DISEASES OF THE URINARY TRACT 1

EVALS 6

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Trans Group: 2A

OUTLINE

1. Urate Nephropathy (Hyperuricemia)
2. Hypercalcemia And Nephrocalcinosis
3. Myeloma Kidney (Light Chain Cast Nephropathy)

Summary

References

REFERENCES:

Dr. Dr. Debbie D. de la Fuente — Lecture

I. INTRODUCTION TO THE PATHOLOGY OF RENAL DISEASES

A. MORPHOLOGIC COMPONENTS OF THE NORMAL KIDNEY

1	**Glomeruli**
2	**Tubules**
3	**Intersitium**
4	**Blood Vessels**

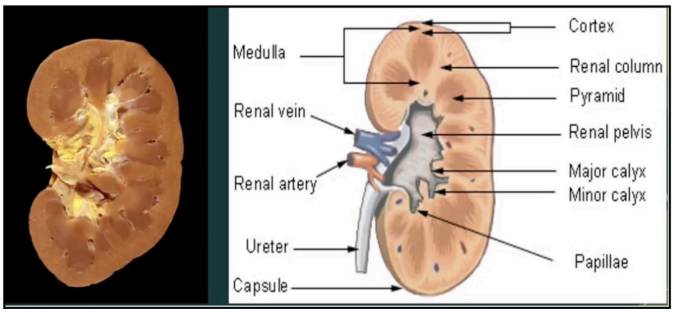


Figure 1. Parts of the kidney and its blood supply

- In most nephrons, the loop of Henle is short, located in the cortex.
- In some, it is long and it plunges into the medulla.
- During tubular reabsorption, substances move from the renal tubules into the interstitium.
  - Diffuse into the peritubular capillaries.
- The proximal convoluted tubules reabsorb 70% of these substances, including:
  - Glucose, water, urea, proteins and creatinine, amino acids, lactic acids, citric and uric acids, phosphates, sulfate, potassium, and sodium ions.

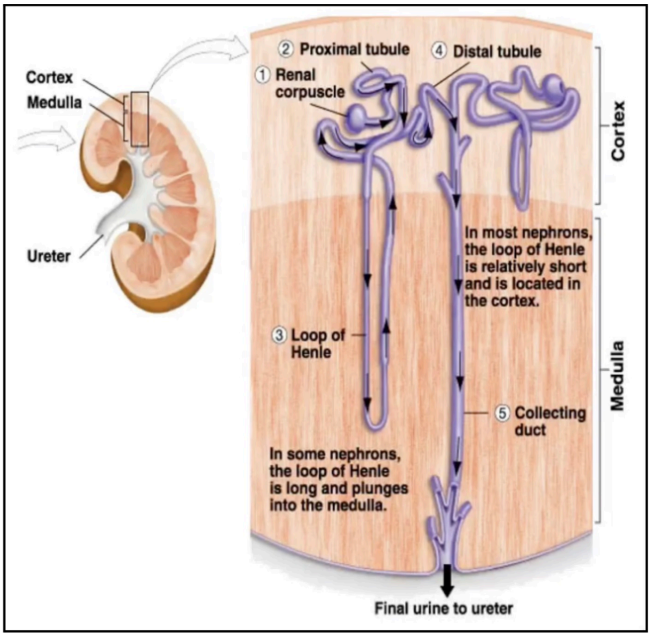


Figure 2. Loop of Henle

- The blood supply to the kidneys, including the one that goes into the glomeruli, comes from the branches of the **Renal Artery.**
  - Venous drainage is through the **Renal Vein.**

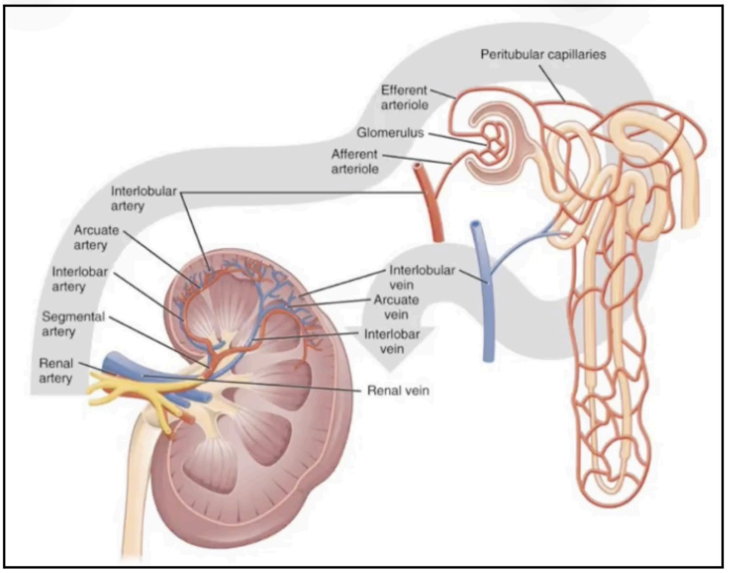


Figure 3. Blood Flow of the Kidney

B. CLINICAL PRESENTATIONS OF RENAL DISEASE

1	**Acute Nephritic Syndrome**
2	**Nephrotic Syndrome**
3	**Asymptomatic Hematuria / Proteinuria**
4	**Acute Kidney Injury or Acute Renal Failure (ARF)**

5	**Chronic Kidney Disease or Chronic Renal Failure (CRF)**
6	**Manifestations of Renal Tubular Defects:** • **Polyuria** • **Nocturia** • **Electrolyte Disorder**
7	**Urinary Tract Infection**
8	**Nephrodolithiasis**
9	**Urinary Tract Obstruction and Renal Tumors**

C. COMPONENTS OF THE GLOMERULUS

- The pathogenesis of glomerulonephritis will involve one or more of these components

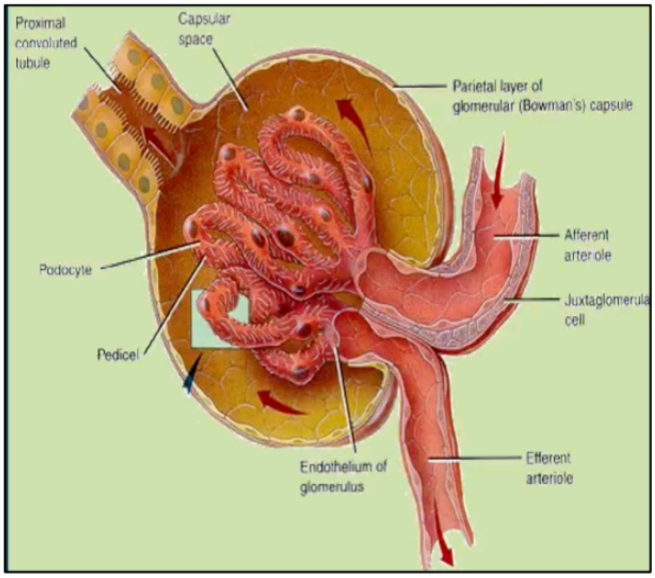


Figure 4. Components of the Glomerulus

1. ENDOTHELIAL CELLS

2. GLOMERULAR BASEMENT MEMBRANE (GBM)

- Made up of collagen, laminin, proteoglycans, fibronectin & glycoproteins that are arranged for maintaining efficient filtration
- **Lamina rara interna**
- **Lamina densa**
- **Lamina rara externa**

3. VISCERAL EPITHELIAL CELLS (PODOCYTES)

- **Foot processes**
  - Embedded in the lamina rara externa
- Adjacent foot processes are separated by filtration slits that are bridged by a thin slit diaphragm

4. MESANGIAL CELLS

- The **glomerular capillaries are supported by mesangial cells scattered** through a (basement membrane - like) mesangial matrix
- Contractile phagocytic capable of:
  - **Proliferating**
  - **Laying down matrix & collagen**
  - **Secreting mediators**

D. FEATURES OF THE FILTRATION BARRIER

- Endothelial cells, GBM, and Podocytes
  - **Slit diaphragm of podocytes = major protein barrier**. Any defect in its proteins results in protein leakage
- Highly permeable to water & solutes
- **Impermeable to proteins:**
  - **Size of proteins**
  - **Charge of proteins**

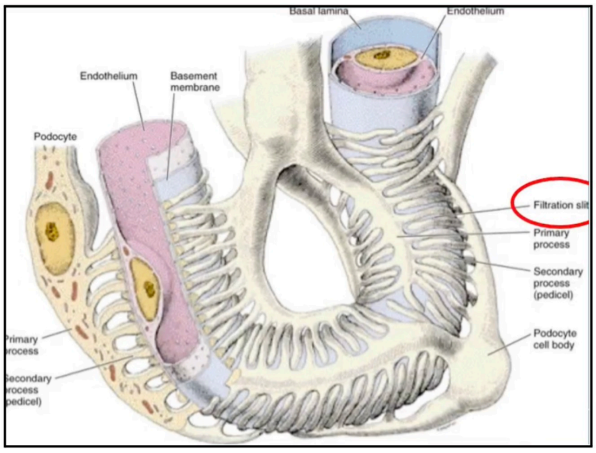


Figure 5. Nature of the Podocytes on the Visceral Epithelial Cells

- The histologic features of progressive reHas foot processes or pedicels that wrap around the capillary wall.
  - In between these foot processes are the filtration slits, which is an important component of the glomerular filtration barrier.

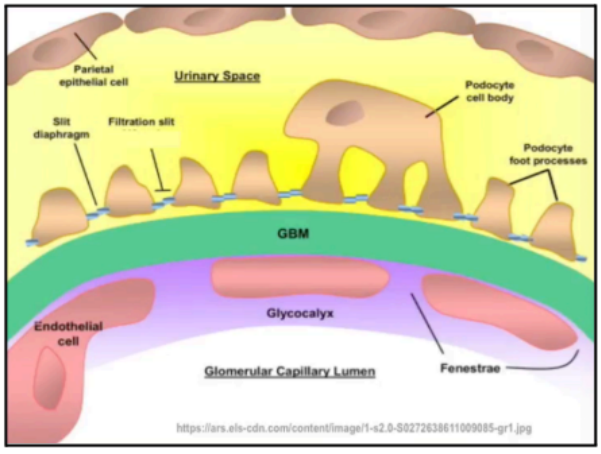


Figure 6. Filtration Barrier

- From the inside of the capillary lumen going outward:
  - The filtration barrier is composed of **fenestrated endothelium**, which is overlaid by the **glycocalyx**
  - Then the **glomerular basement membrane**, which is followed by the **podocytes**, specifically the **filtration slits** that are bridged by the **slit diaphragm**.

1. FILTRATION SLITS

- **Much smaller than the fenestrae of the endothelial cells**
- Each slit is 20-30 nm wide
  - Compared to the endothelial fenestrae which is 70-100 nm wide
- Along with the slit diaphragm, they serve as the **final and most important barrier to the passage of molecules**

2. SLIT DIAPHRAGM

- More complex than it appears to be
- Possess proteins, which when mutated, will result in a defect in its filtration function.

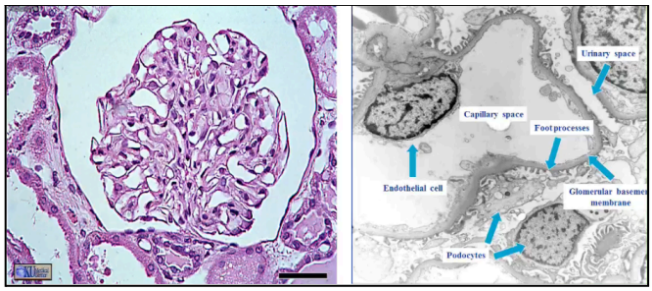


Figure 7. Glomerulus under the Light Microscope (L) and Electron Microscope (R)

1. RENAL BIOPSY

- **Done usually for primary glomerular diseases**
  - Using imaging as a guide, CT scan or ultrasound, a needle is inserted through the skin into the kidney.
  - Pieces of kidney tissues are taken, processed, and viewed using light microscopy, electron microscopy, and immunofluorescence microscopy.
- Special stains are used to better visualize specific structures
- **Ideal renal biopsy should show 10-20 glomeruli**
- **Background sclerosis: (patient's age/ 2) - 10**
  - As a person ages, there will be more sclerotic glomeruli that are NOT ALWAYS associated with the disease.
    - This should be accounted for during renal biopsy evaluation

1. LIGHT MICROSCOPY (No need to memorize)

Stains	Structures Visualized
H&E	Cellularity and architecture
PAS	Carbohydrate moieties of the GBM
Jones-Methenamine Silver	GBM structure
Congo Red	Amyloid
Masson Trichrome	Collagen deposition (glomerulosclerosis and interstitial fibrosis)

2. IMMUNOFLOURESCENCE

- Used to visualize immune deposits
- Two basic patterns:
  - **Granular (coarser) & Linear (well-defined lines)**
- Ultimate examination tool visualizing the ultrastructure

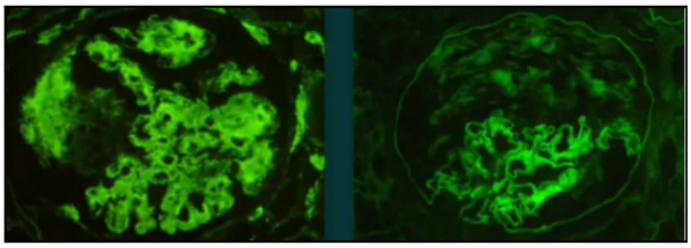


Figure 8. Immune deposits (Bright Green structure)

3. ELECTRON MICROSCOPY

E. AZOTEMIA AND UREMIA (Must know!)

1. AZOTEMIA

- **Biochemical abnormality**
- Characterized by:
  - Elevated BUN
  - Elevated creatinine
  - Related largely to the decrease of GFR

DECREASING GFR	
PRE-RENAL	Hypoperfusion of the kidneys • i.e. volume depletion, hemorrhage, shock, CHF
RENAL	Primary (intrinsic) renal disease
POST-RENAL	Obstruction to urine flow

2. UREMIA

- **Azotemia + clinical signs & symptoms**
  - These are symptoms that are attributable to failure of the renal excretory function, metabolic and endocrine alterations resulting from secondary renal damage
  - Involvement of the GIT, peripheral nervous system, and the heart

F. ACUTE KIDNEY INJURY VS CHRONIC KIDNEY DISEASE

ACUTE KIDNEY INJURY	CHRONIC KIDNEY DISEASE
Acute renal failure (ARF)	**Chronic renal failure (CRF)**
Rapid decline in GFR (within **hours to days**)	Diminished GFR that is persistently less than 60 ml/min/1.73 m2 **for at least 3 months**, from any cause, and/or persistent albuminuria
Manifested by **oliguria** or **anuria** (reduced or no urine flow) → extracellular fluid overload With **recent onset of azotemia**	Milder forms - **silent decline in renal excretory function** Severe forms - **prolonged symptoms and signs of uremia**
Concurrent dysregulation of fluid and electrolyte balance (**electrolyte & acid-base abnormalities**) **Retention** of **metabolic waste** (nitrogenous products)	**Progressive loss in renal function** over a period of months or year **Continuing significant, irreversible reduction** in nephron number
Can result from glomerular, interstitial, vascular, or acute tubular injury (ATI)	End result of all chronic renal parenchymal disease

STAGES OF RENAL FAILURE	
STAGE	**GFR**
Diminished renal reserve	**50%**
Renal insufficiency	**20% to 50%**
Renal failure	**< 20% to 25%**
End-stage renal disease	**< 5%**

G. CLINICAL PRESENTATIONS OF RENAL DISEASE

- Depends on what part of the nephron is affected:

1. GLOMERULI

- Presents with hematuria/proteinuria
- Puffiness of face
- Oliguria/azotemia
- Usually immune-mediated

2. TUBULES

- Presents with inability to concentrate urine
- Polyuria, nocturia, electrolyte imbalance
- Acute renal failure (ARF)
- Azotemia usually due to toxins, infections, inherited

3. INTERSTITUUM

- Presents with inability to concentrate urine
- ARF
- Pyuria
- Usually due to drugs/infections

4. INTERSTITUUM

- Hypertension (HPN); ARF
- Ischemic injury - papillary necrosis/infarcts
- Usually due to congenital disorders / drugs

H. NEPHRITIC VS NEPHROTIC

- Nephritic and Nephrotic are two terms which may be mistakenly used interchangeably

NEPHRITIC	NEPHROTIC
Hematuria	**Heavy proteinuria**
Mild to moderate proteinuria	**Hypoalbuminemia**
Hypertension	**Severe edema**
	Hyperlipidemia
	Lipiduria

- Nephritic disease is characterized by hematuria and hypertension.
- Nephrotic disease is characterized by heavy/massive proteinuria.

PART 2 OBJECTIVES

- Differentiate the glomerular syndromes
- Describe the general histologic changes in the diseased glomerulus
- Explain the immune mechanisms involved in glomerular disease
- Recognize the different mediators involved in glomerular injury
- Name and differentiate the patterns of distribution of glomerular damage.
- Describe epithelial cell injury.
- Explain the sequence of events that leads to FSGS in cases of renal ablation.
- Enumerate the factors that lead to tubulo-interstitial fibrosis.

I. INTRODUCTION TO GLOMERULAR INJURY

A. THE GLOMERULAR SYNDROMES

- Clinical manifestations of glomerular disease

1	Acute Nephritic Syndrome
2	Rapidly Progressive Glomerulonephritis (RPGN)
3	Nephrotic Syndrome
4	Chronic Kidney Disease

5	Glomerular Hematuria or Sub-nephrotic proteinuria (Isolated Urinary Abnormalities)

B. HISTOLOGIC CHANGES IN GLOMERULONEPHRITIS

- The glomerular disease may manifest one or more of these changes.

1. HYPERCELLULARITY

- Cellular proliferation - increase in the number of cells (mesangial cells or endothelial cells of the capillaries)
- Leukocytic infiltration
  - includes neutrophils, monocytes, and lymphocytes
  - Endocapillary proliferation - leukocytic infiltration and swelling along with cellular proliferation
- Formation of crescent-shaped structures - due to an increase in parietal epithelial cells

2. BASEMENT MEMBRANE THICKENING

- Deposition of electron-dense material, which are most often immune complexes, but may be fibrin, globulins or abnormal fibrillary proteins
- It may be thickened due to increased synthesis of the protein components
- Thickening of the basement membrane proper, which may be detected by:
  - LM using PAS stain - thickening of the capillary wall
  - EM - presence of electron-dense material
- Formation of additional layers of basement membrane matrices, which most often occupies subendothelial locations and range from poorly organized matrix to fully duplicated lamina densa

3. HYALINOSIS

- Accumulation of **homogenous and eosinophilic material** (seen by LM)
- Due to accumulation of plasma proteins that have insudated from the circulation

4. SCLEROSIS

- Accumulation of **extracellular collagenous material in the mesangium** and in the **capillary loops** leads to the gradual obliteration of the glomerular tuft
- There is decreased functioning capillaries due to fibrosis

C. PATTERNS OF DISTRIBUTION OF GLOMERULAR CHANGES (MUST KNOW)

Diffuse	**Most glomeruli (>50%)**
Focal	**<50% of the glomeruli**
Global	**Entire glomerulus**
Segmental	**Only a part of the glomerulus**
Mesangial	**Affecting the mesangial region**

D. PATHOGENESIS - IMMUNE MECHANISMS

- Underlie most forms of primary glomerulopathies and may be secondary to glomerular diseases.
- These mechanisms initiate glomerular injury.
- Outcome of the injury will depend on several factors, such as:
  - **Initial severity of the renal damage**
  - **Nature and persistence of the antigens**
  - **Immune status**
  - **Age**
  - **Genetic predisposition**

1. ANTIBODY-MEDIATED MECHANISM

In-situ Immune Complex Deposition

- Antibodies form immune complexes with antigens that are already in the glomerulus (intrinsic glomerular Ags or Ags “planted” in the glomerulus from the circulation)

1. Anti-GBM Antibody-Induced Nephritis [Batch 2027 Trans]

- Antibodies are directed against intrinsic fixed Ags that are normal components of the GBM
- Abs also cross-react with other basement membranes (ex: lungs in Goodpasture’s syndrome)

2. Heymann Nephritis [Batch 2027 Trans]

- Antibody vs antigen located on the visceral epithelial cells
- “Heymann” because in the experimental model, the antigen is called Heymann
- This antigen is “megalin” located at the basal surface of visceral epithelial cells

3. Planted Antigens [Batch 2027 Trans]

- Infection agents, drugs, nuclear proteins, Ig, DNA

Circulating Immune Complex Deposition

- Antibodies form immune complexes with circulating antigens which then deposit in the glomerulus.

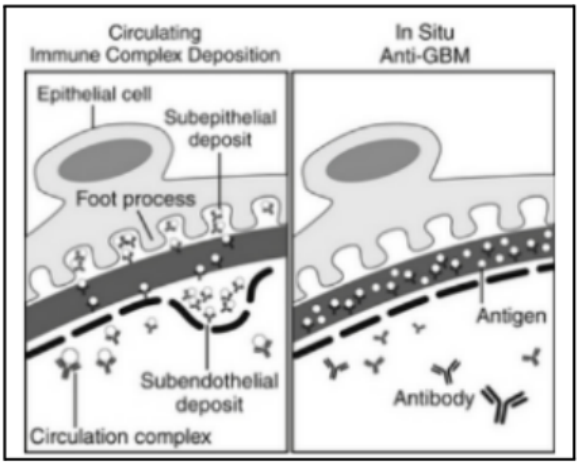


Figure 9. Difference of Antibody-mediated Mechanisms

2. CELL-MEDIATED MECHANISM (SENSITIZED T-CELLS)

- Does not involve antibodies, but rather the activation of phagocytes, antigen-specific cytotoxic T lymphocytes and the release of various cytokines in response to an antigen.
- 📖 Naive T lymphocytes are activated by Ag and proliferate and differentiate into effector cells that migrate to sites where the Ags are present
  - Activated T lymphocytes → release cytokines → inflammation and macrophage activation → T cell-mediated cytotoxicity
  - CD8+ lymphocytes differentiate into CTLs (cytotoxic
- T lymphocytes) that kill cells harboring microbes in the cytoplasm
- 📖 It is thought that T cells in the glomeruli are sensitized to endogenous or exogenous antigens then recruit macrophages resulting in local delayed-type hypersensitivity reaction

3. ALTERNATIVE COMPLEMENT PATHWAY ACTIVATION

- Dysregulation of alternative complement pathway activation either due to antibodies or genetic aberrations resulting in the deposition of C3 in the glomeruli
- 📖 In the absence of antibody, the alternative complement pathway is triggered by microbial surface molecules or other substances, resulting eventually in the cleavage of C3 into C3a & C3b and eventually C5 into C5a & C5b; C5b binds C6-C9 --> membrane attack protein

E. LOCALIZATION OF DEPOSITS

- The distinct pattern of localization is a key determinant of the injury response and the histologic features that subsequently develop.
  - Example: If subendothelial - nearer circulation and therefore more likely associated with circulatory leukocytes, hence may be accompanied by inflammation.
- Localization of deposits may occur in:
  1. **Subepithelial (between the podocytes and GBM)**
     a. **Epimembranous (above the GBM)**
  2. **Basement membrane**
  3. **Subendothelial (beneath the endothelial cells)**
  4. **Mesangial**

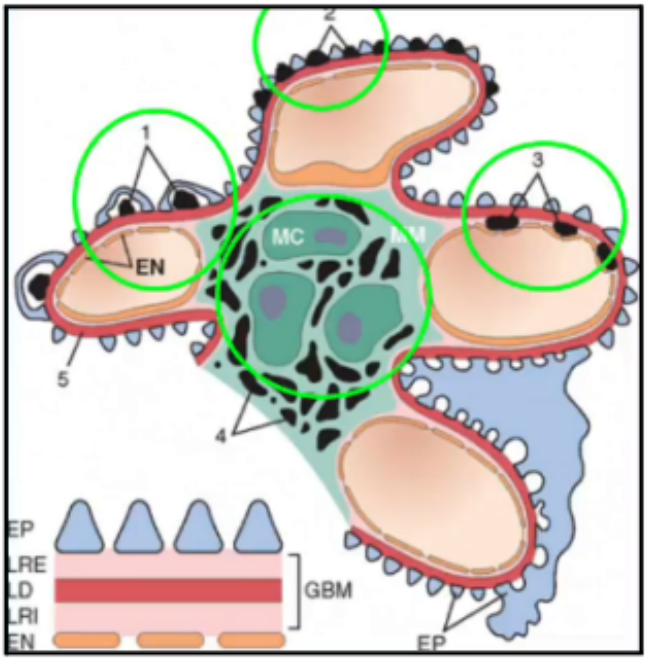


Figure 10. Localization of Deposits; (1) Subepithelial; (2) Basement membrane; (3) Subendothelial; (4) Mesangial

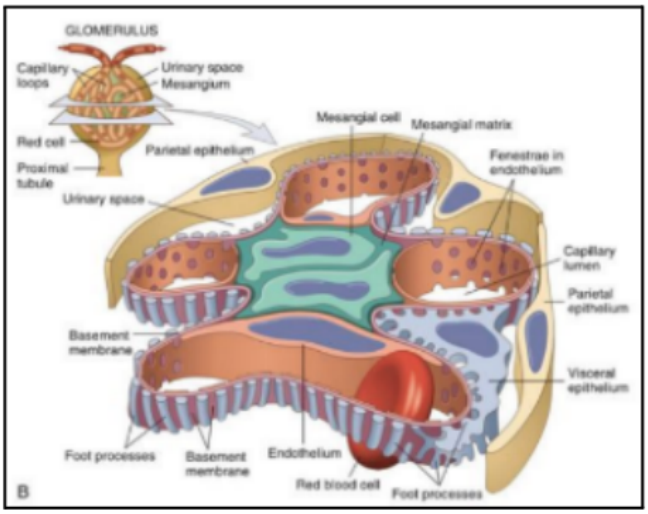


Figure 11. Schematic representation of a Glomerular Lobe

F. MEDIATORS OF GLOMERULAR INJURY

- No need to memorize:

CELLS	CHEMICAL MEDIATORS
Neutrophils & monocytes	Chemotactic factors
Macrophages, T-lymphocytes, NK cells	Cytokines & chemokines
Platelets	Eicosanoids, NO, angiotensin, endothelin
Glomerular cells which may produce	Coagulation system

inflammatory mediators	

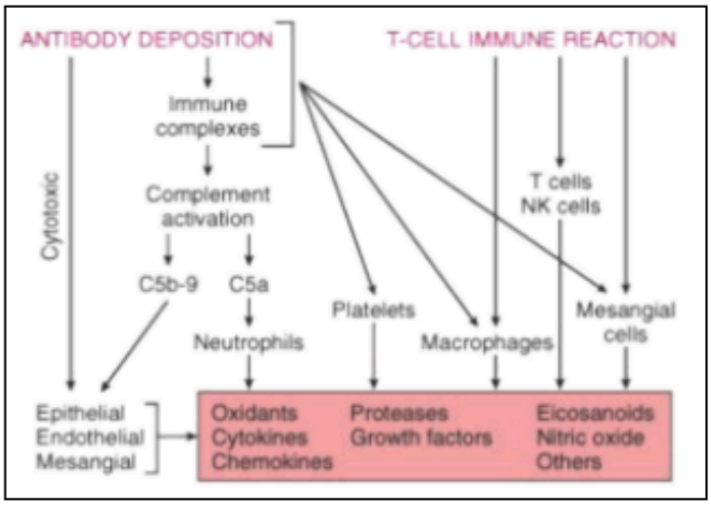


Figure 12. Mechanisms giving rise to chemical mediators

G. EPITHELIAL CELL INJURY

- Podocytes or the visceral epithelial cells have limited capacity for replication and repair
- Podocyte injury is common to both primary and secondary glomerular disease
- The cells may be effaced or detached.
- Injury to the slit diaphragm is often the key event in the development of proteinuria.

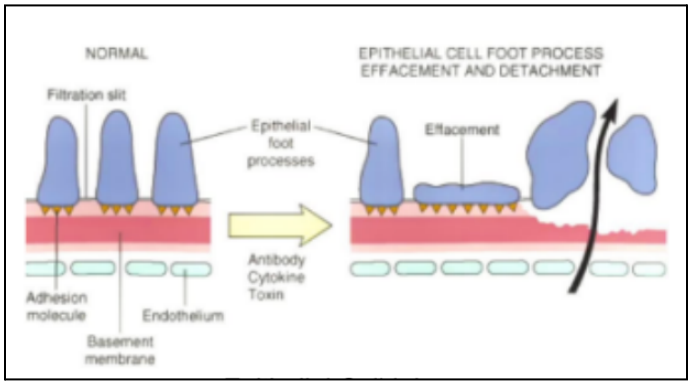


Figure 13. Epithelial Cell Injury

H. MAJOR HISTOLOGIC FEATURES OF PROGRESSIVE RENAL DAMAGE

- Once renal disease destroys functioning nephrons, it reduces the GFR to 30-50% of the normal.
- Progression to the end-stage renal failure proceeds at a constant rate
- The histologic features of progressive renal damage include:
  - Focal Segmental Glomerulosclerosis (FSGS)
  - Tubulo-interstitial Fibrosis

1. FOCAL SEGMENTAL GLOMERULONEPHRITIS (FSGS)

- May occur as a primary disease or it may occur as an advanced stage, a complication of glomerular or non-glomerular diseases that cause reduction in functioning renal mass

Compensatory Glomerular Hypertrophy

- Serves to maintain renal function
- Leads to hemodynamic changes that are associated with the following:
  - Increased glomerular blood flow & filtration
  - Increased transcapillary glomerular hypertension
  - Most often systemic hypertension
- These changes cause epithelial and endothelial cell injury, which results in proteinuria
- Proteins accumulating in the mesangium results in a mesangianous response that involves mesangial cell proliferation and extracellular matrix production
- These changes result to glomerular sclerosis
  - This leads to further reduction in renal mass on going activation of compensatory changes, and the cycle repeats

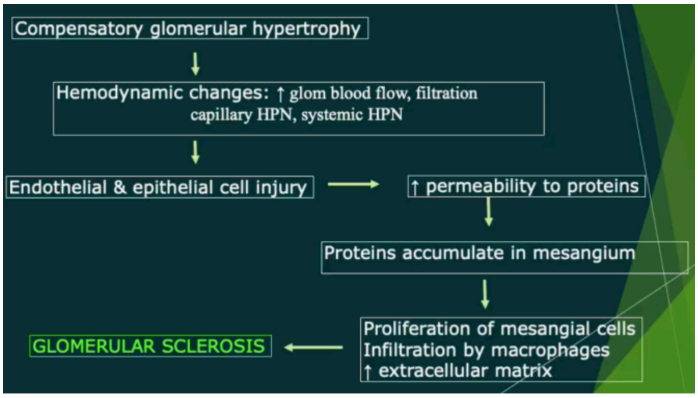


Figure 14. Progressive renal damage: FSGS

Contributing Factor

- Inability of the visceral epithelial cells to proliferate after injury
  - This leads to a decrease in the number of podocytes
  - The remaining podocytes stretch to maintain appropriate filtration barrier
  - Eventually, they are denuded resulting to in abnormal protein filtration and loss of structural support for the glomerular capillary wall
  - This lack of support for the glomerular capillary wall results in the dilatation of that segment of the capillary
  - The bulging capillary loop will subsequently form fibrous attachments to the bowman's capsule, which contributes to the sclerosis

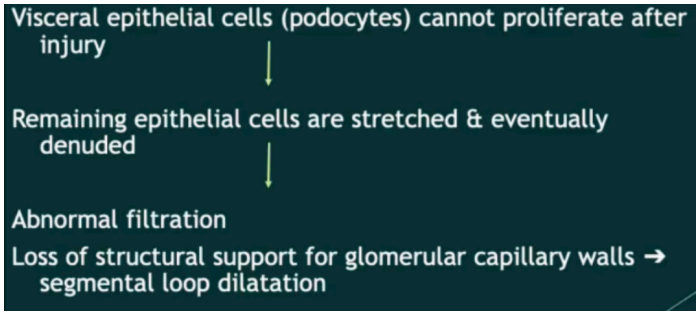


Figure 15. FSGS Contributing Factors

2. TUBULO-INTERSTITIAL FIBROSIS

- Manifested by tubular damage and interstitial inflammation
  - There is often a better correlation of decline in renal function with the extent of tubulo-interstitial damage than with the severity of the glomerular injury
- Contributing factors:
  - Ischemia of tubules
  - Acute or chronic inflammation in adjacent interstitium
  - Damage and loss of peritubular capillary supply
  - Proteinuria
    - Direct injury & activation of tubular cells → expression of mediators that contribute to interstitial fibrosis

SUMMARY

- The clinical manifestations of glomerular disease are clustered into the glomerular syndromes
- Glomerular disease presents with one or more of the following histologic changes:
  - Hypercellularity
  - Basement membrane thickening
  - Hyalinosis
  - Sclerosis
- Glomerular injury is mediated via 3 mechanisms:
  - Antibodies and formation of immune complexes
  - Cell-mediated immune response
  - Activation of the alternative complement pathway
- Glomerular damage is described according to its pattern of distribution.
- Visceral epithelial injury includes:
  - Effacement
  - Detachment
  - Destruction of the slit diaphragm
- FSGS and tubulo-interstitial fibrosis are signs of progression to end-stage renal failure.

PART 3 OBJECTIVES

- Explain the pathophysiology of the essential features of nephrotic syndrome
- Discuss the pathogenesis of post-Streptococcal GN
- Describe the characteristic LM, IF, & EM findings of post-Streptococcal GN
- Differentiate the 3 types of RPGN
- Describe the characteristic gross, LM, IF, & EM findings of RPGN
- Compare the prognosis of post-streptococcal GN and RPGN
- Discuss the pathophysiology of the essential features of nephrotic syndrome
- Differentiate the following as to pathogenesis, histologic morphology (LM, EM, IF) and essential clinical features:
  - Membranous Glomerulopathy
  - Minimal Change Disease
  - Focal Segmental Glomerulosclerosis (FSGS)
  - Membranoproliferative Glomerulonephritis (MPGN)

I. GLOMERULAR SYNDROMES

CLINICAL MANIFESTATIONS OF GLOMERULAR DISEASE	
1	**Acute Nephritic Syndrome**
2	**Rapidly Progressive Glomerulonephritis (RPGN)**
3	**Nephrotic Syndrome**
4	Chronic Renal Failure (CRF)/ Chronic Kidney Disease
5	Asymptomatic Hematuria or Proteinuria

II. NEPHRITIC SYNDROME

- The primary insult in nephritic syndrome appears to be **initiation of inflammation** in the glomeruli
  - Caused by the **presence of immune complexes**

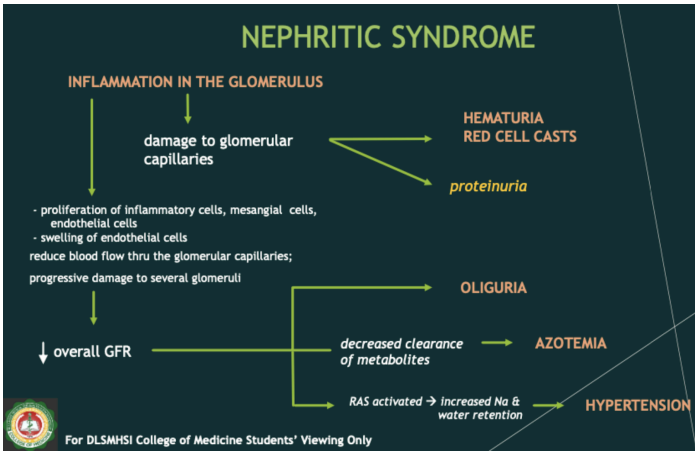


Figure 16. Mechanism of Nephritic Syndrome

1. INFLAMMATION INJURIES IN GLOMERULAR CAPILLARIES

- Allows for the of escape red cells in the urine →hematuria
- Extruded red cells aggregate in the tubule and thus take its shape resulting in characteristic red cell casts in the urine → red cell casts

- Damage to the glomerular capillaries also causes protein to be excreted in the urine → proteinuria
- Causes inflammatory, mesangial, and endothelial
- cellular proliferation

2. CELLULAR PROLIFERATION

- There is also swelling of the endothelial cells (aside from the proliferation of the mentioned cells above)

3. DECLINE IN OVERALL GFR

- All these changes reduce blood flow through the glomerular capillaries → progressive damage to several glomeruli → decline in overall GFR Gives rise to other pathophysiological sequelae

4. SUBSEQUENT EFFECTS

- Reduction in GFR leads to: ↓ capacity for urine formation → oliguria ↓ clearance of metabolites → azotemia Activates the renin-angiotensin system (RAAS) → increased Na+ & water retention → hypertension

A. ACUTE PROLIFERATIVE GLOMERULONEPHRITIS

- Nephritic syndrome is a typical clinical presentation of the most proliferative type of GN or acute proliferative glomerulonephritis.
- The primary event is inflammation in the glomerulus, often due to the immune complexes.
- The inciting antigen may be endogenous or exogenous.
- POST-STREPTOCOCCAL GN: Prototype disease involving exogenous antigen

1. POST-STREPTOCOCCAL GLOMERULONEPHRITIS

- Contractile phagocytic capable of:
- Happens 1 to 4 weeks after a strep infection
  - Follows a streptococcal infection of the pharynx (pharyngitis) or of the skin (impetigo)
  - More than 90% of the cases are traced to Group A β-hemolytic Strep (Types 12, 4, & 1)
- Streptococcal antigens have been used to detect streptococcal infections in humans.
- In the pathogenesis of post-streptococcal glomerulonephritis, two streptococcal antigenic fractions have substantial gain to nephritogenicity:
  - Streptococcal pyogenic exotoxin B (SpeB) -principal antigenic determinant
  - Nephritis-associated plasmin receptor (NaPlr)

1. PATHOPHYSIOLOGY

- Much smaller than the fenestrae of the endothelial cells
- These antigens deposit in the glomerulus and then antibodies are formed against these antigens.
- The antibodies go to the glomerulus and form antigen-antibody complexes, also called in-situ immune complex deposition.
- Antibodies also react with the antigens still in circulation to form immune complexes, which later on are deposited in the glomerulus.
  - In addition, the nephritis-associated plasmin receptor (NaPlr) causes sustained plasmin activity, resulting in glomerular basement membrane (GBM) degradation and facilitating the penetration of the immune complexes through the GBM.

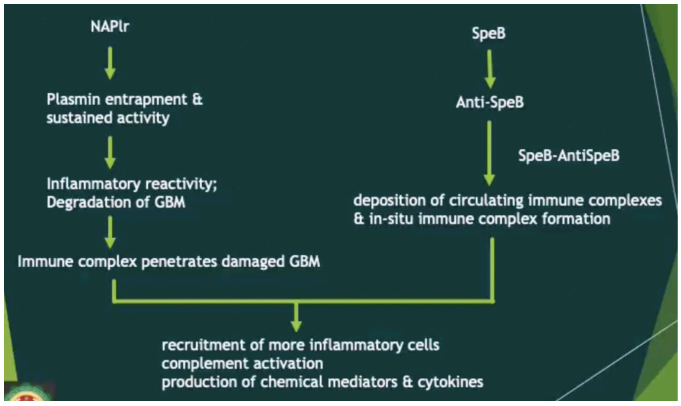


Figure 17. Pathophysiology of Post-Streptococcal GN

2. MORPHOLOGY

- Characterized by enlarged, hypercellular glomeruli
  - Hypercellularity is due to leukocytic infiltration consisting of neutrophils and monocytes
  - There is also proliferation of endothelial and mesangial cells and swelling of endothelial cells
  - Crescent formation may occur in severe cases
  - All of this will lead to the obliteration of glomerular capillary lumina
- Immunofluorescence (IF): granular deposits in the mesangium and GBM (Glomerular Basement Membrane) These deposits consist of IgG, IgM, and C3
- Electron Microscope (EM): subepithelial humps.
  - Diagram of normal glomerulus and another one with black subepithelial deposits.
  - Higher magnification of light microscopic appearance and EM indicates the presence of hump-like subepithelial immune complex deposits

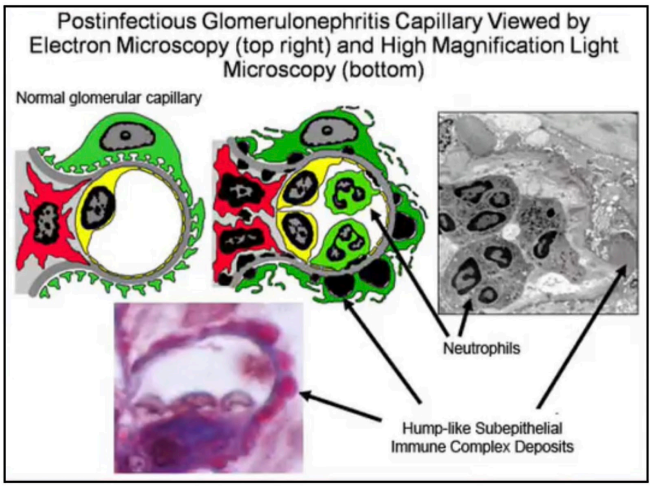


Figure 18. Image showing the microscopic view of the neutrophils and hump-like subepithelial complex deposits

- Essential Features
  - Enlarged hypercellular glomeruli
  - Subepithelial Humps
  - Granular Deposits

3. CLINICAL FEATURES

- Antistreptolysin O (ASO) is elevated
- Serum complements is decreased
- Most patients recover (95%), but a small portion (<1%) may develop rapidly progressive glomerulonephritis (RPGN)
- Clinical course is not as good in adults

B. RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)

- Also known as Crescentic Glomerulonephritis
- Severe glomerular injury
- In many cases it is idiopathic
- Does not denote a specific etiologic form of glomerulonephritis
- It may be associated with renal or extra-renal disease
- Characterized by: Crescents
  - the proliferation of parietal epithelial cells in the Bowman's capsule, and infiltration of monocytes and macrophages
  - Rapid loss of renal function
- Severe oliguria and death within weeks or months, if left untreated

Classification of RPGN

- Diseases that manifest as RPGN have been classified into 3 categories:
  - Type I- Anti-GBM Ab-Induced
    - Renal-limited
    - Goodpasture Syndrome
  - Type II - Immune Complex
  - Type III - Pauci-Immune

Type I - Anti-GBM Ab-Induced

- Characterized by presence of antibodies produced against the glomerular basement membrane (GBM)

DISEASES/CONDITIONS UNDER TYPE I	
1	**Renal-Limited** ● May involve only the kidneys ● Comprise one-fifth (⅕) of cases of RPGN
2	**Goodpasture Syndrome** ● Antibodies cross-react with the GBM in the pulmonary alveolar structure and cause lung lesions as well ○ Anti-GBM Ab cross-react with pulmonary alveolar membrane which has a clinical picture of pulmonary hemorrhage associated with renal failure ● Goodpasture's Ag - A peptide in the collagenous portion of the α3-chain of collagen type IV ○ Causes of Ab production: viruses, hydrocarbon solvents, drugs, cancer, and genetic predisposition ○ The deposits in the glomeruli are IgG and C3

Type II - Immune Complex

- Comprise ¼ of all cases of RPGN
  - Immune complex mediated
  - May be a complication of any of the immune complex nephritides like post-streptococcal GN

DISEASES/CONDITIONS UNDER TYPE II	
1	Idiopathic
2	Post-infectious
3	SLE, Henoch-Schonlein purpura, etc.

Type III - Pauci-Immune

- Does not involve immune complexes or antibodies against GBM, but most of these demonstrate the anti-neutrophil cytoplasmic antibody or ANCA (cytoplasmic ANCA and perinuclear ANCA)
- The ANCA plays a part in vasculitides. In this case, it's vasculitis of the glomerular capillaries.

DISEASES/CONDITIONS UNDER TYPE II	
1	ANCA-associated

2	Idiopathic
3	Wegener's granulomatosis (granulomatosis with polyangiitis)
4	Microscopic Polyangiitis

SUMMARY

- The nephritic syndrome is characterized by **hematuria, oliguria with azotemia, proteinuria, and hypertension**. It is most commonly caused by immune-mediated diseases due to an exogenous or endogenous antigen ○ The predominant nephritogenic antigens associated with PSGN (Post-Streptococcal Glomerulonephritis) are NAPIr (Nephritis Associated Plasmin receptor) and SPEB (Streptococcal Pyogenes Exotoxin B). These antigens cause formation of immune complexes that initiate the inflammation in the glomerulus.
- PSGN is characterized by **enlarged, hypercellular glomeruli, deposition of IgG, IgM, C3 and immune complexes** seen as glomerular deposits on IF and as subepithelial humps on EM.
- RPGN is characterized by features of nephritic syndrome but with rapid and progressive loss of renal function.
- RPGN may be caused by anti-GBM antibodies (Type 1), immune complex deposition (Type 2), or it can also occur in association with ANCAs.
- RPGN is associated with glomerular injury with necrosis and GBM breaks and subsequent proliferation of parietal epithelial cells forming crescents.
- Children with PSGN often recover; adults have poorer outcomes.
- RPGN has poorer prognosis with severe oliguria and rapid loss of renal function.

PART 4 OBJECTIVES

- Discuss the pathophysiology of the essential features of nephrotic syndrome.
- Differentiate the following as to pathogenesis, histologic morphology (LM, EM, IF), and essential clinical features:
  - Membranous glomerulopathy
  - Minimal change disease
  - Focal Segmental Glomerulosclerosis (FSGS)
  - Membranoproliferative Glomerulonephritis (MPGN)

I. NEPHROTIC SYNDROME

- Nephrotic syndrome is clinically characterized by:

1	Massive proteinuria (3.5 g or more/day)
2	Hypoalbuminemia (less than 3 g/dL)
3	Generalized edema
4	Hyperlipidemia and lipiduria

PATHOPHYSIOLOGY

- The pathophysiology of nephrotic syndrome involves the following effects:

1	Glomerular damage results in increased permeability of the glomerular capillary wall, which allows the escape of plasma proteins eventually excreted through the urine (proteinuria). The protein is mainly **albumin**.
2	Proteinuria (≥3.5 g/24 hours) depletes serum albumin leading to **hypoalbuminemia** (albumin <3g/100mL).
3	The decrease in plasma oncotic pressure causes fluid to escape into tissues causing **edema**.
4	The resultant decrease in plasma volume due to decreased oncotic pressure and escape of fluid into the interstitium causes a **reduction in the glomerular filtration rate (GFR)**.
5	The decrease in GFR stimulates aldosterone secretion and fluid retention, thus aggravating edema.
6	Increased hepatic synthesis of lipoproteins, abnormal lipid transport, and decreased lipid catabolism are responsible for **hyperlipidemia**. Since lipid also leaks through the damaged glomeruli, there is **hyperlipiduria**.
7	The increase in the synthesis of lipoproteins is thought to be a compensatory mechanism triggered by a decrease in oncotic pressure.
8	Loss of immunoglobulins (Ig) leads to susceptibility to infection and loss of anticoagulant factors leads to thrombotic/thromboembolic complications.

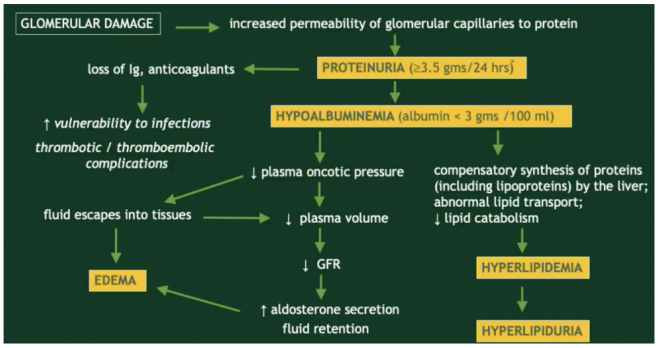


Figure 19. Pathophysiology of nephrotic syndrome

- Urinalysis: a lot of protein, fat globules, fatty casts
- The most important glomerular diseases or lesions that cause nephrotic syndrome are:

1	**Membranous Glomerulopathy**	most common cause of nephrotic syndrome in **adults**

2	**Minimal Change Disease**	most common cause in **children**
3	**Focal Segmental Glomerulosclerosis (FSGS)**	
4	**Membranoproliferative Glomerulonephritis (MPGN)**	
5	**etc.**	

Professor's Notes: Refer to the table on your textbook.

- Renal involvement in systemic disease may also manifest as nephrotic syndrome. Among these systemic diseases, the **most common systemic causes** are:
  - **DM**
  - **Amyloidosis**
  - **SLE**

A. MEMBRANOUS GLOMERULOPATHY

- It is the most common cause of nephrotic syndrome in **ADULTS**
- **Primary** (75%): PLA2R, THSD7A, Neutral endopeptidase
  - In 75% of cases, it occurs as a **primary disease**, recurring as an **autoimmune disease** caused in most cases by antibodies to a renal autoantigen
  - The **phospholipase A2 (PLA2R) receptor** is the antigen that underlies 60-70% of cases
  - Other antigens include: **Thrombospondin Type 1 Domain-containing 7A (THSD7A)** and **neutral endopeptidase or CD10**
- **Secondary**: NSAIDs, malignancy, SLE, infections, other autoimmune diseases
  - The antigens may be endogenous or exogenous
    - The endogenous antigens may be renal or nonrenal
- **Immune complex-mediated** disease
  - **Complex activation**: Antibodies bind with these antigens to form immune complexes, which activate complement and in turn results in a series of events that lead to production of inflammatory chemical mediators

Note: PLA2R, THSD7A, Neutral endopeptidase will not be asked.

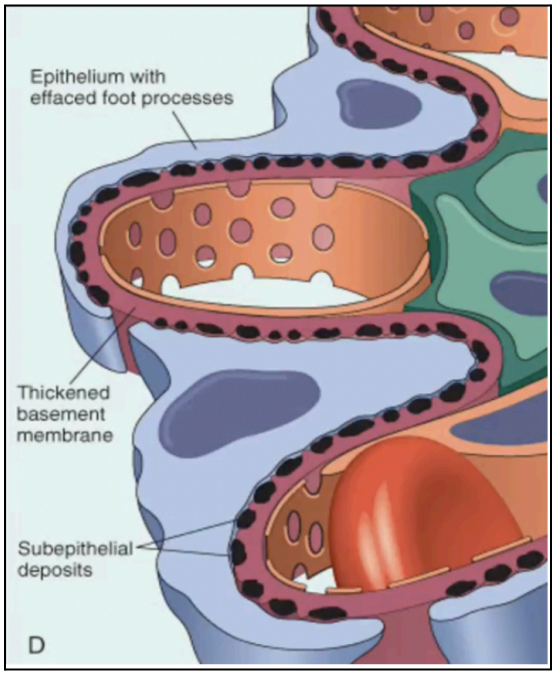
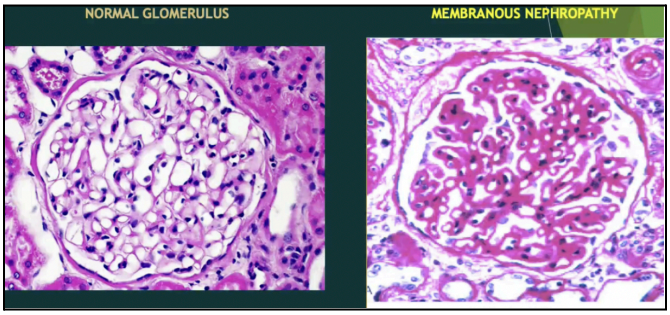


Figure 20. Membranous Glomerulopathy

- **Electron dense deposits**, containing immune complexes, are deposited in the subepithelial region (between podocytes and the basement membrane) (*represented by the black deposits in the image above*)
- **Basement membrane materials** are laid down between deposits (appearing as **spikes** on electron microscopy)
- The deposits + the additional basement membrane material are responsible for the thickening of the basement membrane, hence the term **membranous**
- There is **effacement of the foot processes**, seen here as flattening of the base of the blue-colored cells, hence the distinctive feature of membranous nephropathy as **thickening of the basement membrane**

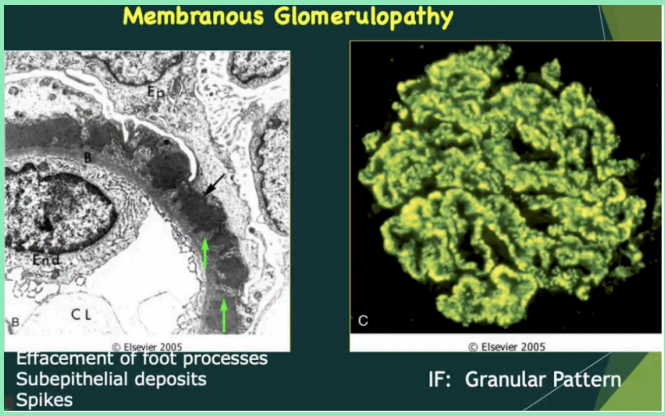
Normal vs Membranous Nephropathy (Glomerulus)



The image on the **left,** shows the **hair-thin outline** of the capillary loops	The image on the **right**, shows **thickening** of this outline

- The glomerulus is not hypercellular and there is paucity of neutrophils, monocytes, and platelets, and therefore, it has

been postulated that **complement activation** with the production of the **membrane attack complex** is responsible for the release of **inflammatory mediators** that cause **capillary wall injury**

Membranous Glomerulopathy	
	
Under the **light microscope**, there is diffuse thickening of the capillary wall	Under the **electron microscope**, this thickening is due to **subepithelial deposits** pointed at by the *black arrow*, and the laying down of basement membrane material
• Basement membrane material insinuates itself between the deposits appearing as **spikes**, shown by the *green arrows* • The **immunofluorescence** would show a **granular** pattern	

- (1) **Non-selective proteinuri**a, (2) **poor response to corticosteroids**, (3) **indolent clinical course**
    - Because of the variable course of the disease, it has been difficult to evaluate the overall effectiveness of **corticosteroids**, or other immunosuppressive therapy, in controlling the **proteinuria** or **progression** of the disease

B. MINIMAL CHANGE DISEASE

- **Most frequent cause** of nephrotic syndrome in **children**
- There are evidences that point an immunologic basis for the disease although immune deposits are absent
- Due to **autoantibodies against nephrin** – component of the slit diaphragm
- Current belief: involvement of an immune dysfunction that results in the elaboration (or production) of factors that damage **visceral epithelial cells**
    - **VISCERAL EPITHELIAL CELL INJURY (PODOCYTOPATHY)**
        - Injury to the visceral epithelial cells, with disruption of the slit diaphragm, is responsible for leakage of proteins

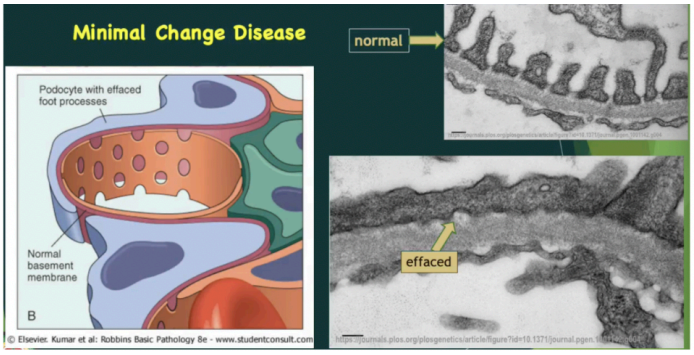


Figure 21. Minimal Change Disease

Morphology	
Under **Light Microscope**	The glomerulus would appear normal • This is the reason why the older term for minimal change disease is **Nil's disease** or **NIL**, which stands for **Nothing In Light**
Under **Electron microscope**	No deposits are seen but there is uniform or **diffuse effacement of podocytes** or foot processes (HALLMARK) • only change that can be seen

- Unlike membranous nephropathy, (1) **proteinuria (albumin) is highly selective** in Minimal Change Disease
- There is (2) **rapid response to corticosteroids, with >90%** of cases in children responding well
- (3) **Excellent long-term prognosis in children**
    - The adults are slower to respond to management or corticosteroid treatment but their long-term prognosis is also excellent

C. FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

- Sclerosis of a portion of the glomerulus (hence, segmental) in some glomeruli (hence, focal)
- Occurs in the following settings:
    - **Idiopathic**
    - In association with **HIV infection**, heroin addiction, sickle cell disease, drug toxicity, and obesity
    - Secondary event in other glomerulonephritis
    - Part of adaptive or compensatory response to loss of renal tissue
    - **Hereditary type** or hereditary nephrotic syndrome with gene mutations, involving **proteins in the slit diaphragm (nephrin and podocin)** and **podocyte cytoskeletal structures (α-actin 4)**

NEPHRIN (NPHS 1) AND PODOCIN (NPHS 2)

- Components of the slit diaphragm
- In the hereditary type, there can be gene mutations in these components
    - results to disruption of the integrity of the slit diaphragm

Professor's Notes:

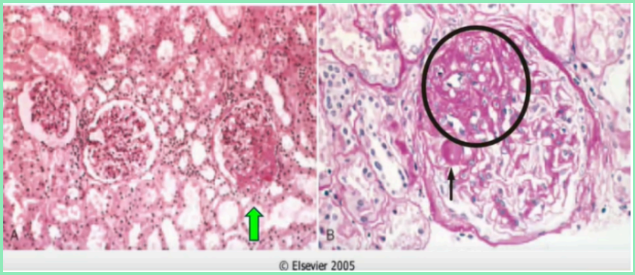
Nice to know

- TRPC6 gene
  - Widely expressed in podocytes
  - Mutation may involve disruption of podocyte function

1. MORPHOLOGY

- **Visceral Epithelial Damage**
  - hallmark of FSGS
  - Seen under EM
  - Consists of:
    - Effacement of foot processes
    - Detachment of epithelial cells
    - Denudation of underlying basement membrane
- **Hyalinosis**
  - Insudation of plasma proteins along the capillary wall
- **Sclerosis**
  - Proteins in mesangium, proliferation of mesangial cells, elaboration of more matrix
  - Under Immunofluorescence: IgM and C3 may be present in sclerotic areas or mesangium

FSGS, PAS Stain



A - LPO; Shows segmental **sclerosis** in one of the three glomeruli (green arrow)	**B -** HPO; Shows hyaline insudation and sclerosis (encircled area)

2. CLINICAL MANIFESTATIONS

- **Collapsing Glomerulopathy**
  - HIV-associated
    - Seen in about 5% to 10% of HIV individuals
  - A **severe form** of FSGS where the glomerulus collapses
- FSGS frequently manifests clinically by acute or chronic or subacute onset of nephrotic syndrome or non-nephrotic proteinuria
- There is little tendency for spontaneous remission in idiopathic FSGS
- 20% of patients follow with an unusually rapid course with intractable massive proteinuria ending in renal failure within 2 years
- Children have better prognosis than adults

QUICK SUMMARY OF HALLMARKS OR KEYWORDS	
POST-STREP GN	Subepithelial humps
RPGN	Ruptures in the GBM; crescents
MEMBRANOUS GN	Diffuse thickening of the capillary wall; "spikes"
MINIMAL CHANGE DISEASE	Uniform, diffuse effacement of foot processes
FSGS	Visceral epithelial cell damage

D. MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS (MPGN)

- Characterized by:
  - **Changes in the basement membrane** (hence, "membrano-"
  - **Proliferation of the glomerular cells** (hence, "-proliferative")
  - **Accumulation of matrix**
  - **Leukocyte infiltration**
- **Two types: Type I and Type II**
- Can manifest as:
  - Nephrotic syndrome
  - Hematuria only
  - Proteinuria only
  - Nephrotic-Nephritic

1. TYPES OF MPGN

TYPES OF MPGN	

TYPE I	• More common
	• **Deposition of immune complexes**, with activation of both classical and alternative complement pathways
	• Antigens involved may be planted (primary) or are part of the immune complexes (secondary) deposited in the glomeruli
	• **Subendothelial electron-dense deposits**
	• Two forms:
	  ○ **Primary/Idiopathic MPGN**
	  ■ Antigens are believed to be derived from Hepatitis B and C
	  ○ **Secondary MPGN**
	  ■ Associated with chronic immune disorders like SLE, alpha-1 antitrypsin deficiency, and malignant disease, particularly lymphoid tumors

TYPE II	• AKA **Dense Deposit Disease** • Involves persistent activation of the complement • Deposition of **unknown dense material within the GBM proper (specifically, lamina densa)**

	• >70% of patients have a circulating autoantibody (C3 nephritic factor or C3Nef) that binds to the alternative pathway C3 convertase
	  ○ This stabilizes the convertase favoring persistent C3 activation
	  ○ Recall that there are inhibitors of the alternative complement pathway (e.g. Factor H and related proteins: Factor I, CD35 and CD46)
	  ■ Mutations in the genes encoding for these factors → lead to dysregulation of the alternative complement pathway

2. CLINICAL FEATURES

CLINICAL FEATURES OF MPGN	
TYPE I	**TYPE II or DENSE DEPOSIT DISEASE**
Primary MPGN: diagnosed for **adolescents** or **young adults** **Secondary MPGN:** more common in **adults**	Affects primarily **children** and **young adults**
Presents **nephrotic** syndrome and a **nephritic** component	Presents with **nephritic** syndrome with **hematuria** and/or **nephrotic** syndrome with **proteinuria**
Follows a **slow progression**, but **unremitting** course. Some develop **rapidly progressive glomerulonephritis (RPGN)** **50% develop chronic renal failure within 10 years**	Poor prognosis with >50% of the patients **progressing to end-stage renal disease (ESRD)** **High recurrence in transplant recipients (90%)**

3. MORPHOLOGY

LIGHT MICROSCOPE

- Similar for Types I and II
- **Large, hypercellular** glomeruli
  - due to proliferation of the following:
    - Mesangial cells
    - Endothelial cells
    - Leukocytes
- **Increased mesangial matrix**
- **Lobular appearance/architecture** of the glomerulus
- **TRAM-TRACK appearance due to thickened GBM (MUST KNOW)**
  - Due to mesangial proliferation → Then, their processes insinuate themselves into the basement membrane
  - Presents with double line or contour of the basement membrane
    - **will look like a "tram track"**

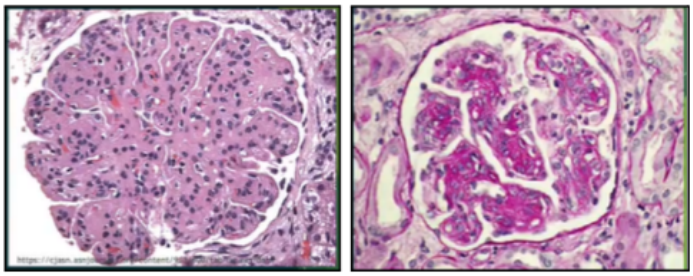


Figure 22. (L) Histologic sections using the PAS stain from a case of MPGN. (R) proliferation of mesangial cells with increased mesangial matrix and accentuation of the lobular architecture of the glomerulus.

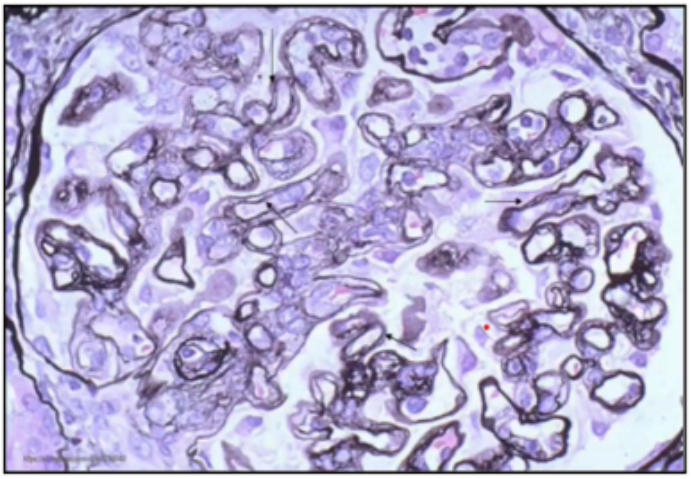


Figure 23. Type I and II MPGN will show this double contour or TRAM-TRACK appearance caused by the duplication of the glomerular basement membrane (GBM) with interposition of the mesangial cell processes shown as thin black arrows

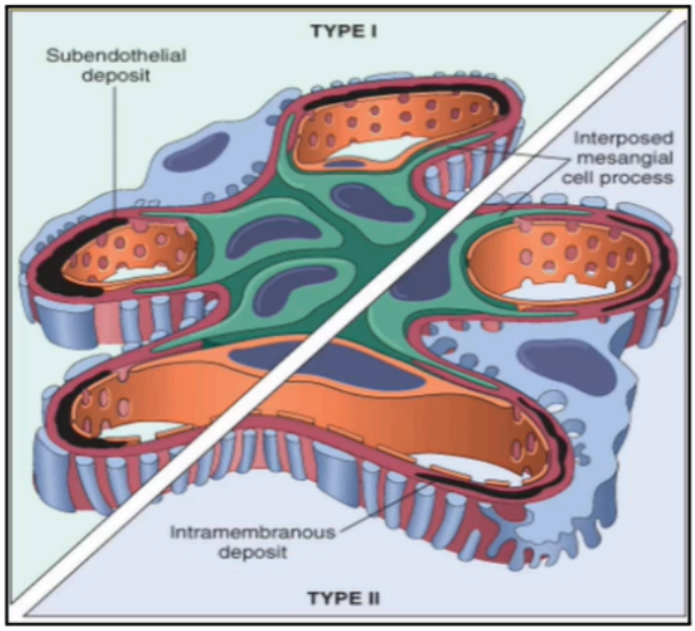
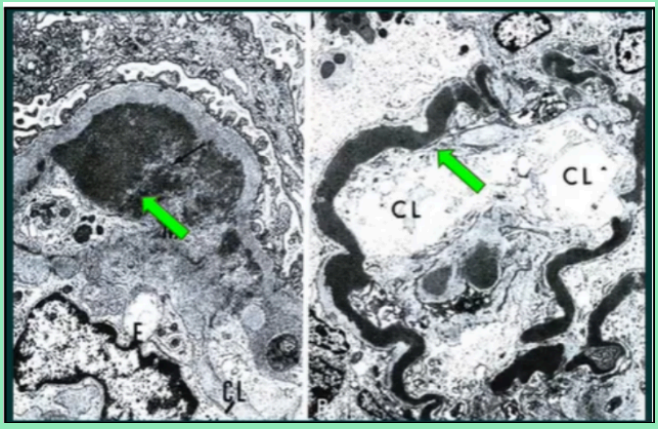


Figure 24. Diagram showing what happens in Type I and Type II MPGN (GBM has a double contour or TRAM-TRACK appearance)

ELECTRON MICROSCOPE (EM)



TYPE I MPGN	TYPE II/DDD
Subendothelial deposits	Lamina densa is electron-dense with packing of unknown material

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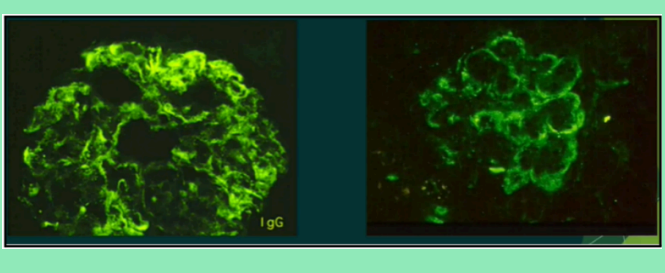


TYPE I MPGN	TYPE II/DDD
Granular pattern	Linear and Granular pattern

COMPARISON OF LM, IF, AND EM FINDINGS			
	LM	**IF**	**EM**
POST STREP GN	Enlarged, hypercellular	Granular	Subepithelial humps
RPGN	Crescents	Anti-GBM: Linear Post-infectious: Granular Pauci-immune: none	Ruptures in the GBM
MINIMAL CHANGE DISEASE	Normal-looking	(-)	Diffuse effacement of foot processes
MEMBRANOUS GN	Diffuse thickening of the capillary wall	Granular	Subepithelial electron dense deposits; "spikes"
FSGS	Focal, segmental sclerosis	Non-diagnostic findings	Degeneration and disruption of visceral epithelial cells
MPGN	Thickened GBM ("tram track appearance"); Hypercellular; ↑Mesangial Matrix	Type I - granular (IgG and C3) DDD (Type II) - granular or linear (C3)	Type I - subendothelial electron dense deposits DDD (Type II) - electron dense deposit in lamina densa of GBM

SUMMARY

- **Nephrotic syndrome** is a manifestation of glomerular diseases where the increased permeability of glomerular capillaries to protein gives rise to heavy proteinuria which leads to hypoalbuminemia and initiates a series of events that give rise to edema, hyperlipidemia and hyperlipiduria.
- **Membranous nephropathy** is caused by autoantibodies to glomerular antigens; it is characterized by granular subepithelial deposits of antibodies with GBM thickening and loss of foot processes but little or no inflammation. The disease has poor response to steroid therapy.

- **Minimal change disease**, the most frequent cause of nephrotic syndrome in children, is characterized by effacement of the foot processes without antibody or immune complex deposits. Response to steroid therapy is good.
- **FSGS** may be idiopathic or secondary. In some cases, mutations in genes that encode for components of the slit diaphragm and podocyte cytoskeletal structures have been identified. The hallmark of FSGS is visceral epithelial cell damage. FSGS is often resistant to therapy and may progress to ESRD.
- **MPGN Type I** is caused by immune complex deposition in both mesangial regions and capillary walls, followed by activation of the complement pathway. It is characterized by subendothelial electron-dense deposits. It may be associated with systemic infections.
- **DDD (formerly called MPGN Type II)** is due to persistent activation of the alternative complement pathway and is characterized by electron-dense material in the lamina densa of the GBM. It is associated with acquired or genetic dysregulation of the alternative complement pathway.
    - MPGN Type I and DDD have similar LM findings and are best differentiated using EM and IF.

PART 5 OBJECTIVES

- Describe the main defect and the characteristic morphologic findings of the isolated abnormalities.
- Describe the morphologic features of chronic glomerulonephritis.
- Describe the distinctive pathologic features of lupus nephritis and diabetic nephropathy.

I. OTHER GLOMERULAR DISEASES

1	**Glomerular disease with Isolated hematuria / Isolated Urinary Abnormalities*** (mainly IgA Nephropathy)
2	**Chronic Glomerulonephritis**
3	**Glomerulonephritis associated with DM and SLE**
*There will be a mention of **Alport Syndrome** and **Benign Familial Hematuria**	

A. GLOMERULAR DISEASE WITH ISOLATED HEMATURIA (OR ISOLATED URINARY ABNORMALITIES)

1	**IgA Nephropathy (Berger Disease)**
2	**Alport's Syndrome**
3	**Benign Familial Hematuria**

1. IgA NEPHROPATHY (BERGER DISEASE)

- The most common cause of glomerulonephritis worldwide.
- Also called **Berger Disease**
- Presents with recurrent gross or microscopic hematuria
- Characterized by **IgA deposits in the mesangium**
- It may occur as:

1	**Isolated disease**
2	**Association with Henoch-Schönlein purpura**
3	**Secondary to liver and intestinal diseases**

1. PATHOGENESIS

- A multi-hit is favored in the pathogenesis of IgA Nephropathy.
- IgA are glycosylated proteins. They become glycosylated or sugars are attached to them prior to the release from the B-cells.
- Genetic/acquired abnormality in immune regulation → increased IgA synthesis in response to exposure to environmental antigens → formation of IgA-containing immune complexes → complexes are trapped in glomeruli → activation of alternative complement pathway → glomerular injury

MECHANISMS

- Circulating immune complex deposition
- Activation of alternative complement pathway

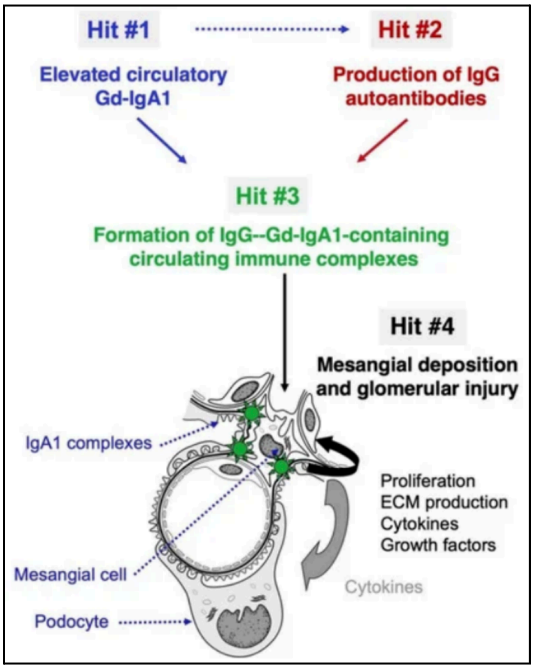


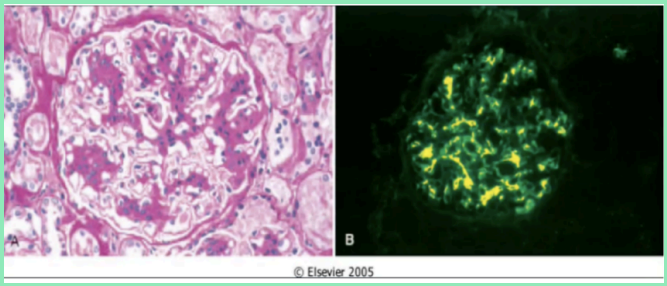
Figure 25. Multi-hit Etiology of IgA Nephropathy

Hit # 1	When there is a hereditary or acquired defect in the glycosylation thus producing abnormal IgA.
Hit # 2	Formation of antibodies against this abnormal IgA.
Hit # 3	When the abnormal IgA and antibodies formed complexes in the glomerulus specifically in the mesangium either by in-situ deposition or by trapping of circulating immunocomplexes.
Hit # 4	• The mesangial immune deposits then activate mesangial cells to proliferate, produce increased amounts of extracellular matrix and secrete numerous cytokines and growth factors.

	• These secreted mediators may not only participate in further mesangial cell activation but may also recruit inflammatory cells into the glomeruli. • The recruited leukocytes contribute to glomerular injury and to our reparative response which can improve opsonization or removal of the immune complexes. • The deposited IgA and IgA-containing immune complexes activate the complement system via the common Alternative complement pathway. Hence, the presence of C3 and the absence of C1, Q, and C4 in the glomeruli in the typical manifestation of this disorder

2. MORPHOLOGY

- **LM:** May be normal
- Mesangial widening and proliferation
- **IF:** Mesangial deposition of IgA
- **EM:** Mesangial electron dense deposits



Microscopic View of the Mesangial Cells in PAS Stain and Immunofluorescence

PICTURE A PAS Stain	**PICTURE B** Immunofluorescence
• Mesangial proliferation • Increased mesangial matrix	IgA deposits in the mesangium

3. EPIDEMIOLOGY AND CLINICAL FEATURES

- The disease may be presented at any age but most commonly older children & young adults are affected.
- Many patients presents with gross hematuria after respiratory infection
- LESS COMMONLY in GIT or Urinary tract infection
- 30-40% have only microscopic hematuria with or without proteinuria.
  - The hematuria typically lasts for several days and then subsides only to return every few months.
  - The subsequent course is highly variable, many patients maintain normal renal function for decades.
  - A slow progression to Chronic Renal Failure occurs in just 15-40% of cases over 20 years.
  - Onset in older age, heavy proteinuria, hypertension, and extent of glomerulus sclerosis and biopsy are clues to an increased risk of progression.

1. ALPORT'S SYNDROME

- Defective GBM synthesis due to production of abnormal collagen type IV
- Alternating thin and thick areas in the GBM
- With nerve deafness and eye disorder
- **X-linked: AR or AD (Must know!)**

2. BENIGN FAMILIAL HEMATURIA

- Diffuse thinning of the GBM (Thin BM Disease)
- Defective genes encoding α3 and α4 chains of type IV collagen

Professor's Notes:

- BOTH Alport & Benign Familial Hematuria involve abnormal collagen formation resulting in alternating thin and thick areas in the GBM (Alport syndrome) and diffuse thinning of the GBM (Benign Familial Hematuria)
- BOTH Alport & Benign Familial Hematuria present with hematuria

B. CHRONIC GLOMERULONEPHRITIS

- Nearly all forms of acute glomerulonephritis have a tendency to progress to chronic glomerulonephritis.
- Characterized by irreversible and progressive glomerular and tubulointerstitial fibrosis ultimately leading to a reduction in the GFR and retention of uremic toxins.
  - If disease progression is not halted with therapy, thenet results are:

1	Chronic kidney disease
2	End-stage renal disease
3	Cardiovascular disease

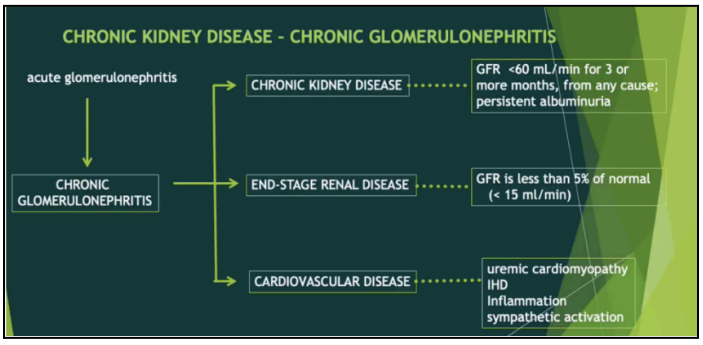


Figure 26. Progression of Chronic Glomerulonephritis

- Chronic glomerulonephritis is where most of the glomerular diseases eventually end, although in some cases there is no antecedent history of any of these diseases.
- These cases may represent the end result of a relatively asymptomatic form of glomerulonephritis that progresses to uremia.

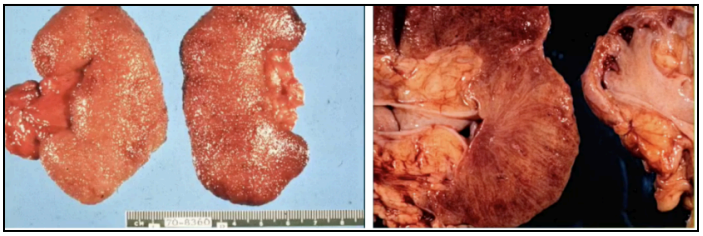


Figure 27. Gross Findings in Chronic Glomerulonephritis

HISTOLOGIC FINDINGS

- In the early stages, the glomeruli may still show the histologic features of the underlying disease, but eventually there is:
  - **Hyaline obliteration of the glomeruli**
  - **Tubular atrophy (thyroidization)**
  - **Interstitial fibrosis**
  - **Leukocytic infiltration**
  - **Arterial and arteriolar sclerosis** (associated with hypertension)
    - Hypertension is almost always an accompaniment of chronic GN, one also sees arterial and arteriolar sclerosis.

HISTOLOGIC FINDINGS IN CHRONIC GN	
1	Hyaline obliteration of the glomeruli
2	Tubular atrophy (thyroidization)
3	Arterial and arteriolar sclerosis
4	Interstitial fibrosis
5	Leukocytic infiltration

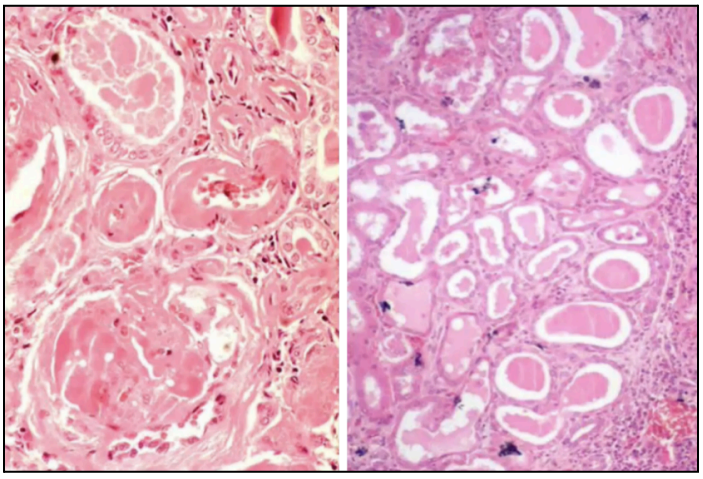


Figure 28. Gross Findings in Chronic Glomerulonephritis

📖 CAUSES OF PRECEDENT GLOMERULAR CONDITIONS	
1	RPGN
2	FSGS
3	Membranoproliferative GN
4	Membranous GN
5	IgA Nephropathy
6	Poststreptococcal GN

DIALYSIS CHANGES	
1	Arterial intimal thickening
2	Deposition of calcium oxalate crystals in tubules & interstitium
3	Acquired cystic disease
4	Increased risk for renal adenomas & adenocarcinomas

- 📖 Dialysis changes: Since most patients with CGN undergo dialysis, there are changes in the kidneys that are unrelated to the primary disease.

📖 UREMIC COMPLICATIONS	
1	Uremic pericarditis
2	Gastroenteritis
3	Secondary hyperparathyroidism
4	Nephrocalcinosis
5	Left ventricular hypertrophy (due to HPN)
6	Uremic pneumonitis – diffuse alveolar damage

- 📖 Uremic complications: These changes are seen not just in CGN but in other forms of chronic renal failure with uremia.

C. GLOMERULAR LESIONS IN SYSTEMIC DISEASE

1	Systemic Lupus Erythematosus (SLE)
2	Diabetes Mellitus (DM)
3	📖 Amyloidosis

1. SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- Characterized by a vast array of autoantibodies, particularly antinuclear antibodies, in which injury is caused mainly by deposition of immune complexes and binding of antibodies to various cells and tissues in the body.
- These are antibodies to double stranded DNA and the so-called Smith antigen. These findings are virtually diagnostic of SLE.
- Up tp 50% have clinically significant renal disease
- Lesions result from deposition of immune complexes on the glomerular basement membrane in the mesangium and sometimes throughout the glomerulus is seen in lupus nephritis.

OCCURS EITHER AS:

1	In situ immune complex deposition

2	Deposition of preformed circulating immune complexes

- According to the currently accepted classifications, 6 patterns of glomerular diseases are seen in SLE.
  - It should be noted that there is some overlap between these patterns
- 📖 Kidney is involved in 60% - 70% of cases
- 📖 Deposition of immune complexes in blood vessels, kidneys, connective tissue & skin → acute necrotizing vasculitis

Professor's and Editor's Notes:

- The details of how SLE affects the kidneys is more extensively explained in Robbin's.
- Dra. De La Fuente only briefly mentioned the different classes of SLE renal involvement and does not expect us to fully memorize them, but asked to only take note Class IV, the most common and severe

PATTERNS OF RENAL INVOLVEMENT	
Class I	Minimal Mesangial Lupus Nephritis
Class II	Mesangial Proliferative Lupus Nephritis
Class III	Focal Lupus Nephritis
Class IV	Diffuse Proliferative Lupus Nephritis
Class V	Membranous Lupus Nephritis
Class VI	Advanced Sclerosing Lupus Nephritis

Class I: Minimal Mesangial Lupus Nephritis

- Normal by light microscopy
- Least common

Class II: Mesangial Proliferative Lupus Nephritis

- Proliferation of mesangial cells and immune complex deposition without involvement of the glomerular capillaries

Class III: Focal Lupus Nephritis

- Involvement of < 50% of glomeruli

Class IV: Diffuse Proliferative Lupus Nephritis

- **Most common and most severe**
- proliferation of endothelial, mesangial and epithelial cells (crescents)
- **"wire loop"** lesion
  - due to circumferential thickening of the capillary walls due to subendothelial deposits

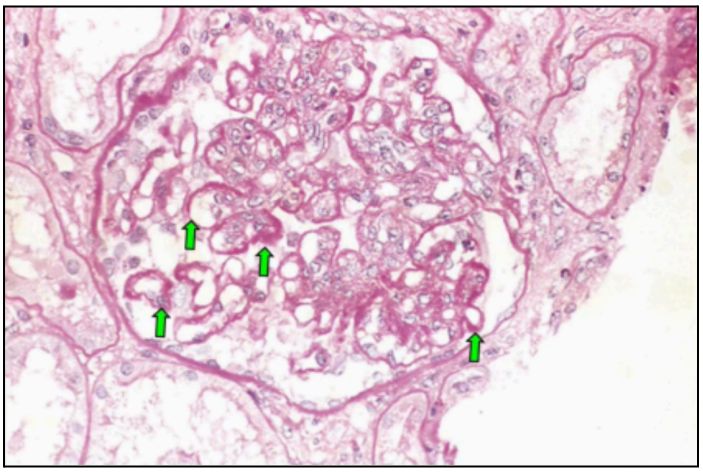


Figure 29. Wire loop lesions (green arrows)

Class V: Membranous Lupus Nephritis

- Diffuse thickening of capillary wall caused by subendothelial deposits

Class VI: AdvancedSclerosing Lupus Nephritis

- Global sclerosis of >= 90% of glomeruli

2. DIABETES MELLITUS (DM)

- Nephropathy is linked with generalized diabetic microangiopathy
- Metabolic defects are responsible for:
  - Biological changes in the GBM:
    - Advanced glycosylated end-products (AGE)
      - ➢ Form cross-linkages with collagen molecules in the GBM (structural & functional defects in the GBM and enhanced protein deposition)
      - ➢ Bind to receptors in many cells (increased synthesis of ECM)
  - Hemodynamic changes also with glomerular hypertrophy
    - Similar to compensatory hypertrophy
  - Glomerular lesions are associated with 3 glomerular syndromes:
    - non-nephrotic proteinuria
    - Nephrotic syndrome
    - CRF

GLOMERULAR LESIONS IN DIABETIC NEUROPATHY	
1	Capillary Basement Thickening
2	Diffuse Mesangial Sclerosis
3	Nodular Glomerulosclerosis
4	Renal Atherosclerosis/Arteriosclerosis
5	Pyelonephritis, Necrotizing Papillitis

1. Capillary Basement Thickening

- Seen in almost all cases of diabetic neuropathy

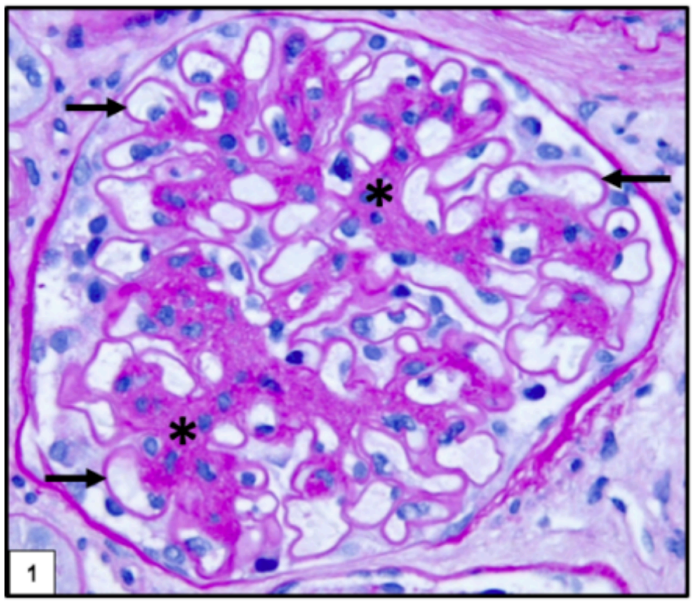


Figure 30. Capillary basement membrane thickening (black arrow) and diffuse mesangial sclerosis (asterisk)

2. Diffuse Mesangial Sclerosis

- Diffuse increase in the mesangial matrix
- Progressive expansion of the mesangium correlates well with the deteriorating renal function

3. Nodular Glomerulosclerosis

- Also known as intercapillary glomerulosclerosis and **Kimmelstiel-Wilson lesion**
- ball-like deposits of laminated matrix
- Enlarged and compressed capillaries leads to renal ischemia and tubular atrophy
  - Fibrin or hyaline cap
  - Capsular drop

4. Renal Atherosclerosis/Arteriosclerosis

- Also contribute to the renal dysfunction in patients with diabetes

5. Pyelonephritis, Necrotizing Papillitis

- Acute or chronic inflammation of the kidneys that usually begins in the interstitial tissue and spreads to affect the tubules

3. AMYLOIDOSIS

- Renal involvement in the most serious form
- Deposits in:
  - Glomeruli
  - Interstitial peritubular tissue
  - arteries and arterioles
- Most commonly, renal amyloid is light chain (AL) or AA type

SUMMARY

- **IgA nephropathy** is characterized by **mesangial deposits of IgA**-containing immune complexes
  - Its pathogenesis involves the production of abnormal IGA, deposition of immune complexes and activation of alternative complement pathway leading to mesangial proliferation, ECM production and activation of cytokines and growth factors.
  - It is a frequent cause of both isolated and frequently recurrent hematuria commonly affecting children and young adults
- **Alport's syndrome** and **Benign Familial Hematuria** both present as gross and/or microscopic hematuria
  - Both involve abnormal collagen formation resulting in alternating thick and thin areas in the GBM in Alport's syndrome and diffuse thinning of the GBM in Benign Familial Hematuria
- **Chronic glomerulonephritis** is characterized by symmetrically contracted kidneys with granular cortical surfaces, thinned out cortex, obliteration of the glomeruli, tubular atrophy, interstitial fibrosis and chronic inflammation
- **Lupus nephritis** is caused by deposition of the immune complexes in the glomerulus.
- There are 6 patterns of glomerular pathology, the most common and the most severe of which is the **Diffuse Proliferative Lupus Nephritis** characterized by the **"wire-loop"** lesion.
- The glomerular lesions in DM are linked with the generalized microangiopathy that accompanies the disease.
  - The lesions include capillary basement thickening, diffuse mesangial sclerosis and the **Kimmelstiel-Wilson lesion**.

PART 6 OBJECTIVES

- Discuss the pathogenesis of Acute Tubular Injury.
  - Cite the main causes.
  - Cite the 2 important factors in its pathogenesis
- Differentiate acute and chronic tubulo-interstitial (T-I) nephritis in terms of the histologic features.
- Discuss the pathogenesis of pyelonephritis
  - Name the predisposing factors
  - Explain vesico-ureteral reflux
- Differentiate acute and chronic pyelonephritis in terms of their morphologic features.
- Discuss the pathogenesis of drug-induced nephropathy (NSAID nephropathy and analgesic nephropathy).
- Briefly describe the 3 types of urate nephropathy.
- Enumerate the conditions that can lead to hypercalcemia and nephrocalcinosis.
- Discuss how multiple myeloma can cause nephropathy.

I. DISEASES OF THE TUBULES AND INTERSTITIUM

Acute Tubular Injury (ATI)	• Ischemic ATI
	• Toxic ATI

Tubulointerstitial Nephritis	• Pyelonephritis - Acute & Chronic • Nephritis induced by drugs and toxins • Others

A. ACUTE TUBULAR INJURY (ATI)

- Characterized by **acute renal failure** and often but not invariably, morphologic evidence of tubular injury in the form of **necrosis of the tubular epithelial cells**
  - Destruction of tubular epithelial cells
  - Acute diminution or loss of renal function
  - Acute tubular epithelial cell injury with acute reduction in renal function
- Used to be called **Acute Tubular Necrosis (ATN)**
  - Since necrosis is sometimes not visible, the term "Acute Tubular Injury" is preferred.
- **Most common cause of acute kidney injury or acute renal failure (ARF)**

1. CAUSES OF ATI

- ATI is not a single disease. It is a **clinico-pathologic entity** that may be caused by a variety of conditions:

1	• Ischemia
2	• Direct toxic injury to tubules by endogenous and exogenous agents (drugs, myoglobin, hemoglobin, radiation, dyes)
3	• Acute tubulointerstitial nephritis - hypersensitivity reaction to drugs *[Batch 2027]*
4	• Urinary obstruction *[Batch 2027]*

2. CLASSIFICATION OF ATI

- ATI may be classified based on the mechanisms or cause of the tubular injury:

1	**Ischemic**	Due to decreased or interrupted blood flow secondary to decreased blood volume or to diseases that involve blood vessels like polyangiitis, malignant hypertension, thrombosis, microangiopathies, and DIC.
2	**Nephrotoxic / Toxin-induced / Direct Toxic Injury**	Endogenous agents (e.g., myoglobin, hemoglobin, monoclonal light chains, bile & bilirubin)
		Exogenous agents (e.g., drugs, radiocontrast dyes, heavy metals & organic solvents)
3	**Mixed**	

3. PATHOGENESIS OF ATI

TWO IMPORTANT FACTORS IN ATI PATHOGENESIS		
1	**Tubule Cell Injury**	Mainly leads to the **death of tubular cells**, either by **apoptosis** or **necrosis**, and the **detachment** of these cells, causing **obstruction in the renal tubules**.
		• Cells detach → luminal tubule obstruction → increased intratubular pressure & decreased tubular flow → decreased GFR and oliguria • Fluid leaks into interstitium → interstitial edema → increased interstitial pressure → further tubular damage
2	**Persistent & Severe Disturbances in Blood Flow**	The major hemodynamic disturbance is **vasoconstriction** mediated by various mechanisms
		Intrarenal vasoconstriction → **decreased GFR and oxygen delivery to the tubules**

Handout:

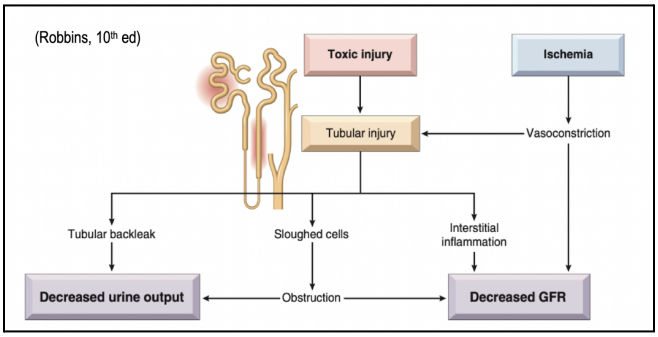


Figure 20.21 Postulated sequence in ischemic or toxic acute tubular injury. *GFR,* Glomerular filtration rate. *[Robbins 10th ed., pg. 924]*

Batch 2027:

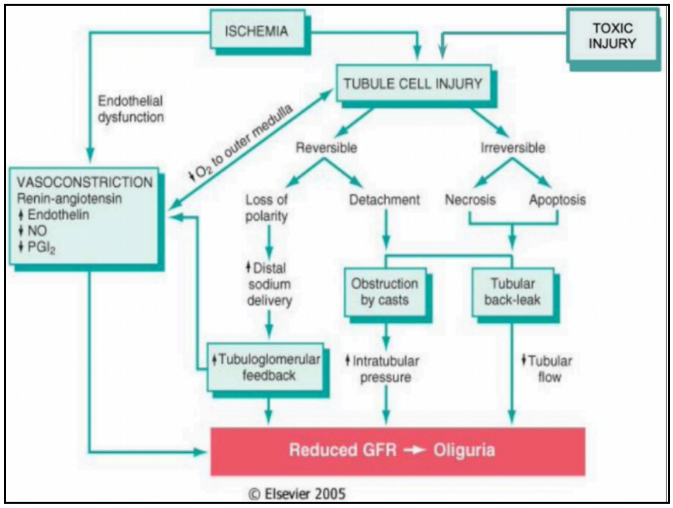


Figure 31. Pathogenesis of ATI.

- Both **ischemia** and **toxic injury** cause **tubule cell injury.**

- When exposed to ischemic stress, tubular cells are prone to loss of polarity and even detachment of viable cells due to destruction of key structural anchors.

- Both **apoptosis** and **necrosis** can be detected in **ATN**.
- With **detachment** and **cell death**, **loss of tubular epithelial barrier o**ccurs.
  - This leads to some reabsorption of filtered solutes into the circulation leading to increase in substances used to estimate GFR including creatinine and inulin.
  - This is known as tubular backleak and accounts for around 10% of the decrease in GFR.
- **Intrarenal vasoconstriction**, which results in both reduced glomerular blood flow and reduced oxygen delivery to the functionally important tubules in the outer medulla (thick ascending limb and straight segment of the proximal tubule).
- Several **vasoconstrictor pathways** have been implicated, including the **renin-angiotensin system**, stimulated by decreased sodium in the tubules as a result of decreased blood pressure, and sublethal endothelial injury, leading to **increased release of vasoconstrictor endothelin** and **decreased production of the vasodilators nitric oxide and prostacyclin (prostaglandin I2)**.
- **Pathogenesis emphasized:**
  - Tubular cell detachment → luminal obstruction → increased tubular pressure → decreased GFR
  - Interstitial edema → worsens tubular injury
  - Persistent blood flow disturbances

4. MORPHOLOGY OF ATI

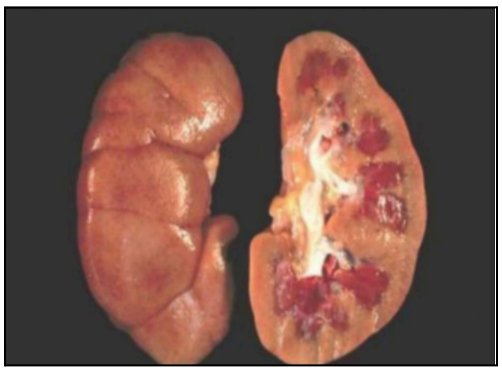


Figure 32. Gross image of a kidney with Acute tubular Injury.

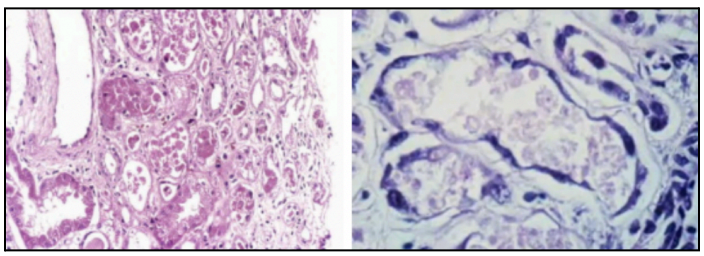
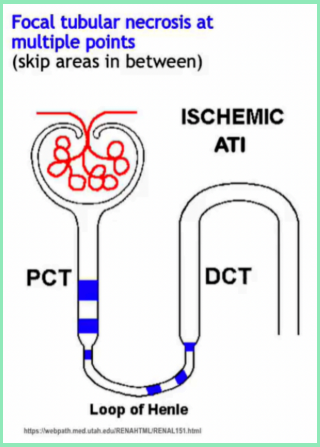
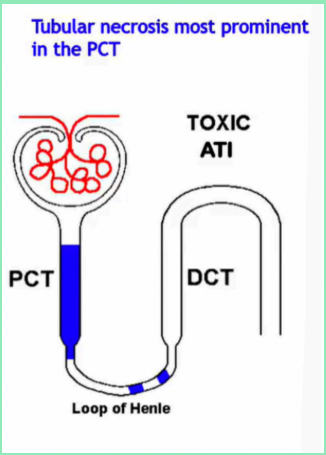


Figure 33. Microscopic images of Acute Tubular Injury.

G	• A kidney with acute tubular injury appears **swollen with a pale cortex and relatively darker medulla.**
M	• **Necrotic** and **detached** tubular epithelial cells (may be patchy) • **Swollen**, **vacuolated** epithelial cells

MORPHOLOGY OF ISCHEMIC VS. NEPHROTOXIC ATI

ISCHEMIC ATI	NEPHROTOXIC ATI
	

• **Tubulorrhexis** (ruptured glomerular basement membrane)
• **Casts** occluding tubular lumen
  ○ Eosinophilic hyaline casts
  ○ Pigmented granular casts "**Muddy brown granular casts**"
• **Interstitial Edema**
• **Leukocytes in vasa recta**	

• Characterized by **multiple points of necrosis** with **skip areas** in between.	• Characterized by **tubular continuous necrosis** that is most prominent at the **proximal convoluted tubule** • **Casts** also present
***[Batch 2027]* Editor's Note**: The lecturer enumerated the similarities (2nd row) between the morphology of ischemic and nephrotoxic ATI. HOWEVER, these enumerated features are only listed under ischemic ATI on the handout provided.	

5. CLINICAL COURSE OF ATI

- The clinical course of acute tubular injury follows three major stages:

1. INITIATION PHASE

- Occurs during the first **36 hours after the start of injury**
- Clinical picture is dominated by the inciting medical, surgical or obstetric event
  - But there is already a **slight decrease in urine output and increase in BUN**
- At this point, **sublethal injury** has occurred.

- If the inciting event is removed, complete recovery would ensue.
- If not, this is followed by an **extension phase**, which is characterized by significant cell necrosis, desquamation, inflammation, and tubular lumen obstruction

2. MAINTENANCE PHASE

- This stage is reached after the **irreversible renal parenchymal injury** has been established.
- Clinically presents as **oliguria (40 - 400 mL/day)**, with **signs of uremia**
- Salt and water overload, elevated BUN, hyperkalemia, and metabolic acidosis *[Batch 2027]*

3. RECOVERY PHASE

- Ushered in by **regeneration** of tubular epithelial cells
- **Increasing urine output** (diuresis; may reach up to 3 L/day) with **loss of sodium and potassium**
  - Hypokalemia *[Batch 2027]*
- BUN and creatinine slowly return to normal

B. TUBULOINTERSTITIAL NEPHRITIS

- Inflammatory injuries of the tubules and interstitium
- Often **insidious** in onset and are principally manifested by **azotemia**
- Can be **acute or chronic**
- **Distinguished** from glomerular diseases by:
  - **Absence of nephrotic or nephritic syndrome** (early)
  - **Presence of defects in tubular function:**
    - Inability to concentrate urine (evidenced clinically by polyuria or nocturia)
    - Salt wasting
    - Decreased ability to secrete acids
    - Defects in tubular reabsorption & secretion
  - In **advanced stages**, it may be **clinically difficult to differentiate from other renal diseases,** including glomerular diseases.

CAUSES OF TUBULOINTERSTITIAL NEPHRITIS	
1	• **Pyelonephritis** - acute & chronic
2	• **Nephritis induced by drugs & toxins** ○ Acute drug-induced interstitial nephritis ○ Analgesic nephropathy
3	• Others

ACUTE	CHRONIC
Rapid clinical onset	Mononuclear leukocytes
Interstitial edema	**Interstitial fibrosis**
Neutrophils and eosinophils in interstitium and tubules	**Widespread tubular atrophy**
Focal tubular necrosis	

***Note**: Acute and chronic tubulointerstitial nephritis are best differentiated by histologic findings.*

1. PYELONEPHRITIS

- **Inflammation** affecting the **tubules**, **interstitium**, and **renal pelvis**
- May be acute or chronic
  - **Acute** – bacterial infection (UTI)
  - **Chronic** – bacterial infection + other factors
    - Vesicoureteral reflux and urine outflow obstructions
- **Most cases** caused by **gram-negative bacilli (>85%)** from the fecal flora in most patients
  - *E. coli*
  - *Proteus*
  - *Klebsiella*
  - *Enterobacter*
- **Routes of infection to the kidneys:**
  - **Hematogenous**
  - **Ascending (more common)**

1. ASCENDING INFECTION

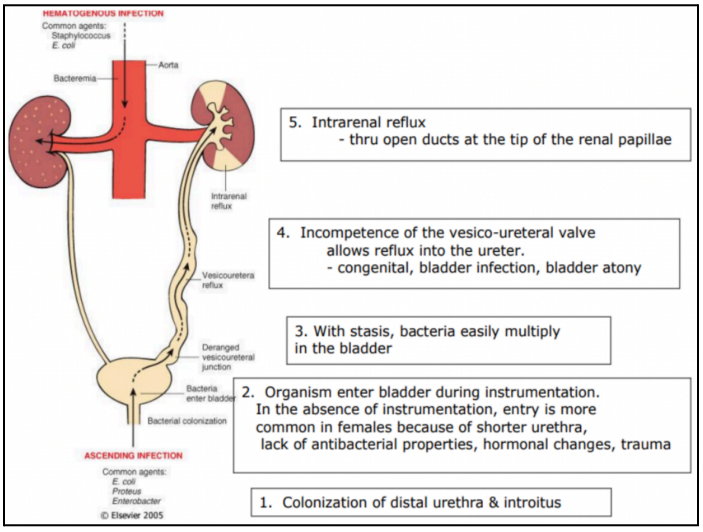


Figure 34. Ascending Infection in Pyelonephritis

1	• Colonization of distal urethra & introitus
2	• **Organism enter bladder during instrumentation** ○ In the absence of instrumentation, entry is more common in females because of shorter urethra, lack of antibacterial properties, hormonal changes, and trauma
3	• With status, **bacterial easily multiplies** in the bladder
4	• **Incompetence of the vesico-ureteral valve** allows reflux into the ureter ○ congenital, bladder infection, bladder atony
5	• **Intrarenal reflux** ○ Through open ducts at the tip of the renal papillae

- The important **factors that predispose** the movement of organisms from the bladder to the kidneys are:
  - **Urinary obstruction & stasis**
  - **Vesico-ureteral reflux**
  - **Intrarenal reflux**

2. VESICOURETERAL REFLUX

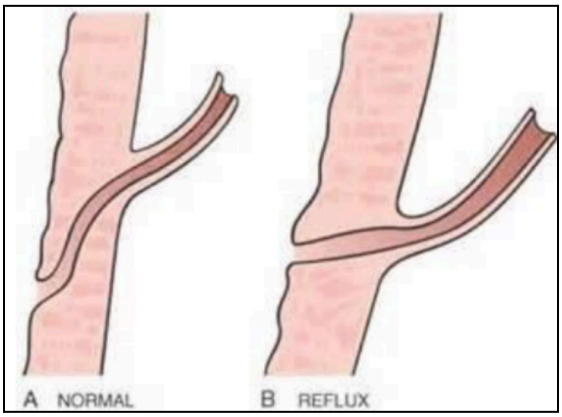


Figure 35. Vesicoureteral reflux

- Reflux of bladder urine into the ureters

CAUSES OF VESICOURETERAL REFLUX	
1	• **Congenital absence or shortening of the intravesical portion of the ureter** ○ Ureter is not compressed during micturition
2	• **Bladder infection** - accentuates reflux
3	• **Persistent bladder atony** due to spinal cord injury

2. ACUTE PYELONEPHRITIS

1. Morphology of Acute Pyelonephritis

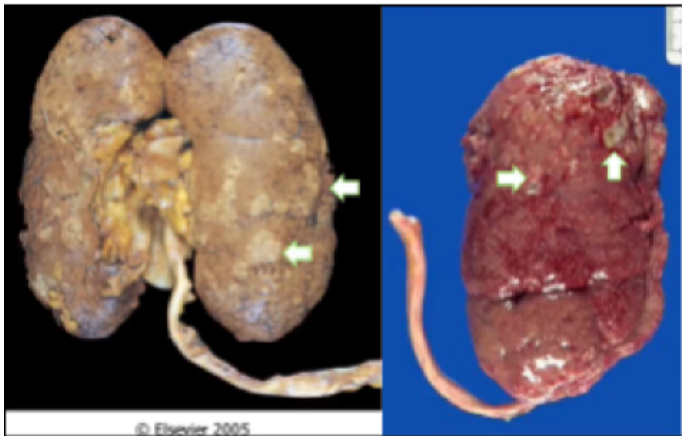


Figure 36. Abscesses in Acute Pyelonephritis (Gross)

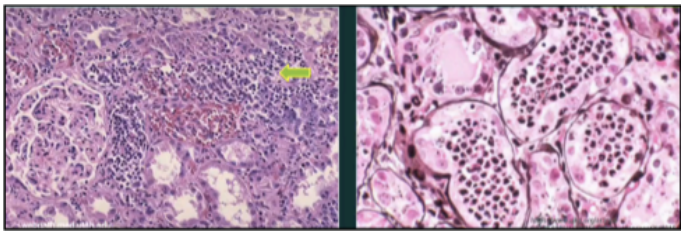


Figure 37. Hallmarks of Acute Pyelonephritis (Microscopic)

G	• **Abscesses** are seen in the cortical surfaces and cut sections in acute pyelonephritis pointed out by the arrows.
M	• **Hallmarks** ○ Foci of patchy interstitial **suppurative inflammation** → abscesses ○ Intratubular aggregates of **neutrophils** ○ Tubular **necrosis**

2. Complications of Acute Pyelonephritis

1	**Papillary necrosis**	• In diabetics and those with UTI • Usually bilateral • Necrosis of tips or distal ⅔ of the pyramids
		• The **renal medulla** and **papilla** are particularly vulnerable to ischemic necrosis because of the peculiar arrangement of their blood supply and the hypertonic environment. • Even when healthy, they exist in a **state of relative hypoxia** because of the slow rate of blood flow in the vasa recta • Thus, conditions that further reduce blood flow may produce **ischemic necrosis.**
2	**Pyonephrosis**	• Condition that arises when **pus is not drained** and fills the renal pelvis, calyces, and ureters due to obstruction.
3	**Perinephric abscess**	• Forms when **suppurative inflammation** extends through the renal capsule into the perinephric tissue

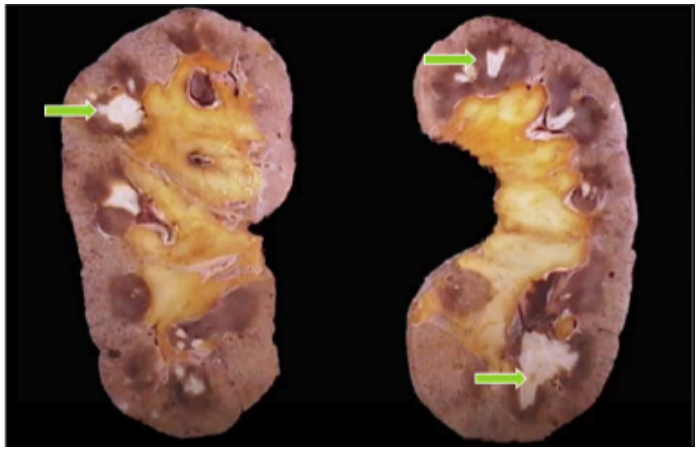


Figure 38. Necrotic papillae (green arrow) in papillary necrosis

3. Associated/Predisposing Conditions

1	Urinary tract obstruction
2	Instrumentation
3	Vesico-ureteral reflux
4	Pregnancy
5	Patient's sex and age - congenital anomalies, NPH
6	Pre-existing renal lesions
7	DM
8	Immunosupression and immunodeficiency

4. Healing and Progression to Chronic Pyelonephritis

1	Mononuclear cells replace neutrophils
2	Irregular scars replace areas of inflammation and necrosis • Followed by interstitial fibrosis, tubular atrophy, and presence of lymphocytes • The scarring causes deformation of underlying calyces and renal pelvis
3	Chronic pyelonephritis ensues

3. CHRONIC PYELONEPHRITIS

- Chronic tubulointerstitial inflammation and scarring with involvement of the pelvis and calyces
- Among the tubulointerstitial diseases, only chronic pyelonephritis and analgesic nephropathy affect the calyces
- Represents repeated episodes, usually with reflux or obstructions (e.g. staghorn calculi)

Associated with	
Reflux Nephropathy	• UTI + congenital vesico-ureteral or intrarenal reflux • Renal involvement occurs during childhood
Chronic Obstructive Pyelonephritis	Effects are due to infection and obstruction

1. Gross Morphology of Chronic Pyelonephritis

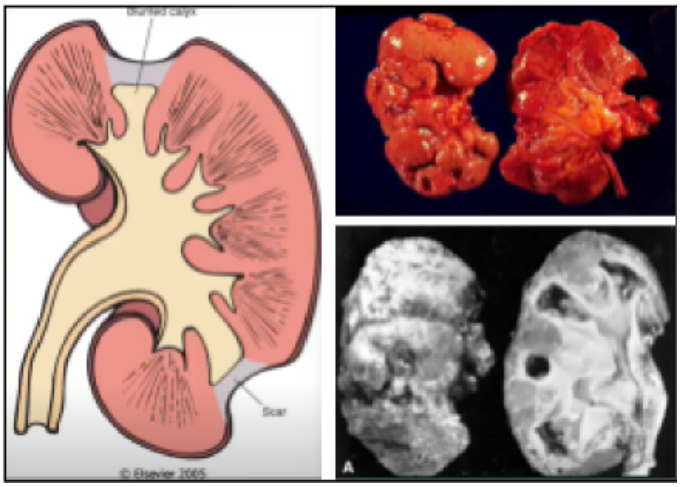


Figure 39. Gross Morphology of Chronic Pyelonephritis

1	• **Asymmetric** involvement
2	• **Deep Irregular scars** ○ Coarse, discrete, corticomedullary scars ○ Overlying blunted or **deformed calyces**

2. Microscopic Morphology of Chronic Pyelonephritis

1	• **Tubular atrophy** in some areas **with dilation or hypertrophy in others**
2	**Thyroidization** • Dilated tubules with flattened epithelium may be filled with eosinophilic secretions resembling thyroid colloids, hence, the term thyroidization
3	**Chronic interstitial inflammation** • At varying degrees in the cortex and medulla
4	**Fibrosis** • At varying degrees in the cortex and medulla • Often around the calyceal epithelium and marked chronic inflammation
5	**Glomeruli may appear** as **round and normal** except for a variety of ischemic changes including: • Periglomerular fibrosis • Fibrous obliteration

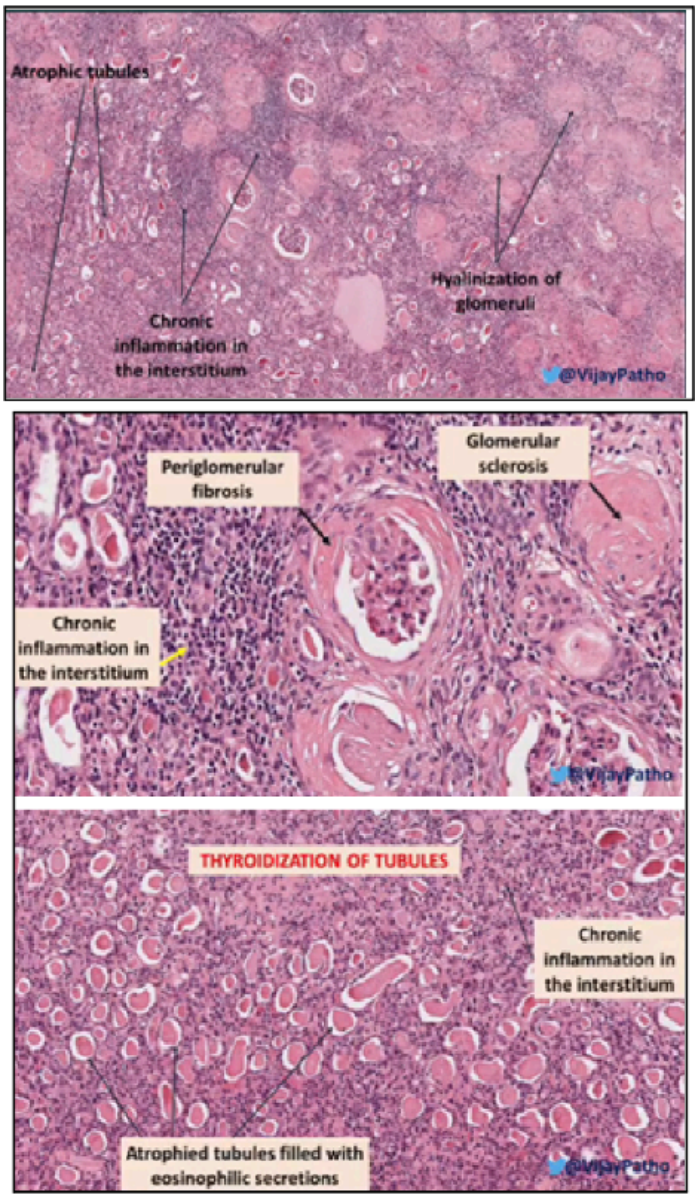


Figure 40. Histologic features chronic pyelonephritis

Professor's Notes:

- *Chronic GN:* diffuse coarse granular surface, bilateral symmetric
- *Chronic pyelonephritis:* deep scars, calyceal deformity, often asymmetric

4. NEPHRITIS INDUCED BY DRUGS AND TOXINS

- Drug and toxin induced tubulointerstitial nephritis is the **second most common cause of acute kidney injury**
  - The pathogenesis involves an immune mechanism that is not dose related

TOXINS/DRUGS PRODUCE RENAL INJURY BY:	
1	Triggering interstitial immunologic reaction
2	Causing acute renal failure (often via ATI/ATN pattern) • Occurs in 50% of cases
3	Causing subtle but progressive damage to the tubules

DRUGS CAUSING RENAL INJURY:	
1	Sulfonamides
2	Synthetic antibiotics
3	Thiazide diuretics
4	NSAIDs
5	Phenacetin-containing analgesics • Causes a condition called **analgesic nephropathy**

Acute Drug-Induced Interstitial Nephritis

- Begins 2-40 days after drug exposure (📖 15 days)
- **Pathogenesis:** Involves an immune mechanism that is not dose-related
- 📖 **Caused by:** synthetic penicillins, rifampin, thiazides, NSAIDs

SIGNS AND SYMPTOMS	
1	• **Fever** (may be transient)
2	• **Eosinophilia** (may be transient) **!!**
3	• **Rash** (25% of patients) **!!**
4	• **Renal Abnormalities** ○ Hematuria ○ Mild proteinuria ○ Leukocyturia (often including eosinophils)
5	• 📖 **Hypersensitivity reaction**
	NOTE: A rise in serum creatinine, or acute kidney injury with oliguria develops in about 50% of cases.

MECHANISMS	
1	**Drugs functions as haptens** ○ It covalently bind to plasma membrane or extracellular components of the tubular cells
2	Modified to **form immunologic self-antigens**
3	Resulting in injury caused by **IgE or cell-mediated immune reactions** directed **against tubular cells** or their basement membrane

MORPHOLOGY	
G	**Marked edema**
M	• Lymphocytes and macrophages interstitial infiltration • Infiltration of tubules **(tubulis)**

1. Nephropathy Associated with NSAIDS

- NSAIDs inhibit the cyclooxygenase-dependent prostaglandin synthesis

CLINICAL FEATURES	
1	**Acute kidney injury (o**r acute renal failure) due to the inhibition of the vasodilatory effects of prostaglandin leading to ischemia

2	Acute hypersensitivity interstitial nephritis
3	Acute interstitial nephritis plus minimal change disease
4	Membranous glomerulonephritis

2. Analgesic Nephropathy

- Associated with intake of phenacetin
  - 📖 Mixture of at least 2: Caffeine, aspirin, acetaminophen, codeine

1	**Papillary necrosis** due to the edema compressing the small vessels in the medulla causing ischemia and necrosis of the renal papilla
2	**Chronic Tubulointerstitial Nephritis**

MECHANISMS	
1	**Direct toxicity of phenacetin/acetaminophen** ○ Depletes glutathione ○ Generates oxidative metabolite
2	**Inhibition of vasodilatory effects of prostaglandin** (aspirin) resulting to ischemia

MORPHOLOGY	
G	• Normal or slightly small kidneys • Depressed and raised areas in the cortex • **Various stages of necrosis** in papillae (vs DM: one stage only)
M	• Loss of atrophy of tubules • Interstitial fibrosis and inflammation • Patchy of diffuse necrosis of papillae • Dystrophic calcification

CLINICAL FEATURES	
1	**Inability to concentrate urine**
2	**Predisposition to renal stone formation**
3	**Anemia** due to renal damage and damage to RBCs
4	**UTI** in 50% of cases
5	**Hematuria** due to excretion of necrotic tissue
6	Development of **transitional papillary CA** of the renal pelvis

3. Other Tubulointerstitial Diseases

1	**Urate Nephropathy (Hyperuricemia)** ○ Acute Uric Acid Nephropathy ○ Chronic Urate Nephropathy ○ Nephrolithiasis
2	**Hypercalcemia and nephrocalcinosis**
3	**Myeloma Kidney** (Light Chain Cast Nephropathy)

1. URATE NEPHROPATHY (HYPERURICEMIA)

- Three types of nephropathy can occur in persons with hyperuricemic disorders

1. Acute Uric Acid Nephropathy

- Occurs in patients with l**eukemia or lymphoma undergoing chemotherapy**
  - 📖 Hyperuricemia is due to accelerated purine breakdown as a result of **rapid cell proliferation and turnover** (in blast crisis of leukemia) or cell death (due to chemotherapeutic drugs)
  - Drugs cause death of tumor cells, eventually releasing uric acid from breakdown of nucleic acids
  - Uric acids may precipitate to form **uric acid crystals** in the tubules

2. Chronic Urate Nephropathy

- Also known as **Gouty nephropathy**
- Characterized by deposition or precipitation of **monosodium urate crystals** in the acidic environment of the distal and collecting tubules or in the interstitium
  - Appear as birefringent crystals and may cause the formation of tophus
  - The obstruction causes **cortical atrophy and scarring**

3. Nephrolithiasis

- Renal Stones
- Form in patients with **gout** or those with **secondary hyperuricemia**

2. HYPERCALCEMIA AND NEPHROCALCINOSIS

- In conditions that cause hypercalcemia, nephrocalcinosis can occur including:
  - Hyperparathyroidism
  - Multiple myeloma
  - Vitamin D intoxication
  - Excess Calcium intake
  - Metastatic bone disease
- If severe, it causes chronic tubulo-interstitial disease and renal insufficiency
- 📖 **Nephrocalcinosis** refers to calcium deposition and stone formation in the cells, basement membrane and tubules.

3. MYELOMA KIDNEY (LIGHT CHAIN CAST NEPHROPATHY)

- About 50% of patients develop renal manifestations
  - Most commonly those of chronic kidney disease as light chains are most responsible for these manifestations

MECHANISMS	
1	**Bence-Jones proteins are excreted in the urine** • Toxic to epithelial cells • Can combine with Tammm-Horsfall glycoprotein to form casts
2	Light chains may **accumulate and form amyloid fibrils**
3	**Light chains** may be **deposited in the GBM**

4	**Hypercalcemia and hyperuricemia** often accompany multiple myeloma

SUMMARY

- **Acute Tubular Injury** is caused by ischemia and/or toxicity. **Tubular epithelial injury and intrarenal hemodynamics** are the main contributors to its pathogenesis.
- **Interstitial edema and neutrophils** characterize acute T-I nephritis while interstitial fibrosis and widespread tubular atrophy characterizes chronic T-I nephritis.
- **Acute and chronic pyelonephritis** are both caused by infections via the ascending (more common) or hematogenous route. Obstruction and vesico-ureteral reflux are important predisposing factors.
- While acute pyelonephritis is characterized by suppurative inflammation and abscesses, **chronic pyelonephritis** is marked by scarring and deformed calyces.
- Inhibition of the vasodilatory effects of prostaglandin, thus leading to ischemia, plays an important role in NSAID nephropathy and analgesic (phenacetin) nephropathy.
- **Hyperuricemia** can cause deposition of uric acid crystals in the tubules (acute uric nephropathy), deposition of monosodium urate crystals (chronic urate nephropathy) or formation of renal stone (nephrolithiasis).
- **Nephrocalcinosis** may occur in hyperparathyroidism, multiple myeloma, Vit D intoxication, excess calcium intake or metastatic bone disease.
- **Light chains of multiple myeloma** are toxic to epithelial cells and can form casts, may accumulate to form amyloid fibrils or may be deposited in the GBM.

REFERENCES

- Face-to-face lecture and Handouts
- Batch 2027 Trans
- Robbins 10th ed.