Renal Pathology
Nephrotic Syndrome
&
Nephritic Syndrome

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Reference: Robbins & Cotran Pathology and Rubin's Pathology

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Objectives for pathology lectures 5 & 6:
Rapid Progressive Glomerulonephritis, Chronic kidney Disease, AND Nephrotic and Nephritic Syndrome:

At the end of the activity (2 lectures) the students will be able to:

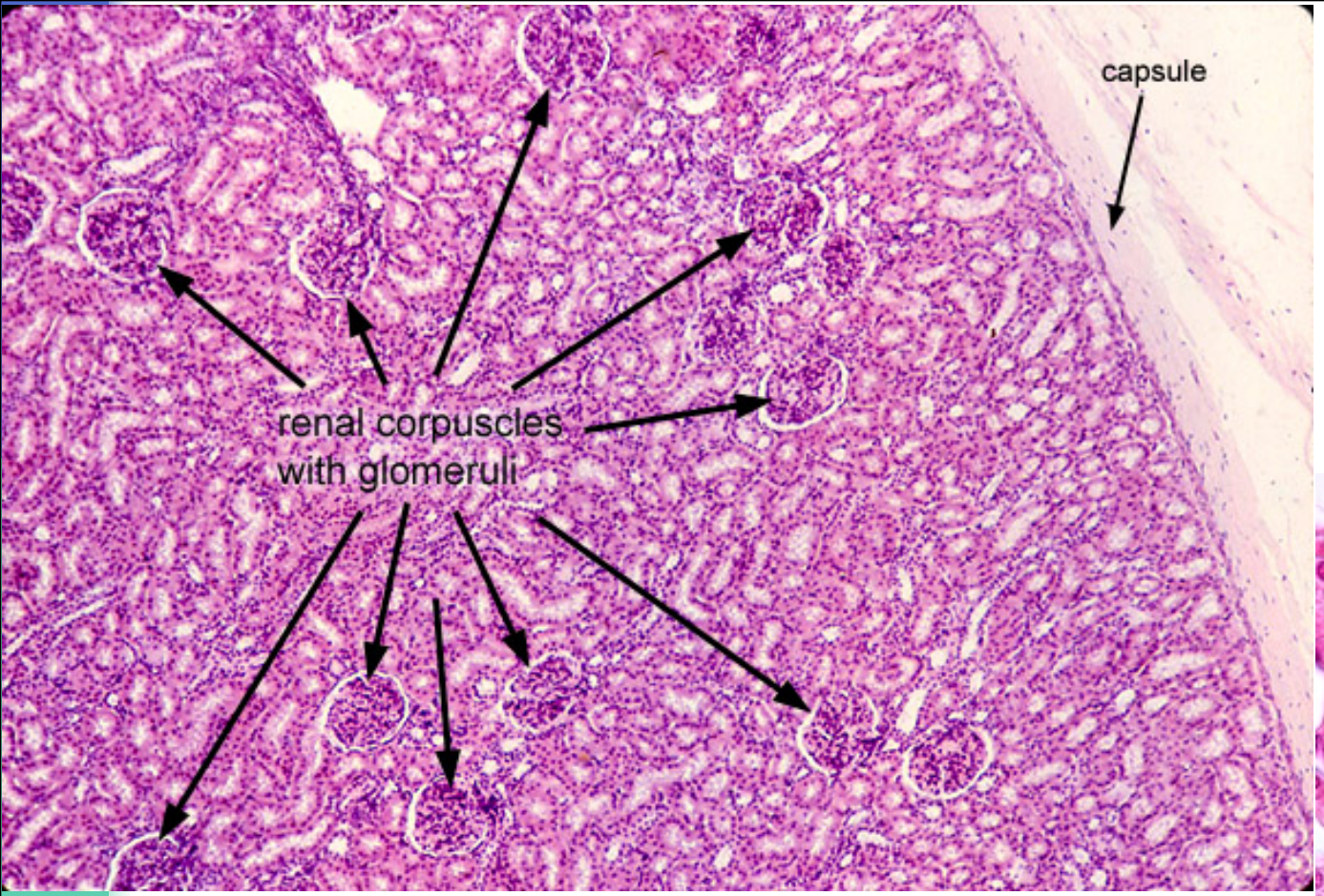
- Recognize the five major renal glomerular syndromes.
- Describe the main differential pathological diagnosis for each syndrome.
- Perform a clinico-pathological correlation.
- Describe the patterns of injury of each syndrome.

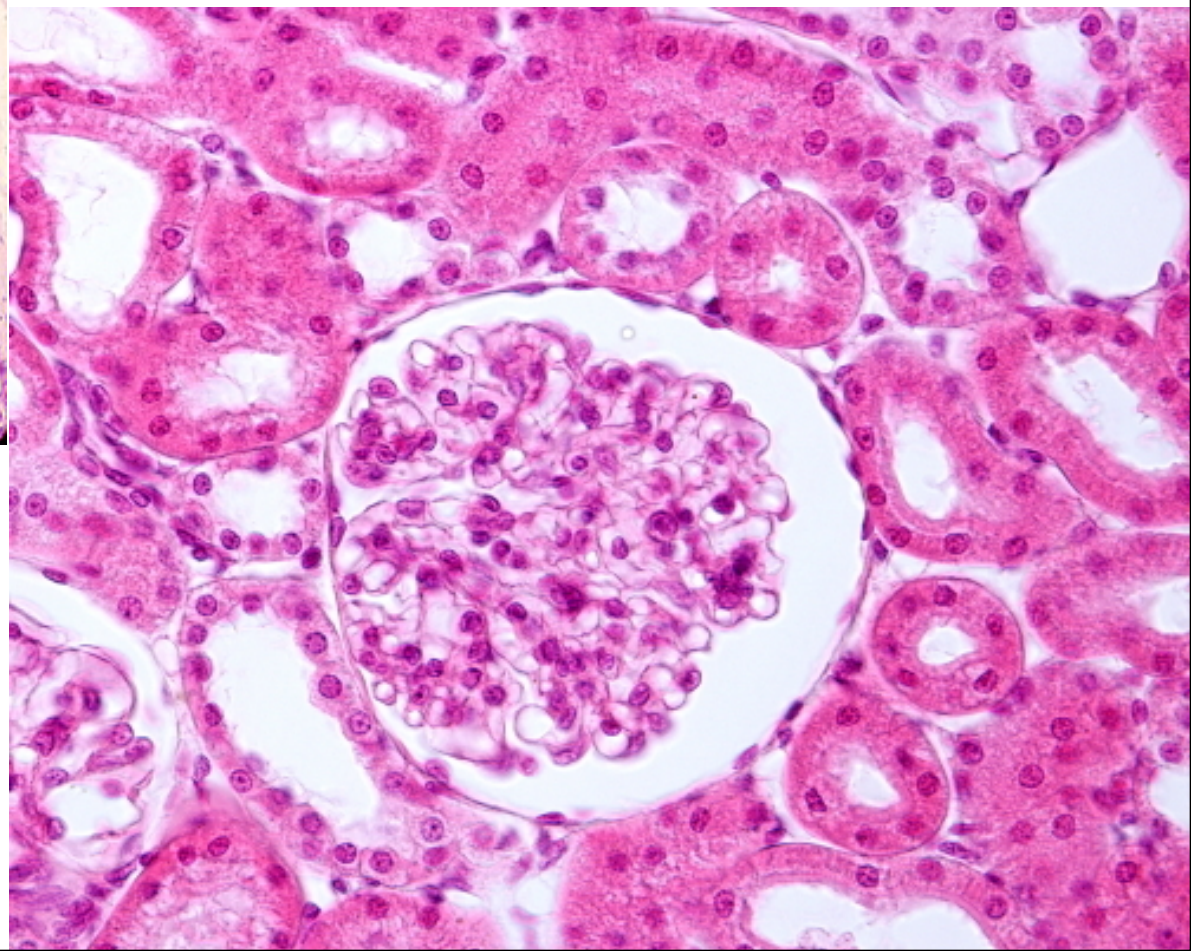
Key Outlines:

- The nephrotic syndrome: (Minimal change, FSGS, membranous, diabetes).
- The nephritic syndrome: (Acute post streptococcal Glomerulonephritis GN, Lupus nephritis).
- Asymptomatic Hematuria: IgA Nephropathy.
- Rapidly progressive GN: (Crescentic GN)
- The Chronic Renal Failure.

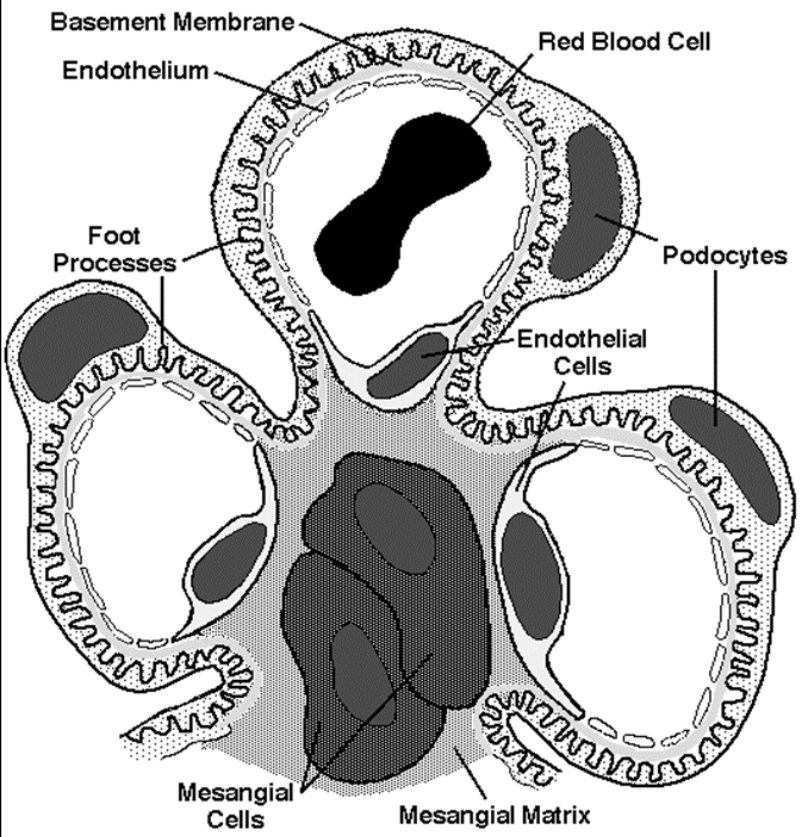
Outline for lecture 5

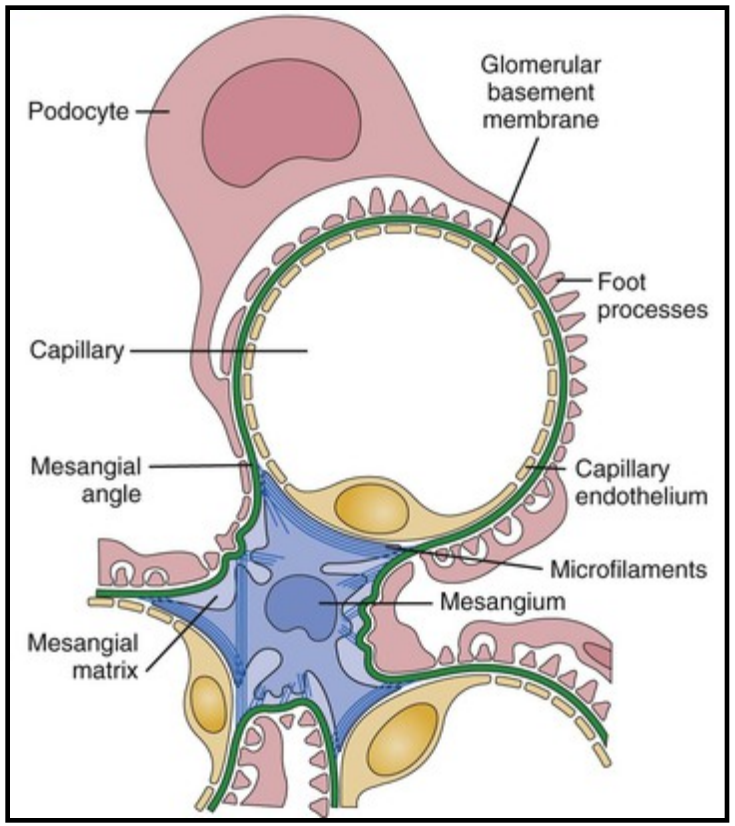
- Introduction, kidney biopsy
- Location of electron dense immune deposits
- Pathogenesis of glomerular disease
- Common markers of renal diseases
- Clinical manifestation of kidney disease
- **Nephrotic Syndrome**
  - Minimal change disease
  - Focal segmental glomerulosclerosis
  - Membranous GN
  - Diabetes mellitus
- **Nephritic Syndrome**
  - Acute post-streptococcal GN
  - Introduction to lupus nephritis
- **Hematuria**
  - IgA Nephropathy

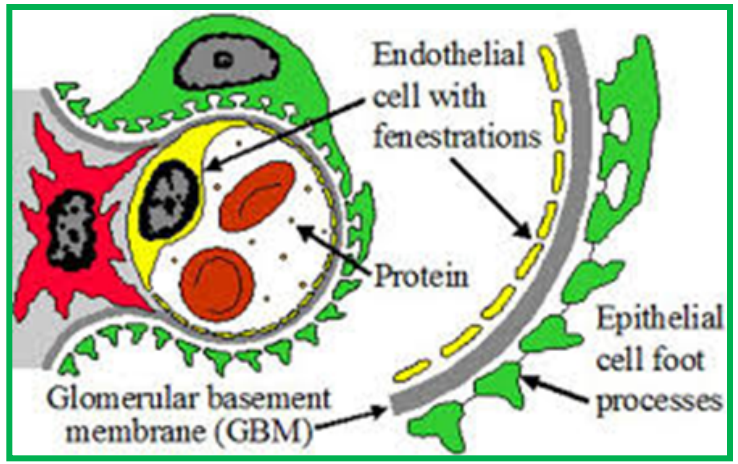

capsule
renal corpuscles
with glomeruli

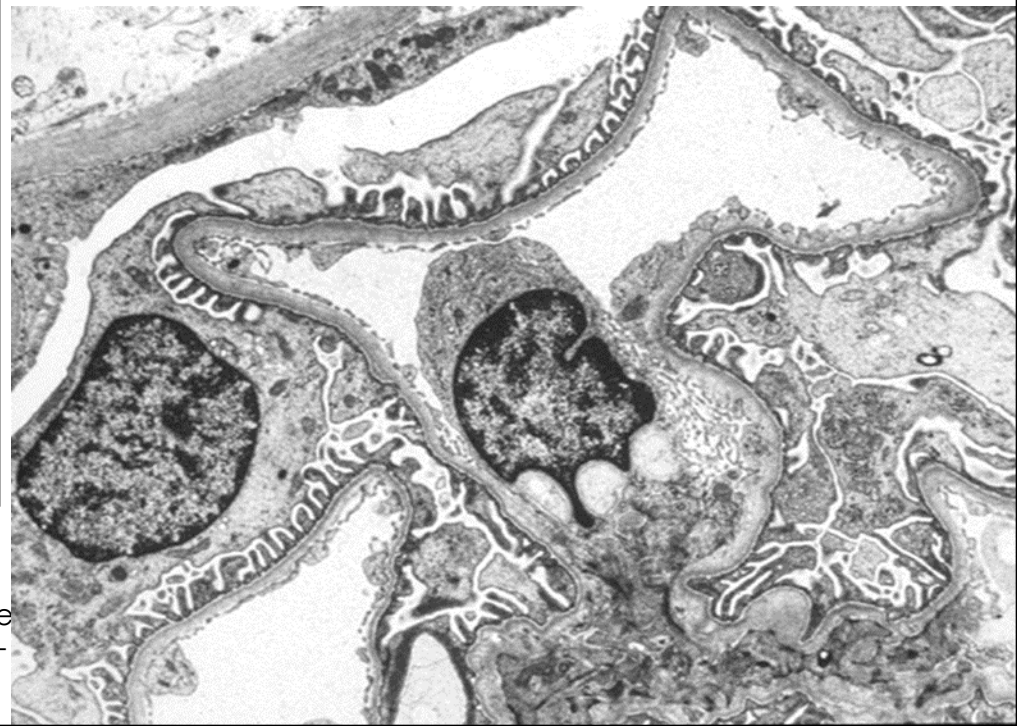


Glomerulus n Transmission EM

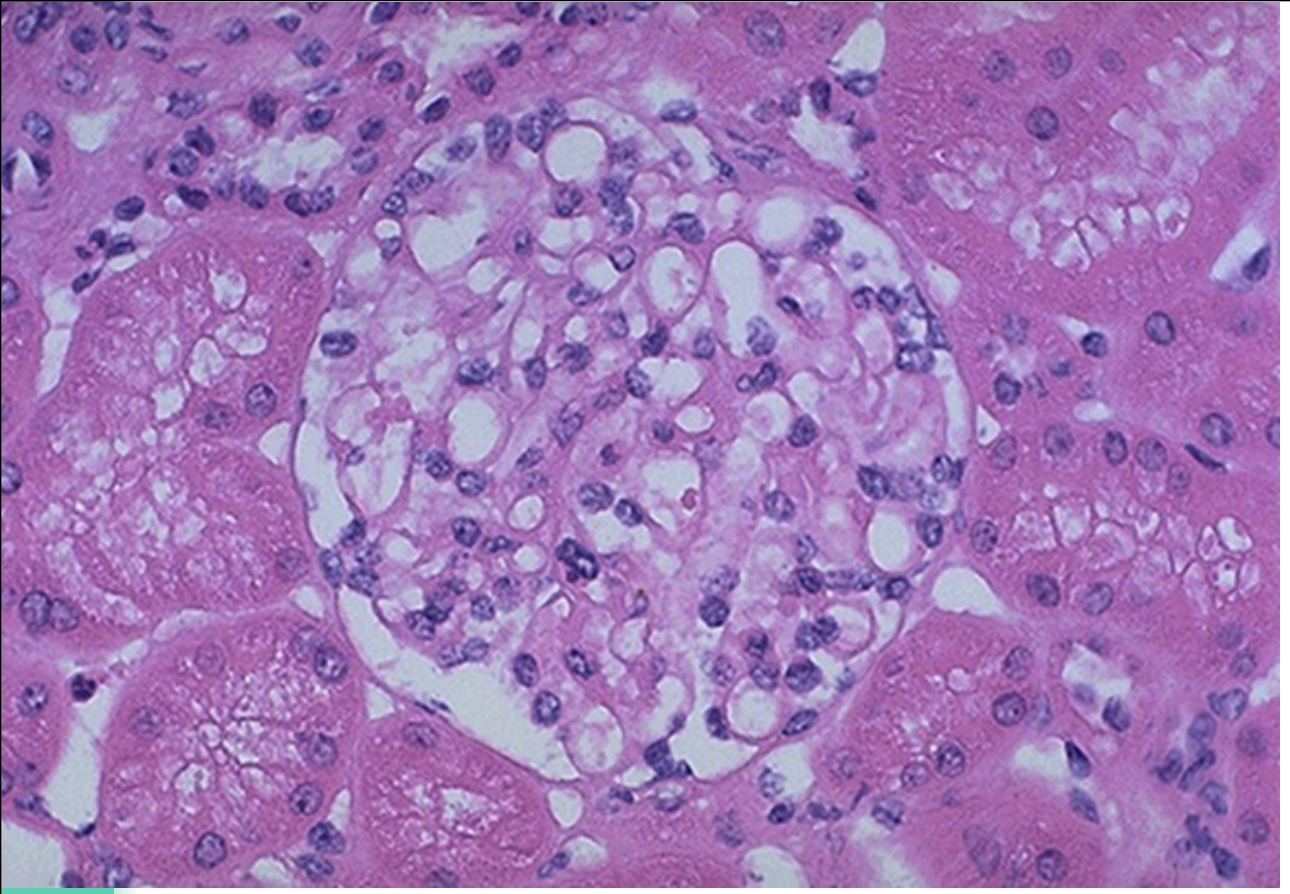




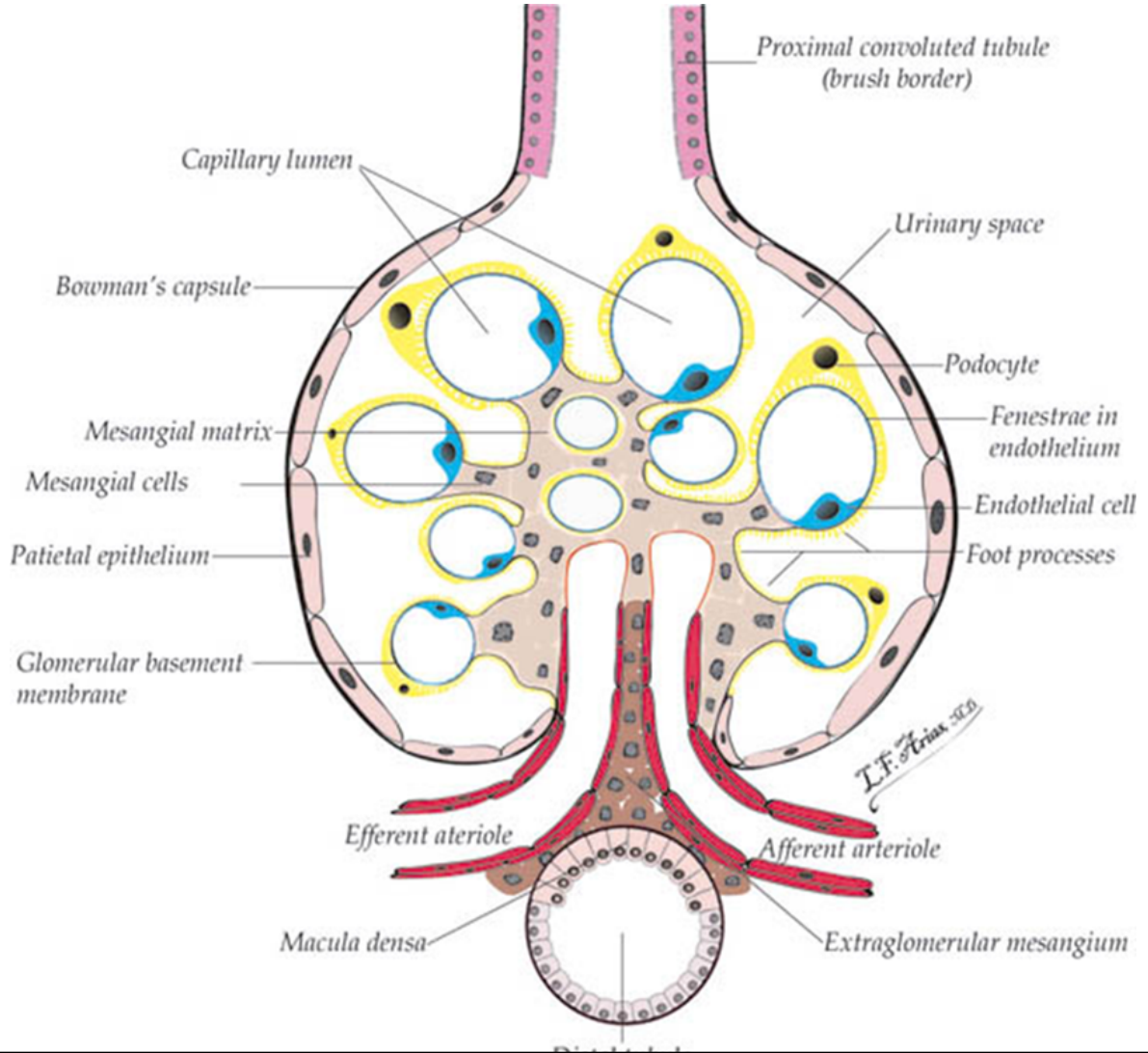




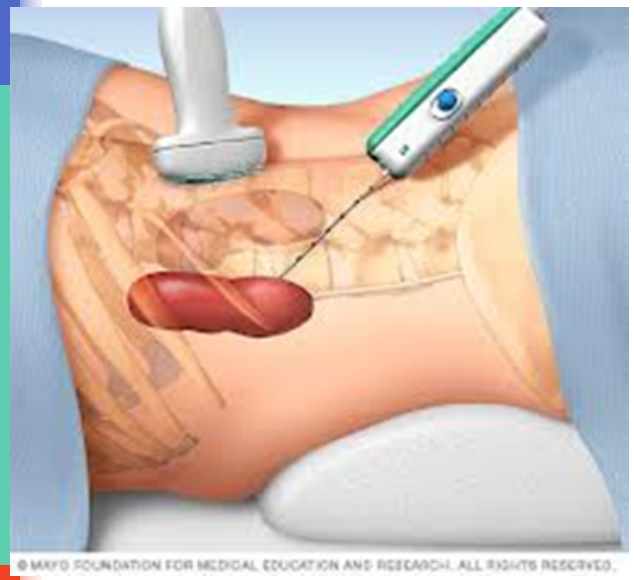
https://www.niddk.nih.gov/research-funding/at-niddk/labs-branches/kidney-diseases-branch/kidne disease-section/glomerular-disease-primer/normal-kidney

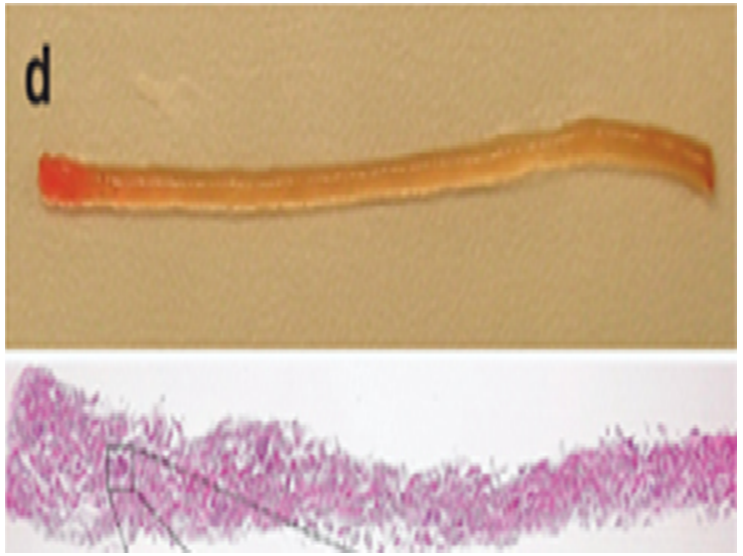


Kidney histology



Kidney biopsy

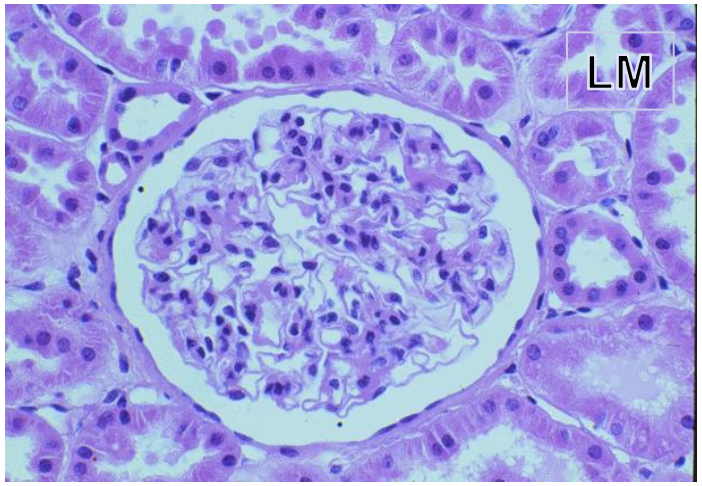


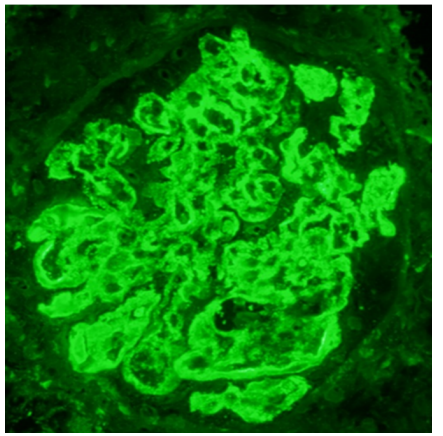


Kidney biopsy

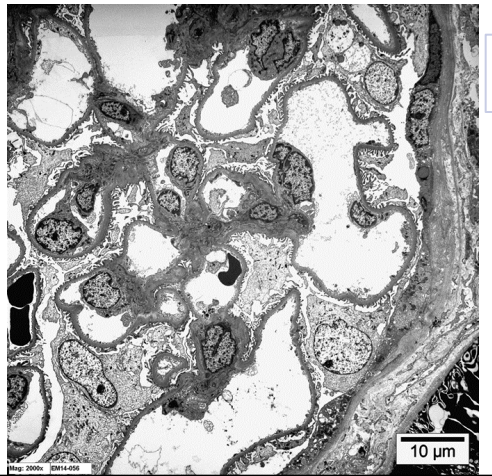
The tissue obtained is used to make slides for

1. **Light microscopy (LM)** to study renal histology.
2. **Immunofluorescence (IF)** study is to detect
   - the presence of immunoglobulins (IgA, IgG, IgM) and complements (C3 and C1q) in the glomeruli (in the mesangium or in the glomerular capillary loop wall.
3. **Electron microscopy (EM) (ultrastructural)** study is to detect the presence or absence of
   - effacement of the epithelial cell (podocytes)foot processes.
   - electron dense immune complex deposits
   - And if deposits are present then to identify the location of the deposits in the glomeruli (mesangial/paramesangial, subepithelial, subendothelial).





IF

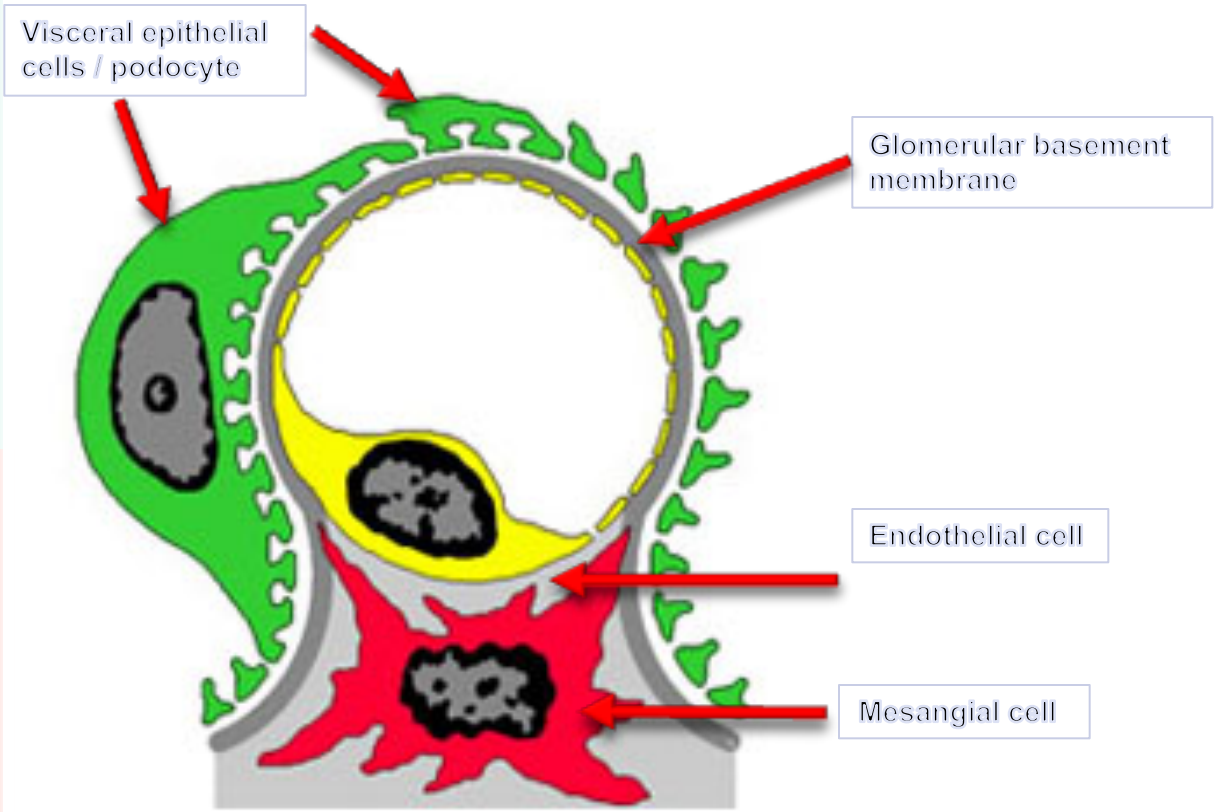


EM

LOCATIONS OF ELECTRON DENSE IMMUNE DEPOSITS

Common locations of electron dense immune deposits. Note: the locations are different in different diseases.

Normal glomerular capillary loop



Deposits (depicted in black)

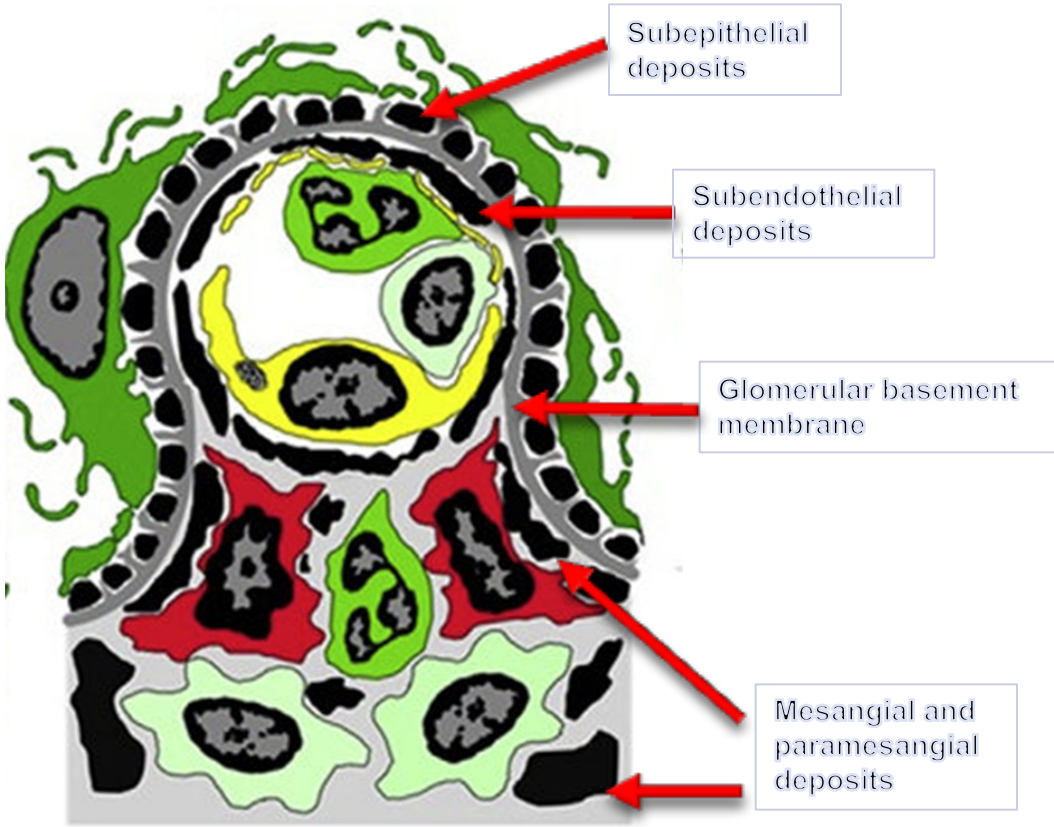


Image from IM Bajema et al.: Revision of lupus nephritis classification. Kidney International ·February 2018 DOI: 10.1016/j.kint.2017.11.023

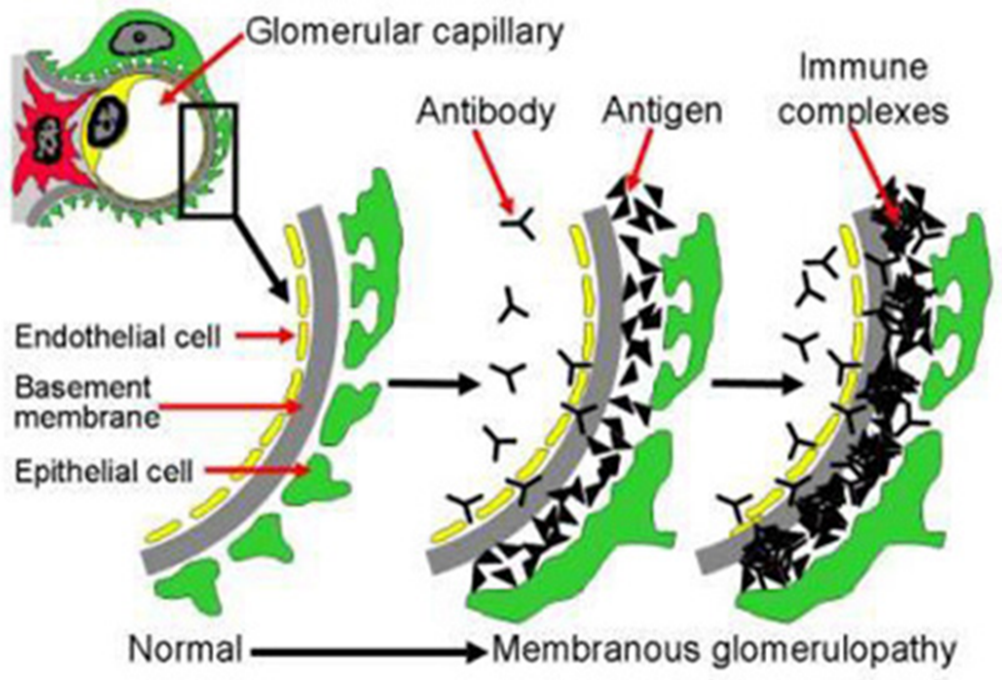
PATHOGENESIS OF GLOMERULAR INJURY

Pathogenesis of glomerular injury

Glomerulonephritis (GN) is frequently caused by immunologic mechanisms →both antibody-mediated (mainly) and cell-mediated types of immunity play roles in the production of glomerular inflammation.

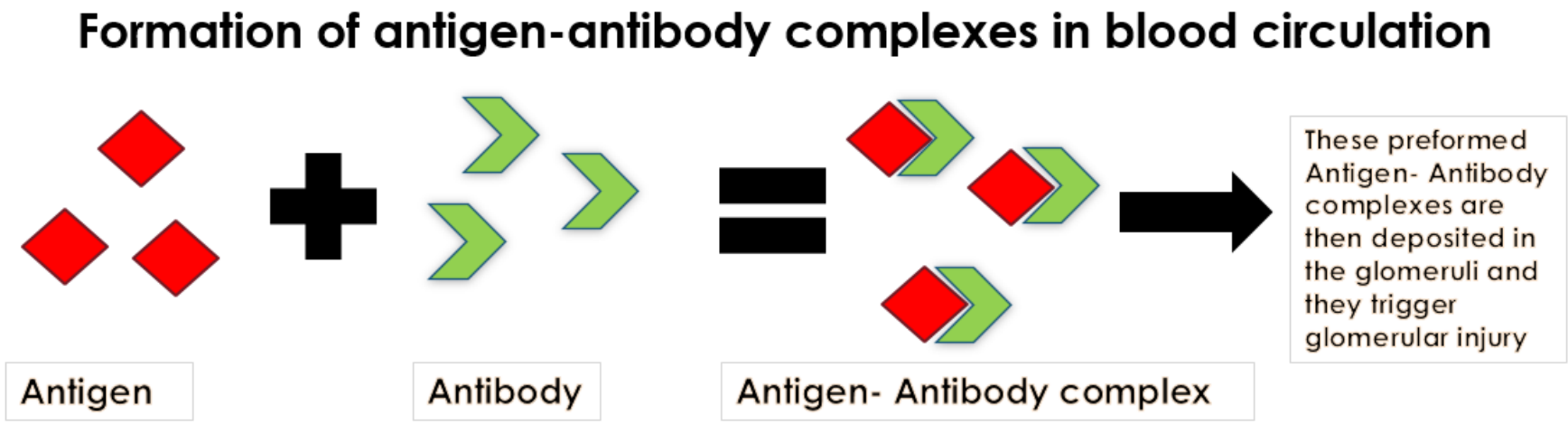
1. **<u>Antibody-mediated immune GN</u>**: there are 3 major mechanisms of antibody-mediated inflammation. They are:

   a) **In situ immune complex formation:** certain circulating antibodies react with certain antigens that are already present in glomeruli → formation deposition of these immune complexes in the glomeruli. These deposits attract leukocytes and activate complement →glomerular injury.



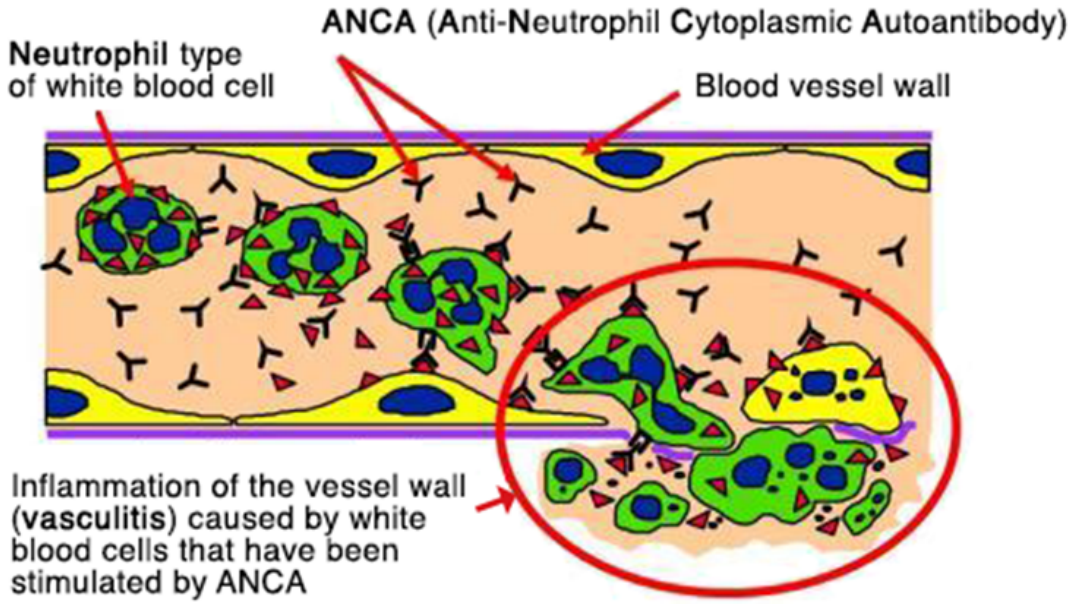
Pathogenesis of glomerular injury contd..

b) Antigen-antibody reaction take place in circulation and these **preformed circulating immune complexes are deposited in the glomeruli** → deposits trigger glomerular injury (by attracting inflammatory cells and activate complements). (the antigen can be a bacteria, virus etc.)



Pathogenesis of glomerular injury contd..

c) **Antineutrophil cytoplasmic autoantibodies (ANCAs):** they cause a severe type of GN in which the patients have circulating autoantibodies against antigens present in neutrophil cytoplasm. This interaction leads to activation and adhesion of the neutrophils to endothelial cells lining the capillaries especially the glomerular capillaries. The neutrophils release injurious products that promote endothelial injury, vascular inflammation (vasculitis) and GN.



https://unckidneycenter.org/files/2017/10/anca-vasculitis-vessel-wall.png

All 3 initiate of glomerular inflammatory injury by attraction and activation of leukocytes.

2. **Cell mediated immune GN:** sensitized T cells also cause glomerular injury.

COMMON MARKERS OF RENAL DISEASES

Common markers of renal diseases

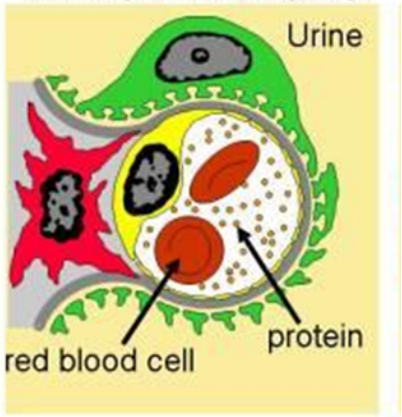
In blood

- **Serum creatinine and BUN**

In urine analysis

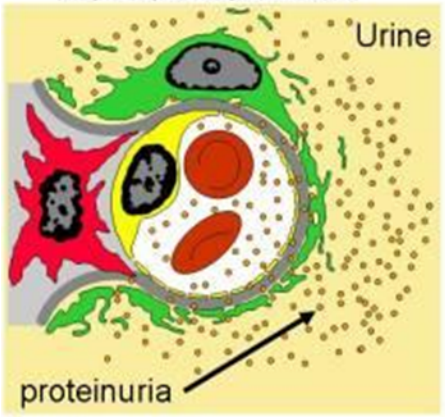
- **Proteinuria:** presence of abnormal quantities of protein in the urine
- **Hematuria:** presence of rbcs in urine (smoky brown urine). It is a result of glomerular injury and rupture of the glomerular capillaries with resultant bleeding into the Bowman's/ urinary space.
- **Urinary casts** are microscopic clusters of urinary particles or cells wrapped in a protein matrix and found in the urine, e.g. rbcs mix with proteinaceous material in the tubules and forms rbc casts. Casts are formed in the distal convoluted tubule and collecting ducts of nephrons, then dislodge and pass into the urine, where they can be detected by microscopy. The presence of casts indicates kidney disease.

Normal glomerular capillary



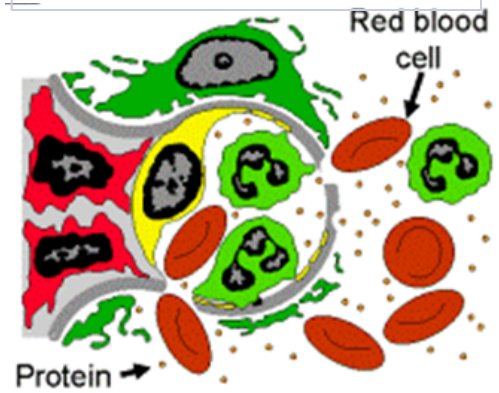
In a normal glomerulus: the capillary loops retains the rbcs, wbcs and most of the protein in the blood that is passing through. The ultrafiltrate is mainly watery fluid going into the urinary space.

Capillary with proteinuria



Protein molecules spill out into the urinary space due to filtration abnormality in the glomerular capillary wall.

Proteinuria and hematuria



In certain types of glomerular injury the injured capillary loop has abnormal permeability and ruptured GBM with allows rbcs (hematuria) and proteins (proteinuria) to leak into the urinary space.

Urine in hematuria

https://unckidneycenter.org/files

CLINICAL MANIFESTATION OF KIDNEY DISEASE

Clinical manifestation of kidney disease

▪ **Nephritic syndrome**	Results from glomerular injury → hematuria (rbcs in urine), azotemia, oliguria & hypertension, may have mild edema and proteinuria.
▪ **Nephrotic syndrome**	heavy proteinuria (excretion of more than 3.5 g of protein/day in urine), hypoalbuminemia, severe edema, hyperlipidemia, and lipiduria.
▪ **Asymptomatic hematuria &/or non-nephrotic proteinuria**	a sign of mild glomerular abnormalities e.g. IgA nephropathy.
▪ **Rapidly progressive glomerulonephritis**	Results from severe glomerular injury → loss of renal function within days or weeks → hematuria, dysmorphic rbcs, rbc casts in urine, mild to moderate proteinuria.
▪ **Acute kidney injury**	oliguria or anuria with recent onset of azotemia; can result from glomerular injury (e.g. crescentic glomerulonephritis), interstitial injury, vascular injury (e.g. TMA) or acute tubular injury/necrosis.
▪ **Chronic kidney disease**	any chronic renal diseases that progresses to end stage kidney requiring dialysis and transplantation.
▪ **Urinary tract infection**	affect the kidney (pyelonephritis) or the bladder (cystitis) → bacteriuria and pyuria (bacteria and leukocytes in urine).
▪ **Nephrolithiasis (renal stones)**	renal colic, hematuria (without rbc casts).

Terminology

- DIFFUSE: majority of the glomeruli are involved
- FOCAL: some of the glomeruli are involved
- SEGMENTAL: only part of a glomerular tuft is involved
- GLOBAL: involving the total glomerular tuft

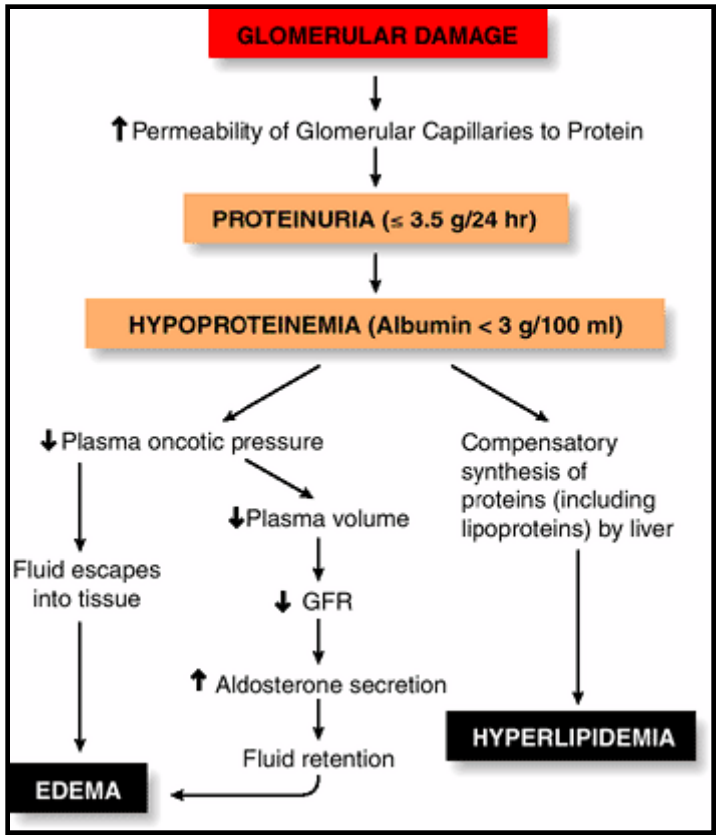
NEPHROTIC SYNDROME

Nephrotic syndrome

Nephrotic syndrome is a group of clinical features that include the following:

1. **Massive proteinuria**: is the loss in the urine of >3.5 g of protein/day. This is due abnormal permeability of the glomerular capillary wall.
2. **Hypoproteinemia or hypoalbuminemia**: plasma albumin levels <3g/dL (this due to the loss of protein in the urine)
3. **Odema**: Hypoproteinemia causes reduced plasma colloid osmotic pressure, salt and water retention and odema.
4. **Hyperlipidemia and lipiduria**: hypoalbuminemia causes compensatory increase in lipoprotein secretion by the liver leading to hyperlipidemia. At the same time there is increased loss of lipid in the urine, lipiduria (due to abnormal permeability of the GBM).

Note: in the beginning there is little or no azotemia, hematuria, or hypertension (not part of definition of nephrotic syndrome).



Causes of nephrotic syndrome

PRIMARY CAUSES

- Minimal change disease
- Membranous GN
- Focal segmental glomerulosclerosis (FSGS)
- Membranoproliferative GN (can also present as nephritic syndrome)
- Others

SECONDARY CAUSES

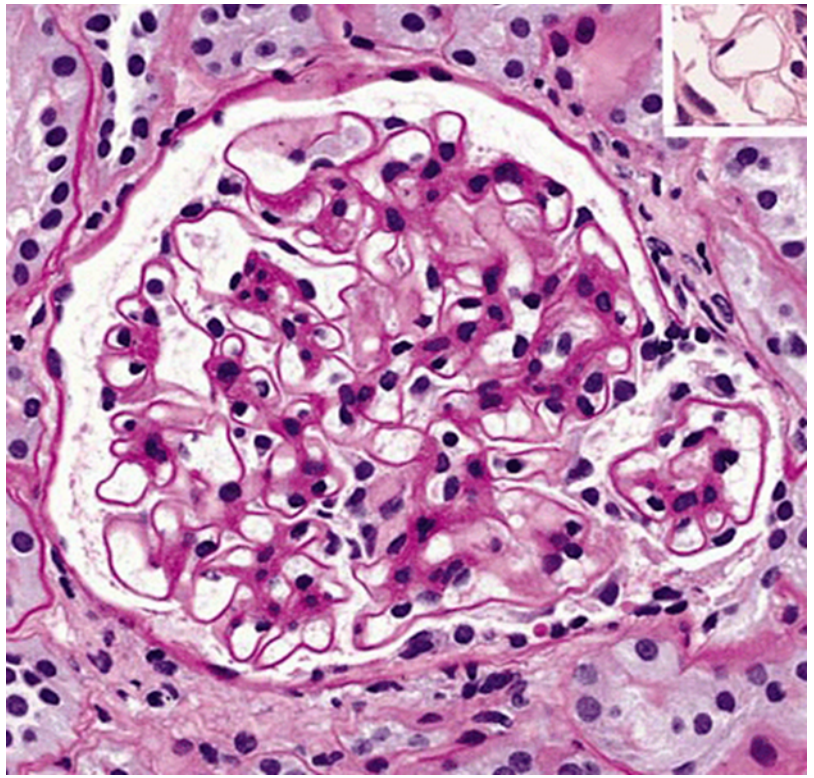
- Diabetes mellitus (most common systemic causes)
- Amyloidosis
- Systemic lupus erythematosus (it can also present as nephritic syndrome)
- Drugs (gold, penicillamine, "street heroin")
- Others

NOTE: In children the most common cause of nephrotic syndrome is minimal-change disease. In adults the most common primary glomerular diseases that causes nephrotic syndrome are membranous glomerulopathy in Caucasians and Asians, and FSGS is the most common etiology in American blacks.

Minimal change disease

Minimal change disease /glomerulopathy

- Minimal change disease (MCD) is also known as lipoid nephrosis.
- It causes nephrotic syndrome.
- Pathogenesis: unknown → usually idiopathic.
- It is characterized by effacement of the foot processes of the visceral epithelial cells (podocytes).



Light microscopy:

- Glomeruli → look normal.
- The proximal convoluted tubular cells are heavily laden with protein droplets and lipids.
- There is no tubular atrophy or interstitial fibrosis.

Immunofluorescence microscopy:

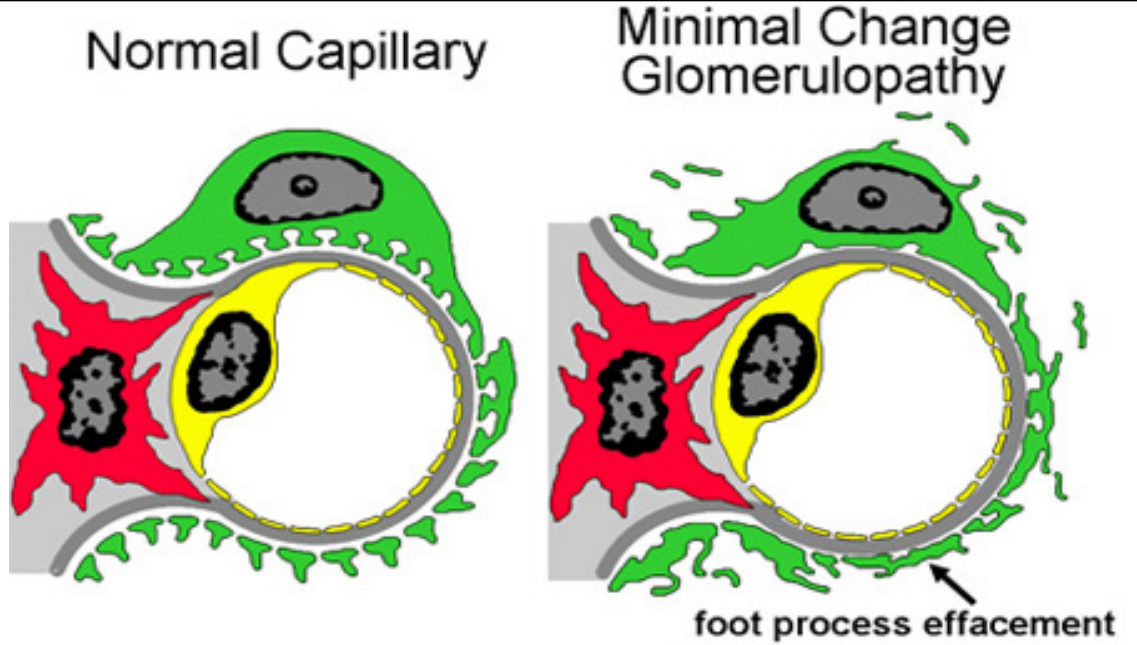
- Is negative for immunoglobulins and complement.

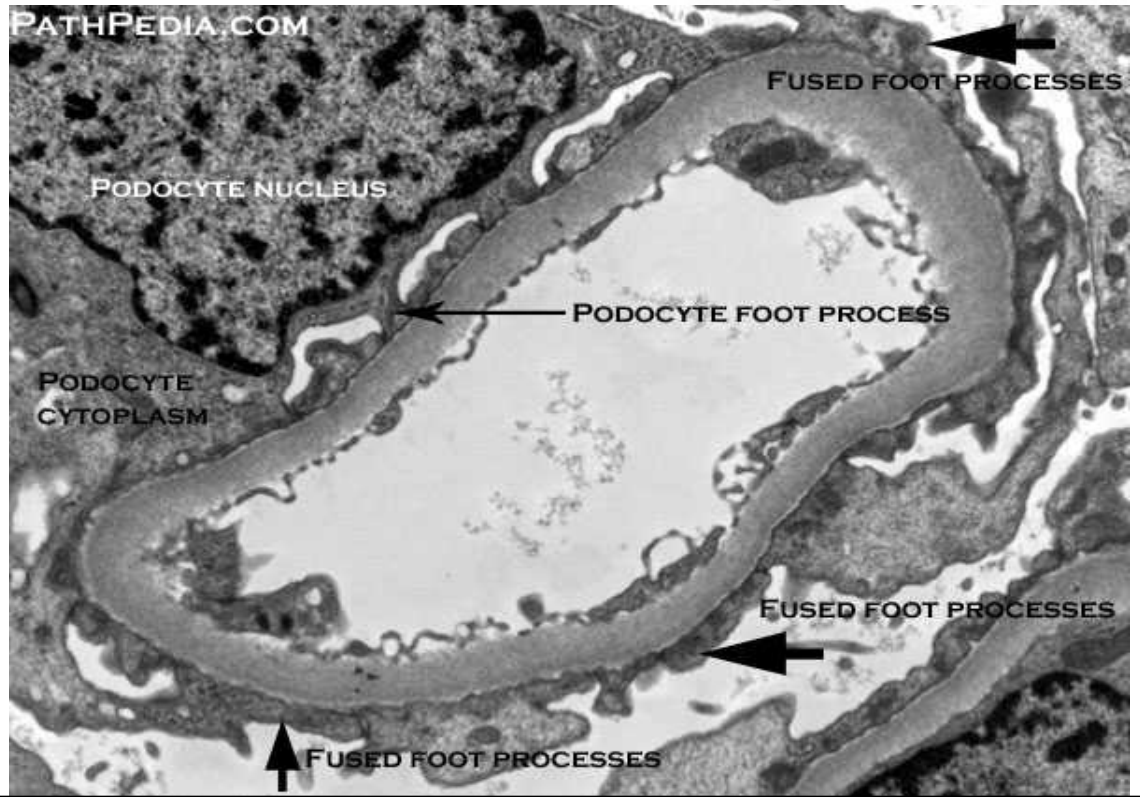
MCD:

Electron microscopy:

- MCD is characterized by diffuse fusion or effacement of the epithelial cell (podocyte) foot processes.
- This effacement is due to the retraction of the foot processes as a result of extensive cell swelling.

NOTE: effacement occurs in virtually all cases of nephrotic proteinuria; it is not specific for minimal-change glomerulopathy.





MCD: clinical features, treatment and prognosis

- C/F include:
  - Nephrotic syndrome
- Treatment and prognosis:
  - Over 90% of children and few adults have complete remission with corticosteroid therapy.
  - Prognosis: good, especially in children.
  - Some patients become steroid dependent i.e. they relapse each time corticosteroid treatment is stopped.
  - Less than 5% develop chronic renal failure

FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

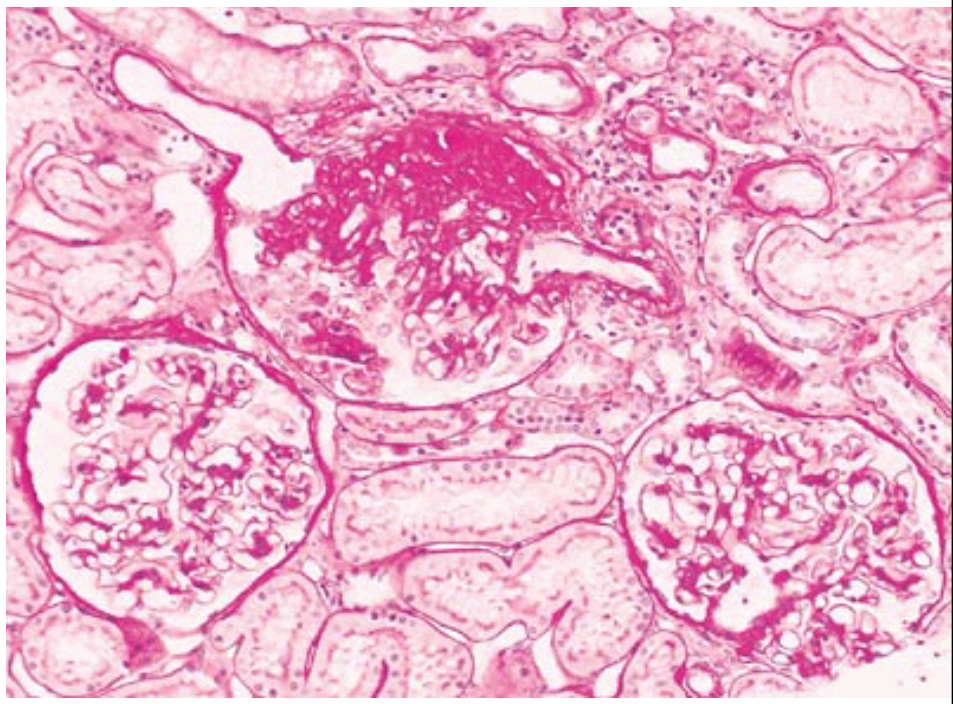
FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

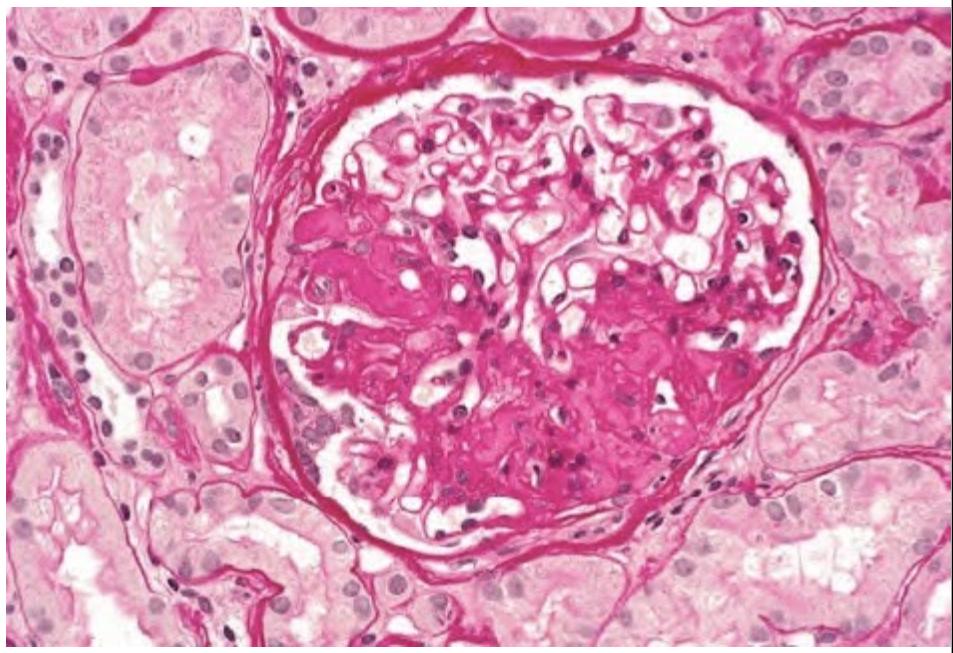
LM:

- Occurs in older children and adults.
- Glomeruli at the corticomedullary junction are commonly affected.
- Only some of the glomeruli are involved (i.e. focal).
- There is focal and segmental sclerosis of the glomeruli (i.e. some glomeruli show sclerosis in a segment of the glomerular tuft).
- Adhesions and hyalinosis +/-

IF: Usually negative. Sometimes IgM is positive.

EM: There is patchy/focal effacement of podocyte foot processes.

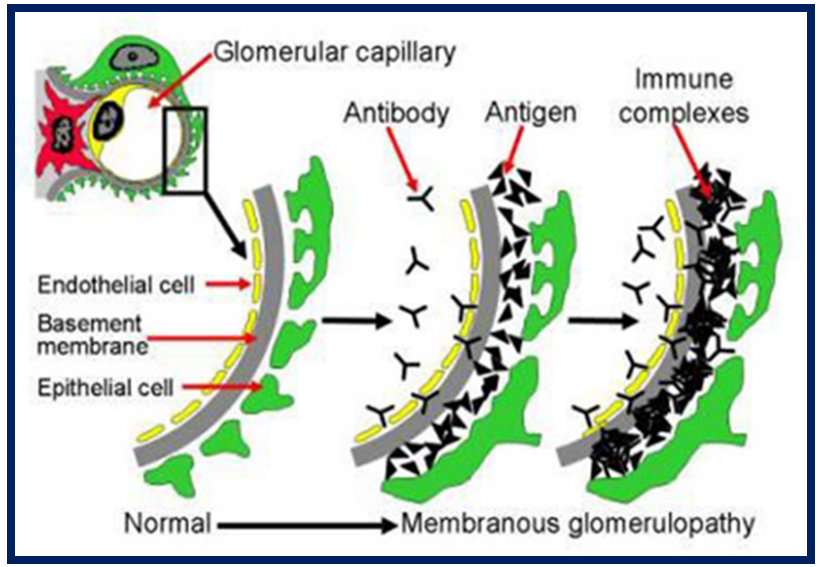


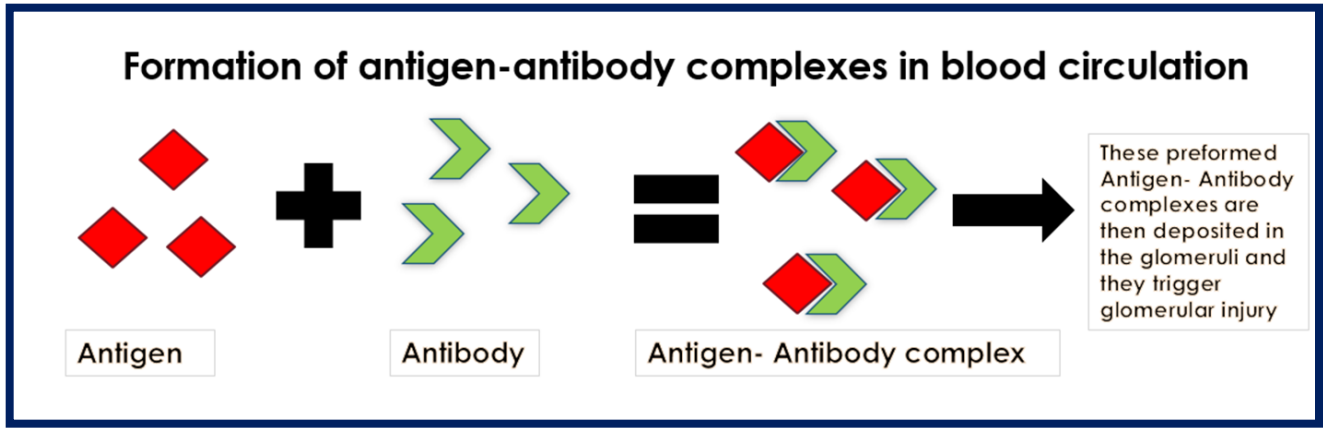


Membranous glomerulopathy/ membranous glomerulonephritis (GN)/ membranous nephropathy

Membranous glomerulopathy/ nephropathy/ GN

- A frequent cause of the nephrotic syndrome in adults (commonly 30-50 years).
- The proteinuria does not usually respond to corticosteroid therapy
- Is an immune complex disease. The antigen-antibody immune complexes are formed either in-situ in the glomeruli or are pre-formed in circulation and then deposited in the glomeruli.





- It is characterized by deposition of electron dense immune complexes in the subepithelial area in the glomeruli (between the podocytes and the GBM).
- It is a slowly progressive disease. If not treated some cases → progress to fibrosis of the kidneys (glomerular sclerosis, atrophy of tubules and interstitial fibrosis) and end stage disease/ renal failure.
- 10% to 30% have a more benign course with good prognosis.

Membranous glomerulopathy/ nephropathy/ GN

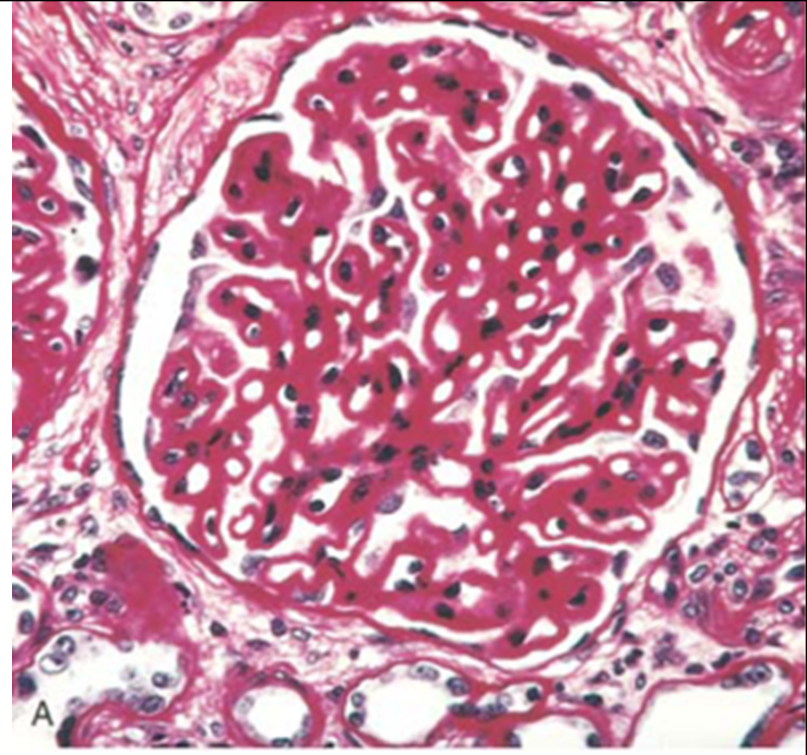
Membranous glomerulopathy can be:

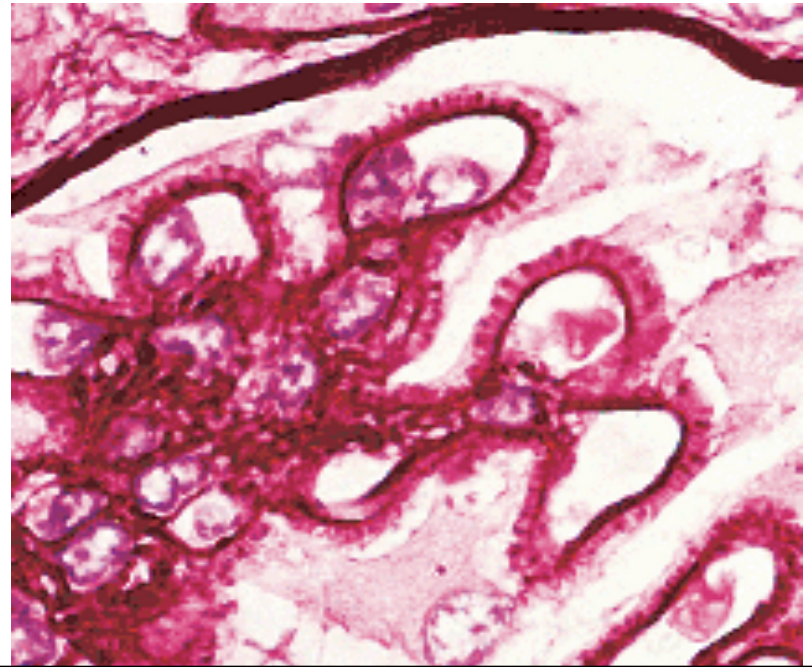
- Primary/idiopathic membranous GN (80% of cases): in primary MN there are autoantibodies against phospholipase A2 receptor 1 (PLA2R1) antigen.
- Secondary membranous GN: causes include autoimmune disease (SLE), infectious disease (hepatitis B virus infection), therapeutic agents (penicillamine), neoplasms (lung cancer). Patient should be investigated for secondary causes.

Membranous glomerulopathy/ nephropathy/ GN

Light microscopy:

- The capillary walls of the glomeruli are diffusely thickened (due to the subepithelial deposits seen on EM).
- The deposits are separated from each other by protrusions of GBM matrix called spikes (bottom picture).
- As the disease progresses there is glomerular sclerosis and interstitial fibrosis.

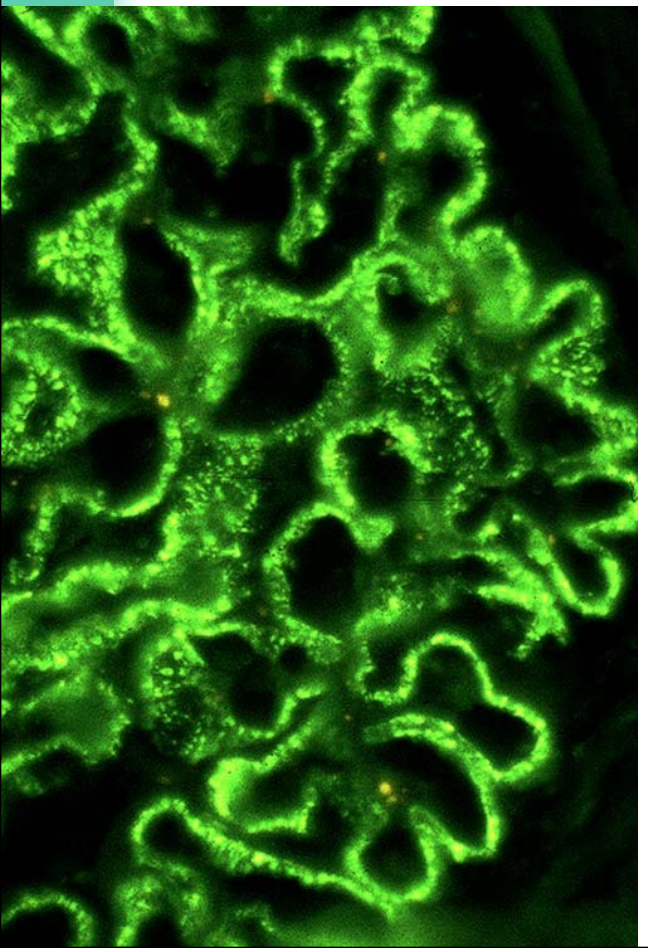


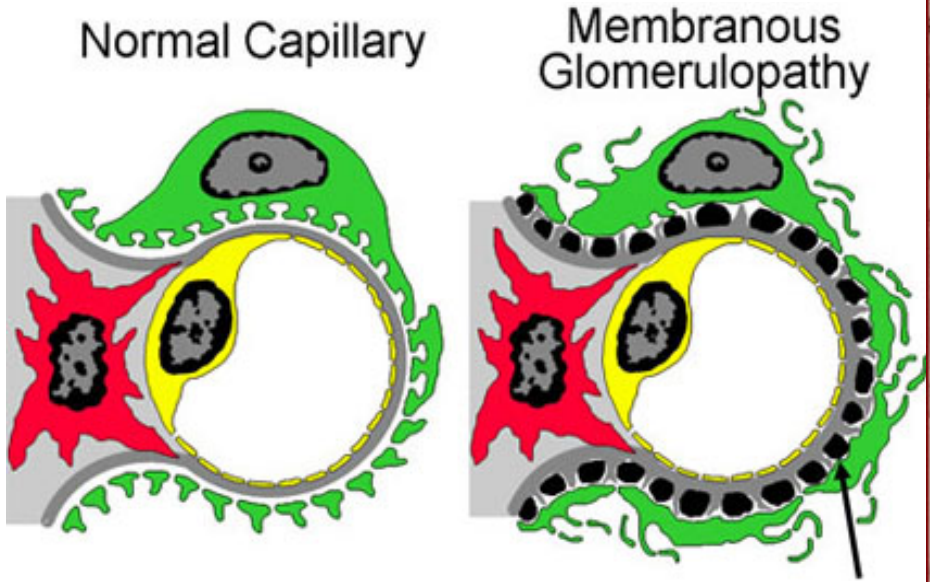


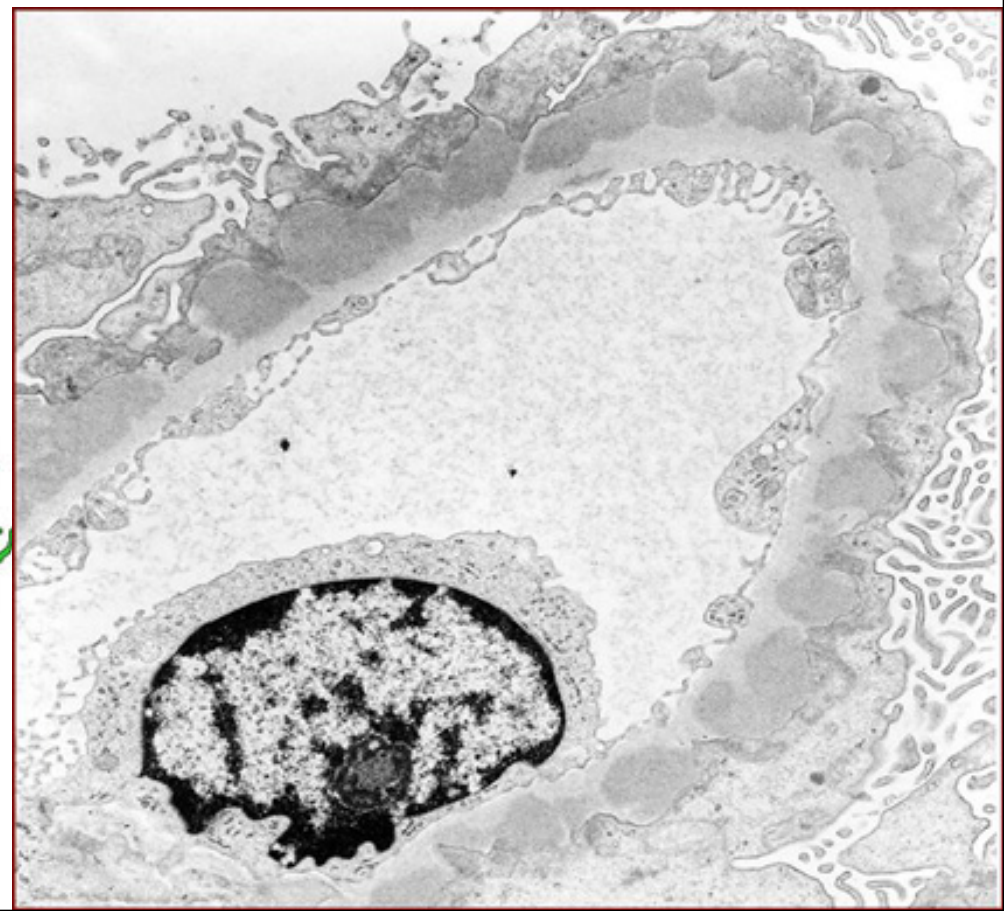
Membranous GN

IF: granular positivity for immunoglobulin IgG and complement C3 along the GBM.

EM: the immune complex appear in capillary walls as electron-dense deposits in the subepithelial space. There is diffuse effacement of epithelial cell foot processes also.







DIABETIC NEPHROPATHY

DIABETIC NEPHROPATHY (DM)

Long standing poorly controlled DM → leads to kidney disease. Is a common cause of secondary nephrotic syndrome.

LM: shows 2 types of lesions:

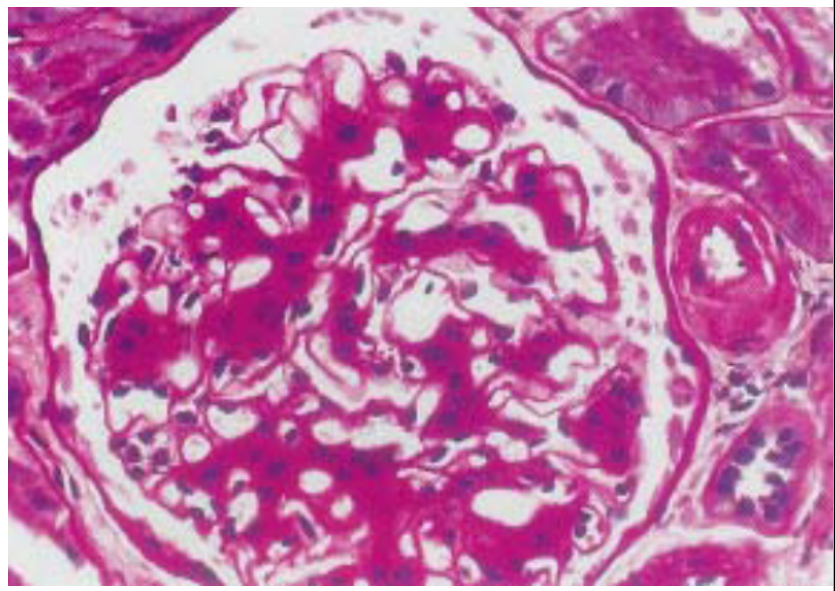
1. **Diffuse glomerulosclerosis:** all the glomeruli show increase in mesangial matrix ending in sclerosis (top photo).
2. **Nodular glomerulosclerosis (Kimmelstiel Wilson nodules):** there are nodules in the mesangium. These nodules are spherical and eosinophilic, with a central acellular area. It is pathogonomic of diabetic nephropathy (bottom photo).

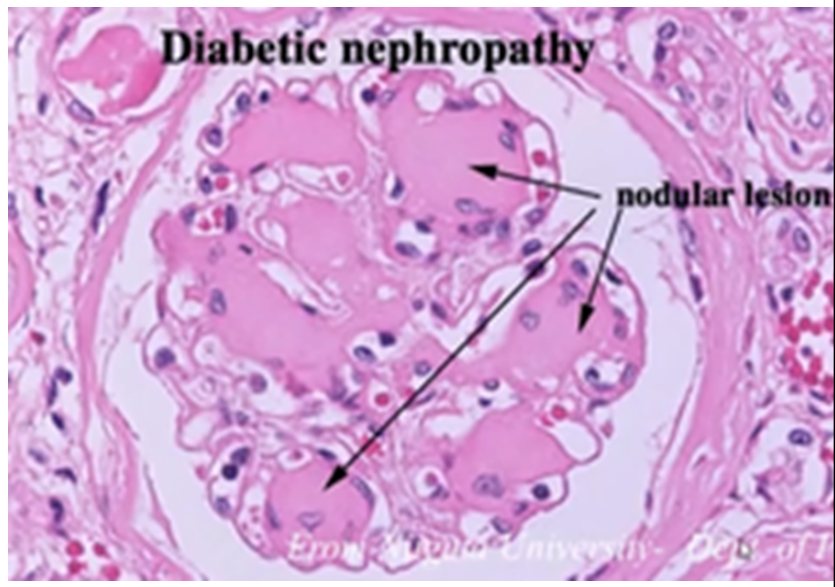
Both show diffuse thickening of the glomerular basement membrane

If not treated can progress to → end staged kidney/ renal failure.

IF: negative.

EM: there is diffuse increase in the thickness of the glomerular basement membrane.





NEPHRITIC SYNDROME

Nephritic syndrome

Nephritic syndrome is a clinical complex characterized by acute onset of:

- **Hematuria** (smoky brown urine). The hematuria is a result of glomerular injury and inflammatory rupture of the glomerular capillaries with resultant bleeding into the Bowman's space. The rbcs pass into the tubules and mix with proteinaceous material in the tubules and forms rbc casts (which are passed in the urine). The hemodynamic changes caused by the rupture lead to a reduction in the glomerular filtration rate (GFR).
- **Oliguria:** is a result of the reduced GFR.
- **Azotemia:** increased blood urea nitrogen and creatinine. It is also a result of reduced GRF.
- **Hypertension:** it is a result of the fluid retention and renin release from the ischemic kidneys.

NOTE: There may be mild proteinuria and edema.

The example of nephritic syndrome include:

- Post-infectious glomerulonephritis: it is the most classical example.
- Lupus nephritis: it can also present as nephrotic syndrome

Post-infectious glomerulonephritis (PIGN)

Post-infectious glomerulonephritis (PIGN)

- It is a type of acute diffuse proliferative GN.
- It is caused by deposition of immune complexes in glomeruli.
- The most common cause of post-infectious glomerulonephritis is infection with group A, beta-hemolytic streptococci and is therefore also called **post-streptococcal glomerulonephritis** . Other infections include pneumococcal and staphylococcal infections and viral diseases (mumps, measles, chickenpox etc.).
- Usually there is a latent period between the exposure and the occurrence of glomerulonephritis
- Classically PIGN develops in children 1 to 4 weeks after streptococcal infection of the pharynx (pharyngitis) or tonsils (tonsillitis) or the skin (impetigo or infected insect bite).
- This disease was more common in the past (because now we have antibiotics), but it is still one of the common childhood renal diseases.

Post-infectious GN: pathogenesis

- The immune complexes are deposited in the glomeruli in the subepithelial area and are composed of IgG and C3. The deposits initiate inflammation by
  - activating complements: this way the complements get used up leading to development of hypocomplementemia (serum C3 levels are low during the acute phase of disease).
  - And activating various other inflammatory mediators

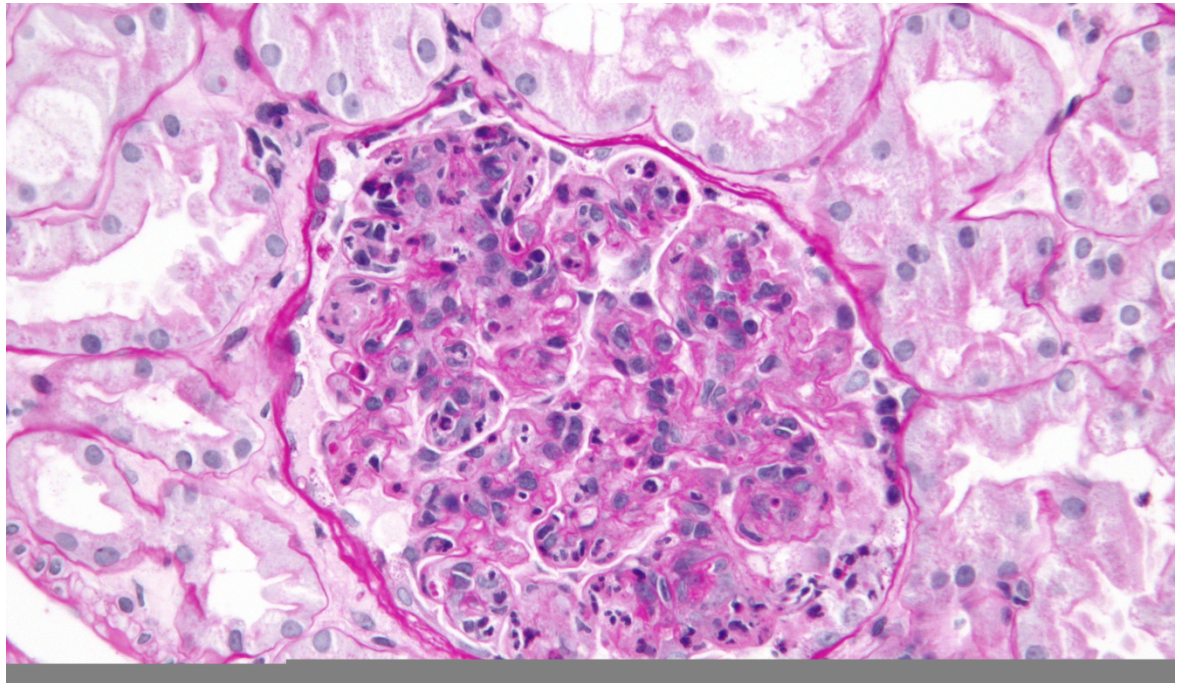
All these inflammatory mediators:

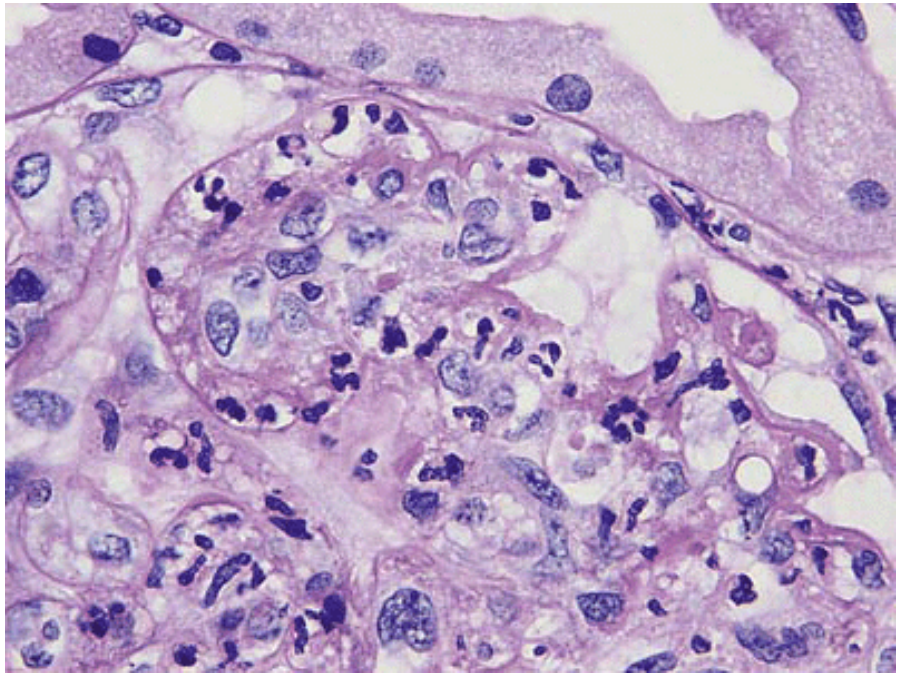
- attracts and activate neutrophils and monocytes
- stimulates proliferation of mesangial and endothelial cell proliferation.

These effects result in marked glomerular hypercellularity → resulting in diffuse proliferative glomerulonephritis.

Post-infectious GN: Light microscopy

- There is diffuse enlargement and hypercellularity of glomeruli due to proliferation of endothelial cells and mesangial cells and infiltration of neutrophils and monocytes.
- Crescents maybe present.
- Glomerular necrosis maybe present.
- All histologic changes resolve completely in most patients after several months

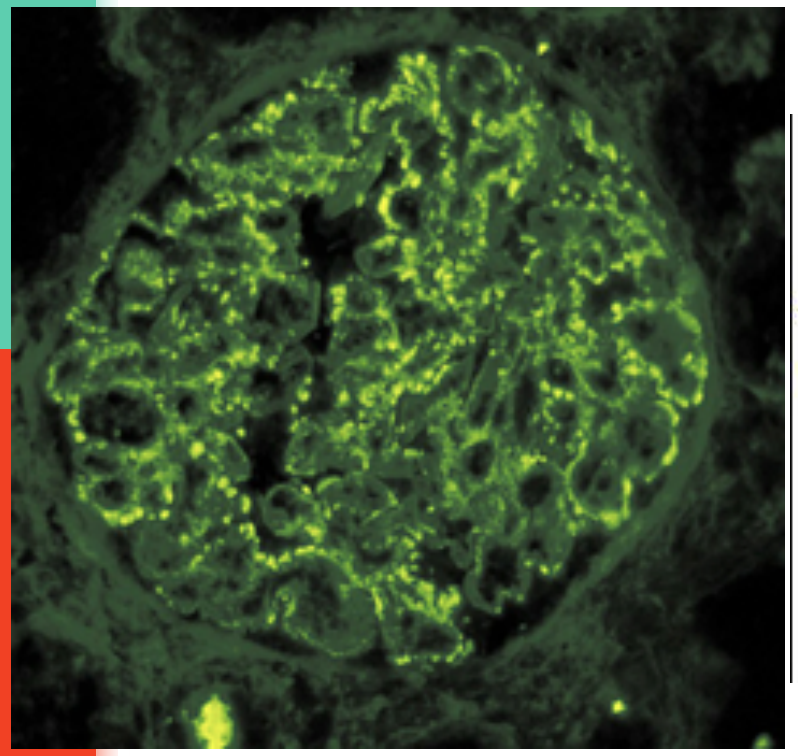




Post-infectious GN

IF: coarse granular (lumpy bumpy) IgG and C3 are positive along the capillary walls.

EM: characteristic subepithelial electron dense immune deposits. They look like dome shaped humps (called subepithelial humps). The deposits clear up and disappear in a few months.



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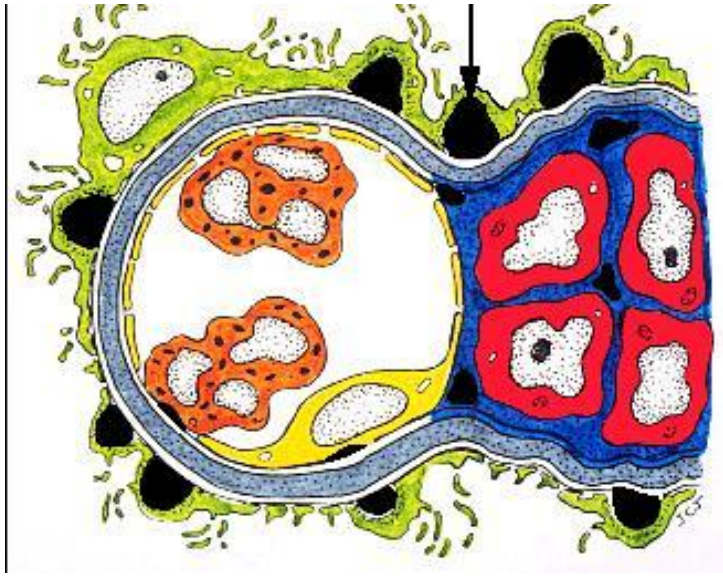

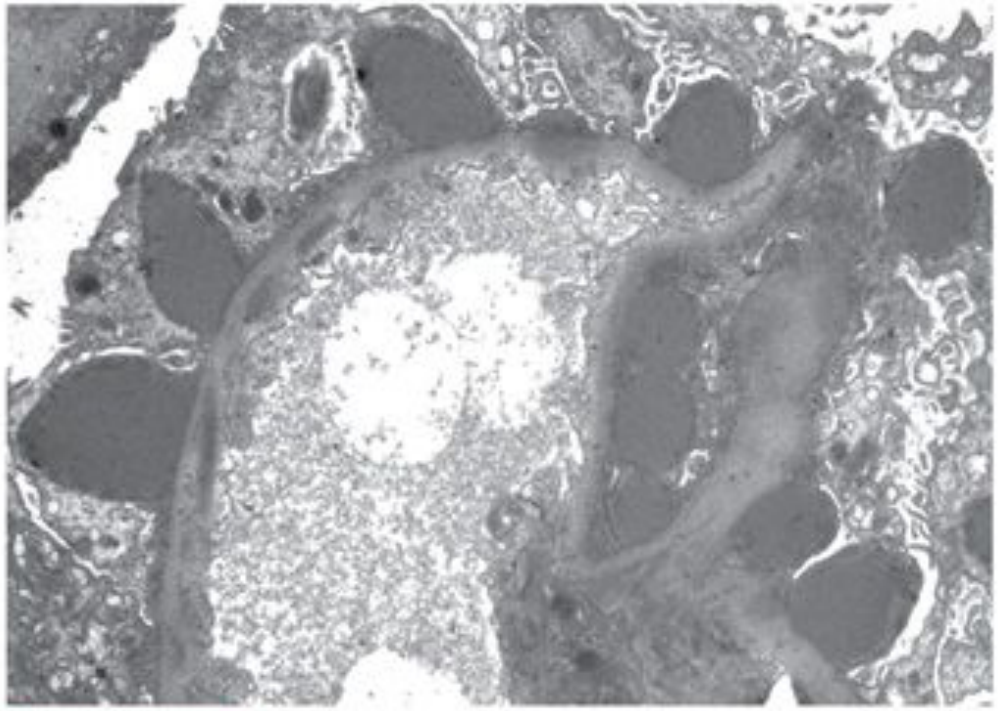

FIGURE 41.6 Postinfectious glomerulonephritis. Note the discrete, electron-dense glomerular subepithelial deposit (hump) (uranyl acetate, lead citrate; ×9,000).

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Post-infectious GN: clinical features

- The onset of kidney disease is sudden.
- Present as nephritic syndrome (oliguria, hematuria, hypertension and azotemia).
- Serum C3 levels are low during the acute phase.
- Diagnosis depends on serologic evidence of a rise in antibody titers to streptococcal products e.g. ASO titre is positive.
- This disease resolves in over 90% of patients. Rarely patients (usually adults) develop progressive renal failure.
- Grossly there is multiple punctate hemorrhagic spots on the kidney surface.

LUPUS NEPHROPATHY/ NEPHRITIS (LN)

LUPUS NEPHROPATHY/ NEPHRITIS (LN)

- LN is seen in patients with the autoimmune disease **called systemic lupus erythematosus (SLE).**
- When SLE patients have associated renal disease its is called as lupus nephritis (LN).
- These patients classically have high levels of **Antinuclear antibodies (ANA)** and double stranded **DNA (dsDNA)**
- It can present as **nephrotic or nephritic syndrome.**
- **LN is an immune complex mediated disease** in which there is the deposition of antigen antibody complexes in the glomeruli. The deposits trigger an inflammatory response which in turn triggers the proliferation of the epithelial, endothelial and mesangial cells of the glomeruli. It can even lead to glomerular necrosis.
- LN can be active or chronic or a combination of both.
- The LN lesions have been classified into 6 classes or groups by the International Society of Nephrology/Renal Pathology Society (ISN/RPS). This classification helps give information regarding the activity, chronicity and the prognosis of the disease.

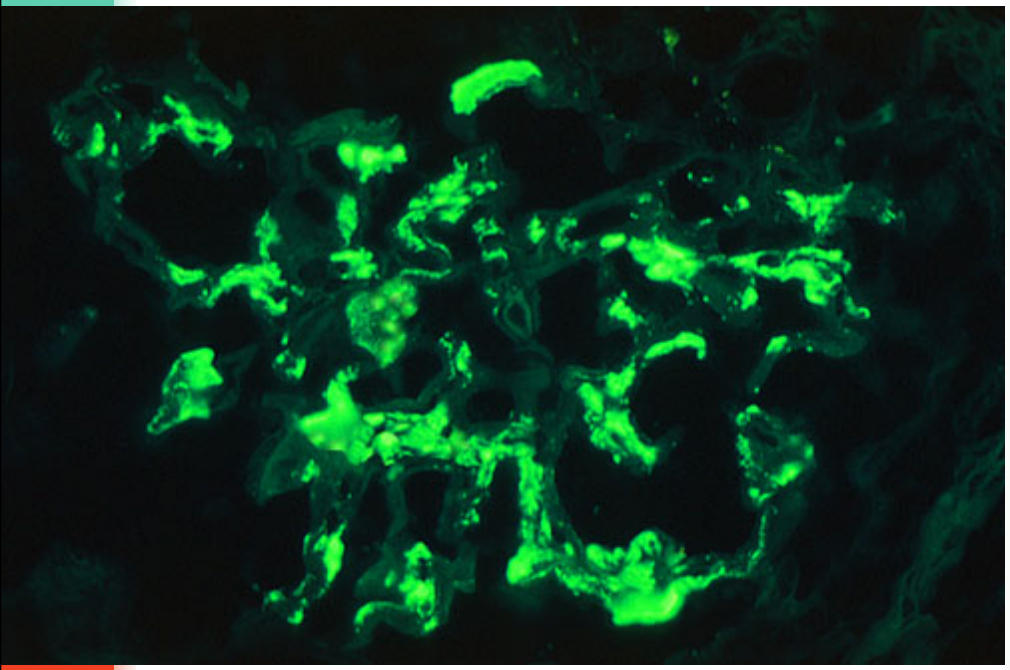
HEMATURIA

Hematuria

- IgA nephropathy (IgAN) is one of the most common type of primary glomerulonephritis that presents as hematuria
- IgAN is characterized by the deposition of IgA immunoglobulin in the mesangium/ paramesangium of glomeruli.
- It usually present as hematuria only and sometimes as nephritic syndrome.
- When it occurs in combination with vasculitis (leukocytoclastic vasculitis) and multiorgan involvement then is referred to as Henoch-Schonlein purpura.

IgA Nephropathy/Bergers disease

- **LM**: is very variable (may or may not show → mesangial hypercellularity, endocapillary hypercellularity, glomerular sclerosis, tubulo-interstitial scarring).
- **IF**: dominant IgA stain positivity in the mesangium.
- **EM**: immune complex deposits positive in the mesangium and paramesangial area.



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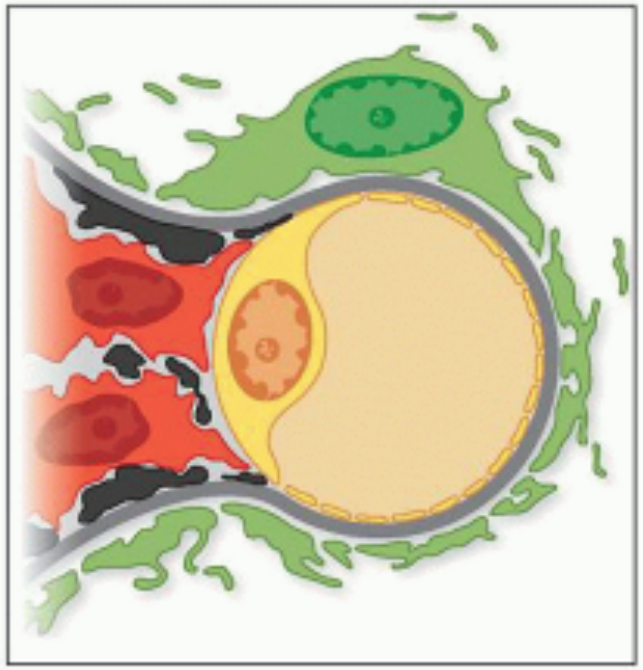

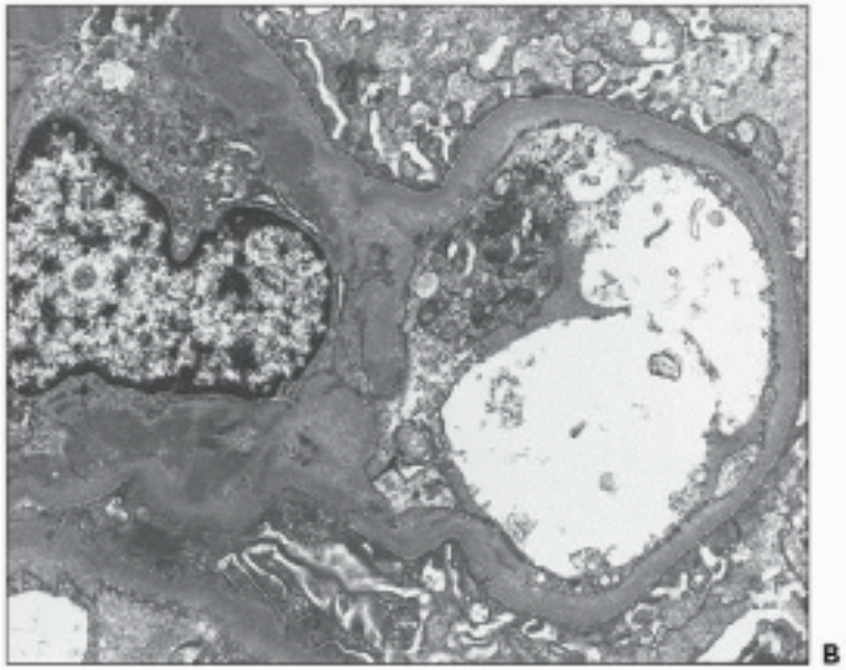

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