KIDNEY-3

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Nephrotic Syndrome

- **Massive Proteinuria ("nephrotic range" >3.5g/24h)**
- **Hypoalbumimenia (<3 gm/dl)**
- **Edema**
- **Hyperlipidemia**
- **Lipiduria**

PATHOPHYSIOLOGY

- Derangement in glomerular capillary wall resulting in to massive proteinuria.

- Depletion of serum albumin level below the compensatory synthetic ability of liver leading to hypoalbuminamia and reversal of albumin:globulin ratio.

- Loss of osmotic pressure and generalized edema. Sodium and water retention also aggravates edema. Edema is soft and pitting, most marked in periorbital region and dependant portions.

- Most patients have hyperlipidemia: increase cholesterol, triglyceride, VLDL,LDL and decrease HDL in some patients. Lipiduria follows as free fat or oval fat bodies.

- Patients are more vulnerable to infections because of loss of immunoglobulin in urine.

- Thrombotic and thromboembolic complications are common because of loss of anticoagulant factors and antiplasmin activity through leaky glomerulus.

Primary Causes of Nephrotic Syndrome

- Membranous GN
- Minimal change disease
- Focal segmental glomerulosclerosis
- Membrano Proliferative GN
- C3 glomerulopathy
  (dense deposit disease and C3 glomerulonephritis)

Secondary causes of Nephrotic syndrome

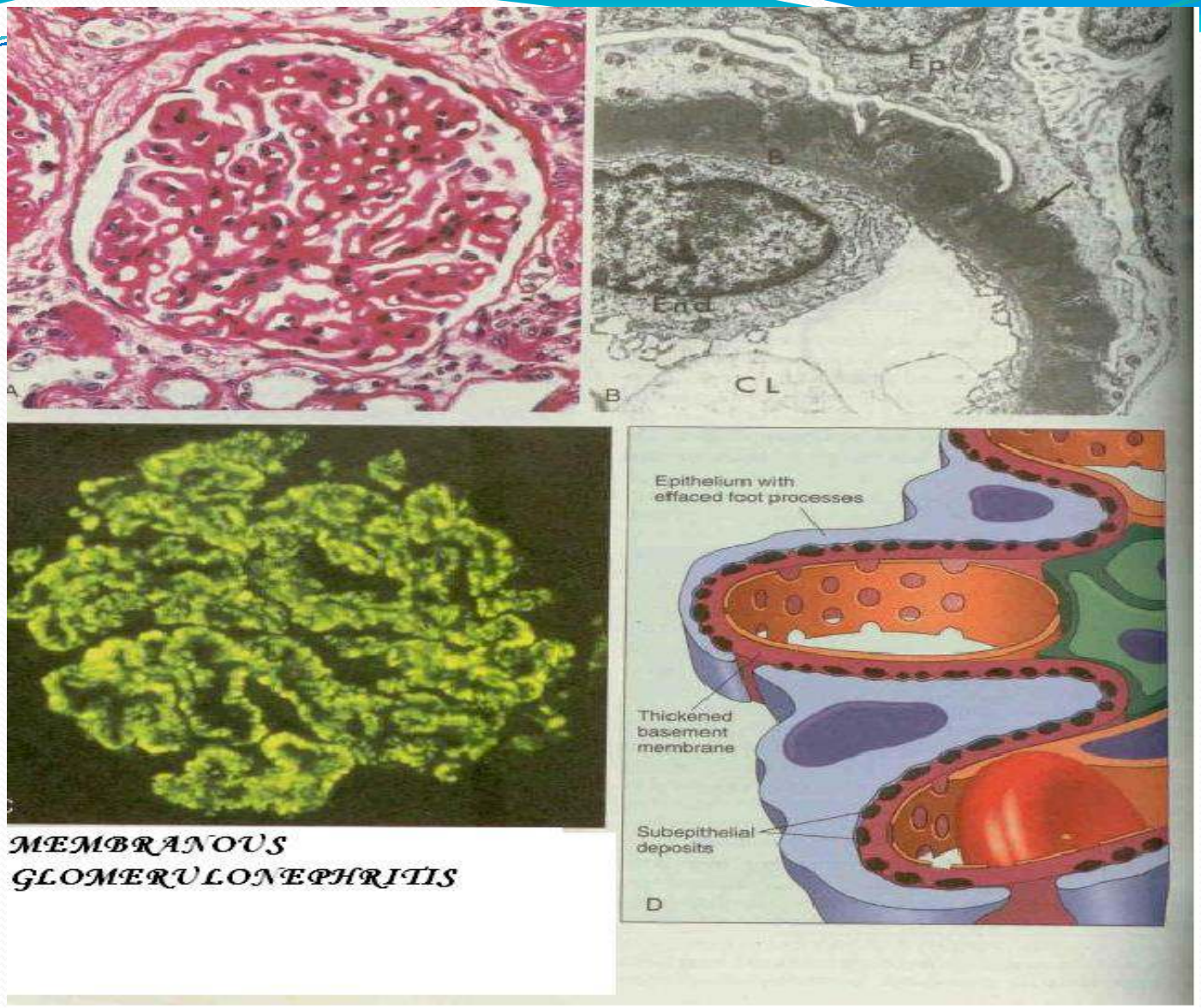
- Diabetes Mellitus
- Amyloidosis
- Systemic Lupus Erythematosus
- Drugs (Penicillamine,Street heroin)
- Infections (Malaria,syphilis,AIDS,Hepatitis)
- Malignant diseases.

Membranous Glomerulonephritis

- Commonest cause of NS in adults.
- Characterized by diffuse thickening of glomerular capillary wall and marked sub epithelial deposits
- **Pathogenesis**-Striking resemblance to *Heymann nephritis*. It results from reaction of antibody to an antigen located on basal surface of visceral epithelial cells .
- Antibodies against the podocyte antigen phospholipase A2 receptor (PLA2R) are frequently present but it is not established that they are causative.
- Direct activation of C5b-c9,the membrane attack complex of complement causes activation of glomerular cells and inducing them to liberate damaging chemical mediators and protein leakage.

MORPHOLOGY

- L.M.-Uniform diffuse thickening of glomerular capillary wall.
- E.M.-Irregular dense deposits between B.M. and epithelial cells which has lost their foot processes. Basement membrane material is laid down between these deposits as irregular spikes and dome like protrusions leading to markedly thickened irregular B.M.
- IFM-Granular deposits containing both immunoglobulins & complements.
- With progression, glomeruli become totally hyalinized and sclerosed.



MEMBRANOUS GLOMERULONEPHRITIS

Ref- Robbins and Cotran: Pathologic basis of disease: South Asia Edition, Pg:916

MINIMAL CHANGE DISEASE

- Relatively benign disorder, frequent cause of N.S. in children of 2-6 yrs of age.
- Characterized by diffuse loss of foot processes of epithelial cells that appear virtually normal by L.M.
- May follow respiratory infection or prophylactic immunization .

Minimal change disease

- Lipoid nephrosis- Cells of proximal tubules are often laden with lipids.
- Despite massive proteinuria (selective proteinuria),renal function remains good.
- Prognosis is excellent.
- Respond rapidly to steroids.

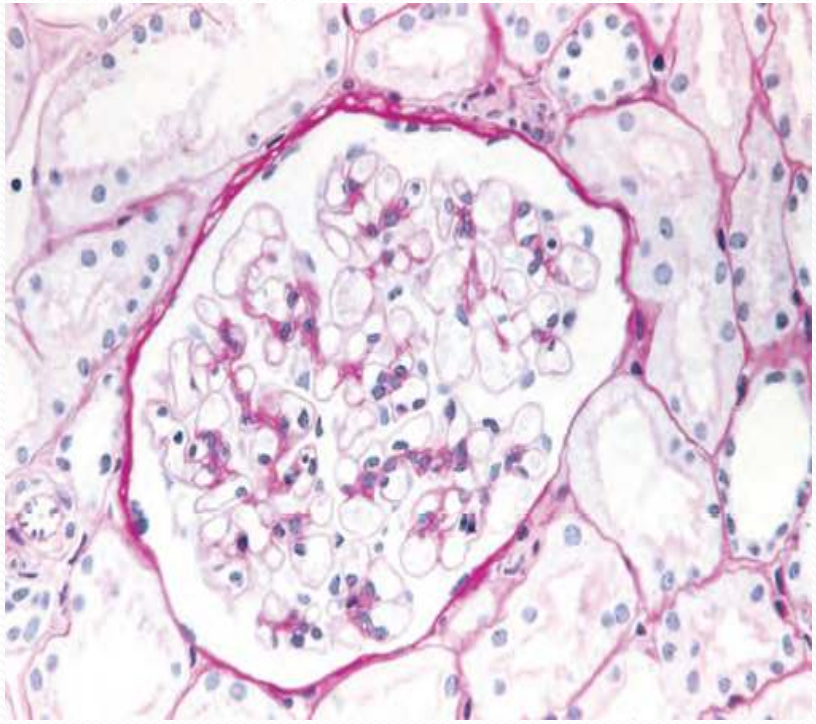
Pathogenesis

- Although absence of immune deposits in glomeruli excludes classic immune mechanism, several features favor immunologic basis.
- Current hypothesis suggest involvement of some immune dysfunction particularly a disorder of T cells results in to elaboration of cytokine like circulating substances(IL-8,TNF or other poorly defined permeability factors) that affect nephrin synthesis, detachment of epithelial cells and protein loss. Mutation in nephrin gene gives rise to congenital N.S.

MORPHOLOGY

- Glomeruli are normal by L.M.
- By E.M,No electron dense material is deposited. Visceral epithelial cells show uniform and diffuse effacement of foot processes often showing vacuolization and swelling (simplification of epithelial cells). It is diagnosed only when fusion is associated with normal glomeruli light microscopically. Epithelial changes are reversible after steroid therapy.
- I.F.M.-No immunoglobulin or complement deposits

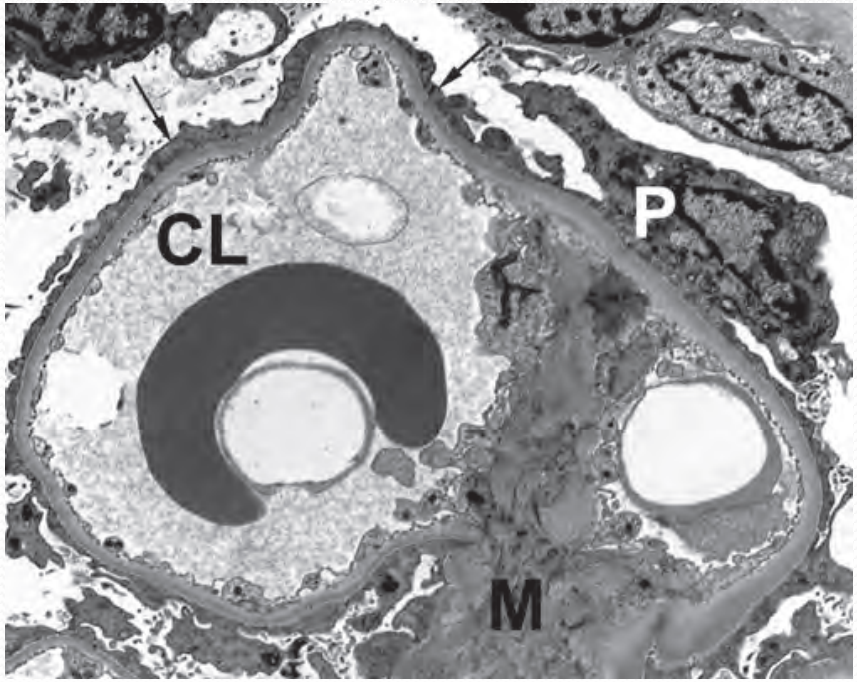
Kidney, nephrotic syndrome, minimal change disease (MCD), PAS stain



- The glomerulus has normal appearance. The basement membrane is of uniform thickness. No inflammation is seen. The tubules are of normal shape and size. The interstitium is also unremarkable. MCD is the most common cause of nephrotic syndrome in children.

Ref- Robbins and Cotran: Pathologic basis of disease: South Asia Edition, Pg:917

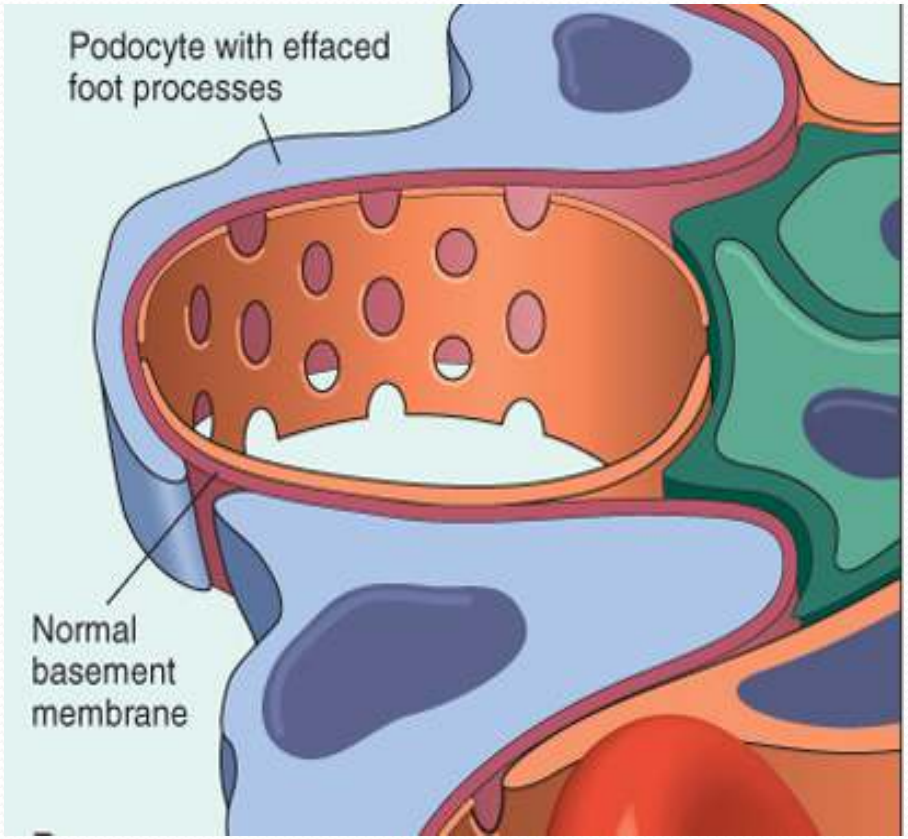
Glomerulus, minimal change disease - Electron micrograph



- In minimal change disease (MCD), electron microscopy (EM) shows effacement of the foot processes.

Ref- Robbins and Cotran: Pathologic basis of disease: South Asia Edition, Pg:917

Glomerulus, minimal change disease - Electron micrograph



- In minimal change disease (MCD), electron microscopy (EM) shows effacement of the foot processes.

Ref- Robbins and Cotran: Pathologic basis of disease: 7th edition page-982

Focal segmental Glomerulo sclerosis

Frequently presents as N.S. or heavy proteinuria, Progression to renal failure occurs at a variable rate.

Causes:

- human immunodeficiency virus infection
- heroin abuse
- as a secondary event in other forms of GN (e.g., immunoglobulin A [IgA] nephropathy)
- as a maladaptation after nephron loss
- Inherited forms of N.S.,linked to mutations in genes encoding for nephrin & its related proteins
- as a primary disease

Patients of FSGS differs from MCD

MCD	FSGS
• in children	• It is seen in adults & children.
• there is a lower incidence of hematuria and hypertension in persons with this lesion	• there is a higher incidence of hematuria and hypertension in persons with this lesion
• proteinuria is selective	• their proteinuria is nonselective
• their response to corticosteroid therapy is good	• their response to corticosteroid therapy is poor.
• The prognosis in children with this disorder is good- No CGN	• More chances of progression to CGN.

MORPHOLOGY

- L.M.-Focal & segmental sclerotic lesions : collapse of B.M, increase mesangial matrix, deposition of hyaline masses, lipoid droplets and foam cells.

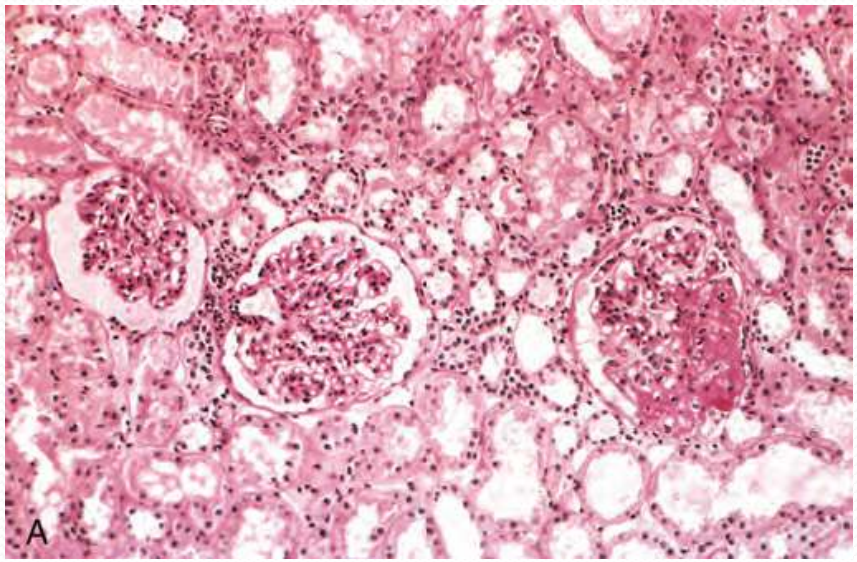
- E.M.-Diffuse loss of foot processes, focal detachment of epithelial cells with denudation of underlying GBM.

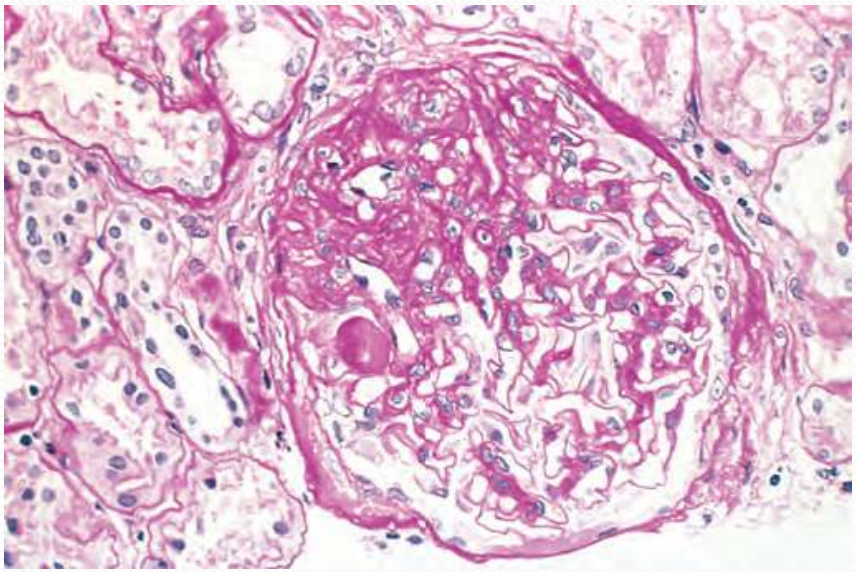
- I.F.M.-IgM & C3 in hyaline masses.

Pathogenesis FSGS

- Pathogenesis-Distinct entity or aggressive variant of MCD. In any case, *injury to the podocytes is thought to represent the initiating event of primary FSGS.*
- The recurrence of proteinuria in patients undergoing renal transplantation for FSGS, sometimes within 24 hours of transplantation, supports the idea that a circulating mediator leads to podocyte damage.

Focal segmental glomerulosclerosis
Segmental sclerosis in one of three glomeruli (PAS stain)

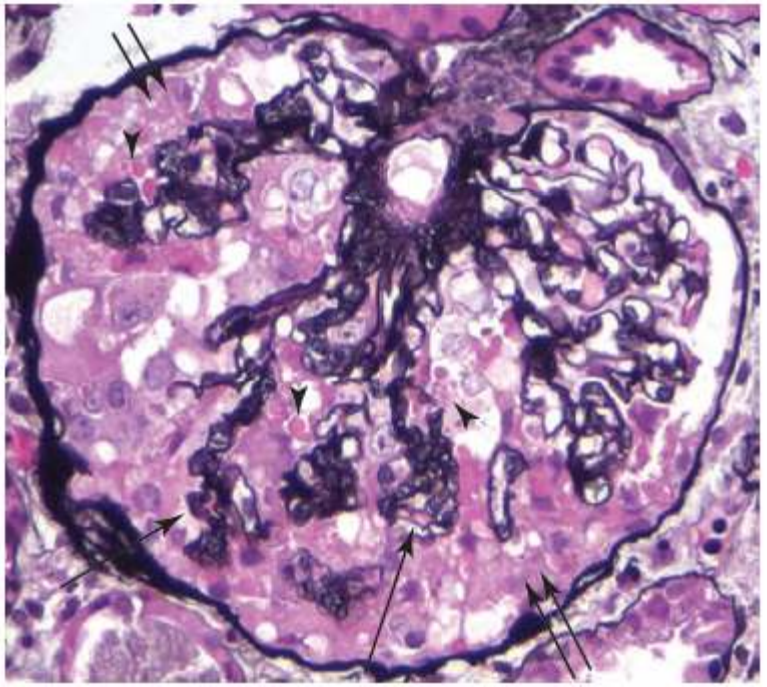




Ref- Robbins and Cotran: Pathologic basis of disease: South Asia Edition, Pg:917

Collapsing glomerulopathy

- A morphologic variant of FSGS, called collapsing glomerulopathy; characterized by collapse of the glomerular tuft and epithelial cell hyperplasia. This more severe manifestation of FSGS may be idiopathic or may be associated with HIV infection, drug-induced toxicities, and some microvascular injuries.
- It carries a particularly poor prognosis.



Ref- Robbins and Cotran: Pathologic basis of disease: South Asia Edition, Pg:-919

MEMBRANO PROLIFERATIVE GN (MPGN)

- Characterized histologically by alteration in GBM, proliferation of glomerular cells, endocapillary proliferation and leukocytic infiltration. (Mesangiocapillary GN)
- Clinical presentation- Nephrotic syndrome or combined nephrotic-nephritic picture.

- TYPES-Primary / secondary. Primary MPGN is further divided in to two types on the basis of distinct ultrastructural,IF and pathogenic findings in to type 1 and type 2 MPGN. Secondary causes are SLE, HIV, Hepatitis, schistosomiasis,malignant diseases, hereditary complement def. states etc..
- These are now recognized to be distinct entities,

  termed *MPGN type I and dense deposit disease (formerly MPGN type II).*

MPGN

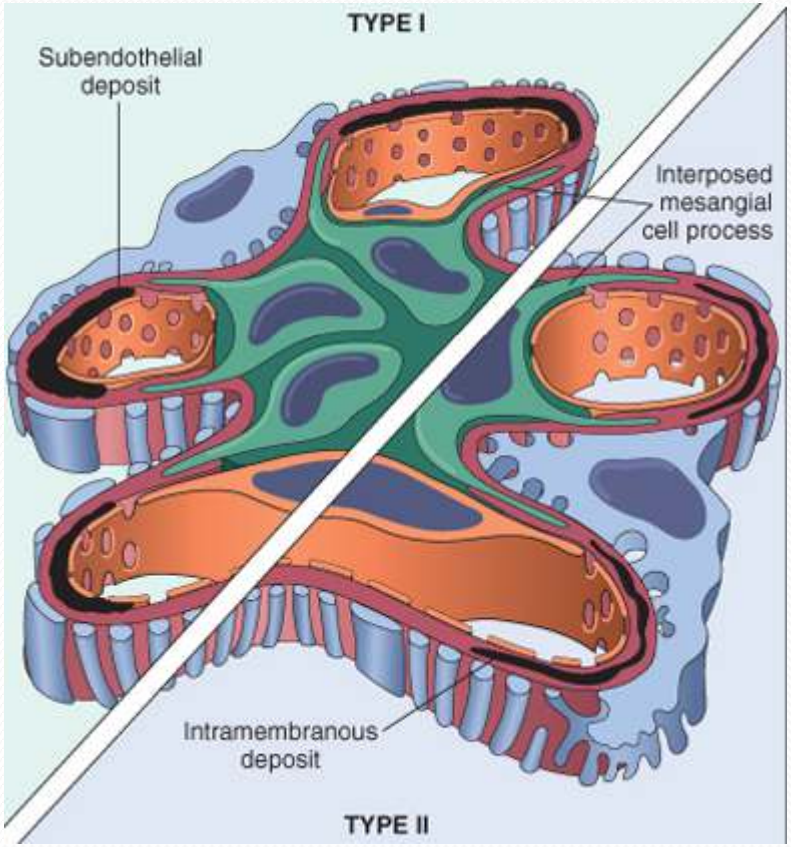
- MORPHOLOGY-By L.M, both types are similar. Glomeruli are large and hypercellular caused by proliferation of mesangial cells and leukocytic infiltration. Glomeruli have a lobular appearance.

- GBM is thickened and shows a double contour or tram track appearance. Duplication of basement membrane (split membrane) is because of inclusion of mesangial cell processes.

  (mesangial interposition)

Different ultrastructural and immunofluorescence microscopic features of Type I & II

	Types I	Types II
Ultrastructural	subendothelial electron-dense deposits	Intramembranous Dense-deposit disease.
Immunofluorescence	C3 is deposited in an irregular granular pattern.	C3 is present in linear foci in the basement membranes and in the mesangium in characteristic circular aggregates (mesangial rings).
	IgG and early complement components present	IgG & early components of the classical complement pathway are absent



Ref- Robbins and Cotran: Pathologic basis of disease: South Asia Edition, Pg:-921

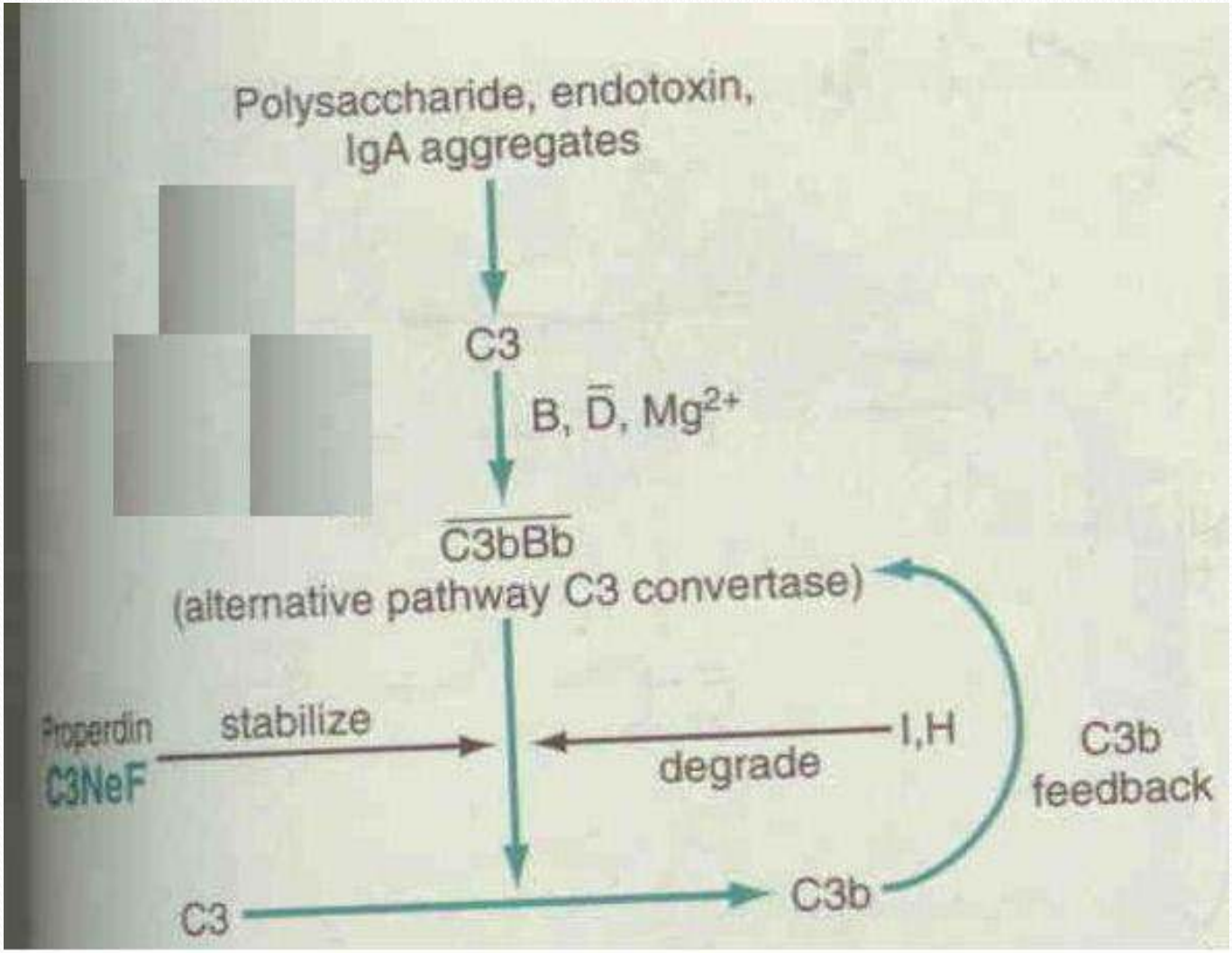
Pathogenesis:

Type I MPGN:

- *Circulating immune complexes*, but the inciting antigen is not known.

Type II MPGN (*dense-deposit disease*):

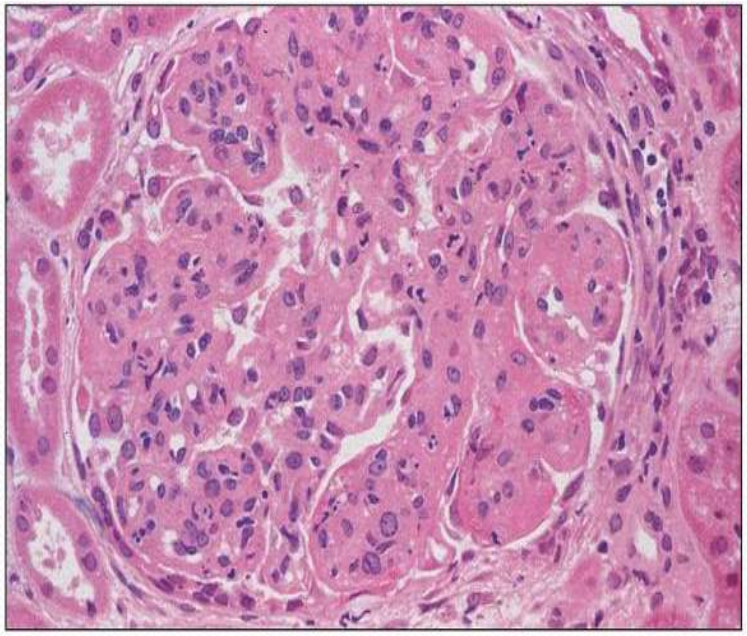
- The pathogenesis of type II MPGN is less clear
- *The fundamental abnormality appears to be excessive alternate complement pathway activation*



ALTERNATE COMPLEMENT PATHWAY

- More than 70% patients with type-2 MPGN have circulating antibodies termed as C3 nephritic factor (C3 NeF), autoantibody binds to C3 convertase ,stabilizes it and enhancing C3 break down leading to hypocomplementemia.
- Decrease C3 synthesis by liver.
- How the C3 Nef is related to glomerular injury and nature of dense deposits are unknown.
- Disease follows slowly progressive but unremitting course.

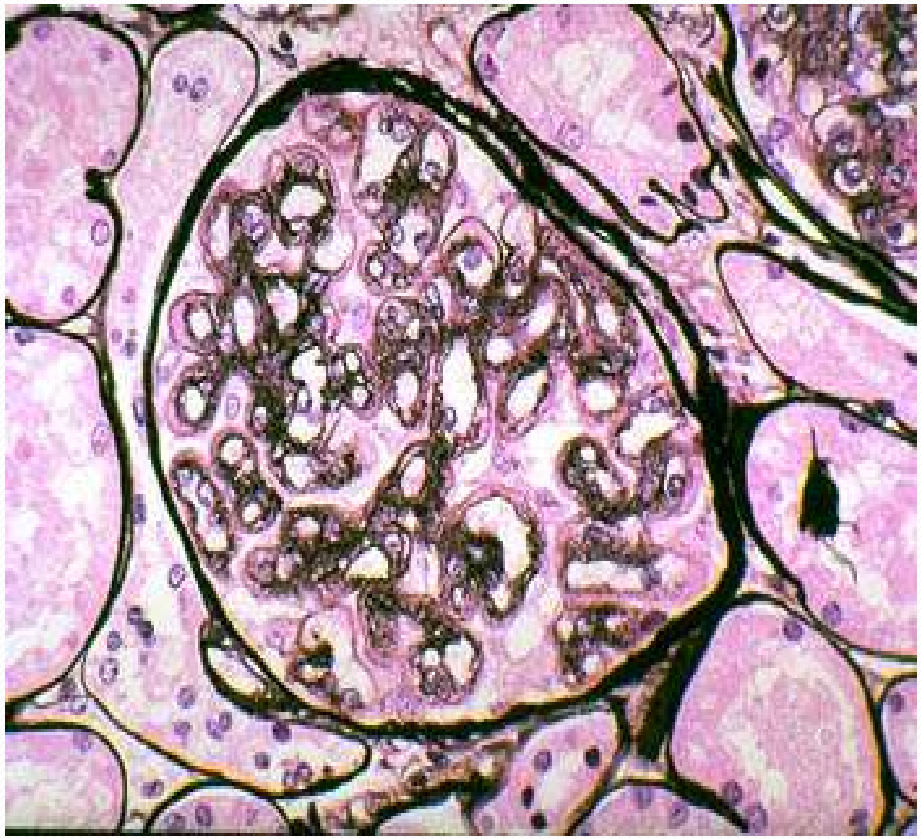
Glomerulus, membranoproliferative glomerulonephritis (MPGN)



Ref: Heptinstall Pathology of the Kidney ,7th Edition ,Pg.576

- MPGN is another relatively common primary renal cause of nephrotic syndrome in both children and adults. Notice the lobular pattern, the hypercellularity, and the collapse of the capillaries.

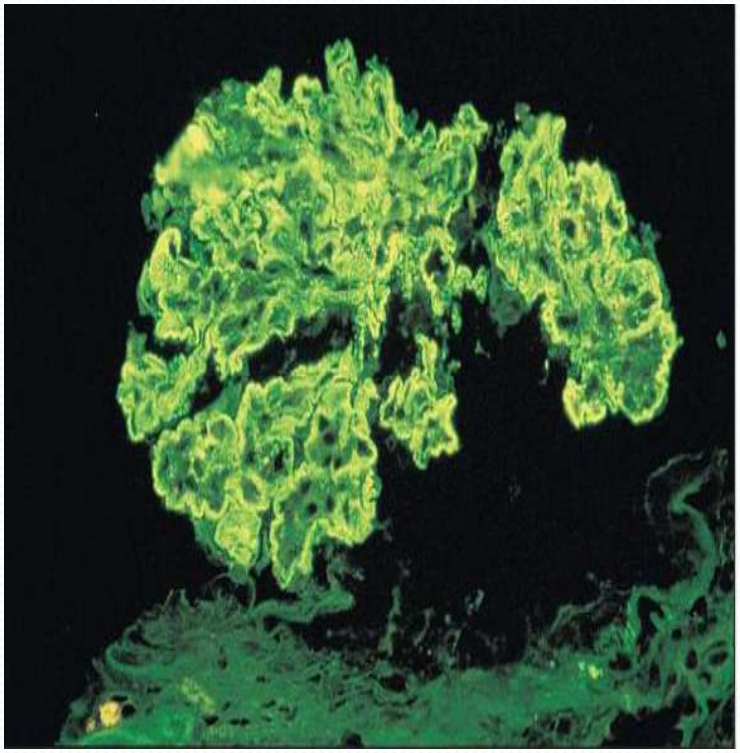
Kidney, membranoproliferative glomerulonephritis (MPGN), later stage, silver stain



- At a later stage of MPGN, many of the capillary loops show a double contour, or "tram-track," appearance.

Ref: https://medicine.tamu.edu/class-files/robbinscases/ren1/record0014.html

Membranoproliferative glomerulonephritis - immunofluorescence



- Intense glomerular mesangial and capillary wall staining with anti-IgG antiserum.

Ref: Heptinstall Pathology of the Kidney ,7th Edition ,Pg.584

C3 Glomerulopathy

- The term *C3 glomerulopathy encompasses two conditions, Dense deposit disease (formerly MPGN, type II) and C3 glomerulonephritis.*
- These are relatively rare diseases with certain shared clinical, morphologic, and pathogenic features. They are set apart by differences in the electron microscopic appearance.
- Patients may present with nephrotic or nephritic syndrome, however, cases with only mild proteinuria also occur.

Pathogenesis

- Complement dysregulation due to acquired or hereditary abnormalities of the alternative complement pathway is the underlying cause.
- Some patients have an autoantibody, called *C3 nephritic factor (C3NeF),* that causes uncontrolled cleavage of C3 by the alternative complement pathway. In other patients, mutations in various complement regulatory proteins, such as Factor H, Factor I, and membrane cofactor protein (MCP), or autoantibodies to Factor H, are the cause of unregulated activation of the alternative pathway of complement

MORPHOLOGY

- Light microscopic presentation is similar to that seen in MPGN,type 1. The glomeruli are hypercellular, the capillary walls show duplicated basement membranes, and the mesangial matrix is increased.
- By immunofluorescence microscopy, there is bright mesangial and glomerular capillary wall staining for C3 in both dense deposit disease and C3 GN. IgG and the early components of the classical complement pathway (C1q and C4) are usually absent in both conditions.

- By electron microscopy, C3 GN shows mesangial and subendothelial electron-dense “waxy” deposits; similar deposits also may be seen along the tubular basement membranes.
- By contrast, in dense deposit disease, the lamina densa of the GBM are transformed into an irregular, ribbon like, extremely electron dense structure, resulting from the deposition of C3-containing material.
- Both dense deposit disease and C3 GN carry a relatively poor prognosis.

Disease	Most Frequent Clinical Presentation	Pathogenesis	Glomerular Pathology		
			Light Microscopy	Fluorescence Microscopy	Electron Microscopy
Minimal-change disease	Nephrotic syndrome	Unknown; podocyte injury	Normal	Negative	Effacement of foot processes; no deposits
Focal segmental glomerulosclerosis	Nephrotic syndrome; nonnephrotic range proteinuria	Unknown: reaction to loss of renal mass; plasma factor?	Focal and segmental sclerosis and hyalinosis	Usually negative; IgM and C3 may be present in areas of scarring	Effacement of foot processes; epithelial denudation
Membranous nephropathy	Nephrotic syndrome	In situ immune complex formation; PLA2R antigen in most cases of primary disease	Diffuse capillary wall thickening and subepithelial "spike" formation	Granular IgG and C3 along GBM	Subepithelial deposits
Membranoproliferative glomerulonephritis (MPGN) type I	Nephrotic/nephritic syndrome	Immune complex	Membranoproliferative pattern; GBM splitting	Granular IgG, C3, C1q and C4 along GBM and mesangium	Subendothelial deposits
C3 glomerulopathy (dense deposit disease and C3 glomerulonephritis)	Nephrotic/nephritic syndrome; nonnephrotic proteinuria	Activation of alternative complement pathway; antibody-mediated or hereditary defect in regulation	Mesangial proliferative or membranoproliferative patterns	C3	Mesangial, intramembranous and subendothelial electron-dense or "waxy" deposits
Acute postinfectious glomerulonephritis	Nephritic syndrome	Immune complex mediated; circulating or planted antigen	Diffuse endocapillary proliferation; leukocytic infiltration	Granular IgG and C3 along GBM and mesangium	Primarily subepithelial humps
IgA nephropathy	Recurrent hematuria or proteinuria	Immune complexes containing IgA	Mesangial or focal endocapillary proliferative glomerulonephritis	IgA ± IgG, IgM, and C3 in mesangium	Mesangial and paramesangial dense deposits
Anti-GBM disease (e.g. Goodpasture syndrome)	Rapidly progressive glomerulonephritis	Autoantibodies against collagen type IV α3 chain	Extracapillary proliferation with crescents; necrosis	Linear IgG and C3; fibrin in crescents	No deposits; GBM disruptions; fibrin
Pauci-immune glomerulonephritis	Rapidly progressive glomerulonephritis	Anti-neutrophil cytoplasmic antibody	Extracapillary proliferation with crescents; necrosis	Fibrin in crescents	No deposits; GBM disruptions; fibrin

Thank You