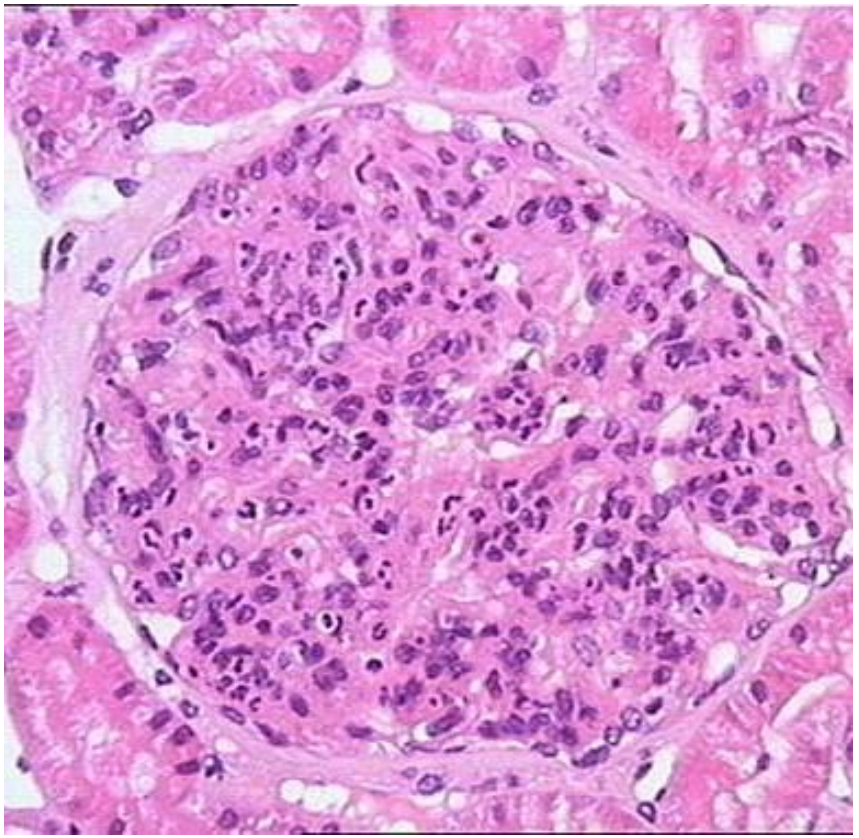
Are clinically; described as **Nephretic >>> typically has:**

Hematuria, variable amount of proteinuria, active urinary sediments, edema, high BP and reduced GFR (AKI)

Normal Glom.



Glom. with prolif. GN

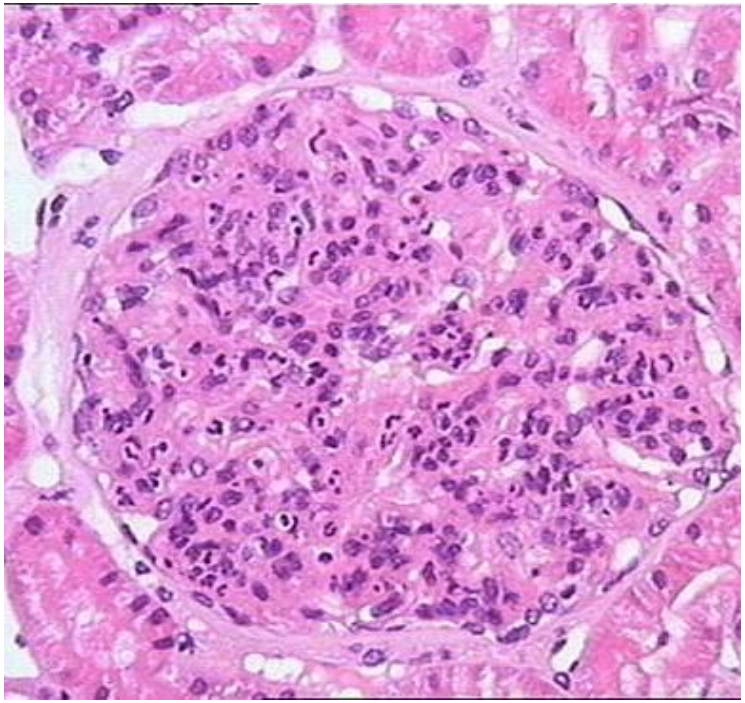


Nephritic Glomerular Diseases:

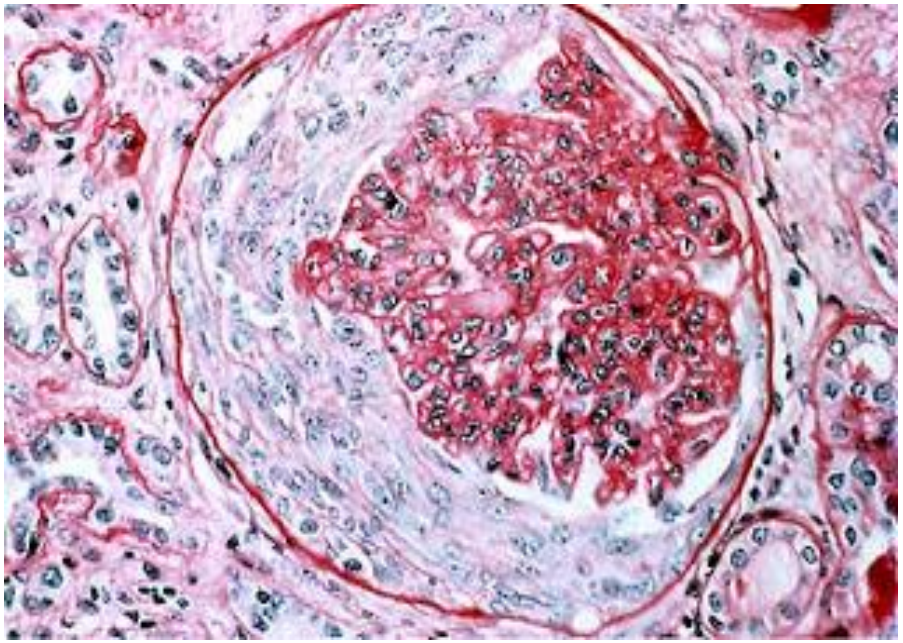
- IgA Nephropathy / HSP (**Henoch-Schönlein Purpura)**
- Poststreptococcal glomerulonephritis (PSGN)
- Lupus Nephritis
- Membranoproliferative GN (MPGN)
- Anti-GBM (Goodpasture's)
- ANCA vasculitis: *granulomatosis with polyangiitis* (Wegener's), *microscopic polyangiitis,* Churg-Strauss syndrome(Eosinophilic granulomatosis with polyangiitis)

Crescentic GN

- Glom. with prolif. GN



- Crescentic GN



In most Nephritic Glomerular Diseases

RPGN=Rapidly Progressive Glomerulonephritis (Crescentic GN); can occur and it means

Extensive crescent formation associated with rapid progression to end-stage renal disease in most untreated patients within a period of weeks to months.

On Biopsy: =>50% of Gloms show Crescent formation.

But what if urine analysis shows only persistent microscopic hematuria without protineura!

Then it could be Glomerular. Vs Non-Glomerular in origin

Causes of **Isolated Glomerular Hematuria:**

- Thin Basement Membrane (Hereditary & benign entity)
- Hereditary Nephritis (Alport syndrome)
- IgA Nephropathy

Common causes of isolated Hematuria (Glom & Non-Glom)

Origin	<50 Yr of Age	≥50 Yr of Age
Glomerular:		
	IgA nephropathy	IgA nephropathy
	Thin basement membrane dz	Hereditary nephritis
	Hereditary nephritis	Mild focal glomerulonephritis
	Mild focal glomerulonephritis	
Nonglomerular:		
Upper urinary tract		
	Nephrolithiasis	Nephrolithiasis
	Pyelonephritis	Renal cell carcinoma
	PCKD	PCKD
	MSK	Pyelonephritis
	Hypercalciuria	TCC
	Renal trauma	Papillary necrosis
	Papillary necrosis	Renal infarction
	Ureteral stricture / hydro	Ureteral stricture / hydro
	Sickle cell trait	Renal TB
	Renal infarction / AVM	
Lower urinary tract		
	Cystitis, prostatitis, urethritis	Cystitis, prostatitis, urethritis
	Bladder Ca + benign tumours	Bladder Ca
	Prostate Ca	Prostate Ca
	Urethral / meatal strictures	Benign bladder tumours
Uncertain		
	Exercise hematuria	Exercise hematuria
	Idiopathic	Over-anticoagulation
	Over-anticoagulation	

Medications that can cause Hematuria:

Aminoglycosides
Amitriptyline
Analgesics
ASA
Busulfan
Chlorpromazine
Warfarin overdose
Cyclophosphamide
Diuretics
OCPs
Penicillins
Quinine
Vincristine

When should you suspect a **Non-Glomerular** Hematuria?

If Microscopic OR Gross hematuria is **NOT** accompanied by: proteinuria, dysmorphic RBC or RBC casts.

With both Renal function & blood pressure remaining normal.

Non-Glomerular is concerning:

if any of the following is/are present:

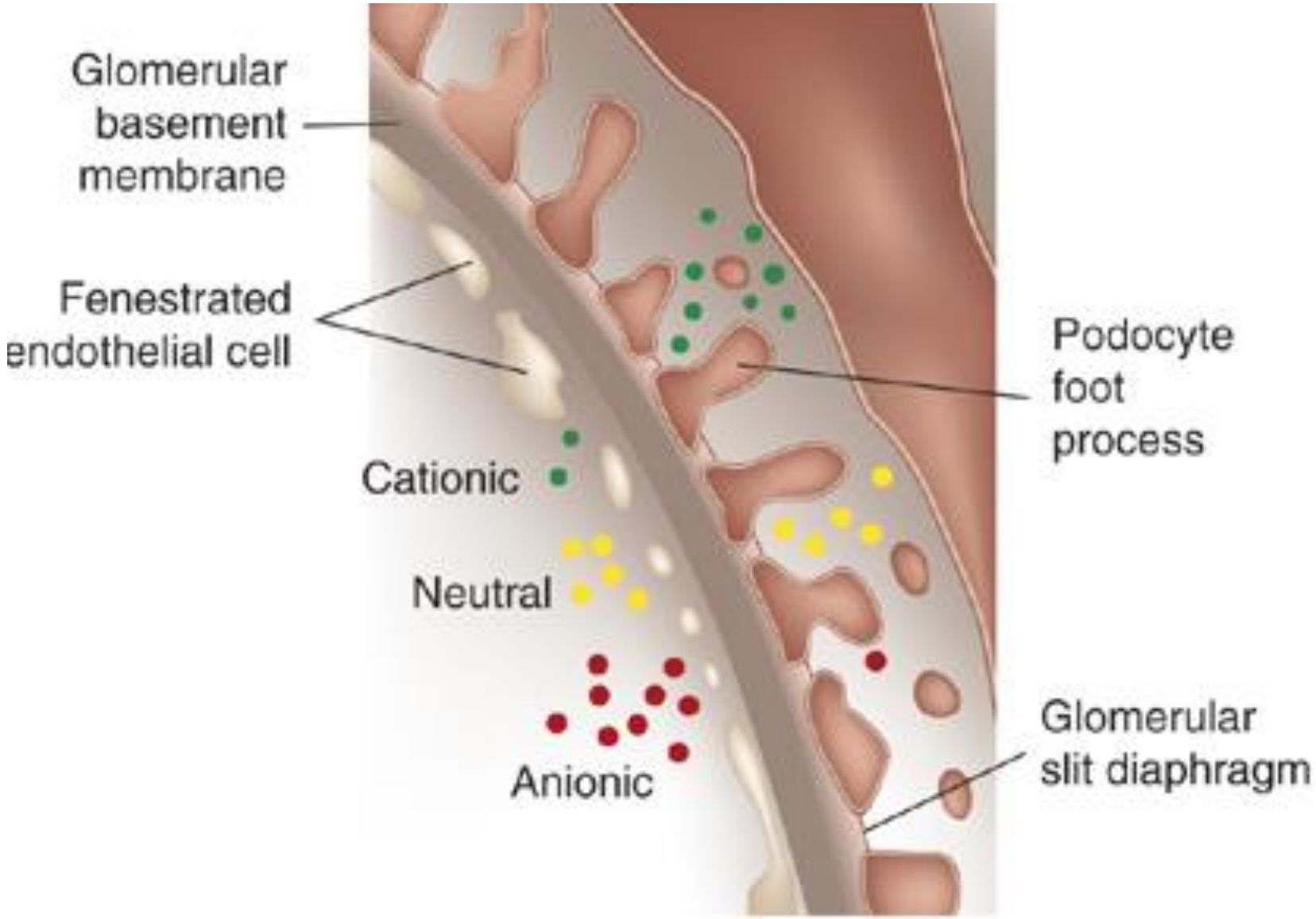
- *Tobacco use*
- *Occupational toxins exposure*
- *Gross hematuria with blood clots*
- *Age > 35-40*
- *Previous urologic disorder*
- *Irritative LUTS*
- *Recurrent UTIs despite appropriate antibiotics*

Risk factors for urinary tract malignancies:

- Age > 50
- Heavy smoking
- Exposure to certain dyes & rubber compounds
- History of analgesics abuse
- History of pelvic irradiation
- Cyclophosphamide exposure

Then what to do for Non-Glom. Hematuria?

- Hx & Physical.
- MSU, also rule out infection
- Urine Cytology (Looking for malignant cells)
- +/- PSA
- Imaging: US, if suspicious: CT or MRI.
- If a lesion was found (e.g. Renal mass, suspicious renal cystic mass or bladder lesion); then get help from urology (patient might require cystoscopy).


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

Proteinuria

Is it **Persistent** or **Transient**?

Transient proteinuria is seen in young healthy patients, always not heavy and always benign.

Causes: fever and exercise

Persistent proteinuria: is abnormal & needs workup

Orthostatic Proteinuria

How to diagnose?

Proteinuria

How much protein in the urine is considered Normal?

- **< 150 mg/day of all proteins is normal**.
- More than that is Proteinuria and is abnormal.
- If Albumin is detected in the urine; it only comes from the Glomerulus.
- < 30 mg/day of Albumin is Normally secreted in the urine (average 4-7mg/day) and this is included in the <150 mg of the total normal protein secretion in the urine per day.

Proteinuria ranges: presented by Alb

Albuminuria: 30-300 mg/day = HIGH ALBUMINURIA (microalbuminuria)

- Indicative of renal disease, specially Diabetic Nephropathy in pts. with DM.
- Associated with an increased risk for cardiovascular disease in non-diabetics.
- Needs chemical analysis to detect, can't detect by simple urine dipstick.

Proteinuria

To estimate the degree (amount) of proteinuria : do

- Albumin / Creatinine ratio on spot urine.

  (close estimation value)

  Normal ratio: 0 - 30 mg Albumin/g Creatinine

  e.g. ACR: 400 mg/g = 400mg/day of albuminuria

OR

- 24 h urine collection

  (**gold standard**; true value, but cumbersome)

Proteinuria

Albuminuria > 300 mg/day called:

OVERT PROTEINURIA (macroalbuminuria).

- Urine dipstick will be positive.

Proteinuria ranges:

- **Sub-Nephrotic** proteinuria: **< 3.5 gm**/day
- **Nephrotic Range** Proteinuria: **> 3.5 gm**/day

Nephrotic urine sediment: Heavy proteinuria + lipiduria (oval fat bodies, fatty casts & fat droplets) with few cells or casts.

- If suspecting Albuminuria < 300mg/day (e.g. early stage of diabetic nephropathy) **OR**

  urine dipstick is positive for protein--> Quantify by

  - 24 h urine collection
  - Albumin/ Creatinine ratio

    or Protein/ratio

Nephrotic syndrome:

- **Hypoalbuminemia (<30 g/L)**
- **Heavy proteinuria (> 3.5 g/24 hours)**
- **peripheral edema**
- Hyperlipidemia
- Thrombosis

Causes of Nephrotic Syndrome in Adults:

Systemic diseases: 30% of adults.

DM, amyloidosis, SLE

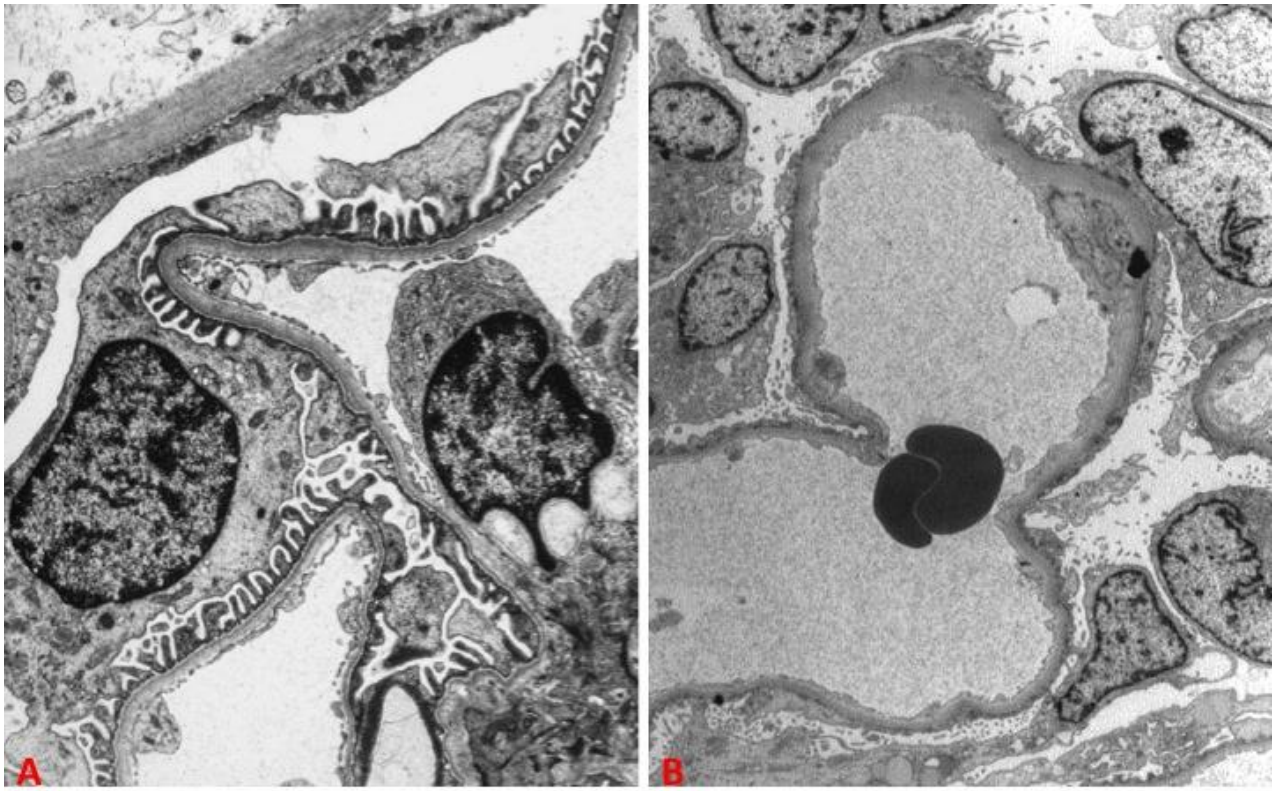
Minimal change disease:

90 % of nephrotic syndrome in children < 10 years of age (Primary)

> 50% in older children

15 % in adults (could be secondary: NSAIDS, malignancy eg HL)

Minimal change disease (only foot process effacement in Electron microscopy)



Focal Segmental Glomerulosclerosis (FSGS)

16 - 35 % in adult with nephrotic syndrome

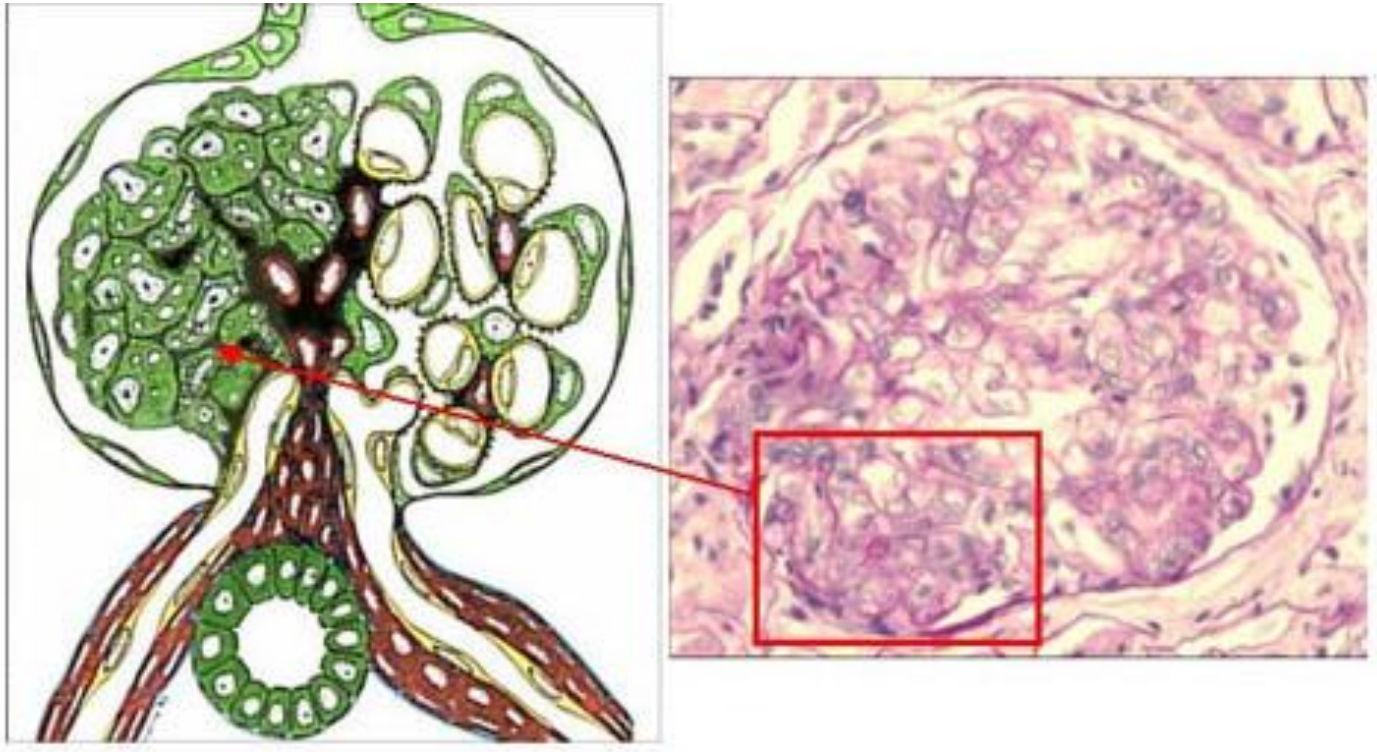
Focal = some gloms are affected

Segmental= parts of the affected glom is sclerosed

-> Idiopathic (usually acute onset of nephrotic syndrome)

-> Secondary: HIV, HTN, healed glom injury, reflux, obesity.

Focal segmental glomerulosclerosis (FSGS)



Membranous nephropathy

24 % of Nephrotic adults patients

- Primary *(Idiopathic):*

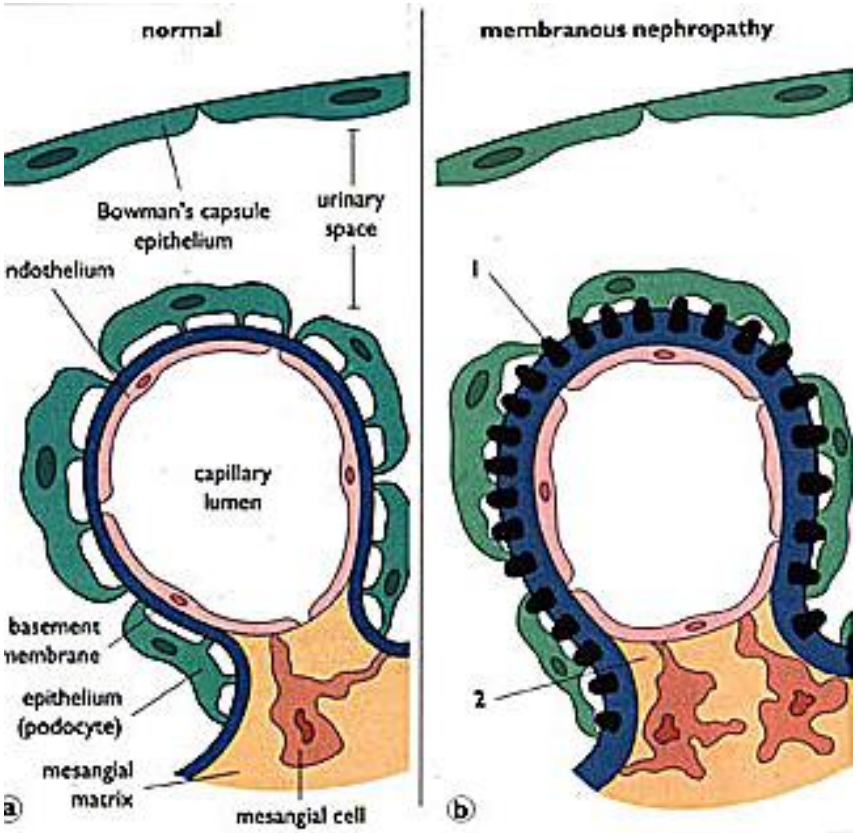
Autoantibodies against the phospholipase A2 receptor on podocytes (PLA2R)

- *Secondary* :

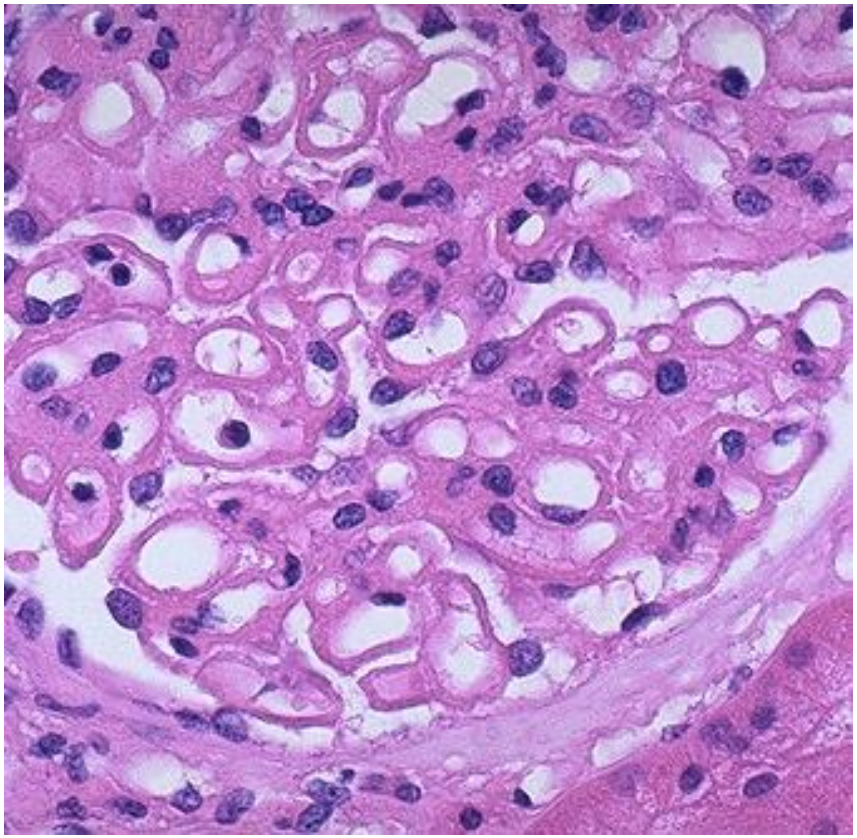
- Infection: Hep B antigenemia, Hep C, Syphilis
- Autoimmune diseases (SLE: class V LN, Thyroiditis)
- Solid tumors (5-20% in > 65ys; Prostate, Lung, GI)
- certain drugs(gold, penicillamine, captopril, NSAIDS)

Membranous nephropathy

IgG deposition



Thickened Capillary Loops



Amyloidosis

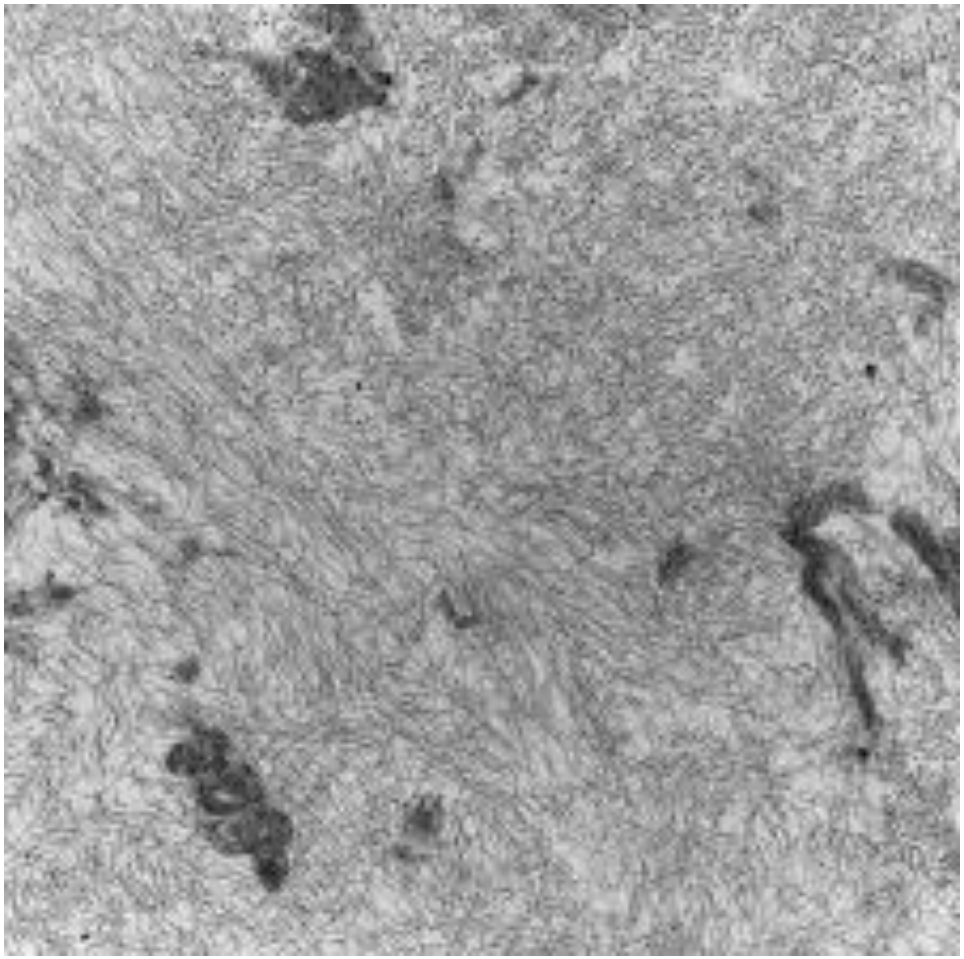
4 to 17% of idiopathic Nephrotic syndrome in adults.

- **Primary amyloid** (**AL**): is a light chain dyscrasia, fragments of Monoclonal Light Chains (MLC) form the amyloid fibrils

Presentation: Heavy Proteinuria, nephrotic syndrome and renal insufficiency. Fatigue and weight loss.

- **Secondary amyloidosis** (**AA)**: acute phase reactant serum amyloid A forms the amyloid fibrils.

Fibrils in Amyloidosis



Membranoproliferative GN (MPGN)

- Presentation ranging from microscopic hematuria with or without mild proteinuria to nephrotic syndrome or severe glomerulonephritis (Nephritic)
- Hypocomplementemia.
- Immune complex-mediated and complement-mediated processes.
- Causes: Hep C, endocarditis, shunt nephritis, abscesses, fungal and parasitic infections (eg, schistosomiasis).
- Also Sjögren's syndrome, SLE, CLL, Dysproteinemias and mixed cryoglobulinemia

Summary -1

- If urine dipstick is positive for blood only:

  - patient is young & healthy>> just repeat in one week.

  If disappeared > reassure the patient

  If persistent, but everything else is normal>>likely benign condition and nothing to worry about. Just follow

  -If older than 35 ys, need to investigate for a lesion

  like ultrasound,CT, urine cytology and ? Cystoscopy

>>>High Cr, High BP, & presence of proteinuria>>>Investigate for possible GN

Summary-2

- If urine dipstick is positive for blood and protein >>> do microscopy (looking for active sediments) and measure the amount of protein/day. Also assess Renal function and BP, renal imaging: US

  You are likely dealing with Glomerular disease. Renal biopsy might be warranted & order serological markers of possible GN.

Scenario 1

A 15 y male, otherwise healthy. You are seeing him in your clinic because of a complaint happened a month ago: he had cola colored urine, for one day started 3 days after symptoms of upper respiratory tract infection. At the same time he experienced bilateral flank discomfort. Physical exam was Normal with BP 140/90. No edema. No skin rash.

Serum Creatinine: 85, Urea 5. Serum ALBUMIN 40.

Urine: 2+ blood, 2+ protein

24h urine collection for protein: 1.8 g/day.

Urine Microscopy: RBCs, RBCs Casts.

US kidneys:Normal

Is this picture Nephritic or Nephrotic?

Differential diagnosis?

- IgA Nephropathy
- Post-infectious GN
- Thin Basement Membrane
- Hereditary Nephritis (Alport syndrome)
- Polycystic kidney disease

Whats next?

- Diagnosis :

IgA nephropathy, confirmed by biopsy.

Scenario 2

45 y lady, long time smoker and has HTN controlled with Rx. Came to ER with SOB, Hemoptysis x 1 wk. Has new onset edema and headache. Noticed decreased urine output. BP was 180/100. Chest: inspiratory crackles with wheezing. 2+ LL edema. No skin rashes.

Creatinine 800 mcmol/L. K+ 7.0. CBC: Hgb 8.5g/dl

Urine: 3+ blood, 2+ protein.

Urine microscopy: Dysmorphic RBCs & RBCs casts.

Serum Albumin 30 gm/L

Chest X-ray: Bilateral air space disease.

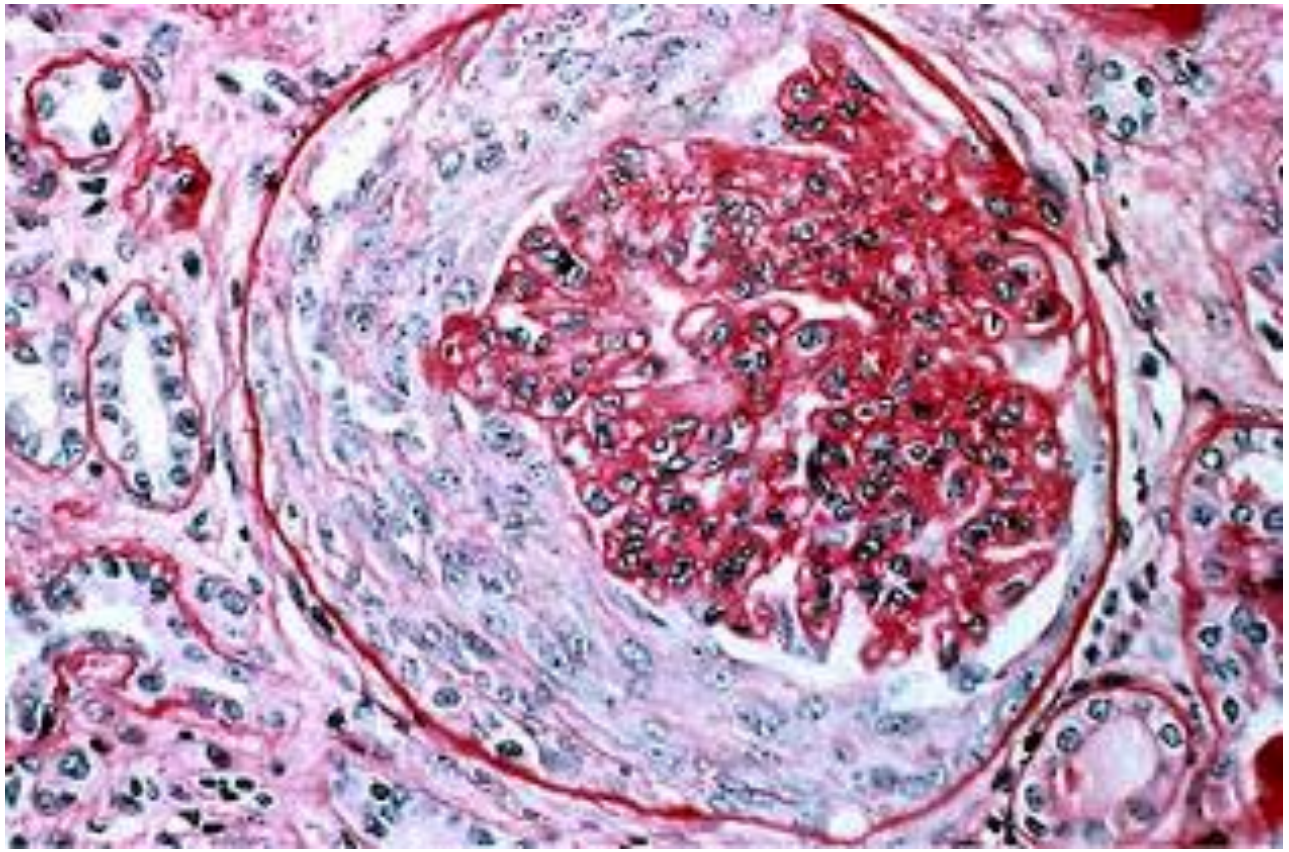
US: increased renal cortex echogenicity, but normal size.

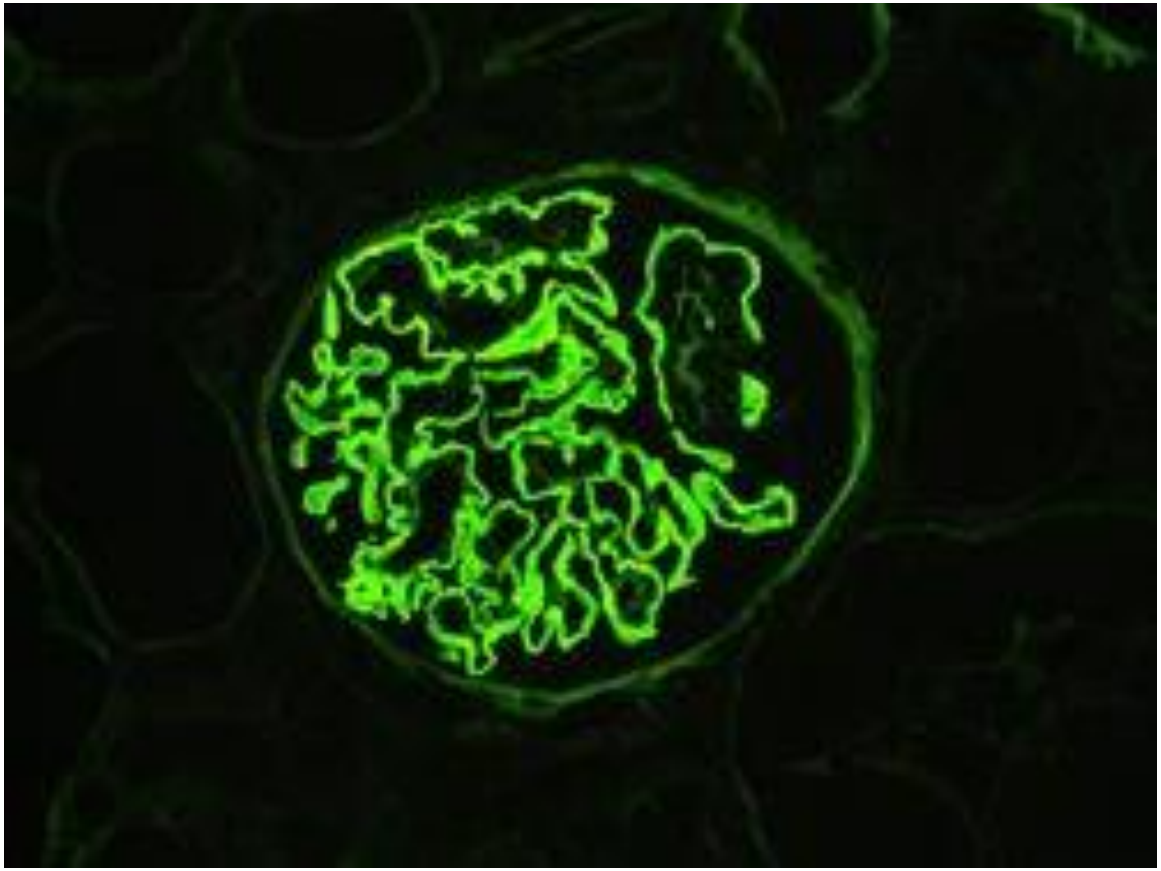
DDX:

- **Anti-GBM (Goodpasture's syndrome)**
- **ANCA vasculitis**
- **Lupus Nephritis (III , IV)**
- HSP (IgA systemic vasculitis)
- Infective endocarditis (immun-complex GN)
- Pulmonary edema due to fluid overload

First 3; Called: Pulmonary-Renal syndromes;
because of Renal & Pulmonary vasculitis

Her biopsy

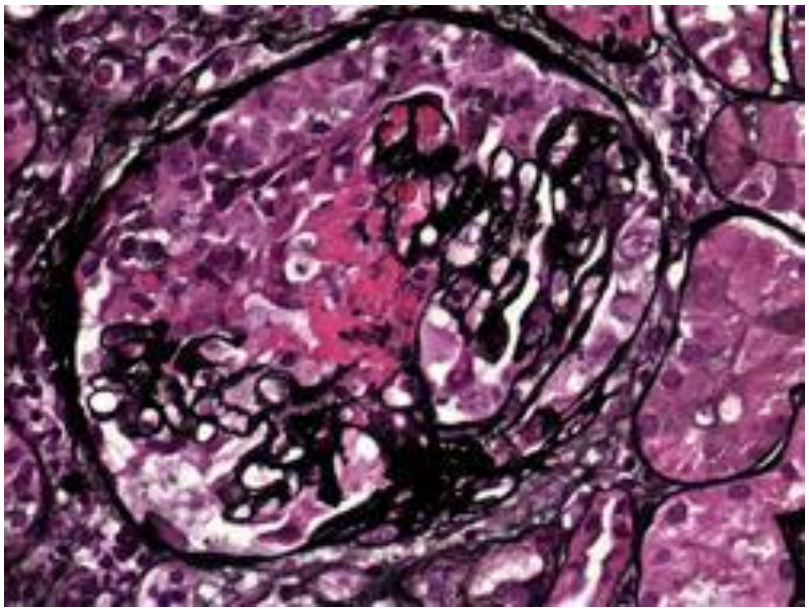


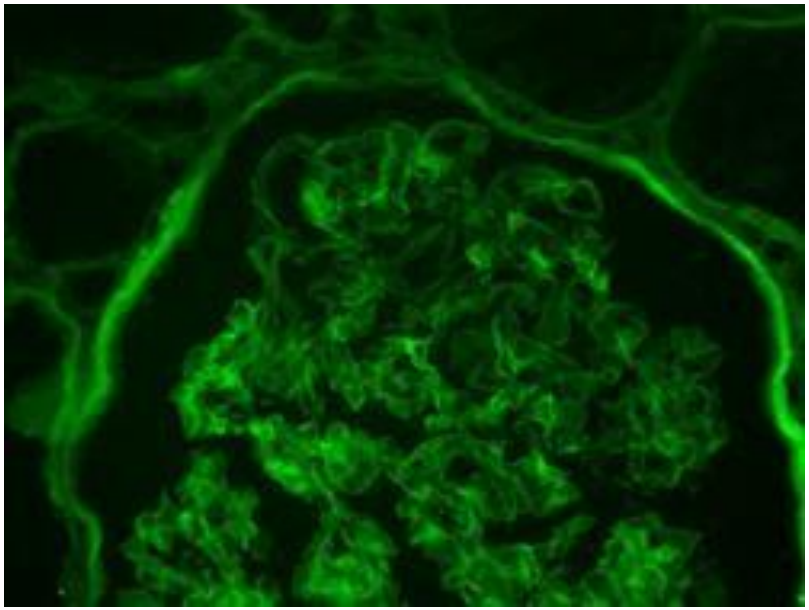


Diagnosis: Anti GBM disease

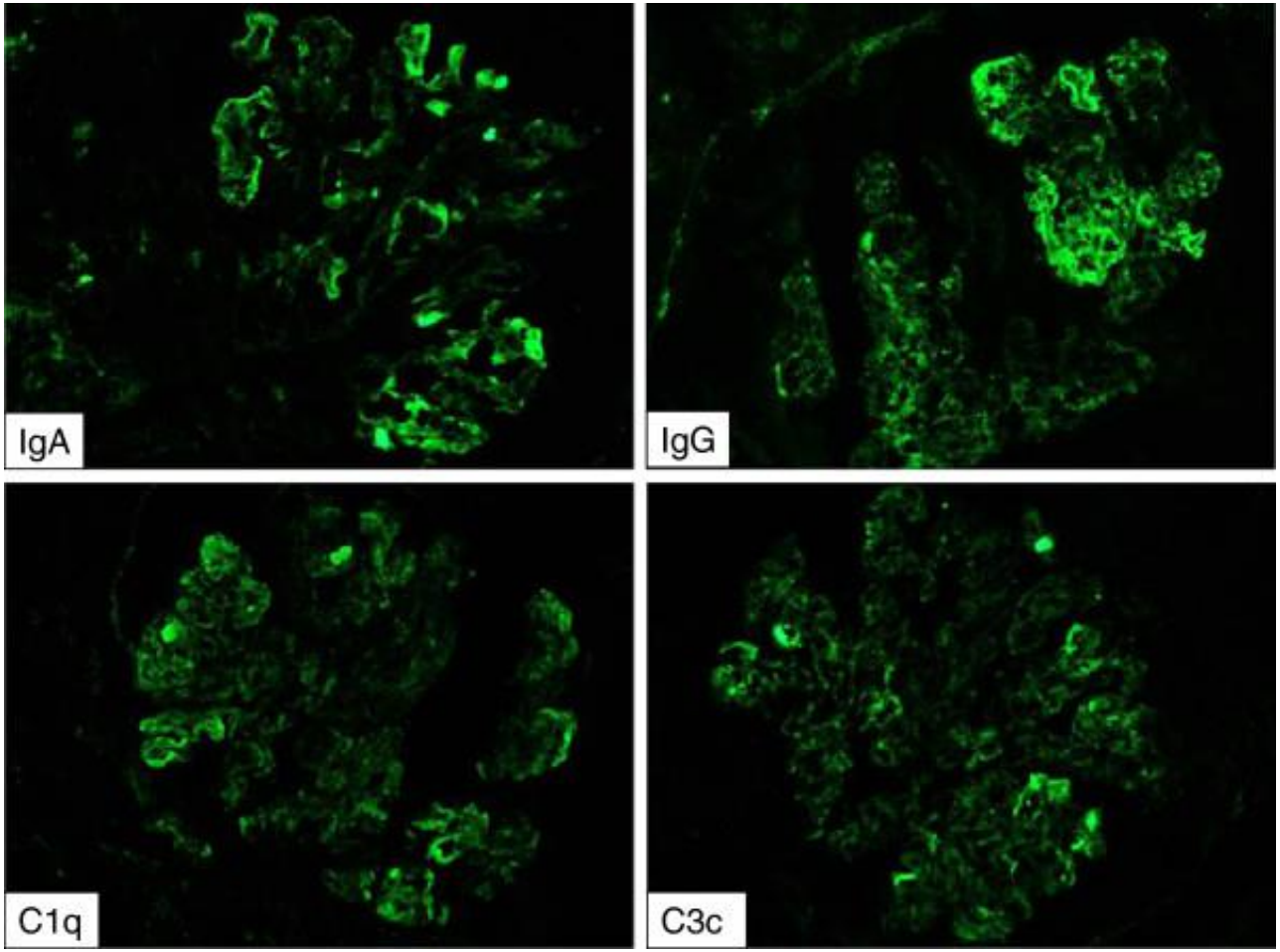
Linear deposition of Anti-GBM on immunofluorescence staining

ANCA vasculitis **= Pauci-immune**





Lupus Nephritis (full house)



What to do next:

- Stabilize patient first.
- Urgent first line therapy.
- Same time Investigate:
- Serology:

  ANA, Anti-DNA, Anti-GBM, ANCA , CRP, compl

- R/O infection: ASO, sputum culture.
- Confirm Diffuse Alveolar hemo: PFT, CT chest, Bronchoscopy. PTT/INR
- Definitive diagnosis: Kidney biopsy

SCENARIO 3

60 ys man, has DM x 14 ys. Had laser treatment for retinopathy x 4. Also has Peripheral Neuropathy. CAD and Hx. of TIA. He admitted a poorly controlled Diabetes. Takes only Insulin & ASA. Seen in clinic with a complaint of lower limbs 2+ edema up to the knees. BP 167/96 .

S. Creatinine 280 mcmol/L (was 190 mcmol/L; 12 months ago) urea 18mmol/L. K+ 5.0

HgA1C 11%, Fasting sugar: 18.

Ultrasound : Normal size kidneys

Serum Alb 36, Urine 2+ protein, microscopy: 3 RBCs, No casts.

Spot Urine Albumin to Creatinine ratio 3000mg/g.

24h urine collection for protein: 3.4 g/day

DDX?

- Diabetic Nephropathy
- Membranous Nephropathy
- FSGS
- IgA Nephropathy
- Amyloidosis

- Dx: Diabetic Nephropathy

Biopsy is not needed, disease course and history is very suggestive.

Scenario 4

60 ys male, has HTN for 10 ys. On Thiazide, came to ER because of 3 days onset of LL swelling extending to groins. Has SOB on exertion. On questing reported frothy urine for 2 month. Has wt. gain and lost appetite.

Exam: BP 130/90. 3+ edema. Bilateral P. effusion. +ve shifting dullness.

Creat 80. urea 4. K+4.8 . Serum Albumin 10 g/L

Urine dipstick: 3+ protein. NO blood

24 h urine collection for protein: 12 g/ day.

What clinical term used to describe his clinical presentation?

DDx

- Membranous Nephropathy
- FSGS
- Amyloidosis (AL)
- Minimal change disease

What you should do for diagnosis?

- Biopsy showed: Membranous Nephropathy