Glomerulonephritis

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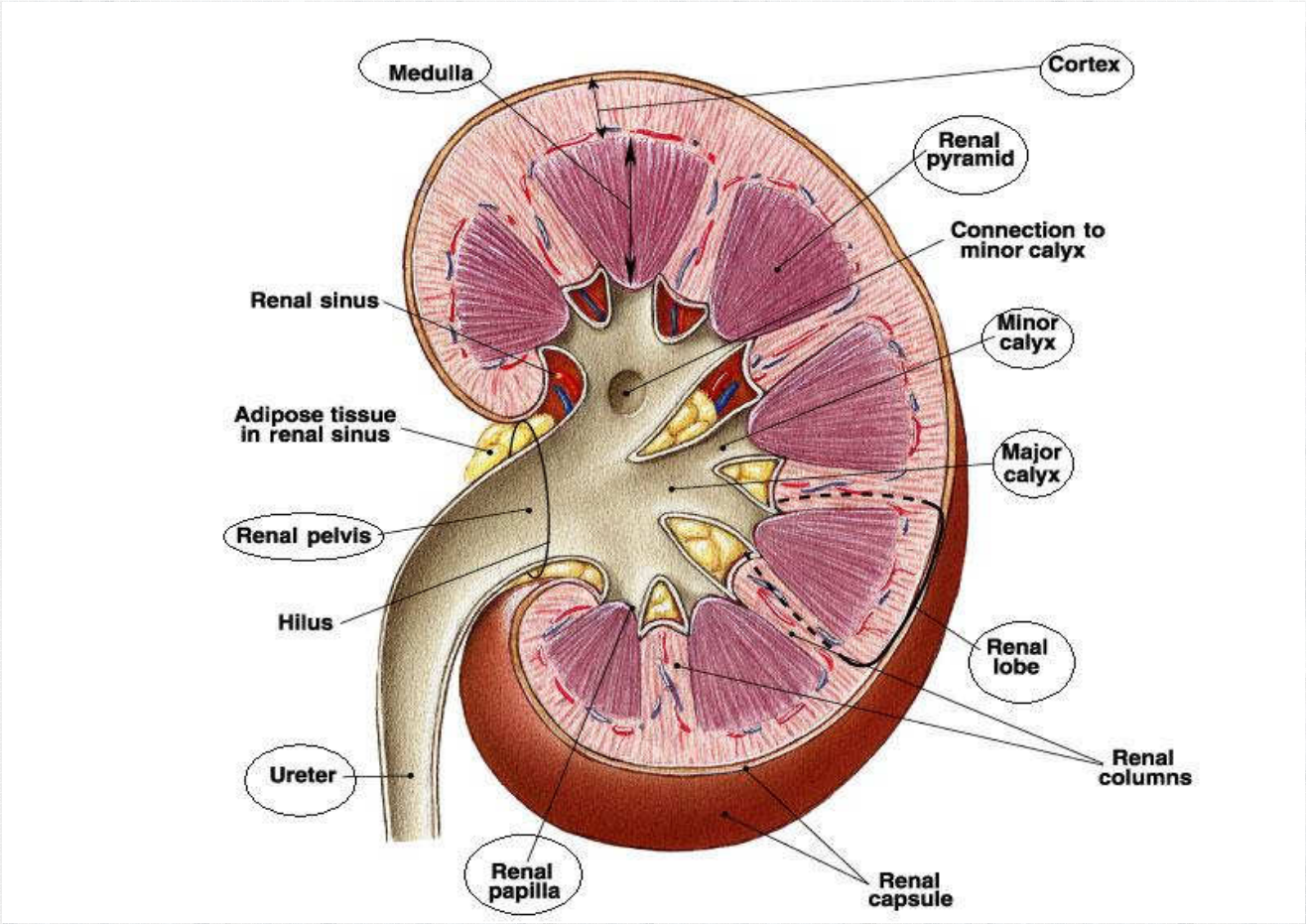
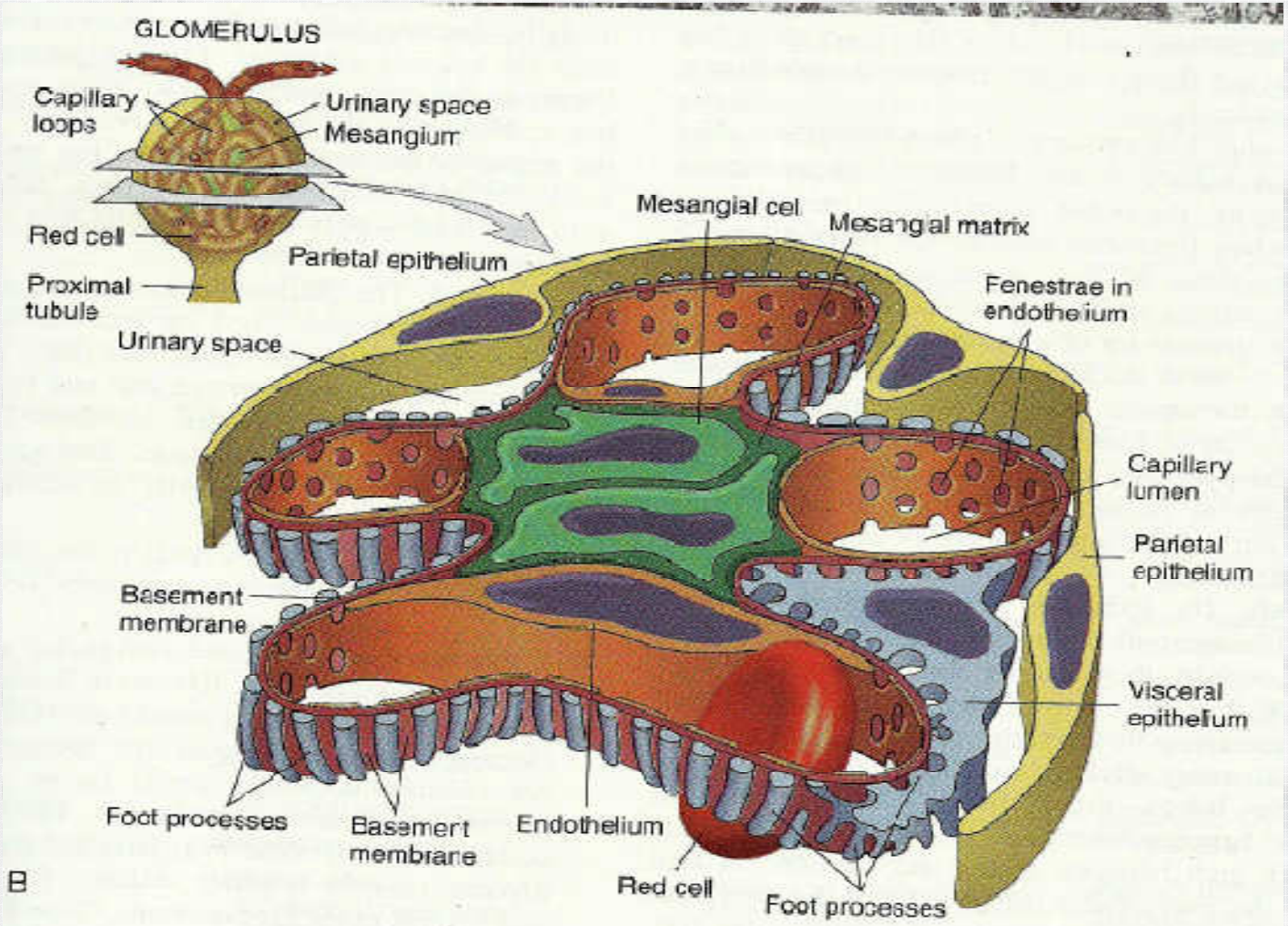
Gross anatomy



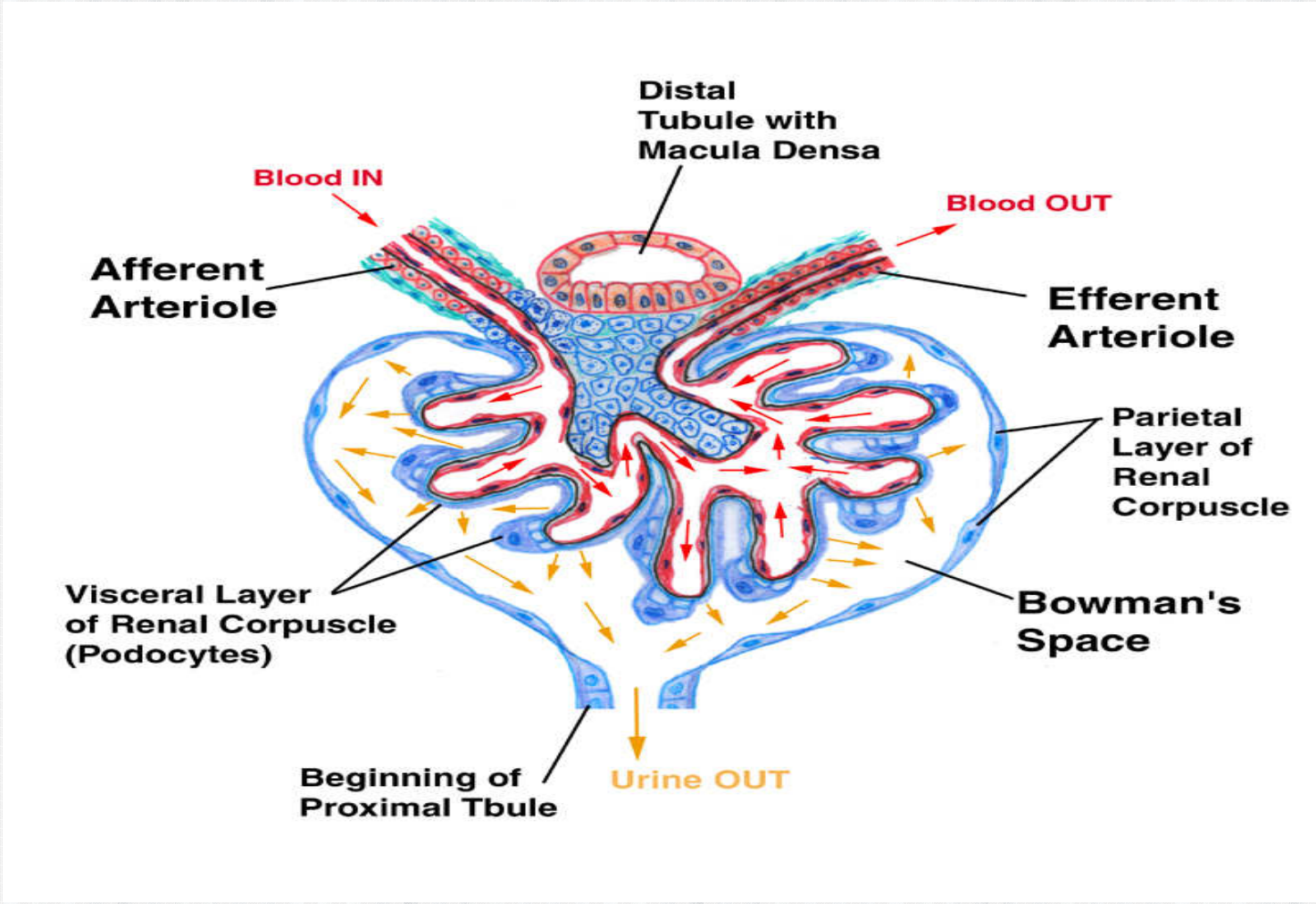
Ref: Goggle Images

Microanatomy

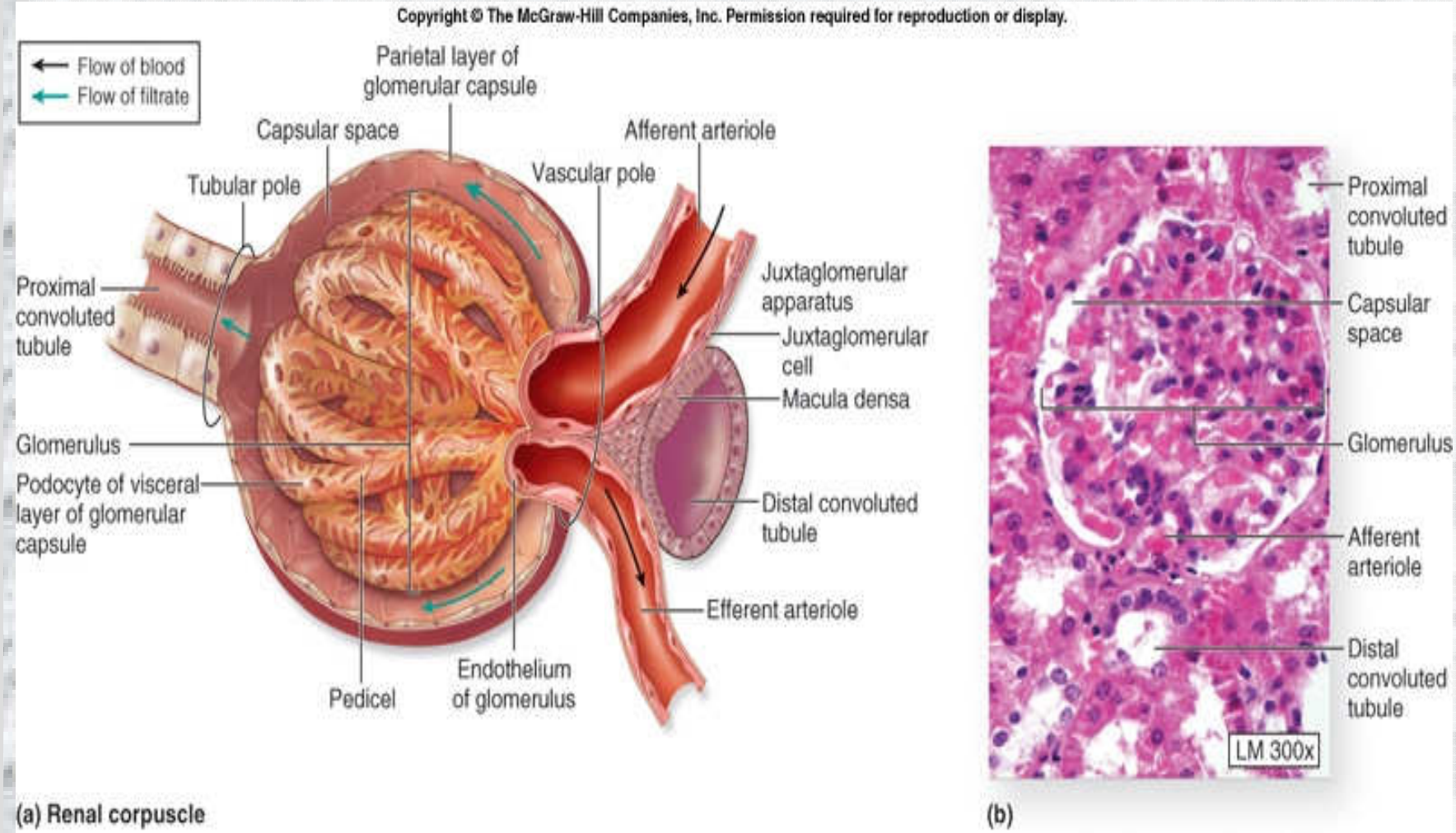


Robins Pathological Basis of Diseases, 6th Ed. Figure 21.1

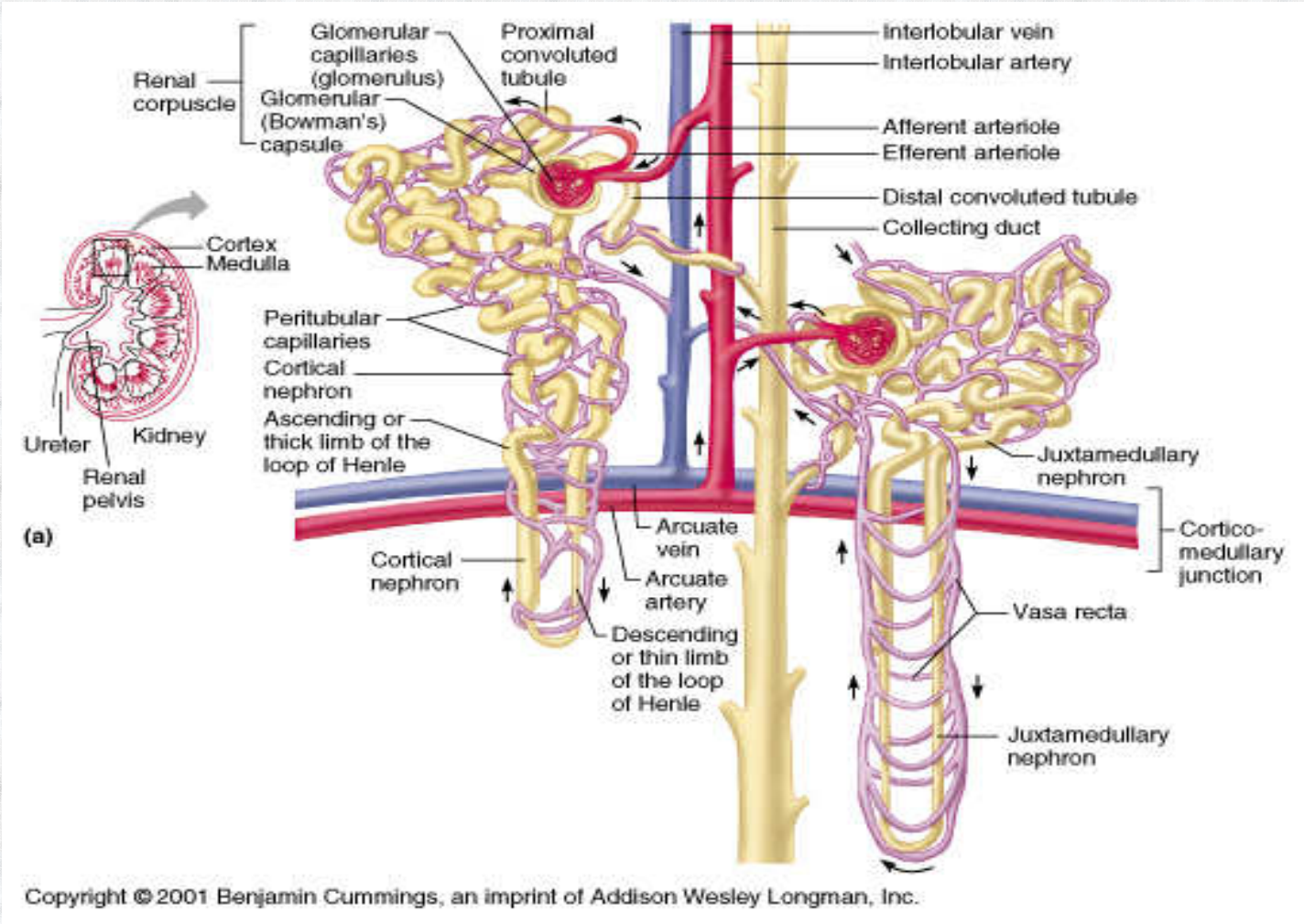
Glomeruli - Ultra filtration



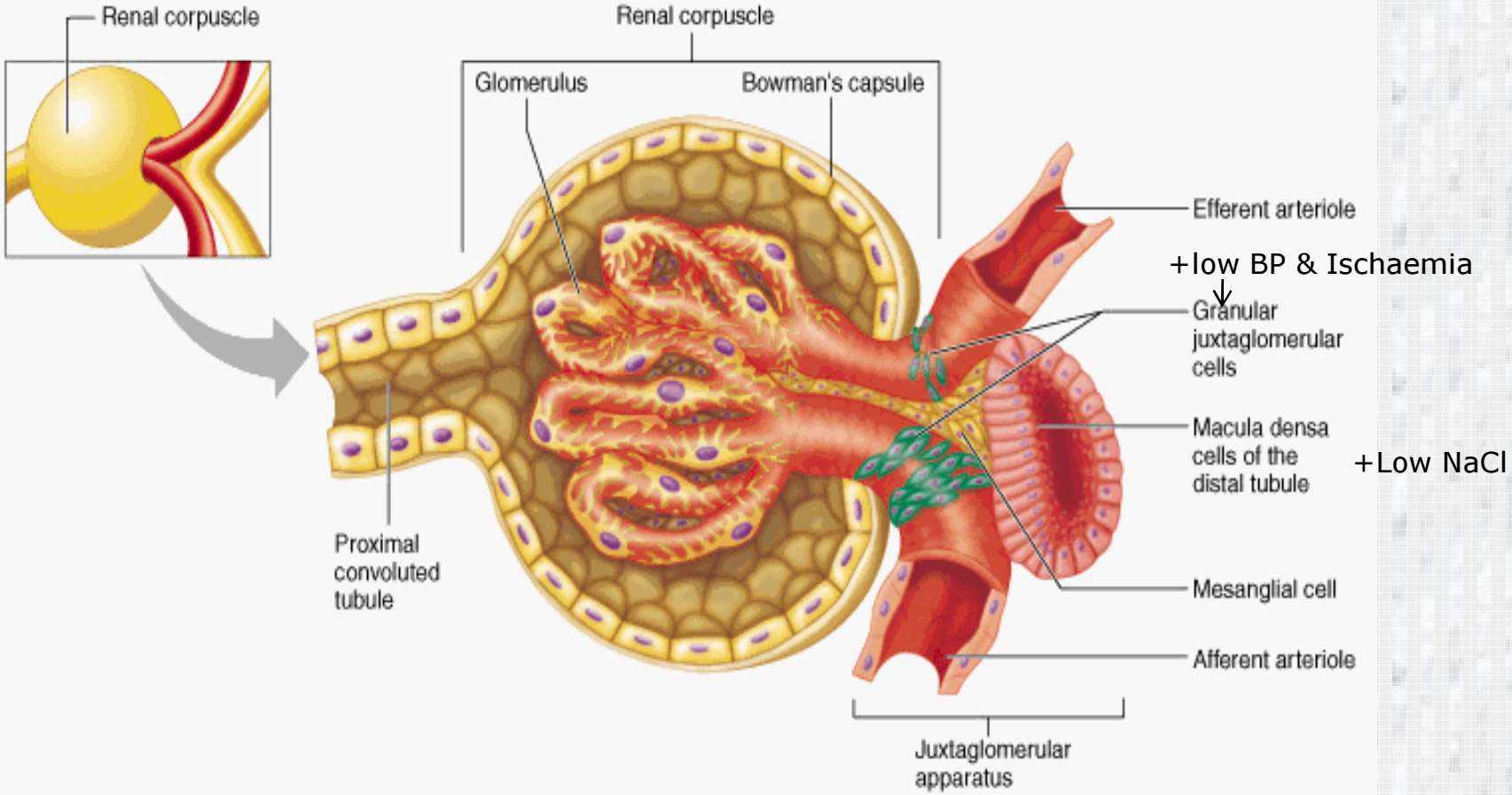
Glomeruli & Renal Capsule

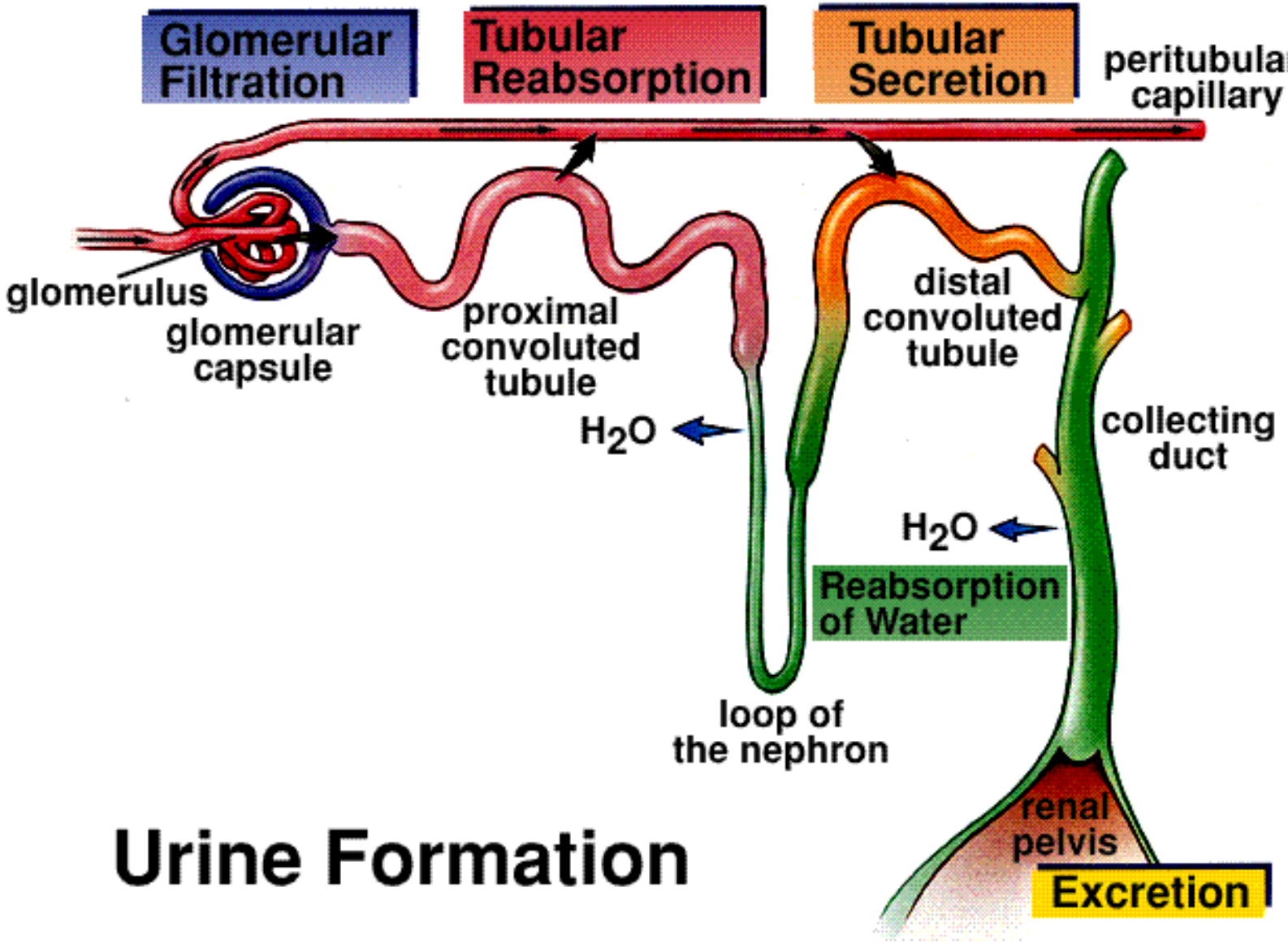


Blood Supply



Juxtaglomerular Apparatus





Urine Formation

Glomerular Pathology

Pathophysiology of Glomerular Diseases

- **Types:**
  - Immune or
  - Non-immune mediated injury

Immune mediated Glomerular Diseases

- **Immune mechanism can be of antibody-associated injury. Two forms are known:**
  - Immune response resulting in injury due to deposition of soluble circulating antigen-antibody complexes in the glomeruli. Referred to as ***Circulating Immune complex injury*****.**
  - Immune response resulting injury due to antibodies reacting in situ within the glomerulus. Referred to as ***Cell Mediated Injury.***
- **Others may be due to cytotoxic antibodies directed against the glomerular cells.**

Non-immune Mediated Glomerular Diseases

- *1.* ***Metabolic glomerular injury.***
  - Diabetic nephropathy: the glomerular lesion is glomerulosclerosis whereby there is thickening of the glomeular basement membrane.
- 2. ***Hemodynamic glomerular injury.***
  - This is due to the high intra-glomerular pressure caused by systemic hypertension or local change in glomerular hemodynamics (glomerular hypertension).
- 3. ***Toxic glomerulopathies.***
  - The toxic verotoxin from the E.Coli is directly toxic to renal endothelium and induces hemolytic-uremic syndrome in patients with infective diarrhea caused by E.Coli. Verotoxin interacts with specific cell membrane receptor inducing thrombotic microangiopathy.

Non-immune Mediated Glomerular Diseases

- ***4. Deposition disease.***
  - There is deposition of abnormal proteins in the glomeruli inducing inflammatory reaction or glomerulosclerosis. For e.g. amyloidosis, cryoglobulins, light and heavy chain deposition disease.

- ***5. Infectious glomerulopathies.***
  - Infectious microorganisms can cause injury by:
  - Direct infection of renal cell
  - Elaboration of nephrotoxins e.g. E.Coli
  - Intraglomerular deposition of immune complexes e.g. post-infectious glomerulonephritis.
  - Providing chronic stimulus for amyloidosis.

- **6. *Inherited glomerular diseases.***
  - A common e.g. is:
  - Alport's disease: Transmitted, as X-linked dominant trait. There is mutation in COL4A5 gene that encodes α-5 chain of type IV collagen located on X-chromosome. The glomerular basement membrane (GBM) is affected.

The determinants of the severity of glomerular damage are

1. The nature of primary insult and secondary mediator system that evoke it.
2. The site of injury within the glomerulus.
3. The speed of onset, extend and intensity of disease.

Classification Glomerulonephritis

Table 21–3. GLOMERULAR DISEASES

Primary Glomerulopathies
Acute diffuse proliferative glomerulonephritis
Poststreptococcal
Non-poststreptococcal
Rapidly progressive (crescentic) glomerulonephritis
Membranous glomerulopathy
Lipoid nephrosis (minimal change disease)
Focal segmental glomerulosclerosis
Membranoproliferative glomerulonephritis
IgA nephropathy
Focal proliferative glomerulonephritis
Chronic glomerulonephritis

Systemic Diseases
Systemic lupus erythematosus
Diabetes mellitus
Amyloidosis
Goodpasture syndrome
Polyarteritis nodosa
Wegener granulomatosis
Henoch-Schönlein purpura
Bacterial endocarditis

Hereditary Disorders
Alport syndrome
Thin membrane disease
Fabry disease

Ref: Robins Pathological Basis of Diseases, 6th Ed. Table 21.3

Primary Glomerulonephritis

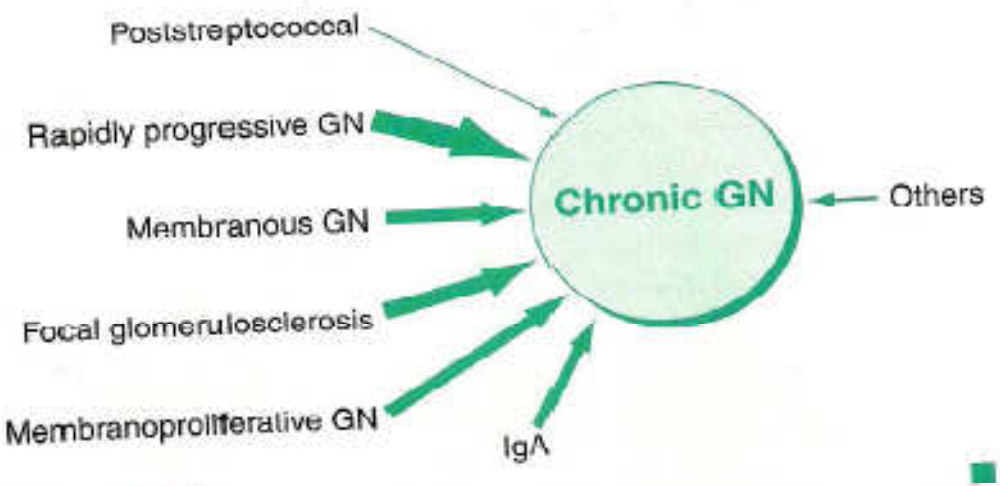


Figure 21–29

Primary glomerular diseases leading to chronic glomerulonephritis (GN). The thickness of the arrows reflects the approximate proportion of patients in each group who progress to chronic glomerulonephritis: poststreptococcal (1% to 2%); rapidly progressive (crescentic) (90%); membranous (50%); focal glomerulosclerosis (50% to 80%); membranoproliferative glomerulonephritis (50%); IgA nephropathy (30% to 50%).

Ref. Robins Pathological Basis of Diseases, 6th Ed. Figure 21.29

Clinical Presentation

- Nephrotic Syndrome
- Nephritic Syndrome
- Others – mixture of symptoms of nephrotic & nephritic syndrome

Diagnostic Criteria - Nephrotic Syndrome

- *Increased BM permeability – increased urinary loss of plasma proteins esp. albumin*
- Massive Proteinuria - >4grams per day. 24 Hr Urine.
- Hypoalbuminemia – from proteinuria. Serum concerntration of <3gm/100ml.
- Generalised oedema – decreased plasma colloid oncotic pressure.
- Hyperlipidemia & hypercholesterolemia – increased hepatic lipoprotein synthesis.

Diagnostic Criteria - Nephritic Syndrome

- *Inflammatory rapture of glomerular capillaries resulting in bleeding into urinary space (Bowman's capsule). Proteinuria and oedema mild.*
- Oliguria – Reduced GFR causing reduced urine output.
- Azotemia – elevated BUN.
- Hypertension – increased fluid retention & Renin-Angiotension-Aldosterone activation by ischaemic kindneys
- Hematuria – form RBC casts & granular casts

Summary of Glomerular Diseases

Disorders manifest by Nephrotic Syndrome	Disorders manifest by Nephritic Syndrome	Other glomerular disorders
• Minimal Change Disease (Lipoid nephrosis)	•Poststreptococcal glomerulonephritis	•IgA nephropathty (Berger disease)
• Focal Segmental glomerulosclerosis	•Rapidly progressive (crescentic) glomerulonephritis	•Membranoproliferative glomerulonephritis
• Membranous glomerulonephritis	•Goodpasture syndrome	
• Diabetic nephropathy	•Alport syndrome	
• Renal amyloidosis		
• Lupus nephropathy		

Disorders Manifest as Nephrotic Syndrome

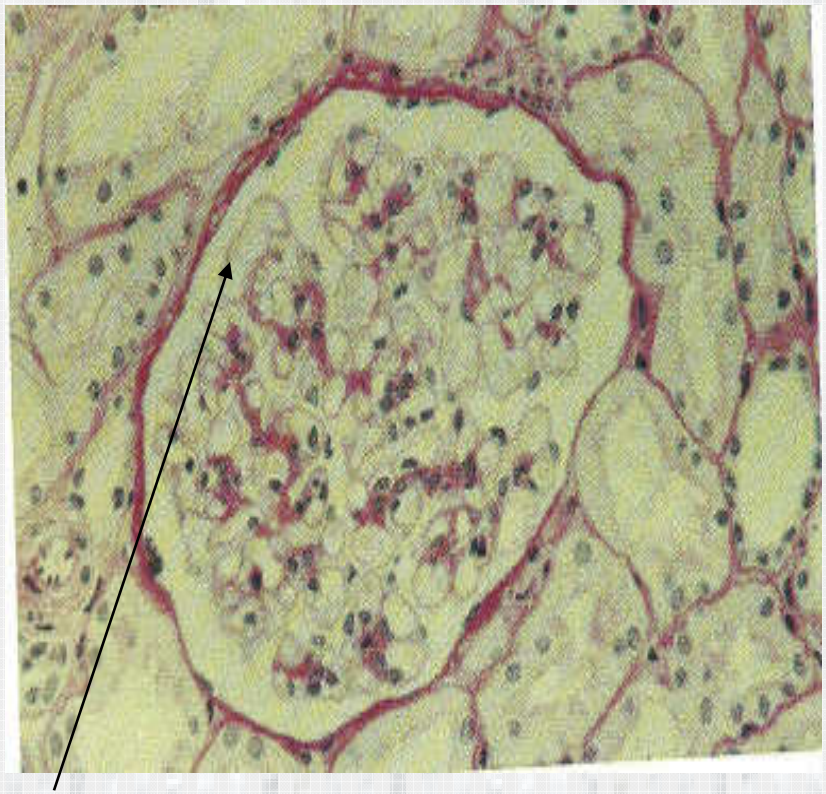
- Minimal Change Disease (Lipoid nephrosis)
- Focal Segmental glomerulosclerosis
- Membranous glomerulonephritis
- Diabetic nephropathy
- Renal amyloidosis
- Lupus nephropathy

Minimal Change (lipoid nephrosis) Disease

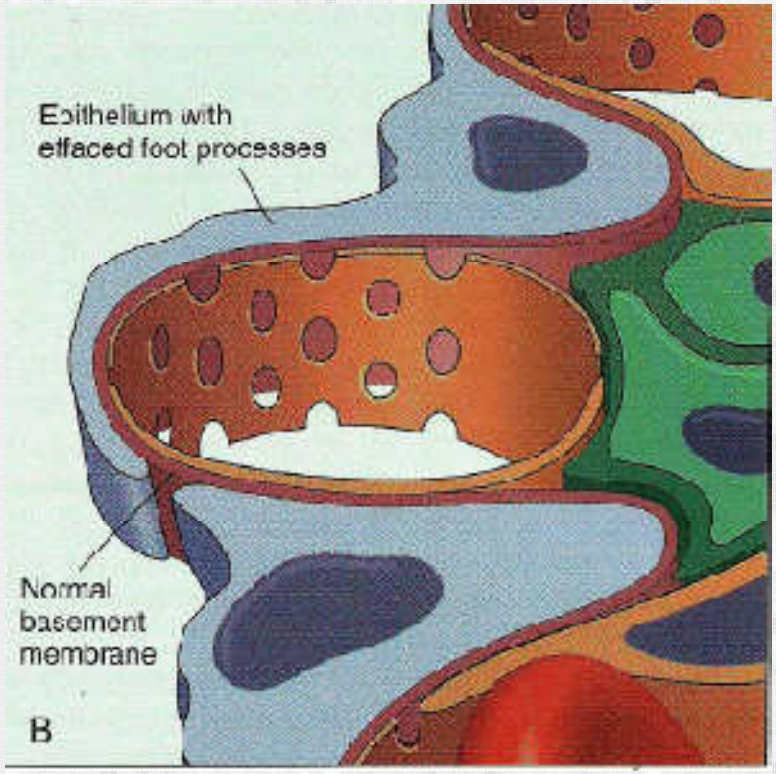
- Common cause of nephrotic syndrome in children.
- Immune mediated
- Characterized by loss of foot processes of epithelial cells (podocytes) in glomeruli.
- Responds to steroid therapy

Minimal Change Disease (Lipoid Nephrosis)

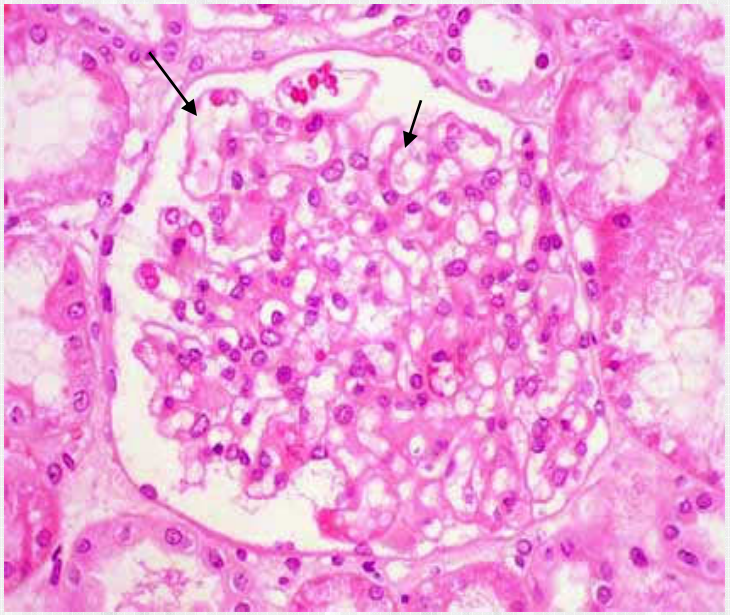
Visceral epithelial cells show uniform and diffuse effacement of foot process

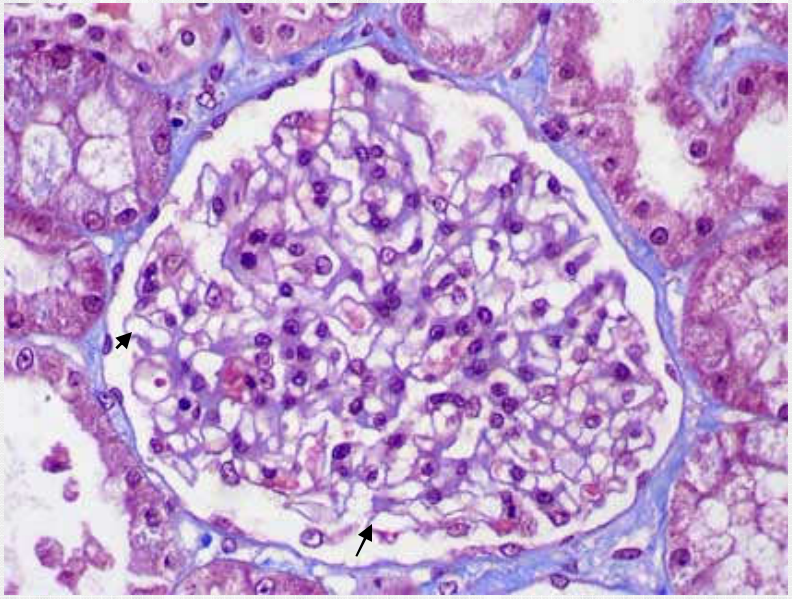


Thin BN. No proliferation



Minimal Change Disease





Normal glomerular tuft. No hypercellularity. Thin BM.

Ref: www.kidneypathology.com

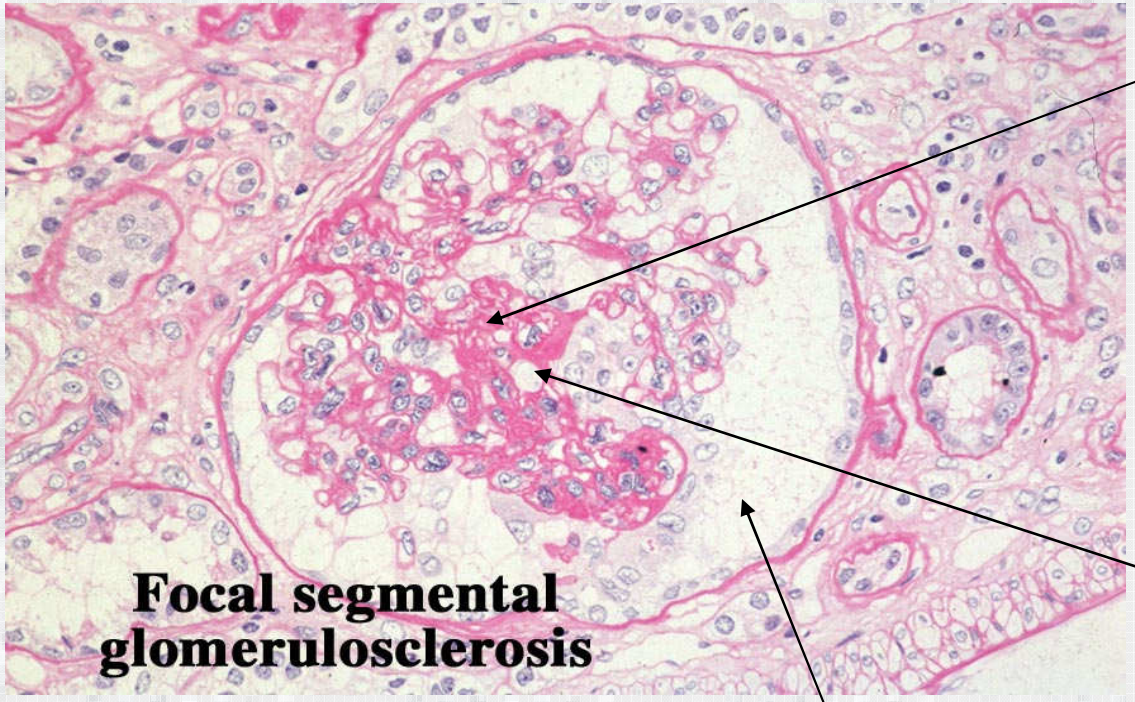
Focal Segmental Glomerulosclerosis

- Clinically similar to minimal change disease but occurs in older patients
- Can occurs as primary or secondary disorder.
- Primary – idiopathic focal segmental glomerulosclerosis
- Secondary – HIV, heroine addiction, sickle cell disease, IgA nephropathy, certain forms of inherited nephrotic syndrome.

Idiopathic FSG

- 10-15% of nephrotic syndrome in adults and children.
- Higher incidence of hematuria, reduced GFR and hypertension
- Non-selective proteinuria
- Respond poorly to steroid therapy
- Many progress to chronic GN & 50% develop end stage renal disease in 10 years
- Immunoflurescence microscopy shows IgM & C3 in sclerotic glomerular segments

Focal Segmental Glomerular Sclerosis



- Sclerotic segment shows deposition of hyaline masses
- Lipid in sclerotic area (small vacuoles)

Foam cells

Ref:www.med.niigata-u.ac.jp

Membranous Glomerulonephritis

- Most common cause of nephrotic syndrome in adults (40%).
- Characterised by: diffuse thickening of glomerular capillary wall & accumulation of electron-dense immunoglobulin containing deposits along epithelial and subepithelial side of BM

Membranous Glomerulonephritis

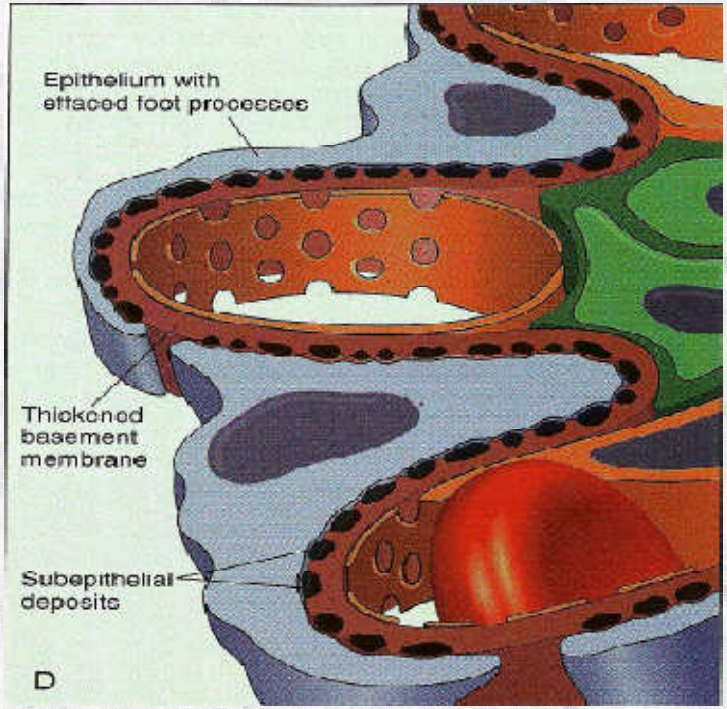
- Primary – 85% of cases no association with any condition.
- Secondary – association with drugs (e.g. NSAIDS), tumors (e.g. CA lung and colon), SLE (15% of GN), infections (e.g. chronic Hep B, C, malaria, syphilis, schistosomiasis) & metablic disorders (e.g. DM & throiditis)

Membranous Glomerulonephritis

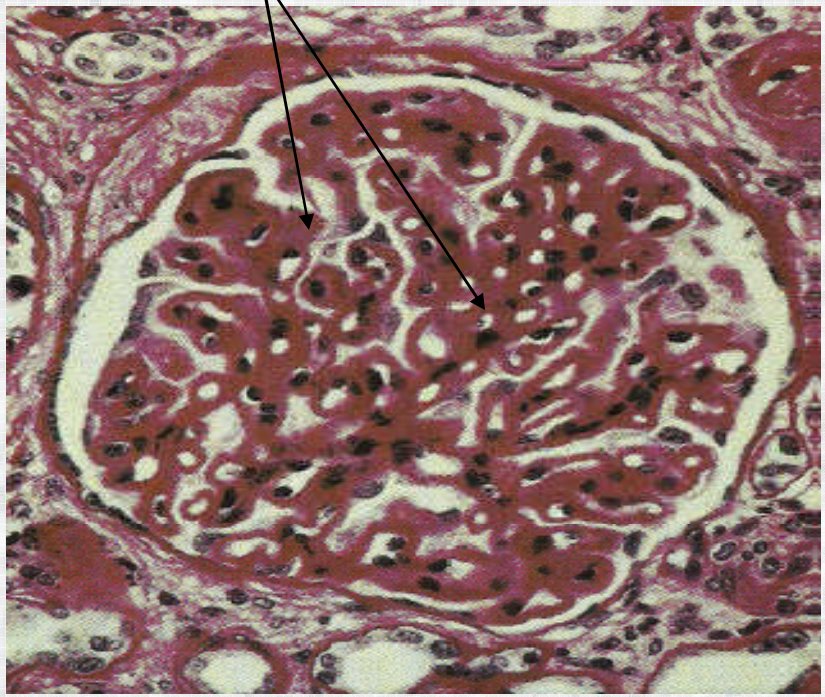
- Primary – Auto-Immune disorder caused by antibodies to renal autoantigen.
- Secondary – chronic antigen-antibody mediated disorder.
- Activation of compliment pathway cause injury to capillary wall and cause increased protein leakage.

Membranous GN

Diagrammatic representation



Diffuse thickening of capillary wall without increase in number of cells



Ref: Robins Pathological basis of Diseases, 6th Ed. Fig. 21.19

Diabetic Nephropathy

Characterised by:

- BM markedly thickened.
- Diffuse or nodular mesangial accumulations of BM like material.

Diabetic Nephropathy

Table 20-4. RELEVANT CHEMICAL AND BIOLOGIC PROPERTIES OF ADVANCED GLYCOSYLATION END PRODUCTS

Chemical

Cross-link polypeptides of same protein (e.g., collagen)
Trap nonglycosylated proteins (e.g., LDL, Ig, complement)
Confer resistance to proteolytic digestion
Induce lipid oxidation
Inactivate nitric oxide
Bind nucleic acids

Biologic

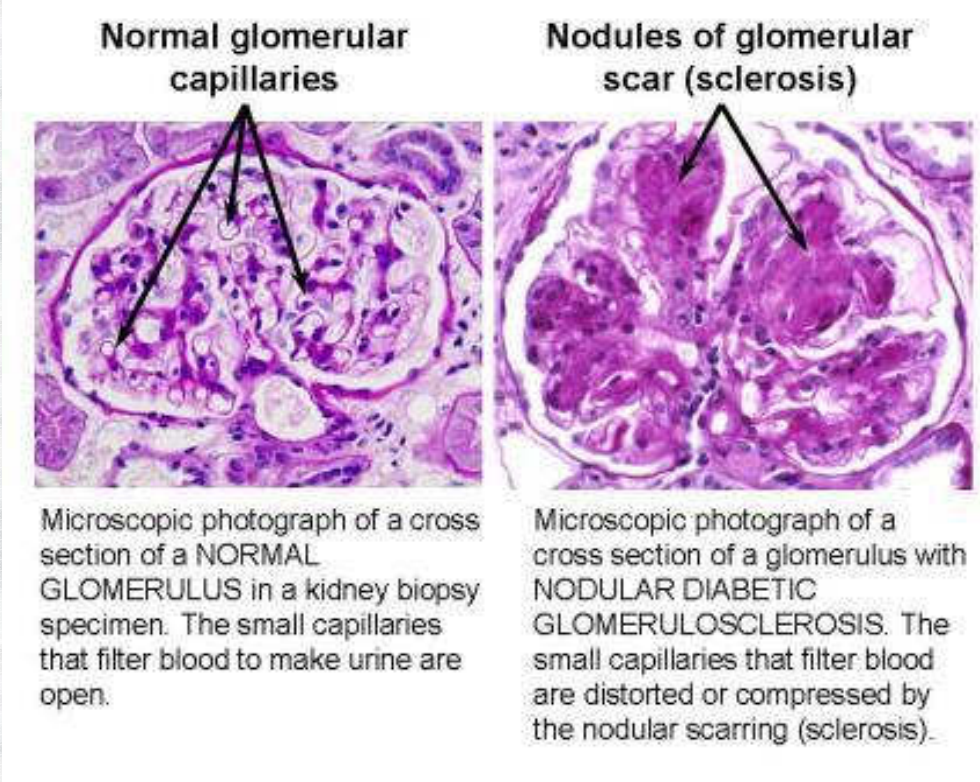
Bind to AGE receptors on monocytes and mesenchymal cells
Induce: Monocyte emigration
Cytokines and growth factor secretion
Increased vascular permeability
Procoagulant activity
Enhanced cellular proliferation
Enhanced ECM production

Ref: Robins Pathological Basis of Diseases, 6th E. Table 20.1

Diabetic Nephropathy

- Capillary BM thickening.
- Diffuse glomerulosclerosis.
- Nodular glomerulosclerosis.

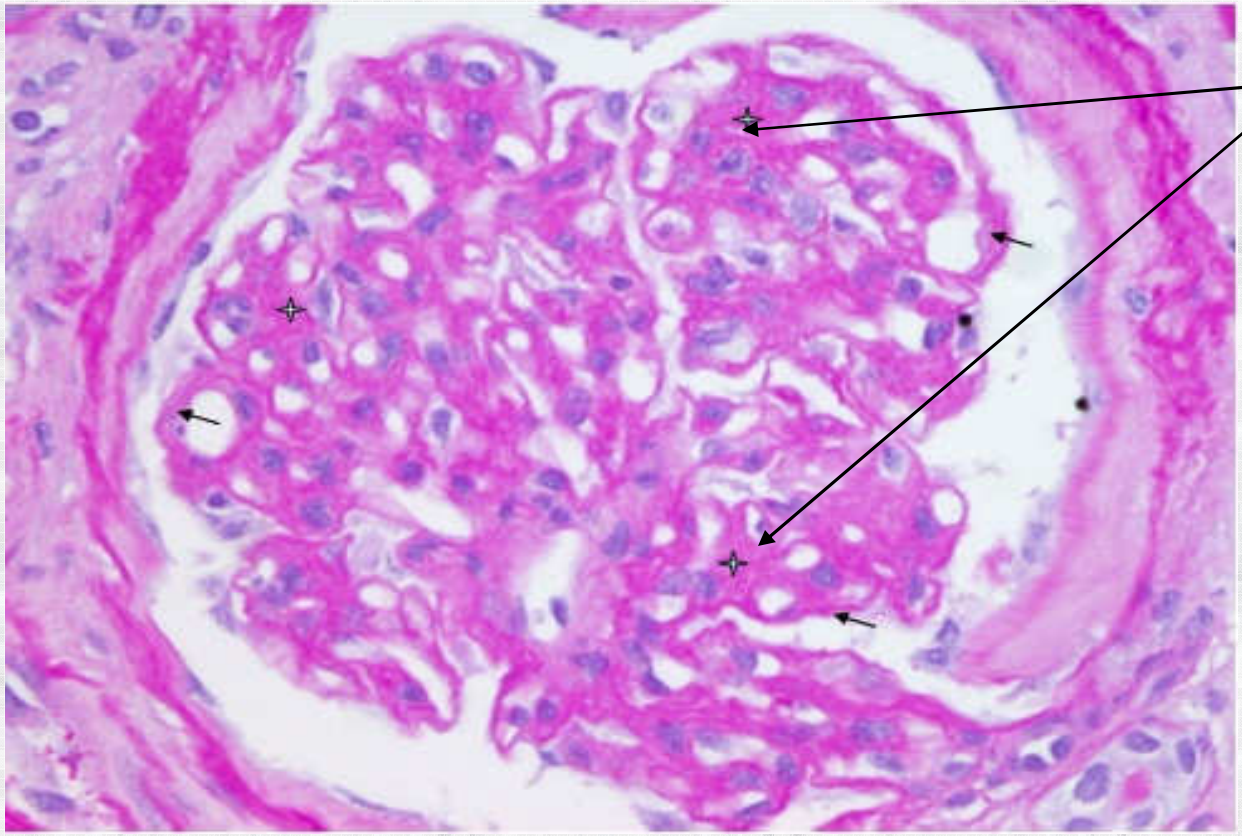
Ref:
www.unckidneycentre.org



Microscopic photograph of a cross section of a NORMAL GLOMERULUS in a kidney biopsy specimen. The small capillaries that filter blood to make urine are open.

Microscopic photograph of a cross section of a glomerulus with NODULAR DIABETIC GLOMERULOSCLEROSIS. The small capillaries that filter blood are distorted or compressed by the nodular scarring (sclerosis).

Basement membrane Thickening



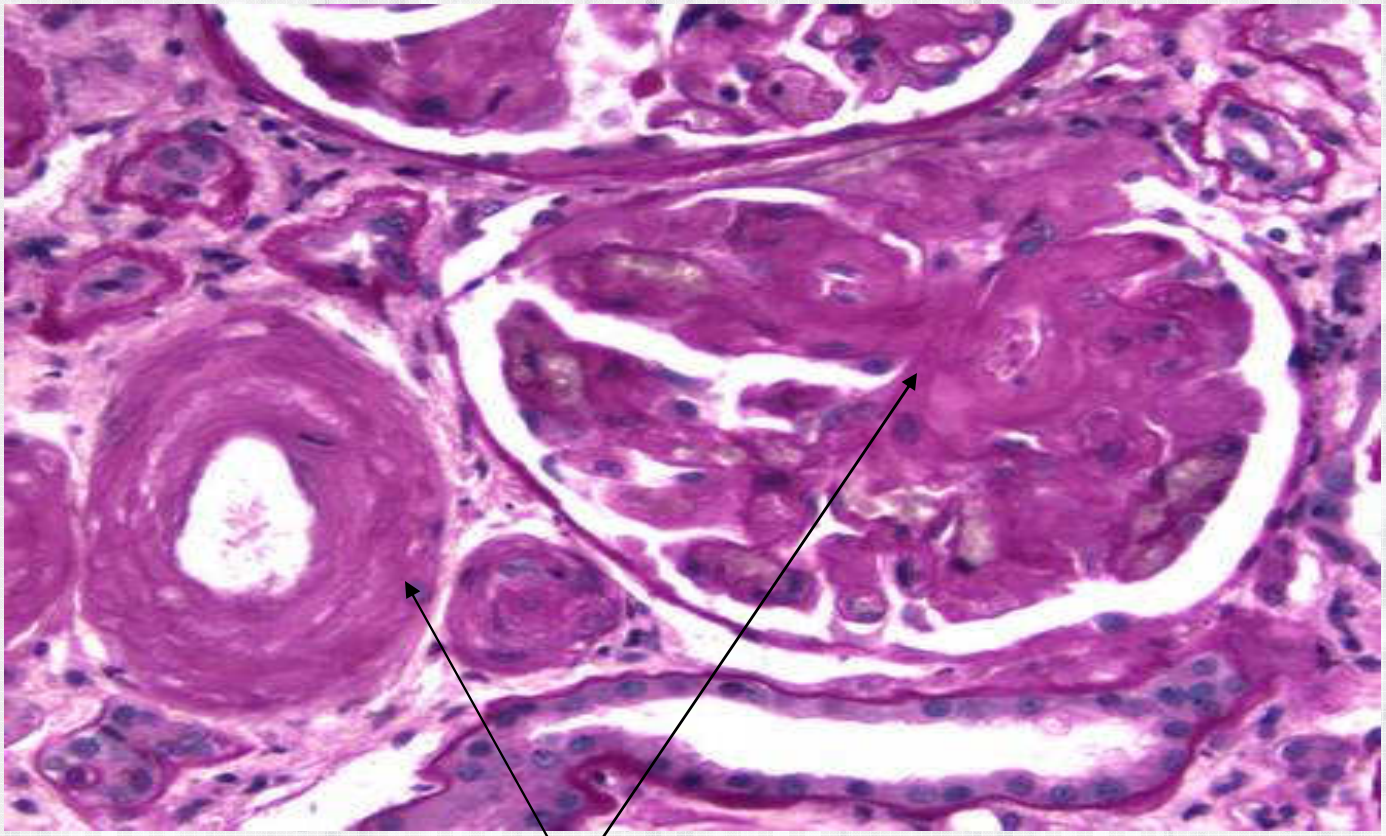
Ref: www.intechopen.com

Renal Amyloidosis

- Deposition of amyloid protein in glomeruli.
- Early stage present as Nehprotic Syndrome.
- End stage – Chronic renal failure.

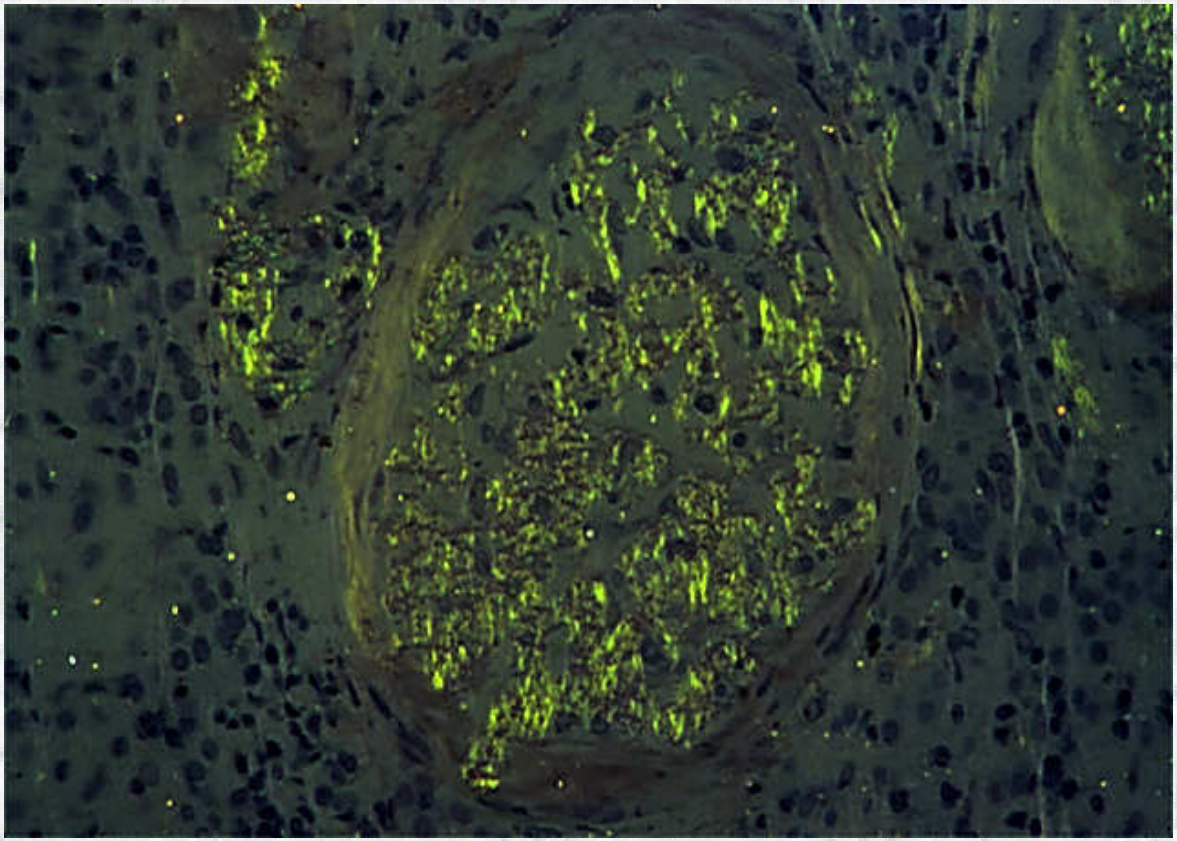
Amyloidosis

- Deposition of abnormal protein in the glomerulus & blood vessel wall



Amyloid deposits

Amyloidosis



Congo red stain. Examined under polarization microscopy. "Apple-green" birefringence.

Ref: www.pathology.vcu.edu

Lupus Nephropathy

- SLE – auto-immune disorder.
- Lupus Nephropathy is renal component of SLE.
- Immune Complex disposition in subendothelial location causing immune mediated injury to glomeruli.
- May have features of Nephritic syndrome as well
- Histologically: various forms. None specific for SLE

Disroders Manifest By Nephritic Syndrome

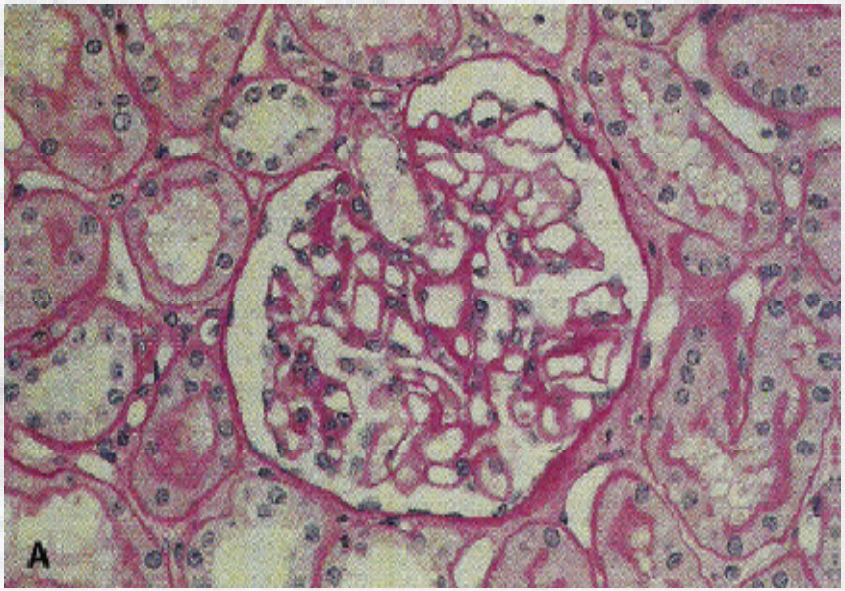
- Poststreptococcal GN
- Rapidly Progressive (crescentic) GN
- Goodpasture syndrome
- Alport Syndrome

Poststreptococcal GN (Acute Proliferative GN)

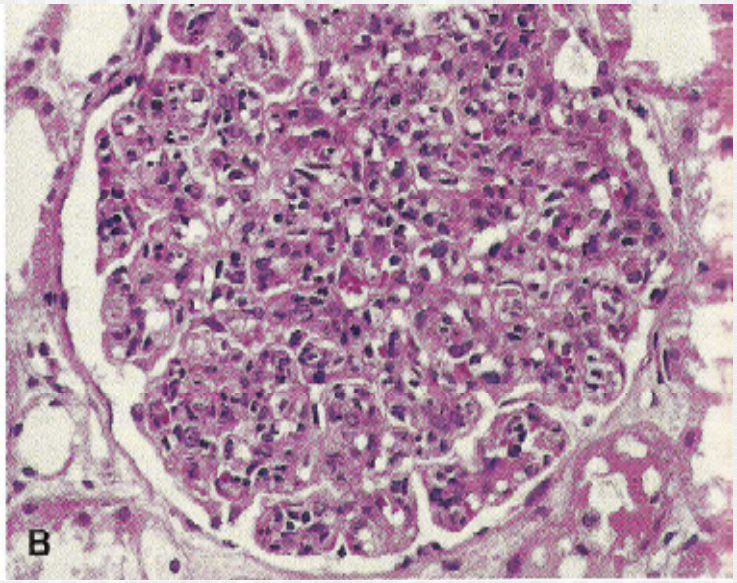
- Immune mediated.
- Sequelae of nephritogenic strains of Group A beta-hemolytic streptococcal skin infection or pharyngitis.
- Deposition of immune complexes in glomeruli cause inflammation and damage BM.
- Common in children age 6-10 yrs.

Post-streptococcal GN

Normal glomerulus



Acute proliferate GN



Hypercellularity due to intercapillary leucocytes & proliferation of glomerular cells (mesangial cells, endothelial cells)

Ref: Robins Pathological Basis of Diseases, 6th Ed. Fig 21.16

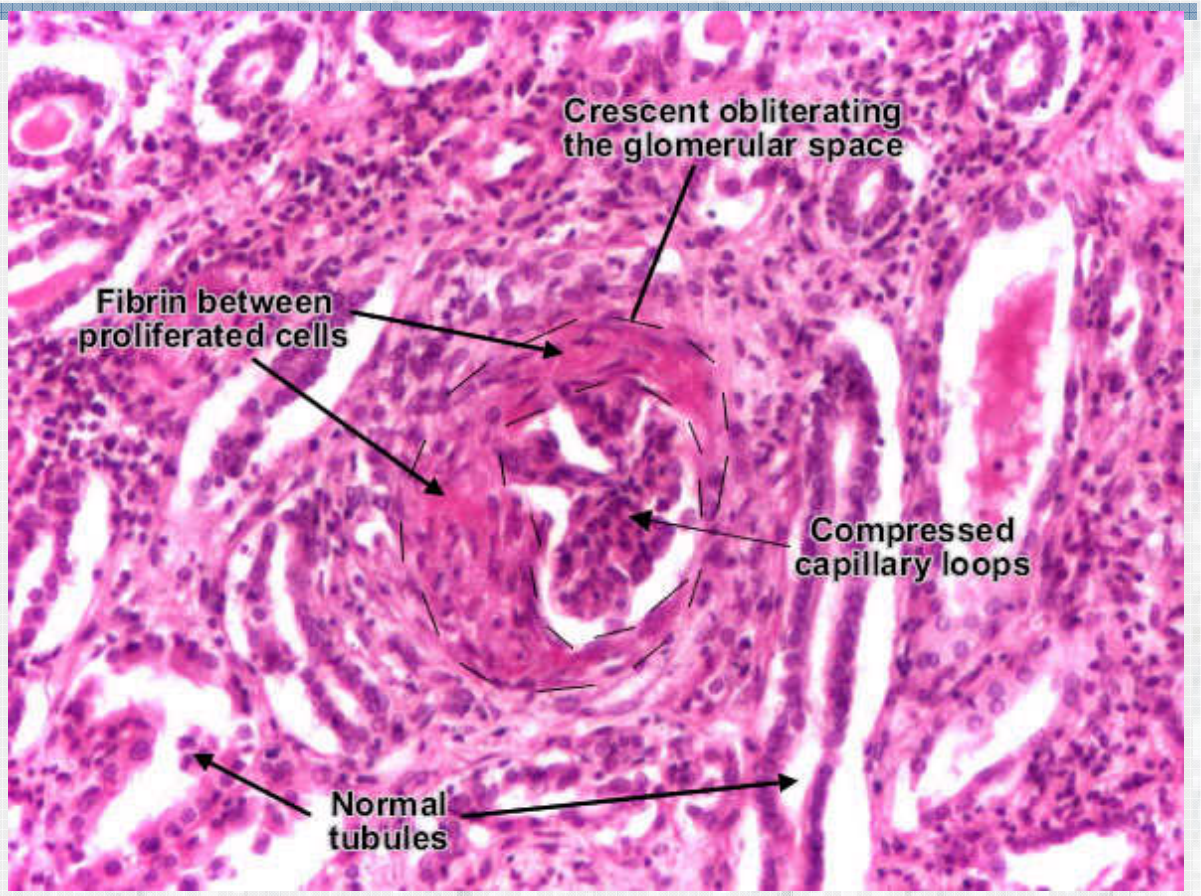
Rapidly Progressive (crescentic) GN

- A syndrome and not a specific diagnosis. Immune mediated.
- 3 types – Type I (ANCA Neg, Anti glomerular BM antibodies), II (Immune complex) & II (ANCA Pos pauci-immune form).
- Can occur as primary or in association with other diseases.
- Disease association: E.g. Goodpasture syndrome (Type I), SLE (Type II) Wegener granulomatosis (Type II).

Rapidly Progressive GN

- Clinically can progress rapidly to renal failure in weeks or months.
- 50% poststreptococcal with immune complex deposition.
- 10% due to antiglomerular BM antibodies (Type I, ANCA Neg) and present as clinically as Goodpasture syndrome.

Rapidly Progressive (Crescentic) GN



Ref: www.geekymedics.com

RPGN or Crescent GN

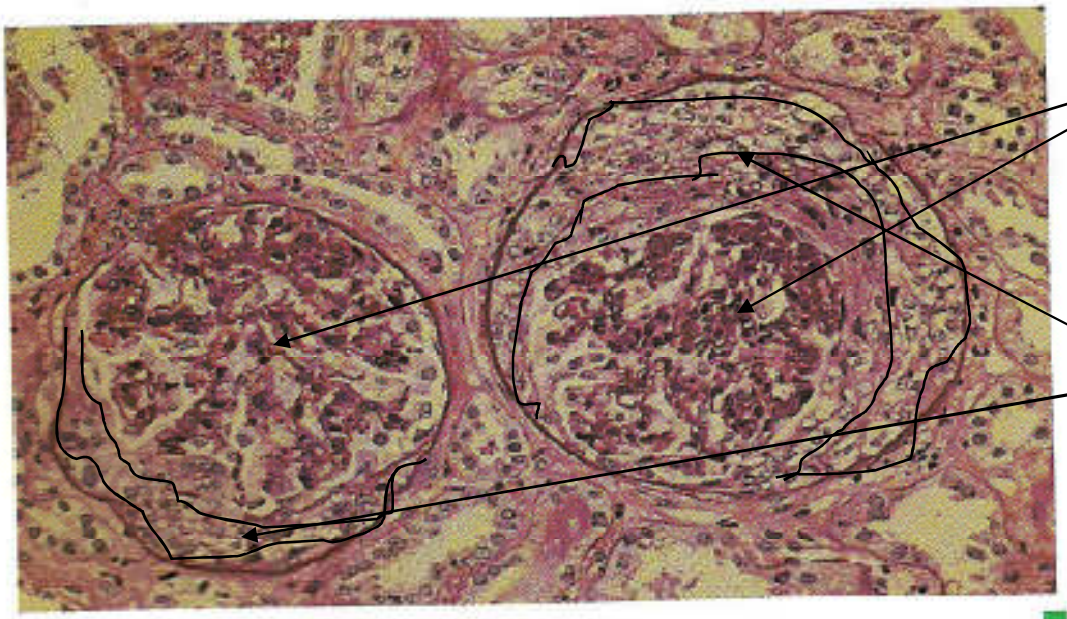


Figure 21–17

Crescentic glomerulonephritis (PAS stain). Note the collapsed glomerular tufts and the crescent-shaped mass of proliferating cells and leukocytes internal to Bowman capsule. (Courtesy of Dr. M.A. Venkatachalam, Department of Pathology, University of Texas Health Sciences Center, San Antonio, TX.)

Collapsed glomerular tufts

Mass of crescent shaped proliferating cells & leucocytes

Ref: Robins Pathological Basis of Diseases, 6th Ed.
Fig 21.17

Goodpasture Syndrome

- Also known as Antiglomerular BM disease
- Immune mediated: Antibodies directed against antigens in glomerular and alveolar BM
- Clinically present as Nephritic syndrome & pneumonitis with hemoptysis
- Peak incidence in male in mid 20s
- Histology shows RPGN crescentic morphology with linear immunofluorescence staining.

Alport Syndrome

- Hereditary nehpritis with nerve deafness & ocular disorders (lens dislocation & cataracts)
- Inherited disorder. Heterogenous mode of inheritance. Most patients have X-linked dominant pattern.
- Genetic basis: mutation in gene for alpha 5 chain of type IV collagen resulting in defective GBM synthesis.
- Symptoms appear between 5-20 yrs and renal failure by 20-50 years.
- Histology: irregular BM thickening with foci of splitting of the lamina densa

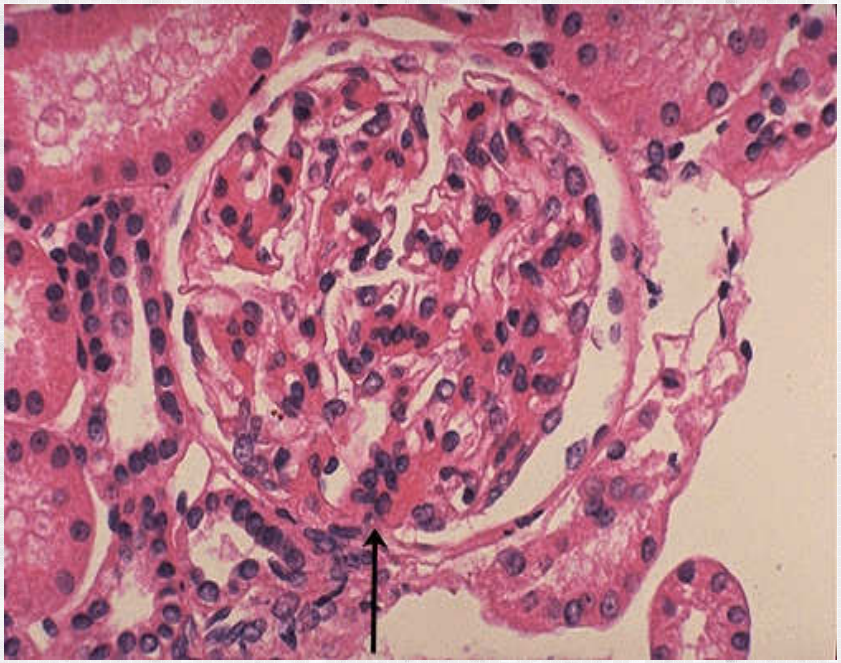
Other Glomerular Disorders (Not Nephrotic or Nephritic

- IgA Nephropathy (Berger Disease)
- Membranoproliferative GN

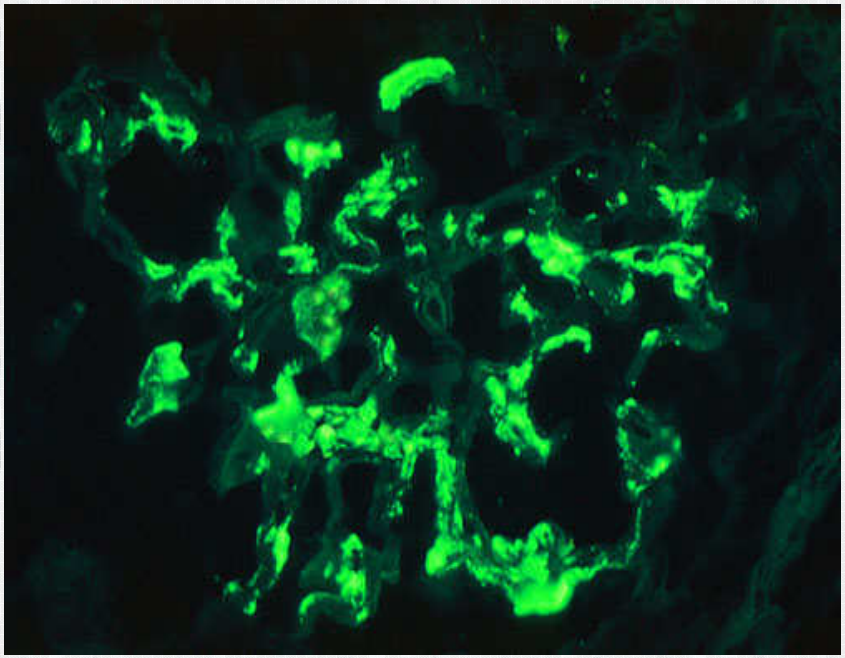
IgA Nephropathy (Berger Disease)

- Very common entity
- Defined by deposition of IgA in the mesangium
- Frequent cause of recurrent gross or microscopic hematuria.
- Can occur as Primary or secondary to other disorders (liver and celiac disease)
- Affects children and adults
- Slow progression to chronic renal failure occurs

IgA Nephropathy (Berger Disease)



IgA deposited within mesangium increasing its cellularity



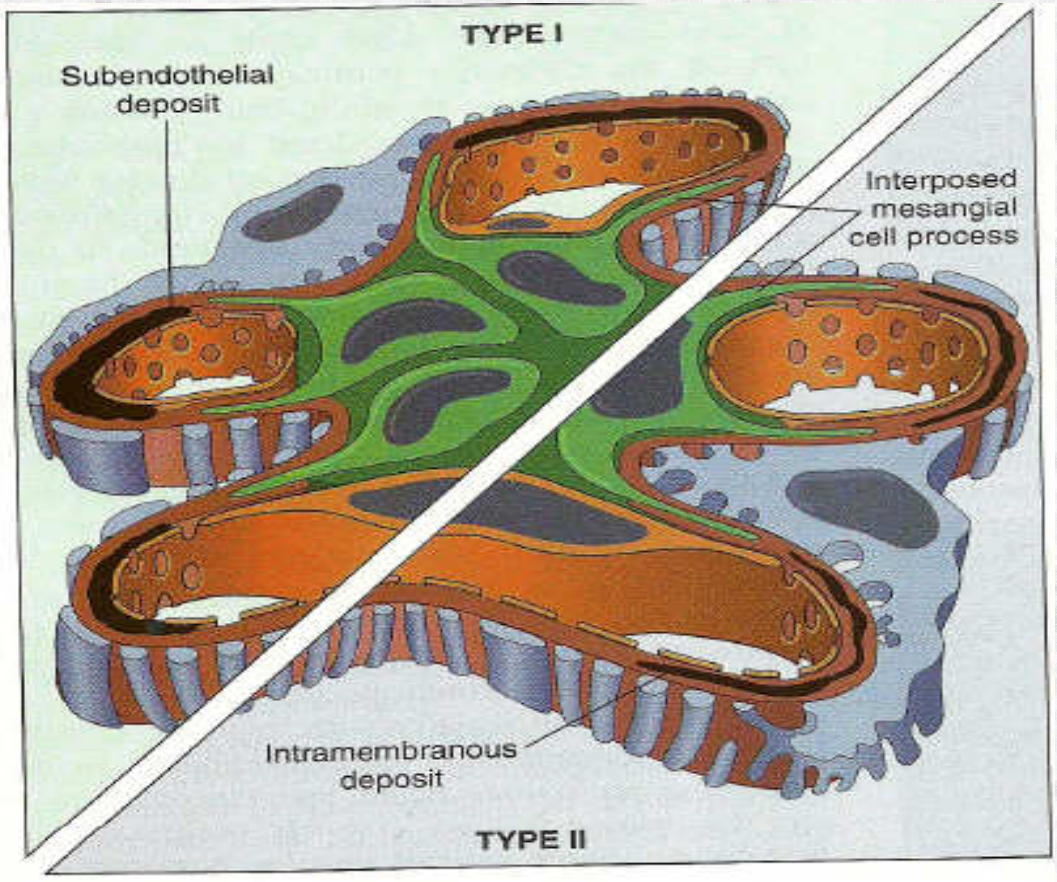
Immunofluorescence demonstrating positivity with antibody to IgA.

Ref: www.pathologyoutlines.com

Membranoproliferative GN (Mesangiocapillary GN – MPGN)

- 5-10% of idiopathic nephrotic syndrome in children and young adults.
- Immune mediated disorder.
- Types I and II based on histological features.
- Clinical: features of nephrotic and nephritic syndrome. 50% develop CRF in 20 years.

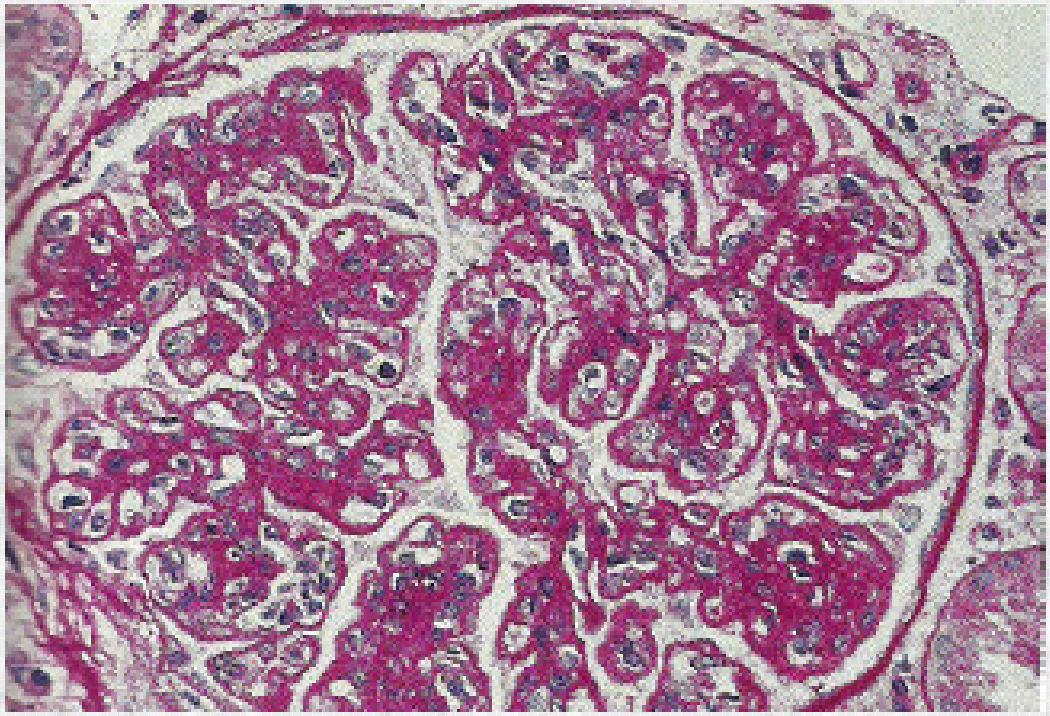
Membranoproliferative GN



Differentiation based on electron microscopy

Ref: Robins Pathological Basis of Diseases, 6th Ed. Fig 21.24

Membranoproliferative GN



Ref: Robins Pathological Basis of Diseases, 6th Ed. Fig 21.23

- Thickened in BM
- Proliferation of mesangial cells (glomerular cells)
- Leukocyte infiltration

Laboratory Diagnosis

- Clinical features
- Urine analysis
- BUN and UEC including albumin
- Lipid profile
- FBC
- ASO titre where indicated
- Compliment levels
- Renal biopsy and immunohistochemistry (do coagulation profile before renal biospy)

Prognosis

- Depends on underlying pathology of either Nephrotic or Nephritic Syndrome

END

- Main reference: Robins Pathological Basis of Diseases, 6th Ed. Chapter on Kidney.

Download seminar notes at

www.pathologyatsmhs.wordpress.com