chapter 8:

DISORDERS OF WATER, ELECTROLYTES AND URATE BALANCES

OBJECTIVES

After studying this chapter you should be able to:

- describe the structure of the kidney;
- list the functions of the kidney;
- describe renal function tests;
- describe the types of renal failure;
- explain the causes and clinical consequences of selected disorders of water, electrolyte and urate homeostases;
- describe the investigation of selected disorders of water, electrolyte and urate homeostases;
- discuss the management and treatment of such disorders.

8.1 INTRODUCTION

Homeostasis is the maintenance of a stable internal environment within the body. This stability is necessary for optimum functioning of proteins, particularly enzymes, cells, tissues, organs and systems. Many substances have to be maintained at appropriate concentrations, including water, electrolytes, such as Na^+, K^+, Ca^{2+}, Mg^{2+} and P_i, and the acid–base components H^+ and HCO_3^-. In addition, waste products, such as urea and urate, must be kept below toxic levels. Normally biochemical and physiological mechanisms regulate and control the concentrations of all these components and, in general, homeostatic controls involve negative feedback mechanisms. A receptor detects unacceptable levels of a particular substance under homeostatic control and sends a signal to a regulatory center that initiates a response that corrects the imbalance and returns conditions to a physiologically acceptable state (*Figure 8.1*). Once normality returns, the receptor is no longer stimulated and the center ceases to respond. Disorders of homeostasis can occur, often as a result of failures in the control mechanisms or because of damage to the regulatory center by external agents.

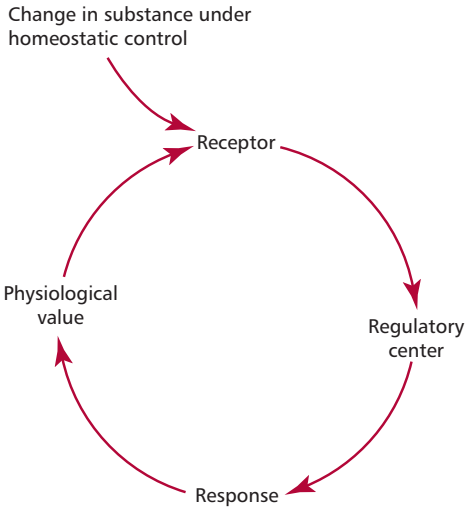

Figure 8.1 A generalized feedback mechanism. See text for details.

Within the body, the kidneys regulate water, electrolyte concentrations, including acid–base balance (*Chapter 9*), and excrete nitrogenous wastes, for example urate. Disorders of water, electrolyte and acid–base homeostasis and urate excretion account for a large number of investigations that are carried out in hospital laboratories.

8.2 KIDNEYS

The functions of the kidney include maintaining the volume of the plasma and its concentrations of electrolytes, such as Na^+ and K^+, and keeping its pH within normal physiological ranges. This is largely achieved by varying the amounts of water and salts excreted, the removal of excess H^+ (*Chapter 9*) and the regeneration of HCO_3^-. Kidneys also excrete waste products, such as urea, urate and creatinine, and produce the enzyme rennin and the hormones erythropoietin and calcitriol (also called 1α,25-dihydroxycholecalciferol, 1α,25DHCC). These control blood pressure, stimulate the production of erythrocytes by the bone marrow (*Chapter 13*) and regulate the absorption of Ca^{2+} by the gastrointestinal tract (GIT) (*Chapter 11*) respectively. Kidneys also synthesize prostaglandins and degrade hormones, such as insulin.

Each kidney is composed of an outer fibrous capsule, a cortex, a middle medulla and an inner pelvis region (*Figure 8.2A*). The tough capsule surrounding each kidney offers protection against trauma and prevents the entry of bacteria (*Chapter 3*). Kidneys are composed of about a million functional units called **nephrons** each composed of a tuft of capillaries called a glomerulus and a tubule. Tubules have four different regions: the proximal tubule, the loop of Henle, the distal tubule and the collecting duct (*Figure 8.2B*). The cortex

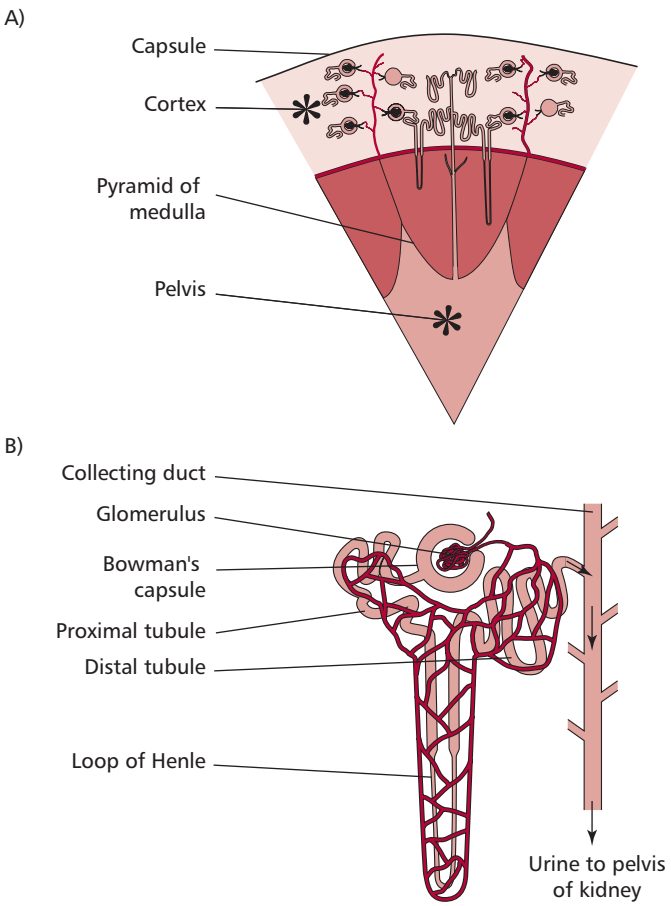

Figure 8.2 (A) Schematic showing the structure of the kidney. (B) The structural relationships between the glomerulus, proximal tubule, loop of Henle and distal tubule (nephron).

contains the Bowman's capsules and their glomeruli. The medulla is composed of the tubules arranged in pyramids that lead into calyces that, in turn, lead into the pelvis of the kidney. The pelvis drains into the ureters that take urine from the kidneys to the bladder.

Kidneys have a rich blood supply and normally receive about 25% of the cardiac output. The renal artery supplies blood at a high pressure to afferent arterioles that supply the glomerular capillaries. Glomerular capillaries drain into efferent arterioles that, in turn, divide to form a capillary network covering the nephron (*Figure 8.2B*). Blood eventually leaves each kidney in a renal vein. Blood is separated from the lumen of the tubules by three layers: the capillary endothelial cells, a basement membrane and specialized epithelial cells of the Bowman's capsule, called podocytes (*Figure 8.3*). Openings between the extensions of the podocytes are called fenestra. The basement membrane contains negatively charged glycoproteins that give the basement membrane an overall negative charge. The hydrostatic pressure of blood in the glomerulus is high at 10 kPa because of its direct route from the heart and because the diameters of afferent arterioles supplying the glomeruli are less than the efferent arterioles collecting blood from them. This forces the plasma to filter through the layers into the lumen of the capsule. The hydrostatic pressure of blood in the glomerulus is opposed by osmotic pressure of 4 kPa generated by its plasma proteins and a back pressure of 2.7 kPa exerted by the filtrate in the Bowman's capsule. Thus the effective pressure, P*eff*, is:

$$\mathbf{P}\mathit{\mathbf{eff}} = 10 - (4 + 2.7) = 3.3 \text{ kPa}$$

Water and small molecules are passively filtered into the Bowman's capsule leaving blood cells and plasma proteins in the capillary. Particles with a M_r less than 5000, such as electrolytes, sugars, amino acid, urea and some small polypeptides and proteins pass freely from the plasma through the glomerular wall into the lumen of the capsule. Substances with M_r up to 68 000, can penetrate to some extent but larger molecules, such as proteins above 68 000 are excluded because of their size and to some extent their charge, given that most plasma proteins are negatively charged at pH 7.4. Hence the initial filtrate in the capsule lumen has a composition similar to that of plasma except that it is largely free of protein. Most of the filtrate is reabsorbed as it passes along the nephron. The proximal tubule is responsible for bulk reabsorption of filtrate while the distal tubule is important for fine tuning its composition depending upon the needs of the body. Normally all the glucose, amino acids, K^+ and HCO_3^- and about 75% of the Na^+ are absorbed by energy dependent mechanisms. The reabsorption of water occurs passively and follows Na^+ reabsorption. Approximately 90% of the filtered Na^+ and 80% of water is reabsorbed in the distal tubule. More Na^+ is reabsorbed in the distal tubule by the cells exchanging it for K^+ and H^+. This exchange is controlled by

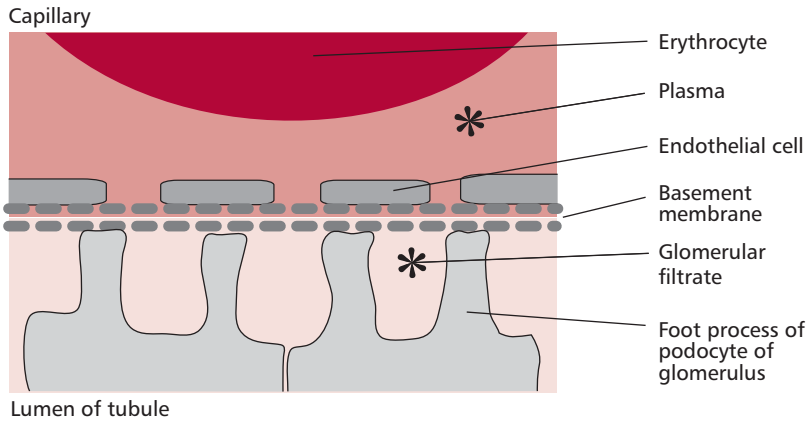

Figure 8.3 Schematic of the filtration unit of the glomerulus. See text for details.

aldosterone (*Chapter 7*). Between 6 and 12% of the filtered urate is excreted by the kidneys with the remainder being reabsorbed in the proximal convoluted tubule. Tubular fluid passes into collecting ducts that extend into the renal medulla and discharge urine into the renal pelvis. About 1 to 2 dm^3 of urine is produced per day depending on the amount of fluid intake with larger volumes being produced after increased intake of water.

RENAL FUNCTION TESTS

Renal function tests are used to detect the presence of renal diseases and assess their progress. They are, however, of little use in determining the causes of renal disease. The most widely used test is to measure the glomerular filtration rate (GFR), that is, the rate of filtrate formation by the kidneys. The value of the GFR depends on the net pressure across the glomerular membrane, the physical nature of the membrane and the surface area of the membrane that reflects the number of functioning glomeruli. All three factors can change as a result of disease and this will be reflected in the value of the GFR. In adults, the GFR is about 120 cm^3 per minute although it is related to body size, being higher in men than women. The GFR is also affected by age and declines in the elderly.

Measuring the GFR

The GFR is determined by measuring the concentration of a substance in the urine and plasma that is known to be completely filtered from the plasma at the glomerulus. This substance must not be reabsorbed nor secreted by renal tubules and must remain at a constant concentration in the plasma throughout the period of urine collection. It should also be possible to measure the concentration of this substance in the plasma and urine both conveniently and reliably. Inulin and creatinine have been used to assess GFR using the equation:

$$\mathbf{GFR} = (\mathbf{U_c} \times \mathbf{V}) \,/\, \mathbf{P_c}$$

where U_c is the concentration of substance in urine, P_c is the concentration of substance in plasma, V is rate of formation of urine in cm^3 per min giving the GFR units of $cm^3\ min^{-1}$.

Creatinine is derived from creatine phosphate in the muscle and the amount produced daily is relatively constant. An estimate of creatinine clearance can be made by a determination of the creatinine concentration in the plasma (*Figure 1.17*) and the creatinine content in a 24-h urine collection. Normal creatinine clearance in adults is between 115 and 125 $cm^3\ min^{-1}$. Reliable measurements of creatinine clearance are often difficult because of the need to obtain a complete and accurately timed urine sample.

Measurements of the concentration of serum creatinine may be used to assess renal function and they are easier to determine than creatinine clearance values. The concentration of creatinine in serum increases with deteriorating renal function but this test lacks sensitivity. For example, the GFR must fall to less than 50% of the original value before there is a significant increase in serum creatinine. This means that a normal serum creatinine value does not necessarily exclude the presence of renal disease.

RENAL FAILURE

Renal failure is the cessation of renal function and it can be acute or chronic. In acute renal failure there is rapid loss of renal function within hours or days, although the condition is potentially reversible and normal renal function can be regained. The deterioration is sudden, with increases in the concentrations of urea, creatinine and H^+ in serum. Patients with acute renal failure often, but not always, present with **oliguria**, where there is less than 400 cm^3 of urine

passed per day. Indeed, patients are sometimes **anuric** and do not pass any urine at all. Chronic renal failure is the gradual, progressive deterioration of kidney function. As kidney function declines, there is accumulation of waste products that eventually reach toxic levels in the blood and may affect other organs.

Acute renal failure

Acute renal failure can be categorized as prerenal, where the loss in renal function is due to a decrease in renal blood flow, postrenal, where the loss is due to an obstruction of the urinary tract, or intrinsic, where the loss is due to damage to the kidney itself.

Prerenal kidney failure can occur because of a decreased plasma volume following blood loss, burns, prolonged diarrhea or vomiting, decreased cardiac output or occlusion of the renal artery. Whatever the reason, prerenal acute renal failure results in a low GFR and decreased blood flow to kidneys. Aldosterone and antidiuretic hormone (*Section 8.3* and *Chapter 7*) release is stimulated by the low blood pressure and the kidneys respond by producing smaller volumes of concentrated urine. The biochemical indicators of prerenal acute renal failure include increased amounts of urea and creatinine in serum due to the low GFR, metabolic acidosis (*Chapter 9*), because of an inability of the kidneys to excrete H^+, and hyperkalemia (*Section 8.5*) because of the low GFR and acidosis. Postrenal kidney damage can be the consequence of a blockage of the urinary tract by, for example, renal calculi, kidney stones or neoplasms. These obstructions increase the hydrostatic pressure that opposes glomerular filtration. If this persists for a sufficiently long time it can cause **intrinsic** renal damage. If pre- or postrenal acute failures are not corrected, patients can develop intrinsic renal damage. A variety of conditions cause intrinsic acute renal failure. These include nephrotoxins, for example drugs such as aminoglycosides and analgesics, septic shock (*Chapters 2* and *4*), a low cardiac output (*Chapter 14*), burns or crush injuries and renal diseases, such as glomerulonephritis. Glomerulonephritis is inflammation of the renal cortex which affects the filtration mechanism of the kidney. It may develop following an infection (*Chapters 2, 3* and *5*).

Three phases occur in acute renal failure. The first is an oliguric phase with a low urine output. The second is a diuretic phase where the urine output increases while the third is a recovery phase when normal function returns. The oliguric phase is characterized by increased concentrations of K^+, urea, creatinine and H^+ in the serum. If the patient survives the oliguric phase, then urine output increases after a few days when the diuretic phase starts. The GFR increases during the diuretic phase and as the output of urine increases the amounts of urea and creatinine in the serum gradually fall. Tubular function may still be abnormal in this phase so that the acidosis may still persist. In the recovery phase, tubular cells regenerate and tubular function is restored to normal. The concentrations of urea and creatinine in serum decrease and K^+ returns to normal levels as the GFR improves.

The management of acute renal failure includes correction of prerenal factors if they are present. This could be achieved, for example by increasing the extracellular fluid volume by administering fluids. Biochemical monitoring of creatinine and K^+ is required and dialysis may be necessary when K^+ concentrations are high or when severe acidosis is present. The cause of the renal failure should be identified and treated wherever possible.

Chronic renal failure

Many diseases, such as glomerulonephritis, diabetes mellitus, hypertension and polycystic kidney disease, can lead to irreversible renal damage. All these conditions effectively decrease the number of functioning nephrons. Patients

may remain asymptomatic until the GFR falls below 15 $cm^3\ min^{-1}$. Chronic renal failure progresses to end-stage renal failure (ESRF) where dialysis or a kidney transplant is necessary for survival. Metabolic features of ESRF include the impairment of urinary concentration and dilution, abnormal electrolyte and H^+ homeostasis, the retention of waste products and decreased syntheses of erythropoietin and calcitriol. Chronic renal failure is accompanied by increases in the concentrations of K^+, urea, creatinine, P_i and H^+ and decreased Ca^{2+} in the plasma.

Patients with chronic renal failure often present with a number of clinical features including neurological symptoms, such as lethargy, growth failure, myopathy, anorexia, nausea, vomiting, anemia, hypertension, *nocturia* and impotence. The causes of many of these are not known but are probably due to the retention of toxins that cannot be excreted.

In some cases, it is possible to delay the progression of the disease by treating its cause. A number of measures may be taken to alleviate symptoms before dialysis becomes necessary. These include careful matching of water and Na^+ intake with their losses. High blood K^+ is controlled with oral ion exchange resins given as their Ca^{2+} or Na^+ salts (*Section 8.5*) whereas a high blood P_i is controlled by oral aluminum or magnesium salts that precipitate ingested phosphate in the GIT. A restriction of dietary protein may reduce the formation of nitrogenous waste.

8.3 DISORDERS OF WATER HOMEOSTASIS

Water is necessary to maintain the volumes of body compartments, for excretion of waste products and as a medium in which biochemical reactions occur. Water intake is variable and can depend, to some extent, on social habits but is supplied in the diet, from food as well as water and as a product of oxidative metabolism. Its loss is variable although an almost fixed amount, called the insensible loss, occurs from the GIT, skin and lungs. An average 70 kg man has 42 dm^3 of water distributed between various body compartments (*Figure 8.4*). Water accounts for 60% of body weight in men but only 55% in women given they have a higher proportion of fat. In disease, patients can be **dehydrated**, where water loss caused by vomiting and diarrhea exceeds gain, or **overhydrated**, with an accumulation of water in body compartments. The clinical features of dehydration and over hydration are listed in *Table 8.1*. A reduced extracellular fluid (ECF) volume causes a decline in blood circulation with decreased excretion of wastes and reduced oxygen and nutrient supply to the cells. Humans deprived of fluid intake die after a few days because the reduced total body fluid leads to a circulatory collapse.

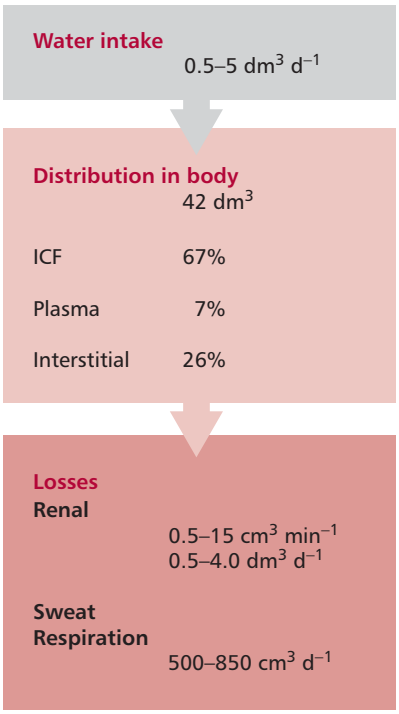

Figure 8.4 The distribution of body water. (ICF, intracellular fluid.)

Clinical feature affected	Dehydration	Overhydration
Pulse	increased	normal
Blood pressure	decreased	normal/increased
Skin turgor	decreased	increased
Eyeballs	soft/sunken	normal
Mucous membranes	dry	normal
Urine output	decreased	normal/decreased
Consciousness	decreased	decreased

Table 8.1 Clinical features affected in patients suffering dehydration and overhydration

The kidneys regulate water balance by varying the output of urine from 0.5 to 15 cm^3 min^{-1} to match water intake. When there is an excess of water, the kidneys lose water rapidly but in times of shortage it is conserved. The total body water is therefore kept constant. Water loss from the kidneys can be regulated by the hormone arginine vasopressin also called antidiuretic hormone (ADH). Antidiuretic hormone acts by altering the permeability to water of the collecting ducts in the kidneys. Osmoreceptor cells in the hypothalamus detect an increase or decrease in osmolality between the intracellular fluid (ICF) and ECF. An increase in the osmolality of the ECF stimulates the receptors and these, in turn, stimulate the release of ADH from the posterior pituitary gland (*Chapter 7*). Antidiuretic hormone then stimulates the kidneys to retain water and produce a more concentrated urine. The retention of water helps return the osmolality of the ECF back to normal. If the osmolality of the ECF is low, the osmoreceptors are not stimulated and ADH is not released. This results in water loss from the kidneys in dilute urine. The loss of water helps to increase the osmolality of the ECF back to normal values. A low blood or ECF volume can be detected by baroreceptors in the aortic arch and carotid sinus (*Chapter 14*). These receptors also stimulate a release of ADH and, indeed, this mechanism can override the release of ADH by osmolality to maintain blood volume and therefore circulation. Antidiuretic hormone interacts with a second hormone, aldosterone to maintain the normal volume and concentration of the ECF. Aldosterone, a steroid hormone, is produced by the adrenal cortex (*Chapter 7*) and released in response to a low ECF volume or blood pressure. It stimulates retention of Na^+ together with water in the kidneys returning the ECF volume back to normal.

There are distinctive signs and symptoms associated with loss of water from body compartments. For example, loss of water from the ICF results in cell dysfunction that presents clinically as confusion, lethargy and coma. Loss of water from the ECF decreases blood pressure, leading to renal shutdown and shock. A reduction in total body water (ICF and ECF) produces a combination of both effects.

All body fluids contain electrolytes (*Table 8.2*). The regulation of water content by ADH helps to maintain normal electrolyte concentrations within the body. The concentration of Na^+ and K^+ in the ICF and ECF are maintained largely by the activity of the plasma membrane Na^+/K^+-ATPase (*Chapter 11*). This enzyme acts as an energy-dependent pump that expels Na^+ from the cell in exchange for an intake of K^+ to maintain both at physiological concentrations. The concentrations of these ions are maintained within narrow ranges and, since water can flow freely through most membranes, the concentrations of Na^+ and K^+ are responsible for maintaining the appropriate osmolalities of these compartments. The movement of water from one compartment to another is mainly responsible for determining their volumes.

Homeostatic mechanisms exist to minimize changes in body water and electrolyte composition and are particularly important in maintaining the

	Intracellular Fluid	Extracellular Fluid
K^+ / mmol dm^{-3}	110	4
Na^+ / mmol dm^{-3}	10	135
Cl^- / mmol dm^{-3}	5	100
HCO_3^- / mmol dm^{-3}	15	28
PO_4^{2-} / mmol dm^{-3}	31	1

Table 8.2 Typical compositions of the ICF and ECF

Margin Note 8.1 Osmolality and the movement of water

Osmolality is the concentration of particles (molecules or ions) dissolved in a fluid. Compartments of cells and, indeed, the body in general are divided by selectively permeable membranes. Most biological membranes are freely permeable to water. If the osmolality is not the same on both sides of the membrane, then there will be a net movement of water from the side of low to high osmolality since the osmolality of a body compartment is proportional to the concentration of a compartment expressed as mmoles of solute per kg of water. In humans, the osmolality of serum is approximately 285 mmol kg^{-1}. Serum osmolality can be measured directly using an osmometer or, if the concentration of solute particles is known, it can be calculated in units of mmol kg^{-1} using the expression:

$$\text{Osmolality} = 2[Na^+] + 2[K^+] + [\text{glucose}] + [\text{urea}]$$

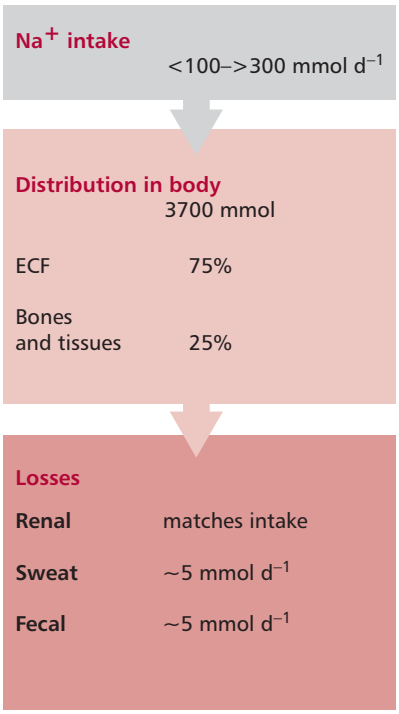

Figure 8.5 The distribution of body Na^+.

volume of the ECF. Water will remain in the extracellular compartment only if its osmolality is sufficiently high.

The assessment of fluid and electrolyte disorders in patients is a significant workload in the hospital pathology laboratory. In most cases, clinical tests to determine the concentrations of electrolytes in blood must be interpreted in conjunction with a clinical examination which involves taking the patient's clinical history, looking for signs and symptoms of hydration or dehydration and assessing kidney function.

8.4 DISORDERS OF Na^+ HOMEOSTASIS

Sodium ions are significant constituents of tissues, including bone, they control the volume of ECF and are required for normal neuromuscular functions. The intake of Na^+ is variable, from less than 100 mmol to more than 300 mmol day^{-1}. Losses are also variable, but renal loss is normally matched to intake. Small amounts of Na^+ are lost via skin and in feces and, under some circumstances, the GIT (*Chapter 11*) can be a major route of Na^+ loss, as in diarrhea.

The average 70 kg man contains 3700 mmol of Na^+ (*Figure 8.5*), of which 75% is found in the ECF. Hyponatremia and hypernatremia refer to serum concentrations of Na^+ below and above the reference range of 135–145 mmol dm^{-3}. Hyponatremia is caused by an excessive retention of water or the loss of Na^+, these two conditions resulting in different clinical features. The retention of water produces behavioral disturbances, headaches, confusion, convulsions and eventually coma. The symptoms associated with excessive loss of Na^+ are weakness, apathy, dizziness, weight loss and hypotension. Hyponatremia due to water retention is the more common. Water may be retained with or without an increase in total body Na^+. The former produces an **edema**, giving an edematous hyponatremia, whereas the latter results in nonedematous hyponatremia.

Edema is the excessive accumulation of fluid in interstitial compartments of the body, resulting from an increase in the concentration of Na^+ in the ECF. It results in swelling, which may be localized in, for example, legs and ankles (*Figure 8.6*) but can be more general in the chest cavity, abdomen and lungs. The major causes of edematous hyponatremia are heart failure, nephrotic syndrome and liver disease. All three reduce blood volume and stimulate aldosterone secretion, which, in turn, stimulates the retention of Na^+. The reduced blood volume also stimulates release of ADH from the posterior pituitary. Both result in more water than Na^+ being retained, giving rise to hyponatremia. Nephrotic syndrome leads to a loss of blood proteins to the urine, reduced concentrations of albumin leading to edema. The commonest cause of nephrotic syndrome is renal damage by diseases such as glomerulonephritis (*Chapter 3*). The treatment of edematous hyponatremia is aimed at its underlying cause, for example heart failure, kidney or liver diseases, and at removing the excess water and Na^+ using diuretics, and restricting water intake.

Nonedematous hyponatremia, the result of water overload without an increase in total body Na^+, is due to a decreased excretion of water from the syndrome of inappropriate secretion of ADH (SIADH), a severe renal failure or an increased intake by compulsive drinking or excessive parenteral fluid. The SIADH is a common finding in clinical practice. Patients present with reduced plasma osmolality, normal kidney function and a low output of urine. This syndrome is associated with many conditions, including malignancies, for example carcinoma of the lungs or bowel (*Chapter 17*), infections, such as pneumonia and tuberculosis (*Chapter 3*), trauma following, for example abdominal surgery, or it may be induced with drugs, such as chlorpropamide. All these conditions result in SIADH with water retention and a low urinary

output. The excessive water is distributed between ICF and ECF and so the clinical signs of water overload, edema, may be mild or absent. Treatment of SIADH is to reduce water intake to less than 750 cm^3 day^{-1} and to correct its underlying cause.

Hyponatremia from loss of Na^+ decreases the total body Na^+ of patients. The losses may occur from vomiting, diarrhea, kidneys (aldosterone deficiency), the effects of drugs, such as spironolactone, or a decreased dietary intake of Na^+, although this is very rare. The loss of Na^+ is always accompanied by water loss; as the volume of the ECF decreases the release of ADH is stimulated and the increased reabsorption of water produces hyponatremia. The decreased volume of ECF means that the patient presents with the clinical symptoms of dehydration. Treatment is aimed at correcting the Na^+ losses with intravenous infusions of 0.9% NaCl, and treating the underlying cause, for example steroid therapy for aldosterone deficiency as in Addison's disease (*Chapter 7*).

Hypernatremia is caused by water depletion, water and Na^+ depletion with the loss of water predominating, or to an excess of Na^+ (*Figure 8.7*). Its clinical features are variable but, in general, patients present with muscular weakness, hypertension, intense thirst (**polydipsia**) and polyuria. If fluid loss occurs, the features associated with dehydration may be present. However, if Na^+ is in excess, raised blood pressure or edema may be seen.

Water depletion results from a decreased intake, such as in comatose patients, infants or the elderly. The body conserves water by producing a low volume of concentrated urine. Increased water losses can also occur in diseases such as diabetes insipidus that result in large quantities of dilute urine (*Chapter 7*). Hypernatremia with water and Na^+ depletion occurs only if relatively more water than Na^+ is lost. It is commonly caused in children by excessive sweating or diarrhea. Patients respond by producing low volumes of concentrated urine. The condition may also occur during osmotic diuresis in patients with diabetes mellitus (*Chapter 7*) where both water and Na^+ are lost, together with other electrolytes in large volumes of dilute urine, producing hypernatremia and a decreased ECF. An excess of Na^+ in the ECF is caused by an increased intake or decreased excretion of Na^+. The intake may be oral, for example salt tablets or seawater, or parenteral as in the treatment of Conn's or Cushing's syndromes (*Chapter 7*). Both disorders produce dilute urine due to retention of Na^+ by the kidneys.

Hypernatremia is treated by oral administration of water. If this is not possible, then 5% dextrose is administered parenterally. If hypernatremia is due to an excessive Na^+ intake, measures to remove it must be considered.

8.5 DISORDERS OF K^+ HOMEOSTASIS

Potassium ions are necessary to maintain cell volume, for the optimal activities of a number of enzymes, and to maintain the resting potential of cell membranes and therefore neuromuscular functions, especially in the heart (*Chapter 14*). The intake of K^+ varies between 30 and 100 mmol day^{-1} and losses are equally variable. The kidneys excrete most ingested K^+ with a smaller amount being eliminated by the GIT. A high concentration of plasma K^+ stimulates the release of aldosterone (*Chapter 7*) that, in turn, increases the renal excretion of K^+. Gastrointestinal losses can be significant during vomiting and diarrhea. Only very small amounts of K^+ are lost in sweat. The average 70 kg human contains about 3600 mmol of K^+ (*Figure 8.8*), almost all being found in the ICF. Values for the concentration of K^+ in the serum below and above the reference range of 3.4 to 4.9 mmol dm^{-3} are called hypokalemia and hyperkalemia respectively. Hyperkalemia is the more common clinical condition.

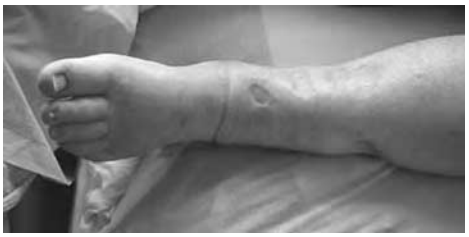

Figure 8.6 A massive edema of the lower limb. Courtesy of Charlie Goldberg, M.D., medicine.ucsd.edu/clinicalmed.

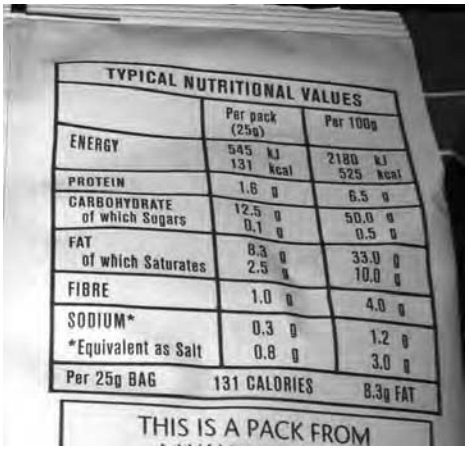

Figure 8.7 Many highly processed foods and snacks, such as potato crisps, contain high levels of Na^+ as its chloride salt (NaCl).

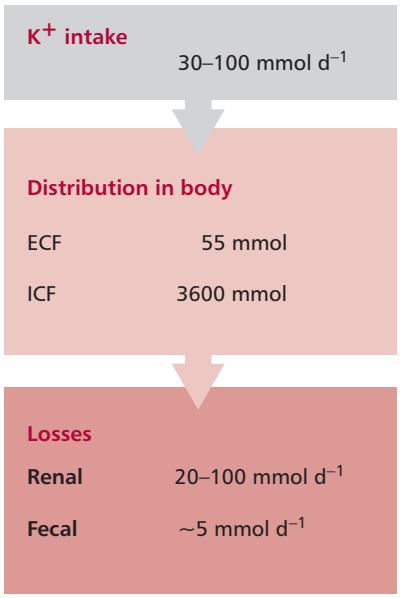

Figure 8.8 The distribution of body K^+.

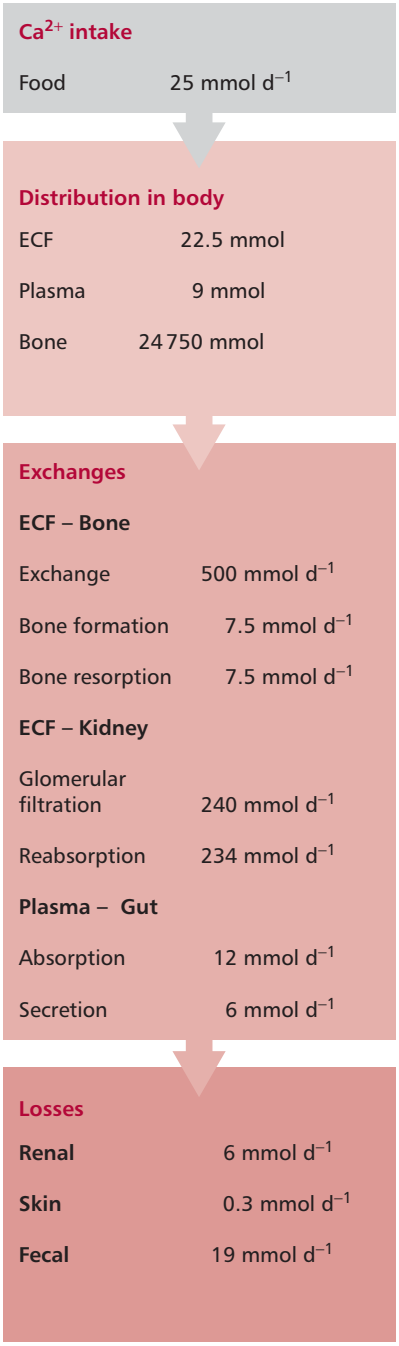

Figure 8.9 The distribution of body Ca^{2+}.

Unlike Na^+, the plasma K^+ concentration does not vary significantly with water loss or overload. However, hyperkalemia must be identified because concentrations of serum K^+ above 7 mmol dm^{-3} can result in cardiac arrest and death. Renal failure, acidosis, aldosterone deficiency, damage to cells and an excess intake of K^+ can all cause hyperkalemia. In renal failure, the kidneys are unable to excrete K^+ because of the low GFR. Further, acidosis, a common feature of renal failure, leads to hyperkalemia because the low pH of the ECF means that K^+ moves out of cells in exchange for H^+, to return the pH to reference values. A deficiency of aldosterone, such as in Addison's disease where the kidneys lose their ability to excrete K^+, can result in hyperkalemia. The destruction of cells during trauma can release large amounts of K^+ causing hyperkalemia. Lastly, an excessive oral or parenteral intake of K^+ is a rare cause of hyperkalemia. The treatment of hyperkalemia includes infusion of insulin and glucose to promote the entry of K^+ into cells. Severe hyperkalemia may require dialysis.

Hypokalemia is clinically significant, giving rise to muscular weakness and cardiac arrhythmias, hence patients often present with breathlessness and chest pain. The causes of hypokalemia include increased K^+ losses from the GIT or kidneys, alkalosis, certain clinical disorders, some drugs, or a decreased K^+ intake. Excessive losses from the GIT can occur during vomiting and diarrhea. Hypokalemia occurs in alkalosis because the pH of the ECF is high and H^+ moves from the ICF to the ECF as part of the buffering process, while K^+ moves in the opposite direction leading to hypokalemia. A number of disorders, for example, Cushing's and Conn's syndromes, are associated with increased cortisol and aldosterone production respectively. Both hormones have mineralocorticoid activity and stimulate the renal retention of Na^+ in exchange for K^+ causing hypokalemia. Drugs, such as carbenoxolone used to treat gastric ulcers (*Chapter 11*), can cause hypokalemia because of their mineralocorticoid activity. Decreases in oral or parenteral intakes of K^+ are rare but can lead to hypokalemia. Patients with hypokalemia are treated with oral K^+ salts. Severe hypokalemia may require intravenous infusions of K^+.

8.6 DISORDERS OF Ca^{2+} HOMEOSTASIS

Calcium is required for bone and teeth structure, the release of neurotransmitters and initiation of muscle contraction, as a cofactor for coagulation factors (*Chapter 13*), some enzyme activities and it also acts as an intracellular second messenger for a number of hormones (*Chapter 7*).

The normal dietary intake of Ca^{2+} of about 25 mmol day^{-1} is supplemented by the reabsorption of Ca^{2+} from gastrointestinal secretions. Approximately 19 mmol of Ca^{2+} is lost in the feces daily. The kidneys normally filter about 240 mmol of Ca^{2+} daily but, as most of this is reabsorbed by the tubules, normal renal loss of Ca^{2+} is only about 6 mmol per day (*Figure 8.9*). Calcium is the most abundant mineral in the body and the average adult contains approximately 1 kg or 25 000 mmol of Ca^{2+}. Approximately 99% of Ca^{2+} is present in the bone. About 500 mmol of Ca^{2+} is exchanged daily between bone and the ECF. The ECF contains about 22.5 mmol of Ca^{2+}, of which 9.0 mmol is present in the plasma. Approximately 47% of Ca^{2+} in plasma occurs as free ionized Ca^{2+}, 46% is protein bound and 7% is complexed with citrate or phosphate. Only free Ca^{2+} is physiologically active and its plasma concentration is controlled by homeostatic mechanisms involving the hormones parathyroid hormone (PTH), calcitriol and calcitonin (*Figure 8.10*). Parathyroid hormone is secreted by the parathyroid glands in response to a fall in the concentration of plasma ionized Ca^{2+} and *vice versa*. It stimulates the release of Ca^{2+} from bone, a process called **bone resorption**, and a decreased reabsorption of HCO_3^- by the kidneys that produces an acidosis, which helps to increase plasma ionized Ca^{2+} and stimulates the synthesis of calcitriol from cholecalciferol in the liver.

This hormone is also formed in the skin by the action of ultraviolet light on 7-dehydrocholesterol. Calcitriol increases Ca^{2+} and P_i absorption from the GIT and increases bone resorption. The physiological function of calcitonin remains unclear but it is known to reduce the concentration of Ca^{2+} in plasma by inhibiting both bone resorption and the renal reabsorption of Ca^{2+}.

The serum reference range for total Ca^{2+} is 2.20–2.60 mmol dm^{-3} and for free 1.20–1.37 mmol dm^{-3}. Values above and below these are called hypercalcemia and hypocalcemia respectively.

The renal damage associated with hypercalcemia is its most serious consequence. Hypercalcemia may suppress neuromuscular excitability causing constipation and abdominal pain and affect the CNS, resulting in depression, nausea and anorexia. The nausea may cause vomiting and therefore dehydration. Calcium can stimulate gastrin and therefore gastric acid secretion and so hypercalcemia may be associated with peptic ulcers (*Chapter 11*). Hypercalcemia may cause arrhythmias and in severe cases may result in cardiac arrest (*Chapter 14*). The commonest causes of hypercalcemia are malignant disease or primary hyperparathyroidism. Less common causes include thyrotoxicosis, vitamin D intoxication, thiazide diuretics and familial hypocalciuric hypercalcemia. Rare causes are tuberculosis, sarcoidosis, acromegaly, milk-alkali syndrome and idiopathic hypercalcemia of infancy.

Cancerous tumors of the lungs stimulate an increase in plasma Ca^{2+} by producing a PTH related protein (PTHrp) that resembles the structure of PTH (*Figure 8.11*). Cytokines and prostaglandins released by tumors that have metastasized to the bones, may lead to increased resorption of Ca^{2}**.** Primary hyperparathyroidism occurs most commonly due to a parathyroid adenoma, which is a benign tumor, and only rarely due to a parathyroid carcinoma. It affects both men and women at any age but is most common in postmenopausal women. In primary hyperparathyroidism, there is excessive PTH secretion that causes hypercalcemia and sometimes hypophosphatemia (*Section 8.7*), which increases bone turnover particularly of the metaphyses (*Figure 8.12*). Thyroid hormones have no direct effect on Ca^{2+} homeostasis but can cause increased bone turnover by increasing osteoclastic activity and giving rise to mild hypercalcemia during thyrotoxicosis. An excessive iatrogenic or accidental ingestion of vitamin D or thiazide diuretics that interfere with renal Ca^{2+} loss can also cause hypercalcemia.

Familial hypocalciuric hypercalcemia is a recently recognized autosomal dominant (*Chapter 15*) condition that develops from childhood. It is

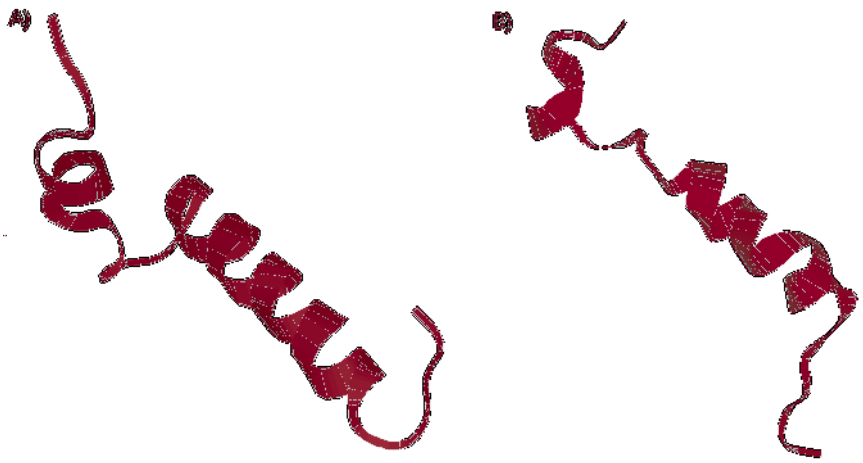

Figure 8.11 Molecular models of (A) PTH and (B) PTHrp. PDB files 1BWX and 1BZG respectively. Note the similarity in overall structures.

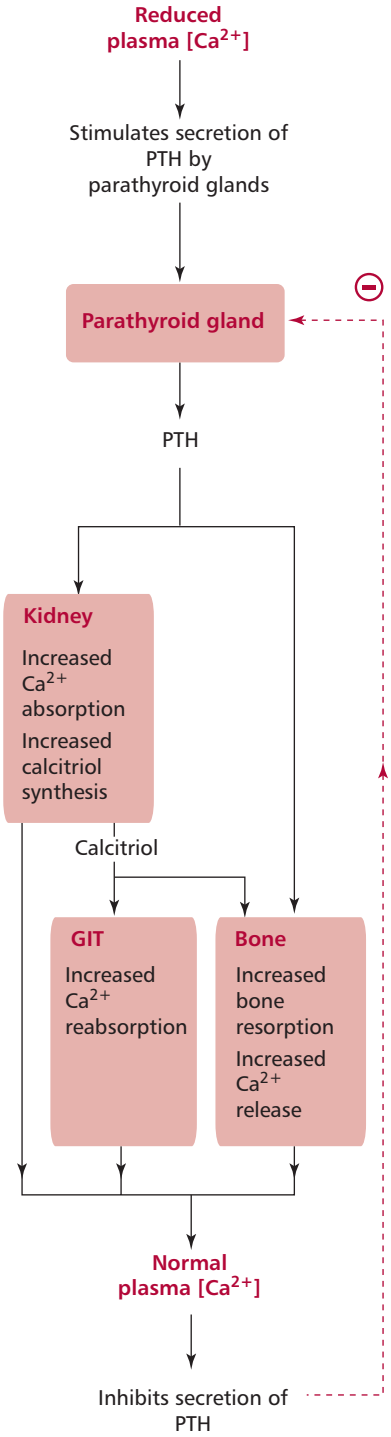

Figure 8.10 The hormonal regulation of the concentration of plasma Ca^{2+}.

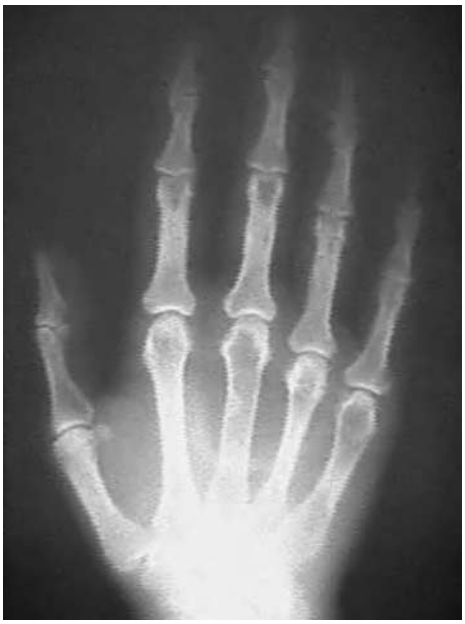

Figure 8.12 An isotope scan of hand and finger bones showing sites in the fingers with a decreased opacity where greater bone turnover has occurred because of increased Ca^{2+} resorption. Courtesy of Dr I. Maddison, London South Bank University, UK.

characterized by chronic hypercalcemia but is usually asymptomatic, with normal levels of PTH and no parathyroid adenoma. The mechanism underlying this condition is unknown. Both sarcoidosis and tuberculosis are granulomatous diseases. In these conditions, hypercalcemia occurs as there is increased production of calcitriol by macrophages in the granulomas. Hypercalcemia is occasionally seen in acromegaly, probably due to stimulation of calcitriol production by excess growth hormone. Hypercalcemia may occur in people who ingest large amounts of milk together with alkali antacids, such as HCO_3^-, to relieve symptoms of peptic ulceration. An alkalosis occurs that is believed to reduce renal Ca^{2+} excretion although the precise mechanism is still unclear. This milk-alkali syndrome is very rare as antacid treatment of peptic ulcers has been replaced by drugs that inhibit gastric acid secretion. The condition idiopathic hypercalcemia of infancy is associated with hypercalcemia because of an increased sensitivity to vitamin D in bone and the GIT but the precise mechanism underlying this hypercalcemia is unknown.

Patients who present with hypercalcemia are investigated for malignancy or primary hyperparathyroidism as this accounts for up to 90% of cases. If both malignancy and primary hyperparathyroidism are excluded, other causes must be considered and investigated (*Figure 8.13* and *Box 8.1*). A number

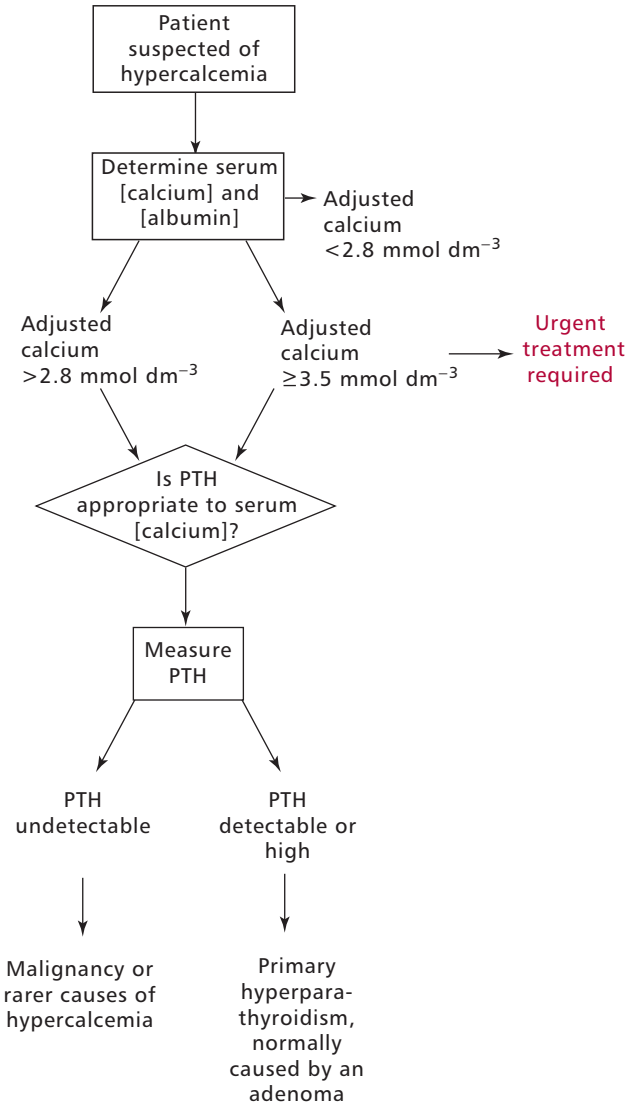

Figure 8.13 Overview of the clinical investigation of hypercalcemia. ***See also Box 8.1.***

BOX 8.1 Albumin and Ca^{2+}

Changes in the concentration of albumin (*Figure 8.14(A)*) in plasma affect the total Ca^{2+} concentration but not the free Ca^{2+} content. A high plasma albumin concentration gives rise to a high total plasma Ca^{2+} concentration and, conversely, a low plasma albumin concentration produces a low total plasma Ca^{2+} concentration (*Figure 8.14(B)*). The determination of total plasma or serum Ca^{2+} concentration can be misleading since it is affected by conditions that change the concentration of albumin. The effect of these changes can be overcome by measuring free Ca^{2+}. However, its determination is difficult and expensive and the usual solution is to calculate an adjusted value for total Ca^{2+} using the following formulae if the [albumin] is given in g dm^{-3} and [Ca^{2+}] in mmol dm^{-3}.

When [albumin] is less than 40 g dm^{-3} then:

$$\text{adjusted } [Ca^{2+}] = \text{measured concentration of total } Ca^{2+} + 0.02\,(40 - [\text{albumin}])$$

When [albumin] is more than 45 g dm^{-3} then:

$$\text{adjusted } [Ca^{2+}] = \text{measured concentration of total } Ca^{2+} - 0.02\,([\text{albumin}] - 45)$$

Since the free Ca^{2+} concentration is unaffected by variations in the concentration of albumin, clinical symptoms are not manifested. However, free Ca^{2+} competes with H^+ for negatively charged binding sites on albumin and changes in the concentration of free Ca^{2+} may occur in acute acid–base disorders, with clinical consequences (*Figure 8.15*). These do not, however, affect the total plasma Ca^{2+} concentration. In alkalosis, more H^+ dissociates from albumin allowing increased amounts of free Ca^{2+} to bind to it. This has the effect of increasing the protein bound Ca^{2+} fraction but at the expense of decreasing the free plasma Ca^{2+} leading to hypocalcemia. In acidosis, increasing amounts of H^+ bind to albumin as Ca^{2+} dissociates from it, decreasing the protein bound Ca^{2+} and increasing free plasma Ca^{2+} producing hypercalcemia.

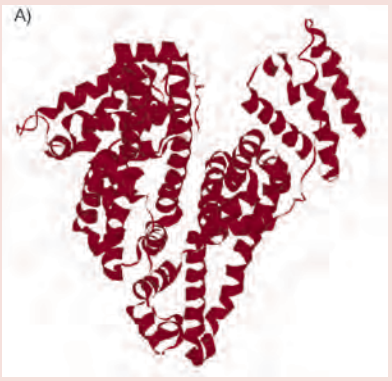

Figure 8.14 (A) Molecular model of human serum albumin. PDB file 1E78. (B) The effect of changes in the concentration of albumin on the concentration of total plasma Ca^{2+}.

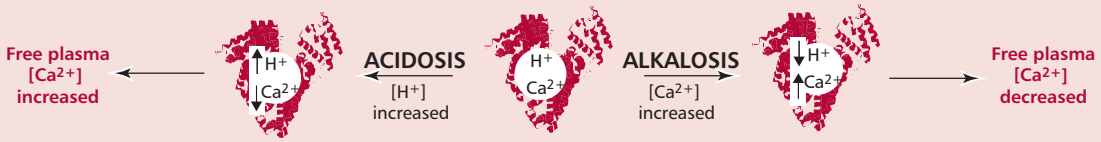

Figure 8.15 Effect of acidosis and alkalosis on the concentration of free Ca^{2+} in the plasma.

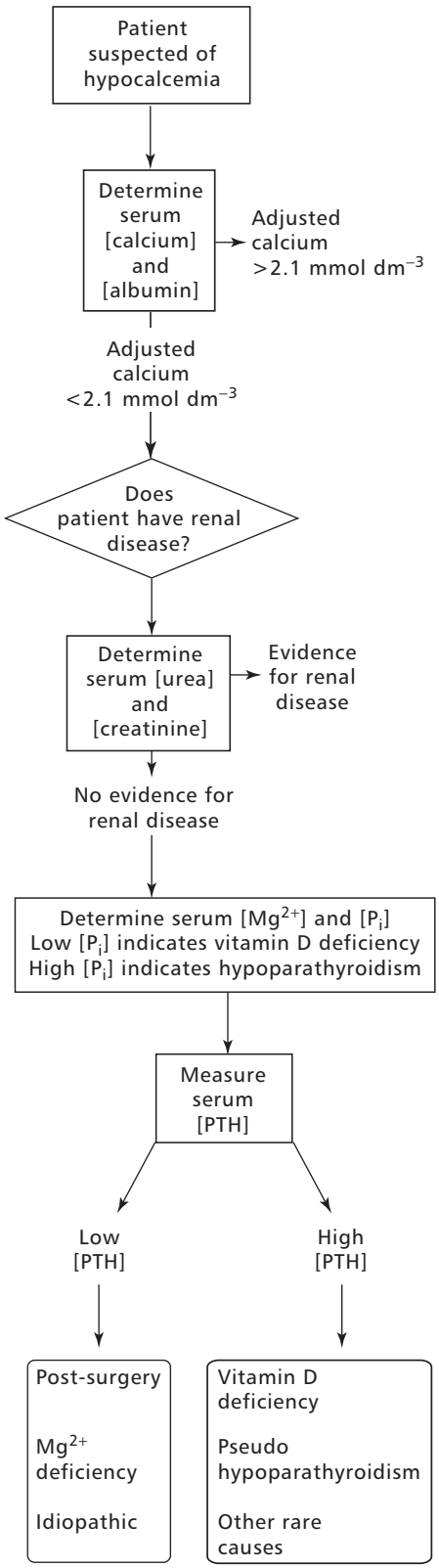

Figure 8.16 Overview of the clinical investigation of hypocalcemia.

of approaches are taken to managing hypercalcemia. The underlying cause should be treated wherever possible. Intravenous saline may be administered in dehydrated patients to restore the glomerular filtration rate and enhance Ca^{2+} loss and hydration. Drugs, such as frusemide, inhibit renal reabsorption of Ca^{2+} and promote its excretion while bisphosphonates lower Ca^{2+} levels by inhibiting bone resorption. In very severe cases, dialysis or emergency parathyroidectomy may be necessary. In some cases, an artefactual hypocalcemia may be reported when blood samples are erroneously collected into tubes containing ethylene diaminetetraacetic acid (EDTA). This anticoagulant is a chelator of Ca^{2+} and its use will lead to low values for Ca^{2+} concentrations.

The clinical effects of hypocalcemia include behavioral disturbances, paresthesiae, tetany, convulsions and cataracts. Its major causes are renal failure, Mg^{2+} and vitamin D deficiencies, hypoparathyroidism and pseudohypoparathyroidism. Chronic renal failure may decrease the reabsorption of Ca^{2+} by decreasing the synthesis of calcitriol leading to hypocalcemia. This may lead to bone disease because the increased output of PTH arising from the hypocalcemia can increase osteoclast activity. Magnesium ions are required for PTH secretion and its action and a deficiency produces hypocalcemia. A deficiency in vitamin D may arise from a poor diet, malabsorption (*Chapters 10* and *11*) or inadequate exposure to sunlight leading to an inadequate absorption of Ca^{2+} from food. Hypoparathyroidism, or a reduced activity of the parathyroid glands with decreased production of PTH, results in hypocalcemia. The condition can be congenital, where there is an absence of the parathyroid glands, or acquired hypoparathyroidism that may be idiopathic, or caused by autoimmune conditions or surgery, for example thyroidectomy. In pseudohypoparathyroidism, there is excessive PTH secretion because target tissues fail to respond to the hormone, producing a persistent hypocalcemia. This condition is more common in males than females and patients present with skeletal abnormalities including short stature, mental retardation, cataracts and testicular atrophy.

The investigation of hypocalcemia is outlined in *Figure 8.16*. The underlying cause of hypocalcemia should be treated wherever possible. Magnesium supplements may be prescribed in hypocalcemia due to Mg^{2+} deficiency, whereas calcitriol and its precursors may be prescribed in vitamin D deficiency. Oral Ca^{2+} supplements are prescribed in mild cases of hypocalcemia.

8.7 DISORDERS OF PHOSPHATE HOMEOSTASIS

Phosphate (P_i) combines with Ca^{2+} to form hydroxyapatite, the mineral component of bone and teeth and is also required for some enzymic activities, oxidative phosphorylation and the synthesis of 2,3-bisphosphoglycerate that regulates the dissociation of oxyhemoglobin (*Chapter 13*), the excretion of H^+ (*Chapter 9*) and for cell membrane integrity. The daily intake of P_i is about 40 mmol. The kidneys lose approximately 26 mmol daily and 14 mmol are lost in feces. The total body content of P_i in the average male is over 20 000 mmol (*Figure 8.17*) with 17 000 occurring in bone and 3000 in soft tissues, largely attached to lipids and proteins. Thus about 85% occurs in bone while the ICF and the ECF contain 15% and 0.1% respectively. The plasma concentration is about 1 mmol dm^{-3}. Approximately 80% of the plasma content occurs as free inorganic P_i, 15% is protein-bound and about 5% is complexed with Ca^{2+} and Mg^{2+}. Parathyroid hormone (*Figure 8.11*) and the hormone, calcitriol, control the homeostasis of P_i; the former decreasing the reabsorption by the kidneys and reducing its plasma concentration, the latter stimulating P_i absorption in the GIT and increasing the concentration.

The reference range for total serum P_i is 0.8–1.4 mmol dm^{-3} but a higher reference range applies in infancy and childhood. Hyperphosphatemia and hypophosphatemia are used to describe concentrations above and below the reference range respectively. Hypophosphatemia causes more damage than hyperphosphatemia but, fortunately, is less common.

Hyperphosphatemia may cause metastatic calcification, for example the deposition of calcium phosphate in soft tissues as the excess P_i precipitates with Ca^{2+} and causes hypocalcemia and tetany in affected patients. The commonest cause of hyperphosphatemia is renal failure where the GFR and P_i excretion decline. Hypoparathyroidism reduces renal excretion of P_i giving rise to hyperphosphatemia. In diabetic ketoacidosis (*Chapter 7*), a deficiency of insulin prevents the uptake of P_i by cells leading to hyperphosphatemia. Other causes are an increased intake of P_i or its release from damaged cells in intravascular hemolysis. Indeed, any condition where there is increased turnover of cells, for example following treatment of malignant disease with chemotherapy, results in release of P_i during cell destruction. Excessive intake, either oral or intravenous, is a rare cause and is more likely when there is also renal failure as in pseudohypoparathyroidism where there is resistance by the kidneys to PTH that decreases their excretion of P_i. A delay in the separation of plasma or serum from blood before analysis for P_i or hemolysis of a blood sample prior to its analysis can indicate artefactual hyperphosphatemia but this does not reflect the true clinical situation.

A number of biochemical tests are useful when investigating hyperphosphatemia. These include determining the concentrations of P_i, Ca^{2+}, urea and creatinine in serum and the concentration of P_i in urine. The following strategy has proved useful in investigating obscure causes of hyperphosphatemia. First, it is necessary to exclude artefactual causes. Secondly, serum concentrations of creatinine and urea should be determined to exclude renal failure. If the serum concentration of Ca^{2+} is normal or above reference values, vitamin D intoxication or untreated diabetes mellitus should be considered. Thirdly, if the plasma or serum concentration of Ca^{2+} is low, then hypoparathyroidism should be investigated. Finally, if the urinary concentration of P_i is low, then hypoparathyroidism is, again, a consideration, whereas a high urinary concentration indicates increased intake, malignancy or intravascular hemolysis. Patients with hyperphosphatemia are managed by treating the underlying cause wherever possible. The oral intake of aluminum, Ca^{2+} and Mg^{2+} salts may be used as these can bind P_i in the GIT reducing its absorption.

The clinical features of hypophosphatemia include paresthesiae, ataxia, coma, osteomalacia and muscle weakness. There may be increased susceptibility to infection possibly due to defective phagocytosis. The causes of hypophosphatemia are varied. Vitamin D deficiency results in a decreased synthesis of calcitriol and therefore decreased P_i absorption in the GIT. Increased renal loss of P_i may occur in primary hyperparathyroidism where increased secretion of PTH causes excessive renal loss of P_i. Certain diuretics that increase renal loss of P_i can cause hypophosphatemia. It may also occur during the recovery phase of diabetic ketoacidosis when patients are administered insulin, which promotes cellular uptake of P_i. Total body P_i may be depleted as a consequence of osmotic diuresis. There are a number of rare causes of hypophosphatemia. These include an inadequate dietary intake usually associated with parenteral nutrition, or when agents, such as aluminum hydroxide are used as antacids and prevent its absorption in the GIT, and in chronic alcoholics who have a complex and multifactorial condition with poor diet and reduced GIT absorption (*Chapter 11*).

Determination of the serum concentrations of P_i and Ca^{2+} and the urinary concentration of P_i are useful in investigating hypophosphatemia. The

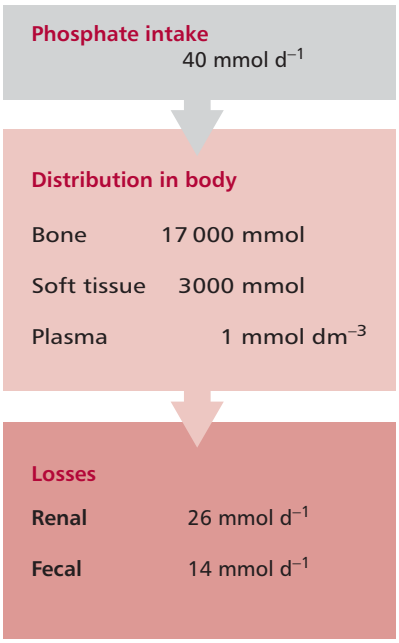

Figure 8.17 The distribution of body P_i.

following strategy may be used when its cause is not obvious. First, exclude causes such as alkalosis and chronic alcoholism. Secondly, a reduced urinary P_i suggests decreased dietary or parenteral intakes or increased cellular uptake, for example in insulin therapy. Thirdly, if the urinary concentration of P_i is above its reference range then excessive renal losses are occurring and the concentration of Ca^{2+} in the plasma or serum should be determined. If this is increased, then primary hyperparathyroidism or malignancy may be present. If, however, the concentration is low or normal, renal defects or inappropriate diuretic therapy are considerations. Hypophosphatemia should be managed by treating the underlying cause wherever possible. In some situations it may be necessary to administer oral or parenteral P_i.

8.8 DISORDERS OF Mg^{2+} HOMEOSTASIS

Magnesium is required to maintain the structures of ribosomes, nucleic acids and numerous proteins and acts as a cofactor for over 300 enzymes, including those involved in energy metabolism and protein synthesis. It is also required for normal cell permeability and neuromuscular functions. The usual dietary intake of Mg^{2+} is about 15 mmol day^{-1} and approximately 30% of this is absorbed in the GIT, the rest is lost in the feces. The adult human body contains over 1200 mmol of Mg^{2+} (*Figure 8.18*). Approximately 750 mmol is found in bone and about 450 mmol in muscle and soft tissues. The ECF contains only 15 mmol. Approximately 55% of plasma Mg^{2+} occurs as free ionized Mg^{2+}, 32% is protein-bound and 13% complexed with P_i or citrate.

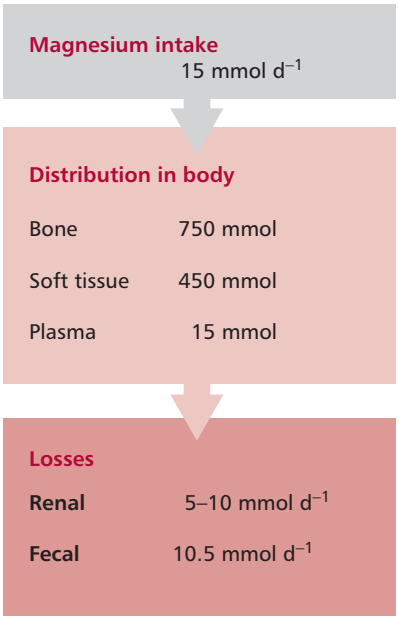

Figure 8.18 The distribution of body Mg^{2+}.

The kidneys lose 5 to10 mmol of Mg^{2+} daily but losses are adjusted to control Mg^{2+} homeostasis. An increased dietary intake of Mg^{2+} results in increased renal loss and *vice versa*. This is achieved principally by adjusting the reabsorption of Mg^{2+} by cells of the proximal tubules and loop of Henle. A number of factors influence the rate of excretion of Mg^{2+} including hypercalcemia and hypophosphatemia (*Section 8.6*) that decrease renal reabsorption and PTH, which stimulates renal retention.

The reference range for serum Mg^{2+} is 0.8–1.2 mmol dm^{-3}. Hypo- and hypermagnesemia refer to concentrations below and above the reference range respectively. Note that measurements of the concentration of Mg^{2+} in plasma or serum are unreliable indicators of its body status since only 1% of body Mg^{2+} occurs in the ECF.

The clinical effects of hypomagnesemia are similar to those seen in hypocalcemia and include tetany, muscle weakness, convulsions and cardiac arrhythmias. These effects are related to the role of Mg^{2+} in neuromuscular function. The causes of hypomagnesemia include decreased intake as in starvation (*Chapter 11*), poorly managed parenteral nutrition or malabsorption. Increased losses of Mg^{2+} as in osmotic diuresis in diabetics (*Chapter 7*), diuretic therapy, hyperaldosteronism and excessive losses from the GIT in prolonged diarrhea, GIT fistula and laxative abuse can also cause hypomagnesemia. The use of anticancer drugs (*Chapter 17*), such as cisplatinum, can damage the kidneys and prevent the renal reabsorption of Mg^{2+}. In alcoholism (*Chapter 12*), hypomagnesemia is believed to occur due to increased renal excretion, inadequate dietary intake, vomiting and diarrhea.

In many cases, the cause of hypomagnesemia is determined by clinical examination. However, measuring the urinary Mg^{2+} may be useful as the amount of Mg^{2+} excreted per day decreases with decreased intake. If hypomagnesemia occurs with increased renal excretion then losses are likely to be due to renal damage. Hypercalcemia may increase renal Mg^{2+} excretion

causing hypomagnesemia but hypocalcemia may occur in hypomagnesemia due to hypoparathyroidism.

In hypomagnesemia, the underlying cause should be treated wherever possible. Oral Mg^{2+} supplements may be adequate for mild cases but severe Mg^{2+} deficiency together with malabsorption may require intravenous infusions of Mg^{2+}.

The clinical effects of hypermagnesemia are also largely related to the role of Mg^{2+} in neuromuscular activities and include muscular weakness, respiratory paralysis and, in very severe cases, cardiac arrest. Acute or chronic renal failures are the commonest causes of hypermagnesemia; others include its release from damaged cells from, for example, crush injuries. Mild hypermagnesemia may occur in mineralocorticoid deficiency, as in Addison's disease. In rare cases, hypermagnesemia may occur from an increased oral or parenteral intake of Mg^{2+} or from the use of Mg^{2+} containing antacids or laxatives. When this does occur, it is usually combined with renal failure. The management of hypermagnesemia involves treating the underlying cause wherever possible. Hypermagnesemia due to renal failure may require dialysis.

8.9 DISORDERS OF URATE METABOLISM

In humans, the end product of the metabolism of the purines, adenine and guanine is urate (*Figure 8.19*). There are three sources of purines namely diet, the breakdown of endogenous nucleotides and nucleic acids and *de novo* synthesis. Most dietary nucleic acids are ingested in the form of nucleoproteins from which urate is produced by the GIT (*Chapter 11*). The degradation and *de novo* synthesis of purines are linked (*Figure 8.20*). The body urate pool, and therefore plasma concentration, depends upon the relative rates of urate formation and excretion. Both the kidneys and the GIT excrete urate with renal excretion accounting for approximately 66% of the total. Almost all the urate is filtered at the glomerulus but most is reabsorbed by the proximal tubule. However, both reabsorption and secretion occur in the distal tubule, so that the net effect is to excrete about 10% of the urate. Urate secreted into the GIT is metabolized to CO_2 and NH_3 by bacterial action or **uricolysis**.

The reference range for serum urate is 0.1 to 0.4 mmol dm^{-3}. However, there is a wide variation in the concentration of urate in plasma or serum even in health. Plasma urate concentration tends to be higher in males than females, is highest in obese individuals, those from affluent social classes and those with a high protein and alcohol intake. Thus hyperuricemia is defined as a concentration greater than 0.42 mmol dm^{-3} in men and more than 0.36 mmol dm^{-3} in women.

Hyperuricemia may arise as a result of increased production of uric acid or decreased excretion or both. Excessive synthesis may occur because of a defective synthetic metabolic pathway, stimulation of *de novo* purine synthesis by alcohol or by increased nucleic acid turnover, as in malignant disease, or the use of cytotoxic drugs. An excessive dietary intake of purines will also produce hyperuricemia. A decreased urate excretion may be due to a reduced GFR giving rise to hyperuricemia. Increased proximal tubular reabsorption and decreased distal tubular secretion of urate have similar effects. Lactate and β-hydroxybutyrate compete with urate for excretion by the distal tubule. Therefore lactic acidosis or ketosis (*Chapter 7*) are often associated with hyperuricemia. Some drugs, for example low doses of aspirin, can inhibit the distal tubular secretion of urate causing hyperuricemia.

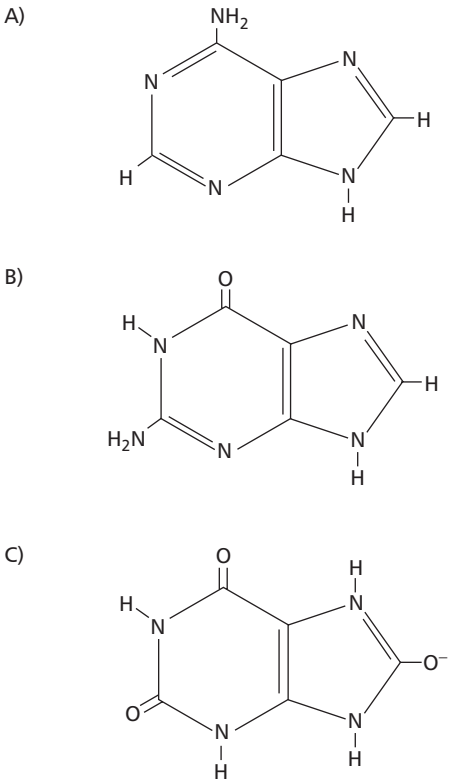

Figure 8.19 (A) Adenine, (B) guanine and (C) urate.

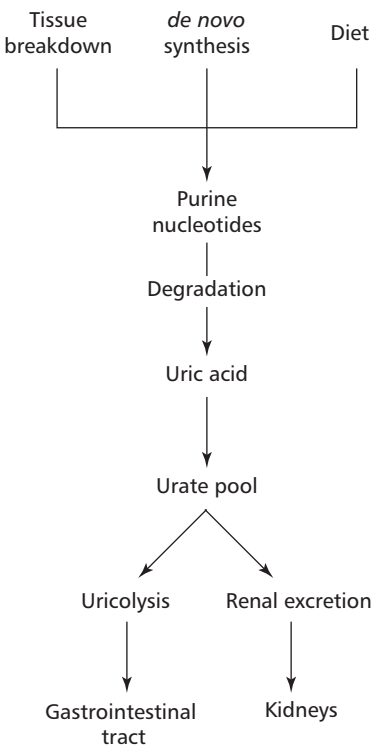

Figure 8.20 The synthesis and degradation of purine bases.

Urate has low solubility and the ECF easily becomes saturated at concentrations just above the upper limit of the reference range. There is a tendency for crystalline monosodium urate to form in people with hyperuricemia, giving rise to gout. Crystals of monosodium urate (*Figure 8.21(A)*) tend to form in cartilage and synovial fluid of joints and particularly those of the big toe causing gout (*Figure 8.21(B)*). The crystals are phagocytosed by neutrophil leukocytes and may cause damage to lysosomal membranes within these cells (*Chapter 16*). As a consequence, lysosomal contents are released, causing damage to both leukocytes and surrounding tissues with an associated inflammatory response (*Chapter 4*). Gout may be primary, with no known cause, or secondary, as a consequence of another disorder. Primary gout is characterized by recurrent attacks of arthritis. It is more common in men than women. The metabolic defect in patients is unknown but a number of abnormalities may be responsible for the overproduction of urate and therefore increased urinary urate output. In many patients there is a combined defect of urate overproduction together with its impaired renal excretion. Patients with primary gout often have deposits of urate in their soft tissues and some can develop renal stones composed of urate salts. The risk that a normal person will develop gout varies with their urate concentration. The annual incidence of gout in men is low, about 0.1%, when the urate concentration is less than 0.42 mmol dm^{-3}. This increases to 0.6% when the concentration is 0.42–0.54 mmol dm^{-3} and 5% when urate concentrations are greater than 0.54 mmol dm^{-3}. The reason for the onset of acute attacks in gout is unclear since a sharp rise in the concentration of urate is not usually demonstrable.

Secondary gout is rare but can arise from a number of other disorders including myeloproliferative disorders (*Chapter 17*) such as polycythemia vera, where the hyperuricemia is due to an increased cell turnover, the use of cytotoxic drug therapy that increases cell destruction and the breakdown of nucleic acids, and psoriasis with its increased turnover of skin cells.

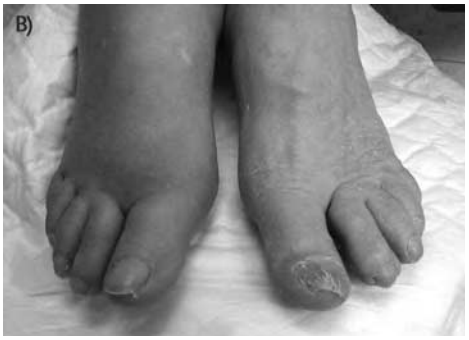

Figure 8.21 (A) Crystals of monosodium urate viewed using polarized light. (B) Gout of the right big toe showing diffuse swelling and inflammation centered where the toes join the foot but also extending over much of the foot. Courtesy of Charlie Goldberg, M.D., medicine.ucsd.edu/clinicalmed.

A diagnosis of gout is made on clinical grounds, a demonstration of hyperuricemia and a satisfactory response to uricosuric drugs. A high plasma urate concentration does not always mean that the patient has gout, that is high plasma urate concentration makes the diagnosis of gout more likely, whereas a consistently low plasma urate concentration excludes the diagnosis. To confirm diagnosis it is necessary to aspirate the joint fluid during an acute attack. The finding of urate crystals, 2–10 μm long and needle shaped, within neutrophils will confirm the diagnosis.

Anti-inflammatory drugs, such as indomethacin, are used to treat acute attacks of gout but have no effect on the hyperuricemia which is treated with a diet low in protein and alcohol. Urate lowering drugs, for example allopurinol, that prevent the formation of urate and decrease *de novo* synthesis of purines, are used in long-term treatment or when plasma urate levels are persistently higher than 0.6 mmol dm^{-3}.

Hypouricemia, where the concentration of urate in serum is below the reference range, is uncommon and not of clinical significance. Its occurrence is due to a decreased urate synthesis, as in congenital xanthine oxidase deficiency and severe liver disease, or to increased excretion of urate as seen in renal tubular disorders, such as the Fanconi syndrome. Hypouricemia may also result from excessive use of drugs such as allopurinol.

CASE STUDY 8.1

Ted was admitted to hospital following a car accident. The following results were obtained on a serum specimen three days later. Reference ranges are given in parentheses.

Urea	45 mmol dm^{-3}	(2.4–6.5 mmol dm^{-3})
Na^+	132 mmol dm^{-3}	(133–145 mmol dm^{-3})
K^+	6.9 mmol dm^{-3}	(3.4–4.8 mmol dm^{-3})
HCO_3^-	13 mmol dm^{-3}	(21–28 mmol dm^{-3})
Osmolality	332 mmol kg^{-1}	(280–290 mmol kg^{-1})

Questions

(a) What may be the primary cause of these results?

(b) Suggest reasons why Ted shows hyperkalemia and low serum HCO_3^-.

CASE STUDY 8.2

Arnie, a 25-year-old man, presented with a history of severe diarrhea, abdominal pain, weight loss, cramp in the arms and legs and tetany. He had suffered several previous episodes of diarrhea and abdominal pain. His serum was investigated and yielded the following results. Reference ranges are given in parentheses.

Na^+	140 mmol dm^{-3}	(133–145 mmol dm^{-3})
K^+	3.3 mmol dm^{-3}	(3.4–4.8 mmol dm^{-3})
Urea	5.8 mmol dm^{-3}	(2.4–6.5 mmol dm^{-3})
Total Ca^{2+}	2.40 mmol dm^{-3}	(2.15–2.46 mmol dm^{-3})
Phosphate	1.0 mmol dm^{-3}	(0.8–1.44 mmol dm^{-3})
Albumin	42 g dm^{-3}	(38–48 g dm^{-3})
Mg^{2+}	0.39 mmol dm^{-3}	(0.8–1.2 mmol dm^{-3})

Questions

(a) Explain the significance of these results.

(b) Suggest ways in which Arnold should be treated.

CASE STUDY 8.3

John, a 58-year-old obese lecturer woke in the middle of the night with severe pain in his large toe which was hot, swollen and red. The pain was so intense he could not place his foot on the floor. John had been to a dinner party the night before. In the morning he visited the local hospital where a blood sample was taken and analyzed for serum urate. Reference ranges are given in parentheses.

Serum urate 0.81 mmol dm^{-3} (0.1–0.4 mmol dm^{-3})

Questions

(a) What is the most likely diagnosis?

(b) What further investigations should be performed?

(c) How should John be treated?

8.10 SUMMARY

It is essential to maintain appropriate levels of water and electrolytes in the body so that metabolic reactions can function effectively. The stable environment within the body is maintained by homeostatic mechanisms, which return levels to normal, following a shift in equilibrium. In addition, waste products such as urate need to be removed to prevent toxicity. The kidneys help to maintain the balance of water, electrolytes and waste products and a number of renal function tests are available to assess their function in cases of suspected renal failure. Dehydration, possibly as a result of gastrointestinal disease causing diarrhea and vomiting, is a severe, life-threatening condition. Disorders of electrolyte balance can involve a lack or excess of the electrolyte in question. Thus distinct syndromes can occur with disorders affecting the levels of Na^+, K^+, Ca^{2+}, Mg^{2+} and P_i. Disorders of urate metabolism may result in high levels of urate in the blood, leading to gout and renal stones, whereas low levels of urate in the blood are rare.

QUESTIONS

1. Robin was rescued from a raft at sea. He had been without food or water for several days.
   a) What will have happened to Robin's body compartments?
   b) Should he have drunk seawater to survive?

2. Jane, an 80-year-old woman who lives alone was suffering from a urinary tract infection and had little food or water for several days. She was found in a drowsy confused state by her neighbors and taken to hospital. An analysis of her serum gave Na^+ and urea of 160 and 20 mmol dm^{-3} respectively. Glucose and K^+ concentrations were within their references ranges. Account for Jane's symptoms and test results.

3. Hyperkalemia may be caused by which one of the following?
   a) hemolysis;
   b) delayed separation of plasma;
   c) increased intake of K^+ supplements;
   d) renal failure;
   e) all of the above.

4. What is the adjusted serum Ca^{2+} concentration for a patient with a serum albumin concentration of 29 g dm^{-3} and a total serum Ca^{2+} of 1.78 mmol dm^{-3}?

5. Which one of the following does NOT cause hyperuricemia?
   a) excessive dietary purine intake;
   b) malignant disease;
   c) chronic renal failure;
   d) hypomagnesemia;
   e) psoriasis.

6. Alice, a 48-year-old woman, was treated by parathyroidectomy for her hyperparathyroidism. Unfortunately, she developed hypocalcemia and was placed on vitamin D therapy although the hypocalcemia proved difficult to control. Eventually, Alice was seen in outpatients complaining of feeling unwell and vomiting. Her blood results showed her to be hypercalcemic but other values were within their reference ranges. Suggest the most plausible reason for Alice's hypercalcemia.

7. Explain why hypercalcemia is often associated with malignancy.

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