KIDNEY-2

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Pathogenesis of glomerular injury

Immune Glomerulonephritis:

(A) Antibody mediated injury

- In situ immune complex deposition
  - Tissue antigens – Good pasture anti GBM Ag
  - Planted antigens – infections, toxins, drugs.

- Circulating immune complex deposition.
  - Endogenous – DNA as in SLE
  - Exogenous – infections.

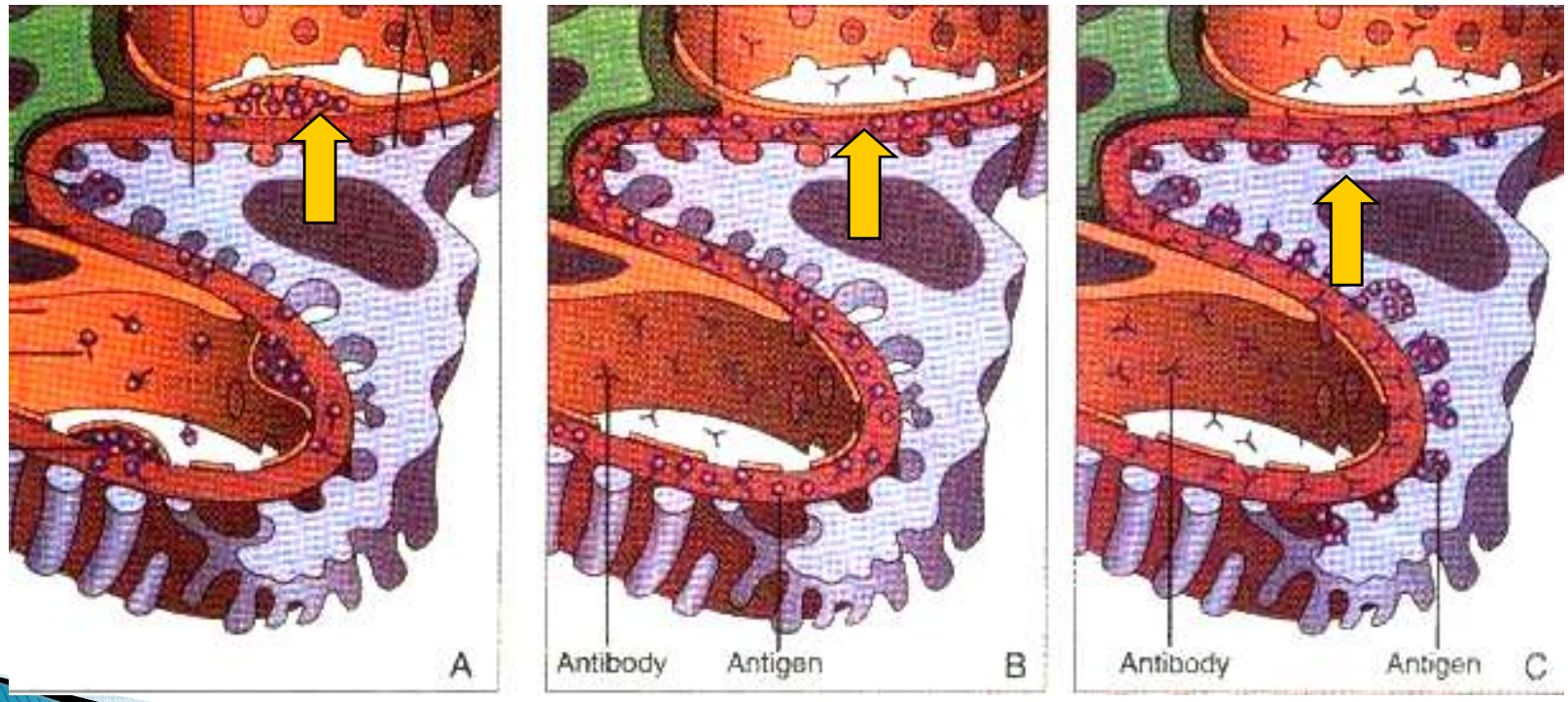
- Cytotoxic antibodies

(B) Cell mediated Immune injury

(C) Activation of alternate complement pathway

Immune Glomerulonephritis:

Immune Complex **ANTI-GBM** **HEYMANN**



(A) Antibody mediated injury
In situ immune complex deposition

- Antibody react directly with intrinsic tissue or planted antigens.
- *1.Anti GBM nephritis* –Antibodies directed against fixed antigens. Experimental model produced in rats by injecting anti rat kidney antibody prepared in rabbits. Homogenous diffuse linear pattern by I.F. technique. Deposited immunoglobulin of rabbit is foreign to the host producing more glomerular injury. Characterized by rapidly progressive form of glomerulonephritis.

- Antibodies cross react with other basement membrane. GOOD PASTURE SYNDROME
- GBM antigen –Component of NC domain of alpha 3 chain of collagen type 4.
- 2 HEYMANN NEPHRITIS –Experimental model of rat. GN induced by immunizing animals with an antigen made up of preparation of proximal tubular brush border.(Membranous GN)
- MGN results from reaction of ab to ag located on basal surface of visceral epithelial cells and cross reactive with brush border antigen.

- Heymann antigen –large 330 KD protein (Megalin) complexed to a smaller 44KD protein (receptor associated protein).
- On E.M, numerous electron dense deposits along the sub epithelial side of B.M.
- By I.F.M, Granular and interrupted pattern of immune deposition is seen.

Antibody against planted antigens

- Cationic molecules –bind to glomerular capillary anionic sites.
- DNA –GBM components.
- Bacterial products – deposited in mesangium.
- IFM –Granular pattern of immunoglobulin deposition.

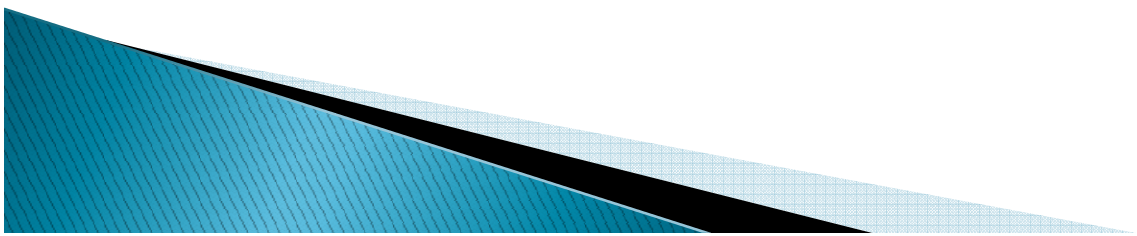
CIRCULATING IMMUNE COMPLEX DEPOSITION

- Glomerular injury occurs because of deposition of circulating ag-ab complexes within glomeruli. Antibodies have no immunologic specificity to glomerular constituents, but they localize because of their physicochemical properties and hemodynamic factors. (innocent bystander)
- E.M.-electron dense deposits.
- I.F.M-granular deposits
- Antigen exposure is short lived in post streptococcal GN and continuous exposure in Membranoproliferative GN.

Cytotoxic antibodies–

Antibodies to glomerular cells

(B) Cell mediated immunity –Sensitized nephritogenic T cells cause some form of glomerular injury, and are involved in progression of many GN.

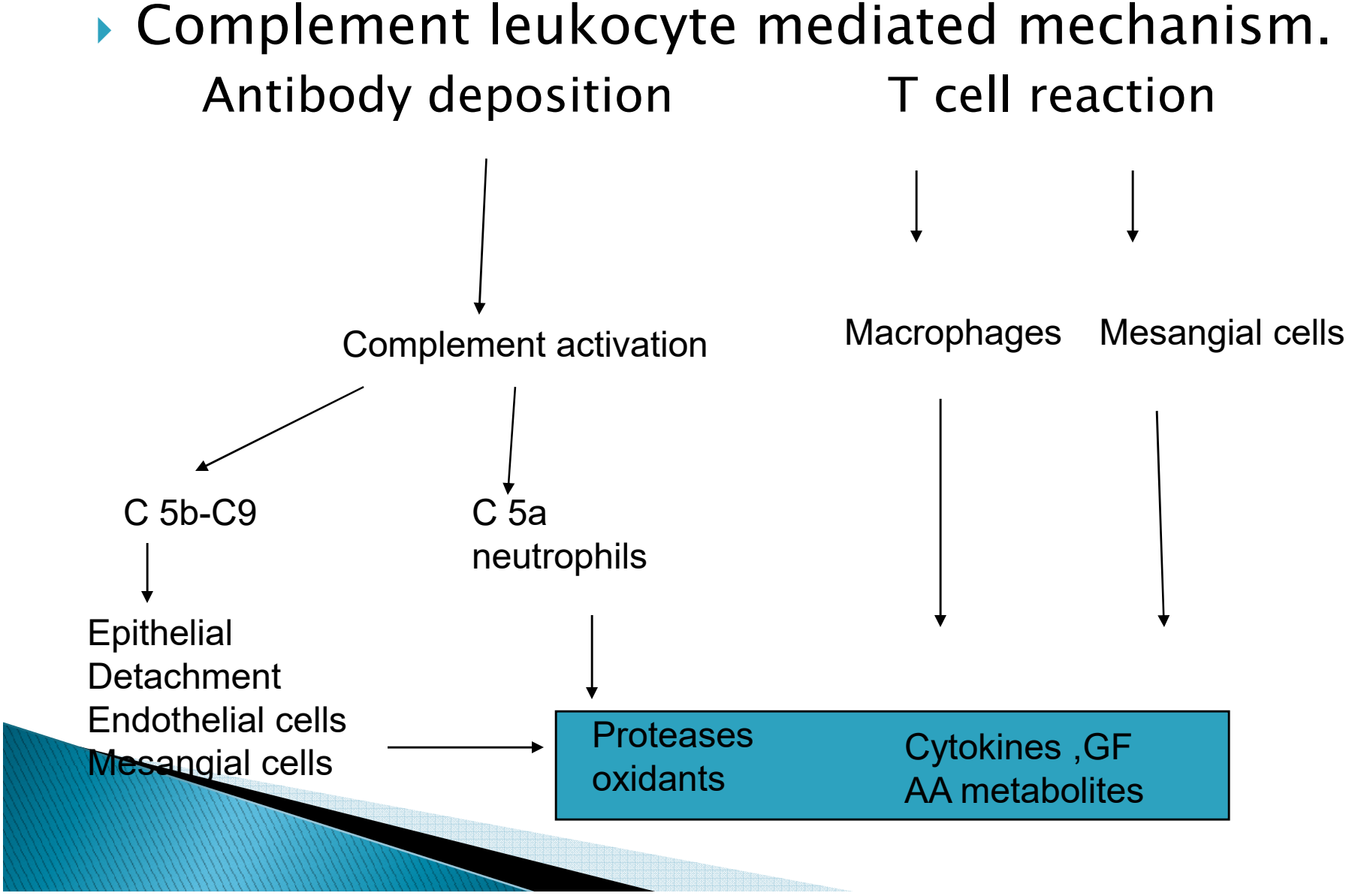


(c) Glomerular Diseases Caused by Complement Activation

- The primary cause of these diseases is unregulated activation of the alternative complement pathway, *which may* be triggered by acquired autoantibodies or inherited abnormalities of complement regulatory proteins.
- Two forms of GN (dense deposit disease and C3 GN) and a systemic disease with significant renal manifestations (complement-mediated thrombotic microangiopathy [TMA] or atypical hemolytic uremic syndrome).

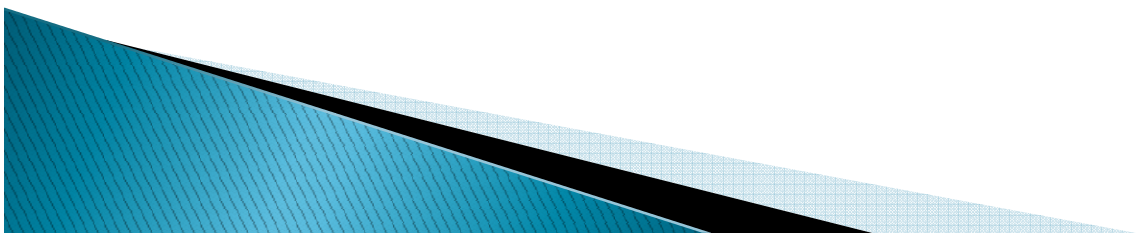
MEDIATORS

- Complement leukocyte mediated mechanism.



OTHER MEDIATORS

- Monocytes and macrophages –When activated release a vast number of biologically active molecules.
- Platelets –aggregate in glomerulus and release Prostaglandins and growth factors.
- Resident glomerular cells –can be stimulated to secrete mediators like cytokines IL-1 arachidonic acid metabolites, GF, NO, endothelin etc..
- Fibrin related products- causes leukocyte infiltration and glomerular cell proliferation.

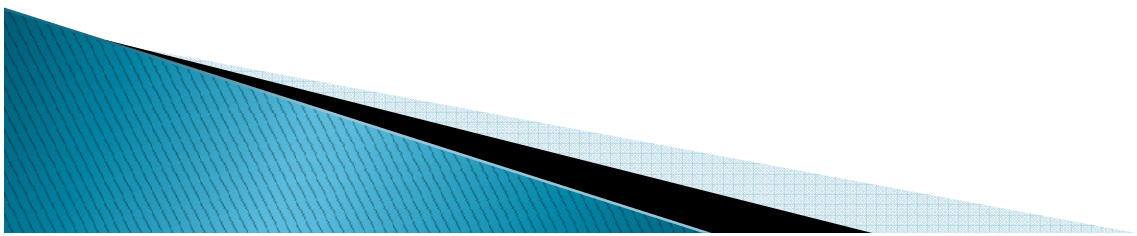


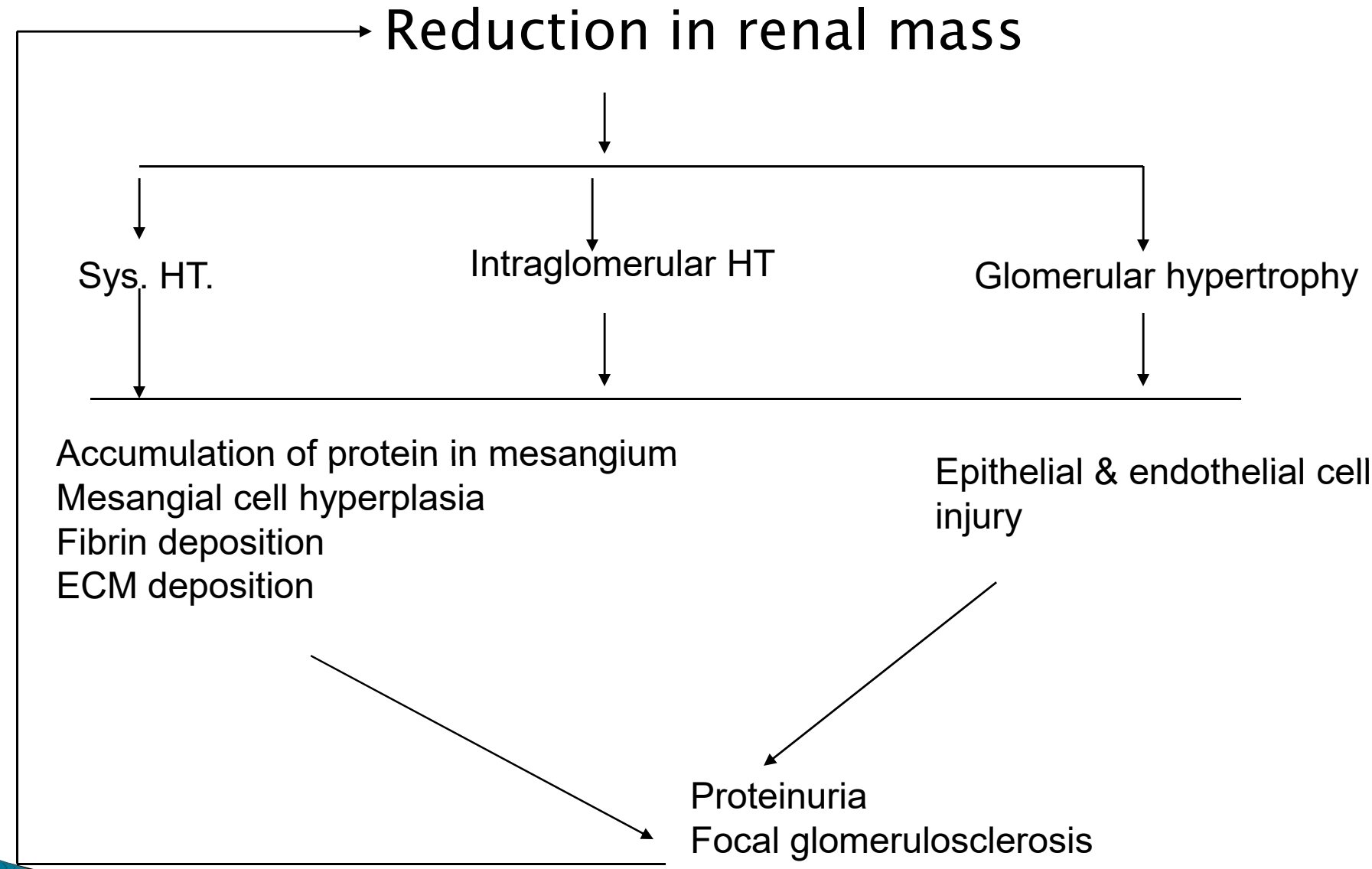
Other mechanisms of glomerular injury

- Epithelial cell injury –detachment of epithelial cells caused by alteration in Nephrin and its associated protein. It is an important protein to maintain selective glomerular permeability .
- Examples –Minimal change disease and Focal segmental glomerulosclerosis
- Reflected morphologically by loss of foot processes, vacuolization, retraction and detachment of epithelial cells.
- Functionally by proteinuria.

Nephron Loss

- Renal ablation glomerulopathy –
- Once any renal disease which reduces GFR to 30–50% of normal, progression to end stage renal failure proceeds at a relatively constant rate.
- Initiated as an adaptive change, initially seen in relatively unaffected glomeruli of diseased kidney.
- Patients develop priteinuria and glomerulosclerosis




Reduction in renal mass
Sys. HT.
Intraglomerular HT
Glomerular hypertrophy
Accumulation of protein in mesangium
Mesangial cell hyperplasia
Fibrin deposition
ECM deposition
Epithelial & endothelial cell injury
Proteinuria
Focal glomerulosclerosis

Acute nephritic Syndromes :

- Diffuse Proliferative GN
  - *Post Streptococcal*
  - *Non post streptococcal*
- RPGN
- Berger's disease (IgA Nephropathy)
- MPGN
- C3 Glomerulopathy
- Hereditary nephritis
- SLE

Diffuse Proliferative GN:

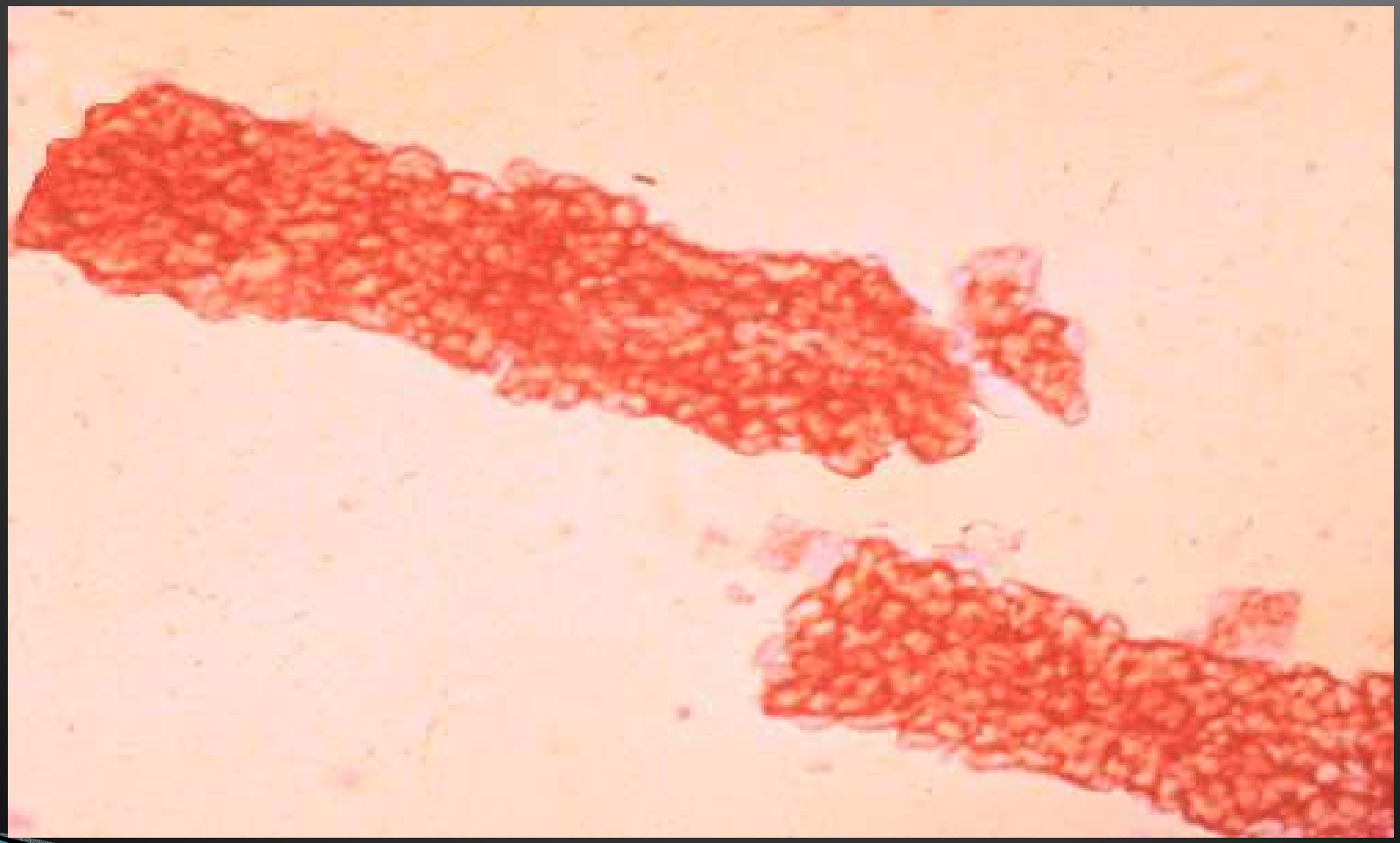
- **Post streptococcal GN**- Seen in children (age 6 to10 yrs), 10 days following a group A ß-hemolytic streptococcal pharyngitis or 2 weeks after a skin infection (most commonly M types 1,2, 4, 12,18,25, 49,55, 57 and 60 nephritogenic strains)
- **Primary infection** – Pharynx, skin, ear etc..
- **Kidney damage** – 1-4 weeks after infection.
- Malaise, fever, nausea, edema, hematuria, ↑ASO, ↓C3
- **Resolution** in 6-8 weeks.

Post-Streptococcal glomerulonephritis

- Circulating immune complex deposition. Alternate complement pathway is activated; serum complement levels are decreased.

- Patients have high ASO titers (80%),high antiDNAase B titers (90%), antistreptokinase (ASKase), anti-nicotinyl adenine dinucleotidase (antiNADase), and antihyaluronidase (AHase)

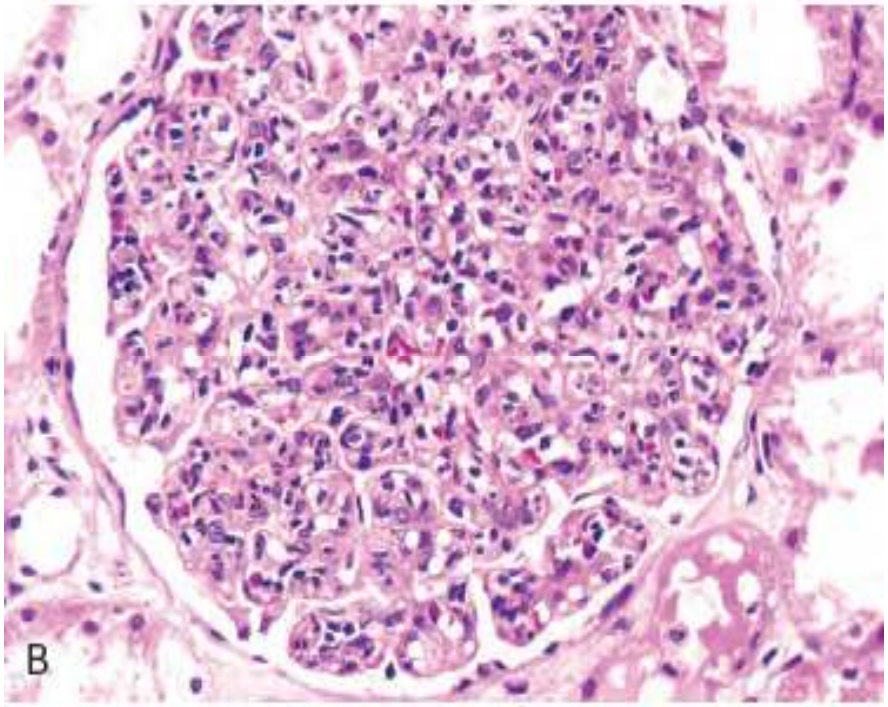
Red cell Casts in Urine:



Acute Nephritic Syndrome

- Test tubes of urine showing normal at the top; grossly bloody in the middle; and smoky urine on the bottom consistent with nephritic syndrome

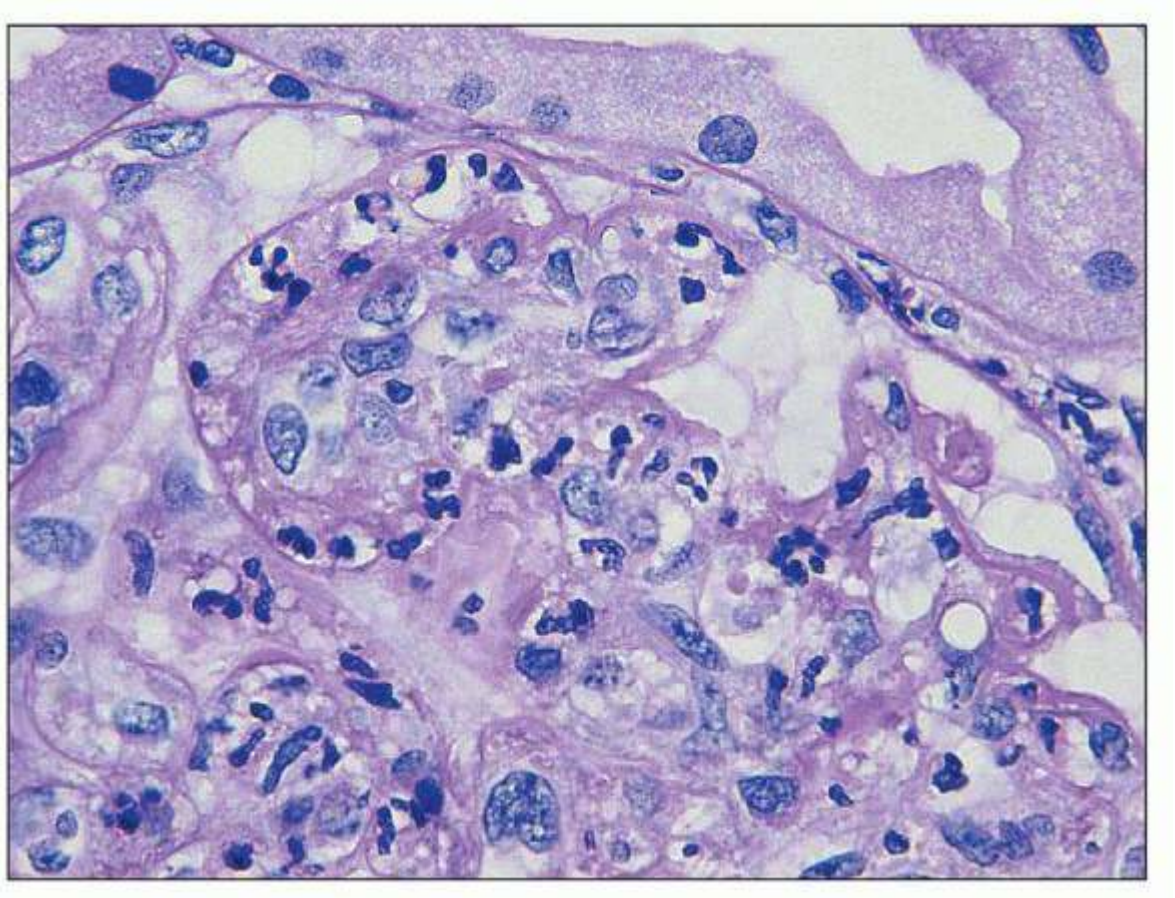
Diffuse Proliferative GN:



Ref- Robbins and Cotran: Pathologic basis of disease: South Asia Edition, Pg:911

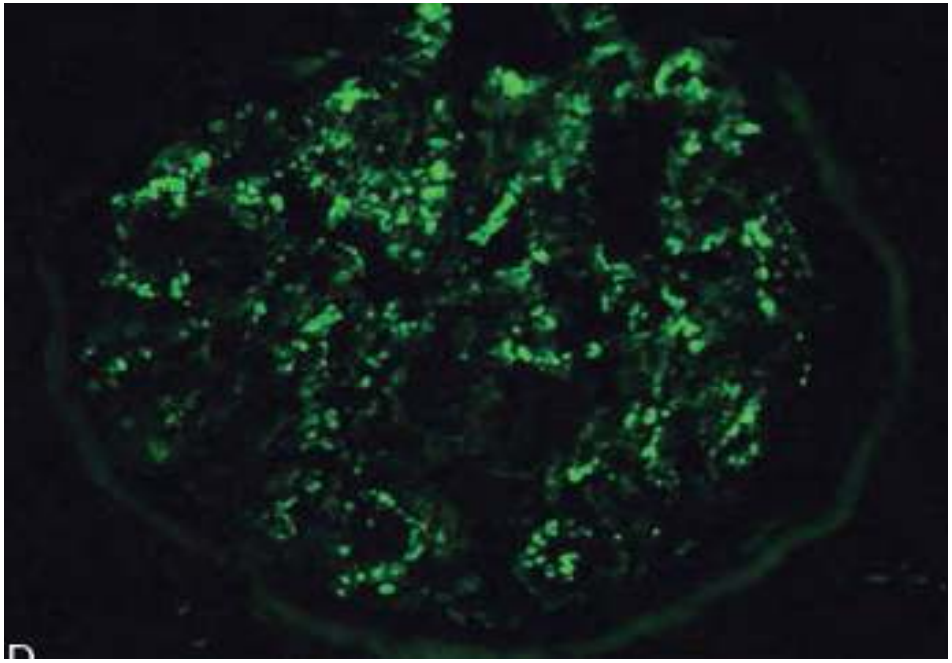
- Enlarged hypercellular glomeruli.
- Hyperplasia of endothelium & mesangial cells. Cell Swelling.
- Inflammatory cells.
- Collapsed capillaries. Obstruction to blood flow.

The hypercellularity of post-streptococcal glomerulonephritis is due to increased numbers of epithelial, endothelial, and mesangial cells as well as neutrophils in and around the capillary loops.



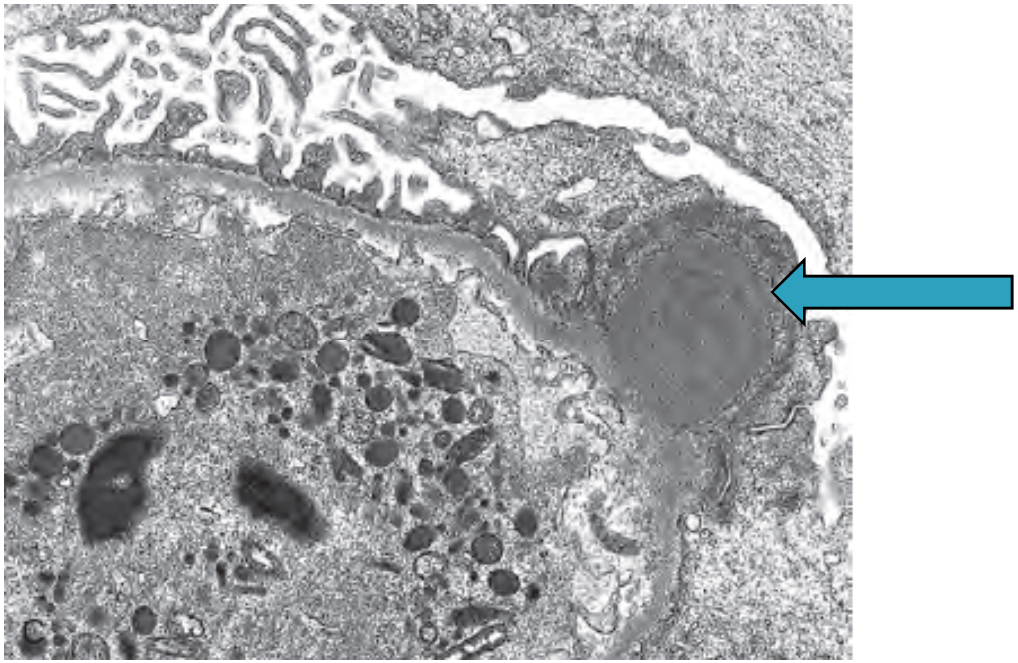
Ref: Heptinstall Pathology of the Kidney 7th Edition ,Pg.691

IF- Diffuse Proliferative GN



Ref- Robbins and Cotran: Pathologic basis of disease: South Asia Edition, Pg:911

Subepithelial deposit
Post –streptococcal glomerulonephritis

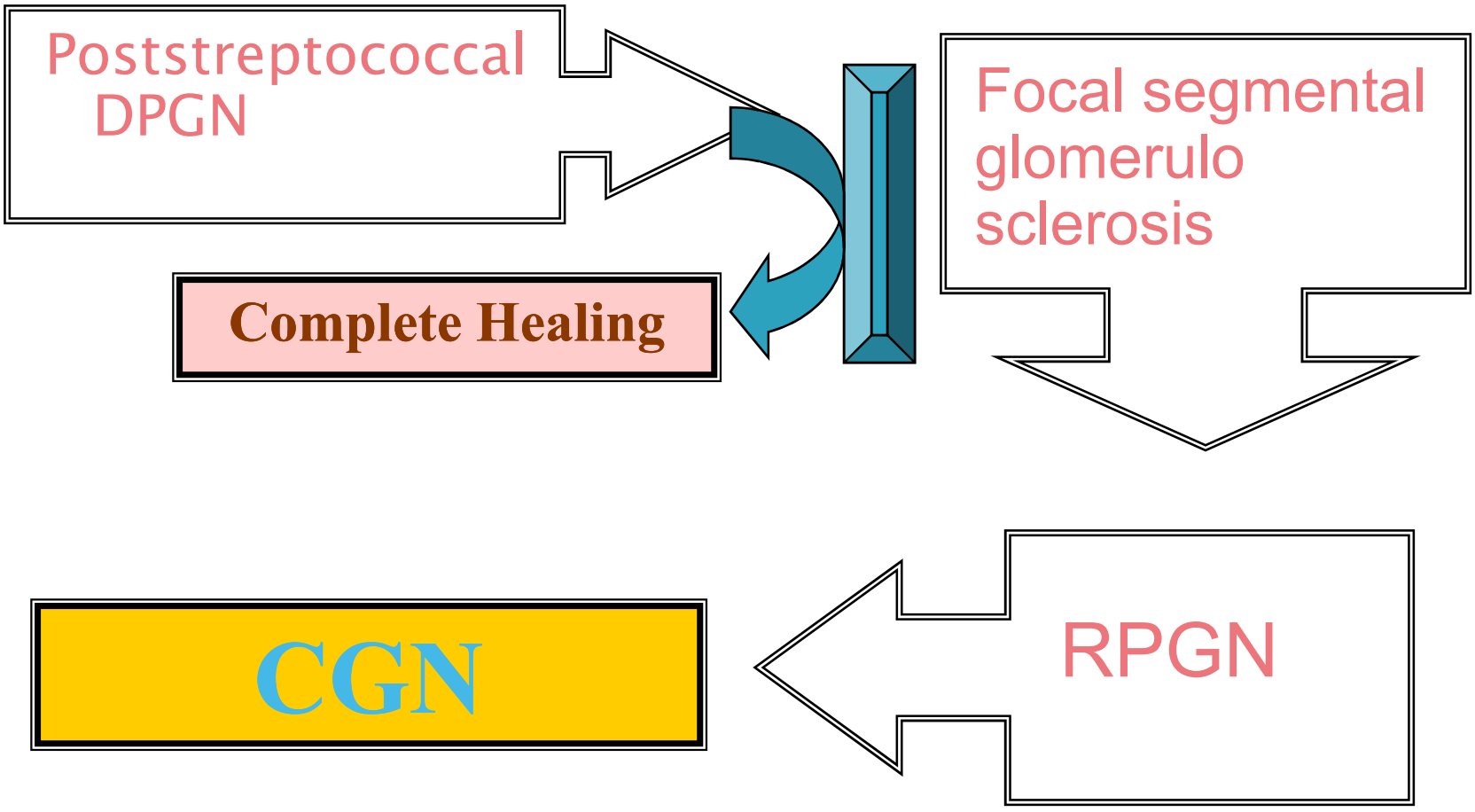


Ref- Robbins and Cotran: Pathologic basis of disease: South Asia Edition, Pg:911

Post-Streptococcal glomerulonephritis

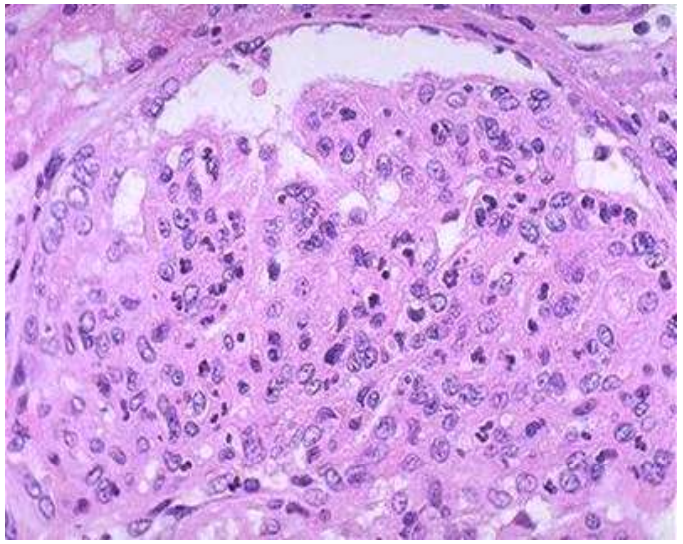
- Clinical course determined by:
  - Age of the patient (children-most recover; adults-50% progress to RPGN or CGN)
  - Whether disease is sporadic (poor prognosis) or epidemic (better prognosis)

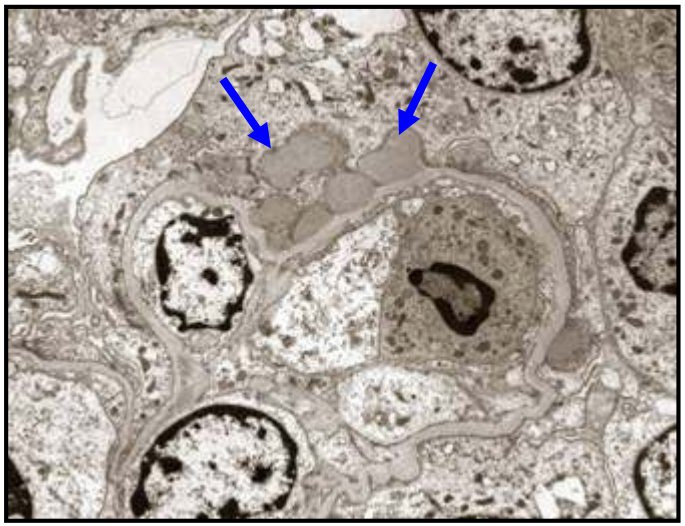
Progression of DPGN:



Acute Post Strepto. GN:

Synonyms:	**Acute diffuse proliferative GN , Acute post-infectious GN .**
Incidence:	**Peak incidence in children (3-14). Sporadic, mostly winter and spring.**
Etiology:	**Glomerular trapping of circulating anti-streptococcal immune complexes. Group A, B-hemolytic streptococci.**
Clinical:	**Acute nephritic syndrome post-strept pharyngitis or pyoderma. Other infections.**
Lab:	**Nephritic urine with RBC casts. Evidence of streptococcal infection or serologic evidence of recent infection. Decreased serum complement.**
Pathology	**Enlarged, hypercellular glomeruli with endothelial and mesangial cell proliferation & Acute inflammation. IgG and C3 in granular pattern along GBMs. Discrete, subepithelial "hump-like" deposits.**
Clinical Course:	**Children - Excellent prognosis. Adults - Worse prognosis, some develop progressive disease.**





Crescentic or Rapidly Progressive Glomerulonephritis (RPGN)

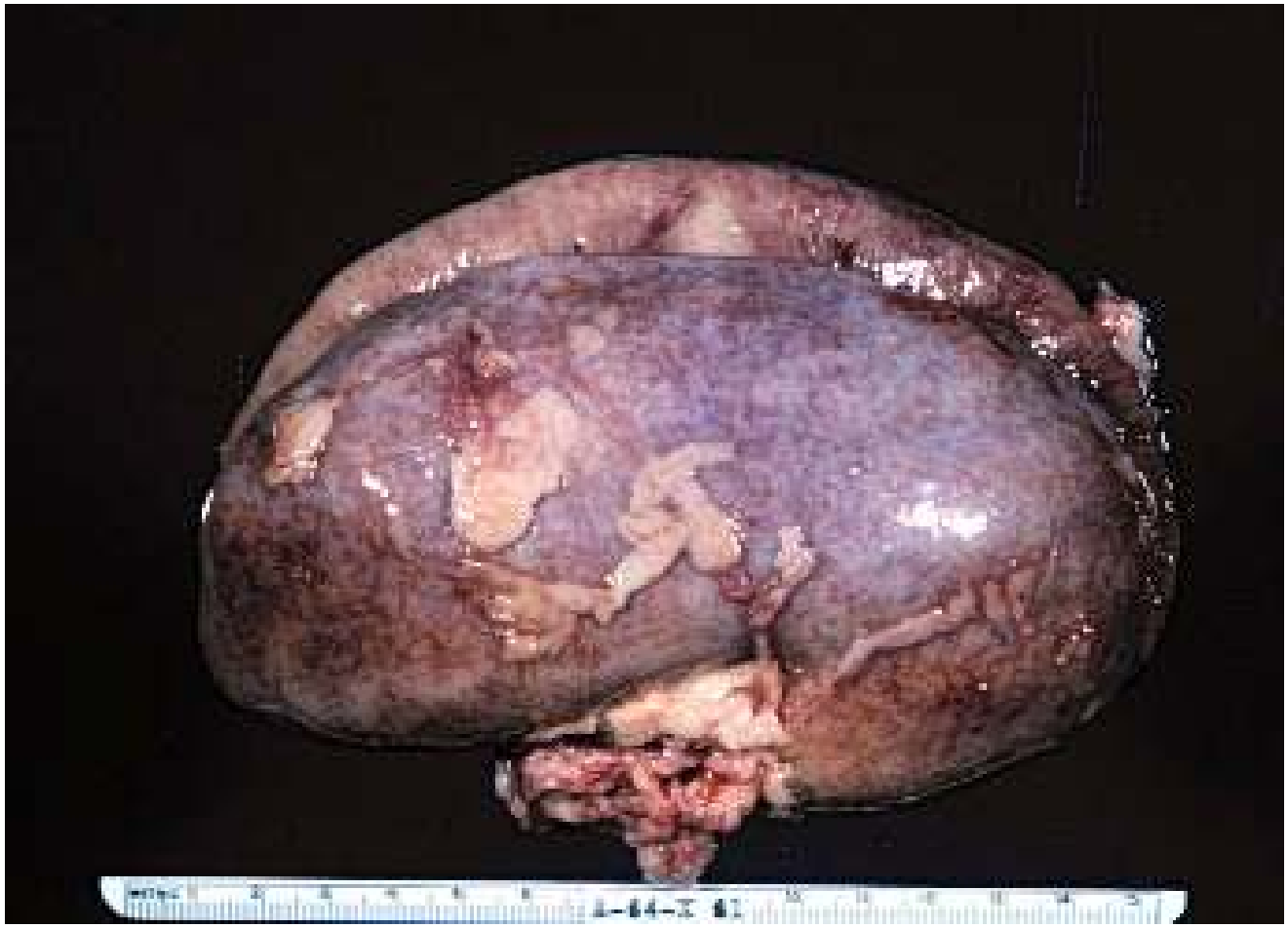
- Glomerular damage is accompanied by rapid and progressive decline in renal function; usually severe oliguria / anuria leading to irreversible renal failure within weeks to months.

- The classic pathologic finding is crescent formation. Proliferation of Parietal epithelial cells & infiltration of monocytes & macrophages in Bowman's space form- "CRESCENTS".

Classification

- Type 1: Anti- GBM disease (Idiopathic, Good pasture syndrome)
- Type 2: Immune complex mediated disease (Idiopathic, Post infectious, SLE, IgA nephropathy, others)
- Type 3 : ANCA associated {Pauci immune} (idiopathic, microscopic Polyangitis, Granulomatosis with polyangitis)

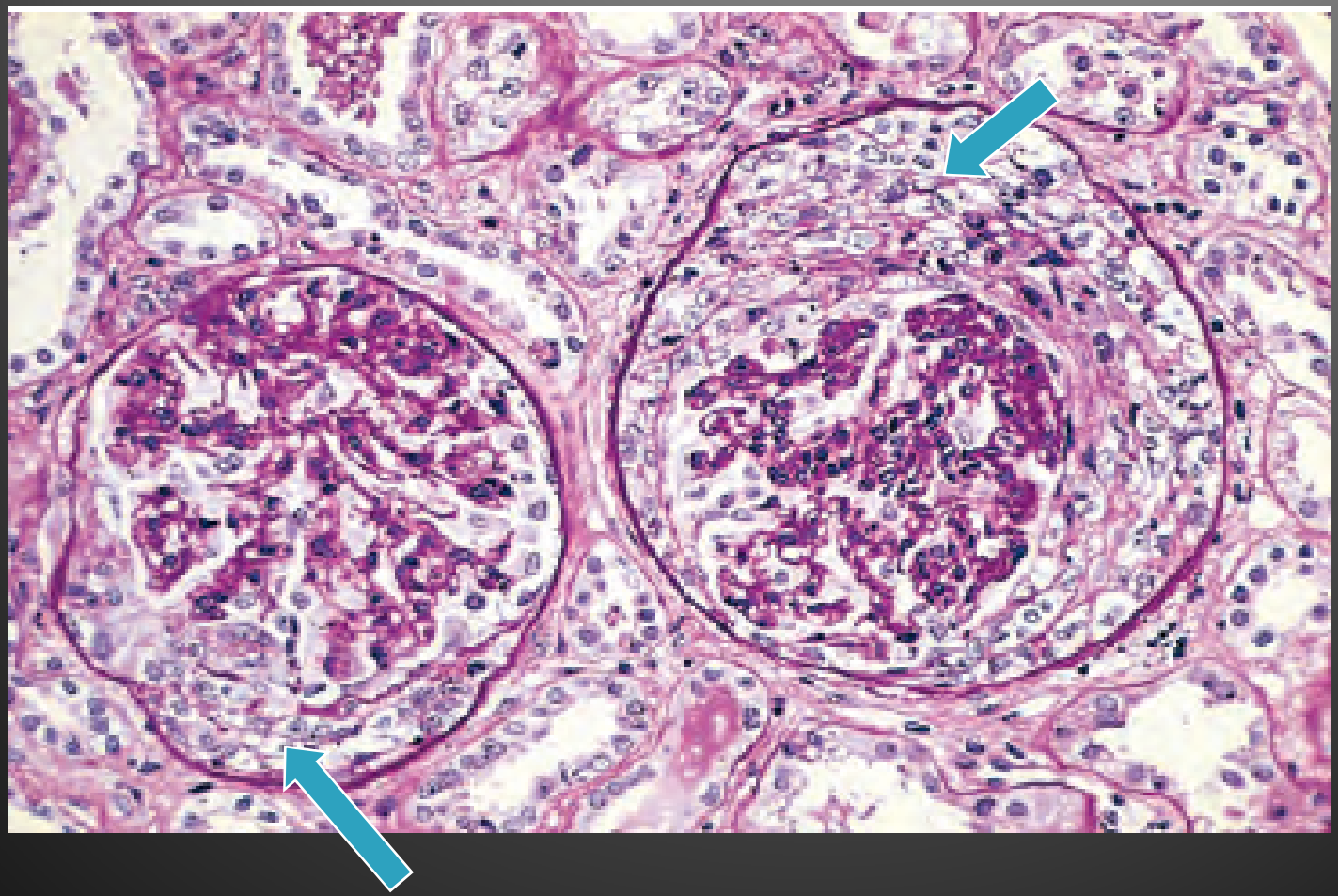
Rapidly progressive glomerulonephritis



Kidney – Enlarge and pale with petechial hemorrhages

Ref: https://www.slideshare.net/vmshashi/pathology-of-glomerulonephritis

Crescentic GN – (RPGN)



Ref- Robbins and Cotran: Pathologic basis of disease: South Asia Edition, Pg:913

RPGN

- Immunoflurescence:

-Type 1: Linear (GPS)

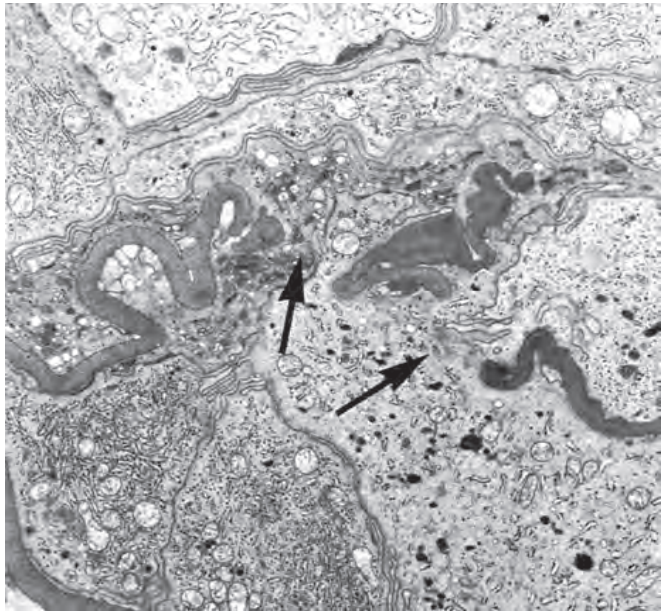
-Type 2 : granular

-Type 3 : No deposition

-Idiopathic:
granular/linear

- Electron microscopy:

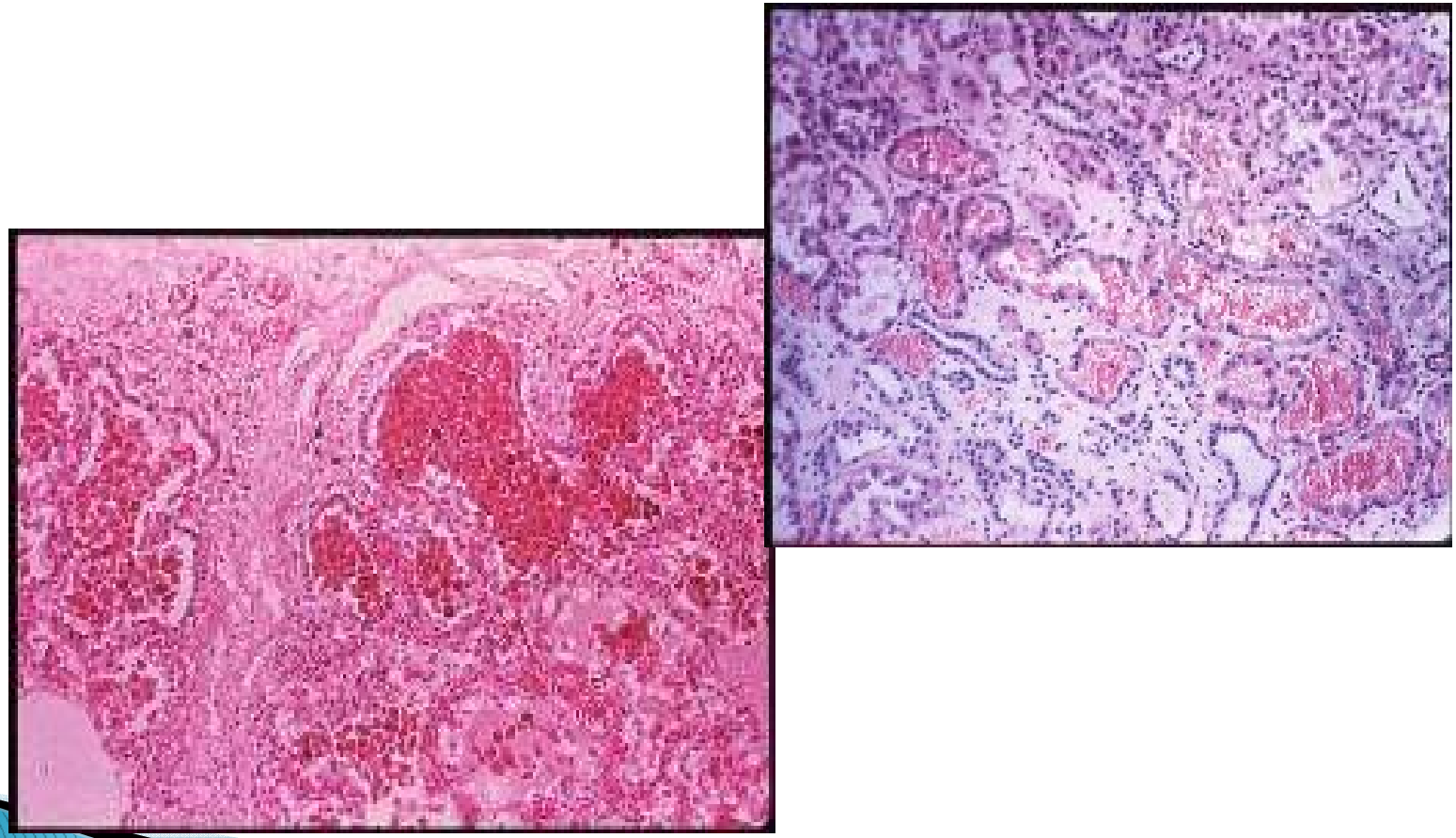
Wrinkling of GBM with focal disruption in continuity



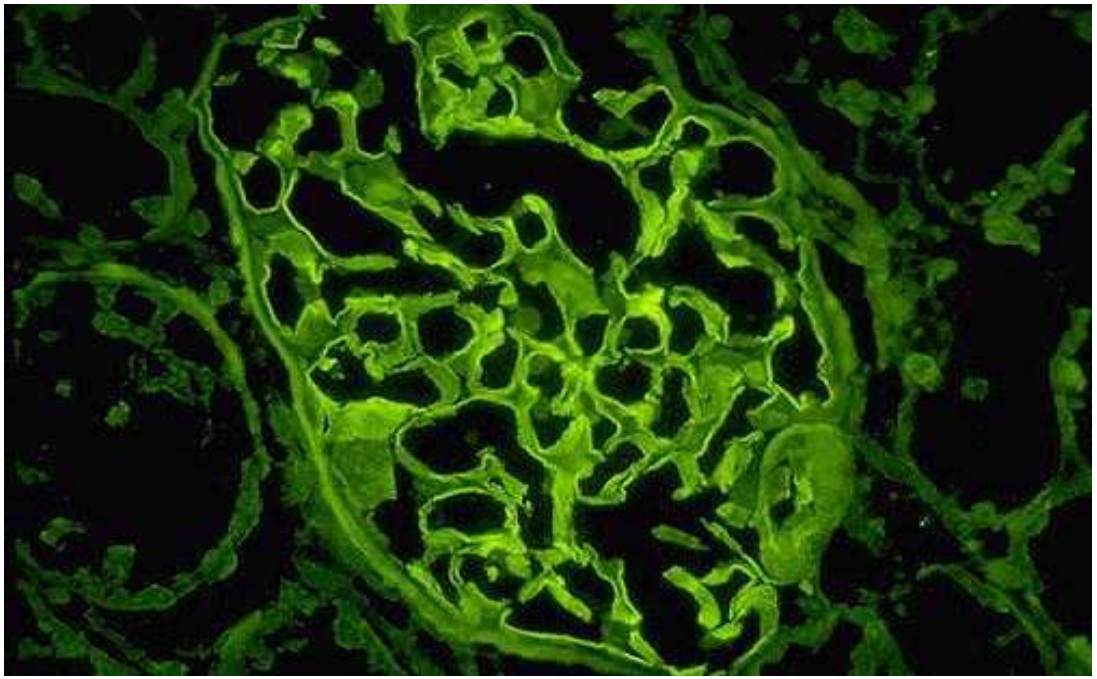
Ref- Robbins and Cotran: Pathologic basis of disease: South Asia Edition, Pg:913

Goodpasture's Syndrome

- A section of lung on the left and kidney on the right showing hemorrhage



Goodpasture Syndrome:

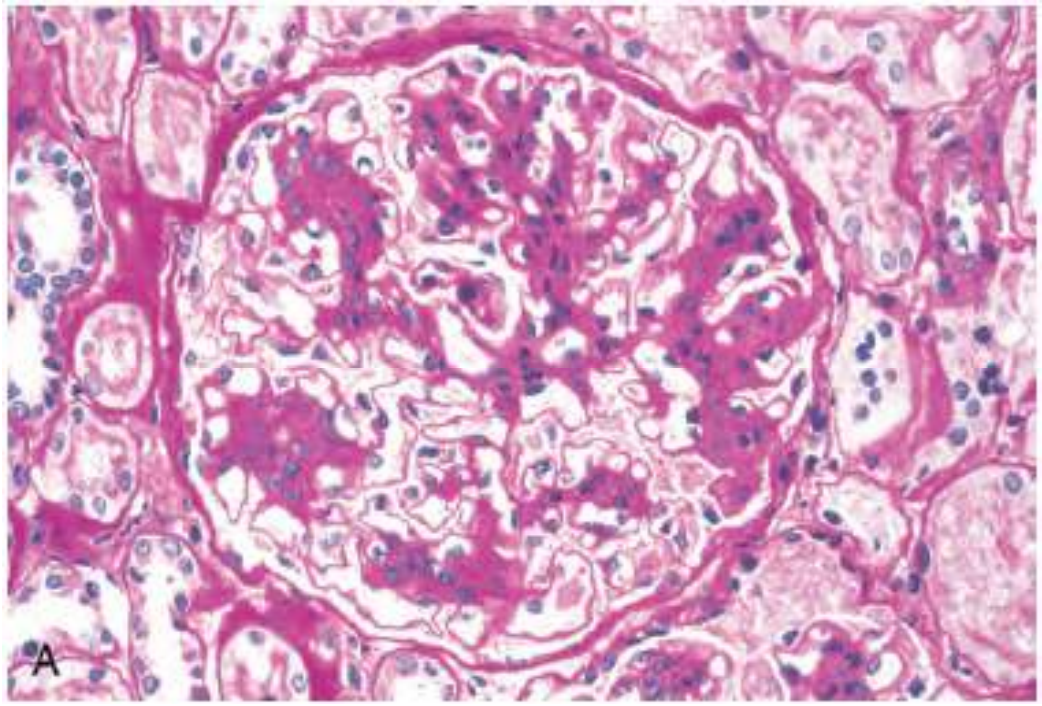


Ref: https://webpath.med.utah.edu/RENAHTML/RENAL093.html

IgA Nephropathy

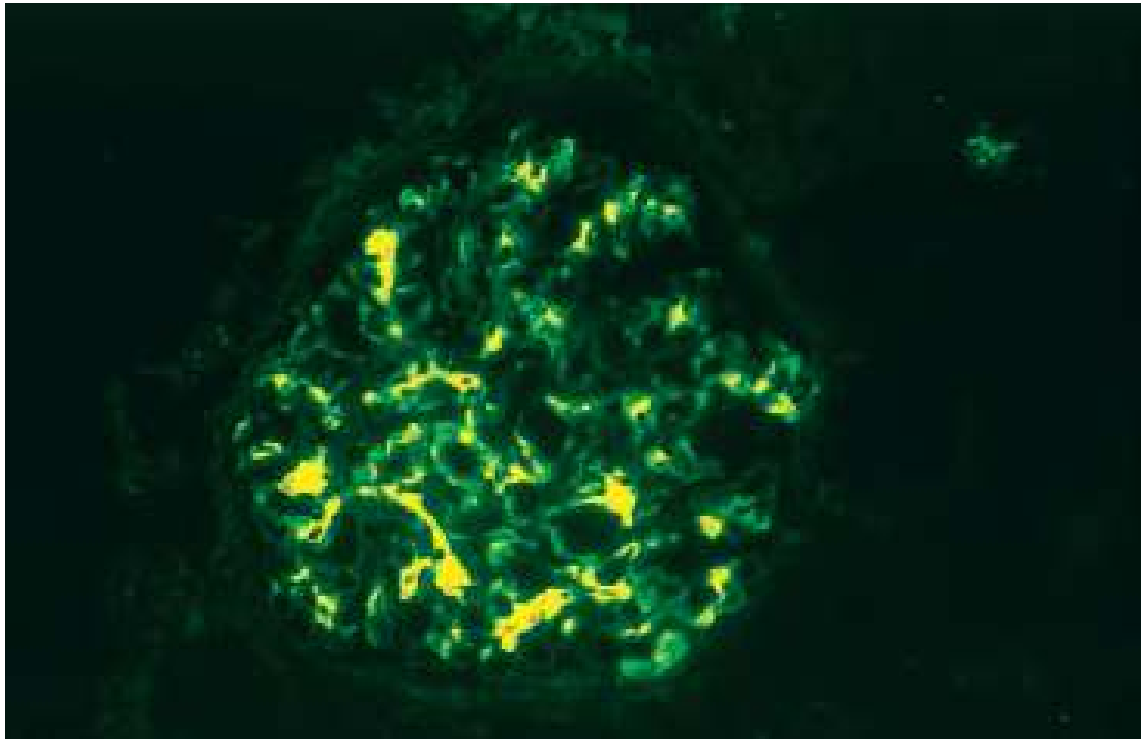
- Most common type of G.N, frequent cause of gross or microscopic hematuria.
- Entrapment of IgA immune complexes in mesangium with activation of alternate pathway.

This is Berger's disease, or IgA nephropathy. The IgA is deposited mainly in mesangium, which then increases mesangial cellularity as shown at the arrow. Patients with IgA nephropathy usually present with hematuria.



Ref- Robbins and Cotran: Pathologic basis of disease: South Asia Edition, Pg:923

This immunofluorescence micrograph demonstrates positivity with antibody to IgA. Note that the pattern is that of mesangial staining. This is IgA nephropathy



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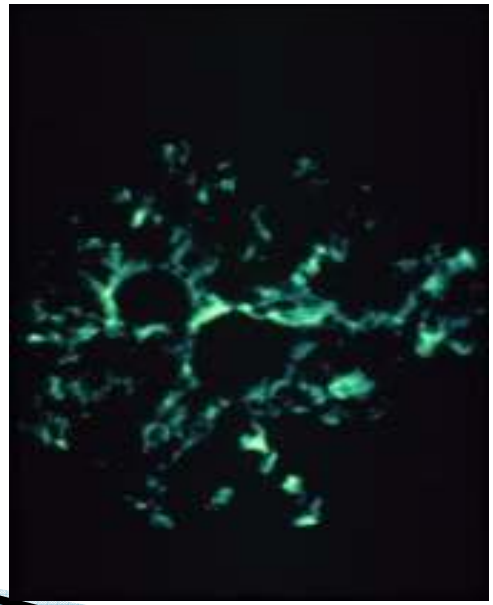
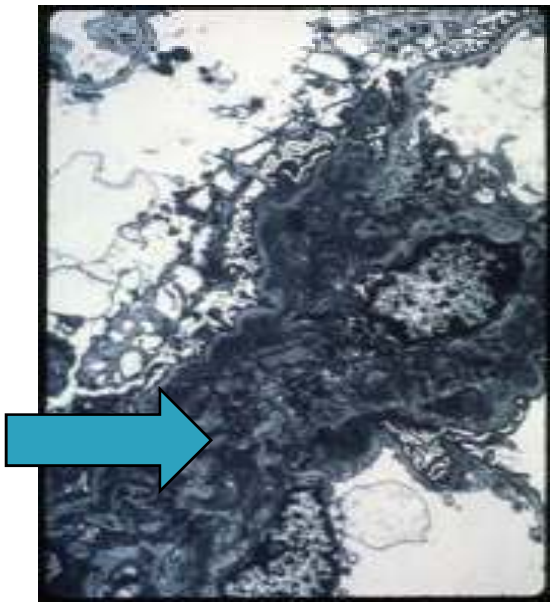
IgA Nephropathy

- Immunofluorescence staining for IgA
- EM showing thickening of the mesangium





Alport's syndrome

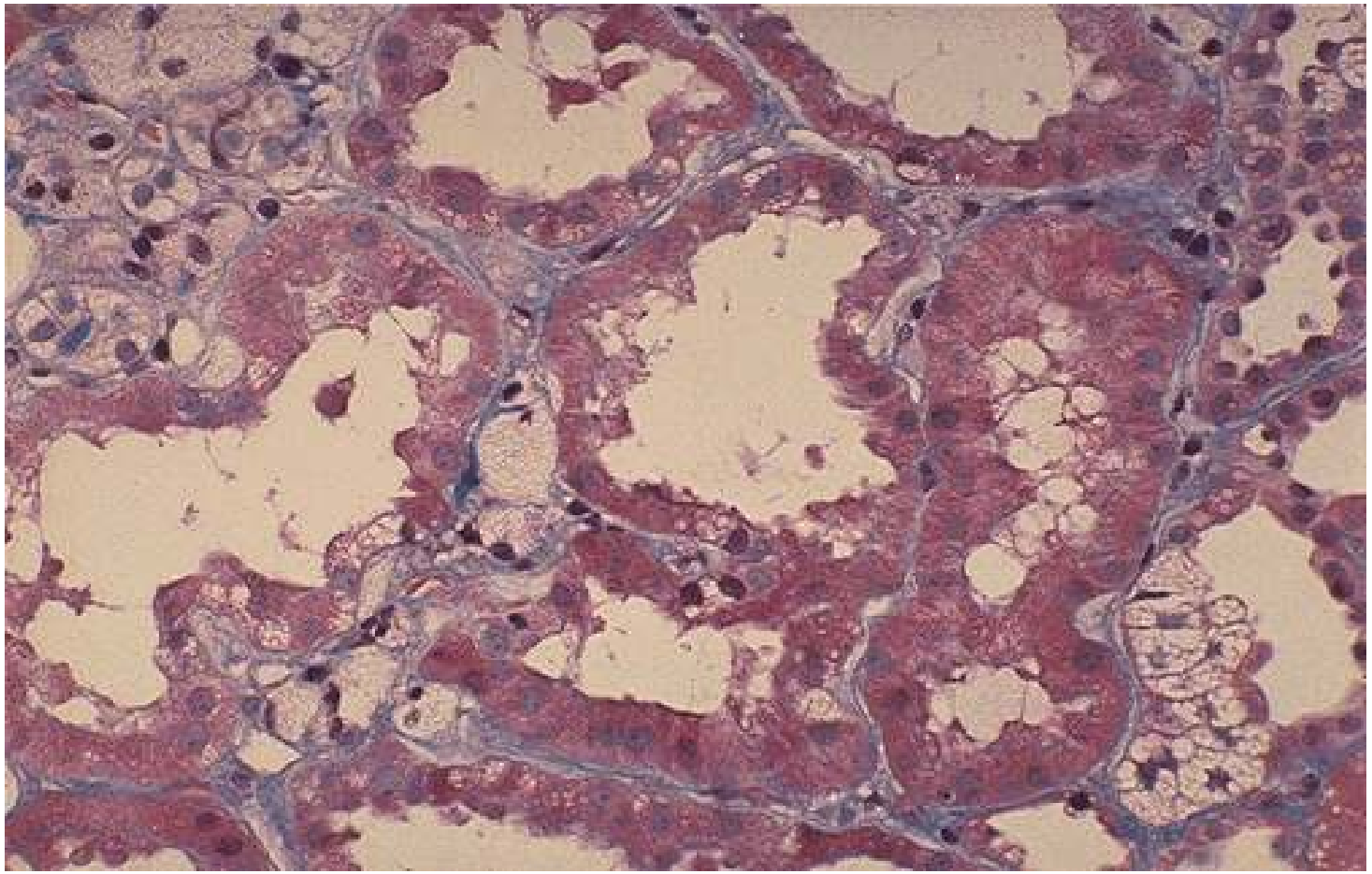
- X-linked recessive transmission.
- Male predominance (5-20 yrs)
- Associated with sensorineural hearing loss and eye diseases.
- Problem is defective Type IV collagen
- Segmental GS, interstitial fibrosis, tubular atrophy.
- Foam cells in interstitial tissue.
- Progressive nephritis leading to renal failure by the ages of 20 to 50 years.

Alport's syndrome

- The GBM is composed largely of type IV collagen, which is made up of heterotrimers of α3, α4, and α5 type IV collagen. This form of type IV collagen is crucial for normal function of the lens, cochlea, and glomerulus. Mutation of any one of the α chains results in defective heterotrimer assembly.

- The majority of Alport syndrome patients have X-linked disease as a result of mutation of the gene on the X chromosome encoding the α5 chain of type IV collagen. Rare autosomal recessive or dominant cases are linked to defects in the genes that encode α3 or α4 type IV collagen.

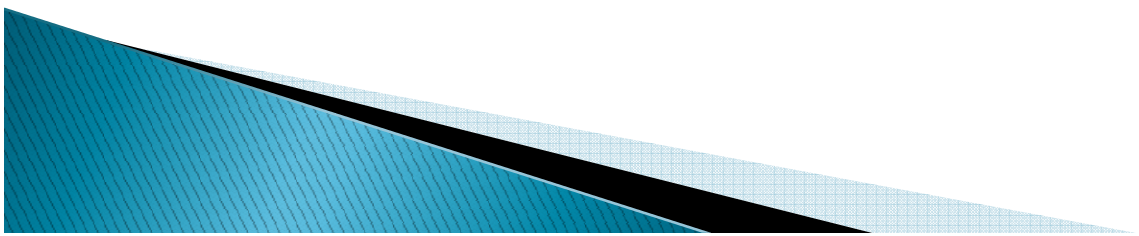
Alport's syndrome in which patients may also manifest nerve deafness and eye problems. The renal tubular cells appear foamy because of the accumulation of neutral fats and mucopolysaccharides.



https://webpath.med.utah.edu/RENAHTML/RENAL100.html

Systemic Lupus Erythematosus

- Kidney involvement occurs in 60-70% of cases; more common in black women
- Clinical Presentation:
- Class I,II: microscopic hematuria
- Class III, IV : nephritic synd with/ without nephrotic range proteinurea
- Class V : severe nephotic range proteinurea with microhematuria
- Class VI : Chronic renal failure



Systemic Lupus Erythematosus

- **Lupus nephritis** is subdivided into 6 WHO classes
  - Class I–minimal lesions
  - Class II–mesangial GN
  - Class III–focal segmental GN
  - **Class IV–diffuse proliferative GN (50% of cases)**
    - 50% present with nephritic syndrome and up to 50% with nephrotic syndrome
    - **Most aggressive renal lesion–30% progress to terminal renal failure**
  - Class V–membranous GN
  - Class VI –chronic sclerosing lupus nephritis

Lupus Nephritis

- *REMEMBER:* ALL PATIENTS WITH SLE have immune deposits in glomeruli; the basic location of the deposits is in the mesangial regions
- Additional deposits and accumulations of cells in various locations are superimposed on the mesangial deposits and result in different morphologies and clinical manifestations

SLE- Immunoflurescence

- Class I, II: Deposits in mesangium
- Class III, IV: Mesangium & entending to glomerular capillary wall
- Class V, VI : Full house IF.

  Strong glomerular C1q staining is rarely seen in conditions other than lupus nephritis

Thank You