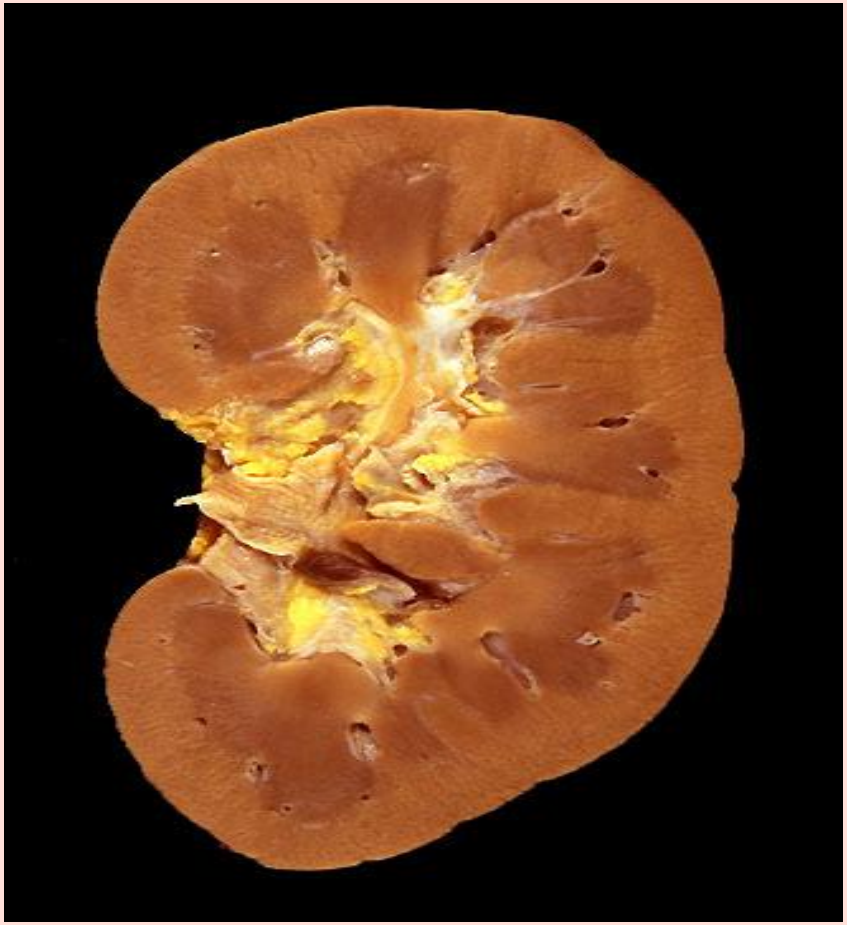
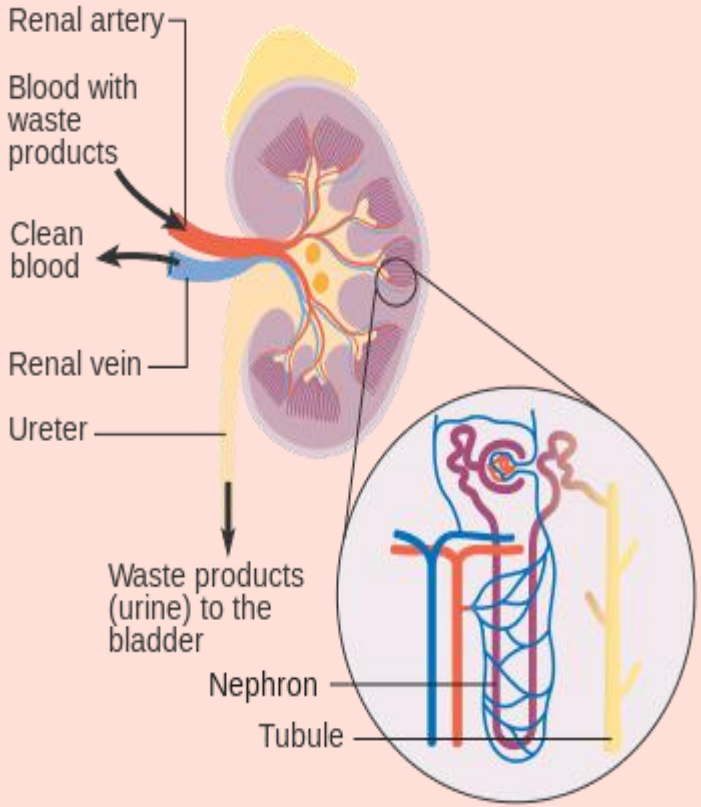
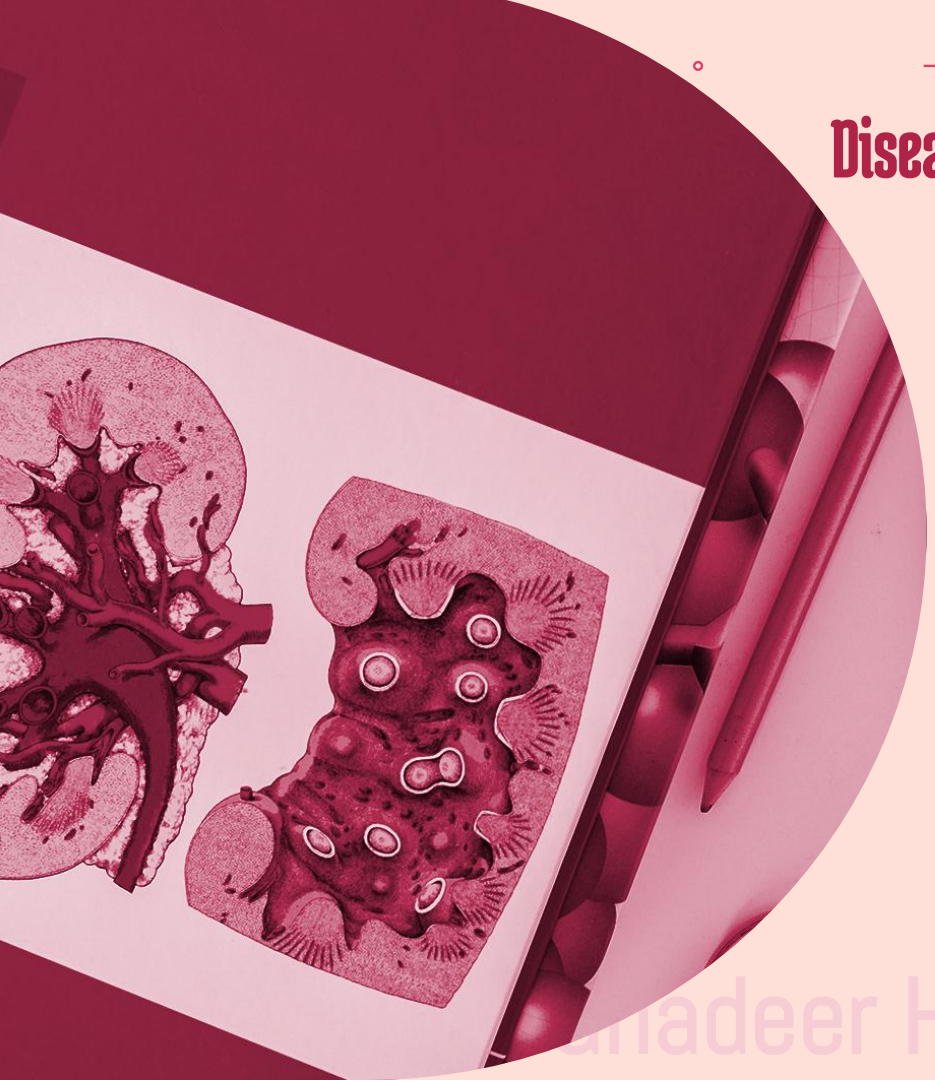
Renal Diseases I

Ghadeer Hayel, M.D.

April 21-22, 2021







Diseases of the kidney

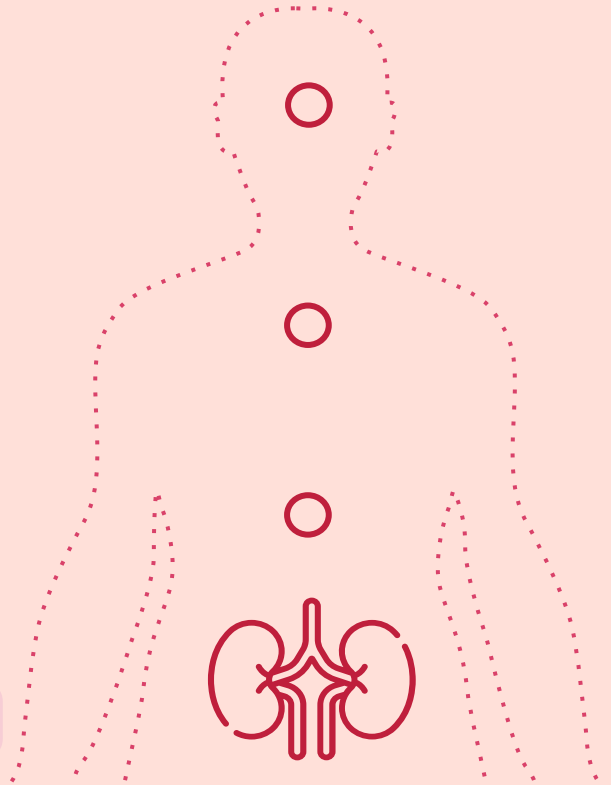
- Kidneys carry out many functions that require a high degree of structural complexity.
- Renal diseases are responsible for a great deal of morbidity & mortality
- Four basic morphologic components: glomeruli, tubules, interstitium, & blood vessels.

Jamadeer Hayel, MD

CLINICAL MANIFESTATIONS OF RENAL DISEASES

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

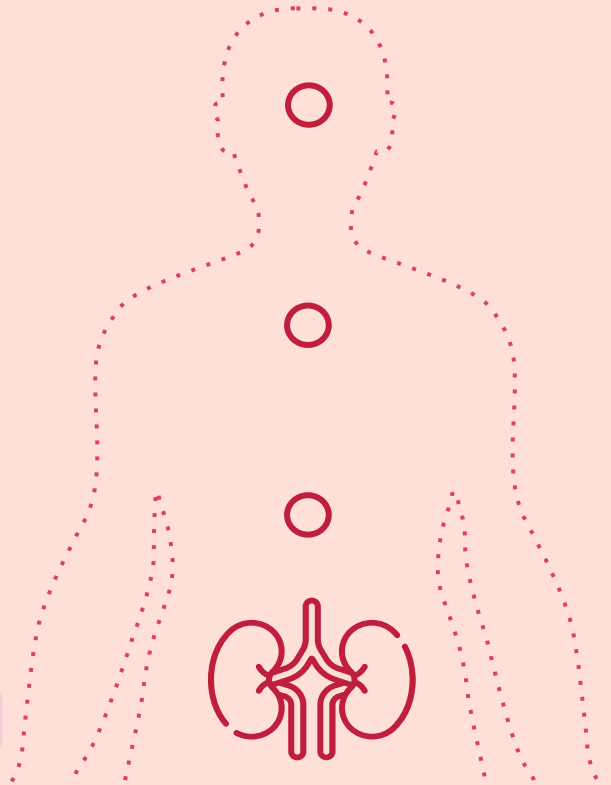
Uremia: When azotemia gives rise to clinical manifestations & systemic biochemical abnormalities.
Failure of renal excretory function + metabolic & endocrine alterations incident to renal damage.



CLINICAL MANIFESTATIONS 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.

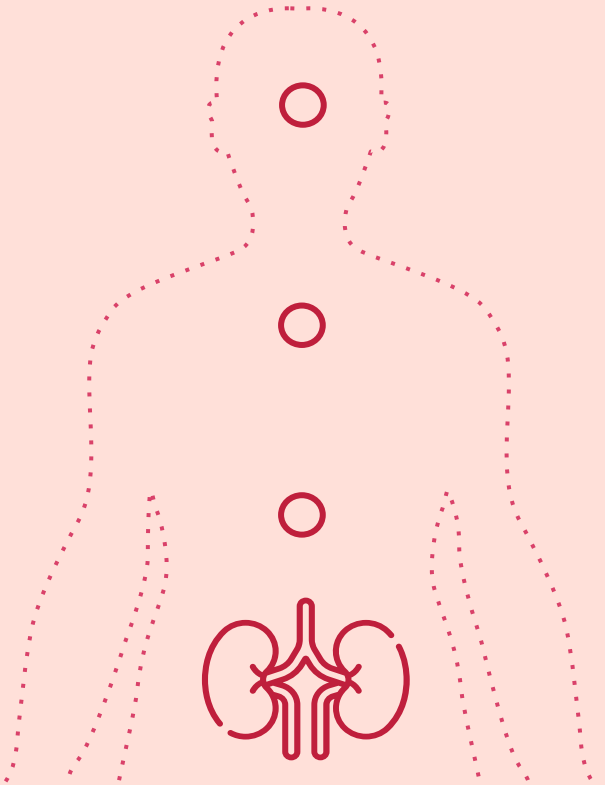


CLINICAL MANIFESTATIONS OF RENAL DISEASES

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



01

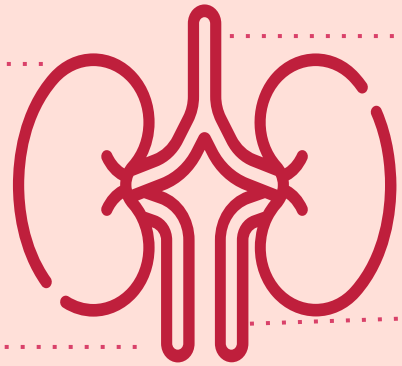
GLOMERULAR DISEASES

Ghadeer Hayel, MD

GLOMERULAR DISEASES

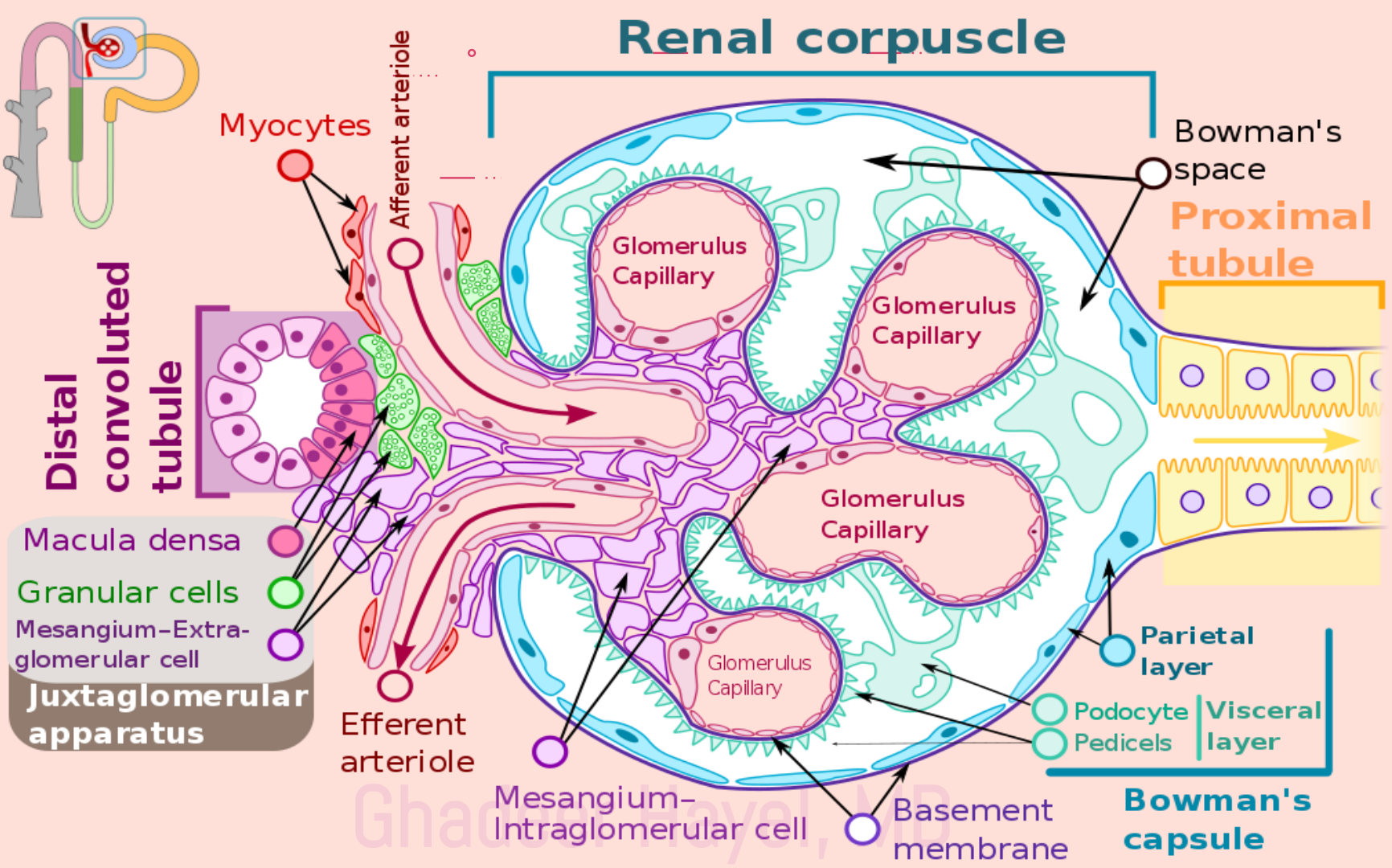
01 A major problems in nephrology; Chronic glomerulonephritis is one of the most common causes of chronic kidney disease

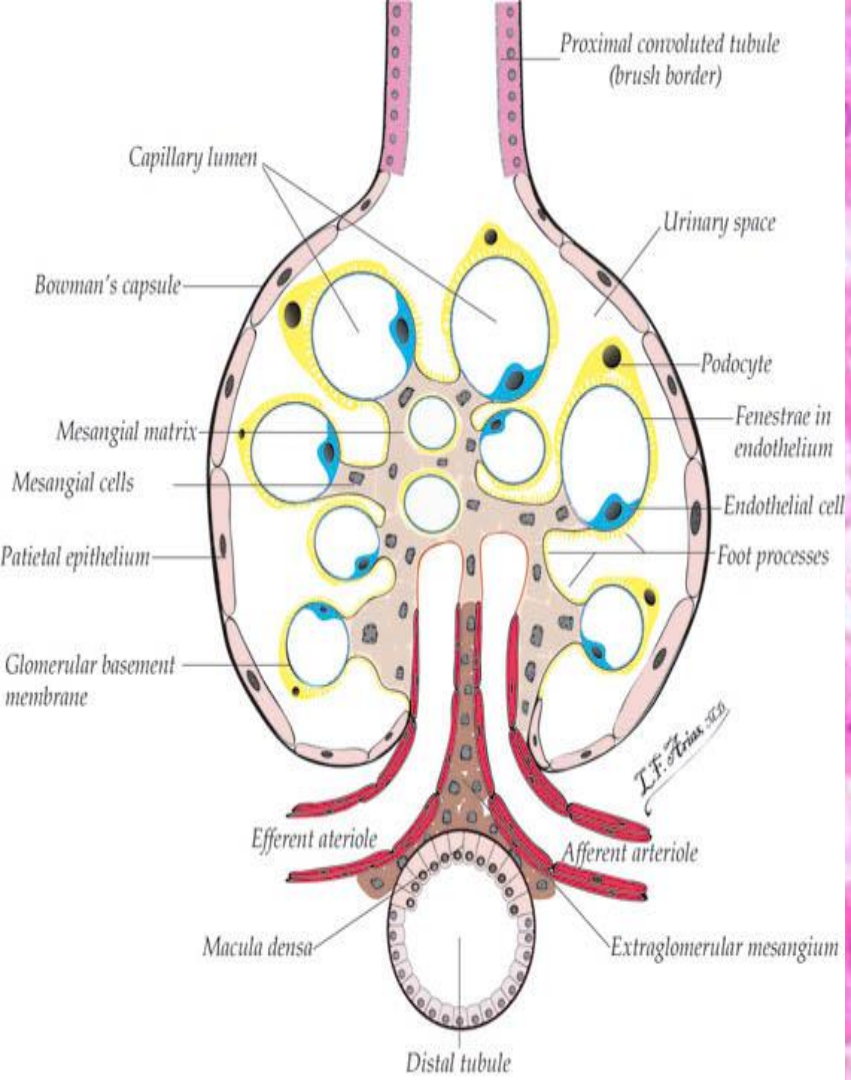
02 The glomerulus: anastomosing network of capillaries invested by two layers of epithelium: visceral & parietal epithelium

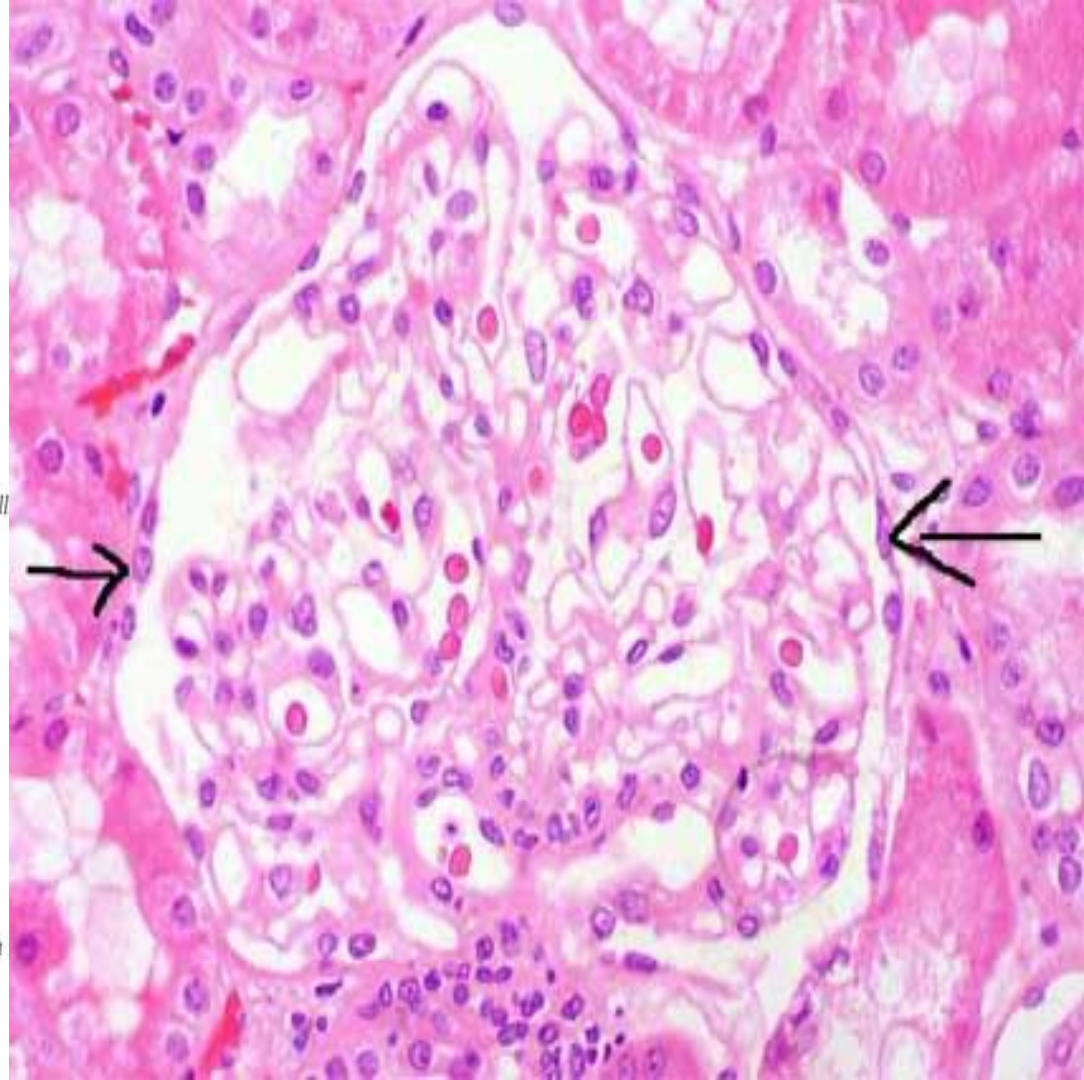


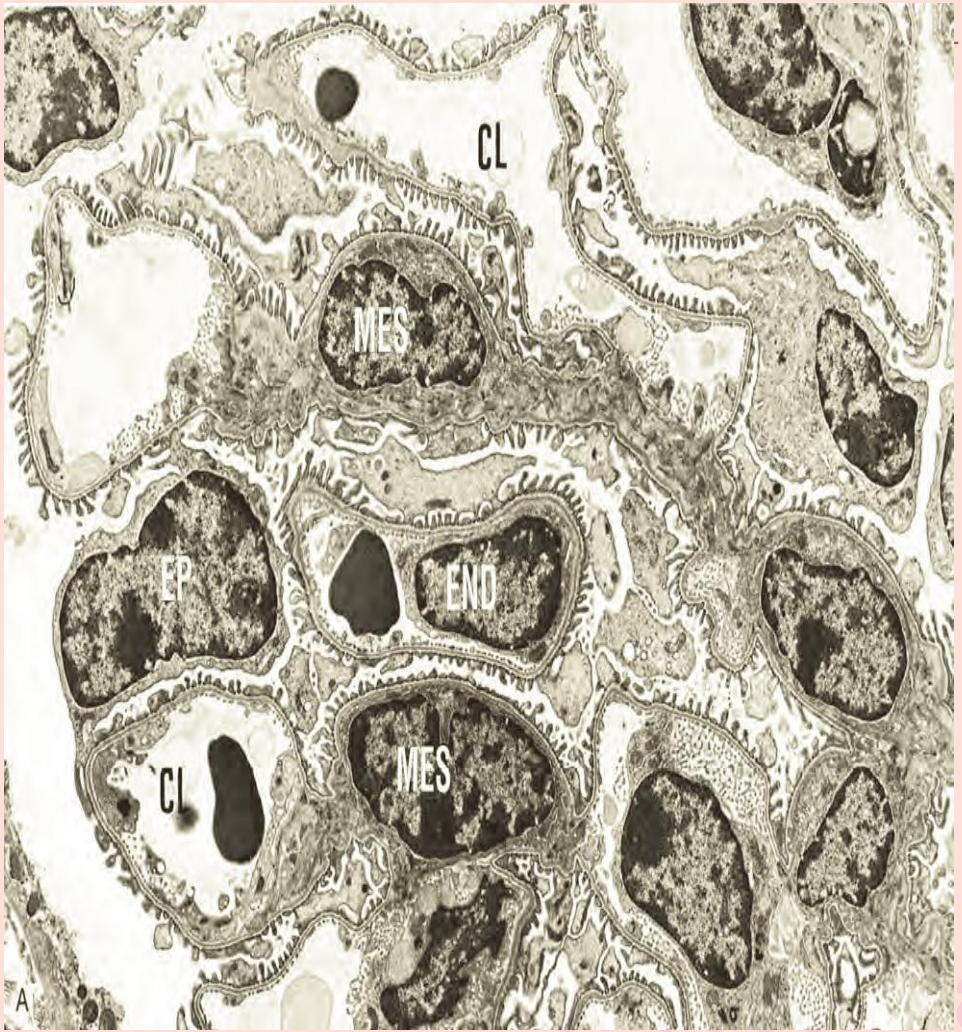
03 The visceral epithelium (composed of podocytes) part of the capillary wall

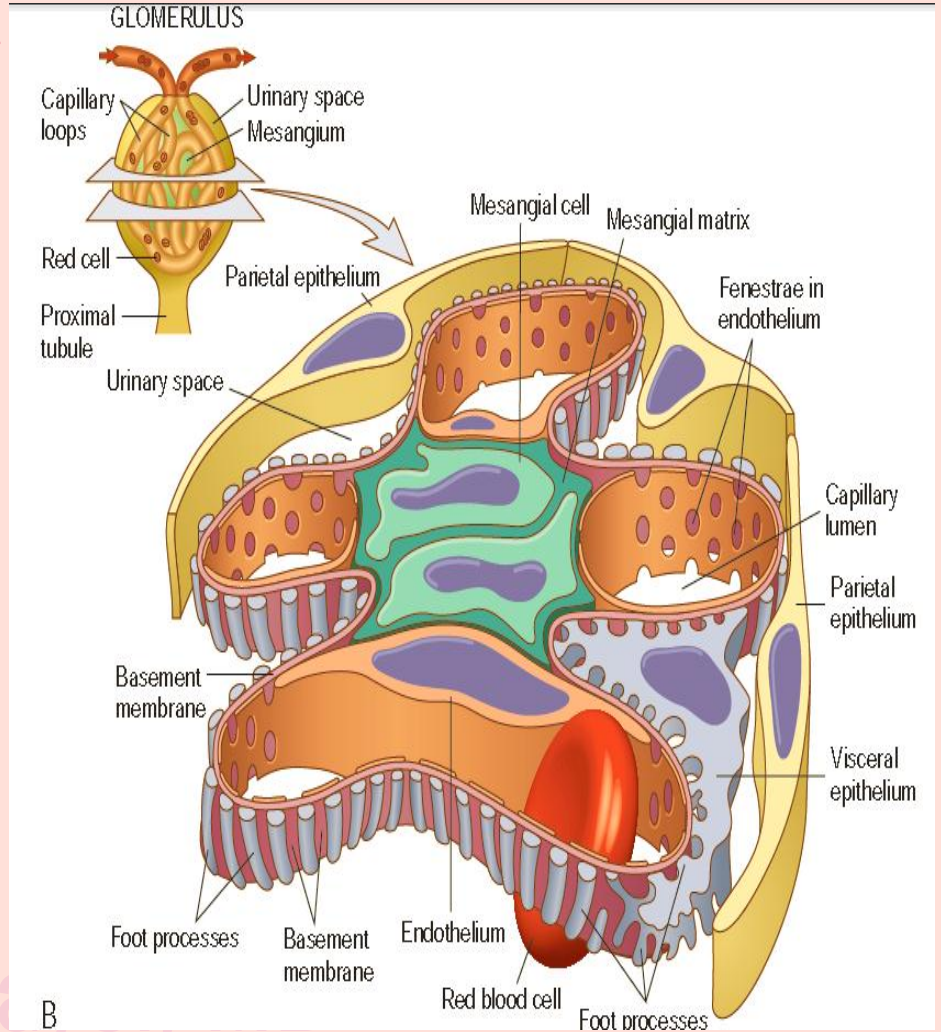
04 The parietal epithelium encircles Bowman space (urinary space), the cavity in which filtrate of plasma collects.

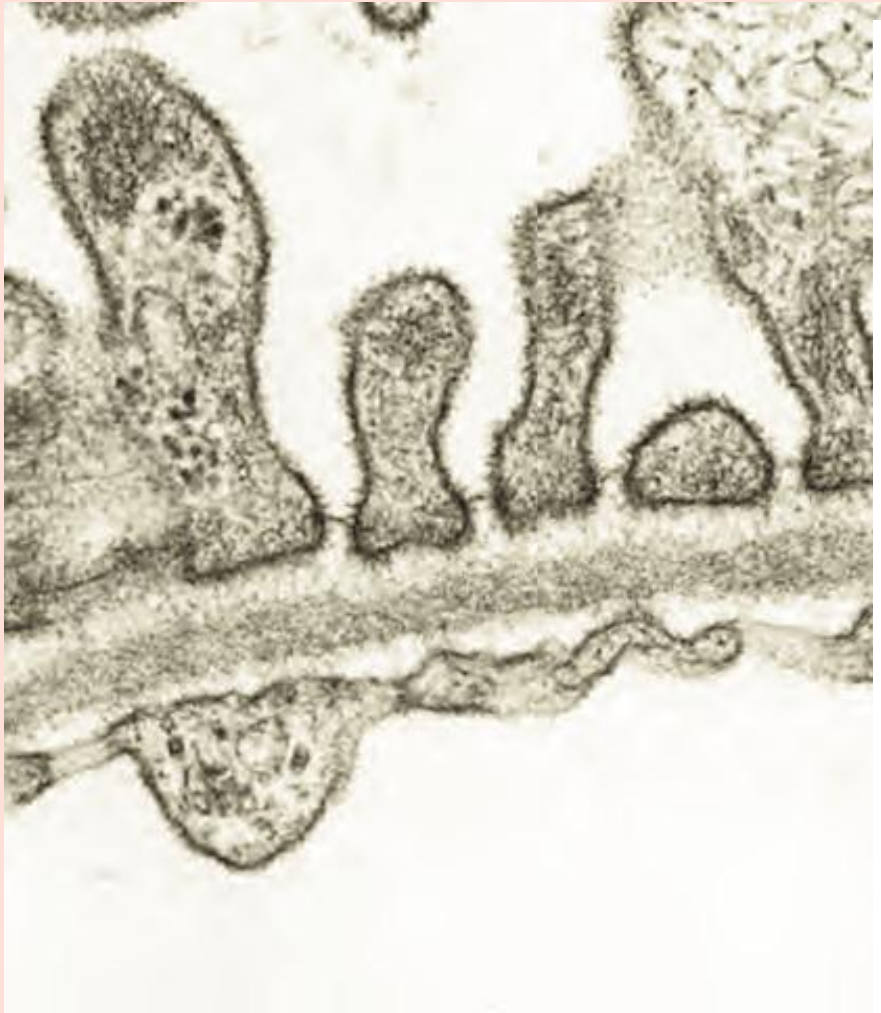


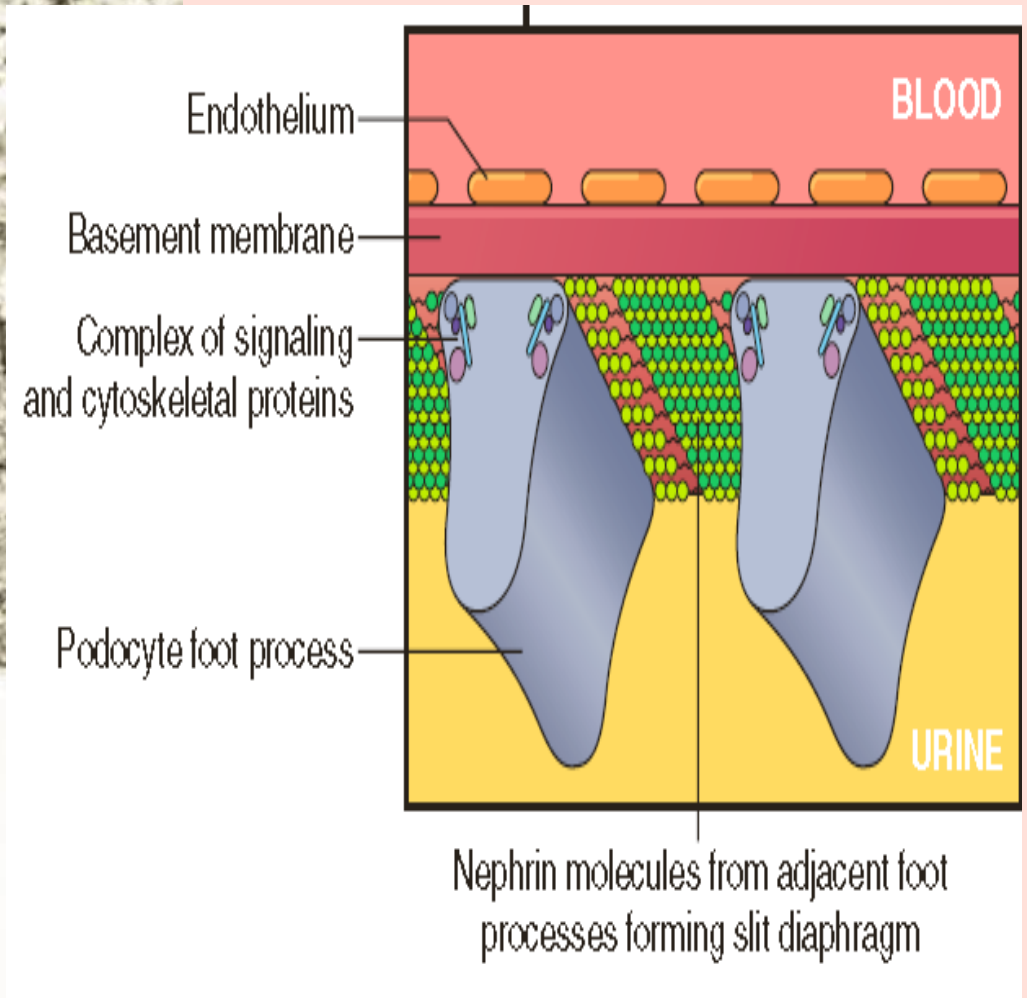

Proximal convoluted tubule
(brush border)
Capillary lumen
Urinary space
Bowman's capsule
Podocyte
Fenestrae in
endothelium
Mesangial matrix
Mesangial cells
Endothelial cell
Patietal epithelium
Foot processes
Glomerular basement
membrane
Efferent ateriole
Afferent arteriole
Macula densa
Extraglomerular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




CL
MES
EP
END
CL
MES
A


GLOMERULUS
Capillary loops
Urinary space
Mesangium
Red cell
Proximal tubule
Parietal epithelium
Mesangial cell
Mesangial matrix
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

Mechanisms of Glomerular Injury & Disease

01 Glomerular diseases

- Primary: kidney is the only or predominant organ involved
- Secondary: Injured in the course of a systemic diseases

02 Immune mechanisms

most types of primary diseases & many of the secondary

- Deposition of circulating antigen-antibody complexes in the glomerular capillary wall or mesangium,
- Antibodies reacting in situ within the glomerulus, either with fixed (intrinsic) glomerular antigens or with extrinsic molecules that are planted in the glomerulus

The two most common clinical syndromes associated with glomerular diseases:

01 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

Nephritic syndrome 02

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

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)

01

A relatively benign disorder. The most frequent cause of nephrotic syndrome in children.

02

Characterized by glomeruli that have a normal appearance by light microscopy (minimal).

03

Develop at any age, most common at 1-7 years of age.

04

Pathogenesis: Unknown ?, T-cell dysfunction → release factors that damage podocytes & efface foot processes.

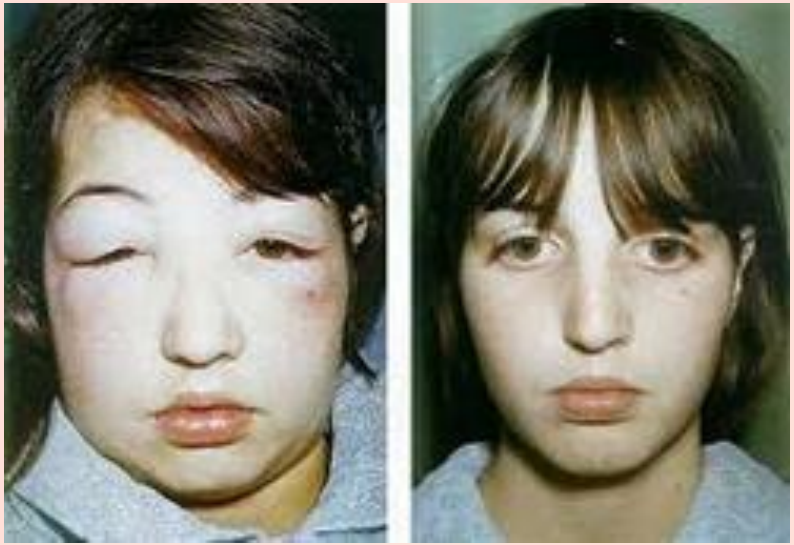
05

Normal glomeruli on light microscopy (LM) & negative IF

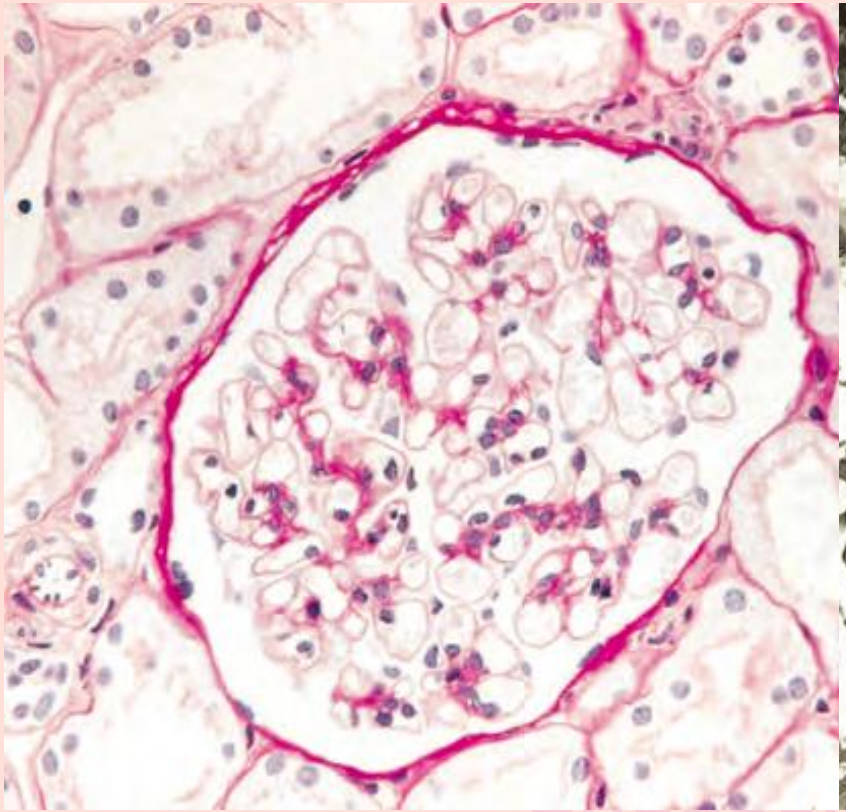
06

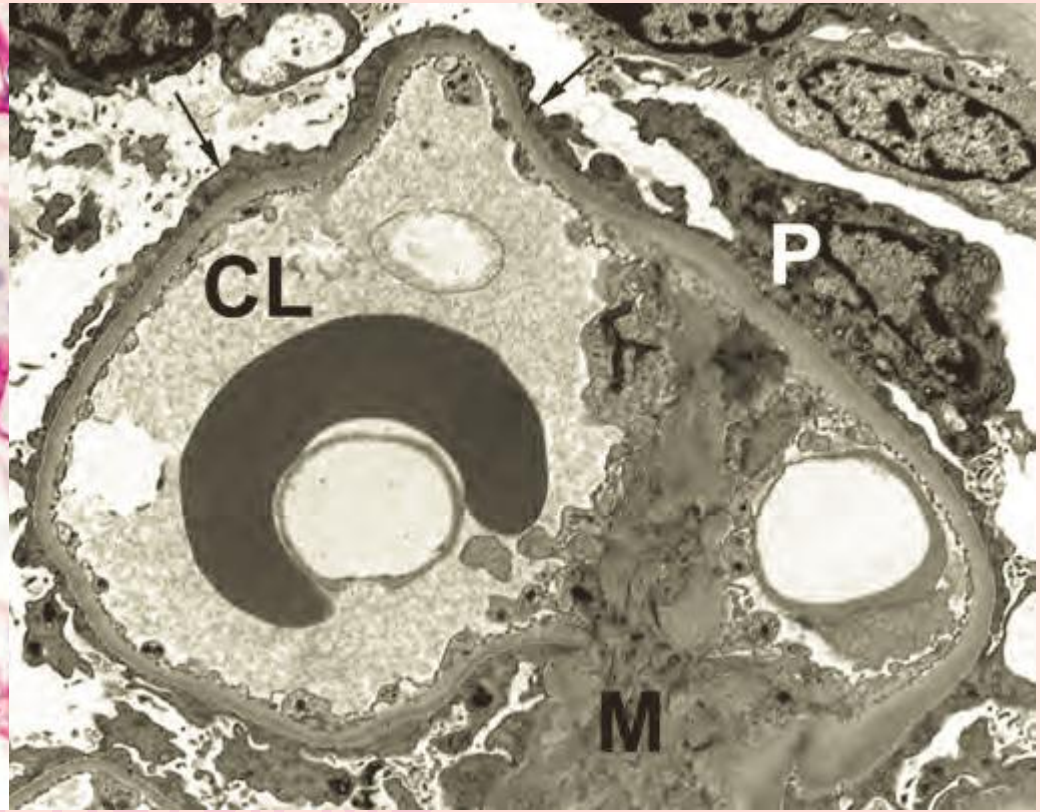
The only obvious glomerular abnormality is the diffuse effacement of the foot processes of the podocytes on EM.

Minimal-Change Disease (MCD)



Minimal change disease





Minimal change disease -Clinical

- Typically abrupt nephrotic syndrome in an otherwise healthy child.
- No hypertension, & renal function is often preserved.
- Protein loss chiefly albumin → selective proteinuria
- Prognosis for children is favorable; > 90% of children respond to a short course of corticosteroid therapy.
- Adults with also respond to steroid therapy, but slower & relapses are more common.
- Less than 5% develop chronic kidney disease after 25 years.

Focal segmental glomerulosclerosis (FSGS)

01

Characterized by sclerosis of some (but not all) glomeruli (focal) that involves only a part of each affected glomerulus (segmental).

02

May be primary (idiopathic) or secondary

03

Secondary causes: HIV infection (5-10% of HIV patients), Heroin abuse, other forms of GN (IgA nephropathy), nephron loss

04

Pathogenesis: not fully understood; Injury to podocytes is thought to represent the initiating event of primary FSGS

05

Hyaline deposition in glomeruli → caused by entrapment of plasma proteins & lipids in foci of injury → sclerosis.

06

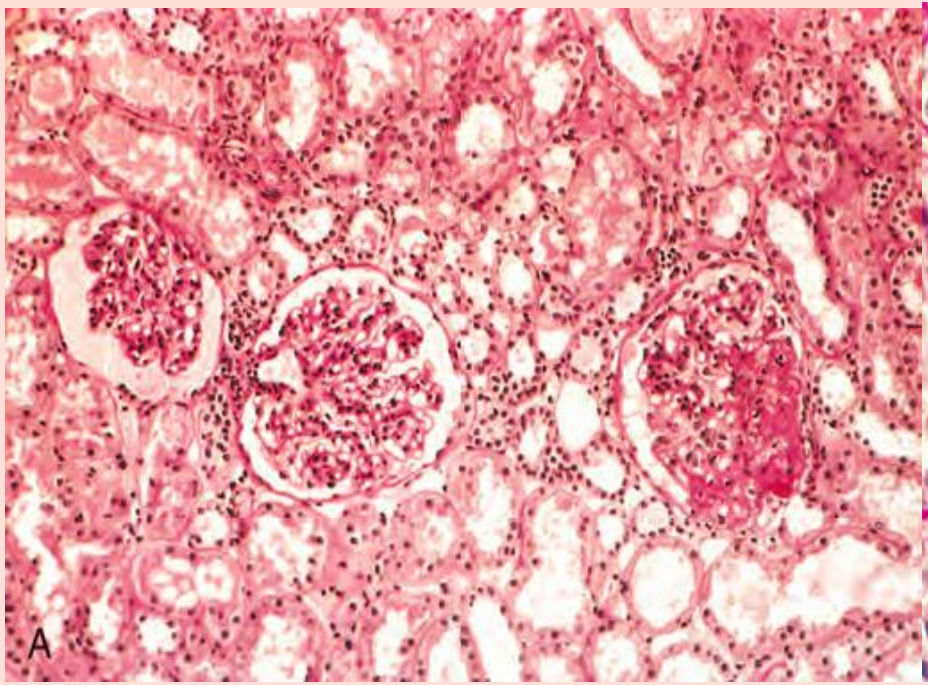
50% develop renal failure in 10 years . The response to corticosteroid therapy is poor.

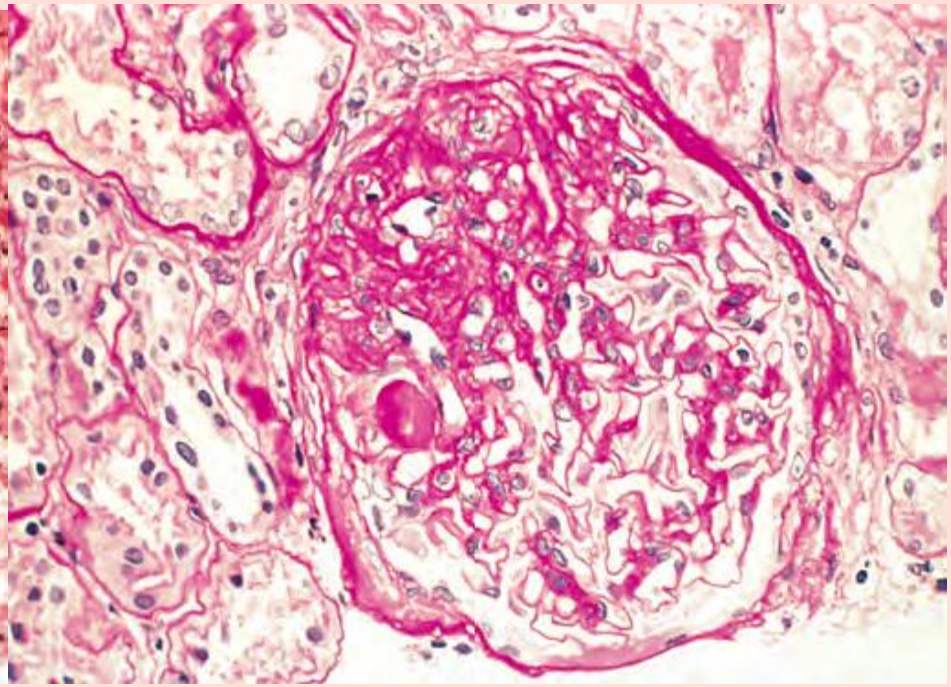
FSGS - Morphology

- 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.

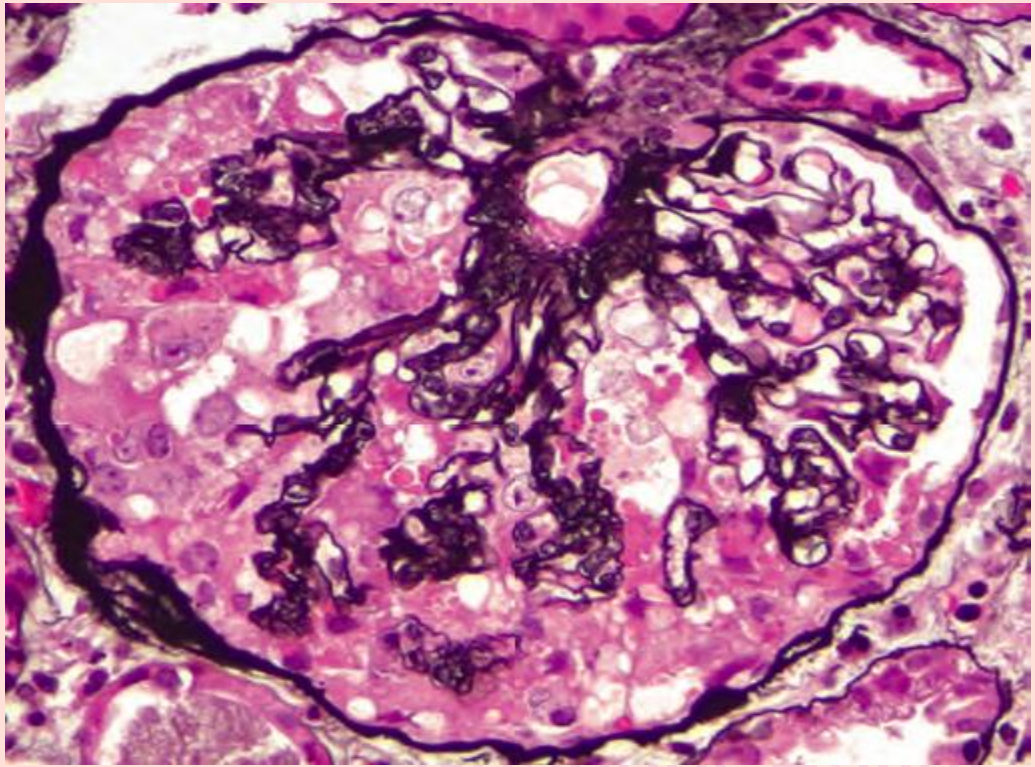
- Collapsing glomerulopathy- FSGS morphologic variant
  - Collapse glomerular tuft & epithelial cell hyperplasia.
  - severe form with worse prognosis
  - Can be: idiopathic, ass/with HIV infection, or drug-induced toxicities

FSGS - Morphology





FSGS - Morphology



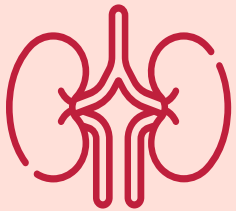
Collapsing glomerulopathy- FSGS morphologic variant

MCD vs FSGS

It is important to distinguish FSGS from minimal-change disease, because the clinical courses &responses to therapy are markedly different.

	MCD	FSGS
Hematuria.	Absent	Present
Hypertension	Absent	Present
Proteinuria	Selective	nonselective
Response to corticosteroid	Excellent	Poor

Membranous Nephropathy



01 Chronic immune complex mediated disease

- Antibodies reacting in situ to endogenous antigens
- Antibodies reacting in situ to planted glomerular antigens

02 75% of cases are Primary (called idiopathic)

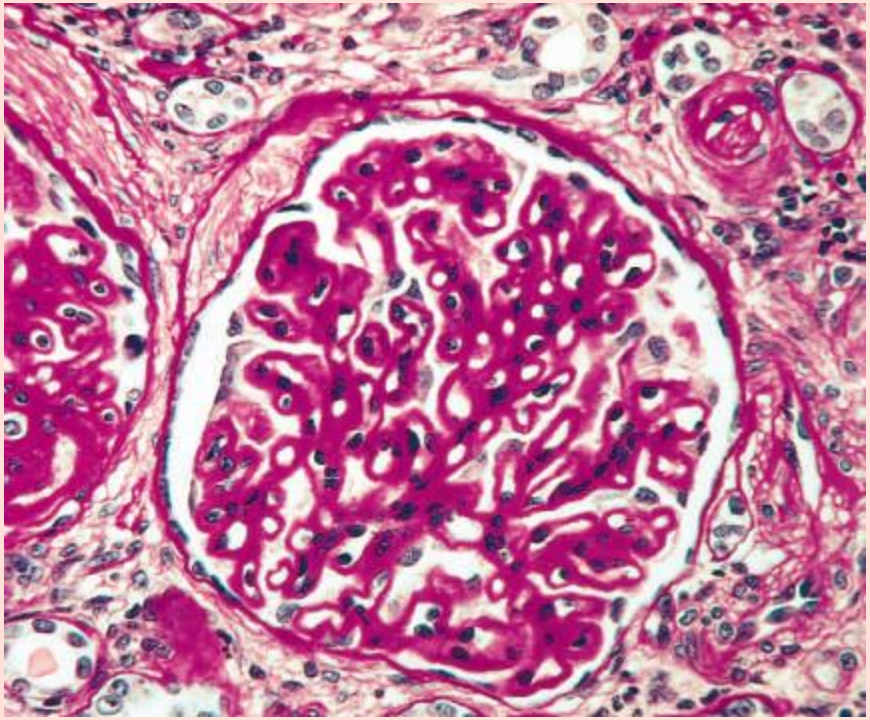
Antibodies against the podocyte antigen phospholipase A2 receptor (**PLA2R**)

03 Secondary

- **Infections**: chronic HBV, malaria , syphilis
- **Malignancies** ; Ca. of lung & colon, melanoma
- **Autoimmune diseases**, particularly SLE
- Exposure to **inorganic salts** (gold, mercury)
- **Drugs** (penicillamine, captopril, NSAIDs).

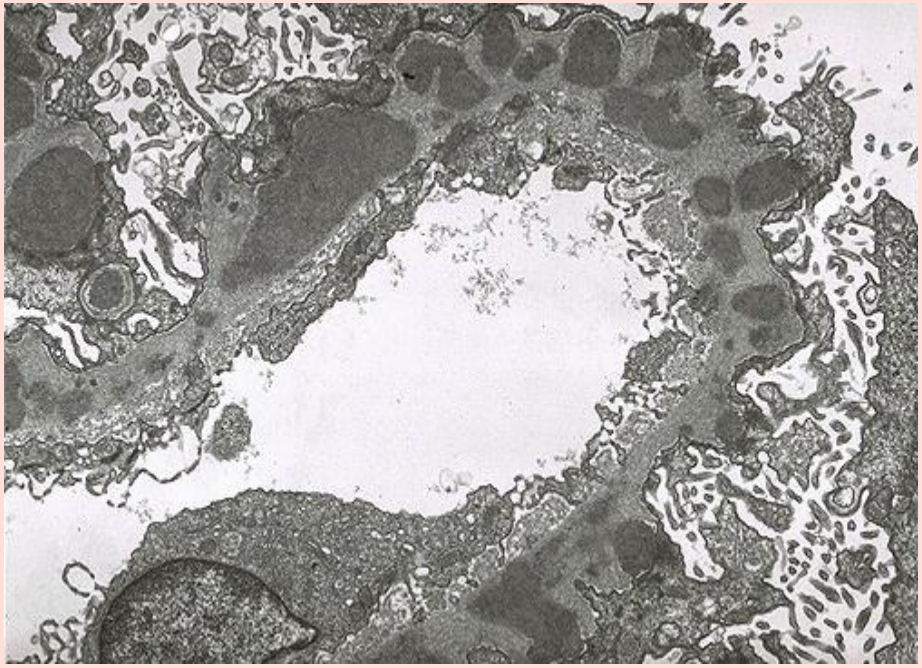
Membranous Nephropathy - Morphology -LM

The main histologic feature is **diffuse thickening** of the capillary wall (GBM glomerular basement membrane)on routine H&E stains



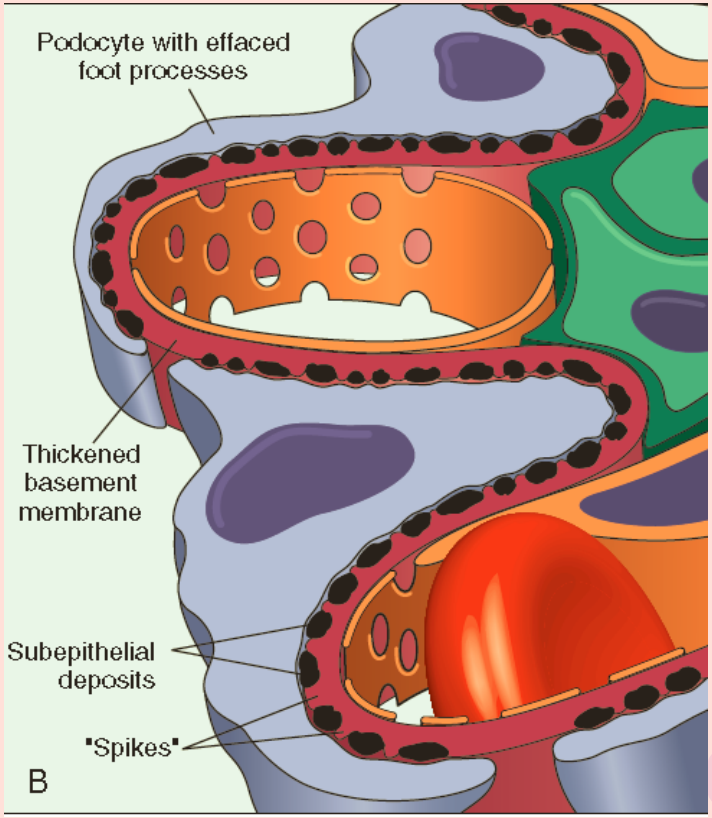
Membranous Nephropathy - Morphology - EM

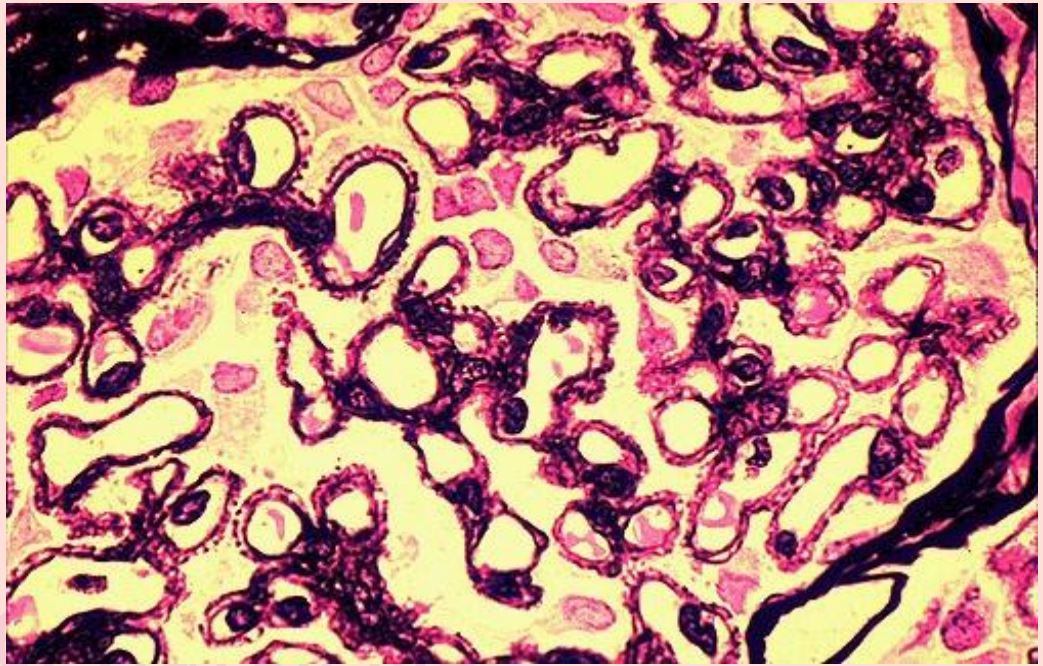
EM reveals that thickening is caused by subepithelial deposits, which nestle against the GBM & are separated from each other by small, spike-like protrusions of GBM matrix that form in reaction to the deposits (**spike & dome pattern**)



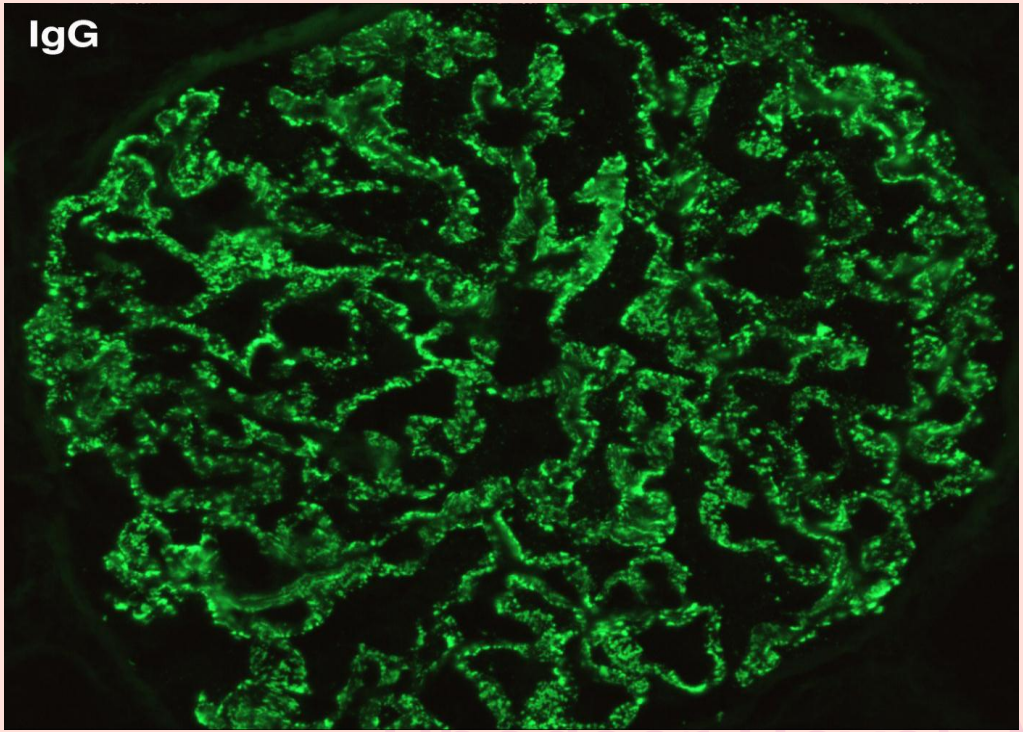
Membranous Nephropathy - Morphology -LM

A silver stain (black) of the GBM → appears with characteristics spikes (projections in capillary loops)





Membranous Nephropathy - Morphology -IF



IF microscopy demonstrates that the **granular** deposits contain both immunoglobulins & complement

Membranous Nephropathy -Clinical

- Sudden onset full-blown nephrotic syndrome
- In contrast to MCD, the proteinuria is nonselective
- Usually fails to respond to corticosteroid therapy
- Secondary causes should always be ruled out
- Variable prognosis:
  - Proteinuria persists in > 60% of patients
  - ~ 40% progress to renal failure over 2 to 20 years.
  - 10-30% benign course → partial or complete remission of proteinuria.

Nephritic syndrome

- **Often characterized by inflammation in the glomeruli, proliferation of the cells in glomeruli & leukocytic infiltrate.**
- Inflammation causes injury in capillaries → permeable to RBCs & other contents → **hematuria**
- ↓↓ GFR + augmented Renin/aldosterone (fluid retention & ↑↑ plasma volume) → **Hypertension**
- The acute nephritic syndrome may be caused by primary glomerular diseases; postinfectious glomerulonephritis (GN) & various forms of crescentic GN, diffuse proliferative GN, IgA nephropathy or as a result of systemic disorders e.g., SLE

Membrano-proliferative Glomerulonephritis (MPGN)

01 Best considered as a pattern of immune mediated injury rather than a specific disease:

Alterations in the GBM & mesangium, & proliferation of glomerular cells.

02 Presentation

50% of cases → nephrotic syndrome.
It may begin as acute nephritis or as mild proteinuria

03 MPGN type I

80% of cases.
Immune complex activate both classical & alternative complement pathways.

04 Dense Deposit Disease

Formly MPGN type II.
Excessive complement activation

Ghadeer Hayel, MD

MPGN - Pathogenesis

Type I

- The antigens Mostly are proteins derived from infectious agents e.g., hepatitis C & B viruses;

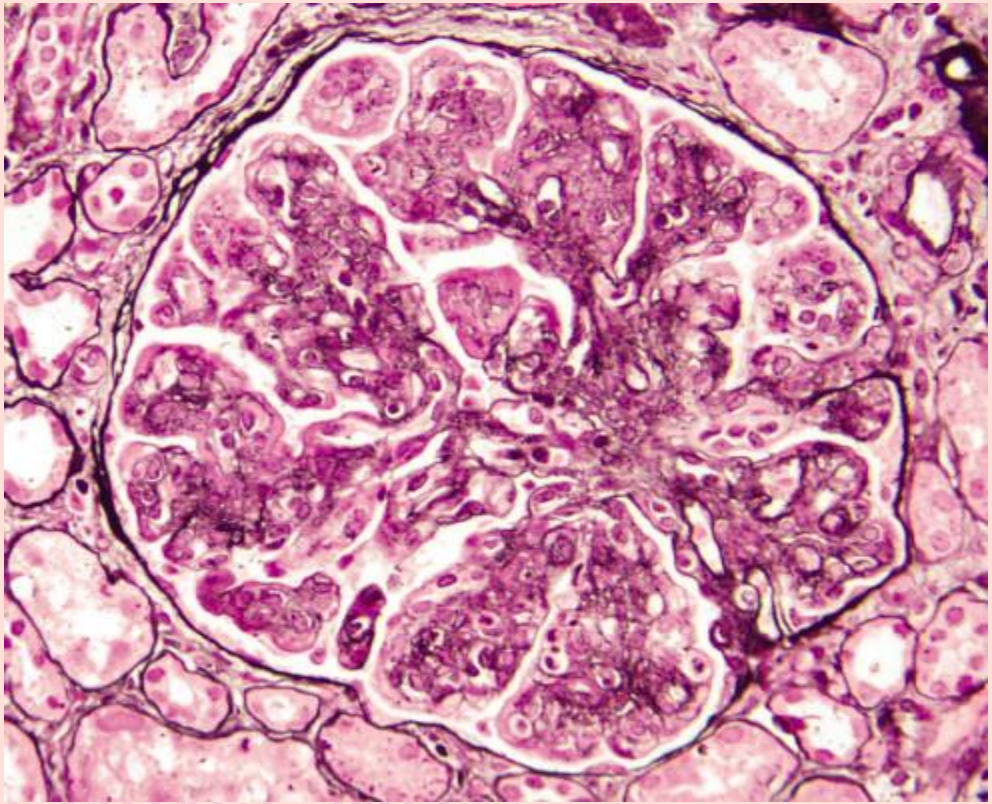
1. "planted" antigens: after first binding to or becoming trapped within glomerular structures.
2. Contained in preformed immune complexes deposited from the circulation.

Dense Deposit Disease

- **Complement dysregulation**
- Autoantibody against C3 convertase (called C3 nephritic factor)
- Ab stabilizes the enzyme → uncontrolled cleavage of C3 & activation of the alternative complement pathway

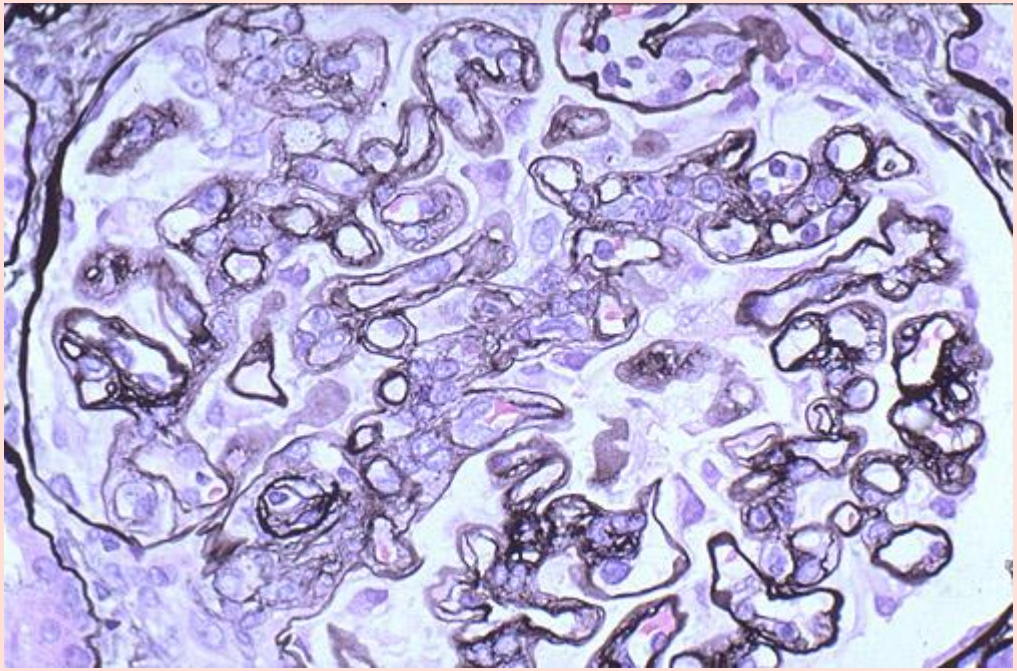
MPGN- Morphology -LM

Glomeruli are large, have an accentuated **lobular** appearance; proliferation of mesangial & endothelial cells as well as infiltrating leukocytes



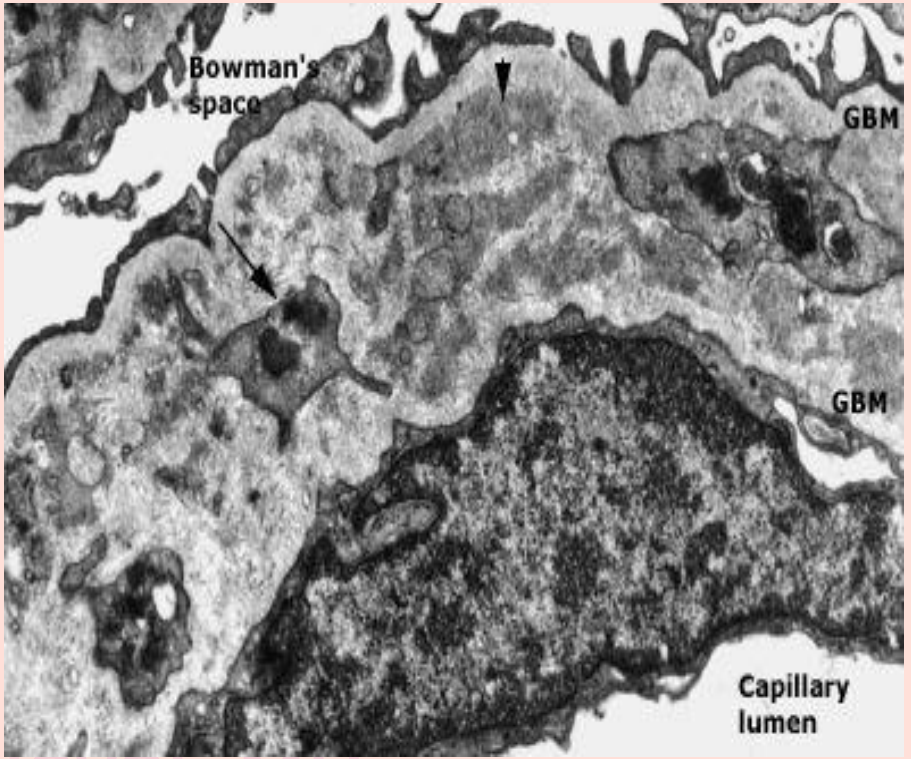
MPGN- Morphology -LM

The GBM is thickened, and the glomerular capillary wall often shows a **double contour**, or "**tram track**," appearance, especially evident with use of silver



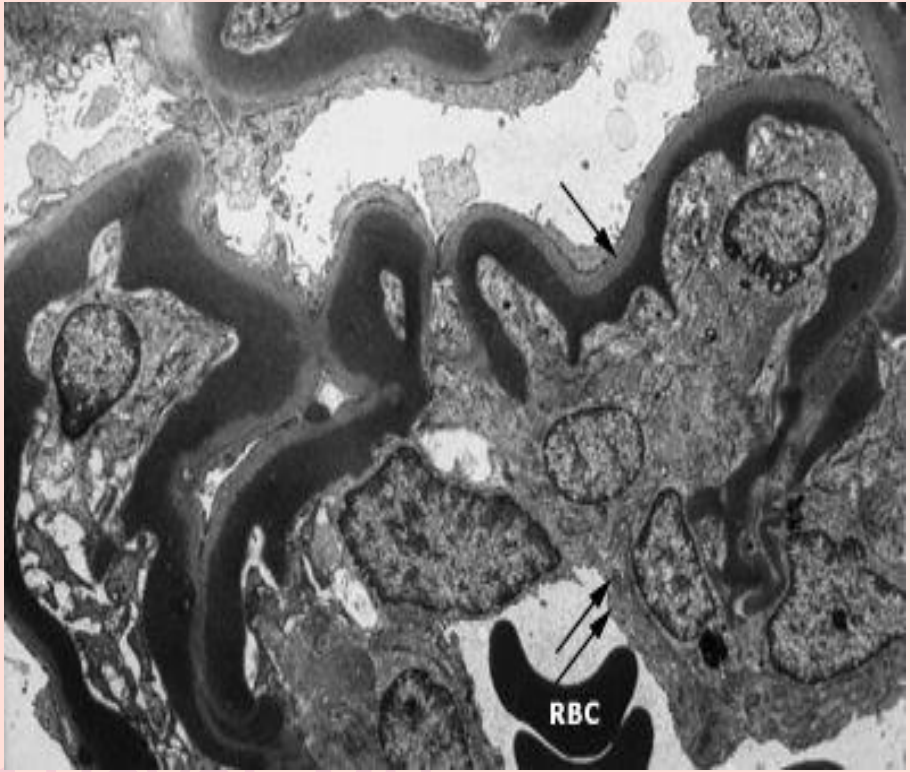
MPGN I - Morphology -EM

Marked thickening of the glomerular capillary wall by immune deposits (short arrow) & by interposition of mesangial cell processes (long arrow).



MPGN II/DDD - Morphology -EM

There are **dense** homogeneous deposits within the basement membrane. Ribbon-like appearance of subendothelial & intramembranous material



MPGN - IF

Type I

C3 is deposited in an irregular granular pattern, IgG and early complement components (C1q & C4)

Dense Deposit Disease

Only C3 is present in irregular foci in the GBM on either side but **not within the dense deposits**.

MPGN-Clinical

- The prognosis generally is poor.
- No complete remission;
- 40% progressed to renal failure
- 30% had variable degrees of renal insufficiency, & the remaining 30% had persistent nephrotic syndrome without renal failure.

Acute Postinfectious (Poststreptococcal) Glomerulonephritis

01 About the Disease

Glomerular deposition of immune complexes resulting in (1) proliferation of & damage to glomerular cells (2) infiltration of leukocytes, (esp. neutrophils)

Typically 02

develops in a child 1-4 weeks after he/she recovers from a group A streptococcal infection.

03 Association

Initial infection in pharynx or skin.
Classic pattern/most common → poststreptococcal GN. (but ass/w other organisms; viral or bacterial)

Pathogenesis 04

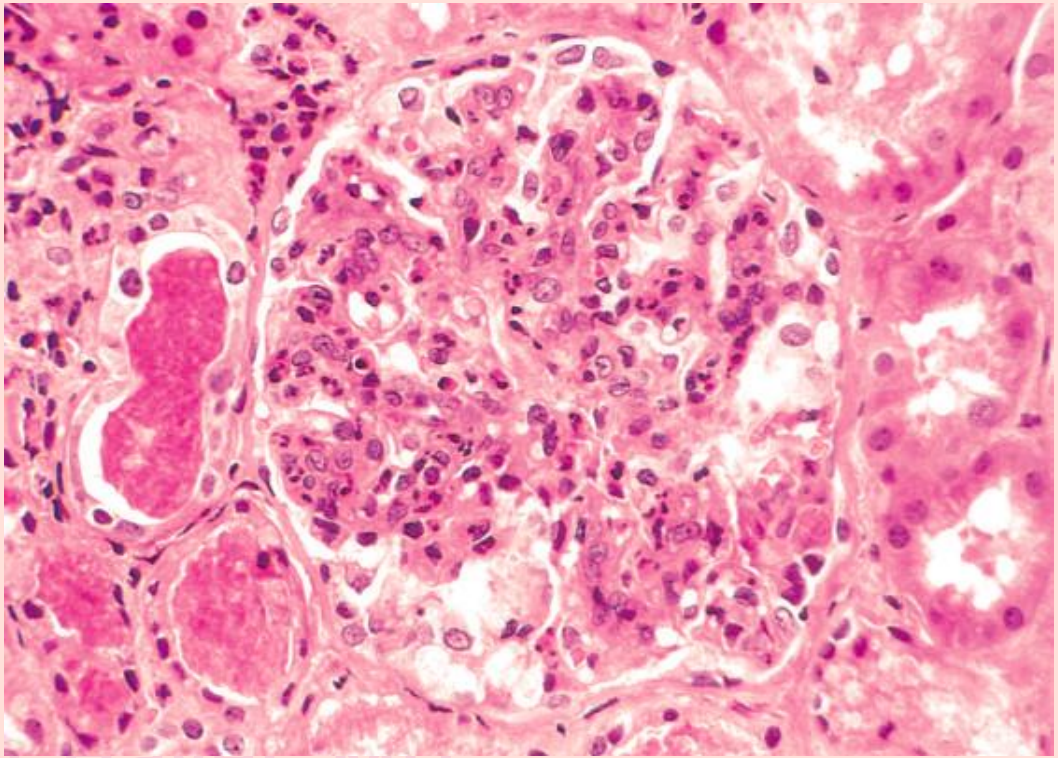
Immune complexes containing streptococcal antigens & specific antibodies formed in situ → activate complement system

Ghadeer Hayel, MD

Acute Postinfectious Glomerulonephritis

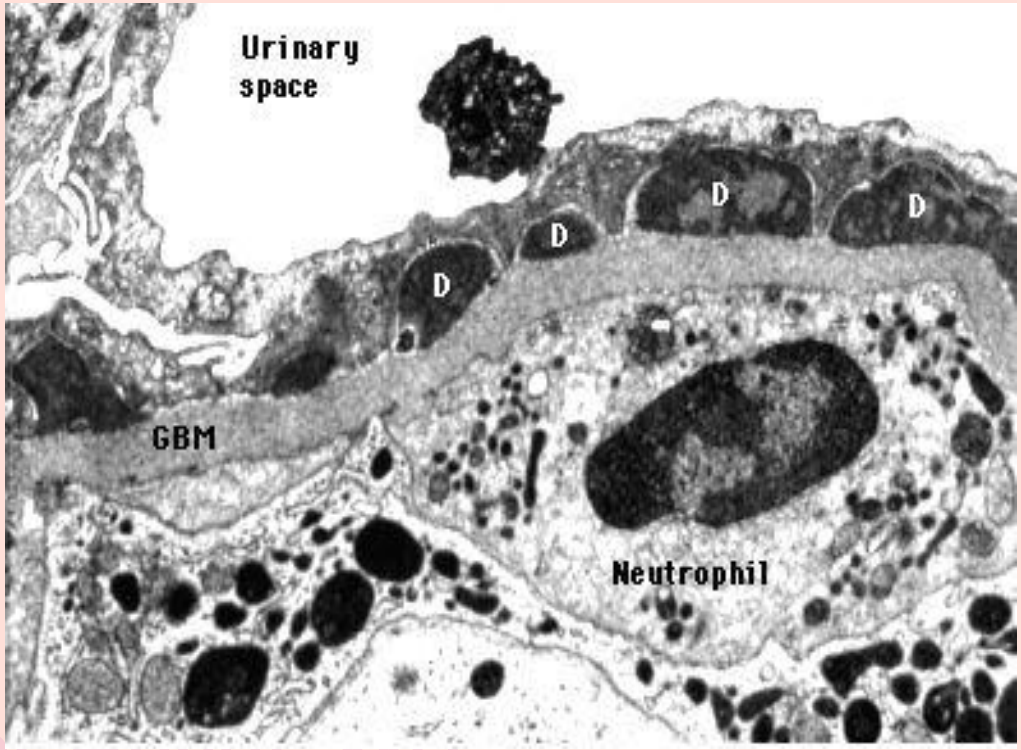
Morphology -LM

Most characteristic change → increased cellularity of all glomeruli (nearly all glomeruli) → caused by (1) proliferation & swelling of endothelial & mesangial cells (2)by infiltrating neutrophils & monocytes.



Acute Postinfectious Glomerulonephritis
Morphology — IF & EM

EM: shows deposited immune complexes as **subepithelial "humps"** (on the epithelial side of GBM)
IF: scattered granular deposits of IgG & complement within the capillary walls



Acute Postinfectious Glomerulonephritis

Clinical

- Most commonly present as acute nephritic syndrome
- Fever, nausea, gross hematuria, & mild proteinuria.
- Serum complement levels are low during the active phase of the disease.
- Serum anti–streptolysin O antibody titers are elevated in poststreptococcal cases.
- Recovery occurs in most children with poststreptococcal disease

IgA Nephropathy (Berger Disease)

01 About the Disease

One of the most common causes of recurrent microscopic or gross hematuria. Usually affects children & young adults

02 Presentation

An episode of gross hematuria (within 1-2 days of a nonspecific URTI), hematuria lasts days & subsides, but it recurs periodically.

03 Association

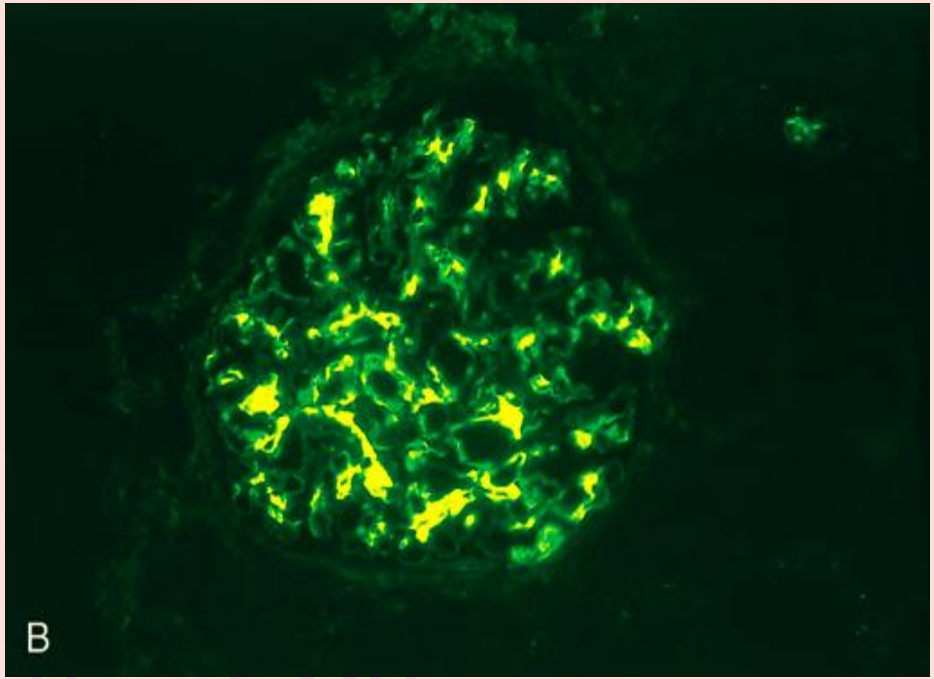
Similar IgA deposits are present in a systemic disorder of children, Henoch-Schonlein purpura. Renal manifestations occur in one third of patients. (same deposition pattern as IgA nephropathy)

04 Pathogenesis

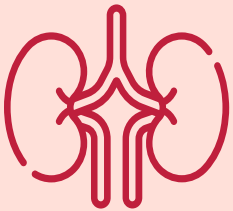
A genetically susceptible individual + URTI or GIT exposure to microbial or other antigens → ↑↑↑ IgA synthesis → deposition of IgA & immune complexes in the mesangium

IgA Nephropathy - Morphology

Different **LM** findings but whatever the histologic lesions, the pathognomonic feature by **IF** is the deposition of IgA and C3, in the mesangial region. (diagnostic)



Rapidly Progressive (Crescentic) Glomerulonephritis



01 It is a clinical syndrome & not a specific etiologic form of GN

- Rapid loss of renal function if untreated; (nephritic syndrome → oliguria→ renal failure) in weeks to months

02 Characterized by the presence of crescents (crescentic GN)

- Formed by : (1) proliferation of epithelial cells & (2) migration of monocytes/ macrophages into Bowman's space in response to injury

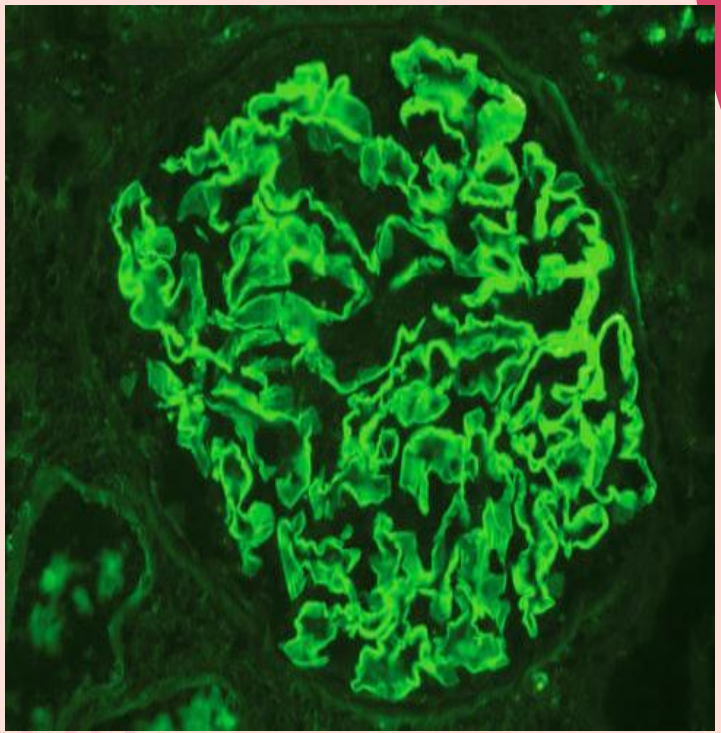
03 Associated with number of disease

- Anti-GBM antibody–mediated crescentic GN (Goodpasture disease)
- Any of the immune complex nephritides
- Pauci-immune RPGN, Serum ANCA

RPGN — Goodpasture disease

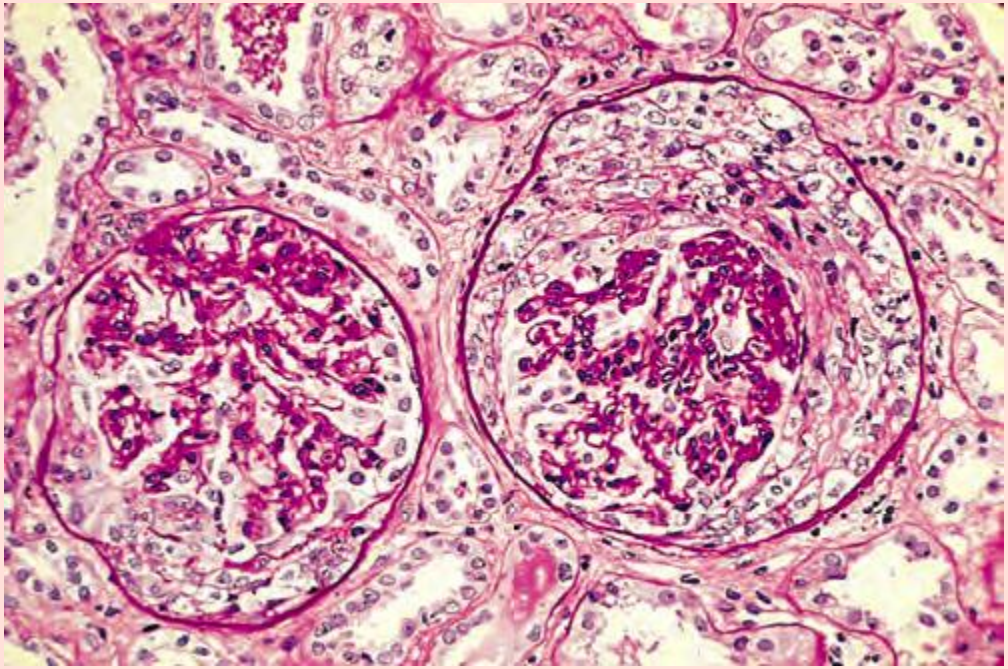
Anti-GBM antibody–mediated crescentic GN

- Characterized by **linear** deposits of IgG in GBM.
- In some patients, anti-GBM antibodies bind to pulmonary alveolar capillary BM to produce the clinical picture of pulmonary hemorrhages ass/w renal failure → Goodpasture syndrome.
- Anti-GBM Abs are in the serum → Diagnosis.
- It is important to recognize Goodpasture disease → benefit from **plasmapheresis** → removes pathogenic antibodies from the circulation.



RPGN - Morphology -LM

Collapsed glomerular tufts and **crescent-shaped** mass of proliferating parietal epithelial cells & leukocytes internal to Bowman capsule

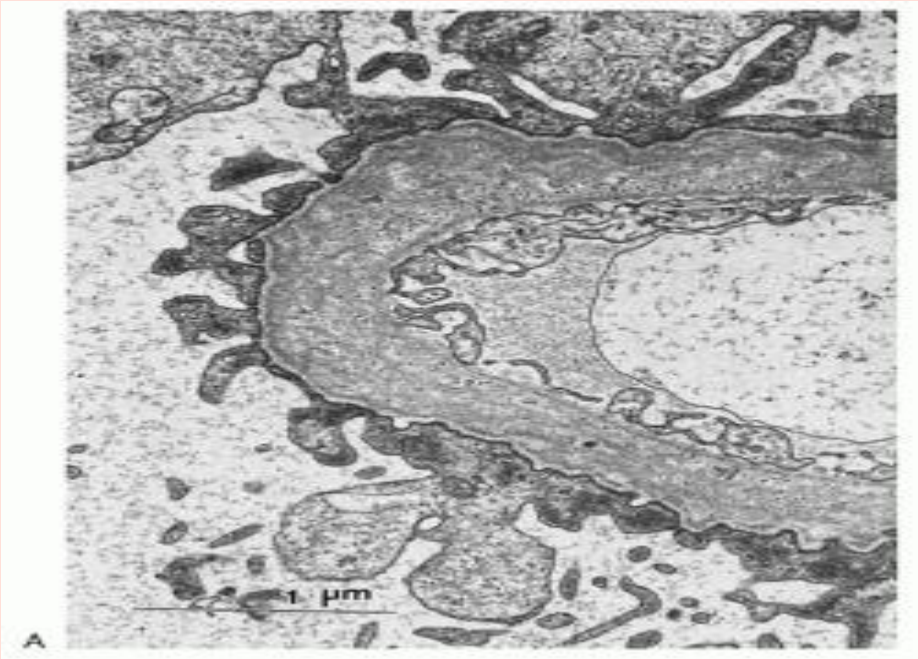


Hereditary Nephritis - Alport Syndrome

- **Hereditary nephritis:** a group of heterogeneous familial renal diseases ass/w mutations in collagen genes & manifest primarily with glomerular injury.
- **Alport syndrome** manifest by nephritis + sensorineural deafness + various eye disorders (lens dislocation, posterior cataracts, & corneal dystrophy)
- Inherited as an X-linked trait in ~ 85% of cases
- GBM is composed of type IV collagen, heterotrimers of α3, α4, & α5 type IV collagen. This form of type IV collagen is crucial for function of the lens, cochlea, & glomerulus.
- Mutation of any one of the α chains results in defective heterotrimer assembly → manifestations of Alport syndrome

Alport Syndrome - Morphology

Early: GBM is thin & attenuated
Later: develops irregular foci of thickening, splitting and lamination, yielding a "**basket-weave**" appearance.



"**Public opinion is a weak tyrant**, compared with our own private **opinion**. What a man thinks of himself, that is what determines, or rather indicates, his fate."

—Henry David Thoreau