GLOMERULAR DISEASES

- **Primary Glomerulonephritis**
  Acute diffuse proliferative GN
  Rapidly progressive GN
  Membranous GN
  Lipoid nephrosis (minimal change disease)
  Focal segmental glomerulosclerosis
  Membranoproliferative GN
  IgA Nephropathy
  Chronic GN

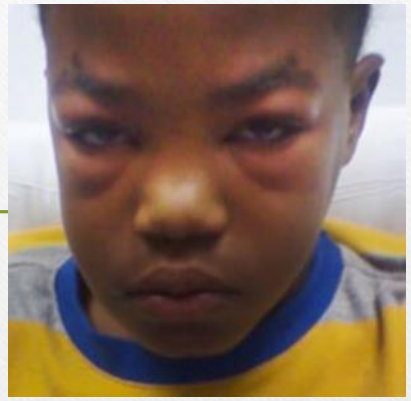
- **Secondary (Systemic) Diseases**
  Systemic lupus erythematosus
  Diabetes mellitus
  Amyloidosis
  Goodpasture's syndrome
  Polyarteritis nodosa
  Wagener's granulomatosis
  Henoch-Scholein purpura
  Bacterial endocarditis

. **Hereditary Disorders**

  Alport's syndrome

  Fabry's disease

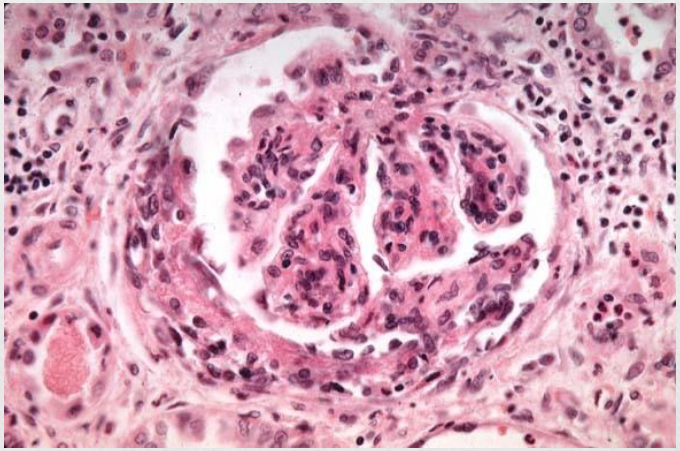
ACUTE GLOMERULONEPHRITIS



- Nephr**i**tic
- **H**oles in BM
- **H**ematuria, **H**ypertension,
- **H**ardly any urine (Oliguria), Azotemia
- in children following a strep infection
- POSTSTREPTOCOCCAL (old term)
- **H**YPERCELLULAR GLOMERULI
- INCREASED ENDOTHELIUM AND MESANGIUM
- IgG, IgM, C3 along GMB FOCALLY(**H**ump)
- 95% full recovery

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

- **Clinical definition, NOT a specific pathologic one**
- **“CRESCENTIC”**
- **Anti-GBM Ab**
- **Immune complex**
- **Anti-Neut. Ab**



NEPHROTIC SYNDROME

- **Only MASSIVE PROTEINURIA**
- **HYPOALBUMINEMIA**
- **EDEMA**
- **LIPIDEMIA/LIPIDURIA**
- **NUMEROUS CAUSES:**
  - **MEMBRANOUS, MINIMAL CHANGE, FOCAL SEGMTL.**
  - **DIABETES, AMYLOID, SLE, DRUGS**

Acute proliferative Glomerulonephritis:

This group is characterized by inflammatory alterations in the glomeruli and clinically by acute **nephritic** syndrome

Postsreptococcal type

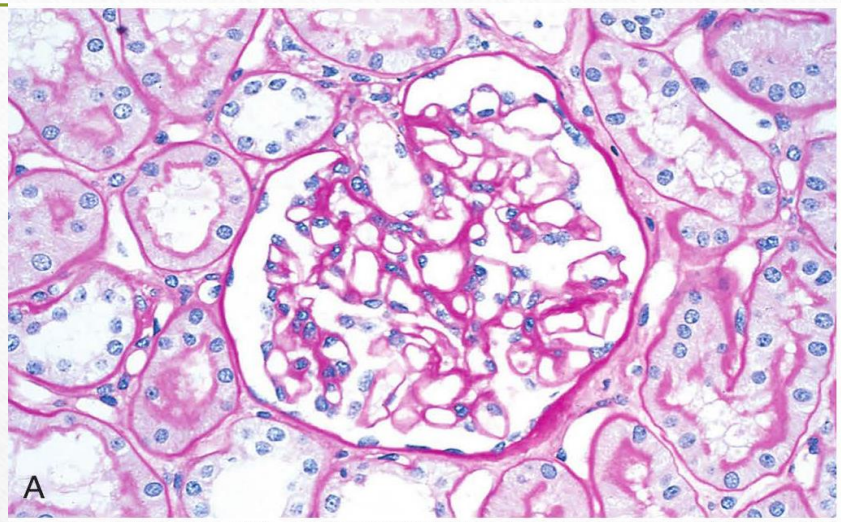
- Typically occurs 1-4 weeks after a streptococcal infection of the pharynx or skin.
- It affects most frequently children aging 6-10 years, but adults of any age can be involved.
- Only certain strains of group A, beta-hemolytic streptococci are **nephrogenic**.
- Many infections can cause glomerulonephritis e.g. Streptococci, Pneumococci, Staphylococci, & viruses like mumps, measles, HBV, HCV.

Postsreptococcal type-cont

- It is not known if these represent planted Ag, part of circulating immune complexes, or both.
- GBM proteins altered by streptococcal enzymes have also been implicated as an Ag.
- The classic diagnostic morphologic change is enlarged, hypercellular glomeruli, due to;
  - 1. Infiltration by leukocytes, both neutrophils and monocytes.
  - 2. Proliferation of endothelial and mesangial cells.
  - 3. Crescent formation, in severe cases.

Postsreptococcal

- The changes are both diffuse and global.
- By immunofluoresence microscopy, there are granular deposits of IgG, IgM and C3 in the mesangium and along the basement membrane.
- By electron microscope reveals **subepithelial humps**
- In the classic case, a young child abruptly develops fever, malaise, oliguria and hematuria, 1-4 weeks after recovery from a sore throat.
- The patient exhibits red cell cast in the urine, mild proteinuria, periorbital edema and mild to moderate hypertension.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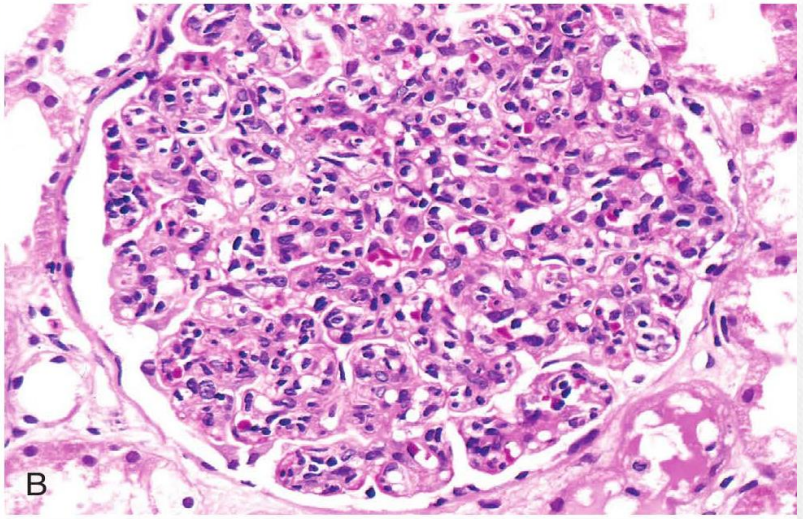
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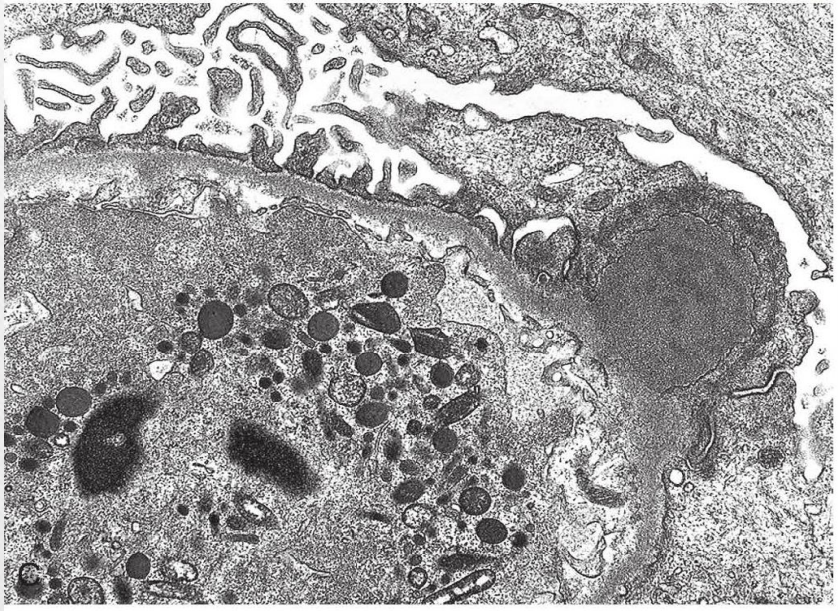

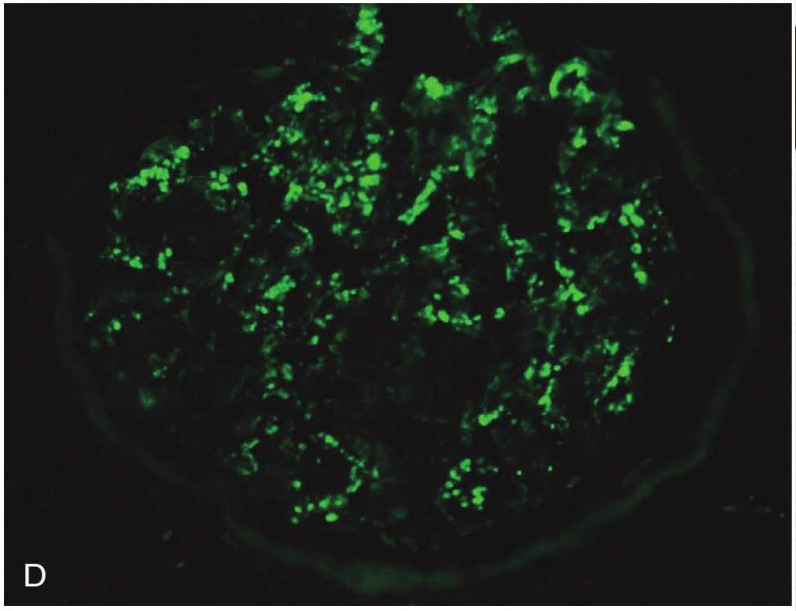
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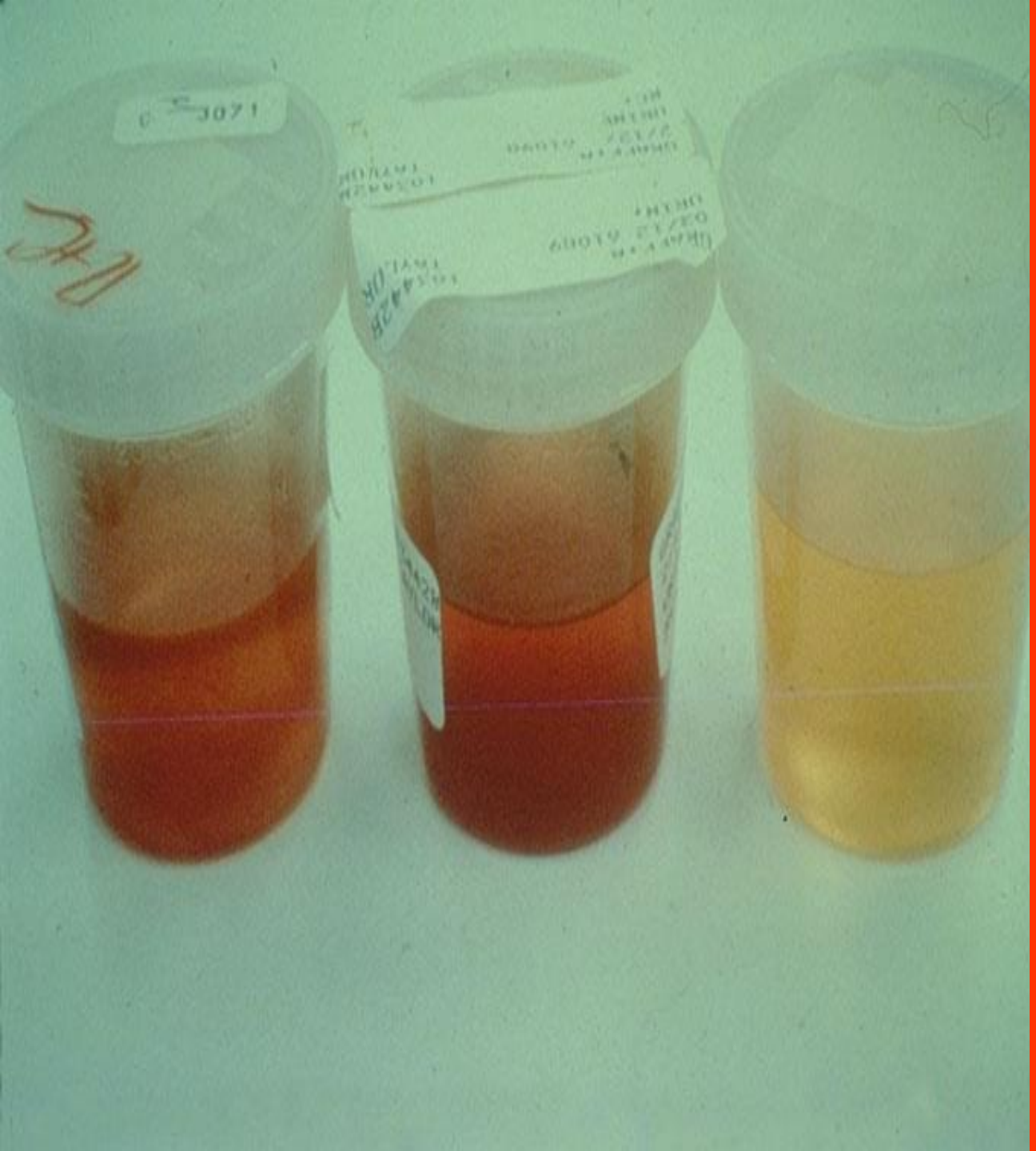
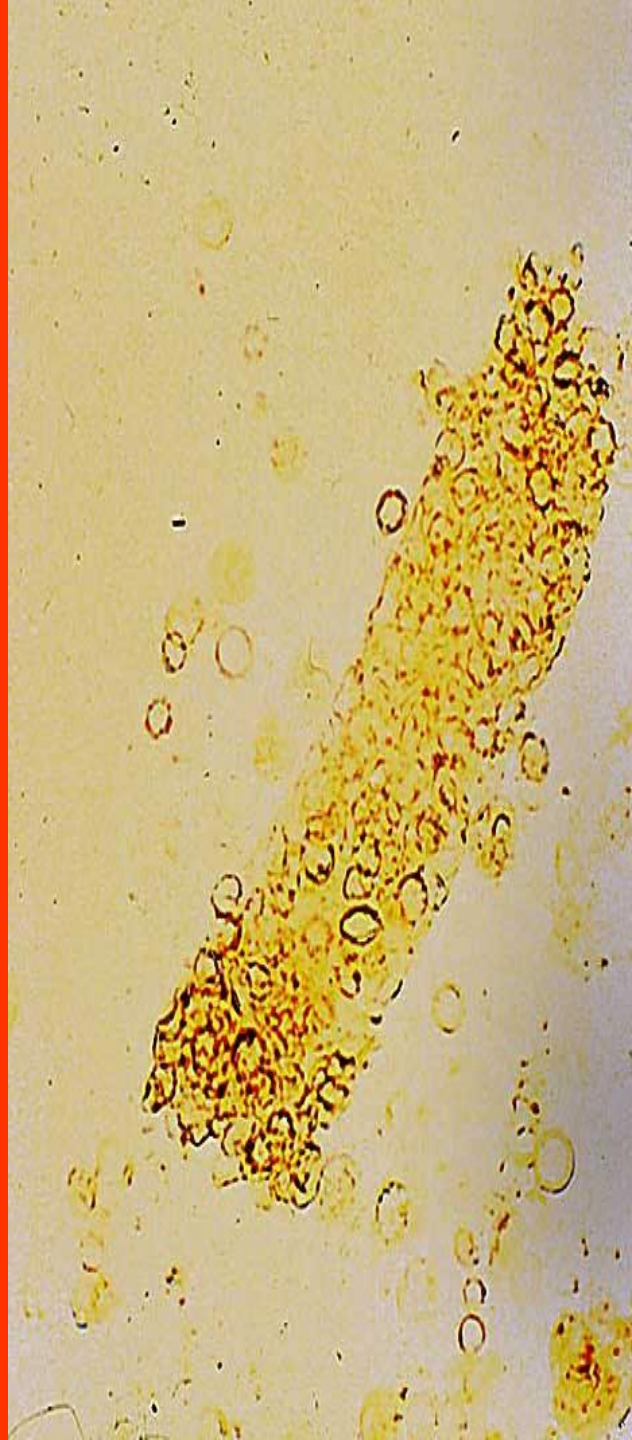




Postsreptococcal-cont

- More than 95% of affected children eventually recover completely with conservative therapy.
- Perhaps less than 1% do not improve, and develop a rapidly progressive form of glomerulonephropathy.
- Some of the remaining patients undergo slow progression to chronic glomerulonephropathy.
- In adults, the disease is less benign, as only 60% of patients do recover promptly

Rapidly Progressive (Crescentic) Glomerulonephropathy

- It is a syndrome associated with severe glomerular injury and is characterized clinically by rapid and progressive loss of renal function, and if untreated, death from renal failure within weeks or months .
- Regardless of the cause, the classic histologic picture is the **presence of crescents** in most of the glomeruli
- obliteration of Bowman's space & compression of glomerular tuft
- fibrin strands are prominent between the cell layers and crescent; distinct **ruptures of the BM**

Classification and pathogenesis

- In most of the cases, immunologic injury of the glomeruli is present. Accordingly 3 groups are identified

1. Type I RPGN (Anti-GBM AB-Mediated)

Idiopathic

Goodpasture Syndrome

2. Type II RPGN (Immune complex-Mediated)

Idiopathic

Postinfectious

Systemic lupus erythemotosus

Henoch-Schonlein purpura (IgA)

Others

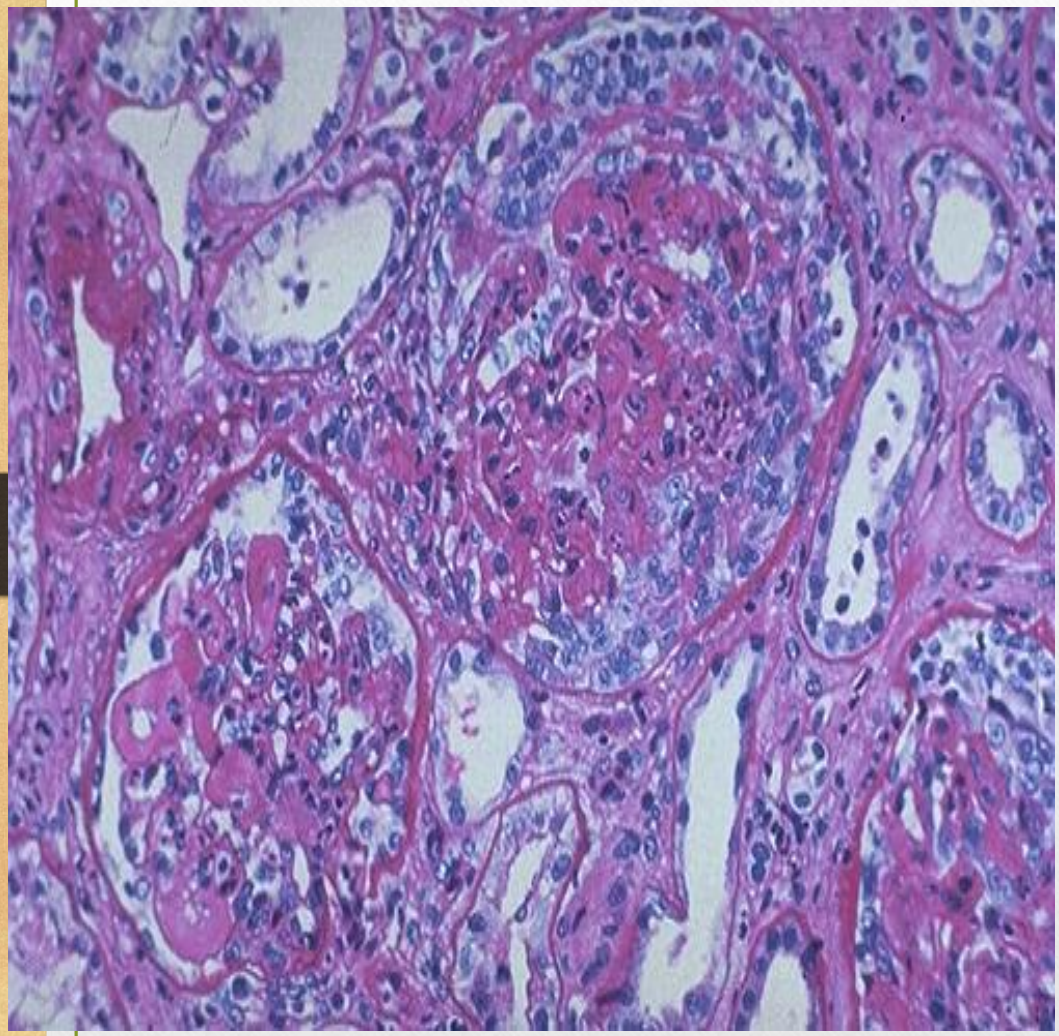
3. Type III RPGN (Pauci-Immune)

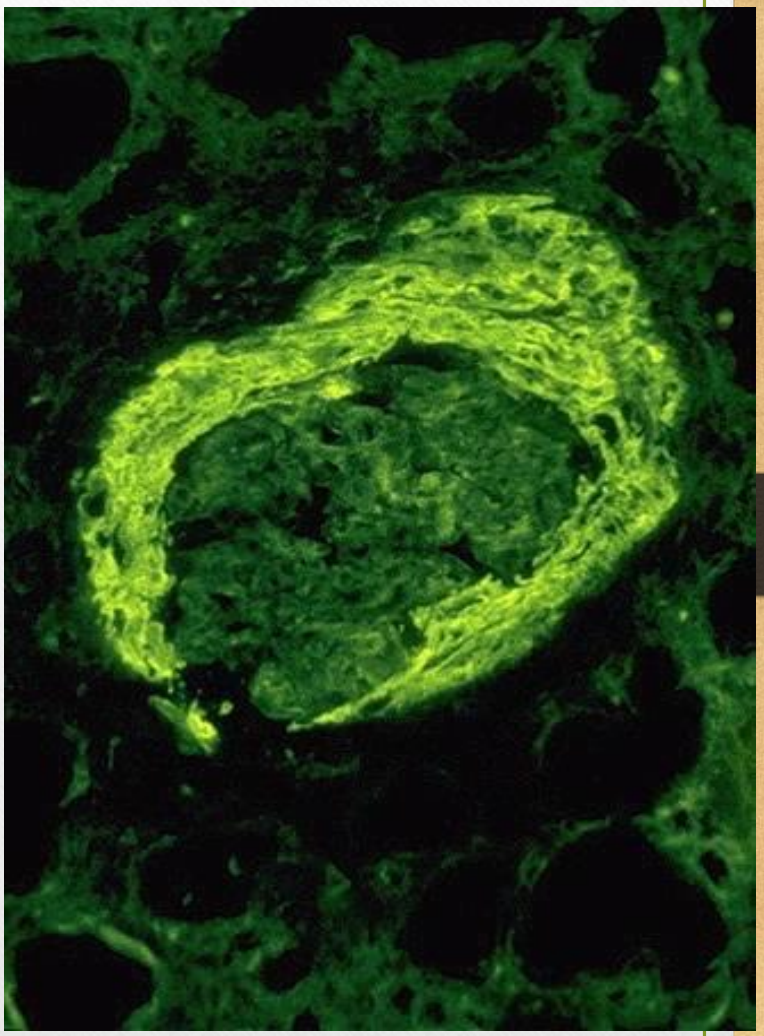
ANCA associated

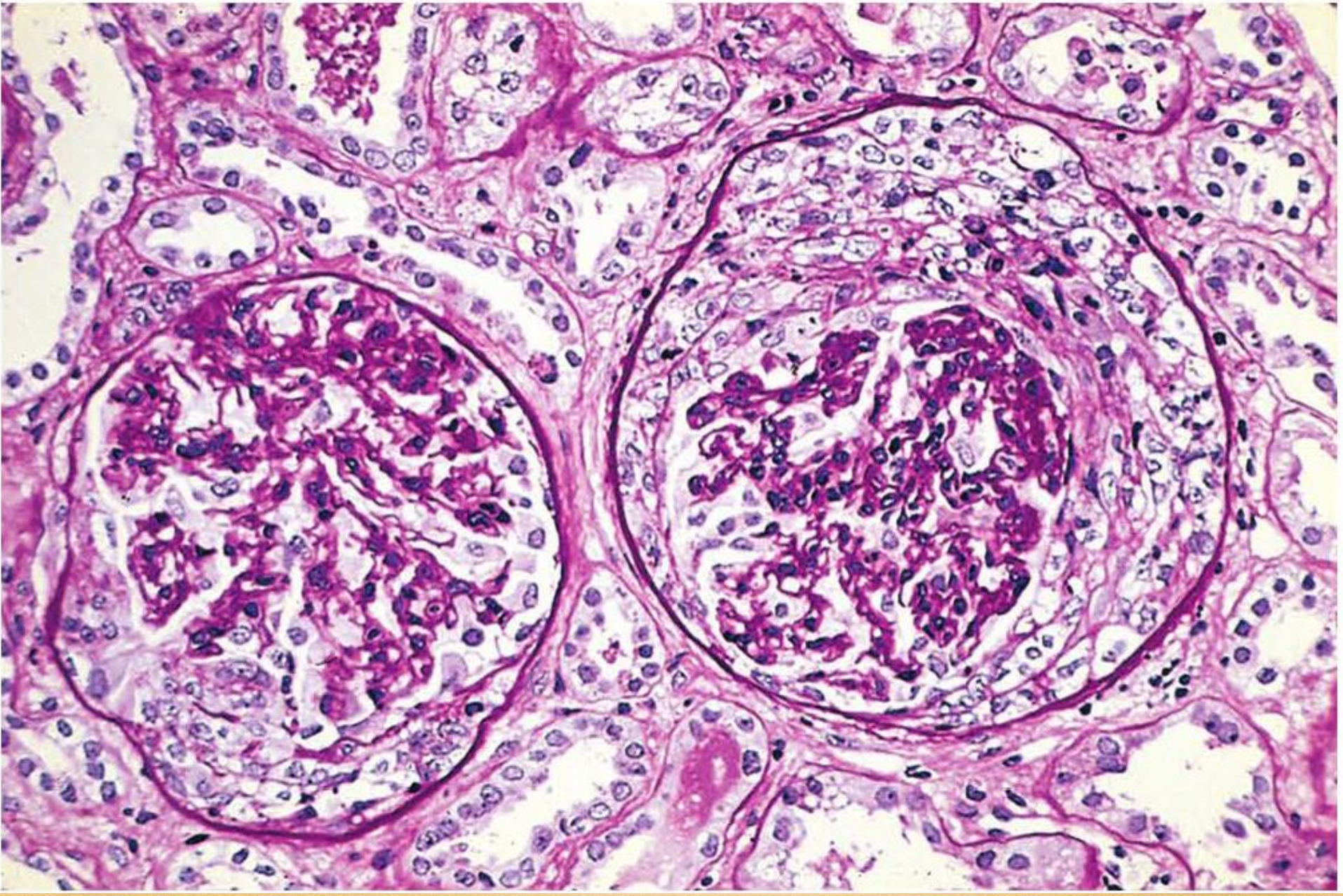
Idiopathic

Wegener granulomatosis

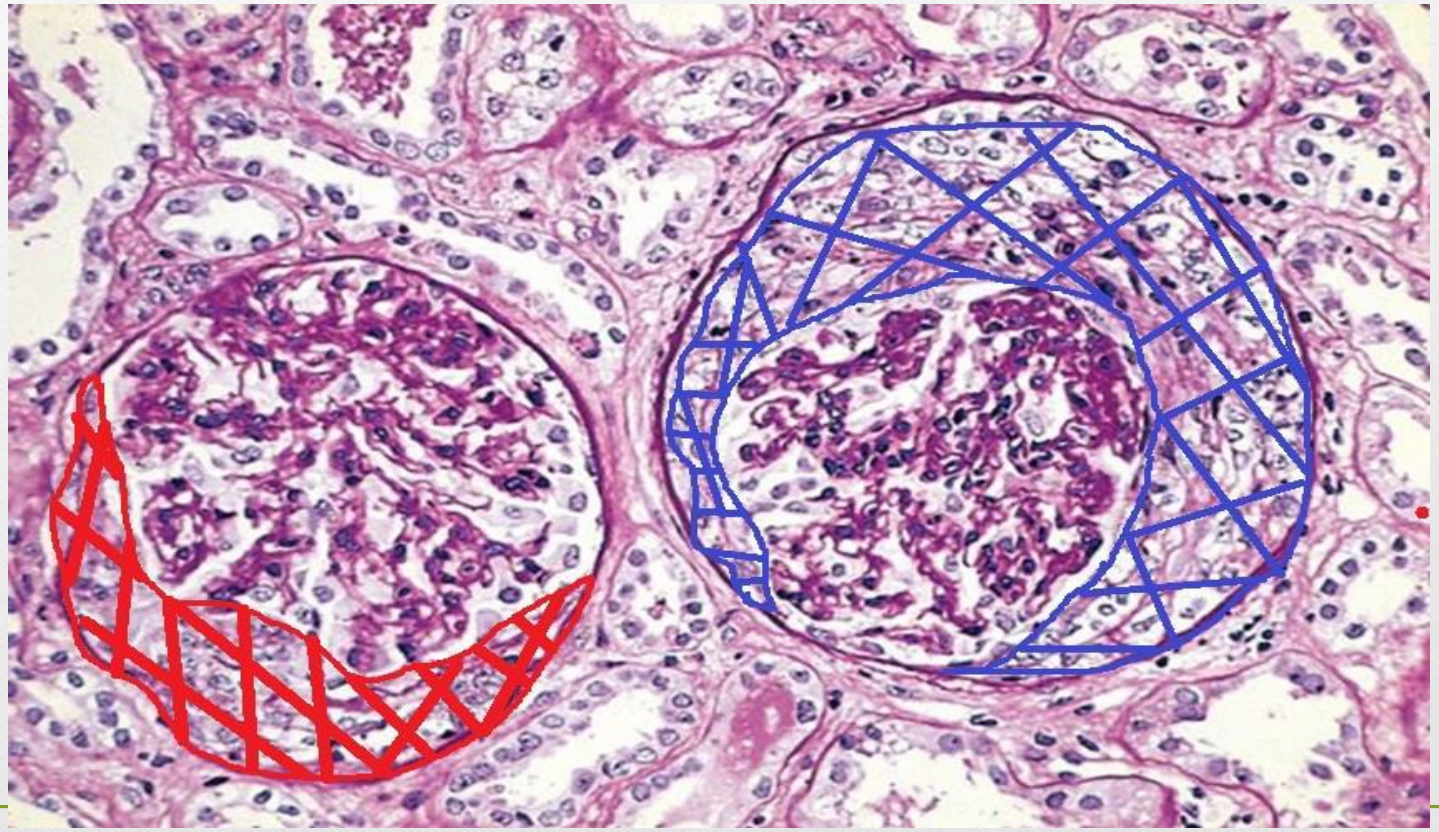
Microscopic polyarteritis nodosa

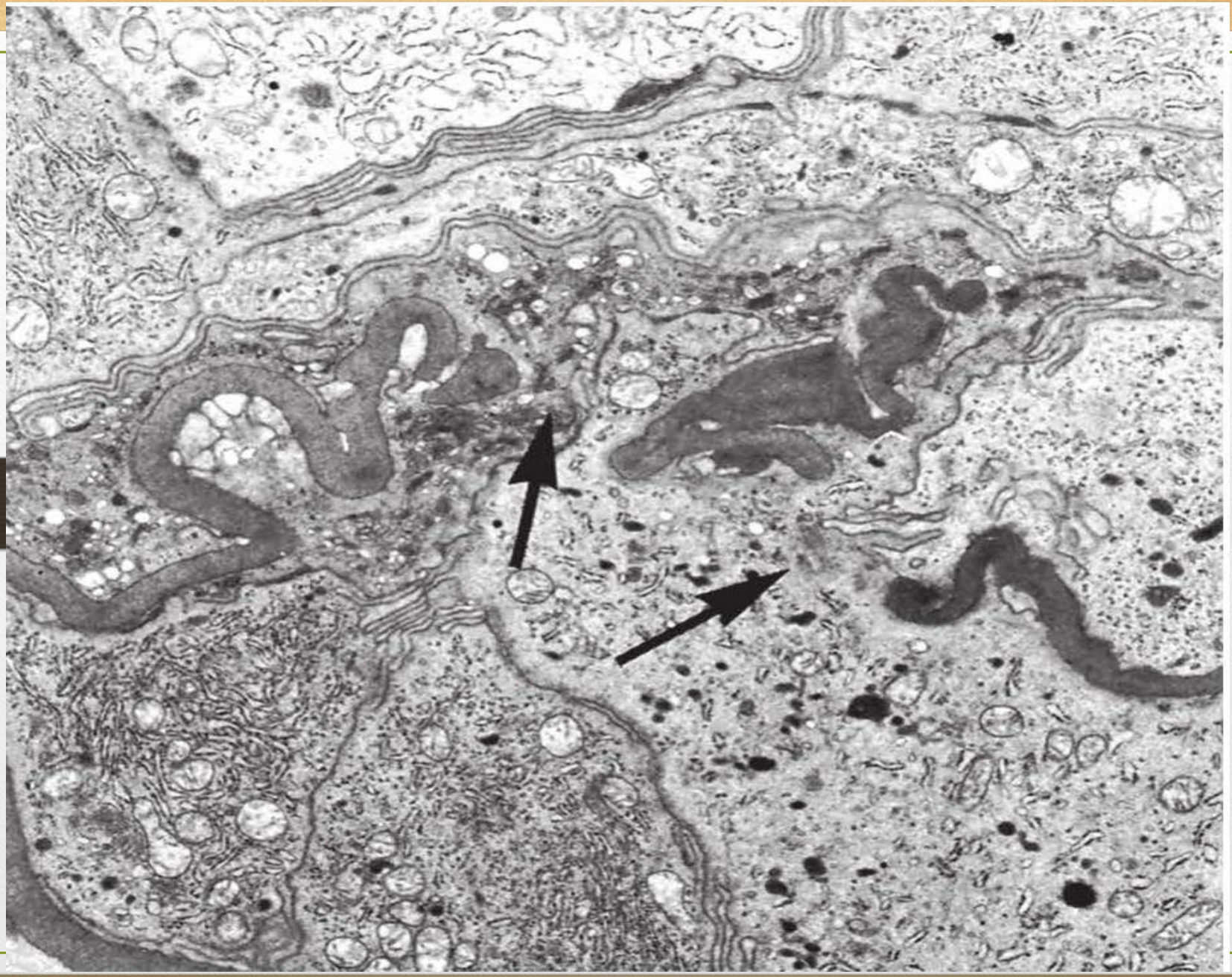






Crescentic glomerulonephritis (PAS stain)





Morphology,

- Gross: The kidneys are enlarged and pale, often with petechial hemorrhages on the cortical surfaces(flea bitten kidney).

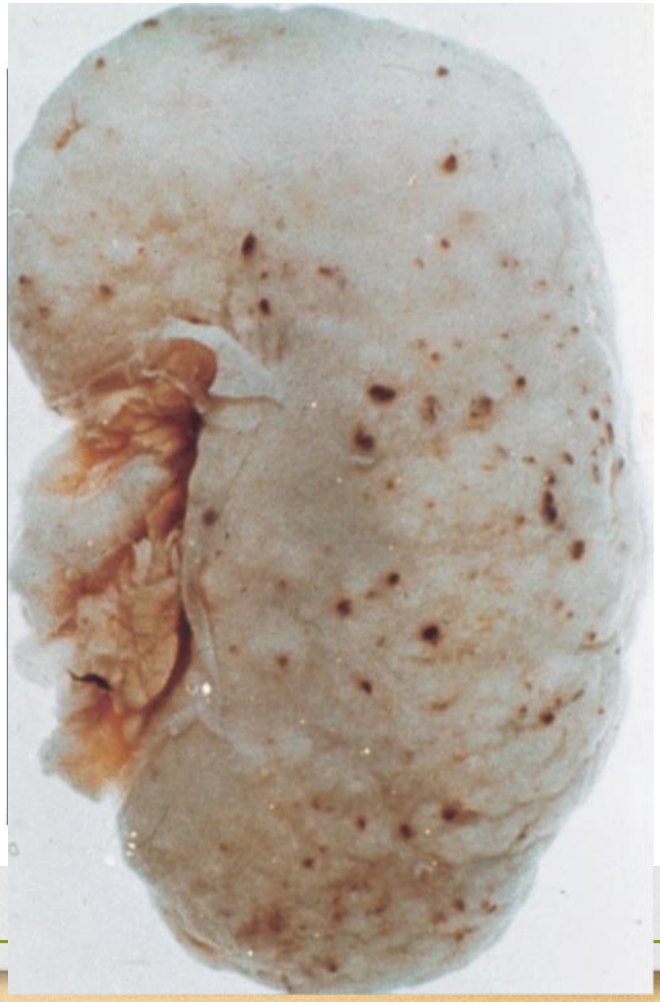
- Mic.: The histologic picture is dominated by the formation of crescents.
- Electron microscopy shows distinct rupture in the basement membrane.
- By immunofluorescence microscopy, postinfectious cases exhibit granular immune deposits; Goodpasture syndrome cases show linear deposits and pauci-immune cases have little or no deposits.

FLEA-BITTEN KIDNEY

SEEN IN

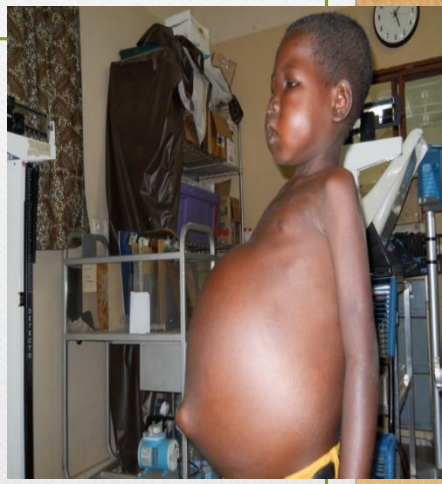
- Malignant hypertension
- Infective endocarditis
- Wegener's granulomatosis
- RPGN (including Good-Pasteur's syndrome)
- SLE (type IV)
- Leptos

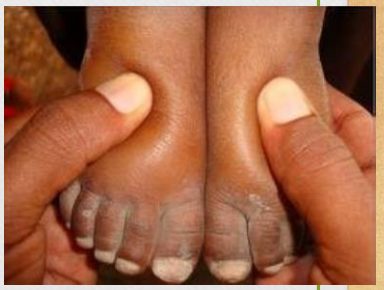
Thought to be due to thrombosis or embolism of glomerular capillaries with fibrinoid necrosis, causing tiny haemorrhagic microinfarcts in the cortex



NEPHROTIC SYNDROME

- Syndrome of Glomerular dysfunction that is characterized by *increased loss of proteins in the urin*e due to increased basement membrane permeability
- **CLINICAL MANIFESTATIONS**
- Massive proteinuria without hematuria [>3.5g/ day]
- Hypoalbuminemia [<3g/dl]
- Periorbital edema then …
- Generalized edema – Due to ↓'d plasma oncotic pressure
- Hyperlipiduria and Oval Fat Bodies
- Hyperlidemia and Hypercholesterolemia – due to loss of lipoproteins and alterations in liver production of lipoproteins
- Increase in Infections due to loss of low weight globulins and complement
- Loss of anticoagulants → hypercoagulable state





Nephrotic Syndrome

- Certain glomerular diseases virtually always produce the nephrotic syndrome.

- The manifestations include;
  - Massive proteinuria (selective albuminuria) > 3.5 gram of protein / day.
  - Hypoalbuminemia (plasma albumin less than 3 gram / dl).
  - Generalized edema.
  - Hyperlipidemia & lipiduria.
  - Little or no Azotemia or hypertension.

Albuminuria is due to derangement of Glomerular capillary wall.

Minimal Change Disease

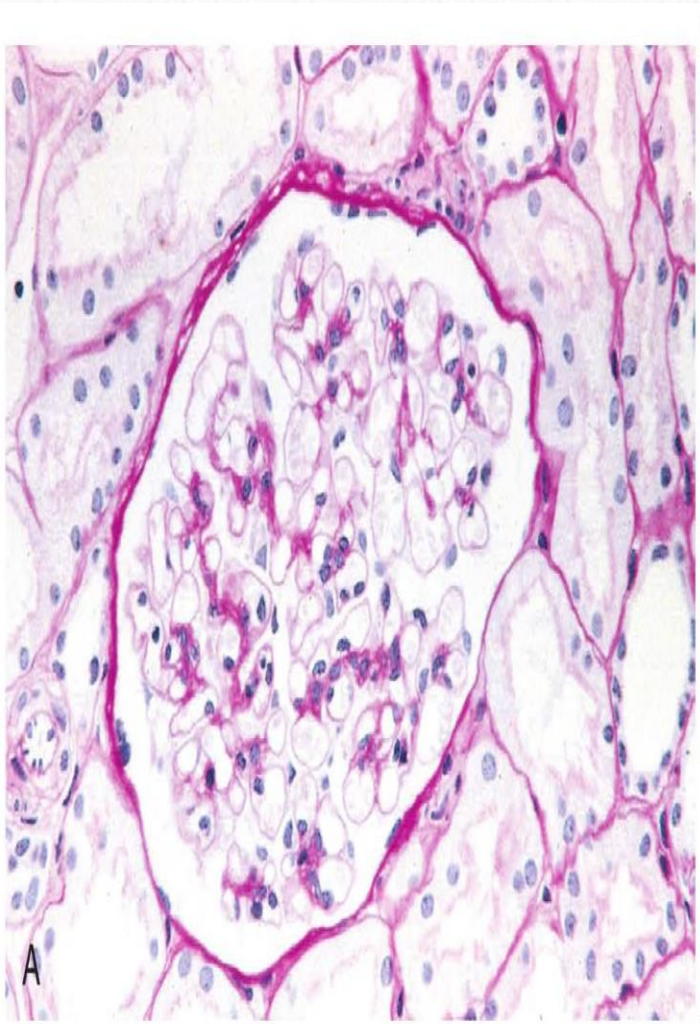
- This relatively benign disorder is the most frequent cause of nephrotic syndrome in children.
- The peak incidence is at 2-6 years of age.
- The disease sometimes follows a respiratory infection or routine immunization.

Pathogenesis of Minimal Change disease

- 1. Disorders of T- Cells (unknown mechanism).
- 2. Nephrin gene mutation (recently discovered) & mainly seen in congenital type of nephrotic syndrome (Finnish Syndrome).

Morphology

- The glomeruli are normal by light microscopy and immunoflurecent study.
- tubules are laden with lipid (secondary to hyperlipidemia) = “lipid nephrosis”
- By electron microscopy, the basement membrane appears normal; the principal lesion is the uniform and diffuse effacement of foot processes of the visceral epithelial cells.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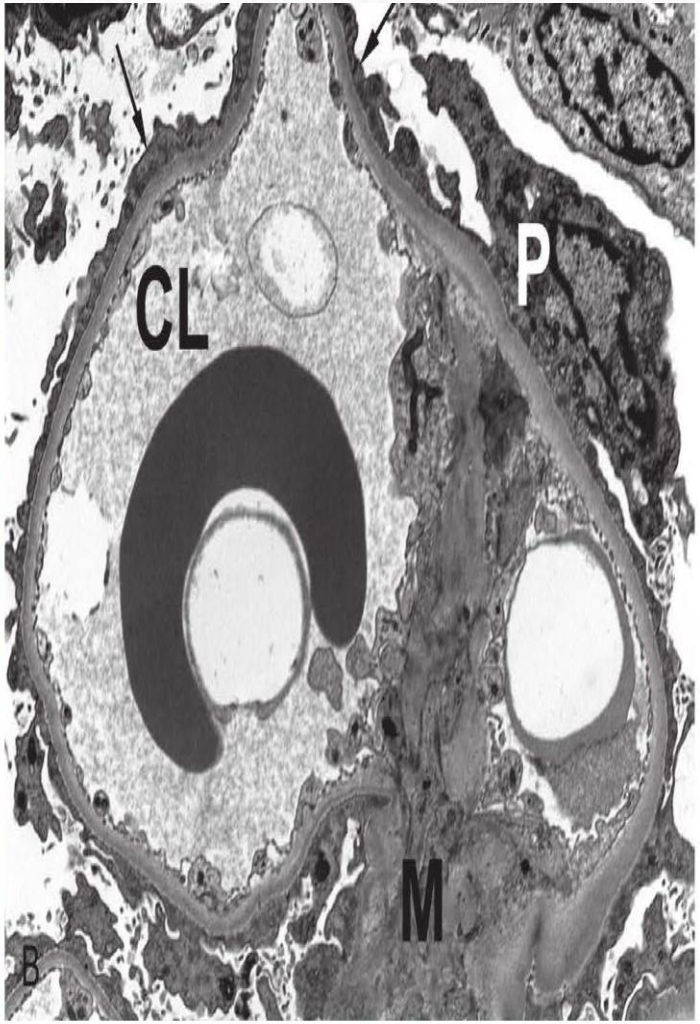
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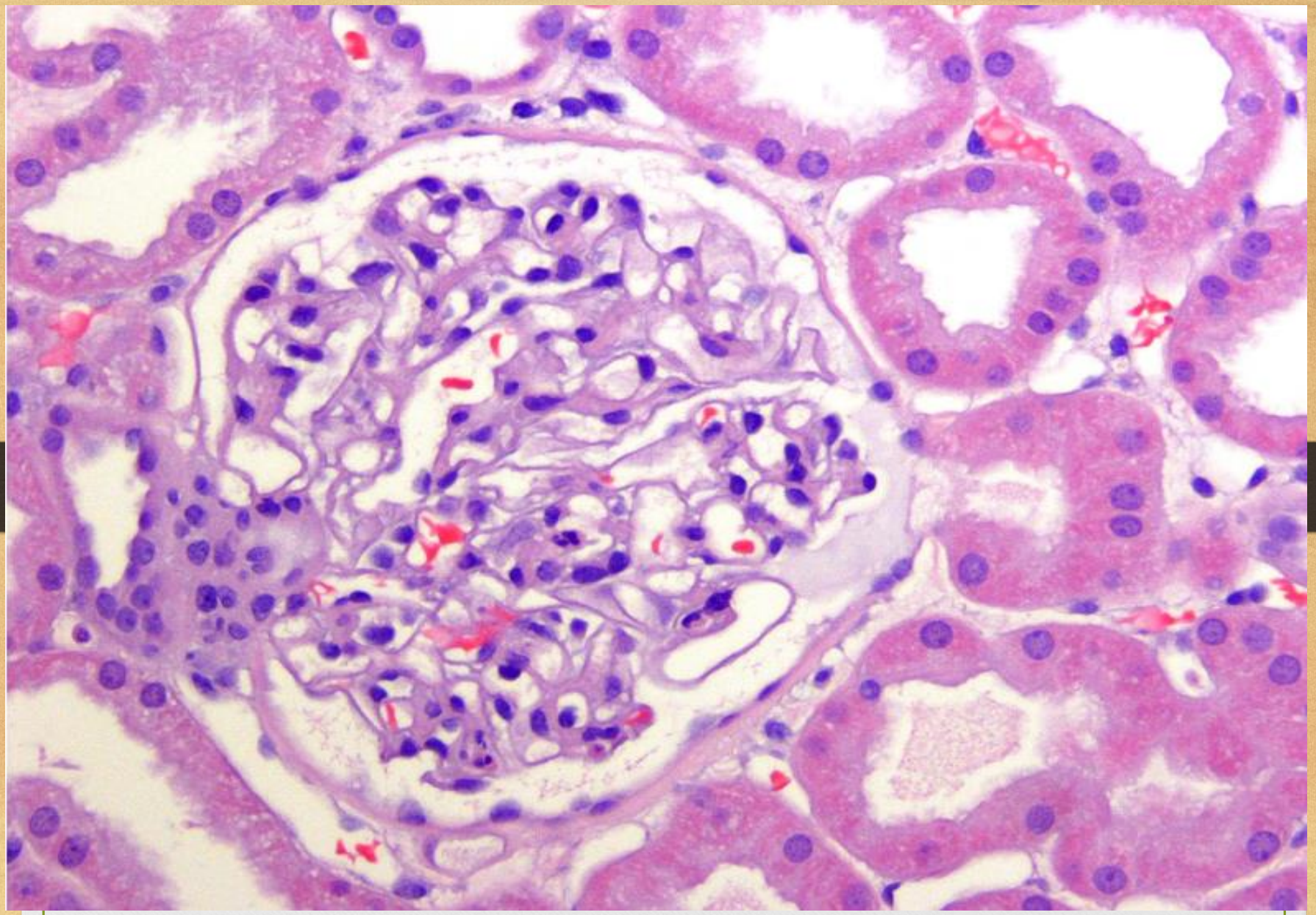
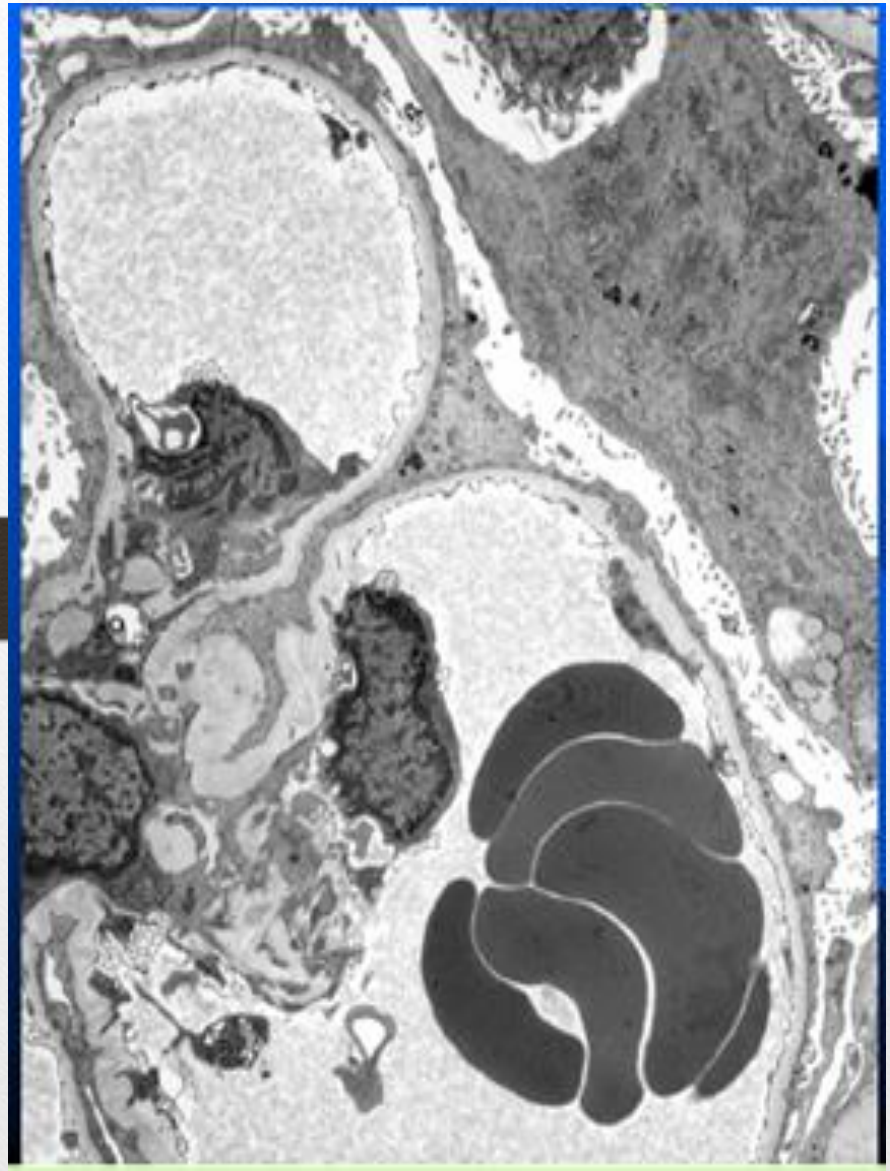
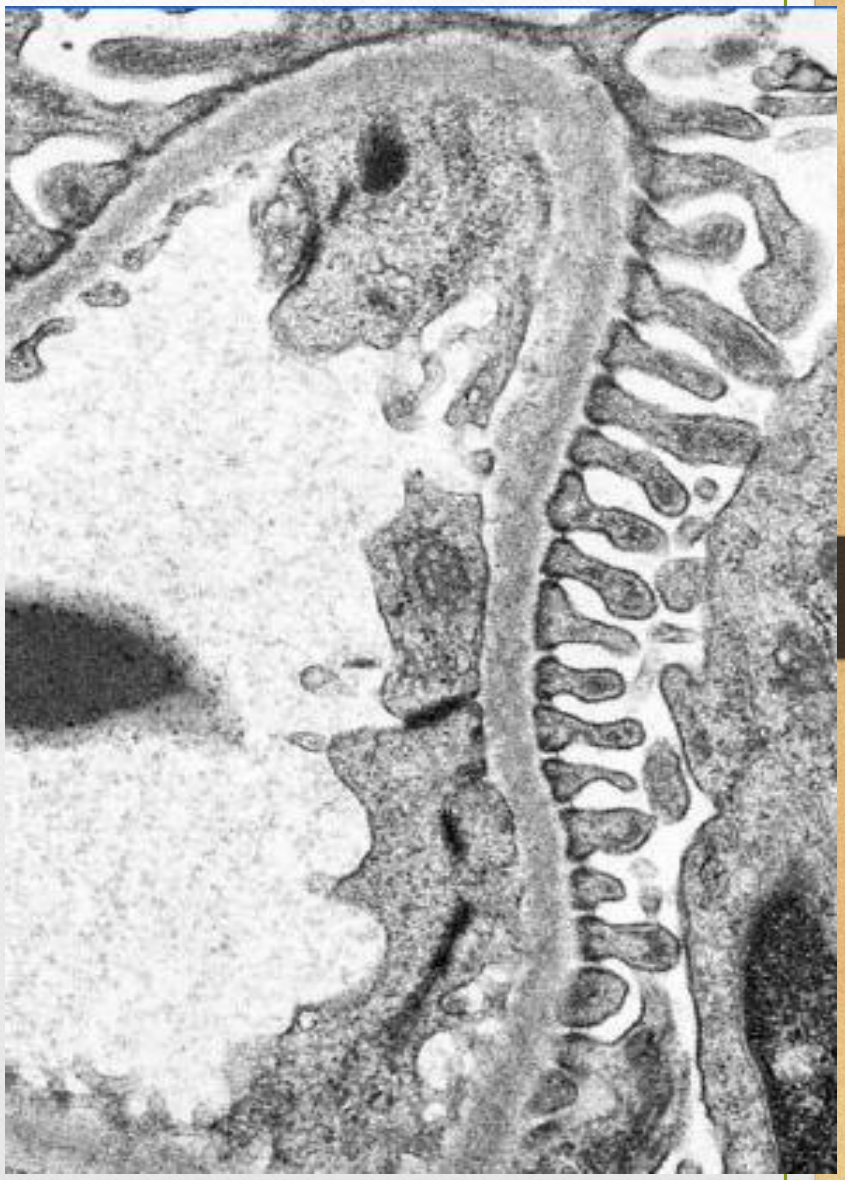
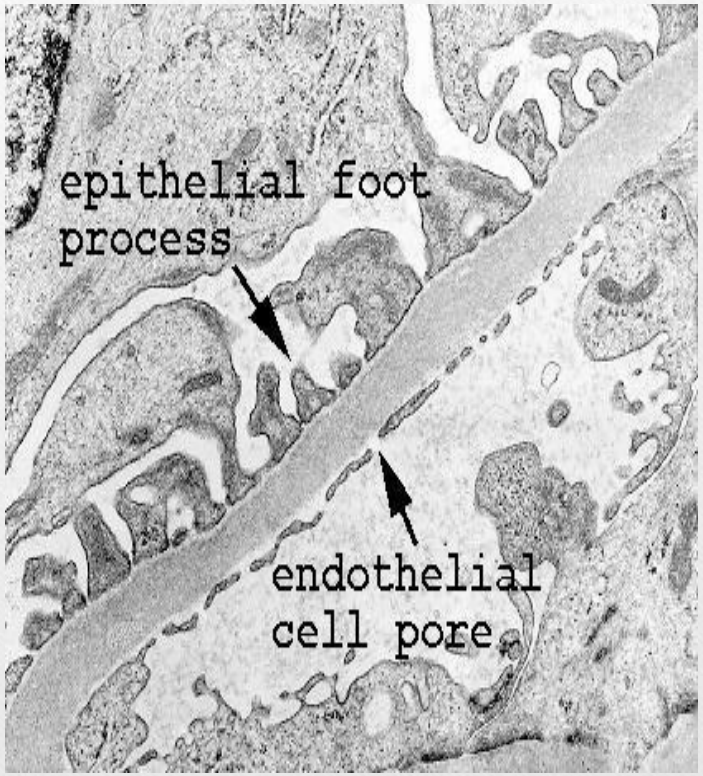


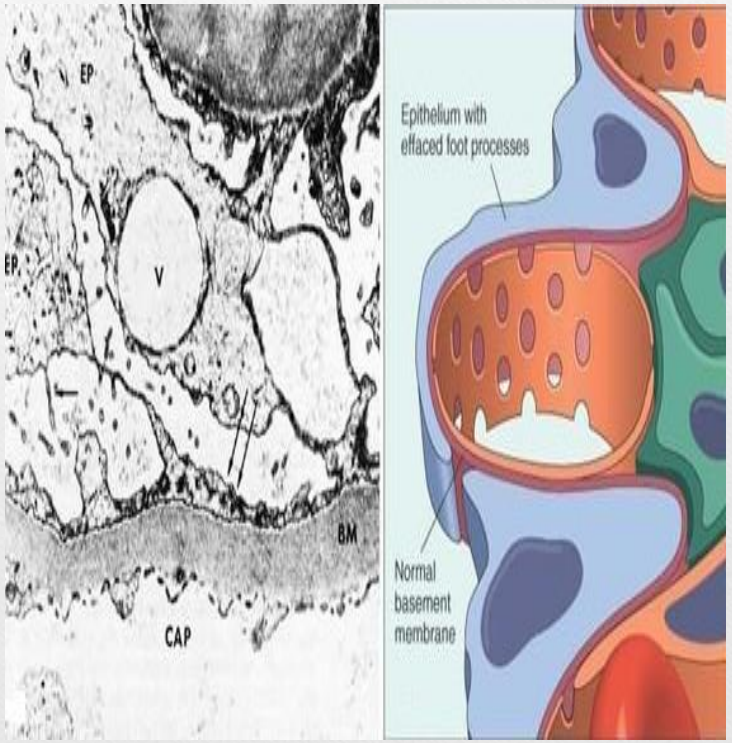




MINIMAL CHANGE GLOM. (LIPOID NEPHROSIS)

- **MOST COMMON CAUSE of NEPHROTIC SYNDROME in CHILDREN**
- **EFFACEMENT of FOOT PROCESSES**





prognosis

- Despite massive SELECTIVE proteinuria, renal function remains good.
- More than 90% of children respond rapidly to corticosteroid therapy. However, some patients may become steroid dependent or resistant.
- The long-term prognosis is excellent, and even steroid dependent disease resolves when children reach puberty.
- Although adults are slower to respond, the long-term prognosis is also excellent.

Membranous Glomerulonephropathy

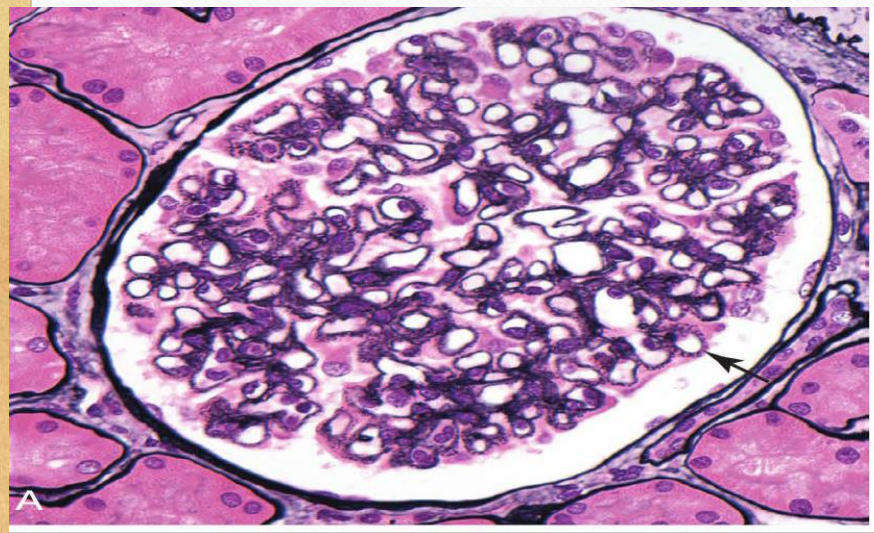
- It is the most common cause of nephrotic syndrome in adults.
- It is characterized by diffuse thickening of the glomerular capillary wall and the accumulation of electron-dense deposits along the **subepithelial** side of the basement membrane.

Etiology and pathogenesis,

- it is a form of chronic immune-complex-mediated disease.
- A-The disease is idiopathic in about 85% of cases, and is called primary MGN.
- B- secondary forms are identified in association with;
- 1. Drugs (penicillamine, captopril, NSAIDS).
- 2. Underlying malignant tumors, particularly bronchogenic carcinoma, carcinoma of colon and melanoma.
- 3. SLE.
- 4. Infections (Chronic hepatitis B and C, syphilis, malaria).
- 5. Autoimmune diseases such as thyroiditis.

Morphology,

- By light microscopy, the glomeruli exhibit diffuse thickening of the glomerular capillary wall.
- By electron microscopy, there are irregular dense deposits between the basement membrane and the epithelial cells, appearing as irregular spikes, which are best seen by silver stains as black in color .These spikes by time thicken to produce dome-like protrusions.
- Immunofluorescence microscopy demonstrates the granular deposits to contain immunoglobulins and various amounts of complement.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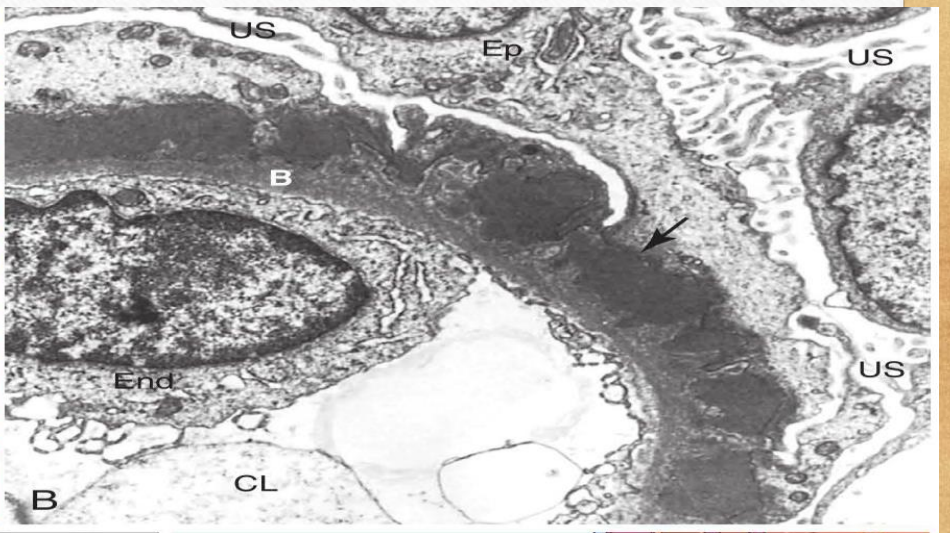
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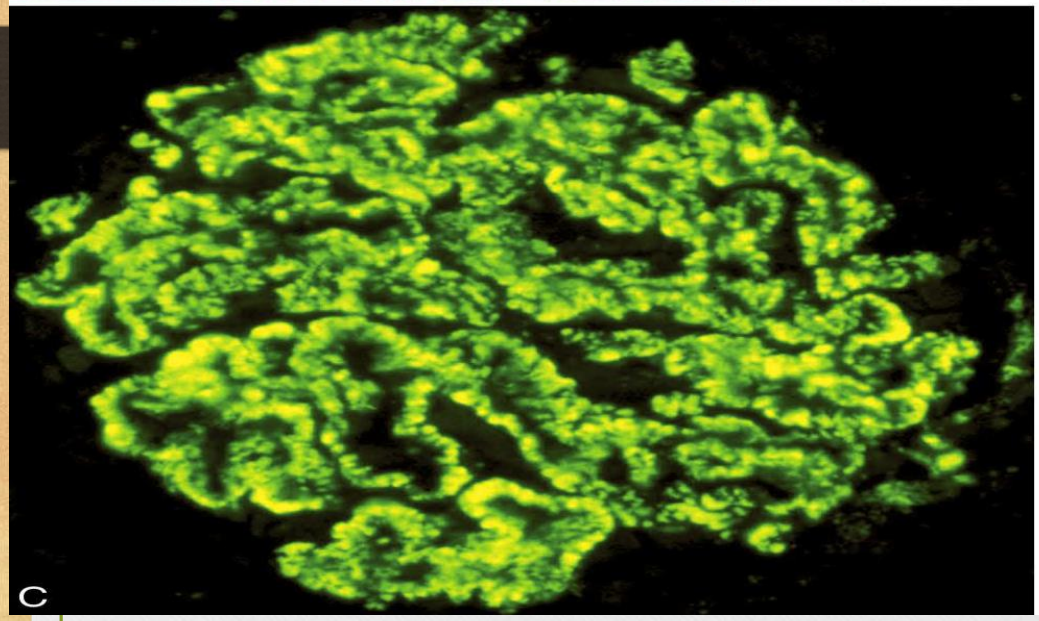
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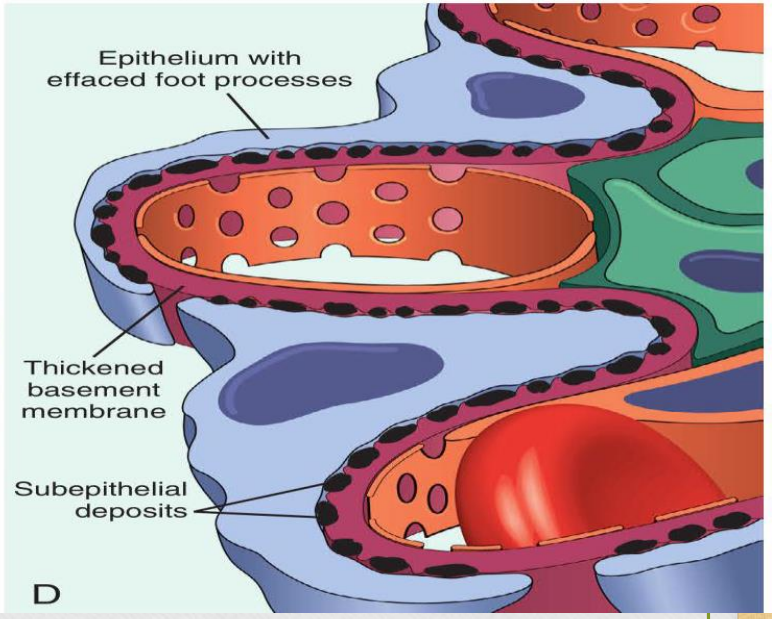
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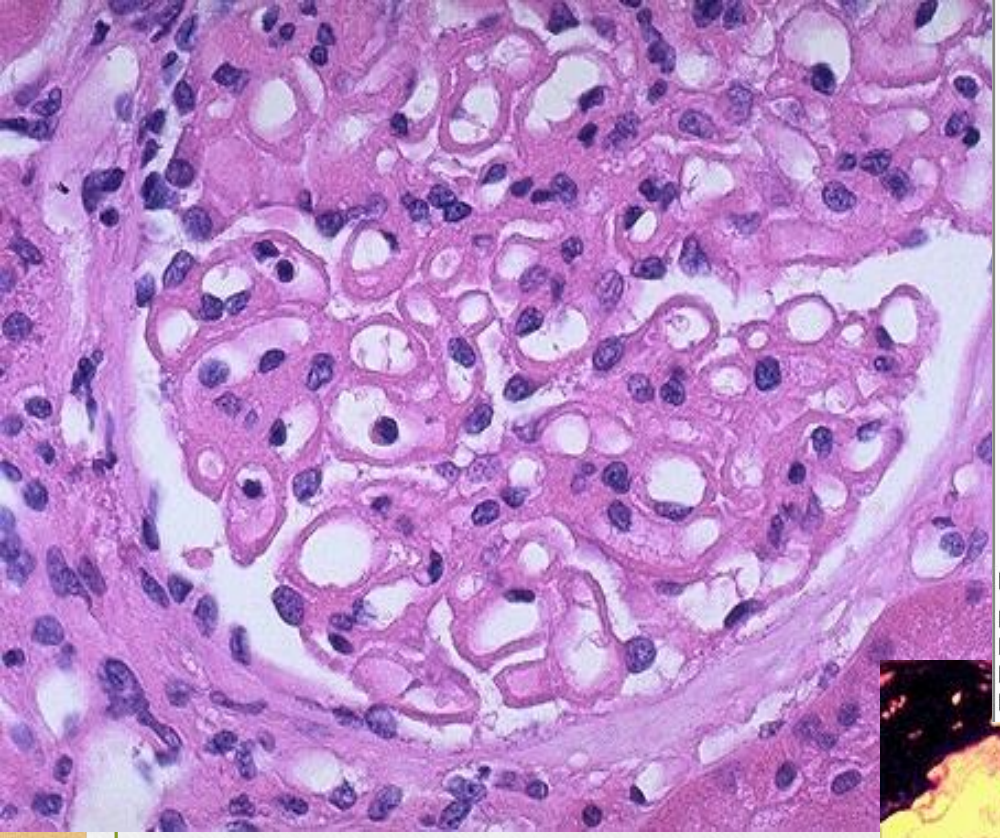

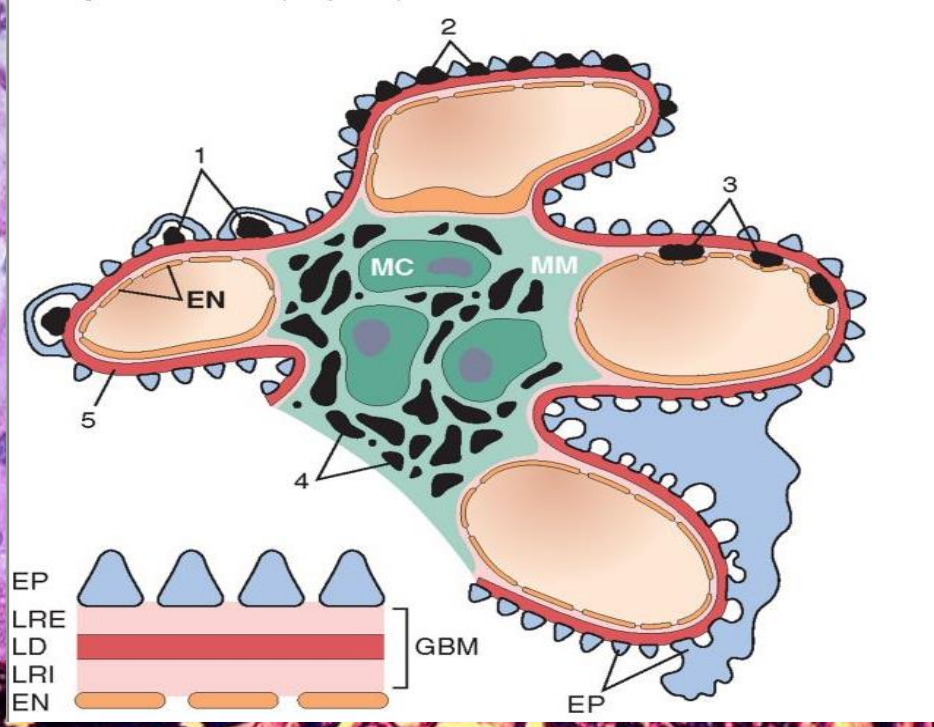
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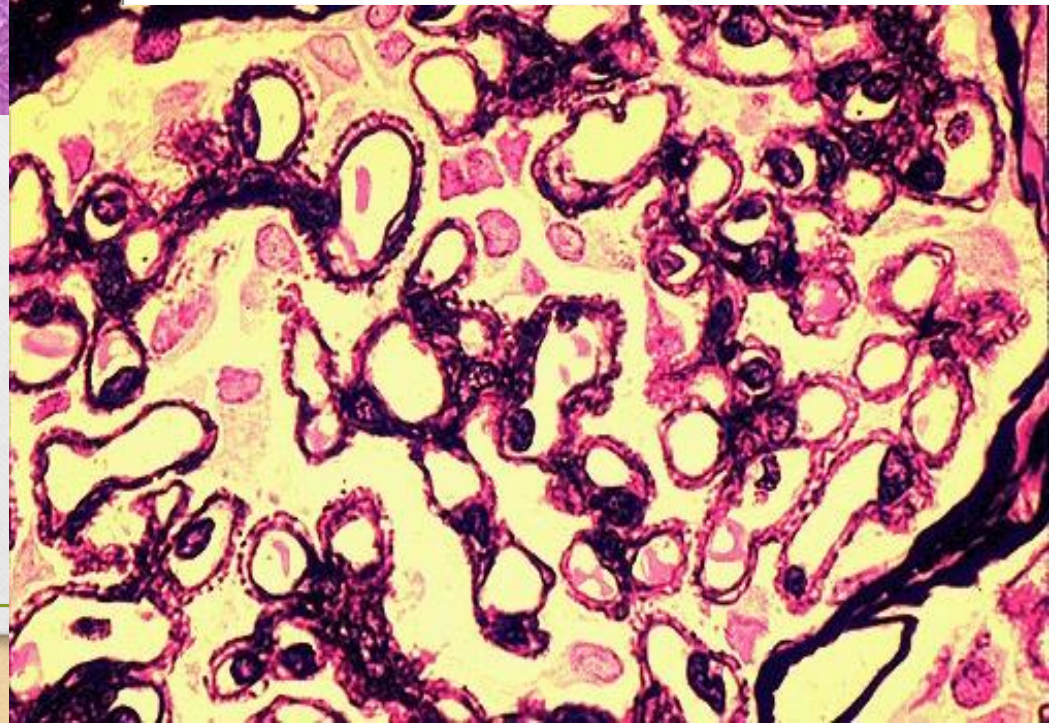

Prognosis:

- The disorder begins with the insidious onset of nephrotic syndrome.
- The course of the disease is variable but generally indolent.
- Spontaneous remission and a relatively benign course occur more commonly in women and in those with proteinuria in the non-nephrotic range
- 60% show persist proteinuria, 40% show progressive renal failure.

Focal Segmental Glomerulosclerosis

- It occurs in the following settings;

- 1. In association with other conditions (HIV infection, heroin addiction, sickle cell disease and massive obesity).
- 2. Secondary to glomerular disease (e.g. IgA nephropathy).
- 3. Idiopathic (primary disease).

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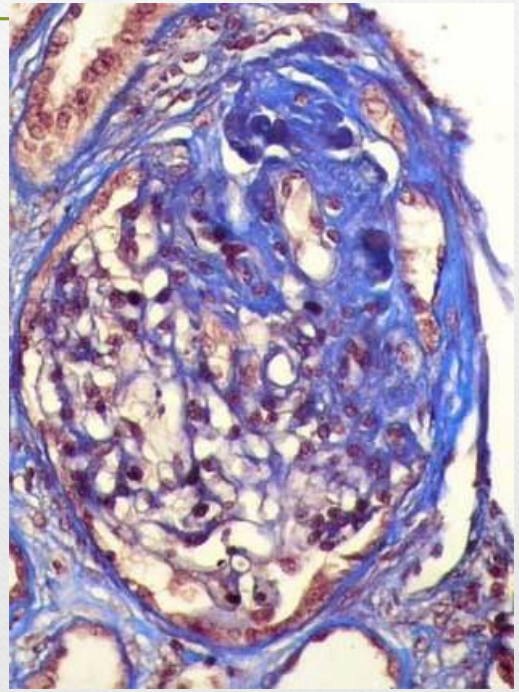
FOCAL SEGMENTAL GLOMERULO-SCLEROSIS

- **Just like its name**
  - **Focal**
  - **Segmental**
  - **Glomerulo-SCLEROSIS (NOT –itis)**
- **HIV, Heroine, Sickle Cell, Obesity**

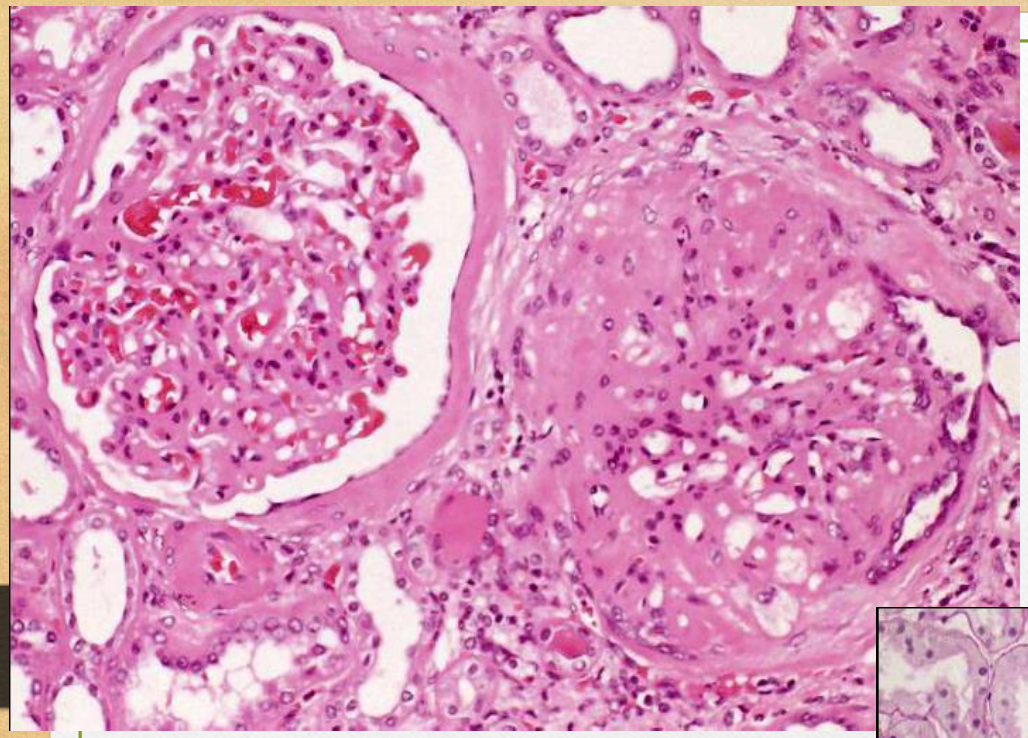


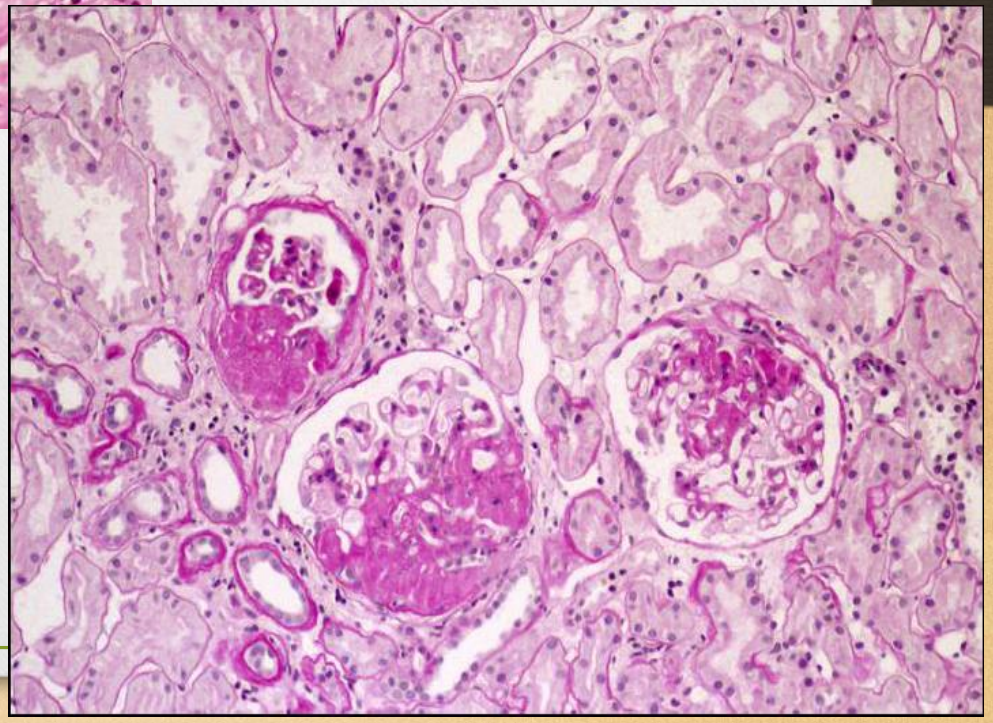
Morphology,

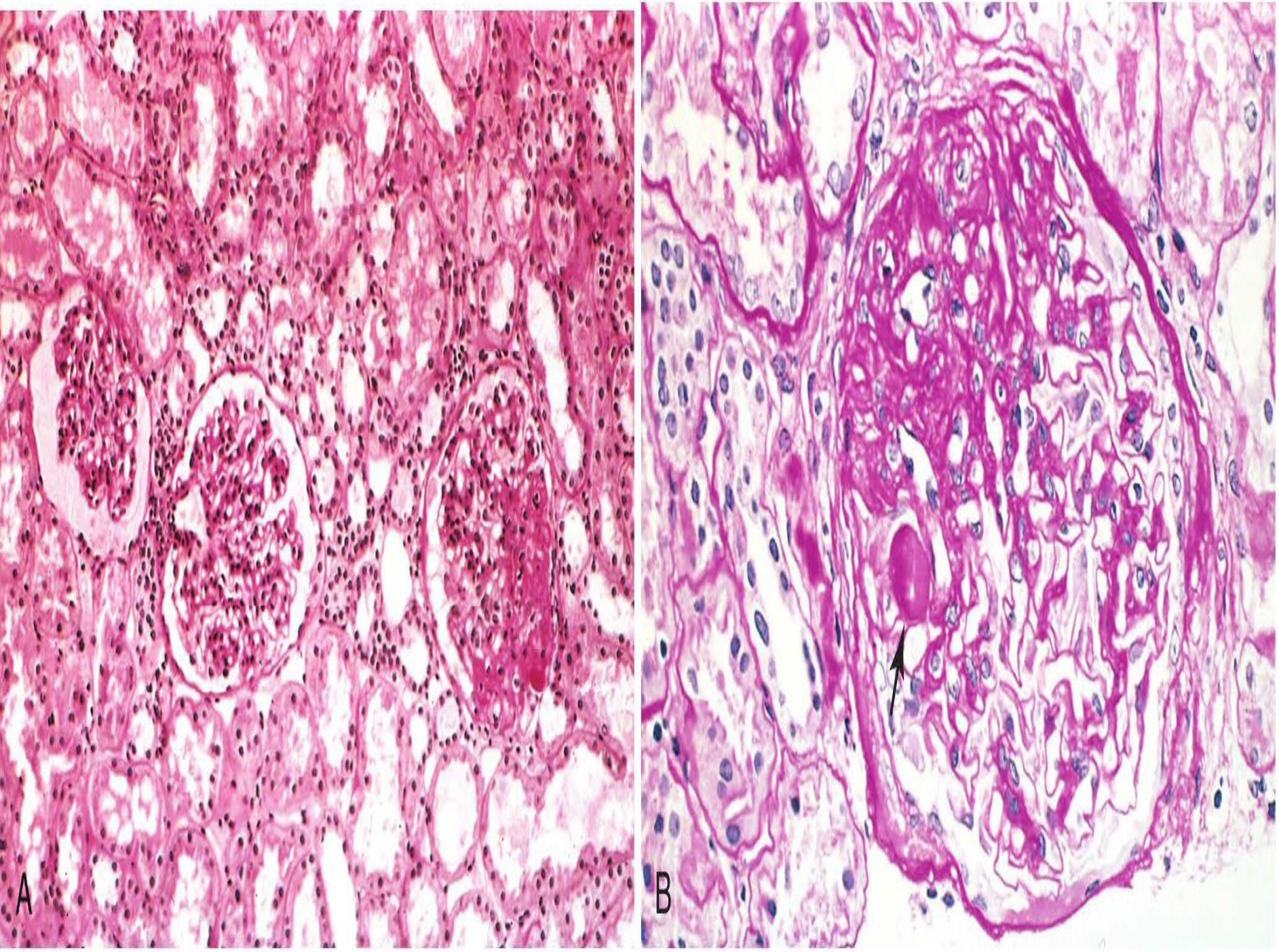
- By light microscopy, the lesion may involve few glomeruli.
- In the sclerotic segments, there is collapse of basement membranes, and increase in matrix.

- By electron microscopy, both sclerotic and non-sclerotic glomeruli show diffuse loss of foot processes of visceral epithelial cells and in addition, there may be focal detachment of the epithelial cells.

- By Immunofluorescence microscopy, IgM and C3 may be present in the sclerotic areas and/or in the mesangium.



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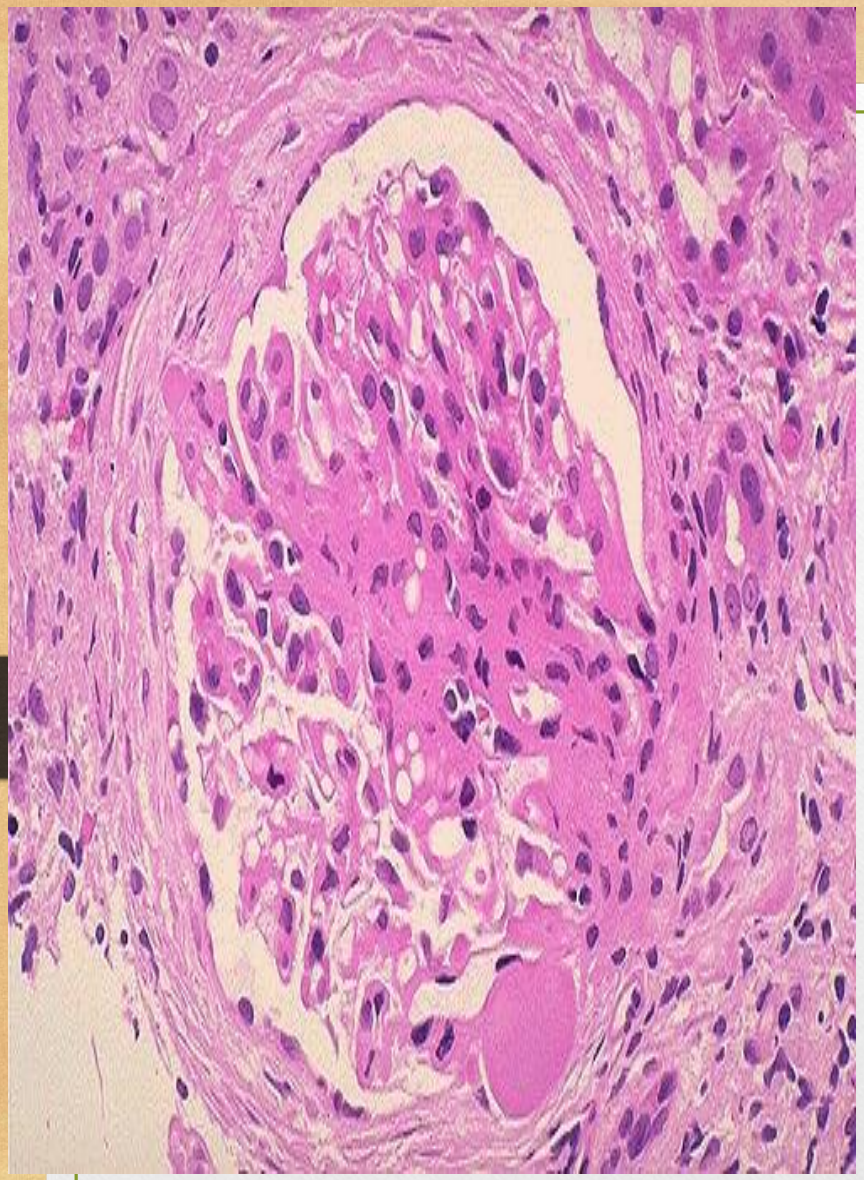
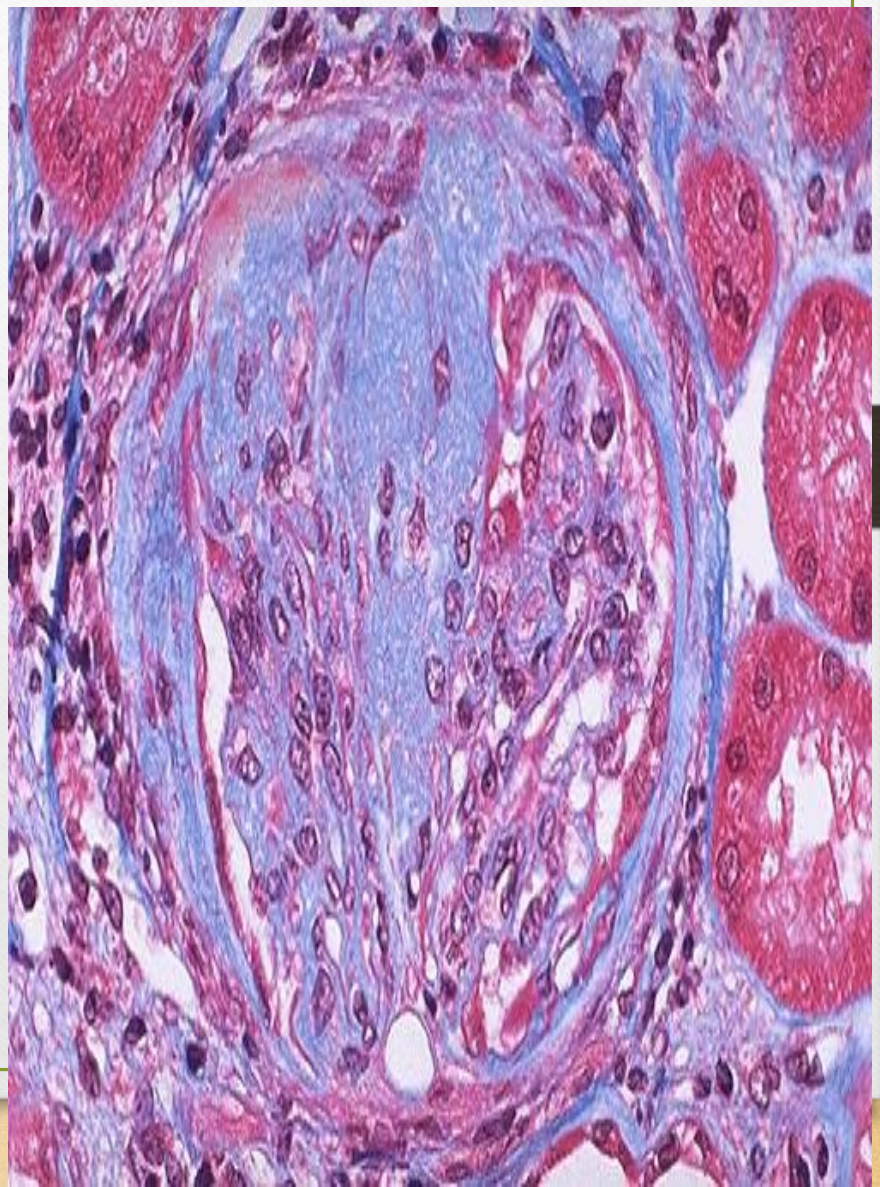




prognosis

- There is little tendency of spontaneous remission and responses to corticosteroid therapy are variable.

- In general, children have a better prognosis than adults do.
- About 20% of patients follow an unusually rapid course ending in renal failure within 2 years.
- Recurrences are seen in 25%-50% of patients receiving allografts.

Membranoproliferative Glomerulonephropathy:

- Sometimes referred as mesangioproliferative GN.
  - MPGN is classified into;

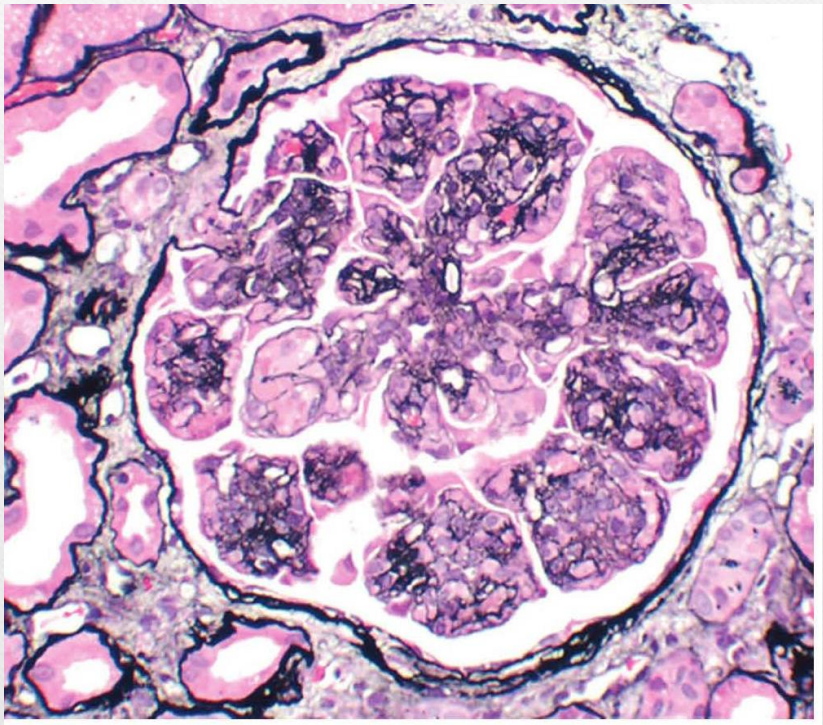
    1. Primary (idiopathic).
    2. secondary, associated with;

    - Chronic immune complex disorders (SLE, hepatitis B and C infection, HIV infection).
    - Alfa1-antitrypsin deficiency.
    - Malignant tumors (leukemia, lymphoma).
    - Hereditary deficiency of complement regulatory proteins.

Morphology

- By light microscopy, the glomeruli are large due to hypercellularity secondary to proliferation of measngial cells, capillary endothelial cells and leukocytic infiltration.
- The glomeruli have a lobular appearance
- The GBM is clearly thickened. The glomerular capillary wall often shows a double contour or "tram-track" appearance that caused by reduplication of glomerular basement membrane
- Primary MPGN is divided into 2 major types :

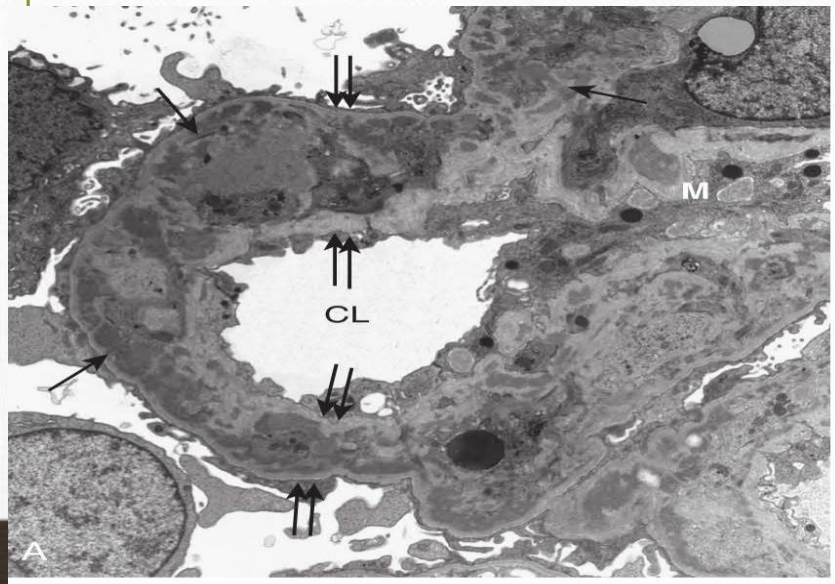
Membranoproliferative glomerulonephritis, showing mesangial cell proliferation, increased mesangial matrix (staining black with silver stain), basement membrane thickening with segmental splitting, accentuation of lobular architecture, swelling of cells lining peripheral capillaries, and influx of leukocytes (endocapillary proliferation).



1. **Type I (great majority of cases),** is characterized by the presence of subendothelial electron-dense deposits. By the IF:

- C3 is deposited in a granular pattern,
- IgG and early complement components (C1q and C4) are often present, suggesting an immune complex pathogenesis.

1. **Type II (dense-deposit disease DDD),** the GBM is transformed into an irregular, ribbon-like, extremely electron-dense structure, because of the deposition of dense material of unknown composition in the GBM proper. C3 is present in granular or linear pattern. IgG is usually absent, as are the early complement factors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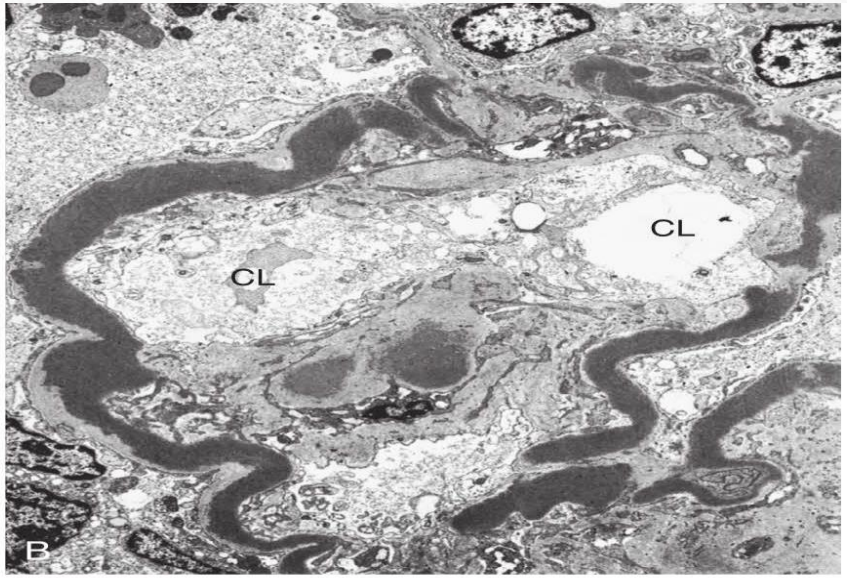
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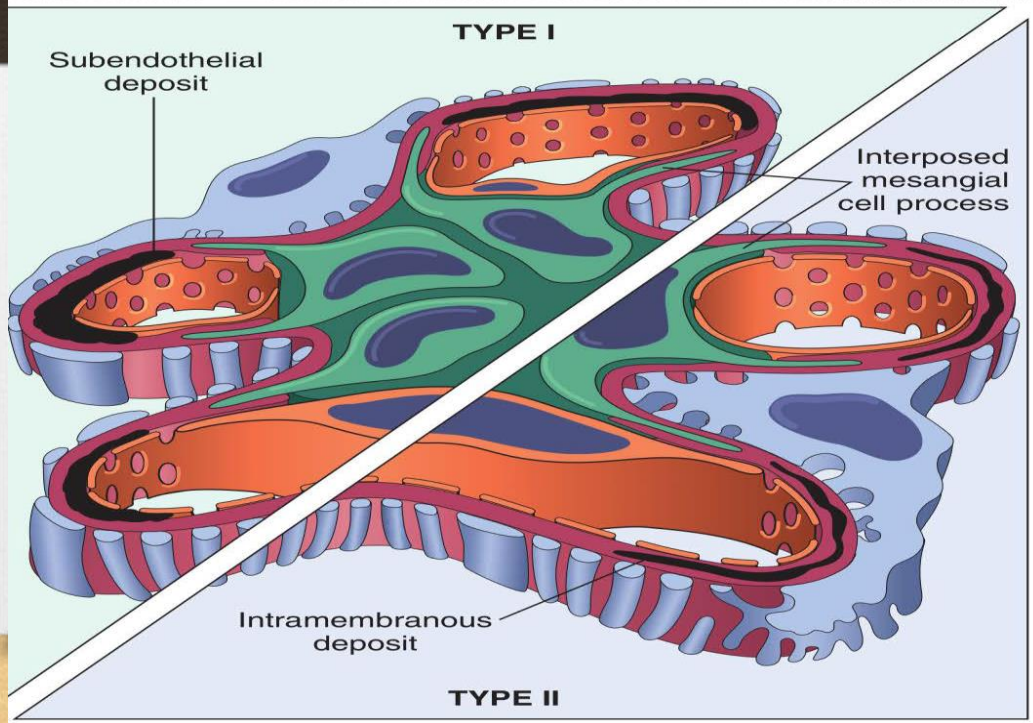
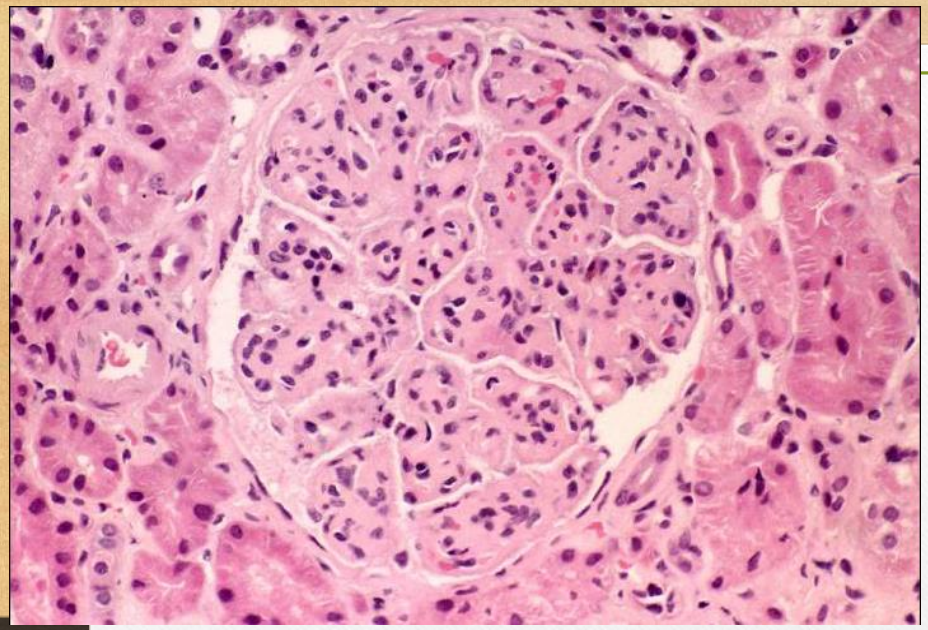
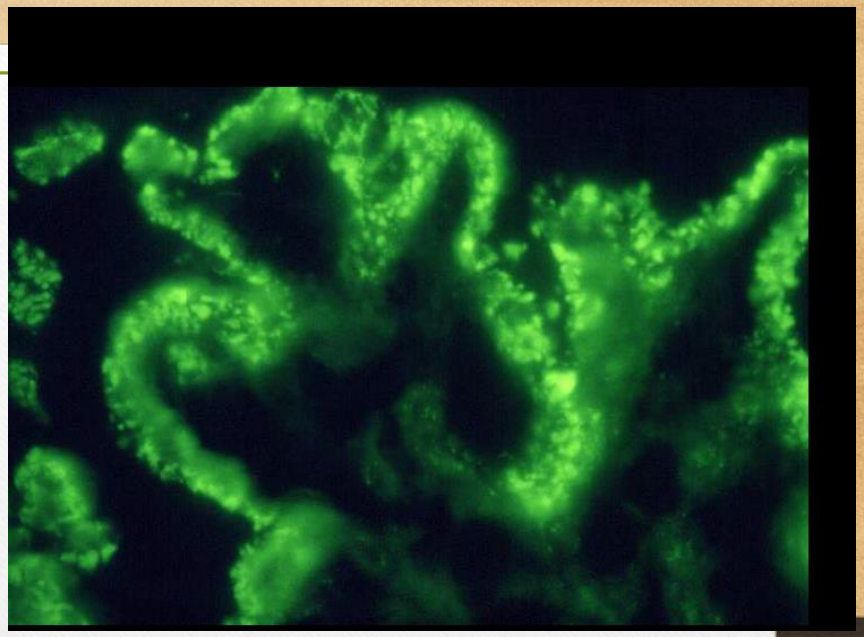
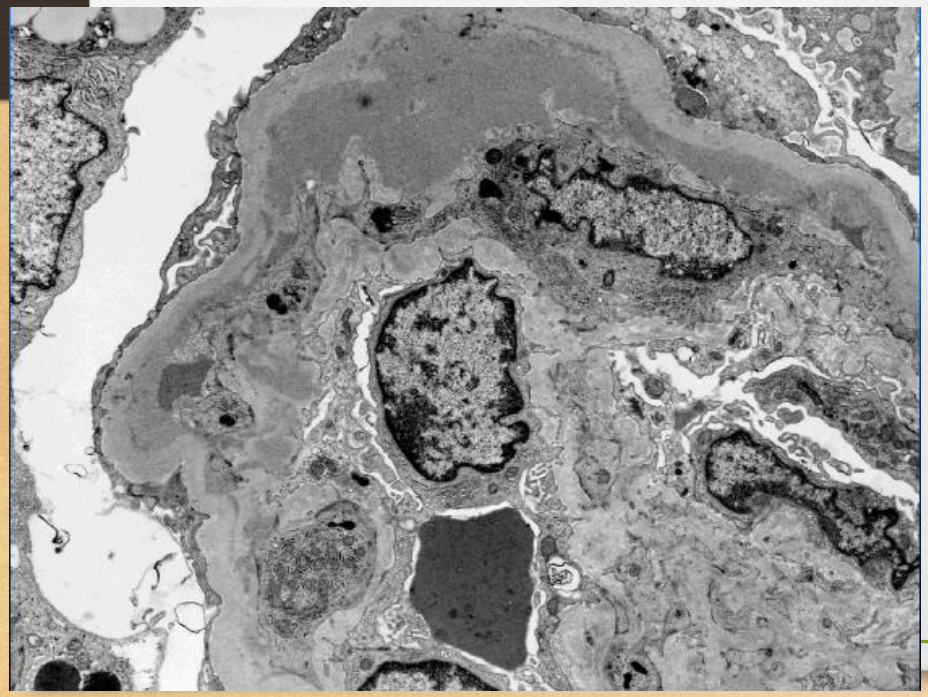
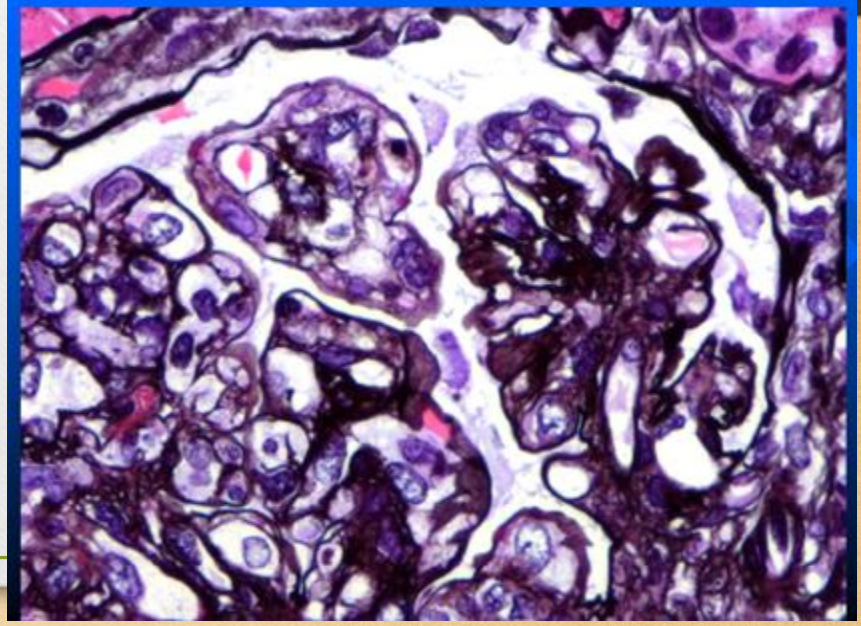

TYPE I
Subendothelial deposit
Interposed mesangial cell process
Intramembranous deposit
TYPE II







MPGN with GBM duplication



Pathogenesis,

- In most cases of type I MPGN, there is evidence of immune complexes in the glomerulus and activation of both classical and alternative complement pathways.

- Most patients with type II MPGN, have abnormalities that suggest activation of the alternative complement pathway.

Clinical course

- The principal mode of presentation is the nephrotic syndrome occurring in older children or young adults.
- Few remissions occur spontaneously.
- 50% develop chronic renal failure within 10 years.
- Medical treatment has NOT been proved to be effective.
- There is high incidence of recurrence in transplant recipients, particularly in dense-deposit disease.

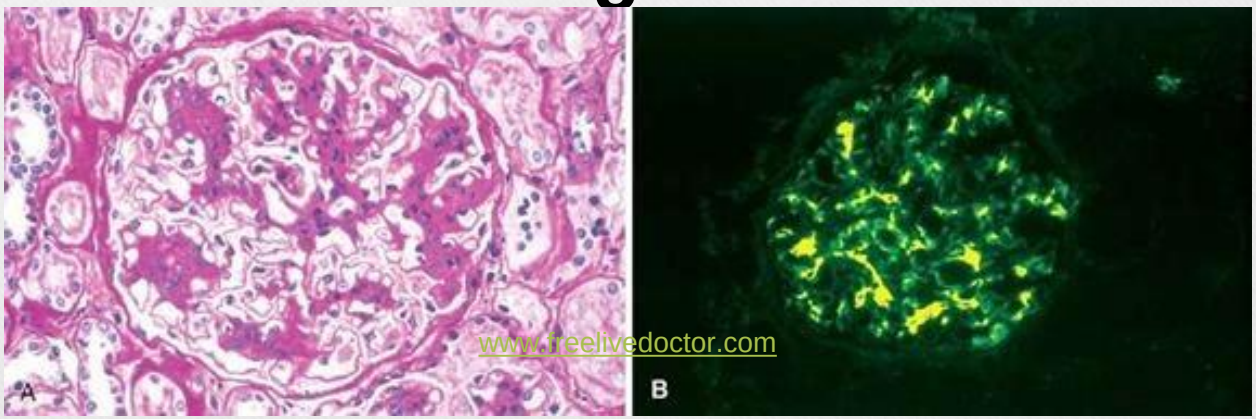
IgA Nephropathy (Berger Disease):

- It is the frequent cause of recurrent gross or microscopic hematuria and is probably the most common type of glomerulo-nephropathy worldwide.

- Mild proteinuria is usually present,
- Nephritic syndrome may occasionally develop.
- Rarely, patients may present with RPGN

IgA NEPHROPATHY (BERGER DISEASE)

- Mild hematuria
- Mild proteinuria
- IgA deposits in mesangium



Pathogenesis

- There is either a genetic or acquired abnormality of immune regulation leading to increased mucosal IgA synthesis in response to respiratory or gastrointestinal exposure to environmental agents (viruses, bacteria, food proteins).

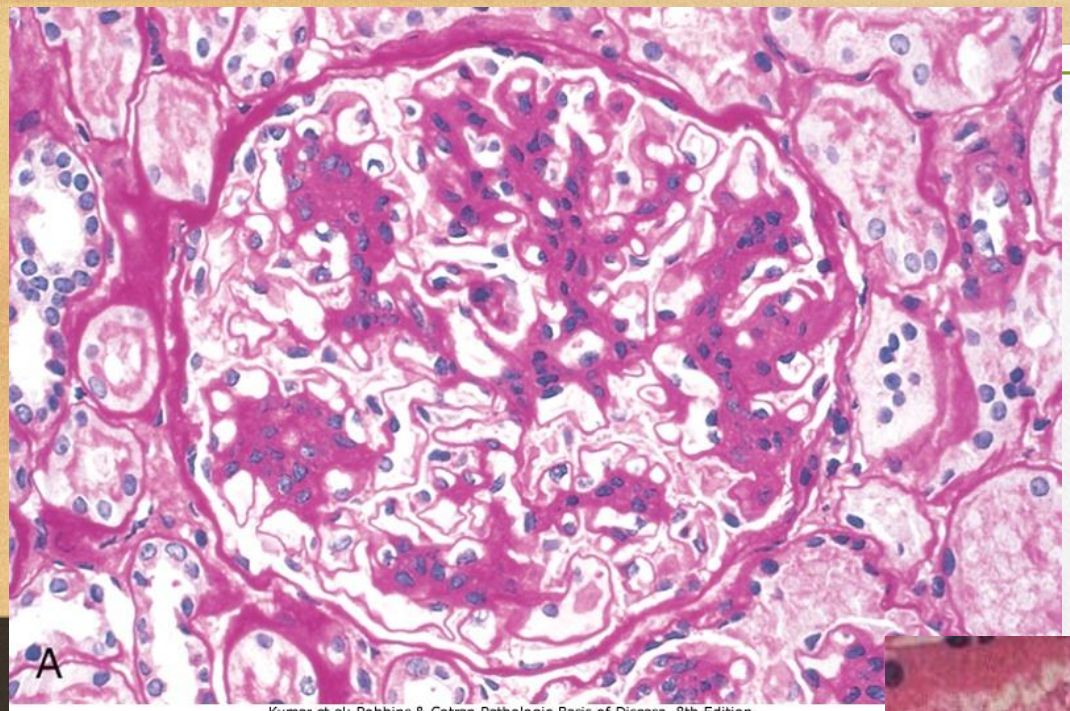
- IgA1 then trapped in the mesangium.

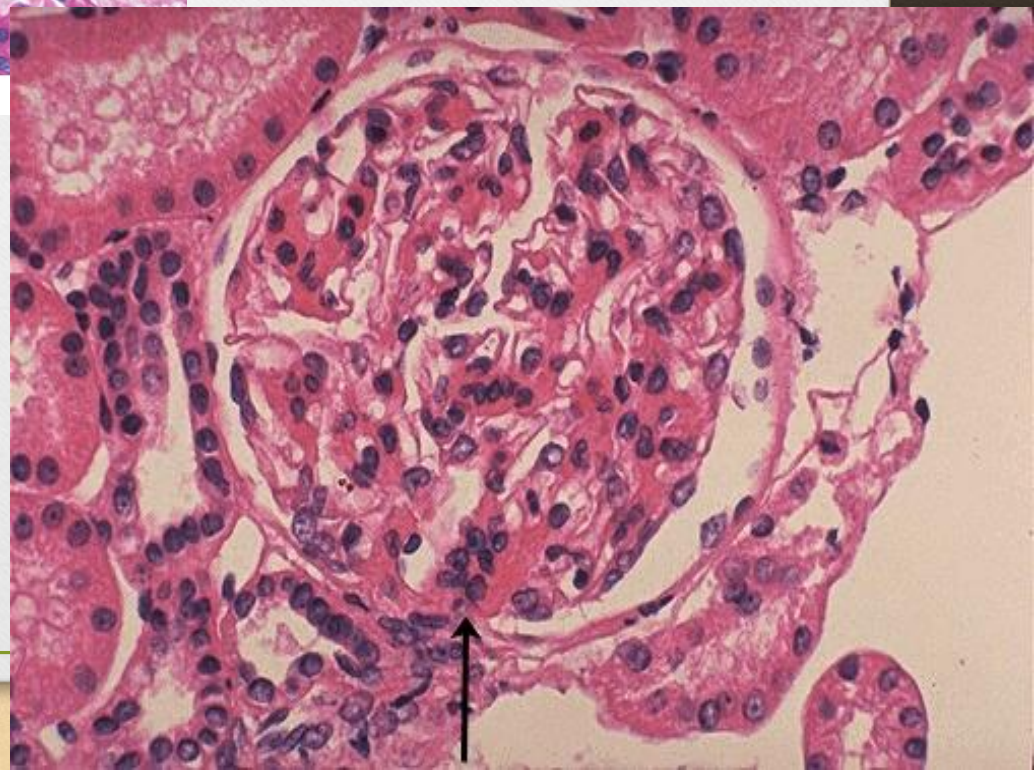
Morphology

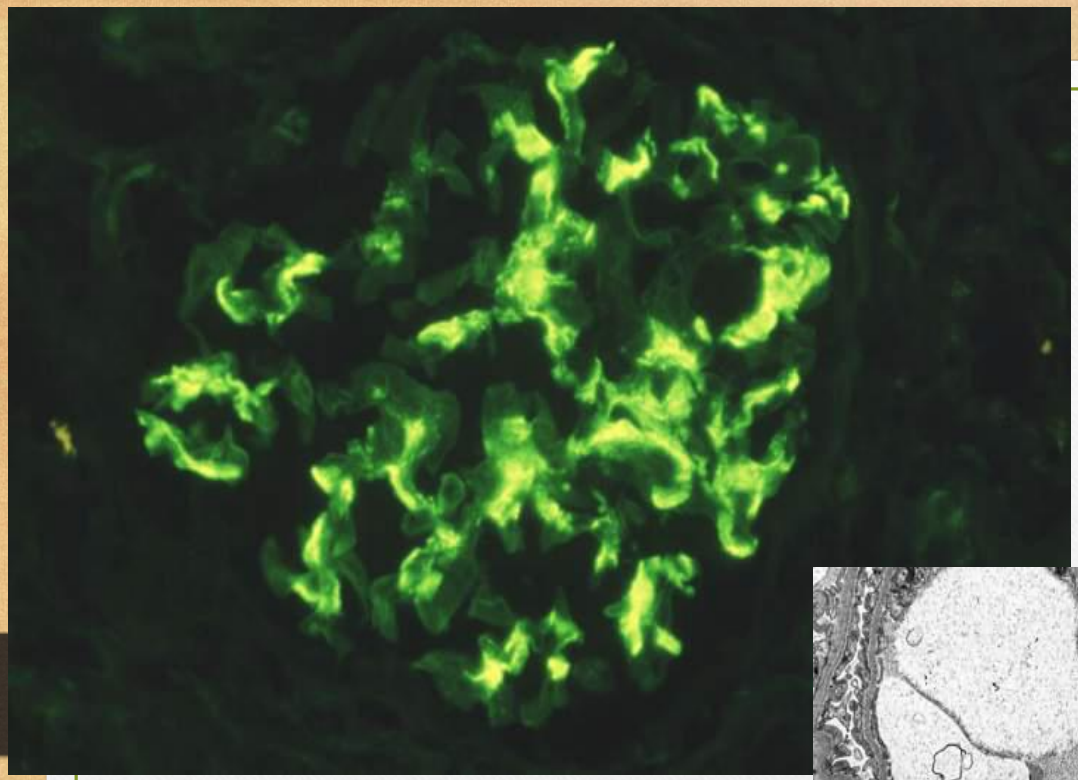
- By light microscope, there is variable mesangial proliferation +/- sclerosis.
- lesions vary considerably

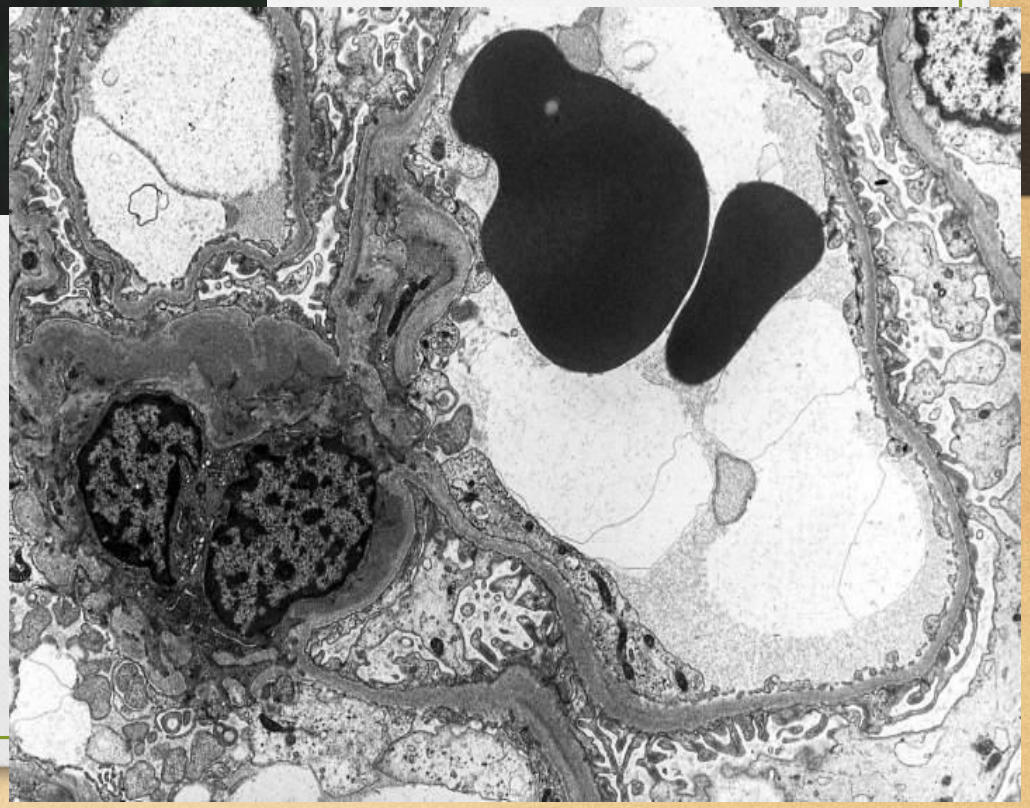
- focal proliferative glomerulonephritis
- focal segmental sclerosis
- crescentic glomerulonephritis
- The characteristic picture is seen under fluorescent microscopy in form of mesangial deposition of IgA often with C3.

- Electron microscopy confirms the presence of electron dense deposits in the mesangium.







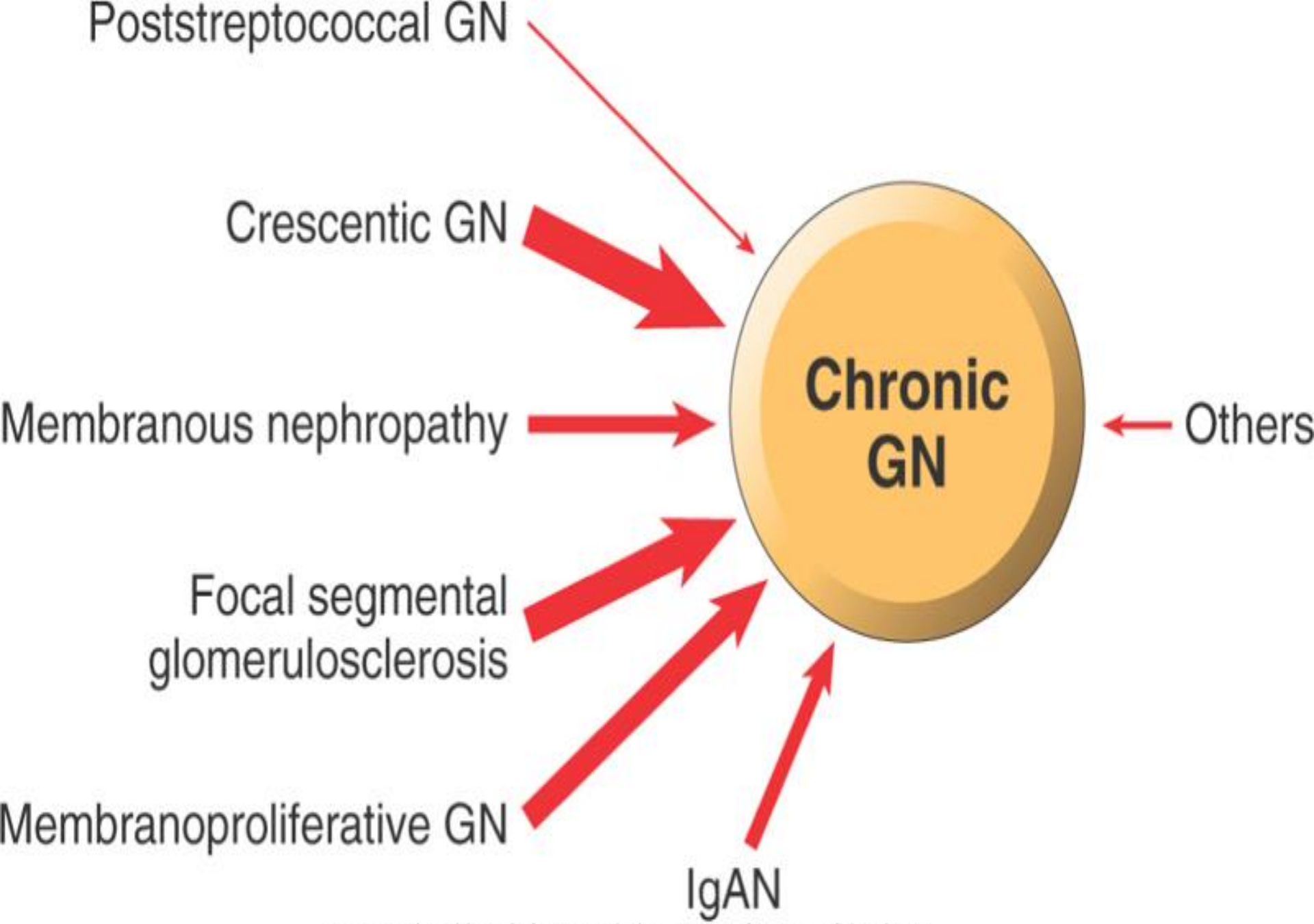


prognosis

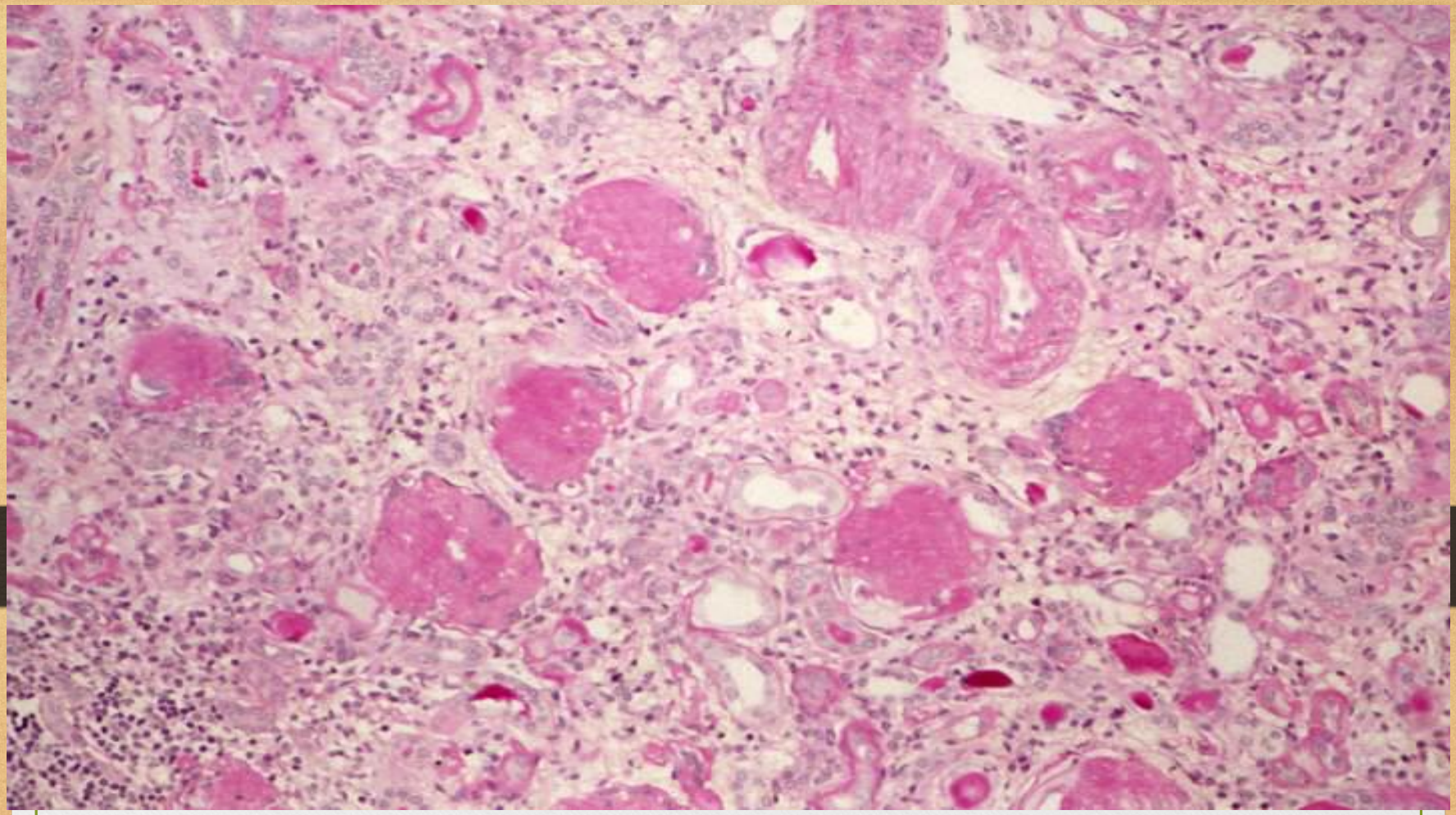
- The disease affects people of any age, but older children and young adults are most commonly involved.
- Many patients present with gross hematuria after an infection of respiratory tract, or GIT
- Many patients maintain normal renal function for decades. Slow progression to chronic renal failure occurs in 15-40% of cases over a period of 20 years.
- Recurrence of IgA deposits in transplanted kidneys is frequent.

Chronic Glomerulonephropathy

- It is an important cause of (end stage renal disease ESRD).
- It is an important outcome of many Acute glomerulonephritis e.g. membranoproliferative, rapid progressive glomerulonephritis.
- Gross:
- Contracted kidneys (symmetrically), with red- brown granular surface.



- **Mic:**
- **HYALINIZED (fibrotic) GLOMERULI**
- Scarring of glomeruli & Bowman space.
- Interstitial fibrosis and lymphocytic infiltration
- Tubular atrophy.
- Thick wall arteries.
- **Clinical features:**
- Proteinuria, Azotemia on routine medical investigations.
- Unexplained edema.
- **Prognosis:**
- Poor without treatment.



Chronic GN: Defined by the presence of > 2/3 sclerotic glomeruli

prognosis

- In most patients, chronic glomerulonephropathy develops insidiously and slowly progresses to renal insufficiency.

Disease	Most Frequent Clinical Presentation	Pathogenesis	Glomerular Pathology		
			Light Microscopy	Fluorescence Microscopy	Electron Microscopy
Postinfectious glomerulonephritis	Nephritic syndrome	Immune complex mediated; circulating or planted antigen	Diffuse endocapillary proliferation; leukocytic infiltration	Granular IgG and C3 in GBM and mesangium; Granular IgA in some cases	Primarily subepithelial humps; subendothelial deposits in early disease stages.
Goodpasture syndrome	Rapidly progressive glomerulonephritis	Anti-GBM COL4-A3 antigen	Extracapillary proliferation with crescents; necrosis	Linear IgG and C3; fibrin in crescents	No deposits; GBM disruptions; fibrin
Chronic glomerulonephritis	Chronic renal failure	Variable	Hyalinized glomeruli	Granular or negative	
Membranous nephropathy	Nephrotic syndrome	In situ immune complex formation; PLA_2Rantigen in most cases of primary disease mostly unknown	Diffuse capillary wall thickening	Granular IgG and C3; diffuse	Subepithelial deposits
Minimal change disease	Nephrotic syndrome	Unknown; loss of glomerular polyanion; podocyte injury	Normal; lipid in tubules	Negative	Loss of foot processes; no deposits
Focal segmental glomerulosclerosis	Nephrotic syndrome; nonnephrotic proteinuria	Unknown Ablation nephropathy Plasma factor (?); podocyte injury	Focal and segmental sclerosis and hyalinosis	Focal; IgM + C3 in many cases	Loss of foot processes; epithelial denudation
Membranoproliferative glomerulonephritis (MPGN) type I	Nephrotic/nephrotic syndrome	Immune complex	Mesangial proliferative or membranoproliferative patterns of proliferation; GBM thickening; splitting	IgG ++ C3; C1q ++ C4	Subendothelial deposits
Dense-deposit disease (MPGN type II)	Hematuria Chronic renal failure	Autoantibody; alternative complement pathway	Mesangial proliferative or membranoproliferative patterns of proliferation; GBM thickening; splitting	C3; no C1q or C4	Dense deposits
IgA nephropathy	Recurrent hematuria or proteinuria	Unknown	Focal mesangial proliferative glomerulonephritis; mesangial widening	IgA ± IgG, IgM, and C3 in mesangium	Mesangial and paramesangial dense deposits

GBM, Glomerular basement membrane.

SECONDARY (2º) GLUMERULONEPHROPATHIES

- **SLE**
- **Henoch-Schonlein Purpura (IgA-NEPH)**
- **BACTERIAL ENDOCARDITIS**
- **DIABETES (Nodular Glomerulosclerosis, or K-W Kidney)**
- **AMYLOIDOSIS**
- **GOODPASTURE**
- **WEGENER**
- **MYELOMA**