NEPHROLOGY
FOR
MEDICAL STUDENTS

by
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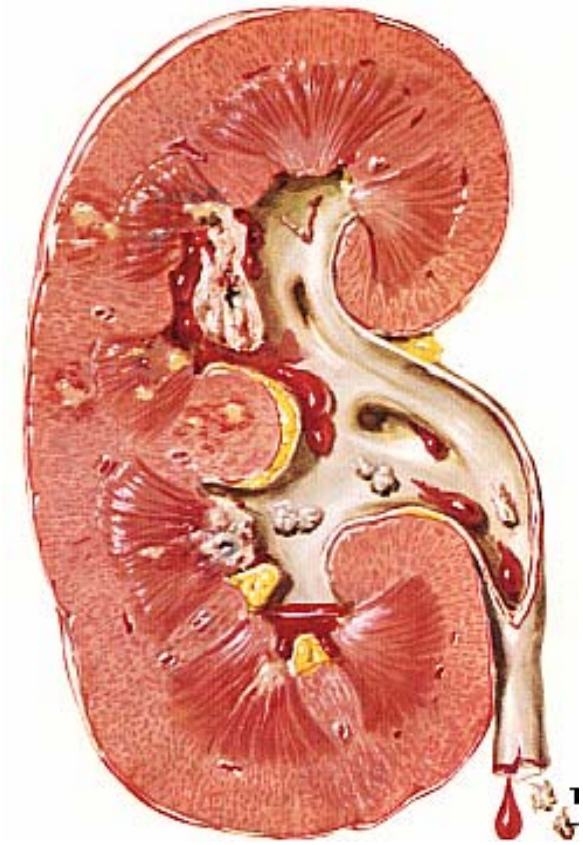

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Dedication

To the soul of my dear father

To my dear mother

To my lovely wife, and

To my children.

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PREFACE

Renal diseases are increasing worldwide. Doctors in all specialties are facing renal diseases either as isolated disorder or in association with other disease. For these reasons it became mandatory to give more attention for better education of renal diseases especially for young doctors and medical students.

This book is written essentially for medical students and general practionares. It covers most of the items of renal diseases in a simple fashion with sufficient number of illustrations and figures.

For those who are seeking for more details, this could be easily obtained from the more comprehensive version of this book entitled "Essentials of Clinical Nephrology".

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CONTENTS

RENAL FUNCTIONS AND STRUCTURE

KIDNEY FUNCTIONS:

The function of the kidney is to keep the **internal environment** (internal milieu) of the body stable within the physiologic limits. This is achieved through the following functions:

1. **EXCRETORY FUNCTION AND PRODUCTION OF URINE:**
   Through urine production there are: **1.** elimination of wastes (metabolic products, ingested toxins such as drugs). **2.** control of water balance (maintenance of total body water and plasma osmolarity), and **3.** control of electrolyte balance (sodium, chloride, calcium, phosphate, potassium, acid-base, magnesium and others).

2. **REGULATION OF THE ACID-BASE BALANCE OF THE BODY:**
   This is achieved through the following:
   Proximal tubular reabsorption of bicarbonate which is filtered from blood through the glomeruli.
   Renal tubules through the increase in the formation of ammonia and titratable acids (phosphates, sulphates and phenols).

3. **HEMOPOIETIC FUNCTION :**
   Kidney has an important role in erythropioesis in the bone marrow through secretion of erythropoietin.
   Human recombinant erythropoietin is now commercially available for the treatment of anaemia in uraemic patients.

4. ENDOCRINE FUNCTIONS OF THE KIDNEY:

Many hormones and vasoactive substances are either formed (Renin, Prostaglandins), activated (Vitamine D), or degraded (Insulin, Parathormone, Prolactin) by the kidney.

ANATOMY OF THE KIDNEY:

Each kidney is a bean-shaped structure measuring approximately 11 cm x 6 cm x 3 cm and weighing 120-170 grams in adult. The kidney is contained in a fibrous capsule. The hilum of the kidney which is present medially contains renal artery, vein, lymphatics and pelvis of the ureter. The kidney is contained in peri-renal fat. The kidney lies in the paravertebral gutter on the posterior abdominal wall retroperitoneally and opposite the twelfth thoracic down to the third lumbar vertebra. The right kidney is slightly lower than the left (liver effect), lower pole reaches one finger breadth above the iliac crest. **Figure 1.1** shows a longitudinal section of the kidney. It shows the hilum containing the renal vessels and pelvis of the ureter which branches inside the kidney into 2-4 major calyces, each of which in turn branches into several minor calyces. The kidney parenchyma is divided into outer cortex (1 cm thick) and inner medulla. The medulla is formed of 8-18 pyramids which are conical-shaped, with its base at cortico-medullary junction and its apex projects into minor calyces as papillae. The medullary pyramids are striated in shape. The cortex which is granular-looking may extend between pyramids forming columns of Bertini. Medullary rays are striated elements which radiates from the pyramids through the cortex.

THE NEPHRON:

Is the functional unit of the kidney **(Fig. 1.2)**. Each kidney contains approximately one million nephrons. The first part of the nephron is the *glomerulus* (renal corpuscle) which lies mainly in the renal cortex, followed by *proximal convoluted tubule* which also lies mainly in the renal cortex. This is followed by a *loop of Henle* which is partly in the cortex and partly extends deep into the medulla. Loop of Henle is composed of a thin part and a thick part. This is followed by the *distal convoluted tubule* which lies in the renal cortex. Part of the distal convoluted tubule comes into contact with the hilum of the glomerulus and afferent arteriole. Cells in the hilum of the glomerulus and those in distal convoluted tubule and afferent arteriole are modified to form the *Juxta glomerular apparatus***.** Distal convoluted tubule ends into the *collecting duct* which lies partly in the cortex and partly in the medulla. In the medulla, collecting ducts descend in the pyramids, at the renal papillae collecting ducts unite together to form ducts of Bertini which discharge urine into renal pelvis.

The glomerulus (renal corpuscle):

The renal corpuscle is formed essentially of two modified structures of different embryonic origins:

A. *The first* is the Bowman's capsule which is present at the beginning of the proximal convoluted tubule and is formed of a space lined by basement membrane and flat epithelial cells.

B. *The second* is modification of the end of the afferent arteriole, which divides into several primary branches. These in turn give rise to several lobules of capillaries (tuft of capillaries). The other end of this capillary tuft gives rise to the efferent arteriole. Each capillary is lined with basement membrane, lined from inside by endothelial cells and from outside by epithelial cells which lie on the capillary basement membrane by foot process (so it is called

podocyte). The capillary tuft will invaginate and occupy the Bowman's capsule to form the renal corpuscle.

Figure 1.3 shows a cross section of the glomerulus which is composed of:

1. Bowman's capsule with its outer (parietal) layer lined by flat epithelial cells, and inner visceral layer in contact with capillary tuft lined with visceral epithelial cells (podocytes). Between the two layers there is a space called urinary space.
2. Glomerular capillaries are lined by basement membrane which is covered from inside with endothelial cells and from outside by epithelial cells (podocytes).
3. Mesangium is composed of special cells and matrix. It is located mainly at the hilum of the glomerulus, and extends between capillary loops. Its main function is to support the capillary tuft, also, it may have a phagocytic function and contractile function.

   Phagocytic property of the mesangium helps in clearing the glomerulus from any circulating immune complexes or antigens. The contractile function may help in modulating the renal blood flow and the capillary wall filtration surface.

Juxta-glomerular apparatus:

Juxta-glomerular apparatus is a specialized structure which is present at the hilum (vascular pole) of the glomerulus **(Figure 1.4)**. It is composed of four groups of cells which contain granules in their cytoplasm (most probably renin). These cells are:

1. The macula densa cells which are modified cells in distal convoluted tubules.
2. The epithelioid cells which are modified cells in the wall of the afferent and-to less extent-efferent arterioles.

3. The lacis cells which are interstitial cells in continuity with mesangial cells.
4. The peripolar cells which are present at the vascular pole of the glomerulus, separating the podocytes from the flat parietal epithelial cells of Bowman's capsule.

Concentration And Dilution Of Urine:

This function is very important to regulate body water and tissue osmolarity. Normal body tissue and fluid osmolarity is 280-300 mosmol/Liter. This is maintained despite the wide variation in fluid intake (increased intake decreases osmolarity and vice versa) and load of osmotically active substances e.g. salt. Through biologic activity, there is a basal production of 600 mosmol/day. This can increase to over 1200 mosmol/day in states of severe catabolism as in patients with extensive burns.

The kidney is responsible for the control of secretion of water and solutes through process of urine formation so as to keep normal plasma osmolarity. The normal urine volume is around 1.5 liter/day but can vary from 400 ml to over 20 liter/day according to water and solute intake.

The urine osmolarity may vary from 30 mosmol/liter (when urine is maximally diluted) to 1400 mosmol/liter (when urine is maximally concentrated). The minimum urine output to maintain adequate excretion of waste products (600 mosmol/day) is 400 ml with maximum osmolarity of 1400 mosmol/liter.

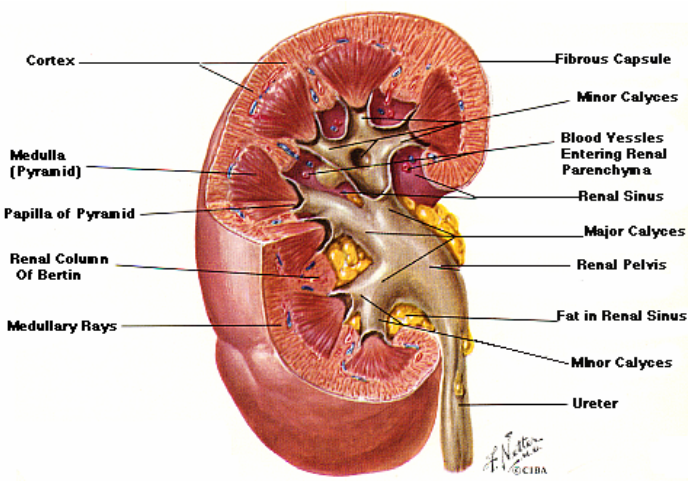
Under normal circumstances, over 99% of filtered water is reabsorbed. Water is reabsorbed in an iso-osmotic fashion with sodium chloride i.e. as NaCl is reabsorbed, water flows back into the circulation.

In addition, further water is reabsorbed in the process of urine concentration which occurs in the distal nephron.

Dilution of urine is achieved through the removal of NaCl from the tubular lumen fluid in the segment which is impermeable to H_2O (thick part of the ascending loop of Henle, DCT), or from the segment which becomes impermeable to H_2O as an effect of ADH (collecting tubule and duct). The most important of them is the loop of Henle which secretes more H_2O and less Nacl in urine making it hypotonic (diluted).

Urine concentration results from the reabsorption of water in excess of nitrogenous wastes and other solutes. Therefore, in urine the concentration of urea is about 60 times that in plasma. In states of maximal urine concentration, urine osmolarity is about 1200 mosmol/liter. Further increase in urine osmolarity to 1400 mosmol/liter can be achieved with persistence of the stimulus for urine concentration. Urine concentration, through excess reabsorption of free water occurs mainly in collecting tubules.

The mechanism of urine concentration depends on passage of collecting tubules through the hypertonic renal medulla. The tonicity of renal medulla is maximum at the tip of renal papillae and decreases gradually towards the direction of the corticomedullary junction. ADH when secreted will increase the collecting tubule permeability to water which gets out to the interstitium leaving tubular contents hypertonic. The interstitial water is picked up by the vasa recta and renal venules and will be drained away.



(Fig. 1.1)

Right kidney sectioned in several planes exposing the parenchyma and renal sinus.

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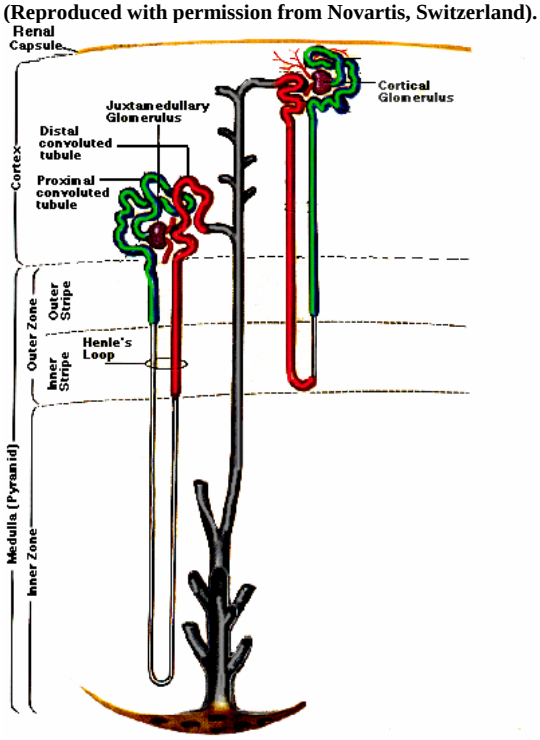
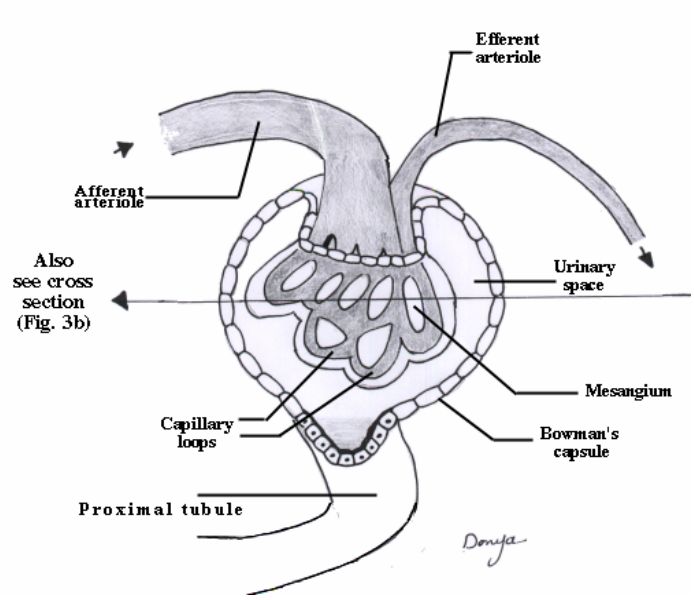


(Fig. 1.2)
Diagrammatic illustration of the nephrons and collecting tubules.



(Fig. 1.3.a)
Diagramatic representation of the glomerulus

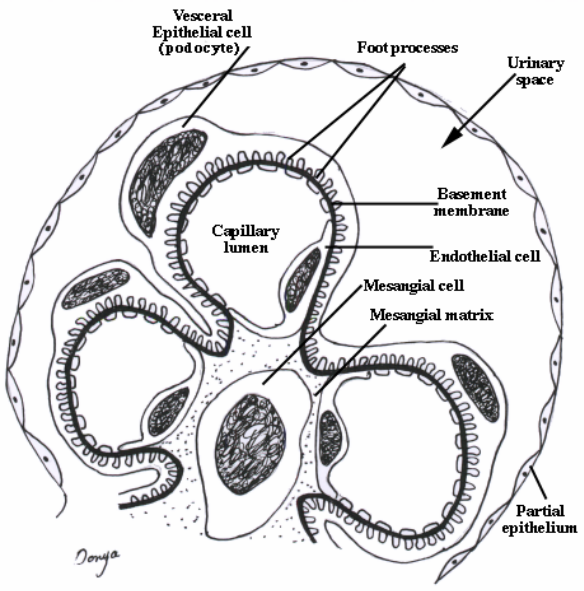
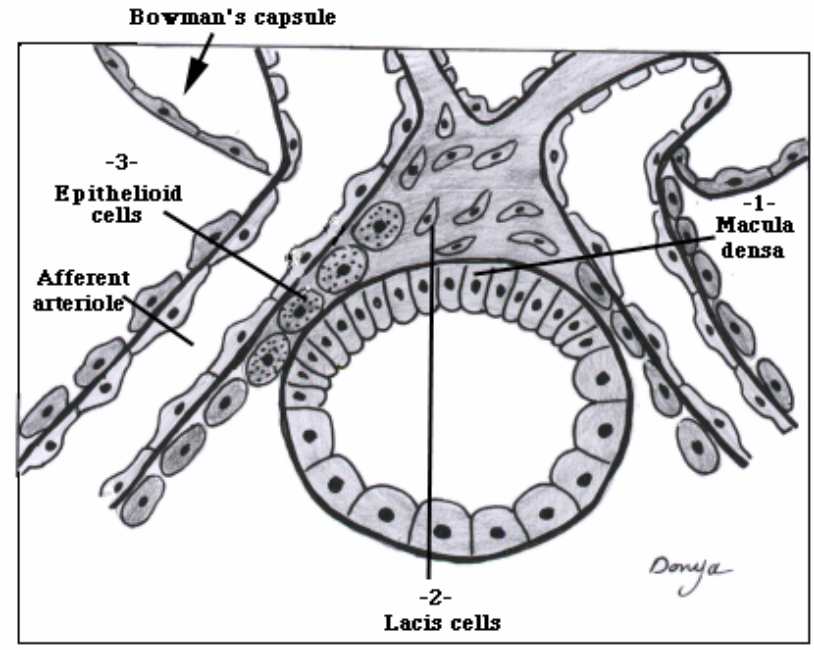
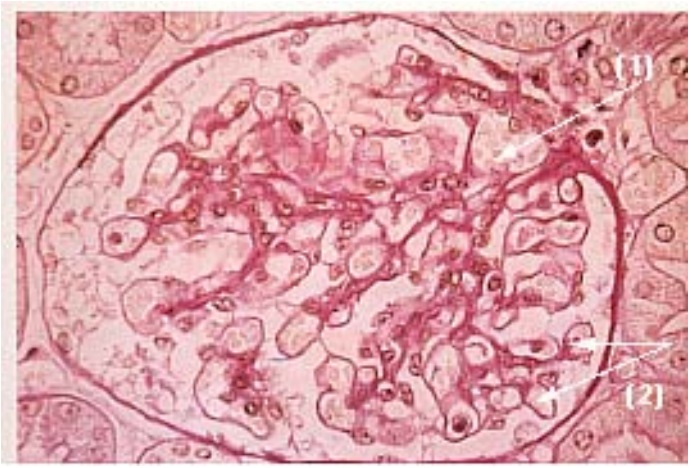


Fig. 1.3b
Cross-section of a glomerlus showing the details of the glomerular tuft.



(Fig. 1.4a)
The Juxtaglomerular apparatus. Note: (1) Macula densa of distal tubule.
(2) Juxtaglomerular (lacis) cells.
(3) Granular renin-secreting epithelial cells of afferent arterioles.



(Fig. 1.4b)
PAS stained kidney section (X 260), which shows a normal glomerulus cut through the hilus. The branching mesangial stalk is clearly seen (arrow-1). The capillaries are attached to the stalk, forming peripheral capillary loops (arrow-2).

INVESTIGATIONS FOR KIDNEY DISEASES

These include biochemical, microbiologic, immunologic, histopathologic and radiologic investigations.

A. BIOCHEMICAL INVESTIGATIONS:

Include the examination of urine, tests for kidney functions, microbiologic and immunologic tests.

I. URINE EXAMINATION:

Simple urinalysis and blood pressure measurement could be a valuable method for screening for renal diseases. However, negative urinalysis does not exclude renal disease. Urinalysis is an essential part of physical examination for kidney disease. The urine should be **fresh** and examined for the following :

1. Physical characteristics: these include examination for colour, odour, transparency, froth and foreign materials.

   Normal colour of urine is amber yellow due to the pigment urochrome, it could be diluted or concentrated according to the patient hydration status and the diluting and concentrating capacity of the kidney.

   A red coloured urine is seen mainly with haematuria, hemoglobinuria which could be differentiated by microscopic examination which can demonstrate RBC's in cases of haematuria but not in cases of haemoglobinuria.

   A milky urine is seen in chyluria (lymph in urine). Turbid urine is seen with pyuria or presence of salts (phosphate, urate or oxalates). Cloudy and offensive urine could be seen with infection. Abnormal

foreign bodies seen in urine are for example gravels or sloughed renal papillae.

2. Dip-stick test: These are plastic strips, attached to it are pieces of paper impregnated with different enzymes. Each piece contains an enzyme which reacts specifically with certain urine chemicals (e.g. glucose, albumin, acetone, H+, nitrite, haemoglobin, etc.). According to the concentration of the chemical tested, a certain change in colour occurs (0, 1+, 2+, 3+, 4+).
3. Microscopic examination of urine is a method for detection of cells (RBC's, leukocytes, pus, epithelial cells), casts (hyaline casts, red cells casts, leucocyte casts, granular casts or broad casts), or crystals (triple phosphate, uric acid, oxalate or cystine) **(Figure 2.1)** .
4. Quantitative estimation of proteinuria: This is achieved through quantitation of protein in 24 hours urine collection (normally less than 150 mg/24hours)
5. Examination of urine for Bence Jones protein: Normally this could not be detected by Dip-Stix and needs immunoelectrophoresis. This protein precipitates on heating at 56°C and redissolves at 100°C or more. It is present in cases of multiple myeloma, amyloidosis and other types of macroglobulinemias.

II. RENAL FUNCTION TESTS:

These includes tests for glomerular and tubular functions.

a. TESTS FOR GLOMERULAR FUNCTION

These include test for serum creatinine, blood urea nitrogen and glomerular filtration rate (GFR).

1- Serum creatinine : In routine practice serum creatinine level is the best indicator of kidney function (normally is 0.6-1.2 mg/dl).

2- **Plasma urea and Blood Urea Nitrogen (BUN) :** The normal value of blood urea is 15-40 mg/dl. Normal value of BUN is 8-13 mg/dl.

3- **Glomerular Filtration Rate (GFR):** This is measured by studying the clearance of a substance which is ideally freely filtered through the glomerulus; and not reabsorbed or excreted by the renal tubules (e.g. inulin). In practice, we use endogenous creatinine which is filtered through the glomerulus but some excretion occurs by the renal tubules, so creatinine clearance slightly overestimates GFR.

Normal creatinine clearance in adult male is 90 -150 ml/minute. To estimate creatinine clearance, the patient should collect 24 hours urine from which V and U could be estimated then, blood is withdrawn for P estimation.

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

C= creatinine clearance
U= urine concentration of creatinine
V= urine flow rate (minute or second)
P= plasma concentration of creatinine

99mTc-DTPA or 151Cr-labeled EDTA or iothalamate isotope renal scan is an alternative method which does not require urine collection.

b. TESTS FOR TUBULAR FUNCTIONS:

1. Urine Acidification Test.
2. Urine Concentration Test.
3. Urinary B_2-microglobulin.
4. Urinary Enzymes.
5. Urinary excretion of sodium (UNa)

B. MICROBIOLOGICAL EXAMINATION OF URINE:

In cases of urinary tract infection, urine specimens are examined for identification of bacteria as well as for its sensitivity to antibiotics by culture techniques. Taking a proper urine sample is mandatory to avoid false results.

A midstream urine sample is required i.e. when the bladder is full, the first 200 c.c. is passed to clean the urethra. Then, 10 c.c. is taken in a sterile container from the urine stream. In the male, glans penis should be cleaned by sterile water, and in the female the vulva is cleaned properly and during micturition labia are held away by fingers. In neonates and young children suprapubic aspiration of urine by fine needle is safe.

C. IMMUNOLOGICAL TESTS FOR DIAGNOSIS OF KIDNEY DISEASES:

1. Complement:

Complement System is activated and consumed in immune-complex formation. Hypocomplementemia consequently occur in diseases such as: post infectious glomerulonephritis, shunt nephritis, nephritis associating subacute bacterial endocarditis, lupus nephritis and idiopathic mesangio-capillary (membrano-proliferative) glomerulonephritis. Usually, the complement system is assessed by measuring the total haemolytic complement (CH50) activity, C3 and C4 concentrations.

2. Immunoglobulins:

Such as serum IgA concentrations could be high in IgA nephropathy and Henoch-Schönlein disease.

3. Circulating Immune Complexes (C.I.C.):

Circulating immune complexes (C.I.C.) are detected in diseases such as cryoglobulinaemias, SLE and collagen diseases. C.I.C. assays have a limited role in clinical practice.

4. Autoantibodies:

These include antinuclear antibodies (ANA), anti-DNA, anti-neutrophil cytoplasm auto antibodies (ANCA), and anti-glomerular basement membrane antibodies (anti-GBM).

D. KIDNEY BIOPSY:

Kidney Biopsy is performed to obtain kidney tissue for histological examination in order to take therapeutic decision and to judge the prognosis of the renal disease.

Indications:

For all adults with nephrotic syndrome, children with steroid resistant nephrotic syndrome and patients with renal impairment of unknown etiology.

Complications:

1. Peri-renal haematoma which is extremely common but of significance only in 1% of cases.
2. Bleeding which could be microscopic or gross with clot retention.
3. Intra-renal A-V fistula which usually closes spontaneously.

E. RADIOLOGIC EXAMINATION OF THE KIDNEY AND THE URINARY TRACT:

During the last decade a great progress has been achieved in imaging techniques of the kidney and urinary tract. We have to select the procedure which is the simplest, least invasive, most informative and which saves time for the patient.

1. Ultrasonography (U.S.):

Ultrasound examination of the kidney and urinary tract is either through B-mode scan, Doppler flow examination of renal vessels or duplex ultrasound scanning.

B-mode U.S. imaging is the usual examination requested. Renal ultrasonography should be the first radiologic procedure performed on

patient with renal or urologic disorder; and in most instances it will be the only one that is required. Renal ultrasonography carries the advantages of being non-invasive, less costly and does not require special preparation. It can demonstrate clearly the renal size, contour, echotexture **(Figure 2.2),** stone, back pressure (due to chronic obstruction), renal mass or cyst **(Figure 2.3)**, and perirenal collection. Pelvic ultrasonography may show bladder mass and calculate the residual urine (amount of urine remaining in the bladder after micturition). Ultrasonography can also show the upper and lower parts of the ureter. In addition, ultrasonography can help in examining surrounding organs and help in guiding needle for renal biopsy or aspiration of peri renal or peri-vesical collection.

Doppler flow imaging of the renal vessels will assess the integrity of the blood supply of the kidney **(Figure 2.4)**. It may be displayed with standard gray scale or in colour (colour Doppler). It may help in diagnosis of renal artery occlusion or stenosis, renal vein thrombosis and kidney transplant rejection.

Duplex ultrasonography shows the standard B-mode image with superimposed Doppler flow informations **(Figure 2.5)**.

2. Plain abdominal X-Ray:

For examination of urinary system, this is called plain X-ray abdomen or KUB (kidney, ureter, bladder). KUB may show : 1-stones (80-90% of stones are radio-opaque), 2-Calcification of the kidney, urinary bladder, seminal vesicles or prostate, and 3-In a well prepared patient with no bowel gases, or by nephrotomogram, soft tissue shadow and renal contour could be seen (size and shape of the kidney) **(Fig. 2.6)**.

3. Intravenous urography (IVU):

The patient should come for this investigation after a thorough bowel evacuation (laxative is to be given the night before and enema on the morning of the day of examination) and with the fluid intake restricted (to allow concentration of the dye and consequently proper visualization of the urinary tract). An iodinated contrast media is injected intravenously and x-ray films are taken immediately, 1 minute and 15 minutes after injection. Sometimes late films are taken (e.g. when artery stenosis is suspected).

Nephrogram is the film obtained immediately after injection of contrast medium. It shows the dye concentrated in the nephrons and the kidney appears opacified but no dye yet in the renal pelvis. This film shows the site, the size, the contour of the two kidneys. It also shows whether the kidneys are functioning equally or not. In cases of renal artery stenosis, the nephrogram of the affected kidney appears delayed than the other healthy kidney. After nephrogram, dye will appear in the renal pelvis, ureter then the bladder **(Fig. 2.7)**. So, IVU shows the anatomy of the kidney and urinary system (any mass, stones, back pressure changes) and also demonstrates the kidney function.

As the contrast media used is ionic and with high viscosity and the technique is done with dehydration, this can result in kidney damage (contrast media nephropathy) with rise in serum creatinine-even acute renal failure may occur. There is a group of patients who are more vulnerable to contrast media nephropathy. These are diabetics, elderly, hyperuricaemics, patients with multiple myeloma, presence of renal dysfunction, patients receiving other nephrotoxic drugs (e.g. gentamycin), and those with congestive heart failure.

Anaphylactoid reaction is another possible risk of the contrast media. Therefore, steroids and antihistaminic drugs should be at hand.

4. Cystography and voiding cystourethrography:

Diluted contrast is injected into the bladder through urethral or suprapubic catheter. When the bladder becomes full, the patient is asked to micturate and films are taken. This is called micturating or voiding cystourethrogram (VCU). Normally the dye does not appear in the ureters because of the normally present antireflux mechanism at ureterovesical junction. If the dye appears in the ureters during VCU, this is called vesicoureteric reflux (VUR).

5. Urodynamic studies:

Measuring the intravesical pressure (cystometry) and urine flow will give full anatomic and physiologic assessment of the lower urinary tract.

6. Angiography: This includes

a. Renal Arteriography

A catheter is introduced percutaneously into the femoral artery and proceeded under television (screen) control through the aorta. The dye could be injected into the aorta, above the level of renal arteries (flush aortography) and films are taken which will show renal arteries and nearby vessels or the catheter could be advanced selectively into renal artery and dye is injected (selective renal angiography).

Renal arteriography is mainly indicated for diagnosis of renovascular hypertension or persistent haematuria following trauma.

b. Renal Venography

This is indicated mainly for diagnosis of renal vein thrombosis. A catheter is introduced percutaneously into the femoral vein then advanced through inferior vena cava to the renal vein where the contrast medium is injected.

7. Computerized tomography (C.T.)

This scanning may be superior to other radiologic investigations in the following areas: 1. To characterize lesions in peri-renal, para-renal and retroperitoneal space as lymphadenopathy, tumours or retroperitoneal fibrosis. 2. Solid renal masses, for diagnosis and staging of the tumour. 3. Low density or radiolucent stones. Therefore it is strongly indicated in patients with obstructive uropathy with non-evident cause **(Fig. 2.8)**.

8. Radionuclide Imaging

There are two types of isotope renal scanning: 1. Static imaging, in which the tracer injected is retained by proximal convoluted tubules, giving best chance to visualize the morphology of functioning part of the kidney using gamma camera. So, it is helpful in diagnosing renal scarring **(Figure 2.9)**, renal tumours and anatomic abnormalities. The tracer used for this type of scan is 99m technetium-labelled dimercaptosuccinic acid (DMSA). 2. Dynamic renal imaging in which the tracer is not retained by the kidney, but is immediately excreted, either by glomerular filtration alone e.g. 99m TC- diethylenetriamine penta acetic acid (DTPA) or by glomerular filtration and tubular secretion (MAG3), and 123I, sodium iodohippurate (Hippuran). This type of scan is helpful in diagnosing renal vascular occlusion (embolism or thrombosis) or narrowing (renal artery stenosis). The dynamic parenchymal imaging **(Figure 2.10)** helps in diagnosis of ureteric obstruction in which delayed washout of the tracer from the kidney will be observed. Furthermore, the dynamic scan can be

helpful in the measurement of the total or individual kidney GFR (DTPA) or effective renal plasma flow (MAG3 or Hippuran).

9. Magentic Resonance Imaging (MRI)

The principle of MRI is the excitation of the nuclei of atoms such as hydrogen in tissues with radiowaves, and detection of echo radiation from these nuclei when the radio source is removed. Thus, the MRI provides information at the cellular level. Currently, this recent technique provides excellent anatomical informations **(Figure 2.11)** which are very helpful in studying malignancies of the urinary tract and assessment of renal vessels.

Normal Values

Plasma

• Creatinine (Cr)	0.6-1.2 mg/dl.
• Sodium (Na)	134-145 mEq/L
• Potassium (K)	3.5-5.0 mEq/L
• Chloride (CL)	96-106 mEq/L
• Bicarbonate (HCO_3^-)	23-30 mEq/L
• Blood urea nitrogen (BUN)	8-13 mg/dl
• Osmolality (osmol)	280-295 mosmol/kg

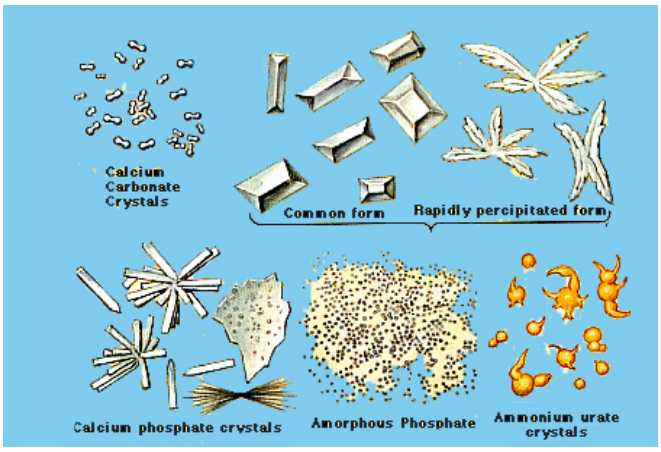
Serum

• Uric acid	2.6-7.2 m/dl
• Calcium (Ca)	8.8-10.5mg/dl
• Phosphorus (Po_4)	2.4-4.9 mg/dl
• Albumin	3.5-5.0gm/dl
• Magnisium	1.8-2.4 mg/dl
• Complement (C_3)	85-193 mg/dl
• Complement (C_4)	12-36 mg/dl

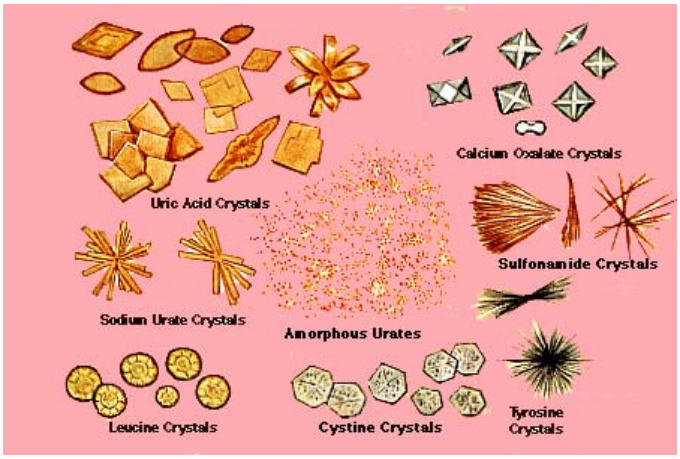
24 hour urinary excretion

• Protein	< 150 mg
• Albumin	< 20 mg

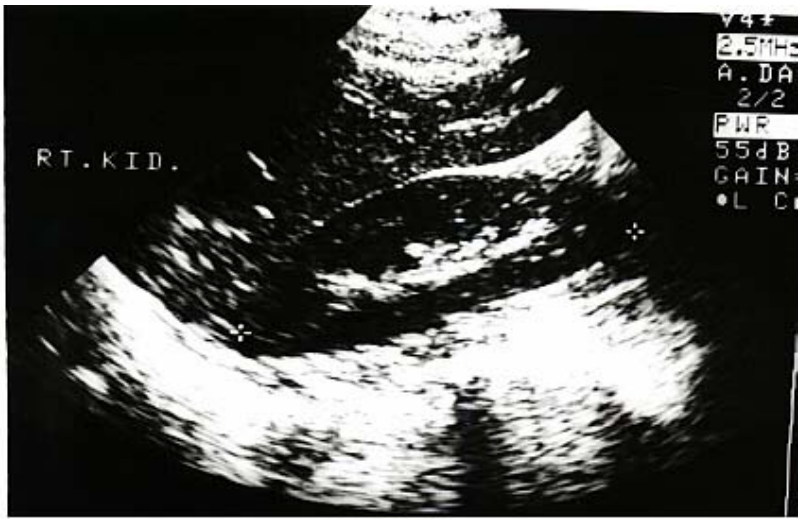
Urine Osmolality	500-800 mosmol/kg H_20
Creatinine clerance	90-150 ml/min.



(Fig. 2.1 a) Shows different crystals which could be seen by microscopy of urine with alkaline pH.

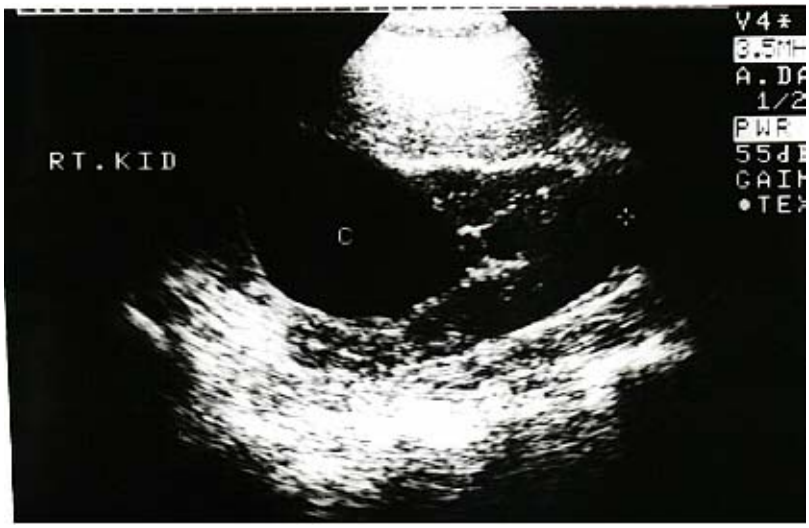


(Fig. 2.1b) Shows different crystals which could be seen by microscopy of urine with acidic pH.



(Fig. 2.2)

Normal renal ultrasound: it shows longitudinal scan through the right kidney demonstrating the relationship to the right lobe of the liver anteriorly and the paraspinal muscle posteriorly. The kidney shows echogenecity less than that of the adjacent liver



(Fig. 2.3a)

It shows a well-circumscribed right upper polar cyst (c) with a sonolucent "echo-free" pattern, thin wall, well-defined posterior margin and posterior echo-enhancement (due to good transmission of the ultrasound waves through the fluid content).

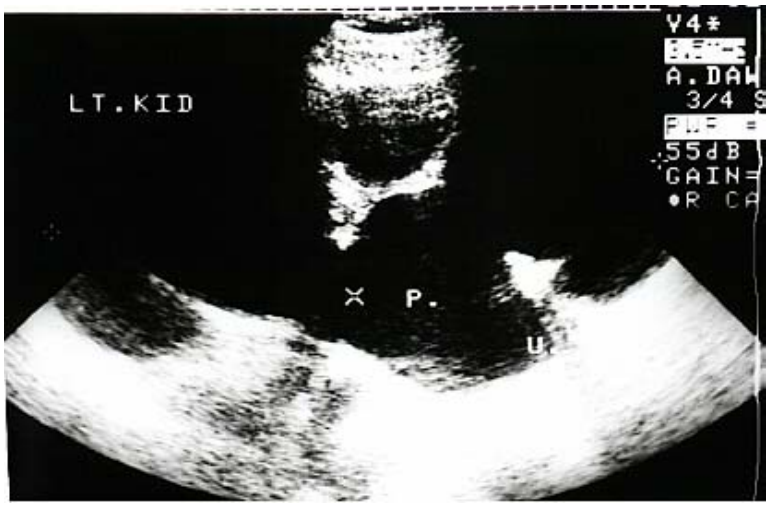
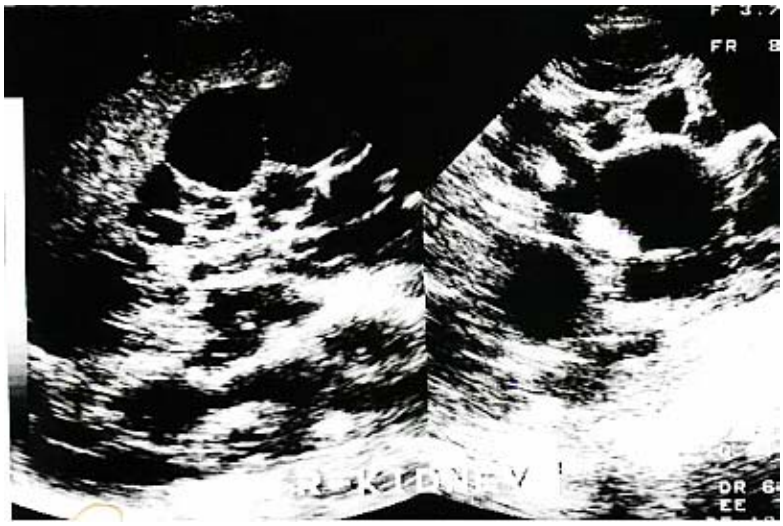


Fig. (2.3b)

It shows marked left hydronephrosis demonstrating marked dilatation of the calyces and the renal pelvis with thinning of the renal parenchyma.



(Fig. 2.3c)

It shows a longitudinal scan of each kidney with bilateral variably sized non-communicating cyst throughout renal parenchyma. Neither back-pressure changes nor communication with the collecting system can be identified.

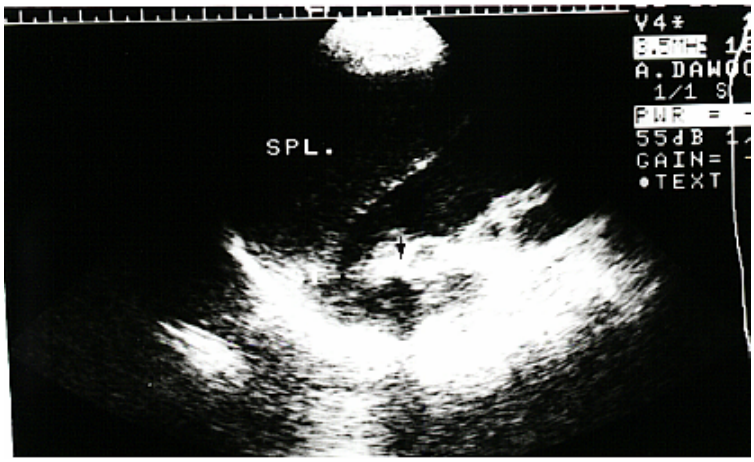
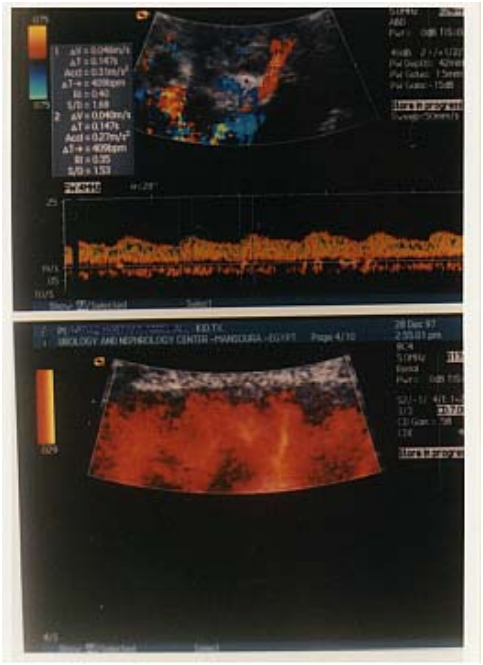


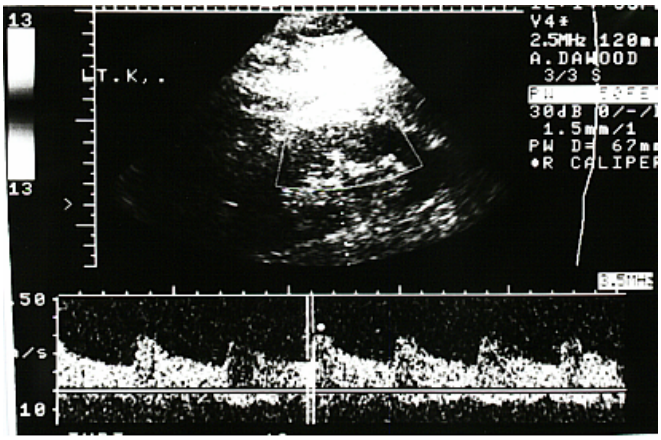
Fig. (2.3d)

It shows a LS of the left kidney with a stone upper calyx (arrow) as echo-dense focus casting posterior acoustic shadow.



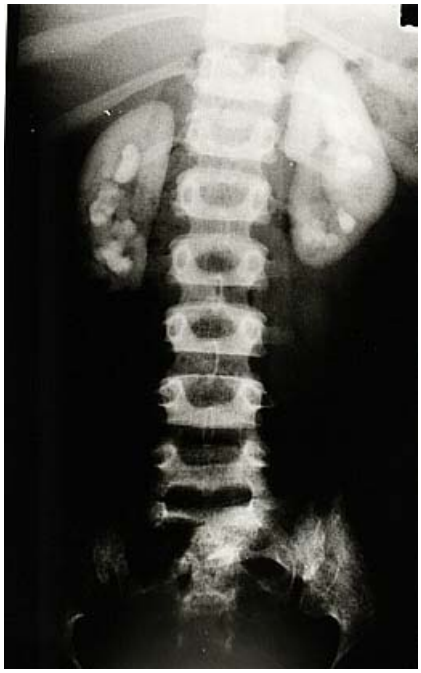
(Fig. 2.4)

Doppler US of a case with renal artery stenosis, it shows Damped wave form with marked delay in the systolic rise time, a reduction in the pulsatility index with low flow velocities (Parvus tradus pattern). Sampling was from an intrarenal vessel.



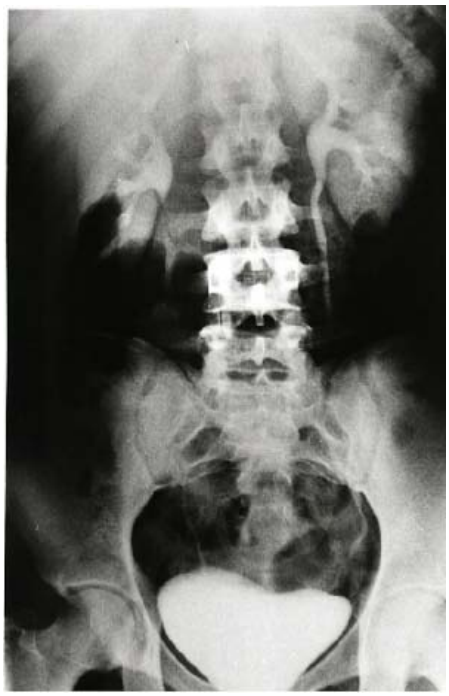
(Fig. 2.5)

Duplex US (Normal)
Combined real time US (top) and Doppler US (bottom) showing normal low-resistance waveform with high forward flow throughout systole and diastole.



(Fig. 2.6)

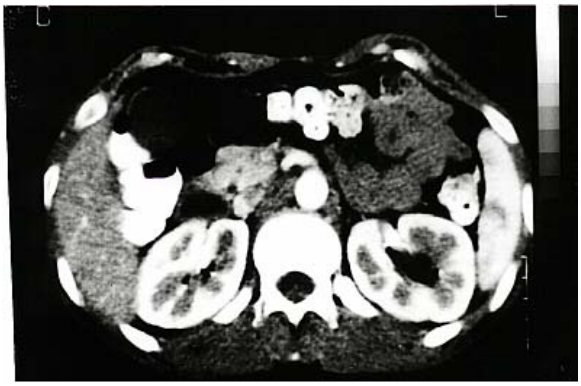
Oxalosis (UTP)
Calcified soft tissue shadow of both kidney (simulating a nephrogram of IVU). Multiple, bilateral radioopaque stones are noted as well.



(Fig. 2.7)

Intravenous urography (IVU) showing:

- Normal excretion and concentration of contrast medium by both kidneys.
- Normal configuration of both kidneys.
- Normal course and calibre of both ureters
- Normal cystogram.



(Fig. 2.8)

CT scan of the kidney (Normal)

- Axial CT scan of the kidney early after administration of I.V. contrast medium showing normal corticomedullary definition as the medullary pyramids are less enhancing than the cortex. The central hypodense structure represents the renal sinus.

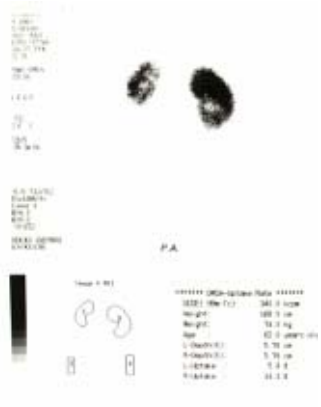
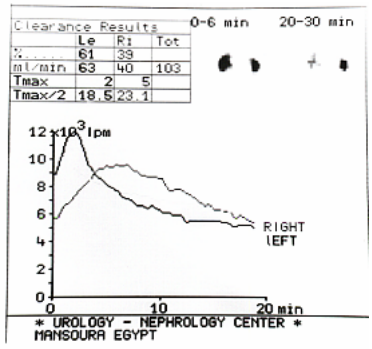
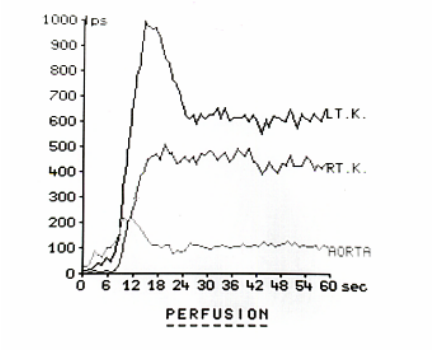


Fig. (2.9)
DMSA scan (chronic pyelonephritis) small-sized left kidney with irregular outline and multiple photopenic areas. A photodeficient area is also noted at the lower pole of right kidney.

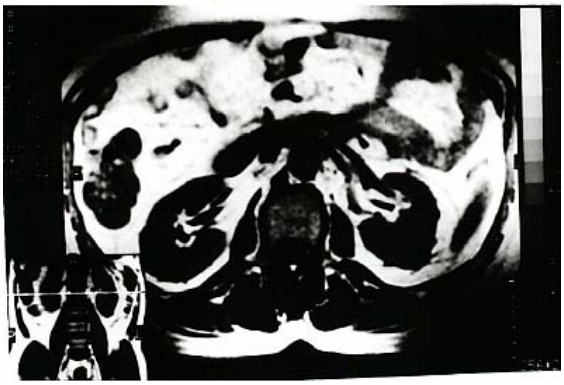




(Fig. 2.10)

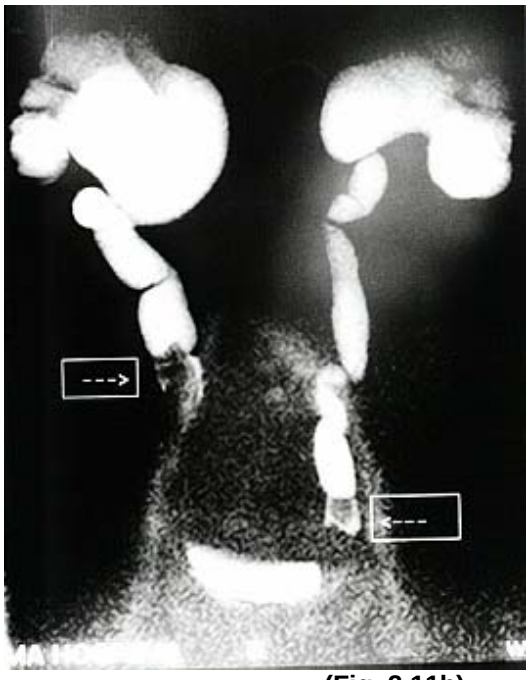
(a) Perfusion study: Reduced perfusion of the right kidney, in comparison to the normal left kidney, with loss of the flow peak.

(b) Renogram:
The right kidney shows prolonged time maximum activity (second, accumulation phase), flat peak, and slow rate of excretion.



(Fig. 2.11a)

MRI Kidenys (Normal)
Axial T1-weighted sequence demonstrating hypointensity of the renal parenchyma. The perinephric fat is hyperintense and easily demarkated from the adjacent renal cortex. The renal sinus fat is hyperintense as well.



(Fig. 2.11b)

MR urography (obstruction)
Bilateral hydroureteronephrosis in a patient with 4.8 mg/dl serum creatinine (IVU is not feasible). Note the hypointense ureteric stone bilaterally (arrows).

GLOMERULONEPHRITIS
(GN)

Are group of diseases of inflammatory or non-inflammatory nature involving the renal glomeruli.

PATHOGENESIS OF GLOMERULONEPHRITIS:

Many pathogenic mechanisms are responsible for the development of glomerular injury. These mechanisms are:

I. Immunologic mechanisms
II. Metabolic abnormalities
III. Hyperfiltration injury
IV. Hereditary abnormalities

I. Immunologic Mechanisms:

Most of the cases of glomerulonephritis encountered in clinical practice are secondary to immunologic attack affecting the renal glomeruli. This attack usually occurs in genetically predisposed person after exposure to toxin or an infection. This will provocate the immune system to attack the glomerular structures. This could be through the formation of antibodies or through a cell mediated glomerular injury.

II- Metabolic Abnormalities: See diabetic nephropathy, gouty nephropathy and renal amyloidosis.

III- Hyperfiltration injury: See diabetic nephropathy.

IV- Hereditary Abnormalities: See Alport's Syndrome.

CLASSIFICATION OF GLOMERULONEPHRITIS:

Glomerulonephritis can be classified on the basis of (I) the etiologic cause; (II) the histopathologic findings on examination of kidney biopsy; (III) or according to the clinical presentation.

(I) Etiology of glomerulonephritis:

This could be either:

a) Primary (idiopathic) when the glomerular disease is not part of systemic disease and the cause is unknown.

b) Secondary when glomerular disease is part of a systemic disease (e.g. diabetes mellitus) or due to a known cause (e.g. post-streptococcal glomerulonephritis).

Secondary glomerulonephritis may be the result of:

1. *Infection* which may be bacterial (e.g. post-streptococcal), viral (e.g. HBV, HCV, CMV), parasitic (e.g. Schistosoma mansoni, malaria).
2. *Collagen disease* (e.g. SLE, polyarteritis nodosa, rheumatoid arthritis).
3. *Drug* (e.g. Penicillamine, Paradione, Aspirin, Heroin).
4. *Metabolic disease* (e.g. Diabetes mellitus, amyloidosis).
5. *Malignancy* (e.g. lymphoma).
6. *Heredofamilial* (e.g. Alport syndrome).

(II) Histopathologic classification of glomerulonephritis:

A paraffin section from a percutaneous needle biopsy of the kidney of a patient with glomerulonephritis (whether primary or secondary), when examined by light microscopy may show any of the following:

1. Minimal change (Nil-change) disease (lipoid nephrosis) (Figure 3.1):

Light microscopy may show either no abnormality or minimal increase in mesangial cellularity. Also, immunofluorescent microscopy may show no immune deposits. Electron microscopy may show fusion of foot processes of epithelial cells (podocytes).
Idiopathic type of this lesion usually clinically presents as steroid sensitive nephrotic syndrome with good prognosis.

2. **Focal and segmental glomerulosclerosis (Figure 3.2):**
The glomerular lesions under light microscopy are sclerotic. These lesions involve only parts of the affected glomeruli (i.e. segmental) and some glomeruli look normal, but in between a glomerulus is affected (i.e. focal).
This disease usually presents with nephrotic syndrome with impairement of kidney function and hypertension. Response to steroid treatment is much less than that in minimal change glomerulonephritis.

3. **Membranous glomerulonephritis** (**Figure 3.3):**
In this type of glomerulopathy, light microscopic examination shows diffuse thickening of the glomerular capillary basement membrane with no proliferation in the mesangium.
This disease usually presents as nephrotic syndrome with spontaneous remissions and exacerbations. It may be steroid sensitive.

4. Proliferative glomerulonephritis:

According to the site of proliferation within the renal glomeruli, this type could be sub-divided into:

a. *Mesangial proliferative glomerulonephritis* **(Figure 3.4)**: There is an increase in mesangial matrix and mesangial nuclei by light microscopic examination.
This disease usually presents with haematuria or with nephrotic syndrome.

b. *Mesangiocapillary* (or membranoproliferative) glomerulonephritis **(Figure 3.5)**: There are both diffuse thickening of glomerular capillary wall and mesangial proliferation.
This disease may present as nephrotic syndrome. The disease is usually steroid resistant and slowly progresses to chronic renal failure.

c. *Crescentic glomerulonephritis* **(Figure 3.6)**: There is extensive cellular proliferations in the Bowman's capsule giving the appearance of crescent surrounding the glomerular tufts. This disease is serious and usually presents as rapidly progressive glomerulonephritis.

d. *IgA nephropathy:* This is a proliferative type of glomerulonephritis characterized with predominant immunoglobulin A deposition in renal glomeruli when kidney sections are examined by immunofluorescence.
IgA nephropathy is the commonest glomerular disease presenting with gross or microscopic haematuria.

(III) Clinical manifestations of glomerulonephritis:

Patient with glomerulonephritis may present with any of the following five syndromes:

1. **Nephrotic syndrome:**

   This is characterized clinically with massive oedema of insidious onset. In some cases, it may progress slowly to renal failure. Urine analysis shows massive proteinuria (> 3.5 gm/24 hr/1.73 m^2), microscopic haematuria and lipiduria. Serum analysis may show hypoalbuminaemia and hypercholesterolaemia. Serum creatinine is usually normal.

2. **Acute nephritic syndrome (acute nephritis):**

   Characterized clinically with rapid onset of oedema (less in severity than in nephrotic syndrome), oliguria and hypertension. Urine analysis may show red cell casts, proteinuria (less in amount than in nephrotic syndrome), haematuria and leukocyturia. Serum analysis may show increased serum creatinine, normal serum albumin and cholesterol. Prognosis is usually good and recovery occurs.

3. **Rapidly progressive glomerulonephritis (RPGN):**

   Characterized clinically with rapid (within days to weeks) loss of kidney function with development of manifestations of uraemia and the patient needs dialysis treatment. If not treated early and aggressively, the renal damage may be irreversible. Urine analysis may show findings which are similar to acute nephritic syndrome. Serum analysis shows rapidly increasing serum creatinine while serum albumin remains within normal.

4. **Chronic nephritic syndrome:**

Characterized by slowly (over months to years) progressive uraemia and the patient usually presents with manifestations of chronic renal failure. Urine analysis may show broad casts, loss of ability to concentrate urine (urine specific gravity is equal to plasma), proteinuria (mild) and microscopic haematuria. Serum analysis shows high serum creatinine and phosphate, low calcium, anaemia and metabolic acidosis.

5. Asymptomatic urinary abnormality:

As microscopic haematuria or proteinuria or both. The prognosis is usually excellent and no treatment is required.

NEPHROTIC SYNDROME (NS)

Definition: is a syndrome characterized by heavy proteinuria (more than 3.5gm/24h/1.73m^2), hypoalbuminaemia, hyperlipidaemia and edema.

Etiology:

Nephrotic syndrome could be primary or a part of a systemic disease (i.e. secondary).

Secondary nephrotic syndrome may be due to any of the following:

1. Postinfection (e.g. Schistosoma and malaria).
2. Drug (e.g. penicillamine, phenytoin, gold and nonsteroidal anti-inflammatory drugs as aspirin).
3. Metabolic (e.g. D.M., amyloidosis).
4. Collagen and autoimmune disease (e.g. SLE, rheumatoid).
5. Malignancy (e.g. Lymphoma, multiple myeloma).

6. Renal vein thrombosis.
7. Congenital and familial conditions.

Pathology:

See pathologic classification of glomerular diseases (Page 16).

Pathogenesis:

Hypoalbuminemia

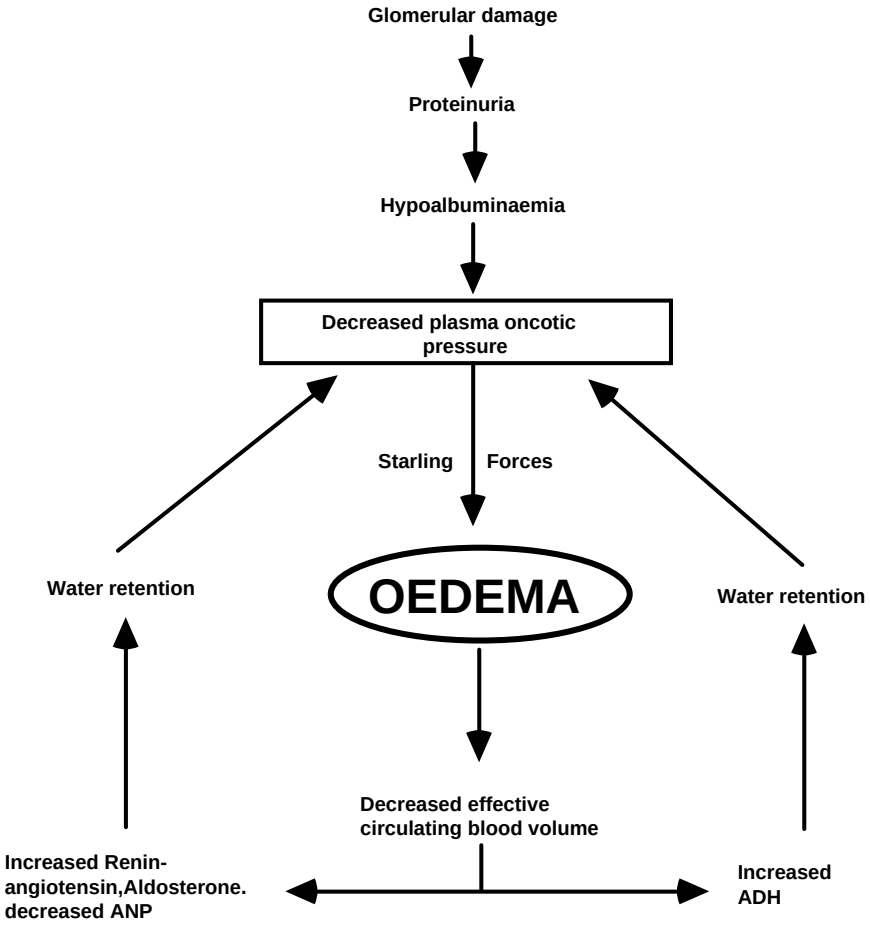
Is mainly due to loss of albumin through the kidney as a result of the glomerular disease. However, there are other factors which increase the magnitude of this problem such as:

1. The decreased intake (due to anorexia) and decreased absorption (due to oedema of the intestinal wall).
2. The increased concentration of albumin in the glomerular filtrate which is accompanied by increase in its catabolism by the renal tubules.
3. The partitioning of albumin between extra-and intravascular spaces; and
4. Sometimes decreased rate of hepatic biosynthesis of albumin.

Oedema:

The mechanisms incriminated in pathogenesis of oedema in nephrotic patient include the following **(Fig. 3.7).**

1. Hypoalbuminaemia results in a decrease in plasma oncotic (osmotic) pressure which is the power keeping water in the intravascular space. Consequently, water leaks to the interstitial space with formation of edema.



(Fig. 3.7)
Mechanisms of oedema formation in patients with nephrotic syndrome

2. Loss of intravascular fluids results in hypovolaemia (reduction of circulating blood volume) which a. stimulates the kidney (juxtaglomerular apparatus) to secrete Renin, b. stimulates volume receptors which stimulate the hypothalamus that stimulates pituitary secretion of antidiuretic hormone (ADH), and c. stimulates volume

receptors which will result in a decrease in secretion of atrial natriuretic peptide (ANP).

3- Renin secreted by juxta glomerular apparatus converts plasma angiotensinogen into angiotensin I which is converted by angiotensin converting enzyme (ACE) to angiotensin II. The latter stimulates secretion of aldosterone from the suprarenal gland. Aldosterone stimulates reabsorption of salt and water from the distal convoluted tubules.

4- Antidiuretic hormone stimulates reabsorption of water from the collecting ducts.

5- The decrease in the secretion of the atrial natriuretic peptide (ANP) decreases water and salt excretion by the kidney; and

6- Salt and water retained through the stimulation of Renin, and antidiuretic hormone secretion, and suppression of atrial natriuretic peptide secretion-leak from the vascular space (due to low oncotic pressure) to the interstitial space with more oedema formation.

Hyperlipidemia:

Hyperlipidemia is secondary to hypoalbuminemia. This condition is accompanied with increase in concentration of plasma cholesterol, triglycerides, VLDL and a decrease in HDL. Urine examination may show lipiduria and oval fat bodies.

Clinical Picture of Nephrotic Syndrome:

1. *Edema:* is the main clinical feature of nephrotic syndrome. It starts as morning puffiness of the face. Then, gradually progresses to edema of lower limbs; especially on prolonged standing and at the end of the day. In severe cases edema may progress to be generalized anasarca with ascites- even pleural and pericardial effusion.

2. *Hypertension:* may be detected in nearly 50% of the cases, according to the etiologic and pathologic type of nephrotic syndrome. For example idiopathic minimal change nephrotic syndrome cases are always normotensive while cases with mesangiocapillary glomerulonephritis whether idiopathic or secondary are always hypertensive. Hypertension is either due to salt and water retention or it may be due to the excess secretion of renin.

3. *Other manifestations of nephrotic syndrome* include lassitude, anorexia, loss of appetite and pallor.

4. *Manifestations of the etiologic cause* in secondary cases as manifestations of diabetes in cases with diabetic nephropathy.

Complications:

1. *Subnutritional State:* Due to poor dieting, and urinary losses of protein and other substances.

2. *Infection:* Especially upper respiratory, urinary, skin and peritoneal infections.
   Recurrent infection is due to nutritional deficiencies, urinary loss of immunoglobulins and complements.

3. *Clotting episodes:* These manifest as a recurrent deep vein thrombosis (DVT), or renal vein thrombosis. It may be complicated by pulmonary embolism. This clotting tendency in nephrotic patients is due to:

a. Increased concentration of coagulation factors resulting from an increased hepatic synthesis e.g. fibrinogen, factor III, and VIII.
b. Urinary loss of antithrombin III and protein C which normally act against intravascular clotting.
c. Abnormal vascular endothelium.
d. Hypovolemic state.

4. *Premature atherosclerosis:* it is due to hyperlipidaemia. This complication occurs mainly in cases with frequent relapses or cases resistant to treatment.

5. *Hypovolaemia:* Which causes postural hypotension.

6. *Drug related complications:* This category includes:
   a. Diuretics which may cause hypovolaemia, hypokalaemia, or hyponatraemia.
   b. Corticosteroids that may cause diabetes mellitus, cataract, D.U., infections, and bone disease.
   c. Other Immunosuppressive drugs as cyclophosphamide which may cause haemorrhagic cystitis, alopecia, infection and malignancy.

7. *Acute renal failure,* this may be due to severe hypovolaemia (due to the severe hypoalbuminaemia and use of big doses of diuretics), or due to acute interstitial nephritis (drug induced as large dose of furosemide).
8. *Bone disease:* Due to hypocalcemia (resulting from deficient intake and urinary loss of vitamin D binding globulin). It causes secondary hyperparathyroidism.

9. *Anemia*: Due to nutritional deficiencies and urinary loss of transferrin.

Investigations of Nephrotic Syndrome:

1. *Urine analysis* for proteinuria, microscopic haematuria, pus cells, casts, also collect 24 hours urine for quantitation of urinary protein excretion.

2. *Blood* for hypoalbuminaemia, hyperlipidaemia, hypocalcaemia and for serum creatinine level.

3. *Investigations for diagnosis of the cause in secondary cases* e.g. fasting and postprandial blood sugar for diabetes and anti-DNA for SLE.

4. *Kidney biopsy:* in children, kidney biopsy is indicated only in steroid resistant or steroid dependent cases as well as in frequent relapsers and those with impaired kidney functions. But in adults, it is wise to routinely obtain kidney biopsy to determine the underlying pathology so that specific treatment can be initiated if indicated.

Treatment of nephrotic syndrome:

The regimen for the treatment of NS is as follows:

1. *Treatment of the cause in secondary cases*- for example- by proper control of blood sugar in D.M. and steroids and immunosuppressive drugs in SLE.

2. *Treatment of complications* as infection by antibiotics and under nutrition by giving proper dieting, minerals and vitamins.

3. *Rest in bed* during exacerbation to promote diuresis and early ambulation with remission to avoid DVT.

4. *Diet:* salt restricted supported with vitamins especially vitamin D and calcium. Protein content should equal the daily physiologic needs (1g/kg) plus the amount of daily urinary protein loss e.g. a 60 kg patient who loses 10 gm daily should be given 70 gm protein containing diet.

5. *Diuretics:* Mainly loop diuretics (e.g. Frusemide) initially can be given orally in variable doses (according to severity and response e.g. 20-60 mg/d.). In severe resistant cases doses up to 120 mg. I.V. may be given. Addition of metolazone (a thiazide diuretic) may have a potentiating effect for frusemide in diuretic resistant cases.

6. *Salt poor albumin* is expensive and when given is lost quickly in urine. So it is indicated only when there is severe oedema resistant to large doses of diuretics and if the nephrotic patient is to be subjected to surgery or invasive procedure (e.g. biopsy). Albumin infusion will improve the plasma oncotic pressure.

This improves circulating blood volume and prevents hypotension or shock during the procedure.

7. *Corticosteroids* are given when there is no response to previous lines of treatment. Minimal change glomerulonephritis gives the best response while mesangiocapillary glomerulonephritis is always steroid resistant. Other types of primary glomerulopathy are in between. For patients with secondary glomerulonephritis, steroids are given if indicated for the causative disease as in SLE but not in D.M. The dose and duration of steroid treatment depends on the type of disease and response. In primary (idiopathic) minimal change nephritis 40-60 mg daily prednisone are given orally (for children 1-2 mg/kg/d), for 4-6 weeks followed by gradual withdrawal.

8. *Other immunosuppressive drugs* as cyclophosphamide, azathioprine and ciclosporin are indicated in selected cases.

ACUTE POST-STREPTOCOCCAL GLOMERULONEPHRITIS

10% of patients infected with nephritogenic strains of group A, ß-haemolytic streptococci will develop glomerulonephritis.

Streptococcal infection may be pharyngeal or skin infection. The period between infection and the appearance of glomerulonephritis (latent period) is 1-3 weeks for pharyngeal infection and 2-4 weeks for skin infection.

Children are more affected than adults and males are more than females.

Clinical picture:

Usually the patients present with manifestations of acute nephritic syndrome with oliguria, smoky urine, puffiness of the face and headache (as a result of hypertension). 20% of patients may manifest as nephrotic syndrome, 5% may present as rapidly progressive glomerulonephritis and some patients may be with asymptomatic urinary abnormalities.

Some patients may develop encephalopathy as a result of severe hypertension or hyponatraemia or they develop heart failure because of hypertension and fluid retention.

Pathogenesis:

1. Nephritogenic strains of streptococci may secrete substances e.g. neuraminidase and sialic acid which may modify autologous immunoglobulin for which antibodies are formed by the patient (autoantibodies) and immune complexes are formed which will be trapped by the renal glomeruli and cause the disease.
2. Streptococcal antigens stimulate the body to form antibodies against them with the subsequent immune complex formation.

Laboratory investigations:

1. Urine may show red cell casts, proteinuria (less than in nephrotic syndrome), haematuria or leucocyturia.
2. Pharyngeal or skin culture may show streptococci.
3. Markers of streptococcal infection as ASO titre and C-reactive protein are positive.
4. Hypocomplementaemia (C3, C4) which is transient (for few weeks only).
5. Serum creatinine is usually high.
6. Kidney biopsy **(Fig. 3.8)** may show diffuse proliferative glomerulonephritis with neutrophil and monocyte infiltration of the

glomeruli. Severe cases may show glomerular crescents (cases presenting clinically with rapidly progressive glomerulonephritis).

Treatment:

Treatment of poststreptococcal glomerulonephritis is mainly symptomatic (rest, salt restriction, diuretics, antihypertensives, treatment of infection and dialysis if renal failure develops). Sometimes steroids and immunosuppressive drugs are given for cases presenting with RPGN.

Prognosis:

Most of the cases (85%) recover completely, 5% die in early phases from complications (hypertensive encephalopathy or heart failure). The rest of the cases pass to chronic glomerulonephritis and develop chronic renal failure.

Prognosis is better in children than in adults. Signs of bad prognosis are persistently rising serum creatinine, heavy proteinuria, persistent hypertension with gross haematuria and presence of glomerular crescents in renal biopsy.

SECONDARY GLOMERULAR DISEASES

In many diseases renal involvement is a part of a generalized process e.g. diabetes mellitus and systemic lupus erythematosus.
Renal involvement may be the dominant lesion or may be just an incidental finding. Generally, when the kidney is involved, the prognosis and type of treatment are changed drastically.

Systemic lupus Erythematosus and lupus nephritis

SLE is an autoimmune disease with systemic manifestations. It affects 1/10,000 population. The incidence is higher in females than in males (9 : 1). It affects caucasian more than black and occurs more in adolescents than in elderly. Most probably the disease reflects an exaggerated response to common environmental agents in a genetically susceptible host.

Circulating and in-situ formation of DNA-anti-DNA immune complexes are thought to be the main pathogenic mechanisms for SLE. Complement deficiency may be a promoting factor. Not all SLE patients will show clinically evident renal involvement. But, if kidney biopsies are obtained and examined thoroughly, all patients will show glomerular disease.

In clinical practice lupus nephritis is responsible for more than 5% of patients presenting with glomerulonephritis. Sometimes renal manifestations are the main presentation of SLE patient with minor systemic disease.

Clinical Manifestations of Lupus Nephritis:

It is known that 50-90% of lupus patients will show manifestation(s) of renal disease. Many of such patients may not show any clinically apparent renal disease, but when subjected to kidney biopsy glomerular lesions will be detected.

Clinical presentation of lupus nephritis patient may vary from asymptomatic urine abnormality to rapidly progressive glomerulonephritis. Furthermore, some patients show manifestations of tubulointerstitial nephritis (e.g. RTA) or vasculitis.

Diagnosis:

The diagnosis should be confirmed by screening for Anti-nuclear antibodies (ANA) and the more specific anti-double stranded DNA (anti-dsDNA). Measurement of ESR, complement component C3, C4 and Circulating Immune Complexes (CIC) may help in assessing disease activity.

The ARA criteria for diagnosis of SLE include:

1- Malar rash.
2- Discoid rash
3- Photosensitivity
4- Oral ulcers
5- Arthritis
6- Serositis
7- Renal disease
8- Neurological disorders (seizures, psychosis)
9- Hematologic disorders (haemolytic anaemia, lymphopenia, leukopenia, thrombocytopenia)
10- Immunologic disorders (positive LE cell test, anti-DNA, anti-sm antibody)
11- Positive anti nuclear antibody.

Treatment:

There is no standard regimen for the treatment of lupus nephritis patient. But there are many therapeutic tools which has to be tailored for every case. Patient's age, sex, disease class, activity and chronicity indices (pathologic criteria) and clinical presentation all determine the choice of the treatment. The available treatment protocols include: (1) Prednisolone, oral, 1mg/kg/d, (2) 3-5 days pulses of methyl prednisolone 500-1000 mg each, (3) Cytoxan (cyclophosphamide) 2-3 mg/kg orally/d (4) cytoxan 0.5-1.0 gm/m2 surface area monthly for 6 months, (5) Azathioprine 2-3

mg/kg/d, (6) Cyclosporin A 5mg/kg/d, orally; and/or (7) Plasma exchange.

Generally, the target of treatment is to induce remission, then to maintain it by small doses of either one drug (Prednisolone) or combined (e.g. Prednisolone and Azathioprine). The more active the disease, the more aggressive the treatment will be and vice versa.

Beside the specific treatment for SLE, the patient may need other drugs such as hypotensives for hypertension, diuretics for oedema, and supportive dialysis for renal failure.

Renal Involvement In Vasculitis

Among different types of vasculitis, polyarteritis nodosa (PAN) and Wegener's Granulomatosis (W.G.) stand as the more common diseases affecting the kidney. Polyarteritis nodosa is either classic (involving medium sized-vessels as renal arteries with aneurysm formation) or microscopic involving small arteries and arterioles presenting with manifestation of glomerulopathies (mostly PRGN).

The classic type of polyarteritis nodosa may present with ischaemic renal changes, hypertension, immobilization with renal infarctions or haemorrhage related to the kidney (haematuria, peri-renal hematoma resulting from rupture of aneurysm).
Concomitant mesenteric, coronary or cerebral vessels affection could be detected.

Wegener's granulomatosus mainly involves small vessels with early, major disease of respiratory tract excluding asthma. Granulomata are characteristic but not essential feature for diagnosis of W.G.

Clinical Features:

1- Renal manifestations are variable from asymptomatic urinary findings to RPGN.
2- Constitutional symptoms as fever, weight loss, fatigue.
3- Extrarenal manifestations including mononeuritis, myositis, arthritis, cutaneous vasculitis, angina and in classic PAN mesentric ischaemia or cerebral strokes.
4- Upper respiratory symptoms including sinusitis, epistaxis, pharyngel lesions and otitis media or externa. These are more common in W.G. than PAN.

Treatment:

Patients with active urine sediment (proteinuria, haematuria, casts), renal impairment and documented lesions in renal biopsy should be treated by immunosuppressive drugs to achieve remission. The standard treatment is prednisolone and cyclophosphamide. The dose and whether prednisolone alone or combined drug regimen, depend on disease activity and initial reponse to treatment. Cyclosporin A 5mg/kg/d can be used when these drugs are toxic or have no satisfactory response.

Plasma exchange has been reported for treatment of severe cases. Use of azathioprine alone has been disappointing.

Henoch-Schönlein Purpura (HSP)

HSP is a multisystem disease with renal, gastrointestinal and cutaneous manifestations. It usually affects children 5-15 years old with a slight preponderance of males. Full recovery is common in children. But in adults, the course could be problematic. Renal involvement is documented in 10-30% of the cases, but in some series, it reaches up to 90% of the cases. The primary abnormality is most probably defective handling of mucosally presented antigen.

Pathology (Fig. 3.9):

There is a great similarity between HSP and IgA nephropathy. Light microscopy usually shows changes variable from minimal abnormalities, mesangial proliferation, focal mesangial proliferation with crescent formation to membranoproliferative glomerulonephritis. Immunofluorescent microscopy will show predominant IgA deposits which are mainly mesangial, and this is usually accompanied with C3, IgG and to a lesser extent IgM.

Clinical features:

1- The disease usually occurs in winter, following upper respiratory infection or following exposure to allergen.
2- Renal manifestations varies from haematuria (macroscopic or microscopic), N.S., to RPGN. Severe forms of the disease are more encountered in adults.
3- Extrarenal manifestations include:
    a. Purpuric rash which involves mainly the buttocks and lower limbs. It does not blanch on pressure and may extend to other areas.
    b. Polyarthralgia or arthritis.
    c. Gastrointestinal manifestations including abdominal pain, bloody diarrhea and or melena.

d. Fever, malaise, epistaxis and haemoptysis.

e. In more than 50% of cases serum IgA is high.

Treatment and Prognosis:

Generally, the disease is self-limiting. However 5-20% of cases (especially adults) may show persistence or even progression to uraemia.

Signs of bad prognosis include patients with: severe disease at presentation, persistent nephrotic syndrome, severe renal impairment and crescentic G.N.

Cases with mild disease may be treated symptomatically while severe cases should be treated with steroids, cytotoxic drugs and plasma exchange.

Essential Mixed Cryoglobulinaemia (EMC)

Cryoglobulinaemia is a wide range of diseases associated with formation of cryoglobulins. The cryoglobulin complex is mainly an immunoglobulin (antibody) attached to another immunoglobulin (antigen). The complex has the character of precipitation at cold. According to the nature of the two immunoglobulins, three types of cryoglobulinaemia are recognized: 1- monoclonal cryoglobulinaemia (i.e. both components are monoclonal immunoglobulins), detected in Myeloma, macroglobulinaemia, chronic lymphatic leukaemia and essential cryoglobulinaemia. 2- mixed polyclonal-monoclonal cryoglobulinaemia detected in Sjögren's disease, rheumatoid arthritis and essential mixed cryoglobulinaemia. 3- mixed polyclonal cryoglobulinaemia (i.e. poly-poly)

in essential mixed cryoglobulinaemia, autoimmune disease as SLE, PAN, HSP, infection as CMV, malaria and HBV.

While patients with cryoglobulinaemia usually present with the manifestation of the original disease, 20-30% of patients with mixed cryoglobulinaemia present with disease (vasculitis) caused by cryoglobulin itself. This is termed essential mixed cryoglobulinaemia.

Clinical features:

Clinical manifestations of EMC include the following:

1- Renal, including nephrotic syndrome, nephritic syndrome or RPGN.
2- Extrarenal, including purpura, arthritis and hepatic dysfunction.

Treatment:

Steroid and cyclophosphamide are usually given in combination to treat EMC. Plasma exchange is indicated with severe disease to lower the level of circulating cryoglobulin.

Diabetic Nephropathy

Microangiopathy with neuropathy, retinopathy and nephropathy are complications known to develop in the majority of long-term diabetics.

Renal failure causes death in up to 40% of diabetics, being 17 times more common than in non-diabetics.

The better the control of diabetes, the longer the survival is and the more the chance to manifest nephropathy and other microangiopathy will be. This explains the prevelence of this disease in countries with better health programs.

The disease affects both juvenile and adult onset diabetics, but juvenile diabetics manifest the disease more; since they survive longer with the disease. Adult onset diabetics usually die earlier with coronary or cerebral strokes.

In Juvenile diabetics, nephropathy passes into 6 stages: 1- very early stage in which GFR is supernormal, 2- stage of microalbuminuria, 3- stage of clinical proteinuria, 4- stage of nephrotic syndrome, and hypertension, 5- stage of renal impairment then, 6- stage of end stage renal failure.

In type II diabetics, the renal disease is usually well established when first discovered clinically.

Treatment:

Prevention of diabetic nephropathy is ideally achieved by proper control of diabetes and avoidance of smoking and obesity.

If microalbuminuria; which is a marker of very early disease; is detected, proper control of diabetes and use of small dose of ACE inhibitors (e.g. captopril 6.25 mg twice daily before meals) will help the normalization of glomerular haemodynamics and prevent progression to diabetic glomerulopathy.

In the stage of clinical proteinuria and nephrotic syndrome, hypertension has to be controlled preferably with ACEI. This in addition to the control of diabetes and hyperlipidemia besides the measures for management of nephrotic syndrome.

When renal failure manifests, supportive treatment and renal replacement therapy (RRT) may be provided. Renal replacement therapy is usually provided earlier for diabetics (i.e. at GFR 10-15 ml/min). CAPD is superior to haemodialysis. If transplantation is to be provided, combined kidney and pancreas transplantation is the choice for type I diabetics and generally steroid sparing immunosuppressive protocols are preferable.

In the near future, Pancreas islet-cell transplantation would revolutionize the management of diabetic nephropathy.

Hereditary Glomerulopathies

1- Alport Syndrome

Alport Syndrome is an autosomal dominant inherited disease with variable penetrance, sometimes with X-linkage. Clinically, the patients show combination of renal disease, nerve deafness ocular defects (anterior Lenticonus, cataract, macular lesions) and platelet defect (macrothrombocytopathic thrombocytopenia).

The basic defect is in the type IV collagen which is normally present in the GBM, lens and cochlea.

2- Fabry's Disease
(Angiokeratoma Corporis Diffusum Universale)

Fabry's disease results from the deficiency of the enzyme a-galactosidase. This, in turn, results in an accumulation in all tissues of glycosphingo-lipids, cerebroside dihexoside and cerebroside trihexoside. The disease is inherited as X-linked, the homozygous males are severely affected while the heterozygous females are asymptomatic.

Clinical Features:

1- Skin lesions in the form of angiokeratomas which are red papules in the mouth, lower abdomen, buttocks and pubic region.
2- Neurologic manifestations in the form of periodic episodes of severe pain due to involvement of dorsal root ganglia.
3- Cardiac manifestations as hypotension and ischaemic heart disease.
4- Renal manifestations include, haematuria, proteinuria and progressive uraemia.

3- Nail-Patella Syndrome
(Hereditary onycho-Osteo-dysplasia)

This is characterized by a generalized disturbance in collagen synthesis leading to dysplasia of nails, skeletal deformities (especially hypoplastic displaced patella, deformed elbow, iliac horns, scoliosis) and renal involvement.

Renal manifestations include haematuria and proteinuria, but rarely nephrotic syndrome or renal failure occure.

Malarial Nephropathy

The disease is common in malarial endemic areas. It affects children more than adults. It occurs in both quartan and falciparum malaria. Quartan malarial nephropathy tends to be chronic and progressive while falciparum malarial nephropathy tends to resolve completely after antimalarial treatment.

Schistosomal Nephropathy

Incidence:

In Egypt, proteinuria was detected in 20 percent of asymptomatic patients with active schistosoma mansoni infection. In the same centre, schistosomal specific kidney lesions were documented in 65 per cent of patients with active schistosoma mansoni who present with overt nephrotic syndrome.

the disease is more common in patients with advanced hepatosplenic disease in comparison with early intestinal disease.

Clinical and histopathologic manifestations of schistosomal glomerulopathy:

The disease passes through three distinct phases which are: occult glomerulopathy, overt glomerulopathy and end-stage glomerulopathy.

- **Occult glomerulopathy** is usually silent. Asymptomatic proteinuria is an early expression of the disease which was reported in 20% of Egyptian patients and 26% of Brazilian patients with active schistosoma mansoni infection. Patients in this phase have less hepatic and more intestinal schistosomal disease. Histopathologic examination of kidney biopsy by light microscopy will show either no change or mild mesangioproliferative lesion, with little or no expansion of mesangial matrix but with occasional focal thickening of the basement membrane. Immunofluorescence shows mostly mesangial deposits of IgM- containing immune complexes, schistosomal antigens and complement C3.

- **Overt glomerulopathy** nephrotic syndrome with or without renal impairment is the commonest presentation in this phase. Hypertension is noticed in 30-50 percent of patients. Less commonly, patients may present with non-nephrotic proteinuria.

Patients in this phase always have hepatosplenic disease. The liver is firm and shrunken. The spleen is enlarged. Ascites may be present and oesophageal varices may be detected. Histopathologic examination of a kidney biopsy shows focal segmental glomerulosclerosis or mesangio-capillary glomerulonephritis **(Fig. 3.10)**.

- **End-stage glomerulopathy:** Patients usually present with uraemic manifestation in association with hepatosplenic schistosomiasis. Histopathologic examination of kidney biopsy may show glomerulosclerosis, interstitial fibrosis and tubular atrophy.

Treatment:

The results of treatment with both anti-parasitic agents and immunosuppressive drugs have been disappointing. Very early treatment of schistosomiasis may be the only available way of preventing the poor outcome of schistosomal nephropathy.

Glomerulopathy Secondary To Virus Infection

A variety of viral infections may be associated with features of acute glomerulonephritis. However, it is usually milder than it is in post streptococcal glomerulonephritis.

Classification:-

(1) Herpes virus:	- cytomegalovirus
	- Epestien Bar virus.
(2) Paramyxovirus:	- measles
	- mumps
(3) Parovirus	
(4) Hepatitis viruses:	- hepatitis B
	- hepatitis C
(5) Retroviruses:	- human immunodeficiency virus.

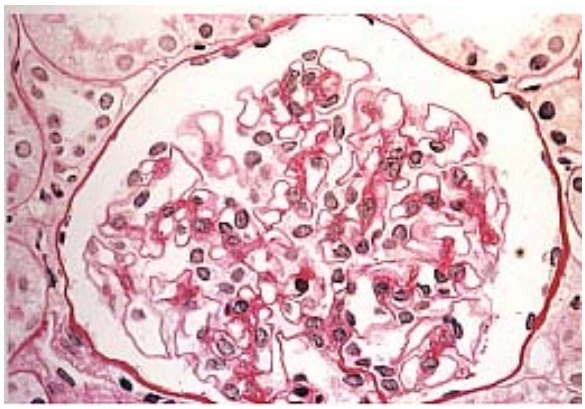
(6) Influenza viruses: - Influenza A & B

Mechanism of Renal affection in viral infection:

(1) Direct cytopathic effect of the virus on the glomerular cells.

(2) Immune complex mediated which is due to stimulation of antibody response.

(3) Direct effect on T-cells.



(Fig. 3.1)
PAS stained kidney section (X 410) from a patient with minimal change nephritis. Light microscopic examination shows a normal glomerulus.
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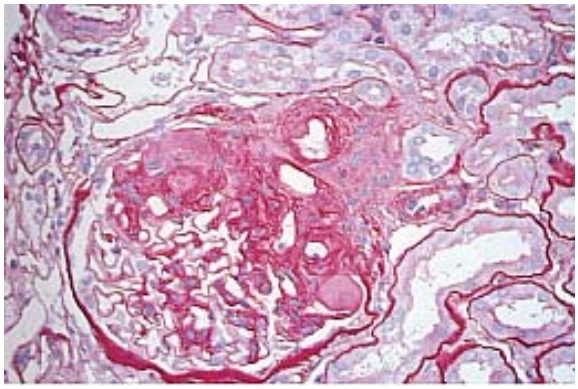

(Fig. 3.2a)
PAS stained kidney section (X260) from a patient with FSGS. Light microscopic examination of an affected glomerulus shows segmental sclerosis in the hilar region.
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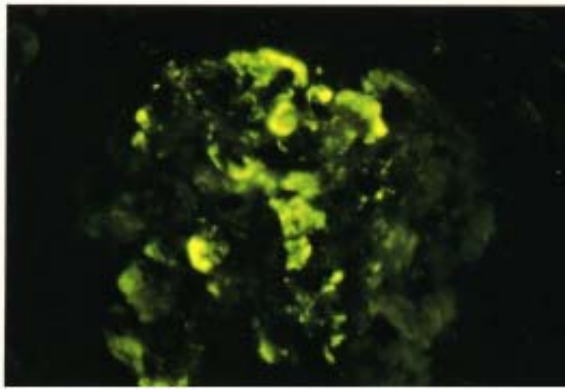

(Fig. 3.2b)
The same case when examined by immunofluorescent microscope shows segmental deposits of complement (C3).
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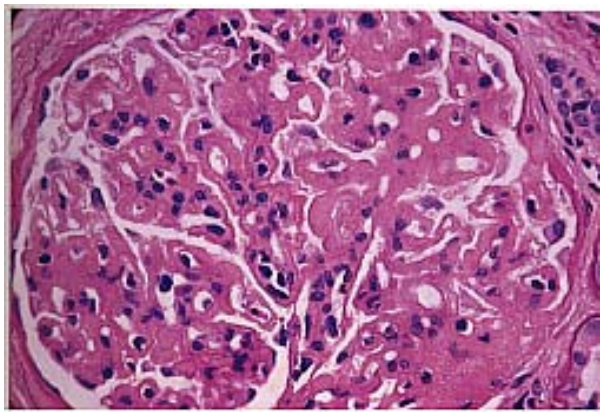

(Fig. 3.3a)
PAS stained kidney section (X320) from a patient with membranous glomerulonephritis. Light microscopic examination shows marked thickening of the capillary walls with no cellular proliferation.

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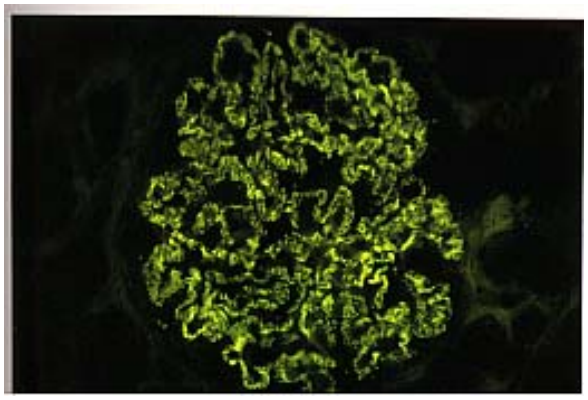

(Fig. 3.3b)
The same case in Fig. 3a, examined by I.F., it shows diffuse granular deposits of IgG along the capillary walls (X260).

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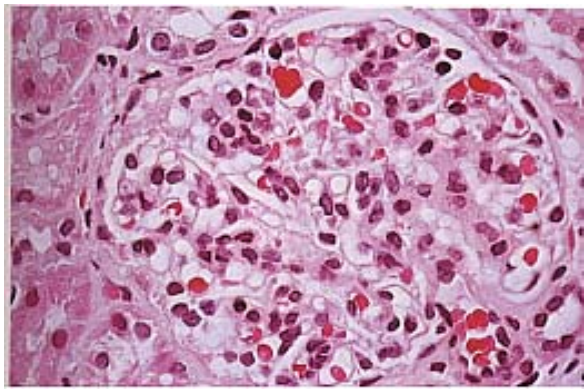

(Fig. 3.4)
PAS stained kidney section (X 410) from a patient with mesangial proliferative glomerulonephritis. Light microscopic examination shows diffuse proliferation in the mesangium with normal capillary walls

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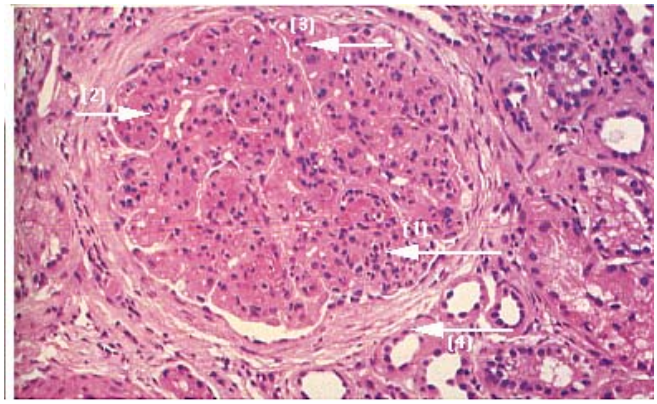

(Fig. 3.5)
Hx & E stain of a case of mesangio-capillary glomerulo-nephritis,there is mesangial prolifera-tion (arrow-1) with lobulation, (arrow-2), thickening of the GBM (arrow-3), also there is periglomerular fibrosis (arrow-4)

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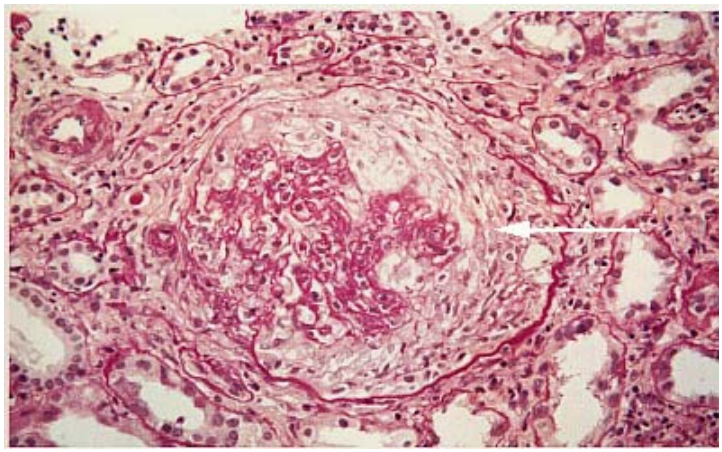

(Fig. 3.6)
Periodic acid-schiff stain. High power view of a glomerulus showing crescentic glomerulonephritis (arrow)

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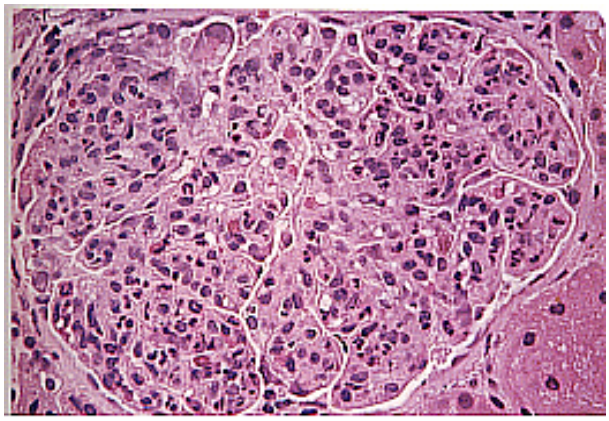

(Fig. 3.8)
Hx & E stained kidney section (X 260) from a patient with post infection glomerulonephritis. Light microscopic examination shows diffuse proliferative endocapillary glomerulo-nephritis with marked cellularity caused by both mononuclear cells and polymorphoneuclear leukocytes.

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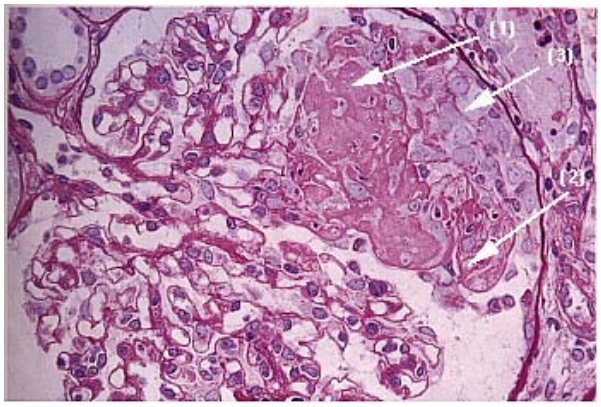

(Fig. 3.9a)
PAS stained kidney section (X310) from a patient with Henoch-Schonlein purpura, it shows segmental involvment of the glomerulus wth thrombosis (arrow 1) necrosis (arrow-2), and a small crescent (arrow 3). The remaining of the glomerulus looks normal.

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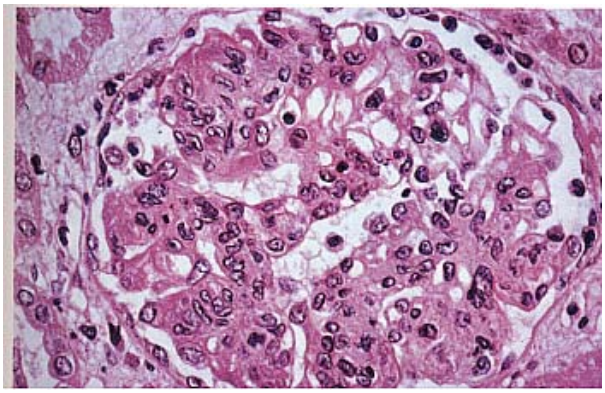

(Fig. 3.9b)
PAS stained kidney section (X410) from a patient with Henoch-Schonlein purpura. It shows diffuse endocapillary glomerulonephritis.

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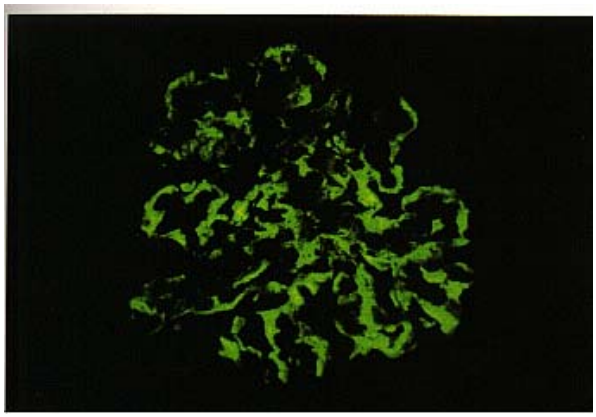

(Fig. 3.9c)
Immunofluorescent stained kidney section (X410) from a patient with Henoch-Schonlein purpura. It shows deposits of IgA along the GBM.

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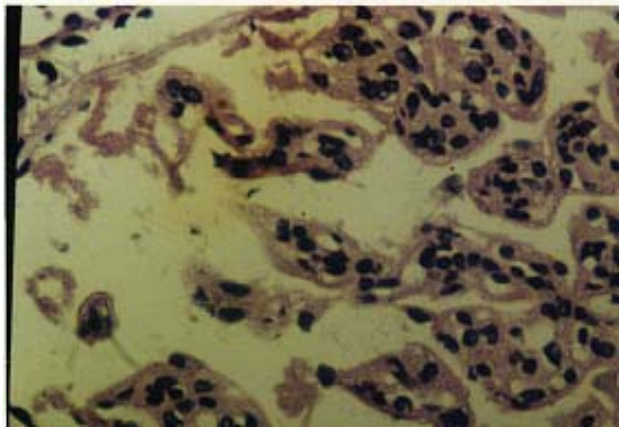


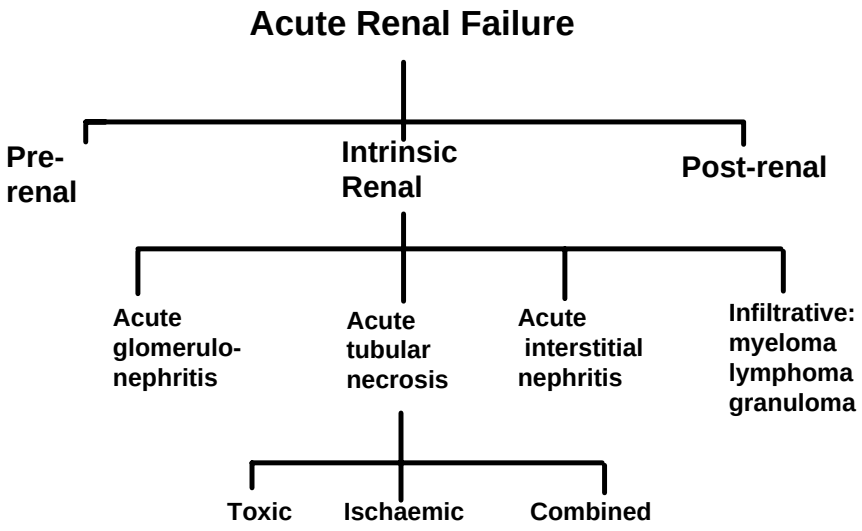
(Fig. 3.10)
Renal biopsy of a patient with schistosomal-specific nephropathy showing mesangiocapillary glomerulonephritis (HX & E X 400).

ACUTE RENAL FAILURE
(ARF)

Definitions:

ARF is a syndrome that can be broadly defined as a rapid deterioration of renal functions resulting in the accumulation of nitrogenous wastes such as urea and creatinine.

Acute renal failure may be pre-renal, renal or post-renal **(Fig. 4.1)**:



(Fig. 4.1)
Different types of acute renal failure

In pre-renal failure, the renal tissue is intact and kidney biopsy shows normal renal histology. Oliguria and high serum creatinine are due

to functional impairment; since there is no sufficient blood reaching the kidney to be cleared of these toxins.

In post-renal failure, the obstruction of the urinary tract results in increasing the pressure above the level of the obstruction up to the nephron including the urinary space of the renal glomeruli. When this back pressure exceeds that of the filtration pressure in the renal glomeruli, the process of urine formation will stop with progressive accumulation of wastes and increase of serum creatinine and blood urea.

In renal failure (intrinsic renal failure), there is a damage involving the glomeruli, renal tubules or tubulointerstitium with loss of their functions. Consequently wastes accumulate with increase in serum creatinine and blood urea.

I. Pre-renal Failure

Combination of hypotension, hypovolaemia resulting in diminished renal perfusion is the most common cause of acute renal failure in hospitalized patients.

When renal hypoperfusion (due to hypotension and/or hypovolaemia) is not severe enough to cause renal tubular damage, it will manifest as pre-renal failure in the form of oliguria and a rise in serum creatinine and blood urea. Since there is no structural renal damage, early diagnosis and correction of renal hypoperfusion results in immediate diuresis and rapid drop in serum creatinine and blood urea levels. If hypoperfusion is severe or neglected, renal compensatory mechanisms will fail and acute tubular necrosis occurs. In this new situation, correction of hypoperfusion will not be followed by diuresis or drop in serum

creatinine. Few days or weeks (mean 2-3 weeks) are needed for tubular regeneration and recovery of kidney function to occur.

II. Acute Intrinsic Renal Failure

This includes acute tubular necrosis (ATN), acute interstitial nephritis and acute glomerulonephritis. In this chapter we will focus on ATN. Details of the other two categories are found in chapters 3&6.

Acute Tubular Necrosis

Acute tubular necrosis can be induced by renal hypoperfusion (ischemia) or exposure to nephrotoxins (exogenous or endogenous toxins) and frequently by a combination of both. These two types of insults (ischaemic and toxic) will now be reviewed individually.

Causes of Ischaemic ATN:

A- Blood Loss

- Haemorrhage (post partum, surgical or gastrointestinal).
- Major trauma

B- Fluid Loss

- Gastrointestinal (vomiting or diarrhoea)
- Renal (aggressive diuresis or polyuria)

C- Third Space

- Haematoma
- Illius
- Peritonitis

D- Severe vasodilatation as in septicaemia, rapid oedema formation, liver cell failure.

E- Renovascular disease

- Renal artery occlusion by stenosis, embolism or compression.
- Renal vein thrombosis or compression.

Causes of Toxic ATN

(A) Exogenous nephrotoxins include:

Antibiotics:	Aminoglycosides	Amphotericin
	Cephalosporin	Acyclovir
	Sulfonamide	
	Tetracyclines	Bacitracin
Anaesthetic agents:	Methoxy fluorane	
Contrast Media:		
Analgesics:	Phenacetin	
Metals:	as Mercury, lead, arsenic, bismuth, cadmium, antimony,	
organic solvents:	Glycols	
Poisons:	paraquat, snake bite, stings, bacterial toxins.	

(B) Endogenous nephrotoxins include

Pigments:	**Crystals:**
Myoglobin	Uric acid
Hemoglobin	Calcium
Methemoglobin	Oxalate

Clinical features of ARF:

1- Usually, the patient gives history of the etiologic cause such as trauma, shock, haemolysis, drug intake, infection, or stone disease.

2- Patient may notice a change in urine volume and character, oliguria is common, but in 10-50% of cases urine volume will be normal or even higher (as in toxic ATN) this is called polyuric ATN. Absolute anuria is highly suggestive of obstructive ARF (post-renal) or very severe form of ATN (cortical necrosis).

3- Manifestation of salt and water retention (oedema, puffiness, hypertension and even heart failure).

4- By time, manifestations of uraemia appear as acidotic breathing, dyspnea, nausea, vomiting, headache, muscle twitches and even frank encephalopathy and coma.

5- Patient may present as well with any of the following complications:

Complications Of Acute Renal Failure:

Cardiovascular

- pulmonary odema
- hypertension
- myocardial infarction
- arrhythmias
- pericardial effusion
- pulmonary embolism

Metabolic

- hyponatremia
- hyperkalemia
- acidosis
- hypocalcemia
- hyperphosphatemia

Neurologic

- coma
- seizures

Gastrointestinal

- gastritis
- gastroduodenal ulcers

Haematologic

- anaemia
- hemorrhagic diathesis

Infections

- pneumonia
- septicemia
- UTI

Investigations of ARF:

A- Urinary indices:-

May be helpful in the differentiation between pre-renal failure and acute tubular necrosis. Diuretics should not be given at least during the preceeding 48 hours for these parameters to be valid.

Parameter	Prerenal	ATN
Concentration of urine:		
Urine specific gravity	> 1.020	< 1.010
Urine Osmolarity (mosm/lit))	> 500	< 350
GFR and overall tubular reabsorption:		
Creatinine clearance	> 20	< 20
Urine/Plasma urea	> 8	< 3
Urine/Plasma creatinine	> 40	< 20
Tubular handling of solutes		
UNa (mEq/L)	< 20	> 40
FeNa (%)	< 1	> 1

B- Urinary sediment:

Centrifugation of fresh urine sample and examination of the urinary sediment may be helpful in diagnosing different causes of ARF. See the chapter on value of urine examination in medical diagnosis. In pre-renal failure and in ischaemic ATN urinary sediment is usually free.

C- Renal Imaging:

1. **Plain film of the abdomen:**

   This will show kidney parity, size, shape, calcification and stones.

2. **Renal Ultrasonography and echo-doppler of renal vessels:**

Ultrasonography safely assesses kidney size, shape and echo-genicity. Cortical thinning or oedema can sometimes be seen clearly.

Also, it can exclude obstructive uropathy (back pressure changes).

Echo-Doppler of renal vessels can exclude occlusion of the renal arteries and veins.

3. **Retrograde and antegrade pyelography:**

   Provide the most reliable information on the patency of the ureter.

4. **Radionuclide studies (Renogram):**

   The vascular phase of the isotope renogram can show the pattern of renal perfusion (for diagnosis of reno-vascular diseases). Diuretic renogram can help in diagnosis of urinary tract obstruction. Also, renogram may help in diagnosis of renal parenchymal diseases, but cannot discriminate their different etiologic causes.

5. **Angiography:**

   Is useful mainly when an acute reversible renovascular event is suspected such as embolization, thrombosis or involvement in a dissecting aortic aneurysm. It carries the risk of exposure to contrast media which could be nephrotoxic.

6. **C.T. studies:**

   Provide reliable information on kidney parity, size, shape and presence of hydronephrosis.

7. **Magnetic Resonance urography:**

   Recently MRI urography (MRU) without use of contrast media can provide films similar to IVP. It is thus of great value to exclude U.T. obstruction without the risk of contrast media nephropathy **(Fig. 4.2)**.

D. Renal biopsy:

The indications of renal biopsy in ARF are:

1. Equivocal case history.
2. Renal signs suggesting glomerular, vascular or interstitial lesions.
3. Extrarenal manifestation in patients with a systemic disease identifiable by biopsy.
4. Prolonged renal failure (more than 3 weeks).

Acute cortical necrosis:

Is a subset of ATN in which there is a massive necrosis of the tubules and glomeruli of the renal cortex. The condition may be focal or diffuse with irreversible damage of the kidneys. It is suspected when ATN fails to recover after 4-6 weeks.

Acute cortical necrosis usually occurs with complicated pregnancy as postpartum haemorrhage and abruptio placenta.

TREATMENT OF ARF:

A- Treatment of the cause e.g. any condition causing renal hypoperfusion, exposure to toxic drug or chemical or systemic disease.

B- Prevention of acute renal failure:

The timing of intervention to prevent ATN is important. Protective agents must be administered at the time of, or immediately following potential renal insult. This intervention may prevent or at least blunt the severity of ATN.

The intervention could be through the following approaches. In different combinations according to the clinical situation:

- Volume expansion by saline loading.
- Diuretic as mannitol and furosemide.

- Calcium channel blockers as verapamil and nifedipine.
- Vasodilating agents as dopamine in renal dose 1-2 ug/kg/min
- ATP-magnesium chloride.

In case of contrast media, the following additional points should be adopted, these are:-

- Avoid unnecessary contrast procedures.
- Avoid multiple contrast exposure within a few days.
- Avoid contrast exposure in high risk patient.
- Use the smallest dose possible.
- Use of non-ionic contrast is to somewhat safer.
- In high risk patient with renal impairment we can manage to wash the contrast out immediately after the technique (e.g. coronary angiography) by haemodialysis.
- MRU is good alternative for visualization of the urinary tract obstruction.

C- Conservative measures:

1- fluid balance:

Careful monitoring of intake/output and body weight is very important to avoid overload and hypovolaemia. The first may lead to pulmonary oedema while the second may aggravate renal ischaemia.

Patient should receive fluids equal the daily urine output plus the other sensible losses e.g. vomitus or diarrhea fluid; plus an amount equals the insensible loss which is around 600 c.c. for 60kg body weight patient. For example, a 60kg b.w. patient with ARF who produces 200 c.c. urine daily with no vomiting or diarrhea will need a daily fluid intake of about 600 + 200 = 800 c.c. With every 1°c increase in body temperature, 200

c.c. should be added to the daily fluid intake. Fluid requirement will increase with the increase in the body surface area and the atmospheric temperature and humidity (leading to increase in sweating). Fluids could be given orally or (if not possible), it could be given intravenously.

2- Electrolytes and acid-base balance:

- Prevent and treat hyperkalemia.
- Avoid hyponatremia.
- Keep serum bicarbonate above 16 mmol/L.
- Minimize hyperphosphatemia by giving phosphate binders (e.g. Ca Co_3 & AL hydroxide) with meals.
- Treat hypocalcaemia.

3- Nutritional support:

- Restrict protein (to 0.5gm/kg/day) but maintain sufficient caloric intake.
- Carbohydrate intake should be at least 100 gm/day to minimize ketosis and endogenous protein catabolism.

4- Drugs:

- Review all medications.
- Stop magnesium-containing medications.
- Adjust dosage for renal failure.

5- Treatment of hyperkalemia:

- Calcium gluconate I.V.
- Glucose 50% + Insulin
- Na Hco_3 I.V.
- Salbutamol
- K-exchange resins (e.g. resonium)
- Dialysis
- Avoid diets and drugs causing hyperkalaemia

6- Dialysis:

The indications of dialysis in ARF are:

a. **Clinical:**
- Poor clinical state, nausea, confusion.
- Fluid overload, pulmonary oedema.
- Preoperatively.

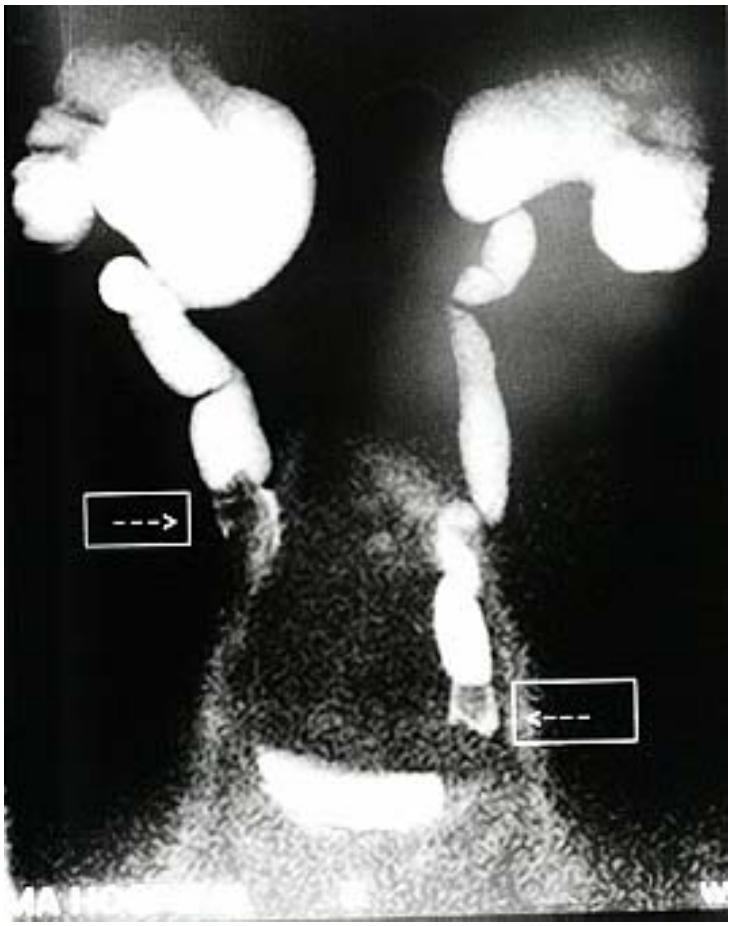
b. **Biochemical:**
- Plasma $K^+ > 7$ mmol/L.
- Plasma bicarbonate < 12 mmol/L
- Arterial pH < 7.15.

Prognosis of AFR:

The mortality of AFR remains high, ranging between 50-80% in surgical and post-traumatic cases. It is generally lower in ARF due to drugs and toxins. About 75% of deaths occur in the first week of ARF, and 25-50% of these deaths are due to the underlying disease. The overall prognosis is better in non-oliguric than in oliguric renal failure.

The factors influencing patient survival in acute renal failure include the following:

- Aetiology of ARF.
- Severity of ARF.
- Number and severity of coexisting illness.
- Patient's age.
- Presence of complications.



(Fig. 4.2)

MR urography shows bilateral hydroureteronephrosis in a patient with 4.8 mg/dl serum creatinine (IVU is not feasible). Note the hypointense ureteric stone bilaterally (arrows).

CHRONIC RENAL FAILURE
(CRF)

DEFINITIONS:

Chronic renal failure is a progressive loss of kidney functions due to progressive damage of kidney tissue by a disease involving the two kidneys.

In chronic renal failure, there is a persistent and irreversible reduction in the overall renal function. Not only the excretory functions are disturbed but also the endocrine and the haemopoietic functions as well as the regulation of acid-base balance become abnormal. These derangements in the internal environment (internal milieu) of the body will result in the uraemic syndrome.

Disease involving one kidney (even if very severe and damaging this kidney) will not result in renal impairment or failure as the other kidney is capable to maintain the internal milieu or environment within normal. In this setting we may say compromised or non-functioning right or left kidney (according to the kidney damaged right or left). Sometimes we say solitary functioning right or left kidney (according to the side of the healthy kidney).

AETIOLOGY OF CHRONIC RENAL FAILURE:

The common causes of CFR are diabetic nephropathy, chronic pyelonephritis, obstructive uropathy, reflux nephropathy, chronic glomerulonephritis and polycystic kidney disease. The complete list of causes include the following:

1. **Primary glomerular diseases:**

Such as idiopathic crescentic glomerulonephritis, primary focal segmental glomerulosclerosis and primary mesangiocapillary glomerulonephritis.

2. **Tubulo-interstitial diseases:**

These include the following:

- Chronic heavy metal poisoning such as lead, cadmium and mercury may result in chronic tubulo-interstitial nephritis and renal failure.
- Chronic hypercalcaemia as with vitamin D intoxication and primary hyperparathyroidism.
- Chronic potassium depletion resulting from prolonged use of diuretics without potassium supplementation as in patients with ascites or congestive heart failure.

3. **Renal vascular diseases:**

Bilateral advanced renal artery stenosis or a unilateral renal artery stenosis in a solitary kidney.

Renal artery stenosis usually occurs due to advanced atherosclerosis which is more common in elderly males or due to fibromuscular dysplasia which is more common in middle aged females.

Bilateral renal vein thrombosis; which is more common in patients with nephrotic syndrome.

Nephrosclerosis secondary to long standing hypertension (very common), polyarteritis nodosa (less common).

4. Chronic urinary tract infection

5. Chronic urinary tract obstruction:

This may be upper or lower urinary tract obstruction. It results in hydronephrosis which if left untreated may result in CFR.

Causes of upper urinary tract obstruction include bilateral ureteric or renal stones, bilateral neoplasms and bilateral ureteric stricture.

Causes of lower urinary tract obstruction include bladder tumour, senile prostatic enlargement, huge bladder stones and stricture urethra

Association of infection and obstruction is the most common cause of renal failure as obstruction may invite infection and infection may lead to obstruction.

6. Collagen diseases:

Collagen diseases such as S.L.E. and polyarteritis nodosa, rheumatoid arthritis, and systemic sclerosis may cause chronic renal failure.

7. Metabolic diseases:

Renal amyloidosis; which is usually a complication of Familial Mediterranean Fever (FMF) or chronic suppuration (e.g. osteomyelitis) may end by chronic renal failure.

Gout may cause chronic renal failure either directly (gouty nephropathy) or secondary to abuse of NSAIDs. More commonly it develops by the two mechanisms.

Diabetic nephropathy is one of the common causes of CFR.

Analgesic nephropathy occurs with most of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin. Analgesic nephropathy is a cumulative effect needing a long term drug administration. Nearly an amount of 2-3 kgm of aspirin is needed for chronic renal failure to occur. This condition is frequently seen in patients with chronic pain as those with osteoarthritis and rheumatoid arthritis.

CLINICAL FEATURES OF CHRONIC RENAL FAILURE:

Fig. 5.1 summarizes the clinical features of the uraemic syndrome. The details of this features include:

I. Gastrointestinal Manifestations:

a. Mouth:

The high concentration of urea in saliva causes unpleasant taste (taste of ammonia) and uraemic odour of the mouth (ammoniacal smell).

The tongue appears dry, dirty, brown or white coated and may be ulcerated. Later, stomatitis, ulceration of the mouth and pharynx may occur. The mouth is always dry due to dehydration and mouth breathing. Dental caries is also common.

b- Stomach:

Gastritis and sometimes gastric erosions may occur. This occurs due to the high concentration of urea in saliva and gastric juice causing chronic irritation of the gastric mucosa. The patient may suffer from anorexia, nausea and vomiting. Upper G.I.T. bleeding (haematemesis) and melena may even occur.

Hiccough occurs in terminal stages of uraemia and is aggravated by food. The cause of hiccough in uraemic patient is most probably due to irritation of the phrenic nerve or may be due to a central effect induced by uraemic toxins.

c- Intestine:

Usually, there is constipation due to dehydration, but diarrhea or even bloody dysentery (uraemic dysentery) may occur in terminal uraemia. This is due to urea deposition in the mucosa of the colon which leads to mucosal ulceration which is liable to superadded infection which may cause diarrhea. In severe cases of mucosal ulceration, there may be bleeding per rectum.

II. Neurological manifestations:

These include the following:

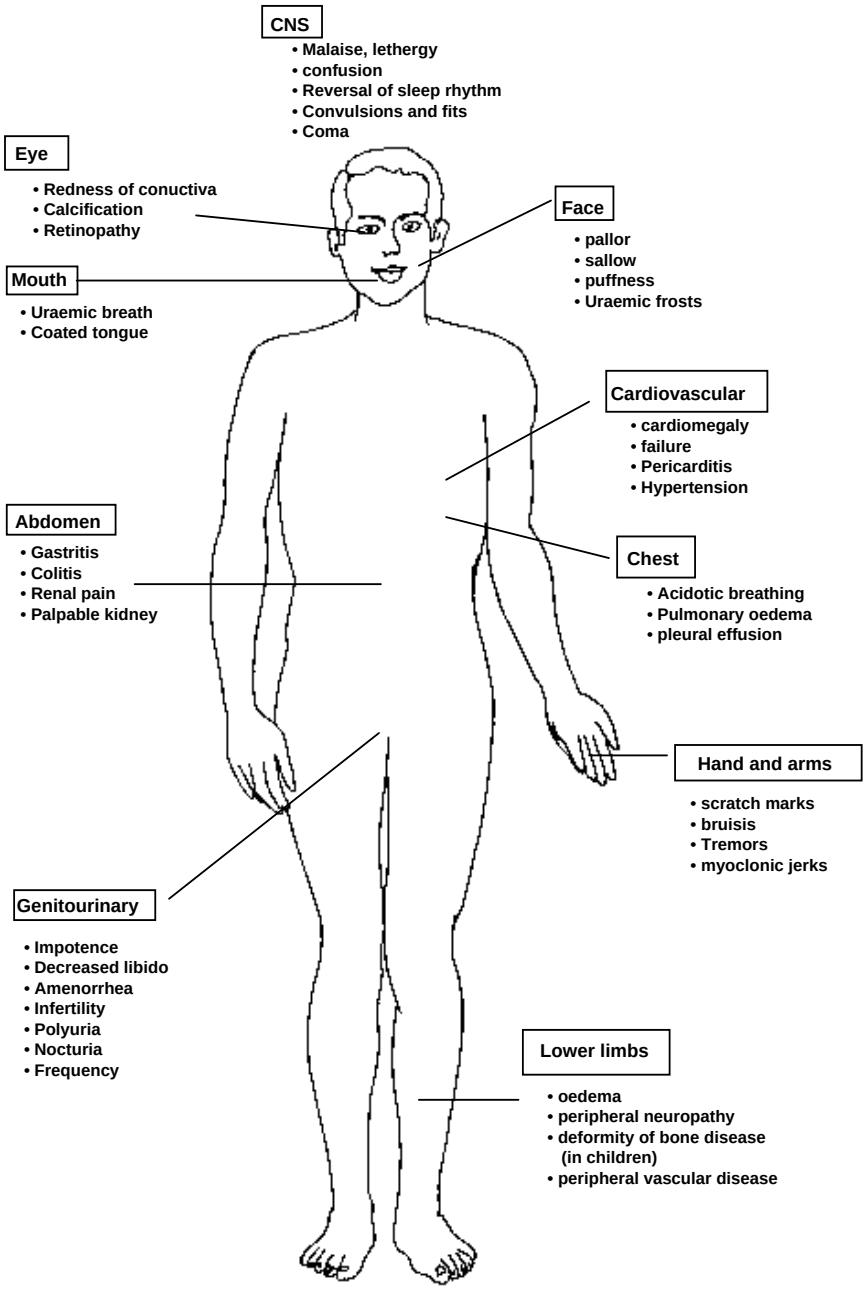
a- Cerebral:

Headache, lassitude, drowsiness, insomnia, sometimes inverted sleep rhythm, and vertigo are common manifestations of uraemia. These manifestations are caused by the retained uraemic toxins. Uraemic coma occurs in advanced cases.

b- Neuromuscular:

The following are the common neuromuscular manifestations of uraemia:

- Flabbing tremors (asterixis) and proximal myopathy with paradoxically brisk tendon reflexes.
- Peripheral neuropathy is usually mixed (motor and sensory) and mainly affecting legs. Patients present mainly with parasthesia.
- Muscle twitches and convulsions are mainly due to hypokalaemia and hypocalcaemia.
- Muscle weakness is due to hyperkalaemia, hyponatraemia and hypovitaminosis D.



(Fig. 5.1)
Clinical Features of the Uraemic Syndrome

III. Hematologic and cardiovascular Manifestations:

a- Anaemia:

Anaemia is a common feature of uraemia and is usually normocytic normochromic. It is partly responsible for many of the debilitating symptoms of uraemia such as lethargy, tiredness and exertional dyspnea. The main causes of anaemia in uraemic patient are the followings:

- Bone marrow depression by the uraemic toxins and due to erythropoietin deficiency.
- Short life span of R.B.Cs due to the uraemic toxins.
- Nutritional deficiency due to dietatic restrictions and dyspepsia (protein, Vit. B12, and folic acid)
- Iatrogenic causes as frequent blood sampling in hospitalized patients and the blood loss in the dialyzer at the end of each haemodialysis session.
- Bleeding tendency as GIT bleeding and metrorrhagia.
- Aluminium toxicity.
- Bone marrow fibrosis due to hyperparathyroidism.
- Hypersplenism especially in multiple transfused patient.

Sometimes anaemia is microcytic hypochromic due to iron deficiency. White cell count and platelet count are normal but with decreased functions.

b- Bleeding tendency:

May result from:

- Qualitative platelet defects:

Platelet aggregation is reduced and ADP release is inhibited leading to increased capillary fragility and prolongation of bleeding time.

- Increased fibrinolytic activity of the blood because fibrinolysin is normally eliminated by the kidney.
- Anaemia:

  This bleeding tendency is corrected by dialysis, correction of anaemia or administration of DDAVP or oestrogen.

c- Hypertension:

Hypertension in uraemic patients is either due to high renin secretion or salt and water retention. It occurs in about 80% of cases. In uraemics, hypertension is characterised by resistance to drug treatment and by tendency to develop malignant hypertension more than in other forms of hypertension. Hypertension aggravates the renal disease which further increases the blood pressure and a vicious circle is produced.

d- Uraemic pericarditis:

This occurs due to deposition of urea on the smooth inner surface of the pericardial sac changing it into rough surface. Continuous friction between the visceral and parietal pericardium during cardiac systole and diastole results in dry pericarditis which manifests by pericardial pain and pericardial rub on auscultation. Later, haemopericardium develops which progresses to cause cardiac compression (tamponade). This manifests clinically by a triad of:

1. progressive systemic venous congestion with congested neck veins, congested liver, and anasarca.

2. Progressive hypotension due to reduction of stroke volume as venous return is progressively decreasing.

3. Progressive increase in cardiac size on clinical examination and by plain X-ray. Echo cardiography shows that the increase is mainly due to fluid collection in the pericardium. It also shows the defective cardiac filling and reduced stroke volume.

   Cardiac tamponade, if not treated urgently, will be fatal. Treatment is by pericardiocentesis.

e- Heart failure:

This is usually a left sided heart failure which is due to:

1- hypertension 2- anaemia 3- fluid overload
4- uraemic cardiomyopathy.

IV. Cutaneous manifestations:

- Muddy face (sallow skin), due to retention of some toxins (urochromogens).
- Puffy face, due to salt and water retention.
- Pallor, due to anaemia.
- Dry skin with urea frost. Also the skin is fragile, thin and bruises easily.
- Pruritis results from skin dryness or from irritation of the cutaneous sensory nerves by calcium deposits or by parathormone.
- Purpura and skin infection.
- Nails may be white with tips discoloured brown.

V. Respiratory manifestations:

These include the following:

- Kaussmaul's (acidotic or hissing) breathing
- Exertional dyspnea, paroxysmal nocturnal dyspnea with heart failure.
- Increased incidence of pulmonary infection.
- Rarely, dry uraemic pleurisy.

VI. Ocular manifestations:

These include the following:

- Retinopathy.
- Uraemic amaurosis (rare): which is sudden transient loss of vision.
- Red eye due to conjunctival congestion and calcium deposition.
- Calcium may be deposited as plaques in the conjunctiva.

VII. Musculo-Skeletal and soft tissue manifestations:

These include the following:

a- *Muscular* : fatigue, and wasting (myopathy) which is mainly proximal in lower limbs (Waddling gait). It is due to retained uraemic toxins, electrolyte disturbances, vitamin D deficiency, hyperparathyroidism and nutritional deficiency.

b- *Skeletal* : include bone aches, fractures, and deformity in childhood cases.

c- *Soft tissue calcification* which manifests according to the tissue involved e.g. pruritus when skin and sensory nerves are involved, red eye when conjunctiva is affected, arthritis when calcium deposition involves periarticular tissues, and finger tips gangrene when small arterioles are involved (Calciphylaxis).

VIII. Gonadal disturbances:

The following gonadal disorders are commonly seen in uraemic patients:

- In males: decreased libido, impotence, gynecomastia, reduced spermatogenesis.
- In females: decreased libido, infertility and menstrual dysfunctions.

IX. Endocrinal disturbances:

The following are the endocrine disorders which are common in uraemic patients:

- Hyperparathyroidism
- Lack in activation of vit. D.
- Increased renin activity
- Lack of erythropoietin
- Decreased testosterone level resulting in a decreased libido, potency and spermatogenesis.
- Increased prolactin and L.H. causing menstrual disorders, gynecomastia and infertility.
- Insulin: there are two opposing effects of uraemia on insulin. The first effect is tissue resistance to insulin due to the uraemic milieu. The second is decreased renal tubular degradation of insulin with a consequent increase in the insulin half life. The upper hand is usually for the second effect with consequent fall in insulin requirement (insulin daily dose) in diabetic patients when they become uraemic.

X. Features of the underlying disease may be present:

As manifestations of D.M., SLE or renal stone disease.

INVESTIGATIONS OF A CASE WITH CHRONIC RENAL FAILURE:

1. Urine examination may show the following :

- Polyuria especially nocturia and anuria in terminal cases.
- Urine specific gravity is low and fixed to 1010 (osmolarity 300 mosm/l).
- Urine aspect is pale and watery.
- Albuminuria and granular casts.

2. Blood Changes:

There is an increase in blood urea, creatinine and uric acid levels, metabolic acidosis, normochromic normocytic anaemia, hyperkalaemia, and hyperphosphataemia. Serum calcium may be normal or low in early phases, but it becomes high in stage of tertiary hyperparathyroidism.

3. Kidney Function Tests:

Marked impairment of the renal functions (increase in s. creatinine and decrease in cr. clearance). Plasma creatinine is elevated once GFR is decreased to less than 60 ml/min.

4. Fundus Examination:

May show uraemic retinopathy.

5. Investigations To Know The Cause Of Renal Failure :

Such as Plain X-ray for urinary tract (stone), ultrasonography (obstruction), blood sugar (diabetes), and anti DNA (SLE). Renal biopsy is indicated in cases with average kidney size and unknown etiology of uraemia.

MANAGEMENT OF CHRONIC RENAL FAILURE :

The following steps should be adopted for a proper management of patients with chronic renal failure.

Step 1. CONFIRMATION OF CHRONICITY OF THE KIDNEY DISEASE.

This could be achieved through the following:

a. History: A long history of renal disease suggests chronicity while absent previous history suggests acute renal failure.

b. Kidney size as detected by ultrasonography: A small atrophic kidney favours the diagnosis of chronic renal failure, while a normal sized kidneys is more in favour of acute renal failure.

c. Magnitude of the increase in serum creatinine in relation to the presenting symptoms: High serum creatinine with minimal symptoms is in favour of chronic renal disease, while relatively low serum creatinine with severe symptoms is in favour of acute renal disease.

d. Hyperphosphataemia and osteodystrophy are present more with chronic cases.

e. Anaemia is more with chronic cases.

f. Renal biopsy: extensive renal interstitial fibrosis and tubular atrophy in renal biopsy are features of chronic cases.

Step 2. SEARCHING FOR REVERSIBLE FACTORS:

These factors are classified as the following:

a. Pre-renal factors such as:

• Bilateral renal artery stenosis.
• Severe cardiac failure.
• Malignant hypertension.
• Hypotension.
• Dehydration and hypovolaemia.

b. Renal causes factors such as:

• Active glomerular disease
• Active tubulo-interstitial disease
• Pyelonephritis

c. Postrenal factors:

Causing obstruction of urine flow from both kidneys such as:

• Stone
• Stricture ureters
• Enlarged prostate
• Bladder neck obstruction

Step 3. CONSERVATIVE TREATMENT OF CHRONIC RENAL FAILURE:

a. Dietary control:

- *Protein* is usually restricted to 0.6-1 gm/kg/day (an amount which satisfies the physiologic requirements.
- *Fluid restriction* equivalent to the patient's daily fluid loss. This equals: the sensible water loss (e.g. urine, vomitus and diarrhea) plus the Insensible water loss (respiratory and sweat) which is

about 600 ml/d in an adult of 70 kg. Extra 200 ml fluid should be added in febrile patient for every one degree centigrade increase in the body temperature.

- *Electrolytes:* Sodium restriction with hypertension or oedema, and potassium restriction with severe oliguria and with hyperkalaemia
- *Calories:* Patient should receive about 35 K. calories/kg/day with carbohydrate 60% of non protein calories and fat 40%.

b. Treatment of Bone disease:

- *Phosphate Binders* such as aluminium hydroxide, magnesium oxide and calcium carbonate or acetate which combine with phosphorus in the gut and are excreted with the stool. Calcium containing compounds are better than aluminium and magnesium salts which could be dangerous on long term use. Calcium carbonate or acetate may be given orally t.d.s. with meals in a dose of 500-1000 mg orally.
- *Active vitamin D* " 1-OH vitamin D" which is given orally in a daily dose of 0.25-1.0 ug.
- *Acidosis is corrected* by oral Na bicarbonate supplementation.
- *Parathyroidectomy* may be done for cases with tertiary hyperpara- thyroidism. Three glands and part of the fourth are removed and the remaining is implanted subcutaneously.

c. Anaemia:

Is responsible for major part of uraemic symptoms. The first line of treatment is by giving proper nutrition, iron, folic acid, and vitamins especially B12. Failure to respond may indicate repeated blood transfusion or treatment with recombinant human Erythropoietin. Blood transfusion carries the advantage of being cheap but have the disadvantage of transmitting diseases (especially HIV, HBV and HCV) beside other

risks of blood transfusion. Erythropoietin (EPO) is given S.C. 4000u three times weekly, it carries the advantage of being safe and effective, but it is very expensive. The dose of EPO has to be readjusted to maintain haemoglobin value of 9-11 gm/dl.

d. Symptomatic treatment of:

- *Hypertension* is controlled by hypotensive drugs.
- *Itching* is treated by skin soothing creams, anti-histaminics, treatment of hyperphosphataemia, hyper and hypocalcaemia. For severe, intractable cases, parathyroidectomy may be of help.
- *G.I.T. manifestations* as vomiting could be controlled by antacids and H_2-receptors blockers.

Failure of conservative treatment to provide the patient with a reasonable quality of life is an indication for renal replacement therapy, i.e. dialysis or renal transplantation.

Step 4. RENAL REPLACEMENT THERAPY (RRT):

This includes dialysis (haemodialysis and peritoneal dialysis) and renal transplantation. Early induction of RRT and good nutritional support provide better response to the treatment (less patient morbidity and mortality).

Indications for RRT:

- Failure of conservative treatment with progressive deterioration in patient's general condition and blood chemistry.
- Persistent nausea and vomiting.
- Circulatory overload which is unresponsive to loop diuretics (e.g. frusemide)
- Severe motor neuropathy.
- Uraemic encephalopathy.
- Pericarditis
- Bleeding diathesis.
- Hypertension unresponsive to treatment.
- Hyperkalaemia (serum K^+ level > 7 mEq./litre).
- High creatinine levels and decreased creatinine clearance (Cr. clearance < 10ml/min).

Contraindications for dialysis treatment.

1. **Absolute:**
   - Patient's refusing dialysis.
   - Severe extrarenal illness e.g. severe cardiac disease, end stage liver disease, severe cerebrovascular disease and advanced malignancy.

2. **Relative:**
   - Severe disability or handicapping.
   - Paraplegia or hemiplegia

DIALYSIS THERAPY

Definition:

Dialysis is a process in which the solute composition of blood is altered by exposing it to a physiological solution (dialysate) across a semipermeable membrane (dialysis membrane). Solutes will move from one compartment to another through the dialysis membrane.

Types of Dialysis

There are two forms of dialysis therapy: (A) Haemodialysis, and
(B) Peritoneal dialysis

(A) Haemodialysis

Definition:

It is the movement of solutes and water from the patient's blood across a semipermeable membrane which is the dialyzer.

This is carried out via vascular access where the blood is pumped by a haemodialysis machine into the dialyzer then the blood returns back filtered to the patients circulation **(Fig. 5.2).**

Complications:

(I) Common complications:

(A) Hypotension: This is the commonest complication and may be due to:

- High ultrafiltration rate
- Dialysis solution sodium level is too low
- Acetate-containing dialysis solution
- Dialysis solution is too warm
- Food ingestion (splanchnic vasodilatation)

- Autonomic neuropathy (e.g. diabetic patients)
- Diastolic dysfunction
- haemorrhage
- Arrhythmia
- Septicaemia
- Dialyzer reaction

(B) Muscle Cramps.

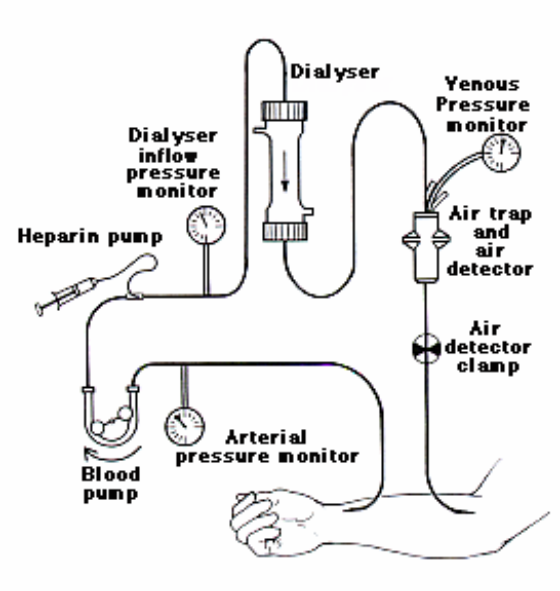
(C) Nausea and Vomiting.

(D) Headache.

(E) Chest pain and back pain.

(F) Itching.

(G) Fever and chills.



(Fig. 5.2)
The extracorporeal blood circuit showing the usual location of the different dialysis monitors.

(II) Less Common Complications:

Although they are less common, they are serious complications. They include:

(A) Disequilibrium Syndrome:

Definition:

Disequilibrium syndrome is a set of systemic and neurologic symptoms which are often associated with characteristic EEG findings that can occur either during or soon after dialysis.

Early manifestations include headache, nausea, vomiting, convulsions and may be coma. In severe cases, death can occur if not treated properly.

(B) Dialyzer reactions:

Type A (anaphylactic type):

The manifestations of this type may be mild in the form of itching, cough, urticaria, sneezing, coryza or watery eyes; or may be severe in the form of dyspnea, chest tightness, cardiac arrest or even death.

Treatment:

- Stop dialysis immediately
- Antihistaminics
- Steroids

Type B (Non specific type):

The patients may complain of back pain or chest pain.

Etiology:

Complement activation

Treatment:

No specific treatment

(C) Arrhythmia:

Arrhythmias during dialysis are common especially in patients receiving digitalis

(D) Cardiac tamponade:

Unexpected or recurrent hypotension during dialysis may be a sign of pericardial effusion or impending tamponade.

(E) Intracranial bleeding:

Underlying vascular disease and hypertension combined with heparin administration can sometimes result in intracarnial bleeding.

(F) Seizures: This occur more often in children

(G) Haemolysis:

Acute haemolysis during dialysis may be a medical emergency

(H) Air embolism:

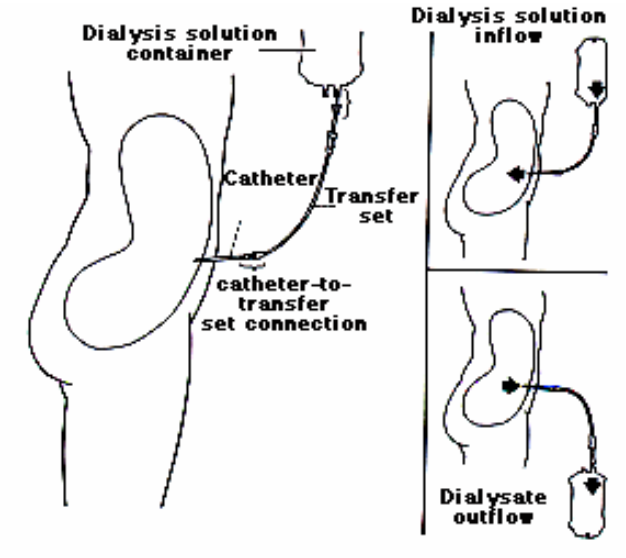
It is a potential catastrophe that can lead to death if not quickly detected and treated.

(B) Peritoneal Dialysis

Definition:

It is the movement of solutes and water from patient's blood across a semipermeable membrane (which is the peritoneal membrane) to the dialysis solution (dialysate).

This is carried out via a peritoneal catheter which is inserted into the peritoneal cavity for infusion of the dialysate which is left to dwell then; drained out via the catheter **(Fig. 5.3)**.



(Fig. 5.3)
Basic continuous ambulatory peritoneal dialysis system, with catheter, and dialysis solution container. On the right, inflow and outflow are depicted.

Types:-

(1) CAPD (Continuous Ambulatory Peritoneal Dialysis):

In which the dialysate is always present in the peritoneal cavity and is exchanged every 4-6 hours/day. This is the commonly used form of P.D worldwide.

(2) CCPD (Continuous Cyclic Peritoneal Dialysis):

In which the dialysate is exchanged at bed time via a cycler (P.D. machine) 3-4 times and the last exchange fluid is left in the abdomen during the daytime.

(3) NIPD (Nocturnal Intermittent Peritoneal Dialysis):

In which the dialysate is exchanged at bed time via a cycler 5-8 times/day and the abdomen is left dry the rest of the day.

This is the new trend nowadays, but it is limited because of the high cost of the cycler.

(4) TPD (Tidal Peritoneal Dialysis):

This is still an experimental form of NIPD which was designed to optimize solute clearance by leaving large volume of dialysate in the peritoneal cavity throughout the dialysis session.

Indications for PD:

Because it provides the best rehabilitation potential as it is safe and easy, it is used for all ages and all sizes of patients with end stage renal failure.

Specific indications for peritoneal dialysis include the following:

1- Infant and very young children
2- End stage renal failure patients with cardiovascular or haemodynamic instability.
3- Haemodialysis patients with vascular access failure (especially diabetics)
4- Patients for whom vascular access can not be created (especially diabetics)

5- High risk of anticoagulants
6- Patients who desire greater freedom to travel

Contraindications:

Absolute:
1- Extensive peritoneal fibrosis
2- Pleuroperitoneal leak

Relative:
1- The same as those in haemodialysis
2- Presence of colostomy or nephrostomy
3- Recent thoracic or abdominal surgery
4- Inguinal or abdominal hernia
5- Blindness
6 - Mental retardation
7- Poor motivation and compliance

Complications:

Mechanical:

- Pain during inflow owing to hot dialysate or rapid jetting
- Pain during outflow due to ball-valve effect
- Outflow failure due to constipation, obstruction or malposition of the catheter
- Pericatheter leakage because of very early usage of the catheter
- Scrotal odema

Pulmonary:

- Atelectasis
- Hydrothorax
- Restricted chest movement

Metabolic:

- Hyperglycaemia
- Hyperlipidaemia
- Protein depletion
- Obesity

Infectious and inflammatory

- Peritonitis
- Exit site infection
- Tunnel infection

KIDNEY TRANSPLANTATION

Definition:

Kidney transplantation means the treatment of chronic renal failure by surgical implantation of a kidney that is obtained from either healthy kidney donor or brain stem dead cadaver.

Principle:

- Kidney transplantation is performed by doing a unilateral nephrectomy for the donor to be implanted into the patient with end stage renal disease "The recipient".
- The new kidney is placed in the patient's abdomen, usually in the right iliac fossa. The artery and vein are anastomosed to patient's vessels (usually internal iliac) and the ureter is implanted into the bladder **(Fig. 5.4)**.

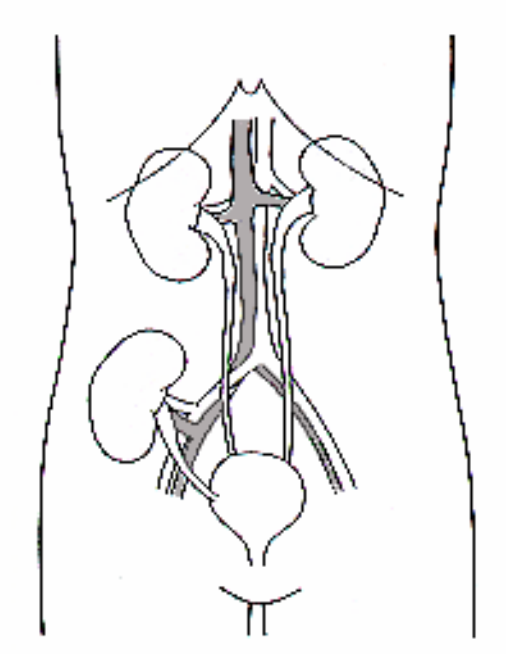


Fig. (5.4)
Kidney transplant in recipient's right iliac fossa with native kidneys left in place.

- The native kidneys are left in place, unless there is an indication to be removed e.g. uncontrollable hypertension, infection or if they are hugely enlarged.
- The immune system of the recipient considers the transplanted kidney as a foreign body and tries to destroy it. This is called "rejection" which can be prevented by:
  - Pre operative immunological investigations to be sure that tissue typing of the recipient and the donor is identical or similar and via
  - Post operative suppression of the recipient's immune system by immunosuppression therapy.

Indications:

Patients with end stage renal failure requiring renal replacement therapy.

Contraindications:

1- Patient refusal
2- Psychosis
3- Age more than 60 years (relative)
4- Recurrent disease, if the original kidney disease that caused renal failure can recur in the transplanted kidney and destroy it e.g. oxalosis.
5- Systemic disease: Some co-existing systemic diseases may contraindicate transplantation because of their effect on the patient's survival or because of the danger of post transplant immunosuppression therapy. These include the following:
   - Severe respiratory disease e.g. C.O.P.D.
   - Severe cardiovascular disease e.g. severe left ventricular failure
   - Severe hepatic disease e.g. liver cirrhosis
   - Central nervous system e.g. cerebral hemorrhage
   - Active peptic ulceration
   - Malignancy
   - Active infection
6- Unrepairable urologic abnormalities.

Immunosuppression after transplantation:

- **Definition:** Immunosuppression therapy is used after kidney transplantation in order to modify the recipient's immune system so that rejection is prevented.
- **Duration:** Immunosuppression therapy continues for life.

- **Mode of action:**

- Immunosuppression can be achieved by different drugs.
- Each drug has a different mechanism by which it can depress leukocytes which are responsible for the immune response.

- **Regimens:**
  - Many regimens are present
  - Steroids are the corner stone drug used
  - Triple regimen (steroids-azathioprine-cyclosporine) is the commonest regimen
  - Other new drugs: (FK-506, Mycophenolate and Rapamycin).
  - Polyclonal antibodies as ATG and ALG
  - Monoclonal antibodies as OKT3
  - Cymeric and humanized antibodies as simulect (Novartis) and zenapax (Roche).

Complications after kidney transplantation:

1- Rejections:

• **Hyperacute:** usually occurs Immediately postoperative.

• **Acute:** Usually occurs days or weeks to months postoperatively

• **Chronic:** Usually occurs months to years postoperatively.

2- Complications of immunosuppression therapy:

a. General complications:

1. Infection
2. Increased incidence of malignancy

b. Complications due to individual drugs:

1. **Steroids:** hypertension, D.M., atherosclerosis, Bone disease, GIT bleeding and cataract.
2. **Azathioprine:** Bone marrow depression and hepatic dysfunction
3- **Cyclosporine:** Nephrotoxicity, hepatotoxicity, hypertension and D.M.

*3- **Recurrence of the original kidney disease into the graft*** (e.g. FSGS, MPGN)

Outcome after transplantation:

- The outcome of kidney transplantation is continuously improving with the advances in the immunosuppressive drugs and the immunologic assessment of donors and recipients, technique of surgery and the postoperative care.
- The current 1 year graft survival is about 90-95% and 5 years graft survival is about 60-70%.
- Continuous advancement in immunosuppressive drugs aims to an ideal drug with maximal ability to prevent rejection and minimal side effects.

TUBULAR DISORDERS AND TUBULOINTERSTITIAL DISEASES

This group of diseases are either specific tubular disorders or a tubulointerstitial nephritis.

I. Specific tubular disorders

These includes the following:

1- Carbohydrate tubular transport defect
- Renal glycosuria

2- Amino acid tubular transport defects
- Hartnups disease
- Cystinuria and cystinosis

3- Renal Tubular Acidosis (RTA)
- Classic (Distal) RTA
- Proximal RTA

4- Abnormal water Handling
- Nephrogenic diabetes inspidus (NDI)
- Water Retention

5- Others
- Wilson's Disease
- Barters Syndrome
- Oxalosis
- Vitamin D Resistant Rickets
- Fanconi Syndrome
- Pseudohypoparathyroidism

II. Tubulointerstitial Nephritis:

- Acute tubulointerstitial nephritis
- Chronic tubulointerstitial nephritis
- Analgesic Nephropathy
- Reflux Nephropathy
- Pyelonephritis

Renal Glycosuria

Normally glucose does not appear in the urine until plasma concentration reaches up to 180 mg/dl (10 mmol/L). This is called renal threshold. Maximum glucose excretion is reached at plasma concentration of 270 mg/dl (15 mmol/L). This is called (tubular maximum or Tm).

Renal glucosuria means the detection of glucose in urine while plasma glucose is less than 180 mg/dl (i.e. decreased renal threshold). There are two types of renal glycosuria, type A in which both renal threshold and Tm are reduced; and type B in which renal threshold is decreased but Tm is not.

Genetics: It is transmitted as autosomal recessive, few families have been reported with autosomal dominant inheritance.

Clinical features: These are persistent throughout the life with no symptoms unless starvation occurs, the patients will suffer from severe hypoglycemia, hypovolaemia and ketosis.

Diagnosis: By detection of glycosuria while plasma glucose is less than 135 mg/dl (7.3 mmol/L).

Differential diagnosis: Renal glycosuria should be differentiated from: (1) Diabetes mellitus (by glucose tolerance curve); (2) Fanconi's syndrome (multiple tubular defects not isolated glycosuria); (3) Glucose-Galactose malabsorption (combined renal and jejunal defect); (4) Gluco-glycinuria; and (5) phosphate diabetes.

Treatment: No treatment is required.

Renal Tubular Acidosis (RTA)

Is a systemic metabolic acidosis resulting from specific tubular abnormality in handling of H^+. Usually the patient presents with metabolic acidosis out of proportion to the renal functional impairment. There are four types of RTA; distal (classic, type I) , proximal (type II) , type III (distal with bicarbonate wastage), and type IV (hyperkalaemic, hyporeninaemic, hypoaldosteronaemic) .

Distal (classic) RTA

The normal daily production of hydrogen ions (H^+) is approximately 1mmol/kg/d in adults and 3 mmol/kg/d in children. This H^+ load is excreted by the kidney, through distal nephron. Failure to secrete this hydrogen load will result in metabolic acidosis. Normally, there is a pump mechanism in the distal convoluted tubules pushing H^+ to the lumen (urine). In distal RTA, there is a reduced pump activity or there is back diffusion of H^+ (from lumen to tubular cells and systemic circulation) resulting in systemic acidosis.

Normally, with systemic accumulation of hydrogen ions the kidney will secrete these H^+ to the urine which will be acidified to a urine pH of 5.2 or less. In distal RTA, this is not possible and urine pH is always above 5.7 even with severe metabolic acidosis.

Serum Bicarbonate (HCO_3) is used as a buffer for the retained H^+ ($HCO_3 + H^+ \text{---> } H_2CO_3 \text{----> } H_2O + CO_2$), so its blood level will be low in metabolic acidosis. As the proximal convoluted tubular function is intact in distal RTA, more HCO_3 and chloride (CL^-) will be reabsorped from its lumen. Reabsorped HCO_3 will be used for buffering more H^+.

Etiology:

1. **Primary**
   - idiopathic
   - genetic (autosomal dominant)
2. **Autoimmune disease**
   - SLE
   - Sjogren's Syndrome
   - Chronic active hepatitis
3. **Tubulo-interstitial disease**
   - Chronic pyelonephritis
   - Acute tubular necrosis
   - Obstructive uropathy
   - Renal transplant glomerulopathy
4. **Drugs and toxins**
   - Analgesics
   - Amphotericin B
   - Lithium
   - Toluene
5. **Uretero-sigmoidostomy**

Clinical Features:

1. Male to female ratio is always 1 : 1. Primary RTA usually manifests clinically between the first and the third decade of life **(Fig. 6.1)**.
2. Hypokalemia due to defective handling of K^+ in distal nephron this will manifest as muscle weakness even paralysis and may be complicated by rhabdomyolysis, respiratory arrest or cardiac arrhythmia. Prolonged hypokalaemia may lead to renal concentration defect which will manifest as polyuria and nocturia.
3. Nephrocalcinosis and stone disease that is due to the decreased solubility of calcium salts (oxalate, carbonate or phosphate) due to persistently alkaline urine and reduced urinary citrate, Mg and hypercalcuria (in 50% of congenital and hereditary RTA).
   This will result in obstructive uropathy, infection and finally renal failure.
4. Osteomalacia with bone pains and fractures. It is due to acidosis and use of bone as buffer with release of calcium carbonate from bone, also hypophosphataemia causing hyperparathyroidism and suppression of activation of vitamin D and hypocalcaemia.
5. Severe acidaemia will cause tachypnea, dizziness and even coma.
6. Severe acidaemia may decrease extracellular fluid volume and GFR.
7. Incomplete RTA will manifest only as nephrocalcinosis or as a stone disease.

Treatment:

Except in drug induced cases of RTA, the disease is always persistent and needs permanent treatment.

1. First treat hypokalaemia and hypocalcaemia.
2. Then give sodium bicarbonate to correct acidosis.
   After correction of acidosis no need to give potassium supplementation.
3. Treatment of infection or obstruction if present.

Proximal RTA

Normally all the filtered bicarbonate is reabsorped unless the concentration of bicarbonate in the glomerular filtrate is above the HCO3Tmax which is 25 mmol/L. 80% of reabsorption of HCO_3 occurs in the proximal tubules through H^+ pump. In Proximal RTA, there is a degree of weakness in H^+ pump resulting in a decrease in its HCO_3 reabsorption capacity and a new steady state is settled in which Tmax of HCO_3 is decreased (e.g. to 10 mmol/L or 14 mmol/L). All HCO_3 filtered above this level will be lost in urine (bicarbonaturia) and blood level of HCO_3 will be decreased.

The HCO_3 reaching the distal nephron will turn the urine alkaline. This will interfere with ammonium ion and titratable acids excretion and consequent retention of H^+ in the body.

In this phase, the condition is characterized by metabolic acidosis, hyperchloraemia (excess reabsorption of CL^- by PCT on expense of HCO_3), alkaline urine, decrease titratable acids and ammonium ion excretion.

When a new steady state is reached (new Tmax) all the filtered HCO_3 will be reabsorped. The condition is characterized by metabolic acidosis, low plasma HCO_3, hyperchloraemia, normal acidic urine (less than 5.2), no bicarbonaturia and normal excretion of ammonium ions and titratable acids.

Etiology:

PRTA is more rare than distal RTA. The list of causes of PRTA includes:

1. Primary single tubular defect
   - Genetic (very rare)
   - Idiopathic
   - Transient in infants
2. Autoimmune disease
   - Sjogren's Syndrome
3. Tubulo-interstitial disease
   - Medullary cystic disease
   - Renal transplant rejection
4. Drug and Toxins
   - Outdated tetracyclines
   - Streptozotocin
   - Lead, mercury, sulfonamide
5. Dysproteinaemia
   - Multiple myeloma
6. Other renal diseases
   - Amyloidosis
   - Nephrotic Syndrome

Clinical features and diagnosis:

1. Usually metabolic acidosis with manifestations of other proximal tubular defects e.g. Fanconi Syndrome.
2. Hypokalemia

3. Nephrocalcinosis and renal stone disease
4. Manifestations of acidosis with failure to thrive in children, hypovolaemia, and tachypnea.
5. In contrary to distal RTA, the urine pH is variable. The morning urine pH is less than 5.2. Infusion of $NaHCO_3$ to increase plasma HCO_3 to normal will be followed by bicarbonaturia and increase in urine pH (alkaline) in proximal RTA and not in distal RTA; since in PRTA all HCO_3 above Tmax will be lost in urine.

Treatment:

A large amount of alkali is needed (3-10 mmol/kg/d). Potassium supplement ($KHCO_3$) is needed because the correction of systemic acidosis will lead to bicarbonaturia with more renal loss of potassium.

Abnormal Water Handling:

A. Nephrogenic diabetes Insipidus (NDI)

Normally, anti-diuretic hormone (ADH) will make the distal nephron tubular basement membrane permeable to water with its reabsorption from the tubular lumen. In NDI, the tubular basement membrane is not responsive to ADH either due to defect in receptor site for ADH or in the effector site; defect in adenylate cyclase enzyme with reduced formation of cyclic AMP. Other mechanisms could be reduction of the medullary hypertonicity as in chronic renal failure, prolonged low protein intake and with the use of osmotic diuretics (mannitol).

Failure to respond to ADH will result in polyuria.

Etiology of Nephrogenic Diabetes Insipidus

1. Hereditary.
   - Congenital
   - Fabry's disease
2. Non-Hereditary.
   - Idiopathic
   - Cystic disease
   - Obstructive nephropathy
   - Interstitial nephritis
   - Chronic renal failure
3. Electrolyte disorder
   - Hypokalaemia
   - Hypercalcaemia
4. Drugs
   - Diuretics
   - Lithium
   - Demeclocycline (tetracycline)
   - Methoxyflurane
   - Colchicine
   - Amphotericin B
   - Propoxyphene
   - Chlorpromazine
5. Miscellaneous
   - Amyloidosis
   - Multiple myeloma
   - Sjogren's Syndrome
   - Low protein intake

Clinical features and diagnosis

1. Mainly polyuria (3-6 litres/day) and polydepsia.
2. Hypernatraemia will develop only in infants or unconscious patients who cannot ask for water or in patients with impaired thirst mechanism (hypokalaemia, hypocalcemia or hypothalamic lesion). This will be manifested by dehydration, hypotension, restlessness, ataxia, seizures and grand mal fits.

3. NDI should be differentiated from central diabetes insipidus (CDI) and psychogenic polydepsia. Both NDI and CDI could be complete or partial syndrome.

   The three conditions could be differentiated by water deprivation test which aims to increase plasma osmolality to 295 mosmol/kg by water deprivation (alternatively by giving hypertonic saline 5% Nacl in a dose of 0.05 ml/kg/min for 2 hours) then looking for urine volume and urine osmolarity.

   - Normally, as plasma osmolarity increases to 295 mosmol/kg, the urine volume will decrease and urine osmolality will increase to 800-1400 mosmol/kg.
   - In psychogenic polydepsia, urine volume will gradually decrease and urine osmolality will increase up to 800 mosmol/kg.
   - In complete NDI or CDI the urine volume and osmolarity will not change (even the patient may become shocked from hypovolaemia so blood pressure should be watched hourly and body weight should not be allowed to decrease by more than 3-5%).

     When plasma osmolality reaches 295 mosmol/kg or hypotension occurs, ADH is given in the form of DDVAP intranasally or 5 units of aqueous vasopressin i.v. Urine volume will decrease and osmolality will increase up to 800 in CDI but no change will occur in NDI.

     In partial syndrome (NDI or CDI) water deprivation will increase osmolality to 400-500 mosmol/kg and some decrease in urine volume occurs. On giving vasopressin or DDVAP, urine osmolarity will increase to 800 in CDI and not in NDI.

Treatment:

1. Treatment of the cause.

2. Adequate free water intake (without salt) to compensate for water loss and avoid dehydration and hypernatraemia.
3. Thiazide diuretic may help. The mechanism is mostly through induction of hypovolaemia. This will increase proximal tubular water reabsorption and thus reduces the amount of urine reaching to the distal nephron (the site of abnormality).

B. Water Retention:

This is usually caused by drugs increasing sensitivity of distal nephron to ADH leading to excess water reabsorption which will lead to dilutional hyponatraemia. These drugs are: cyclophosphamide, indomethacin, sulfonylureas (chlorpropamide, tolbutamide), acetaminophen, oxytocin and vasopressin.

Clinical Features and Diagnosis:

The picture is similar to that of the syndrome of inappropriate secretion of ADH (SIADH) but with low plasma ADH level. There is euvolaemic or hypervolaemic state (oedema, high blood pressure, decreased haematocrit ratio), dilutional hyponatraemia and hypoosmolality (irritability, disorientation, lethergy, twitching, nausea, seizures, and even coma), mortality is 10% in chronic hyponatremia and 50% in acute hyponatremia.

Treatment:

Withdrawal of the causative drug. If this is not possible, give demeclocycline 200-600 mg/d.

ACUTE INTERSTITIAL NEPHRITIS (AIN)

Etiology:

1. **Drug or Toxin induced:**

Antibiotics are the most commonly implicated drugs, in acute interstitial nephritis. Methicillin is the most frequent but penicillin, ampicillin, rifampicin, phenandione, sulfonamides, co-trimoxazole, thiazides and phenytoin are frequently implicated and are more important clinically. Drugs involved but less frequently are non-steroidal anti-inflammatory drugs (NSAIDS), diuretics, analgesics and H_2-antagonists. Toxins which can induce tubulointerstitial nephritis are organic solvents, ochratoxin (fungal toxin).

2. **Infection-related acute interstitial nephritis:**

May result from direct invasion of the renal interstitium by the organism (mainly the renal medulla which is involved with picture of acute pyelonephritis) or may be associated with a systemic infection without direct renal involvement by bacteria. The lesion will be caused by bacterial toxin or through an immunologic process triggered by bacterial infection.

3. **Idiopathic and immune mediated disease:** Such as Sjogren's syndrome, SLE and transplant rejection.

Pathology:

Macroscopically, the kidney looks normal or increased in size. *Microscopically*, there is interstitial edema and cellular infiltrate. Tubules may look normal or show necrosis, glomeruli; and blood vessels are intact. The infiltrating inflammatory cells are predominantly lymphocytes and

plasma cells. In addition, neutrophils and eosinophils will be seen in drug induced AIN.

The condition may regress completely or progress to chronic interstitial nephritis if the offending cause is persistent.

Clinical Presentation:

The disease varies from severe hypersensitivity syndrome with fever, rash, eosinophilia and acute renal failure to asymptomatic increase in plasma creatinine or abnormal urinary sediment without evidence of renal insufficiency.

In cases of drug induced AIN the interval between exposure to drug and the onset of symptoms varies from hours to months.

Differential diagnosis:

This includes acute tubular necrosis, rapidly progressive glomerulonephritis and athero-embolic renal artery disease.

History of drug intake or exposure to toxic substance or infection is important. Presence of skin rash, fever, eosinophilia, tubular proteinuria (usually < 1g/24 h), leucocyturia, microscopic haematuria and eosinophiluria are findings supporting the diagnosis of AIN. Kidney biopsy will settle the final diagnosis.

N.B. Absence of eosinophilia or eosinophiluria does not exclude AIN.

Treatment:

1. Discontinuation of the causative drug and treatment of infection and supportive treatment may be sufficient to induce recovery.
2. Steroids are sometimes given (unless there are contraindications) to shorten the course of illness and prevent permanent renal damage.

CHRONIC INTERSTITIAL NEPHRITIS (CIN)

There are many conditions that may lead to CIN. The most common are analgesic nephropathy, reflux nephropathy, gouty nephropathy, obstructive nephropathy and chronic pyelonephritis. The complete list of causes of CIN is in table 1.

TABLE 1
CAUSES OF CHRONIC INTERSTITIAL NEPHRITIS

1.	Chronic phase following acute interstitial nephritis.
2.	Drugs (analgesics, lithium).
3.	Heavy metals (cadmium, mercury, lead).
4.	Reflux nephropathy.
5.	Metabolic (gout, hyperoxaluria, hypercalcaemia).
6.	Radiation.
7.	Sarcoidosis.
8.	Balkan endemic nephropathy.
9.	Sjögren syndrome.
10.	Neoplastic disorders (multiple myeloma, leukemia, lymphoma, light chain nephropathy).
11.	Transplant rejection.

Pathology:

Macroscopically, the kidney is small, atrophic.

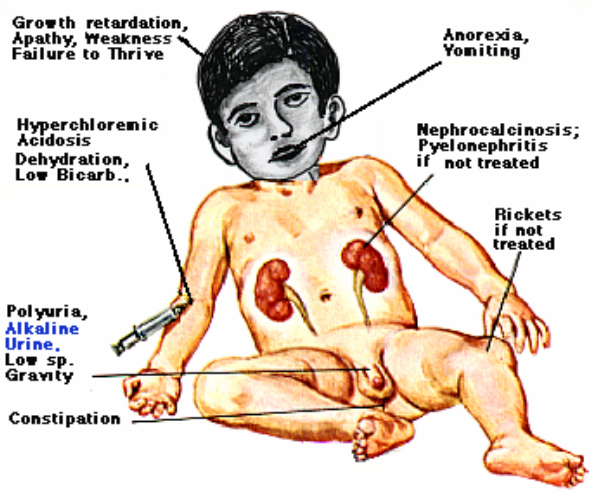
Microscopically, non-specific changes are seen including interstitial fibrosis, chronic inflammatory cellular infiltration and tubular atrophy.

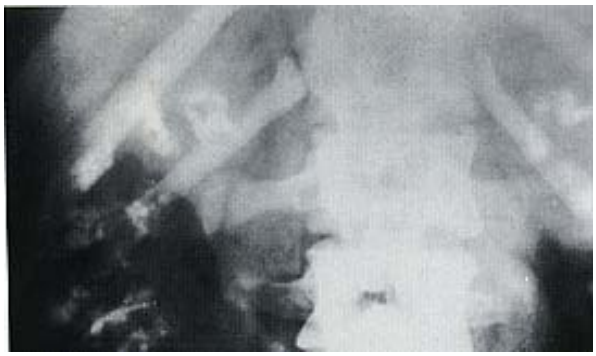
Clinical presentation :

1. Manifestations of the etiologic cause.
2. Manifestations of chronic renal impairment (see page 47) which may progress to end stage renal disease.

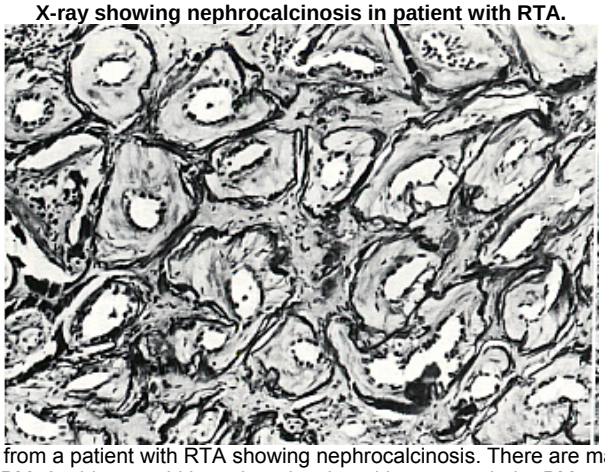
Treatment:

1. Of the etiologic cause, and
2. Treatment of the chronic renal failure, whether conservative or with renal replacement therapy in advanced stages (dialysis and transplantation).





X-ray showing nephrocalcinosis in patient with RTA.



Kidney section from a patient with RTA showing nephrocalcinosis. There are massive calcium deposits in tubular BM. A wide mucoid layer has developed between tubular BM and epithelium. PAS (X90).

(Fig. 6.1)

Clinical Features of Renal Tubular Acidosis

ANALGESIC NEPHROPATHY

Analgesic nephropathy is a chronic tubulointerstitial disease, it represents an important cause of end stage renal failure.

Pathology:

The following pathologic features could be seen in analgesic nephropathy:

1. Renal Papillary Necrosis (RPN).
2. Chronic Interstitial Nephritis.
3. Vascular (Capillary) Sclerosis.
4. Transitional Cell Carcinoma of the Urothelium.

Macroscopic appearance:

The kidney is small in size. The capsule is thick and adherent, with prominent scars and multiple small cysts seen on the surface. Cut surface will show the brownish-black necrotic shrunken papillae with atrophy of the overlying cortical tissue and hypertrophy of the intervening columns of Bertini **(Figure 6.2)**.

Microscopic appearance:

1. Renal papillary necrosis (RPN):

Is the primary feature of analgesic nephropathy, resulting from medullary cytotoxicity and ischemic infarct. Histologically, RPN may be divided into three stages according to the extent of necrosis, starting by papillary tip necrosis to complete papillary necrosis. A striking feature is absence of inflammatory infiltrate and the presence of calcification of the involved papillae. Separation and loss of a necrotic papilla result in the formation of a cavity which becomes lined by fibrous tissue.

2. Chronic interstitial nephritis:

There is tubular atrophy, interstitial fibrosis and round cell infiltration.

3. Vascular sclerosis:

Affecting small arterioles, venules in the renal medulla and the submucosa of the renal pelvis and the urinary tract.

4. Transitional cell carcinoma (TCC) of urothelium:

TCC is commonest analgesic-associated tumour.

Clinical manifestations:

Female to male ratio is 7 : 1, in spite of ratio of analgesic consumption is only 2 : 1 denoting female sex preponderance. The patient's age is usually 40-60 years.

Analgesic nephropathy may be asymptomatic and is discovered only on routine medical examination.

The patient may present with manifestations of progressive renal impairment with more marked manifestations of tubular dysfunctions including more severe metabolic acidosis than expected (if we consider serum creatinine), early loss of concentrating ability with polyuria and nocturia, sodium losing state, more osteodystrophy (renal bone disease) and enzymuria.

Hypertension occurs in more than 60% of cases.

Gout occurs in 20% of cases. It is more common in males.

Proteinuria occurs in 40% of cases, usually mixed tubular and glomerular (up to 3g/24h).

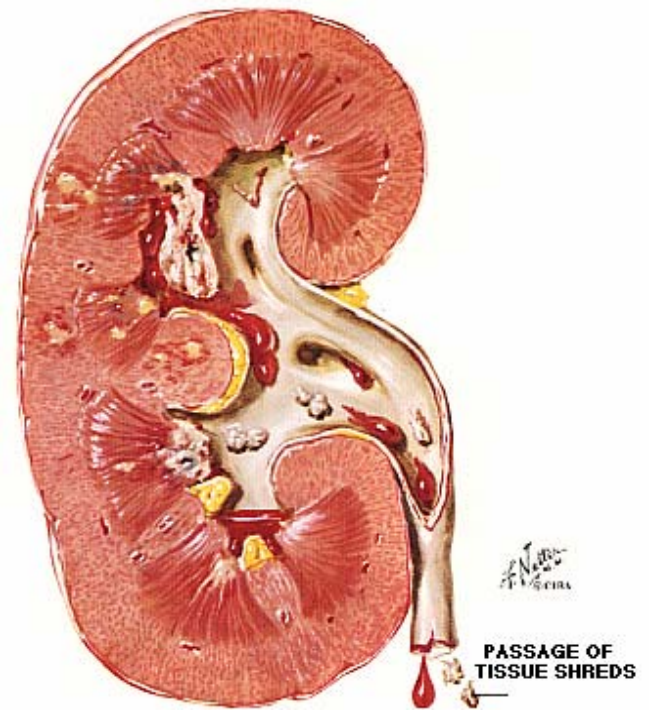
Haematuria secondary to cystitis, renal calculi, malignant hypertension, malignancy.

Urinary tract infection may occur in up to 50% of cases, due to epithelial shedding, stones, stasis and instrumentation. Sterile pyuria is very common due to renal calculi or renal tubular epithelial celluria.

Ureteric obstruction by necrotic papillary tissue, stone, tumour or stricture-if associated with infections-may result in a life threatening acute renal failure.

Management:

1. Total avoidance of all NSAIDs is the most important therapeutic approach.
2. Maintenance of a high fluid intake (greater than two liters/d).
3. Treatment of complications e.g. hypertension, acidosis, infection.
4. Careful long-term follow-up for early discovery of complications e.g. malignancy, infection, stones and renal artery stenosis.



(Fig. 6.2) - Gross appearance of a kidney with necrotizing papillitis it shows sloughing of the Renal papillae

(Reproduced with permission from Novartis-Switzerland)

REFLUX NEPHROPATHY

Vesicoureteric reflux (VUR) is the back flow of urine from the bladder to the ureter; and reflux nephropathy (RN) is the kidney disease characterized by coarse renal scars as a complication of VUR.

Pathogenesis of Renal scarring in RN:

Renal scars develop during infancy or during early childhood. Three factors are interacting to cause renal scarring. These are:

1. Vesicoureteric reflux.
2. Intra-renal reflux.
3. Urinary infection. As infection reaches renal pyramids in the immature kidney, scars will develop.

Prevalence of RN:

About 0.5% of neonates have VUR, but small proportion of them develop R.N., scarring occurs in female more than in male (5 : 1).

1-2% of school girls have bacteruria, and of these 20-30% have VUR. Prevalence of RN in school girls is 0.3-0.5%.

Clinical Features:

1. **Recurrent urinary tract infections:** This is the commonest presentation. In neonates it may present as fever and failure to thrive, in older children it is associated with fever, dysuria, frequency and loin pain. Usually it is recurrent.
2. **Hypertension:** VUR is responsible for more than 60% of hypertension in children and 60% of adults with VUR are hypertensive.

3. **Renal failure:** 10% of patients coming for dialysis have RN, usually at age of 30 years. Renal failure occurs due to scarring, infection, and FSGS.
4. **Other clinical presentations:** As loin pain on voiding, childhood enuresis, renal stone, positive family history, and presence of other congenital anomaly as duplex ureter and posterior urethral valve.

Diagnosis:

1. IVU will show cortical scarring and clubbing of calyx, disparity in kidney size and shape.
2. Renal radionuclear imaging. Using DMSA scan to show scarring or area of inflammation.
3. MCU and cystoscopy.
4. Renal biopsy is indicated only when IVU and DMSA show no scarring.

Management of RN:

1. Control of infection by prophylactic antibiotics which should be given daily (e.g. septrin once daily) till puberty or reflux disappears. If infection occurs it should be treated aggressively.
2. Control of hypertension.
3. Anti-reflux surgery: The indication of surgery in treatment of VUR is still controversial. Surgery will not prevent progression of renal disease. It may be indicated with recurrent pyelonephritis or when prophylactic antibiotics could not be given especially with high grade reflux. Either ureter is reimplanted into the bladder with special anti-reflux technique or cystoscopic injection of material (e.g. collagen or polytetrafluoro- ethylene) around ureteric orifice to narrow it and to prevent refluxing.

PYELONEPHRITIS

Is a microbial infection involving renal pelvis and renal parenchyma. Pyelitis means an infection mainly affecting the renal pelvis. Pyelonephritis is usually associated with constitutional symptoms (fever, rigors,...) due to parenchymatous involvement, while pyelitis like other viscous organ infection (e.g. cystitis and urethritis) is not.

Pyelonephritis may be acute or chronic:

ACUTE PYELONEPHRITIS

Predisposing factors:

1. Anatomical abnormalities: as vesico-ureteric reflux, ureteric stricture or congenital kidney disease as horse shoe kidney.
2. Renal stones.
3. Obstruction of the urinary tract causing stasis of urine as in cases of senile prostatic enlargement and bladder neck obstruction.
4. Diabetes mellitus: due to its predisposition to infection, this risk will be magnified on presence of diabetic nephropathy.
5. Analgesic nephropathy: due to the interstitial fibrosis and the abnormal urinary epithelium caused by chronic exposure to these drugs.
6. Instrumentation: as cystoscopy which may introduce organisms into the urinary tract.
7. Neurogenic bladder which leads to residual urine in the bladder and stasis creating a good medium for bacterial multiplication.
8. Following primary renal disease e.g. nephrotic syndrome.

Precipitating factors specific for female patients:

1. Short urethra allowing easy passage of bacteria from the perineal area to the bladder.

2. Trauma such as honey moon cystitis (cystitis occurring in early marriage).
3. Stasis with pregnancy: due to hormones secreted during pregnancy causing relaxation of ureteric muscles and ureteric dilatation.

Symptoms:

Fever, malaise, aches, dysuria, frequency of micturition, hematuria and papillae may pass in urine causing renal colic (especially in diabetic patients). In children, abdominal pain and screaming on micturation.

Signs:

Tender loin and suprapubic area and the urine may look turbid and may smell fishy (in Proteus infection).

Investigations:

1. Urine examination including:

(a) Microscopic examination which will show pus cells and sometimes
bacteria .

(b) Urine culture to detect bacterial count (significant count is > 100,000 bacteria/ml urine), for identification of type of organism, and to detect degree of sensitivity to antibiotics which is important for treatment, especially in complicated cases.

For urine culture, the urine should be free of contamination. This could be achieved by using midstream urine sample in adults or suprapubic aspiration of urine in children. This is done by puncturing the full bladder by a fine needle after disinfecting the skin of suprapubic area.

The most common organism causing acute pyelonephritis is E.coli, followed by coliforms bacteria. In cases with anatomic abnormality in urinary tract or with instrumentation the common organisms are pseudomonas, proteus, and k. aurogenosa.

Causes of sterile pyuria (pus cells with negative repeated cultures) are:

1. Urinary T.B. (needs special media to grow).
2. Renal stones.
3. Urethritis (caused by virus, fungus or chlamydia.... etc.)
4. Analgesic nephropathy.
5. Nonspecific inflammation of the bladder.

2. **Kidney function tests:** Serum creatinine and creatinine clearance. Renal dysfunction could be a preceding event or a complication of pyelonephritis and its presence will affect the mode of treatment of acute pyelonephritis.

3. **Renal ultrasonography** to diagnose precipitating factors as stone or back pressure.

4. **IVP:** After single attack in male and repeated attacks in females to diagnose stone disease or anatomic abnormality, e.g. ureteric stricture, back pressure changes.

5. **Kidney biopsy:** Is not indicated for diagnosis as it may disseminate infection.

Treatment:

1. High fluid intake to induce diuresis to wash pus and bacteria out.

2. Antimicrobial therapy:

For first or uncomplicated infection we may start with Ampicillin, Amoxycillin or Septrin for 7-10 days. For resistant, recurrent or complicated infection antibiotic may be chosen according to urine culture and antibiotic sensitivity test.

Changing urine pH is indicated with anatomic abnormalities especially when the sensitivity test shows garamycin as the best choice. Alkaline urine is needed for garamycin, sulfonamide, streptomycin. Acidic urine is needed for tetracycline and mandelamine.

Relapse of infection (same organism) or reinfection (different organism) is usually due to wrong choice of antibiotic, inadequate dose or duration of treatment, female sex and anatomic abnormality. This could be managed through a proper vulval hygiene, long antibiotic suppressive therapy (after full course of antibiotic give a daily evening dose for 3-6 months) and correcting any anatomic abnormality.

CHRONIC PYELONEPHRITIS

Is believed to be the result of chronic or repeated renal bacterial infection. Often at presentation, proof of the bacterial etiology is unavailable.

Pathology:

Gross Appearance: Affected kidney is decreased in size with irregular outline (due to underlying scars).

Microscopy: A nonspecific appearance is similar to any type of chronic interstitial nephritis. There is irregular, patchy, cortical infiltration with inflammatory cells, tubular atrophy and interstitial fibrosis. Vascular changes of hypertension may be evident (thickening of the wall with duplication of internal elastic lamina and narrowing of arterial lumen).

Clinical presentation:

1. History of recurrent episodes of urinary tract infection.
2. Hypertension.
3. Insidious onset of renal failure.
4. Sometimes patient may be asymptomatic with non-nephrotic proteinuria.

Investigations:

1. **Urine culture:** should be repeated 3-4 times. A positive culture is obtained only in 30% of cases.
2. **Ultrasound and IVP:** may show asymmetry in kidney size and distortion of calyx.

3. **GFR:** may be reduced, increase in 24-hour proteinuria and manifestations of distal tubular dysfunction (e.g. renal tubular acidosis, inability to concentrate urine).
4. **Renal biopsy:** is **not** indicated.

Treatment:

1. Antimicrobial therapy: according to culture and sensitivity testing and a long suppressive regimen is indicated.
2. Surgical treatment for anatomic abnormality or stone disease.
3. Treatment of hypertension.
4. If the patient presents with chronic renal failure, treatment will be provided as described in section on chronic renal failure.

URINARY TUBERCULOSIS

Clinical picture of genitourinary tuberculosis:

Tuberculosis should be considered in the presence of:

1- Chronic cystitis non responding to adequate treatment.
2- Sterile pyuria
3- Gross and microscopic hematuria
4- Non tender and enlarged epididymis with beaded thick vas
5- Chronic scrotal sinus
6- Nodular prostate and thick seminal vesicle in young males.

Symptoms:

1- Asymptomatic
2- Constitutional symptoms: malaise, night fever and sweating and weight loss
3- Symptoms related to kidney and ureter:
   - May be asymptomatic

- Loin dull aching pain
- Renal colic (due to blood clot, caseous material or stone)
- Painless mass (rare).

4- Symptoms related to the urinary bladder
- Cystitis (burning micturition, frequency, nocturia)
- Hematuria (gross in 10%- microscopic in 50%)
- Suprapubic pain (due to bladder ulcers)
- Recurrent E. Coli cystitis.

5- Others:
- Painless scrotal swelling or sinus
- Haemospermia
- Incidental discovery after TURP
- Swollen painful inguinal lymph node in a tuberculous female may direct the attention to husband tuberculosis.

Investigations:

Laboratory:

1- Urine: - Persistent pyuria with sterile culture (secondary infection occurs in 15-20%)
- Collection of 3-5 consecutive early morning urine for examination by ZN staining for detection of the acid fast bacilli (positive in 60% of cases).
- Urine culture for tuberculosis
- Animal inoculation.

2- Blood: ESR for assessment of disease activity, serum creatinine and complete blood picture.

Radiological investigations:

1- Plain X-ray for the abdomen usually shows:

- Increased soft tissue shadow in one kidney
- Obliterated renal and psoas shadow (abscess)
- Punctate calcification (60%)
- Stones
- Ureteric calcification casting the ureter
- Large prostatic calculi

2- Intravenous urography (IVU)

- Moth-eaten appearance of ulcerated calyces.
- Obliterated calyces
- Dilated calyces with narrow neck
- Abscess cavity connected to calyces
- Ureteric stricture
- Straightening and shortening of the ureter
- Non functioning kidney (autonephrectomy)
- Small contracted bladder

Cystoscopy

- May show ulcers or contracted bladder
- Mucosal biopsy: Is contraindicated if acute tuberculous cystitis is suspected or tuberculous affection is close to ureteric orifices

Treatment Of Genitourinary Tuberculosis

Aim of the therapy:

- Treating active disease
- Making the patient non infectious as soon as possible
- Preservation of the maximum amount of renal tissue

Different drug Regimens

6- month regimen:

Rifampicin	600mg/day	2month
INH	300mg/day	
Pyrazinamide	1gm/d	

Followed by

Rifampicin	900mg/day	3 times/week for 4 month
INH	600mg/day	

4 -month Regimen:

Pyrazinamide	25 mg/kg/day (maximum 2gm)	2 month
INH	300mg/day	
Rifampicin	450 gm/day	

Followed by

INH	600 mg thrice weekly	for further 2 month
Rifampicin	900 gm/day	

Some precautions for drug usage:

- All the drugs should be administered in one dose, if they are to be divided, they may achieve subtherapeutic levels.
- It is adviced to take all drugs prior to bed times.

- Streptomycin adds nothing to the other three drugs in the initial phase, but it is advantageous in extensive disease with severe bladder symptoms; because it has a high concentration in urine.

Recent methods for diagnosis of tuberculosis

(A)Bacteriologic:

1- Polymerase chain reaction (PCR)

Advantages:

- Capable of detection of single organism in biological fluid
- Can differentiate between typical and atypical mycobacteria.

Disadvantages:

- Needs experience and equipments
- Liable to contamination

2- Radiometric detection method e.g. Bactec 460 system

(B) Immunochemical:

1- Adenosine deaminase activity (ADA)

2- ELISA

CYSTIC RENAL DISEASES

Renal cyst is an isolated segment of the nephron which is dilated to a diameter of 200 um or more. Cystic kidney is a kidney containing 3 or more cysts.

Classification of Renal Cystic Disorders

I. Polycystic kidney disease.
- Autosomal dominant polycystic kidney disease.
- Autosomal recessive polycystic kidney disease.

II. Renal Medullary cysts.
- Medullary cystic disease
- Medullary sponge kidney
- Juvenile Nephronopthisis

III. Acquired renal cystic disease

IV. Renal cyst in hereditary syndrome
- Tuberous sclerosis
- Von Hippel-Lindau disease
- Others

V. Simple renal cyst
- Single
- Multiple

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

It is one of the most common genetic disorders and is responsible for approximately 10% of patients with end stage renal failure. It affects 1:400-1:1000 of people allover the world.

Genetics

The disease is transmitted by autosomal dominant inheritance. So, 50% of offsprings inherit the abnormal gene.

Clinical Features

A. Renal Manifestations

- Less than 5% of nephrons are involved in cyst formation. Clinically, most patients will have no detectable cyst at birth. Several small cysts will appear in childhood, and during adulthood, the cysts grow and kidney may be as large as 40 cm in length and over 8 kg in weight.
- By the age of 50, nearly 30% of patients, will develop end stage renal failure and by the age of 73 the figure becomes nearly 50%. Hypertension will manifest before the development of renal failure in 60% of cases. Also, the inability to concentrate urine (polyuria and nocturia) and metabolic acidosis will appear earlier. Episodic dull aching abdominal pain which is due to cyst enlargement and persistent abdominal fullness by large kidneys are other common complaints.
- Renal complications include:
  (a) Increased incidence of renal adenoma, and renal cell carcinoma.
  (b) Haematuria which may be gross or microscopic in 50% of cases secondary to cyst rupture into the pelvis, infection, nephrolithiasis or owing to malignancy.
  (c) Infection which may be difficult to treat if involving the cysts.
  (d) Nephrolithiasis.
  (f) Non-nephrotic range proteinuria in 30% of cases.

B. Extra-Renal Manifestations

1. Cardiovascular involvement.

With ADPKD, there is a higher incidence of mitral valve prolapse (30% while it is only 6% among normal population). In addition to aortic

and tricuspid valve incompetence and left ventricular hypertrophy that are most probably secondary to hypertension.

2. Gastrointestinal involvement

Hepatic cysts are the commonest extrarenal manifestations of ADPKD as they occur in 40% of cases. Other gastrointestinal manifestations include diverticulosis (may be complicated by diverticulitis, abscess formation or perforation), pancreatic and splenic cysts and inguinal hernias.

3. Neurological involvement

Intracranial aneurysm occurs in 10% of cases. It may rupture leading to subarachnoid haemorrhage.

Pathology:

The two kidneys are massively enlarged **(Fig. 7.1)**, in 80% of cases, the enlargement is symmetrical. Cross section will show hundreds of cysts occupying the cortex and medulla and compressing the normal renal tissue in between.

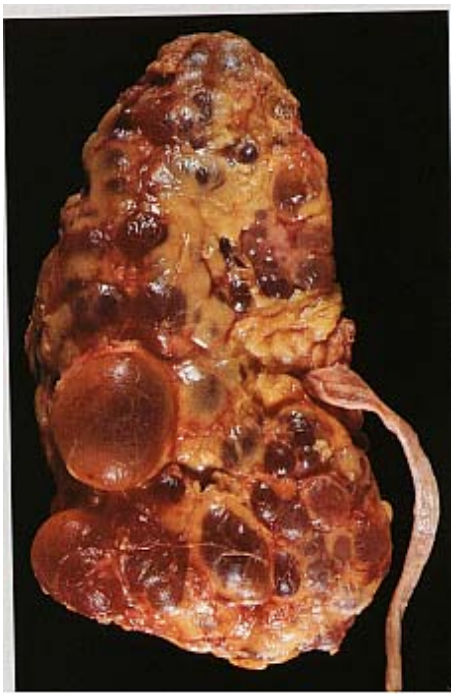
Diagnosis:

1. By detecting renal cysts by US or CT scanning.
2. Gene linkage analysis for the detection of responsible gene on chromosome 16.

Management:

1. Abdominal and flank pain which is due to enlarging cyst is managed by non-narcotic analgesics, rarely percutaneous cyst rupture may be indicated for persistent severe pain.

2. Hypertension should be treated aggressively to prevent progression of the kidney damage and to guard against aneurysm rupture in cases of families with a history of cerebral haemorrhage.
3. Restriction of dietary protein to slow progression of kidney damage.
4. If infection occurred, give proper antibiotics, especially those which could penetrate into the renal cysts (trimethoprim-sulphamethoxazole, chloramphenicol, and fluoroquinolone drugs as norfloxacin and ciprofloxacin). If cyst infection occurred, drainage may be required.
5. Screening for intracranial aneurysm is indicated in cases with hypertension and positive family history for cerebral haemorrhage.



(Fig. 7.1)
Kidney of a patient with ADPCK, the renal tissue is replaced by large cysts.

RENAL STONE DISEASES

Renal stone disease is a frequent illness. In the West, it is estimated that approximately 12% of males and 5% of females will have an episode of renal colic during their lifetime. In countries with hot weather as in Egypt higher incidence is expected especially in the presence of other predisposing factors as bilharziasis.

Type of Stones:

Stones could be classified according to their radiologic and structural features into:

1. Radio opaque stones.
   - Calcium oxalate which represents 60% of renal calculi.
   - Calcium apatite or phosphates which represents 20% of renal calculi.
2. Radiolucent stones:
   - Uric acid stones (7%)
   - Magnesium ammonium phosphate (struvit or infection) stones (7%). These are caused by infection with urea-splitting organisms, particularly proteus and pseudomonas.
   - Cystine stones (3%)

Pathogenesis of renal stones:

Always there are several factors playing together for stone formation:

1. **Supersaturation of urine by salt** (e.g. calcium oxalate).
2. **Increased urinary acidity**.

3. **Loss of inhibitors of crystallization.**

Specific factors contributing in stone formation:

1. **Hypercalciuria**
2. **Hyperuricosuria**
3. **Hypocitraturia**
4. **Hyperoxaluria**
5. **Cystinuria**
6. **Xanthinuria**
7. **Inflammatory bowel diseases**

Clinical Manifestations of Renal Calculi:

Renal colic is the commonest presentation. Other manifestations include incidental discovery (during routine X-ray), or may present by complications (e.g. urinary tract obstruction, hematuria, or infection).

Investigations:

Not all investigations are indicated for every patient with renal stone. The more recurrent and aggressive the stone disease, the more the investigations needed.

The investigations include:

1. **Blood tests:**

Serum creatinine (for kidney function), HCO_3 (for diagnosis of metabolic acidosis and RTA), uric acid (for hyperuricaemia) and serum calcium (for hypercalcaemia). In cases of hypercalcaemia, Vitamin D and parathormone (PTH) levels should be determined.

2. **Renal ultrasonography and pyelography:**
   For detection of renal stones, back pressure changes, infection, kidney size, parenchymal echogenecity, kidney function (secretion of contrast media) and for diagnosis of medullary sponge kidney.

3. **Urine microscopy**
   For diagnosis of infection, haematuria. The presence of calcium oxalate or uric acid crystals is of doubtful value since it could be detected in normal subjects.

4. **Urine analysis** for pH, 24 hours calcium, uric acid and cystine excretion.

5. **Stone analysis** to identify its nature. It may help in the treatment of stone formers.

Medical Treatment:

1. High fluid intake to achieve a urine volume of at least 2 liters per 24 hours.

2. Dietary modification: Reduction of sodium, calcium, protein and oxalate:
   - Sodium restriction to 100 mmol/d since excess sodium intake results in excess excretion in urine which inevitably increases calcium urinary excretion.
   - Calcium should be restricted to 1 gm/d to decrease urinary calcium excretion.

- Protein restriction is adopted because high protein diet increases urine acidity, uric acid and calcium excretion; and decreases citrate excretion.
- Oxalate should be restricted to decrease urinary oxalate. Oxalate rich food as spinach, strawberry, rhubarb, tea, chocolate and Vitamin C.

3. Potassium citrate increases urinary citrate, decreases urinary calcium and increase urine pH.
4. Treatment of hypercalciuria: Thiazide diuretic will treat renal hypercalciuria (hydrochlorothiazide 50 mg twice daily). If this is proved ineffective, cellulose phosphate will treat the absorptive hypercalciuria.
5. Allopurinol: which may be given in a dose of 300 mg/d plus alkalinization of urine and restriction of dietary protein in patients with uric acid stones.
6. Cystine calculi could be treated by high fluid intake, alkalinization of urine to pH 7-7.5 and diet low in methionine and cystine. Penicillamine 1.5 g/d may decrease urinary cystine but with high side effects (allergic reactions affecting kidney, skin and bone marrow).

WATER AND ELECTROLYTE DISTURBANCES

Hyponatraemia

Definition:

Hyponatraemia is a state where plasma sodium concentration is less than 135 mmol/L.

Causes:

Hyponatraemia is the commonest electrolyte abnormality in hospitalized patients. Usually this is dilutional hyponatraemia due to defective renal water excretion as a result of excess secretion or potentiation of ADH. The complete list of causes of hyponatraemia classified according to changes in total body water include:

1. **Hypovolaemic Hyponatraemic states:**
   - Diuretic therapy.
   - Mineralocorticoid deficit (Addison's disease).
   - Salt-losing nephropathy (analgesic nephropathy, chronic tubulo- interstitial nephritis, incomplete urinary tract obstruction, after recovery from acute tubular necrosis and after release of urinary obstruction).
   - Gastrointestinal losses (diarrhea or vomiting).
   - Fluid loss in third space (peritonitis, ileus, burn or crush injury).

     In these conditions volume receptors are stimulated with secretion of ADH which will then stimulate water reabsorption from the distal nephron. This process will continue even with development of hyponatraemia and

hypoosmolality owing to the fact that volume receptors are more potent than the osmoreceptors.

2. **Hypervolaemic (oedematous) Hyponatraemic states:**
   - Liver cirrhosis
   - Congestive heart failure.
   - Nephrotic syndrome
   - Renal failure with water overload.

   In these conditions, although total body water is increased, the effective circulating blood volume is decreased as the excess fluid is extravascular and is interstitial. The decreased effective circulating volume results in excessive stimulation and secretion of ADH with more water retention.

3. **Euvolaemic (Normal volume) Hyponatraemic States:**
   - Hormonal (Myxoedema, glucocorticoid deficiency or exogenous ADH vasopressin).
   - Massive water load (psychogenic polydipsia, parenteral fluid or excessive water absorption during bladder irrigation at transurethral prostatectomy).
   - Syndrome of inappropriate secretion of ADH (SIADH)
   - Essential hyponatraemia: Occurs mostly with chronic illness, under nutrition or with T.B. There is a resetting of the osmostat (in the hypothalamus) for lower level of osmolality and consequently lower plasma sodium concentration.

Clinical Features of Hyponatraemia:

- Manifestations of hyponatraemia depend greatly on the rate of its development. A very slowly progressive hyponatraemia can be asymptomatic while acutely developing hyponatraemia could be very serious.
- With hyponatraemia, plasma will be hypotonic while cells (especially brain cells) will be hypertonic. To achieve osmotic equilibrium, water will move from plasma to cells with a consequent cell oedema (brain oedema).
- Plasma sodium concentrations above 120 mmol/L are usually well tolerated, while the majority of patients will have severe cerebral dysfunction once plasma sodium is below 110 mmol/L (lethargy, anorexia, nausea, vomiting, confusion, disorientation, convulsions, coma and even permanent brain damage).

Treatment of Hyponatraemia:

- In severe hyponatraemia, rapid correction with hypertonic saline is contraindicated as it may lead to fatal central pontine myelinolysis. It is wise to increase plasma sodium by only 5-10 mmol/Litre per 24 hours. This is achieved through the administration of loop-diuretic and normal saline and in severe cases, small amounts (100-200 ml) of hypertonic (double strength i.e. 300 mmol/L) saline may be infused.
- Correction of the underlying cause, in the overloaded patient water restriction can be combined with loop-diuretics as furosemide and sometimes salt supplements.
- In SIADH, lithium or demeclocycline may be given to induce a renal concentration defect.

Hypernatraemia

Hypernatraemia is considered when plasma sodium is more than 145 mmol/litre.

Causes:

Hypernatraemia is usually a consequence of water depletion and-to much lesser extent- is due to excess sodium intake. In normal situations water loss (renal or non-renal) or excess sodium intake will induce hyperosmolar state with stimulation of osmoreceptors which will lead to thirst (water intake) and secretion of ADH (water reabsorption from the distal nephron). Water gain will correct the hyperosmolar state and hypernatraemia will not persist. Hypernatraemia persists only when either water intake is not possible (unconscious, very young or very old patient unable to ask for water or absent water supply) or when there is a lesion affecting thirst center in the hypothalamus (tumour) or abnormal osmoreceptors (essential hypernatraemia).

A- Renal causes of water loss:

1. **Osmotic diuresis**
   - Enteral (through a nasogastric tube) or parenteral (intravenous hyperalimentation) feeding, usually hypertonic constituents are used.
   - Hyperglycaemia
2. **Nephrogenic diabetes insipidus (NDI)** which results in renal tubular concentration defect. This could be due to:
   a. Toxin e.g. drug (lithium, amphotericin, demeclocycline) or Bence-Jones protein.

b. Renal tubular disease as in post obstructive diuresis, recovering ATN, PCKD, chronic tubulointerstitial nephritis, medullary cystic disease and congenital NDI.

3. **Pituitary ADH deficiency (CDI)** which is due to either trauma, neoplasm, vincristine or idiopathic (50%).

B- Non-renal causes of water loss: gastrointestinal loss.

C- Sodium intake in excess of water.

Clinical features:

1- Manifestations of the etiologic cause.
2- Polyuria, polydipsia, nocturia and functional dilatation of the bladder and ureters, this is seen in patients with D.I.
3- Hypernatraemia occurs only if there is lesion in osmostat (hypothalamic lesion) or patients unable to drink, it manifests as muscle twitches, lethargy, weakness, seizures or even coma and death.

With hypernatraemia, there is a shrinkage of brain cells and a decrease in brain size which if severe it may lead to rupture of blood vessels with focal intracerebral or subarachnoid hemorrhage. If the patient survived, brain cells will adapt and regain size.

Treatment:

1- Acute hypernatraemia could be corrected quickly but chronic hypernatraemia must be corrected slowly to prevent cerebral oedema (decrease plasma sodium by about 2 mmol/litre/hour).

Usually the hypernatraemic patient is hypovolaemic, we can calculate the water deficit by the equation:

$$\text{Water deficit (litre)} = \frac{\text{Plasma Na}}{140} - 1\text{x (0.6 Xbody weight)}$$

For example, a patient of 60 kg with plasma sodium 160 mmol/L, his water deficit is 5.1 litre.

The water deficit could be given orally as water or intravenous as 5% dextrose in water. If there is Na^+ loss as well give D 5%/1/2 saline (glucose 5% in half tonic saline) is given.

Rarely the hypernatraemic patient is hypervolaemic, in this situation we have to give furosemide (lasix) and compensate urine loss with either oral water or D 5% I.V.

2- Treatment of the etiologic cause as DDAVP intranasally for CDI.

III. DISTURBANCES IN PLASMA POTASSIUM CONCENTRATION

Most of body K^+ is intracellular. The intracellular K^+ is about 150 mmol/litre, while plasma K^+ is only 3.5-5.5 mmol/litre. The capacity of the kidney to excrete K^+ load is large but relatively slow (> 30 min). The shift between intra- and extracellular compartments is quick and fast.

Hyperkalaemia

It is plasma K^+ concentration which is more than 5.5 mmol/litre.

Causes of hyperkalaemia:

These could be summarized as the following:

A- Increased Potassium Intake

- Dietary excess (Banana, citrus fruits...)
- Intravenous load with K^+ containing fluids
- Drugs containing K^+ e.g. potassium penicillin
- Salt substitutes containing KCL rather than NaCL

B- Shift of Intracellular K^+ to extracellular Compartment

- Acidosis
- Cell damage (cancer chemotherapy, crush injury, incompatible blood transfusion).
- Muscle disease
- Convulsions, myositis, periodic paralysis, suxamethonium anaesthesia.

C- Decreased excretion of K^+ by the kidneys

- Renal failure
- mineralocorticoid deficiency
- drug interference as ACEI, cyclosporine, NSAIDS, Tacrolimus and K^+ sparing diuretics.

D- Factitious:

Haemolysis of blood sample, severe leucocytosis or thrombocytosis.

As a result of the strong defence mechanisms against hyperkalaemia, usually more than one factor is present for hyperkalaemia to occur. In practice, usually there is impaired renal excretion combined with other factor as drug intake e.g. ACEI.

Normal K^+ homeostasis involves about 100 mmol/day oral intake and about 10 mmol/d faecal output and about 90 mmol/day being excreted by the kidney. Hyperkalaemia usually occurs only when renal failure is

severe (GFR < 10ml/min) or when a defect in tubular excretion is present, as in salt-depletion, mineralocorticoid deficiency, drug interference or renal tubular disease.

Hyporeninaemic hypoaldosteronism is a common cause of hyperkalaemia in diabetics. This is seen usually in elderly diabetic with mild renal impairment, hyperkalaemia is mild (K= 5.5-6.5), the condition is aggravated by hyperglycaemia and/or salt depletion.

Clinical features of hyperkalaemia:

These are due to the effect of hyperkalaemia on cell membrane excitability especially those of the heart and the neuromuscular junctions. The toxic effect of K^+ depends on the rate of development and severity of hyperkalaemia. In patients with chronic renal failure, since the development is usually very slow, there will be a cell membrane adaptation and toxicity to occur needs relatively very high level in comparison with that occurring with acute renal failure.

The manifestations include tingling, numbness, circumoral paraesthesia, muscle weakness with loss of tendon reflexes. The more serious, which can even be the first to appear, is the cardiac toxicity.

ECG tracing in hyperkalaemic patient may show:

- Tall T waves
- Prolongation of the PR interval
- Widening of the QRS complex
- Finally cardiac arrest in diastole

Treatment:

It includes the following:

A- Immediate correction (Emergency) of hyperkalaemia

- 50 ml of I.V. 50% glucose + 20 units soluble insulin every 30 min.
- B – adrenergic agonists (e.g. salbutamol)
- Correct acidosis with I.V. $NaHCO_3$ 8.4%(25 – 100ml)

} Shift K^+ into cells

- Caclium gluconate slow I.V. (5ml of 10% solution)

} Physiologic anatagonist of K+ on cardiac cell membrane

B- Increase renal excretion of K^+

Diuresis with saline and furosemide

C- Potassium exchange resin

- Sodium phase e.g. Resonium A, kayexalate
- Calcium phase e.g. sorbosterit
- 25-100 g orally or by enema.
- They will increase faecal K^+.

D- Dialysis:

Preferably K^+ low Dialysate haemodialysis for patients with renal failure.

The condition is considered medical emergency if ECG abnormalities are present.

Beside the above therapeutic approaches, we must not forget treating the etiologic cause, restrict K^+ containing food and drugs.

Hypokalaemia

It is a condition of plasma potassium which is less than 3.5 mmol/litre.

Causes:

Causes of hypokalaemia are numerous. The more common are due to renal or gastrointestinal loss. Less commonly it is due to deficient intake or redistribution between intra and extracellular compartments. The list of causes includes the following:

A- Renal K^+ loss

1- Causes associated with alkalosis

- Diuretic therapy (the commonest)
- Primary mineralocorticoid excess (Conn's Syndrome)
- Secondary aldosteronism (e.g. renal artery stenosis)
- Glucocorticoid excess (Cushing's syndrome)
- Bartter's syndrome

2- Causes associated with acidosis

- Diabetic ketoacidosis during recovery phase.
- RTA
- Ureterosigmoidostomy
- Acetazolamide therapy

3- Causes associated with polyuria

- Recovery phase of ATN or post-obstructive ARF
- Tubulotoxicity as cisplatin, amphotericin
- Diabetic hyperglycaemia

B- Gastrointestinal loss

1- Prolonged or severe diarrhoea
2- Laxative abuse
3- Prolonged vomiting
4- Ileus with massive intestinal dilatation.

C- Redistribution of K^+ into cells

1- Metabolic alkalosis
2- Periodic muscle paralysis
3- Beta-adrenergic agonists e.g. salbutamol
4- Insulin.

D- Inadequate K^+ intake

Intravenous fluid without K^+ in patient without oral intake.

Bartter's Syndrome is a rare disease characterized with hypokalaemic alkalosis, hyperreninaemic hyperaldosteronism, high urinary prostaglandin E and prostacyclin concentration and normal blood pressure. Kidney biopsy will show hypertrophied juxtaglomerular apparatus.

In the non renal causes of hypokalaemia when the kidney is intact, it can decrease urinary K^+ to <20 mmol/day:

Clinical features:

Usually appear when plasma K^+ is less than 2.5 mmol/L

1- Muscle weakness especially proximal muscles. Tendon reflexes are depressed. In severe cases, muscle necrosis may occur.
2- Gastrointestinal hypomotility up to paralytic ileus may occur with further K^+ loss into dilated intestinal loops.
3- In chronic hypokalaemia, renal tubular damage with chronic tubulointerstitial nephritis may occur.
4- With severe hypokalaemia fatal cardiac arrhythmia may cause death.

ECG will show the following:

- Depressed T waves and S-T segments
- Appearance of U waves
- Widening of the QRS
- Finally, ventricular ectopics and fibrillation may occur.

Treatment:

1- Treatment of the etiology
2- Potassium supplement either oral or parenteral according to the severity of hypokalaemia. As a rule, we have not to give KCL intravenous more than 10 mmol/hour.

IV. Disorders of Plasma Calcium Concentration

Generally, the kidney, the gastrointestinal tract and the skeleton play a key role in body calcium and phosphate homeostasis.

The contribution of the kidney in calcium and phosphate metabolism includes:

1- Synthesis of 1,25 dihydroxycholecalciferol

Inactive vitamin D (cholecalciferol) is activated in the liver by hydroxylation to 25, hydroxycholecalciferol, the second step of its activation is in the kidney to be 1, 25, dihydroxycholecalciferol. The active vitamin D promotes the gut calcium absorption and the normal calcification of bone.

2- Renal excretion of calcium

85-90% of the filtered Ca^{2+} is reabsorbed by the PCT while the rest is reabsorbed by the DCT, under the influence of PTH, only <2% of filtered calcium is excreted in the urine (equals about 5.5 mmol/day).

3- Renal excretion of phosphate

Urinary excretion of phosphate varies from 5-40 mmol/day. 80-95% of the filtered load is absorbed in PCT (as Ca^{2+}, glucose, aminoacids and low molecular weight proteins). Phosphate is the major buffer for H^{+} excretion.

Hypercalcaemia

Is a total plasma Ca^{2+} concentration more than 2.6 mmol/litre (10.5 mg/dl)

Causes of hypercalcaemia

1- Malignancy
   - Multiple myeloma.
   - Boney metastasis
   - Hormonal factors (PTH-like substance) secreted by tumour cells.
2- Hyperparathyroidism
3- Sarcoidosis
4- Bone disease
   - Paget's disease
   - Aluminium osteodystrophy
5- Calcium or vitamin D related
   - Vitamin D intoxication
   - Thiazide diuretics
   - Milk-alkali syndrome
   - Renal failure
6- Endocrine disease
   - Thyrotoxicosis
   - Addison's disease
7- Hyperproteinaemia
   (only non-ionised calcium is raised)

Clinical features

1- Manifestations of the etiologic cause
2- Renal manifestations
   - Polyuria and polydepsia resulting from urinary concentration defect
   - Stone disease and nephrocalcinosis
   - Acute renal failure may occur with severe hypercalcaemia and the associated dehydration owing to polyuria
   - Chronic renal failure due to stone disease, nephrocalcinosis and chronic tubulointerstitial nephritis.

3- Gastrointestinal manifestations

- Nausea and vomiting which are central effects of hypercalcaemia. These may aggravate dehydration induced by polyuria
- Peptic ulcer disease
- Pancreatitis

4- Nervous system

Nausea, vomiting, malaise, fatigue, and even psychosis are all central effects of hypercalcaemia.

5- Tissue deposition of calcium may lead to nephrocalcinosis, vascular calcification, pruritis, conjunctival calcification (red-eye) and band keratopathy.

Treatment:

A- Treatment of the etiologic cause

B- Treatment of hypercalcaemia

1- Saline diuresis in patients with reasonable kidney function. If there is no response we can inforce diuresis by furosemide and intravenous saline. Loop diuretics in contrary to thiazide diuretics increase urinary calcium excretion.

2- Glucocorticoids are effective in all conditions other than hyperparathyroidism. In sarcoidosis and Vit. D intoxication 10 mg prednisolone may be sufficient while in malignancy doses up to 60 mg/d may be required.

3- Others:

- Methramycin is particularly useful in malignancy related hypercalcaemia, a dose of 20-30 ug/kg may induce fall in serum Ca^{2+} within hours and last for few days.
- Calcitonin 50-100 units S.C.
- Phosphate oral or intravenous, but carries the risk of metastatic calcification.

- Diphosphonate will suppresses hypercalcaemia in hyperpara- thyroidism

4- Dialysis in renal failure especially on using low Ca^{2+} dialysate will be very effective in decreasing serum calcium.

Hypocalcaemia

It is plasma calcium concentration less than 2.20 mmol/litre (8.5 mg/dl).

Causes of hypocalcaemia

1- Renal failure
2- Hypoparathyroidism
(surgical, idiopathic, pseudohypoparathyroidism)
3- Vitamin D deficiency
4- Hypoalbuminaemia
5- Acute pancreatitis

In renal failure, hypocalcaemia is due to the lack of activation of vitamin D and to the hyperphosphataemia which will cause drop of serum calcium. The presence of acidosis will delay the manifestations of hypocalcaemia by increasing serum ionised calcium.

Vitamin D deficiency may be due to decreased intake, decreased exposure to sun light, defective gut absorption or lack of its activation. Hypovitaminosis D is characterized with hypocalcaemia, hypophosphataemia and hyperparathyroidism.

Clinical features of hypocalcaemia

1- Manifestations of the etiologic cause.

2- Neuromuscular; in acute hypocalcaemia it takes the form of tetany, tingling, numbness, parasthaesia, even convulsions. While in chronic hypocalcaemia the main features are depression, irritability, intracarnial calcification.
3- Bone disease as osteomalacia in vitamin D deficiency and renal failure and hyperparathyroid disease in hyperparathyroidism
4- Cataract may be seen with chronic hypocalcemia

Treatment:

1- Treatment of the cause
2- Calcium and vitamin D supplementation

DISORDERS OF ACID-BASE BALANCE

Plasma pH is normally 7.35-7.45 which represents a H^+ concentration of 36-44 mmol/litre. The normal plasma HCo_3^- concentration is 20 to 30 mmol/litre. The lowest urinary pH is 4.5 units (with severe metabolic acidosis in presence of normal kidneys) and the highest urinary pH is 10 units (with severe metabolic alkalosis).

Metabolic Acidosis

Metabolic acidosis can result from the generation or the ingestion of acid; or from the loss of bicarbonate ions with consequent accumulation of H^+ in the circulation.

This will be compensated for by the increase in ventilation with a consequent drop in the level of Co_2 and HCo_3^-.

The term acidaemia is sometimes used when compensatory mechanisms fail to maintain the pH level within the normal range. But in practice, the term acidosis is usually used whether the pH level is within the normal range or lower.

Features of metabolic acidosis:

- Low plasma HCo_3^- concentration (< 20 mmol/litre).
- Low arterial Co_2 concentration (< 40 mmol/litre).
- Low plasma pH (< 7.35).

Causes of metabolic acidosis:

First we have to know about the concept of *anion gap* which is the difference between plasma concentration of Na^+ and the sum of chloride and bicarbonate [Na^+ — (CL + HCo_3^-) = 6 — 16 mmol]. This gap represents substances which combine with Na^+ other than CL^- and HCo_3^- which are not measured in routine chemistry such as amino acids.

We may classify metabolic acidosis into those with high anion gap [Na^+ — (CL + HCo_3^-) > 16 mmol] and those with normal anion gap:

I- *Metabolic acidosis with high anion gap:*

The high anion gap is due to the addition of anionic toxic substances into the circulation which combine with Na^+ at the expense of chloride and HCo_3^-. Since these substances are not measured, the anion gap will be high.

Causes of metabolic acidosis with high anion gap are:

- Lactic acidosis; the anion toxic substance here is lactate
- Diabetic ketoacidosis with accumulation of acetoacetic acid; B-hydroxybuteric acid
- Intoxication with methyl alcohol; Ethylene glycol, paraldehyde and salicylates.
- Renal failure with accumulation of sulfates; phosphates and phenols.

II- *Metabolic acidosis with normal anion gap* (hyperchloraemic metabolic acidosis).

This could be due to renal, gastrointestinal or other defects.

A. Renal causes of metabolic acidosis with normal Anion gap:

1- Diamox, a diuretic which causes bicarbonate wastage (bicarbonaturia).
2- Renal tubular acidosis (RTA); resulting from either:
    a. Type I, classic (Distal) RTA: In this condition, there is inability to secrete H^+ load.
    b. Type II, proximal RTA: In this condition, the PCT is unable to reabsorb HCo_3^- as there is a set up of HCo_3^- Tm at low level e.g. HCo_3^- Tm of 16 mmol/l, so any HCo_3^- above this concentration will be lost in urine.
    c. Type III RTA: There is both inability to secrete H^+ load and proximal HCo_3^- wastage.
    d. Type IV RTA: There is hyperkalaemic hyperchloraemic metabolic acidosis with hyporeninaemic hypoaldosteronism. This is usually seen in diabetics with mild renal impairment.

B- Gastrointestinal causes of metabolic acidosis with normal anion gap:

1- Diarrhoea; There is loss of K^+ and HCo_3^-, every litre of diarrhoea fluid contains 30-50 mmol of HCo_3^-.
2- Fistula or tube drainage: Each litre of the small intestinal fluid contains 60 mmol HCo_3^- while pancreatic fluid contains 120 mmol/litre.
3- Ureterosigmoid or ileal loop urine diversion: In these conditions there is loss of mucosal HCo_3^- (normally present in high concentration in intestinal mucous) in exchange with the urinary CL^- (hyperchloraemia).

4- Anion exchange (CL^- versus HCo_3^-) as with the use of cholestyramine.
5- Ingestion of Ca and Mg chlorides.

Treatment of metabolic acidosis:

1- Treatment of the cause and compensate for the deficit
2- In distal RTA, $NaHCo_3$ should be provided 1-3 mmol/kg/d, sometimes K^+ supplementation is required. In children $NaHCo_3$ will be provided in a dose of 5-15 mmol/kg/d.
3- In proximal RTA large amounts of alkali are provided (10-25 mmol/kg/d) and K^+ supplementation.

Respiratory Acidosis

In respiratory acidosis, Co_2 retention occurs and the reaction ($Co_2 + H_2O \varnothing H_2Co_3 \times H^+ + HCo3^-$) results in accumulation of H^+ in circulation and acidosis. The kidney compensates by the secretion of H^+ and reabsorption of $HCo3^-$.

In acute respiratory acidosis blood Hco_3^- increases by 1 mmol/L for every 10 mmHg increase in PCo_2 while in chronic respiratory acidosis $HCo3^-$ increases by 3.5 mmol for very 10 mmHg increase in PCo_2.

Features of respiratory acidosis:

- high PCo_2
- low pH
- high HCo_3^-
- urine pH is low <5.4

Etiology:

- Severe respiratory disease e.g. obstructive air way disease and severe obesity.
- Central depression of respiratory drive.

Clinical features:

1- Manifestations of the cause.
2- Confusion, hyperreactivity, headache, tremor, stupor and coma in severe cases.
3- Papilloedema and increased CSF pressure due to V.D.
4- Pulmonary and splanchnic V.C.

Treatment:

1- Treatment of the etiologic cause
2- If there is respiratory failure, assisted respiration (ventilator) should be provided.

Metabolic Alkalosis

Because of the high capacity of the kidney to secrete HCo_3^-, metabolic alkalosis can only persist if there is a renal dysfunction with a reduction in HCo_3^- excretion or enhanced renal generation of HCo_3^-.

Features:

- High plasma HCo_3^- (> 30 mmol/litre)
- High plasma pH (pH > 7.45)
- High Pco_2, for every 1 mmol/litre increase in plasma HCo_3^- there will be a 0.6-0.7 increase in Pco_2. Hypoxaemia stands as a limiting factor for the respiratory compensation. So, if it exists, we have to give oxygen support.

- Chloride and K^+ are also usually low. K^+ is low as a result of the renal loss and the intracellular shift.

Causes:

A- Renal:

1- Adrenocorticoid and adrenocorticoid-like effect (HCo_3^- retention with K^+ and H^+ excretion).
   - Secondary aldosteronism (e.g. cirrhosis)
   - Primary aldosteronism
   - Cushing's syndrome
   - Bartter's syndrome
   - Liquorice ingestion

2- Volume depletion (Cl^- depletion and HCo_3^- reabsorption)
   - diuretics
   - diarrhea
   - cirrhosis

B- Gastrointestinal loss of acid:

- Vomiting
- Gastric aspiration

C- Ingestion of alkali:

- $NaHCo_3$
- Milk-alkali syndrome

Hyperaldosteronism stands as a common mediator in metabolic alkalosis as it lead to enhanced K^+ and H^+ excretion, with sodium and bicarbonate retention (hypokalaemic alkalosis). Diuretic therapy, secondary aldosteronism in cirrhotics and severe vomiting are the common causes of metabolic alkalosis.

Clinical features:

1- Manifestations of the cause
2- Manifestations of neuromuscular irritability owing to the decreased ionized calcium.

Treatment:

1- Of the cause
2- Support respiratory and renal compensatory mechanisms.
3- If there is renal failure with severe metabolic alkalosis, dialysis may be provided.

Respiratory Alkalosis

Excessive pulmonary wash of Co_2 will result in alkalosis owing to directing the reaction ($H_2O + Co_2$ ´ H_2CO_3 ´ H^+ HCo_3^-) to the left with consequent reduction in H^+.

The renal defence mechanism will include the increase in HCo_3^- secretion and retention of H^+. This mechanism is relatively slow. It needs 24 hours to be established.

For each 10 mmHg increase in PCo_2, there is a 2.5 mmol/L decrease in plasma HCo_3.

Features:

- ↓ PCo2
- ↑ pH
- ↓ HCo_3

Causes of respiratory Alkalosis:

1- Iatrogenic in patients under ventilatory support.
2- Liver cirrhosis, salicylate intoxication, exercise and hypotension.
3- Hyperventilation syndrome in neurotic patients
4- Cerebral hypoxia and intracranial disease

Clinical features:

1- Manifestations of the cause
2- Parasthesia, tinnitus, neuromuscular irritability and/or cerebral vasoconstriction

Treatment:

1- Of the cause
2- Breathing into a mask (rebreathing of expired air with its high level of Co_2).

HYPERTENSION AND THE KIDNEY

Most physicians, consider the blood pressure above 140/90 mmHg in patients under the age of 50 years as hypertension thus deserves treatment.

Etiology And Classification Of Hypertension:

Hypertension, according to severity and target organ damage (of retina, kidney, heart) could be classified into benign or malignant. Etiologically, hypertension may be classified as essential (primary) or secondary.

Secondary hypertension may be:

1- Renal:

a- Renovascular hypertension:

- Renal artery stenosis
- Polyarteritis nodosa
- Renal artery aneurysm
- Renal artery malformation

b- Renoparenchymal:

- Glomerulonephritis
- Polycystic kidney disease
- Analgesic nephropathy
- Renal tumour as Wilms' tumour
- Other renal parenchymal diseases

2- Endocrinal:

a. Adrenal cortex:

• Cushing's syndrome

• Conn's syndrome

b- Adrenal medulla and splanchnic sympathetic chain:

• Pheochromocytoma

c- Others:

• Acromegaly

• Hyperparathyroidism

3- Iatrogenic:

• Oral contraceptives

• Sympathomimetic amines
(nasal decongestants and bronchodilators)

• Corticosteroids

• Cyclosporine

• Nonsteroidal anti-inflammatory drugs (NSAIDs)

• Tricyclic antidepressants

• Liquorice

• Pregnancy-associated hypertension

• Acute intermittent porphyria

Secondary Hypertension

A- Renal Hypertension:

Renal hypertension is the commonest type of secondary hypertension. This may be due to diseases of the renal artery as renal artery

stenosis (renovascular hypertension) or disease of the renal parenchyma as glomerulonephritis (Renoparenchymal hypertension).

Pathogenesis:

Hypertension may develop owing to either:

- Excess secretion of renin with a consequent more angiotensin II activity.
- Vasopressor substances as Endothelin will be released by the diseased kidney. Endothelins are cyclic peptides released by arteriolar endothelium. They may have a vasoconstrictor action and strong platelet activation.
- Failure to secrete salt and water load because of the decreased nephron mass. This will lead to the expansion of the extracellular volume and hypertension.
- Failure to secrete vasodilator substances such as prostaglandins, platelet activating factor and kinins due to decreased nephron mass.

Treatment:

1- Treatment of renal disease as renal artery stenosis by balloon dilatation or bypass surgery and SLE by steroids and immunosuppressive drugs.

2- Control of hypertension in renal patients may be a part of the treatment of the renal disease as it is known that uncontrolled hypertension is one of the major factors causing progression of renal damage and scarring.

3- Any drug which controls hypertension will be valuable but it seems that, in the presence of significant proteinuria, ACEIs may be superior in the prevention of glomerular scarring. On the contrary, in the

presence of renal artery stenosis this group of drugs are contraindicated.

B- Conn's Syndrome-Primary hyperaldosteronism:

This is characterized with excess aldosterone which is due to excess secretion by adenoma or hyperplasia of the zona glomerulosa of the adrenal cortex. This will result in hypokalaemia and metabolic alkalosis. Plasma sodium will be high and bicarbonate will be above 30 mmol/L, also plasma renin will be low. Patients with Conn's syndrome usually present with muscle weakness and mild hypertension. In few cases with Conn's syndrome, the course of this disease will be marked with malignant hypertension and stroke.

Treatment depends mainly on surgical excision and in bilateral cases steroid replacement may be needed.

C- Pheochromocytoma:

This is a tumour of chromaffin cells occurring in all age stages. In children, the tumour is always highly malignant (neuroblastoma and medulloblastoma), while in adults the tumour is always benign. Yet, hypertension will have a sinister prognosis if untreated properly.

In 90% of cases the tumours is in adrenal medulla while in 10% the tumour is extra-adrenal affecting the sympathetic chain. It could be multiple and malignant. The extra-adrenal tumour could be abdominal or even thoracic.

Beside the clinical criteria of this tumour, serum and urinary catecholamine assay will confirm the diagnosis.

Localization of tumour site is mandatory for surgical excision. This is usually carried out by isotope scanning using the tracer meta-iodo benzaguanin (MIBG). The tumour is extremely sensitive to X-ray contrast media, on exposure it will secrete a huge amount of catecholamine with fatal outcome. So, in hypertensive patient if pheochromocytoma is expected, this should be excluded first; by catecholamine assay before the patient is subjected to the contrast media.

Treatment is by hypotensive drugs having A and B-adrenergic blocking properties as labetalol and carvedilol. They are the drugs of choice. The definitive treatment is surgical excision.

RENAL DISEASES IN HEPATIC PATIENTS

There are many renal disorders which are known to occur in cirrhotic patients. These are:

1- Hepatorenal syndrome
2- Cirrhotic glomerulopathy
3- Glomerulopathy induced by infection common in cirrhotic patients such as:
   - Malaria
   - Bilharziasis
   - HBV
   - HCV

4- Tubulointerstitial disorders that are due to:
   - Infection (brucellosis, mononucleosis, tuberculosis)
   - Systemic disease (sarcoidosis, Sjogren's syndrome, lymphoma)
   - Drugs (methicillin, ampicillin, penicillin, sulfonamides, rifampicin, acetaminophen, Allopurinol).

5- Drugs and toxins producing combined Hepatic and Renal damage.

A- Drugs causing hepatic injury and acute tubular necrosis:

- Hallogenated hydrocarbons as carbon tetrachloride, chloroform and chlorethylene
- Hallogenated anaesthetics as Halothane and Methoxyflurane
- Tetracycline
- Rifampicin
- Methotrexate
- Copper sulphate
- Sulfonamides
- Acetaminophen
- Arsenic

B- Hepatic injury and acute interstitial nephritis

- Sulfonamides
- Rifampicin
- Phenindione
- Allopurinol

Hepatorenal Syndrome (HRS)

Definitions :-

HRS is an unexplained, functional renal failure occurring in patients with advanced liver disease. The diagnosis of HRS is considered when there is no laboratory or anatomic evidence of other known cause of renal failure.

HRS occurs in patients with cirrhosis, acute hepatitis, fulminant hepatic failure and with hepatic malignancy.

Etiology :-

HRS usually develops in hospitalized patient, indicating that iatrogenic factors are playing important role in the pathogenesis of this disorder.

Abdominal paracentesis, vigorous diuretic therapy and bleeding-especially gastrointestinal-are known precipitating factors. Sometimes HRS is idiopathic.

Clinical features of HRS

The patient usually presents with manifestations of advanced liver disease and on development of HRS, there will be further progression of the bad general condition, disturbance of consciousness, mental concentration, increase in oedema, ascites and progressive oliguria and even anuria. Laboratory assessment will show a progressive increase in serum creatinine and blood urea.

Differential Diagnosis:

HRS should be differentiated from other causes of azotaemia in patient with advanced liver disease especially prerenal azotaemia and acute tubular necrosis. The following table presents the important differentiating points.

	Pre renal azotemia	Hepatorenal syndrome	Acute tubular Necrosis
Urinary sodium (mmol/L)	<10	<10	>20
Urine/plasma creatinine ratio	>30/1	>20/1	<20/1
Urine osmolarity (mosmol/l)	≥200 higher than plasma	≥200 higher than plasma	Relatively similar to plasma (isothenuric)
Urine sediment	Normal	Unremarkable	Casts, cellular debris

Treatment of Hepatorenal Syndrome

- Treatment of HRS is largely supportive.
- Prevention is more important. Toxic agents as NSAIDs, demeclocycline, aggressive diuresis or aggressive paracentesis have to be avoided.
- If azotaemia is discovered in hepatic patient, the precipitating factor as volume contraction, cardiac decompensation and urinary tract obstruction have to be discovered and promptly treated.
- If prerenal azotemia is possible we have to give a volume expander (colloid as albumin or crystalloid as saline) .
- Abdominal paracentesis with plasma volume expansion (e.g. by salt free albumin) may decrease the intra-abdominal pressure, decrease

inferior vena cava obstruction and may increase the cardiac output and the renal perfusion.

- Dialysis may be indicated in selected patients with HRS. Mainly those with potentially reversible acute liver disease and those awaiting orthotopic liver transplantation.

- Orthotopic liver transplantation is the definitive line of treatment in patients with end stage liver disease and HRS. The renal function is resumed immediately after transplantation.

PROTEINURIA

Proteinuria is a rare presenting complaint of patients. Yet, when severe enough, it may cause hypoalbuminaemia and oedema. As protein in urine decreases the surface tension, it causes frothy urine which may be observed by some patients (bile salts and detergents used in toilets do the same).

The urine is tested for proteinuria by dip stick test. Dipstick is a plastic strip, attached to it is a paper impregnated with chemical substance (tetrabromophenol) which is normally yellow in colour and changes according to amount of protein in urine (0, +, ++, +++). It can detect a protein down to a concentration of 300 mg/l. Proteinuria detected by dip stick test should be confirmed by collecting the 24 hours urine and testing for quantity of proteinuria using chemical methods.

Definitions:

- *Proteinuria* is a secretion of an abnormal amount of protein in urine. Normal protein excretion per 24 hours in adults is less than 200 mg.

Most of this protein is albumin and Tamm Horsfall protein with smaller amounts of immunoglobulins.

- *False positive proteinuria* by dip stick occurs mainly when urine is alkaline and very concentrated; or if the stick test is left in urine for long time.

  False negative proteinuria is observed when protein excretion is mainly Bence Jones proteinuria and when urine is very diluted.
- *Bence Jones protein* which is the light chain fraction of immunoglobulin appears in abnormal amounts in urine in cases of multiple myeloma, clots at temperature 45-55°C, above and below that range it dissolves in urine. Presence of Bence Jones proteinuria should be confirmed by immunoelectrophoresis.
- The causes of Bence Jone's proteinuria include: multiple myeloma, amyloidosis, adult Fanconi syndrome, benign monoclonal gammopathy and hyperparathyroidism.

Mechanism of proteinuria:

There are four known mechanisms for proteinuria. These are:

1. Abnormality in permeability of the glomerular basement membrane because of glomerular disease or abnormal glomerular hemodynamics.
2. Increased concentration of small molecular weight protein in blood (MW 60000- 70000) e.g. hemoglobin, myoglobin and immunoglobulin light chains. These will pass easily through the normal GBM
3. Tubular disease with inadequate reabsorption of normally filtered proteins of MW <60000 e.g. B2-microglobulin.
4. Secretion by renal tubular cells of Tamm-Horsfall protein (urinary glycoprotein).

Differential Diagnosis of Proteinuria:

I. Functional proteinuria:

There is no organic change in the kidney tissue: it is usually less than 1 gm/d and is reversible. Possibly, it is due to hemodynamic changes or to minor glomerular disease which are reversible.

a. Strenuous exercise
b. Fever
c. Orthostatic proteinuria
d. Miscellaneous
(Thyrotoxicosis, severe anaemia, CNS lesions)

II. Patients with proteinuria of 0.5-3.5 gm/d:

a. Acute interstitial nephritis.
b. Chronic interstitial nephritis such as bacterial (pyelonephritis), gouty nephropathy, analgesic nephropathy or nephrolithiasis.
c. Tubular proteinuria such as Fanconi syndrome, heavy metal intoxication (lead, cadmium), multiple myeloma, hypokalaemic nephropathy, polycystic kidney disease and medullary cystic kidney disease.

III. Patients with proteinuria of more than 3.5 gm/d:

Usually caused by glomerular disease.

a. **Primary glomerular disease:** refers to all types previously discussed under glomerulonephritis.
b. **Secondary glomerular disease** is Previously discussed under glomerulonephritis.

Investigations of a case of proteinuria:

1. **Characterization of proteinuria:** After diagnosis of proteinuria by dip stick test, it should be confirmed by quantitative estimation of 24 hours proteinuria. Further assessment may include electrophoresis or immunoelectrophoresis to determine the type of abnormal protein excreted.

2. **Urine analysis:** For pus cells (to diagnose U.T. infection), RBCs and casts (to diagnose glomerular disease), also urine volume (oliguria or polyuria), pH of urine, specific gravity and test for glycosuria; and aminoaciduria and B_2 microglobulin (may help in the diagnosis of tubular disease).

3. **Blood and serologic examination:**
   a. Kidney function tests: serum creatinine, creatinine clearance, electrolytes (Na, K, Ca, Po_4).
   b. Total protein, albumin, cholesterol to diagnose nephrotic syndrome.
   c. Serologic examination e.g. for anti-DNA and complement component C_3 and C_4 for diagnosis of lupus erythematosus.

4. **Radiologic assessment including:**
   a. Examination of the kidney for its size, state of parenchyma, the presence of stone, back pressure change or pyelonephritic changes. It is achieved through ultrasound examination, plain X-ray, and IVP (if the kidney function is normal).
   b. Investigations to discover malignancy which could be the etiologic cause of proteinuria e.g. skeletal survey for multiple myeloma, X-ray chest and bronchogram or CT scan for bronchogenic carcinoma.

5. **Renal biopsy** will give the final answer for the diagnosis of the kidney lesion causing proteinuria.

HAEMATURIA

Definitions

- Normally the number of RBC's in urine should not be more than 5 RBCs/high power field on microscopic examination of fresh centrifuged urine sample. So, haematuria is defined as a secretion of more than 5 RBCs/HPF in urine.
- Haematuria may be the only symptom or associated with other symptoms, according to the etiologic cause e.g. loin pain and fever with infection and renal colic with renal stones.
- Haematuria could be gross (causing red-coloured urine) or microscopic (urine appears normal. But RBCs are seen on microscopic examination).

  In gross hematuria, urine looks red if alkaline, but brown or coca-cola like if urine is acidic due to denaturation of the hemoglobin.
- Also, hematuria could be glomerular (because of glomerular disease, sometimes called medical); or non glomerular (sometimes called surgical). Glomerular could be differentiated from non glomerular haematuria by:
  1. The shape of RBCs in urine is dysmorphic in cases with glomerular haematuria while it will be normal in case of non glomerular haematuria.
  2. The size of RBCs whose mean corpuscular volume in urine of patient with glomerular haematuria which is smaller than it is in peripheral blood. But in non glomerular cases it is equal.

3. Proteinuria is present in most cases of glomerular hematuria but not in cases of non glomerular hematuria.
4. Casts such as proteinuria.
5. Blood clots indicate non-glomerular bleeding and can be associated with pain & colic.

Differential Diagnosis of Hematuria:

A. First, hematuria should be differentiated from other causes of red or brownish urine:

- Microscopy will show RBC's only with hematuria.
- Dipsticks (Hemastix) will be positive with hemoglobinuria (hemolysis) and myoglobinuria (muscle damage) but negative with other causes e.g. porphyrins (in porphyria), bile (in jaundice), melanin (in melanoma), alkaptonuria, food dyes and drugs as PAS or phenylphthalein.

B. Hematuria may be of renal, ureteral, bladder or urethral origin.

I. Haematuria of renal origin:

a. **Glomerular haematuria:** Either primary glomerular disease (e.g. IgA nephropathy, mesangial proliferative glomerulonephritis or crescentic glomerulonephritis); or secondary glomerulonephritis i.e. renal involvement is a part of systemic disease (e.g. post-streptococcal glomerulonephritis, Henoch-Schönlein purpura, SLE, polyarteritis nodosa).

b. **Renal infection:** Pyelonephritis (especially with papillary necrosis) or renal tuberculosis.

c. **Renal neoplastic disease:** Renal cell carcinoma, transitional cell carcinoma of the renal pelvis and others.

d. **Hereditary renal disease:** Medullary sponge kidney or polycystic kidney disease.

e. **Coagulation defect:** Use of anticoagulant, liver disease and thrombocytopaenia.
f. **Renal vascular disease:** Renal infarction, renal vein thrombosis or malignant hypertension.
g. **Exertional haematuria.**

II. Hematuria of ureteral origin:

a. Malignancy.
b. Nephrolithiasis
c. Ureteral inflammatory condition secondary to nearby inflammation e.g. diverticulitis, appendicitis or salpingitis.
d. Ureteral trauma e.g. during ureteroscopy.

III. Hematuria of bladder origin:

a. Infection: schistosoma, viral or bacterial cystitis.
b. Neoplasms.
c. Foreign body in the bladder e.g. stones.
d. Trauma: During instrumentation or accidental.
e. Drug: e.g. cyclophosphamide induced haemorrhagic cystitis.

IV. Hematuria of urethral or associated structures:

a. Prostate: acute prostatitis, benign prostatic hypertrophy.
b. Urethritis, foreign body or local trauma to the urethra.

Investigations of a case of hematuria:

1. First exclude haemoglobinuria and myoglobinuria since both of them can also cause positive dipstick test for haematuria. This is done by microscopic examination of fresh urine sample. In case of haematuria, RBCs could be seen while in the other two conditions no RBC's could be seen.

   In case of myoglobinuria, clinical examination may show manifestations of muscle disease and the examination of urine by immunoelectrophoresis may show myoglobin. In case of haemoglobinuria, manifestations of haemolysis may be evident.
2. Examination of urine for proteinuria and casts (to diagnose glomerular disease), pus cells and urine culture (for diagnosis of infection), Zeil-Nelson stain and specific media (for diagnosis of T.B.).
3. Plain X-ray, I.V.P. (if serum creatinine is normal), ultrasound and possibly angiography, for the diagnosis of surgical diseases e.g. stone, malignancy or infection.
4. RBCs in urine could be examined for its shape to differentiate glomerular from non glomerular causes (by phase contrast microscopy).
5. Kidney function tests.
6. Specific investigations for diagnosis of systemic diseases causing haematuria e.g. SLE.
7. Kidney biopsy for glomerular haematuria.

VALUE OF URINE EXAMINATION IN MEDICAL DIAGNOSIS

Normal Urine Characters:

1. Volume is 600-2500 ml/24 h (average is 1200 ml/24 h).
2. Colour is umber yellow.
3. Specific gravity is 1003-1030 (represents amount of solids in urine).
4. pH is 4.6-8.8 (average 6.0)
5. Protein: The amount as detected by semiqualitative methods is 0.0-0.1 gm/24 hr urine.
6. Cells and casts:
   - R.B.C.s and W.B.C.s. < 5 by H.P.F.
   - Hyaline casts occasionally present (protein collected in the renal tubules taking a cylinderical shape producing occasional hyaline casts).
7. Glucose: should be negative.
8. Some other substances may be present e.g.:
   - Calcium < 150 mg/24 hr.
   - Phosphate : 1mg/24 h.
   - Amylase: 260-950 mg/24h.
   - Creatinine: 1.6 gm/24 h (15-25 mg/kg/24h).
   - Porphyrin: 50-300 mg/24h.
   - Ketones: qualitative amounts.

How to examine urine:

We have to comment on the following items:

- Volume/24 h
- Specific gravity (osmolality)

- Colour of urine
- Dip stick examination of urine
- Microscopic examination.

1. **Volume of urine:**

Changes in urine volume may be oliguria or polyuria:

Polyuria:

(Urine volume > 2500 ml/day) may occur with:

- Diuretics
- Excessive water intake (within the normal range).
- Compulsive water drinking in psychological cases (psychogenic polydepsia).
- Uncontrolled D.M.
- Diabetes insipidus which may be central or nephrogenic.
  - In central D.I. there is a decreased A.D.H. secretion.
  - In nephrogenic D.I. the renal response to A.D.H. is defective as in analgesic nephropathy and medullary cystic kidney disease.
- Early stage of chronic renal failure.
- Diuretic phase of acute renal failure.

(for more details see chapter on hypernatraemia)

Oliguria:

(Urine volume < 600 ml/day), may occur with:

i. **Obstructive causes:**

Mainly produce anuria i.e. no urine at all, should be differentiated from urine retention by detecting urine in the bladder (suprapubic dullness, by U.S., or by urethral catheter).

- Removal of solitary functioning kidney.

- Bilateral ureteric obstruction (or unilateral ureteric obstruction of a solitary functioning kidney).
- Retro-peritoneal fibrosis blocking ureteric flow.

ii. **Nonobstructive causes:**

Mainly produce oliguria:

- Inadequate renal perfusion e.g. with vomiting, or diarrhea will cause depletion of body salts and fluids.
- Intravascular volume depletion e.g. with internal haemorrhage or rapidly developing ascites.

iii. **Oliguria with intrinsic renal disease:**

- Oliguric phase of acute tubular necrosis.
- Rapidly progressive glomerulonephritis.
- Bilateral cortical necrosis.
- End stage renal failure.
- Acute nephritic syndrome.
- Nephrotic syndrome.

2. **Specific gravity:**

Specific gravity represents the amount of solids in urine:

- Specific gravity is measured by urinometer or by another special complicated apparatus which is more perfect (osmometer).
- Specific gravity is one of the kidney function tests. In D.I. repeated measurement of urine specific gravity in face of water deprivation and after vasopressin administration is mandatory for proper diagnosis.

3. **Colour:**

- Normal: umber yellow
- Examples of colour changes of urine:
  - Red urine: with hematuria, myoglobinuria and haemoglobulinuria
    (with haemoglobinuria the colour is red brown).
  - Pink: with rifampicin.
  - Orange: concentrated normal urine, urobilin, bilirubin,
  - Deep yellow: Mepacrine.
  - Milky: Chyluria.
  - Smoky: acute glomerulonephritis.

4. **Dip stick examination of urine:**

- Dip stick is a plastic strip with squares of paper impregnated with enzymes which change in colour on exposure to target chemicals.
- Dip stick is used for detection of protein, ketones, glucose, pH, haemoglobin, bile, bacteria, pus cells and leucocytes....

i. **Proteinuria:**

- Normal protein in urine (by quantitative assessment) is <0.1 gm/d by dip stick. It is mainly albumin and Tamm Horsfall protein which is synthesized by renal tubules.
- Abnormal proteinuria may contain albumin, globulin, Bence Jones protein and low molecular weight protein (e.g. B-microglobulin).
- Proteinuria may be of:
  - Glomerular origin e.g post infectious G.N., drug induced G.N., collagen disease and idiopathic G.N.
  - Tubular origin (usually low molecular weight proteins) e.g. heavy metals intoxication, analgesic nephropathy.
- For more details see chapter on proteinuria (page 122)

ii. **pH:**

- Normal urine is acidic, average 6.
- Highly acidic in uric acid stones.
- Alkaline in stones caused by infection and in renal tubular acidosis.
- pH is important in:
  - The treatment of stones, it is advised to give alkalies e.g. Na HCo_3 in acidic stones, or acids e.g. vitamin C in alkaline stones.
  - Drug intoxication, it is advised to give alkalies in acidic drug intoxication as salicylates and acids in alkaline drug intoxication as pethidine.
  - Increase potency of some antibiotics in urinary tract infection, alkalies with aminoglycosides and acids with tetracyclines are given.

iii. **Haemoglobinuria:**

- Haemoglobin may be present in urine in haemoglubinuria or haematuria (differentiated by presence of R.B.C.s in case of haematuria).
- RBCs may rupture in cases of hypotonic urine but RBCs ghosts could still be seen.
- Ascorbic acid may produce false test for haemoglobinuria.

Causes of Haemoglobinuria:

- Intravascular haemolysis e.g. in severe exercises or severe burns.
- Chemicals e.g. naphthalene and hydroquinone derivatives.
- Mismatched blood transfusion.
- Black water fever.
- Paroxysmal cold Haemoglobulinuria.
- Paroxysmal nocturnal Haemoglobulinuria.
- Snake bites.
- Vegetable toxins e.g. mushroom poisoning.
- False Haemoglobinuria.
- Trans-urethral prostatectomy with post operative washing with water, which when absorped cause hypotenicity of blood with consequent haemolysis.

iv. **Bacteruria:**

- To collect a urine sample one of the following methods should be used:
  - Cleaning of the area around the urethra and a midstream urine is collected.
  - Urine specimen may be obtained by a urethral catheter (especially in females).
  - Supra-pubic puncture in children.
- Detection of bacteruria is by colony count which is significant if >100,000/ml (indicate infection). False low count may occur with high urine flow, antibiotic treatment or contaminated container.

- Direct microscopic examination of urine (stained or unstained) has the reliability of about 85-90% of colony count.
- Microscopic detection of pus cells in urine is less sensitive and produces more negative results.
- **Bacteruria may occur in:**
  - 10% of pregnant ladies.
  - 15% of diabetic patients.
  - 20% of patients with prostatic enlargement.
  - 95% of patients with catheter for more than 2 days without prophylactic antibiotics.

v. **Glycosuria:**

May occur in:

- Hyperglycaemia which may be endocrinal (e.g. in D.M.) or non endocrinal (as liver disease) or due to administration of hormones (e.g. corticosteroids, A.C.T.H., thyroid and adrenaline drugs).
- In renal tubular defects e.g. renal diabetes, heavy metal poisoning or Fanconi syndrome.

N.B.

In renal glycosuria, hypoglycaemic attacks may occur. At the same time someone may wrongly give hypoglycaemic drugs which are dangerous in such cases so caution should be taken on diet and treatment of glycosuria.

Concomitant hyperglycaemia should be detected before giving hypoglycaemic drugs.

5. **Microscopic examination of urine:**

- For cells (type and count).
- For casts (type and count). Casts may be:
  - Fine granular casts (in chronic renal disease).
  - Hyaline casts (in chronic renal disease).
  - RBCs casts (acute nephritic syndrome).
  - WBCs casts (in U.T.I.).
  - Fat casts (in nephrotic syndrome).

6. **Crystals (Fig.2.1):**

- Crystals mainly appear in alkaline urine e.g. urate, phosphate (Treatment depends on the acidification of urine by vitamin C then follow up of pH by dip sticks).
- Crystals in acidic urine e.g. oxalate or uric acid.

7. **Chemicals:**

Determination of 24 hours urine of some chemical substances e.g.

- Calcium:
  Increases in hyper-parathyroidism, Vitamin D intoxication.
  Decreases in hypo-parathyroidism, rickets.
- Porphyrin: Increases in lead poisoning, liver cirrhosis or infective hepatitis.
- Urinary L.D.H. (lactic dehydrogenase): increases in carcinoma of the kidney, prostate and bladder, glomerular disease or myocardial infarction.
- Urine catecholamine : Increase in pheochromocytoma (also increases level of V.M.A.) and neuroblastoma.

ENVIRONMENTALLY-INDUCED KIDNEY DISEASES

The extent of the contribution of environment in causing renal disease is unknown. This is largely due to the following: 1- The fact that multiple environmental factors could be working together, 2- Difficulty in confirming and quantifying the exposure to a certain environmental toxin; and 3- The lack of specific clinical or pathologic presentation of different environmental toxin.

In the USA, 19% of patients with end stage renal failure have disease of unknown cause and in 30 per cent of those presenting with glomerulonephritis the aetiology is unrecognized, possibly environmental toxins are responsible at least in part for these cases.

The kidney is more prone to environmental toxins for the following reasons:

1- The kidney is the principal organ for excretion of different toxins;
2- High renal blood flow;
3- Extensive surface of endothelial contact with toxins;
4- Positive intraglomerular hydrostatic pressure;
5- The medullary counter-current multiplier system leading to more accumulation of toxic agents and their metabolites in the renal medulla.

The environmentally-induced renal injury may be tubulo-interstitial, glomerular or combined. Tubulo-interstitial lesions may be in the form of acute tubular necrosis (such as exposure to high concentration of mercury) or chronic tubulointerstitial nephritis (such as chronic exposure to low doses of lead). Glomerular lesions may be due to direct toxicity (such as deposition of gold in basement membrane and silica in

the mesangium) or immunologically-induced (for example immune complex disease in chronic exposure to hydrocarbons).

Environmental chemicals with nephrotoxicity includes solvents, hydrocarbons, heavy metals and fungal toxins. Other environmental nephrotoxins include physical agents (e.g. radiation injury) and biological (e.g. parasite as bilharziasis and malaria).

Volatile Hydrocarbons (Organic Solvents) As Environmental Nephrotoxins

Types of exposure include:

- Ingestion or inhalation of carbon tetrachloride;
- Intentional sniffing of cleaning fluid (toluene-containing glues, trichlorethylene, 1,1,1,-trichloroethane);
- Suicide attempts by ingestion of tetralin;
- Occupational exposure (inhalation of trichloroethylene, diesel fuel and toluene, paints, glue, degreasing solvents);
- Washing hands and hair with diesel fuel;
- Domestic solvent inhalation.

Kidney lesions induced by organic solvents include:

- Acute tubular necrosis owing to exposure to high doses of organic solvent;
- Chronic tubulo-interstitial nephritis as a consequence of acute exposure;
- Glomerulonephritis owing to chronic exposure with possibly genetic predisposition, which may result in either anti-GBM glomerulonephritis, membranous glomerulonephritis or proliferative glomerulonephritis.

- Clinically, renal lesions may present as acute renal failure, chronic renal failure or nephrotic syndrome; and neoplasia especially renal cell carcinoma.

Heavy Metals As Environmental Nephrotoxins

These include lead, cadmium, mercury, uranium and arsenic. Moreover, therapeutic forms of gold, bismuth and platinum can cause nephrotoxicity. Silicon, beryllium, lithium, barium and selenium are not heavy metals (specific gravity <5) but may cause nephrotoxicity.

Lead nephrotoxicity:

Prior to the industrial revolution the normal total body burden of lead was 2mg. In a typical modern industrialized society, it is now about 200 mg. About 10-15 per cent of ingested and 40 per cent of inhaled lead is absorbed.

Exposure:

a) Occupational: metal smelting workers, miners, storage battery workers, pottery makers, automanufacturers, ship builders, paint manufacturers and painting industry.
b) Household: lead-glazed pottery, moonshine whisky, lead added to aphrodisiacs, herbal and folk medicines.
c) Others: retained bullet, leaded gasoline.

Acute lead nephropathy:

This may manifest as acute renal failure with Fanconi syndrome and systemic disease including abdominal colic, anorexia, vomiting, constipation, anaemia, peripheral neuropathy and encephalopathy.

Lead containing inclusion bodies will be detected in renal tubular cells, urine, liver, neural tissue and osteoblasts.

Good responses can be achieved by chelation therapy (EDTA, BAL and Penicillamine).

Chronic lead nephropathy:

Histologically, it will appear as a slowly progressive tubulointerstitial nephritis. Clinically, this manifests as chronic renal failure, hypertension, hyperuricaemia and gout. These manifestations are associated with others, including gastrointestinal, haematologic and neurologic. The diagnosis is confirmed with the detection of an abnormal body lead level >80 ug/L and positive EDTA lead chelation test. In the hypertensive gouty patient with chronic renal failure and without stone disease, chelation test may detect an unrecognized lead exposure.

Chronic lead nephropathy, especially if diagnosed and treated early could be arrested or its progression is retarded.

Ca Na_2 EDTA is given in combination with BAL for symptomatic cases.

Cadmium nephropathy:

Source of exposure: Cadmium is a component of metal alloys, in the manufacture of electrical conductors, electroplating storage batteries, aircraft industries, as a by-product of iron smelting, as a pigment, in ceramics, glass, in plastic stabilizer, in photographic developer, rubber or dental prosthetics. Also, the burning of coal, oil and cigarettes.

Cadmium toxicity: The acute absorption of as little as 10 mg of dust or fumes will cause severe gastrointestinal symptoms; and 12 hours later, pulmonary oedema. Chronic low dose exposure will cause emphysema, anosmia and renal disease. Early renal manifestations are those of adult Fanconi syndrome, tubular proteinuria and renal tubular acidosis. Urinary calculi are detected in 40 per cent of cases. In late phases chronic renal failure appears.

Treatment: Ca Na_2 EDTA is of little value after cadmium has fixed in tissues. Vitamin D and calcium may be of help for bone disease, but may aggravate renal disease (by more stone formation).

Mercury nephrotoxicity:

Mercury toxicity depends on its chemical form and route of administration. Elemental mercury is harmless when ingested but when its vapour is inhaled will be very toxic. Environmentally, mercury is either organic or inorganic salt. Toxicity is usually caused by methyl, ethyl, or phenoxyethyl organic salts and the chloride salt.

Acute mercury nephrotoxicity will manifest as acute renal failure due to acute tubular necrosis associated with erosive gastritis, haematemesis and melena.

Chronic mercury nephrotoxicity will manifest as tubulo-interstitial nephritis or nephrotic syndrome (due to membranous nephropathy or nil-change disease or less commonly anti-GBM disease) which is associated with neurologic deficits.

Treatment: Acute toxicity is treated with BAL and chronic toxicity by removal from the source of exposure.

Arsenic nephrotoxicity:

Elemental arsenic is not toxic, but the pentavalent, trivalent salts and arsine gas (Arsine) are very toxic.

Exposure:

- Industry: glass, pigment, bronze plating or metal alloys.
- Wood preservation, veterinary medicine, herbicides, insecticides and rodenticides.
- Certain herbal preparations, burning of arsenic-treated wood or arsenic containing prescription medicines.
- Arsine can be released from sewage plants.

Clinical manifestations of arsenic nephrotoxicity:

a) Acute exposure (for example arsine gas): Acute renal failure (ATN), haemolytic anemia, cardiomyopathy, encephalopathy, epigastric pain, vomiting and explosive diarrhoea. This is usually fatal and those who recover develop chronic renal failure.

b) Chronic exposure: slowly progressive renal failure, encephalopathy, polyneuropathy, cardiomyopathy, anemia, liver cirrhosis, abdominal cramps, diarrhoea and vomiting and hyperpigmentation.

Diagnosis and treatment:

Arsenic may be detected in urine, blood, hair and nail. Treatment is with BAL, exchange transfusion or haemodialysis which should be performed within 24 hours of exposure.

Radiation injury

It may be defined as any somatic or genetic disruption of function or form caused by electromagnetic waves or accelerated particles. These could be ultraviolet radiation, microwave radiation, high intensity ultrasound and ionized radiation from natural or man made sources.

Exposure:

a) Medical: Staff or the public may be affected by a malfunction or during repair of machinery in radiotherapy departments. Patients subjected to radiotherapy may be affected and can be a source of irradiation to others.
b) Industrial and military: atomic weapon testing, catastrophes (such as Chernobyl reactor), industrial and laboratory exposure. This could be through ingestion or inhalation of long-lived isotopes (such as radium and plutonium).

Radiobiology of kidney tissue:

After exposure to a dose of radiation of 10 Gray (GY) or more, the renal tubular cells are reduced in number, exhibiting flattening in the tubule lining. Whole nephrons are lost over 4-18 months after exposure.

Radiation Nephrotoxicity:

a) Immediate: decreased renal blood flow and glomerular filtration rate.
b) Early: acute nephritis
c) Late: chronic nephritis, obstructive uropathy, urinary fistula and fluid and electrolyte depletion.

Infective (biological) environmental risk factors

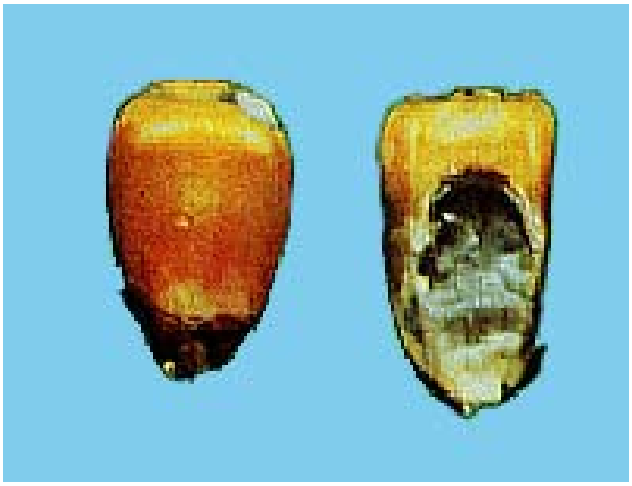
a) Parasitic: for example malaria, schistosoma and hydatid disease.
b) Bacterial: for example tuberculosis.
c) Viral: for example viral hepatitis and HIV.
d) Fungal toxins: especially ochratoxin and aflatoxin.

Ochratoxins arise from fungus Aspergillus ochraceus, discovered in the mid 1960s during a search for new toxic substances from moulds. It was discovered to be a natural contaminant of maize **(Fig. 11.1)**, and to be the cause of porcine nephropathy in Scandinavia by 1978. It is established as grain contaminant and a cause of porcine nephropathy in Europe and USA.

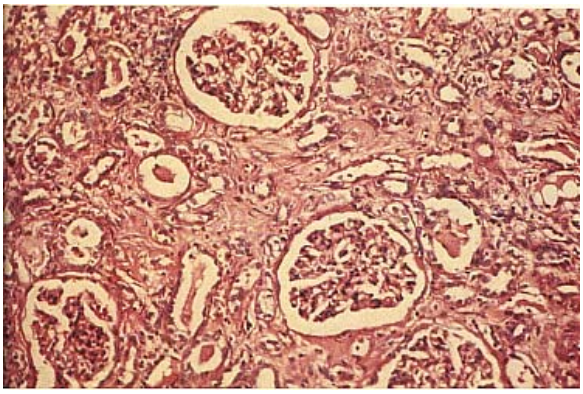
Ochratoxin nephrotoxicity

- Ochratoxins induce nephropathy and kidney tumours in rodents, dogs, pigs and birds.
- It induces endemic porcine nephropathy in central and northern European countries.
- It most probably has a major role in the aetiology of Balkan endemic nephropathy which is characterised by chronic tubulo-interstitial disease **(Fig. 11.2)** progressing to end stage renal failure and urethral tumours, a picture similar to porcine nephropathy.

- Recently it has been reported to be responsible for nephropathy in Tunisia and possibly in Egypt.



(Fig.11.1)
Normal and fungus-invaded Kernels of maize. The later, as other fungus-contaminated grains, could produce nephropathy in animals and human.



(Fig. 11.2)
Kidney section of case with chronic tubulointerstitial nephritis, most probably produced by ochratoxicosis