

# ACID–BASE BALANCE AND REGULATION OF pH



## Chapter objectives

After studying this chapter you should be able to:

- ① Define the normal range for plasma pH.
- ② Explain the role of the kidney in the steady state elimination of acid produced daily by metabolism.
- ③ Outline the defence mechanisms which act to prevent an abrupt change in pH in response to an acid load.
- ④ Describe the mechanism for acid transport in the different nephron segments.
- ⑤ Recognize the clinical and biochemical features of metabolic acidosis, list some causes and give an approach to the differential diagnosis.
- ⑥ Recognize metabolic alkalosis, list some causes, and explain the pathophysiology of this disturbance during prolonged vomiting.



## Introduction

Just as the kidney is a critical organ in defending the normal set points for extracellular fluid (ECF) volume, osmolality and potassium concentration, it also plays a central role in the homeostasis of the plasma pH. While chemical buffering mechanisms and respiratory elimination of carbon dioxide are important in immediate responses to disturbances in acid-base balance, it falls to the kidney to make long-term adjustments in the rate of acid excretion which allows the external balance with respect to hydrogen ion concentration to be maintained. This chapter will focus on the mechanisms whereby the kidney achieves this role, and the origin of some disturbances of this system in disease.

*See box 1.*

The clue in this case that there is a disturbance of acid-base metabolism is that the bicarbonate concentration, representing the base component of the principal physiological buffer system, is greatly reduced below the normal range. This is consistent with acid accumulation in the ECF, for which we must explore both the cause and the consequences.

The key parameter involved in acid-base regulation is the concentration of  $H^+$  in the ECF. The physiological set point for this parameter is 40 nmol/L, usually expressed (using the negative base 10 logarithm) as the pH, which is normally 7.40. So important is homeostasis of this parameter to the normal operation of metabolism and cellular function that pH is tightly regulated in the range 7.38–7.42, although a somewhat wider range is compatible with life (7.0–7.8).

Two forms of acid are generated as a result of normal metabolic processes. Oxidative metabolism produces a large amount of  $CO_2$  daily, and this so-called 'volatile acid' is excreted through the lungs. Carbon dioxide effectively acts as an acid in body fluids because of the following reactions:



The first reaction (formation of carbonic acid,  $H_2CO_3$ ) is the rate-limiting step and is normally slow, but in the presence of the enzyme carbonic anhydrase (c.a.) the reaction is greatly accelerated. The subsequent ionization of carbonic acid proceeds almost instantaneously. This equation can be rearranged to enhance its physiological utility in the form shown in Fig. 4.1, as the Henderson–Hasselbalch equation.

The other form of acid, the so-called 'non-volatile acid', results from the metabolism of dietary protein, resulting in the accumulation of some 70 mmol of acid per day in an average adult on a typical western meat-containing diet.

## Acid-base balance and regulation of pH box 1

### A case of acidosis

Mrs Mary Loy is a 48-year-old woman of Chinese background who has been sent by her family doctor to the Emergency Department because of his concern about her clinical condition and some biochemical results.

She had been complaining for some weeks of increasing lethargy, an extensive rash and 'heavy breathing'. She had been receiving treatment for 4 years for systemic lupus erythematosus (SLE), a multiorgan autoimmune condition for which a consultant rheumatologist had prescribed prednisone. However, Mrs Loy confessed to having discontinued this medication some 10 months earlier because she was unhappy about its side effects.

On examination she was febrile, unwell and had an erythematous rash on her face and limbs. Her blood pressure was 110/80, pulse rate 100 beats/min and respiratory rate 20/min, the breathing being deep and sighing. The referring doctor's letter indicated that he had obtained a urinalysis result that morning showing: pH 7, blood +++ and protein ++.

He had also obtained plasma biochemistry the previous day, the results of which are as follows:

Sodium 135 mmol/L  
 \*Potassium 3.1 mmol/L  
 \*Chloride 113 mmol/L  
 \*Bicarbonate 13 mmol/L  
 Urea 8.0 mmol/L  
 Creatinine 0.09 mmol/L.

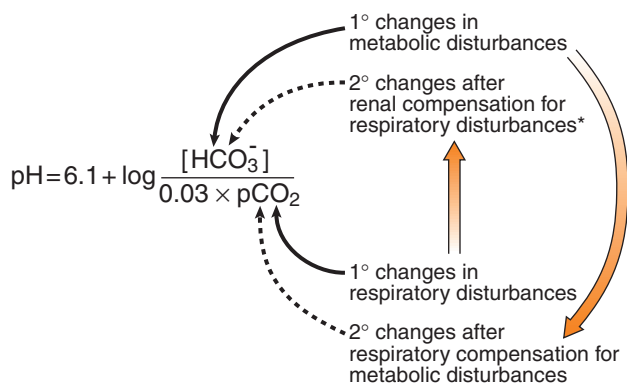
The family doctor is particularly concerned about the low bicarbonate, which he interprets as a sign of acid build-up, and seeks full evaluation of her clinical and metabolic problem.

(\*Results outside the normal range; see Appendix.)

The most important mechanism preventing change in the pH of the ECF is the carbonic acid/bicarbonate buffer system outlined above. The importance of this buffer pair relates to certain key properties: bicarbonate is present in a relatively high concentration in the ECF (24 mmol/L) and the components of the buffer system are effectively under physiological control: the  $CO_2$  by the lungs, and the bicarbonate by the kidneys. These relationships are illustrated in Fig. 4.1.

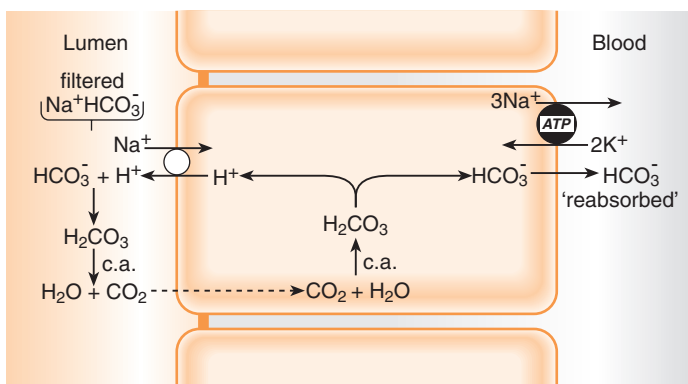
It is clear from this relationship that a shift in pH can be brought about by either a primary change in the bicarbonate concentration (metabolic disturbances) or

in the partial pressure of  $\text{CO}_2$  in the blood (respiratory disturbances). However, it can also be seen that alterations in each of these parameters may represent a compensatory change whereby either the kidney or the lung can act to limit the extent of pH change which would occur because of a primary disturbance in respiratory function or in metabolism, respectively. The patterns of resulting clinical acid–base disturbances will be discussed later in this chapter.



**Fig. 4.1**

Effect of changes in  $\text{HCO}_3^-$  and  $\text{pCO}_2$  on net pH of the plasma. This is an applied version of the Henderson–Hasselbalch equation. Normal plasma  $[\text{HCO}_3^-] = 24 \text{ mmol/L}$ , normal  $\text{pCO}_2 = 40 \text{ mmHg}$ , giving a normal plasma pH of 7.40. The pH will return to 7.40 as long as the ratio of  $[\text{HCO}_3^-]:[0.03 \times \text{pCO}_2]$  is 20:1. \*Note that changes in  $\text{HCO}_3^-$  concentration are also made as part of the renal correction of sustained metabolic acid–base disturbances as long as the kidney itself is not the cause of the primary disturbance.



**Fig. 4.2**

Mechanism of proximal tubular bicarbonate reabsorption. Details of the bicarbonate exit mechanism across the basolateral membrane are not shown in this or subsequent figures. c.a., carbonic anhydrase.

### Role of the kidney in $\text{H}^+$ balance

Before we can make further progress in analysing the acid–base problem in our patient, it is necessary to consider the role the kidney plays in maintaining acid–base balance under normal conditions. Given that bicarbonate buffer is freely filtered at the glomerulus and that there is a daily load of non-volatile acid to be excreted into the urine, there must be two components to the nephron's task: reabsorption of filtered bicarbonate, and addition of net acid to the tubular fluid.

### Bicarbonate reabsorption

Bicarbonate is the principal physiological buffer in the plasma and it is freely filtered at the glomerulus. If this bicarbonate were not fully reabsorbed by the tubular system, there would be ongoing losses of essential buffer into the urine, resulting in progressive acidification of the body fluids as metabolic acid production continued. In fact, bicarbonate excretion is essentially zero under normal conditions because of the extensive and efficient reabsorption of bicarbonate, principally in the proximal tubule as shown in Fig. 4.2.

As discussed in Chapter 2, the cells in this tubular segment contain a sodium–hydrogen exchange carrier molecule known as NHE-3 in the apical cell membrane. As sodium enters the cell from the luminal fluid down its electrochemical gradient via this carrier, it effectively removes hydrogen ions from the cell cytoplasm and adds them to the luminal fluid. The hydrogen ions are generated within the cell by the action of the enzyme carbonic anhydrase, which catalyses the reaction between  $\text{CO}_2$  and water to produce carbonic acid. This rapidly breaks down to produce the hydrogen ions that are secreted into the lumen, and a bicarbonate ion which is transported across the basolateral cell membrane into the plasma. (Note that this is equivalent to saying that the dissociation of cellular water yields a hydrogen ion and a hydroxyl ion, which reacts with cytoplasmic  $\text{CO}_2$  under the influence of carbonic anhydrase to produce the bicarbonate for basolateral extrusion.) Carbonic anhydrase also exists on the brush border membrane on the luminal surface of these cells. Here it catalyses the breakdown of carbonic acid formed as the secreted hydrogen ion reacts with filtered bicarbonate, releasing water and  $\text{CO}_2$  which passes freely across the cell membrane, allowing the cycle to repeat.

The net outcome of this process is that the filtered sodium bicarbonate passing through the proximal tubule is effectively reabsorbed, although the bicarbonate added to the plasma in a given turn of the cycle



is not the same one appearing in the lumen with sodium. This process accounts for reabsorption of some 85% of filtered bicarbonate, and operates at a high capacity but generates a low gradient of hydrogen ion concentration across the epithelium, with the luminal pH falling only slightly from 7.4 at the glomerulus to around 7.0 at the end of the proximal tubule. This is both because of the presence of carbonic anhydrase in the luminal compartment and because the epithelium is 'leaky' to hydrogen ions.

### Net acid excretion

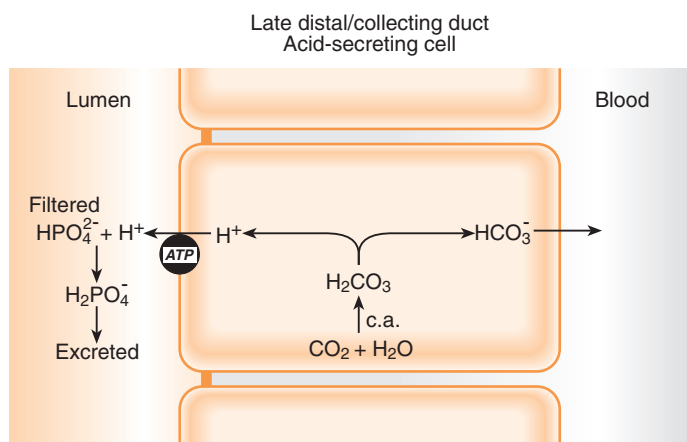
It is important to understand that the process described above has not done anything to remove net acid from the body, since the fate of the secreted  $H^+$  in this segment is effectively to conserve most of the filtered bicarbonate. Under circumstances requiring removal of net acid from the body, the tubules must still carry out two more steps.

- Secrete further acid into the tubular lumen beyond that needed to reabsorb all filtered bicarbonate.
- Provide a buffer in the tubular fluid to assist in the removal of this acid (this is necessary since the maximum acidification which can be achieved in the lumen – around pH 4.5 – would not allow for excretion of the metabolic acid load needing elimination).

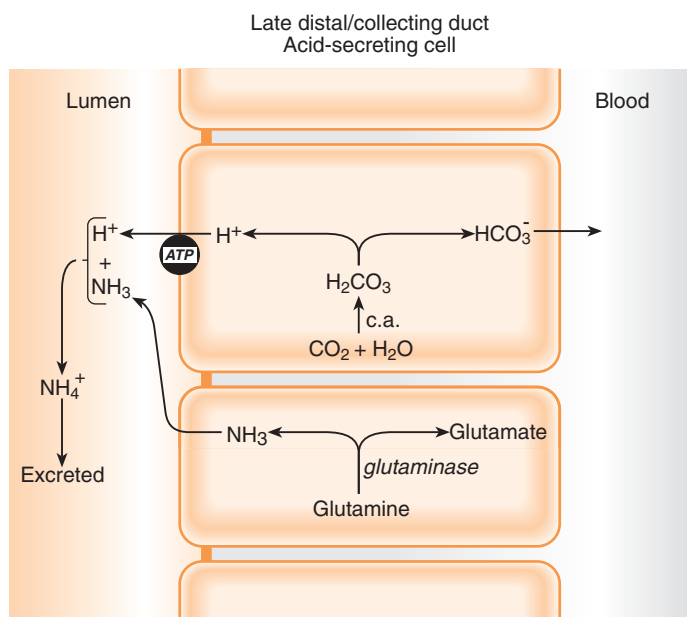
These two requirements are fulfilled in more distal nephron segments. As shown in Figs 4.3 and 4.4, acid is secreted into the lumen of the late distal tubule and collecting ducts by an  $H^+$ -ATPase located in the apical cell membrane. This pump has been found in the intercalated cells within the cortical collecting duct and in the apical membrane of the outer medullary collecting duct cells. The  $H^+$  undergoing secretion in this way is generated within the tubular cells by a reaction facilitated by carbonic anhydrase, as described for the proximal tubule. Again, the bicarbonate generated within the cell by this process passes across the basolateral membrane (actually via a chloride-bicarbonate exchange carrier not shown in Fig. 4.3) into the plasma. However, here the bicarbonate does not replace a filtered bicarbonate molecule, but represents a 'new' bicarbonate, effectively counteracting the consumption of buffer which would have occurred had the excreted acid been retained in the body.

Two types of buffer are involved in excretion of this net acid. The glomerular filtrate contains a limited amount of non-bicarbonate buffer which is capable of taking up some of the  $H^+$ , as shown in Fig. 4.3. The main molecule involved is monohydrogen phosphate

( $HPO_4^{2-}$ ), which is titrated in the distal lumen to dihydrogen phosphate ( $H_2PO_4^-$ ), which is excreted in the urine with sodium. This reaction has limited capacity (removing up to 30mmol of  $H^+$ /day) and tends to proceed as the urine pH falls along the distal nephron segments, typically from 7 down to 6 and below, the



**Fig. 4.3**  
Titration of filtered buffer (phosphate) by acid secreted in the distal nephron. Movements of filtered sodium ions are not shown. c.a., carbonic anhydrase.



**Fig. 4.4**  
Titration of manufactured buffer (ammonia) by acid secreted in the distal nephron. Ammonia synthesis is shown for convenience occurring in an adjacent distal cell; in fact, it is largely synthesized in proximal tubular cells. c.a., carbonic anhydrase.

pK (acid dissociation constant) of this buffer system being 6.8. This form of excreted  $H^+$  is sometimes called 'titratable acid' as it can be quantitated by back-titrating a specimen of urine.

The other form of buffer involved in removal of secreted acid is that manufactured by the kidney itself, namely ammonia ( $NH_3$ ). Renal tubular cells, especially those of the proximal tubule, contain the enzyme glutaminase, which catalyses the production of  $NH_3$  from the nitrogen-rich amino acid glutamine. Ammonia itself is a lipid-soluble gas, which diffuses freely through the kidney tissue and is converted to its protonated form ammonium ( $NH_4^+$ ) in acidic environments (it is also concentrated in the renal medulla by recirculation in the loop of Henle). As the luminal pH falls from the proximal to the distal nephron segments, the  $NH_4^+$  becomes increasingly 'trapped' in the luminal fluid compartment where it is washed away into the urine, associated with chloride ions. Again this constitutes removal of an unwanted  $H^+$  from the body, with restoration of a 'new' bicarbonate molecule to the ECF. The importance of this mechanism for acid excretion is that it is linked to an abundant and regulated source of buffer production ( $NH_3$ ) of essentially unlimited capacity. Thus, under conditions of acid build-up (especially chronic acidosis),  $NH_3$  synthesis is stimulated and acid excretion (as ammonium) is greatly increased, allowing systemic acid-base balance to be maintained.

Note that despite the action of  $NH_3$  to buffer the build-up of free acid in the late segments of the nephron, the pH of the tubular fluid does fall along the collecting duct system, resulting in final urinary pH as low as 4.5. This occurs both because the distal nephron is relatively impermeable to  $H^+$  and because there is no carbonic anhydrase in the luminal compartment in these tubular segments. This means that the dehydration of carbonic acid formed in the lumen is slow, allowing  $H^+$  to accumulate.

In summary, under conditions of normal dietary protein consumption, a slightly alkaline plasma pH of 7.40 is maintained despite the generation of about 70 mmol of hydrogen ion (as non-volatile acid) per day. The kidney's role in maintaining this pH homeostasis is achieved by generating an acidic urine in which the net daily excess of acid can be removed. It does this in the following ways.

- Reabsorbing all bicarbonate buffer filtered into the urine.
- Secreting  $H^+$  for excretion with filtered buffers such as phosphate.
- Secreting  $H^+$  for excretion with the manufactured buffer ammonia.

### Disturbances of acid-base balance: acidosis

Following from the above principles, we can now examine how the kidney is involved in the response to acid-base disturbances, and will consider first the situation of excess acid accumulation, or acidosis. This may arise as a result of either of two primary disturbances.

#### Respiratory acidosis

Respiratory acidosis results from the accumulation of  $CO_2$  in the body as a result of failure of pulmonary ventilation. This itself may occur after lesions either in the central nervous system (e.g. depression of cerebral function, spinal cord injury) or in peripheral nervous pathways involved in ventilating the lungs (peripheral nerve and muscle disorders), or in some forms of lung disease involving impaired gas diffusion.

The decrease in body fluid pH resulting from carbonic acid generation is initially buffered to a limited extent by the reaction of carbonic acid with intracellular buffers such as haemoglobin, leading to the release of small amounts of bicarbonate into the plasma. However, longer term restoration of body fluid pH balance requires the excretion by the kidney of the net acid retained during the period of hypoventilation.

This is achieved by the three steps described above, namely total reabsorption of filtered bicarbonate, titration of all available filtered buffers, and increased generation of ammonia within the kidney to allow for a higher-than-baseline level of net acid excretion as ammonium ion. This latter step is stimulated both by intracellular acidosis and by the elevated  $pCO_2$  which is associated with respiratory acidosis. Over a few days, a new steady state is achieved in which renal excretion of net acid matches that being retained by the lungs, the urine pH being low and the plasma bicarbonate being raised above baseline values (Fig. 4.5).

#### Metabolic acidosis

Metabolic acidosis (or, more correctly, non-respiratory acidosis), on the other hand, is associated with the accumulation of non-volatile acid within the body. There are essentially three components to the protective response which limits the fall in pH which would otherwise occur.

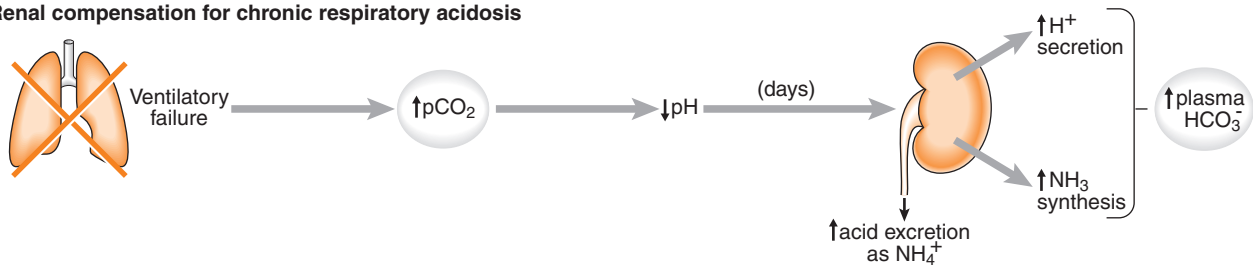
#### Physicochemical buffering

The first defence against a fall in the pH of the body fluids after addition of an acid load is the buffering of  $H^+$  by available bases, particularly bicarbonate which is abundant in the ECF. This results in a fall in the plasma bicarbonate, and hence a lesser fall in the plasma pH

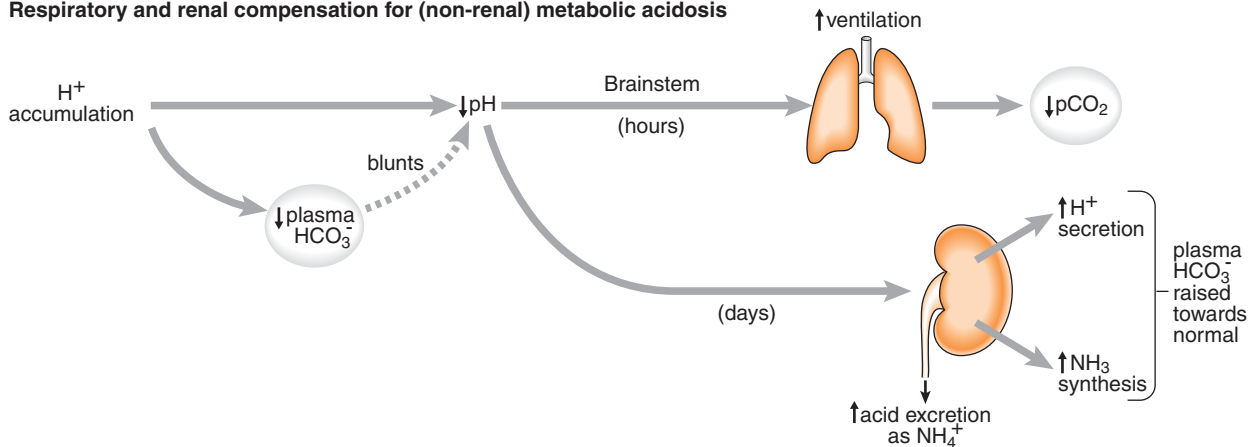




### Renal compensation for chronic respiratory acidosis



### Respiratory and renal compensation for (non-renal) metabolic acidosis



**Fig. 4.5**

Mechanisms of renal and respiratory compensation for acid–base disturbances. The immediate action of physicochemical buffers is omitted for clarity.

than would otherwise have occurred. A variety of extracellular and intracellular proteins provide a further reserve of  $\text{H}^+$  binding sites, and a limited amount of tissue phosphate also contributes some buffer capacity. These reactions are essentially complete within a few minutes of addition of acid to the body fluids, though further buffering occurs in bone and other tissues over the ensuing hours and days.

#### Respiratory response

Despite initial buffering, the pH of the plasma will still fall somewhat during acidosis, and this acts as a potent stimulus to increase the ventilation rate via the activation of chemoreceptors within the brainstem (ventral medulla) which respond to a fall in pH of the cerebrospinal fluid. Clinically this manifests as a deep, rapid breathing pattern (Kussmaul respiration). Over a matter of minutes to hours, this response drives the  $\text{CO}_2$  below normal, and thus serves to blunt the fall in ECF pH by shifting the carbonic acid equilibrium reaction (see Fig. 4.1). This respiratory response provides a medium-term compensation for the acidosis produced by the metabolic disturbance. Note that while the resulting plasma pH is brought up towards 7.40, it

is not fully normalized, and never ‘overshoots’, as a result of respiratory compensation alone.

#### Renal response

Steady state correction of the acid–base disturbance requires the development over several days of an increased capacity by the kidney to excrete the metabolic acid load. This involves reabsorption of all filtered bicarbonate, maximum titration of filtered buffers with secreted  $\text{H}^+$ , and increased intrarenal synthesis of ammonia, which combines with secreted hydrogen ions in the luminal compartment and appears in the urine as large quantities of ammonium. The urine pH falls to minimum levels (around 4.5) and the plasma bicarbonate, lowered initially by the reaction with added acid and subsequently by the hyperventilation response, is elevated back up into the normal range. The net result is a restoration of plasma pH to normal.

Before leaving the subject of renal acid secretion, a number of factors which have been identified as regulators of this process should be listed. The principal factors causing an increase in  $\text{H}^+$  secretion by the nephron include:

### Acid–base balance and regulation of pH box 2

#### The arterial blood gases

Returning to the case of Mrs Loy, crucial early data needed to clarify her acid–base status are the pH and  $p\text{CO}_2$  of the arterial blood. These are obtained immediately after her admission to hospital, and give the following results:

pH 7.37  
 $*p\text{CO}_2$  22 mmHg  
 $*\text{HCO}_3^-$  13 mmol/L  
 $p\text{O}_2$  103 mmHg.

These data confirm that her problem is primarily an acidosis ( $\text{pH} < 7.40$ ) of metabolic origin (low  $\text{HCO}_3^-$ ) which has undergone a considerable degree of respiratory compensation (low  $p\text{CO}_2$ ). However, the presence of the low bicarbonate concentration implies that the kidney has not achieved long-term correction of the underlying acid accumulation.

The question now arises: what is the source of the metabolic acid load that is playing a major part in this presentation?

Before completing an analysis of her acid–base problem, we might take note of one clue present in the data available already. Whatever the cause of metabolic acid build-up, there is some problem with kidney function in this case since urinalysis showed a pH of 7. According to the description above of an expected renal response to acidosis involving excretion of a maximally acidic urine ( $\text{pH} < 5$ ), the urine pH in this case is quite inappropriate and would appear to point to a primary problem located within the kidney itself. As will be seen, this was indeed the case.

- increase in filtered load of bicarbonate
- decrease in ECF volume
- decrease in plasma pH
- increase in blood  $p\text{CO}_2$
- hypokalaemia
- aldosterone.

Note that the first two factors listed result in increased proximal bicarbonate reabsorption, while the later factors act in distal nephron segments to enhance net acid excretion. The common mediator in the case of the last four factors is probably a decrease in the intracellular pH of the tubular cells, which not only activates the hydrogen ion secretory mechanism but also enhances tubular ammonia synthesis.

See box 2.

#### Patterns of metabolic acidosis

Two basic types of metabolic acidosis can be distinguished, on the basis of the effect they have on readily measurable plasma parameters. In one type, acid might be added as hydrochloric (mineral) acid, or there might be a primary loss of bicarbonate buffer from the ECF. In this pattern, there is no addition to the plasma of a new acid anion. In the second type, the accumulating acid might be in the form of an organic acid where the acid anion accumulates in the plasma to replace the falling bicarbonate.

These concepts are shown in diagrammatic form in Fig. 4.6. When the concentrations of the commonly measured cations in the blood (sodium and potassium) are added, there is in normal plasma an apparent discrepancy of some 15 mmol/L over and above the sum of the two commonly measured anions (chloride and bicarbonate). This ‘anion gap’ is largely explained by the multiple negative charges on plasma protein molecules. It can be seen that, where mineral acid is added or bicarbonate is lost (pattern A), the fall in plasma bicarbonate is compensated by a rise in chloride, resulting in no change in the apparent anion gap. In pattern B, however, the bicarbonate may fall to the same extent, but this is accounted for by the addition of the organic acid anion, which, being itself unmeasured, adds to the apparent anion gap, and the plasma chloride does not change from normal. This simple analysis provides an initial tool for the diagnosis of the cause of a metabolic acidosis, where this is not obvious.

Some causes of normal anion gap metabolic acidosis are given in Table 4.1. Rarely, the cause is addition of hydrochloric acid or ammonium chloride, usually in a setting of medical investigation or treatment. More commonly, there is a problem either in the gastrointestinal tract involving loss of bicarbonate from the lower bowel, or in the kidney. In the latter case, the normal mechanisms for  $\text{H}^+$  secretion into the lumen of the nephron may be impaired, either in the proximal tubule (such as by the carbonic anhydrase inhibitor acetazolamide), or in the distal nephron (where the processes involved in urinary acidification are defective). As a group, these disorders of renal acid excretion are called renal tubular acidoses, and will be discussed further later in this chapter.

Causes of the increased anion gap pattern of metabolic acidosis are given in Table 4.2. The organic acid load in these conditions may be classified as to whether it is of endogenous or exogenous origin. In some cases, when specifically suspected, such as lactate in lactic acidosis, the organic acid anion can be measured in the blood. In other cases, however, the

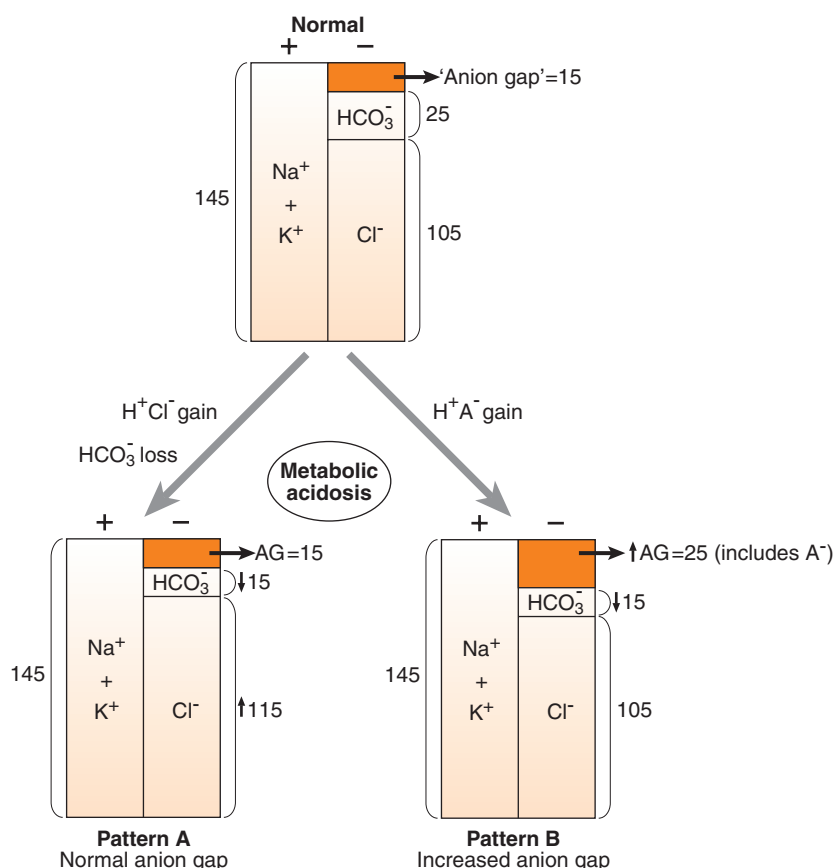


Fig. 4.6

Patterns of metabolic acidosis. All figures are in mmol/L. AG, anion gap.

clinical history provides a strong clue as to the cause, e.g. the accumulation of ketoacids in diabetic ketoacidosis, or of salicylate following aspirin intoxication (this latter disorder being complicated by respiratory alkalosis because of ventilatory stimulation). Of note is the predisposition of alcoholic patients to a number of forms of increased anion gap metabolic acidosis. These include starvation ketosis, lactic acidosis and intoxication by methanol or ethylene glycol (when consumed as alternatives to alcohol). Where metabolic acidosis is associated with advanced renal failure, the cause is usually the accumulation of complex organic acids normally excreted by filtration and proximal tubular secretion, and the result is an increased anion gap.

See box 3.

### Renal tubular acidosis

Metabolic acidosis can arise as a result of failure of renal tubular segments to secrete hydrogen ions in the absence of any major impairment of glomerular filtration rate. This acidosis of renal tubular origin is

Table 4.1

Causes of normal anion gap metabolic acidosis

Disorder	Mechanism
Inorganic acid addition: Infusion/ingestion of HCl, NH <sub>4</sub> Cl	Exogenous acid load
Gastrointestinal base loss: *Diarrhoea Small bowel fistula/drainage Surgical diversion of urine into gut loops	Loss of bicarbonate from gut Loss of bicarbonate from gut Secretion of KHCO <sub>3</sub> by bowel mucosa
Renal base loss/acid retention: Proximal renal tubular acidosis Distal renal tubular acidosis	Renal tubular bicarbonate wasting Impaired renal tubular acid secretion

\*Diarrhoea alone is rarely associated with marked acidosis unless it is severe and prolonged.

not associated with accumulation of any organic acid anion, and so the anion gap remains normal. Two basic variants of the condition, which can be either congenital or acquired, are described.



**Table 4.2**  
**Causes of increased anion gap metabolic acidosis**

<i>Disorder</i>	<i>Anion(s)</i>	<i>Clues to diagnosis</i>
Endogenous acid load:		
Diabetic ketoacidosis	Acetoacetate, beta-OH butyrate	Hyperglycaemia, ketonuria
Starvation ketosis	Acetoacetate, beta-OH butyrate	Hypoglycaemia
Lactic acidosis	Lactate	Shock, hypoxia, liver disease
Renal failure	Organic acids	Reduced glomerular filtration rate
Exogenous acid load:		
Salicylate poisoning	Salicylate	Associated with respiratory alkalosis
Methanol poisoning	Formate	Visual complaints, often alcoholic
Ethylene glycol poisoning	Glycolate, oxalate	Oxalate crystalluria, often alcoholic

### Acid–base balance and regulation of pH box 3

#### The diagnosis

Mrs Loy's electrolyte profile was examined and an anion gap of 12 mmol/L was calculated (see original biochemistry data). There was no history of gastrointestinal disturbance and the urine pH was noted to be inappropriately high at 7. An interim diagnosis of renal tubular acidosis was made.

Further investigation, directed toward defining the immunological activity of her underlying connective tissue disease, revealed that the levels of **antinuclear antibodies** (including antibodies to double-stranded DNA) were elevated, and serum **complement** levels were low, consistent with activated SLE. In addition, the urine contained many red cells and red cell casts (see Chapter 7), and a large amount of protein. Renal biopsy confirmed severe diffuse inflammation affecting the glomeruli as well as the **tubulointerstitium**.

A diagnosis of reactivated SLE was made, with the complications of diffuse lupus nephritis (see Chapter 7) and renal tubular acidosis. The distal tubular dysfunction in this setting reflects a disruptive effect of the interstitial inflammatory changes on the transport properties of the tubules.

- In proximal renal tubular acidosis (RTA), the defect lies in the mechanism normally present within the proximal tubular epithelium for reabsorbing bicarbonate (refer to Fig. 4.2). Thus, either because of a specific defect in one of the components of the cellular acid secretory mechanism in this segment or because of non-specific damage to, or malfunction of, the proximal tubular epithelium as a whole, filtered bicarbonate is incompletely reabsorbed. This results in a large flow of bicarbonate, together with sodium,

**Table 4.3**  
**Some causes of renal tubular acidosis (RTA)**

#### Proximal RTA

Congenital (Fanconi syndrome, cystinosis, Wilson's disease)  
Paraproteinaemia (e.g. myeloma)  
Hyperparathyroidism  
Drugs (carbonic anhydrase inhibitors)

#### Distal RTA ('classic' type)

Congenital  
Hyperglobulinaemia  
Autoimmune connective tissue diseases (e.g. systemic lupus erythematosus)  
Toxins and drugs (toluene, lithium, amphotericin)

#### Hyperkalaemic distal RTA

Hypoaldosteronism  
Obstructive nephropathy  
Renal transplant rejection  
Drugs (amiloride, spironolactone)

through later nephron segments. Plasma bicarbonate falls, blood pH falls, and bicarbonate appears in the urine.

- In distal RTA, the defect is in the late distal tubule and collecting duct segments, where acid secretion is mediated by an  $H^+$ -ATPase. In the classic form of this disorder, the hydrogen pump itself is probably defective. In other forms, such as that induced by amphotericin (an antifungal antibiotic), the impairment of net acid secretion results from back-leak of hydrogen ions across an epithelium which is made abnormally permeable to these ions.

Some causes of proximal and distal RTA are given in Table 4.3. Both proximal and distal RTA may be inherited as a primary defect, but a number of other conditions may produce secondary RTA in either segment. Notably, an alteration in proximal tubular function can be induced by high **paraprotein** levels as in **myeloma**, or by hyperparathyroidism, or by the carbonic anhydrase inhibitor acetazolamide. Distal



RTA, on the other hand, can be caused by conditions associated with polyclonal **hyperglobulinaemia**, including SLE, as in the patient studied in this chapter. Other forms of structural tubulointerstitial disease can produce the same defect, and a number of drugs and toxins are also prone to damage this segment selectively.

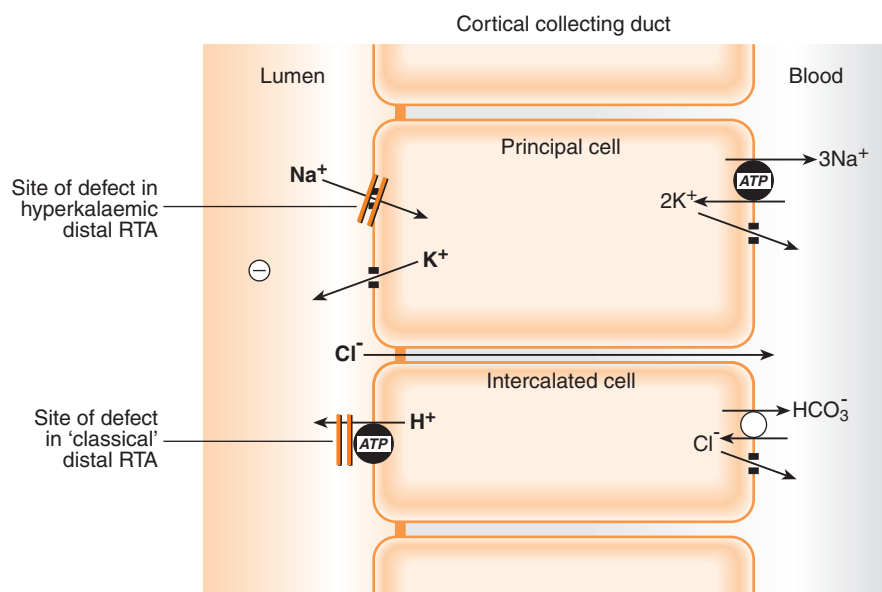
Apart from the differences in clinical setting and aetiology between the proximal and distal types of RTA, a number of physiological differences exist. In the distal form, the impaired operation of the collecting duct  $H^+$  pump means that, no matter how severe the systemic acidosis, the urine pH can never be lowered appropriately, and generally remains above 5.5. Bicarbonate loss is not prominent since proximal reabsorption is generally intact. However, in early or mild forms of proximal RTA there is considerable leak of bicarbonate into the urine, which again has an inappropriately high pH since the distal segments are unable to acidify the urine as long as large amounts of bicarbonate are flooding through the lumen from the proximal segments. However, when acidosis is more severe in proximal RTA, the plasma bicarbonate falls because of buffering of the accumulated acid. As a result, a point may be reached where the reduced filtered amount of bicarbonate can be largely reabsorbed by the defective proximal tubular reabsorptive mechanism. The intact distal segments can then reabsorb a small distal leak of bicarbonate, as normally occurs. In this situation the distal tubular secretory pump can operate normally and generate a transtubular  $H^+$  concentration gradient, resulting in a lowering of the final urine pH. When this occurs, bicarbonate loss ceases and ammonium excretion rises so that a new steady state arises in which acid

retention stabilizes, albeit at a reduced plasma bicarbonate concentration.

There are also differences in some of the associated features of proximal *versus* distal RTA. The proximal type may be associated with loss of other molecules normally reabsorbed in the proximal tubule, giving rise to amino aciduria, glycosuria and phosphaturia. A different problem occurs in distal RTA as a result of progressive accumulation of acid over many years. As a consequence of buffering of  $H^+$  in bone, calcium is released from the skeleton and may be deposited in the tissues, including the kidney (nephrocalcinosis). Furthermore, the high urinary excretion of calcium may result in stone formation (see Chapter 10), often associated with urinary tract infection. Impairment of skeletal growth can occur in this condition, and also in proximal RTA when the disorder is congenital or starts in early childhood.

Much of the symptomatology of both kinds of RTA relates to electrolyte depletion. Urinary losses of sodium are abnormally high in both forms, resulting in a degree of hypovolaemia. Both forms are typically also associated with hypokalaemia because of stimulated potassium secretion in the late distal and cortical collecting ducts. This is caused by a high luminal flow of sodium and bicarbonate in proximal RTA, and by electrically-driven potassium secretion to replace faulty  $H^+$  secretion in distal RTA.

An important variant of distal RTA is hyperkalaemic distal RTA (sometimes called type 4 RTA). In this case the normal anion gap metabolic acidosis is associated with hyperkalaemia, which points to a different site of defect in the acid-secreting segment of the nephron. As shown in Fig. 4.7, if a disruption occurs in the normal



**Fig. 4.7**  
Site of defect in two variants of distal renal tubular acidosis (RTA).

operation of the principal cell type in this tubular segment, sodium reabsorption will be impaired, resulting in a loss of the normal lumen negativity (see Chapter 2). This electrical change impairs the rate of secretion of both potassium and hydrogen ions into the lumen, resulting in systemic acidosis with hyperkalaemia. This lesion has been described in a variety of conditions causing distal tubulointerstitial damage (such as urinary tract obstruction with infection), and also during treatment with drugs interfering with principal cell sodium transport (such as amiloride). A similar defect results from deficiencies in aldosterone secretion or action, including diseases of the adrenal cortex and of the renin secretory mechanism in the kidney.

The management of all forms of RTA is directed in the first instance toward reversing the underlying condition affecting tubular function, if possible. The next principle is that sufficient bicarbonate buffer must be provided to replace that consumed by the acid being accumulated. Provision of some of this bicarbonate as potassium salt will help replete potassium lost in classic forms of the disorder, while in the hyperkalaemic variant of distal RTA, measures to assist in the excretion of potassium (e.g. loop or thiazide diuretics, or corticosteroids, as appropriate) may be necessary. Treatment may also be required for specific complications in the various forms of the condition, such as removal of stones and treatment of infections which sometimes complicate classic distal RTA.

#### Acid-base balance and regulation of pH box 4

##### Treatment and outcome

Mrs Loy's treatment focused on the control of her underlying connective tissue disease. Immunosuppression using prednisone and cyclophosphamide was initiated with a view to reducing the activity of her SLE. The metabolic acidosis and hypokalaemia were corrected initially with infusions, and later with oral supplements, of alkaline salts of sodium and potassium.

Over the ensuing weeks her condition improved dramatically, with the fevers and rash subsiding, urinary protein and red cell excretion reduced, and plasma electrolyte profile reverted towards normal. Within several weeks it was possible to discontinue her electrolyte and buffer therapy, and ongoing management was directed towards long-term stabilization of the connective tissue disease.

#### Disturbances of acid-base balance: alkalosis

To complete our survey of acid-base disturbances, we can consider the two primary perturbations which might result in alkalosis.

##### Respiratory alkalosis

Any form of sustained hyperventilation will produce a reduction in the blood  $p\text{CO}_2$  with a resulting increase in plasma pH. The respiratory stimulus most commonly arises from anxiety states, but it may also be due to drugs stimulating the respiratory centre, other brain disorders and chronic liver disease.

The homeostatic response to respiratory alkalosis involves an initial phase of physicochemical buffering by intracellular proteins, which give up  $\text{H}^+$ , resulting in a small decrease in the plasma bicarbonate. More sustained compensation occurs over the ensuing days, during which renal tubular  $\text{H}^+$  secretion is inhibited by the high extracellular pH and the reduced  $p\text{CO}_2$ . Bicarbonate reabsorption is inhibited, as is ammonium excretion, and the result is a reduction in net acid excretion and a fall in the plasma bicarbonate. In many cases the respiratory disturbance is not unduly prolonged, and the renal compensation subsides as ventilation is normalized.

##### Metabolic alkalosis

In this disorder there is a primary increase in the plasma bicarbonate concentration and the plasma pH. The causes fall into two groups according to whether there is associated contraction of the ECF volume or not.

*Hypovolaemic metabolic alkalosis* is the commonest pattern, and includes disorders such as vomiting and gastric suction, in which acid-rich gastric juices are lost from the body. Metabolic alkalosis associated with volume contraction also occurs during treatment with most diuretics (other than carbonic anhydrase inhibitors and potassium-sparing drugs). Here there is increased acid loss into the urine related to the diuretic action on the tubules. The alkalosis associated with volume contraction is perpetuated by secondary renal responses, described in more detail below.

*Normovolaemic (or hypervolaemic) metabolic alkalosis* occurs when the primary disturbance provokes both bicarbonate retention and a degree of volume expansion. This most commonly occurs in corticosteroid



excess states such as primary hyperaldosteronism (Conn's syndrome), Cushing's syndrome and related disorders. Occasionally, overuse of antacid salts can produce a similar pattern.

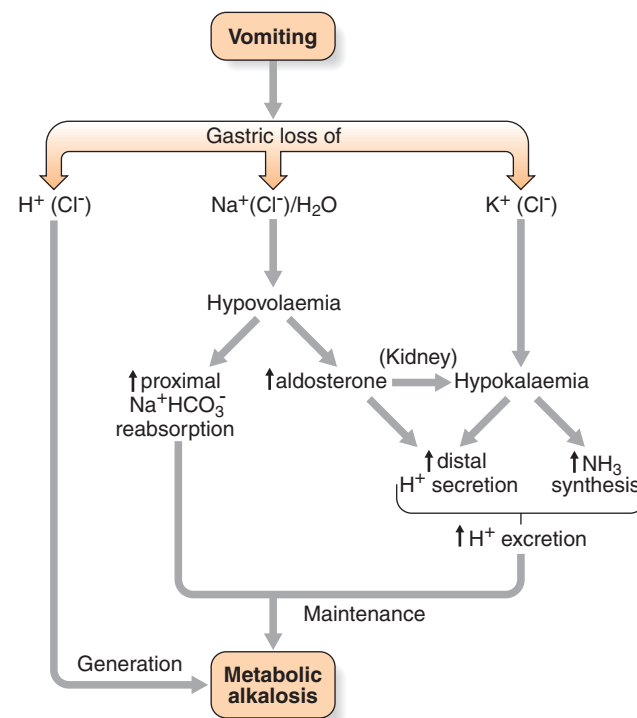
The homeostatic response to metabolic alkalosis involves initial buffering of the rise in plasma bicarbonate by titration of extracellular and intracellular buffers, including plasma proteins. Soon afterwards, the increased pH acts to inhibit ventilation through the medullary chemoreceptors, such that the  $p\text{CO}_2$  starts to rise. Since, however, this is ultimately associated with an unacceptable degree of hypoxia, the extent to which this form of compensation occurs is limited, such that the maximum  $p\text{CO}_2$  attained is rarely more than 55 mmHg.

In the absence of counterbalancing stimuli, the expected renal response to sustained metabolic alkalosis would be to decrease tubular acid secretion, inhibit bicarbonate reabsorption and excrete the excess bicarbonate into the urine. However, in the commonest form of metabolic alkalosis, that caused by sustained vomiting, this response is distorted by other changes associated with the loss of gastric fluid. As shown in Fig. 4.8, the loss of  $\text{H}^+$  initiates the alkalosis ('generation' phase), which is actually worsened by the losses of sodium, water and potassium ('maintenance' phase). The sodium losses are associated with hypovolaemia, which triggers both proximal bicarbonate reabsorption and aldosterone release, which stimulates distal acid secretion, thereby aggravating the systemic alkalosis. Furthermore, the hypokalaemia resulting from potassium loss (more through the kidney than from gastric fluid) also stimulates distal acid secretion and tubular ammonia synthesis (see earlier), both of which enhance acid excretion and maintain the alkalosis. The net result is an inappropriately acid urine and a failure of the kidney to effect long-term correction of the systemic pH disturbance.

The cornerstone of management in hypovolaemic metabolic alkalosis states, exemplified by vomiting, is to provide adequate volume replacement as sodium chloride (isotonic saline infusions), which switches off the volume-conserving mechanisms mentioned above and allows the kidney to excrete the excess

alkali in the urine. Replacement of potassium helps correct the hypokalaemia and its consequences in the kidney.

The non-hypovolaemic forms of metabolic alkalosis, by way of contrast, are resistant to treatment with sodium chloride, but can usually be managed by cessation of alkali therapy or correction of mineralocorticoid excess. The latter may involve either adrenal gland surgery or blockade of mineralocorticoid effect in the kidney by treatment with spironolactone.



**Fig. 4.8** Vomiting: generation and maintenance of metabolic alkalosis. Note that the gastric loss of  $\text{H}^+$  is primarily responsible for generating the systemic alkalosis, while the other mechanisms shown act through the kidney to maintain the alkalosis as long as sodium and potassium losses are uncorrected. Chloride is the deficient anion accompanying all cations shown.

**Table 4.4**  
Summary of 'simple' acid-base disturbances

Disorder	pH	Primary change	Compensatory response
Metabolic acidosis	Decreased	Decreased $\text{HCO}_3^-$	Decreased $p\text{CO}_2$
Metabolic alkalosis	Increased	Increased $\text{HCO}_3^-$	Increased $p\text{CO}_2$
Respiratory acidosis	Decreased	Increased $p\text{CO}_2$	Increased $\text{HCO}_3^-$
Respiratory alkalosis	Increased	Decreased $p\text{CO}_2$	Decreased $\text{HCO}_3^-$

### Summary of findings in principal acid-base disturbances

Table 4.4 provides an overview of the changes in pH, bicarbonate concentration and  $p\text{CO}_2$  in the four major simple acid-base disorders. Taken in conjunction with clinical information, the results of these analyses are usually sufficient to enable a diagnosis to be made of the nature and cause of the disturbance. Rules of

thumb are available to indicate the predicted compensatory change in  $p\text{CO}_2$  or bicarbonate levels expected in each of the simple (uncomplicated) acid-base disorders. When the available data for a given patient are not consistent with these changes, a complex or 'mixed' acid-base disorder can be inferred, and the elements of the disturbance usually deduced in conjunction with a thorough clinical evaluation.

### Self-assessment case study

A consultation is requested on an 81-year-old man who has been admitted to the hospital with an acute myocardial infarction (heart attack). There has been significant damage to the left ventricle such that cardiac output is markedly reduced. Furthermore, on day 5 after admission his course is complicated by the development of acute ischaemia in the left leg, attributed to occlusion of a major leg artery following embolization of a thrombus from the left ventricular cavity.

The patient's plasma electrolyte results are as follows:

Sodium 135 mmol/L

\*Potassium 5.2 mmol/L

Chloride 97 mmol/L

\*Bicarbonate 14 mmol/L

\*Urea 14.0 mmol/L

\*Creatinine 0.14 mmol/L.

(\*Values outside normal range; see Appendix.)

Arterial blood gas analysis reveal the following: pH 7.33,  $p\text{CO}_2$  29 mmHg,  $p\text{O}_2$  (breathing room air) 58 mmHg.

After studying this chapter you should be able to answer the following questions:

- ① What is the overall pattern of acid-base disturbance in this patient?
- ② What is the anion gap in this patient?

- ③ What is the likely cause of the disturbance in this case?
- ④ What would you expect the urine pH to be?
- ⑤ What are the principles of treatment?
- ⑥ What would the effect of a bicarbonate infusion be on his plasma potassium concentration?

Answers see page 146

### Self-assessment questions

- ① What would the effect on systemic acid-base balance be if a patient were given long-term treatment with a carbonic anhydrase inhibitor such as acetazolamide?
- ② Where in the nephron is the steepest gradient of pH between the plasma and the luminal fluid?
- ③ Name three changes in the plasma which stimulate an increase in hydrogen ion secretion by the nephron.
- ④ Give three causes of a metabolic acidosis with a normal anion gap.
- ⑤ Name three factors which perpetuate the systemic alkalosis which follows prolonged vomiting.

Answers see page 146



