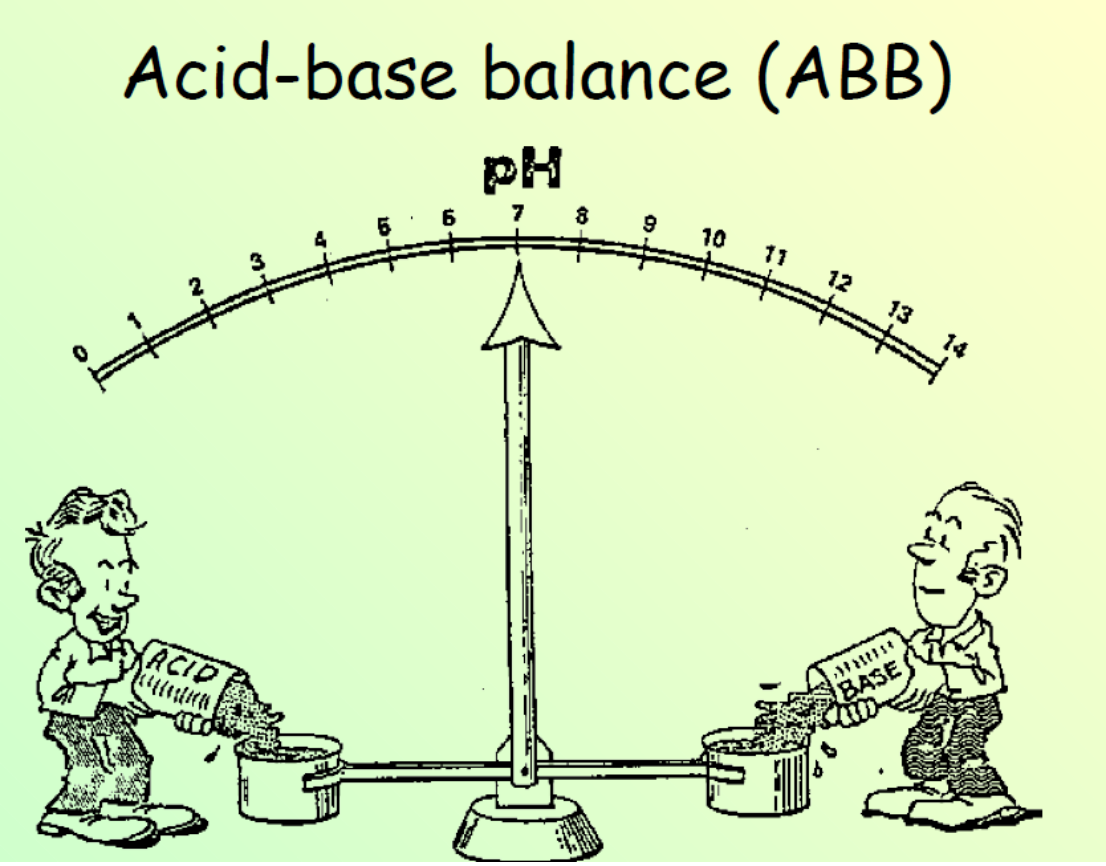

After studying this lecture you should confidently be able to :

Describe the mechanisms that control the blood pH.

Explain how changes in blood levels of carbon dioxide and bicarbonate affect blood pH.

Classify the acid-base disorders and describe how compensatory mechanisms restore the pH towards normal.

Relate blood pH to p CO_2 and blood bicarbonate concentration.

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Every day living involves burning fuel to supply energy and removing the waste products that can be toxic if left to accumulate. Normal metabolic turnover by the cells will produce an excess of acid which is in fact hydrogen ions produced in the cells. If the hydrogen ions are not removed their accumulation and therefore the rise in acidity within the cell will eventually lead to cell death. We shall see how acid is formed and transported in the blood to sites of excretion.

The acidity of fluids is measured by pH, which is inversely related to the log of the hydrogen ion concentration. Low pH (high hydrogen ion concentration) values are given by acidic solution, whereas alkaline solutions have a high pH values (low hydrogen ion concentration). In health the pH of the body is very tightly regulated and enzymes work at optimum pH values. If the pH of the cell, or of the body, changes significantly an acid-base disturbance occurs, leading to pathological symptoms and, if left untreated can lead to death.

A number of metabolic pathways contribute to the production of hydrogen ions within the cells. The most important are:

- Oxidation of sulphur containing amino acids giving sulphuric acid. H_2SO_4
- The hydrolysis of phosphorus containing proteins and lipids giving phosphoric acid. H_3PO_4
- The production of ketoacids and lactic acids from triglycerides and carbohydrates metabolism.

Approximately 40-80mmol of the above acids is produced every day, mainly from the breakdown of dietary protein.

To maintain carful control of the pH the body has sophisticated buffering mechanism. The three most important buffer systems are:

- The bicarbonate system.
- Proteins, mainly haemoglobin.
- The phosphate system.

These buffer systems are important because they mop up excess hydrogen ions produced by the cell. The bicarbonate buffering system is the most important, making up approximately three quarters of the body's buffering capacity. Hydrogen ions combine with bicarbonate ions to form carbonic acid which itself dissociates to water and carbon dioxide. Some cells contain an enzyme, carbon anhydrase, which catalyzes this reaction. These reactions are shown below:

$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$

The reaction is driven to the right, which means that hydrogen ions, produced in cells and buffered by the bicarbonate system, generate carbon dioxide and reduce available bicarbonate. Uncontrolled generation of hydrogen ions would lead to high blood levels of dissolved carbon dioxide and low levels of bicarbonate ions. Fortunately there are mechanisms which remove hydrogen ion and maintain blood pH within very tight limits.

Control of pH

Two organs control the pH of the body: the lungs and the kidneys. In health the hydrogen ions from non-volatile and organic acids are removed by the kidneys into the urine, and carbon dioxide from the breakdown of carbonic acid is excreted by the lungs. The blood transports acidic waste products from the site of production in the tissues to the site of excretion, namely the kidneys and lungs. These two excretory pathways form two components of acid-base metabolism. The lungs represent and control the **respiratory component** of acid –base

balance and the kidneys represent and control the **metabolic component**. It is the interaction and balance of these two systems which controls the pH of the body, and diseases affecting either of these two organs can affect the acid-base balance, giving rise to an abnormal pH.

Respiratory component

The lungs are responsible for gas exchange, giving oxygen to the red blood cells and removing carbon dioxide. In the tissues carbon dioxide is produced and diffuses in to erythrocytes where it combines with water to form bicarbonate ions and hydrogen ions. This process is under the influence of carbonic anhydrase. Deoxygenated haemoglobin is reduced by hydrogen ion, acting as a buffer. As bicarbonate diffuse out of the cell, chloride ions diffuse in to restore electrical neutrality; this is known as the **chloride shift.** In the lungs the reverse reaction occurs and reduced haemoglobin absorbs fresh oxygen, releasing hydrogen ions which combine with bicarbonate under the influence of carbonic anhydrase to produce water and carbon dioxide. Carbon dioxide diffuses rapidly into the alveolus and is exhaled.

The erythrocytes return to the tissues in the arterial blood which is oxygenated.

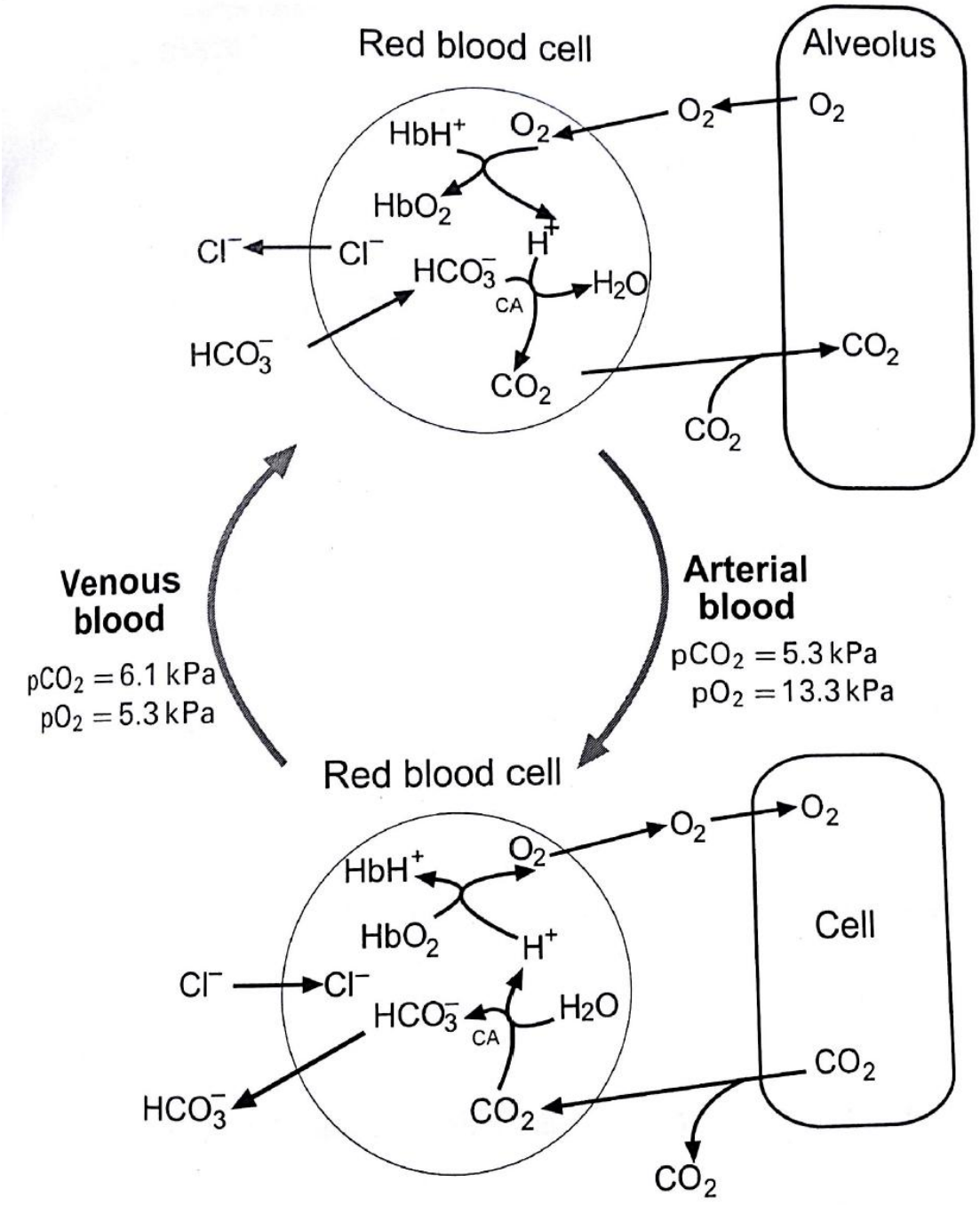

Diagram showing the excretion of carbon dioxide generated within respiring cells and transported in the blood to be lost through the lungs. CA= carbonic anhydrase.

Metabolic component

The kidneys are the site where the hydrogen ions are excreted and also where the bicarbonate is generated. Blood is filtered in the glomerulus to produce the glomerulur filtrate which contains small proteins and dissolved cations and anions, including acid anions such as sulphate and phosphate. In the kidney tubular cells the enzyme carbonic anhydrase catalyses the reaction between carbon and water to form bicarbonate and hydrogen ions. Bicarbonate ions diffuse from the cell into the blood and hydrogen ions are transported into the kidney tubule, this process has the effect of generation of bicarbonate ions. In the kidney tubule there are two main buffer systems which remove the excreted hydrogen ions. Pathway A leads to the generation of ammonium ions from ammonia, mainly derived from glutamine. Pathway B shows the buffering capacity of phosphate via the generation of sodium dihydrogen phosphate. These two pathways occur in the distal tubular cells and the buffering capacity depends somewhat on the amount of phosphate and ammonia excreted. Pathway C involves the reabsorption of bicarbonate ions filtered from the blood. In this case hydrogen ions are exchanged for sodium ions in the glomerular filtrate, a process achieved by sodium pump.

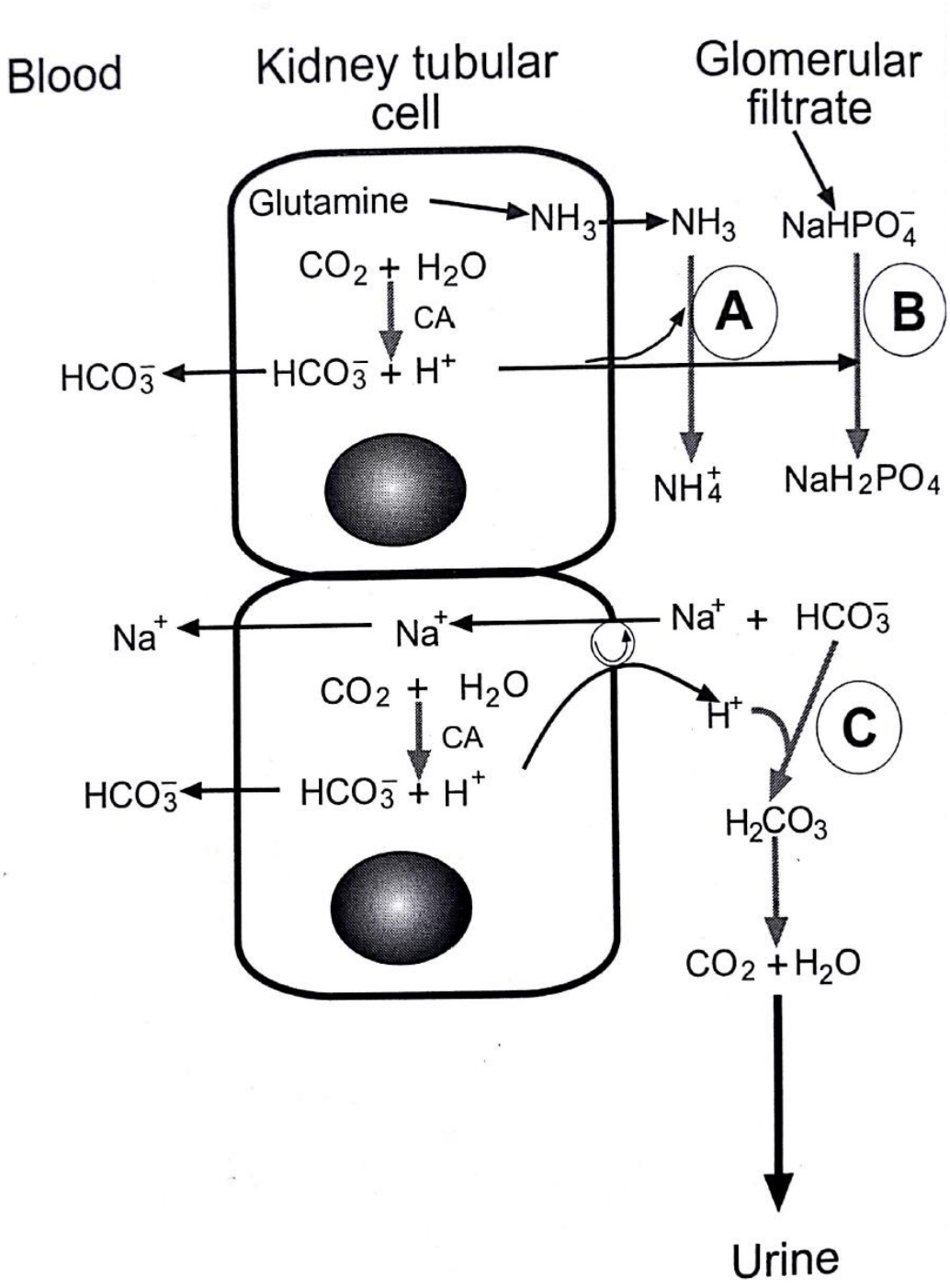

Diagram showing the excretion of hydrogen ions by the kidney.

Normal pH

The normal pH of the body is 7.4. This can be calculated from the Henderso-Hasselbach equation using constants for bicarbonate buffer:

$pH = 6.1 + \log [HCO_3] / [H_2CO_3]$

Where 6.1is the Pk_a of the bicarbonate buffer system, from this equation we can see that:

$pH \alpha [HCO_3] / [H_2CO_3]$ -------- (1)

We have seen that bicarbonate forms carbon dioxide which dissolved in the body's water.

$[H_2CO_3] = pCO_2 \times H_2O$ --------- (2)

Combining (1) and (2) we obtain:

$pH \alpha [HCO_3] / pCO_2$

This shows that the pH is related to the bicarbonate concentration and pCO_2. pH is inversely related to the hydrogen ion concentration and so the above relationship could be written as:

$[H^+] \alpha pCO_2 / [HCO_3]$ ------(3)

In health pH of the blood is 7.4 which is equivalent to a hydrogen ion concentration of 40 nmol l^{-1}. To maintain this value the ratio $[HCO_3] / pCO_2$ is kept constant. This means that in order to restore a low pH (high H^+) either the pCO_2 will need to be increased or $[HCO_3]$ needs to be decreased. Conversely, when pH is high (low H^+) the pCO_2 has to be lowered or $[HCO_3]$ increased to restore normal pH. Referring to equation (3) we can say that: **pCO_2 is the respiratory component and [**

HCO_3] is the metabolic component. The reference range of pCO_2 is 4.5 – 6 kPa, while for [HCO_3] is 20 – 30 mmol/l.

The hydrogen ion concentration of a fluid of pH 7.4 is:

$$7.4 = \log_{10} 1/[H^+] = -\log_{10}[H^+]$$

$$[H^+] = 10^{-7.4} = 3.98 \times 10^{-8} \text{ moles}$$

$$= 40 \text{ nM } (40 \text{ nmol } l^{-1})$$

Disorders of acid base balance

In health the pH is 7.4, if the pH should change due to normal physiological activity such as strenuous exercise, it is rapidly restored to normal. Problems arise when the normal mechanisms are unable to restore the pH. There are two primary causes of this:

- A prolonged production of hydrogen ions or prolonged loss of hydrogen ions too.
- Diseases of the lungs or kidneys which prevents the normal compensation mechanisms.

Disorders of acid base balance are broadly grouped as an acidosis or an alkalosis depending on whether there is a general accumulation of hydrogen ions, an acidosis (low pH), or if there is loss of hydrogen ion, an alkalosis (high pH), these are both further subdivided into two more groups depending on the cause of the disorder. If the pH imbalance is due to metabolic or renal disease it is classified as a metabolic and where the problem is due to lung function it is classified as respiratory.

Knowing the [HCO_3] and pCO_2 enables classification of acid-base disorder. Remember :

$[H^+] \ \alpha \ pCO_2 / [HCO_3]$

pCO_2 reflects respiratory activity and [HCO_3] reflects metabolic activity.

The four main acid-base disorders are as follow:

1- Metabolic acidosis, an accumulation of hydrogen ions resulting in a decreased bicarbonate concentration.

$$[H^+] \ \alpha \ pCO_2 / [HCO_3]$$

$$\uparrow \qquad \downarrow$$

2- Respiratory acidosis, an excess of hydrogen ions due to insufficient gas exchange resulting in increased pCO_2.

$$[H^+] \ \alpha \ pCO_2 / [HCO_3]$$

$$\uparrow \qquad \uparrow$$

3- Metabolic alkalosis, a decrease in hydrogen ion concentration resulting in an elevated bicarbonate concentration.

$$[H^+] \ \alpha \ pCO_2 / [HCO_3]$$

$$\downarrow \qquad \uparrow$$

4- respiratory alkalosis, a decrease in hydrogen ion concentration due to excessive gas exchange resulting in lowered pCO_2.

$$[H^+] \ \alpha \ pCO_2 / [HCO_3]$$

$$\downarrow \qquad \downarrow$$

Compensation

Where the lung function is causing the acid-base disturbance the kidney increases its excretion of hydrogen ions in an attempt to restore blood pH. This is **renal compensation**. Where the acid base disorder is due to metabolic problem or renal insufficiency the lung can offer some compensation by changing the rate of gas exchange. This is **respiratory compensation**. If the compensation mechanism restore the pH within the reference range this is the **fully compensated** disorder. In this case the pH is normal but pCO_2 and HCO_3 are grossly abnormal. **Partial compensation** is when the pH has not been fully restored to normal.

Pathophysiology

Disorders of acid-base balance can be divided into acidosis and alkalosis, each having a metabolic and respiratory origin

Metabolic acidosis – low [HCO_3]

This is due to:

- Increased production of acid
- Decreased excretion of acid
- Excessive loss of bicarbonate ions

Increased acid production is seen in metabolic disease where there is an excess production of organic acids, for example ketoacids seen in diabetes mellitus, or lactic acid seen in cases of lactic acidosis.

Kidney diseases and cases of mineralcorticoid deficiency results in a reduction in excretion of acid from the kidney and accumulation of acid in the blood.

Excess acids are buffered by bicarbonate resulting in reduced bicarbonate concentration and lower pH.

In cases of acute diarrhea there is a loss in bicarbonate resulting in an altered ratio with pCO_2 and a lowered pH.

The high levels of hydrogen ions (low pH):

- Impair cardiac muscles contraction with the possibility of cardiac failure.
- Exchange with potassium in cells leading to hyperkalaemia.
- Enhance mobilization of calcium from bones, thereby decreasing binding of calcium to proteins and calcium reabsorption by the kidney. In prolonged acidosis there can be a generalized loss of calcium from the body and there may be formation of kidney stones.

Compensation of metabolic acidosis is achieved through the respiratory pathway. Respiratory compensation removes more carbon dioxide through the lungs, achieved by hyperventilation. This lowers the pCO_2 and restores the pCO_2 : $[HCO_3]$ ratio and hence the pH. Respiratory compensation rarely returns pH to normal.

Respiratory acidosis – high pCO_2

This is due to:

- Decreased respiration rate.
- Decreased gas exchange due to lung disease.

Decreased respiration rate can result from depression of the central nervous system following infection, tumors, or drug overdose. Injury to the chest can also affect respiratory efficiency.

High levels of carbon dioxide in the blood (hypercapnia) stimulate CNS to induce hyperventilation to lower the pCO_2. When this cannot occur, the high pCO_2 causes cerebral vasodilation leading to headache, drowsiness, and coma.

Compensation of respiratory acidosis occurs by the kidney excreting more acid and generating more bicarbonate, thereby more restoring the pCO_2 : $[HCO_3]$ ratio.

Metabolic (non-respiratory) alkalosis – high $[HCO_3]$

This is due to:

- Loss of hydrogen ions.
- Alkalotic agents: (administrated in cases of peptic ulcer or hyperacidity) or antacids, administered in excess can lead to an alkalosis.

Metabolic alkalosis is a metabolic condition in which the pH of tissue is elevated beyond the normal range (7.35–7.45). This is the result of decreased hydrogen ion concentration, leading to increased bicarbonate, or alternatively a direct result of increased bicarbonate concentrations. The condition typically cannot last long if the kidneys are functioning properly.

Mild cases of metabolic alkalosis often cause no symptoms. Typical manifestations of moderate to severe metabolic alkalosis include abnormal sensations, neuromuscular irritability, tetany, abnormal heart rhythms (usually due to accompanying electrolyte abnormalities such as low levels of potassium in the blood), coma and seizures.

Compensation for metabolic alkalosis occurs mainly in the lungs, which retain carbon dioxide (CO_2) through slower

breathing, or hypoventilation (respiratory compensation) to restore the pCO_2 : $[HCO_3]$ ratio.

Respiratory alkalosis – low pCO_2

This is due to:

- Stress
- Pulmonary disorder
- Salicylate poisoning (aspirin overdose)

The mechanism of respiratory alkalosis generally occurs when some stimulus makes a person hyperventilate. The increased breathing produces increased alveolar respiration, expelling CO_2 from the circulation. This alters the dynamic chemical equilibrium of carbon dioxide in the circulatory system. Circulating hydrogen ions and bicarbonate are shifted through the carbonic acid (H_2CO_3) intermediate to make more CO_2 via the enzyme carbonic anhydrase.

The diagnosis of respiratory alkalosis is done via test that measure the oxygen and carbon dioxide levels (in the blood), chest x-ray and a pulmonary function test of the individual.

Lactic acidosis

Most cells in the body normally metabolize glucose to form water and carbon dioxide in a two-step process: First, glucose is broken down to pyruvate through glycolysis and pyruvate is converted to lactate: glucose $\rightarrow$ 2 lactate + $2H^+$. .
Then, mitochondria oxidize the pyruvate into water and carbon dioxide by means of the Krebs cycle and oxidative phosphorylation. This second step requires oxygen. The net

result is ATP, the energy carrier used by the cell for metabolic activities and to perform work, such as muscle contraction. When the energy in ATP is used during cell work via ATP hydrolysis, hydrogen ions, (positively charged protons) are released. The mitochondria normally incorporate these free hydrogen nuclei back into ATP, thus preventing buildup of unbound hydrogen cations, and maintaining neutral pH.

If oxygen supply is inadequate (hypoxia), the mitochondria are unable to continue creating ATP at a rate sufficient to meet the cell's energy needs. In this situation, glycolysis is increased to provide additional ATP, and the excess pyruvate produced is converted into lactate and released from the cell into the bloodstream, where it accumulates over time. While increased glycolysis helps compensate for less ATP from oxidative phosphorylation, it cannot bind the hydrogen cations that result from ATP hydrolysis. Therefore, hydrogen cation concentration rises and causes acidosis.

Diabetic ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is a potentially life-threatening complication of diabetes mellitus. Diabetic ketoacidosis arises because of a lack of insulin in the body. The lack of insulin and corresponding elevation of glucagon leads to increased release of glucose by the liver (a process that is normally suppressed by insulin) from glycogen via glycogenolysis and also through gluconeogenesis. High glucose levels spill over into the urine, taking water and solutes (such as sodium and potassium) along with it in a process known as osmotic diuresis. This leads to polyuria, dehydration, and polydipsia. The absence of insulin also leads to the release of free fatty acids from adipose tissue (lipolysis), which are converted through a process

called beta oxidation, again in the liver, into ketone bodies (acetoacetate and β-hydroxybutyrate). β-Hydroxybutyrate can serve as an energy source in the absence of insulin-mediated glucose delivery, and is a protective mechanism in case of starvation. The ketone bodies, however, have a low pKa and therefore turn the blood acidic (metabolic acidosis). The body initially buffers the change with the bicarbonate buffering system, but this system is quickly overwhelmed and other mechanisms must work to compensate for the acidosis. One such mechanism is hyperventilation to lower the blood carbon dioxide levels.