Chronic renal failure is a slowly worsening loss of the ability of the kidneys to remove wastes, concentrate urine, and conserve electrolytes.
Stages

- All individuals with a GFR <60 mL/min/1.73 m² for 3 months are classified as having chronic kidney disease, irrespective of the presence or absence of kidney damage.

- The rationale for including these individuals is that reduction in kidney function to this level or lower represents loss of half or more of the adult level of normal kidney function, which may be associated with a number of complications.
Stages

• All individuals with kidney damage are classified as having chronic kidney disease, irrespective of the level of GFR.
• The rationale for including individuals with GFR 60 mL/min/1.73 m² is that GFR may be sustained at normal or increased levels despite substantial kidney damage and that patients with kidney damage are at increased risk of the two major outcomes of chronic kidney disease: loss of kidney function and development of cardiovascular disease.
Stages

- The loss of protein in the urine is regarded as an independent marker for worsening of renal function & cardiovascular disease.
- Hence, British guidelines append the letter "P" to the stage of chronic kidney disease if there is significant protein loss.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1 CKD</strong></td>
<td>Slightly diminished function; Kidney damage with normal or relatively high GFR (&gt;90 mL/min/1.73 m²). Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.</td>
</tr>
<tr>
<td><strong>Stage 2 CKD</strong></td>
<td>Mild reduction in GFR (60-89 mL/min/1.73 m²) with kidney damage. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.</td>
</tr>
<tr>
<td><strong>Stage 3 CKD</strong></td>
<td>Moderate reduction in GFR (30-59 mL/min/1.73 m²). British guidelines distinguish between stage 3A (GFR 45-59) and stage 3B (GFR 30-44) for purposes of screening and referral.</td>
</tr>
<tr>
<td><strong>Stage 4 CKD</strong></td>
<td>Severe reduction in GFR (15-29 mL/min/1.73 m²) Preparation for renal replacement therapy</td>
</tr>
<tr>
<td><strong>Stage 5 CKD</strong></td>
<td>Established kidney failure (GFR &lt;15 mL/min/1.73 m², or permanent renal replacement therapy (RRT))</td>
</tr>
</tbody>
</table>
Clinical course

- Stage I:
  - *Decreased renal reserve*: Cr, BUN normal, patient asymptomatic detected only by severe demands on the kidney.

- Stage II:
  - *Renal insufficiency*: 75% of nephrons of functioning tissue is destroyed, GFR is 25% normal, BUN, Cr begins to increase depending on protein intake, mild azotemia, nocturia, polyuria
Clinical course

- Stage III:
- *ESRD or Uremia*: 90% of nephrons of functioning tissue is destroyed, GFR is 10% normal, BUN, Cr increase sharply depending on protein intake, patient has sever symptoms (uremic syndrome), oliguria.
<table>
<thead>
<tr>
<th>System</th>
<th>Effect</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body fluids</td>
<td>Polyuria</td>
<td>Inability to concentrate urine</td>
</tr>
<tr>
<td></td>
<td>Metabolic acidosis</td>
<td>Reduced H⁺ excretion</td>
</tr>
<tr>
<td></td>
<td>Abnormal levels of Na⁺, K⁺, Ca²⁺, PO₄⁻</td>
<td>Loss of tubular function</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia, excess bleeding</td>
<td>Impaired erythropoietin</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypertension, edema</td>
<td>Activation of renin–angiotensin system</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Anorexia, nausea</td>
<td>Accumulation of metabolic wastes</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Uremic encephalopathy</td>
<td>Accumulation of ammonia and nitrogenous waste</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Muscle and bone weakness (“Renal Osteodystrophy”)</td>
<td>Loss of calcium and minerals</td>
</tr>
</tbody>
</table>
Initially it is without specific symptoms and can only be detected as an increase in serum creatinine or protein in the urine. As the kidney function decreases:

- Blood pressure is increased due to fluid overload & production of vasoactive hormones, increasing one's risk of developing hypertension and/or suffering from congestive heart failure

- Urea accumulates, leading to azotemia & ultimately uremia (symptoms ranging from lethargy to pericarditis and encephalopathy). Urea is excreted by sweating & crystallizes on skin ("uremic frost").
General S & s

• Potassium accumulates in the blood (known as hyperkalemia with a range of symptoms including malaise and potentially fatal cardiac arrhythmias)
• Erythropoietin synthesis is decreased (potentially leading to anemia, which causes fatigue)
• Fluid volume overload - symptoms may range from mild edema to life-threatening pulmonary edema
• Hyperphosphatemia - due to reduced phosphate excretion, associated with hypocalcemia (due to vitamin D3 deficiency). The major sign of hypocalcemia being tetany.
Later this progresses to tertiary hyperparathyroidism, with hypercalcaemia, renal osteodystrophy & vascular calcification that further impairs cardiac function.

- Metabolic acidosis, due to accumulation of sulfates, phosphates, uric acid etc. This may cause altered enzyme activity by excess acid acting on enzymes and also increased excitability of cardiac and neuronal membranes by the promotion of hyperkalemia due to excess acid (acidemia)
People with chronic kidney disease suffer from accelerated atherosclerosis & are more likely to develop CVD than the general population.

Patients afflicted with chronic kidney disease and cardiovascular disease tend to have significantly worse prognoses than those suffering only from the latter.
### General pathophysiology

- **Traditional point**: all the nephron units are diseased to varying degree and specific parts of the nephron concerned with particular functions may be destroyed.

- **Bricker hypothesis (intact nephron hypothesis)**: Nephrons when diseased are totally destroyed and the remaining intact nephrons behave normally.
Bricker hypothesis

- As CRD advance the amount of solute that must be excreted does not change although there is reduction in number of functioning nephrons.
- The remaining nephrons hypertrophy in attempt to increase filtration rate, solute load, tubular reabsorption.
- The increased single nephron GFR (SNGFR) occurs by dilation of the afferent arterioles resulting in enhanced single nephron plasma flow.
General pathophysiology

- When about 75% of nephron mass is destroyed, the FR and solute load per nephron are so high that glomerular-tubular balance is no longer maintained.

- Loss of flexibility & ability of the nephron to concentrate or dilute urine causing the specific gravity to become fixed & account for symptoms of nocturia & polyuria.
It has been noted for some time that CRF is often progressive, even when the inciting cause of injury is removed.

For example, children with chronic pyelonephritis caused by vesicoureteral reflux & recurrent tract infections develop pyelonephritic scars remain even after removal of the cause.
• The most popular current explanation is the hyperfiltration hypothesis. According to this theory the intact nephrons are eventually injured by increased plasma flow & GFR.

• Increased SNGFR is adaptive in the short run, it is mal-adaptive in the long run.

• Most of the evidence for the hyperfiltration theory of secondary injury is derived from the remnant kidney model in the rat. When one kidney in the rat was removed and two thirds of the other kidney destroyed, it was noted that the animal developed end-stage renal failure (ESRF) within 6 months, although a primary renal disease was not present.
• The rate of progression of these CRD varies greatly. The course terminating in ESRD may vary from 2 to 3 months to 30 to 40 years.
FIGURE 76-1. Proposed mechanisms for progression of renal disease.
Major risk factor for developing ESRD

- Age: risk increase with age.
- Race: common in African Americans
- Gender: men more than women
- Family history: increase risk of HTN & DM
# Classification of causes of CRF

<table>
<thead>
<tr>
<th>Disease classification</th>
<th>Disease</th>
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</thead>
<tbody>
<tr>
<td>Infectious tubulointerstetal disease</td>
<td>Chronic pyelonephritis or reflux nephropathy</td>
</tr>
<tr>
<td>Inflammatory disease</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Hypertensive vascular disease</td>
<td>Benign nephrosclerosis</td>
</tr>
<tr>
<td>Connective tissue disorder</td>
<td>SLE, progressive systamic sclerosis</td>
</tr>
<tr>
<td>Congenital and hereditary disorders</td>
<td>Polycystic kidney disease, renal tubular acidosis</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>DM, Hyperparathyriodism, Amyloidosis</td>
</tr>
<tr>
<td>Toxic nephropathy</td>
<td>Analgesic abuse, lead nephropathy</td>
</tr>
</tbody>
</table>
| Obstructive nephropathy                        | Upper urinary tract: calculi, neoplasms, retroperitoneal fibrosis  
                                        | Lower urinary tract: prostatic hypertrophy, urethral stricture, congenital anomalies of the bladder neck & urethra |
Currently, diabetes and hypertension are responsible for the largest proportion of ESRD, accounting for 34% & 21% of the total cases, respectively.

Glomerulonephritis is the third most common cause of ESRD (17%). Infectious tubulointerstitial nephritis (chronic pyelonephritis or reflux nephropathy) & polycystic kidney disease (PKD) each account for 3.4% of ESRD.
Note

- The remaining 21% of the causes of ESRD are relatively uncommon & include obstructive uropathy, systemic lupus erythematosus (SLE), & others.
Infectious & inflammatory disease
Acute pyelonephritis

- Caused by infection.
- When acute PN is complicated by obstruction, recurrent or persistent bacteriuria occurs in 50-80% of patients within 2 years.
- It is not known with certainty how many of these patients will develop significant renal damage or how long the process might take.
Chronic pyelonephritis

- The identification and the causes of chronic PN are controversial. A major problem in identification is that many other inflammatory & ischemic diseases of the kidney produce segmental focalized areas of disease indistinguishable from those produced by bacterial infection.
- For example, nonbacterial disorders such as arteriolar nephrosclerosis & toxic nephropathies caused by analgesic abuse, lead exposure, & certain drugs
Chronic pyelonephritis

- Most of the evidence suggests that the renal involvement in reflux nephropathy occurs early in childhood before the age of 5 to 6 years, because new scar formation rarely occurs after this age.
- *hyperfiltration hypothesis*. According to this theory, the initial infection-induced nephron loss leads to compensatory increases in glomerular capillary pressure & hyperperfusion in the remaining relatively normal nephrons. The intraglomerular hypertension then appears to produce glomerular injury & eventual sclerosis
Chronic pyelonephritis

• Experimental evidence shows that the control of systemic hypertension, especially by the administration of angiotensinconverting enzyme (ACE)-inhibitor drugs such as captopril or enalapril maleate, slows the decline of GFR in many patients with chronic renal failure.

• Protien restrection is also good.

• No clear S & S.
Chronic pyelonephritis

- Typical findings in chronic PN include intermittent bacteriuria & WBCs or white cell casts in the urine.
- Consequently, polyuria, nocturia, & urine with a low specific gravity are prominent early symptoms.
- Many patients also have a tendency to lose salt in the urine. About one half of the patients may develop hypertension. Azotemia is common.
Glomerulonephritis

• *Glomerulonephritis* is a bilateral inflammatory disease of the kidneys that begins in the glomerulus & is demonstrated by proteinuria or hematuria or both.
The classic case of acute GN follows a streptococcal infection of the throat or sometimes of the skin after a latent period of 1 to 2 weeks.
Rapidly progressive

- fulminant renal disease with characteristic clinical and morphologic features. There is hematuria, proteinuria, & rapidly progressive azotemia, resulting in death within 2 years.
- Goodpasture's disease or syndrome, a rare disease most common in young men. The onset may be insidious or acute & is associated with lung hemorrhage & hemoptysis.
- nephrotoxic immune mechanism is involved
Chronic

- CGN is characterized by slow, progressive destruction of the glomeruli from long-standing GN.
- Kidneys are grossly contracted, sometimes weighing as little as 50 g, & the surface is granular. These changes are caused by ischemia and the loss of nephrons.
<table>
<thead>
<tr>
<th>Nephrotic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Although many patients with CGN have persistent, asymptomatic proteinuria throughout the course of the disease, about 50% develop the nephrotic syndrome.</td>
</tr>
<tr>
<td>• The nephrotic syndrome is a clinical state in which there is massive proteinuria (&gt;3.5 g/day), hypoalbuminemia, edema, &amp; hyperlipidemia.</td>
</tr>
<tr>
<td>• Usually the BUN level is normal.</td>
</tr>
</tbody>
</table>
Nephrotic syndrome

- Can be idiopathic or 2ry
- Like DM
Hypertensive Nephrosclerosis

- Hypertension & CRF are closely related.
- Hypertension may be the primary disease & damage the kidneys.
- Conversely, severe CRD may cause hypertension or contribute to its maintenance through the mechanism of sodium & water retention, the vasopressor effects of the renin-angiotensin system, & possibly prostaglandin deficiency.
Essential hypertension & the kidneys

- Long-standing hypertension produces structural changes in the arterioles throughout the body, characterized by fibrosis & hyalinization (sclerosis) of the blood vessel walls.
- The chief target organs of this condition are the heart, brain, kidneys, & eyes. The usual cause of death is myocardial infarction, congestive heart failure, or cerebrovascular accident.
Renal Artery Stenosis

- May be unilateral or bilateral
- Atherosclerotic plaques or fibromuscular dysplasia may occlude the renal artery, causing hypertension that is often of the rapidly progressive type.
Connective tissue disorders
SLE

• Multisystem disease of unknown origin characterized by circulating autoantibodies to (DNA).
• Renal involvement is a major cause of morbidity in patients with SLE. Although renal failure is becoming less common with modern treatment, about 25% of those with SLE eventually develop renal failure.
• Lupus nephritis is caused by circulating immune complexes that become trapped in the glomerular basement membrane (GBM) & cause damage.
Polyarteritis nodosa (PAN)

• is an inflammatory & necrotizing disease involving the medium-size & small arteries throughout the body, with secondary ischemia of the tissues supplied by the affected vessels. Early S&S of PAN are nonspecific, including fever, malaise, weight loss, & abdominal pain. Intractable HTN 2ry to the arteritis is often present.

• Men are more commonly affected than women, & the mean age of onset is 48 years. Although the exact cause and pathogenesis are unknown, evidence suggests some form of hypersensitivity mechanism. In many cases the onset is associated with a sensitivity reaction to drugs.
Progressive systemic sclerosis, or scleroderma

- is an uncommon systemic disease characterized by diffuse sclerosis of the skin and other organs. The disease affects the vasculature of several organs, including the kidneys. Women are affected more.
- As in SLE, a variety of antibodies may be found in the serum, suggesting that immune mechanisms may be involved in the pathogenesis.
Congenital and Hereditary Disorders
Polycystic kidney disease (PKD)

- is characterized by bilateral, multiple, expanding cysts that gradually erode and destroy the normal renal parenchyma by compression.
- Of the children who survive the first month of life, 78% survive beyond 15 years.
- Early diagnosis and aggressive treatment of HTN may improve the diagnosis of these children.
Renal tubular acidosis (RTA)

- Refers to a group of disorders in which defective renal hydrogen ion (H+ tubular excretion or loss of bicarbonate (HCO) in the urine, despite preservation of an adequate GFR. The result is a sustained metabolic acidosis.
Metabolic disorders
Diabetic nephropathy (renal disease in patients with diabetes) is one of the most important causes of death in long-standing DM. More than one third of all new patients entering ESRD programs have diabetic RF.

It has been estimated that about 35-40% of patients with type 1 DM develop CRF within 15-25 years after the onset of diabetes. Fewer individuals with type 2 diabetes develop CRF (about 10-20%) with the exception of Pima Indians where the incidence is nearly 50%. Native Americans & African Americans have a particularly high risk of developing diabetic renal failure.
Persistent hyperglycemia seems to be the most important factor in the pathogenesis of the diabetic glomerulosclerosis & involves several mechanisms, including
DM

• (1) vasodilation with increased permeability of the microcirculation allowing increased leakage of solutes into the vascular walls & surrounding tissues;
• (2) glucose disposal, leading to accumulation of polyols & decreased levels of vital cellular components, including the glomeruli; &
• (3) glycosylation of glomerular structural proteins.
Uric acid kidney disease

- Uric acid, an end product of purine metabolism, can precipitate within the renal medullary interstitium, tubules or collecting system, leading to three types of renal disease:
  - (1) acute uric acid nephropathy,
  - (2) uric acid nephrolithiasis, &
  - (3) chronic urate nephropathy.
Primary hyperparathyroidism, resulting in hypersecretion of parathyroid hormone, is a relatively rare disease that can result in nephrocalcinosis and subsequent renal failure.
Amyloidosis

- is a metabolic condition in which there is a deposition, in many tissues, of an abnormal extracellular fibrillar protein, termed amyloid.
- Amyloid deposition can damage the kidney, liver, spleen, heart, tongue, & nervous system.
- The major causes of death are heart failure & renal failure.
Toxic nephropathy
The kidney is especially vulnerable to the toxic effects of drugs & chemicals for the following reasons:

- (1) it receives 25% of the cardiac output, therefore it may be readily exposed to large amounts of a chemical;
- (2) the hyperosmotic interstitium allows chemicals to be concentrated in a relatively hypovascular region; and
- (3) the kidney is an obligatory excretory route for most drugs, so renal insufficiency results in drug accumulation & increased concentration in the tubular fluid.
Analgesic abuse

- worldwide problem
- most preventable form of renal disease.
- Increase with combination.
Lead nephropathy

• may be ingested.
• when lead-based paints were used.
• Lead is incorporated chiefly into the bone & gradually released over a period of years; it is also incorporated into renal tubular cells.
• What is sclerosis?
• What is scleroderma?