Chapter 3

Water, sodium and potassium

Introduction

Water distribution

Water accounts for approximately 60% of body weight in men and 55% in women, the difference reflecting the typically greater body fat content in women. Approximately 66% of this water is in the intracellular fluid (ICF) and 33% is in the extracellular fluid (ECF); only 8% of body water is in the plasma (Fig. 3.1). Water is not actively transported in the body. It is, in general, freely permeable through the ICF and ECF, and its distribution is determined by the osmotic contents of these compartments. Except in the kidneys, the osmotic concentrations, or osmolalities, of these compartments are always equal: they are isotonic. Any change in the solute content of a compartment engenders a shift of water, which restores isotonicity.

The major contributors to the osmolality of the ECF are sodium (a cation, see p.2) and its associated anions, mainly chloride and bicarbonate; in the ICF, the predominant cation is potassium. Other determinants of ECF osmolality include glucose and urea, although urea diffuses freely across the plasma membranes, so changes in ECF urea concentration do not affect water distribution. Protein makes a numerically small contribution of approximately 0.5%. This is because osmolality is dependent on the molar concentrations of solutes: although the total concentration of plasma proteins is approximately 70 g/L, their high molecular mass results in their combined molar concentrations being <1 mmol/L. However, because the capillary endothelium is relatively impermeable to protein and the protein concentration of interstitial fluid is much less than that of plasma, **the osmotic effect of proteins is an important factor in determining water distribution between these two compartments**. The contribution of proteins to the osmotic pressure of plasma is known as the 'colloid osmotic pressure' or 'oncotic pressure' (see Chapter 16).

Under normal circumstances, the amounts of water taken into the body and lost from it are equal over a period of time. Water is obtained from the diet and oxidative metabolism, and it is lost through the kidneys, skin, lungs and gut (Box 3.1). About 170 L water is filtered by the kidneys every 24 h, and almost all of this is reabsorbed. In adults, the minimum volume of urine necessary for normal excretion of waste products is about 500 mL/24 h, but as a result of obligatory losses by other routes, the minimum daily water intake necessary for the maintenance of water balance is approximately 1100 mL. This increases if losses are abnormally large, for example, with excessive sweating or diarrhoea. Water intake is usually considerably greater than this minimum requirement, but the excess is easily excreted through the kidneys.

Sodium distribution

The body of an adult man contains approximately 4000 mmol sodium, 70% of which is freely exchangeable, the remainder being complexed in bone. The majority of the exchangeable **sodium is extracellular**: normal ECF sodium concentration is 133–146 mmol/L, whereas that of the ICF is only 4–10 mmol/L. Most cell membranes are relatively impermeable to sodium, but some leakage into cells occurs and the gradient is maintained by active pumping of sodium from the ICF to the ECF by Na^+,K^+-ATPase (the sodium–potassium pump).

As with water, sodium input and output normally are balanced. The normal intake of sodium in the developed world is 100–200 mmol/24 h, but the obligatory sodium loss, via the kidneys, skin and gut, is <20 mmol/24 h. Thus, the sodium intake necessary to maintain sodium balance is much less than the normal intake; excess sodium is excreted in the urine. Despite this, excessive sodium intake may be harmful: there is evidence that it is a contributory factor in hypertension.

It is important to appreciate that there is a massive internal turnover of sodium. Sodium is secreted into the gut at

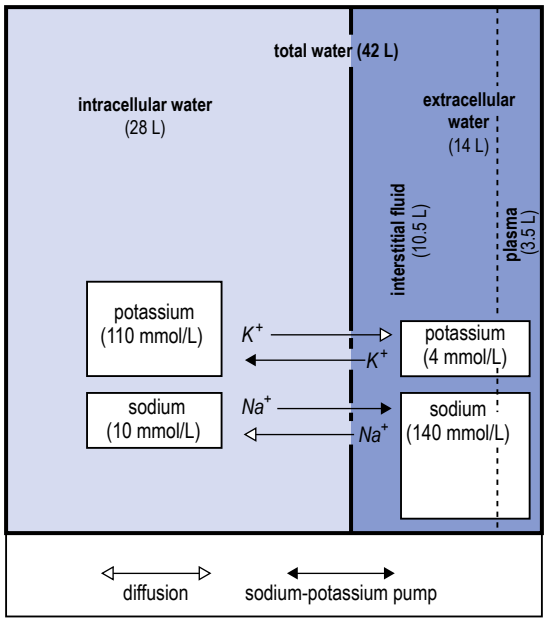

Fig. 3.1 Distribution of water, sodium and potassium in the body of a 70-kg man. In women, the distribution is similar but water accounts for a lower percentage of body weight (50–55%). In children and infants, the proportion of interstitial fluid water is higher and water makes up a higher percentage of body weight (75–80%). Note that although plasma volume is approximately 3.5 L, blood volume in a 70-kg man is approximately 5.5 L.

a rate of approximately 1000 mmol/24 h and is filtered by the kidneys at a rate of 25 000 mmol/24 h, the vast majority being regained by reabsorption in the gut and renal tubules, respectively. If there is even a partial failure of this reabsorption, sodium homoeostasis will be compromised.

Potassium distribution

Potassium is the predominant intracellular cation. Some 90% of the total body potassium is free and therefore exchangeable, whereas the remainder is bound in red blood cells, bone and brain tissue. However, only approximately 2% (50–60 mmol) of the total is located in the extracellular compartment (see Fig. 3.1), where it is readily accessible for measurement. Plasma potassium concentration is not, therefore, a reliable index of total body potassium status, but because of the effect of potassium on membrane excitability, it is important in its own right. The potassium concentration of serum is 0.2–0.3 mmol/L higher than that of plasma (see p.22), because of the release of potassium from platelets during clot formation, but this difference is not usually of practical significance.

Box 3.1 Daily water balance in an adult

Obligatory losses	mL	Sources	mL
skin	500	water from oxidative metabolism	400
lungs	400	minimum in diet	1100
gut	100		
kidneys	500		
total	**1500**	**total**	**1500**

The minimum intake necessary to maintain balance is approximately 1100 mL. Actual water intake in food and drink is usually greater than this: the excess over requirements is excreted in the urine.

There is a constant tendency for potassium to diffuse down its concentration gradient from the ICF to the ECF, opposed by the action of Na^+,K^+-ATPase, which transports potassium into cells. Potassium homoeostasis and its disorders are described later in this chapter.

Water and Sodium Homoeostasis

Water and extracellular fluid osmolality

Changes in body water content independent of the amount of solute will alter the osmolality (Fig. 3.2). The **osmolality of the ECF** is normally maintained in the range 275–295 mmol/kg water. Any loss of water from the ECF, such as occurs with water deprivation, will increase its osmolality and result in movement of water from the ICF to the ECF. However, a slight **increase in ECF osmolality** will still occur, stimulating the hypothalamic thirst centre, causing thirst and thus promoting a desire to drink, and stimulating the hypothalamic osmoreceptors, which causes the release of **vasopressin** (antidiuretic hormone [ADH]).

Vasopressin renders the renal collecting ducts permeable to water (its combination with V2 receptors results in the insertion of aquaporins [water channels] into the normally impermeable apical membrane of the cells of the collecting tubules), permitting water reabsorption and concentration of the urine. The maximum urine concentration that can be achieved in humans is about 1200 mmol/kg. The osmoreceptors are highly sensitive to osmolality, responding to a change of as little as 1%. Plasma vasopressin concentration declines to very low values at an osmolality of 284 mmol/kg, but it increases sharply if osmolality increases above this level (Fig. 3.3A). However, if an

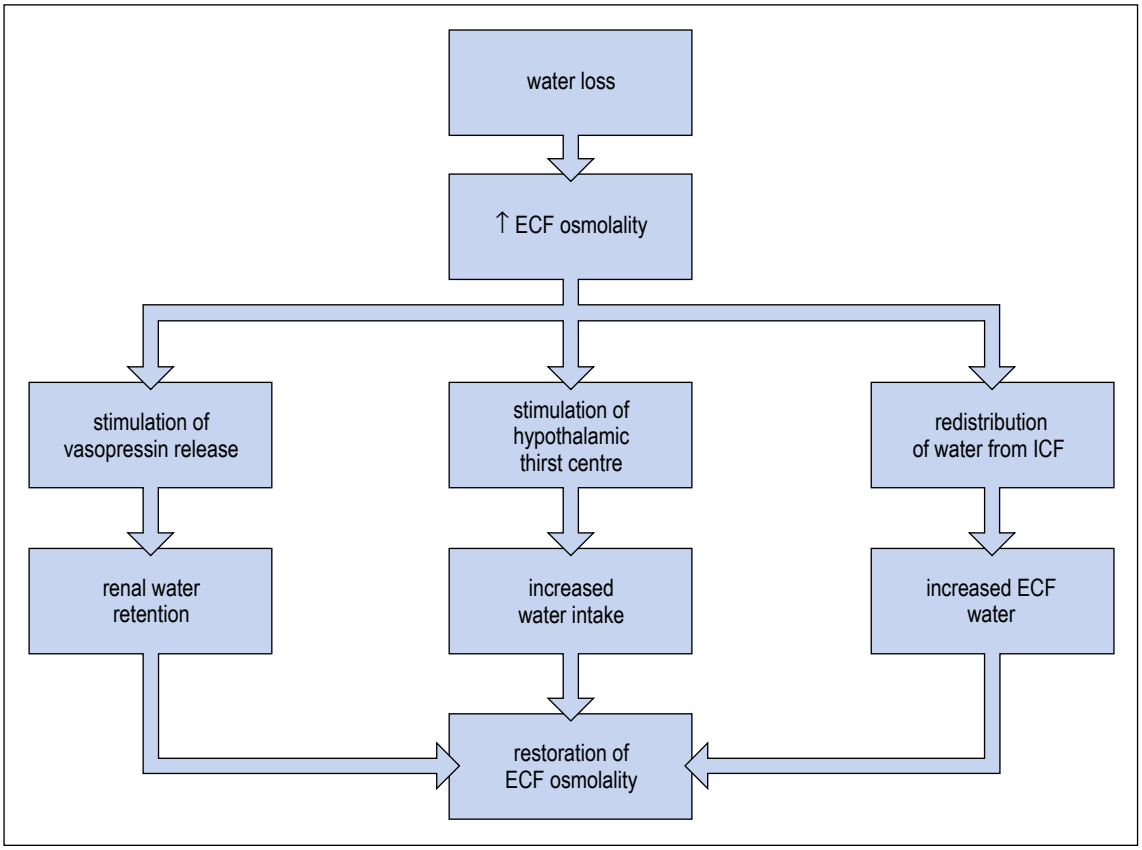

Fig. 3.2 Physiological responses to water loss. ECF, extracellular fluid; ICF, intracellular fluid.

increase in ECF osmolality occurs as a result of the presence of a solute such as urea that diffuses readily across cell membranes, ICF osmolality also increases and osmoreceptors are not stimulated.

If ECF osmolality declines, there is no sensation of thirst and vasopressin secretion is inhibited. Dilute urine is produced, allowing water excretion and restoration of ECF osmolality to normal. The vasopressin responses to changes in osmolality occur rapidly. In health, the ingestion of water surplus to requirements leads to a rapid diuresis, and water depletion leads to a rapid increase in the concentration of the urine.

Other stimuli that affect vasopressin secretion include arterial and venous baroreceptors and angiotensin II (in response to reduced effective blood volume), stress, pain, nausea and a range of drugs (Box 3.2). Hypovolaemia and hypotension increase the slope of the vasopressin response to an increase in osmolality (see Fig. 3.3A) and lower the threshold osmolality for vasopressin secretion. The vasopressin response to a decline in plasma volume is exponential: it is relatively small with small decreases in plasma volume, but greater declines cause a massive increase in vasopressin secretion (see Fig. 3.3B). Also, osmolar controls are overridden, so that ECF volume is defended (by stimulating water retention) at the expense of a decrease in osmolality.

Sodium and extracellular fluid volume

The volume of the ECF is directly dependent on the total body sodium content: sodium is very largely confined to the ECF, and water intake and loss are regulated to maintain a constant ECF osmolality, and hence sodium concentration.

Dietary **sodium intake** is highly variable. Sodium balance is maintained by regulation of its excretion by the kidneys. **Sodium excretion** requires glomerular filtration, but the glomerular filtration rate (GFR) appears to become an important limiting factor in sodium excretion only at extremely low rates of filtration (sodium retention is a late feature of chronic kidney disease). Normally, approximately 70% of filtered sodium is

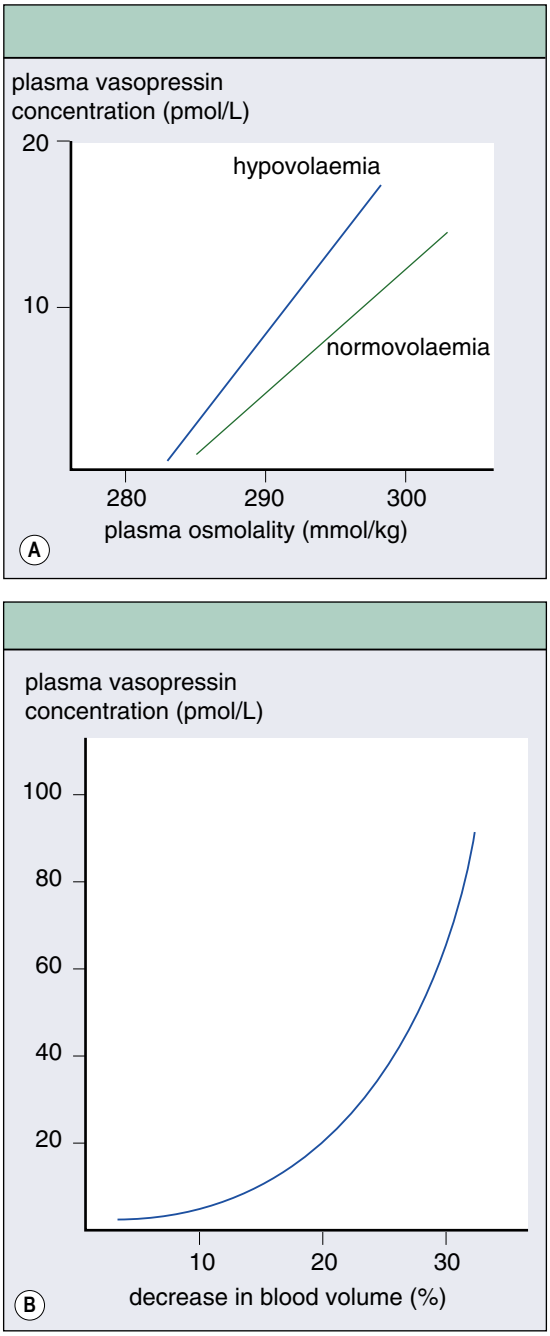

Fig. 3.3 **A,** Vasopressin secretion is stimulated by an increase in extracellular fluid osmolality above a threshold of approximately 284 mmol/kg; in hypovolaemia (blue line), this threshold is reduced and the response is greater. **B,** Vasopressin secretion is stimulated exponentially by hypovolaemia. Note the difference in the scales of the vertical axes.

Box 3.2 Control of vasopressin secretion

Stimulating factors	Inhibiting factors
increased ECF osmolality	decreased ECF osmolality
severe hypovolaemia (via angiotensin II and arterial and venous receptors)	hypervolaemia
stress, including pain	alcohol
nausea	
exercise	
drugs	
amiodarone	
analgesics, e.g. NSAIDs, opiates	
antidepressants, e.g. SSRIs	
anticonvulsants, e.g. carbamazepine, sodium valproate, lamotrigine	
antipsychotics, e.g. phenothiazines, butyrophenones	
anticancer drugs, e.g. vinca alkaloids, platinum compounds, melphalan, cyclophosphamide, methotrexate	
MDMA ('ecstasy')	
proton pump inhibitors	

ECF, extracellular fluid; MDMA, 3,4-methylenedioxymethamphetamine; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

actively reabsorbed in the proximal tubules, with further reabsorption in the loops of Henle. Sodium reabsorption is reduced in the proximal tubules if blood volume increases (because this is associated with a decline in the oncotic pressure in peritubular capillary blood) and if sympathetic activity decreases (such as also tends to occur with an increase in blood volume). Only <5% of filtered sodium reaches the distal tubules and collecting ducts, but these comprise the major site for the fine control of sodium excretion.

Aldosterone, released from the adrenal cortex in response to activation of the renin–angiotensin system, stimulates sodium reabsorption in the distal parts of the distal tubules and collecting ducts, and it is the major factor controlling renal sodium excretion. The control of renin

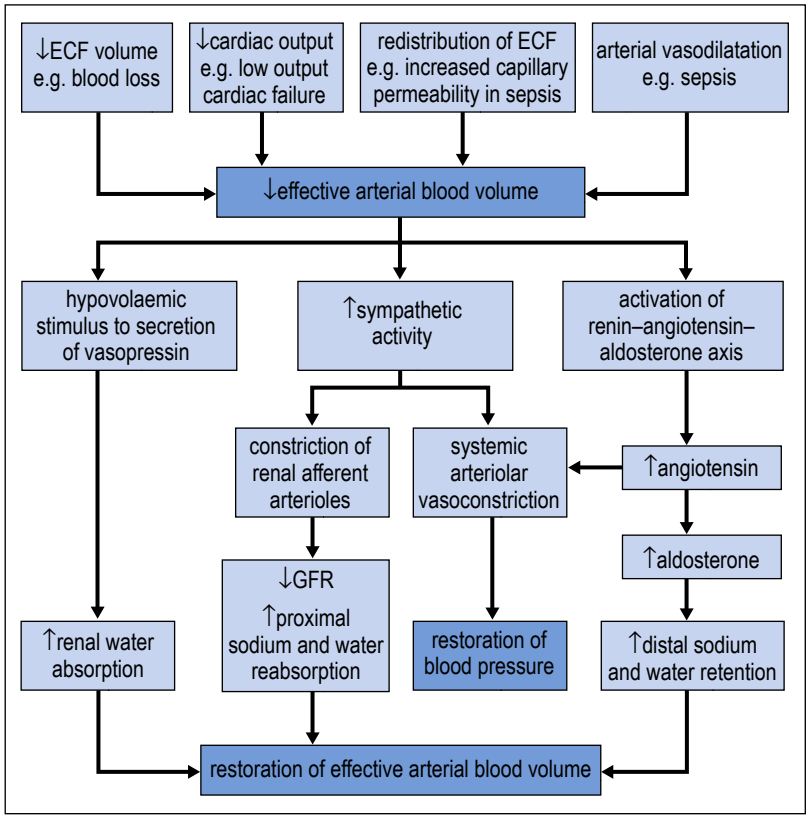

Fig. 3.4 Physiological responses to a decrease in plasma volume. These involve responses to restore plasma volume and to maintain blood pressure. ECF, extracellular fluid; GFR, glomerular filtration rate.

secretion is discussed in detail in Chapter 10, but in essence, renin secretion is stimulated primarily by a decrease in renal perfusion secondary to a decrease in blood volume—specifically a fall in arterial blood volume (effective blood volume, see later).

Natriuretic peptide hormones also have a role in controlling sodium excretion. Atrial natriuretic peptide (ANP) is a 28–amino acid peptide, one of a family of similar peptides, secreted by the cardiac atria in response to atrial stretch after a rise in atrial pressure (e.g. caused by ECF volume expansion). ANP acts both directly by inhibiting distal tubular sodium reabsorption and through decreasing renin (and hence aldosterone) secretion. It also antagonizes the pressor effects of noradrenaline (norepinephrine) and angiotensin II (and thus tends to increase GFR) and has a systemic vasodilatory effect. It appears to provide 'fine-tuning' of sodium homoeostasis but is probably more important in pathological states than physiologically. Two other structurally similar peptides have been identified. One (B-type natriuretic peptide [BNP], originally discovered in brain) is secreted by the cardiac ventricles in response to ventricular stretching and has similar properties to ANP; the other (C-type natriuretic peptide [CNP]) is present in high concentrations in vascular endothelium and is a vasodilator. Measurement of BNP is of value in the management of patients with suspected cardiac failure (see Chapter 17). Increased secretion of natriuretic peptides has been postulated to be, at least in part, responsible for the natriuresis seen in cerebral salt wasting (see p.39).

In summary, the initial response to a decrease in ECF volume is activation of the renin–aldosterone axis, causing an increase in the secretion of aldosterone and leading to sodium retention. Water reabsorption follows along the resulting osmotic gradient. Maintenance of osmolality takes precedence unless there is a very large decline in plasma volume, which stimulates a massive increase in vasopressin (see Fig. 3.3B) and free water retention. In addition to the changes in sodium and water excretion, there are also changes in the tone of

Box 3.3 Causes and clinical features of predominant water depletion

Causes		Clinical features
Decreased intake		**Symptoms**
infancy		thirst
old age		dryness of mouth
unconsciousness		difficulty in swallowing
dysphagia		weakness
restriction of oral intake		confusion
Increased loss		**Signs**
from kidneys	from skin	weight loss
renal tubular disorders	sweating	dryness of mucous membranes
diabetes insipidus	from lungs	decreased saliva secretion
increased osmotic load caused by diabetes mellitus, osmotic diuretics or high protein intake	hyperventilation	decreased urine volume (early)[a]
	from gut	
	diarrhoea (in infants)	

[a]Unless caused by renal water loss.

arteriolar smooth muscle, peripheral vascular resistance, renal blood flow and blood pressure. The physiological responses to a decrease in ECF volume are illustrated in Fig. 3.4.

Water and Sodium Depletion

Water depletion, or combined water and sodium depletion, will occur if losses are greater than intake. Depletion of water alone is seen much less frequently than depletion of both water and sodium. Because sodium cannot be excreted from the body without water, sodium loss never occurs alone but is always accompanied by some loss of water. The fluid lost may be isotonic or hypotonic with respect to ECF.

The clinical and biochemical features of water depletion and of isotonic sodium and water loss are quite different, as are the physiological responses, and it is helpful to consider them separately. In clinical practice, however, states of fluid depletion encompass the whole spectrum between these two extremes, and the clinical and biochemical features will reflect this. Furthermore, it should be appreciated that they may have been modified by previous treatment.

Water depletion

Water depletion will occur if water intake is inadequate or if losses are excessive. Excessive loss of water without any sodium loss is unusual, except in diabetes insipidus, but even if there is loss of sodium as well, provided that this is small, the clinical consequences will be related primarily to the water depletion (Box 3.3).

Loss of water from the ECF causes an **increase** in **osmolality**, which, in turn, causes movement of water from the ICF to the ECF, thus lessening the increase. Nevertheless, the increase in ECF osmolality will be sufficient to stimulate the thirst centre and vasopressin secretion. Plasma sodium concentration increases; plasma protein concentration and the haematocrit are usually only slightly elevated. Unless water depletion is due to uncontrolled loss through the kidneys, the urine becomes highly concentrated and there is a rapid decrease in its volume. Because water loss is borne by the total body water pool, and not just the ECF (Fig. 3.5), **signs of a reduced ECF volume are not usually present**. Furthermore, the increased colloid osmotic pressure of the plasma tends to hold extracellular water in the vascular compartment. Circulatory failure is a very late feature of water depletion: it is much more likely to occur if sodium depletion is also present.

Severe water depletion induces cerebral dehydration, which may cause cerebral bleeding through damage to

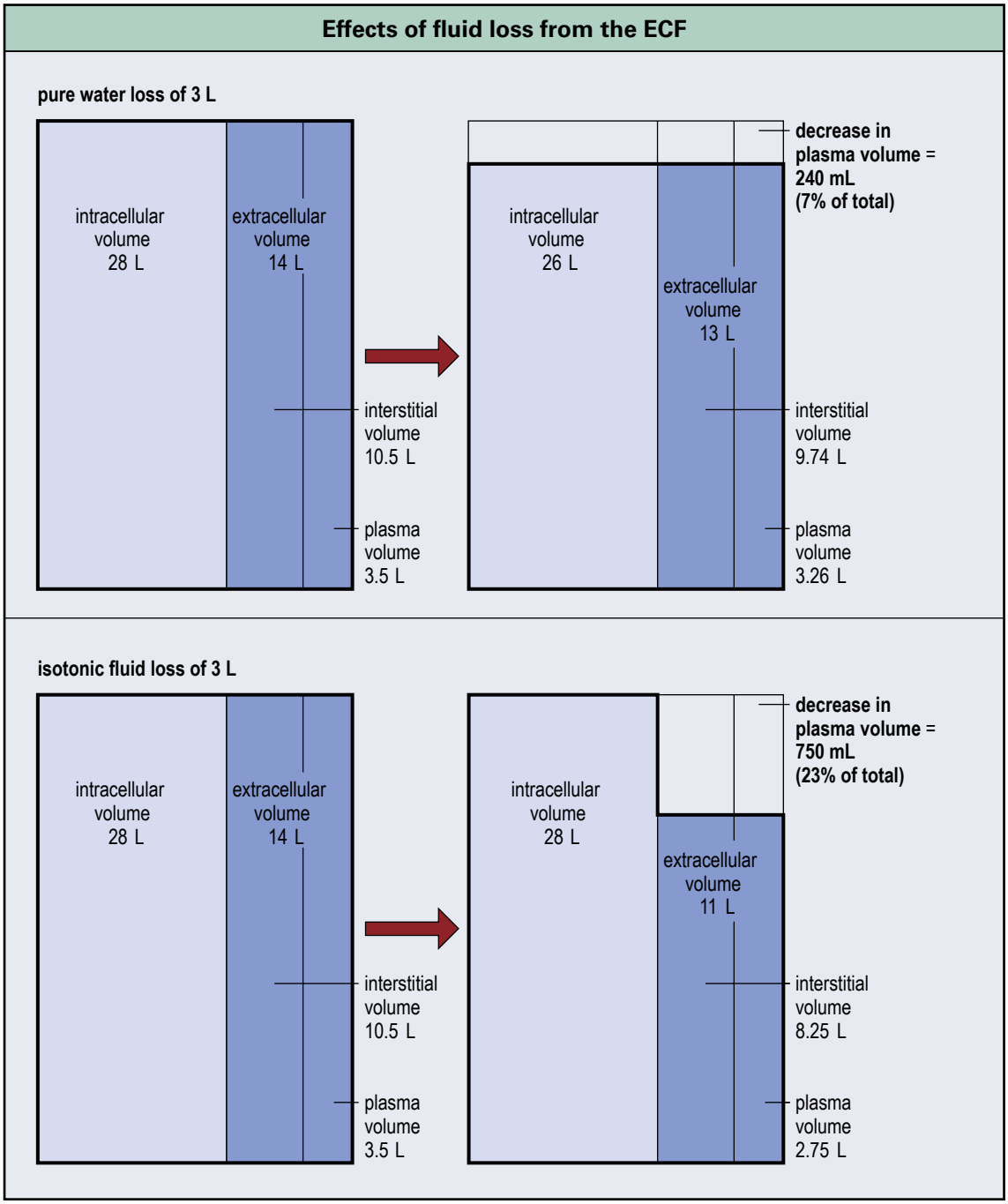

Fig. 3.5 Comparison of the effects of water loss and isotonic fluid loss from the extracellular compartment. When only water is lost from the extracellular fluid (ECF), the increase in osmolality causes water to move from the intracellular fluid (ICF), which minimizes the decrease in plasma volume. When isotonic fluid is lost from the ECF, no osmotic imbalance is produced, there is no movement of water from the ICF and the effect on plasma volume is, therefore, much greater.

blood vessels. In the short term, cerebral shrinkage is mitigated somewhat by movement of extracellular ions into cerebral cells, causing an osmotic intracellular shift of water. If dehydration persists, brain cells adapt by synthesizing osmotically active organic compounds ('osmolytes'), and overzealous fluid replacement may cause cerebral oedema because of rapid intracellular movement of water (Fig. 3.6B).

The **management** of water depletion requires treatment of the underlying cause and replacement of the fluid deficit. Water should preferably be given either orally or via a nasogastric tube. If this is not possible, 5% dextrose should be administered intravenously, together with 0.9% saline if there has been accompanying sodium depletion. As a general guide, the aim should be to correct approximately two- thirds of the deficit in the first 24 h and the remainder in the next 24 h while avoiding a decrease in sodium concentration of >10 mmol/L in the first 24 h. How rapidly the sodium concentration should be normalized depends on how quickly the water depletion has developed. If it is long-standing (as it often is in the elderly), a decrease of no more than 0.5 mmol/L per hour is recommended, but initially more rapid correction (1 mmol/L per hour) may be appropriate in acute water depletion (more common in children).

Sodium depletion

Sodium depletion is seldom due to inadequate oral intake alone, although sometimes inadequate parenteral input is responsible. More often, it is a consequence of excessive sodium loss (Box 3.4). Sodium can be lost from the body either isotonically (e.g. in plasma) or hypotonically (e.g. in sweat or dilute urine). In each case, there will be a **decrease in ECF volume** (see Fig. 3.5), but this will be less if the fluid lost is hypotonic than if it is isotonic, because some of the water loss will be shared with the ICF. The clinical features of sodium depletion (see Box 3.4) are primarily a result of the decrease in ECF volume.

The **normal responses to hypovolaemia** are an increase in aldosterone secretion, stimulating renal sodium reabsorption in the distal convoluted tubules and collecting ducts, and a decline in urine volume as a consequence of a decreased GFR. Significantly increased vasopressin secretion, which stimulates the production of highly concentrated urine, occurs only with more severe ECF volume depletion (see Fig. 3.3).

The decrease in GFR may lead to pre-renal acute kidney injury (see Case history 5.1). In contrast with the effects of pure water depletion, plasma protein concentration and the haematocrit are usually clearly increased in sodium depletion, unless this is a result of the loss of plasma or blood. Furthermore, because the fluid loss is borne mainly by the ECF, signs of a reduced ECF volume are usually present, and there is a greater risk of peripheral circulatory failure than in water depletion. The features of sodium and water depletion are compared in Table 3.1.

The plasma sodium concentration can give an indication of the relative amounts of water and sodium that have been lost: plasma sodium will be normal if the fluid lost is isotonic with respect to the ECF and increased if it is hypotonic. With severe sodium depletion, increased vasopressin secretion secondary to the resulting hypovolaemia may cause water retention; plasma volume is then maintained at the expense of osmolality and hyponatraemia develops. Thus, the plasma sodium concentration in a sodium-depleted patient may be high, normal or low (Table 3.2).

The **management** of sodium depletion involves treatment of the underlying cause and, if necessary, restoration of the intravascular volume by giving isotonic fluid ('normal saline' [0.9% sodium chloride]) by intravenous infusion. This can usually be done rapidly, but any associated free water deficit requires more cautious correction.

Water and Sodium Excess

Excess of water and sodium can result from a failure of normal excretion or from excessive intake. The latter is often iatrogenic. As with the syndromes of depletion, it is helpful to consider the causes and consequences of excess water alone and of sodium excess with isotonic retention of water separately, although in practice there is often a degree of overlap.

Water excess

Water excess is usually related to an impairment of water excretion (Box 3.5). However, the limit to the ability of the healthy kidneys to excrete water is about 20 mL/min, and occasionally, excessive intake is alone sufficient to cause water intoxication. This can sometimes occur in patients with psychiatric disorders. It has also been described in people drinking large amounts of beer with a low solute content, because this results in a low osmotic load for excretion and there is a minimum osmolality below which the urine cannot be diluted further. Increased thirst can occur in organic brain disease (particularly trauma and after surgery), although decreased thirst is more common. Hyponatraemia is invariably present in water overload. The increased water load is shared by the ICF and ECF.

The **clinical features** of water overload (see Box 3.5) are related to cerebral overhydration; their incidence and severity depend on the extent of the water excess and its time course. Thus, a patient with a plasma sodium concentration of 120 mmol/L, in whom water retention has occurred gradually over several days, may be asymptomatic, whereas one in whom this is an acute phenomenon may show signs of severe water intoxication. In the short

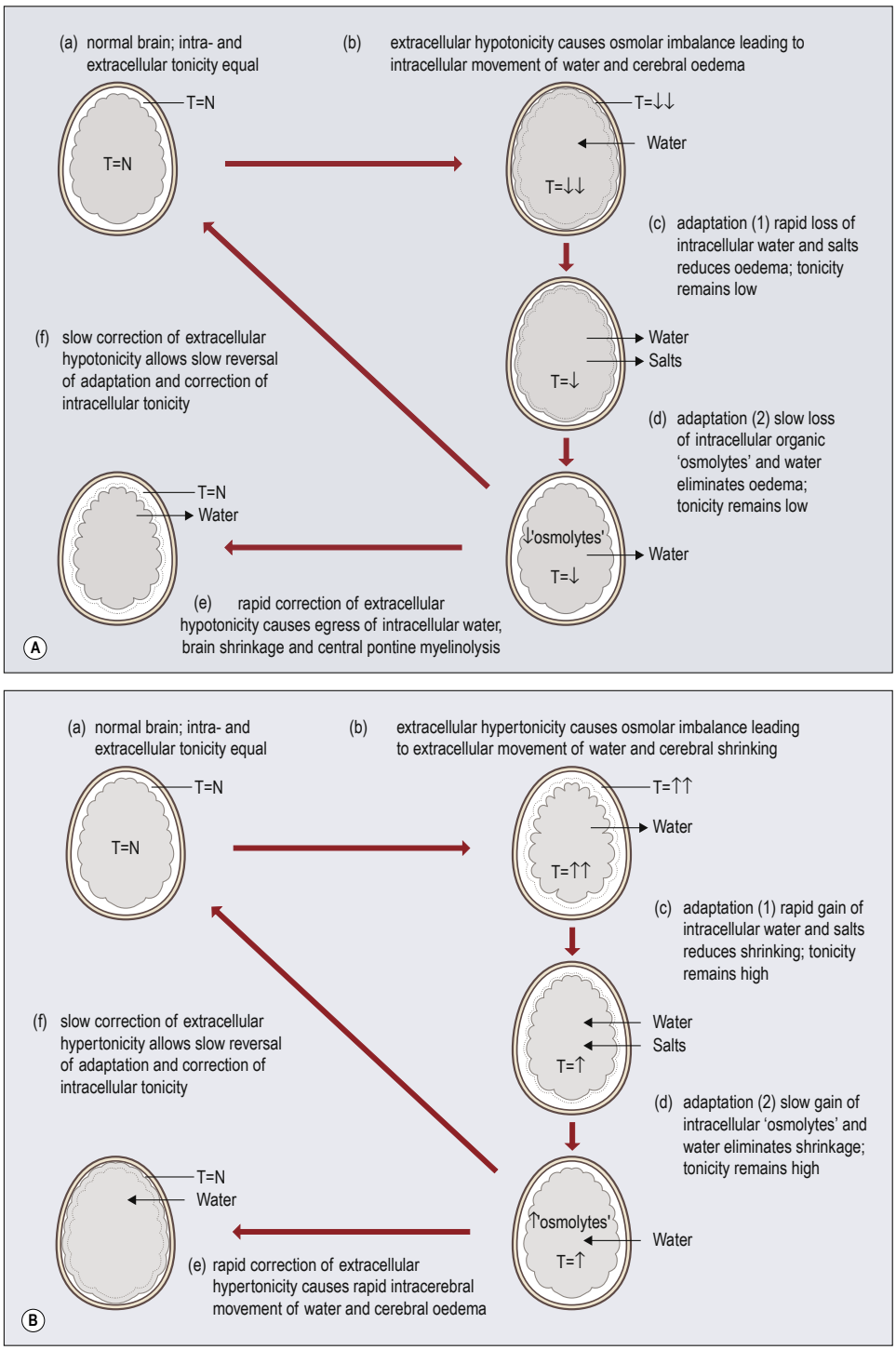

Fig. 3.6 Effects of hyponatraemia **(A)** and hypernatraemia **(B)** on the brain, adaptive changes and the effects of rapid correction. T, tonicity; N, normal.

Box 3.4 **Causes and clinical features of predominant sodium depletion**

Causes	Clinical features
Excessive loss	**Symptoms**
from kidneys	weakness
diuretic phase of acute kidney injury	apathy
diuretic therapy	postural dizziness
mineralocorticoid deficiency	syncope
cerebral salt wasting	confusion, coma (late)
other salt-losing states	
from skin	**Signs**
massively increased sweating	weight loss
cystic fibrosis	related to decreased plasma volume
widespread dermatitis	tachycardia
burns	hypotension (initially postural)
from gut	peripheral circulatory failure
vomiting, diarrhoea	oliguria
fistulae	related to decreased interstitial fluid
ileus	decreased intraocular pressure
intestinal obstruction	decreased skin turgor
Inadequate intake	
sodium deletion will occur whenever intake is inadequate to balance excessive losses; inadequate intake alone is rarely a cause of depletion	

term, the effects of hypotonicity are mitigated to some extent by a movement of ions out of cerebral glial cells; more chronically (days), a decrease in intracellular organic 'osmolytes' further reduces intracellular water content (see Fig. 3.6A). As is the case with water depletion, this adaptation necessitates a cautious approach to treatment, particularly in chronic water overload. The **management** of water overload is discussed together with that of hyponatraemia on p. 38.

Sodium excess

Sodium excess can result from increased intake or decreased excretion. The **clinical features** are related primarily to **expansion of ECF volume** (Box 3.6). When related to excessive intake (e.g. the inappropriate use of hypertonic saline), a rapid shift of water from the intracellular compartment may also cause cerebral dehydration. When sodium overload is due to excessive intake, hypernatraemia is common (see Case history 3.5).

Sodium overload is more often due to impaired excretion than to excessive intake. The most frequent cause is secondary aldosteronism. This is seen in patients who, despite clinical evidence of increased ECF volume (e.g. peripheral oedema), appear to have a decreased effective arterial blood volume, for example, caused by venous pooling or a disturbance in the normal distribution of ECF between the vascular and extravascular compartments. This phenomenon is particularly associated with cardiac failure, hypoalbuminaemia and hepatic cirrhosis. Many such patients with sodium excess are, paradoxically, hyponatraemic, implying the coexistence of a defect in free water excretion. This is probably in part due to an increase in vasopressin secretion as a result of

Table 3.1 Clinical and laboratory findings in sodium and water depletion

	Sodium depletion	Water depletion
plasma [Na[a]]	normal or ↓	↑
haematocrit	↑↑↑[a]	normal or slightly ↑
ECF volume	↓↓↓	usually normal
plasma [urea]	↑	high normal
urine volume	↓	↓↓↓
urine concentration	↑	↑↑↑
thirst	late	early
tachycardia, hypotension	early	late

[a]Unless caused by loss of blood.

Table 3.2 Plasma sodium concentration with various causes of sodium depletion

Mechanism of sodium depletion	Plasma sodium concentration
sodium and water loss, waterloss predominating, e.g.excessive sweating	increased
isotonic sodium and waterloss, e.g. burns, haemorrhage	normal
Sodium loss with water retention, e.g. treatment of isotonic sodium depletion with low sodium fluids	decreased

Box 3.5 Causes and clinical features of excess body water

Causes	Clinical features
Increased intake	behavioural disturbances
compulsive water drinking	confusion
excessive parenteral fluid administration	headache
water absorption during bladder irrigation	convulsions
	coma
Decreased excretion	muscle twitching
chronic kidney disease (severe)	extensor plantar responses
cortisol deficiency	
inappropriate or ectopic secretion of vasopressin	
drugs:	
stimulating vasopressin release (see Box 3.2)	
potentiating the action of vasopressin, e.g. chlorpropamide	
vasopressin (V2) agonists, e.g. oxytocin	
interfering with renal diluting capacity, e.g. thiazide diuretics	

the decreased effective blood volume. Also, the decrease in GFR and consequent increase in proximal tubular sodium reabsorption decreases the delivery of sodium and chloride to the loops of Henle and distal tubules. This reduces the diluting capacity of the kidneys, thereby compromising water excretion. Kidney disease is a relatively uncommon cause of sodium excess, as is increased mineralocorticoid secretion caused by primary adrenal disease (Conn syndrome, see p. 184).

It is noteworthy, however, that oedema is not a feature of Conn syndrome: furthermore, in healthy individuals, the administration of high doses of mineralocorticoids initially leads to sodium retention and modest expansion of the ECF volume (but to an insufficient extent to cause oedema), but sodium balance is then restored and a new steady state is achieved. It is thought that the increased arterial filling leads to a decrease in sympathetic activity and secretion of angiotensin II, with a consequent increase in renal perfusion and GFR, together with the increased secretion of ANP. The net result is an increase in the delivery of sodium to the distal nephrons, which, together with ANP, counters the sodium-retaining action of aldosterone. In oedematous states, relative arterial underfilling leads to a decline in GFR, increased proximal tubular sodium reabsorption, and decreased delivery of sodium to the distal nephrons. Even though there is increased secretion of ANP, its ability to cause natriuresis is limited by this decreased sodium delivery.

The **management** of sodium excess should be directed towards the cause, where possible. In addition, diuretics (including spironolactone if secondary aldosteronism is a contributory factor) can be used to promote sodium excretion. Sodium intake must be controlled. Dialysis or

Box 3.6 **Causes and clinical features of predominant sodium excess**

Causes	Clinical features
Increased intake	peripheral oedema
excessive parenteral administration	dyspnoea
absorption from saline emetics	pulmonary oedema
	venous congestion
Decreased excretion	hypertension
decreased glomerular filtration:	effusions
acute and chronic kidney disease	weight gain
increased tubular reabsorption:	
primary mineralocorticoid excess:	
Cushing syndrome	
Conn syndrome	
secondary mineralocorticoid excess:	
congestive cardiac failure	
nephrotic syndrome	
hepatic cirrhosis with ascites	
renal artery stenosis	

The 'U&E' profile

U&E, standing for urea and electrolytes, is the term given to a long-established profile aimed at testing kidney function and fluid and electrolyte status. In most circumstances, however, creatinine is a better first-line test of kidney (or more precisely glomerular) function. Some laboratories automatically include creatinine in the 'U&E' profile, but creatinine alone should be requested if only a screening test for kidney function is required. An electrolyte is any substance that dissociates into free ions when it dissolves in water, and can therefore conduct electricity and move along an electrochemical gradient. Positively charged electrolytes are cations and negatively charged ones are anions. Conventionally, the two electrolytes included in the U&E profile are sodium and potassium, which are measured by near-identical methods in the laboratory and almost invariably requested and reported as a pair. There are, however, a large number of atomic and molecular ions in plasma, all of which are electrolytes.

haemofiltration may be necessary if kidney function is poor, and it is occasionally necessary in acute sodium overload associated with the use of hypertonic fluids.

Laboratory Assessment of Water and Sodium Status

Plasma **sodium concentration is dependent on the relative amounts of sodium and water** in the plasma. In isolation, therefore, plasma sodium concentration provides no information about the sodium content of the ECF. It may be high, normal or low in states of sodium excess or depletion, according to the amount of water in the ECF.

The plasma sodium concentration is one of the most frequent measurements made in clinical chemistry laboratories (largely for historical reasons), but definite indications for its measurement are few and results are often misinterpreted. Plasma sodium concentration should be measured in the following situations:

- patients with dehydration or excessive fluid loss, as a guide to appropriate replacement
- patients on parenteral fluid replacement
- patients with unexplained confusion, abnormal behaviour or signs of central nervous system (CNS) irritability.

In the assessment of a patient's water and sodium status, **clinical observations**, such as assessment of central venous pressure, fluid balance and body weight, may all provide

vital information, although each is open to inaccuracy or misinterpretation. In the intensive care setting, indicators of cardiac output such as transoesophageal echocardiography provide more precise measures of intravascular volume. An increase in the concentration of plasma proteins or in the haematocrit suggests haemoconcentration. Other abnormal results may suggest specific conditions; for example, hyperkalaemia in a patient with hyponatraemia with clinical evidence of sodium depletion would suggest adrenal failure.

Measurement of urine osmolality and sodium can provide valuable information, although the results may be misleading (e.g. in patients on steroids or diuretics). A urine osmolality of >100 mmol/kg in a patient with hyponatraemia indicates water retention, which may be inappropriate (e.g. in **syndrome of inappropriate antidiuresis (SIAD**, see p. 40), and failure to produce a concentrated urine in hypernatraemia may point to diabetes insipidus. Urine sodium concentration is a useful marker of arterial blood volume because it reflects the renal response to aldosterone: a value ≤30 mmol/L usually indicates intravascular volume depletion, although total ECF volume could be high if there is abnormal fluid distribution between compartments. However, natriuresis in a patient with sodium depletion could imply either a failure of aldosterone secretion or a failure of the kidneys to respond to the hormone (Case history 3.1).

Sodium measurement

Sodium concentration is usually measured by ion-selective electrodes which, strictly speaking, determine the activity of sodium rather than its concentration, that is, the number of atoms that act as true ions in a defined volume of water. Plasma normally comprises around 93% water by volume (the remaining 7% comprises proteins and lipoproteins): ion-selective electrodes are calibrated to allow for this, and they produce results that are a close estimate of plasma sodium concentration.

Laboratory analyzers dilute the plasma before analysis (indirect analysis), whereas most point-of-care testing instruments measure sodium concentration directly in undiluted plasma (direct analysis). Under most circumstances, the two techniques give results that are very similar.

Case history 3.1

History

A 50-year-old woman with a long history of rheumatoid disease complained of fainting episodes after an attack of gastroenteritis.

Examination

Blood pressure 102/72 mmHg when lying down, 78/56 when standing.

Results (see Appendix for reference ranges)

Serum:	sodium	118 mmol/L
	potassium	3.9 mmol/L
	urea	9.1 mmol/L
	creatinine	74 µmol/L
	eGFR	77 mL/min/1.73 m^2
ACTH (tetracosactide [Synacthen]) test: normal cortisol response to ACTH		
Plasma: aldosterone (recumbent)		1420 pmol/L (100–450)
Plasma: renin activity (recumbent)		15.6 nmol/L per hour (1.1–2.7)
24-h urinary sodium excretion		118 mmol

Summary

Severe hyponatraemia with slightly raised urea. High renin and aldosterone and natriuresis.

Interpretation

The hyponatraemia with a slightly raised urea is consistent with sodium depletion producing hypovolaemia. The result of the ACTH stimulation test is normal, excluding adrenal failure, and renin and aldosterone are appropriately raised. The patient's urinary sodium excretion is excessive: although the input was not assessed, the expected response in a volume-depleted patient is sodium retention by the kidneys.

Discussion

Postural hypotension may be caused by hypovolaemia, autonomic neuropathy or hypotensive drugs. This patient was not taking such medication and there was no other evidence of neuropathy. It was important to rule out adrenal insufficiency, and she was shown to have a normal renin and aldosterone response to volume depletion. The normal renal response to volume depletion is to conserve sodium, with a urine sodium concentration of <30 mmol/L.

It was concluded that the patient had a renal salt-losing state such that the kidneys could not respond to the normal physiological stimuli to retain sodium. She became symptomatic only when diarrhoea and vomiting caused further fluid loss. This was later confirmed by sodium balance studies and the patient was found to have renal papillary necrosis, an occasional complication of the use of certain analgesic drugs, which principally affects renal tubular function.

However, if the fractional plasma water content is decreased, as it is in severe hyperlipidaemia or hyperproteinaemia, the sodium concentration, measured (after dilution) by an indirect ion-selective electrode, will be an underestimate of true sodium activity because the dilution is of total plasma volume, not just water volume. Direct ion-selective electrodes give a more accurate estimate of the concentration of sodium in plasma under these circumstances.

This effect, known as **pseudohyponatraemia**, is only seen with severe hyperlipidaemia (when the plasma will usually appear turbid to the naked eye) and with large increases in total protein concentration caused by paraproteinaemia (see p. 292). If it is suspected, plasma osmolality should be measured because it is a direct measure of solute activity in plasma water. Plasma osmolality should be normal in a patient with pseudohyponatraemia.

Measurement of osmolality

Given that it is osmolality, rather than sodium concentration, that is controlled by the hypothalamus, it might appear logical to measure plasma osmolality rather than sodium concentration. The measurement of osmolality is, however, less precise than that of sodium and is not easily automated. It is nevertheless useful under certain circumstances.

Measurement of osmolality can help in the interpretation of a low plasma sodium concentration and is necessary in water deprivation tests for possible diabetes insipidus (see Chapter 9). It can also be useful in the investigation of patients suspected of having ingested substances such as ethanol or ethylene glycol (see Case history 21.5) because, if present, these increase the plasma osmolality. This can be revealed by comparing the measured osmolality with the approximate expected value using a formula that adds together the main osmolar plasma constituents to calculate osmolarity (see the following).

Measured osmolality (in mmol/kg of water) and calculated osmolarity (in mmol/L of solution) are normally numerically very similar. Significant discrepancies (an **osmolar gap**) occur when abnormal osmotically active species are present in plasma (as may occur in poisoning, and perhaps in some cases of the sick cell syndrome) and when the fractional water content of plasma is reduced, as in severe hyperlipidaemia or hyperproteinaemia (**pseudohyponatraemia**).

Osmolality and osmolarity

Plasma **osmolality** is a measure of the number of osmotically active particles per kilogram of plasma water (expressed as **mmol/kg**). It is a true physicochemical entity that determines the colligative properties of a solution, including osmotic pressure. **Osmolarity** is an estimate of osmolality that is derived by adding together the concentrations, in **mmol/L** of the solutes that are present at highest concentration in plasma, but doubling that of sodium to allow for the anions that inevitably accompany cations. The most commonly used formula is:

$$\text{osmolarity} = 2 \times [Na^+] + [\text{urea}] + [\text{glucose}]$$

where all concentrations are measured in mmol/L. The factor 2 is to allow for the major anions (chloride and bicarbonate); other formulae include potassium and a slightly smaller multiplier, to allow for the fact that some anions and cations act as ion pairs rather than as individual moieties

Measurement of anions (bicarbonate and chloride)

A change in plasma sodium concentration must be matched by a change in anion concentration. The major anions of the ECF are chloride and bicarbonate. Bicarbonate (strictly, total carbon dioxide, but this mostly comprises bicarbonate ions, see p. 58) is frequently measured because it reflects the extracellular buffering capacity (note that the measurement must be made on a fresh sample to obtain an accurate result, because of the loss of carbon dioxide to the atmosphere on standing). The measurement of plasma chloride rarely adds useful information in the diagnosis of disorders of sodium and water homoeostasis. However, it may have a role in the detection of harmful hyperchloraemia in patients receiving large volumes of chloride-rich intravenous fluids (see p. 63), and it may occasionally be helpful in the diagnosis of patients with non-respiratory acidoses or rare chloride-losing states (as it is used in the calculation of the anion gap, see p. 59).

Hyponatraemia

A slightly low plasma sodium concentration is a frequent finding. The median plasma sodium concentration of hospital inpatients is ~5 mmol/L lower than in healthy control subjects. Mild hyponatraemia is seen with a wide variety of illnesses and may be multifactorial in origin (see the 'Sick cell syndrome' section, p. 42). It is essentially a secondary phenomenon that reflects the presence of disease; treatment should be directed at the underlying cause and not at the hyponatraemia. Hyponatraemia itself may warrant primary treatment, but usually only when it is severe or is associated with clinical features of water intoxication (see Box 3.5).

Causes

It has been emphasized that plasma sodium concentration depends on the amounts of both sodium and water in the plasma, so a low sodium concentration does not necessarily imply sodium depletion. Indeed, hyponatraemia is more frequently a result of a defect in water homoeostasis that causes water retention and hence dilution of plasma sodium. One of three mechanisms is usually primarily responsible for the development and maintenance of hyponatraemia, although in individual patients more than one factor may be involved. These mechanisms are:

- **sodium depletion** (hypovolaemic hyponatraemia)
- **water excess** (euvolaemic hyponatraemia)
- **water and sodium excess** (hypervolaemic hyponatraemia).

For an explanation of the connection between sodium status and plasma volume, see p. 27

Sodium depletion

Sodium cannot be lost without water, and isotonic or hypotonic loss would not be expected to cause a decline in plasma sodium concentration. However, hyponatraemia can occur in patients with sodium depletion, and it is due either to inappropriate replacement of fluid (e.g. containing insufficient sodium) or, in severe sodium depletion, to the hypovolaemic stimulus to vasopressin secretion, which overrides the osmotic control and permits water retention at the expense of a decrease in osmolality. A patient with adrenal failure with hyponatraemia as a result of sodium depletion is presented in Case history 10.1.

Clinical signs of hypovolaemia (see Box 3.4) may be present in patients with hyponatraemia caused by sodium depletion. Unless the sodium loss is occurring through the kidneys, increased aldosterone secretion should cause maximal renal sodium retention and the urinary sodium concentration will be low (<30 mmol/L). This finding is a valuable aid to the diagnosis of extrarenal sodium depletion as a cause of hyponatraemia. In contrast, in hypovolaemia caused by renal sodium losses, urine sodium concentration is often much greater than 30 mmol/L.

The **management** of hyponatraemia associated with sodium depletion involves correction of the underlying cause and appropriate fluid replacement (e.g. physiological [0.9%] saline). It is important to monitor plasma sodium concentration: restoration of plasma volume will suppress any hypovolaemic stimulus to vasopressin secretion, causing a relative water diuresis.

Plasma sodium concentration is usually normal in patients treated with diuretics, but these drugs have complex effects on sodium and water homoeostasis. Although primarily tending to cause sodium depletion, the blocking of sodium reabsorption in the cortical diluting segment of the nephrons may impair free water excretion. This, perhaps exacerbated by the effect of vasopressin secretion secondary to hypovolaemia and an increase in water intake because of thirst, can result in hyponatraemia. This is usually mild, but it can be more severe, particularly in patients receiving treatment with thiazides. Treatment with diuretics is the most frequent cause of hypovolaemic hyponatraemia in ambulant patients.

Cerebral (or central) salt wasting describes the combination of hyponatraemia and natriuresis in the presence of cerebral pathology. It is particularly associated with brain injury and cranial surgery. The pathogenesis is uncertain: mechanisms may include release of natriuretic peptides by the brain and increased centrally mediated sympathetic activity, leading to dopamine release and increased renal perfusion pressure. It is sometimes mistaken for SIAD (see later). The critical practical difference between cerebral salt wasting and SIAD is that patients with cerebral salt wasting should have clinical and biochemical features of hypovolaemia: indeed, it should not be diagnosed unless there is evidence of hypovolaemia (patients with SIAD are typically euvolaemic), marked natriuresis (urine sodium >100 mmol/L) and diuresis. The distinction is vital, because the management of the two conditions is quite different: patients with cerebral salt wasting require intravenous isotonic saline, often in large volumes, to replace the sodium that is being lost. SIAD, in which the basic problem is water retention, is usually treated by water restriction or, in severe cases, a vasopressin receptor antagonist (see p. 40).

Water excess

Water excess causes **dilutional hyponatraemia** with reduced plasma osmolality. It can occur acutely purely because of excessive water intake, but this is rare. Normal kidneys are capable of excreting 1 L water per hour: water intoxication and hyponatraemia will thus be seen only when very large quantities of fluid are ingested rapidly, as is seen in some patients with psychoses. It can also occur in people who drink large quantities of weak beer (see p. 32). Far more frequently, however, the acute development of water excess and hyponatraemia is a result of a combination of excessive hypotonic fluid intake and impairment of diuresis. Because osmolality is normally precisely controlled, the persistence of dilutional hyponatraemia implies a failure of diuresis, which must be caused by either continued (and inappropriate) production of vasopressin (or the presence of a drug having a vasopressin-like action) or an impairment of the renal diluting mechanism.

SIAD is essentially a diagnosis of exclusion. It is frequently diagnosed on insufficient evidence without regard

Case history 3.2

History

A man who had undergone major abdominal surgery 36 h earlier and was still receiving intravenous fluid replacement was reviewed by the ward junior doctor.

Examination

He was alert and appeared neither underhydrated nor overhydrated. He had received a total of 3.5 L of dextrose-saline since his operation, and examination of the fluid balance chart showed that he had a positive balance of 2 L.

Results

Serum:	sodium	127 mmol/L
	urea	4.0 mmol/L
	creatinine	68 µmol/L
	eGFR	>90 mL/min/1.73 m^2

Summary

Moderate hyponatraemia, other results unremarkable.

Interpretation

Hyponatraemia resulting from excessive administration of hypotonic intravenous fluids.

Discussion

Hyponatraemia is a very common finding in postoperative patients on intravenous fluid infusions. It is usually, as in this case, a reflection of excessive administration of hypotonic fluids (5% dextrose or 'dextrose-saline') at a time when the ability of the body to excrete water is depressed as part of the normal metabolic response to trauma, which includes increased release of vasopressin. If, as is usually the case, there are no clinical features of water intoxication, the only action necessary is adjustment of the fluid input.

to other possible causes of hyponatraemia. Both clinical information and laboratory data are important. It is essential to measure urine and plasma osmolalities: plasma osmolality is low and the urine should be less than maximally dilute (i.e. osmolality >100 mmol/kg). The **laboratory criteria for the diagnosis** are:

- hyponatraemia
- decreased plasma osmolality
- inappropriately concentrated urine (it is sometimes stated that the osmolality of the urine should be greater than that of the plasma, but it is sufficient that it is not maximally dilute)
- continued natriuresis (>30 mmol/L)
- no clinical evidence of volume depletion (e.g. due to diuretics) or oedema
- normal renal function
- normal adrenal function
- normal thyroid function (although only profound hypothyroidism causes hyponatraemia)
- clinical and biochemical response to fluid restriction.

Oedema is not a feature of SIAD: the excess of water is distributed throughout both the ICF and the ECF, and the effect on ECF volume is insufficient to cause oedema. Measurement of vasopressin concentration is seldom helpful in differential diagnosis: raised values are present in the majority of patients with hyponatraemia, irrespective of the cause.

There are at least four different types of SIAD:

- tumours may produce the hormone (ectopic production)
- abnormal regulation of vasopressin release, for example, stimulation of thoracic volume receptors during artificial ventilation or resetting of the 'osmostat' so that osmolality is still controlled but at a lower level, perhaps as a result of decreased intracellular organic solute ('osmolyte') content
- incomplete suppression of vasopressin release when osmolality falls (a 'vasopressin leak')
- inappropriate activation of the aquaporin water channel, because of genetic mutations of the vasopressin V2 receptor gene, has been described in a few patients.

Conditions associated with SIAD are listed in Box 3.7. In addition, certain drugs either stimulate vasopressin release (see Box 3.2) or have a vasopressin-like action on the kidneys.

This syndrome was previously called 'syndrome of inappropriate antidiuretic hormone secretion' or SIADH, but because inappropriate secretion of the hormone is not always present in patients satisfying its diagnostic criteria, and vasopressin is now the accepted name for 'antidiuretic hormone', the newer term syndrome of inappropriate antidiuresis is more appropriate.

Severe hyponatraemia has been reported in individuals undertaking endurance athletic events, such as marathon running. This is due to stress-mediated secretion of vasopressin combined with an inappropriately high intake of low-solute fluids.

The **management of dilutional hyponatraemia** (i.e. water overload) depends on its severity and the time course over which it develops. The latter is relevant because of the adaptive responses to water overload (see Fig. 3.6 and p. 32). As a general principle, hyponatraemia should be corrected at a rate that reflects the rate of its development, but in severely symptomatic patients, it is often necessary to effect partial correction rapidly to control symptoms.

Case history 3.3

History

An elderly man was admitted to hospital in an acute confusional state. No history was available.

Examination

He had finger clubbing and tar staining indicating that he was a heavy smoker. There were signs of a right-sided pleural effusion, but no other obvious abnormality was detected. He was neither dehydrated nor oedematous.

Investigations

A chest radiograph confirmed the presence of the effusion and showed a mass in the right lower zone with an appearance typical of a carcinoma.

Results

Serum:	sodium	114 mmol/L
	potassium	3.6 mmol/L
	bicarbonate	22 mmol/L
	urea	2.5 mmol/L
	creatinine	55 µmol/L
	eGFR	>90 mL/min/1.73 m^2
	total protein	48 g/L
	osmolality	236 mmol/kg
Plasma:	glucose	4.0 mmol/L
Urine:	osmolality	350 mmol/kg
	sodium	50 mmol/L

Summary

Severe hyponatraemia with low serum urea and protein concentrations. Relatively high urine osmolality and ongoing natriuresis in the presence of hypo-osmolal plasma.

Interpretation

The patient is not clinically dehydrated, and the low serum protein and urea concentrations suggest that the hyponatraemia is dilutional. The normal response should be for vasopressin secretion to be inhibited, resulting in the production of dilute urine. However, in this case, the urine is inappropriately concentrated in relation to the serum, implying continuing secretion of vasopressin resulting in SIAD. The chest radiograph indicates that the likely source is ectopic secretion of vasopressin by a bronchial carcinoma.

Discussion

In SIAD, there is inappropriate concentration of the urine and continued natriuresis despite the low plasma sodium concentration because plasma volume is maintained by water retention; therefore, there is no hypovolaemic stimulus to renin, and hence aldosterone, secretion. Hyponatraemia with natriuresis can also occur in adrenal failure and in renal disorders, and these must be excluded before a diagnosis of SIAD can be made. Water intoxication should always be considered as a possible cause of a confusional state, especially in the elderly.

Patients with mild acute and chronic hyponatraemia ([Na^+] 125–130 mmol/L) are usually asymptomatic, although even they may have an increased incidence of osteoporosis and falls. The underlying cause must be addressed, but if this is not possible, the logical treatment is to restrict the patient's water intake to less than that required to maintain normal water balance, for example, to 500–1000 mL/24 h, until the plasma sodium concentration has become normal. However, water restriction is unpleasant and impractical to sustain long term. Demeclocycline, a drug that antagonizes the action of vasopressin on the renal collecting ducts, has been used for this purpose, but it can cause photosensitivity and is potentially nephrotoxic. V2 vasopressin receptor antagonists (vaptans) are now available for the treatment of SIAD, although they are expensive and patients require careful monitoring of water and electrolyte status during treatment.

If patients are severely symptomatic (e.g. experiencing convulsions; see Box 3.5), as is more likely if the hyponatraemia is severe or has developed rapidly, urgent correction of the hyponatraemia will be necessary. Hypertonic saline (1.8%, 2.7% or 3%) should be infused at a rate sufficient to increase the plasma sodium concentration initially by 1 mmol/L per hour (0.5 mmol/L per hour if onset is more than 48 h previously) but not by >10 mmol/L over 24 h. (Note that hypertonic saline should not be given to patients who are experiencing fluid overload.) Paradoxically, giving a loop diuretic at the same time can be beneficial: this reduces the slight increase in ECF volume that is present, stimulates distal renal tubular sodium retention and increases free water excretion. Regular clinical assessment and measurement of plasma sodium concentration are essential. The infusion should be stopped when patients become asymptomatic, irrespective of sodium concentration, or when plasma sodium concentration reaches 120 mmol/L. In chronic dilutional hyponatraemia, correcting the sodium concentration

Box 3.7 **Conditions associated with the syndrome of inappropriate antidiuresis**

Ectopic secretion

bronchial carcinomas
other tumours, e.g. thymus, prostate

Inappropriate secretion

pulmonary diseases
- pneumonia
- tuberculosis
- positive pressure mechanical ventilation

cerebral diseases
- head injury
- encephalitis
- tumours
- aneurysms

miscellaneous
- pain, e.g. postoperative, acute intermittent
- porphyria, Guillain–Barré syndrome,
- hypothyroidism (profound), drugs (see Box 3.2)

too rapidly risks causing central pontine myelinolysis (see Fig. 3.6A), a brain syndrome characterized by spastic quadriplegia, pseudobulbar palsy and cognitive changes. Hypoxaemia, a history of alcohol excess or the presence of chronic liver disease may increase this risk. This condition has a poor prognosis.

It is possible to calculate the approximate infusion rate of hypertonic saline required to achieve a given increase in sodium concentration, but doing so must never be used as a substitute for careful clinical and biochemical monitoring.

Combined water and sodium excess

Combined water and sodium excess is a frequent cause of hyponatraemia. It underlies the hyponatraemia of congestive cardiac failure, hypoproteinaemic states and some patients with liver failure. The mechanism is discussed on p. 34. The fact that there is sodium excess is indicated by signs of increased ECF volume (e.g. peripheral oedema or ascites). The logical treatment in these patients involves measures to treat the underlying cause and remove the excess sodium and water (e.g. with diuretics). Despite the hyponatraemia, saline should not usually be given, because these patients are already experiencing sodium overload.

Other causes of hyponatraemia

Decreased fractional water content of plasma, causing pseudohyponatraemia, can occur with severe hyperproteinaemia and hyperlipidaemia (see p. 38).

Addition of a solute to the plasma that is confined to the ECF will tend to increase ECF osmolality. The most common example is hyperglycaemia (Case history 3.4): a decline in plasma sodium is a normal response to hyperglycaemia, and it is essential to measure plasma glucose concentration in all patients with unexplained hyponatraemia. Acutely, there is a shift of water from the ICF to the ECF, lowering the ECF sodium concentration, and the increase in ECF osmolality stimulates vasopressin secretion, leading to water retention. The resulting increase in ECF volume inhibits aldosterone secretion, leading to natriuresis. Movement of water from the ICF to the ECF does not occur in uraemia because urea equilibrates between the ECF and the ICF, thus preventing an osmotic imbalance.

The 'sick cell syndrome'

Hyponatraemia is frequently observed in patients with either acute or chronic illness, without any obvious cause. The term 'sick cell syndrome' has been used to describe this phenomenon, which previously was attributed to an increase in the permeability of cell membranes to sodium with or without a decrease in the activity of the sodium pump. However, any transmembrane shift of sodium would be expected to be accompanied by an iso-osmotic movement of water, and thus should not affect plasma sodium concentration, although it is possible that sodium could become bound to intracellular macromolecules, thus nullifying its effect on osmolality. A raised osmolar gap (see p. 38), presumed to be due to loss of intracellular organic molecules through leaky cell membranes, has been observed in some patients, and the accompanying iso-osmotic shift of water to the extracellular compartment would dilute its sodium concentration. Depletion of intracellular organic solutes may also reset the hypothalamic osmostat. Many sick patients may have a degree of stress-related increased vasopressin secretion or another cause of SIAD.

In practice, however, the mechanism of the hyponatraemia of the 'sick cell syndrome' is relatively unimportant. The hyponatraemia reflects the presence of the underlying disease, and it is this that should be treated, not the hyponatraemia.

Case history 3.4

History

A patient with insulin-treated diabetes woke up feeling hypoglycaemic and drank two glasses of a sugar-rich drink, which abolished the symptoms. She had a hospital appointment that morning and, worried that she might become hypoglycaemic while driving, decided to omit her usual injection of insulin. She felt quite well on arrival at the hospital. Blood was taken for routine monitoring tests.

Results

Plasma:	glucose	28 mmol/L
Serum:	sodium	126 mmol/L
	osmolality	290 mmol/kg

Serum urea, creatinine, potassium and bicarbonate concentrations were normal.

Summary

Hyponatraemia with hyperglycaemia.

Interpretation

The hyponatraemia is dilutional. It is the result of a movement of water from the ICF to the ECF to maintain isotonicity as the plasma glucose concentration increases. In the short time since onset, there was no significant osmotic diuresis, and thus no dehydration.

Discussion

Lowering of plasma sodium concentration is a normal response to hyperglycaemia. It is observed in patients with diabetes and occasionally when glucose is administered at a rate greater than it can be metabolized during parenteral nutrition. It can also occur after mannitol infusion. Mannitol may be given to patients with cerebral oedema, to reduce intracellular water content, and is also used as an osmotic diuretic.

Investigation of hyponatraemia

In many instances, the cause of hyponatraemia can be recognized clinically and additional investigations add little to the management of the patient. Careful clinical evaluation and study of fluid balance charts (if reliable) will often indicate the underlying mechanism or mechanisms, and thus point the way to a diagnosis. Hyponatraemia caused by sodium depletion may be accompanied by physical signs of a decrease in ECF volume, whereas this will be normal in patients with water excess, and in combined water and sodium excess the signs will be those of ECF expansion. Not infrequently, however, clinical assessment of fluid volume status may be difficult, and a systematic process of biochemical investigation is necessary.

Acute hypervolaemic hyponatraemia may be fatal as it causes cerebral oedema (see Fig. 3.6). Acute-onset hyponatraemia with **sodium <120 mmol/L** requires urgent assessment and management (see p. 41). Children are at higher risk of cerebral oedema so **sodium <130 mmol/L in patients aged <16 years** should be managed with the same degree of urgency.

A simple algorithm for the diagnosis of hyponatraemia is given in Fig. 3.7. Some of the commoner causes of hyponatraemia are indicated in Table 3.3, and some investigations that may help in elucidating its cause are presented in Box 3.8. It must be emphasized, however, that an appreciation of the underlying physiological principles and their clinical correlates is vital for correct interpretation of their results.

Management of hyponatraemia

Hyponatraemia is essentially a feature of a disorder involving water or sodium homoeostasis, or both. As has been discussed, measures to treat the causative condition may need to be supplemented by direct measures to correct the imbalance of sodium and water. These will vary according to the mechanism of the hyponatraemia, and it is therefore essential both to diagnose the cause and to understand the pathogenesis. If symptoms of water intoxication are present, urgent (though cautious) correction will be required.

Hypernatraemia

Hypernatraemia is less common than hyponatraemia but is much more frequently of clinical significance. The causes include pure water depletion, combined sodium and water depletion with water loss predominating, or sodium excess; of these, excess sodium is the least common. Hypernatraemia is a relatively frequent finding in elderly people, as a result of inadequate water intake; in hospitals, it is often iatrogenic.

In most patients with hypernatraemia, the cause is obvious from the history and clinical observations. Diabetes insipidus is an important cause, and the investigation of patients suspected of having this condition is considered in Chapter 9.

Regardless of its cause, hypernatraemia should be treated by administration of hypotonic fluids such as water (orally) or 5% dextrose (parenterally). In patients with sodium overload, measures to remove excess sodium may have to be considered. As already emphasized, it is important that hypernatraemia caused by water depletion is not corrected too rapidly.

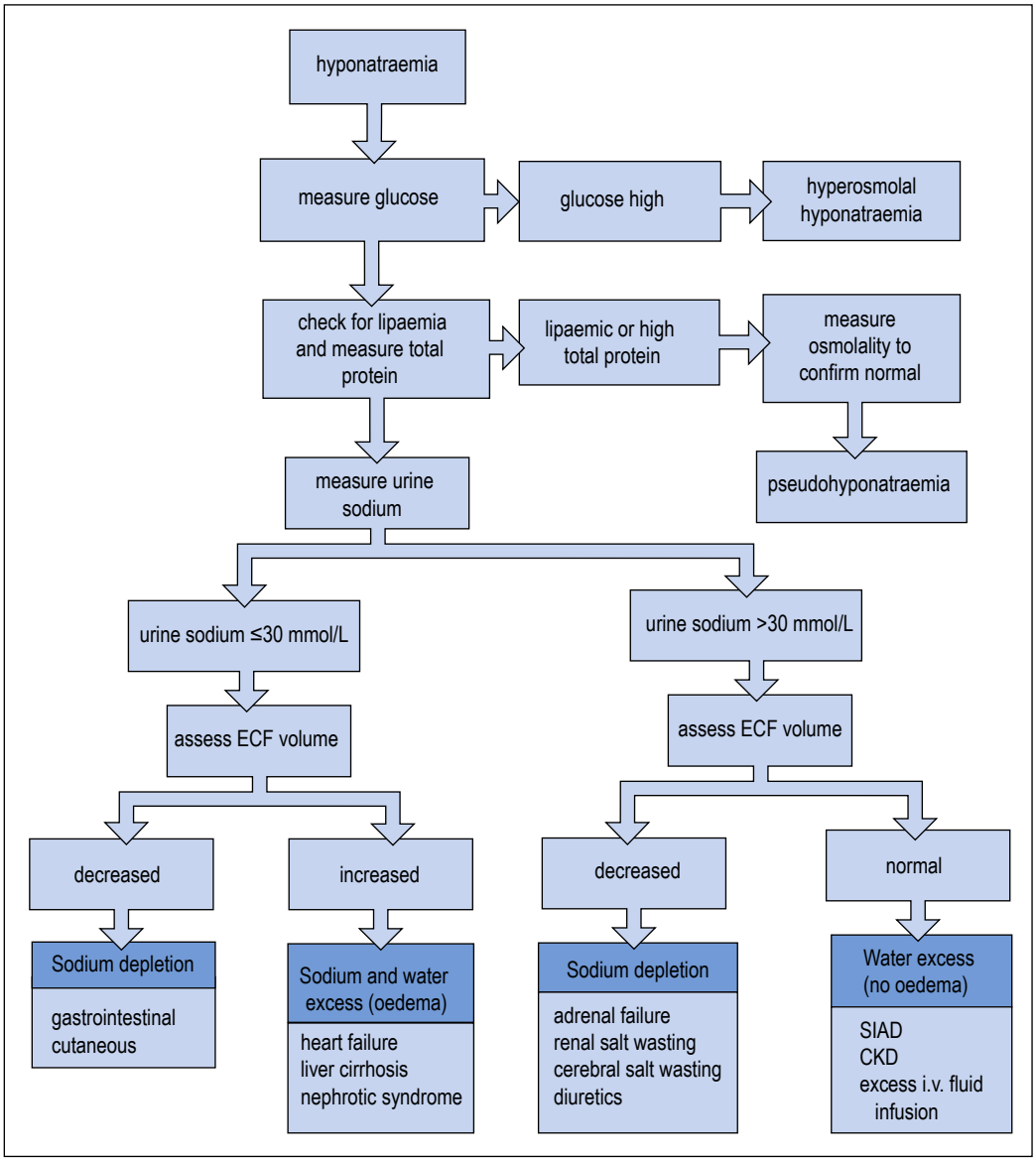

Fig. 3.7 Simple algorithm for the diagnosis of hyponatraemia. In practice, hyponatraemia is often multifactorial, but one cause may predominate and determine the clinical features. ECF, extracellular fluid; i.v., intravenous; SIAD, syndrome of inappropriate antidiuresis; CKD, chronic kidney disease.

Potassium Homoeostasis

Dietary potassium intake is of the order of 75–150 mmol /24 h, values higher in the range being associated with a high intake of fruit and vegetables. Extracellular potassium balance is controlled primarily by the kidneys and, to a lesser extent, by the gastrointestinal tract. In the kidneys, filtered potassium is almost completely reabsorbed in the proximal tubules. Some active potassium secretion takes place in the most distal part of the distal convoluted tubules, but potassium excretion is primarily a passive process. The active reabsorption of sodium generates a membrane potential that is neutralized by the movement of

Table 3.3 Some common causes of hyponatraemia

Cause	Mechanism	ECF volume
syndrome of inappropriate antidiuresis	water excess	normal
increased gastrointestinal output	sodium depletion	decreased
inappropriate i.v. fluids	water excess	normal or increased
congestive cardiac failure and hypoproteinaemic states	sodium and water retention	increased
diuretic therapy	sodium depletion and water retention (see text)	decreased
adrenal insufficiency	sodium and water depletion	decreased
hyperglycaemia	isotonic redistribution	normal
non-specific ('sick cell syndrome')	see text	normal

ECF, extracellular fluid; i.v., intravenous.

Box 3.8 Some laboratory investigations of value in the investigation of hyponatraemia

inspection of serum for limpaemia
serum
- osmolality
- potassium
- urea
- creatinine
- total protein
- TSH and free T4

haematocrit
ACTH (tetracosactide [Synacthen]) stimulation test
urine
- sodium
- osmolality

ACTH, adrenocorticotrophic hormone; TSH, thyroid-stimulaing hormone.

Case history 3.5

History

A male infant aged 15 weeks was admitted to hospital for the investigation of recurrent diarrhoea. He had been well until 8 weeks of age, when the first episode had occurred. Since then, there had been several further attacks.

Examination

There were clinical signs of dehydration and he had lost weight.

Results

Serum:	sodium	167 mmol/L
	potassium	4.9 mmol/L
	urea	2.6 mmol/L
Urine:	sodium	310 mmol/L

Summary

Severe hypernatraemia with high urine sodium concentration.

Interpretation

The combination of high urine sodium excretion with hypernatraemia suggests salt overload. In most patients with chronic diarrhoea, the kidneys conserve sodium in response to dehydration and there is hyponatraemia, because of loss of sodium with inadequate replacement.

Discussion

Stool chromatography revealed the presence of an abnormal sugar, which was identified as lactulose. Lactulose is a non-absorbed osmotic laxative. Careful observation confirmed the suspicion that the child's mother was adding salt and lactulose to his feeds. She was not allowed to stay with him unattended, and the diarrhoea and electrolyte abnormalities resolved rapidly. This was a case of child abuse (fabricated or induced illness, sometimes referred to as 'Munchausen syndrome by proxy').

potassium and hydrogen ions from tubular cells into the lumen. Thus, **urinary potassium excretion** depends on several factors:

- the circulating concentration of aldosterone
- intravascular volume (reduction stimulates aldosterone secretion)
- the relative availability of hydrogen and potassium ions in the cells of the distal tubules and the collecting ducts

- the capacity of these cells to secrete hydrogen ions
- the rate of flow of tubular fluid: a high flow rate (e.g. osmotic diuresis, treatment with diuretics) favours the transfer of potassium into the tubular lumen
- the amount of sodium available for reabsorption in the distal convoluted tubules and the collecting ducts
- dietary potassium intake (the kidneys' capacity to retain potassium is enhanced by low intake, and vice versa): the mechanism for this is uncertain
- magnesium status: magnesium depletion increases potassium secretion from the distal nephron (it also impairs the action of the sodium–potassium pump responsible for the uptake of potassium into the ECF).

In the distal nephrons, potassium is secreted in exchange for either sodium or hydrogen ions: increased delivery of sodium increases the potential secretion of potassium. Aldosterone stimulates potassium excretion both indirectly, by increasing the active reabsorption of sodium in the distal convoluted tubules and the collecting ducts, and directly, by increasing active potassium secretion in the distal part of the distal convoluted tubules. Aldosterone secretion from the adrenal cortex is stimulated indirectly by activation of the renin–angiotensin system in response to hypovolaemia (see p. 28) and directly by hyperkalaemia.

Because both hydrogen and potassium ions can neutralize the nephron membrane potential generated by active sodium reabsorption, there is a **close relationship between potassium and hydrogen ion homoeostasis**. In an acidosis, hydrogen ions will tend to be secreted in preference to potassium; in alkalosis, fewer hydrogen ions will be available for excretion and there will be an increase in potassium excretion. Thus, there is **a tendency towards hyperkalaemia in acidosis** and towards **hypokalaemia in alkalosis**. In addition, the active secretion of hydrogen ions in the distal nephron is partly balanced by a reciprocal reabsorption of potassium. An exception to this tendency is renal tubular acidosis caused by defective renal hydrogen ion excretion (see p. 97). In this condition, because of the decrease in hydrogen ion excretion, potassium secretion must increase to balance sodium reabsorption. The result is the unusual combination of hypokalaemia with acidosis.

The capacity of the distal nephrons to excrete potassium is, in part, determined by intracellular magnesium concentration. Magnesium depletion (e.g. resulting from

Case history 3.6

History

After surgery for major abdominal injuries sustained in a knife fight, a young man was fed parenterally with a regimen including 17 g nitrogen as amino acids and 500 g glucose, and artificially ventilated. On day four he become pyrexial, and positive blood cultures were subsequently obtained.

Examination

His fluid balance chart showed that in the previous 24 h his fluid intake had been 3000 mL, urine output had been steady at 90–100 mL/h, and 300 mL fluid had been aspirated via a nasogastric tube. The sodium intake had been 70 mmol. A request for biochemistry testing was made, and the sample was collected the following morning.

Results

Serum:	sodium	150 mmol/L
	potassium	4.2 mmol/L
	urea	10.2 mmol/L
	creatinine	102 µmol/L
	eGFR	>90 mL/min/1.73 m^2
	glucose	25 mmol/L

Summary

Hypernatraemia with hyperglycaemia with raised urea and normal creatinine concentrations.

Interpretation

Sodium input is not excessive; water depletion is the more likely cause of the hypernatraemia. His measured net fluid balance is only 400 mL positive. This is insufficient to balance insensible losses, which will have been increased by the pyrexia and possibly by ventilation. The urine output has not decreased; therefore there has also been an excessive renal water loss. This is due to an osmotic diuresis as a result of glycosuria and a high urea output. The high urea concentration relative to that of creatinine is typical of fluid depletion (see Box 5.1).

Discussion

Glucose intolerance may be a problem in patients receiving parenteral nutrition and can be exacerbated by sepsis, which causes insulin resistance. Parenteral administration of excessive nitrogen will result in increased formation of urea, which will also contribute to an osmotic diuresis: this patient was receiving amino acids equivalent to >100 g protein/day, more than his probable requirements. Inadequate humidification of inspired air may also be a causative factor in water depletion in such circumstances.

increased gastrointestinal or renal loss) results in increased tubular potassium secretion.

Healthy kidneys are less efficient at conserving potassium than sodium: even on a potassium-free diet, urinary excretion remains at 10–20 mmol/24 h. Because there is also an obligatory loss from the skin and gut of approximately 15–20 mmol/24 h, the kidneys cannot compensate if intake declines to much less than 40 mmol/24 h.

Potassium is secreted in gastric juice (5–10 mmol/L) and much of this, along with dietary potassium, is reabsorbed in the small intestine. In the colon and rectum, potassium is secreted in exchange for sodium, partly under the control of aldosterone. Stools normally contain some potassium, but considerable amounts (up to 30 mmol/L) can be lost in patients with fistulae or chronic diarrhoea, or in patients who are losing gastric secretions through persistent vomiting or nasogastric aspiration.

Movement of potassium between the intracellular and extracellular compartments can have a profound effect on plasma potassium concentration. Potassium ions move into cells from the ECF in exchange for sodium, via the transmembrane, energy-dependent sodium–potassium pump (Na^+,K^+-ATPase). Hyperkalaemia can result if the activity of this pump is impaired or if there is damage to cell membranes. Potassium uptake into cells is stimulated by insulin and β-adrenergic stimulation; α-adrenergic stimulation has the opposite effect. Potassium uptake is impaired in magnesium depletion, but the concurrent increased loss of potassium through the kidneys results in net potassium depletion and hypokalaemia.

Transcellular shifts of hydrogen ions can cause reciprocal shifts in potassium and vice versa. In a systemic acidosis, intracellular buffering of hydrogen ions results in the displacement of potassium into the ECF. In alkalosis, there is a shift of hydrogen ions from the ICF to the ECF, and a net movement of potassium ions in the opposite direction, which tends to produce hypokalaemia. Similarly, potassium depletion can lead to systemic alkalosis (see Chapter 4).

Potassium Depletion and Hypokalaemia

Potassium depletion occurs when output exceeds intake. Except in patients who are fasting, inadequate intake is rarely the sole cause of potassium depletion. However, **increased loss of potassium, either from the gut or (more often) through the kidneys, is a frequent occurrence**. If renal potassium excretion is <20 mmol/L in a patient with hypokalaemia, excessive renal excretion is unlikely to be the cause. Drug therapy is often implicated in the pathogenesis of potassium depletion. Hypokalaemia, although usually only mild (3.0–3.5 mmol/L), is the most frequently occurring electrolyte abnormality.

The **causes of hypokalaemia** are shown in Box 3.9. By far the most common causes are loss of potassium from the gut and treatment with diuretics. When hypokalaemia is a result of potassium depletion, it usually develops slowly and is only corrected slowly when the cause is effectively treated. In contrast, hypokalaemia as a result of redistribution of potassium from the extracellular to the intracellular compartment usually develops acutely and can normalize rapidly. Bartter, Liddle and Gitelman syndromes are rare

Box 3.9 Principal causes of hypokalaemia

Decreased K^+ intake

- oral (rare)
- parenteral

Transcellular K^+ movement

- alkalosis
- insulin administration
- β-adrenergic agonists
- refeeding syndrome
- rapid cellular proliferation (e.g. anabolic phase after starvation)

Increased K^+ excretion

- renal
  - diuretics
  - diuretic phase of acute kidney injury
  - nephrotoxic drugs (e.g. amphotericin)
  - mineralocorticoid excess:
    - primary aldosteronism
    - secondary aldosteronism
    - Cushing syndrome
    - carbenoxolone, liquorice (see p. 184)
    - renal tubular acidosis (types 1 and 2)
  - Bartter, Liddle and Gitelman syndromes (see Table 3.4)
  - magnesium depletion
- extrarenal
  - diarrhoea
  - purgative abuse
  - villous adenoma of the rectum
  - vomiting, gastric aspiration
  - enterocutaneous fistulae
  - excessive sweating

Table 3.4 **Inherited disorders of renal tubular function that are associated with hypokalaemic alkalosis**

Syndrome name	Inheritance	Renin and aldosterone	BP	Other features	Cause	Usual age of clinical onset
Liddle	AD	↓	↑	family history of premature stroke	activating mutation in distal tubule sodium channel	infancy to early adulthood
Gitelman	AR	↑	↓/N	salt wasting hypomagnesaemia hypocalciuria	defect in thiazide-sensitive sodium transporter	adulthood
Bartter	AR	↑	↓/N	salt wasting short stature	impaired sodium reabsorption in loop of Henle	infancy to early childhood

AD, autosomal dominant; AR, autosomal recessive; BP, blood pressure.

inherited disorders caused by mutations in renal tubular ion transport proteins. Their biochemical and clinical features are summarized in Table 3.4.

Clinical features

Even severe hypokalaemia may be asymptomatic. Hypokalaemia causes hyperpolarization of excitable membranes, thus decreasing their excitability. When symptoms are present, they are related primarily to disturbances of neuromuscular function (Table 3.5): muscular weakness, constipation and paralytic ileus are common problems. Cardiac dysrhythmias can be fatal: characteristic electrocardiographic (ECG) findings include ST segment depression and a prominent U wave. Hypokalaemia also potentiates digoxin toxicity. This is an important practical consideration, because diuretics and digoxin may be prescribed together, although the latter drug is now used less frequently than in the past. Hypokalaemia results in increased synthesis of prostaglandins, which antagonize the action of vasopressin, leading to polyuria and secondary polydipsia.

Table 3.5 **Clinical features of hypokalaemia**

Disorder	Feature
neuromuscular	weakness
	constipation, ileus
	hypotonia
	depression
	confusion
cardiac	arrhythmias
	potentiation of digoxin toxicity
	ECG changes (ST depression, T wave depression/inversion, prolonged P-R interval prominent U wave)
renal	impaired concentrating ability leading to polyuria and polydipsia
metabolic	alkalosis

Excitable membranes become hyperpolarized in hypokalaemia, decreasing their excitability The effect on the kidneys is due to increased synthesis of prostaglandins, which antagonize the action of vasopressin.

Investigation of hypokalaemia

As indicated in Box 3.9, the causes of hypokalaemia can be divided into decreased potassium intake, redistribution of potassium into cells and increased potassium excretion. The first two groups are usually clinically apparent: low potassium intake is usually a chronic problem, whereas abnormal transcellular movement of potassium is more likely to be an acute disorder. Current and recent drug treatment should be reviewed for thiazide or loop diuretics and potentially nephrotoxic drugs such as amphotericin or cisplatin, all of which cause increased urinary potassium loss. Because increased potassium losses may be either via the kidneys or via other routes (usually gastrointestinal), it is often informative to measure urine potassium output. A random urine potassium concentration >20 mmol/L in the presence of hypokalaemia is inappropriately high and usually indicates that the kidneys are the route of potassium loss.

Most patients with hypokalaemia also have a metabolic alkalosis, the presence of which is indicated by a

high plasma bicarbonate concentration: measurement of venous or arterial hydrogen ion concentration (pH) is rarely necessary. Important exceptions are renal tubular acidosis and some instances of increased gastrointestinal loss, which may be associated with the low plasma bicarbonate concentrations that characterize metabolic acidosis.

Patients with increased renal or gastrointestinal potassium excretion often also have increased magnesium excretion; magnesium depletion may exacerbate hypokalaemia by impairing the capacity of the kidney tubules appropriately to reabsorb filtered potassium (see p. 46). Plasma magnesium concentration should therefore be measured if the clinical picture indicates that depletion is likely or in any patient with otherwise unexplained hypokalaemia or hypokalaemia that is resistant to replacement.

Management of hypokalaemia

Although the plasma potassium concentration is a poor guide to total body potassium, a plasma concentration of 3.0 mmol/L generally implies a deficit of the order of 300 mmol. The first step in the management of hypokalaemia should be to identify and treat the causative condition, but potassium replacement is frequently required. Oral supplementation may be appropriate in mild, chronic hypokalaemia, but in more severe or acute cases, intravenous administration is necessary. Because any potassium deficit will be almost entirely from the ICF but administered potassium first enters the ECF, replacement must be undertaken with care, particularly when the intravenous route is used.

As a guide, the following potassium dosages should not be exceeded without good reason: a rate of 20 mmol/h, a concentration of 40 mmol/L in intravenous fluid or a total of 240 mmol/24 h. Thorough mixing with the bulk of the fluid to be infused is vital. Plasma concentrations should be monitored during treatment. If unusually large amounts of potassium are necessary, and particularly if there is impaired kidney function, ECG monitoring is essential, because characteristic changes in the waveform occur with changing plasma potassium concentrations.

Case history 3.7

History

A 67-year-old woman presented with severe muscular weakness. She had been in the habit of taking large amounts of purgatives and recently had been prescribed a thiazide diuretic for mild hypertension.

Results

Serum:	potassium	2.4 mmol/L
	bicarbonate	36 mmol/L

Summary

Severe hypokalaemia with high serum bicarbonate concentration.

Interpretation

Hypokalaemic alkalosis resulting from both increased losses from the gut, owing to purgative abuse and from the kidneys as a result of a thiazide diuretic.

Discussion

Thiazides act by inhibiting sodium–chloride cotransport in the distal part of the ascending limbs of the loops of Henle and in the first part of the distal tubules. As a result, there is an increase in the amount of sodium delivered to, and available for reabsorption from, the distal tubules: this will tend to increase potassium and hydrogen ion excretion from the kidneys. Loop diuretics similarly increase renal potassium excretion, although to a lesser extent. The doses of thiazide diuretics used to treat hypertension rarely cause significant hypokalaemia unless, as in this case, other causes of hypokalaemia are present.

If necessary, potassium supplements may be prescribed at the same time as diuretics; combined preparations are available but typically provide insufficient potassium. Alternatively, a potassium-sparing diuretic such as amiloride may be co-prescribed. Potassium supplements are probably unnecessary unless the plasma concentration is <3.0 mmol/L, and they are potentially dangerous in patients with renal impairment because hyperkalaemia may result.

Potassium Excess and Hyperkalaemia

Potassium excess can be caused by excessive intake or decreased excretion. A normal intake may be excessive if excretion is decreased (e.g. in kidney failure). Excessive intake is otherwise virtually always iatrogenic and the result of parenteral administration. Drugs are frequently implicated as causes of hyperkalaemia: combinations of potassium-sparing diuretics with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) or non-steroidal anti-inflammatory drugs (NSAIDs) are particularly hazardous. NSAIDs tend to decrease renal potassium excretion through their effect on eicosanoid synthesis.

Hyperkalaemia (Box 3.10) can result from potassium excess but can also be a result of redistribution of potassium from the intracellular to the extracellular compartment. This mechanism can sometimes cause hyperkalaemia even in a patient with potassium depletion (e.g. in diabetic ketoacidosis). As with hypokalaemia, more than one cause of hyperkalaemia may be present. **Pseudohyperkalaemia**,

Case history 3.8

History

A 60-year-old man underwent total gastrectomy for a carcinoma. He was malnourished before surgery and it was decided to provide parenteral nutrition postoperatively. On the fifth day, his serum potassium concentration was 3.0 mmol/L, despite the provision of 60 mmol potassium/24 h in the intravenous feed.

Interpretation

The patient is hypokalaemic in spite of the provision of sufficient potassium to cover normal obligatory losses.

Discussion

Potassium excretion increases during the metabolic response to trauma but, once a patient becomes anabolic, the body's requirements increase as potassium is taken up into cells. Furthermore, during total parenteral nutrition, glucose is often the predominant energy source, providing a considerable stimulus to insulin release. Potassium requirements may, therefore, be much greater than normal because insulin stimulates its uptake into cells.

This patient had recently undergone abdominal surgery, and an ileus is usual in these circumstances. This will result in decreased reabsorption of any potassium secreted into the gut and can also contribute to the loss of potassium from the ECF.

Severe hypokalaemia is a feature of the refeeding syndrome that may occur when nutrition is started at an inappropriately high rate (see p. 149).

Box 3.10 **Principal causes of hyperkalaemia**

Spurious

haemolysis

delayed separation of serum from blood cells

contamination (e.g. with potassium EDTA anticoagulant)

abnormal blood cells, e.g. leukaemia, thrombocytosis

Excessive K^+ intake

oral, e.g. LoSalt (rare except in chronic kidney disease orf with K^+-sparing diuretics)

parenteral infusion

Transcellular K^+ movement

tissue damage (e.g. trauma, tumour lysis syndrome)

catabolic states

- systematic acidosis
- insulin lack
- vigorous exercise (transient)

Decreased K^+ excretion

acute kidney injury

chronic kidney disease

K^+-sparing diuretics

angiotensin-converting enzyme inhibitors

angiotensin II receptor antagonists

non-steroidal anti-inflammatory drugs

mineralocorticoid deficiency:

- Addison disease
- adrenalectomy
- hyporeninaemic hypoaldosteronism

caused by the leakage of potassium from blood cells *in vitro*, often occurs. Although often caused by frank haemolysis, this is not invariably the case, especially if there has been a delay in separation of the plasma from the blood cells. The normal clotting process releases potassium from white cells and platelets: this normally contributes a negligible amount to serum potassium concentration, but the effect is exaggerated in patients with high white cell or platelet counts (e.g. in leukaemia).

Investigation of hyperkalaemia

Chronic mild hyperkalaemia, with a serum potassium concentration of 5.3–6.0 mmol/L, is a relatively common finding, especially in elderly patients. In some cases, it is clearly attributable to acute or chronic kidney disease, but in others, no such cause is apparent.

It is important to exclude adrenal insufficiency, if necessary, with an adrenocorticotrophic hormone (ACTH; tetracosactide [Synacthen]) stimulation test (see p. 179). Mineralocorticoid deficiency often, but not always, results in hyponatraemia, an increase in urea and hyperkalaemia.

A careful drug history may elicit use of 'potassium-sparing' diuretics such as spironolactone. ACEIs or ARBs cause hyperkalaemia, especially in patients with renal artery stenosis (which may be unsuspected clinically), and it is essential to check 'urea and electrolytes' one week after starting drugs of this class. NSAIDs are particularly prone to cause hyperkalaemia in patients taking diuretics.

Haemolysis is an obvious cause of pseudohyperkalaemia, and most laboratories screen for, and report this on all samples, but the same effect occurs in the absence of

haemolysis if separation of the plasma from the cells is delayed for more than about 4 h, especially at low temperatures. Pseudohyperkalaemia associated with high white cell or platelet counts can be excluded by measuring a full blood count. Some patients have subclinical red cell abnormalities that result in more rapid cell breakdown in vitro: measurement of potassium using a blood tube containing heparin anticoagulant with rapid centrifugation and separation of the plasma may identify this cause. Pseudohyperkalaemia of any cause is not of direct clinical significance, but patients may need to have their blood samples taken in the hospital phlebotomy clinic and processed rapidly to enable accurate measurement of potassium.

If the above causes are excluded, the patient may have hyporeninaemic hypoaldosteronism. This is particularly prevalent in the elderly and often a feature of early (e.g. diabetic) nephropathy, with hyperkalaemia out of proportion to the reduction in GFR. It may be helpful to measure paired serum and urine potassium concentrations and osmolalities to calculate the transtubular potassium gradient (TTKG), a measure of the ability of the nephrons to excrete potassium appropriately. In hyporeninaemic hypoaldosteronism, the TTKG is low.

Clinical features

Hyperkalaemia is less common than hypokalaemia but is more dangerous: through its effect on the heart, it can kill without warning. It lowers the resting membrane potential, shortens the cardiac action potential and increases the speed of repolarization. Cardiac arrest in asystole or slow ventricular fibrillation may be the first sign of hyperkalaemia. The risk increases significantly with potassium concentrations exceeding 6.5 mmol/L (particularly if the increase has occurred rapidly); this should be treated as a medical emergency. It is therefore necessary to be alert for this disorder in appropriate circumstances, for instance, in acute kidney injury, to ensure that effective early management is instituted. Characteristic ECG changes (initially peaking of T waves, followed by loss of P waves and, finally, the development of abnormal QRS complexes) may precede cardiac arrest. Other clinical features of hyperkalaemia include muscle weakness, and in hyperkalaemia associated with acidosis, hyperventilation (Kussmaul respiration, see Case history 13.2) may be present.

Management

In **acute and severe hyperkalaemia,** intravenous calcium gluconate (10 mL of a 10% solution given over 1 min and repeated as necessary) affords some degree of immediate protection to the myocardium by antagonizing the effect of hyperkalaemia on myocardial excitability. Intravenous infusion of glucose and insulin promotes intracellular potassium uptake. Salbutamol, which activates Na^+,K^+-ATPase, has a similar effect. If insulin is used, blood glucose must be monitored for the subsequent 6 h because of the risk of hypoglycaemia. In an acidotic patient, hyperkalaemia can be controlled temporarily by bicarbonate infusion (using a 1.26% solution, not 8.4%, which risks causing ECF volume expansion because of the high sodium concentration).

In acute kidney injury and in other circumstances where the hyperkalaemia is uncontrollable, dialysis or haemofiltration will be required. In chronic kidney disease, restriction of potassium intake and the administration of oral ion-exchange resins are often successful in preventing

Case history 3.9

History

A young man was admitted to hospital after sustaining a fractured femur and ruptured spleen in a motorcycle accident. He underwent splenectomy and was put in traction. Some 24 h after admission, he had passed only 300 mL urine.

Results

Serum:	urea	21.5 mmol/L
	creatinine	168 µmol/L
	eGFR	49 mL/min/1.73m^2
	potassium	6.5 mmol/L

Summary

Severe hyperkalaemia with high serum urea and creatinine concentrations.

Interpretation

Oliguria with high serum urea and creatinine concentrations indicates that the patient has developed acute kidney injury; this might be reversible (i.e. pre-renal; see p. 85). The hyperkalaemia is due to a combination of decreased renal perfusion (hypovolaemic shock) and the loss of potassium either from cells damaged directly by trauma or from cells whose membrane integrity is impaired by hypoxia.

Discussion

This case illustrates the risk of severe hyperkalaemia in patients who sustain acute kidney injury owing to hypovolaemic shock. Similar results may be seen in patients who have sustained a gastrointestinal haemorrhage, which may itself cause hypovolaemia, affecting renal function, but in addition, there will be absorption of potassium from red blood cells undergoing lysis in the gut and increased synthesis of urea from the amino acids released.

Note that although the estimated glomerular filtration rate (eGFR) is stated to be 49 mL/min/1.73 m^2, eGFR calculations overestimate the true GFR in patients who are developing acute kidney injury, see p. 82.

dangerous hyperkalaemia until such time as dialysis becomes necessary for other reasons.

ECG monitoring can be valuable in patients with hyperkalaemia. Changes in the plasma potassium concentration are reflected by changes in the ECG waveform more rapidly than could be determined by biochemical measurement.

Stable chronic hyperkalaemia with potassium concentration <6.5 mmol/L is not a medical emergency, although there is increased risk of cardiac dysrhythmias if the underlying cause worsens or a second contributory factor arises. Treatment is primarily of the underlying cause, with care to avoid use of drugs that promote renal potassium retention and to restrict overconsumption of potassium-rich foods, such as fruits, or high-potassium salt substitutes (e.g. LoSalt).

Patients with hyporeninaemic hypoaldosteronism may need treatment for acute hyperkalaemia should this supervene, but in the longer term, the mineralocorticoid drug fludrocortisone or the potassium-wasting diuretic furosemide may be useful.

Case history 3.10

History

Blood from an outpatient being treated with diuretics was received in the laboratory for biochemical analysis. The serum potassium concentration was 6.7 mmol/L. There was no visible haemolysis, and the blood was freshly drawn. She was recalled and asked to bring all her tablets with her. It transpired that she had initially been prescribed a loop diuretic and potassium supplements for congestive cardiac failure. However, at an outpatient attendance she had been prescribed spironolactone, an antagonist of aldosterone used as a potassium-sparing diuretic, instead of the potassium supplements. She had misunderstood the instructions given to her, and continued to take both the supplements and the diuretic. She was asked to stop taking the potassium supplements, and her serum potassium concentration was normal when checked 1 week later.

Discussion

Therapeutic drugs are a common cause of hyperkalaemia: potassium-sparing diuretics and angiotensin-converting enzyme inhibitors or aldosterone receptor blockers pose a particular risk, especially in the elderly, in whom renal function may be diminished. Salt substitutes (which contain potassium) are also a potential hazard.

Hyperkalaemia is a medical emergency because it causes potentially fatal cardiac dysthymias. Plasma potassium concentrations may increase rapidly, particularly in patients with defective potassium excretion. **Potassium >6.0 mmol/L** requires urgent repeat and if rising rapidly or **potassium >6.5 mmol/L** the patient must be referred for urgent management in hospital.

Intravenous fluid therapy

The safe and effective provision of appropriate intravenous fluids to patients who are unable to maintain adequate sodium, water and potassium balance is learned through supervised clinical practice but must be informed by a thorough understanding of the underlying physiological and pathological principles. Accurate measurement of fluid losses and assessment of insensible losses is important. Biochemical measurements can provide valuable information but are frequently misinterpreted (e.g. that hyponatraemia necessarily indicates sodium depletion).

Initial assessment of an acutely ill patient will include assessment of whether he or she is hypovolaemic and needs fluids as part of **resuscitation**. Blood (or red cell concentrate) may be required if bleeding has occurred. Patients who are unable to meet their ongoing fluid and electrolyte requirements orally or enterally need provision of intravenous fluids. It is helpful to consider separately the amounts of water and electrolytes needed for **routine maintenance** and to **replace abnormal losses** and **redistribution**.

For replacement of gastrointestinal losses, the choice will be determined by the nature of the fluid being lost; for example, gastric aspirates require isovolumetric replacement with 0.9% sodium chloride (sometimes referred to as 'normal' or 'physiological' saline, although it is neither of these).

The most frequent indication for the use of intravenous fluids outside critical care and high-dependency units is in relation to surgery. Before surgery, steps should be taken to ensure that body water, sodium and potassium status are normal. In emergencies, this may require rapid resuscitation with intravenous fluids or blood. Considerable quantities of water can be lost from exposed mucosal surfaces during surgery, in addition to any loss of blood and other continuing insensible losses.

Postoperatively, the requirement is to maintain fluid balance until the patient is able to take fluids orally. In the immediate postoperative period, the metabolic response to trauma causes relative water retention because of increased secretion of vasopressin. Stress also decreases sodium excretion and there is loss of potassium from damaged cells into the ECF. In the first 24 h after surgery, intravenous fluid administration may need to be limited to no more than 1500 mL if overload is to be avoided, and potassium is not usually required. As the metabolic response to trauma resolves, fluid input can be increased to maintain an adequate urine output. A recommended intravenous postoperative fluid regimen after the first 24 h is 25–30 mL/kg per 24 h water and 1 mmol/kg per 24 h sodium and potassium, but account must also be taken of any additional losses (e.g. from fistulae or gastric aspirates) and the results of measurements of plasma concentrations of sodium, potassium, urea and creatinine. Gastrointestinal losses should usually be replaced with 0.9% sodium chloride, but otherwise Hartmann's solution is preferable to replace sodium, because it contains less chloride and reduces the risk of inducing hyperchloraemic acidosis (see p. 63).

The provision of nutrients postoperatively is discussed in Chapter 8.

The composition of some more frequently used intravenous fluids is shown in Table 3.6.

Table 3.6 **The composition of some intravenous fluids**

Fluid	Composition	Use
0.9% sodium chloride[a]	sodium 154 mmol/L chloride 154 mmol/L	isotonic fluid replacement
dextrose-saline	sodium 31 mmol/L chloride 31 mmol/L glucose 222 mmol/L	balanced sodium and water replacement[b,c]
5% dextrose	glucose 278 mmol/L	water replacement[b]
1.26% sodium bicarbonate	sodium 150 mmol/L bicarbonate 150 mmol/L	treatment of acidosis
Hartmann's solution ('Ringer–lactate', compound sodium lactate)	sodium 131 mmol/L potassium 5.4 mmol/L calcium 2.2 mmol/L chloride 112 mmol/L lactate 29 mmol/L	isotonic fluid replacement

[a]Sometimes referred to as physiological or 'normal' saline.
[b]These solutions are isotonic with plasma, but metabolism rapidly removes the glucose so they are effectively hypotonic.
[c]Dextrose–saline contains sodium and water in suitable proportion to provide total daily sodium and water requirement to an adult who has no deficits or abnormal losses, through use of a single infusion fluid: glucose is used to make the solution isotonic. Note that this is often inappropriate in clinical practice, and many patients require both 0.9% saline or Hartmann's solution and 5% dextrose.

SUMMARY

- **Sodium, potassium and water homoeostasis are closely linked.** Sodium is the principal extracellular cation, and the amount of sodium in the body is the major determinant of ECF volume. Potassium is the major intracellular cation.
- **Sodium and potassium are transported actively** in the body; **water moves passively** in response to changes in the solute contents of the body's fluid compartments.
- **Sodium excretion** is primarily controlled by **aldosterone**, a hormone secreted in response to a decrease in ECF volume that causes sodium retention and loss of potassium.
- **Water excretion** is controlled by **vasopressin** (ADH). This promotes water retention and is secreted in response to an increase in ECF osmolality and a decrease in ECF volume.
- **Potassium excretion** is regulated in part by aldosterone but also depends on extracellular hydrogen ion concentration and sodium and water excretion.
- Disturbances of either water or sodium homoeostasis can produce characteristic clinical and biochemical features, but combined disturbances are common and the features may then be less clear-cut.
- Changes in plasma sodium concentration can be caused by changes in the amounts of extracellular sodium or water, or both. **Hyponatraemia is common**; it is sometimes an appropriate physiological response to disease. **Hypernatraemia is less common** than hyponatraemia and usually is related to a decrease in body water.
- **Plasma potassium concentration** is a poor guide to the body's overall potassium status. Depletion is not always associated with hypokalaemia, nor is hypokalaemia always due to potassium depletion; similar considerations apply to potassium excess and hyperkalaemia.
- **Hypokalaemia** is most frequently a result of excessive gastrointestinal or renal loss of potassium and may be exacerbated by poor intake. It can also be a consequence of increased cellular uptake of potassium from the plasma. It can cause skeletal and smooth muscle weakness, and impairment of myocardial contractility and renal concentrating ability. It also potentiates digoxin toxicity.
- **Hyperkalaemia** is most frequently due to decreased renal excretion or loss of potassium from cells; hyperkalaemia is often iatrogenic, occurring as a result of drug treatment or inappropriate potassium administration. Spurious hyperkalaemia, caused by release of potassium from cells *in vitro*, is common. Hyperkalaemia can cause cardiac arrest: this can occur in the absence of any warning clinical symptoms or signs.