and hydrogen ions compete for secretion in exchange for sodium ions. The possible mechanism stimulated by aldosterone is discussed in Chapter 2. The most important stimulus to aldosterone secretion is mediated by the effect of renal blood flow on the release of renin from the juxtaglomerular apparatus; this method of reabsorption is part of the homeostatic mechanism controlling sodium and water balance.

## BIOCHEMISTRY OF RENAL DISORDERS

### Pathophysiology

Different parts of the nephrons are in close anatomical association and are dependent on a common blood supply. Renal dysfunction of any kind affects all parts of the nephrons to some extent, although sometimes either glomerular or tubular dysfunction is predominant. The net effect of renal disease on plasma and urine depends on the proportion of glomeruli to tubules affected and on the number of nephrons involved.

To understand the consequences of renal disease it may be useful to consider the *hypothetical* individual nephrons, first with a low glomerular filtration rate (GFR) and normal tubular function, and then with tubular damage but a normal GFR. It should be emphasized that these are hypothetical examples, as in clinical reality a combination of varying degree may exist.

Uraemia is the term used to describe a raised plasma urea concentration and is almost always accompanied by an elevated creatinine concentration: in North America this is usually referred to as azotaemia (a raised nitrogen concentration).

#### Reduced glomerular filtration rate with normal tubular function

The total amounts of urea and creatinine excreted are affected by the GFR. If the rate of filtration fails to balance that of production, plasma concentrations will rise.

Phosphate and urate are released during cell breakdown. Plasma concentrations rise because less than normal is filtered. Most of the reduced amount reaching the proximal tubule can be reabsorbed, and the capacity for secretion is impaired if the filtered volume is too low to accept the ions; these factors further contribute to high plasma concentrations.

A large proportion of the reduced amount of filtered sodium is reabsorbed by isosmotic mechanisms; less than usual is then available for exchange with hydrogen and potassium ions distally. This has two main outcomes:

- reduced hydrogen ion secretion throughout the nephron: bicarbonate can be reclaimed only if hydrogen ions are secreted; plasma bicarbonate concentrations will fall,
- reduced potassium secretion in the distal tubule, with potassium retention (potassium can still be reabsorbed proximally).

If there is a low GFR accompanied by a low renal blood flow:

- Systemic aldosterone secretion will be maximal: in such cases, any sodium reaching the distal tubule will be almost completely reabsorbed in exchange for $H^+$ and $K^+$, and the urinary sodium concentration will be low.
- ADH secretion will be increased: ADH acting on the collecting ducts allows water to be reabsorbed in excess of solute, further reducing urinary volume and increasing urinary osmolality well above that of plasma and reducing plasma sodium concentration. This high urinary osmolality is mainly due to substances not actively dealt with by the tubules. For example, the urinary urea concentration will be well above that of plasma. This distal response will occur only in the presence of ADH; in its absence, normal nephrons will form a dilute urine.

If the capacity of the proximal tubular cells to reabsorb solute, and therefore water, is normal, a larger proportion than usual of the reduced filtered volume will be reclaimed by isosmotic processes, thus further reducing urinary volume.

In summary, the findings in venous plasma and urine from the affected nephrons will be as follows.

##### *Plasma*

- High urea (uraemia) and creatinine concentrations.
- Low bicarbonate concentration, with low pH (acidosis).
- Hyperkalaemia.
- Hyperuricaemia and hyperphosphataemia.

##### *Urine*

- Reduced volume (oliguria).
- Low (appropriate) sodium concentration – only if renal blood flow is low, stimulating aldosterone secretion.
- High (appropriate) urea concentration and therefore a high osmolality – only if ADH secretion is stimulated.

### Reduced tubular function with normal glomerular filtration rate

Damage to tubular cells impairs adjustment of the composition and volume of the urine. Impaired solute reabsorption from proximal tubules reduces isosmotic water reabsorption. Countercurrent multiplication may also be affected, and therefore the ability of the collecting ducts to respond to ADH is reduced. A large volume of inappropriately dilute urine is produced.

The tubules cannot secrete hydrogen ions and therefore cannot reabsorb bicarbonate normally or acidify the urine. The response to aldosterone and therefore the exchange mechanisms involving reabsorption of sodium are impaired; the urine contains an inappropriately high concentration of sodium for the renal blood flow. Potassium reabsorption from the proximal tubule is impaired and plasma potassium concentrations may be low. Reabsorption of glucose, phosphate, magnesium, urate and amino acids is impaired. Plasma phosphate, magnesium and urate concentrations may be low.

Thus, the findings in venous plasma and urine from the affected nephrons will be as follows.

*Plasma*

- Normal urea and creatinine concentrations (normal glomerular function).
- Due to proximal or distal tubular failure:
  - low bicarbonate concentration and low pH,
  - hypokalaemia.
- Due to proximal tubular failure:
  - hypophosphataemia, hypomagnesaemia and hypouricaemia.

*Urine*

- Due to proximal and/or distal tubular failure:
  - increased volume,
  - pH inappropriately high compared with that in plasma.
- Due to proximal tubular failure:
  - generalized amino aciduria,
  - phosphaturia,
  - glycosuria.
- Due to distal tubular failure:
  - even if renal blood flow is low, an inappropriately high sodium concentration (inability to respond to aldosterone),
  - even if ADH secretion is stimulated, an inappropriately low urea concentration and therefore osmolality (inability of the collecting ducts to respond to ADH).

There may also be tubular proteinuria, which usually refers to low-molecular-weight proteins that are normally produced in the body, filtered across the glomerular membrane and reabsorbed in the proximal tubule, but appear in the urine as a result of proximal tubular damage, for example $\alpha_1$-microglobulin and retinol binding protein. However, tubular proteinuria also occurs when proximal tubular enzymes and proteins, such as *N*-acetyl-β-D-glucosaminidase (NAG), are released into the urine due to tubular cell injury. See Chapter 19.

## Clinical and biochemical features of renal disease

The biochemical findings and urine output in renal disease depend on the relative contributions of glomerular and tubular dysfunction. When the GFR falls, substances that are little affected by tubular action (such as urea and creatinine) are retained. Although their plasma concentrations start rising above the baseline for that individual soon after the GFR falls, they seldom rise above the reference range for the population until the GFR is below about 60 per cent of normal, although in individual patients they do rise above baseline.

Plasma concentrations of urea and creatinine depend largely on glomerular function (Fig. 3.5). By contrast, urinary concentrations depend almost entirely on tubular function. However little is filtered at the glomeruli, the concentrations of substances in the initial filtrate are those of a plasma ultrafiltrate. Any difference between these concentrations and those in the urine is due to tubular activity. The more the tubular function is impaired, the nearer the plasma concentrations will be to those of urine. Urinary concentrations *inappropriate to the state of hydration* suggest tubular damage, whatever the degree of glomerular dysfunction.

The plasma sodium concentration is not primarily affected by renal disease. The urinary volume depends on the balance between the volume filtered and the proportion reabsorbed by the tubules. As 99 per cent of filtered water is normally reabsorbed, a very small impairment of reabsorption causes a large increase in urine volume. Consequently, if tubular dysfunction predominates, impairment of water reabsorption causes polyuria, even though glomerular filtration is reduced (see Chapter 2).

The degree of potassium, phosphate and urate retention depends on the balance between the degree of glomerular retention and the loss as a result of a reduced

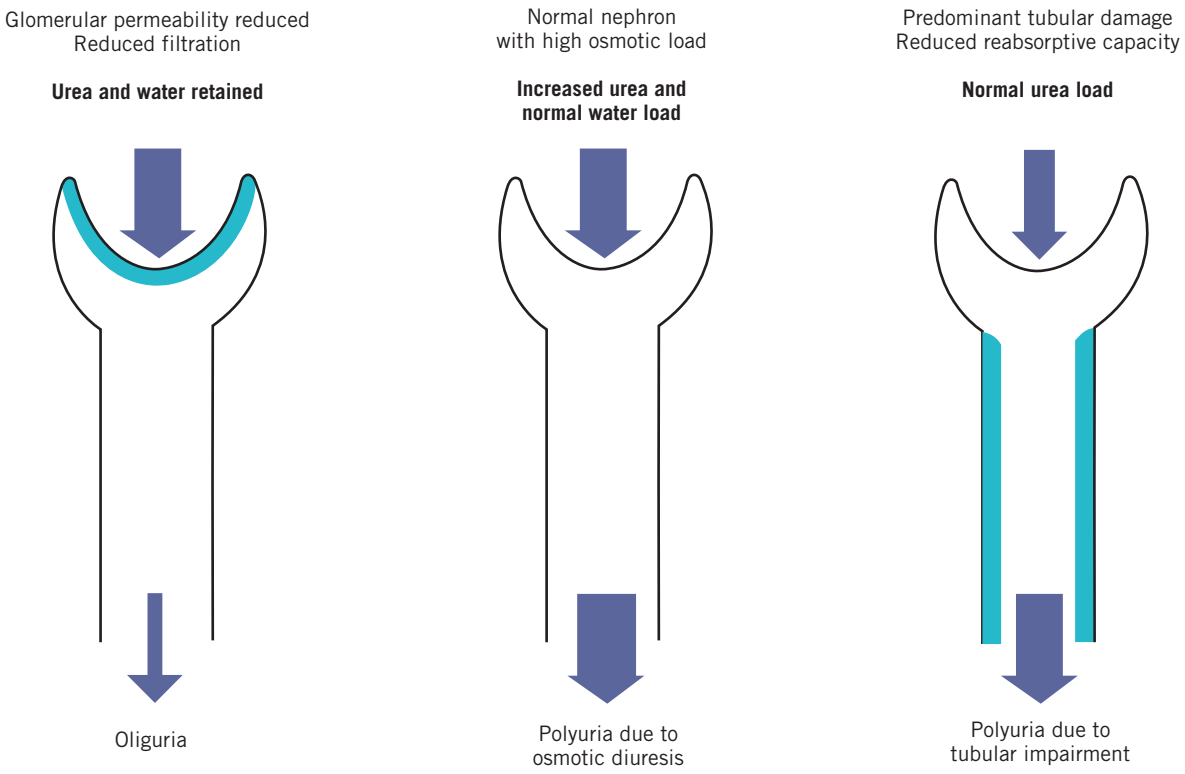


**Figure 3.5** The effects of glomerular and tubular dysfunction on urinary output and on plasma concentrations of retained 'waste' products of metabolism, the volume depending on the proportion of nephrons involved.

proximal tubular reabsorptive capacity. If glomerular dysfunction predominates, so little is filtered that plasma concentrations rise, despite the failure of reabsorption. Conversely, if tubular dysfunction predominates, glomerular retention is more than balanced by impaired reabsorption of filtered potassium, urate and phosphate, and therefore plasma concentrations may be normal or even low. A low plasma bicarbonate concentration is found in association with metabolic acidosis, which may worsen the hyperkalaemia.

## Acute kidney injury

This was previously known as acute renal failure. In adults, oliguria is defined as a urine output of less than 400 mL/day, or less than 15 mL/h; it usually indicates a low GFR and a rapid decline in renal function over hours to weeks, with retention of creatinine and nitrogenous waste products. Oliguria may be caused by the factors discussed below.

### Acute oliguria with reduced GFR (pre-renal)

This is caused by factors that reduce the hydrostatic pressure gradient between the renal capillaries and the tubular lumen. A low intracapillary pressure is the

## CASE 1

A 17-year-old man was involved in a road traffic accident. Both femurs were fractured and his spleen was ruptured. Two days after surgery and transfusion of 16 units of blood, the following results were found:

*Plasma*

Sodium 136 mmol/L (135–145)
Potassium 6.1 mmol/L (3.5–5.0)
Urea 20.9 mmol/L (2.5–7.0)
Creatinine 190 µmol/L (70–110)
Albumin-adjusted calcium 2.40 mmol/L (2.15–2.55)
Phosphate 2.8 mmol/L (0.80–1.35)
Bicarbonate 17 mmol/L (24–32)

The patient was producing only 10 mL of urine per hour and a spot urinary sodium was 8 mmol/L.

**DISCUSSION**

The results are compatible with pre-renal acute kidney injury (AKI), secondary to massive blood loss. Note the oliguria, low urinary sodium concentration, hyperkalaemia, hyperphosphataemia and also low plasma bicarbonate concentration, suggestive of a metabolic acidosis.

most common cause. It is known as *renal circulatory insufficiency* ('pre-renal uraemia') and may be due to:

- intravascular depletion of whole blood (haemorrhage) or plasma volume (usually due to gastrointestinal loss), or reduced intake,
- reduced pressure as a result of the vascular dilatation caused by 'shock', causes of which include myocardial infarction, cardiac failure and intravascular haemolysis, including that due to mismatched blood transfusion.

The patient is usually hypotensive and clinically volume depleted. If renal blood flow is restored within a few hours, the condition is reversible, but, the longer it persists, the greater the danger of intrinsic renal damage.

As most glomeruli are involved and tubular function is relatively normal, the biochemical findings in plasma and urine are those described earlier. Uraemia due to renal dysfunction may be aggravated if there is increased protein breakdown as a result of tissue damage, a large haematoma or the presence of blood in the gastrointestinal lumen. Intravenous amino acid infusion may have the same effect because the urea is derived, by hepatic metabolism, from the amino groups of amino acids. Increased tissue breakdown may also aggravate hyperkalaemia, hyperuricaemia and hyperphosphataemia.

### Acute oliguria due to intrinsic renal damage

This may be due to:

- prolonged renal circulatory insufficiency,
- acute glomerulonephritis, usually in children – the history of a sore throat and the finding of red cells in the urine usually make the diagnosis obvious,
- septicaemia, which should be considered when the cause of oliguria is obscure,
- ingestion of a variety of poisons or drugs,
- myoglobulinuria (see Chapters 18 and 19),
- Bence Jones proteinuria (see Chapter 19).

One problem in the differential diagnosis of acute oliguria is distinguishing between renal circulatory insufficiency and intrinsic renal damage that may have followed it. Acute oliguric renal dysfunction often follows a period of reduced GFR and renal circulatory insufficiency.

The oliguria is due to reduced cortical blood flow with glomerular damage, aggravated by back-pressure on the glomeruli due to obstruction to tubular flow by oedema. At this stage, the concentrations of many constituents in plasma, such as urea and creatinine, are raised with hyperkalaemia; tubular damage results in an inappropriately dilute urine for the degree of hypovolaemia. Fluid must be given with caution, and only until volume depletion has been corrected; there is a danger of overloading the circulation.

During recovery, oliguria is followed by polyuria. When cortical blood flow increases, and as tubular oedema resolves, glomerular function recovers before that of the tubules. The biochemical findings gradually progress to those of tubular dysfunction until they approximate those for 'pure' tubular lesions. Urinary output is further increased by the osmotic diuretic effect of the high load of urea. The polyuria may cause water and electrolyte depletion. The initial hyperkalaemia may be followed by hypokalaemia. Mild acidosis (common to both glomerular and tubular disorders) persists until late. Recovery of the tubules may restore full renal function.

### Acute oliguria due to renal outflow obstruction (post-renal)

Oliguria or anuria (absence of urine) may occur in post-renal failure. The cause is usually, but not always, clinically obvious and may be due to the following:

- *Intrarenal obstruction*, with blockage of the tubular lumina by haemoglobin, myoglobin and, very rarely, urate or calcium. Obstruction caused by casts and oedema of tubular cells is usually the result of true renal damage.
- *Extrarenal obstruction*, due to calculi, neoplasms, for example prostate or cervix, urethral strictures or prostatic hypertrophy, any of which may cause sudden obstruction. The finding of a palpable bladder indicates urethral obstruction, and in males is most likely to be due to prostatic hypertrophy, although there are other, rarer, causes.

Early correction of outflow obstruction may rapidly increase the urine output. The longer it remains untreated, the greater the danger of ischaemic or pressure damage to renal tissue. Imaging studies such as renal tract ultrasound may be useful to confirm post-renal obstruction (Box 3.1).

### Investigation of acute kidney injury

- A careful clinical history, especially of taking nephrotoxic drugs, and examination may give clues to the cause of acute kidney injury (AKI). It is essential to exclude reversible causes of pre-renal failure, including hypovolaemia or hypotension, and also post-renal urinary tract obstruction (renal tract imaging may be useful, such as abdominal

**Box 3.1** Some causes of acute kidney injury (AKI)

**Pre-renal**
Hypotension
Hypovolaemia
Decreased cardiac output
Renal artery stenosis + angiotensin-converting enzyme inhibitor
Hepatorenal syndrome

**Renal or intrinsic renal disease**
Acute tubular necrosis, e.g. hypotension, toxins, contrast media, myoglobinuria, sepsis, drugs, sustained pre-renal oliguria
Vasculitis
Glomerulonephritis
Drugs that are nephrotoxic, e.g non-steroidal anti-inflammatory drugs
Sepsis
Thrombotic microangiopathy or thromboembolism
Atheroembolism
Bence Jones proteinuria
Interstitial nephritis
Infiltration, e.g. lymphoma
Severe hypercalcaemia
Severe hyperuricaemia

**Post-renal**
Calculi
Retroperitoneal fibrosis
Prostate hypertrophy/malignancy
Carcinoma of cervix or bladder

radiograph if calculi are suspected, and renal tract ultrasound); see Box 3.1).

- Monitor urine output, plasma urea and creatinine and electrolytes, as well as acid–base status.
- Hyperkalaemia, hypermagnesaemia, hyperphosphataemia, hyperuricaemia and metabolic acidosis may occur in the oliguric phase of AKI.
- Urine microscopy may show granular casts supportive of the diagnosis of acute tubular necrosis.
- The urinary to plasma urea ratio can be useful, and when more than 10:1 is suggestive of pre-renal problems. The urinary to plasma creatinine or osmolality ratio may also be useful (Table 3.1).
- The fractional excretion of sodium (FENa%) is also useful diagnostically and can be measured using a simultaneous blood sample and spot urine (see above and Fig. 3.6).

## CASE 2

A 56-year-old man attended the renal out-patient clinic because of polycystic kidneys, which had been diagnosed 20 years previously. He was hypertensive and the following blood results were returned:

*Plasma*
Sodium 136 mmol/L (135–145)
Potassium 6.2 mmol/L (3.5–5.0)
Urea 23.7 mmol/L (2.5–7.0)
Creatinine 360 µmol/L (70–110)
Estimated glomerular filtration rate (eGFR) 14 mL/min per 1.73 $m^2$
Albumin-adjusted calcium 1.80 mmol/L (2.15–2.55)
Phosphate 2.6 mmol/L (0.80–1.35)
Bicarbonate 13 mmol/L (24–32)

**DISCUSSION**
These results are typical of a patient with chronic kidney disease (CKD) with raised plasma urea and creatinine concentrations. The patient has hyperkalaemia and a low plasma bicarbonate concentration, suggestive of a metabolic acidosis. The hypocalcaemia and hyperphosphataemia are also in keeping with CKD stage 5.

**Table 3.1** Some laboratory tests used to investigate acute kidney injury

| | Pre-renal failure | Intrinsic renal failure/ acute tubular necrosis |
|---|---|---|
| Urine sodium (mmol/L) | <20 | >20 |
| FENa% | <1 | >1 |
| Urine to plasma creatinine ratio | >40 | <20 |
| Urine to plasma osmolality ratio | >1.2 | <1.2 |
| Urine to plasma urea ratio | >10 | <10 |

Note that in post-renal failure there is usually anuria.
FENa%, fractional excretion of sodium.

$$\text{FENa\%} = \frac{\text{urine [sodium]}}{\text{plasma [sodium]}} \times \frac{\text{plasma [creatinine]}}{\text{urine [creatinine]}} \times 100\% \quad (3.1)$$

- An FENa% of less than 1 per cent is typical of pre-renal failure, as is a urinary sodium concentration more than 20 mmol/L.

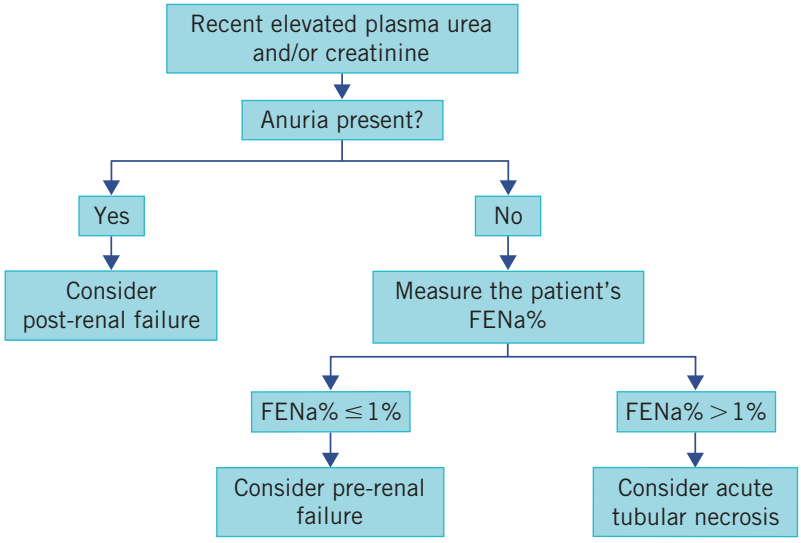


**Figure 3.6** Algorithm for the investigation of acute kidney injury (AKI). FENa%, fractional excretion of sodium.

- Blood may be necessary for full blood count, coagulation screen and blood cultures. Also exclude myeloma, and look for Bence Jones proteinuria and cryoglobulins. Autoantibody screen, including antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), extractable nuclear antigen (ENA) antibody, complement, antiglomerular basement membrane antibodies and double-stranded deoxyribonucleic acid (DNA), myoglobin, plasma creatine kinase and plasma calcium, may also be indicated, depending on the clinical situation.
- In obscure cases, renal biopsy may be necessary to establish a diagnosis.
- Recently, urine neutrophil gelatinase-associated lipocalin (NGAL) has been suggested as a marker of renal injury and predictor of AKI.

## Chronic kidney disease

Chronic renal dysfunction [defined as being reduced eGFR (estimated GFR), proteinuria, haematuria and/or renal structural abnormalities of more than 90 days' duration] is usually the end result of conditions such as diabetes mellitus, hypertension, primary glomerulonephritis, autoimmune disease, obstructive uropathy, polycystic disease, renal artery stenosis, infections and tubular dysfunction and the use of nephrotoxic drugs (Box 3.2). It is common, perhaps affecting about 13 per cent of the population. Acute or chronic renal dysfunction can occur when angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are given to patients with renal artery stenosis; a clue to this is an increase in plasma creatinine of about 20 per cent and/or a decrease in eGFR of about 15 per cent soon after initiation of the drug.

**Box 3.2** Some causes of chronic kidney disease

Diabetes mellitus
Nephrotoxic drugs
Hypertension
Glomerulonephritis
Chronic pyelonephritis
Polycystic kidneys
Urinary tract obstruction
Severe urinary infections
Amyloid and paraproteins
Progression from acute kidney injury
Severe hypothyroidism (rare)

In most cases of acute oliguric renal disease there is diffuse damage involving the majority of nephrons. A patient who survives long enough to develop chronic renal disease must have some functioning nephrons.

Histological examination shows that not all nephrons are equally affected: some may be completely destroyed and others almost normal. Also, some segments of the nephrons may be more affected than others. The effects of chronic renal disease can be explained by this patchy distribution of damage; acute renal disease may sometimes show the same picture.

In chronic kidney disease (CKD) the functional adaptive effects can be divided into three main categories: diminished renal reserve, renal insufficiency, and end-stage uraemia. The loss of 75 per cent of renal tissue produces a fall in GFR of 50 per cent. Although there is a loss of renal function, homeostasis is initially preserved at the expense of various adaptations such as glomerulotubular changes and secondary hyperparathyroidism.

Chronic renal dysfunction may pass through two main phases:

- an initially polyuric phase,
- subsequent oliguria or anuria, sometimes needing dialysis or renal transplantation.

### Polyuric phase

At first, glomerular function may be adequate to maintain plasma urea and creatinine concentrations within the reference range. As more glomeruli are involved, the rate of urea excretion falls and the plasma concentration rises. This causes an osmotic diuresis in functioning nephrons; in other nephrons the tubules may be damaged out of proportion to the glomeruli. Both tubular dysfunction in nephrons with functioning glomeruli and the osmotic diuresis through intact nephrons contribute to the polyuria, other causes of which should be excluded (see Chapter 2).

During the polyuric phase, the plasma concentration of many substances, other than urea and creatinine, may be anywhere between the glomerular and tubular ends of the spectrum, although metabolic acidosis is usually present.

### Oliguric phase

If nephron destruction continues, the findings become more like those of pure glomerular dysfunction. Glomerular filtration decreases significantly and urine output falls; oliguria precipitates a steep rise in plasma urea, creatinine and potassium concentrations; and the metabolic acidosis becomes more severe.

The diagnosis of CKD is usually obvious. In the early phase, before plasma urea and creatinine concentrations have risen significantly, there may be microscopic haematuria or proteinuria. However, haematuria may originate from either the kidney or the urinary tract, and may therefore indicate the presence of other conditions, such as urinary tract infections, renal calculi or tumours (see Box 3.2).

### Other abnormal findings in chronic kidney disease

Apart from uraemia, hyperkalaemia and metabolic acidosis, other abnormalities that may occur in CKD include the following:

- Plasma phosphate concentrations rise and plasma total calcium concentrations fall. The increased hydrogen ion concentration increases the proportion of free ionized calcium, the plasma concentration of which does not fall in parallel with the fall in total calcium concentration. Impaired renal tubular function and the raised phosphate concentration inhibit the conversion of vitamin D to the active metabolite and this contributes to the fall in plasma calcium concentration. Usually, *hypocalcaemia should be treated only after correction of hyperphosphataemia*. After several years of CKD, secondary hyperparathyroidism (see Chapter 6) may cause decalcification of bone, with a rise in the plasma alkaline phosphatase activity. Some of these features of CKD can also evoke renal osteodystrophy, associated with painful bones. The increase in plasma PTH occurs early when the GFR falls below 60 mL/min per 1.73 $m^2$.
- Plasma urate concentrations rise in parallel with plasma urea. A high plasma concentration does not necessarily indicate primary hyperuricaemia; clinical gout is rare unless hyperuricaemia is the cause of the renal damage (see Chapter 20).
- Hypermagnesaemia can also occur (see Chapter 6).
- Normochromic, normocytic anaemia due to erythropoietin deficiency is common and, because haemopoiesis is impaired, does not respond to iron therapy; this can be treated with recombinant erythropoietin.
- One of the commonest causes of death in patients with CKD is cardiovascular disease, in part explained by hypertension and a dyslipidaemia of hypertriglyceridaemia and low high-density lipoprotein cholesterol. Some of these effects may be due to reduced lipoprotein lipase activity.
- Abnormal endocrine function, such as hyperprolactinaemia, insulin resistance, low plasma testosterone and abnormal thyroid function, may also be seen in chronic renal dysfunction.
- Some of the features of CKD may be explained by the presence of 'middle molecules' – compounds that the kidneys would normally excrete. These compounds,

of relatively small molecular weights, can exert toxic effects upon body tissues.

- The presence of increasing proteinuria may be the best single predictor of disease progression.

Irreversible but potentially modifiable complications such as anaemia, metabolic bone disease, undernutrition and cardiovascular disease occur early in the course of CKD. A summary of the clinical features of chronic kidney disease is shown in Table 3.2.

## SYNDROMES REFLECTING PREDOMINANT TUBULAR DAMAGE – RENAL TUBULAR ACIDOSIS

There is a group of conditions that primarily affect tubular function more than the function of the glomeruli. However, scarring involving whole nephrons may eventually cause chronic renal dysfunction. Impaired function may involve a single transport system, particularly disorders associated with amino acid or phosphate transport, or may affect multiple transport systems. Conditions associated with multiple transport defects may cause renal tubular acidoses – renal tubular disorders associated with a systemic metabolic acidosis because of impaired reclamation of bicarbonate or excretion of $H^+$ (see Chapter 4).

Disorders affecting the urine-concentrating mechanism and causing nephrogenic diabetes insipidus but which rarely in themselves cause a metabolic acidosis are discussed elsewhere (see Chapter 2).

## NEPHROTIC SYNDROME

The nephrotic syndrome is caused by increased glomerular basement membrane permeability, resulting in protein loss, usually more than 3 g a day (or a urine protein to creatinine ratio of >300 mg/mmol), with consequent hypoproteinaemia, hypoalbuminaemia and peripheral oedema. All but the highest molecular weight plasma proteins can pass through the glomerular basement membrane. The main effects are on plasma proteins and are associated with hyperlipidaemia and hyperfibrinoginaemia. (This is discussed more fully in Chapter 19.) Uraemia occurs only in late stages of the disorder, when many glomeruli have ceased to function.

## NEPHRITIC SYNDROME

This comprises reduced eGFR, oedema, hypertension and proteinuria with significant haematuria. It is usually associated with systemic disease such as post-infectious glomerulonephritis, e.g. post-streptococcal or immunoglobulin A (IgA) nephropathy, ANCA-associated vasculitis, e.g. Wegener's granulomatosis or microscopic polyarteritis, or antiglomerular basement membrane disease (Goodpasture's disease).

## DIAGNOSIS OF RENAL DYSFUNCTION

### Glomerular function tests

As glomerular function deteriorates, substances that are normally cleared by the kidneys, such as urea and creatinine, accumulate in plasma.

**Table 3.2** Stages of renal dysfunction (chronic kidney disease)[a]

| Stage | Description | GFR (mL/min per 1.73 m²) | Metabolic features |
|---|---|---|---|
| 1 | Presence of kidney damage with normal or raised GFR[b] | >90 | Usually normal |
| 2 | Presence of kidney damage with mildly reduced GFR | 60–89 | Plasma urea and creatinine rise |
| | | | PTH starts to rise |
| 3 | Moderately reduced GFR | 30–59 | Calcium absorption decreased |
| | | | Lipoprotein lipase decreased |
| | | | Anaemia – erythropoietin decreased |
| 4 | Severely reduced GFR (pre-end stage) | 15–29 | Dyslipidaemia |
| | | | Hyperphosphataemia |
| | | | Metabolic acidosis |
| | | | Hyperkalaemia and hyperuricaemia |
| 5 | End-stage kidney disease (may need dialysis or transplant) | <15 | Marked elevation of urea (uraemia) and creatinine |

Note that a suffix of 'p' with staging can be used if proteinuria is present.
[a]National Kidney Foundation.
[b]Such as proteinuria or haematuria.
GFR, glomerular filtration rate; PTH, parathyroid hormone.

### Measurement of plasma concentrations of urea and creatinine

Urea is derived in the liver from amino acids and therefore from protein, whether originating from the diet or from tissues. The normal kidney can excrete large amounts of urea. If the rate of production exceeds the rate of clearance, plasma concentrations rise. The rate of production is accelerated by:

- a high-protein diet,
- absorption of amino acids and peptides from digested blood after haemorrhage into the gastrointestinal lumen or soft tissues,
- increased catabolism due to starvation, tissue damage, sepsis or steroid treatment.

In catabolic states, glomerular function is often impaired due to circulatory factors and this contributes more to the uraemia than does increased production. Conversely, the plasma urea concentration may be lower than 1.0 mmol/L, the causes of which include the following:

- those due to increased GFR or haemodilution (common):
  - pregnancy (the commonest cause in young women),
  - overenthusiastic intravenous infusion (the commonest cause in hospital patients),
  - 'inappropriate' ADH secretion (syndrome of inappropriate ADH secretion, SIADH).
- those due to decreased synthesis:
  - use of amino acids for protein anabolism during growth, especially in children,
  - low protein intake,
  - very severe liver disease (low amino acid deamination),
  - inborn errors of the urea cycle are rare and usually only occur in infants.

Creatinine is largely derived from endogenous sources by muscle creatine breakdown. Plasma creatinine usually correlates with muscle mass, with 95 per cent of creatine occurring in skeletal muscle. The plasma creatinine concentration varies more than that of urea during the day owing to creatine intake in meals. However, sustained high-protein diets and catabolic states probably affect the plasma concentration of creatinine less than that of urea. Creatinine concentration is used to assess renal function; however, its assay may be less precise than that of urea, and can be prone to analytical interference by substances such as bilirubin, ketone bodies and certain drugs.

If the plasma concentration of either urea or creatinine is significantly raised, and especially if it is rising, impaired glomerular function is likely. Serial changes may be used to monitor changes in the GFR and changes greater than 10–15 per cent are likely to be clinically significant.

With a reduced GFR, plasma urea concentrations tend to rise faster than those of creatinine and tend to be disproportionately higher with respect to the upper reference limit. The rate at which urea is reabsorbed from the collecting ducts is dependent on the amount filtered by the glomerulus and by the rate of luminal fluid flow (see Table 3.2).

### Clearance as an assessment of glomerular filtration rate (Fig. 3.7)

For a substance (S) that is filtered by the glomerulus, but not reabsorbed from or secreted into the tubules, the amount filtered (GFR × plasma[S]) must equal the amount excreted in the urine (urinary[S] × volume per unit time):

$$\text{GFR} \times \text{plasma[S]} = \text{urinary[S]} \times \text{urine volume per unit time} \quad (3.2)$$

Thus, rearranging gives:

$$\text{GFR} = \frac{\text{urinary[S]} \times \text{urine volume per unit time}}{\text{plasma[S]}} \quad (3.3)$$

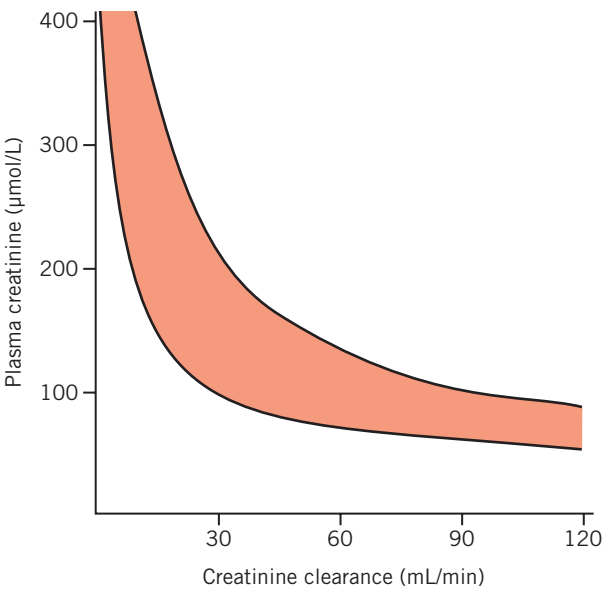


**Figure 3.7** The inverse relationship between plasma creatinine and creatinine clearance. (Shaded area is approximate 95 per cent confidence intervals.)