Module: CLINICAL PATHOLOGY

Unit 3: The Kidney and Urinary Tract

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UNIT OUTLINE

	Topic	Sub Topic	Duration (hrs)
1.	Introduction	Introduction to Urinary Pathology; Review Anatomy and Physiology; Pathogenesis of urinary disease; investigations in urinary disease	1.5
2.	The Kidney	Congenital Malformations and Urinary Calculi	1.5
		Acute Renal Failure (ARF)	2
		Chronic renal failure (CRF) and End Stage Kidney	2
		Glomerular Disease - Glomerulonephritis(AGN, CGN)	2
		Glomerular Disease - Nephrotic and Nephritic syndromes	1
3.	Urinary Tract	Urinary Tract Infections(Pyelonephritis, Ureteritis, Cystitis and Urethritis)	1
		Urinary Tract Obstruction	1
4.	Bladder	Bladder - Infections – cystitis , Neurogenic Disorders	1
5.	Tumours	Tumours - Renal Tumours, Bladder Tumours	1
		Total	**15**

Lesson 1: Introduction to Urinary Pathology

Learning Outcomes

At the end of the unit the learner should be able to: -
1) Describe the structure and function of the urinary system
2) Explain the pathophysiology of urinary disorders
3) Outline Investigations in urinary disorders

1.0 INTRODUCTION

- Renal pathology has a significant impact on **morbidity and mortality** due to the vast functions of the renal system in maintaining optima functioning of body systems
- Primary function of the kidney is regulation of the **extra-cellular fluid** environment a process accomplished through formation of urine (modified form of plasma).
- Kidney develops from the lower end of the mesonephric (Wollffian duct) to the mid vertebral column and then they ascend.
- It accounts for 0.5% of the total body weight.

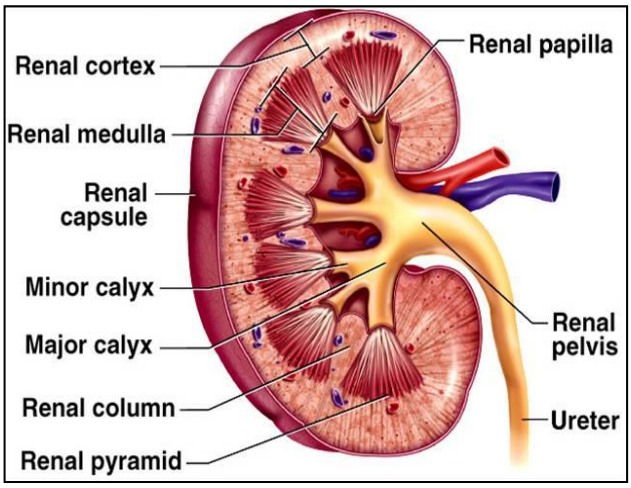
2.0 GROSS STRUCTURE OF THE URINARY SYSTEM

- Kidneys are located in the abdominal cavity below the diaphragm
- Each kidney in adults weighing 160 – 175 gms, 10 – 12 cm long, 5 – 6 cm wide
- Ureters channel urine from the kidney to the bladder
- Bladder is the storage sac for urine and it is drained by the urethra (4 cm [1.5”] in females and 20 cm [8”] in males)

3.0 FINE STRUCTURE

- Fine structure of the kidney reveals the cortex and medulla
- **Cortex is the outer region** generally 15 mm thick but varies in thickness, which is in contact with the renal capsule. It is usually reddish-brown and granular in appearance (due to many capillaries)
- **Medulla is the deeper r**egion that is lighter in colour and stripped in appearance (due to microscopic appearance of tubules and blood vessels) and consists of renal pyramids, renal capsule and the calyces. There are 8 – 15 renal pyramids separated by renal columns
- Each pyramid projects into a small depression called a minor calyx (calyces in plural) several of which unite to form a major calyx.

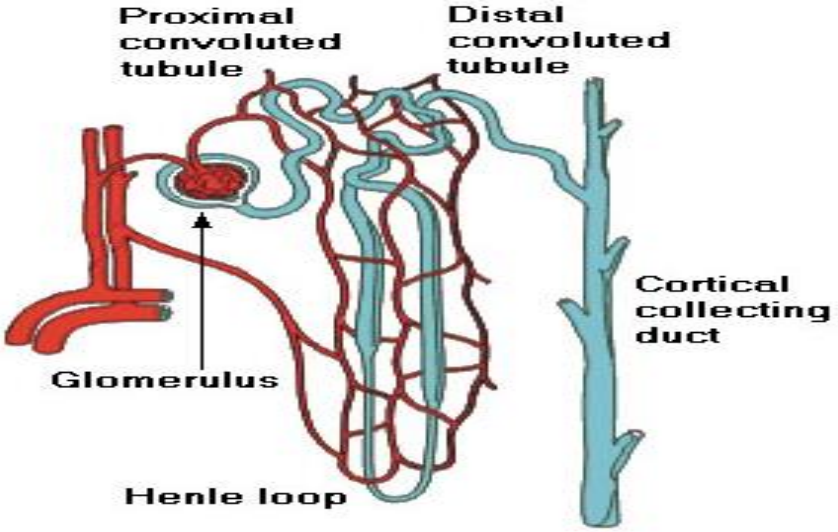
Diagram 1.1: Fine Structure of the Kidney and Nephron



The Nephron

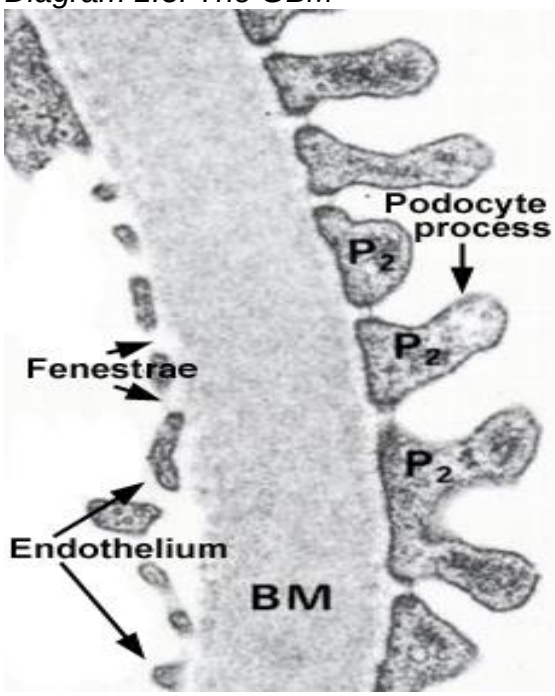
- Basic functional unit of the kidney
- Divided into **glomerulus** and **tubules** (the proximal and distal tubules).
- Nephrons originating in the inner one-third of the cortex (the juxtamedullary nephrons) have longer loops of Henle than the more numerous cortical nephrons those originating in the outer 2/3 of the cortex
- Glomerular capillaries have large pores and a layer of the Bowman's capsule with filtration slits. The barrier to filtration of large macromolecules such as albumin depends on the normal lamina densa, maintenance of a negative charge on both lamina rarae and a healthy covering of the glomerular epithelial cells.

Diagram 1.2: The Nephron



- Main components of the nephron are: -
  1) The Pre-glomerular blood vessels – supply blood to the glomerulus
  2) The Glomerulus
     - Highly vascularized capillary system
     - BM of the lining epithelium is fused to that of the surrounding epithelium forming a highly selective filtration barrier called the GBM
     - GBM is responsible for the differential molecular size segregation. Has messangial cells, which are phagocytic (clear escaping macromolecules) and regulate glomerular blood flow (GBF) by actively contracting

Diagram 1.3: The GBM



The filtration process occurs through structures such as the: -

a) The Endothelium contains fenestrations that are 90 nm in diameter.
b) The Glomerular Basement Membrane (GBM) which is 300 nm thick and consists of three layers viz: - the lamina rara interna, lamina densa and lamina rara externa
c) The Mesangium that contains mesangial cells which form the supportive framework of the glomerular tuft.
d) Visceral epithelial cells (podocytes) which are foot processes separated by filtration slits which are separated by the slit diaphragm

- Proximal tubule loops backwards towards the glomerulus becoming the distal tubule carrying urine towards the collecting ducts and calyces
- Glomerular capillary tuft is situated in the Bowman's capsule (collects ultrafiltrate and passes it to the tubules)
- Produces the **glomerular filtrate (GF)** which passes into the proximal tubule that has cells with long apical microvilli well adapted for the main function of reabsorption of solutes (sodium, potassium, phosphate, glucose and water).

3) The tubular system
   - Divided into several parts
     i) Proximal tubules – selective reabsorption of various components of the glomerular filtrate
     ii) Loop of Henle – creates ionic concentration gradient in the renal medulla
     iii) Distal tubule – acid-base balance and sodium-potassium ion resorption
     iv) The Collecting Tubules and Ducts - reabsorb water from the dilute urine under control of ADH
4) The Post-glomerular vasculature
   - Provide oxygenated blood for the tubular epithelium
   - Participates in homeostasis – ions, water and other molecules pass between the tubular and ductular parts of the nephron and the post-glomerular vasculature

Juxtaglomerular Apparatus (JGA)

- Point where the afferent arteriole enters the glomerulus
- A modified granular smooth muscle cells occupying the media of the afferent arteriole
- Secretes rennin that is essential in blood pressure regulation.

Interstitium

- Renal cortical interstitium is scanty and consists of a small number of fibroblasts. The medullary interstitium is plentiful. The normal cortex has a small compact space that any obvious expansion is pathological. This can occur due to accumulation of fluid (oedema) or inflammatory cells or fibrous tissue.

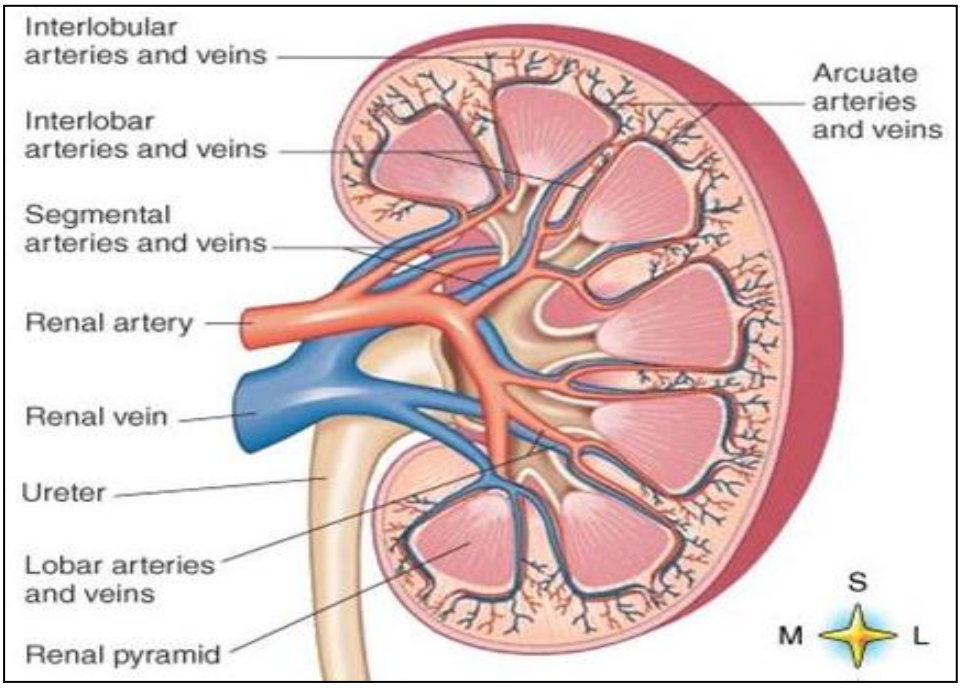
4.0 RENAL VASCULATURE

- Each kidney is supplied with blood by a main renal artery, which arises from the aorta at the level of the 2nd lumbar vertebra
- The artery usually divides into anterior and posterior divisions at the hilum further subdividing into segmental branches forming the interlobar arteries.

Blood Flow

- Blood flow to the kidney is usually 25% of the cardiac output
- Interlobular arteries carry most of the blood to the richly vascularized cortex and arcuate arteries run between the cortex and medulla giving of the interlobular arteries, which run perpendicular to the cortical surface.
- They furnish the afferent arteries that enter the glomerulus and from which capillaries are derived.
- The efferent arteriole emerges from the glomerular and the peripheral arterioles give rise to a rich perivascular network of capsule
- Blood flows through the renal artery, segmental arteries, interlobar arteries, arcuate arteries and interlobular arteries.

Diagram 1.4: Blood Supply



5.0 FUNCTIONS OF THE KIDNEY

1) Excretory function – eliminates waste products and drugs
2) Regulatory function- Blood volume and composition; Electrolytes of body fluids; Acid-base balance; Blood pressure (The kidneys control the blood pressure through the rennin-angiotensin-aldosterone mechanism)
3) Endocrine function – Production of rennin, erythropoietin and prostaglandins
4) Metabolic function - Vitamin D synthesis, synthesis of small molecular weight proteins

6.0 PATHOGENESIS OF RENAL DISEASE

- Grouped into 2 main entities based on the aetiology and morphological changes

Aetiological

- Congenital malformations; Infections; Injury – mechanical, immunological and metabolic; Ischaemia/hypoxia; Tumours – primary and secondary; Toxins, chemicals and drugs; Obstruction

Morphologic

- Morphologic involvement of the kidney in early stages of disease is usually confined to one component either glomeruli, tubules, interstitial or blood vessels but eventually affects all the components resulting in end stage kidney
- Renal disease results in 2 main pathological syndromes of **acute and chronic renal failure**
- When these syndromes are associated with abnormal increase in BUN the term **azotaemia** whereas **uraemia** is used to describe increase in BUN associated with clinical signs and symptoms
- Morphological parameters include glomerular diseases, tubular diseases, interstitial diseases and vascular diseases

7.0 INVESTIGATIONS IN RENAL DISEASE

- Assessment of renal function involves a number of tests geared to giving information regarding renal blood flow, glomerular filtration, renal tubular function and urinary output.
- These tests are grouped into 4 main groups: - urine analysis (urinalysis), concentration and dilution of urine, blood chemistry (Blood analysis) and renal clearance tests

1) Urinalysis
   a. Physical characteristics - volume, colour, turbidity, density and odour,
   b. Chemical characteristics - pH, haemoglobin; glucose; protein, leucocytes, nitrates, bile pigments, bilirubin, urobilinogen and ketones
   c. Urine biochemistry - 24 hour creatinine clearance, urinary electrolytes (– presence of sodium distinguishes pre-renal and intrinsic renal disease), urine osmolarity (the concentrating ability of the kidney) and electrophoresis – detection of light chain
   d. Urine microscopy - cells (white blood cells -neutrophils, lymphocytes, eosinophils; erythrocytes; renal tubular epithelium, uroepithelial; squamous cells); lipids; casts - granular and red cell casts; crystals; organisms (bacteria, Fungi, Trichomonas, Schistosoma haematobium); contaminants

2) Plasma biochemistry (Serum) – Renal Function Tests
   - Serum urea (2.5 – 7 mmol/L); Creatinine levels (1.0 – 2.0 gm/dl); Serum electrophoresis in myeloma; Serum LDH – increased in renal infarction due to embolism; Electrolytes – sodium, potassium; BUN

3) Haematology - Eosinophilia – in allergic interstitial nephritis; Increased ESR; Fragmented RBCs and thrombocytopenia due to haemolysis, uraemia, hypertension; Sickling test

4) Microbiology - Urine for culture and sensitivity

5) Radiological/Imaging Technique
   a. Plain X-ray
   b. Excretion urography; Antegrade and retrograde urography
   c. IVP/IVU
   d. Ultrasonography (ultrasound) and Computerized tomography (CT scan
   e. Micturating cytourography
   f. Renal arteriography
   g. Magnetic resonance imaging
   h. Radionuclide evaluation

6) Immunology and Serological tests
   a. Complement components
   b. Autoantibody screening (for S.L.E, G.P.S)
   c. ASOT; HBV, HCV antibodies and HIV antibodies; Blood slide/QBC

7) Renal Biopsy
   - Renal biopsy – considered in patients with unexplained renal failure and normal sized kidneys.

8) Renal Clearance

   - This is to assess the rate of glomerular filtration (normal 120 ml/minute in an average adult) and renal blood flow. Clearance tests give an indication of glomerular filtration rate.
   - Substances which can be used for clearance tests – **urea** and **creatinine**

$$C = \frac{UV}{P}$$

Where:

C is the clearance of the substance in ml/minute;
U is the concentration of the substance in the urine;
P is the concentration of the substance in the plasma
V is the volume of urine passed per minute.

Lesson 2: Congenital Malformations and Renal Stones

Learning Outcomes

At the end of the lesson the leaner should be able to:
1) Identify congenital malformations of the urinary system
2) Discuss the pathology of renal stones

1.0 EMBRYOLOGY OF THE URINARY SYSTEM

- Kidney arises from the urogenital ridge
- Kidney is formed of 2 main portions from 2 embryological sources as follows:
  1) The **excretory portion** of the kidney develops from the intermediate mesoderm (or called metanephric cap or blastema). This portion consists of **nephron** (which includes Bowman's capsule, proximal convoluted tubule, loop of Henle and distal convoluted tubule).
  2) The **collecting portion** of the kidney develops from the ureteric bud. This portion includes the collecting tubules, minor calyces, major calyces, renal pelvis and ureter.
- Its development passes into 3 stages (or kidneys) in cranio-caudal sequence as follows pronephros (temporary and non-functional), mesonephros (temporary functional at the early foetal stages) and metanephros (the permanent functional kidney)
- **Pronephros (1st kidney) d**evelops from the intermediate (nephrogenic) mesoderm in the cervical region (at the beginning of the 4th week of intrauterine life)
- **Mesonephros (Second Kidney) d**evelops from the intermediate (nephrogenic) mesoderm in the middle part (thoracic and lumbar region). Most of mesonephric tubules disappear except few of them that form the functional tubules opposite the developing testis and join the rete testis to form the ***efferent ductules*** (vasa efferentia) and non-functional tubules, e.g. superior and inferior aberrant ductules, paradidymis and appendix of epididymis in males; non-functional tubules, e.g. of epoophoron and paroophron in females; ureteric bud in both sexes; male genital ducts; epididymis, vas (ductus) deferens, seminal vesicle and ejaculatory duct.
- Metanephros (third or permanent kidney) develops during (the 5th week) when it arises in the pelvis from 2 sources ureteric bud arising from the mesonephric duct and metanephric cap arising from the intermediate mesoderm (lower or pelvic part).

2.0 CONGENITAL ABNORMALITIES OF THE KIDNEY

- Can be classified into 3 main groups namely abnormalities of **amount of renal mass** – deficient renal parenchyma (hypolasia and agenesis) and excess; abnormalities of **position, form and orientation** - renal ectopia (pelvic kidney), renal fusion (horse shoe kidney) and persistent foetal lobation) and cystic disorders

2.1. Renal Agenesis

- Absence of the kidney due to failure of ureteric bud to develop

2.2. Ectopic kidney

- Ectopic (or pelvic) kidney due to failure of the kidney to ascend

2.3. Lobulated kidney

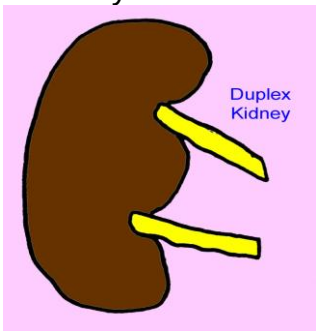
- Due to persistence of the foetal lobulation of the kidney

2.4. Rosette (cake) kidney

- Due to adhesions of the 2 kidneys at the hilum during their ascent. It is a pelvic kidney.

2.5. Double kidney

- Due to early division of the ureteric bud



2.6. Aberrant renal vessels

- A renal artery enters the kidney at its lower pole
- It is due persistence of the normal foetal arteries that normally disappear during growth of kidney and may cause obstruction of the urine flow through the corresponding ureter.

2.7. Cystic Diseases

- Occur due to failure of communication between the distal convoluted tubules (derived from the metanephric cap) and the collecting tubules (derived from the ureteric bud). This results in retention of urine in the excretory portion of the kidney, resulting in formation of retention cysts.
- Cystic diseases of the kidney result from poor differentiation of cells. It can be congenital or acquired, non-neoplastic or neoplastic. They occur at any age from foetal to old age.
- Majority of renal cystic lesions are congenital non-neoplastic lesions. Cystic diseases commonly present as abdominal masses associated with infection, respiratory distress (because of accompanied pulmonary hypoplasia) and haemorrhage (haematuria). Some may become neoplastic.

Polycystic Kidney (PKD)

- Is a disorder of the kidney in which a large portion of the renal parenchyma is changed into cysts of variable size
- PKD occurs in 2 forms - adult PKD (autosomal dominant disease) and infantile PKD (autosomal recessive disease) due to mutations on chromosome 16.

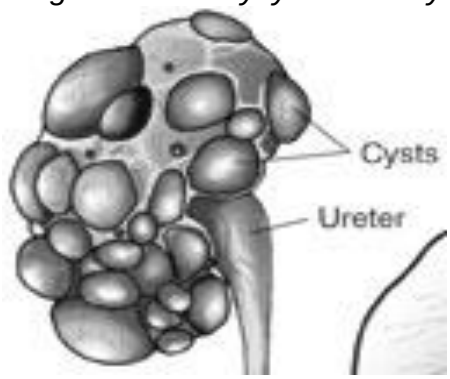
Adult PKD (APKD)

- Occur in 10% of renal diseases; Usually bilateral and diffuse
- The defect is branching of the collecting tubules resulting in formation of normal and abnormal nephrons
- Progresses leading to atrophy of the normal nephrons secondary to pressure (mainly in the 3rd to 4th decade of life).
- Kidneys are normal at birth and renal function is retained only for symptoms to appear later in life
- PKD presents with chronic renal failure, uraemia and hypertension.

Pathology

Macroscopy (Gross): The kidneys are heavy, bilaterally enlarged (up to 4kg). The cysts have clear, straw-yellow fluid or reddish brown material. There is distortion of the renal pelvis and calyces. Cysts do not communicate with the renal pelvis as seen in hydronephrosis.

Diagram 2.1: Polycystic Kidneys



Microscopy: Cysts arising from all parts of the nephrons

Clinical Features

- Dull ache in the lumbar regions; haematuria; passage of blood clots in urine; renal colic; hypertension; urinary tract infection; progressive chronic renal failure with polyuria and proteinuria

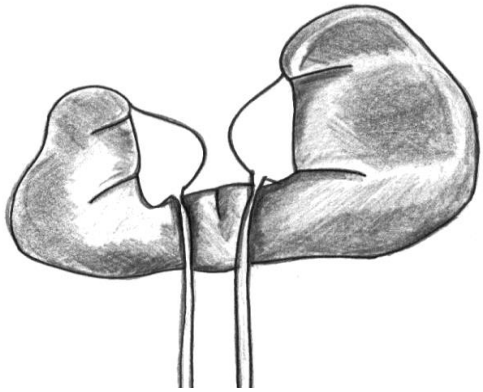
Infantile PKD

- Infantile PKD is rare and may present during perinatal, neonatal, infantile or juvenile stage
- Serious manifestations seen at birth resulting in renal failure in early childhood
- Nephrons are normal in number and function but there is cystic dilatation in the terminal branches of the collecting ducts
- Kidneys are enlarged bilaterally with sponge like appearance on cross section.

2.8. Horse-Shoe Kidney

Due to adhesions of the 2 kidneys at their lower poles. This kidney is located at the level of the lower lumbar vertebra because its ascent is prevented by the origin of the inferior mesenteric artery from the aorta.

Diagram 2.2: Horse Shoe Kidney



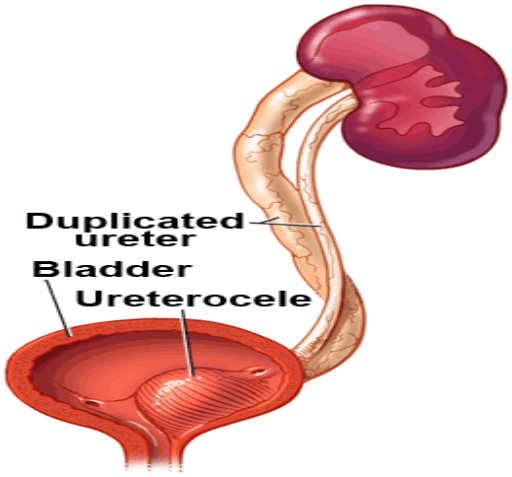
3.0 ABNORMALITIES OF RENAL PELVIS AND URETERS

1) Pelvic-ureteric junction obstruction
2) Duplication of the pelvis and ureters
3) Ureterocoele
4) Chronic ureteric dilatation

Ureterocele

- A congenital abnormality found in the bladder
- The ureter balloons at the opening into the bladder forming a sac-like pouch

Diagram 2.3: Ureterocele



- The signs and symptoms include frequent urinary tract infections, urosepsis, obstructive voiding symptoms, urinary retention, failure to thrive, haematuria, cyclic abdominal pain and ureteral calculus

4.0 DISORDERS OF THE URETHRA

1) Epispadias and hypospadias
2) Phimosis and paraphimosis
3) Urethral valves

4.1. Hypospadias and Epispadias

- Hypospadias is a developmental defect of the urethra in which the urethral meatus opens on the ventral surface of the penis and does not reach the end of the penis whereas in epispadias the defect is on the dorsal aspect of the penis
- Hypospadias and epispadias may be associated with other urogenital malformations such as undescended testis (cryptorchidism) and may produce urethral constriction resulting in lower urinary tract obstruction and they do also interfere with normal ejaculation and insemination leading to sterility.

Types of Epispadias

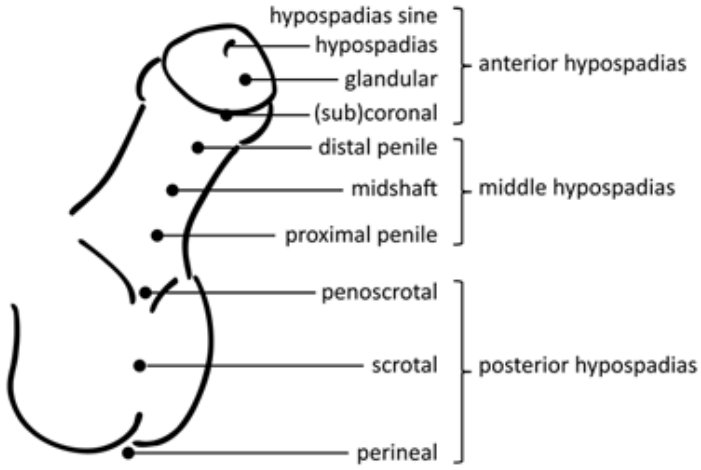
- Include glandular, coronal, penile and penopubic

Types of Hypospadias

- Include glandular, coronal, penile, peno-scrotal and perineal
- Glandular hypospadias is the most common and least severe are requires no treatment

- The perineal hypospadia is the most severe abnormality where the scrotum is split between its two halves and there may be testicular maldescent making it difficult to determine the sex of the child.

Diagram 2.6: Hypospadias



Complications

1) Incontinence
2) UTI
3) Sexual problems
4) Infertility
5) Psychological-social stress

4.2. Phimosis and Paraphimosis

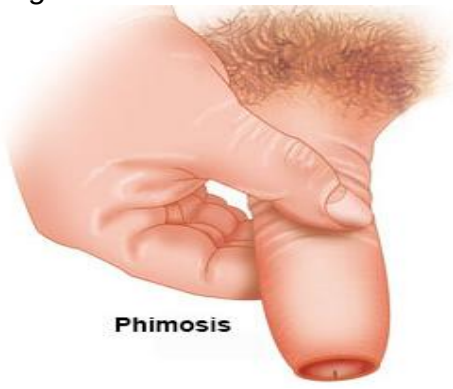
Causes

1) Congenital – a developmental anomaly.
2) Acquired – Inflammation, trauma and oedema

Phimosis

- Condition in which the foreskin is abnormally tight and does not retract easily over the glans penis
- Interferes with cleanliness and predisposes to the development of secondary infection; preputial calculi and squamous cell carcinoma due to chronic accumulation of secretions and other debris under the foreskin.

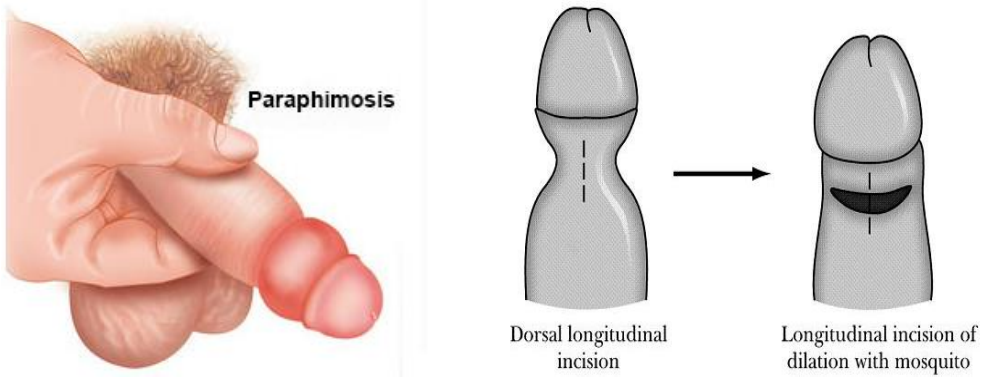
Diagram 2.4: Phimosis



Paraphimosis

- Abnormal, painful swelling of the glans penis after forceful retraction of a phimotic prepuce
- May cause urethral obstruction condition
- Painful swelling of the glans as a complication of inability to release the foreskin after it has been retracted

Diagram 2.5: Paraphimosis

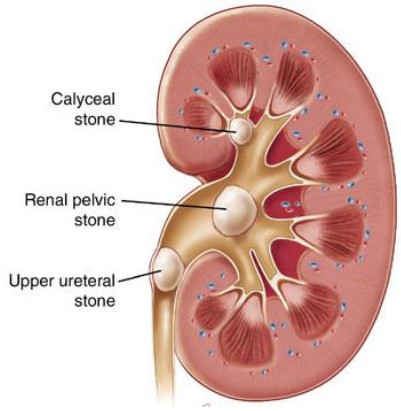


Urinary Stones (Calculi) – Urolithiasis

1.0 INTRODUCTION

- Stones (calculi) are hard masses that form anywhere in the urinary tract and may cause pain, bleeding, obstruction of the flow of urine, or an infection.
- Depending on where a stone forms, it may be called a **kidney stone**, **ureteral stone**, or **bladder stone**. The process of stone formation is called **urolithiasis, renal lithiasis**, or **nephrolithiasis**
- It is estimated that 2% of the population experiences renal stone disease at sometime in their life with more males being victims (male: female ratio is 2:1). The peak incidence is witnessed in the 2nd to 3rd decades of life. The renal stones are called **calculi** (single – calculus) from a Latin word meaning *"little stone" or "pebble"*
- Stones vary in size from too small to be seen with the naked eye to 1 inch (2.5 centimeters) or more in diameter. A large so-called stag horn stone may fill almost the entire renal pelvis (small tubes of the kidney and its collecting area) and the tubes that drain into it (calices).
- A UTI may result when bacteria become trapped in urine that pools above a blockage. When stones block the urinary tract for a long time, urine backs up in the tubes inside the kidney, producing excessive pressure that can distend the kidney (**hydronephrosis**) and eventually damage it.

Diagram 2.7: Renal Stones



2.0 PREDISPOSING FACTORS

i) Certain disorders (e.g. hyperparathyroidism and short bowel syndrome)
ii) Diet is very high in protein or vitamin C
iii) Less consumption of water
iv) Calcium
v) Family history of stone formation

3.0 CAUSES

- Too much saturation of urine with salts that can form stones
- Lack of the normal inhibitors (as citrate which normally binds with calcium) of stone formation

4.0 PATHOGENESIS

- Renal stones are formed by precipitation of urinary constituents with incorporation of a small amount of organic material
- The process of stone formation is complex and ill understood. However, it has two stages of **nucleation** (stone deposition is initiated) and **aggregation** (growth of stone in size).
- The **three main factors** that predispose to stone formation are: - increased concentration of salts in urine, urinary tract infection and urinary tract obstruction.
  i) Increased concentration of salts in urine facilitate precipitation of the same resulting in formation of calculi
  ii) Infection in the urinary tract reduces solubility of the salts in urine and clusters of bacteria can serve as a nidi for crystallization of the salts to form stones
  iii) Obstruction in the urinary tract results in stagnation of urine favouring precipitation of salts and also predisposes to infection, which further increases the likelihood of stone formation.

5.0 TYPES OF URINARY CALCULI

Four (4) main types: -
1) Calcium stones (calcium containing) – 75 – 80 %
2) Mixed (struvite) stones – 15%
3) Uric acid stones - 6%
4) Cysteine stones – 2%

5.1. Calcium Stones

- Most common of the renal stones
- May be pure stones of calcium oxalate or calcium phosphate or a mixture of calcium oxalate and calcium phosphate.

Aetiology
1) Idiopathic hypercalciuria without hypercalcaemia
2) Hypercalcaemia and hypercalciuria due to hyperparathyroidism or a defect in the bowel (absorptive hypercalciuria) or kidney (renal hypercalciuria)
3) Hyperuricosuria with a normal uric acid level
4) Idiopathic calcium stone disease

Pathogenesis

- Occurs an imbalance between the degree of saturation of the ions forming the stone and the concentration of inhibitors in the urine
- The stone grows as more crystals are deposited around the nidus
- Other predisposing factors are: - changes in alkaline urinary pH, decreased urinary volume and increased excretion of oxalate and uric acid.

Diagram 2.8: Urinary Stones

Morphology

- Small (< 1 cm), ovoid, and hard with a granular surface
- They are dark brown due to old blood pigment deposited in them due to repeated trauma by these sharp edged stones.

5.2. Mixed (Struvite) Stones

- Made up of magnesium-ammonium-calcium phosphate
- Often called struvite or triple stones.

Aetiology

- Formed as a result of infection of the urinary tract with urea-splitting organisms that produce urease e.g. Klebsiella, Pseudomonas and Enterobacter.

Morphology

- Mixed stones are yellow-white or grey; soft and friable with an irregular shape e.g. the “Staghorn stone” formed at the renal pelvis.

5.3. Uric Acid Stones

- Uric stones are made of uric acid.

Aetiology

- Formed in cases of hyperuricaemia and hyperuricosuria e.g. due to primary gout or secondary gout due to myeloproliferative disease (e.g. leukaemia)
- Likely in patients on chemotherapy and administration of uricosuric drugs (e.g. salicylates, probenecid). Other factors include – acidic pH (below 6) and low urine volume

Pathogenesis

- The solubility of uric acid at Ph of 7 is 200mg/dl while at pH of 5 is 15mg/dl. Therefore solubility of uric acid decrease as the pH becomes more acidic increasing precipitation of uric acid crystals hence formation of uric acid stones
- Hyperuricosuria is an important factor in uric stone formation.

Morphology

- Are smooth, yellowish-brown, hard and often multiple.

5.4. Cysteine Stones

- Cysteine stones are associated with cystinuria due to genetically determined defect in transport of cystine and other amino acids across the cell membrane of renal tubules and the small intestinal mucosa.

Pathogenesis

- The excessive excretion of less soluble cystine leads to formation of stones

Morphology

- Are small, rounded, smooth and often multiple

6.0 CLINICAL FEATURES

- Stones, especially tiny ones, may not cause any symptoms.
- Stones in the bladder may cause pain in the lower abdomen. Stones that obstruct the ureter or renal pelvis or any of the kidney's drainage tubes may cause back pain or renal colic. Renal colic is characterized by an excruciating intermittent pain, usually in the flank (the area between the ribs and hip), that spreads across the abdomen, often to the genital area and inner thigh. The pain tends to come in waves, gradually increasing to a peak intensity, then fading, over about 20 to 60 minutes. The pain may radiate down the abdomen toward the groin or testicle or vulva.
- Other symptoms include nausea and vomiting, restlessness, sweating, and blood in the urine. A person may have an urge to urinate frequently, particularly as a stone passes down the ureter. Chills, fever, and abdominal distention sometimes occur
- Characteristic colicky pain (renal colic) as the stones pass down along the ureters
- Haematuria
- Features determined by the predisposing factors

- What important features will you look for in a medical history of a patient suspected to have renal stones
- What are the complications of renal stones
- What are the differential diagnosis of renal stones

Lesson 3: Acute Renal Failure (ARF)

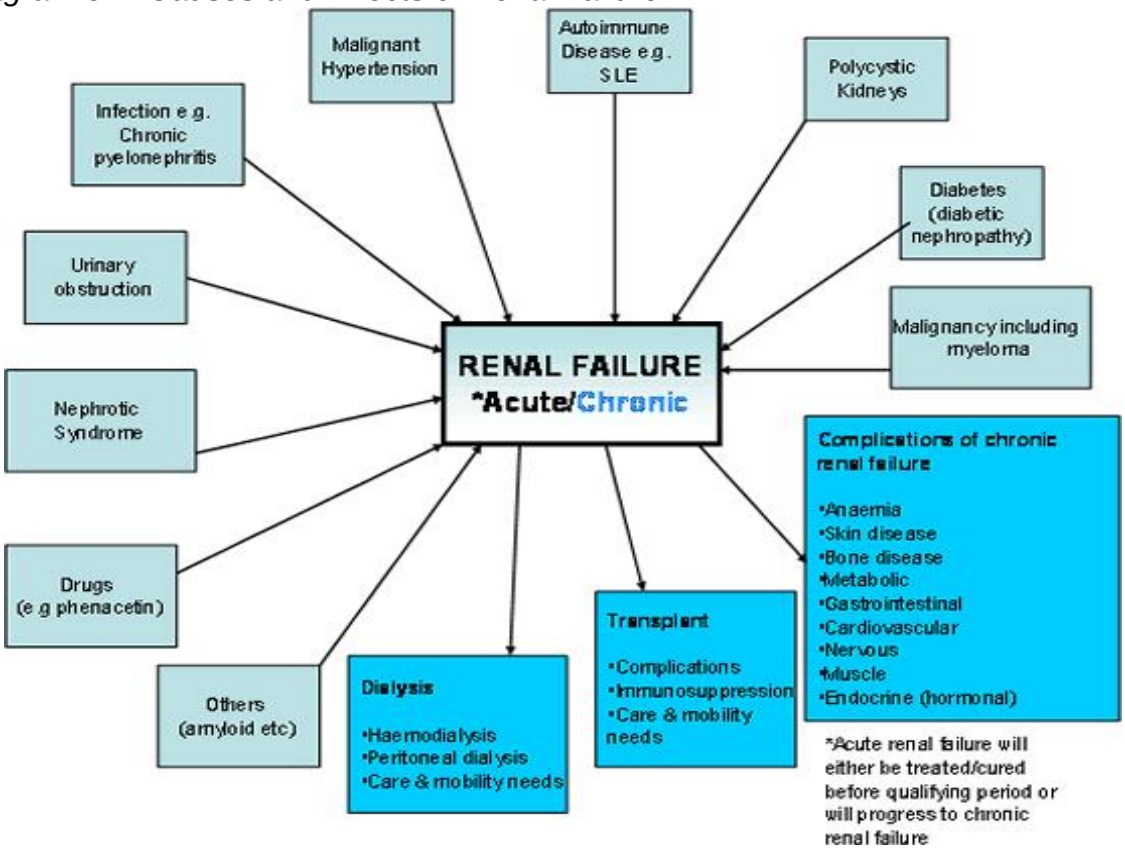
Learning Outcomes

At the end of the lesson the learner should be able to: -
1) Describe the causes pathogenesis, pathophysiology and pathology of renal failure
2) Describe the complications of renal failure
3) Investigate renal failure

1.0 INTRODUCTION

- Renal failure can be acute renal failure (ARF), chronic renal failure (CRF) or End stage kidney disease (ESKD)

Diagram 3.1: Causes and Effects of Renal Failure

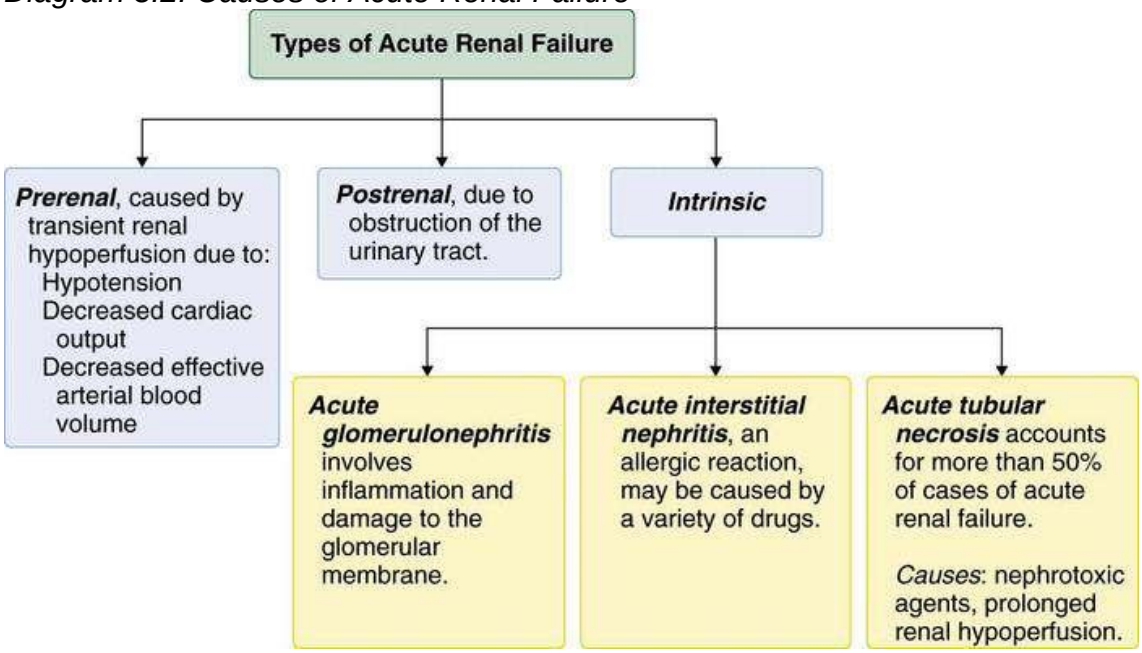


- Acute kidney disease represents a spectrum of disease associated with a sudden onset of renal parenchymal injury most typically characterized by generalized failure of the kidneys to meet the excretory, metabolic, and endocrine demands of the body, i.e. acute renal failure (ARF)Renal failure can be classified as acute renal failure (ARF) and chronic renal failure (CRF)
- **ARF** is a syndrome characterized by rapid decline in GFR (a period of hours to weeks), retention of nitrogenous waste products and disturbance of extracellular fluid volume and electrolyte and acid-base homeostasis
- Commonly defined as an abrupt decline in renal function, manifested by acute elevation in plasma blood urea nitrogen (BUN) and serum creatinine, occurring in hours to days to weeks, and usually reversible.
- Is reversible as the kidney can recover almost complete loss of function
- Form of total renal failure in which majority of the nephrons stop working suddenly and simultaneously resulting in a drastic fall in urine production (**oliguria**) or no urine production (**anuria**)

2.0 AETIOLOGY

1) Pre-renal (pre-renal azotaemia) - 30 - 60% cases
2) Renal (renal azotaemia) - 20 - 40% cases
3) Post-renal (post-renal azotaemia) - 1 - 10% cases

Diagram 3.2: Causes of Acute Renal Failure



3.0 PRE-RENAL FAILURE

- Most common form of renal failure and represents a physiologic response to mild-moderate renal hypofunction
- Rapidly reversible upon restoring renal blood flow and glomerular ultrafiltration pressure
- Epithelial cells of the proximal and distal convoluted tubules are the most sensitive part of the nephron to poor perfusion and anoxia they may undergo marked necrosis (**acute tubular necrosis**).

Causes

1) Decreased effective intravascular volume
   a) Volume depletion
      i) Blood loss – haemorrhage
      ii) Sodium depletion - GIT loss (diarrhoea and vomiting, prolonged nasogastric drainage, prolonged biliary drainage), Renal loss (diuretics, salt-losing nephritis and osmotic diuresis in diabetes) and Skin loss (burns, excessive sweating)
   b) Volume redistribution
      i) Third spacing of fluid – pancreatitis, ascites, peritonitis, burns and nephrotic syndrome
      ii) Peripheral vasodilatation – sepsis, anti-hypertensive agents and anaphylaxis
2) Decreased cardiac output - congestive cardiac failure, cardiomyopathy, myocardial infarction, pericardial tamponade and pulmonary embolism
3) Intra-renal haemodynamic disturbances
   a) Systemic vasodilatation – sepsis, anti-hypertensives, anaphylaxis and anaesthesia
   b) Renal vasoconstriction – hypercalcaemia, norepinephrine and epinephrine
   c) Hepato-renal syndrome
   d) Renal hypoperfusion with impairment of renal autoregulatory responses - ACE inhibitors and NSAIDS
   e) Hyperviscosity (rare) - multiple myeloma and polycythaemia

4.0 RENAL (INTRINSIC RENAL) FAILURE

- Normal renal function requires adequate arterial/venous blood supply and normal glomeruli and tubules
- Intrinsic renal azotaemia can complicate many diverse disease conditions of the renal parenchyma.

Causes

1) Vascular
   a. Renovascular obstruction (bilateral/unilateral) e.g. Renal artery disease e.g. embolism, thrombosis, atherosclerosis, vasculitis and aneurysm.
   b. Renal vein obstruction – thrombosis and compression
   c. Vasculitis;, scleroderma, atheroembolic renal disease, malignant hypertension, and thrombotic angiopathy
2) Glomerular Disease
   a. Glomerulonephritis and vasculitis
   b. Others such as haemolytic uraemia syndrome, Thrombotic thrombocytopenia purpura, D.I.C, toxaemia of pregnancy (P.E.T), accelerated hypertension, radiation nephritis and S.L.E
3) Interstitial
   a. Tubular and Interstitial Damage - Acute tubular necrosis (A.T.N)
      - Ischaemia due to hypovolaemia, low cardiac output, renal artery vasoconstriction
      - Toxins - Exogenous toxins e.g. radiocontrast, antibiotics, chemotherapy, organic solvents and acetaminophen (paracetamol) and endogenous toxins e.g. haemolysis, uric acid, oxalate and plasma cell dyscrasia (e.g. myeloma)
   b. Interstitial nephritis
      - Allergic to antibiotics (Beta-lactams, sulphonamides, trimethoprim, rifampicin), NSAIDS, diuretics and captopril.
      - Infections - bacterial, viral and fungal
      - Infiltration – lymphoma, leukaemia, Sarcoidosis
      - Idiopathic
   c. Intratubular deposition and obstruction - myeloma proteins, uric acid, oxalate, sulphonamides and methotraxate
   d. Renal allograft rejection/immunological reactions

5.0 POST RENAL FAILURE

- Obstruction may occur at any part of the urinary tract

Causes

1) The Kidneys - Stag horn calculus, Cancer of the pelvis, Pelvic-ureteric junction stricture
2) Ureters
   a. Intrinsic – calculi, blood clots, sloughed renal tissue/papillae, fungus ball. Malignancy, congenital defects (congenital megaureter)
   b. Extrinsic – malignancy (cervix, colon), external compression (retroperitoneal fibrosis), ureteral trauma, high impact injury
3) The Bladder
   a. Mechanical: Benign prostatic hyperplasia, prostate cancer, bladder cancer, urethral strictures, phimosis, paraphimosis, urethral valves, obstructed indwelling urinary catheter
   b. Neurogenic: Anticholinergic drugs, UMNL or LMNL

4) Neurogenic bladder(anticholinergic drugs, upper or lower motor neurone lesion), prostatic hypertrophy, calculi, cancer and blood clot
5) Urethra - congenital valve, , phimosis, paraphimosis and urethral stricture secondary to calculi, gonococcal infections and instrumentation

6.0 CLASSIFICATION OF ACUTE RENAL FAILURE – RIFLE Criteria

- Comprises three grades of injury (risk, injury and failure) and two outcomes (loss and end-stage kidney disease)
- Assessment of grade of injury is based on the presence of one of the following parameters: an increase in the serum level of creatinine, a decrease in the rate of glomerular filtration or a change in the volume of urine output.

Diagram 3.3: Classification of ARF

	Change in serum level of creatinine	Change in GFR	Urine output
Risk of kidney dysfunction	Increase > 50%	Decrease > 25%	< 0.5 mL/kg hourly for > 6 h
Injury to the kidney	Twofold increase	Decrease > 50%	< 0.5 mL/kg hourly for > 12 h
Failure of kidney function	Threefold increase or ≥ 350 µmol/L with an acute rise of ≥ 44 µmol/L	Decrease > 75%	< 0.5 mL/kg hourly for > 24 h or anuria for > 12 h
Loss of kidney function	Loss of kidney function, which requires dialysis, lasting longer than 4 w		
End-stage kidney disease	Loss of kidney function, which requires dialysis, lasting longer than 3 mo		

7.0 PATHOPHYSIOLOGY OF ARF

- Nephron functions as a unit that highly depends on tubular integrity as an anatomical channel, a transporting epithelium and adequate blood supply.
- Pathophysiological consequences of renal failure give rise to the complex manifestations of renal failure arise from the following principal disturbances: -
  i) Failure of water and electrolyte homeostasis
  ii) Retention of toxic substances
  iii) Failure of renal endocrine function
  iv) Homeostatic adaptations – the “trade-off” hypothesis

7.1. Pathogenesis

The major events in ARF and ATN are: -
a) Tubule Cell Injury
   - Results from ischemia and toxins causing numerous structural (cellular swelling, loss of brush boarder, blebbing, loss of polarity, cell detachment, necrosis and apoptosis) and functional alterations in epithelial cells
   - The initial insult disrupts cell membrane leading to intracellular anoxia and rapid influx of calcium ions disturbing mitochondrial respiration causing anaerobic glycolysis and intracellular acidosis leading to denaturation of intracellular protein, lysosomal disruption and cell death.

b) Disturbances in Blood Flow
   - Haemodynamic alterations mainly intrarenal vasoconstriction cause reduced GFR and oxygen supply to the tubules in the outer medulla an important functional structure
   - These changes are driven by RAAS, tubuloglomerular feedback mechanism (increased distal sodium delivery), sub-lethal endothelial injury (endothelin) and decreased production of vasodilators nitric oxide and PGI_2.
   - Direct ischemia or toxins cause reduced GFR due to messangial contraction

7.2. Pathophysiology

7.2.1. Prerenal Failure

- Hypovolaemia, hypotension and impaired heart function result in failure of perfusion with blood to the kidney
- Hypovolaemia leads to a fall in the systemic arterial pressure, which is detected by the carotid sinuses and cardiac barorecptors. The neural and hormonal responses are triggered to restore blood volume and arterial pressure. This includes the activation of the sympathetic nervous system, rennin-angiotensin-aldosterone (RAA) mechanism and release of arginine vasopressin (AVP).
- Norepinephrine, angiotensin II and AVP: - cause vasoconstriction in non-essential vascular bed, inhibit salt loss through the sweat glands, stimulate the thirst and salt appetite and promote renal salt and water retention.

7.2.2. Renal Intrinsic

Can be due to
- Acute tubular necrosis
- Glomerular damage
- Interstitial damage
- Obstruction to urine flow within the renal tissues

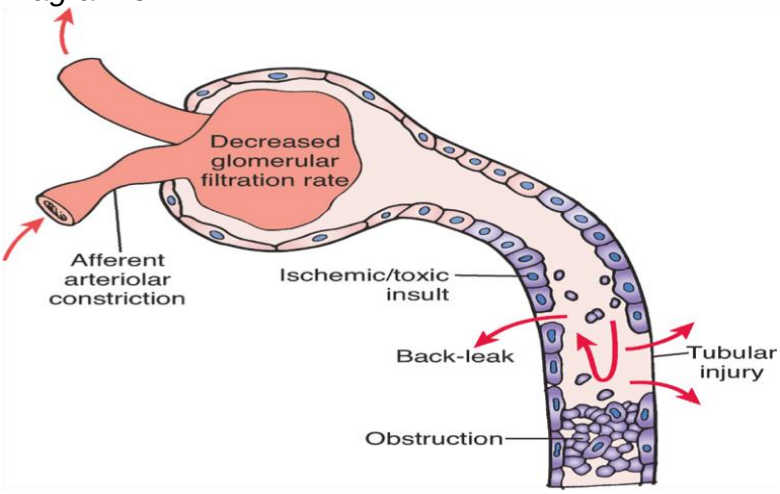
Acute Tubular Necrosis (ATN)

- There is secretory failure manifesting with *persistent alteration of blood flow*, *alteration of kidney capillary ultrafiltration process, renal tubule obstruction and back leakage of filtrate through damaged tubules*
- Has three characteristic phases - *initial (oliguric) phase, maintenance (diuretic) phase and recovery phase*.

Initial (Oliguric) Phase

- Initial period of hypoperfusion that lasts 36 hours where a damaging stimulus causes necrosis of renal tubular epithelium
- Tubular function is disturbed and the GFR declines as a result of reduced glomerular ultrafiltration, obstruction of glomerular filtrate flow by casts (epithelial cells, necrotic debris) and back leak of GF through injured tubular epithelium resulting in production of dark urine of small quantities (40 – 400 mls/24 hours).
- There is progressive rise in urea and other nitrogenous metabolites due to a decline in GFR formation and acidosis due to breakdown of endogenous fats and proteins.
- Decline in urine formation leads to accumulation of waste products of protein metabolism in blood and leading to azotaemia, metabolic acidosis, hyperkalaemia, hypernatraemia and other secondary effects.

Diagram 3.4: ATN



The Polyuric (Diuretic) Phase

- Lasts over 1 – 3 weeks
- Epithelial cell injury is established and urine output is low
- GFR remains low due to persistent intra-renal vasoconstriction and medullary ischaemia and uraemic complications set in hence the name maintenance phase.
- In reversible cases regeneration of renal tubular epithelium takes place with removal of dead material by phagocytic cells
- Tubules open up increasing glomerular blood flow and the patient develops **polyuria (up to 3L/day)** because the regenerated tubular cells have not fully developed for selective reabsorption of various substances
- There is increased drawing of sodium and water by the increased level of urea and creatinine as they move through the nephron to be excreted. The urine is of low specific gravity.
- Fluid replacement is important to compensate for excessive urine loss

Recovery Phase

- Tubular cells re-establish differentiation with restoration of homeostatic renal function
- May take up to 1 year for full recovery of renal function.

7.2.3. Post renal

Obstruction leads to failure of excretion of urine from the system allowing accumulation of the urine within the renal structures subsequently damaging them.

8.0 PATHOLOGY

Macroscopy

1) Kidneys are enlarged and on section
2) Cut surface bulges due to dilatation of tubules and interstitial oedema
3) Cortical vessels contain little blood and cortex appears pale with blurring of normal radial pattern
4) Medulla is dark and congested
5) Petechial haemorrhage in the cortex

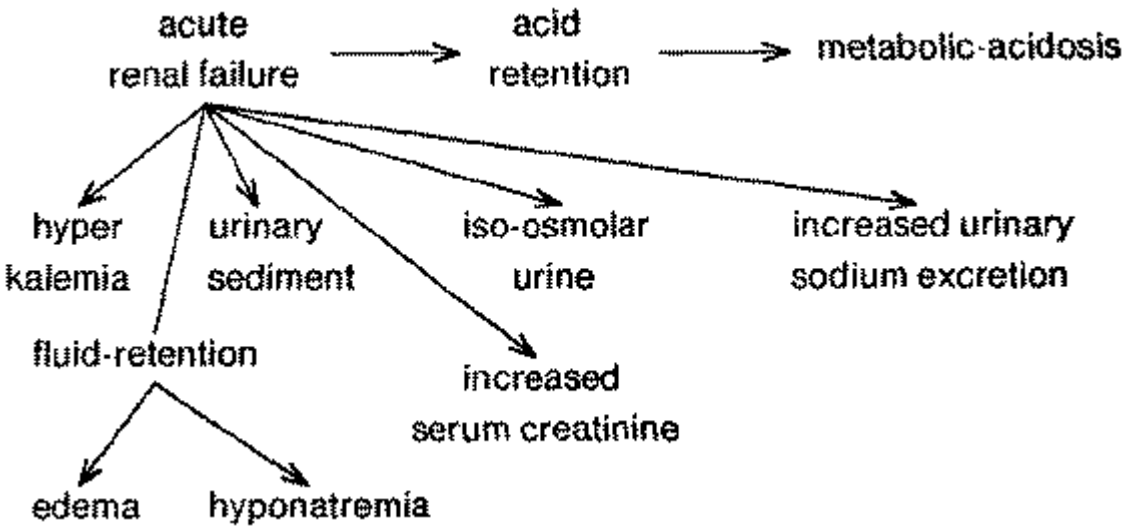
Microscopy

1) Debris and casts form in the ascending limb and distal convoluted tubules
2) Medulla shows oedema, casts and cellular infiltration (polymorphs) with neutrophils, monocytes and macrophages

9.0 SYMPTOMS AND SIGNS

- Initially, weight gain and peripheral oedema may be the only findings
- Often, predominant symptoms are those of the underlying illness or those caused by the surgical complication that precipitated renal deterioration.
- Later, as nitrogenous products accumulate, symptoms of uraemia may develop, including anorexia, nausea and vomiting, weakness, myoclonic jerks, seizures, confusion, and coma; asterixis and hyperreflexia may be present on examination.
- Chest pain (typically worse with inspiration or when recumbent), a pericardial friction rub, and findings of pericardial tamponade may occur if uremic pericarditis is present.
- Fluid accumulation in the lungs may cause dyspnoea and crackles on auscultation.

Diagram 4.4: Features of ARF



10.0 FLUID AND ELECTROLYTE HOMEOSTASIS

- With reduced GFR, tubular reabsorption is decreased and the kidney excretes a much larger fraction of the filtrate
- To correct a given electrolyte imbalance, a large change in fractional excretion is needed (an adaptation called – **magnification phenomenon**)
- These adaptations help in chronic renal failure (CRF) until the GFR is less than 10 mls/min
- Most patients with CRF are able to avoid severe disturbances of water and electrolytes as opposed to in ARF due to this mechanism
- What happens to sodium and water, potassium, acid- base balance and ureamic toxins

11.0 INVESTIGATIONS

1) Full blood counts
2) Serum urea/electrolytes & creatinine clearance (urea ↑, creatinine ↑, Na^+ ↑, K^+↑, Ca^{2+}↓, PO_4^{3-}↑)
3) Urinalysis
4) Autoantibodies
5) ASOT
6) Bence Jones proteins
7) CXR
8) ECG
9) Renal U/S
10) MRI

Study Question

- *How significant are these investigations?*
- *What are the important parameters in each case?*

Lesson 4: Chronic Renal Failure & End Stage Kidney Disease

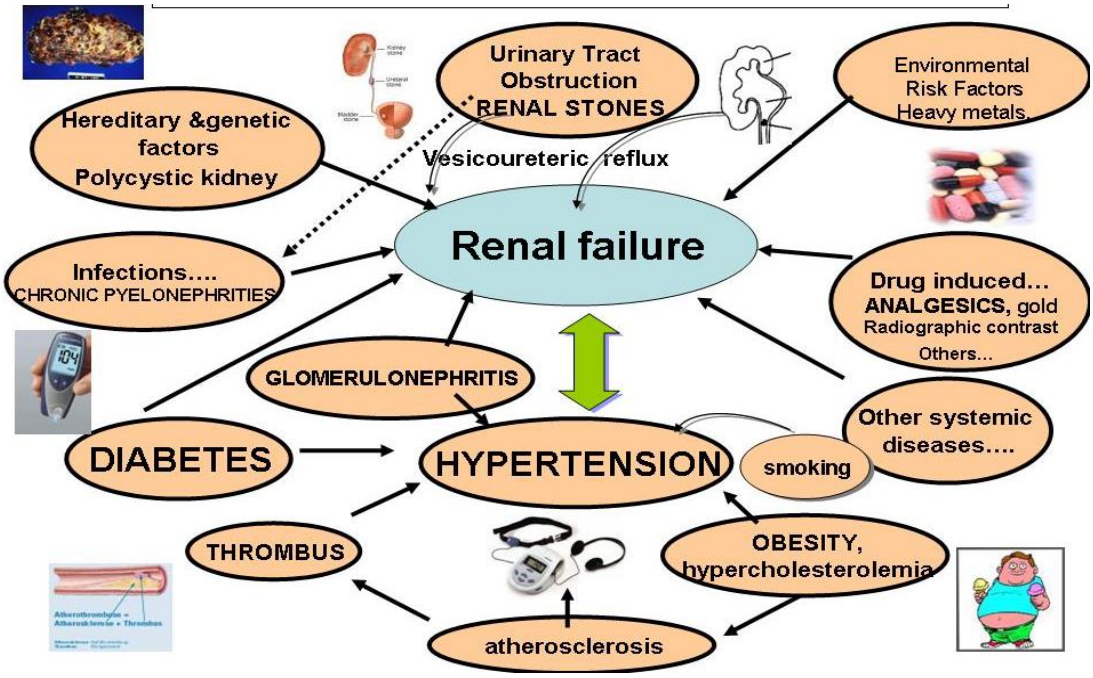
Learning Outcomes

At end of the lesson the learner should be able to: -
1) Explain the pathophysiology and pathology of chronic renal failure
2) Investigate chronic renal failure
3) Discuss the complications of chronic renal failure

1.0 INTRODUCTION

- Chronic renal failure (CRF)
  - Is a syndrome characterized by substantial, progressive and irreversible long standing loss of renal function
  - A GFR below 12 –15 ml/minute (normal GFR is about 100 ml/min) or a GFR of <60mL/min/1.73m2 for ≥ 3 months
- Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood and urine tests or imaging studies.
- Biochemical evidence of renal insufficiency ensues when 75% of the renal function is lost and prolonged renal injury causes progressive and irreversible destruction of the nephrons
- Reduced nephron mass leads to structural and functional hypertrophy of the few surviving nephron
- CRF results in progressive retention of nitrogenous products, progressive failure of tubular function resulting in loss of the capacity to maintain fluid and electrolyte homeostasis, acid-base imbalance and endocrine function failure (excess rennin and less erythropoietin).

2.0 RISK FACTORS



3.0 CAUSES

1) Chronic glomerulonephritis
2) Chronic pyelonephritis
3) Interstitial nephritis
4) Diabetic glomerulosclerosis

5) Hypertension
6) Tumours
7) Drugs and toxins
8) Renovascular and thrombotic disease - unresolved ARF
9) Interstitial disease such as interstitial nephrons, pyelonephrosis, papillary necrosis due to diabetes, SCD, anaemia and analgesic nephropathy, deposits of urates and oxalate and metals, Irradiation/drugs/toxins
10) Cystic diseases - Polycystic kidney
11) Urinary obstruction - as in ARF

4.0 PATHOGENESIS

- Glomerular damage (primary or secondary) causes destruction of the nephrons interfering with the filtration process.
- Damage of the renal tubes and interstitial tissues results in alterations in reabsorption and secretory functions of the kidney
- Vascular pathologies culminate in ischaemia and necrosis of the nephrons
- Infections and toxic agents cause nephron damage
- Obstruction of the urinary tract leads to progressive damage to the nephron due to fluid backpressure and reflux.

5.0 PATHOPHYSIOLOGY

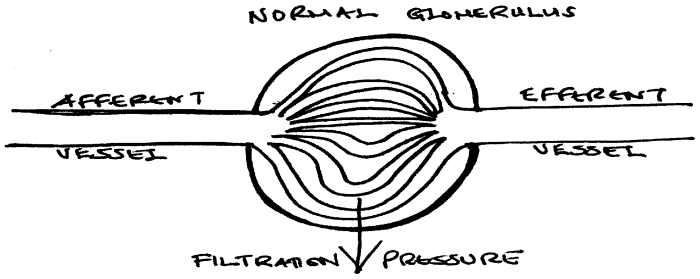
- As the nephrons are lost, the surviving nephrons show compensatory hypertrophy and are continually active without any rest (in the normal kidney, the nephrons do not all function simultaneously)
- Compensatory hypertrophy of the normal nephrons increases individual nephron GFR but the overall GFR fails due to adaptive **hyperfiltration** mediated by increase in glomerular capillary pressures and flow.
- In compensatory hypertrophy there is dilatation of afferent arterioles and constriction of the efferent arteriole which facilitates hyperfiltration. In such circumstances the glomerulus is subjected to increased wear and tear culminating in sclerosis.

Compensatory Mechanisms

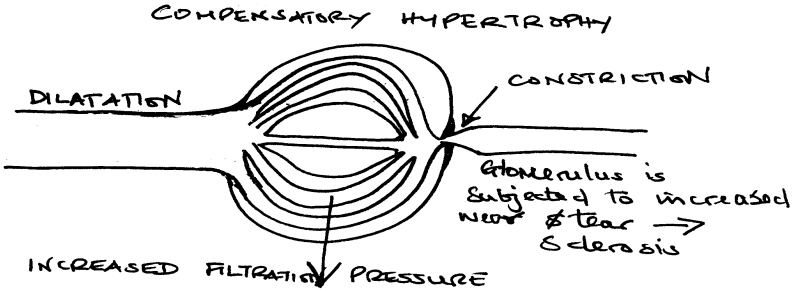
- Hypertrophy of tubules especially the proximal tubules leads to reduced water filtration resulting in reduced water reabsorption to maintain urine volume around 1.5 litres per 24 hours (same holds for sodium)
- Filtration of up to 10% of the normal volume leads to reduced reabsorption to less than 90% and problems arise when there is external water electrolyte balance.
- Increase in GF volume and reduced tubular cell mass results in reduced sodium and chloride reabsorption in the thick ascending loop of Henle causing a reduction in hypertonicity of the medulla on which urine-concentrating mechanisms rely on. This ends up with osmotic diuresis due to high urea, reduced responsiveness of collecting tubes to AVP and reduced acidification of urine results from reduced ammonia production following reduced tubular mass
- Glomerular hyperfiltration stabilizes the amount of nitrogenous waste products (but only at a high level). For example if the GFR is 120 mls/min and urea is 5 mmol/L, therefore urea in glomerular filtrate (GF) is 5/1000 mmol/L X 120 mls/min which equals 0.6 mmol/L per min. Hence if the GFR reduces to 12 mls/min; to maintain homeostasis, urea will be 50 mmol/L. That is U/1000 mmol/L x 12 = 0.6 mmol/L, therefore U = (0.6 x 1000)/12 = 50 mmol/L because 50/1000 x 12 = 0.6 mmol/L.

Diagram 4.1: Compensatory Mechanisms

a) Normal Glomerulus



c) Compensatory Hypertrophy



6.0 EFFECTS OF CRF

The effects of CRF are
1) Water and sodium imbalance
2) Disturbance of acid-base balance
3) Uraemia
4) Hormonal abnormalities
5) Hypertension

- Discuss the pathogenesis and pathophyisology of these effects
- What important findings do you expect on physical examination in a patient having renal failure?

7.0 BIOCHEMICAL CHANGES

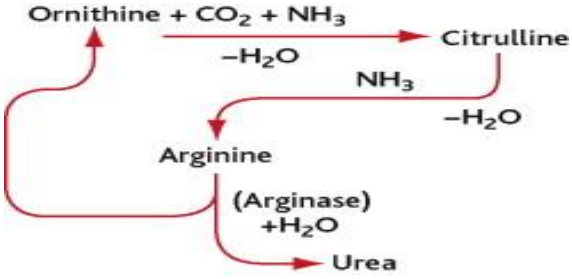
Urea

- Reduced functional renal tissue leads to reduced RBF and GFR and thus the amount of urea removed from the blood is reduced with subsequent increase of urea serum levels.
- Retention of urea indicates retention of non-protein nitrogenous metabolites that are toxic to the body.

Urea Formation

- The body is usually unable to store proteins or amino acids therefore the surplus is destroyed by in liver cells that deaminate excess amino acids brought to the liver by the hepatic portal vein by removal of the amino group NH_2 forming ammonia (NH_3)
- The ammonia released from deammination is removed from the blood by conversion to urea
- The urea that is formed diffuses from the liver cells into the body fluids to the kidney where it is excreted.

$$2NH_3 + CO2 = N_2N{=}C(-NH_2) + H_2O$$
$$\qquad\qquad\qquad\qquad\quad \|$$
$$\qquad\qquad\qquad\qquad\quad O$$



Urea Excretion

- Body forms 25 – 30 gms/day of urea whose excretion is determined by urea concentration in **plasma** and the **GFR**
- The two factors increase urea excretion because a load of urea entering the proximal tubules equals the urea concentration in plasma multiplied by the GFR. Usually 40 – 60% of urea passes the tubules into the urine.
- Reduced GFR leads to reduced urea excretion resulting in urea accumulating in the body tissues until its plasma concentration is very high, then it becomes great enough to be excreted as rapidly as it is formed but the high concentrations are severely damaging to the body

Water

- There is reduced GFR which causes retention of sodium and loss of tubular reabsorptive power leading to retention of water
- Volume variability leads to development of different clinical features: -

  i) With sufficient water intake the kidney produces 2.5 litres of dilute urine.
  ii) With inadequate water intake, urine production continues resulting in dehydration leading to reduced blood volume, reduced blood pressure, reduced urine volume and increased urea.
  iii) With excessive water intake the patient develops water intoxication and pulmonary oedema. There is heart failure as a complication of CRF with hypertension leading to reduced RBF and reduced GFR and increased urea and cardiac oedema
  iv) Polyuria –tubules fail to effect the normal variation in concentration of urine and the high urea in the glomerular filtrate exerts a diuretic effect leading to increased urine production.

Electrolytes

Sodium

- Range of secretion of sodium and potassium is limited because the few functional nephrons in CRF must excrete more Na/K per nephron to maintain homeostasis.
- Sodium deficiency leads to reduced plasma volume and blood pressure causing oliguria, nitrogen retention and acidosis
- Causes of sodium deficiency in CRF are renal loss, restricted dietary intake and diarrhoea and vomiting due to uraemia
- Sodium loss in CRF secondary to chronic pyelonephritis (CPN) is usually severe (DDx: Addison's disease – adrenocortical insufficiency). Injudicious correction may induce systemic and pulmonary oedema

Potassium

- Patients with CRF are able to maintain serum potassium within normal limits until the GFR falls below 5 ml/min

- This is attained through adaptation mechanisms of increased potassium excretion by the nephrons which involve increased fractional excretion of potassium due to increased sodium flow in the DCT and the collecting ducts, adaptive increase in Na^+K^+-ATPase activity and minerocorticoid action
- If the compensatory mechanisms fail, hyperkalaemia may be an early feature of renal failure in patients with metabolic disorders and poses the life threatening risk of cardiac arrthymias.

8.0 CLINICAL FEATURES

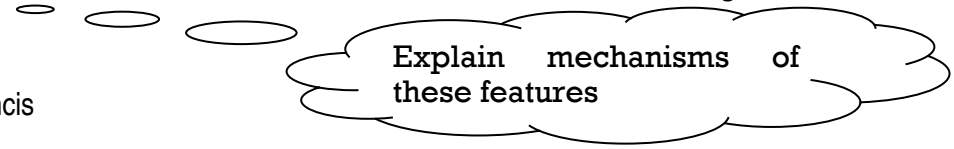
- CRF evolves progressively through five stages
- Manifestations of full-blown CRF resulting in uraemic syndrome can be primary (renal) uraemic manifestations and secondary (systemic and extra-renal) uraemic manifestations.

Primary uraemic (renal) manifestations

1) Metabolic acidosis
   - Results from loss of acid-balance; excess hydrogen ions with declining levels of bicarbonate
   - Features – Kussmaul breathing, hyperkalaemia, hypercalcaemia
2) Hyperkalaemia
   - Accumulation of potassium due to decreased GFR
   - Metabolic acidosis worsens hyperkalaemia
   - Features – cardiac arrthymias, weakness, nausea, intestinal colic, diarrhoea, muscular irritability and flaccid paralysis
3) Sodium and water imbalance
   - Poor passage of water and sodium into the glomerular filtrate due to decreased GFR hence they are retained; Rennin plays a role
   - Features – oedema, hypovolaemia, circulatory overload with congestive cardiac failure
4) Hyperuricaemia
   - Excessive accumulation of uric acid in blood due to a reduced GFR
   - Uric acid crystals can be deposited in joints and soft tissues causing gout.
5) Azotaemia - elevated blood urea nitrogen (BUN) and creatinine due to decreased GFR.

Secondary ureamic (extra-renal) manifestations

1) Anaemia: Due to decreased erythropoietin production as result of reduced renal mass, bleeding, poor intake and bone marrow depression. Features – pallor, lethargy, breathlessness on exercise.
2) Features of platelet abnormality – epistaxis, bruising (explain why)
3) Skin – pigmentation and pruritis (explain why)
4) Respiratory system
   - Dyspnoea – due to hypovolaemia and heart failure that causes pulmonary congestion (pulmonary oedema) and ureamic pneumonitis.
   - Kussmaul's breathing
5) Digestive system
   - Azotaemia causes mucosal ulcerations in the stomach and intestines
   - Bleeding (haemorrhagic ulcers) and anaemia
   - Gastro-intestinal irritation leads to anorexia, nausea, vomiting and diarrhoea



6) Cardiovascular system
   - Ureamic pericarditis
   - Fluid retention
   - Hypertension, heart failure and peripheral vascular disease
7) Endocrine/gonads- Amenorrhoea, Infertility, Erectile impotence
8) Central nervous system – confusion, coma, fits, myopathy, peripheral neuropathy and intellectual deterioration
9) Renal osteodystrophy – osteomalacia, muscle weakness, bone pain, osteosclerosis and hyperparathyroidism
10) Depression of immunological reaction

9.0 STAGES OF CKD

Diagram 4.3: Stages of CKD

Stage	GfR	Description
1	90+	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease
2	60-89	Midly reduced kidney function, and other findings (as for stage 1) point to kidney disease
3A 3B	45-59 30-44	Moderately reduced kidney function
4	15-29	Severely reduced kidney function
5	<15 or on dialysis	Very severe or endstage kidney failure (sometimes call established renal failure)

10.0 PATHOLOGICAL CHANGES AND COMPLICATIONS

1) Anaemia – is present and the causes are as follows
   a. Erythropoietin deficiency
   b. Bone marrow toxins (polyamines, Ar, Cu, Pb and Al)
   c. Bone marrow fibrosis due to hyperparathyroidism
   d. Haematinic deficiency (Fe, vitamin B12 and folate)
   e. Blood loss (G.I.T bleeding, blood loss in haemodialysis, platelet dysfunction, frequent blood sampling)
   f. Cell destruction (mechanical, oxidants)
   g. Abnormal cell membranes increasing osmotic fragility
   h. Drugs (ACE inhibitors)

2) Bone disease
   a. Renal osteodystrophy (osteomalacia, osteoporosis, osteosclerosis)
   b. Decreased renal production of 1, 25 dihydroxycalciferol decreasing calcium absorption.
3) Skin disease
   a. Pruritis due to increased calcium-phosphate product and magnesium, hyperparathroidism, iron deficiency, inadequate dialysis and dry skin.
   b. Photosensitive skin

4) G.I.T complications - decreased gastric emptying increasing the risk of oesophagitis, increased risk of peptic ulcer disease and acute pancreatitis and constipation
5) Nervous system
   a. Central Nervous system - depressed cerebral function and seizure threshold
   b. Autonomic nervous system - increased circulating catecholamine levels, impaired baroreceptor sensitivity and efferent vagal function
   c. Peripheral nervous system - Carpo-tunnel syndrome and restless legs syndrome
6) Cardiovascular system – Hypertension, cardiac enlargement (due to anaemia, hypertension, sympathetic over activity), vascular calcification, uraemic pericarditis and dialysis pericarditis
7) Muscle dysfunction – uraemia interferes with muscle energy metabolism.
8) Metabolic abnormalities - gout due to urate retention, insulin resistance in advanced disease and abnormalities of lipid metabolism (hypercholestearaemia)
9) Endocrine abnormalities
   a. Hyperprolactinemia causes galactorrhoea
   b. Increased LH in both sexes
   c. Reduced serum testosterone (impotence and reduced spermatogenesis)
   d. Disturbed cyclical changes in female hormones (amenorrhoea, oligomennorhoea)
   e. Reduced growth hormone secretion and activity
   f. Abnormal thyroid hormone levels due to altered protein binding

- ✔ Compare and contrast acute and chronic renal failure
- ✔ Explain how and why renal vasculature and renal blood flow is unique
- ✔ What is the pathophysiology of complications in CRF?

11.0 INVESTIGATIONS

1) Full Blood Counts (FBC) – normocytic normochromic anaemia
2) Blood glucose - Hyperglycaemia
3) Urea/electrolytes/creatinine - ↑ urea, ↑ creatinine, ↓ Ca^{2+}, ↑ PO_4^{3-},
4) Serum alkaline phosphotase (renal osteodystrophy) ↑
5) ↑ PTH (hyperparathyroidism)
6) Urates ↑
7) Renal ultrasound – small granular contracted kidney with thinning of the cortex and loss of corticomedullary junction
8) IVU
9) CXR – cardiomegally, pleural and pericardial effusion, pulmonary oedema
10) Bone X-rays – erosive cortical defects in the skull (“pepper pot skull”), a “rugger jersy” appearance of the spine
11) Renal biopsy

End Stage Renal Disease (ESRD/ESKD)

1.0 INTRODUCTION

- Chronic kidney disease (CKD) is defined as the presence of kidney damage, or a decreased level of kidney function, for a period of three months or more.
- End-stage kidney disease (ESKD) is the most severe form of chronic kidney disease, also known as Stage 5 chronic kidney disease (CKD) or kidney failure.
- End-stage renal disease is when the kidneys permanently fail to work.
- ESRD are late stages of renal disease comprising mainly features of CRF and the main stay of management is conservative, haemodialysis and renal transplant.

2.0 FEATURES OF ESRD

	Feature	Description
1.	Polyuria	Damage of Bowman's capsule, tubules and the GBM leads to loss of fluid into the tubules with minimal reabsorption as the proteins entering the tubules exert an osmotic pressure resulting in osmotic diuresis;Increased urea levels contribute to increase in osmotic load.
2.	Nocturia	During the day the patient is ambulant and the fluid moves into the perivascular tissue spaces due to activity and reduction in the osmotic pressure in the vascular tree. At night there is change of osmotic gradient such that fluid moves back into the vascular system. The osmotic load due to increased urea load exerts a diuretic effect throughout 24 hours increasing production of large amounts of dilute urine at night
3.	Polydipsia	Loss of fluid as a result of polyuria and oedema formation leads to dehydration of cells triggering the thirst mechanism hence increased water intake
4.	Anaemia	Reduced production of erythropoietin, bone marrow depression (due to uraemia). Other effects of uraemia are nausea, cell destruction (haemolysis) and bleeding tendencies. Kidney produces factors which when incubated with plasma produce erythropoietin hence the anaemia is normocytic normochromic.
5.	Hypertension	Occurs due to failure of the renal BP control mechanisms.
6.	Oedema	Results from disturbance of fluid balance with retention of fluid in tissues ensuing due to alteration sin the osmotic and hydrostatic pressures.
7.	Acidosis	Kidneys control the acid-base balance and due to reduced bicarbonate ions acidosis sets in leading to *Kussmaul breathing*
8.	Uraemia	Uraemia results from accumulation of urea in the blood as a result of reduced excretion. Uraemia is associated with bleeding tendencies such as: - haematemesis, melena stools, epistaxis, haematochazia, peptic ulcer (duodenal and gastric) and thrombocytopenia purpura. Accumulation of urea and other nitrogenous compounds cause increased excitability hence muscles go into twitches. Ureamia causes nausea, vomiting and hiccups. Uraemia has adverse effects on the brain. With increased urea and other nitrogenous substances, the patient becomes confused and drowsy and ultimately passes into a comatose state – *uraemic coma.*
9.	Bone pains	Bone pains occur due to osteomalacia and osteoporosis resulting from reduced 1-25 dihydrocholecalciferol secondary to reduced calcium absorption. Calcium absorption is controlled by vitamin D_3. Vitamin D (cholecalciferol) is converted to 25 hydroxycholecalciferol in liver and later to 1-25 dihydrocholecalciferol in the kidney. The eventual outcome is reduced serum calcium, spontaneous fractures and renal rickets

3.0 DIFFERENTIAL DIAGNOSIS OF ESKD

- When dealing with end-stage kidney disease, consider chronic renal failure because this condition is contained in CRF
- Chronic glomerulonephritis (CGN); Chronic pyelonephritis (CPN); Metabolic disease – Diabetes mellitus; Idiopathic/essential hypertension; Systemic lupus erythromatosus

(S.L.E); Polyarteritis nodosa; Renal artery disease/renal vein thrombosis; Renal tuberculosis; Congenital disorders – polycystic kidney; Toxins – drugs and heavy metals (lead, mercury); Obstructive nephropathy; Obstruction

4.0 MANAGEMENT OF ESKD

- Includes conservative management, haemodialysis and renal transplant

4.1. Dialysis

- In chemistry dialysis is the separation of particles in a liquid on the basis of differences in their ability to pass through a membrane while in medicine it is the clinical purification of blood by dialysis, as a substitute for the normal function of the kidney
- The artificial process of removing waste substances and fluid from the blood that are normally eliminated by the kidneys

Indications

1. Chronic – CRF and End stage kidney disease
2. Acute - acute poisoning; metabolic acidosis; electrolyte imbalance, fluid overload and uraemia

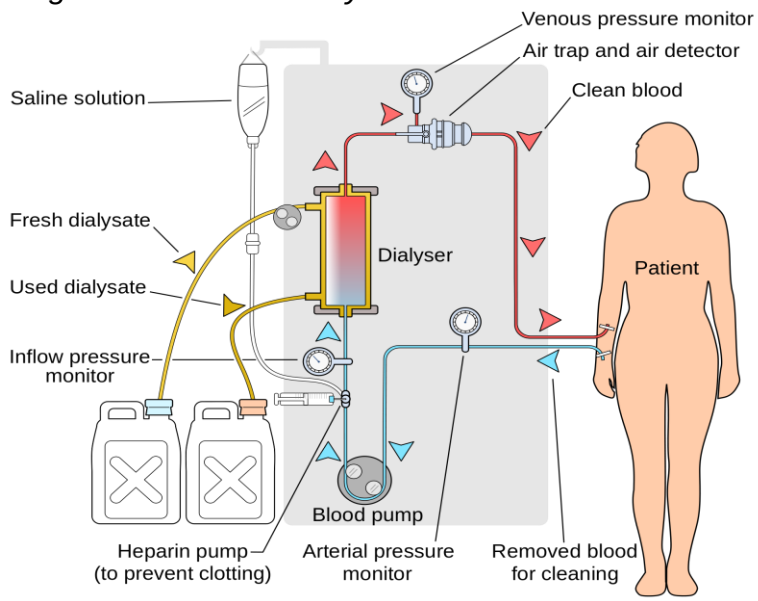
Types of Dialysis

- There are two modes of dialysis – haemodialysis and peritoneal dialysis
- Haemodialysis is a process of diffusion across a semi-permeable membrane removing unwanted substances from blood and adding desired components
- The dialysis equipment consists of blood delivery system, compartment and delivery system of the dialysate and the dialyzer

Haemodialysis

- Procedure to remove fluid and waste products from the blood and to correct electrolyte imbalances.
- Accomplished using a machine and a dialyzer, also referred to as an "artificial kidney."

Diagram 4.4: Haemodialysis



Peritoneal Dialysis

- Uses the peritoneal membrane as a semi-permeable membrane
- There are three different types of peritoneal dialysis: continuous ambulatory peritoneal dialysis (CAPD), continuous cyclic peritoneal dialysis (CCPD), and intermittent peritoneal dialysis (IPD).

Lesson 5: Glomerular Disease - Glomerulonephritis

Learning Outcomes

At the end of the lesson the learner should be able to: -
1) Describe the pathophysiology and pathology of glomerulonephritis
2) Investigate glomerulonephritis
3) Discuss the complications of glomerulonephritis

1.0 INTRODUCTION

- The glomerular plays a crucial role in the process of filtration of plasma through the GBM so as to initiate the tubular process of the kidney
- Glomerular filtration is a process facilitated mainly by the structure of the GBM and hydrostatic and osmotic forces operational in the region
- Glomerulus is the target of many disease processes culminating in temporary or permanent damage resulting in four main features namely reduction in urinary output, proteinuria, haematuria and hypertension.

Diagram 5.1: Glomerulus

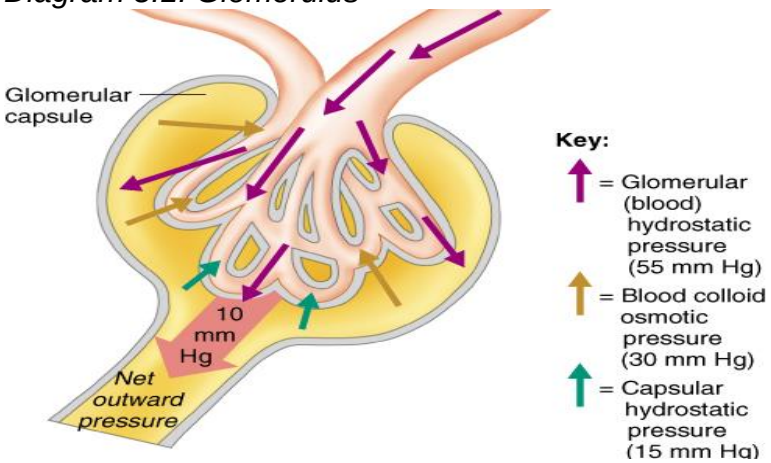


Table 5.1: Physiologic role of glomerular components

Component	Physiologic function	Consequence of injury
Endothelial cells	Maintain glomerular perfusion Prevents leucocyte adhesion Prevents platelet aggregation	Vasoconstriction Leucocyte infiltration Intravascular; Microthrombi
Mesangial cell	Control glomerular filtration	Mesangial proliferation and increased matrix
GBM	Prevents plasma protein filtration	Proteinuria
Visceral epithelial cells	Prevent plasma protein filtration	Proteinuria
Parietal epithelial cells	Maintains Bowman's space	Crescent formation

2.0 GLOMERULONEPHRITIS (GN)

- GN is a group of disorders in which there is immunological mediated glomerular injury; symmetrical involvement of the kidneys; secondary mechanisms of glomerular injury and renal disease being part of a generalized disease
- Lesions are primarily glomerular with other changes being secondary to the injury
- Glomerular disease produces four main features namely: - proteinuria, haematuria, hypertension and disturbed renal function.

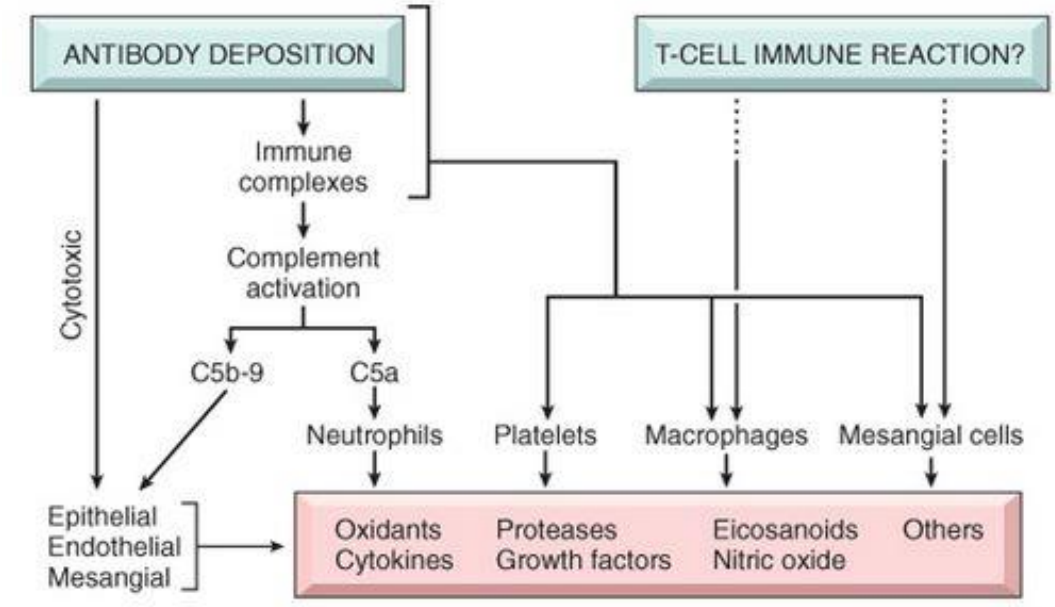
3.0 AETIOLOGY

- Immunological; Metabolic; Haemodynamic; Toxins; Deposition; Infections; Hereditary

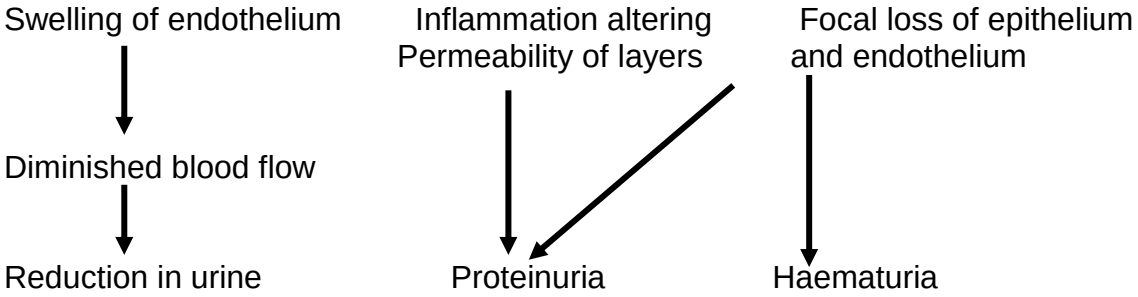
4.0 PATHOGENESIS OF GLOMERULAR INJURY

- Injury can occur at different sites such as the endothelial cells, mesangial cells, visceral epithelium, parietal epithelium and the glomerular basement membrane (GBM)
- Caused by immune mechanisms (cell-mediated or antibody-mediated) and non-immune mechanisms (metabolic, haemodynamics, deposition of substances, infections and inherited glomerular diseases)

Diagram 5.2: Mechanisms of Glomerular Injury



- Consequences of glomerular damage are reduction in urinary output, proteinuria and haematuria
- The mechanisms underlying these changes are as follows: -



4.1. Immune Mechanisms

- Immune reactions that lead to formation of antigen-antibody complexes in the glomerular account for the majority of cases of glomerular injury in glomerulonephritis.

Antibody mediated glomerular injury - Immune complex disease

- Local immune complex deposits – formation of Ag-Ab complexes locally e.g. streptococcal infection, viral infection, parasitic infections.
- Circulating immune complex deposits – Ag-Ab complexes circulating in blood e.g. endogenous (e.g. S.L.E) or exogenous (e.g. syphilis, falciparum malaria, hepatitis B virus).
- Anti-GBM disease –formation of antibodies against the GBM (mainly IgG type)
- Alternate pathway disease – activation of the complement system in the event of an infection may result in destruction of the glomerular. The antibody responsible is IgA.
- Other mechanisms – presence of autoantibodies e.g. anti-neutrophil cytoplasmic antibodies and anti-endothelial cell antibodies.
- Immune complexes are deposited within the glomerulus in the glomerular in three (3) ways namely
  i) Filtration of the circulating immune complexes
  ii) Reaction of the circulating antibodies with non-basement membrane glomerular Ag
  iii) Plasma Ag trapped in the capillary wall and Ab to the intrinsic constituents of the glomerular basement membrane (GBM).
- Deposition of the Ag-Ab complexes within the glomeruli depends on the sizes, shape and the electrical charge of the immune complexes.
- Ag localized within the glomerular epithelial cells can react with the circulating Ab (in-situ immune complex formation). There can also be development of Ab against the GBM. The antibodies are IgM, IgG, and IgA and complement C_3

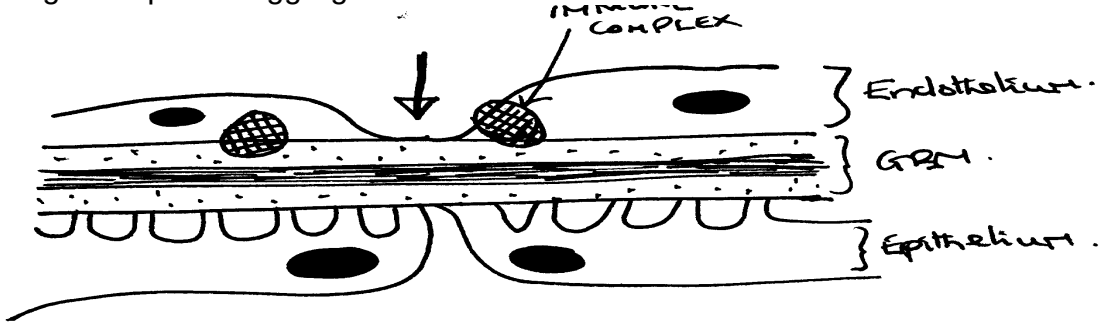
Sites of Deposition

The sites include: -

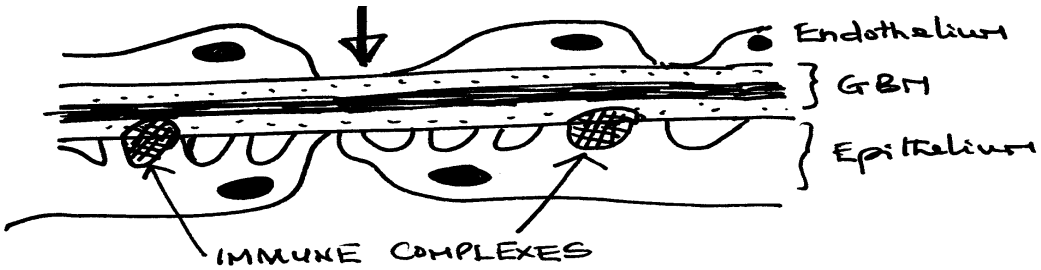
a) Glomerular capillaries - lie between two arterioles hence the glomerular capillary pressure is much greater than other capillary beds.
b) Glomerular wall - normal capillary wall acts as a progressive sieve and the macromolecules and Ag-Ab complexes can penetrate into the glomerular wall. This penetration depends on the size, shape and the electrical charge of the immune complexes.
c) GBM - larger complexes aggregate on the subendothelial side of the GBM while the smaller complexes are deposited on the epithelial side of the GBM.

Diagram 5.4: Deposition of Ag-Ab complexes

Large complexes aggregate on the subendothelial side of the GBM



Smaller complexes are deposited on the epithelial side of the GBM.



Mechanisms of Deposition

- Two main mechanisms - formation and deposition of immune complexes and deposition of anti-GBM antibodies.
- Both mechanisms do activate secondary mechanisms that produce glomerular damage.

a) Immune Complex Nephritis

- Circulating Ag-Ab complexes are deposited in the GBM or locally formed complexes are trapped in the glomerulus.
- Exogenous antibodies are produced elsewhere in the body e.g. following an infection with group A beta haemolytic streptococcus bacteria reaching the GBM leading to Ag-Ab reaction causing migration of leucocytes (by chemotaxis) and activation of the lysosomal enzymatic complement system, which then causes glomerular damage.
- Endogenous antibodies are produced in the body cells when patients form antibodies to the host DNA e.g. systemic lupus erythromatosus (S.L.E), polyarteriris nodosa (P.N) and Good pastures syndrome (G.P.S). The host is unable to clear the immune complexes from the circulation. There is accompanying deficiencies in the complement system.

b) Anti-GBM Antibody

- Reacts with the antigen in the GBM producing damage
- It is IgG type of antibody
- It can react with the alveolar basement membrane causing both lung haemorrhage and glomerulonephritis (e.g. in Good pastures syndrome, G.P.S).

Cell mediated glomerular injury

- Cytokines and other mediators released by activated T cells recruit more leucocytes and fibrogenesis. Injury results from the effect of the CD4+ and CD8+ T lymphocytes.

Secondary pathogenetic mechanism

- Results from the effects of activated neutrophils, mononuclear phagocytes, complement system, platelets, mesangial cells and coagulation student.

Secondary Mechanisms of Glomerular Injury

- After deposition the Ag-Ab complexes and the anti-GBM antibodies several secondary mechanisms cause glomerular damage increasing capillary permeability
- Include complement activation, fibrin deposition, platelet aggregation, inflammation with neutrophils dependant mechanisms and activation of the kinin system

Causes

1) Infections
2) Viruses e.g. mumps, measles, EBV, coxsackie, Hepatitis B and varicella.
3) Bacteria e.g.β–haemolytic streptococci group A, *Strep*. *Viridans*, Staphylococcus. *Trepanoma pallidum*, gonococci and salmonella.

4) Parasites - *plasmodium malariae*, schistosomiasis, filariasis
5) Drugs e.g. penicillamine
6) Host Ag e.g. S.L.E and malignant tumours

4.2. Non-immune Mechanisms

- This result from various mechanisms: -
  i) Metabolic glomerular injury e.g. diabetic nephropathy
  ii) Haemodynamic e.g. systemic hypertension
  iii) Deposition diseases e.g. Amyloidosis
  iv) Infections e.g. HBV, HCV, HIV, E. coli-derived nephrotoxin
  v) Inherited glomerular disease.
  vi) Trauma

5.0 PATHOLOGY

i) Hypercellularity - increased proliferation of cells – mesangial cells, endothelial cells, leucocytes
ii) Basement membrane thickening
iii) Capillary wall necrosis
iv) Hyalinization and Sclerosis

6.0 CLINICAL MANIFESTATIONS

- Four principal manifestations or features of glomerular disease include proteinuria, haematuria, hypertension and disturbed excretory function

Table 5.2: Syndromes of glomerular disease

Syndrome	Features
Asymptomatic proteinuria	Presence of proteinuria in a patient with on complains (unexpectedly in a patient).
Acute nephritic syndrome	Haematuria, proteinuria, hypertension, oedema and oliguria
Nephrotic syndrome	Heavy proteinuria, hypoalbuminaemia, oedema, hyperlipidaemia, lipiduria and hypercoagubility
Acute renal failure	Rapid decline in renal function
Chronic renal failure	Proteinuria, haematuria, hypertension and azotaemia

7.0 CLASSIFICATION

- GN denotes diseases that primarily involve the glomeruli
- Glomerular disease can be primary glomerulonephritis or secondary glomerulonephritis. In primary GN, the glomerular is the predominant site of involvement while in secondary GN, systemic and hereditary disease secondarily affect the glomeruli. Glomerulonephritis can be classified on clinical perspective, pathological or clinico-pathological.

Clinical classification

1) Acute glomerulonephritis (AGN)
2) Chronic glomerulonephritis (CGN) – end stage kidney disease

Pathological classification

- Depends on the pathological features exhibited by different verities of AGN.
  1) Acute diffuse proliferative GN (post-streptococcal, post-infection)

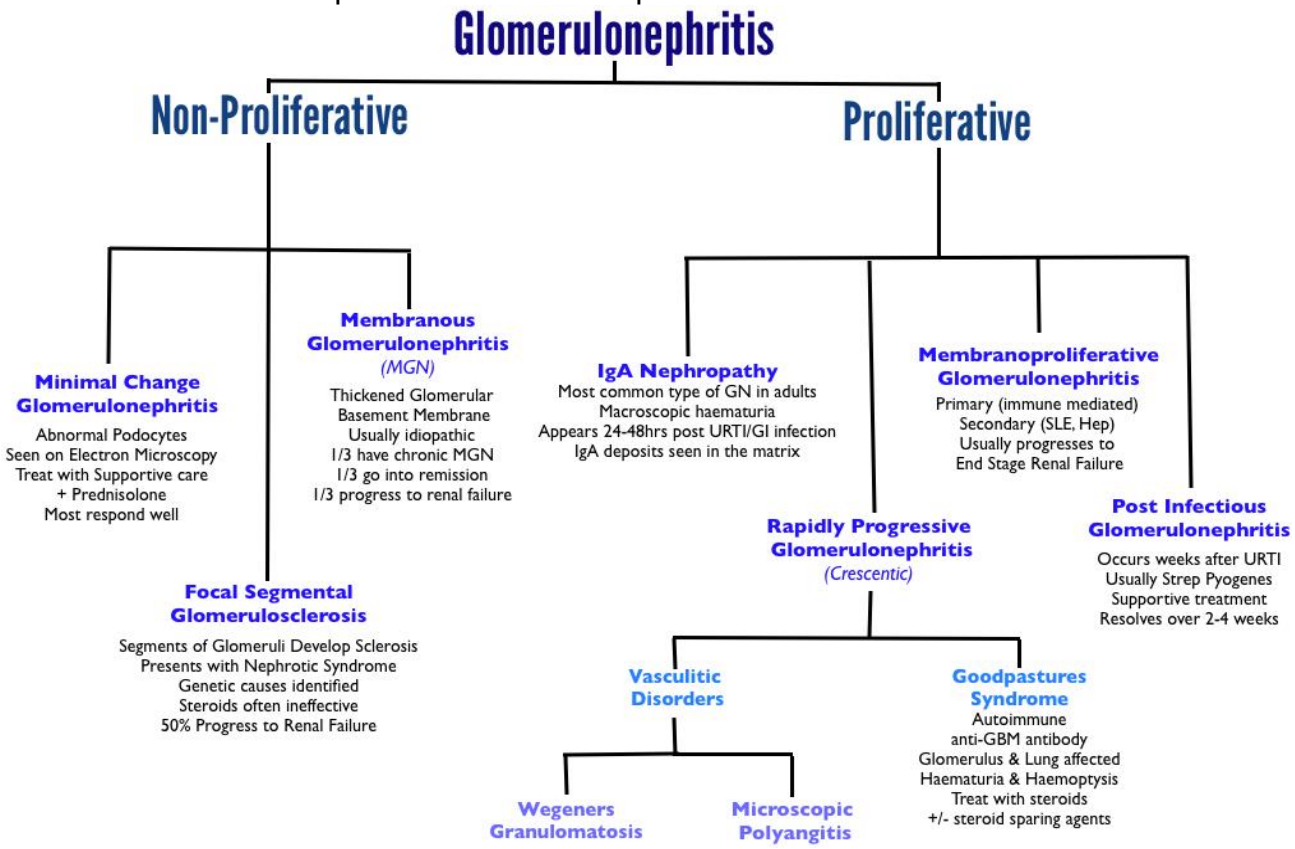
2) Rapidly progressive GN (crescenteric)
3) Diffuse membranous GN (idiopathic)
4) Mesangiocapillary/membranoproliferative GN (type I, II and III)
5) Focal GN (primary and secondary)
6) Minimal change/lesion GN

Clinico-Pathological classification

1) Primary glomerular disease – AGN and CGN
2) Secondary systemic glomerular disease e.g. S.L.E, Diabetes
3) Hereditary - Alport's syndrome (lens dislocation, posterior cataracts, corneal dystrophy and nephritis)

8.0 ACUTE GLOMERULONEPHRITIS (AGN)

- Can be classified as proliferative and non-proliferative



8.1. Acute Diffuse Proliferative Glomerulonephritis (ADPGN)

- ADPGN is synonymous with post-streptococcal GN and post-infection GN. It affects all ages but more prevalent in children affecting more males than females
- Classically the patient has a history of a sore throat ten (10) days back (one – two weeks).

Aetiology

1) Bacteria - Group A beta haemolytic streptococcus, *Streptococcus pneumoniae* and *Staphylococus aureus*
2) Viral – EBV, Herpes and Coxsackie
3) Protozoal - Falciparum malaria
4) Parasitic –Schistosomiasis
5) Fungal - Toxoplasmosis,

Pathogenesis

Global deposition of IgG and components of the complement in the glomerular capillary wall with deposition of immune complexes and an elevated ASOT indicates previous streptococcal infection. There is diffuse inflammation of the renal glands with messangial cell proliferation and an endoarterities that reduces the luminal capacity compromising the glomerular filtration rate (GFR) leading to renal failure.

Clinical Picture

- Patients present with ***nephritic syndrome*** or diffuse oedema, hypertension, proteinuria and oliguria with a predisposition to encephalopathy.

Pathological Features
- Macroscopy **–** a pale swollen renal cortex
- Microscopy – there is diffuse enlargement with increased cellularity (neutrophils, monocytes and macrophages

Diagnosis
- History; Clinical examination; Laboratory data

Investigations
1) Urine - moderate proteinuria; microscopic haematuria (rbcs); grannular casts and rbc casts
2) Blood - Urea and electrolyte levels; Increased creatinine clearance; Increased ASOT; Low serum; complement levels; Serum proteins; Full haemogram and ESR
3) Radiological - Plain abdominal X-ray; Ultrasound; Chest X-ray (in cases of enlarged heart and pulmonary congestion)
4) ECG shows T-wave abnormalities

8.2. Membranous Glomerulonephritis

- A common type of GN characterized by **deposition of irregular discontinuous deposits** of immune complexes, which are mainly IgG on the outer (subepithelial) aspect of the GBM.
- Membranous GN presents as nephrotic syndrome or isolated proteinuria or acute nephritic syndrome.
- Membranous GN affects more males than females. The incidence is higher in adults with peak incidence at middle age.

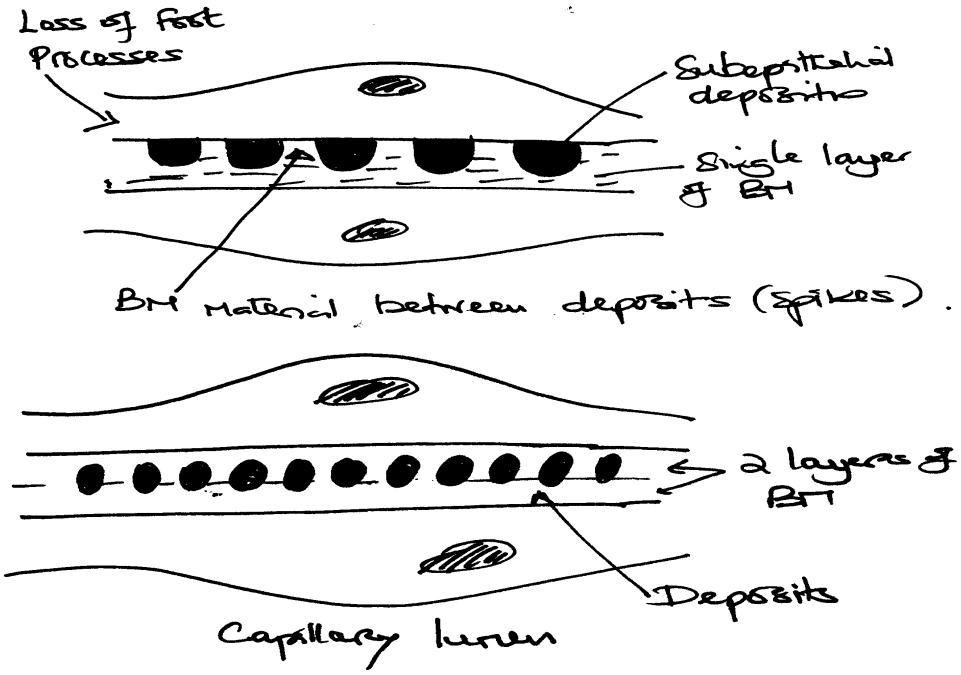
Aetiology
1. Infections e.g. malaria, syphilis, HBV and EBV
2. Drugs e.g. gold compounds, penicillamine and captopril
3. Malignancy e.g. lymphoma
4. S.L.E
5. Idiopathic – majority of the causes

Pathogenesis

- Deposition of immunoglobulins (mainly IgG) along the glomerular capillary walls in small amounts.
- No cellular reaction

- Thickening of the GBM with destruction leading to increased permeability of the Bowman's capsule, which allows escape of proteins.
- Occlusion of capillaries reduces renal blood flow and the GFR leading to uraemia.
- Reduced renal blood flow causes renal ischaemia eventually leads to hypertension.
- Proteinuria results in disturbance of the osmotic gradient leading to oedema formation. The oedema can be massive to cause – ascites, pleural effusion, pericardial effusion and anarsaca.

Diagram 5.4: Membranous GN



Pathology

1. Thickening of the glomerular capillary
2. Narrowing of the lumen
3. Proliferation and swelling of endothelial and mesangial cells.
4. Capillary walls are thickened and are eosinophilic.
5. Tubular atrophy secondary to ischaemia
6. The kidneys are slightly shrunken

In idiopathic GN, 75% of the cases progress slowly to chronic renal failure (CRF) with development of glomerular sclerosis, focal tubular atrophy and interstitial fibrosis.

8.3. Minimal Changen or Minimal Lesion Glomerulonephritis

- Presents as nephrotic syndrome and is characterized by spontaneous remissions
- Common in children and rare in adults. The proteinuria and oedema tend to fluctuate and the blood pressure and renal functions are normal.

Pathogenesis

- Is idiopathic in majority of cases with no evidence of immune complex deposition
- Can occur in Hodgkin's and Non-Hodgkin's lymphoma.
- Shows minimal changes in the mesangial cells
- The epithelial cells have reduced surface area by withdrawing their foot processes.
- There is increased GBM permeability.
- The glomerular capillary wall losses its negative charge allowing negatively charged proteins e.g. albumin to pass more readily leading to heavy proteinuria.
- Heavy proteinuria causes hypovolaemia and increased susceptibility to infections.

- Accumulation of lipids in the proximal convoluted tubule (PCT) and in urine following increased secretion by the liver in response to the low oncotic pressure.

Pathology
1. Glomeruli look normal except for fixed dilatation of capillaries.
2. No thickening of the capillary wall
3. Fusion of fat processes (podocytes)
4. Urine has lipid reach proteins.

8.4. Rapidly Progressive (Crescenteric) Glomerulonephritis

- Less common but fatal type of glomerulonephritis that may follow a streptococcal infection
- May be part of multisystemic disease or a complication of acute diffuse proliferative glomerulonephritis.
- Affects both sexes equally and is common during the middle age.

Aetiology
1. Primary – idiopathic, post-streptococcal or occult visceral sepsis
2. Secondary - Good pastures syndrome, S.L.E, polyarteritis nodosa and infective endocarditis

Clinical Picture and Course
- It runs an insidious onset
- Oedema, dyspnoea; symptoms of uraemia

Pathology

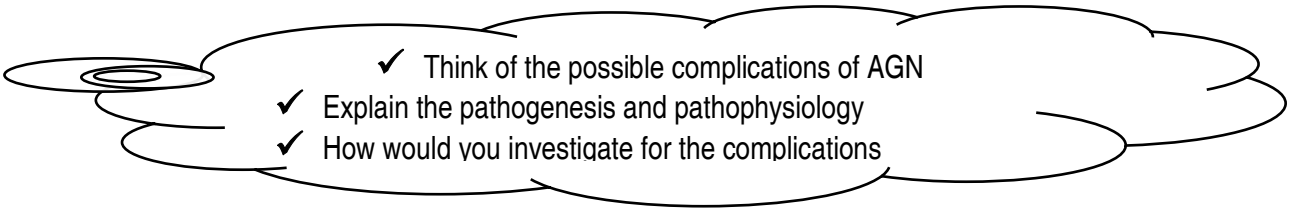
Macroscopy
1. The kidneys are enlarged due to oedema (or may be normal) with a smooth surface, as there is no or little scarring.
2. The cortex is pale with petechial haemorrhage
3. The glomeruli have conspicuous grey dots

Microscopy
1. Proliferation of both the endothelial and mesangial cells
2. Narrowing of the capillary lumina
3. Cellular infiltration with polymorphs
4. Rupture of the basement membrane, thrombosis and haemorrhagic necrosis of capillaries
5. Shows the characteristic histologic feature of a crescent, which comprises of macrophages and fibrin (differential diagnosis- S.A.B.E, malignant hypertension and acute glomerulonephritis).

8.5. Focal Glomerulonephritis

- Affects a portion of the glomeruli (involving only part of glomerular tuft).
- Usually affects children and young adults
- Characterized by proteinuria and haematuria
- Symptoms may subside without impairment of renal function but relapses occur with respiratory infections
- May be primary (IgA nephropathy) or secondary to a number of diseases such as infective endocarditis, S.L.E, polyarteritis nodosa and good pastures syndrome.

- The clinical picture includes -
  - Presents with haematuria and proteinuria
  - Sometimes the patient presents only with haematuria, which is usually worse in the morning and subsides in the evening.
  - When it persists the disease progresses to CGN and eventually CRF.



9.0 CHRONIC GLOMERULONEPHRITIS (CGN)

- A syndrome characterized by persistent proteinuria and/or haematuria and renal insufficiency that progress over years
- Leads to CRF due to extensive glomerular damage with hypertension (mainly malignant hypertension) accelerating the renal damage.

9.1. Aetiology

- May run an insidious course, follow episode of AGN or IgA nephropathy
- CGN is discovered during: -
  i) Routine urinalysis and blood tests for unexplained anaemia, elevated blood urea, nitrogen and creatinine
  ii) Discovery of bilateral small kidneys on ultrasound
  iii) Clinical exacerbation of AGN
  iv) During evaluation for secondary hypertension

9.2. Pathogenesis - Reflects the picture of the offending situation

9.3. Pathology

Macroscopy

a) Kidneys are uniformly and equally reduced in size
b) Renal capsule is firmly adherent
c) Subcapsular surface is uniformly and finely irregular (“granular contracted kidney”)
d) Diffuse thickening of the cortex
e) Medullary pyramids are less markedly shrunken

Microscopy

a) Hyalinization of glomerular
b) Hypertrophy of the normal glomeruli
c) Extensive atrophy of tubules
d) Increased interlobular connective tissue containing lymphocytes and plasma cells
e) Arcuate and interlobular arteries show hypertensive changes leading to ischaemia and scarring.

Lesson 6: Glomerular Disease (Nephrotic & Nephritic Syndromes)

Learning Outcomes

The learner should be able to: -
1) Describe the pathophysiology and pathology of nephrotic and nephritic syndromes
2) Investigate nephrotic and nephritic syndromes
3) Explain the complications in nephrotic and nephritic syndromes

NEPHROTIC SYNDROME

1.0 INTRODUCTION

- Nephrotic syndrome is a clinical complex characterized by a number of renal and extra-renal features – proteinuria/albuminuria of > 3.5 gm per 1.73 m^2 per 24 hours (> 3.5 gm/24 hours), hypoalbuminaemia (< 25 gm/L), massive oedema, EMU[1] protein: creatinine ratio (> 200 mg/mmol), hyperlipidaemia and hypercoagubility [**The key component is proteinuria**, urine protein: creatinine ration – more accurate]

2.0 AETIOLOGY

1) Primary nephrotic syndrome (nephritic nephrosis)
   a. Intrinsic Renal Disease – Glomerulonephritis (nephritic nephrosis)
      i. Adults - Acute diffuse proliferative GN, Membranous GN (middle aged/elderly) and Minimal change lesion (young adults)
      ii. Children - ADPGN, Minimal change (2 – 5 yrs) and Focal GN (6 yrs)
2) Secondary nephrotic syndrome
   a. Infections - Streptococcal (pharyngeal strains – M type 12, skin strains – M types 1, 4, 25, 49, 55, 57 and 60), tropical nephropathy (malaria, HBV, Filariasis, Schistosomiasis (*S. haematobium*),), Syphilis, Endocarditis, Infectious mononucleosis (EBV), Leprosy, HIV,
   b. Systemic Diseases – Diabetes mellitus, Rheumatoid arthritis, S.L.E., Amyloidosis, Good Pastures syndrome (GPS)
   c. Heredito-familial – Sickle cell disease, Congenital nephritic syndrome
   d. Allergies – pollen, bee stings and snake bites
   e. Drugs – Penicillamine, Captopril (high doses), Gold compounds, Mercury
   f. Neoplasms - Hodgikins & Non-Hodgikins lymphoma, Leukaemia, Malignant melanoma, Wilm's tumour
   g. Miscellaneous - Renovascular hypertension, Thyroiditis, Pre-Clampsia Toxaemia (P.E.T), Myoxedema

3.0 PATHOPHYSIOLOGY

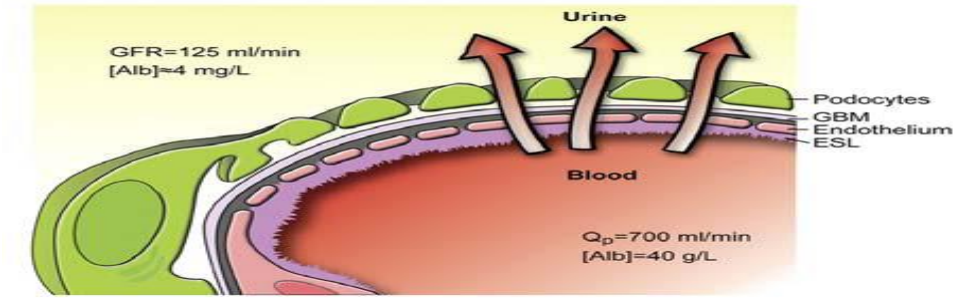
- Revolves around the following features: - proteinuria, hypoalbuminaemia, oedema, hypercholesteraemia (hyperlipidaemia), urine losses, hypercoagubility and lipiduria.

3.1. Proteinuria

- Urinary protein loss that results from: -
  i) Structural damage to the glomerular basement membrane (GBM) leading to increase in the membrane permeability (increase in size and number of pores) allowing larger protein molecules to escape.
  ii) Reduction in the fixed negative electrical charge of the GBM that facilitates a reduction in the repulsion of proteins.

[1] Early Morning Urine

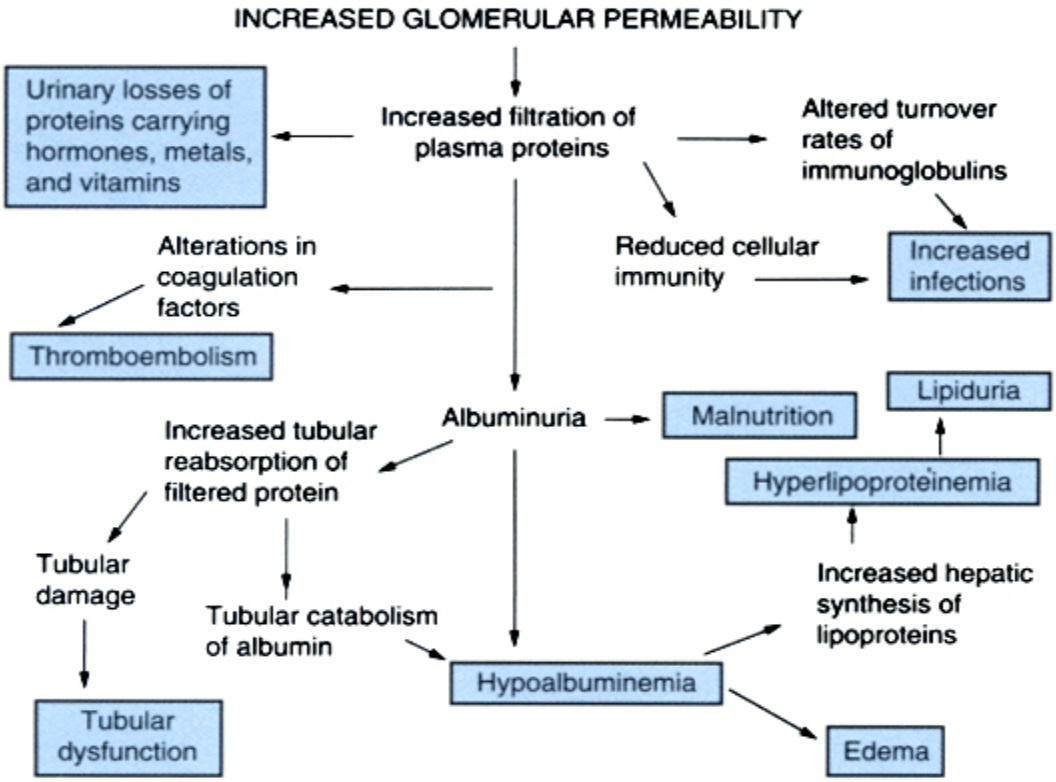
Diagram 6.1: Process of Proteinuria



3.2. Hypoalbuminaemia

- Results from the increased renal loss of albumin (proteinuria), G.I.T losses and increased renal catabolism. Normally the liver synthesizes albumin at the rate of 10 – 12 gm/day therefore with heavy proteinuria, renal catabolism of albumin is substantially increased.
- There is reduced hepatic synthesis to meet the increased demand and urinary loss.

Diagram 6.2: Pathophysiology of Nephrotic Syndrome

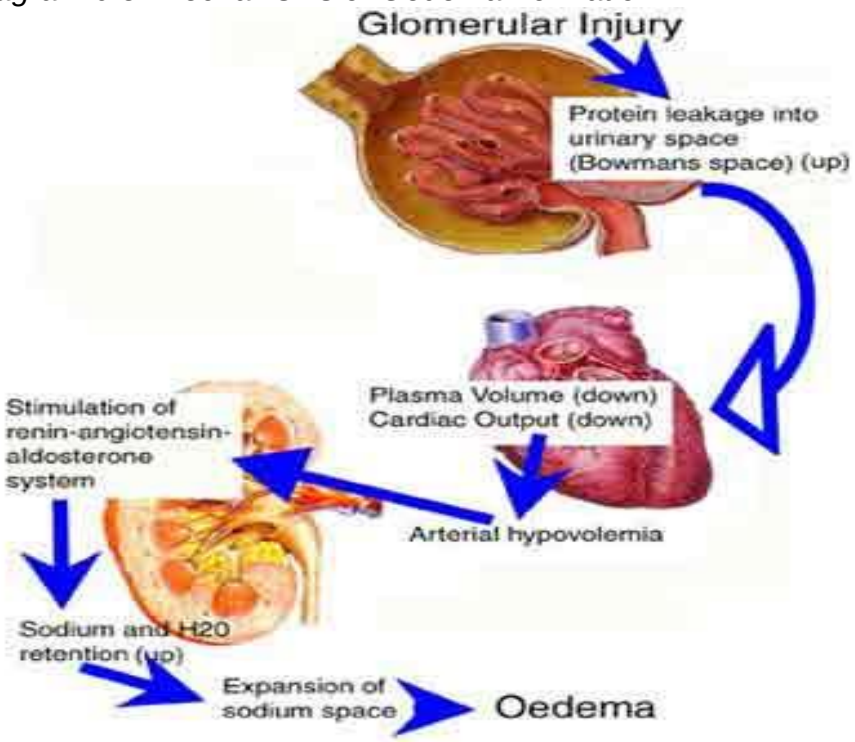


3.3. Oedema

i) Hypoalbuminaemia reduces the oncotic pressure that remains fluid within the blood vessels. This pressure disturbance facilitates shift of fluid into the tissues

ii) Renin-angiotensin-aldosterone response
   - Escape of salt and water causes reduced blood volume and pressure in the afferent glomerular arteries
   - Increased aldosterone promotes Na/water reabsorption in the distal nephron diluting further the plasma proteins.

Diagram 6.3: Mechanisms of Oedema Formation



3.4. Hypercholesteraemia

- Results from
  i) Reduced lipoprotein for carriage of lipids due to increased urine loss
  ii) Increased hepatic synthesis of lipids due to high turnover of proteins
  iii) Metabolic block in lipid metabolism
  iv) Alternate binding sites

3.5. Urine losses

- Due to damage to the glomerular basement membrane there occur a number of losses of various substances through the urine such as: -
  i) Thyroxine binding globulin leads to reduced T_4
  ii) Cholecalciferol binding protein causes reduced vitamin D and calcium
  iii) Transferin causes Fe deficiency anaemia
  iv) Metal binding sites for Zn and Cu
  v) Heparin factors (antithrombin 3) leads to hypercoagubility

3.6. Hypercoagubility

- Results from: -
  i) Increased urinary loss of antithrombin III
  ii) Hyperfirbrinogen due to increased hepatic synthesis
  iii) Impaired fibrinolysis
  iv) Increased platelet aggregation

3.7. Lipiduria

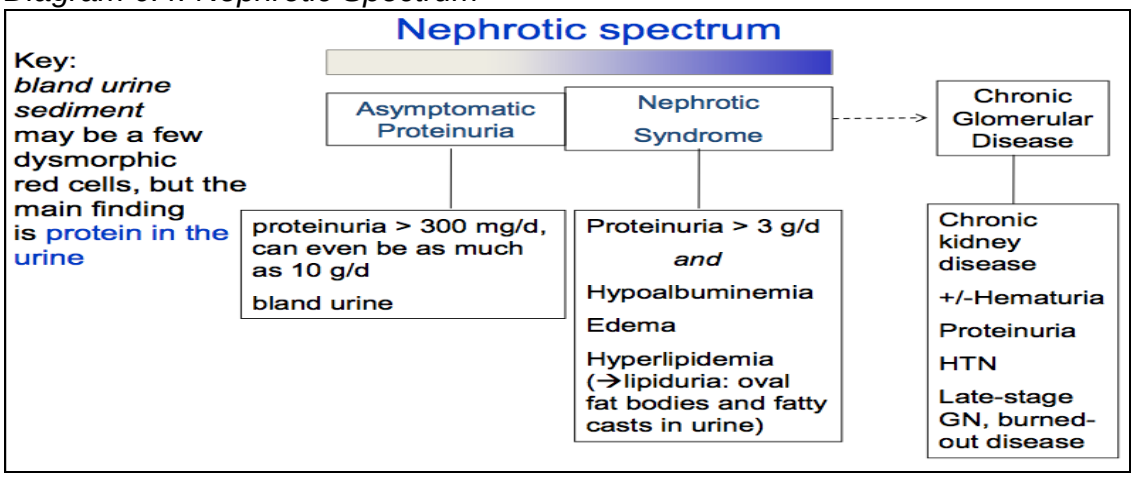
- Follows hyperlipidaemia due to excessive leakiness of glomerular filtration barrier.

4.0 PATHOLOGICAL CHANGES

i) General oedema

ii) Increased risk of infections
iii) The kidneys are pale and enlarged with a yellow radial streaking of the cortex due to lipids
iv) Increased glomerular capillary permeability
v) There is accumulation of "foamy" lipid laden macrophages and giant cell grannulomas around the crystals of cholesterol.
vi) Abundant hyaline deposits

Diagram 6.4: Nephrotic Spectrum



5.0 CLINICAL FEATURES

Symptoms

- History of acute or chronic infections, drug, allergies, systemic symptoms (vasculitis, malignancy)

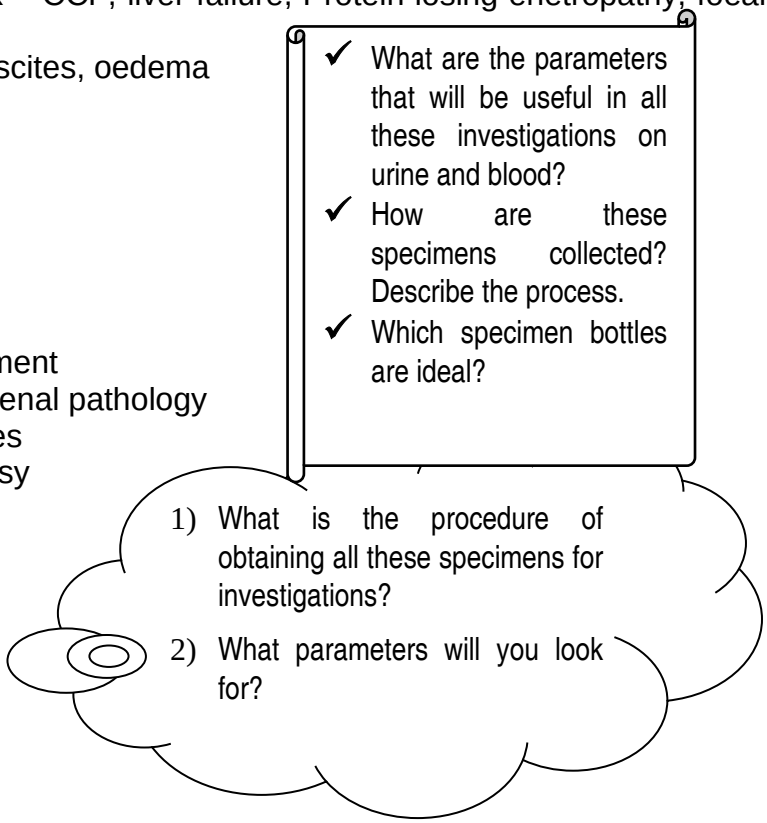
Signs

1) Facial swelling/peripheral oedema(anarsaca - ↑ fluid in organs and cavities with severe oedema + tissue hardening – DDx – CCF, liver failure, Protein losing enetropathy, foeal hydrops)
2) Fluid retention - pleural effusion, ascites, oedema
3) Hepatomegaly
4) Hypertension

6.0 INVESTIGATIONS

Principles of investigations

1. Assess the severity
2. Assess the degree of renal impairment
3. Estimate the nature of underlying renal pathology
4. Specific tests for individual diseases
5. Preparation for possible renal biopsy



Investigations

1) Urine analysis - protein/24 hours, microscopy - red cells, red cell casts; volume and concentration and Bence-Jones proteins
2) Blood
   a. Full haemogram and ESR

b. Serum proteins/albumin
c. Serum fasting cholesterol ↑
d. Urea and electrolytes
e. Blood sugar
f. Serum Electrophoresis
g. ASOT
h. ANF (Anti-Nucleotide Factor)
i. C3 complement concentrations
j. Creatinine
k. Creatinine clearance
l. Differential protein clearance
m. Blood slide/Quantitative buffer coat (QBC)
n. Rheumatoid factor
o. VDRL
p. HIV
q. HBV serology

3) Imaging - CXR – steroid therapy may reactivate TB and Renal ultrasound
4) Renal biopsy

Indications for Biopsy

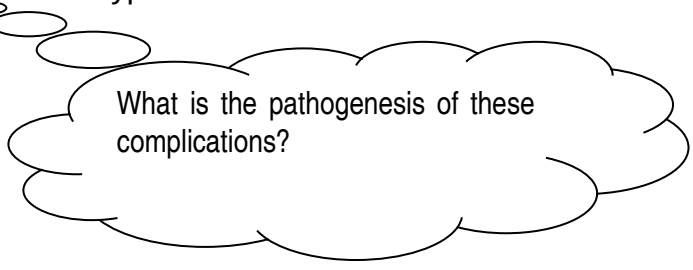
1) Persistent microscopic haematuria
2) Persistent diastolic hypertension
3) Low serum C3 complement
4) Poorly selective differential protein clearance

7.0 DIFFERENTIAL DIAGNOSIS

1) Nephritic syndrome (hematuria, proteinuria, oliguria, HTN)
2) Malnutrition/kwashiorkor (oedema, hypoalbuminaemia, no proteinuria)
3) Allergic reactions (no proteinuria)
4) Liver disease (hypoalbuminaemia)
5) Protein Losing Enteropathy (P.L.E)
6) Diabetic nephropathy
7) ARF/CRF

8.0 COMPLICATIONS

1) Susceptibility to Infections due to low immnunoglobulins (urinary loss), septicaemia, *E. coli*, pneumococcal, stretched skin and oedematous tissue, nephrotic plasma impairs lymphocytic function and immunosuppression (steroid therapy)
2) Thromboembolsism (DVT, renal vein thrombosis.. pulmonary embolism, CNS vessels) due to increased Factor VII and increased fibrinogen concentration due to increased protein synthesis following hypoalbuminaemia
3) Shock
4) Acute renal failure
5) Hypertension
6) Anaemia (Microcytic hypochromic)
7) Bleeding tendencies
8) Vitamin D deficiency
9) Protein malnutrition
10) Hypocalcaemia



NEPHRITIC SYNDROME

1.0 INTRODUCTION

- Is a group of disorders affecting kidney by causing inflammation and pores in glomerulus which results in passage of red blood cells and excess proteins *into* the urine and restores excess fluid in the body
- Follows Group A beta haemolytic streptococcus
- Comprises of:
    i) Haematuria[2] (macroscopic or microscopic)
    ii) Moderate proteinuria
    iii) Hypertension
    iv) Oedema (peri-orbital, leg or sacral)
    v) Oliguria and renal impairment
    vi) Uraemia.

What are the causes of haematuria?

2.0 CAUSES

1) Infections - Group A Streptococcal bacteria
2) Non-Streptococcal post-infectious GN: - mumps, measles, infectious mononucleosis, malaria, schistosomiasis.
3) Primary renal diseases:
    a) Membranoproliferative glomerulonephritis;
    b) Idiopathic rapidly progressive crescenteric glomerulonephritis.
4) Secondary renal diseases:
    a) Subacute bacterial endocarditis;
    b) Infected ventriculoperitoneal shunt;
    c) GN with visceral abscess; bacterial, viral or parasitic infections.
5) Multi-system disease - Systemic lupus erythematosus (SLE) and Goodpasture's syndrome;
6) Allergy:
    a) Acute allergic tubulointerstitial nephritis.

3.0 PATHOGENESIS

- Immunological reaction

4.0 PATHOPHYSIOLOGY

- Damage to the glomerulus occurs by an immune-mediated injury which causes an inflammatory reaction is started an antibody targeted at a component of the glomerulus or immune complexes generated elsewhere in the body are trapped by glomerular filtration
- The antibodies/immune complexes activate the complement cascade and infiltration of inflammatory cells.
- The common histologic features include:
    i) Proliferation of cells within glomerulus; mesangial cells (macrophages of the kidney), endothelial cells reducing capillary lumen diameter, and epithelial cells with Bowman's space given rise to crescent formation.
    ii) Infiltration of inflammatory cells; neutrophils, macrophages etc.

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[2] *Haematuria is* defined *as the presence of 5 or more red blood cells (RBCs) per high-power field in 3 of 3 consecutive centrifuged specimens obtained at least 1 week apart.*

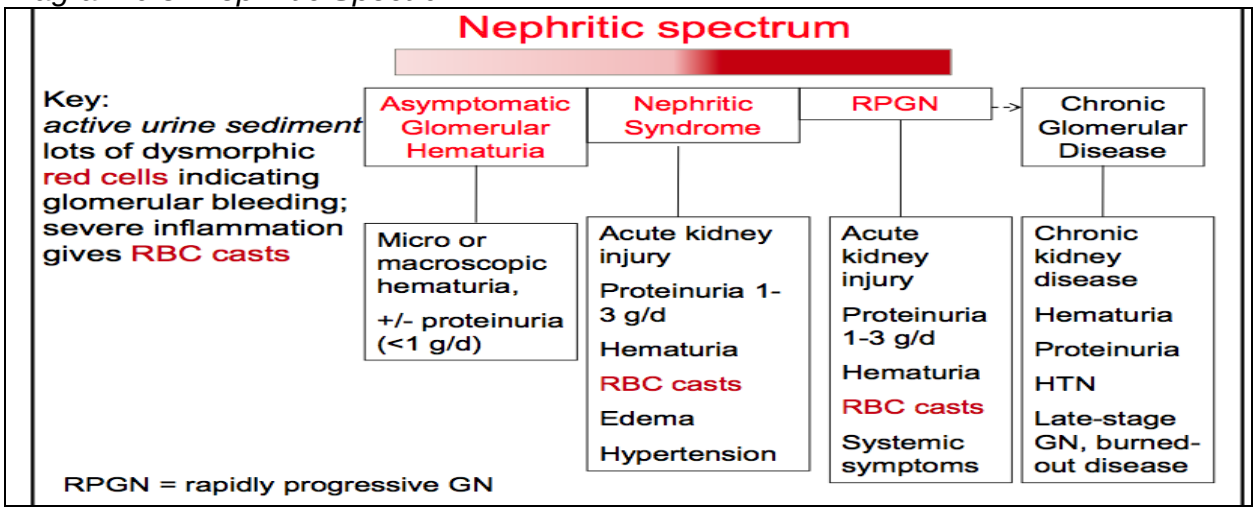
iii) Basement membrane thickening; caused by deposition of antibodies, immune complexes and complement.

- These changes can affect some (segmental) or all (global) of the glomerulus, and can affect some (focal) or all (diffuse) of the glomeruli within the kidneys.
- As a result the filtration capabilities of the glomerulus are affected and thus allows protein and red blood cells to leak through.
- Glomerular filtration rate is reduced stimulating the retention of salt and water culminating in hypertension and oedema.
- As there is decreased filtering of the blood, levels of waste products rise resulting in azotaemia, and the production of urine falls (oliguria).

5.0 SIGNS AND SYMPTOMS

- Haematuria (this can be 'visible' to the naked eye, or 'not visible' when it is detected on urine dipstick); proteinuria; hypertension; oedema (often periorbital, as well as dependent e.g. ankle and sacral); uraemia (symptoms of this include lethargy, pruiritis, nausea and vomiting); oliguria

Diagram 6.5: Nephritic Spectrum



6.0 INVESTIGATIONS

1) Urinalysis - red blood cells
2) Blood - Serum urea (increased); Blood culture (positive); ASOT (increased); C3, C4 levels (decreased); Anti-GBM (positive); Creatinine clearance (decreased); Urine protein (increased); Serum creatinine (increased)
3) Chest X-ray(cardiomegally, pulmonary oedema)
4) Renal imaging (normal)
5) Renal biopsy (glomerulonephritis)

7.0 DIFFERENCES BETWEEN NEPHROTIC & NEPHRITIC SYNDROME

	Feature	Nephrotic	Nephritic
1.	Proteinuria	Massive	Moderate
2.	Hypoalbuminaemia	Marked	Moderate
3.	Oedema	Massive	Moderate
4.	Hyperlipidaemia	Marked	Minimal
5.	Hypertension	Normal BP	Mild hypertension
6.	Haematuria	None	Present

Lesson 7: The Urinary Tract Infection (U.T.I)

Learning Outcomes

At the end of the lesson, the learner should be able to: -
1. Describe defence mechanisms of the urinary tract
2. Discuss the pathogenesis and pathology of UTI
3. Investigate urinary tract infections

1.0 INTRODUCTION

- Most common of all bacterial infections
- Nearly 95% of cases are caused by bacteria that typically multiply at the opening of the urethra and travel up to the bladder.
- UTI can be defined
  - Is defined by the presence of > 100 000 organisms per ml in a midstream specimen urine (MSU).
  - As clinically detectable condition associated with invasion by disease causing microorganism of some part of the urinary tract
- Involves either the kidney and the renal pelvis (pyelonephritis), ureters (ureteritis), the bladder (cystitis) and the urethra (urethritis)
- Can affect the upper part of the tract i.e. upper urinary tract infection (pyelonephritis) or the lower part – lower urinary tract infection (cystitis and urethritis)
- A normal anatomical and physiological urinary tract with intact local and systemic defence mechanisms confine bacteria to the lower end of urethra. Urinary tract infection occurs due to multiplication of organisms in the urinary tract.

2.0 INCIDENCE

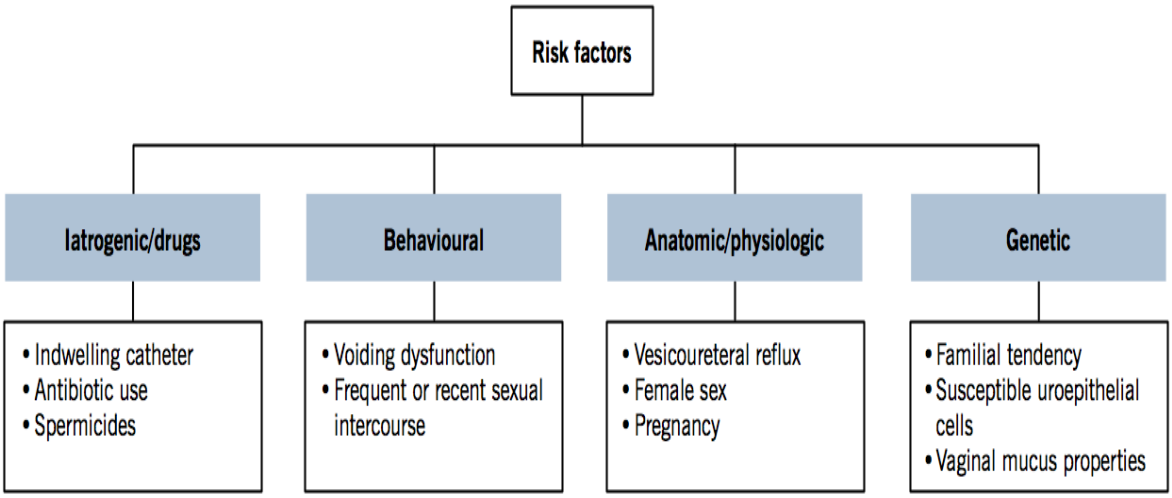
Females > males. In men it is common in 1st year of life and after 60 years

3.0 DEFENCE MECHANISMS

1) Mechanical flushing of urine flow (voiding mechanism allows clearance of mechanisms)
2) Urine acidity (low urine pH) creates a poor culture media; high urine osmolality; urinary inhibitors of bacterial adherence and competitive inhibitors of attachment to uroepithelial cells
3) Mucosal
   i. Muscoal IgA
   ii. Urethral secretion of cytokines and chemokines
   iii. Mucopolysaccharide lining increases difficulty of penetration
   iv. Intrinsic antibacterial properties of prostatic fluid
   v. Intrinsic antibacterial properties of the urethral and bladder mucosa
   vi. Presence of cervico-vaginal antibodies, which coat faecal enterobacteriae and protect against periurethral colonization
4) Anatomical
   i. Urethral length (greater and more effective in males)
   ii. Presence of voiding competent valvular mechanism at the insertion of the ureters into the bladder

4.0 RISK FACTORS

- Age; urinary incontinence; being female; congenital malformations; systemic diseases e.g. diabetes mellitus, sickle cell disease; instrumentation and bladder dysfunction



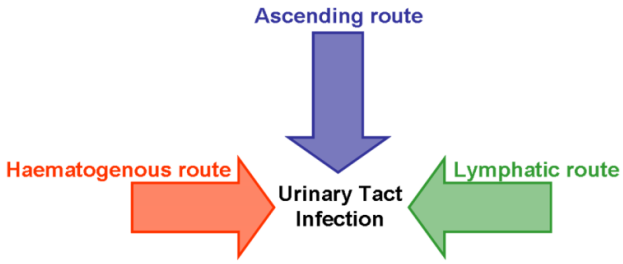
5.0 CAUSES

Males	Females
Proteus mirabilis (30 – 36%) E. coli (11 – 27%) Enterococcus (5 – 24%) Klebsiella pneumoniae (6 – 9%) Enterobacter (2 – 9%)	E. coli (47 – 77%) Proteus mirabilis (2 – 27%) Klebsiella pneumoniae (7 – 11%) Pseudomonas (5 – 9%) Enterococcus (5 – 8%)

6.0 PATHOGENESIS

- Susceptibility of the individuals and presence of risks factors
- Results from multiplication of organisms in the urinary tract
- May be uncomplicated or complicated resulting in permanent renal damage.

Routes of Infection



Stages of UTI development

1) Colonization of the periurethral zone with pathogenic faecal organisms
2) Ascend of organisms
3) Multiplication of organisms

Uncomplicated UTI

- Uncomplicated UTI reveals presence of clinical features of UTI in a patient with normal anatomy and physiology of the urinary tract, normal renal function and no associated disorder that impairs the defence mechanisms

Complicated UTI

- Seen in individuals with abnormalities of the urinary associated with defective or impaired defence mechanisms and results in impaired renal function.

7.0 CLINICAL FEATURES

- Sudden onset frequency of micturition and dysuria; scaling pain during urination; suprapubic pain (cystitis); suprubic tenderness and pain; haematuria and pyuria

8.0 DIAGNOSIS

- Asymptomatic bacteriuria - urine culture
  - ≥10^5 cfu[3]/mL on 2 voided consecutive specimens (women)
  - ≥10^5 cfu/mL on 1 clean-catch urine specimen (men)
  - ≥10^2 ucf/mL on 1 catheterized urine specimen
- Symptomatic bacteriuria - urine culture
  - ≥ 10^5 cfu/mL in a clean-catch or midstream urine specimen
- Pyuria ≥ 10 WBCs per hpf[4]
- Symptoms

9.0 INVESTIGATIONS

1) Urinalysis
2) Full blood count
3) Urea and electrolytes
4) Pelvic and rectal examination
5) IVU
6) Renal ultrasound /abdominal
7) Micturating cysto-urethrography
8) Cystoscopy

What are the significant parameters in these

10.0 URETHRITIS

- What are the causes? , What is the pathogenesis?
- What are the clinical features?
- What are the complications?

11.0 BLADDER – CYSTITIS

1. What are the causes?
2. What is the pathogenesis?
3. What are the clinical features?
4. What are the complications?

12.0 PYELONEPHRITIS

- Is tubulointerstitial infection of the kidney affecting the renal pelvis, calyces and parenchyma
- Part of the tubulointerstitial disease of the kidney predominantly involving the renal interstitial tissues and tubular damage
- Classified as acute pyelonephritis and chronic pyelonephritis.
- Caused by ascending infection (most commonly faecal flora) and septicaemia.

ACUTE PYELONEPHRITIS

1.0 Predisposing Factors

1) Mechanical (urinary tract) obstruction – urine forms a media for bacterial growth and uraemia reduces body resistance.

[3] Colony forming units
[4] High power field

a. Congenital or acquired
b. Structural and functional abnormalities which may be mechanical – e.g. Benign Prostatic Hypertrophy (BPH), urethral stricture and carcinoma of the cervix, Inflammatory and Spasmodic e.g. neurogenic bladder

2) Structural abnormalities
3) Vesicoureteric reflux
4) Instrumentation of urinary tract
5) Pregnancy
6) Diabetes mellitus
7) Immunosuppression
8) Pre-existing or acquired renal lesions which may cause intra-renal scarring and obstruction e.g. gout arthritis, interstitial nephritis
9) Behavioural change in sexual partner

✓ Explain how these predisposing factors facilitate development of pyelonephritis?

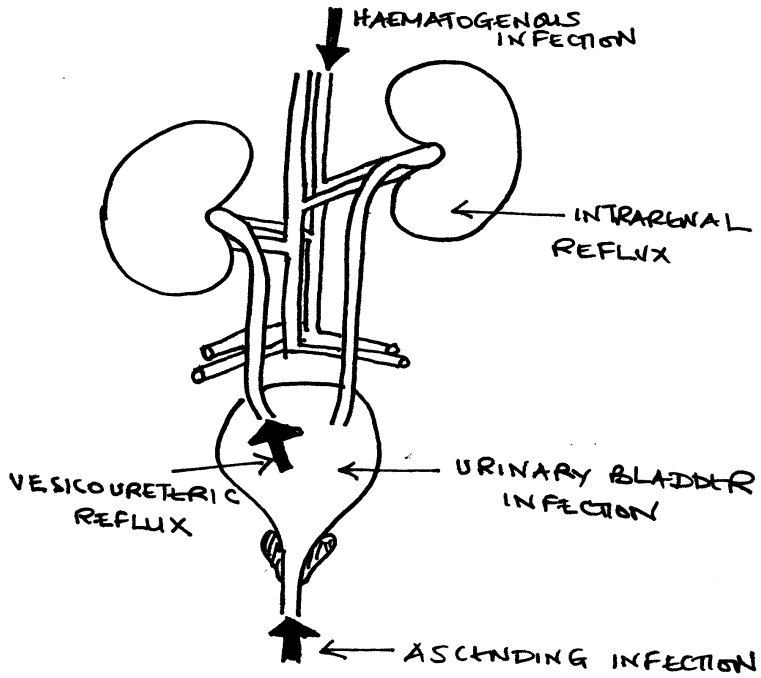
2.0 Aetiology

1) Infection Community acquired - E. coli (90%) and *Enterobacter feacalis,* Proteus, Staphylococcus, *Streptococcus faecalis*, Alcaligenes, a small number of *Pseudomonas aeruginosa*; even for the fungi, protozoa, chlamydia, or HIV infection
2) Hospital acquired – Klebsiella, Pseudomonas, Proteus (especially mirabilis), Staphylococcal and Candida

3.0 Mode of Infection

- Organisms reach the kidney by ascending infection and by blood stream

Diagram 7.1: Mode of Infections



3.1. Ascending Infection

- Most common route of infection involving pathogenic inhabitants of the colon and may cause faecal contamination of the urethral orifice especially in females of the reproductive age group. (WHY?)

- Infection can ascend periurethral, transurethral or establishment in the bladder. It is usually as a consequence of a logical sequence of bacterial colonization of the distal urethra and introitus (in females), multiplication of bacteria in the bladder, vesico-ureteral reflux, intrarenal reflux and haematogenous spread
- Females are prone due to a short urethra liable to faecal contamination, hormonal influences facilitates bacterial adherence to mucosa, absence of prostatic secretions with antibacterial propel, urethra trauma during sexual intercourse .
- The steps in ascending infection include:
  i) Colonization of the distal urethra - vulval and vaginal contamination; local infections; poor personal hygiene and bubble baths and chemicals

  ii) From the urethra to the bladder - female anatomy (short urethra); sexual intercourse; urethral catheterization

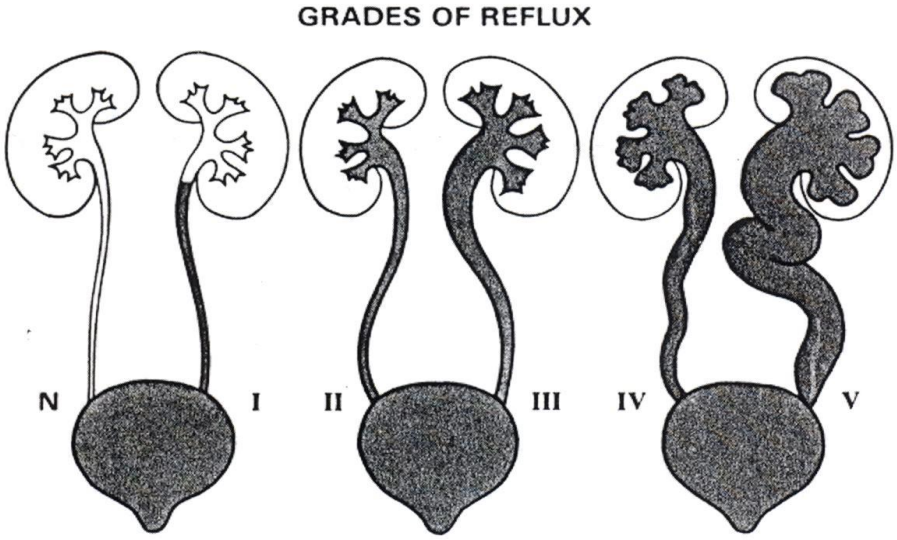
  iii) Multiplication of bacteria in the bladder
    - The bladder and urethra have antibacterial properties, urine is a poor culture medium and urinary pH below 5.5 inhibits bacterial growth
    - Continuous and frequent emptying of the bladder eliminates bacteria from the infected bladder
    - Conditions that hamper flow of urine increase the risk of UTI
    - Incomplete emptying results in increased residual urine and bacteria grow in stagnant urine

  iv) From the bladder to the ureters and renal pelvis (vesicoureteric reflux)
    - Obstruction predisposes for infections of the lower tract but they remain confined to the bladder
    - Only VUR allows bacteria to ascend into the renal pelvis
    - VUR is the retrograde propulsion of bladder urine into the ureter during contractions of the bladder detrusor muscle and micturition

  v) From the renal pelvis into the kidneys (intrarenal reflux)
    - VUR propels the infected bladder urine up to the renal pelvis and calyces and generates a high pressure in the pelvicalyceal system
    - This causes the reversal of normal pressure gradient between the renal parenchyma and the pelvis and allows backflow of urine into the collecting ducts and out into the periphery of the kidney
    - This facilitates bacteria to gain direct access to the renal parenchyma and initiate the infection

Diagram 7.12: Grading of VUR

Grade	Description
I	Reflux into the ureters only
II	Reflux into the renal pelvis and calyces without significant distention
III	Reflex into the pelvicalyceal system with upper tract distention
IV	Gross dilatation of the ureter and moderate dilatation of the renal pelvis and calyces
V	Gross dilatation of the ureter with gross dilatation of the renal pelvis and calyces and non-maintained papillary impression



3.2. Haematogenous (Blood Borne)

- Infection is carried by blood from other foci to the kidney
- Organisms responsible are the: - *Staph aureus,* Actinomycosis spp., Fungi, Yeasts, Mycobacterium tuberculosis and Brucella spp
- Occurs in special circumstances such as debilitated patients and immunosuppressive therapy.

4.0 Pathogenesis of Pyelonephritis

- Infection of the kidney occurs when urinary stasis is present
- This facilitates multiplication of bacteria especially in the bladder
- Causes of stasis include: - benign prostatic hypertrophy (BPH); congenital valves of the posterior urethra; renal calculi; urinary tract neoplasms; cancer of the cervix; pregnancy; nerve damage resulting in atones and dilatation of ureters; obstruction

5.0 Pathological Changes

Macroscopy (Gross appearance)

a) Enlarged swollen kidneys with a bulging surface and adherent capsule
b) Cut section shows: -
    - Focal and discrete suppuration with a haemorrhagic rim
    - Pale linear streaks of pus may extend radially
    - Suppuration filling the pelvis (pyonephrosis)
    - Congestion of pelvis and calyceal mucosa
    - Perinephric abscess

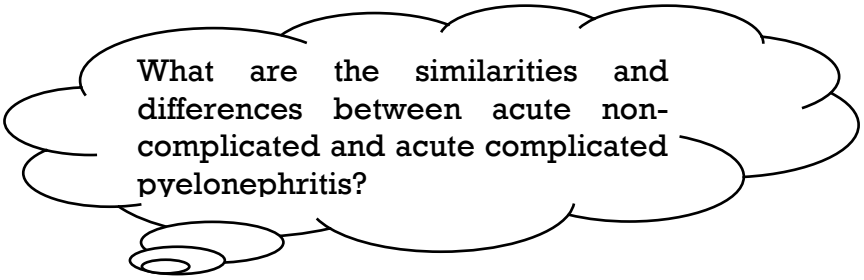
Microscopy

a) Extensive acute inflammation process
b) Extensive destruction of the parenchyma
c) Cellular infiltration – polymorphs

6.0 Clinical Features

1) Triad - Fever, nausea and vomiting, costo-vertebral angle tenderness
2) Chills and fever, rigors

3) Dysuria, polyuria, nocturia
4) Foul-smelling urine
5) Renal colic (presence of stones)
6) Loin pain and lumber tenderness, renal angle tenderness
7) Uncontrollable shivering
8) Anorexia, nausea and vomiting
9) Diarrhoea
10) Haematuria
11) Hypotension (in case of sepsis)
12) Poor feeding, jaundice, irritability in infants
13) Frequency of micturition; urinary urgency
14) ±Signs of cystitis (frequency, dysuria, urgency, strangury, haematuria, suprapubic)
15) Urine reveals - bacteria in excess of 100 000/ml, pus cells and pus cell casts



7.0 Differential Diagnosis

1) Acute abdomen
2) Appendicitis
3) Cystitis
4) PID
5) Urethritis
6) Prostatitis

8.0 Investigations

What investigations will be relevant?

Investigations

1) Urinalysis
   - The urine is often cloudy with an offensive smell
   - Blood, protein, leukocyte esterase and nitrite
   - Microscopy and culture
   - Microscopy of urine shows pyuria
2) Inflammatory markers: CRP, ESR, and plasma viscosity are raised.
3) Recent studies identified procalcitonin as a biological marker in diagnosing acute pyelonephritis in children of 2 years of age or under
4) FBC: this shows elevated white cell count with neutrophilia.
5) Blood cultures: these are positive in approximately 12-20% of patients with pyelonephritis.
6) Radiology
7) Imaging:
   - In children, the choice is between ultrasound and CT scanning. CT is more sensitive but the exposure to radiation may make ultrasound a safer option.

- MRI is also useful in detecting scarring but may require sedation in children. In adults, it is increasingly used where renal infection, masses and urinary obstruction are suspected but its use is limited by cost and availability.

8) Renal biopsy is occasionally employed to exclude papillary necrosis.

9.0 Sequelae of Acute Pyelonephritis

1) Healing
2) Recurrence

10.0 Sequelae and Complications of Acute Pyelonephritis

- Chronic pyelonephritis; Acute renal failure; Chronic renal failure; Sepsis syndromes; Renal papillary necrosis; Abscesses – renal cortical, perinephric, corticopapillary; Emphysematous pyelonephritis

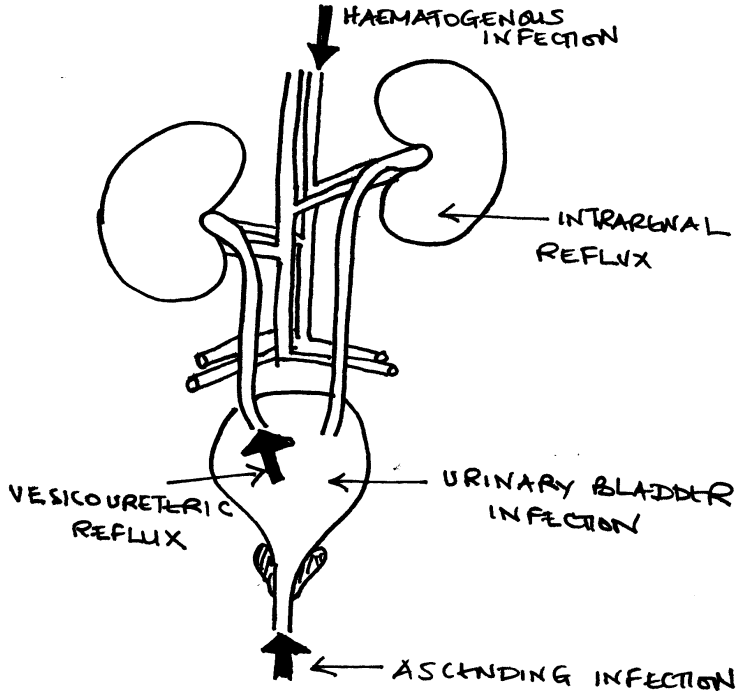
CHRONIC PYELONEPHRITIS

- Is a tubulointerstitial disease resulting from repeated episodes of inflammation and healing by scarring involving the calyces and renal pelvis.
- Accounts for 10 – 20% of end stage kidney.

1.0 Aetiopathology (Classification)

- Two types namely **reflux nephropathy** and **obstructive pyelonephritis**
  i) Reflux Nephropathy
    - Reflux of urine into the ureters during micturation causes chronic inflammation
    - Reflux increase pressure in the renal pelvis forcing urine into the tubules with subsequent damaged to the kidney and scar formation
    - Vesicoureteric reflux is common in children especially girls [due to absence or shortening of intravesical portion of the ureter] and patients with urinary tract obstruction.

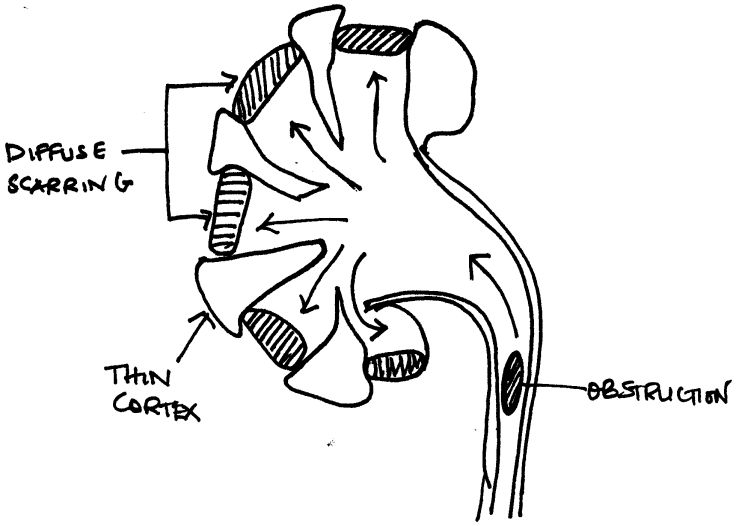
Diagram 7.3: Chronic pyelonephritis by vesicoureteral reflux



Obstructive Pyelonephritis

- Obstruction of urine outflow predisposes the kidney to infection and recurrent episodes of infection results in renal damage and scarring
- Recurrent attacks of acute pyelonephritis rarely cause renal damage and scarring.

Diagram 7.4: Diagram: Chronic pyelonephritis by obstructive uropathy



2.0 Pathological Changes

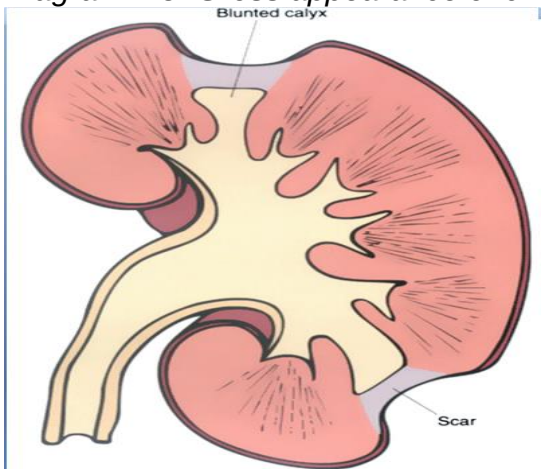
Gross (Macroscopy)

- Small and contracted with irregularly scarred (capsule can be stripped off with difficult) areas
- Scars are of variable sizes and characteristic U-shaped depressions
- Dilatation of the pelvis with blunting of calyces

Microscopy

1) Scarred areas have dilated tubules
2) Glomeruli show: - thickening of Bowman's capsule, necrosis, fibrosis and proliferative changes
3) Cellular infiltration - lymphocytes, plasma cells (prominent), oesinophils and macrophages
4) The renal tubes show atrophy and dilatation
5) Renal calyces are dilated and fibrosed
6) Blood vessels are entrapped in the scarred areas and show obliterative endoarteritis

Diagram 7.5: Gross appearance of chronic pyelonephritis



3.0 Clinical Picture and Diagnosis

- Shows features of chronic renal failure and acute recurrent pyelonephritis.

Diagnosis

1) Diagnostic criteria - irregular scarring, inflammation, fibrosis and deformity of calyces underlying parenchymal scars; tubulo-interstitial histological damage.
2) IVP (intravenous pyelography)
3) Positive urine culture results
4) Ultrasound
5) Haemogram
6) Renal biopsy

4.0 TB Pyelonephritis

- Results from haematogenous spread of T. bacilli from another site, most often from the lungs and less commonly from ascending infection from tuberculosis of the genitourinary system e.g. from the epididymis or fallopian tubes
- Renal TB can spread to involve the ureters, bladder and other pelvic viscera
- May present as TB pyelonephritis or appear as multiple miliary tubercles
- Renal pelvis involvement results in haematuria and renal lesions tend to suppurate leading to pyuria.

Pathology

- Mycobacteria become arrested in the cortex with development of tubercles, which enlarge, caseate and coalese.
- Lymphatic and tubular spread leads to tubercles moving hence the lesion grows with enlarging patch of caseation.
- Spread is common via adjacent papillae
- The lesions may soften and discharge the contents leaving a ragged cavity
- Tubercles in the renal pelvis ulcerate forming multiple lesions with the infection spreading to other parts of the kidney.

Lesson 8: The Urinary Tract Obstruction (U.T.O)

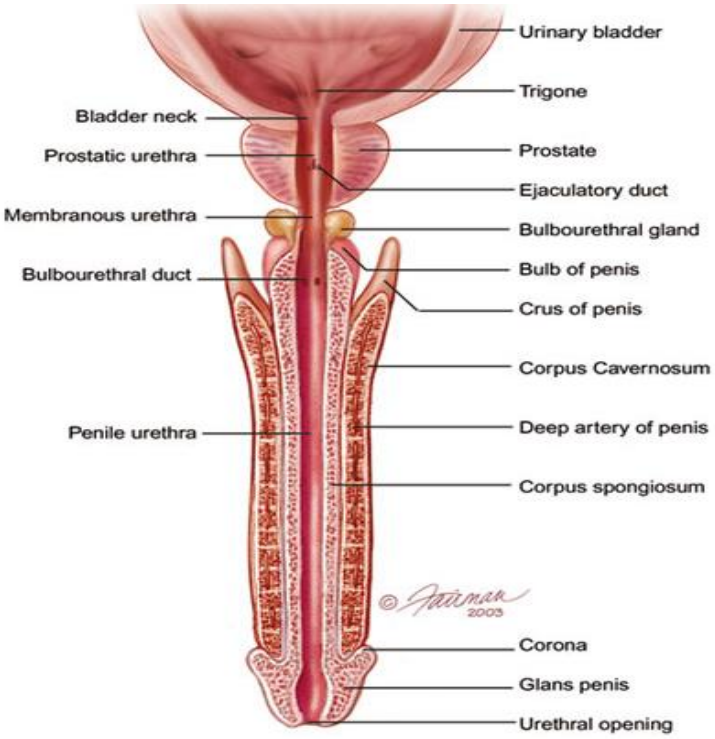
Learning Outcomes

At the end of the lesson the learner should be able to: -
1) Describe the causes and effects urinary tract obstruction
2) Investigate urinary tract obstruction
3) Discuss complications of urinary tract obstruction

1.0 INTRODUCTION

- Obstruction is common and important because it increases susceptibility to infection and stone formation
- May occur at any level of the urinary tract
- Obstruction at the anatomical locations can be due to intraluminal, intramural or extramural causes affecting the renal system unilaterally or bilaterally; partially or completely; insidiously or suddenly.

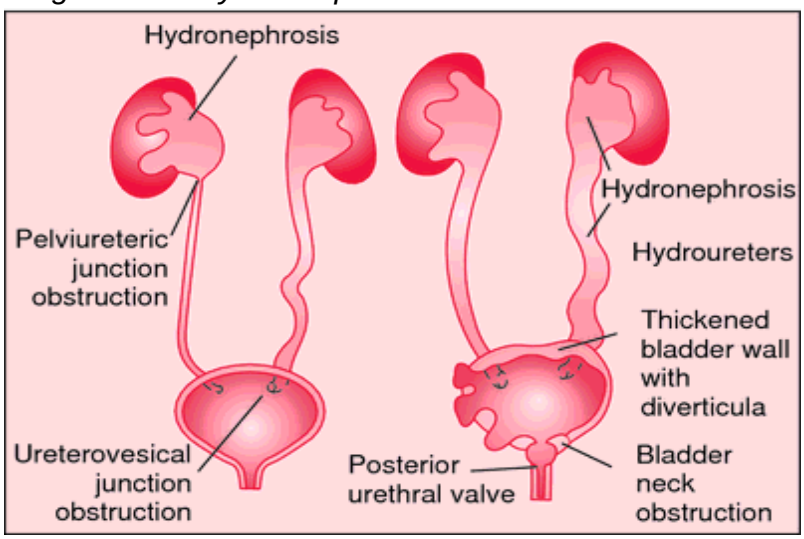
Diagram 8.1: The urethra



- Impaired urinary flow due to physical obstruction may occur at any point in urinary tract from renal calyces to external urethral meatus
- Causes proximal distention of the urinary tract associated with pain and decreased renal function, and urinary stasis carries the attendant risk of UTI and sepsis
- Certain points along the urinary tract are more susceptible to obstruction e.g. pelvi-ureteric junction (PUJ), where the ureters cross the pelvic brim, at the level of the iliac vessels and vesico-ureteric junction (VUJ).
- Obstruction can be unilateral or bilateral
  - Unilateral - commonest causes are calculi and neuromuscular malfunction at the junction of the renal pelvis and ureter
  - Bilateral - in developed world, 75% due to prostate, calculi and bladder tumours.

- Obstruction results in three important sequalae of **hydronephrosis**, **hydroureter** and **hypertrophy** of the bladder.

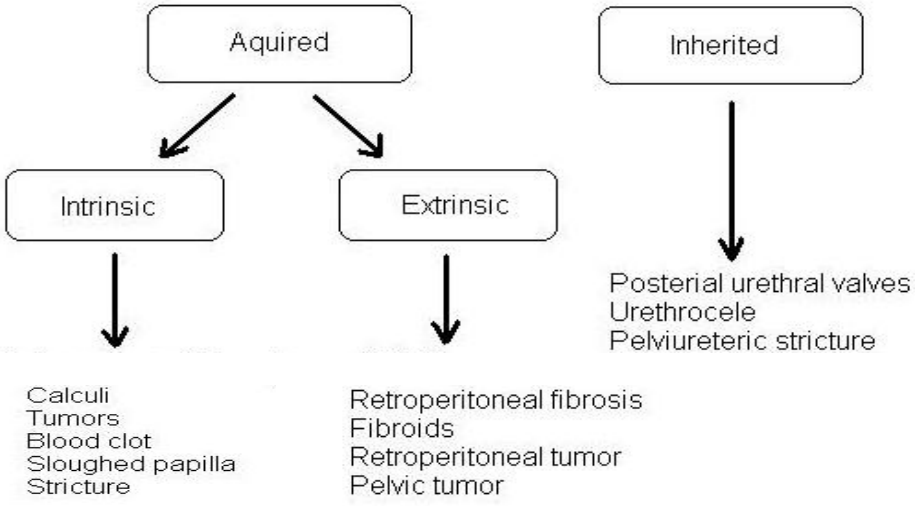
Diagram 8.2: Hydronnephrosis



2.0 EPIDEMIOLOGY

- **Age**: Occurs most commonly in young and the old:
- **Sex**: In men, urinary tract obstruction is most commonly a consequence of BPH or urethral stricture whilst in women, it tends to be related to pelvic tumours (particularly gynaecological malignancies), prolapse of pelvic structures or pregnancy.

3.0 CAUSES OF OBSTRUCTION

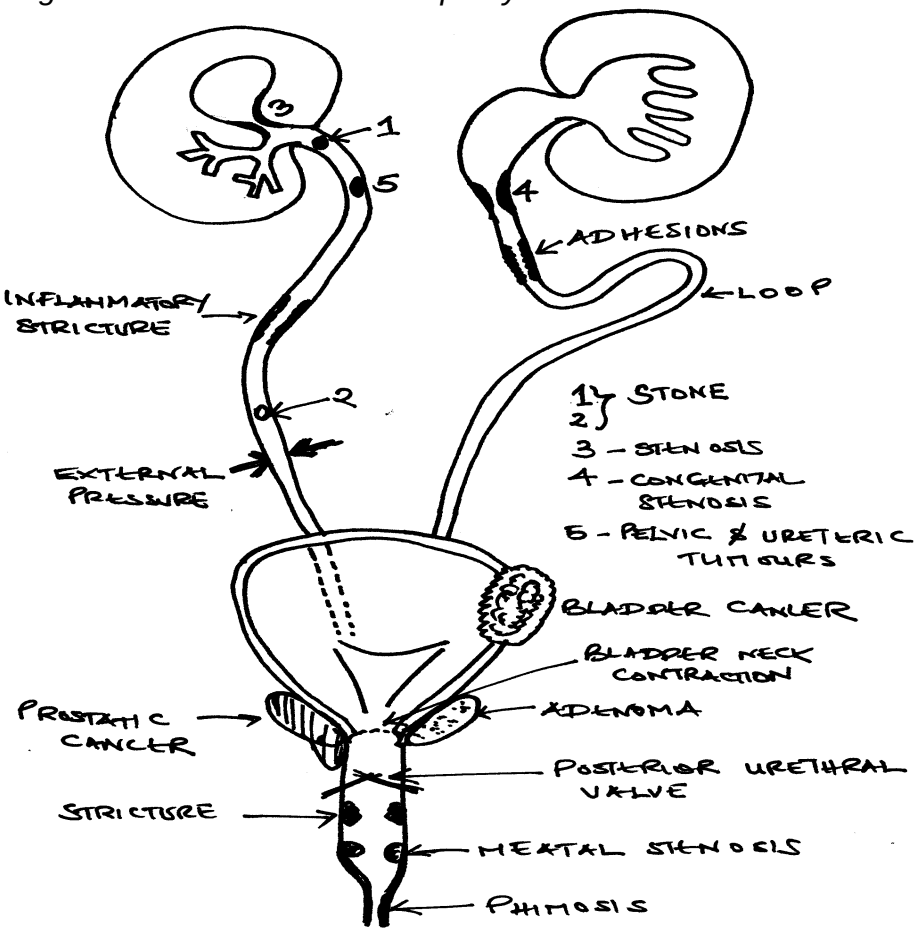


1) Intraluminal (within the lumen)
   - Calculi, tumours (e.g. cancer of the kidney and bladder), sloughed renal papillae, blood clots, foreign body, urethral stricture

2) Intramural
   - Congenital urethrla valves, pelvic-ureteric junction (PUJ) obstruction, vesicoureteric obstruction, uretercic, urethral or ureterovesical stricture, urethral valves, inflammation (e.g. phimosis, cystitis), neuromuscular dysfunction(failed inervation), pin hole meatus and bladder neck obstruction

3) Extramural (pressure from outside)
   - PUJ compression from bands and aberrant vessels, pregnant uterus, retroperitoneal fibrosis, tumours (e.g. carcinoma of the cervix, rectum, colon, caecum), prostatic enlargement, prostatic carcinoma and prostatitis, trauma, pancreatitis, retricaval ureter, chron's disease and phimosis

Diagram 8.3: Obstructive Neuropathy



4.0 PRESENTATION

Acute upper tract obstruction

- Flank pain:
  - Dull, sharp or colicky; intermittent or persistent but usually of varying intensity
  - Often radiates to iliac fossa, inguinal area, testis or labium
  - May be provoked by alcohol, diuretics or high fluid intake
- On palpation, loin tenderness, occasionally enlarged kidney
- Clinical presentation may be dominated by symptoms of UTI and signs of septicaemia.
- Complete anuria suggests bilateral or unilateral complete obstruction.

Chronic upper tract obstruction

- Presents with flank or abdominal pain and/or renal failure.
- Polyuria may be a feature.

Acute lower tract obstruction

- Often follows history of symptoms of obstruction of bladder outflow.
- Usually severe suprapubic pain (but not if superimposed on chronic retention or underlying neuropathy).

Table 2. Some causes of chronic upper urinary tract obstruction

Ureteric	Renal
• Stricture	• Congenital obstruction at the PUJ
• Ureterocele	• Aberrant vessel at the PUJ
• Ureteric valves	• Renal cell carcinoma
• Retrocaval ureter	• Transitional cell carcinoma in the renal pelvis
• Tuberculosis	• Tuberculosis
• Calculi	• Calculi
• Transitional cell carcinoma in the ureter	**Bladder**
• Ureteritis cystica	• Transitional cell carcinoma
• Aortic aneurysm	• Neurogenic bladder
• Radiation	• Pelvic malignancy
• Retroperitoneal fibrosis	
• Pregnancy	
• Para-aortic lymph nodes	
• Iatrogenic	
• Intra-abdominal malignancy	

Chronic lower tract obstruction

- Usual signs and symptoms include
  - Urinary hesitancy
  - Narrow and weak urine stream
  - Dribbling at end of micturition
  - Feeling of incompletely emptied bladder.
- With large volume of residual urine in bladder, may present with frequent passage of small volumes possibly with incontinence.
- May be complicated by acute retention associated with UTI.

5.0 INVESTIGATIONS

1) Check U&Es:
   a. After relieving chronic obstruction there may be sodium and potassium loss, so Na^+ and K^+ levels should be checked subsequently.
   b. Note, normal creatinine and urea do not exclude early mild to moderate renal impairment.
   c. Consider checking creatinine clearance by 24-hour urine collection after acute phase.
2) FBC - looking for anaemia of renal failure and evidence of infection.
3) Urine microscopy and culture in chronic obstruction and after relieving acute obstruction.
4) Blood cultures if septic symptoms/signs.
5) Ultrasound is the first line choice for imaging in suspected chronic upper tract obstruction.
6) IV urography or unenhanced spiral CT, renal scintigraphy, antegrade pyelography and ureterography (contrast agent injected directly into renal pelvis or calyx) by retrograde ureterography are used to investigate suspected acute upper tract obstruction.
7) Ultrasound of distended bladder or a transrectal ultrasound of prostate are used to investigate acute lower tract obstruction. Ascending urethrogram is an option where urethral catheterisation has been unsuccessful following suprapubic catheterisation.

8) Ultrasound with plain abdominal X-ray and measure of urinary flow rates is used to investigate chronic lower tract obstruction.
9) Suspected prostatic enlargement - serum PSA, ultrasound, biopsy as appropriate.

6.0 COMPLICATIONS

- Infection; Renal failure; Urine extravasation; Fistula formation; Pain; Bladder dysfunction

7.0 PROGNOSIS

- Dependents on the cause, location, degree, and duration of obstruction. Bad prognostic factors are longer duration and worse severity of obstruction, together with concomitant infection.

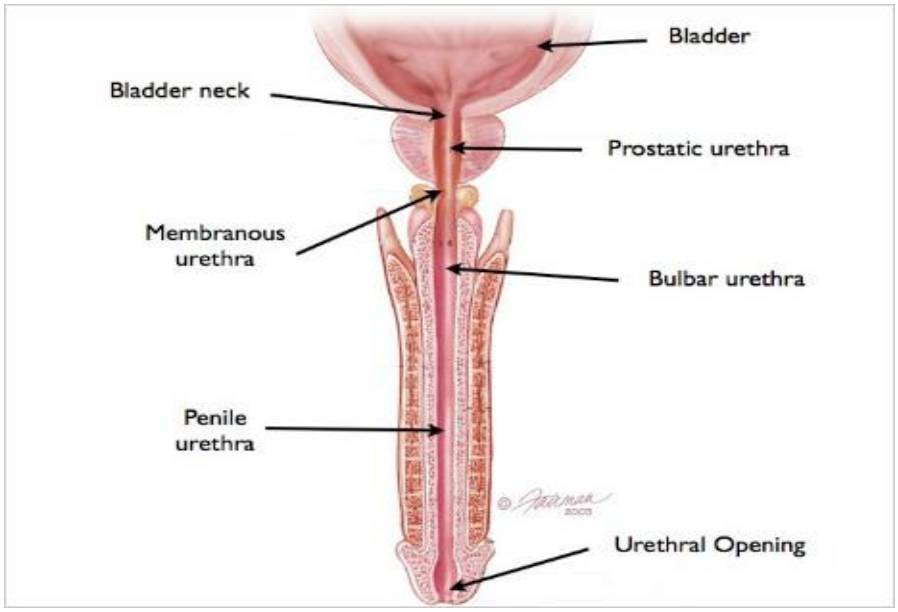
Urethral Stricture

Urethral stricture occurs mainly in the membranous part of the urethra and the bulbar part (prostatic).

Aetiology

1) Congenital - pin hole meatus and urethral valve (a false valve)
2) Traumatic
   a. Direct injury e.g. fracture pelvis, foreign bodies
   b. Instrumentation – e.g. catheterisation, penile amputation, passage of sounds (P.O.S) and urethral endoscopy
3) Post-operative - Open prostatectomy and penile amputation
4) Inflammatory – Gonorrhoea, Meatal ulceration e.g. chancre, Tuberculosis
5) Neoplastic - Primary and Secondary neoplasms

Diagram 8.4: The Urethra



Pathology

- Occurs as a late complication of gonorrhoea
- Can result from persistent suppuration in the peri-urethral glands of the membranous urethra
- The basic pathology is the corpus spongiosum in which fibrosis occurs following thrombophlebitis caused by extravasations of infection urine

- Narrowing of the prostatic urethra may result from gonoccocal prostatitis
- May lead to fistula formation
- A watering can perineum due to multiple strictures.

Complications

- Occur as a result of obstruction to urine flow
- Include cystitis; Pyelonephritis; Hydronpehritis; Hydroureter; Urinary tract obstruction; Urine retention; Urethral diverticuli; Periurerthral abscess; Urethral fistula and hernia, haemorrhoids and rectal prolapse due to straining at stool.

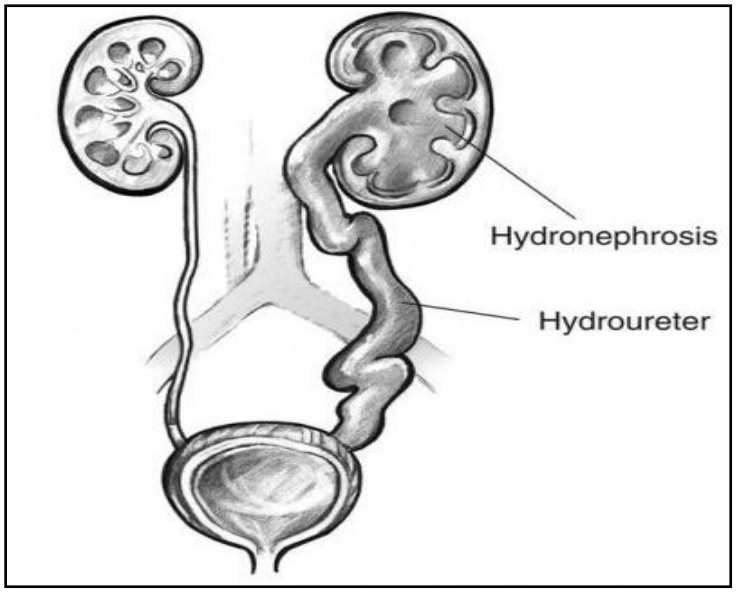
Hydronephrosis

- Is the state of dilatation of renal pelvis and calyces due to partial or intermittent obstruction of outflow of urine
- Develops when one or both pelviureteric sphincters are incompetent. It may be unilateral or bilateral.

Causes

1) Pressure effects of tumours
2) Congenital abnormalities
3) Neurogenic disturbance of bladder control – spinal cord lesions
4) Vesico-ureteric reflex
5) Effects of hormones in pregnancy – relaxing muscles
6) Calculus
7) Inflammatory strictures
8) Traumatic strictures

Diagram 8.5: Hydronephrosis



Lesson 9: Tumours – Renal and Bladder

Learning Outcomes

At the end of the lesson the learner should be able to: -
1) Identify tumours of the urinary system
2) Discuss the clinical effects of tumours
3) Investigate renal tumours

Renal Tumours

1.0 INTRODUCTION

- Kidney tumours may be benign or malignant with the latter being more common
- Arise from renal tubules (adenoma, adenocarcinomas e.g. Grawitz tumour), embryogenic tissue (mesoblastic nephroma, Wilm's tumour), mesencymal tissue (angiomyolipoma, medullary interstitial tumour); epithelium of the renal pelvis (urothelial carcinoma)
- Kidney may also be a site for secondary metastasis of tumours.

2.0 CLASSIFICATION OF KIDNEY TUMOURS

- International cancer units have recommended this classification for staging of tumours
- Detailed classification arrived at by a clinician by considering extend of the primary tumour, lymph nodes involvement and whether metastasis is present or not

Table 1: Classification of Kidney Tumours

Origin	***Benign***	***Malignant***
Epithelial tumours of renal parenchyma	Adenoma	Adenocarcinoma (Grawitz tumour, renal cell carcinoma)
Epithelial tumours of renal pelvis	Transitional cell papilloma	Transitional cell carcinoma Squamous cell carcinoma
Embryonal tumours	Mesoblastic nephroma, Multicystic nephroma	Wilm's tumour (Nephroblastoma)
Non-epithelial tumours	Fibroma Angiomyolipoma	Sarcomas
Metastatic		

TNM classification (staging) of tumours (T – tumour, N – node, M – metastasis)

3.0 BENIGN TUMOURS OF THE KIDNEY

- Benign tumours are usually small
- Are rare hence the rule that any tumour be considered malignant as such until investigations prove it otherwise
- Include fibroma, adenomas and angiolipomas

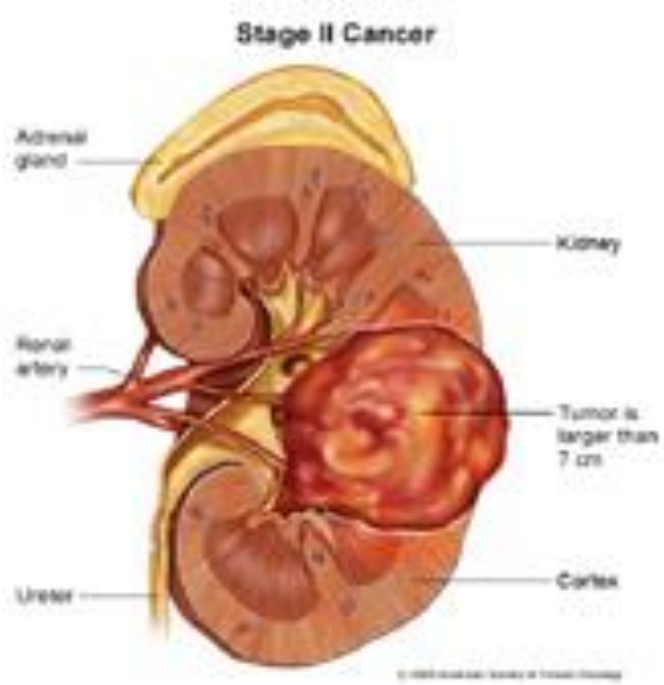
1) Fibroma
- Is the commonest intra-renal tumour of the medulla arising from the interstitial cells?

2) Adenomas
- Develop in the cortex and are commonly seen in patients with end-stage kidney on long-term dialysis or have received a renal transplant
- Usually benign but may become malignant
- Resemble renal adenocarcinomas.

3) **Angiolipomas**
   - Common in patients with tubular sclerosis
   - Comprise a mixture of vessels, smooth muscle and adipose tissue
   - Occur in pyramids or beneath lining of pelvis and lead to severe haematuria.

4.0 MALIGNANT TUMOURS

- May be primary or secondary
- Rare but occur in children below the age of 7 years and adults at the age of 40 – 60 years
- Two most common primary tumours of the kidney are adenocarcinoma (Grawitz's tumour) and Wilm's tumour. Urothelial carcinoma of the renal pelvis is rare.



5.0 ADENOCARCINOMA (RENAL CELL CARCINOMA, GRAWITZ'S TUMOUR)

- Commonest malignant tumour-affecting adults (approx. 75% of the cases).

Origin

The tumours arise from the cortex of the kidney possibly from a pre-existing adenoma. It originates from the renal tubular epithelium usually arising from the upper pole of the kidney but at times the central portion of the kidney. The risk factors include; - cigarette smoking, certain viruses, long-term dialysis and genetic factors.

Pathology

Gross (macroscopic) appearance
1) Solitary or unilateral mass arising from the pole
2) Large, golden yellow and circumscribed
3) Cut surface shows areas of ischaemic necrosis and haemorrhages
4) Presence of tumour thrombus in the renal vein.

Microscopic appearance

1) Shows a variety of patterns within the same tumour – solid, acinar, tubular, trabecular, cord and papillary arrangements in a fibrous stroma.
2) Clear cells – large cells with well-defined borders, abundant clear cytoplasm rich in lipid and glycogen and a relatively regular small pyknotic nuclei
3) Granular cells – moderate amount of pink granular cytoplasm.
4) Greater pleomrphism

Clinical features

1) Intermittent haematuria
2) Dragging dull aching loin pain
3) Palpable renal mass
4) Fatigue and weight loss/cachexia
5) Intermittent fever – suggestive of infection e.g. pyelonephritis
6) Features of metastasis – lungs, brain, bone (haematogenous) and liver, perianal lymph nodes (local spread).
7) Paraneoplastic syndromes due to hormone production; - polycythaemia (erythropoietin), hypercalcaemia (parathyroid hormone and prostaglandins), hypertension (rennin), feminisation or musculinisation (gonadotropins) and Cushing's syndrome (glucosteroids).

Diagnosis

- Triad of gross **haematuria**, **flank pain** and a **palpable abdominal mass**.

Investigations

1) Urinalysis
2) Haemogram
3) IVP/IVU - shows
   a. Filling defect due to invasion of one or more major calyces
   b. There is elongation and compression of the calyces and sometimes the renal pelvis leading to "spider leg" appearance – a diagnostic feature.
4) Abdominal ultrasound
5) Plain abdominal X-ray
6) Tests of Renal function
7) Renal biopsy
8) Chest X-ray

Differential diagnosis

- Polycystic kidney
  - Congenital polycystic kidney has some spider leg deformity but most of the calyces are involved
  - Chest X-ray shows secondary deposition in the lungs in malignancy but not in polycystic kidney disease
  - In polycystic kidney, haematuria may be due to obstruction of renal parenchyma or cysts containing blood rupture into renal pelvis

6.0 NEPHROBLASTOMA (WILM'S TUMOUR)

Introduction

- Is an embryogenic tumour derived from primitive renal epithelial and mesangial components and is the commonest abdominal malignant tumour of young children.
- Comprise epithelial and connective tissue cells (mixed tumour). It is common between 1 – 6 years of age with equal sex incidence
- Usually situated in the poles of the kidney being unilateral but often bilateral.

Pathology

Gross (macroscopic) appearance

1) Quite large and spheroidal
2) Solitary and unilateral (5 – 10% cases bilateral)
3) Cut section shows characteristic variegated appearance - Soft, fish flesh grey white to cream-yellow with necrotic area and haemorrhagic regions
4) Invasion of the renal vein

Microscopic appearance

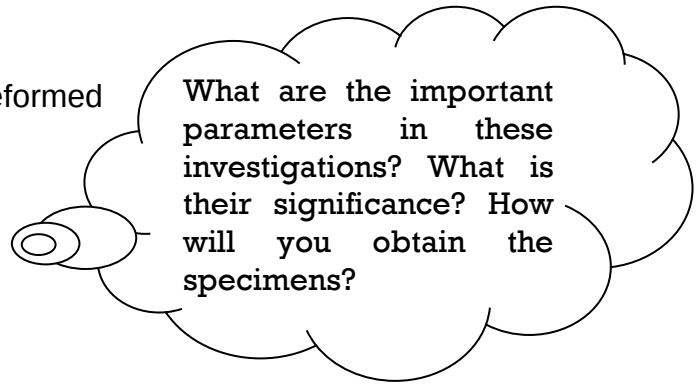
1) Primitive epithelial and connective tissue cells
2) Tumour consists of small, round to spindled cells
3) Smooth muscle cells, skeletal muscle cells, cartilage and bone, fat cells and fibrous tissue may be seen.

Clinical Features

- Abdominal mass (progresses rapidly), haematuria, pain, fever and hypertension

Investigations

1) Urinalysis
2) Haemogram
3) IVP/IVU – shows grossly deformed calyces.
4) Renal biopsy
5) Plain abdominal X-ray
6) Abdominal ultrasound
7) Chest X-ray
8) Renal function tests



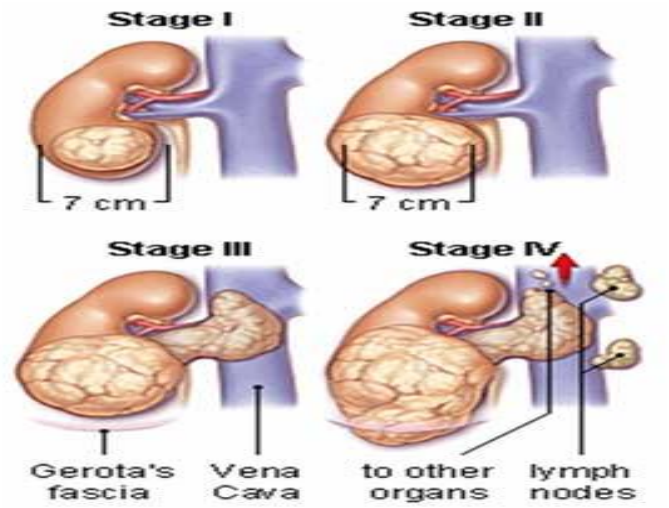
Metastasis

- Occurs early to the lungs, less common to the liver and rarely to the bones. It is exceptional to the brain
- Local spread occurs in the whole kidney and lymphatic spread is much less common.

Differential diagnosis

- Retroperitoneal neuroblastoma - a malignant condition of the adrenal gland that does not cross the midline and metastasis is to the bones only. **Think of other differences.**

Staging



7.0 SECONDARY TUMOURS

- Usually originate from leukaemia (chronic myeloid leukaemia), lungs, breast and the stomach

Tumours of the Bladder

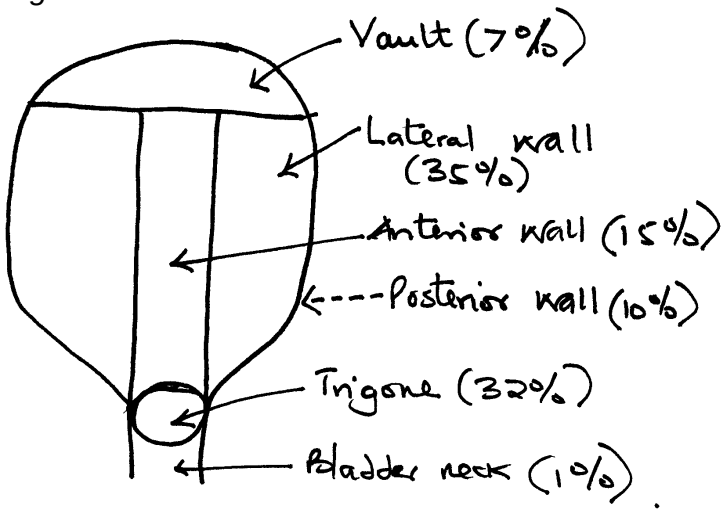
1.0 INTRODUCTION

Majority of the bladder tumours arise from the transitional epithelial (urothelium) of the bladder. Bladder tumours make up 3% of all cancers with most of the cases appearing after the 5th decade of life.

2.0 ETIOPATHOLOGY

- A number of environmental and host factors are associated with increased risk of bladder cancer.
  i) Industrial occupations - Aniline dyes; Rubber; Plastic; Textiles; Cables
  ii) Schistomiasis (*Shistosoma haematonium*) - causes chronic irritation of the mucous membranes, which then undergoes metaplasia, hyperlasia inducing squamous metaplasia and eventually squamous cell carcinoma.
  iii) Dietary factors- metabolites of tryptophan are excreted in urine.
  iv) Local lesions - Ectopia vesicae; Vesical diverticulum; Leukoplakia
  v) Smoking - Increased urinary excretion of carcinogenic substances
  vi) Drugs - Immunosuppressive therapy with cyclophosphamide; Patients with analgesic abuse (phenacetin) nephropathy.

Diagram 9.1: Sites of Bladder tumours



3.0 PATHOLOGY

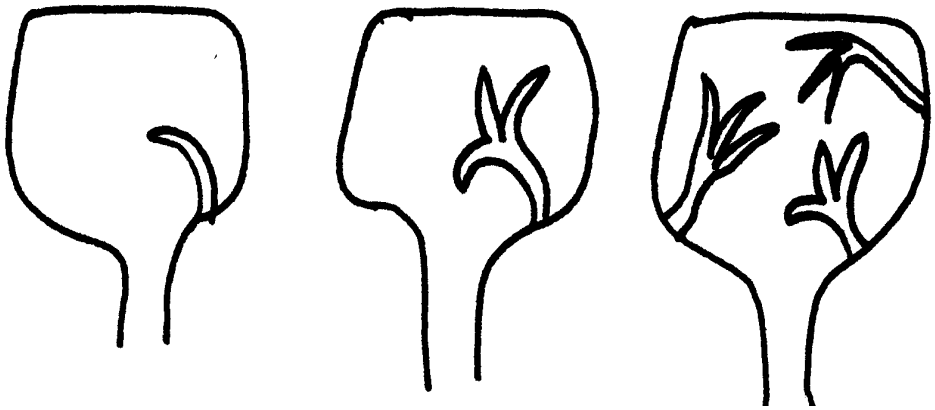
Gross (macroscopic) appearance

- May be single or multiple
- 90% are papillary (invasive or non-invasive)
- Flat indurated (invasive or non-invasive)

Microscopy and histology

- Histologic classification of Urothelial tumours
  i) Transitional cell tumours (90%)
     - Transitional cell papilloma and transitional cell carcinoma (grade 0, I, II and III)
  ii) Squamous cell carcinoma (5%)
  iii) Adenocarcinoma (rare)
  iv) Mixed carcinoma (5%)
  v) Carcinoma in situ.

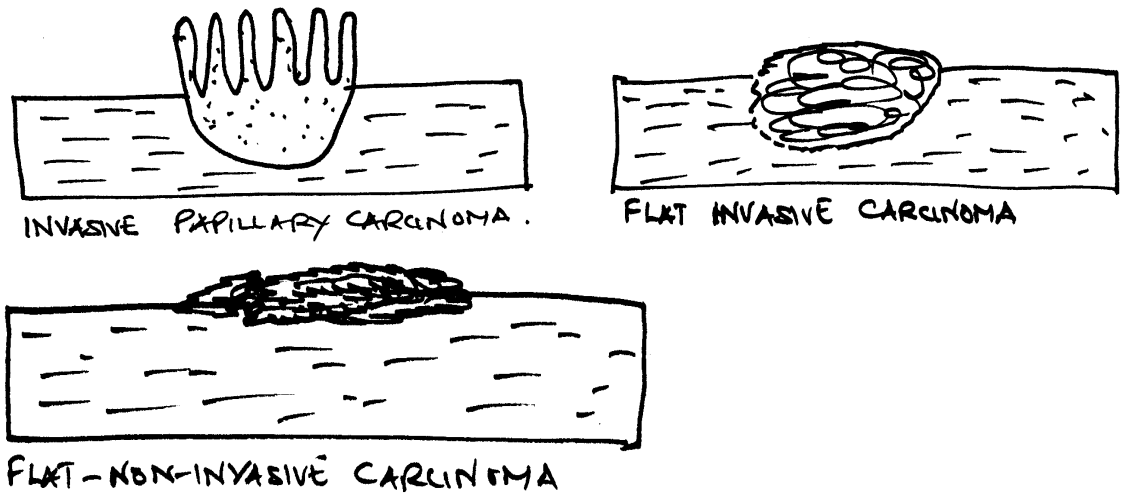
Diagram 9.2: Macroscopic patterns of bladder tumours



Transitional cell papilloma

- Occur singly or may be multiple
- Are small (< 2 cm in diameter)
- Are papillary with branching pattern
- They resemble the normal transitional cells.

Diagram 9.3: Transitional cell papilloma



Transitional cell carcinoma

- Commonest cancer of the bladder
- Has three (3) grades depending on degree of anaplasia and extent of invasion.

Carcinoma in situ

- Characterized by highly anaplastic cells confined to layers superficial to basement membrane of the bladder mucosa.

Squamous cell carcinoma

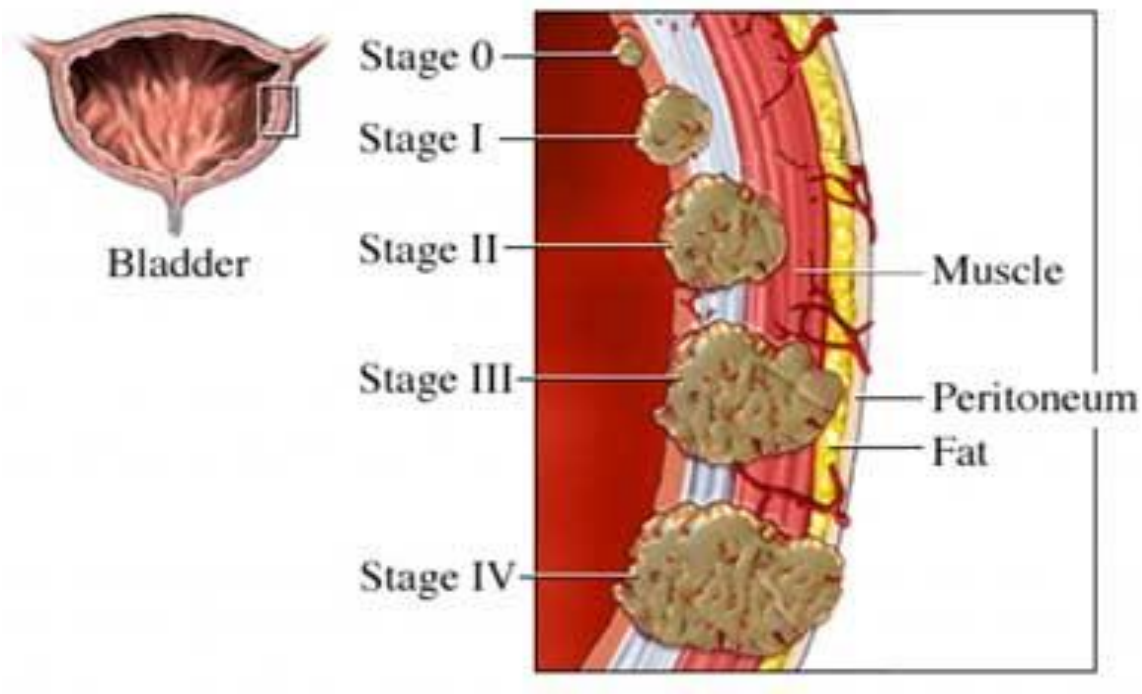
- Sessile, nodular, infiltrating and ulcerating.

Mixed carcinoma

- 50% of bladder tumours show a mixed pattern of transitional and squamous cell combination.

Diagram 9.4: Staging of Bladder Tumours

Staging of Bladder cancer



Stage 0	-	carcinoma confined to the mucosa
Stage I	-	carcinoma invades the lamina propria but not the muscularis
Stage IIa	-	carcinoma invades the superficial muscle layer
Stage IIb	-	carcinoma invades the deep muscle layer
Stage III	-	carcinoma invades perivesical tissues
Stage IVa	-	carcinoma shows regional metastasis
Stage IVb	-	carcinoma shows distant metastases

4.0 INVESTIGATIONS

1) Urinalysis- frank blood, culture and sensitivity, microscopy, sugar, proteins
2) Total blood count (TBC)
3) Cystocopy
4) Renal function tests
5) Excretory pyelography
6) Plain abdominal X-ray
7) IVP/IVU – shows grossly deformed calyces.
8) Renal biopsy
9) Chest X-ray