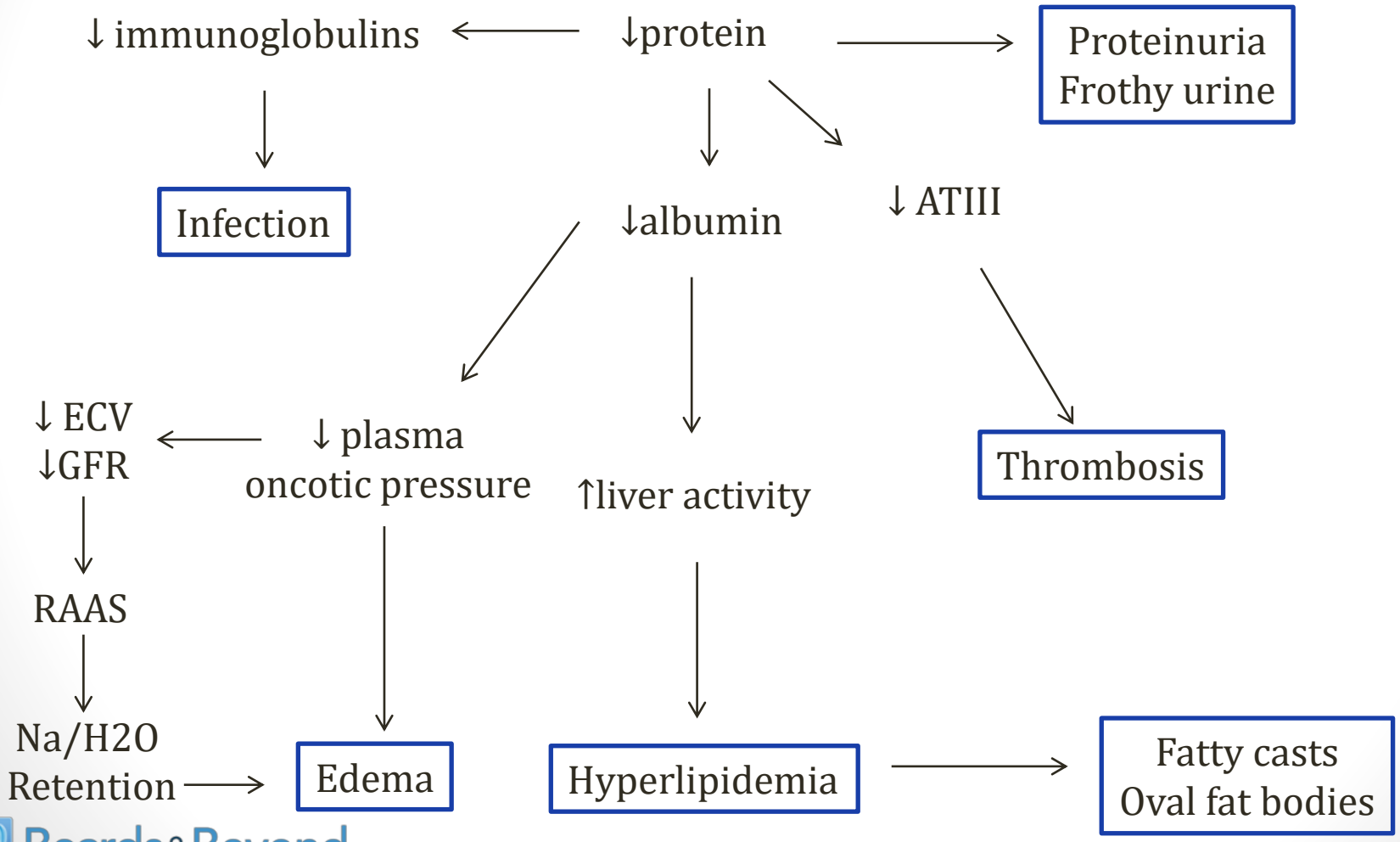
Nephrotic Syndrome

Jason Ryan, MD, MPH

Nephrotic Syndrome



Nephrotic Syndrome

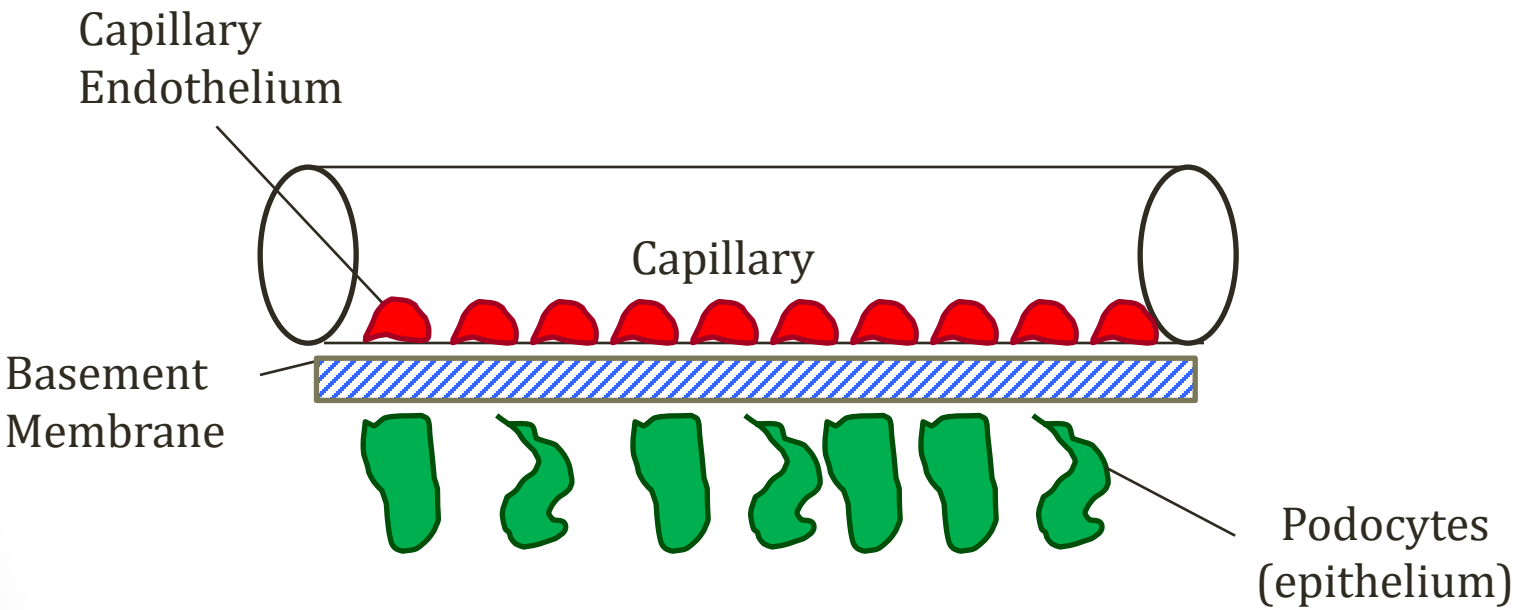
- Classic presentation
  - Frothy urine
  - Swelling of ankles
  - Swelling around eyes (periorbital)
  - Serum total cholesterol >300mg/dl
  - Proteinuria (>3.5g/day)

Nephritic/Nephrotic

Sites of Glomerular Injury

- Major determinant of whether a disease process leads to nephritic or nephrotic syndrome is the **site of glomerular injury**
- **Podocytes**
  - Separated from blood by GBM
  - Injury does not lead to inflammation
  - Damage → loss of filtration barrier to protein only
- Most causes of nephrotic syndrome related to injury of podocytes or epithelial side of GBM

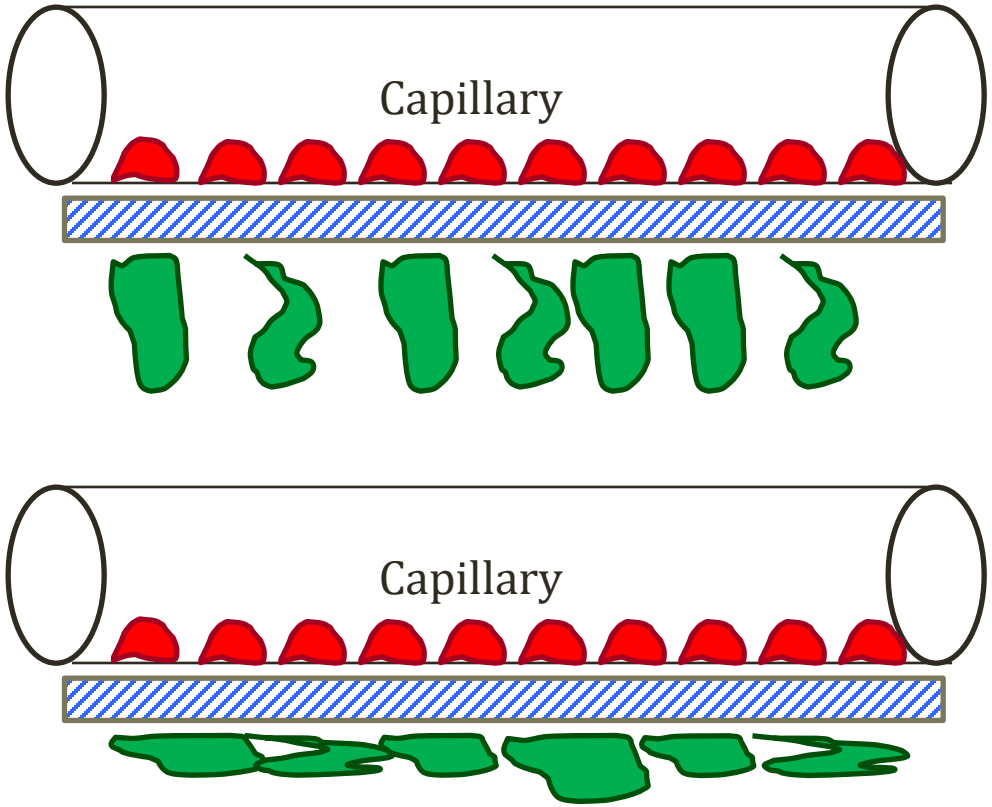
Glomerular Filtration Barrier



Nephrotic Syndrome Causes

1. Minimal change disease
2. Focal segmental glomerulosclerosis (FSGS)
3. Membranous nephropathy
4. Diabetic
5. Amyloidosis
6. Membranoproliferative glomerulonephritis

Minimal Change Disease



Effacement (flattening) Foot Processes

Minimal Change Disease

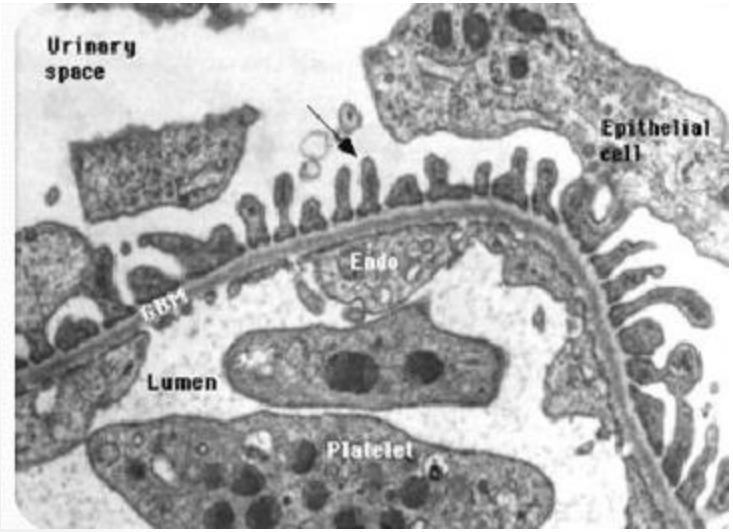
Pathology

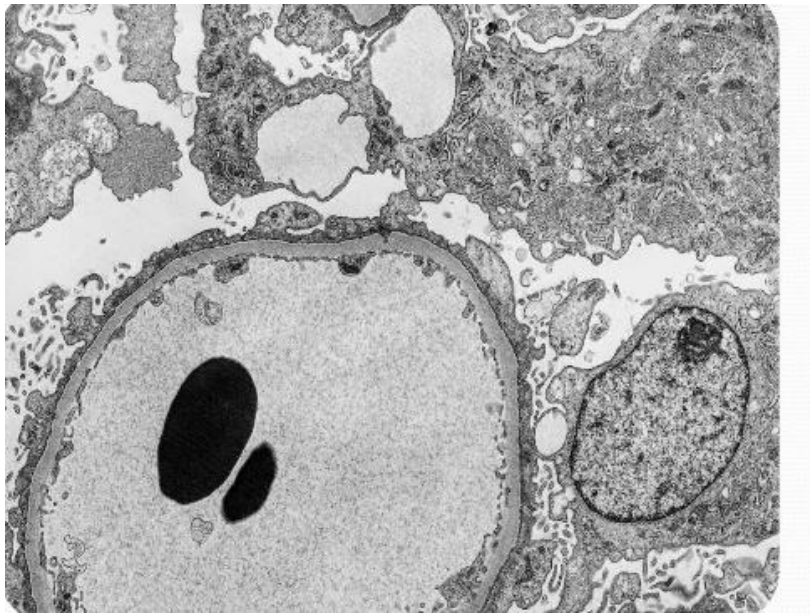
- Caused by **effacement of foot processes**
- Loss of anion (-) charge barrier GBM
- Triggered by **cytokines** → damage to podocytes
- Usually idiopathic
- Associated with Hodgkin Lymphoma

Minimal Change Disease

Renal Biopsy

- Normal light microscopy
- No important findings IF
- Only finding is effacement foot processes EM





Images courtesy of bilalbanday

Minimal Change Disease

Other Features

- Sometimes has immunological trigger (days before)
  - **Viral infection (URI)**
  - Allergic reaction (bee sting)
  - Recent immunization
- **"Selective"** proteinuria
  - Only albumin in urine (not immunoglobulin)
  - Contrast with other glomerular disease "non-selective"
- Most common cause nephrotic syndrome in children
  - Classic presentation is a child with recent URI

Minimal Change Disease

Prognosis and Treatment

- Favorable prognosis
- Responds very well to **steroids**
  - Unique among nephrotic syndrome causes

FSGS

Focal segmental glomerulosclerosis

- Glomerulosclerosis
  - Pink/dense deposition of collagen in glomerulus
- Segmental
  - Only portion of glomerulus involved
- Focal
  - Only some glomeruli involved

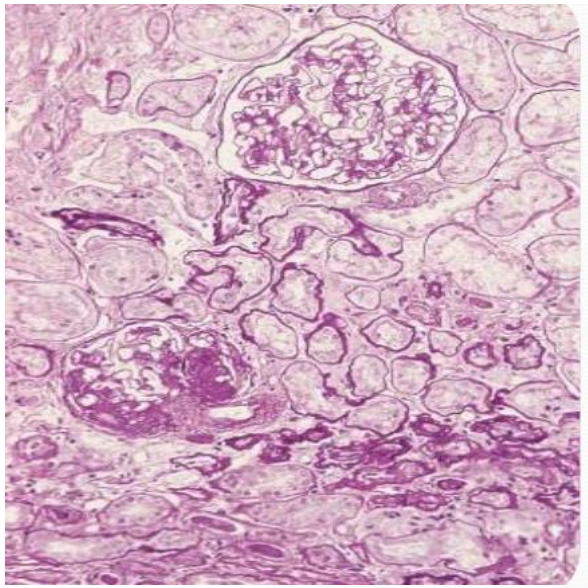


Image courtesy of bilalbanday

FSGS

Pathology

- Sclerotic segments
  - Collapse of basement membranes
  - Hyaline deposition ("hyalinosis")
- Effacement of foot processes
  - Seen on electron microscopy

FSGS

Renal Biopsy

- Light microscopy: focal, segmental lesions
- Electron microscopy: effacement of foot processes
- Immunofluorescence
  - Usually negative (no immune complexes)
  - Sometimes IgM, C3, C1 (nonspecific finding)

FSGS

Focal segmental glomerulosclerosis

- Caused by **podocyte injury**
- Unknown cause
- Often progresses to chronic renal failure
  - 40-60% within 10 to 20 years
  - Does not respond to steroids
  - Severe version of minimal change disease

FSGS

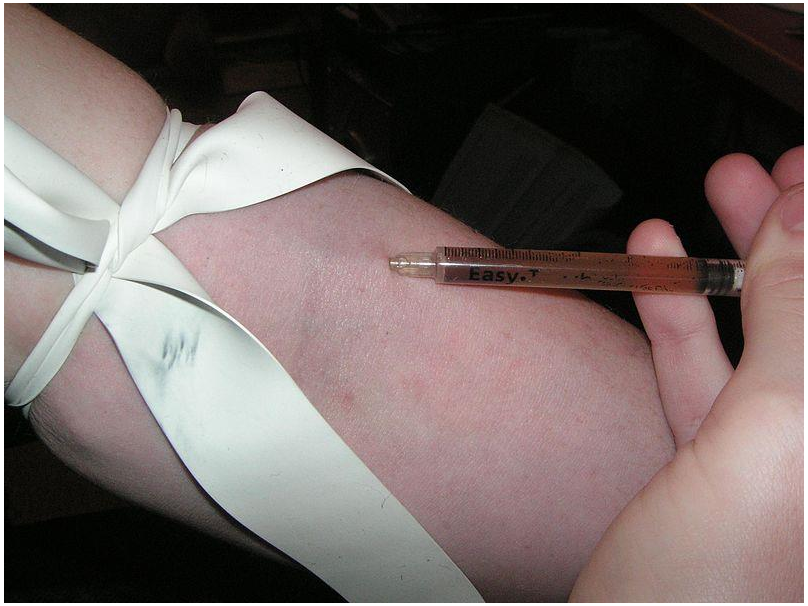
Focal segmental glomerulosclerosis

- Usually idiopathic (primary)
- Many secondary causes

FSGS

Focal segmental glomerulosclerosis

- HIV
- Sickle cell patients
- Heroin users



Psychonaught/Wikipedia

FSGS

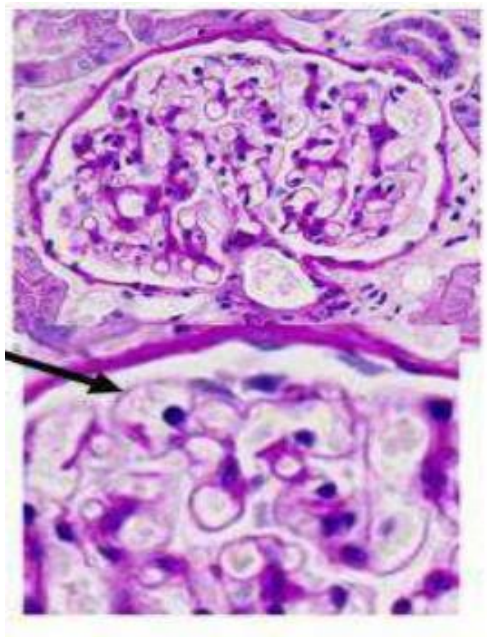
Other Associations

- Massive obesity
- Interferon treatment
  - Used to treat HCV and HBV
  - Some leukemias and lymphomas, melanoma
- Loss of nephrons
  - Single kidney (congenital)
  - Surgical kidney removal

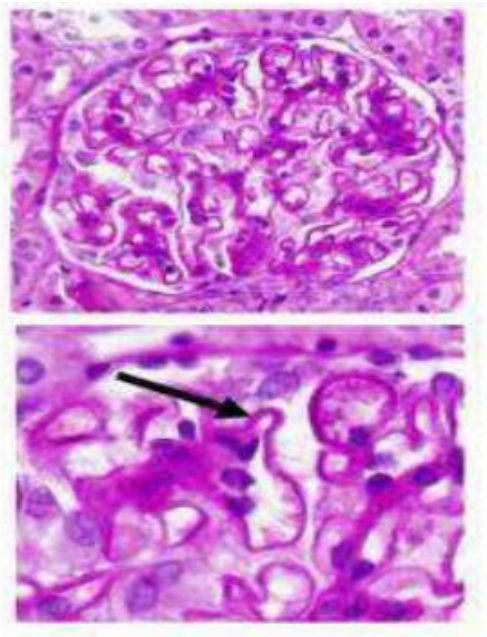
Shutterstock

Membranous Nephropathy

- Thick glomerular basement membrane
  - "Membranous"
- Absence of hypercellularity



Normal



Membranous

Images courtesy of bilalbanday

Membranous Nephropathy

- Membrane thick from **immune complex deposition**
  - IF microscopy very useful
  - "Granular" deposits of IgG and C3 staining

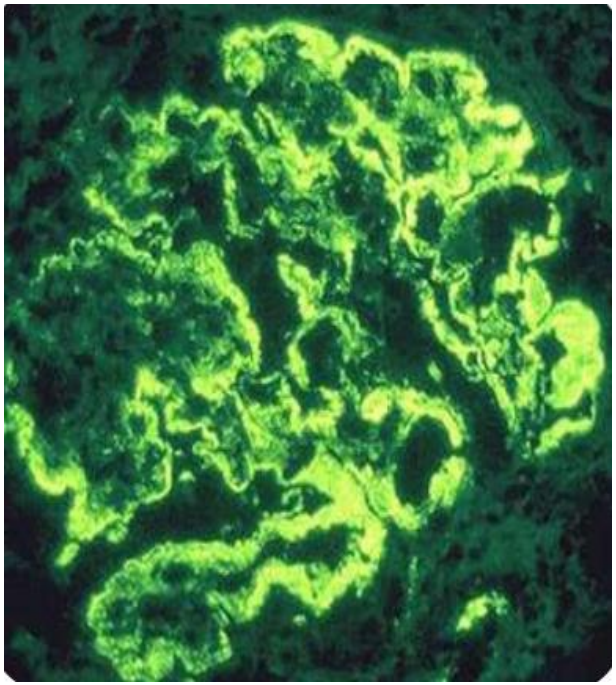
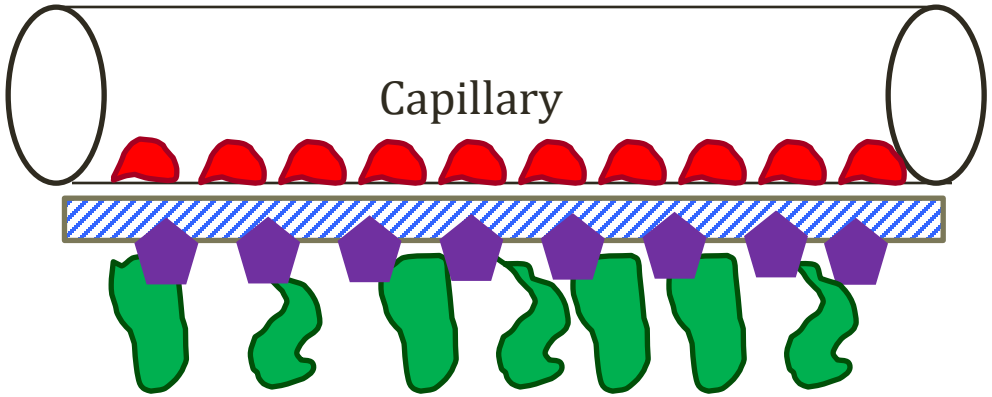


Image courtesy of bilalbanday

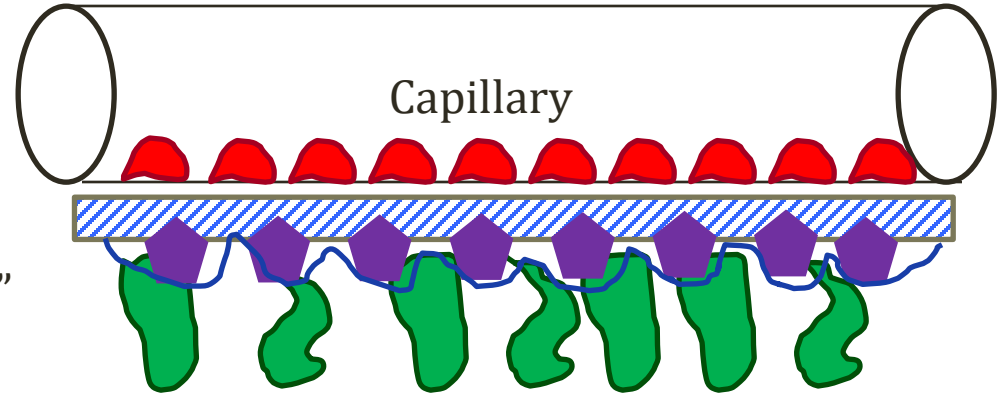
Membranous Nephropathy

Pathophysiology

Subepithelial
Immune
Complex
Deposition
"granular"

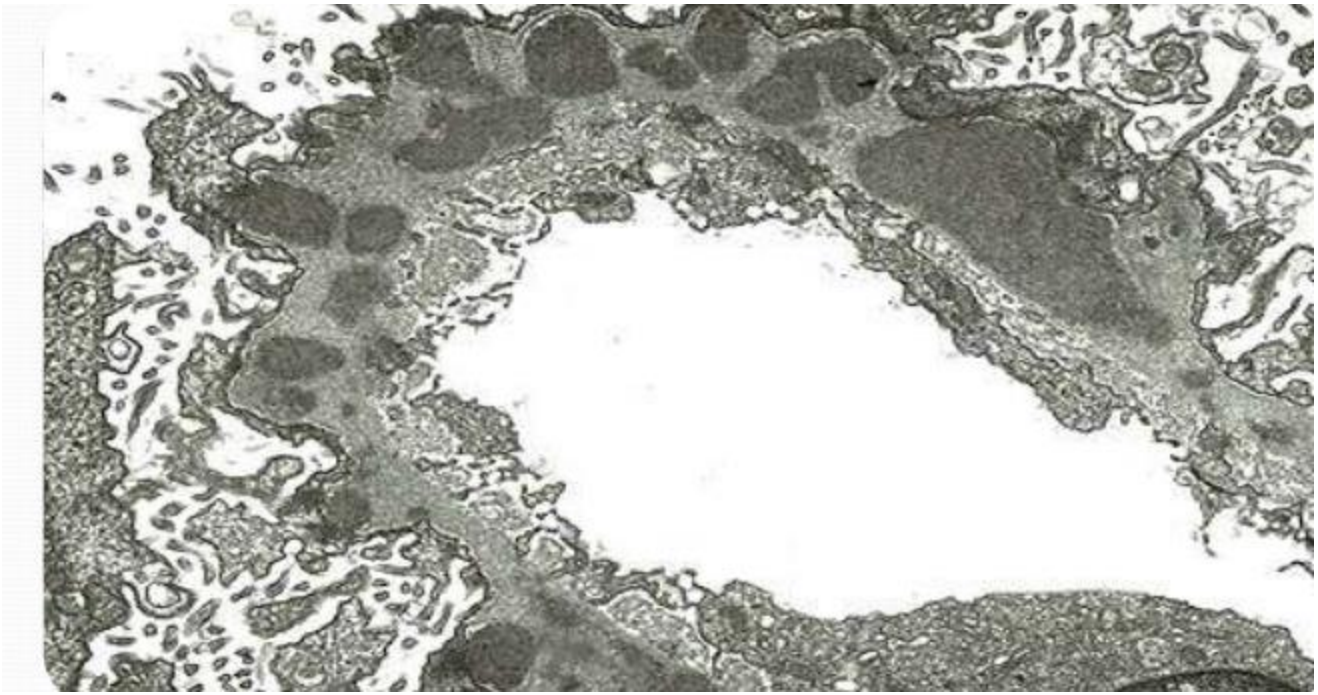


Basement
Membrane
Deposition
"Spike and Dome"



Subepithelial Deposits

"Electron dense deposits"



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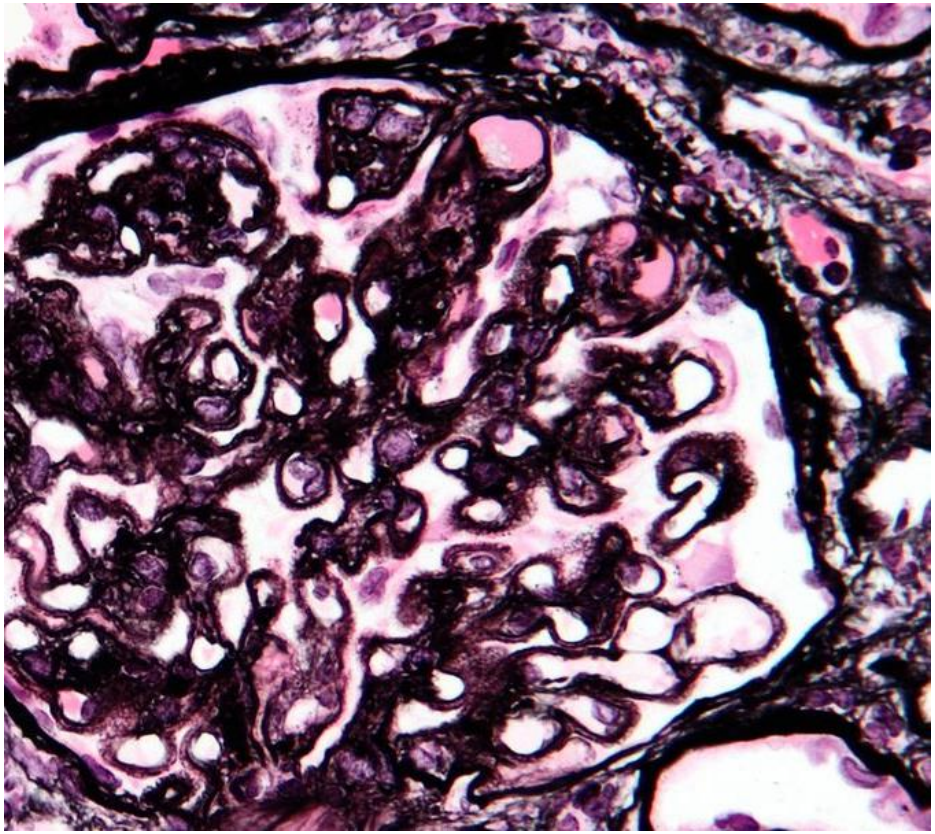
Spike and Dome



Nephron/Wikipedia

Membranous Nephropathy

Renal Biopsy

- Light microscopy: capillary/BM thickening
- Electron microscopy: subepithelial deposits
- Immunofluorescence: granular IgG/C3

Membranous Nephropathy

- Often idiopathic
- **Autoantibodies**
- Antigen: **phospholipase A2 receptor (PLA2R)**
- Expressed on podocytes

Membranous Nephropathy

Secondary Causes

- Systemic lupus erythematosus (SLE)
- Most lupus renal disease in nephritic
- Diffuse proliferative glomerulonephritis
- If nephrotic, this is cause (10-15%)

Wikipedia/Public Domain

Membranous Nephropathy

Secondary Causes

- Solid tumors
  - Colon cancer, lung cancer, melanoma
- Infections
  - Hep B, Hep C
- Drugs
  - Penicillamine, gold, NSAIDs
  - All used to treat **rheumatoid arthritis**

Tumor
Hepatitis
Rheumatoid Arthritis

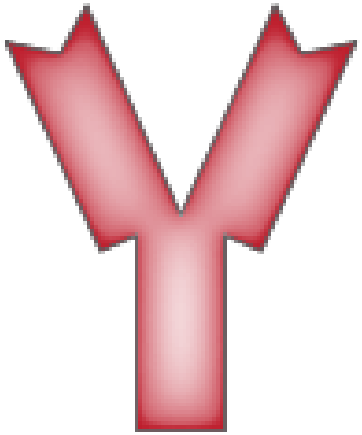
Membranous Nephropathy

Other Features

- Most common cause nephrotic syndrome in adults
- Excellent prognosis in children
- Some adults develop ESRD

Autoantibodies

- Most antibody disorders are nephritic
- IC → inflammation → nephritis → nephritic syndrome
- Membranous is nephrotic
- Subepithelial deposits → nephrotic syndrome



Diabetic Nephropathy

- Non-enzymatic glycosylation
- Basement membranes: leakage of protein
- Long term effect: sclerosis of glomerulus
- Proteinuria
- Can develop nephrotic syndrome

Amyloidosis

- Extracellular buildup of amyloid proteins
- Classic biopsy findings
  - Apple-green birefringence
  - Congo red stain
- Kidney is **most commonly involved organ**

Nephrotic Syndrome Causes

1. Minimal change disease ← Cytokines
2. FSGS ← Podocyte Damage
3. Membranous ← Immune Complexes
4. Diabetic ← Glucose
5. Amyloidosis ← Amyloid
6. Membranoproliferative glomerulonephritis

MPGN

Jason Ryan, MD, MPH

MPGN

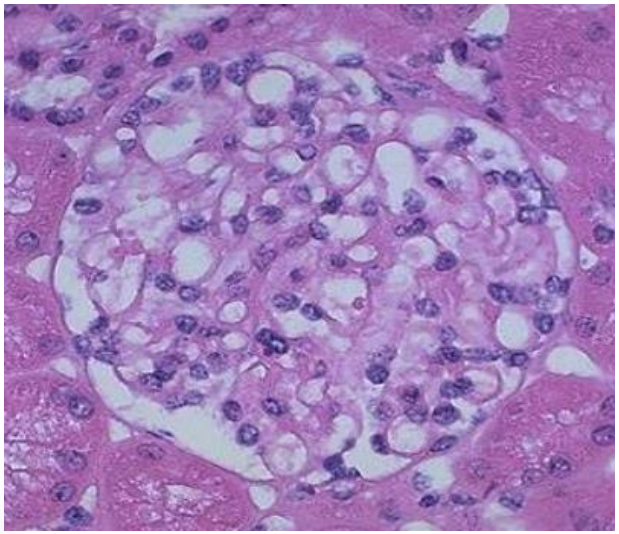
Membranoproliferative Glomerulonephritis

- Rare glomerular disorders
- Can cause nephritic or nephrotic syndrome
- Varying degrees of renal dysfunction
- Renal failure (↑BUN/Cr)
- Hematuria
- Proteinuria (+/- nephrotic range)

MPGN

Membranoproliferative Glomerulonephritis

- Membrano
  - Thick basement membrane
- Proliferative
  - Proliferation of mesangial cells, mesangial matrix



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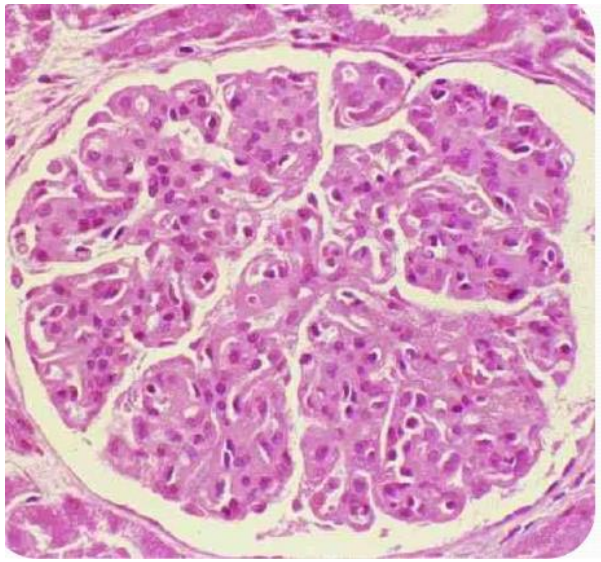


MPGN: Hypercellular, Thick walls

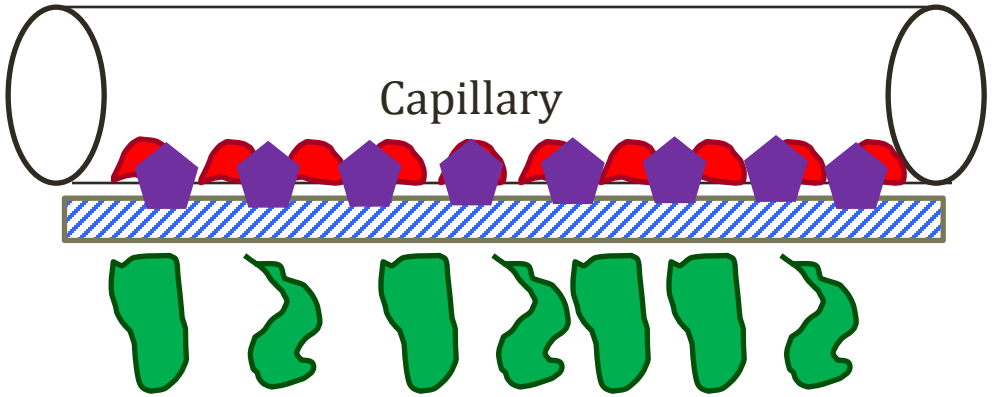
Images courtesy of bilalbanday

MPGN

Membranoproliferative Glomerulonephritis

- Two major types
- Type I much more common
- Type II (dense deposit disease) rare

MPGN Type I

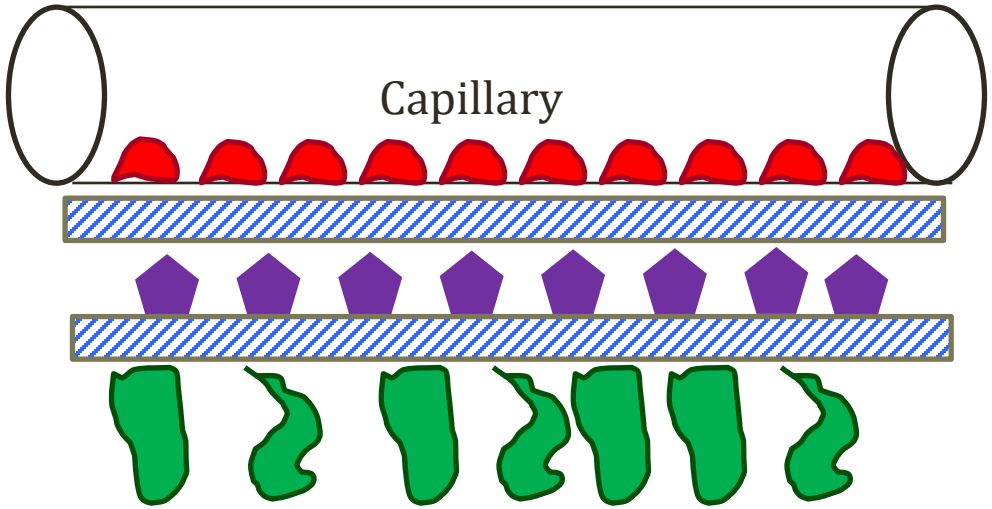


Type I

Subendothelial **immune complex** deposition

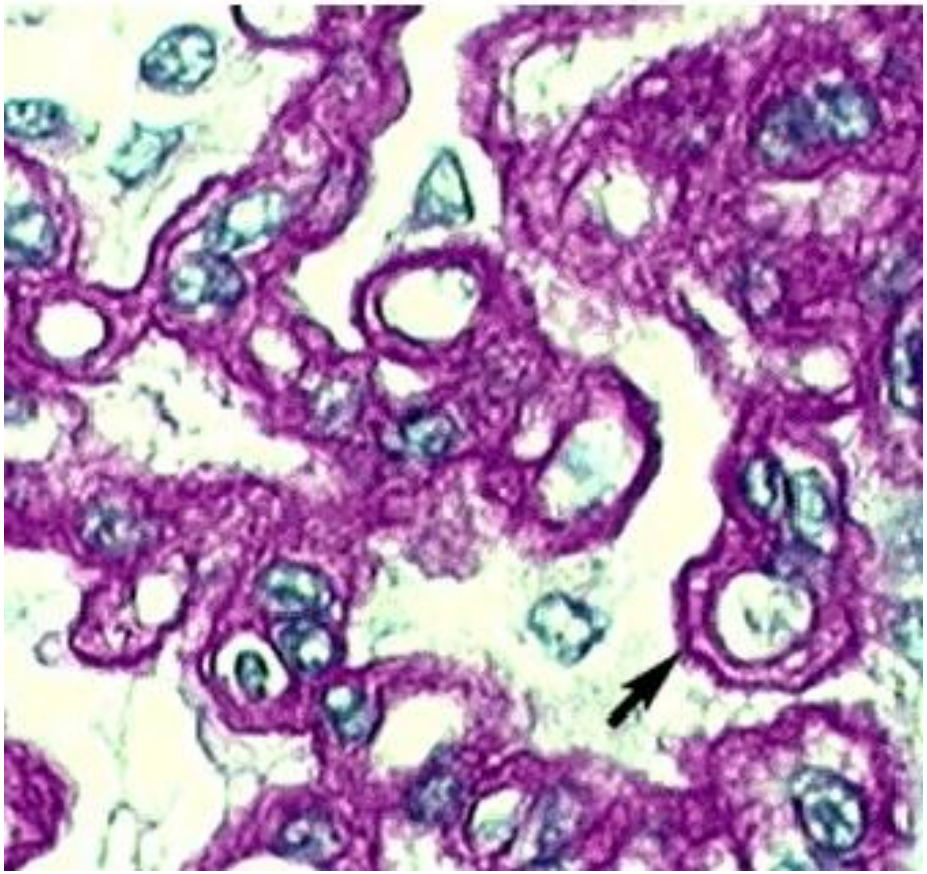
IgG → complement activation

MPGN Type I



IC deposits trigger **mesangial ingrowth**
Splits basement membrane
"Tram track" appearance on light microscopy
Common (80%) in Type I

MPGN Type I

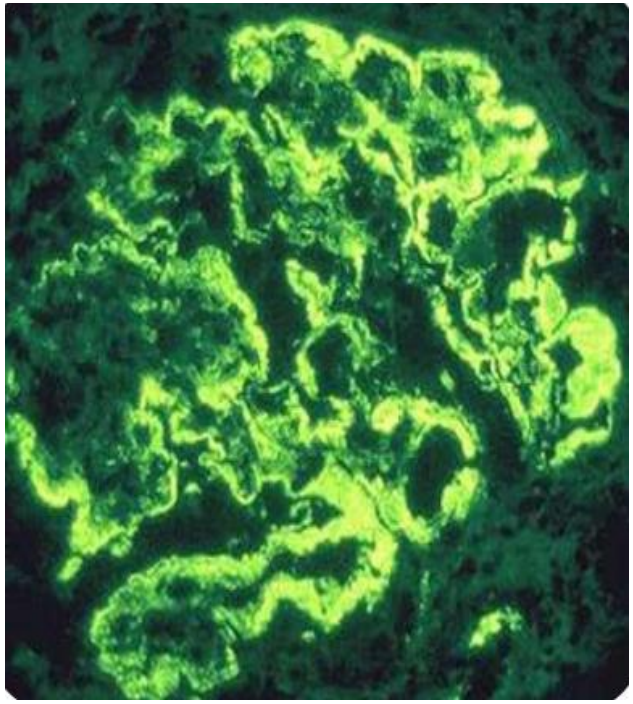


Type I: Tram Tracks

Image courtesy of Shashidhar Venkatesh Murthy

MPGN Type I

- Subendothelial antibodies/complexes
- Granular IF for IgG and C3



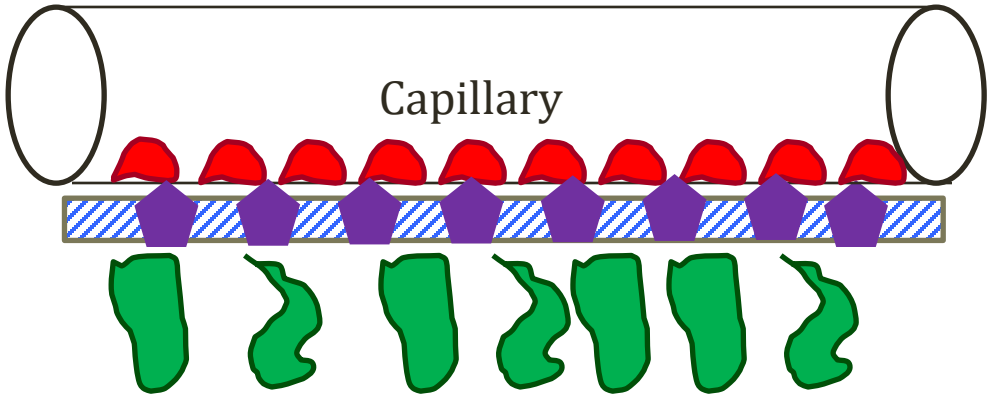
Images courtesy of bilalbanday

MPGN Type I

- May be idiopathic
- Associated with **hepatitis B and C infection**

MPGN Type II

Dense Deposit Disease



Type II

Basement Membrane

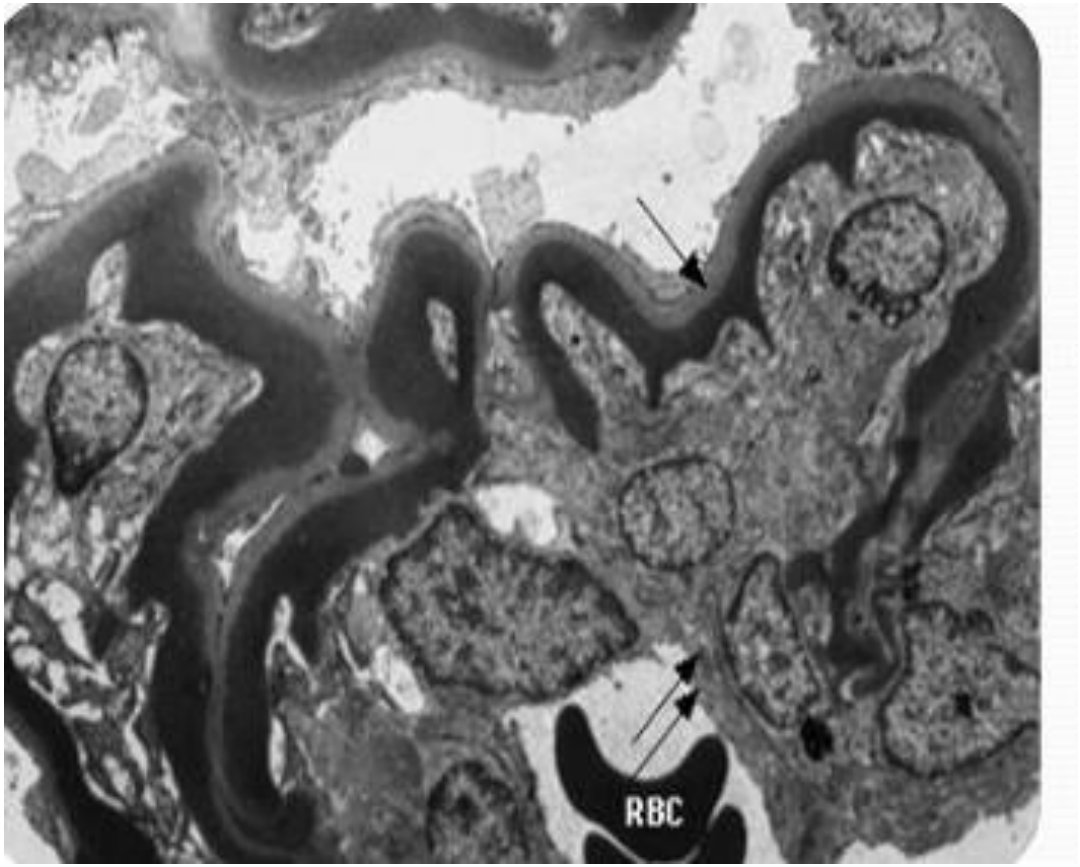
"Electron dense" deposits

Mediated by **complement**

IgG usually absent

MPGN Type II

Dense Deposit Disease



Type II: Dense Deposits
IF shows C3 but not IgG

Image courtesy of bilalbanday

C3 Nephritic Factor

C3 Covertase Stabilizing Antibody

- Found in >80% patients with MPGN II
- C3 convertase activates **alternative pathway**
- Stabilized by C3 nephritic factor
- Over activation of complement system
- Hypocomplementemia (↓C3)

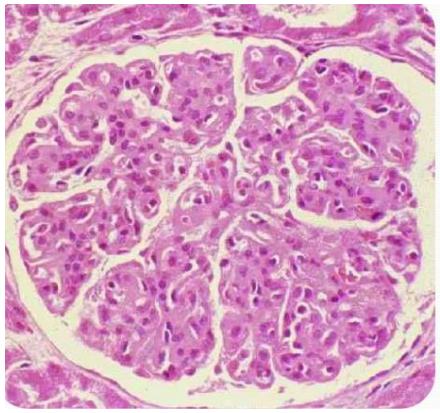
MPGN Type II

Dense Deposit Disease

- Mostly a disease of **children**
- Usually 5 to 15 years old
- 50% develop ESRD within ten years

MPGN

Membranoproliferative Glomerulonephritis



	Type I	Type II
Pathology	Immune Complex	Complement (C3)
Location	Subendothelial	Basement Membrane
Microscopy	LM: Tram Tracks	EM: Dense Deposits
Associations	Hepatitis	Children

Images courtesy of bilalbanday