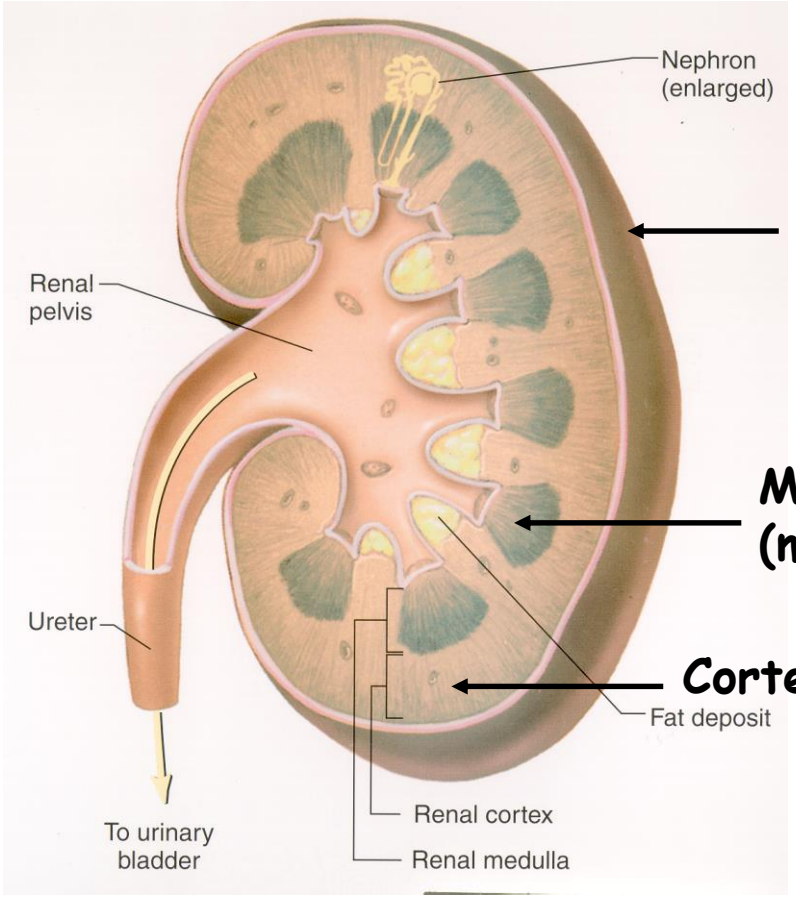
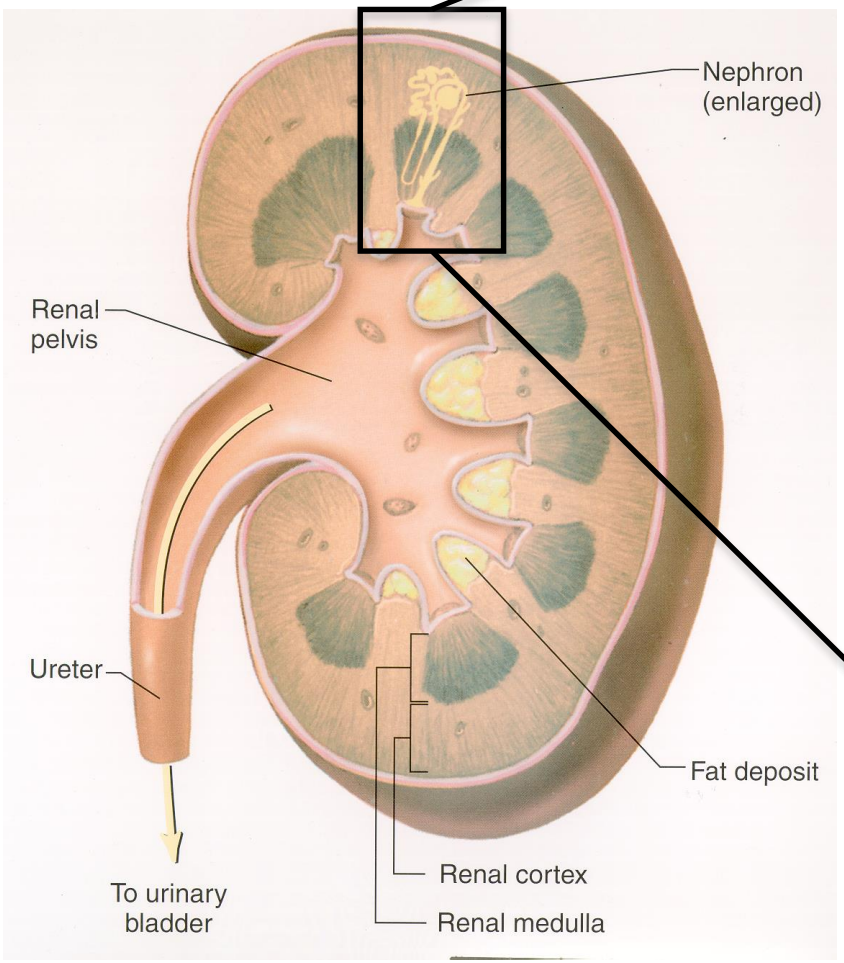
Nephrotic Syndrome

Med 341

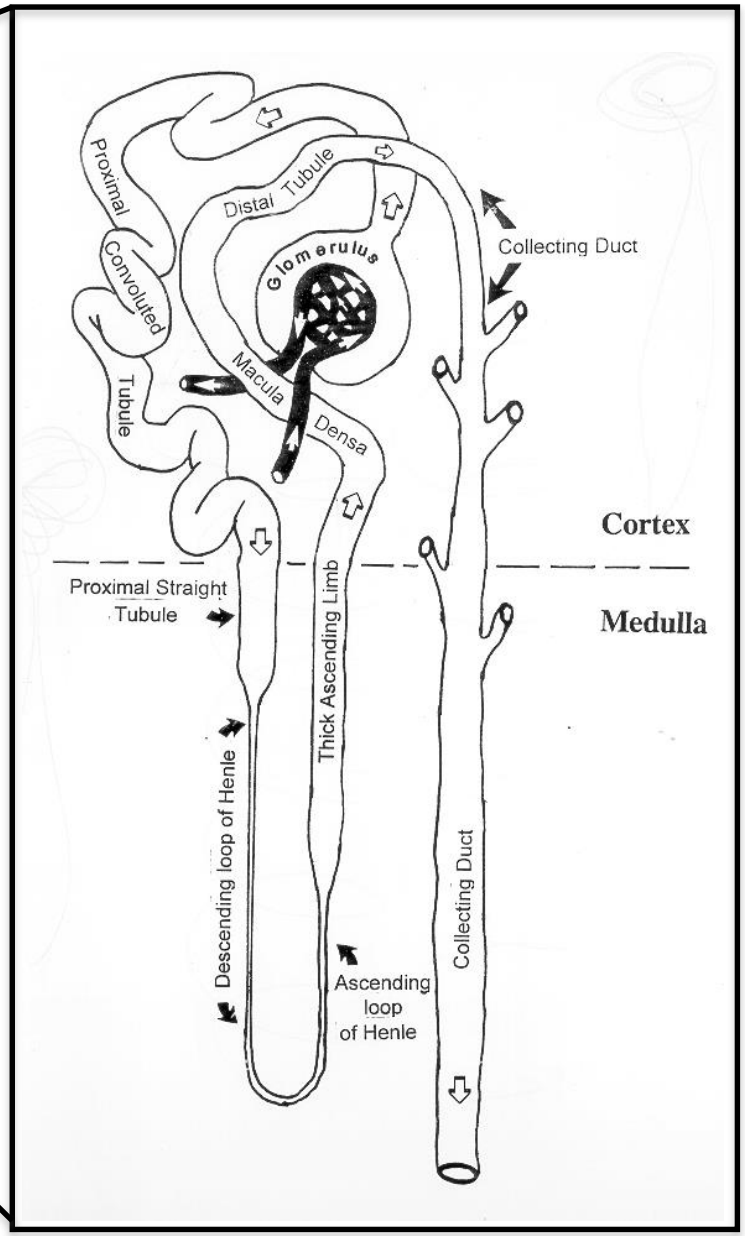
Gross Kidney Anatomy



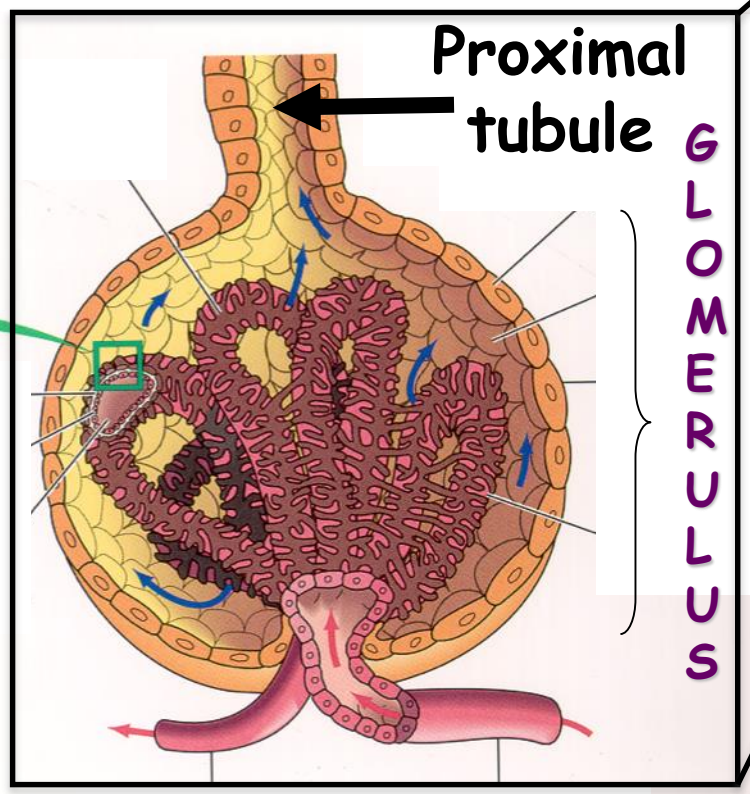
The Nephron

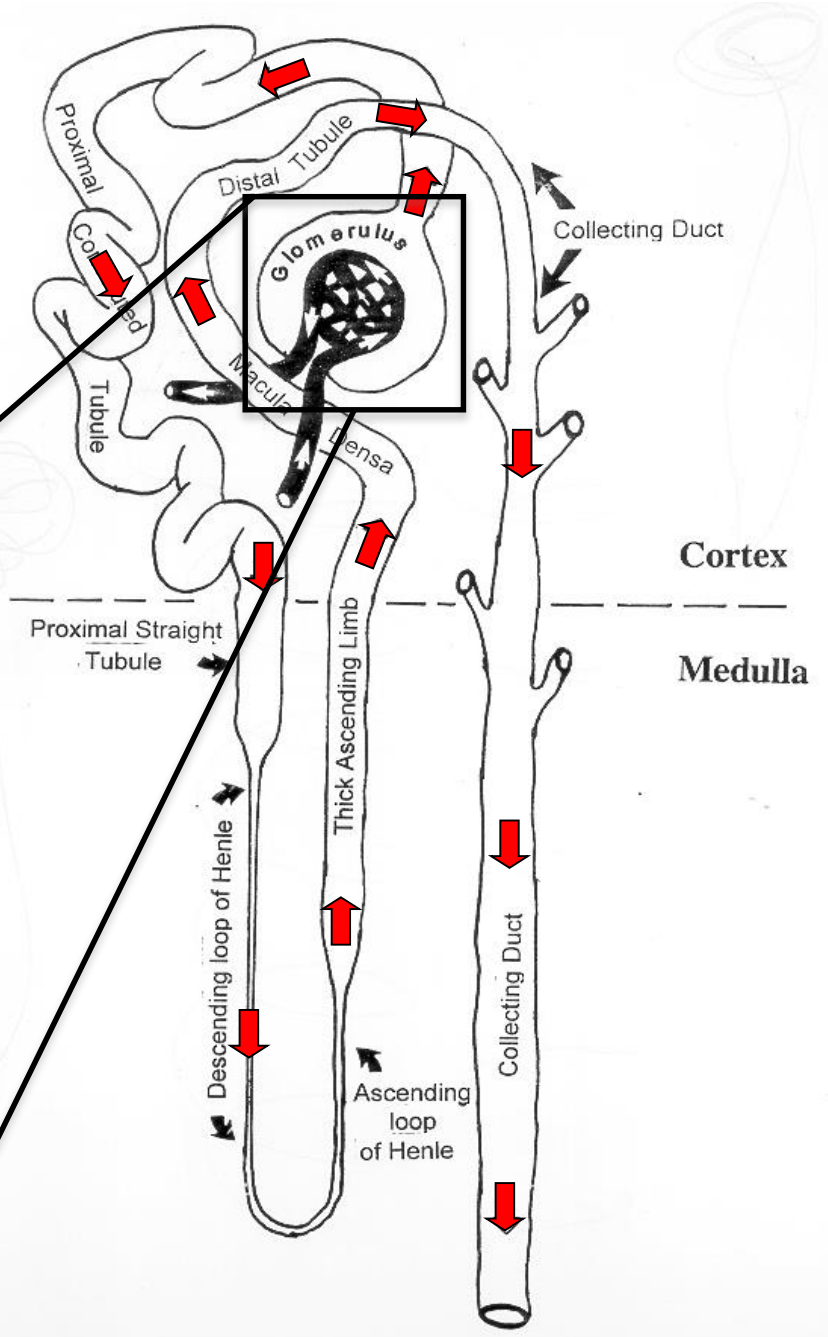


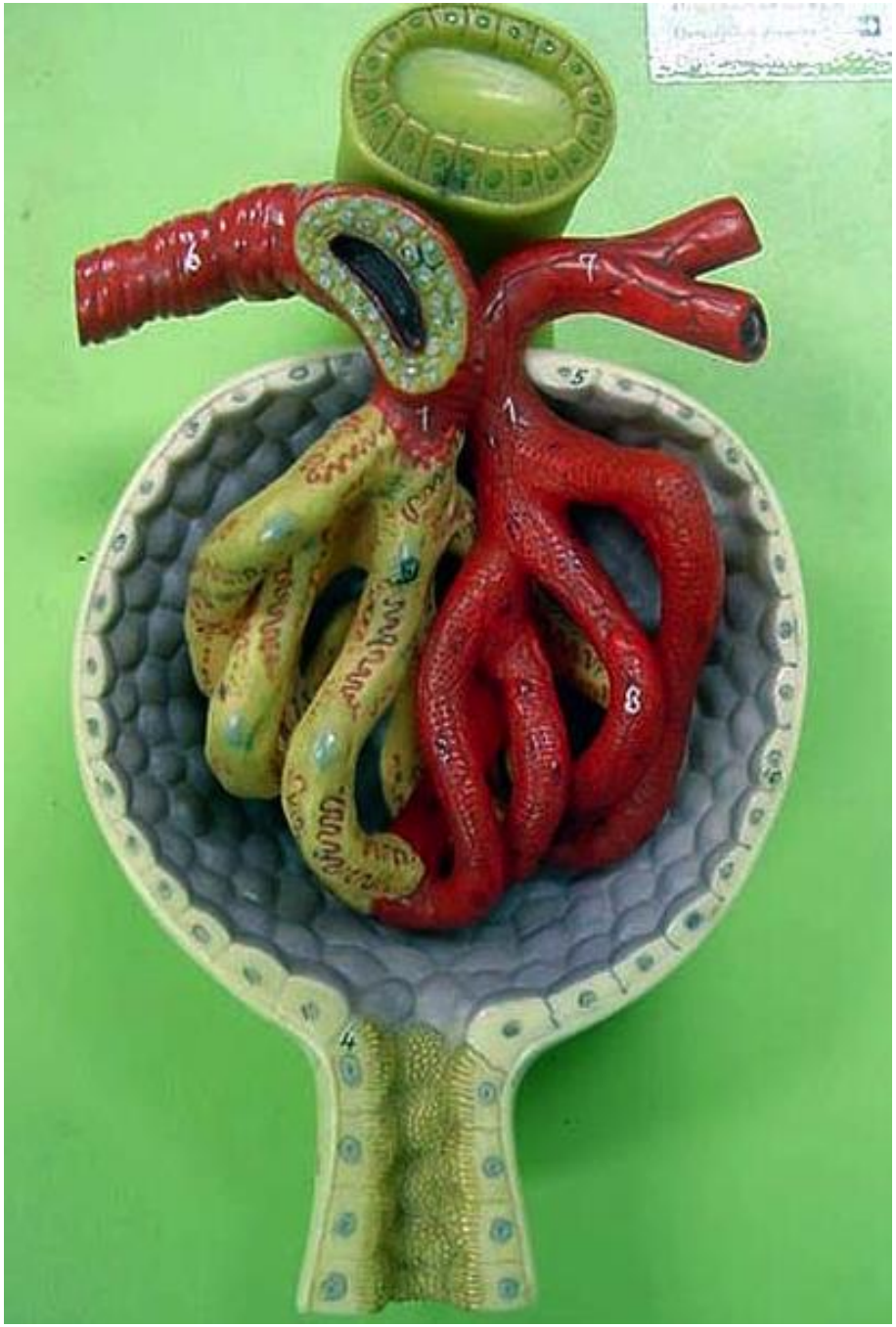
Nephron (zoom)

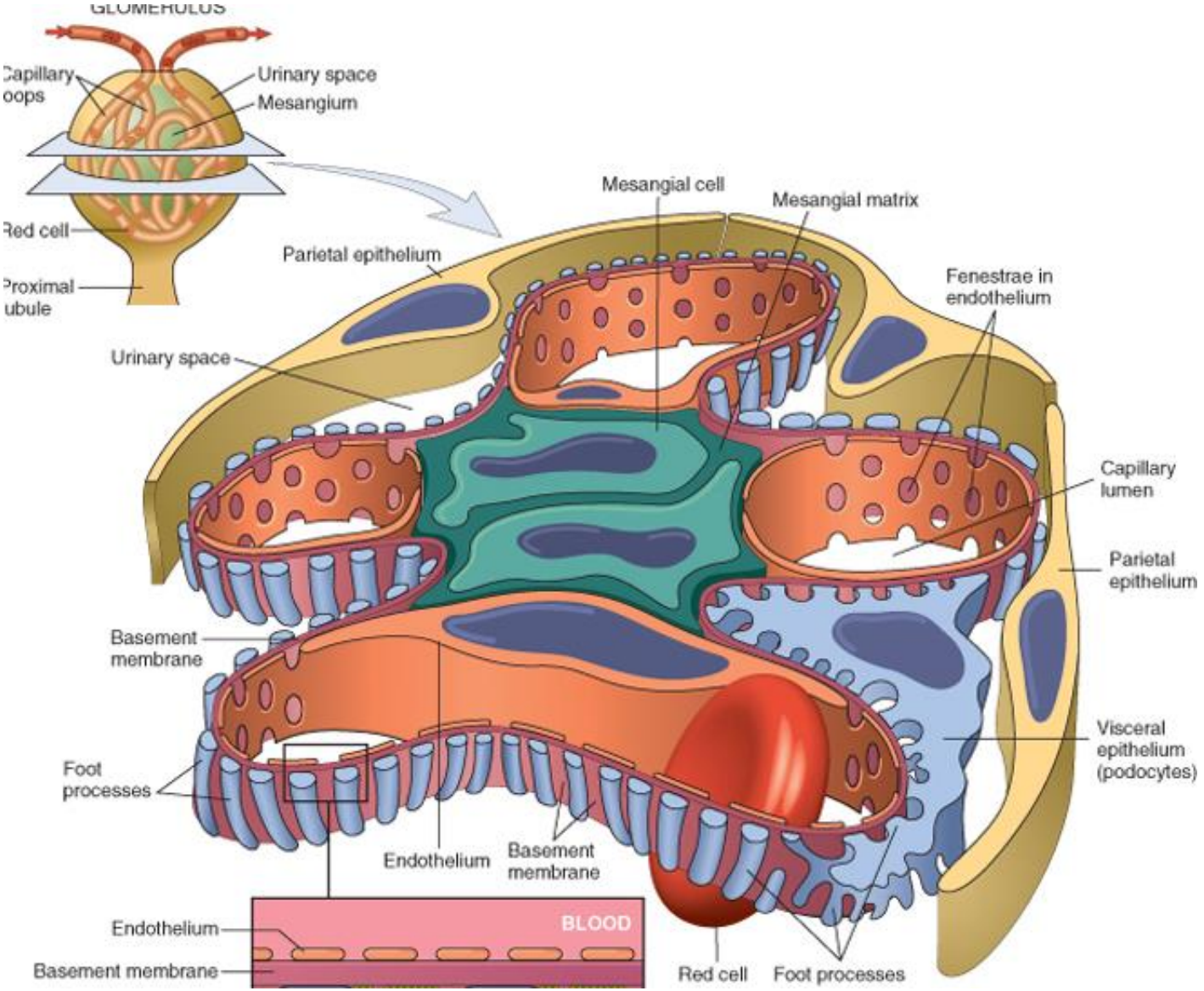


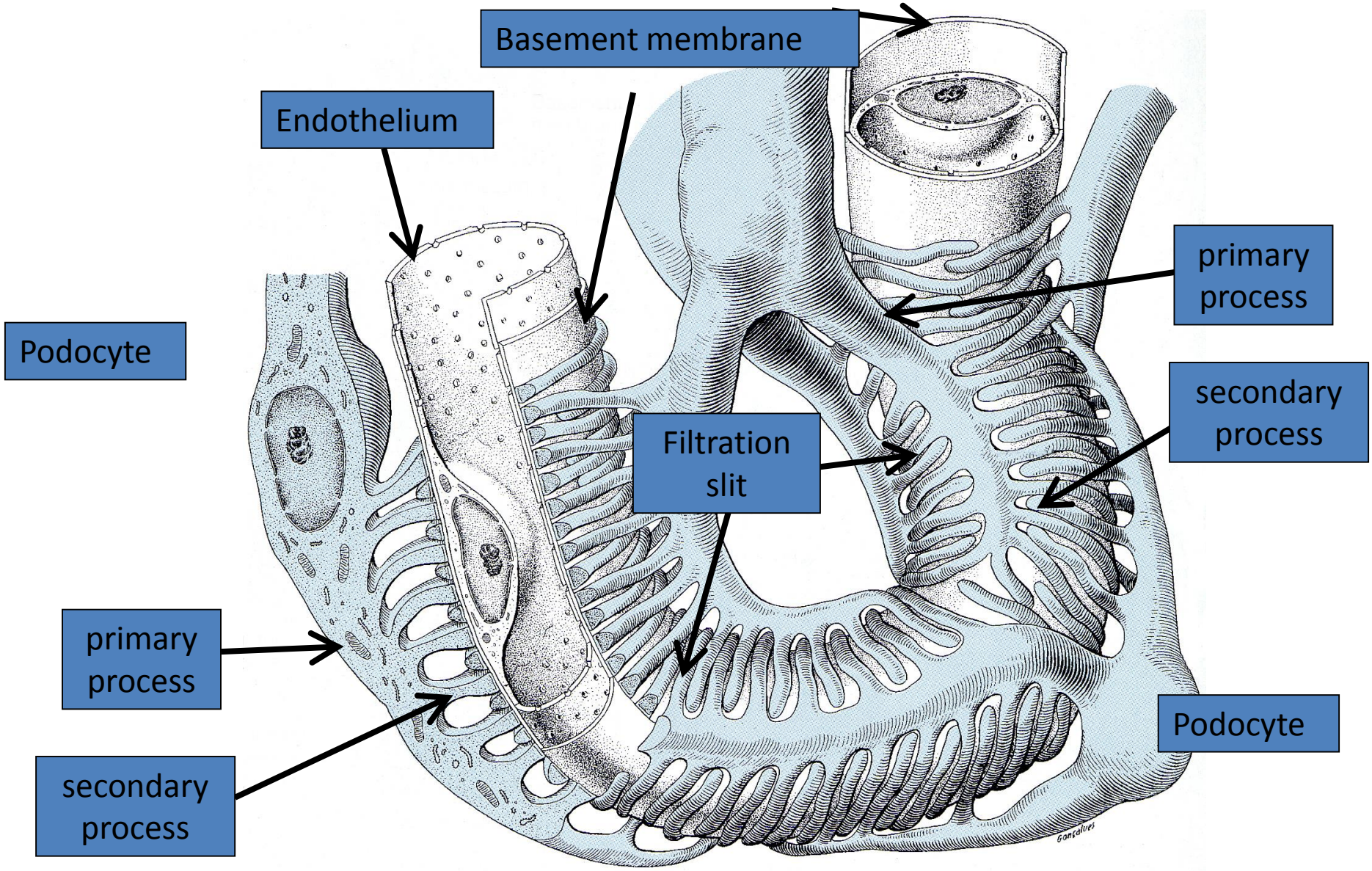
The Nephron


Proximal tubule
GLOMERULUS

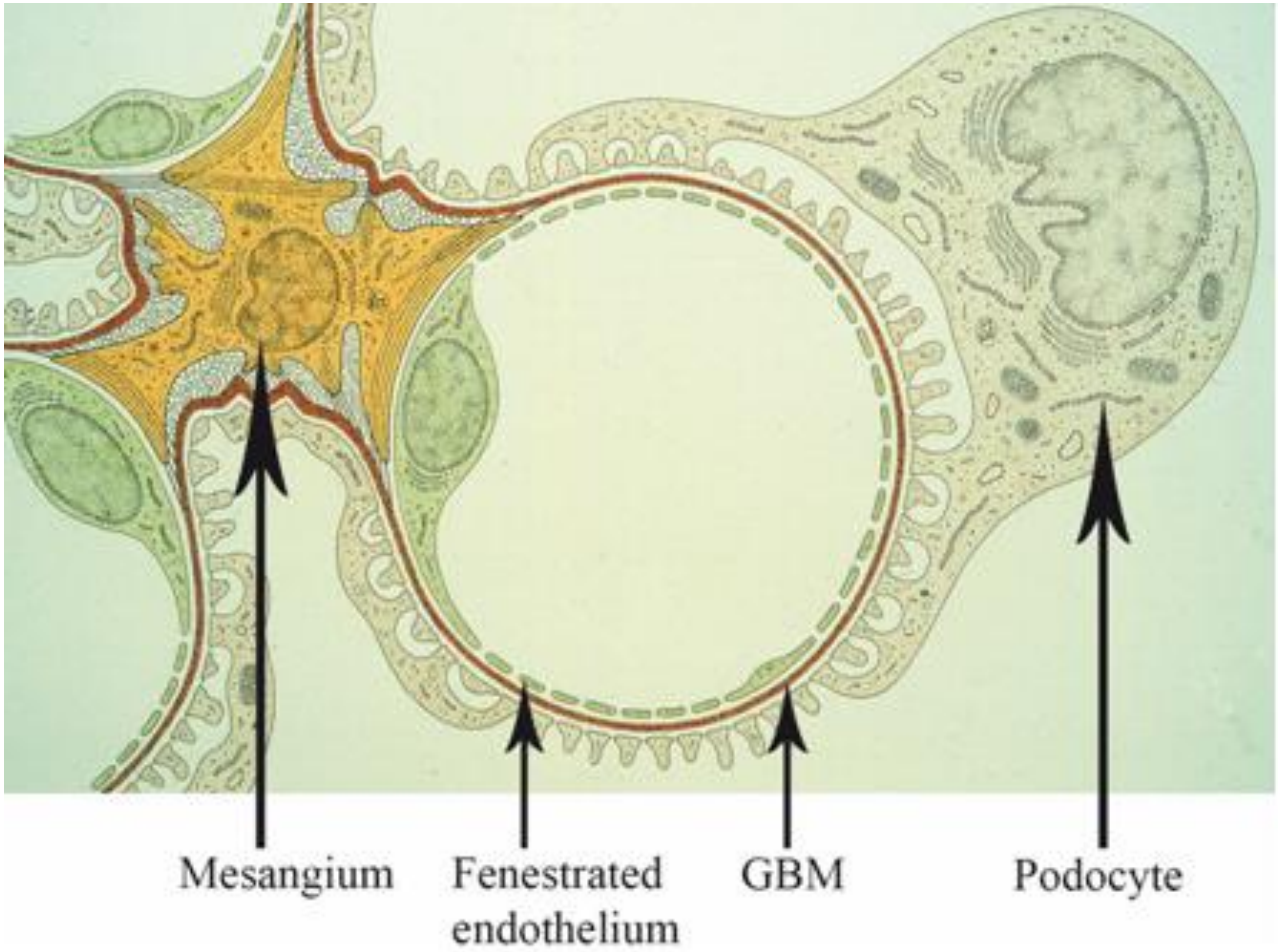

Proximal
Distal Tubule
Glomerulus
Collecting Duct
Tubule
Macula
Densa
Cortex
Proximal Straight Tubule
Medulla
Thick Ascending Limb
Descending loop of Henle
Collecting Duct
Ascending loop of Henle


6
7
5
1
1
8
4

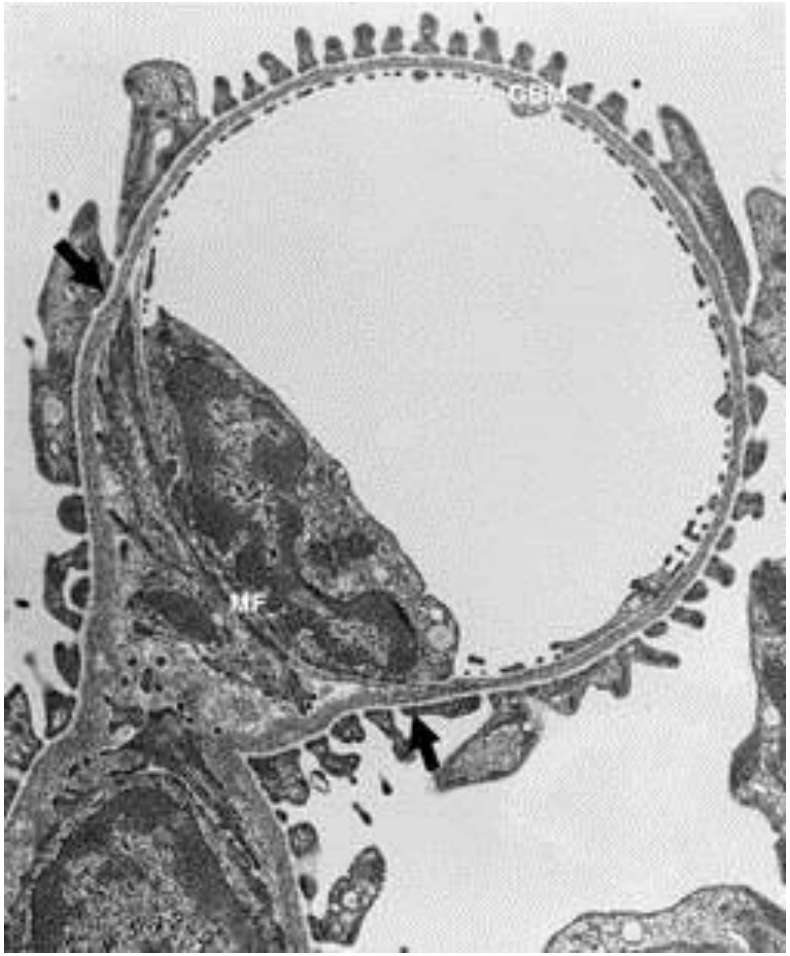

GLOMERULUS
Capillary loops
Urinary space
Mesangium
Red cell
Proximal tubule
Mesangial cell
Mesangial matrix
Parietal epithelium
Fenestrae in endothelium
Urinary space
Capillary lumen
Parietal epithelium
Basement membrane
Visceral epithelium (podocytes)
Foot processes
Endothelium
Basement membrane
BLOOD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


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

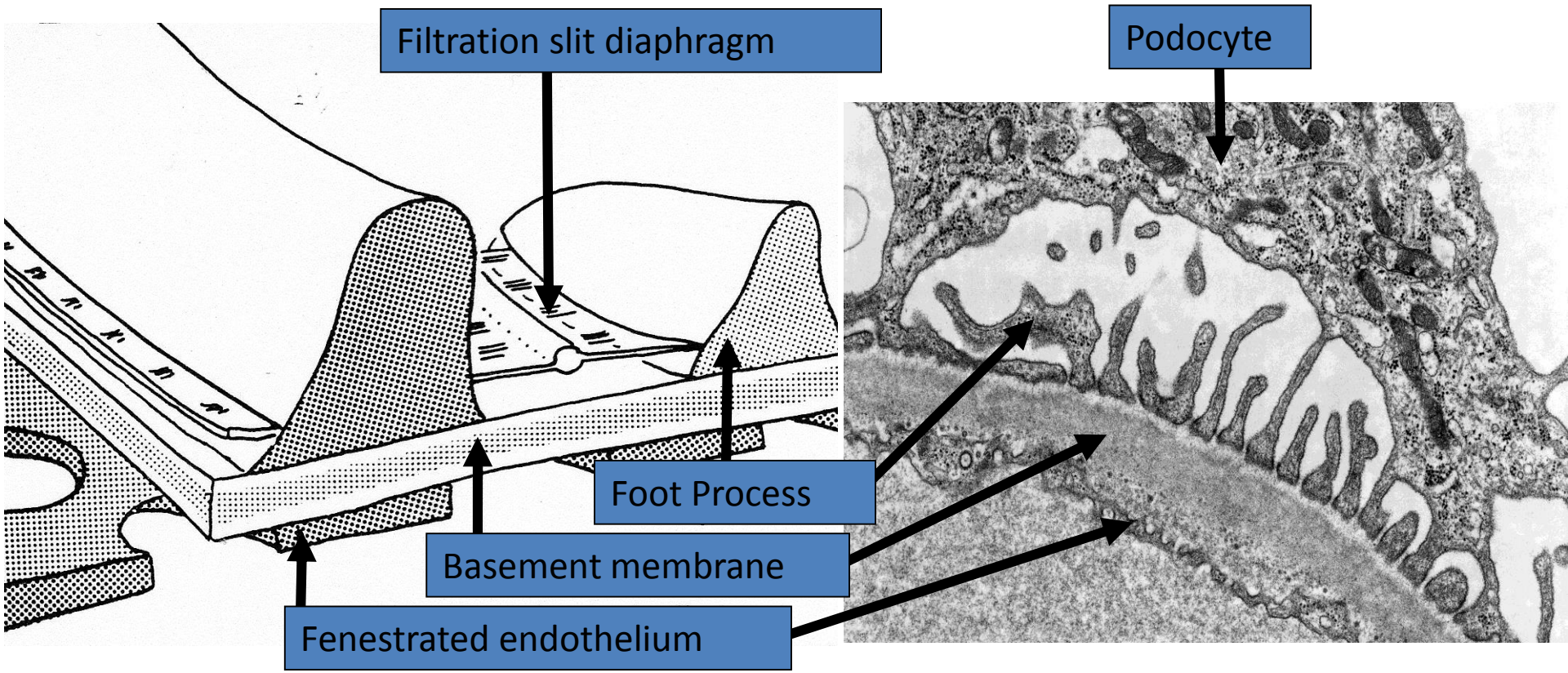
Capillary loop has 3 layers wall



Normal Capillary Loop (Electron Microscopy)



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



Albumin

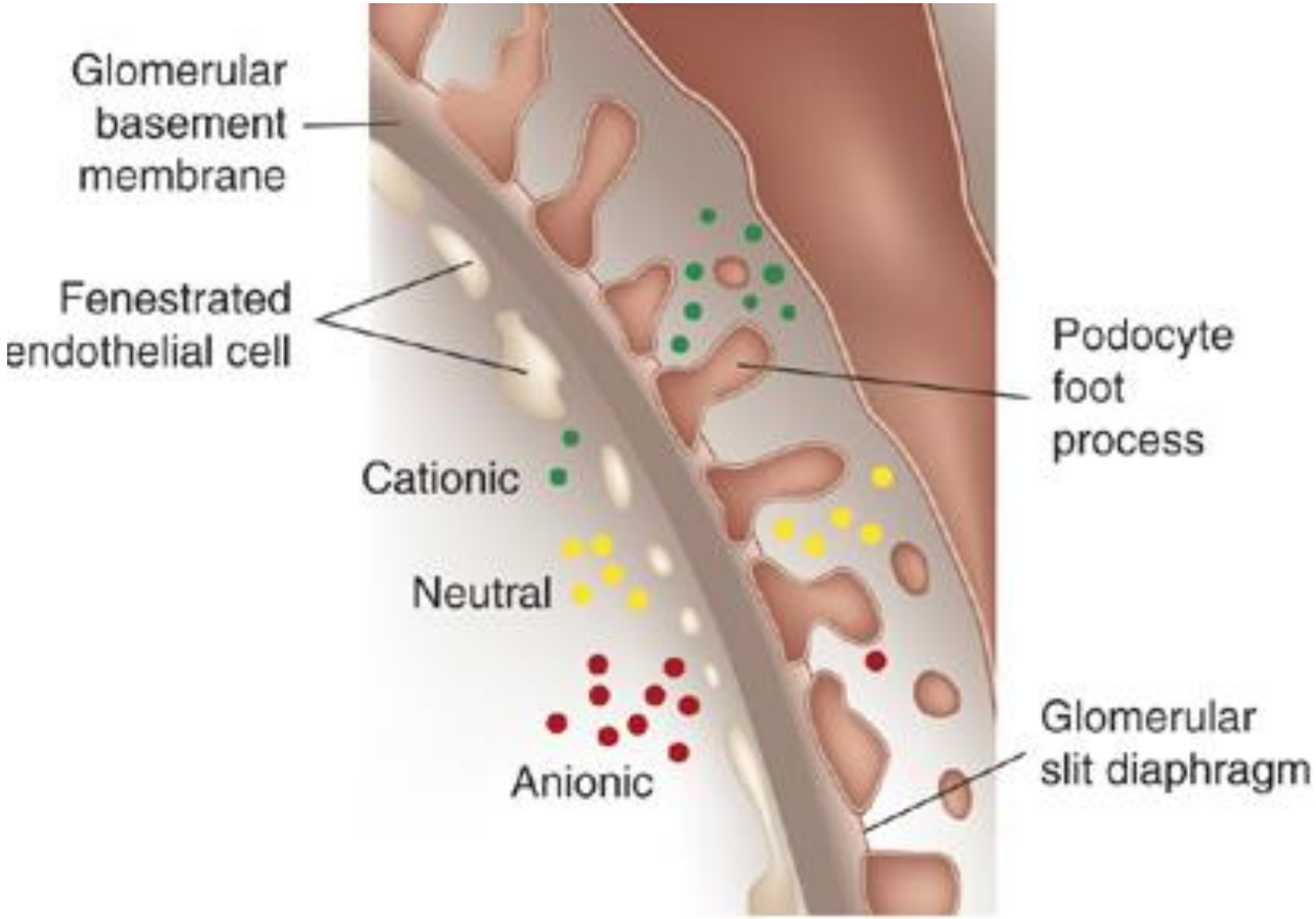
Synthesized in the liver

½ of the total serum protein is Albumin

- A major contributor to oncotic pressure (stabilizing the extracellular fluid volume)
- As a carrier protein for steroids, fatty acids, and thyroid hormones

What keeps Albumin in?

- Endothelium and the GBM are strongly anionic with the electronegative charges.
- Albumin is negatively charged at neutral pH.
- The negative charge of GBM repulses the negative charge of the Albumin; preventing Albumin leaving the capillary lumen.
- Proteinuria is a manifestation of defected GBMs Albumin repulsion mechanism.


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

Normal urine analysis

- NO PROTEIN.
- NO RED BLOOD CELLS (Accept: 1-2 RBCs/HPF)
- NO HEME.
- NO CELLULAR CASTS.

Urine Analysis in Nephrotic Syndrome

- **Lots of protein (Proteinuria)**
- No RBCs (occasionally few seen)
- No RBCs casts
- **Lots of fat (Lipiduria)**(Fatty casts, oval fat bodies & fat droplets)
- No WBCs (few may be seen)

Proteinuria

How much protein in the urine is considered Normal?

- **< 150 mg/day of all proteins**.
- Albumin in the urine only comes from the Glomerulus.
- < 20 mg/day of Albumin is Normal (average 4-7mg/day).

Detecting Proteinuria

Urine dipstick

Detecting Proteinuria

Urine chemical Analysis:

- True measurement: 24h urine collection

- Estimated measurement :
  Urine Albumin/Creatinine ratio

Detecting Proteinuria

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 find, can't detect by dipstick.

Detecting Proteinuria

Albuminuria > 300 mg/day called:

OVERT PROTEINURIA or VERY HIGH ALBUMINURIA (macroalbuminuria)

- Urine dipstick will be positive.
- Most of this protein is Albumin.

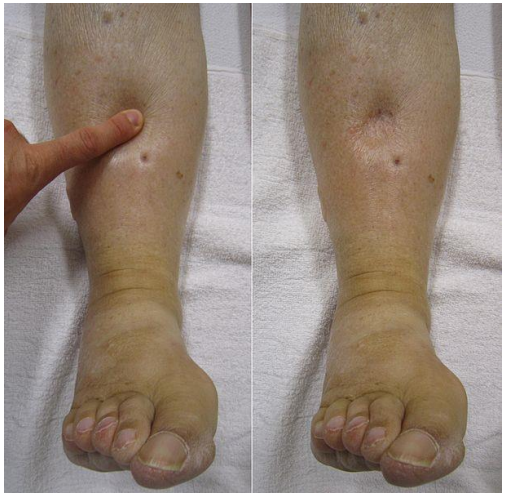
- **Sub-Nephrotic** proteinuria: **< 3.5 gm**/day
- **Nephrotic Range** Proteinuria: **> 3.5 gm**/day

Nephrotic syndrome:

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

- **Heavy proteinuria** (> 3.5 g/24 hours)
- **Hypoalbuminemia** <30 g/L (Normal:35-55 g/L)
- Peripheral or generalized **edema**

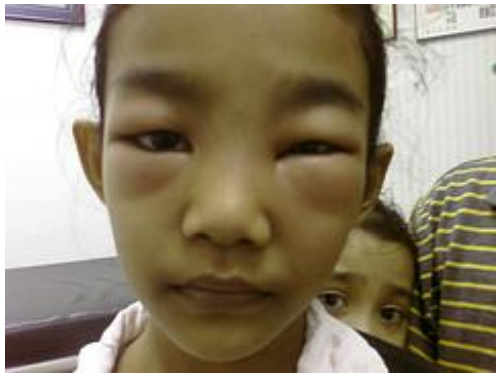
Clinical Presentation

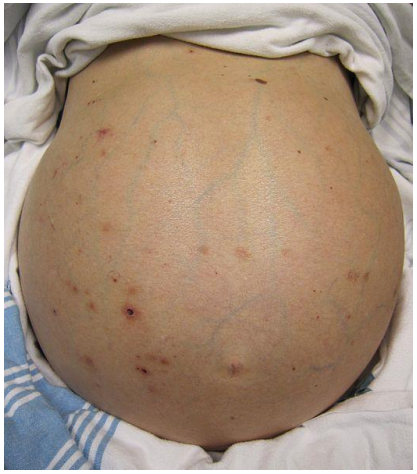


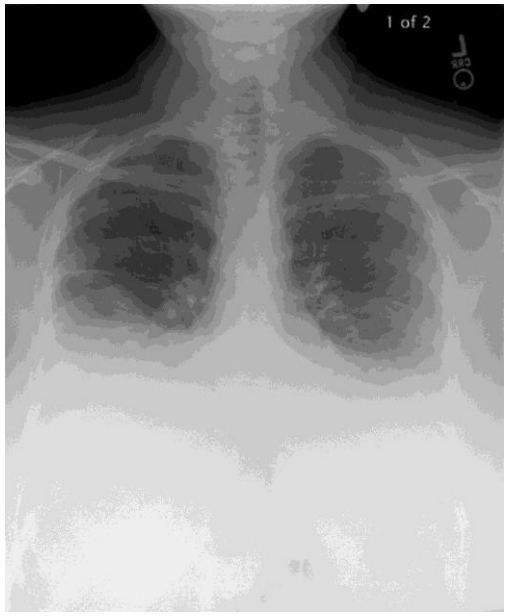
Edema

- Low serum Albumin
- Increase Renal sodium retention

uncontrolled activation of the epithelial sodium channels (ENaC)







Clinical Presentation

- Fatigue
- Foamy urine that persists
- Anorexia
- Nausea & vomiting
- Abdominal pain
- Weight gain
- Shortness of breath
- Signs & symptoms of DVT, PE

Complications of Nephrotic Syndrome

- If left untreated: *potentially fatal complications*
  - Thromboembolism
  - Infections & sepsis
  - Hyperlipidemia
  - Acute kidney injury
  - ESRD if heavy proteinuria not going into remission

Thromboembolism

- In 10 to 40% of patients
- Arterial and venous thrombosis
  (DVT, PE &renal vein thrombosis)
- Membranous Nephropathy
  ⇧Renal vein thrombosis risk
- Mechanism is not clearly understood

May be renal loss of antithrombin and plasminogen. And platelets activation.

Increased risk of infections

the mechanism is not well understood

- Renal loss of IgG may be play a rule
- Impaired ability to make specific antibodies
- Low alternative complement pathway

--*Pneumococcal* infections are more common; should get *Pneumococcal* vaccine

Hyperlipidemia

- *Hypercholesterolemia*

Decreased plasma oncotic pressure stimulates hepatic lipoprotein synthesis

- *Hypertriglyceridemia*

Due to impaired metabolism

➔ ⇧risk for atherosclerotic disease

Lipiduria is a common finding in Nephrotic syndrome

Acute kidney injury (Acute Renal Failure)

Seen more in adult patients. (MCD)

Possible causes:

-Hypovolemia

-Interstitial edema of the kidneys

- ATN

-NSAIDs

Other complications:

-Impaired thyroid function

Low thyroxine-binding globulins

-vitamin D deficiency

-Proximal Tubular dysfunction

-Protein malnutrition : loss in lean body mass with negative nitrogen balance

DDx

- Congestive heart failure
- Liver cirrhosis (portal hypertension)
- Protein losing enteropathy
- Protein malnutrition
- Increased capillary permeability due to an allergic reaction

Causes of Nephrotic Syndrome

- Approximately **30%** is due to systemic diseases (**DM, Amyloidosis, SLE**)
- Membranous Nephropathy (MN)
- Focal Segmental GlomeruloSclerosis (FSGS)
- Minimal Change Disease (MCD)

Microscopy

Light Microscope 2000x

EM 10,000,000

Minimal **C**hange **D**isease **(MCD)**

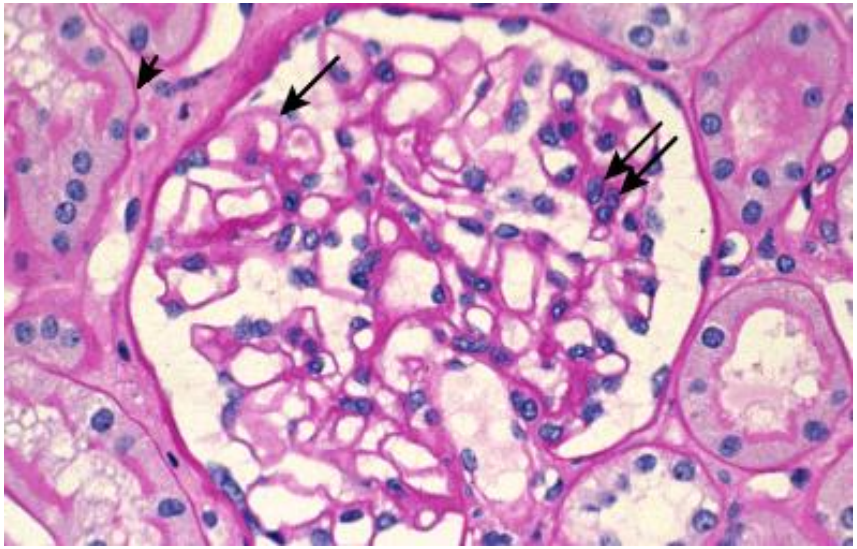
- light microscopy: *is either normal or reveals only mild mesangial cell proliferation*

So called: nil disease

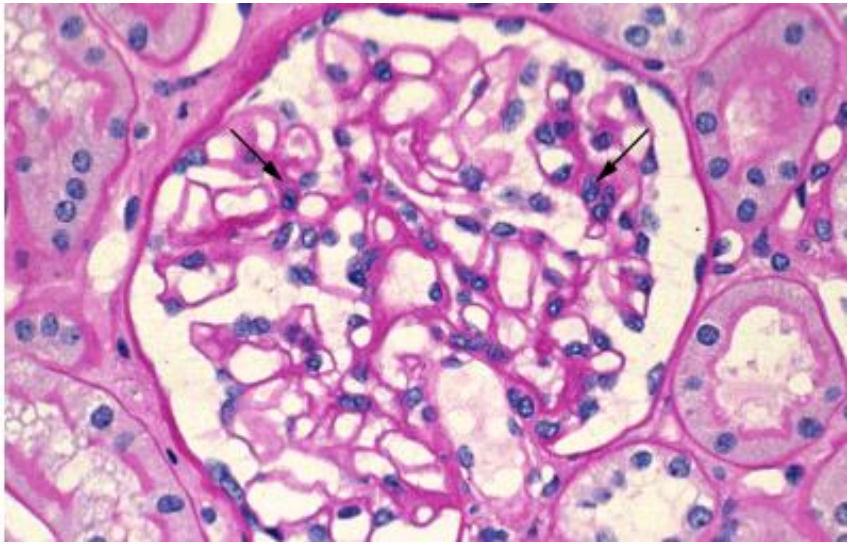
- electron microscopy: *diffuse effacement of the epithelial cell foot processes*

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

Normal Glomerulus

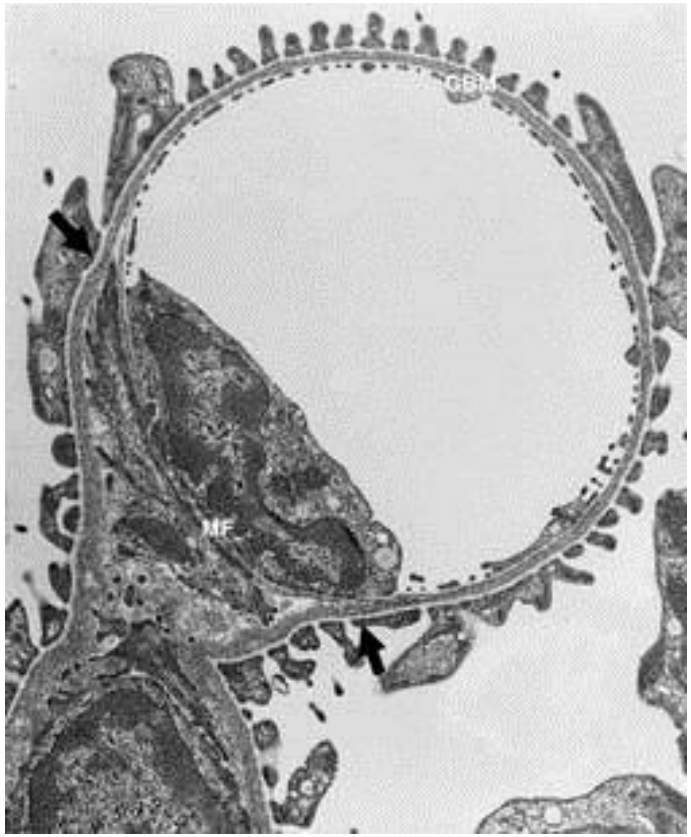


MCD

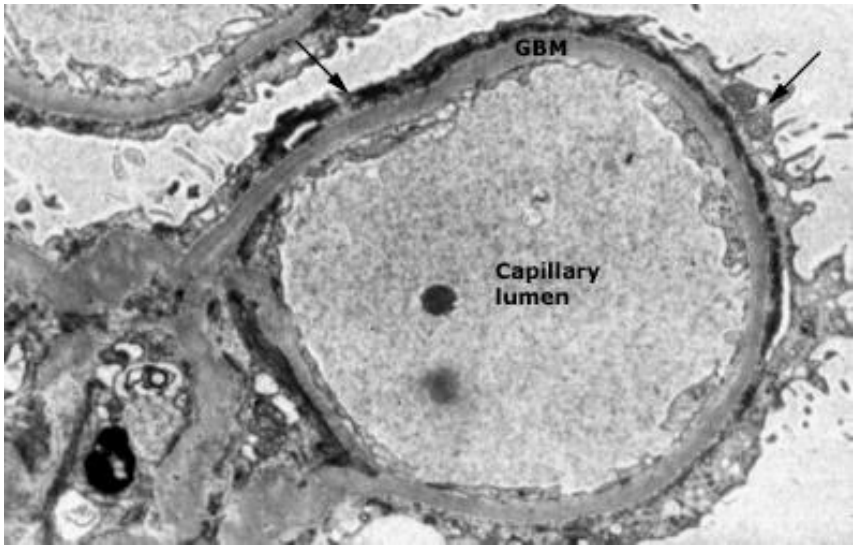


Cont. **Minimal Change Disease (MCD)**

Normal Glomerulus



MCD



Cont. **M**inimal **C**hange **D**isease **(MCD)**

<u>Causes Idiopathic Nephrotic syndrome mainly in children:</u>

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

In children; typically is corticosteroid responsive in > 90% children, thus kidney biopsy is commonly not done.

- **10-25 %** of Nephrotic syndrome in **adults**

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

Idiopathic (Primary) or

Secondary:

- *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 sudden onset Edema
- BP may be normal or slightly elevated
- Heavy proteinuria, Lipiduria
- Hypoalbuminmia
- Hyperlipidemia
- Creatinine is normal or slightly elevated

Cont. **M**inimal **C**hange **D**isease **(MCD)**

Diagnosis:

Must do kidney biopsy in adult patients with this presentation

Treatment:

First line: Corticosteroids (response 8- 16 weeks)

Given x 3-4 months then taper over 6 months

Second line: oral Cyclophosphamide, Cyclosporin or Tacrolimus, Rituximab

Focal **S**egmental **G**lomerulo**S**clerosis (**FSGS**)

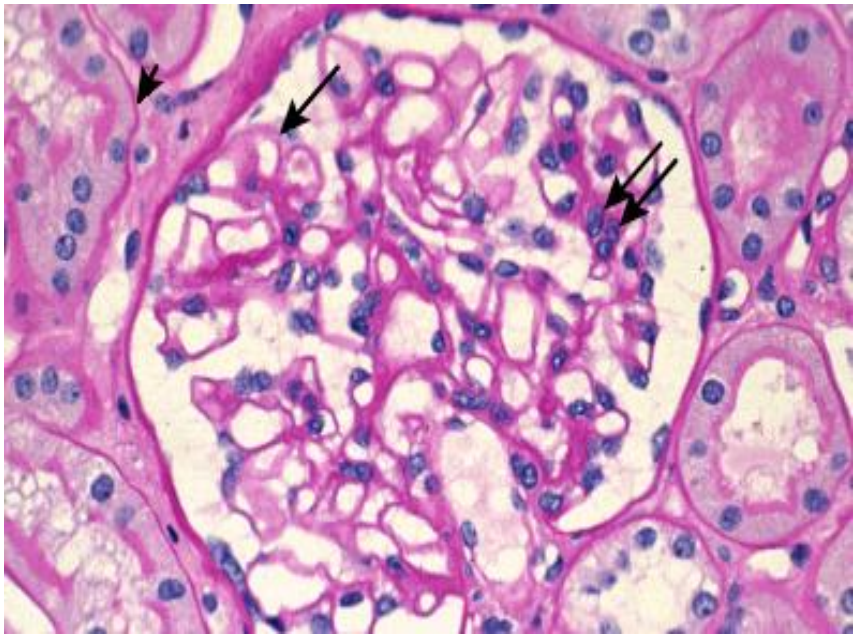
- *Focal*: some glomeruli are affected
- *Segmental*: only a segment of the affected glomerulus is sclerosed.

Focal Segmental GlomeruloSclerosis (FSGS)

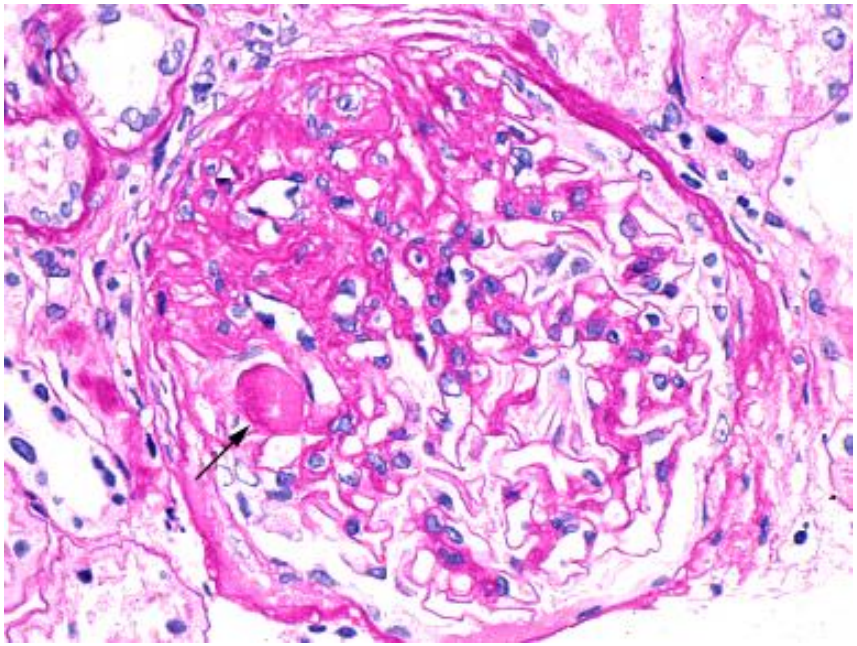
- A more common cause of Nephrotic synd in adults (specially African American)
- Causes 12 – 35 % of the cases in adults.

Focal Segmental GlomeruloSclerosis (FSGS)

Normal

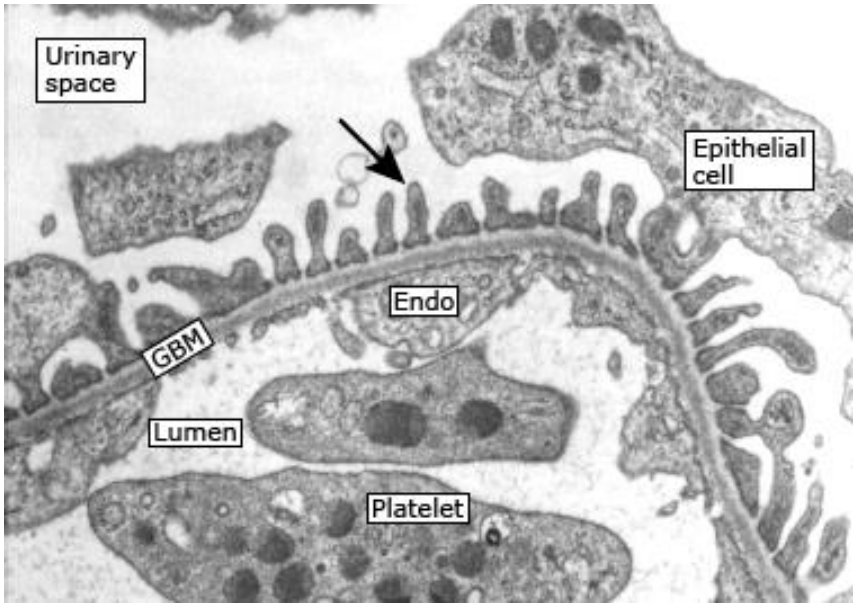


FSGS

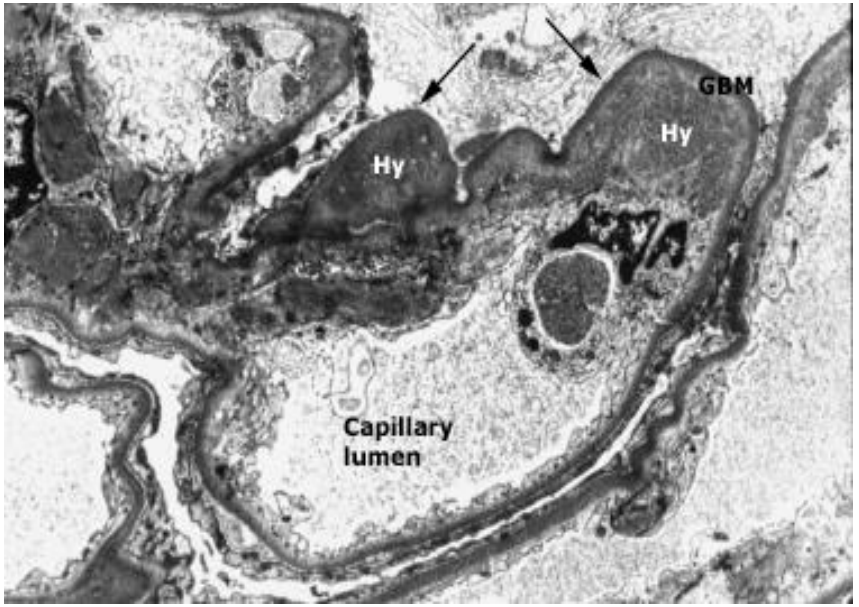


Focal Segmental GlomeruloSclerosis (FSGS)

Normal



FSGS



Focal Segmental GlomeruloSclerosis (FSGS)

Can be:

Primary FSGS:

- Presents suddenly like MCD with heavy proteinuria and other manifistations of nephrotic syndrome
- Typically responds to corticosteroids

Focal **S**egmental **G**lomerulo**S**clerosis (**FSGS**)

Secondary FSGS:

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

-Albumin is not very low

-Renal impairment is commonly seen

Focal Segmental GlomeruloSclerosis (FSGS)

Possible causes of Secondary FSGS:

- Massive obesity
- Nephron loss (> 75% of renal mass)
  Hypertension & reflux nephropathy
- Renal agenesis
- Healing of prior inflammatory injury(IgA, Lupus)
- Anabolic steroid abuse
- Severe preeclampsia
- Drugs: Interferon, Pamidronate, Heroin
- Infections: HIV

Focal **S**egmental **G**lomerulo**S**clerosis (**FSGS**)

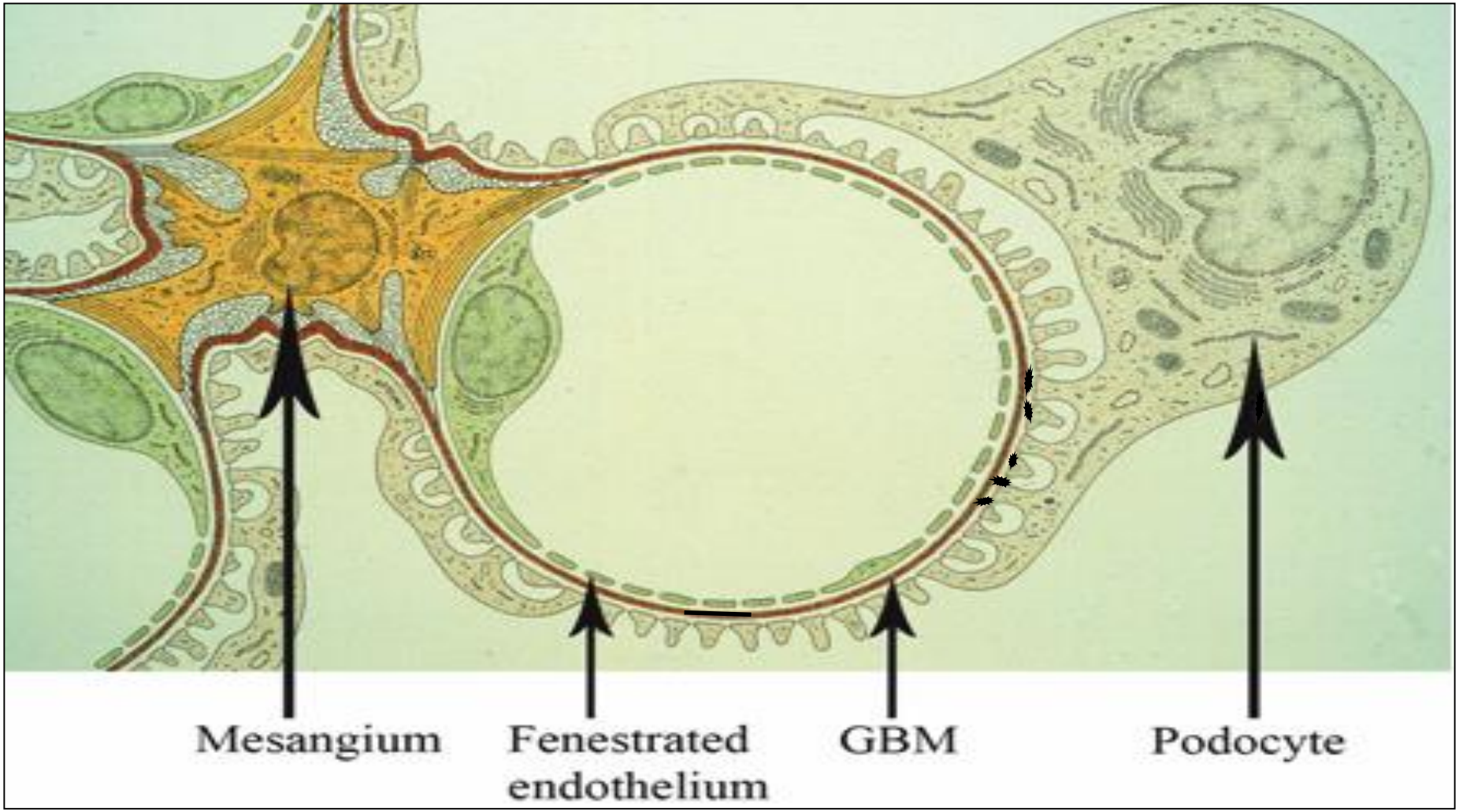
Immunosuppressive therapy is indicated in most patients with **primary FSGS**

- First line: corticosteroids
- Second line: cyclosporine
- Third line: MMF

Secondary FSGS: not typically treated with Immunosuppression, treat the primary cause and add supportive measures.

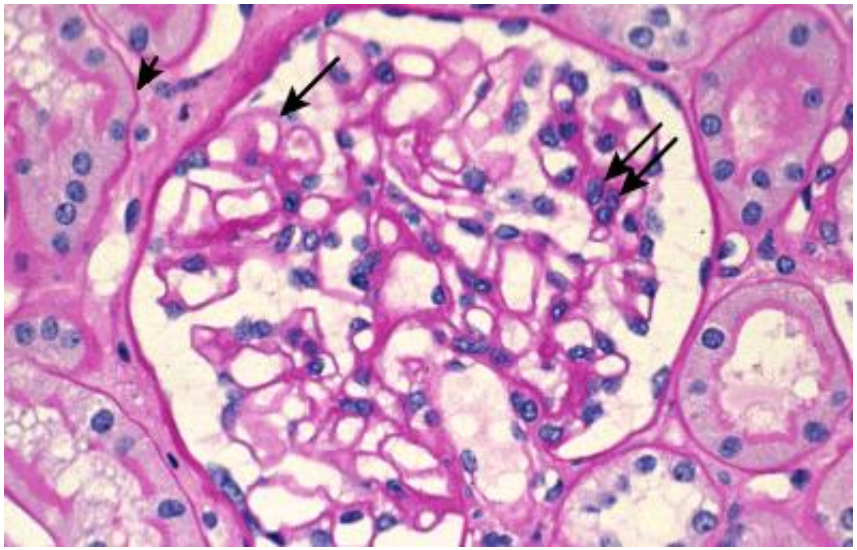
Membranous **N**ephropathy (MN)

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

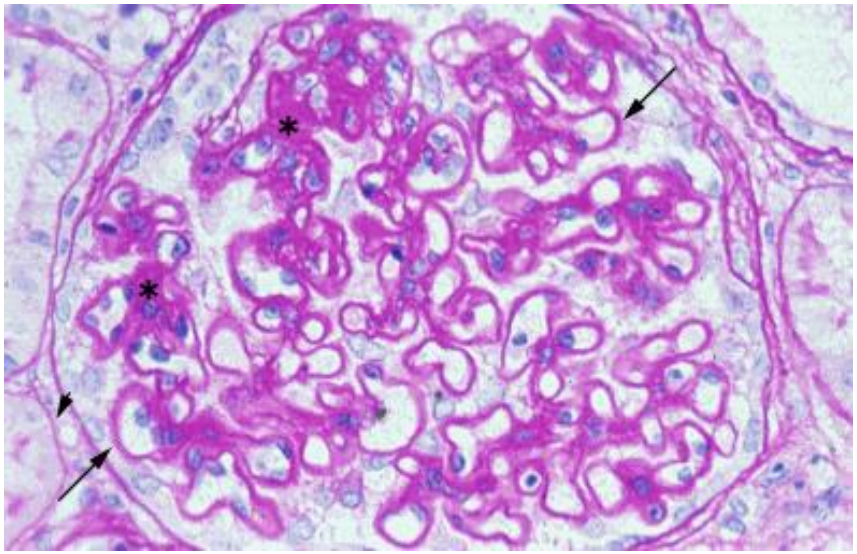

Mesangium
Fenestrated endothelium
GBM
Podocyte

Membranous Nephropathy (MN)

Normal



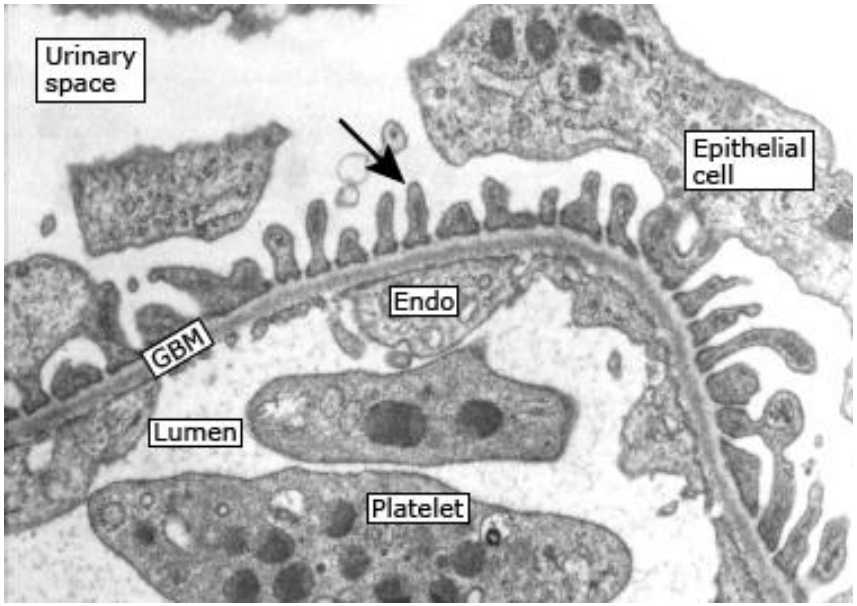
MN



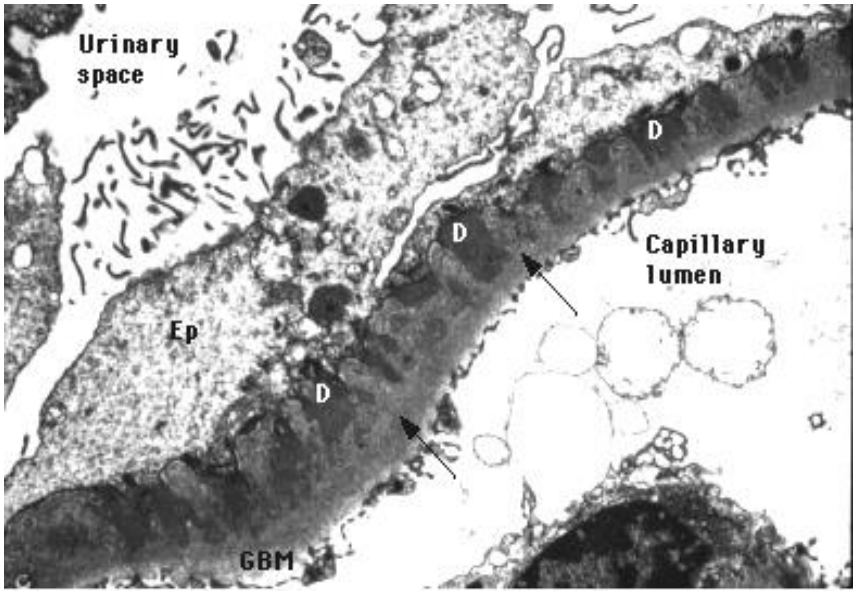
Diffuse thickening of the glomerular basement membrane (GBM) throughout all glomeruli (IgG and C3)

Membranous Nephropathy (MN)

Normal



MN



Membranous **N**ephropathy (MN)

Etiology:

- Idiopathic (Primary)

  Approximately 75% of cases

Membranous **N**ephropathy (MN)

Secondary MN

- Systemic lupus erythematosus (SLE)

  Class V Lupus Nephritis (10-20%)
- Drugs: penicillamine, gold, high dose Captopril, and NSAIDs, Anti-TNF
- Infections: Hepatitis B, Hepatitis C, syphilis
- Malignancy: solid tumors prostate, lung, or GI track

Membranous **N**ephropathy (MN)

Treatment of Primary MN

- Corticosteroids plus
- Cyclophosphamide or cyclosporine
- May be Rituximab

Secondary MN

- Mainly target the primary disease, and the Nephrotic complications.

Amyloidosis

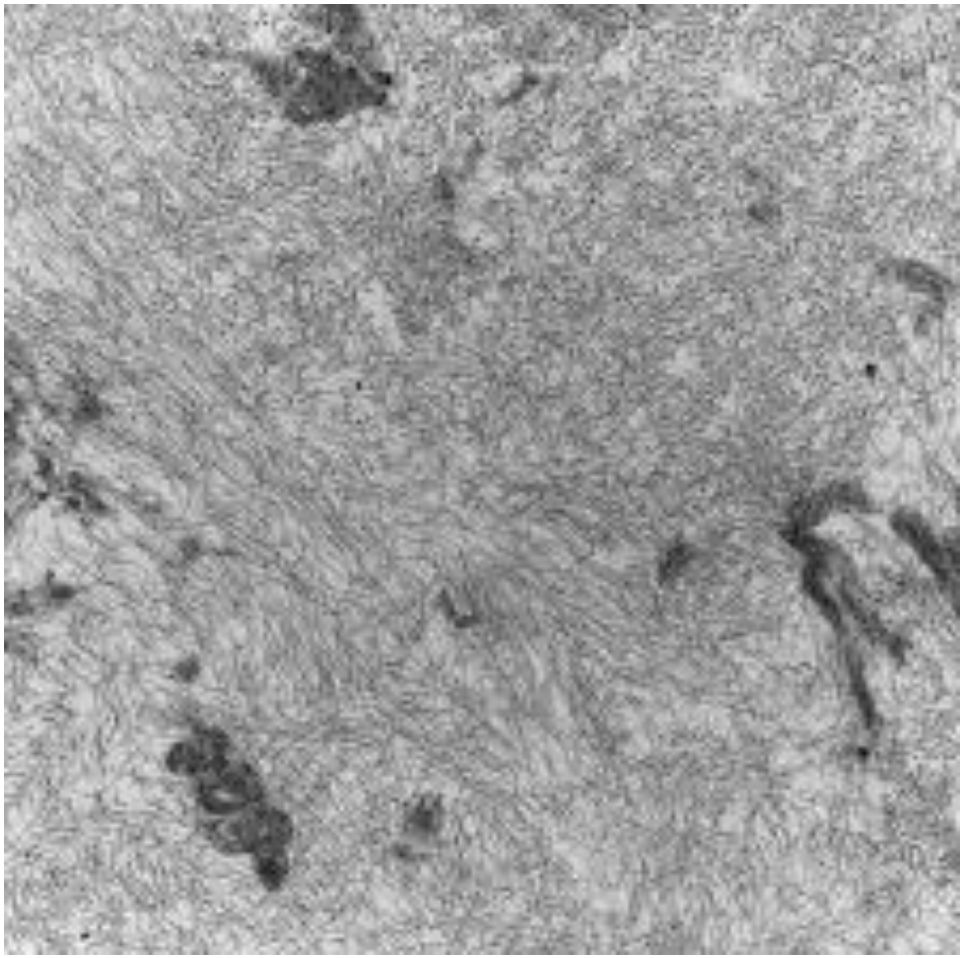
4 to 17% of idiopathic NS in adults.

- **Primary amyloid** : **AL**, light chain dyscrasia, fragments of MLC form the amyloid fibrils)

- **Secondary amyloidosis** : **AA**, acute phase reactant serum amyloid A forms the amyloid fibrils

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

Fibrils in Amyloidosis



GN + Nephrotic Syndrome

- Postinfectious glomerulonephritis
- Membranoproliferative glomerulonephritis
- IgA nephropathy

General management issues in patients with nephrotic syndrome

- **Proteinuria**

  Heaavy proteinuria is toxic to renal tubules

  - *lower intraglomerular pressure* by angiotensin converting enzyme inhibitor or angiotensin receptor blockers

General management issues in patients with nephrotic syndrome

- **Edema**

Peripheral edema and ascites is due to primary renal sodium retention

- *Salt intake restriction*
- *Diuretics (Loop Diuretics, ususally high doses)*

General management issues in patients with nephrotic syndrome

- Hyperlipidemia

  Ususally resolves with resolution of proteinuria

  Accelarate Atherosclerosis

- *HMG CoA reductase inhibitor (statin)*
- *Dietary modification*

General management issues in patients with nephrotic syndrome

- Prevent infection by vaccination.

- Search for the possible cause of secondary Nephrtic syndrome

ANA

Hepatitis serology

Protein Electrophoresis

Complements level