The GFR thus measured is referred to as the *clearance* – the volume of plasma that could theoretically be completely cleared of a substance in 1 min. Only substances freely filtered by glomeruli and not acted on by the tubules can be used to give true measurement of GFR. There is no such endogenous substance, but inulin, a polysaccharide, fulfils the criteria closely. Inulin is not produced by the body; it must be given either by constant infusion in order to maintain steady plasma concentrations during the period of the test, or by a single injection followed by serial blood sampling to enable the concentration at the midpoint of the collection to be calculated.

Radiochromium-labelled ethylenediamine tetra-acetic acid (EDTA) is another exogenous compound that some consider the 'gold standard' for calculating patient GFR, although this requires the use of nuclear medicine tests and is rarely used.

For endogenously produced substances such as creatinine, with its relatively constant production, the following equation can be used to calculate a clearance that acts as an approximation for GFR:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{urinary [creatinine]} \times \text{urine volume (mL)}}{\text{plasma [creatinine]} \times \text{urine collection period (min)}} \quad (3.4)$$

The modification of diet in renal disease (MDRD) formula can be used to estimate GFR (eGFR) and has generally superseded the need to use creatinine clearances in clinical practice and is also used to titrate drug dosing in patients with renal impairment. This is calculated by the isotope dilution mass spectrometry (IDMS) traceable MDRD equation recommended in the UK as: $175 \times ([\text{plasma creatinine}]/88.4)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$.

The equation has not been validated in the following groups: those under 18 years old, those acutely ill, patients with limb amputations, pregnant women, the very elderly and the obese and malnourished. In some of these situations there may be differences in muscle mass and hence in creatine concentrations and ultimately creatinine. Those with muscle breakdown may show higher plasma creatinine concentration and the converse may be seen in those with reduced muscle bulk. There may be increased muscle bulk in black compared with white people. Individuals taking creatine supplements for body building may show increased plasma creatinine and also plasma creatine kinase (CK).

Creatinine clearance is higher than inulin clearance because some creatinine is secreted by the tubules. Urea clearance is lower than inulin clearance as some urea is reabsorbed into the tubules (urea and inulin clearance are now essentially obsolete in clinical practice).

However, there are various factors that make the measurement of creatinine clearance inaccurate:

- All laboratory assays have an inherent imprecision. The combined imprecision of two assays is greater than that of one. Urine as well as plasma is assayed for clearance measurements.
- The most significant error of any method depending on a timed urine collection is in the measurement of urine volume. Inaccurate urine collection may yield misleading results. The difficulties are increased in infants and young children, and in patients who have difficulty in bladder emptying or are incontinent.
- Both creatinine and urea may be partly destroyed by bacterial action in infected or old urine.

For an individual patient, plasma creatinine concentrations may rise above the baseline level but remain within the population reference range despite a deterioration in glomerular function. The reciprocal of the plasma creatinine concentration is called the *renal index*.

The plasma creatinine concentration may not exceed the upper limit of the reference range until the GFR, and therefore the creatinine clearance, has been reduced by approximately 60 per cent (see Fig. 3.7). Thus the measurement of creatinine clearance should be a more sensitive but less accurate indicator of early glomerular dysfunction than of plasma creatinine concentration.

Clearance values will be low whether the reduced GFR is due to renal circulatory insufficiency, intrinsic renal damage or 'post-renal' causes, and it cannot distinguish among them. Creatinine clearance has been said to be useful in deciding the dose of a renally excreted drug.

Cystatin C

Another endogenous substance that can be used as a marker of GFR is plasma cystatin C (Cys C), and its use may alleviate some of the problems associated with creatinine clearance determinations. This is a 13-kDa protein that is a member of the family of cystine proteinase inhibitors. Unlike other endogenous

compounds such as creatinine, Cys C is not secreted by the renal tubules and does not return to the bloodstream after glomerular filtration. It has been suggested that plasma Cys C may approximate to the 'ideal' endogenous marker for GFR, as blood concentrations are independent of patient age and sex, although currently this test is not routinely available in most laboratories.

Renal tubular function tests

Reduced tubular function, with normal glomerular function, impairs the adjustment of the composition and volume of the urine with minimal effect on the plasma urea or creatinine concentration. The investigations used to diagnose tubular disorders can be divided into those that predominantly identify proximal tubular dysfunction and those that predominantly identify distal tubular dysfunction.

Proximal tubular function tests

Impaired solute reabsorption from the proximal tubules reduces isosmotic water reabsorption. Countercurrent multiplication may also be affected, and hence the ability to respond to ADH is reduced. A large volume of inappropriately dilute urine is produced.

The tubules cannot secrete hydrogen ions and so cannot reabsorb bicarbonate normally and therefore the urine is inappropriately alkaline for the degree of acidosis in the blood.

The reabsorption of potassium, phosphate, magnesium, urate, glucose and amino acids is impaired. The following findings may be present, and measurement may occasionally be useful.

Plasma

- Normal urea and creatinine concentrations (normal glomerular function).
- Low bicarbonate concentration with low pH (metabolic acidosis).
- Hypokalaemia, hypophosphataemia, hypomagnesaemia and hypouricaemia.

Urine

- Increased volume (polyuria).
- pH may be inappropriately high.
- Phosphaturia, glycosuria, uricosuria.
- Generalized amino aciduria.

Tubular proteinuria can be diagnosed by measuring specific low-molecular-weight proteins such as retinol-binding protein, NAG or α_1-microglobulin, which are increased in the urine because of reduced tubular reabsorption and increased renal tubular secretion. If there is detectable glycosuria, phosphaturia and non-selective amino aciduria, the condition is known as Fanconi's syndrome.

Distal tubular function tests

Impaired distal tubular function primarily affects urine acidification, with a failure to excrete hydrogen ions; the urinary pH rarely falls below 5.5. There is an impaired response to aldosterone involving reabsorption of sodium, and the urine contains an inappropriately high concentration of sodium for the renal blood flow. The associated findings may include the following.

Plasma

- Low bicarbonate and high chloride concentration with low pH (hyperchloraemic acidosis), hypokalaemia.

Urine

- Increased volume.
- pH inappropriately high.
- An inappropriately high sodium concentration, even if renal blood flow is low (inability to respond to aldosterone).
- An inappropriately low urea concentration, and therefore osmolality, even if ADH secretion is stimulated.

The ability to form concentrated urine in response to fluid deprivation depends on normal tubular function (countercurrent multiplication) and on the presence of ADH. Failure of this ability is usually due to renal disease, or cranial diabetes insipidus (see Chapter 2 for discussion of the fluid deprivation test). The investigation of renal tubular acidosis is covered in Chapter 4.

URINARY SODIUM AND OSMOLALITY

Urinary sodium estimation

Urinary sodium estimation may be used to differentiate acute oliguria due to renal damage from that due to renal circulatory insufficiency. *Aldosterone secretion will be maximal only if renal blood flow is reduced*; in such circumstances, functioning tubules respond appropriately by selectively reabsorbing sodium by distal tubular exchange mechanisms. A urinary sodium concentration of less than about 20 mmol/L is usually taken to indicate that tubular function is not significantly impaired.

Measurement of urinary osmolality

Measurement of urinary osmolality or other indicators of selective water reabsorption, such as urinary urea or creatinine concentrations, is less valuable than assaying urinary sodium concentration, as ADH secretion is stimulated for many other causes (see Table 3.1).

BIOCHEMICAL PRINCIPLES OF THE TREATMENT OF RENAL DYSFUNCTION

Acute kidney injury

Pre-renal AKI can sometimes be reversed by careful control of fluid balance and prompt treatment of hypovolaemia. Sometimes furosemide with mannitol or dopamine infusion may re-establish normal urine flow. If oliguria is due to parenchymal/intrinsic damage, some clinicians may restrict fluid and sodium intake, giving only enough fluid to replace losses and provide an adequate low-protein energy intake to minimize aggravation of uraemia. If possible, the cause of the intrinsic renal failure should be treated. Careful attention should be given to nephrotoxic drugs in AKI. In post-renal failure, prompt relief of the obstruction may reverse the situation.

A polyuric phase may occur, particularly on relief of urinary obstruction with excretion of potassium and magnesium, and this can result in hypovolaemia, hypokalaemia and hypomagnesaemia, which may need correcting.

Renal replacement therapy (RRT) such as dialysis or haemofiltration may improve fluid and electrolyte imbalances (see below). RRT is important to prevent dangerous hyperkalaemia or if resistant pulmonary oedema is present. Other indications for RRT include severe acidosis of pH less than 7.1, encephalopathy and uraemic pericarditis.

Chronic kidney disease

Careful control of fluid and electrolyte balance is important; water intake is usually only restricted if the plasma sodium concentration is not maintained. Similarly, sodium intake should be unrestricted unless contraindications such as hypertension or oedema exist. Plasma potassium monitoring is essential and potassium restriction may become necessary (and avoidance of potassium-retaining medication) if there is hyperkalaemia, which may need specific therapy and can be life threatening (see Chapter 5).

Control of blood pressure, lipids and, if present, diabetes mellitus (optimization of glycaemic control) is important and may help slow decline of eGFR and reduce cardiovascular risk, which is common in these patients. Angiotensin-converting enzyme inhibitors may slow the decline in renal function, although patients should be monitored for hyperkalaemia. Dietary modification with increased caloric intake along with reduced dietary protein intake may slow the decline in GFR by reducing protein catabolism. Nevertheless, it is also important to ensure that the patient is well nourished.

Tissue precipitation of calcium to phosphate may occur early in renal disease and is related to hyperphosphataemia and the calcium phosphate product (calcium concentration × phosphate concentration). This precipitation can be reduced by adequate fluid intake. Dietary phosphate restriction is used in the early stages of chronic renal dysfunction. If the plasma phosphate concentration is raised, phosphate-binding agents such as calcium acetate or carbonate may be indicated. When GFR is below 60 mL/min per 1.73 m^2, secondary hyperparathyroidism with elevated PTH concentration occurs. Giving small doses of active vitamin D, such as calcitriol or alfacalcidol, reduces the serum PTH, and improves bone histology, and leads to increased bone mineral density and helps avoid renal osteodystrophy, hypocalcaemia and tertiary hyperparathyroidism (see Chapter 6).

Recombinant erythropoietin and iron therapy may be indicated to treat anaemia when haemoglobin is less than 11 g/dL; this may slow progression of chronic renal disease.

Dialysis removes urea and other toxic substances from the plasma and corrects electrolyte balance by dialysing the patient's blood against fluid containing no urea and appropriate concentrations of electrolytes, free ionized calcium and other plasma constituents. The following are the principal forms of dialysis:

- Haemofiltration is a form of haemodialysis in which large volumes of fluid and solute can be removed through a highly permeable membrane; dialysis is dependent primarily on the blood pressure. Haemofiltration is mainly used for AKI whereas the following forms of dialysis are mainly for CKD.
- In haemodialysis, blood is passed through an extracorporeal circulation and dialysed across an artificial membrane with a solution of low solute concentration before being returned to the body.

Negative pressure on the dialysate side of the membrane can be varied to adjust the amount of water removed.

- In intermittent and continuous ambulatory peritoneal dialysis, the folds of the peritoneum are used as the dialysing membrane with capillaries on one side, and an appropriate fluid of higher osmolality is infused into the peritoneal cavity on the other. After a suitable time to allow for equilibration of diffusible solutes, depending on the type of peritoneal dialysis, the peritoneal cavity is drained and the cycle is repeated.

Dialysis is used in some cases of acute kidney injury until renal function improves, or as a regularly repeated procedure in suitable cases of end-stage kidney disease. It may also be used to prepare patients for renal transplantation.

RENAL CALCULI

Renal calculi are usually composed of products of metabolism present in normal glomerular filtrate, often at concentrations near their maximum solubility (Fig. 3.8).

Conditions favouring renal calculus formation

- A high urinary concentration of one or more constituents of the glomerular filtrate, due to:
  - a low urinary volume with normal renal function, because of restricted fluid intake or excessive fluid loss over a long period of time (particularly common in hot climates) – this favours formation of most types of calculi, especially if one of the other conditions listed below is also present,
  - a high rate of excretion of the metabolic product forming the stone, due either to high plasma and therefore filtrate levels or to impairment of normal tubular reabsorption from the filtrate.
- Changes in pH of the urine, often due to bacterial infection, which favour precipitation of different salts at different hydrogen ion concentrations.
- Urinary stagnation due to obstruction to urinary outflow or renal tract structural abnormality.
- Lack of normal inhibitors: urine normally contains inhibitors, such as citrate, pyrophosphate and glycoproteins, which inhibit the growth of calcium phosphate and calcium oxalate crystals respectively. Hypocitraturia may partly explain the renal calculi found in distal or type 1 renal tubular acidosis (see Chapter 4).

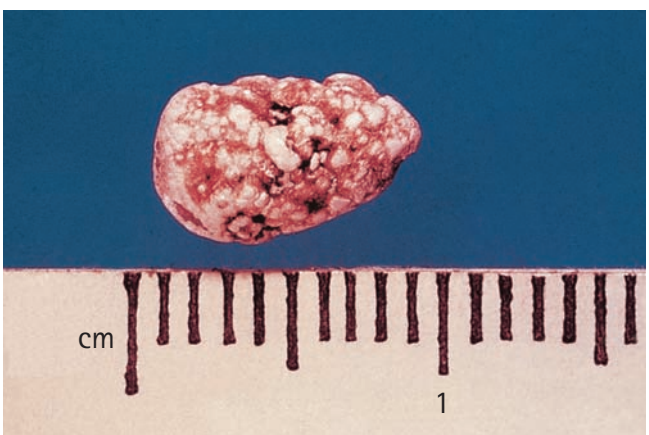

Figure 3.8 A renal calculus. Reproduced with permission from Nyhan WL and Barshop BA. *Atlas of Inherited Metabolic Diseases*, 3rd edition. London: Hodder Arnold, 2012.

Constituents of urinary calculi

Renal calculi may consist of the following (Box 3.3):

- calcium-containing salts:
  - calcium oxalate,
  - calcium phosphate,
- urate,
- cystine,
- xanthine.

Calculi composed of calcium salts

About 80 per cent of all renal stones contain calcium. Precipitation is favoured by hypercalciuria, and the type of salt depends on urinary pH and on the availability of oxalate. Any patient presenting with calcium-containing calculi should have plasma calcium and phosphate estimations performed, and, if the results are normal, they should be repeated at regular intervals to exclude primary hyperparathyroidism.

Hypercalcaemia causes hypercalciuria if glomerular function is normal. The causes and differential

Box 3.3 Some causes of renal calculi

Calcium phosphate or oxalate
Triple phosphate stones
Urate
Cystine
Complex/mixture stones
Rarities, e.g. xanthine, dihydroxyadenine or indinavir
Artefacts, e.g. fibrin/clots/Munchausen's syndrome

diagnosis of hypercalcaemia are discussed in Chapter 6. In many subjects with calcium-containing renal calculi the plasma calcium concentration is normal. Any increased release of calcium from bone (as in actively progressing osteoporosis, in which loss of matrix causes secondary decalcification, or in prolonged acidosis, in which ionization of calcium is increased) causes hypercalciuria; hypercalcaemia is unusual in such cases. In distal renal tubular acidosis there is an increased calcium load and, because of the relative alkalinity of the urine, calcium precipitation in the kidney and renal tract may occur – nephrocalcinosis.

Hypercalciuria has been defined as a daily urinary calcium excretion of more than 6.2 mmol in adult females and 7.5 mmol in adult males.

A significant proportion of cases remain in which there is no apparent cause for calcium precipitation. A common cause is hypercalciuria despite normocalcaemia (see Chapter 6).

Hyperoxaluria favours the formation of the very poorly soluble calcium oxalate, even if calcium excretion is normal. The source of the oxalate may be derived exogenously from the diet. Oxalate absorption is increased by fat malabsorption: calcium in the bowel is bound to fat instead of precipitating with oxalate, which is then free to be absorbed. Foods rich in oxalate include rhubarb, chocolate, beetroot, spinach, nuts and tea.

Primary hyperoxaluria, a rare inborn error, should be considered if renal calculi occur in childhood. There are two main types, 1 and 2, the former being more common. Type 1 is due to deficiency of alanine glyoxylate aminotransferase, and type 2 is due to deficient D-glycerate dehydrogenase. Hyperoxaluria (urinary oxalate greater than 400 µmol/24 h) is a more important risk factor for formation of renal stones than is hypercalciuria.

Calcium-containing calculi are usually hard, white and radio-opaque. Calcium phosphate may form 'staghorn' calculi in the renal pelvis, while calcium oxalate stones tend to be smaller and to lodge in the ureters, where they are compressed into a fusiform shape. Alkaline conditions favouring calcium phosphate precipitation and stone formation are particularly common in patients with chronic renal infection.

The treatment of calcium-containing calculi depends on the cause. Urinary calcium concentration should be reduced:

- by treating hypercalcaemia if present,
- if this is not possible, by reducing dietary calcium (although this alone may exacerbate hyperoxaluria) and oxalate intake,
- by maintaining a high fluid intake, unless there is glomerular failure.

Thiazide diuretics reduce urinary calcium excretion, and treatment of urinary tract infection may reduce the risk of calculi formation.

Struvite (magnesium ammonium phosphate)

These stones (about 10 per cent of all renal calculi) are associated with chronic urinary tract infections by organisms such as *Proteus* species capable of splitting ammonium. The urinary pH is usually greater than 7. These urease-containing bacteria convert urea to ammonia and bicarbonate.

Uric acid stones

About 8 per cent of renal calculi contain uric acid; these are sometimes associated with hyperuricaemia, with or without clinical gout. In most cases, no predisposing cause can be found. Precipitation is favoured in an acid urine. Uric acid stones are usually small, friable and yellowish brown, but can occasionally be large enough to form 'staghorn' calculi. They are radiolucent but may be visualized by ultrasound or by an intravenous pyelogram.

The treatment of hyperuricaemia is discussed in Chapter 20. If the plasma urate concentration is normal, fluid intake should be kept high and the urine alkalinized. A low-purine diet may help to reduce urate production and excretion.

Cystine stones

Cystine stones are rare. In normal subjects the concentration of cystine in urine is soluble, but in homozygous cystinuria this may be exceeded and the patient may present with radio-opaque renal calculi. Like urate, cystine is more soluble in alkaline than in acidic urine; the principles of treatment are the same as for uric acid stones. Penicillamine can also be used to treat the condition (see Chapter 27).

Miscellaneous stones

Xanthine stones

Xanthine stones are very uncommon and may be the result of the rare inborn error xanthinuria.

Indinavir stones

These are seen in patients with human immunodeficiency virus (HIV) infection who have been treated with the protease inhibitor indinavir. The stones are composed of pure protease inhibitor.

Other stones

Other rare stones may consist of dihydroxyadenine (due to adenine phosphoribosyltransferase deficiency) or poorly calcified mucoproteinaceous material associated with chronically infected kidneys (matrix stone). Some stones may be factitious, as sometimes found in patients with Munchausen's syndrome, who may add 'stones' to their urine.

Investigation of a patient with renal calculi

- If the stone is available, send it to the laboratory for analysis (Fig. 3.9).
- Exclude hypercalcaemia (see Chapter 6) and hyperuricaemia (see Chapter 20).
- Collect a 24-h specimen of urine for urinary volume, calcium and oxalate estimations. These tests will help to detect hypercalciuria or hyperoxaluria.
- If all these tests are negative, and especially if there is a family history of calculi, screen the urine for cystine. If the qualitative test is positive, the 24-h excretion of cystine and basic amino acids should be estimated.
- If fresh uninfected urine is alkaline despite a systemic metabolic acidosis, the diagnosis of renal tubular acidosis is likely (see Chapter 4). A pH more than 7 is suggestive of a urinary infection with a urea-splitting organism such as *Proteus vulgaris*, in which case consider struvite calculi. A midstream urine specimen is useful to exclude infection before diagnosing renal tubular acidosis.

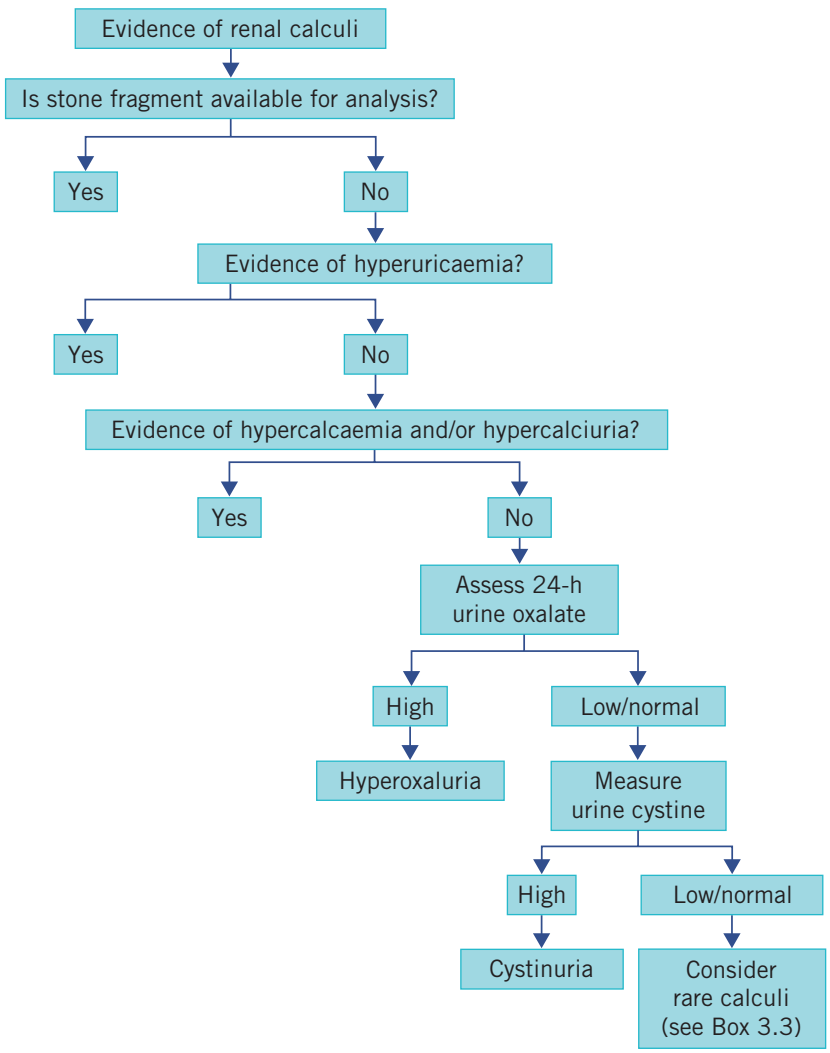

Figure 3.9 Algorithm for the investigation of renal calculi.

CASE 3

A 21-year-old man presented to the urology outpatient clinic because of renal calculi. There was also a family history of renal calculi.

Plasma

Sodium 137 mmol/L (135–145)
Potassium 4.2 mmol/L (3.5–5.0)
Urea 5.9 mmol/L (2.5–7.0)
Creatinine 108 µmol/L (70–110)
Estimated glomerular filtration rate (eGFR) > 90 mL/min per 1.73m^2
Albumin-adjusted calcium 2.43 mmol/L (2.15–2.55)
Phosphate 1.1 mmol/L (0.80–1.35)
Bicarbonate 27 mmol/L (24–32)
Urate 0.33 mmol/L (0.20–0.43)

Urinary excretion of both calcium and oxalate fell within the laboratory reference ranges. However, cystine was detected in the urine.

DISCUSSION

In conjunction with the family history and relatively young age of presentation, the results are suggestive of cystinuria manifesting cystine stones. This is one of the most common amino acidurias, although a rare cause of renal calculi, and is treated by increasing fluid intake and alkalinizing the urine.

- Low plasma urate and high urinary xanthine concentrations suggest xanthinuria, particularly in a child.
- Determination of urinary citrate (an inhibitor of some renal calculi) concentrations may sometimes be useful, as low concentrations may be found.
- If the cause is still unclear, consider the rare causes of renal calculi shown in Box 3.3.
- Renal tract imaging techniques to clarify the anatomy, such as ultrasound or intravenous pyelogram, may also be necessary.

Treatment of renal calculi

Apart from specific treatments (see above), patients with a tendency to form calculi are generally advised to drink more water. The aim is usually to increase the urinary volume to about 2–3 L in 24 h. Reducing calcium intake may not be advisable, as it may increase oxalate absorption and excretion. Calculi removal by fragmentation using extracorporeal shock wave lithotripsy has in some cases reduced the need for surgical intervention.

SUMMARY

- The kidneys are vital organs for the excretion of various waste products as well as for acid–base balance, fluid volume control, hormone production and metabolic function, such as calcium homeostasis.
- Plasma creatinine determination is a useful test of renal function, but plasma creatinine concentration can still remain within the reference range in the presence of a significant decline in renal function.
- Acute kidney injury (AKI) can be due to pre-renal, renal or post-renal causes. Raised plasma urea and creatinine concentrations occur along with fluid retention, anuria or oliguria, hyperkalaemia, hyperphosphataemia and metabolic acidosis.
- End-stage chronic kidney disease (CKD5) implies slow, irreversible renal disease. Raised plasma urea and creatinine concentrations occur initially and, as renal reserve declines, there is further hyperkalaemia, hyperphosphataemia, metabolic acidosis, hypocalcaemia and anaemia. This may necessitate renal support such as dialysis.
- Renal calculi can be the result of urinary stasis or infection associated with urinary supersaturation. The commonest calculi are calcium containing.
- Nephrotic syndrome is defined as gross proteinuria associated with oedema and hypoproteinaemia (discussed further in Chapter 19). This is a disorder of the renal glomerular membrane.
- Renal tubular disease can result in Fanconi's syndrome associated with acid–base and potassium disturbance, glycosuria, amino aciduria, hypouricaemia and hypophosphataemia.
- Renal replacement therapy, such as dialysis (Fig. 3.10), may be indicated in AKI and CKD5.