Renal Pathology
Glomerular diseases
L1

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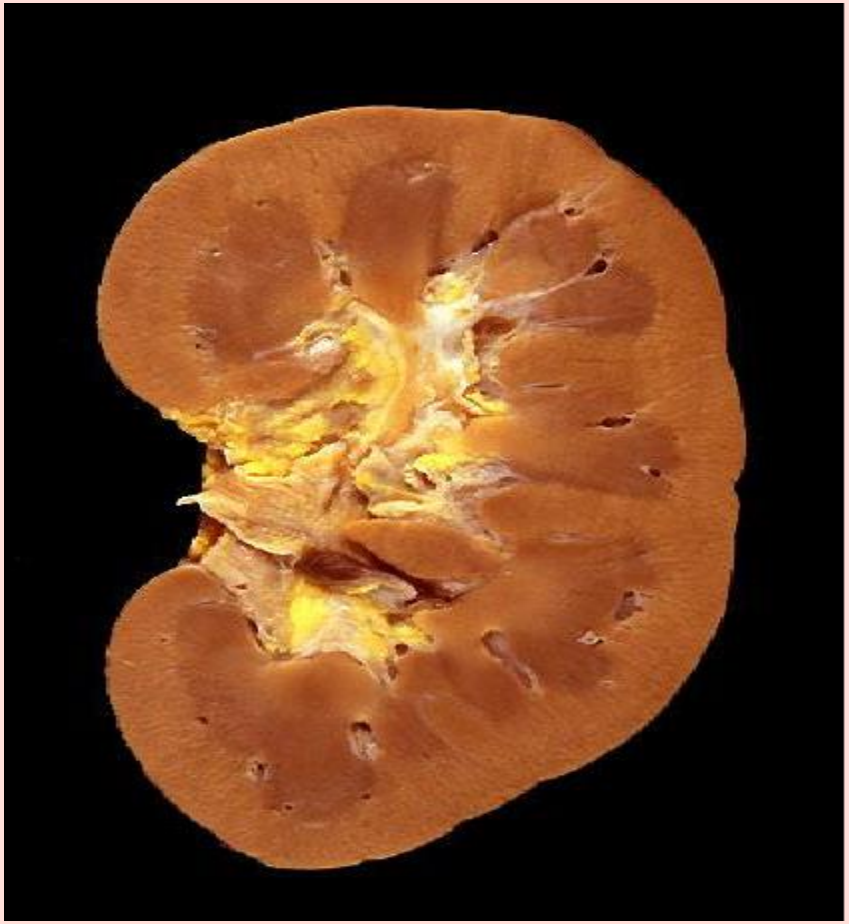
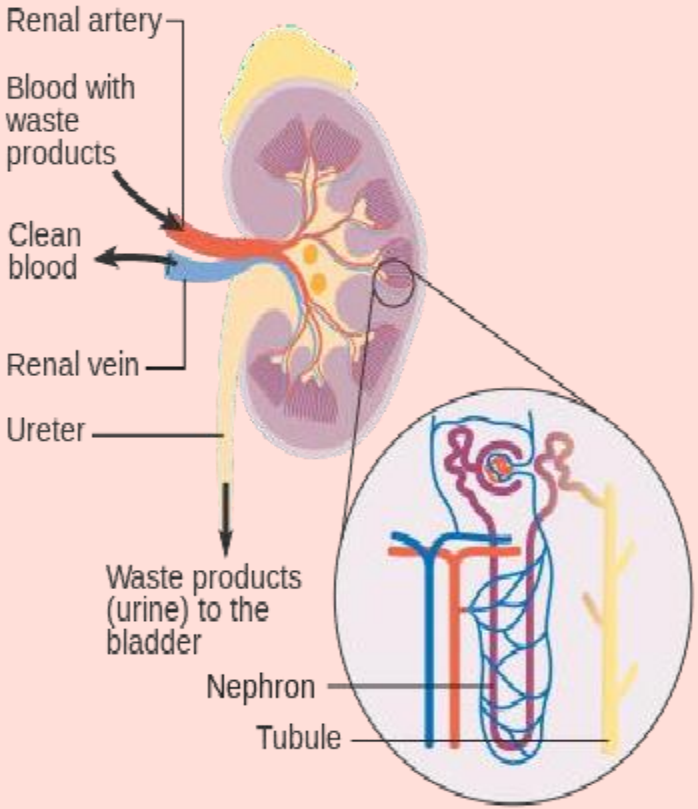
Introduction

- Important functions of the kidney:
- Excretion of the waste products of metabolism
- Regulation of body water and salt
- Maintenance of acid balance
- Secretion of a variety of hormones and prostaglandins

- Structures are divided into those that affect its four components:

1. Glomeruli
2. Tubules
3. Interstitium
4. Blood vessels




Renal artery
Blood with waste products
Clean blood
Renal vein
Ureter
Waste products (urine) to the bladder
Nephron
Tubule

Clinical manifestation of renal diseases

- **Azotemia** an elevation of blood urea nitrogen(BUN) & creatinine levels usually reflects a decreased glomerular filtration rate (GFR).

- **Uremia**: When azotemia gives rise to clinical manifestations & systemic biochemical abnormalities.
- Failure of renal excretory function + metabolic & endocrine alterations incident to renal damage

Clinical manifestation of renal diseases

- **End-stage renal disease (ESRD)** is irreversible loss of renal function requiring dialysis or transplantation typically due to severe progressive scarring in the kidney from any cause.
- **Urinary tract infection** (UTI) bacteriuria & pyuria (bacteria and leukocytes in the urine). Symptomatic or asymptomatic. Affect the kidney (pyelonephritis) or the bladder (cystitis) only.
- **Nephrolithiasis** formation of stones in the collecting system. Manifested by renal colic & hematuria

Clinical manifestation of renal diseases

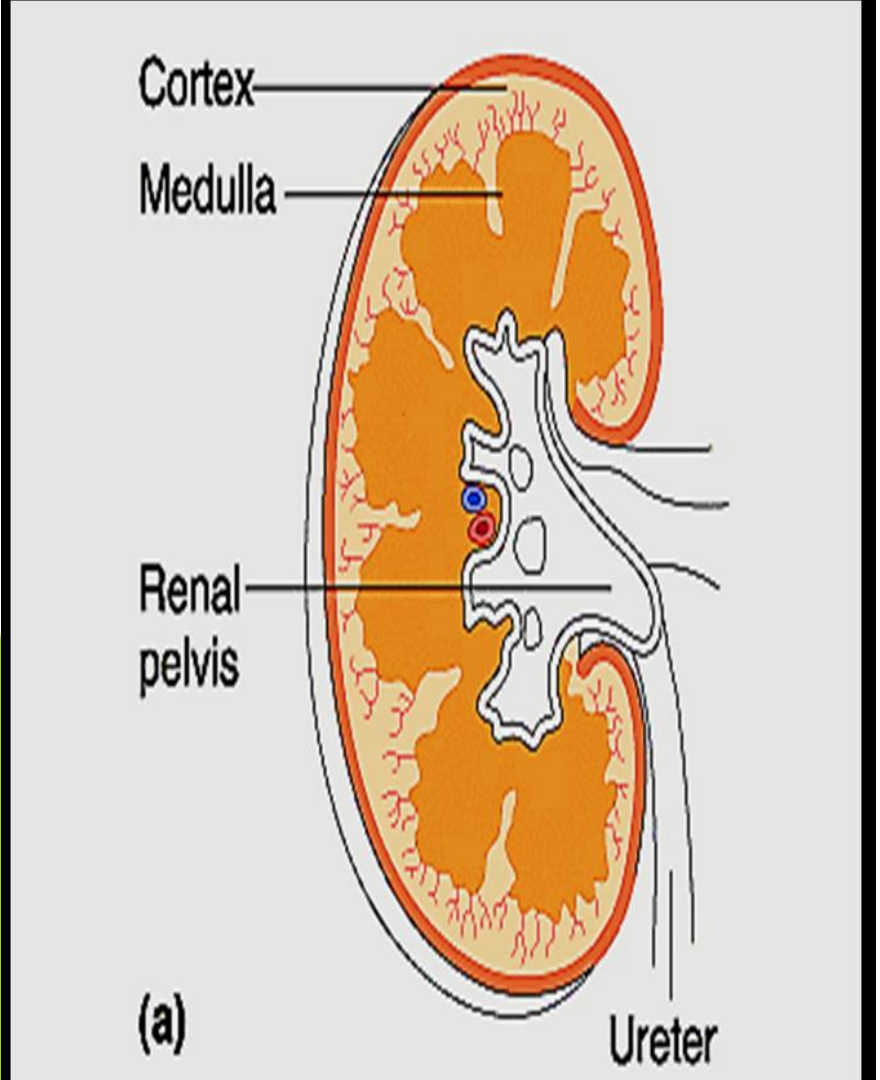
- **Acute kidney injury** abrupt onset of renal dysfunction; an acute increase in serum creatinine often ass/w oliguria or anuria (decreased or no urine flow).
- **Chronic kidney disease:**

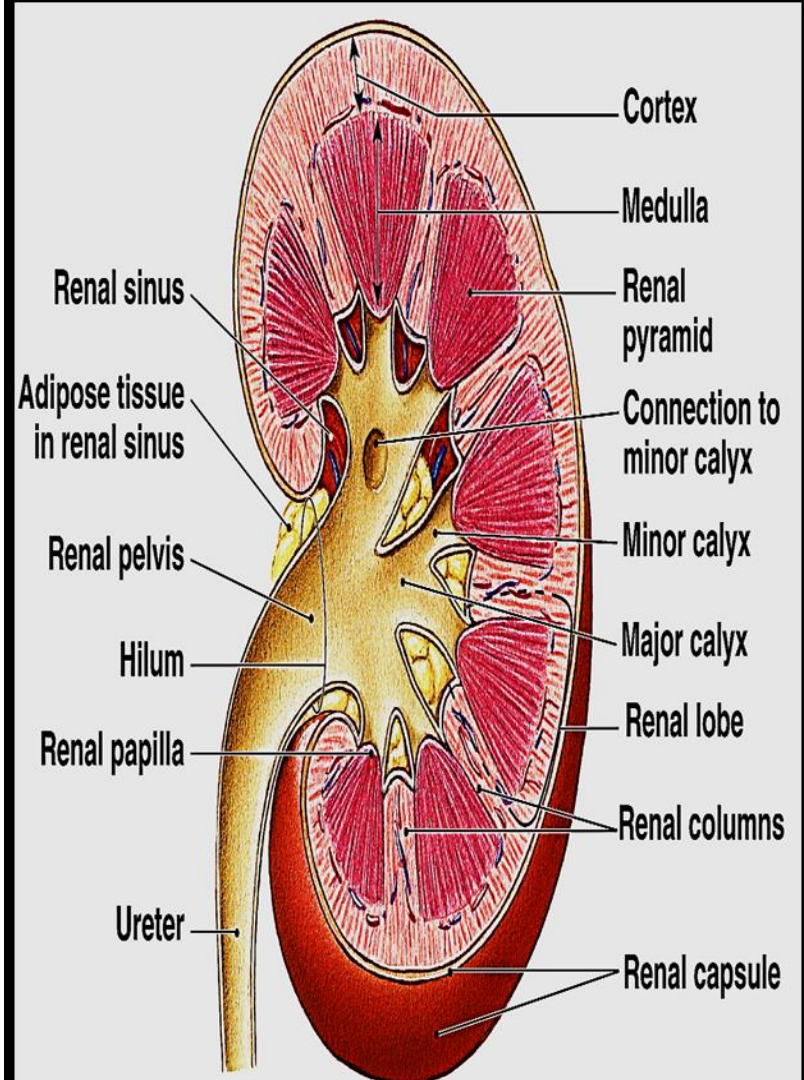
- Results from progressive scarring in the kidney of any cause.

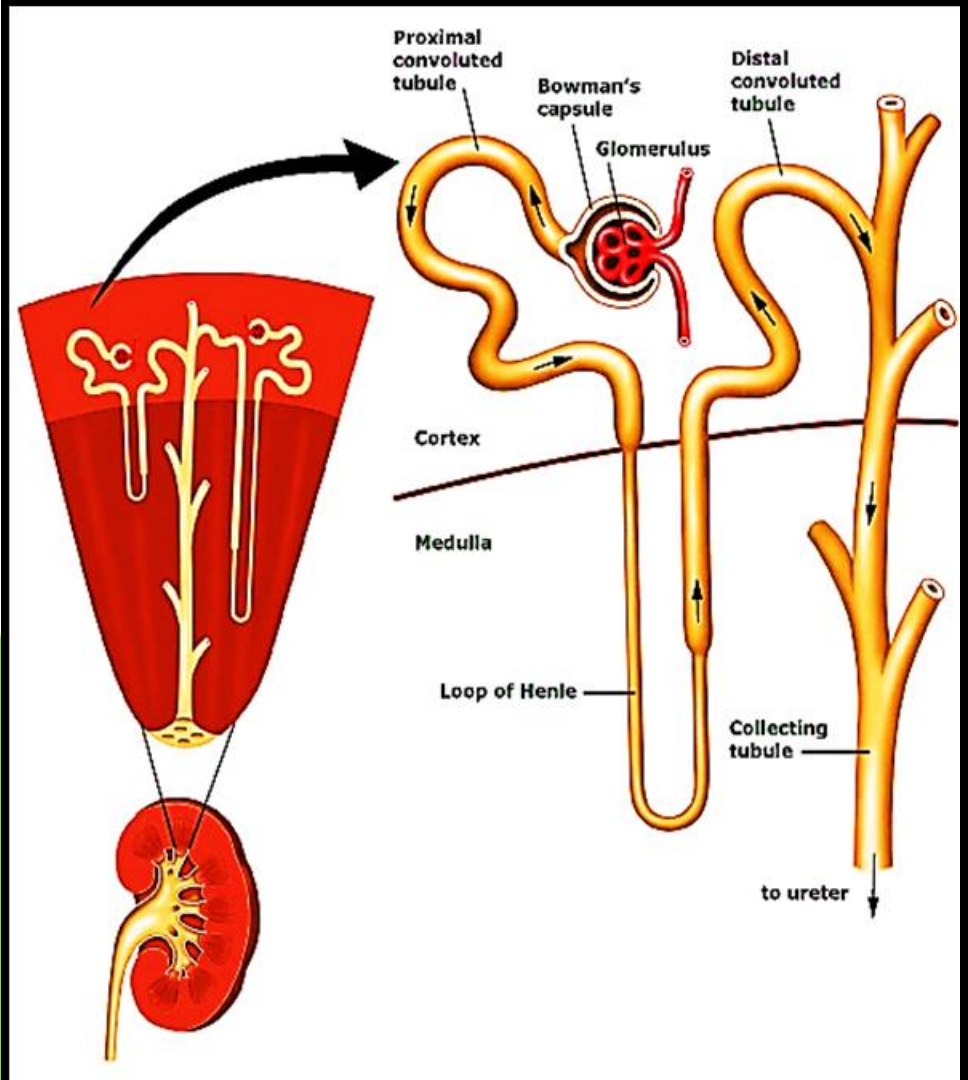
- Metabolic & electrolyte abnormalities such as hyperphosphatemia, dyslipidemia, & metabolic acidosis.

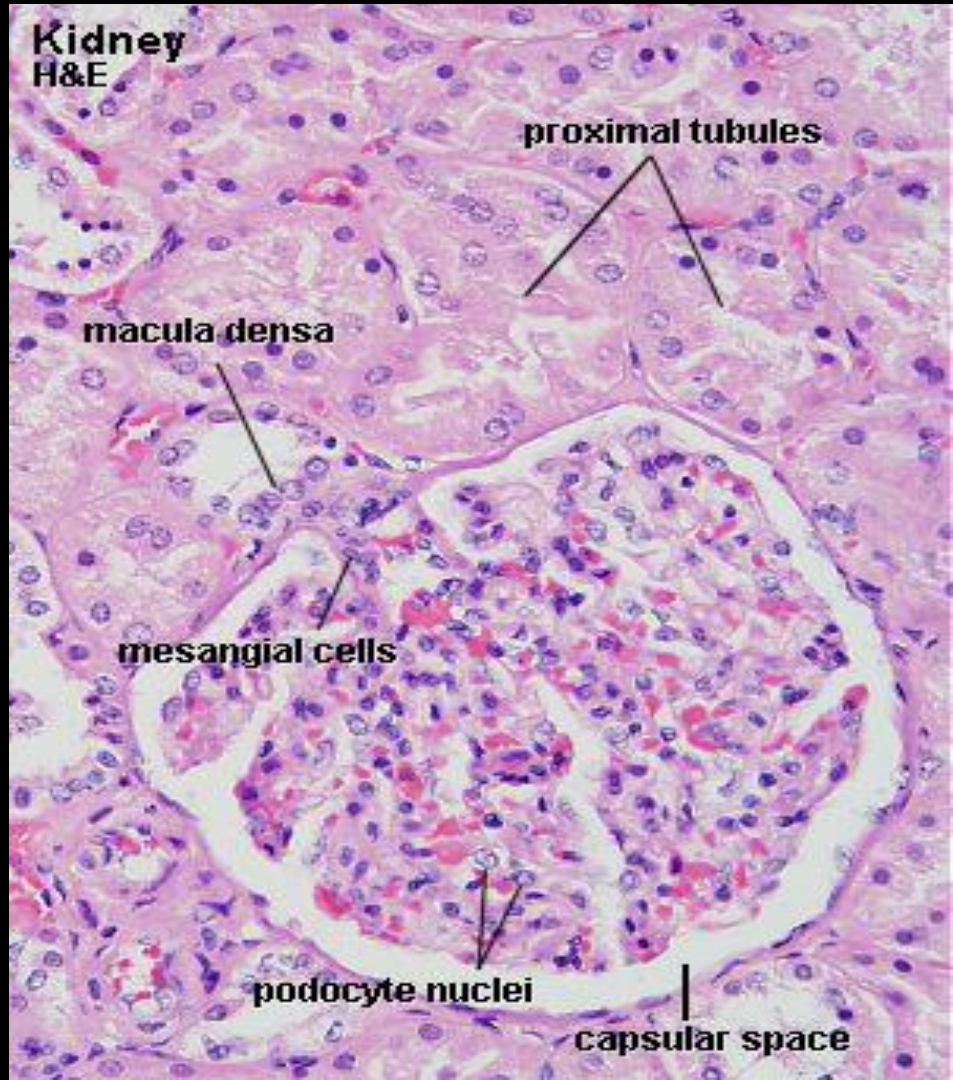
- Often asymptomatic until the most advanced stages symptoms of uremia develop.

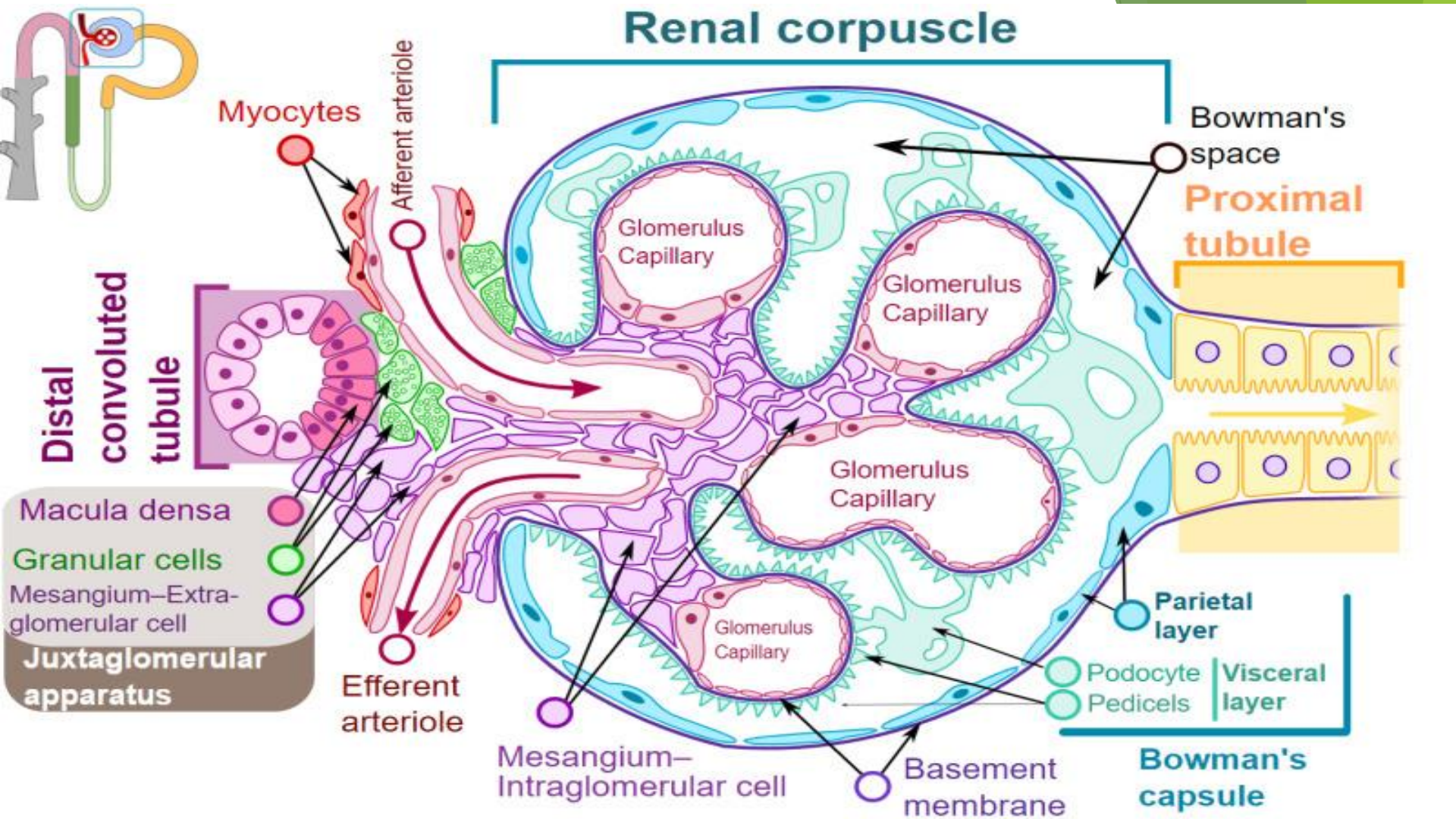
GLOMERULAR DISEASES

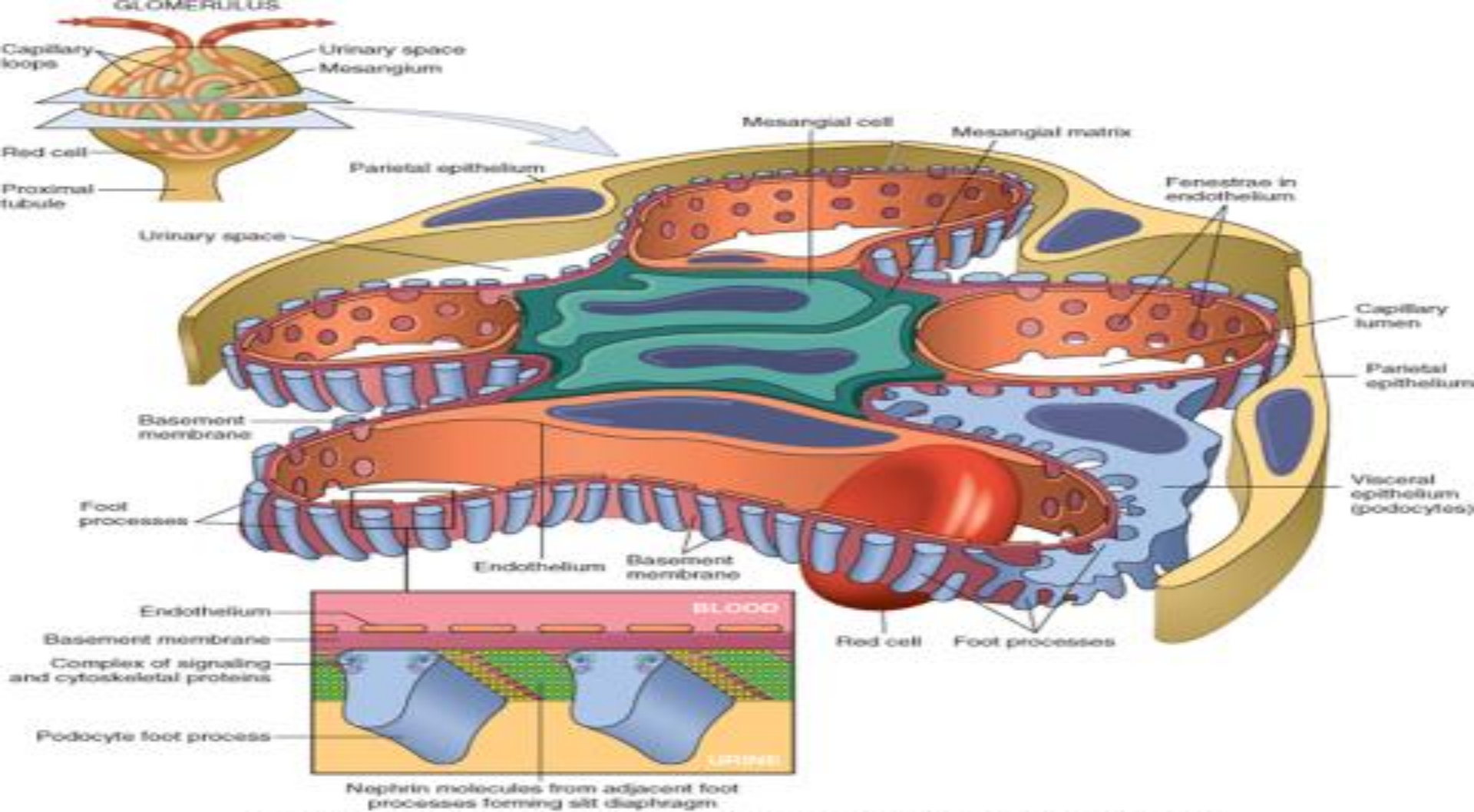

Cortex
Medulla
Renal pelvis
(a)
Ureter


Cortex
Medulla
Renal sinus
Renal pyramid
Adipose tissue in renal sinus
Connection to minor calyx
Renal pelvis
Minor calyx
Major calyx
Hilum
Renal lobe
Renal papilla
Renal columns
Ureter
Renal capsule


Proximal convoluted tubule
Bowman's capsule
Glomerulus
Distal convoluted tubule
Cortex
Medulla
Loop of Henle
Collecting tubule
to ureter


Kidney
H&E
proximal tubules
macula densa
mesangial cells
podocyte nuclei
capsular space

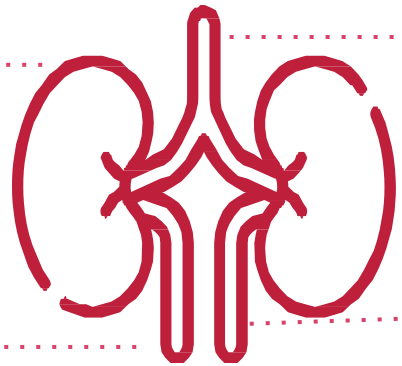

Renal corpuscle
Myocytes
Afferent arteriole
Bowman's space
Proximal tubule
Glomerulus Capillary
Glomerulus Capillary
Glomerulus Capillary
Glomerulus Capillary
Distal convoluted tubule
Macula densa
Granular cells
Mesangium–Extra-glomerular cell
Juxtaglomerular apparatus
Efferent arteriole
Parietal layer
Podocyte
Pedicels
Visceral layer
Mesangium–Intraglomerular cell
Basement membrane
Bowman's capsule



GLOMERULAR DISEASES

01 A major problems in nephrology; Chronic glomerulonephritis is one of the most common causes of chronic kidney disease

02 The glomerulus: anastomosing network of capillaries invested by two layers of epithelium: visceral & parietal epithelium



03 The visceral epithelium (composed of podocytes) part of the capillary wall

04 The parietal epithelium encircles Bowman space (urinary space), the cavity in which filtrate of plasma collects.

Normal glomerulus

- The glomerulus is a specialized net work of capillaries with an arteriole at each end.
- It has a central connective tissue material known as mesangium containing cells known as mesangial cells
- The glomerular capillaries are lined by fenestrated endothelium lying on a basement membrane , which is covered by specialized epithelial cells.

Normal glomerulus

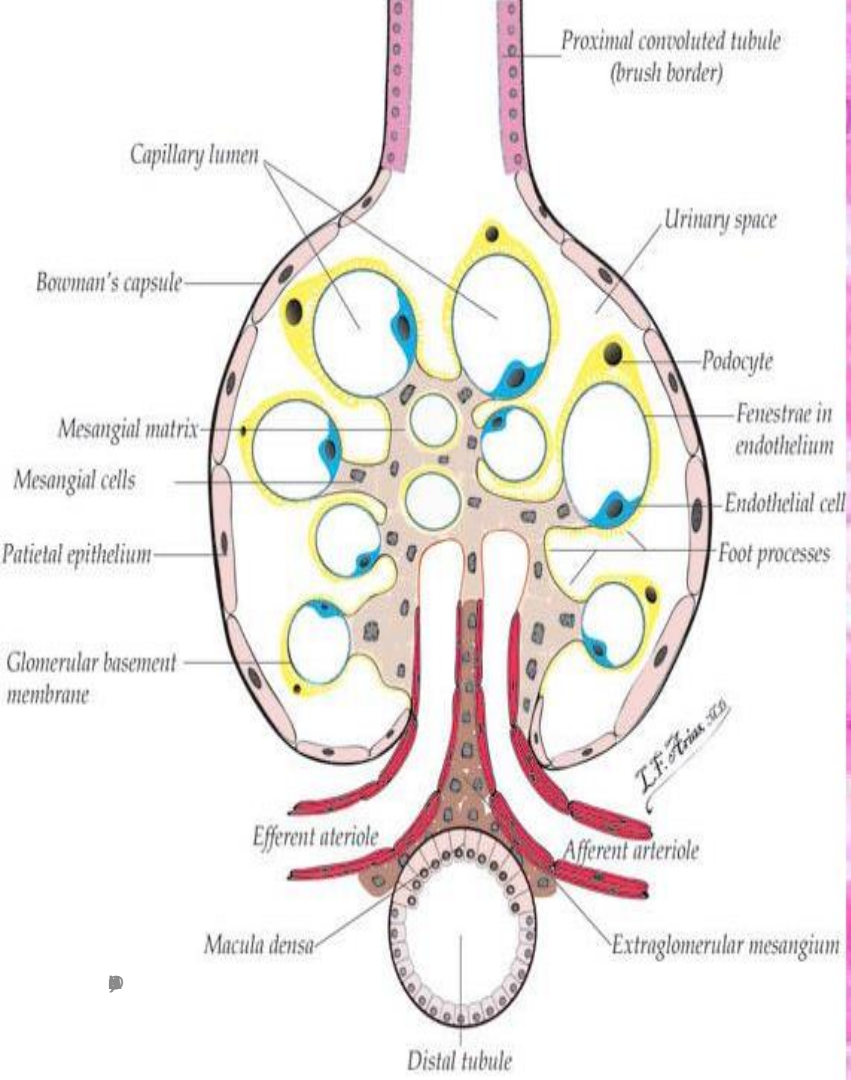
- **Epithelial cells**
- Two types:
  - **Parietal cells** line Bowman's capsule
  - **Visceral rest** on GBM;

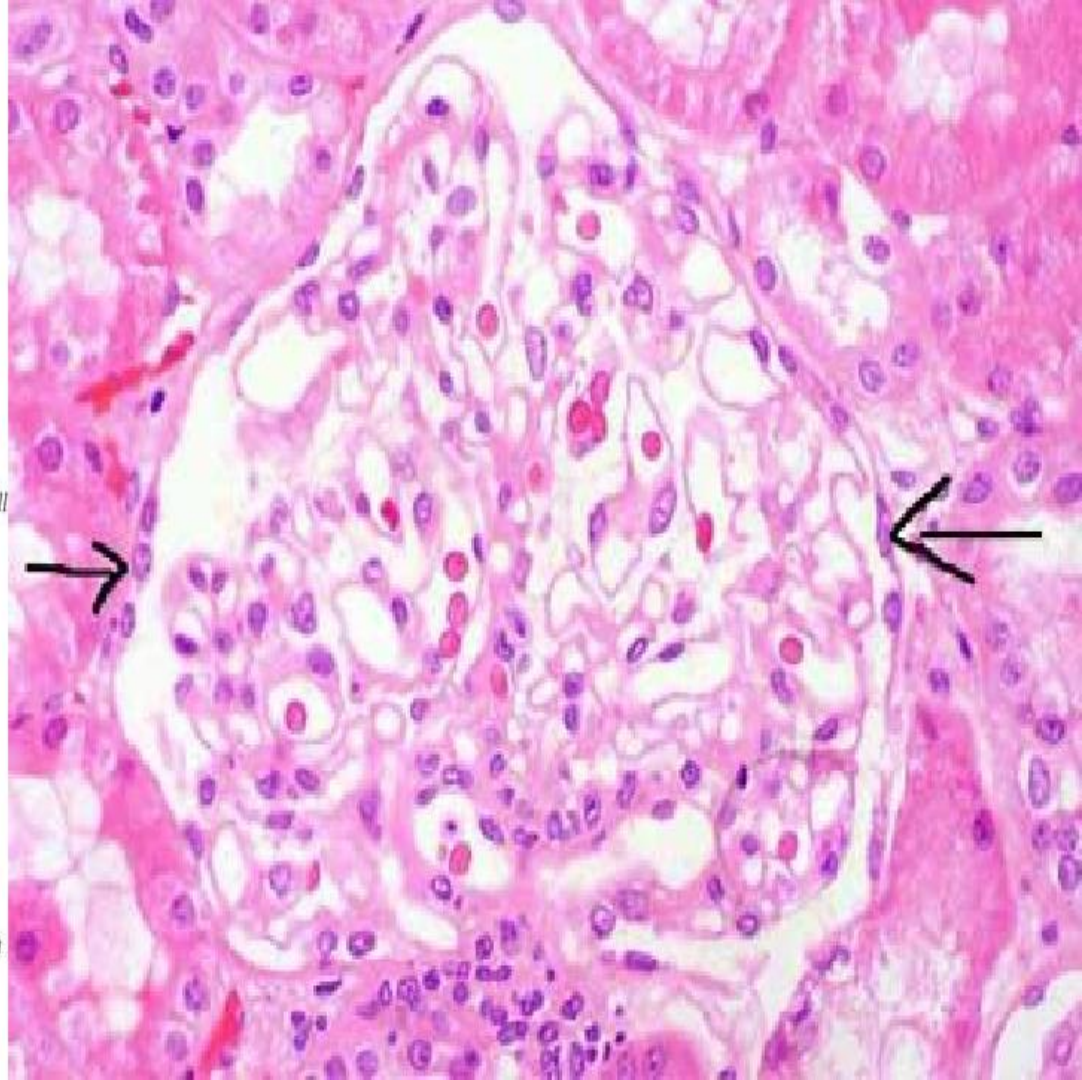
They have cytoplasmic projections known as foot processes (**podocytes**) that surround the GBM . Between the processes there are the slit membranes.

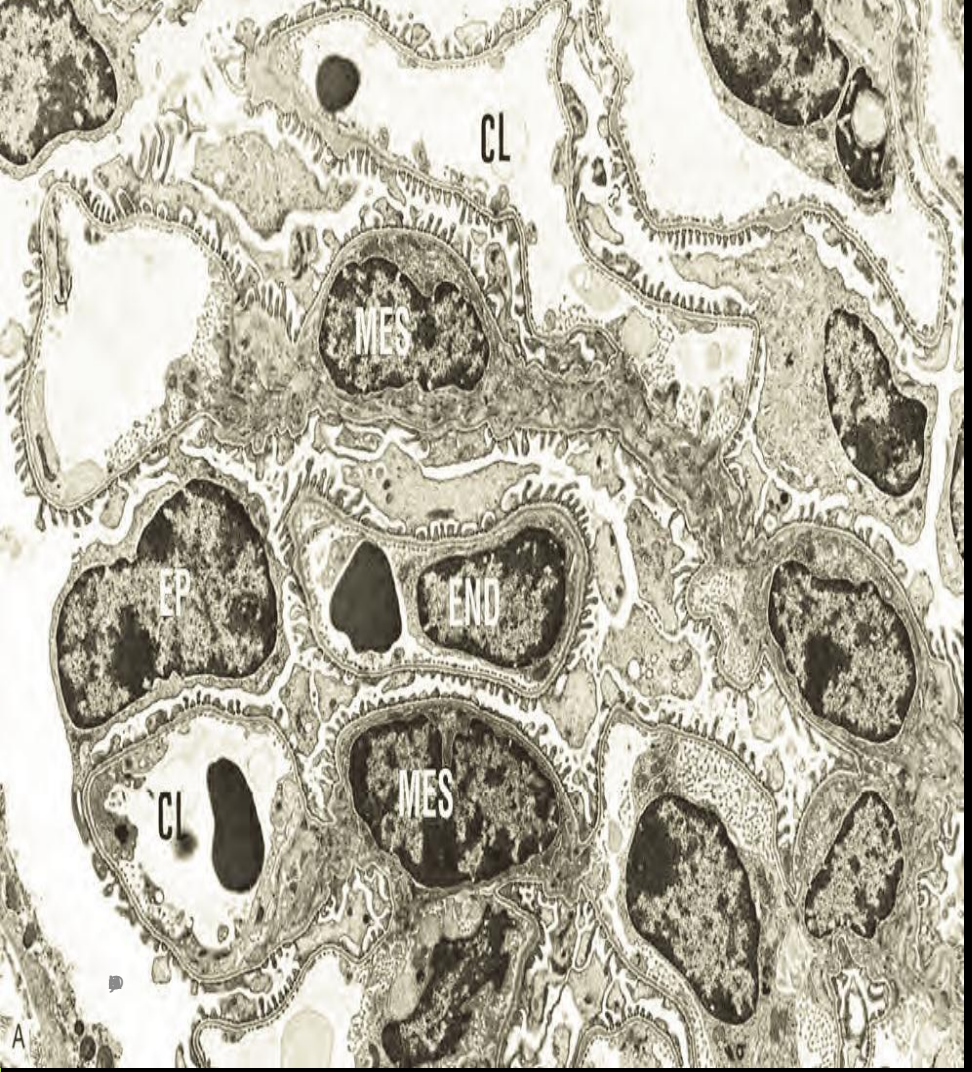
The visceral epithelial cells are the major glomerular filter barrier.

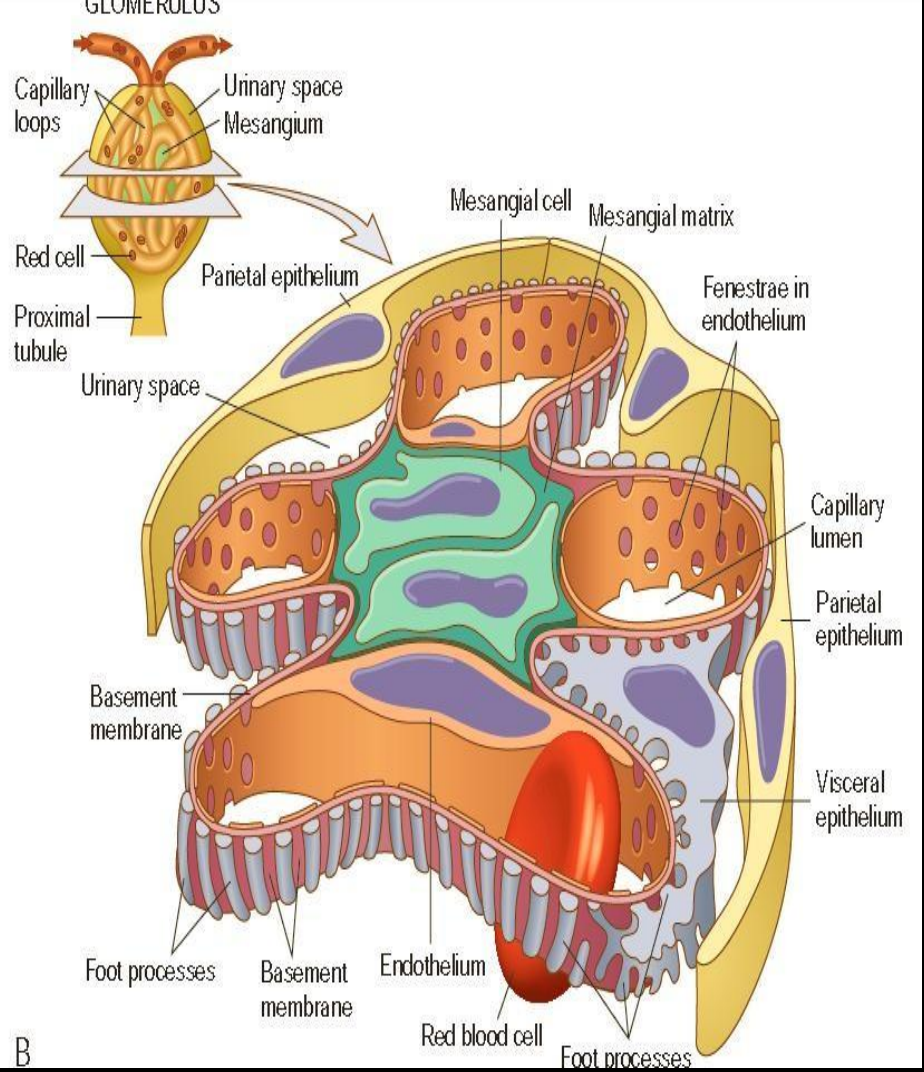
Normal glomerulus

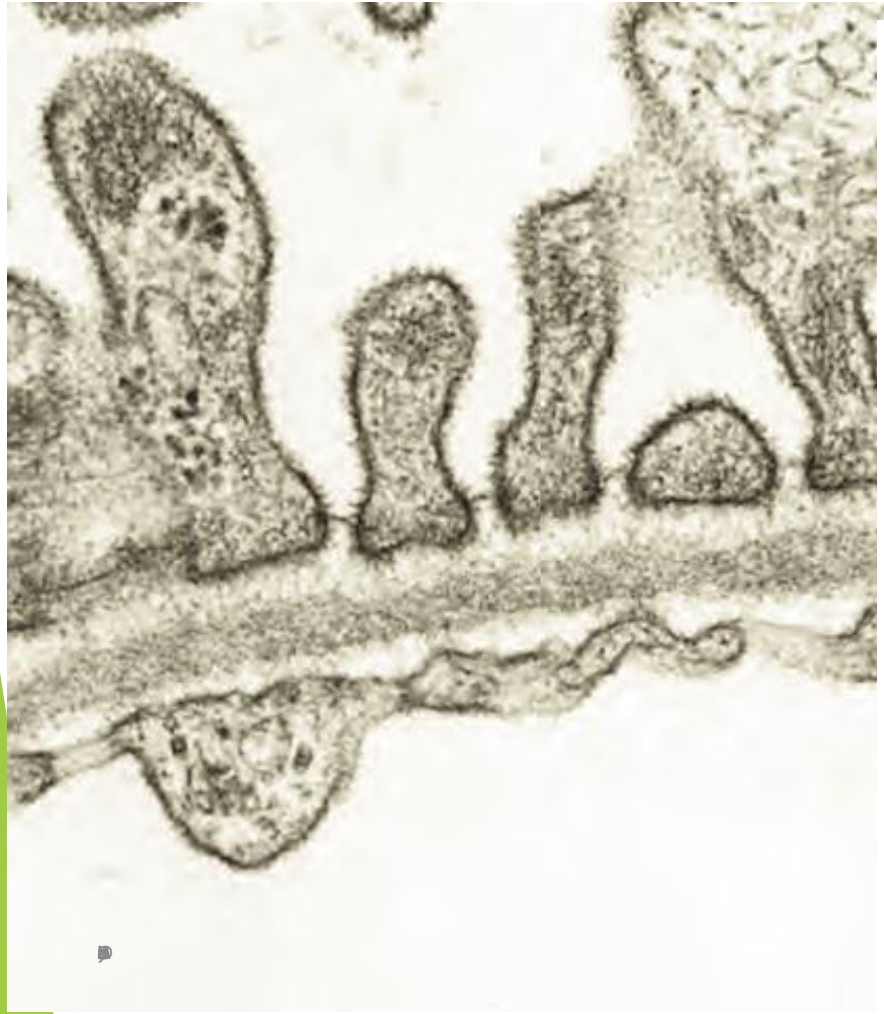
- **Mesangium**
  - Acellular mesangial matrix + mesangial cells which has similarities to smooth muscle cells in the center of glomerulus between capillaries.
  - Mechanical support, modulation of glomerular filtration, generation of active mediators.
  - Important players in many forms of human Glomerulonephritis (GN)

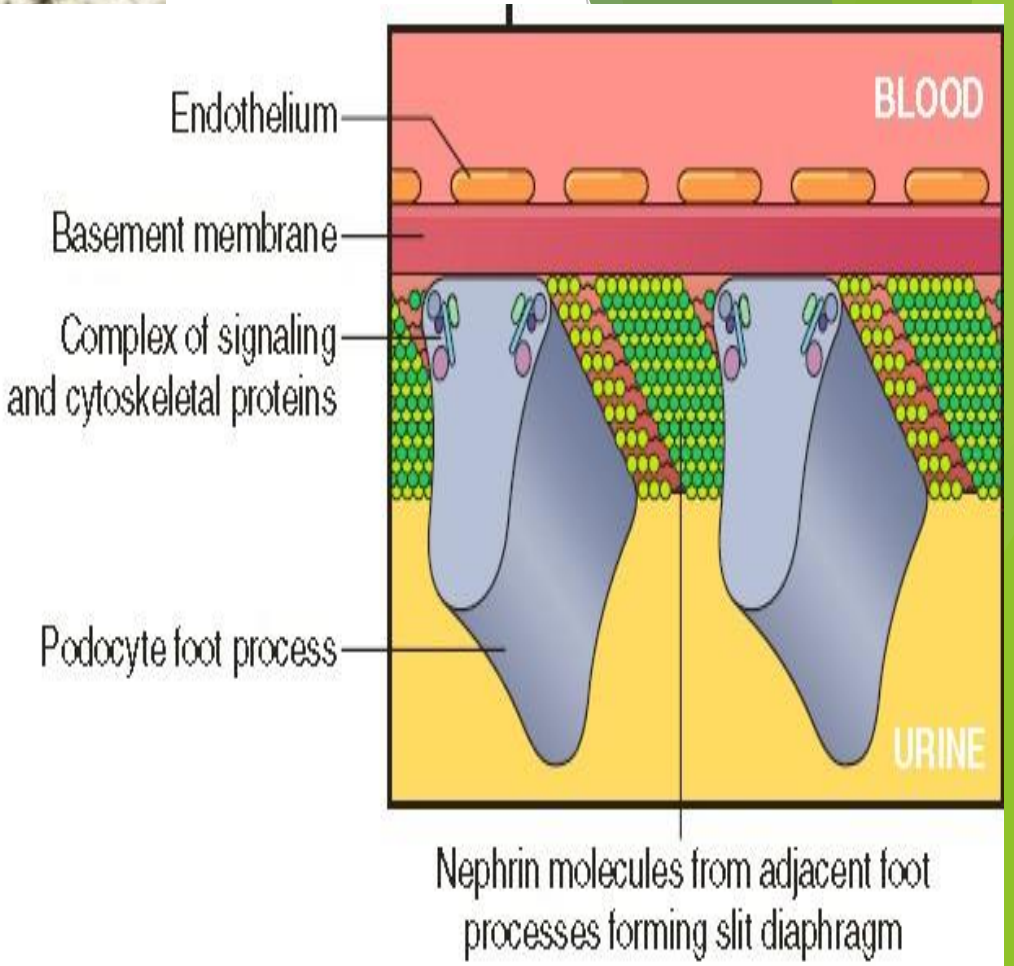

Proximal convoluted tubule
(brush border)
Capillary lumen
Urinary space
Bowman's capsule
Podocyte
Fenestrae in
endothelium
Mesangial matrix
Mesangial cells
Endothelial cell
Patietal epithelium
Foot processes
Glomerular basement
membrane
Efferent ateriole
Afferent arteriole
Macula densa
Extraglomerular mesangium
Distal tubule




CL
MES
EP
END
CL
MES
A


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
Foot processes
Basement membrane
Endothelium
Red blood cell
Foot processes
B




Endothelium
Basement membrane
Complex of signaling and cytoskeletal proteins
Podocyte foot process
BLOOD
URINE
Nephrin molecules from adjacent foot processes forming slit diaphragm

Glomerulonephritis (GN)

- A heterogeneous group of renal diseases in which the glomeruli are primarily affected. Lesion is bilateral and symmetrical.
- Acute and chronic types
- Primary and secondary types

Mechanisms of Glomerular Injury & Diseases

TABLE 14.1 Glomerular Diseases

Primary Glomerular Diseases
Minimal-change disease
Focal segmental glomerulosclerosis
Membranous nephropathy
Acute postinfectious glomerulonephritis
Membranoproliferative glomerulonephritis
IgA nephropathy
Dense deposit disease
C3 glomerulonephritis
Glomerulopathies Secondary to Systemic Diseases
Lupus nephritis (systemic lupus erythematosus)
Diabetic nephropathy
Amyloidosis
Glomerulopathy secondary to multiple myeloma
Goodpasture syndrome
Microscopic polyangiitis
Granulomatosis with polyangiitis
Henoch-Schönlein purpura
Bacterial endocarditis–related glomerulonephritis
Thrombotic microangiopathy
Hereditary Disorders
Alport syndrome
Fabry disease
Podocyte/slit-diaphragm protein mutations

IgA, Immunoglobulin A.

PATHOGENESIS OF GLOMERULAR INJURY

- **1- MAJORITY ARE IMMUNOLOGICAL**
  - Antibody mediated:

(1)Deposition of circulating antigen-antibody complexes in the glomerular capillary wall or mesangium

(2) Antibodies reacting in situ within the glomerulus, either with fixed (intrinsic) glomerular antigens or with extrinsic molecules that are planted in the glomerulus

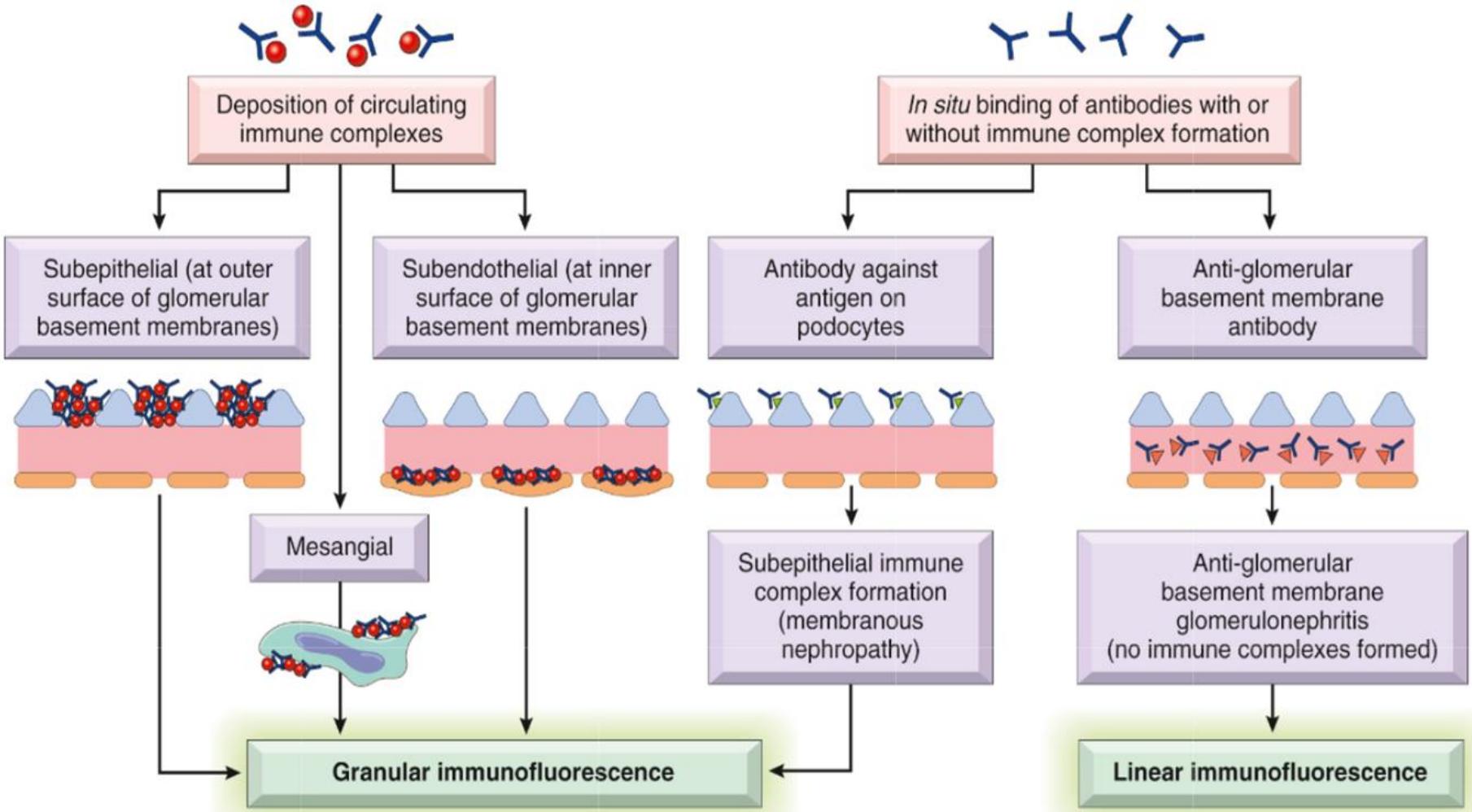
Deposition of circulating immune complexes in the glomerulus initiates complement (and/or Fc receptor) mediated leukocyte activation, resulting in glomerular injury.

PATHOGENESIS OF GLOMERULAR INJURY

- Other less frequent:
- Cell mediated
- Activation of alternative pathway of complement:

--Two forms of GN (dense deposit disease and C3 GN)

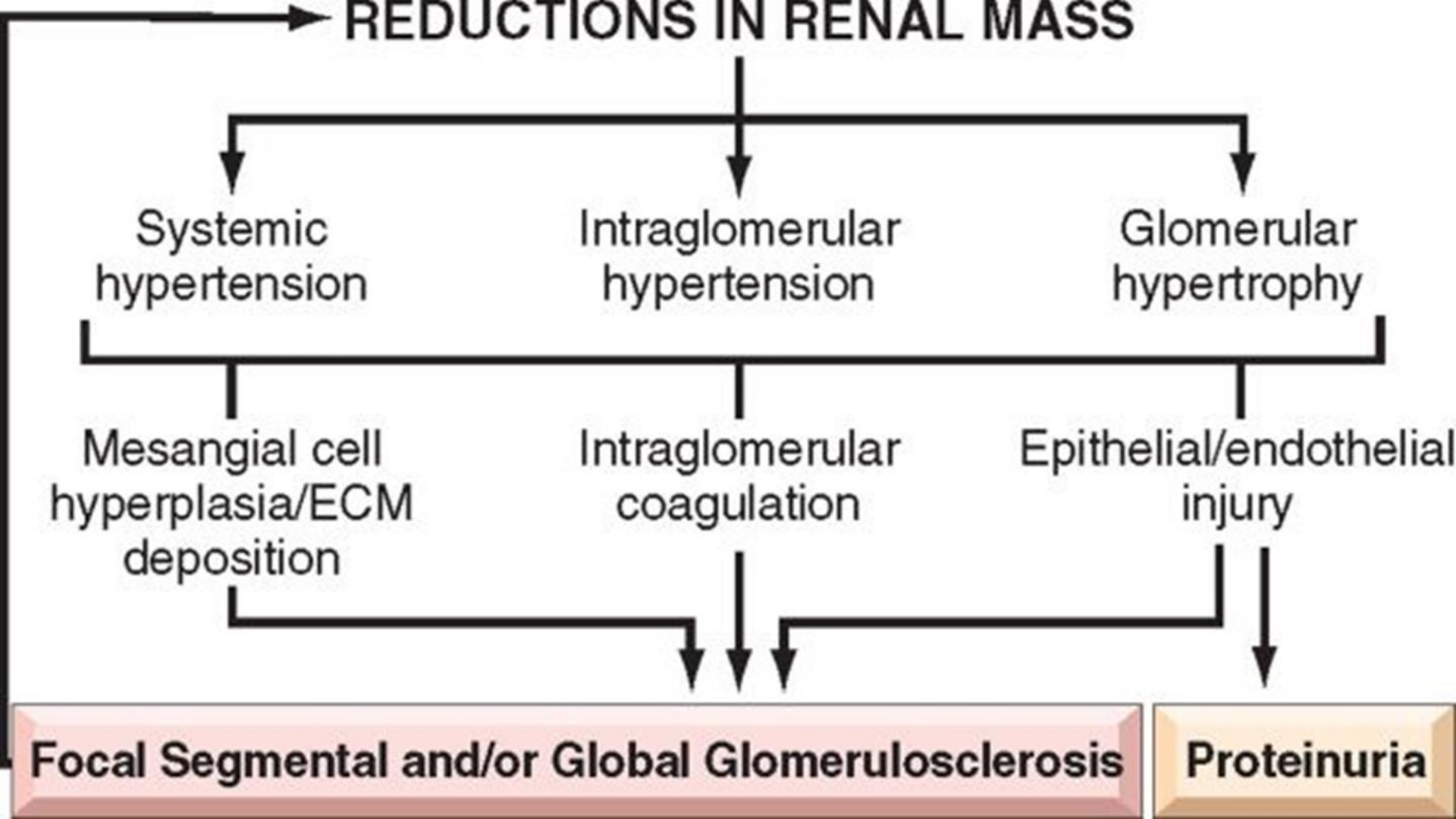
--One form of a systemic disease with significant renal manifestations (complement-mediated thrombotic microangiopathy [TMA] or atypical hemolytic uremic syndrome)


Deposition of circulating immune complexes
In situ binding of antibodies with or without immune complex formation
Subepithelial (at outer surface of glomerular basement membranes)
Subendothelial (at inner surface of glomerular basement membranes)
Antibody against antigen on podocytes
Anti-glomerular basement membrane antibody
Mesangial
Subepithelial immune complex formation (membranous nephropathy)
Anti-glomerular basement membrane glomerulonephritis (no immune complexes formed)
Granular immunofluorescence
Linear immunofluorescence

PATHOGENESIS OF GLOMERULAR INJURY

- 2- **Non- immune mechanism**
  - Podocyte injury: induced by antibodies to podocyte antigens; by toxins; certain cytokines; or poorly characterized circulating factors
  - Injury produces morphologic changes including effacement of foot processes, vacuolization, and retraction and detachment of cells from the GBM, and often results in the development of proteinuria

- **Nephron loss**
- As an adaptive changes intact glomeruli undergo hypertrophy to maintain renal function associated with hemodynamic changes, including increases in single-nephron GFR, blood flow, and transcapillary pressure (capillary hypertension).
- Maladaptive response will lead to further endothelial and podocyte injury, increased glomerular permeability to proteins, and accumulation of proteins and lipids in the mesangial matrix.
- followed by capillary obliteration, increased deposition of mesangial matrix and plasma proteins, and finally segmental or global sclerosis of glomeruli.
- Results in further reduction of nephron mass, initiating a vicious cycle of progressive glomerulosclerosis.


REDUCTIONS IN RENAL MASS
Systemic hypertension
Intraglomerular hypertension
Glomerular hypertrophy
Mesangial cell hyperplasia/ECM deposition
Intraglomerular coagulation
Epithelial/endothelial injury
Focal Segmental and/or Global Glomerulosclerosis
Proteinuria

Reaction of glomeruli to injury

- **Cellular proliferation**
  - endothelial cells, mesangial cells & epithelial cells
- **presence of inflammatory cells**
  - mononuclear cells & polymorphs
- **Formation of crescents**
  - parietal epithelial cells proliferation & monocytes infiltration in Bowman's space
- **Thickening of capillary wall**
  - thickening of GBM
  - presence of immune complexes
  - interposition of mesangial cells
- Others
  - sclerosis, necrosis & thrombi

Classification of Glomerulonephritis

- Primary GN
  - ACUTE DIFFUSE PROLIFERATIVE GN
    - POSTSTREPTOCOCCAL
    - NON-POSTSTREPTOCOCCAL
  - CRESCENTIC (RAPIDLY PROGRESSIVE) GN
  - MEMBRANOUS GN
  - MINIMAL CHANGE DISEASE
  - FOCAL SEGMENTAL GLOMERULOSCLEROSIS
  - MEMBRANOPROLIFERATIVE GN
  - IgA NEPHROPATHY
  - CHRONIC GN

Classification of GN (cont)

Glomerulopathies Secondary to Systemic Diseases

- Lupus nephritis (systemic lupus erythematosus)
- Diabetic nephropathy
- Amyloidosis
- GN secondary to lymphoplasmacytic disorders
- Goodpasture syndrome
- Microscopic polyangiitis
- Wegener's granulomatosis
- Henoch-Schönlein purpura
- Bacterial endocarditis-related GN
- GN secondary to extrarenal infection
- Thrombotic microangiopathy

Classification of GN (cont)

Hereditary Disorders

- Alport syndrome
- Fabry disease
- Podocyte/slit-diaphragm protein mutations

The two most common clinical syndromes associated with glomerular diseases

- 1- **Nephrotic syndrome**
- **Massive Proteinuria**, daily protein loss in the urine of = > 3.5 g
- **Hypoalbuminemia**, with plasma
- **albumin < 3 g/dL**
- **Generalized edema**, the most obvious clinical manifestation
- **Hyperlipidemia and lipiduria**

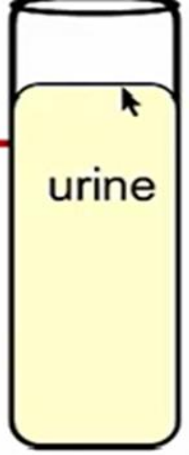
- 2- **Nephritic syndrome**
- **Hematuria (red cells & red cell casts in urine)**
- **Proteinuria** (subnephrotic range) with or without edema
- **Azotemia**
- **Hypertension**

Nephrotic Syndrome

- Insidious onset
- Manifestations
  - Proteinuria >3.5 gm / 24 hr
  - Hypoalbuminemia
  - Edema
  - Hyperlipidemia
  - Lipiduria

AGN: Nephrotic Sy: (non inflammatory)

Massive albuminuria, hypo-albuminemia, hyperlipidemia.



Primary glomerular diseases

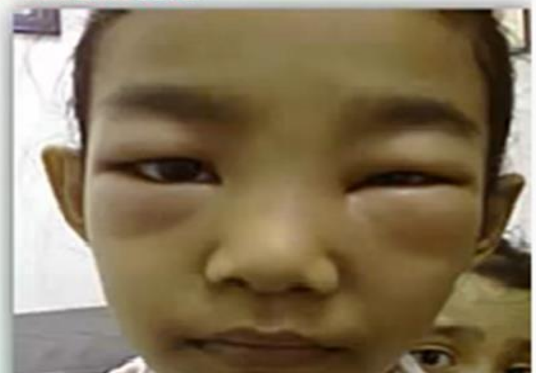
1. Minimal Change Disease (MCD)
2. Focal Segmental Glomerulo Sclerosis (FSGS)
3. Membranous GN (MGN)
   - Membrano-proliferative GN (MPGN subtype 1 & 2)

Inherited disease

Congenital nephrotic sy. (Alport's)

Secondary glomerular disease

- SLE (membranous)
- Henoch-Schönlein purpura
- Malignancy, tumours, infections HIV, drugs (gold, penicillamine, phenytoin etc)
- SBE, Diabetes mellitus
- Amyloidosis
- bee sting.



Nephrotic Syndrome

- In children , it is almost always ass/w a primary kidney lesion.
- Among adult, in contrast , it is often associated with systemic disease
- The most frequent systemic causes of nephrotic syndrome are; diabetes, amyloidosis, and SLE (systemic lupus erythematosus)
- The most important primary kidney diseases that mostly manifest as Nephrotic Syndrome:

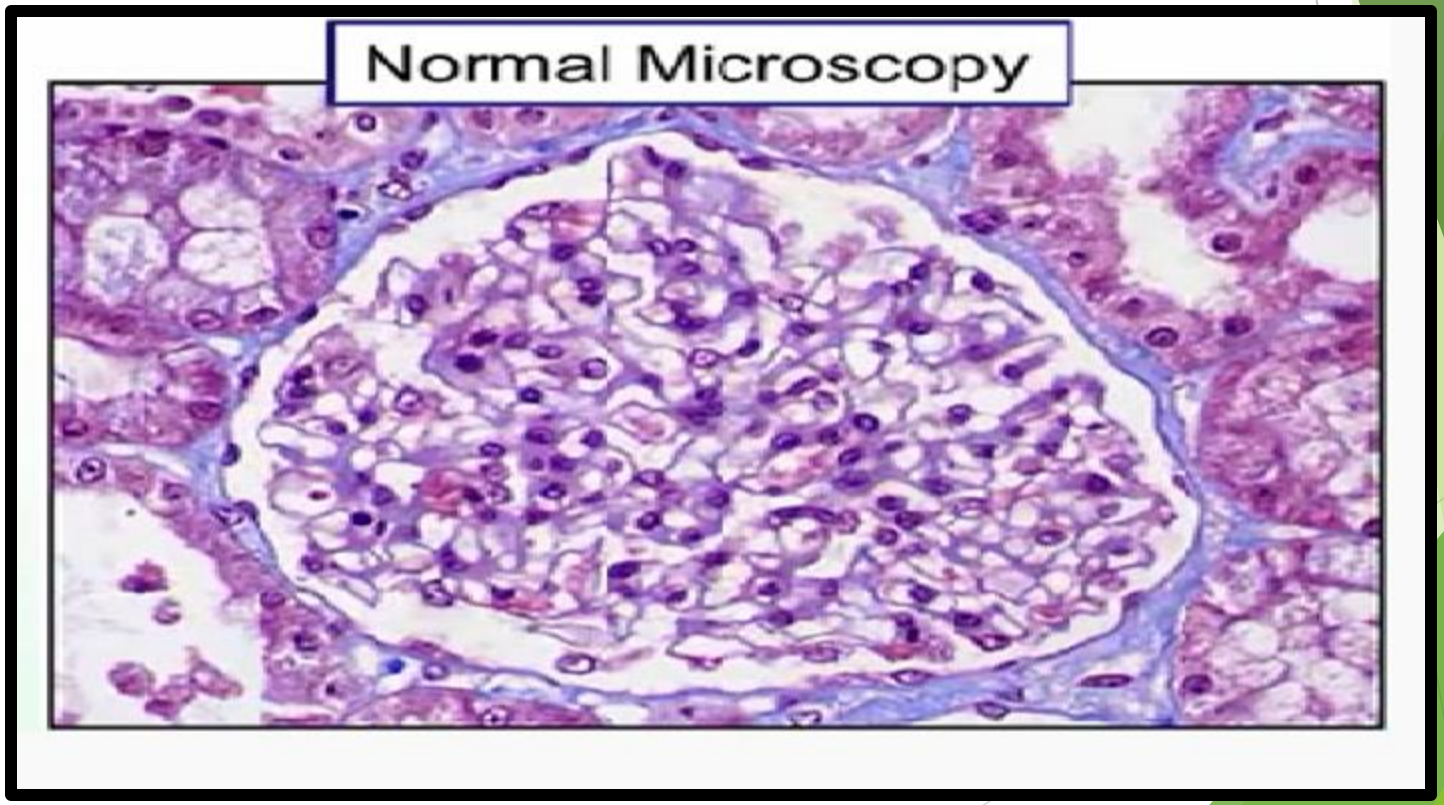
1. Minimal-Change Disease, most common in children
2. Focal Segmental Glomerulosclerosis, highest prevalence in adults
3. Membranous Nephropathy, most common in older adults

Minimal change disease (MCD)

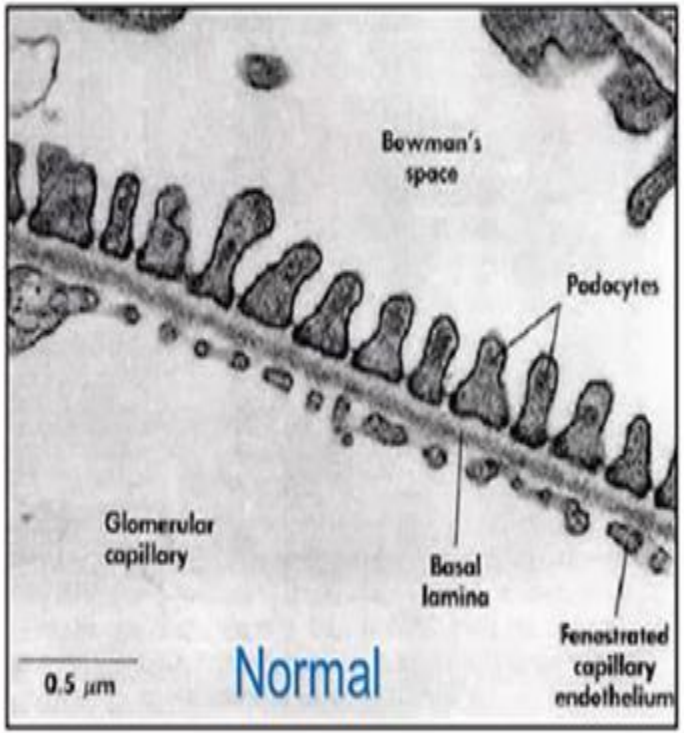
- (Lipoid nephrosis , nil change disease , normal by L mic.)
- A disorder in which NS is associated with fusion of the podocytes (foot processes) of epithelial cells with almost normal glomerulus by light microscopy .
- LM IF EM

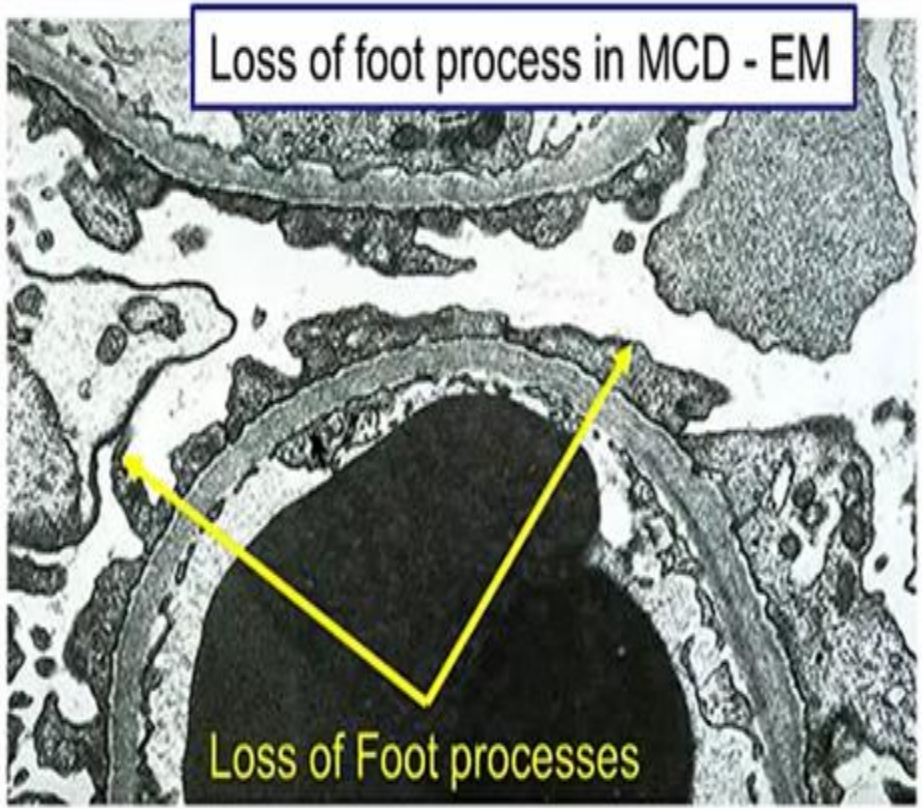
  normal normal fusion of podocyte
- Etiology & Pathogenesis
  - ? Dysfunction of T-cells

Minimal Change Disease



Minimal Change Disease





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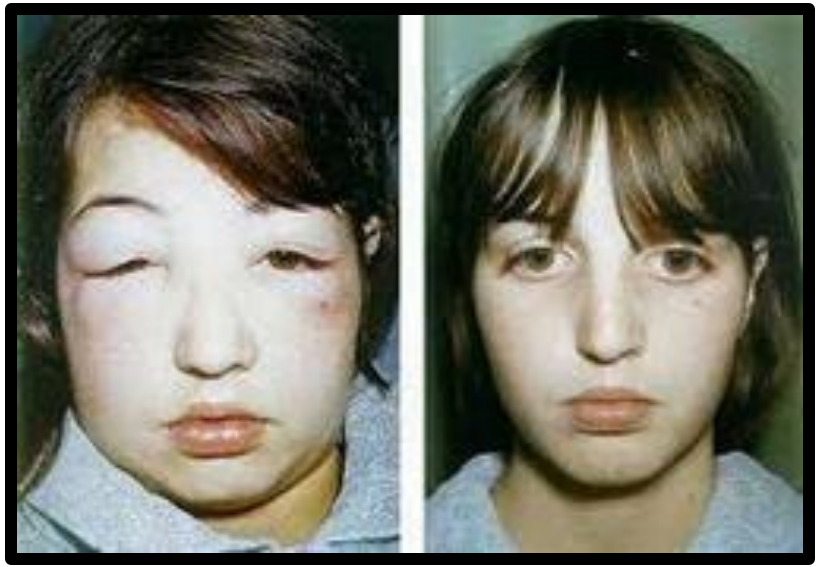
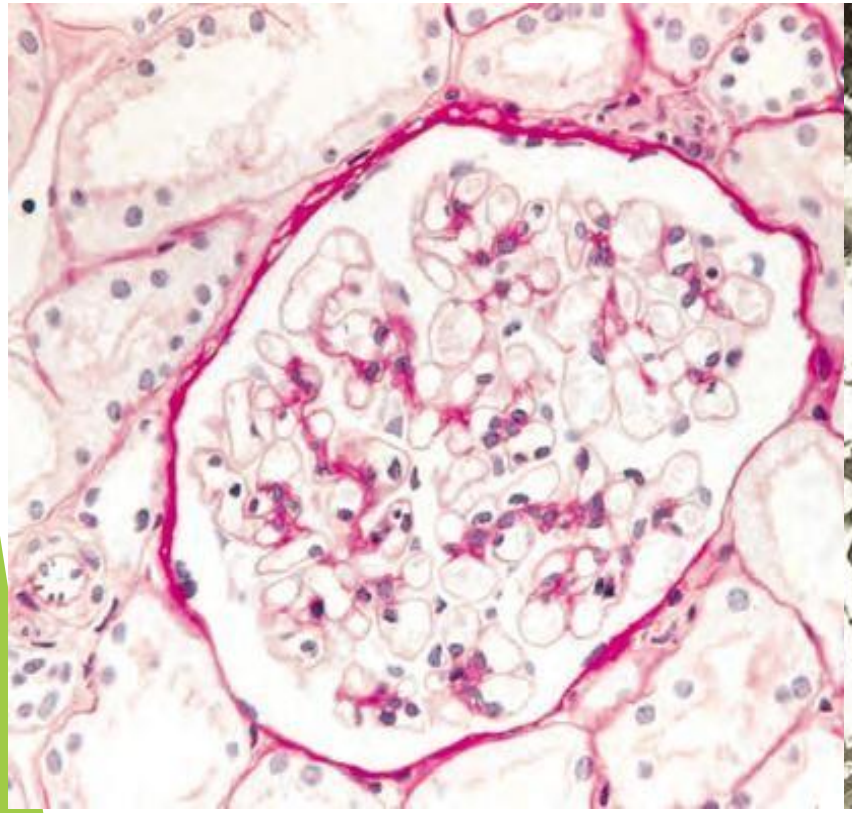
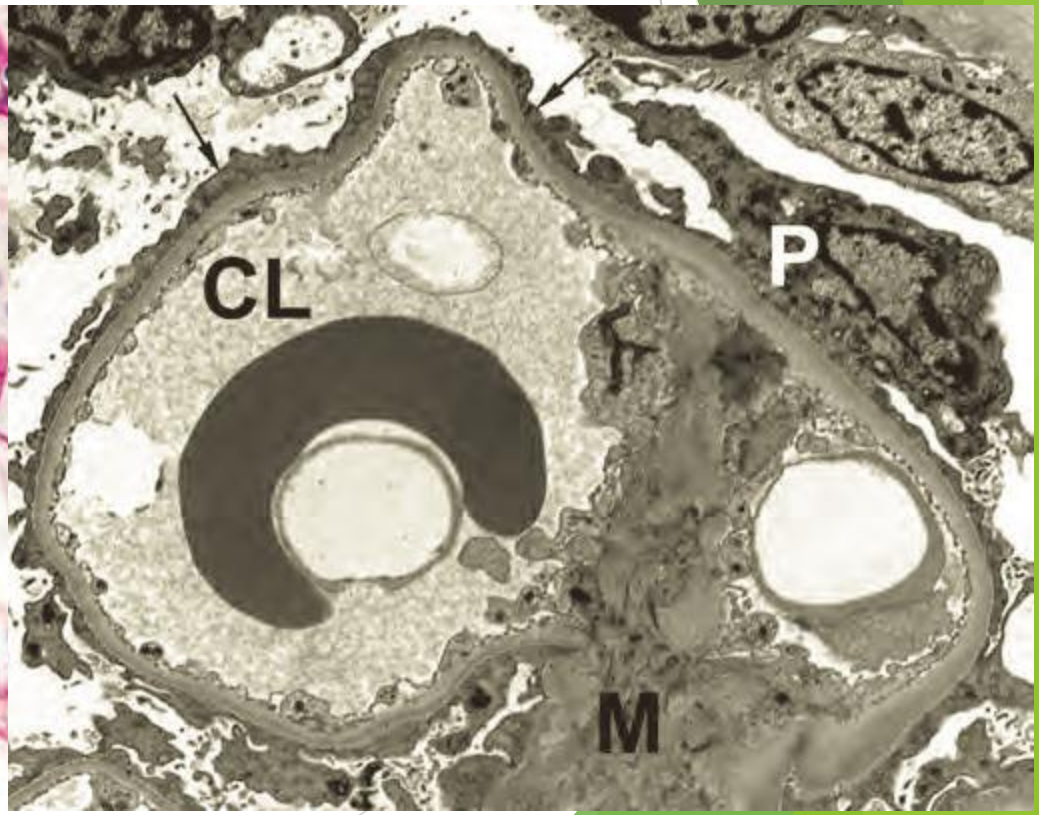


Minimal change disease (MCD)





MCD (cont)

- Clinical picture
  - most common cause of NS in children 65%, adults (10%)
  - 2 - 6 years
  - may follow URTI or immunization
  - selective proteinuria
  - respond to steroids
  - renal function normal
- Prognosis
  - excellent in both children & adults.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

- Sclerosis of some, but not all glomeruli and only part of the glomerulus is involved.

- Can occur in:

  (1) Association with known conditions: HIV, Heroin addiction, sickle cell disease and Obesity.

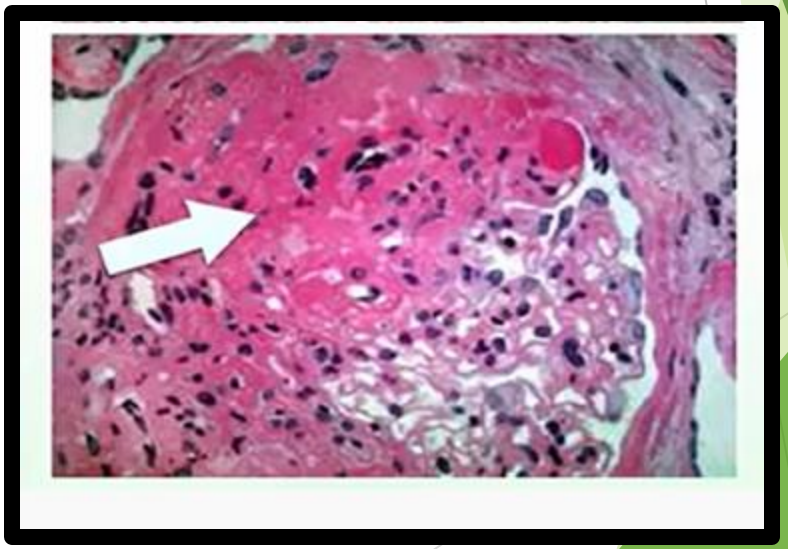
  (2)Glomerular scarring in other forms of GN. e.g IgA nephropathy

  (3) as a maladaptation after nephron loss.

FSGS (cont.)

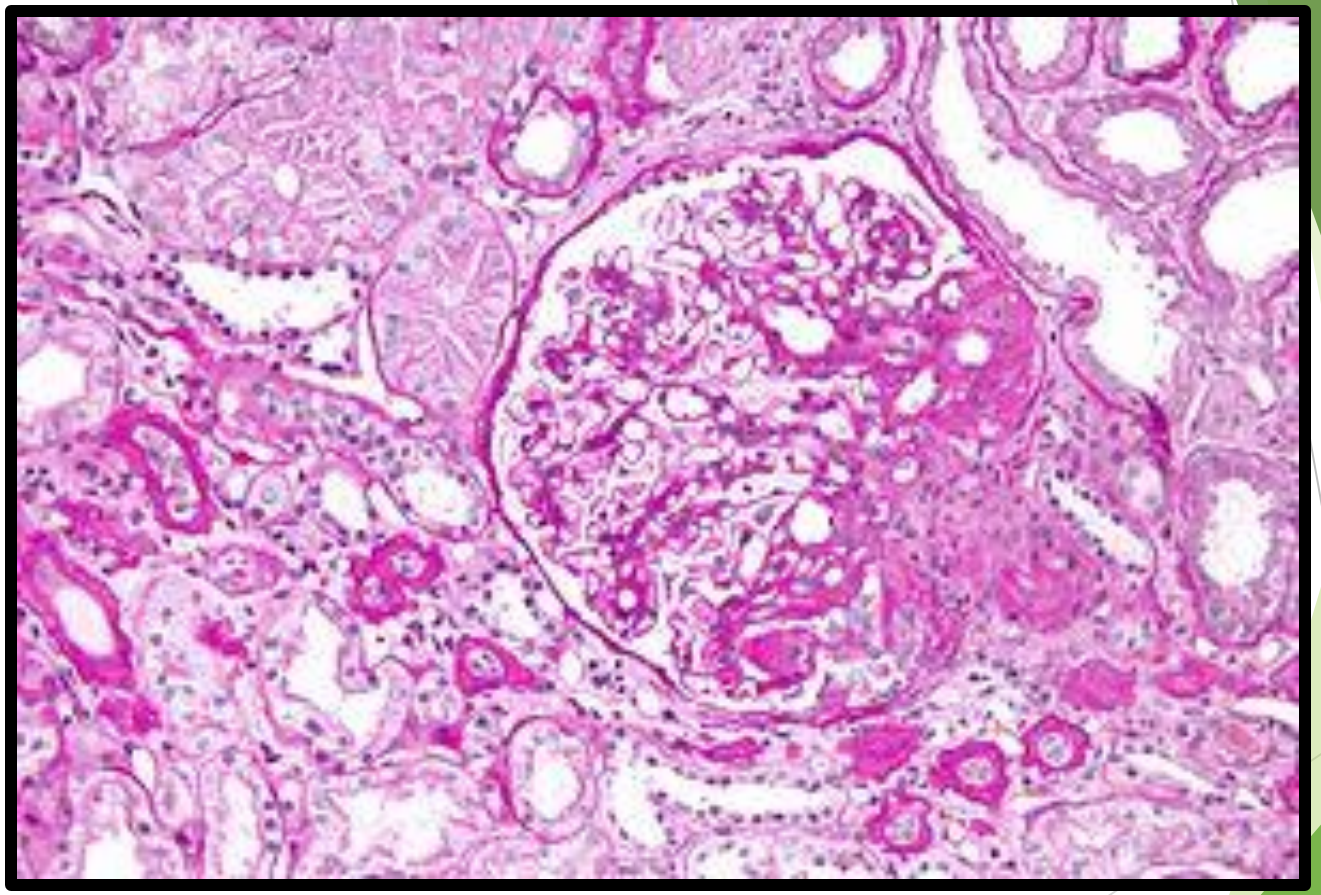
- (4) in inherited or congenital forms resulting from mutations affecting cytoskeletal or related proteins expressed in podocytes (e.g., nephrin); APOL1 gene on CH.22 appears to be strongly associated with an increased risk of FSGS and renal failure in individuals of African descent.

- (5) as a primary disease.



FSGS (cont.)

- **Light microscopy**
  - SCLEROTIC SEGMENTS SHOW COLLAPSE OF B.M. INCREASED MESANGIAL MATRIX , DEPOSITION OF HYALINE MASSES (HYALINOSIS)
- **EM**
  - NON -SCLEROTIC SEGMENTS SHOW LOSS OF PODOCYTES & FOCAL DENUDATION OF EPITHELIAL CELLS
- **IF**
  - IgM & C3 IN SCLEROTIC SEGMENTS



FSGS(cont.)

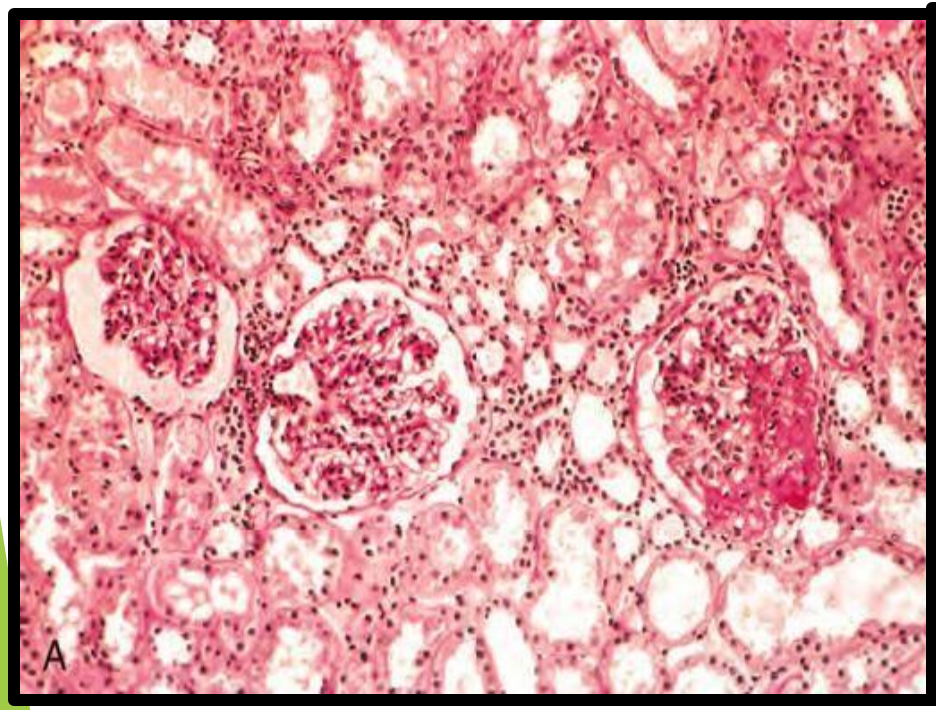
- CLINICAL PRESENTATION
  - NEPHROTIC SYNDROME
    - 10% CHILDREN
    - 35% ADULTS
  - PROTEINURIA
  - A higher incidence of hematuria, reduced GFR, and HT.
  - Nonselective proteinuria
  - poor response to steroids.
  - 50% will develop end-stage renal failure in 10 yrs
- DIFFERENTIAL DIAGNOSIS
  - MCD & MGN

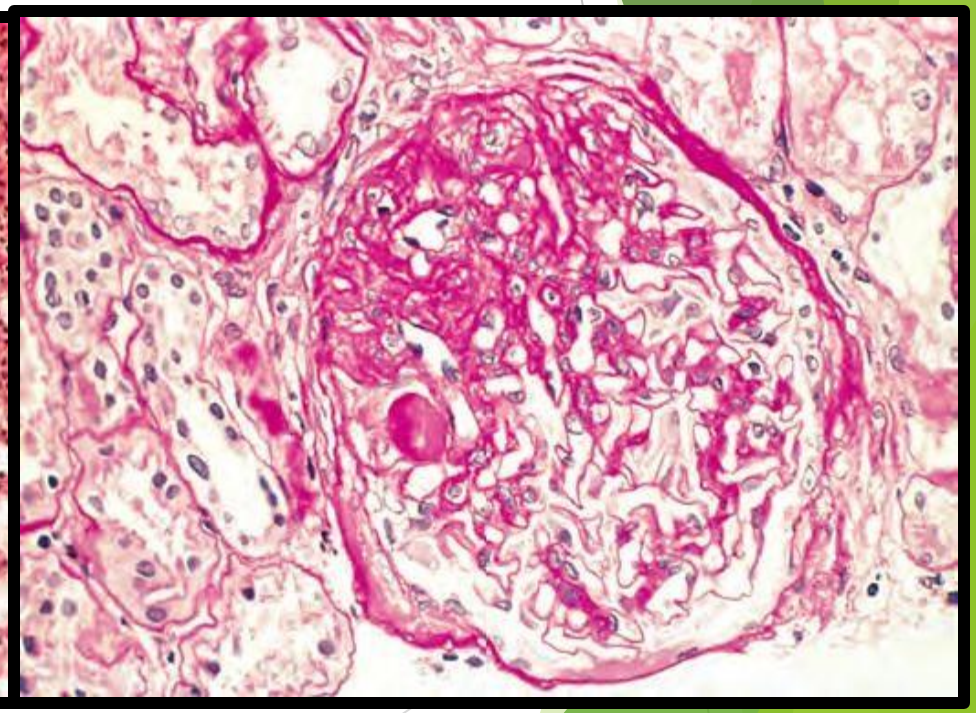
FSGS - Morphology

- **LM:** Sclerosis in some glomeruli not all of them; & in a segment not all of the affected glomerulus
- **IF:** In affected glomeruli, negative or nonspecific trapping of immunoglobulins,
- **EM:** Podocytes exhibit effacement of foot processes as in minimal-change disease.

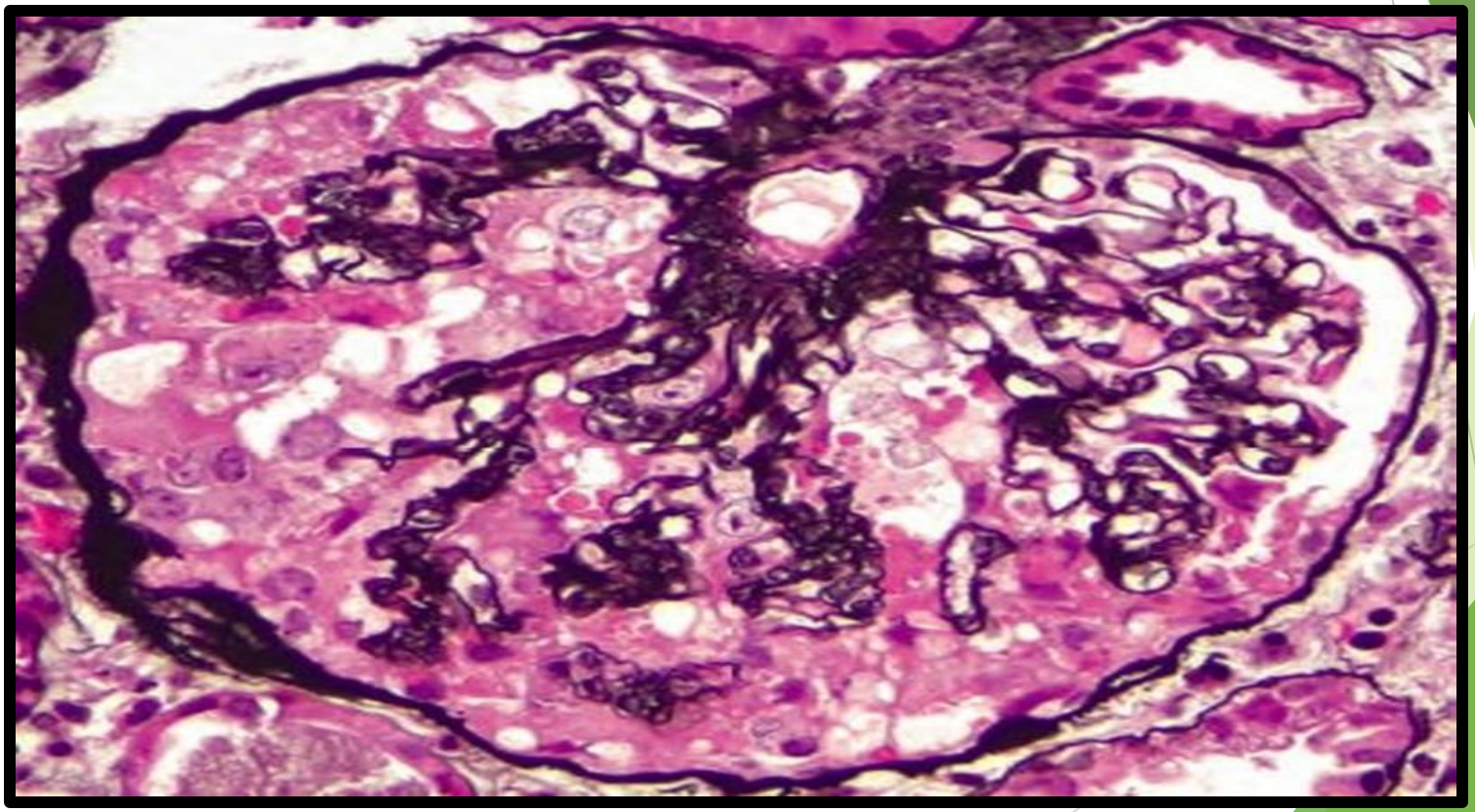
- **Collapsing glomerulopathy- FSGS** morphologic variant
  - Collapse glomerular tuft & epithelial cell hyperplasia.
  - severe form with worse prognosis
  - Can be: idiopathic, ass/with HIV infection, or drug-induced toxicities

FSGS - Morphology





FSGS - Morphology



The End

Good Luck