Acid –Base Balance

Outlines

- Production of H^+ ions
- Mechanism for H^+ removal:
  1. Buffer systems
  2. Exhalation of CO_2
  3. Real secretion

- Disorders of hydrogen ion homeostasis:
  1. Metabolic acidosis
  2. Metabolic alkalosis
  3. Respiratory acidosis
  4. Respiratory alkalosis
  - Laboratory assessment of hydrogen status
  - Clinical cases

Production of Hydrogen Ions

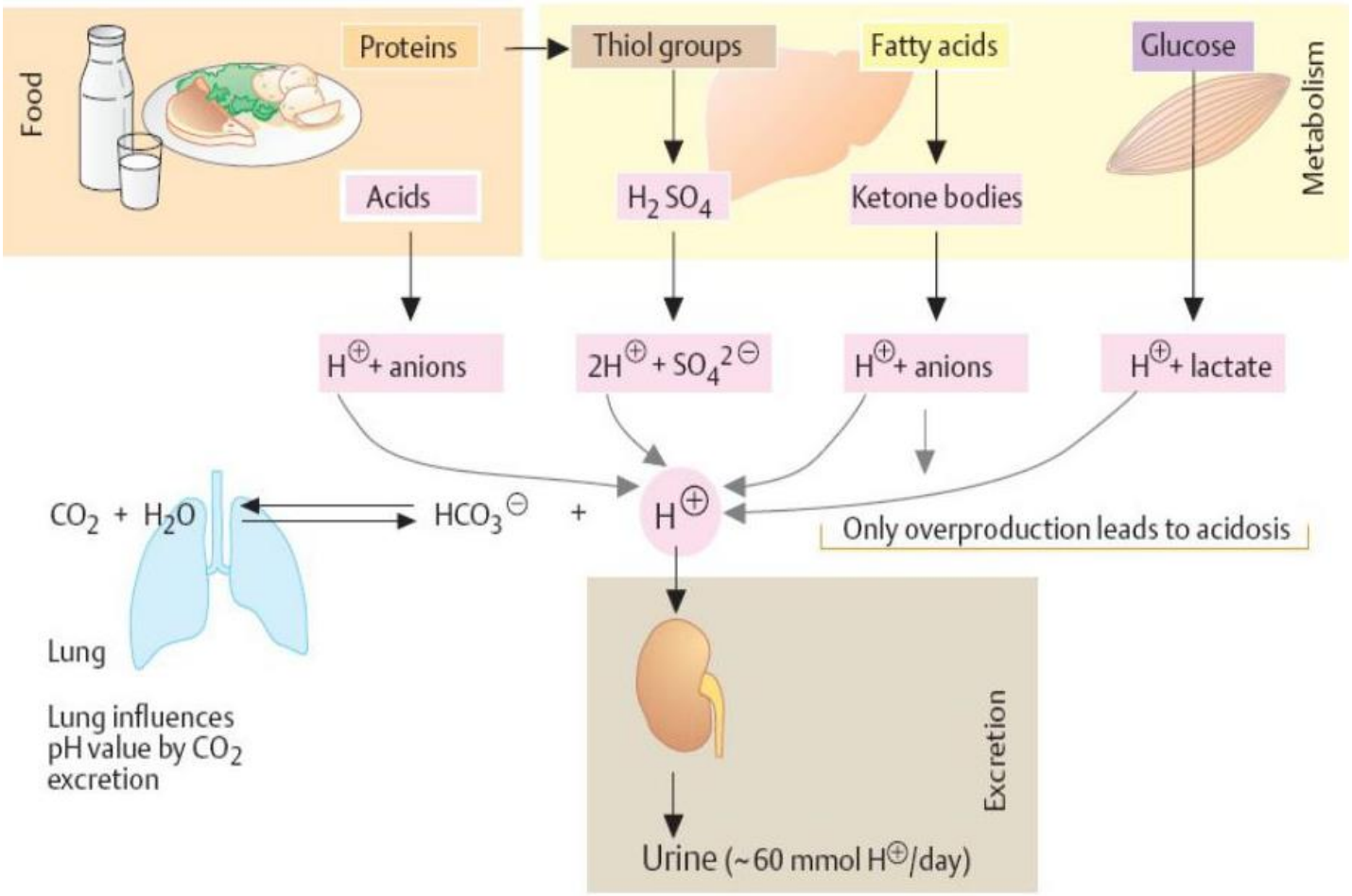
- The processes of metabolism generate hydrogen ions

1. Oxidation amino acids (particularly S-containing a.a.), glucose, and fatty acids produce small amounts of acids (40-80 mmol/24h)
2. CO_2 that is released from oxidative metabolism of carbohydrates, lipids and proteins produce large amounts of acids (15,000 mmol/24h) Although CO_2 does not contain H+ ions it rapidly reacts with H_2O to form carbonic acid (H_2CO_3), which further dissociates into H and HCO_3^- ions

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

This reaction occurs throughout the body and in certain circumstances is speeded up by the enzyme carbonic anhydrase.

3. Acids or bases that are ingested however it is uncommon for these to make a significant contribution to the body's H+ concentration.



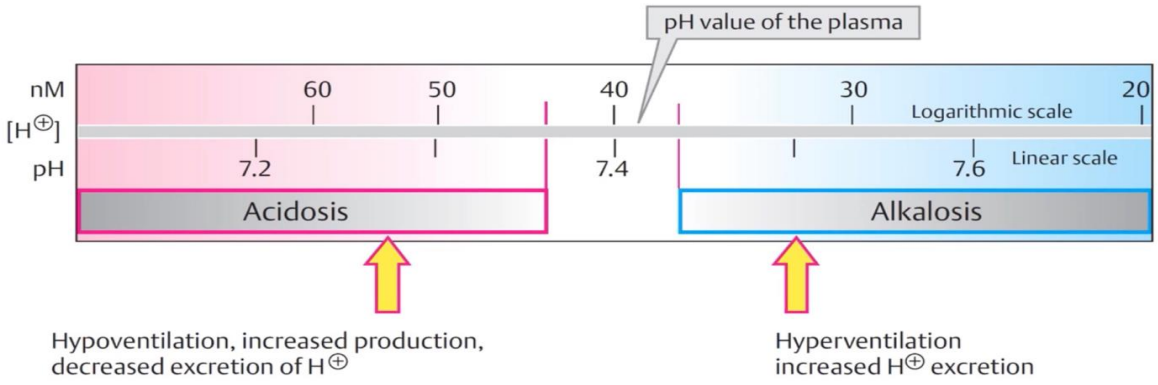
Production of Hydrogen Ions

- **The H^+ ion concentration [H^+] in the blood and ECF (body fluids) is approximately between 35 45 nmol/L (pH 7.35 - 7.45)**
- **The body tries to keep this value constant within tight limits (as large shifts in pH are incompatible with life). A reduction by > 0.03 units is as acidosis, and an increase is alkalosis**
- **There are 3 major mechanisms:**

A. Buffer systems: Buffer systems react quickly to bind H^+ or OH^- ions to prevent drastic changes in the pH

B. Exhalation of CO_2 : Because of the relationship between CO_2 and H^+, alterations in respiratory rate affect changes in pH by changing the CO_2 concentration of the body

C. Kidney secretion of H^+ and regeneration of HCO_3^- : H^+ secretion from distal tubules of the nephrons directly into filtrate acidifies urine and removes the H^+ form the body

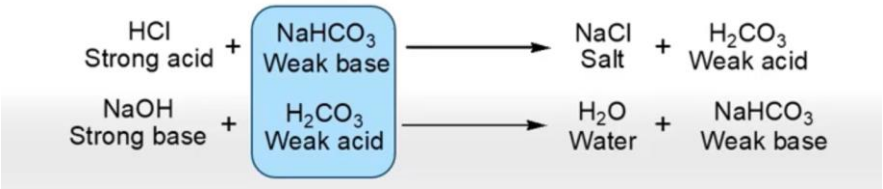


- **Acid base balance or homeostasis: is the equilibrium between the acid production and the rate of its removal.**

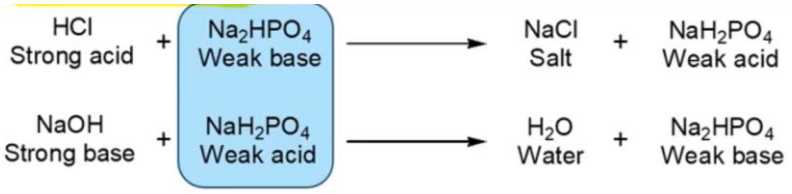
A. Buffer systems

- **Buffers: are solutions which resist the change in pH when an acid or alkali is added to it. They do not remove H^+ from the body, rather they temporarily mop up any excess H+ that are produced.**
- **Buffers are usually a mixture of:**
  - **A weak acid and its salt with a strong base e.g: carbonic acid/sodium bicarbonate mixture (H_2CO_3/$NaHCO_3$)**
  - **A weak base and its salt with a strong acid e.g: ammonium hydroxide/ammonium chloride mixture (NH_4OH/NH_4CI):**

1. **Carbonic acid–bicarbonate buffer system: (ECF only) this buffer remove excess H^+ from the ECF at the expense of bicarbonate**

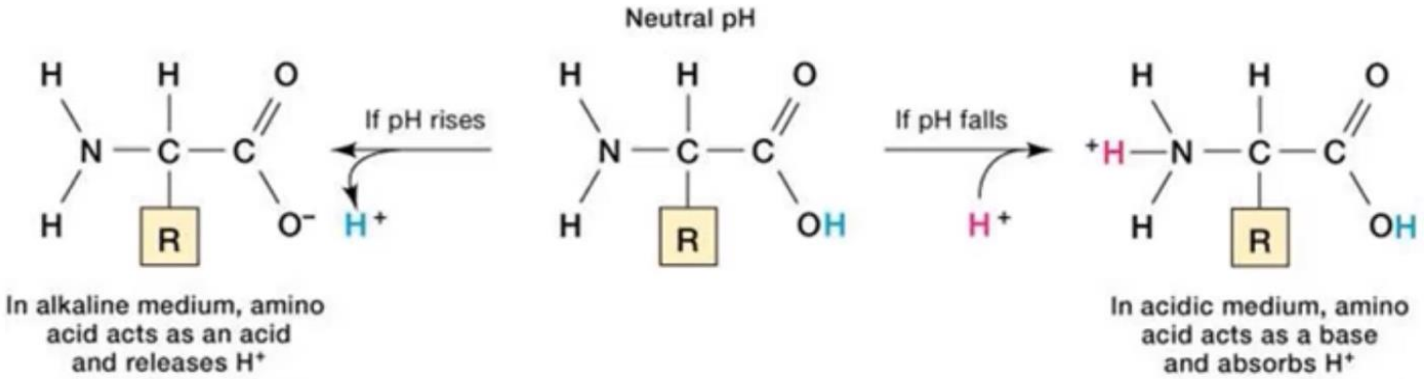


2. **Phosphate Buffer System : ECF, ICF and urine**



3. **Protein Buffer System: ECF and ICF**

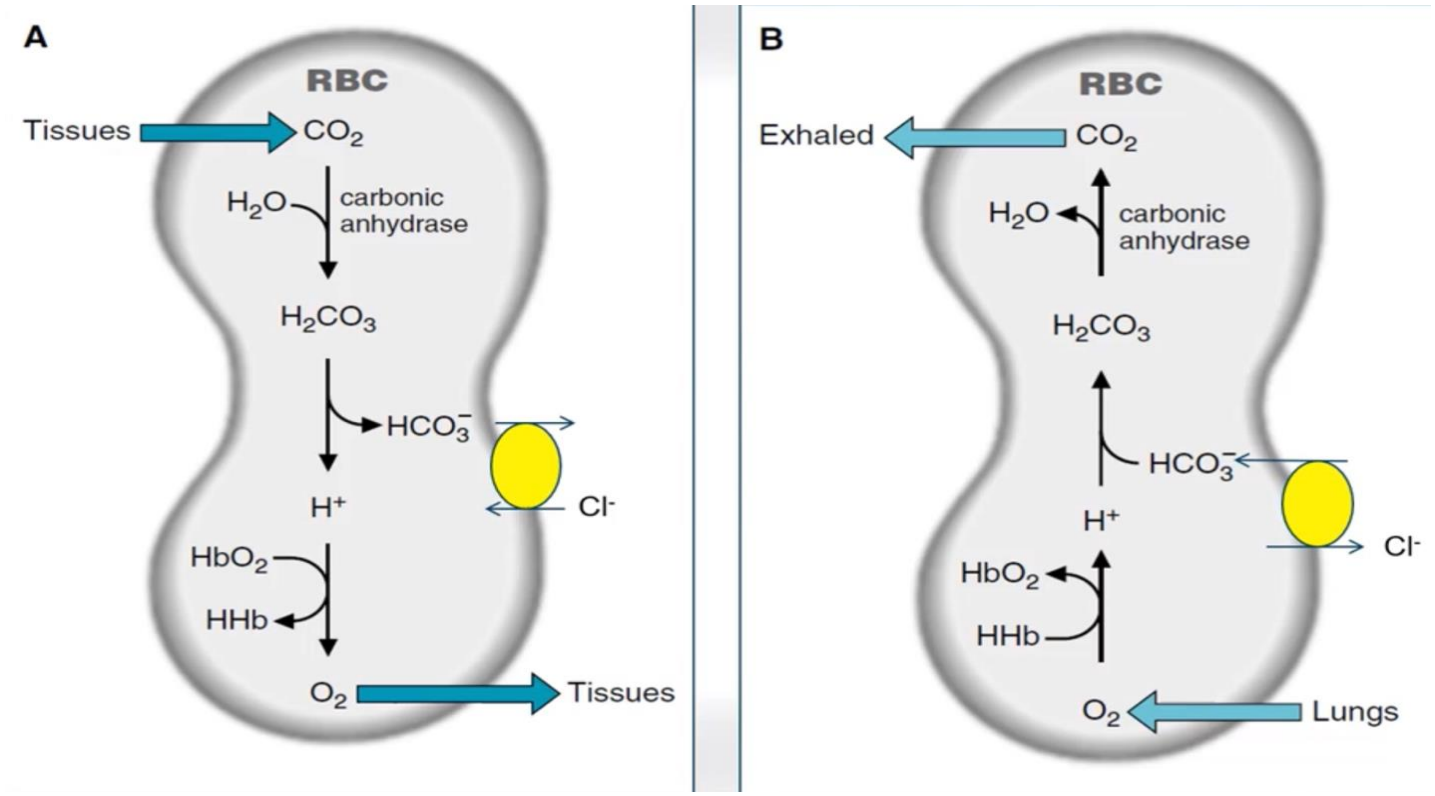
The protein buffer system is the most abundant buffer in cells and plasma Proteins act as both acidic and basic buffer because they have a free carboxyl group and a free amino group



4. Haemoglobin as buffer (Bohr Effect)

- **Haemoglobin is not only important in the carriage of oxygen to the tissues but also in the transport of CO_2 and in buffering H+ ions**
- **Haemoglobin binds both CO_2 and H+ and so is a powerful buffer**

1. **In the tissues dissolved CO_2 passes into the RBC down its concentration gradient where it combines with water to form carbonic acid. This reaction is catalyzed by the enzyme carbonic anhydrase.**
2. **Carbonic acid then dissociates into bicarbonate and hydrogen ions**
3. **The hydrogen ions bind to reduced haemoglobin to form HHb**
4. **HCO_3^- generated by this process pass back into the plasma in exchange for Cl^- . This ensures that there is no change of negative ions by RBC**
5. **In the lungs this process is reversed and H+ bound to haemoglobin recombine with HCO_3^- to form CO_2 which passes into the alveoli.**

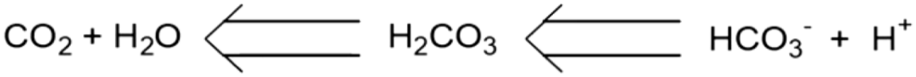


B. Exhalation of CO_2

- ***Breathing plays a most important role in the control of acid-base balance***

- ***In the tissues where CO_2 is abundant, the reaction is shifted to the right***

- ***In the lung where H+ are liberated from Hb, the reaction is shifted to the left***



C. Kidney

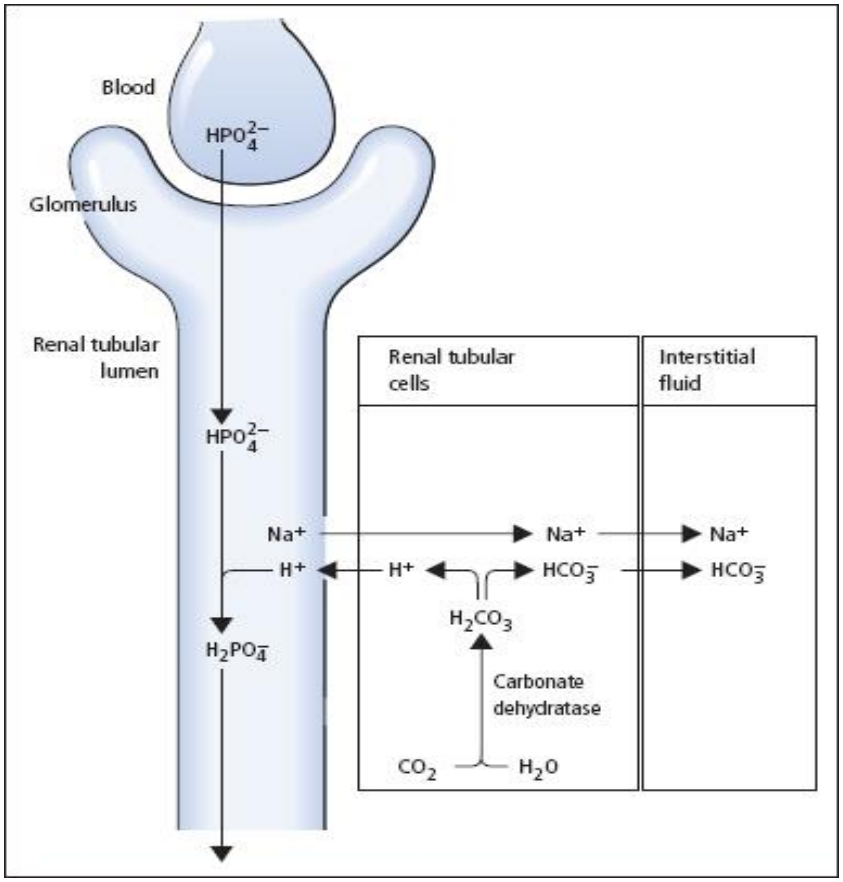
a) Excretion of H+

- **Distal tubules of the kidneys secrete H+ directly into the filtrate so that urine is acidified and the H^+ are lost from the body.**
- **H^+ ions are actively secrete in the proximal and distal tubules, but the maximum urinary [H^+] is around 0.025 mmol/l (pH 4.6). Therefore, in order to excrete the 30-40 mmol of H^+ required per day ,a urine volume of 1200 L would have to be produced**
- **However, buffering of H^+ also occurs in the urine. This allows the excretion of these large quantities of H^+ without requiring such huge urine volumes.**
- **The predominant buffer in the urine are phosphate and ammonia**
- **H^+ ion secretion is an active process and requires energy in the form of ATP.**

- **Phosphate buffering for urine.**

Phosphate is freely filtered by the glomerulus and passes down the tubule where it combines with H^+ to form $H_2PO_4^-$.

Hydrogen ions are secrete in exchange for sodium ions; the energy for this exchange comes from the Na-K-ATPase that maintains the concentration gradient for sodium

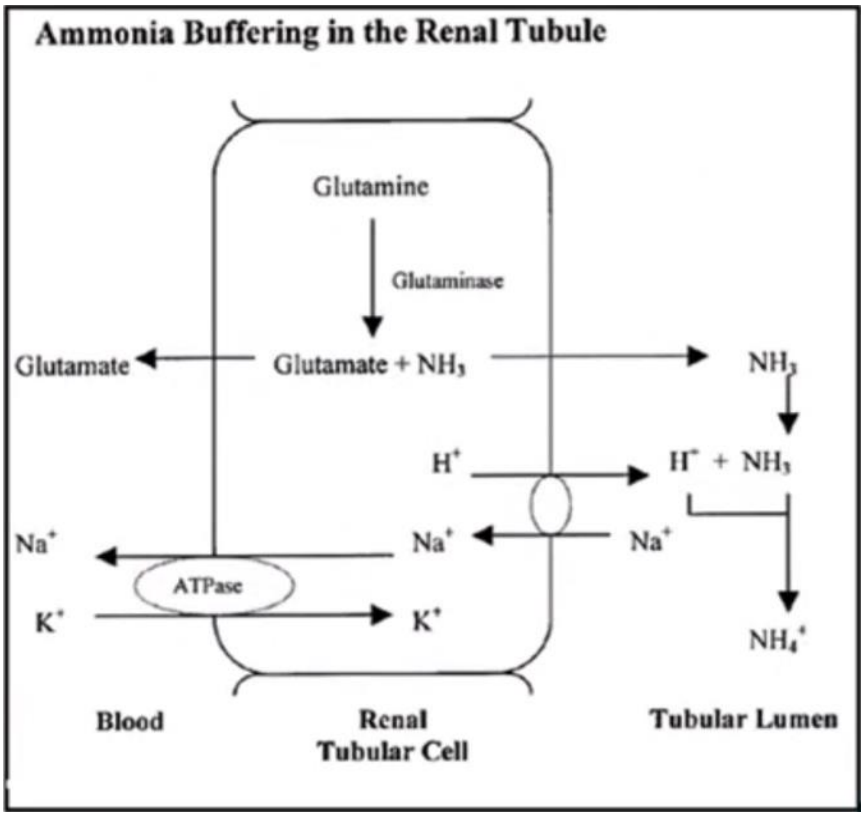


- **Ammonia buffering for Urine**

Ammonia is produced in renal tubular cells by the action of the enzyme glutaminase on the amino acid glutamine

Ammonia is unionize and so rapidly crosses into the renal tubule down its concentration gradient

The ammonia combines with H^+ to form the ammonium ion, which being ionized does not pass back into the tubular cell.

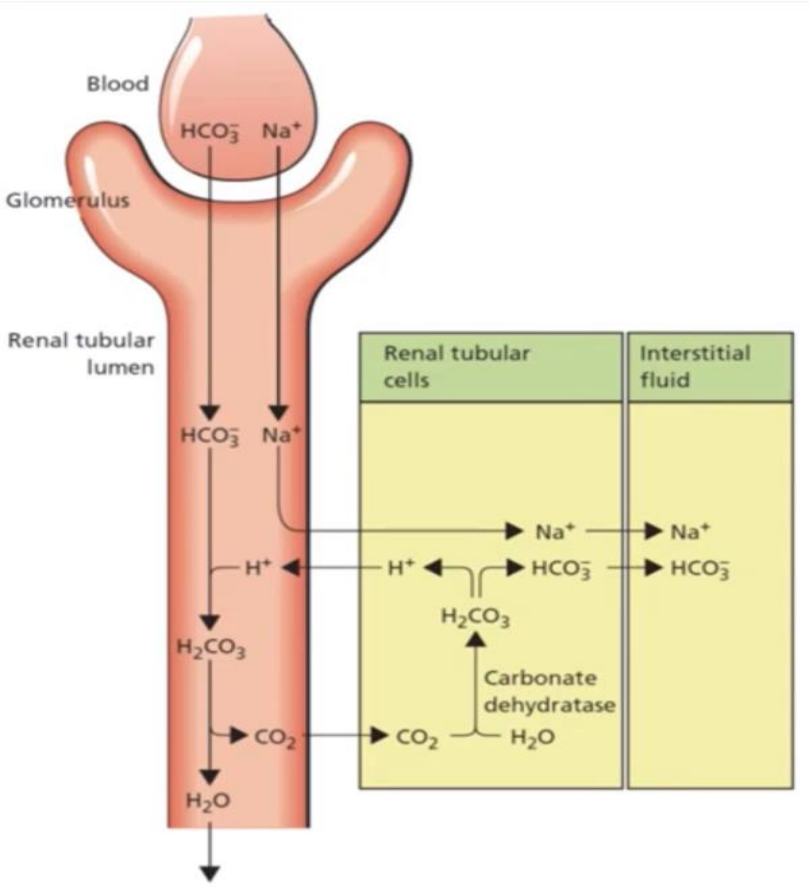


b) Regeneration of Bicarbonate

Bicarbonate ions are freely filtered by the glomerulus.

The concentration of bicarbonate in the tubular fluid is equivalent to that of plasma.

If bicarbonate were not reabsorbed the buffering capacity of the blood would rapidly be depleted.



c) Electrolytes balance

- **Sodium/Potassium: sodium reabsorption and hydrogen ion excretion are interlinked. Sodium reabsorption is controlled by the action of aldosterone on ion exchange proteins in the distal tubule. These ion exchange proteins exchange sodium for hydrogen or potassium ions. Thus, changes in aldosterone secretion may result in altered acid secretion.**

- **Chloride: The number of positive and negative ions in the plasma must balance at all times. Aside from the plasma proteins, bicarbonate and chloride are the two most abundant negative ions (anions) in the plasma In order to maintain electrical neutrality any change in chloride must be accompanied by the opposite change in bicarbonate concentration. Therefore, the chloride concentration may influence acid base balance.**

Disorders of hydrogen ion homeostasis

- **Disturbance of the body's acid-base balance results in the plasma containing either too many H+ (acidaemia or acidosis) or too few H+ (alkalaemia or alkalosis) .**
- **These disturbances may be due to respiratory causes or non-respiratory (metabolic) causes.**
- **Metabolic acid-base disorders affect directly the HCO_3 concentration:**

1. **Metabolic acidosis: decreased HCO_3 concentration**

2. **Metabolic alkalosis: increased HCO_3 concentration**

- **Respiratory acid-base disorders affect directly the PCO_2:**

1. **Respiratory acidosis: increased PCO_2**
2. **Respiratory alkalosis: decreased PCO_2**

Compensation

- **Rena Compensation (slow to take effect /2 to 3 days)**

For the primary respiratory disorders, renal tubules attempt to compensate by increase or decrease the H^+ secretion.

Respiratory acidosis ⟶ compensated by increased tubular H+ secretion

Respiratory alkalosis ⟶ compensated by decreased tubular H+ secretion

- **Respiratory Compensation (quick to take effect)**

For the primary metabolic disorders, lung attempt to compensate by increase or decrease CO2 exhalation

Metabolic acidosis ⟶ compensated by hyperventilation (*Kussmaul breathing*)

Metabolic alkalosis ⟶ compensated by hypoventilation

Primary disorder	Compensatory response
↑ PCO_2 (Respiratory acidosis)	↑ H^+ secretion ↑ HCO_3 reabsorption
↓ PCO_2 (Respiratory alkalosis)	↓ H^+ secretion ↓ HCO_3 reabsorption
↓ HCO_3 (Metabolic acidosis)	Hyperventilation ↓ PCO_2
↑ HCO_3 (Metabolic alkalosis)	Hypoventilation ↑ PCO_2

Disorders of hydrogen ion homeostasis

1. Metabolic Acidosis:

1. **Excess H+ Production:** due to increase organic acids (usually lactic or pyruvic) as a result of anaerobic metabolism. This may result from local or global tissue hypoxia. Increased ketone bodies in diabetic ketoacidosis .

2. **Ingestion of Acids (salicylate overdose)**

3. **Inadequate Excretion of H+:** This results from renal tubular dysfunction and usually occurs in conjunction with inadequate reabsorption of bicarbonate. Any form of renal failure may result in metabolic acidosis.

4. **Excessive Loss of Bicarbonate:** Gastro-intestinal secretion are high in sodium bicarbonate. The loss of small bowel contents or excessive diarrhea results in the loss of large amounts of bicarbonate resulting in metabolic acidosis. This may be seen in such conditions as Cholera

Anion gap

- The body fluids are electrochemical neutral (anions = cations)
- It is not easy to measure all the anions in the body.
- The anion gap is the difference in the measured cation and the measured anions in serum, plasma, or urine
- The concentrations are expressed in units of (mmol/L)
- It is calculated as the difference between the sum of the 2 main cations (Na & K) and the sum of the 2 main anions (Cl & HCO_3)

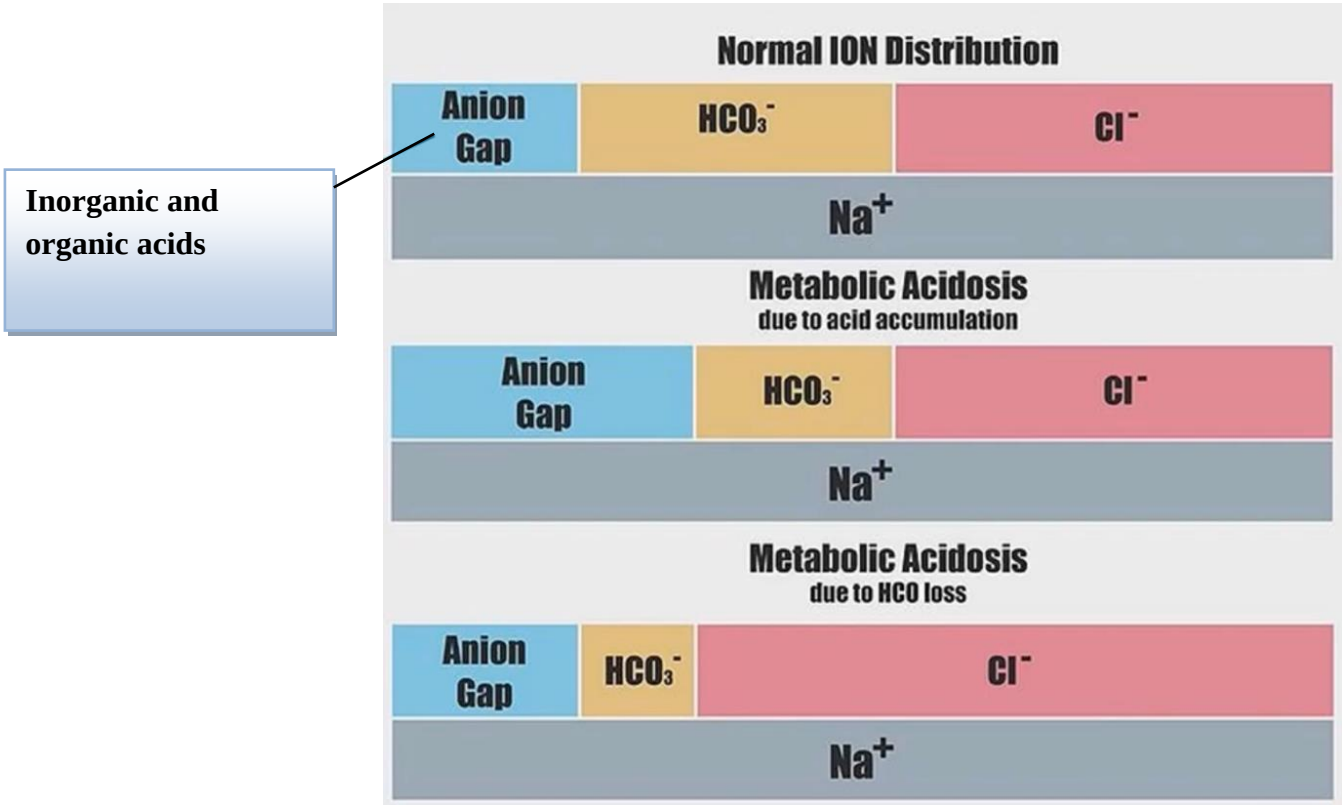
$$= ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$$

- Omission of potassium has become widely accepted, as potassium concentrations, being very Iow, usually have little effect on the calculated gap.

$$= [Na^+] ([Cl^-] + [HCO_3^-]) \text{ normal is } 6 - 18 \text{ mmol/L}$$

- Anion gap is used to determine the cause of metabolic acidosis (increased H+ production or HCO3 loss)
- Normally unmeasured anions exceed unmeasured cation by the anion gap

- When the [HCO_3] increases or decreases, other ions must take its place to maintain electrochemical neutrality
  1. HCO_3 ↓ and the anion gap ↑ this means increased levels of other acids (sulphuric, lactic, acetoacetate or salicylate) (its metabolic acidosis due to increased H+ production)
  2. If HCO_3 ↓ and the <u>anion gap does not change</u> this means Cl^- substitutes for HCO_3 (its metabolic acidosis due lo HCO3 loss)



2. Metabolic Alkalosis:

1. **Excess H+ loss:** Gastric secretion contain large quantities of hydrogen ions. Loss of gastric secretions, therefore, results in a metabolic alkalosis. This occurs in prolonged vomiting for example pyloric stenosis or anorexia nervosa.

2. **Excessive Reabsorption of Bicarbonate**: Bicarbonate and chloride concentrations are linked. If chloride losses are excessive then bicarbonate will be reabsorbed to maintain electrical neutrality. Chloride may be lost from the GIT in prolonged vomiting. Chloride losses may also occur in the kidney usually as a result of diuretic drugs. These drugs cause increased loss of chloride in the urine resulting in excessive bicarbonate reabsorption.

3. **Ingestion of Alkalis (overdose of sodium bicarbonate)**

3. **Respiratory Acidosis: most commonly due to decreased alveolar ventilation causing decreased excretion of CO2. Less commonly it is due to excessive production of CO2 by aerobic metabolism.**

- **Causes:**

1. **Inadequate CO_2 Excretion: The causes of decreased alveolar ventilation are numerous such as airway obstruction, central causes (stroke, trauma in brain, anathesia and opioids) and lung diseases (sever asthma)**
2. **Excess CO_2 Production: This may occur in syndrome such as malignant hyperpyrexia, hyperthyroidism**

Acute respiratory acidosis is uncompensated because the renal compensation requires long time. While chronic respiratory acidosis is compensated by kidneys.

4. **Respiratory Alkalosis: it is much common than respiratory acidosis**

Results from the excessive excretion of CO_2 this is commonly seen in hyperventilation (due to anxiety, pain, shock or high altitude).

Treatment: Increasing the inspired Co_2 by making the patient re- breath into a paper bag.

$$H^+ = 24 \times \frac{pCO_2}{HCO_3^-}$$

Lab. Assessment of hydrogen status

- **Specimen for Blood gases analysis:**
  1. **Arterial blood is used (or arterialized capillary)**
  2. **Heparin is used as anticoagulant**
  3. **Exclude air from the syringe before and after the blood is collected.**

4. **The sample should be placed in ice during transit**

- **The assessment of acid-base status is carried out by measuring [H+], [HCO_3] and PCO_2 however, in practice, we measure [H+] and PCO_2 and there is no need to measure HCO_3 as it can be calculated when the other 2 variables are known.**

- **From the above equation:**
  - **Adding H+, removing HCO_3, or increasing the PCO_2 ⟶ increase [H+]**
  - **Removing H+, adding HCO_3 or decreasing the PCO_2 ⟶ decrease [H+]**

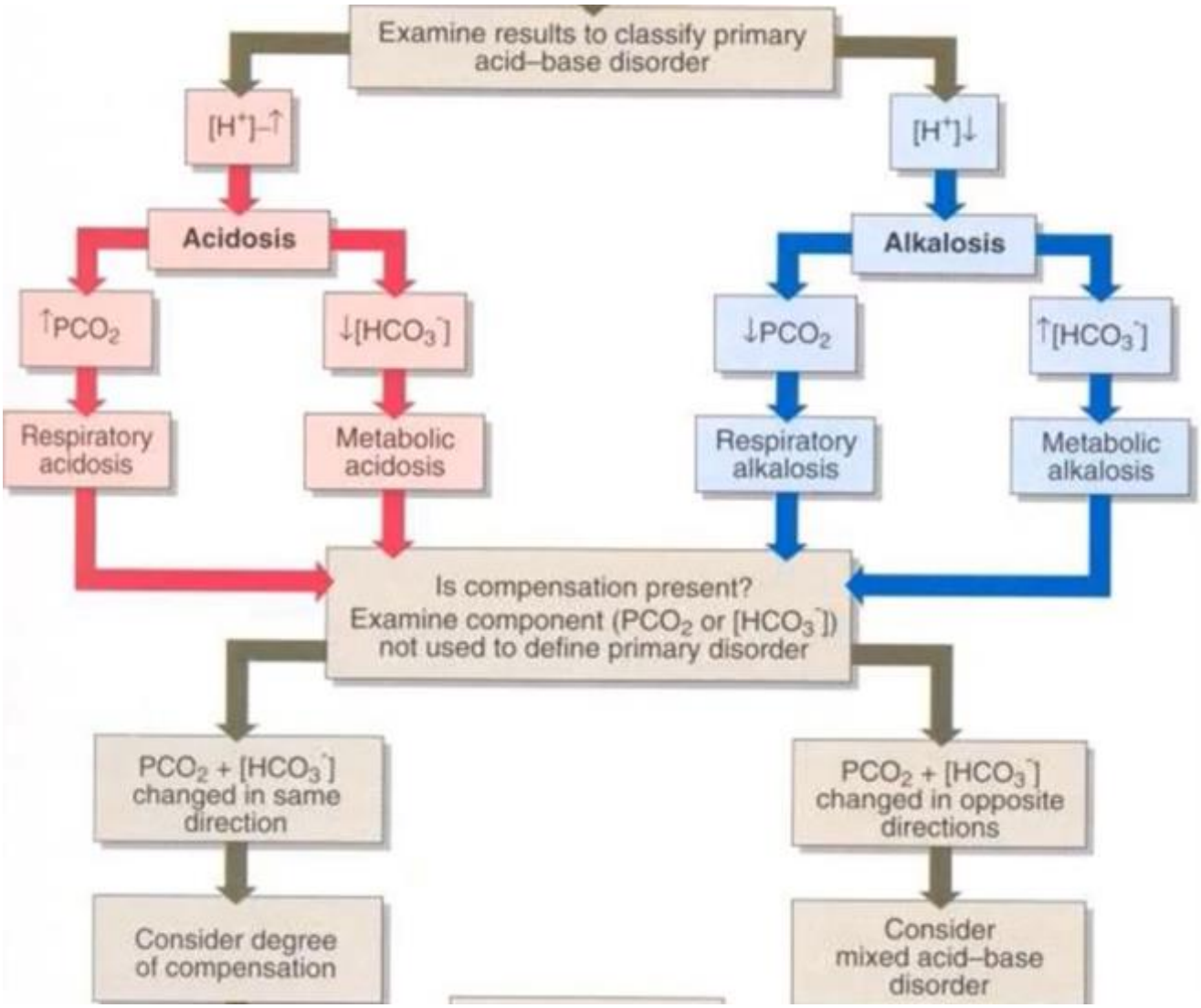
Interpreting the results

- **The practical approach to the interpretation of blood gas results:**

1. **Look at the [H+]: Decide if an acidosis or an alkalosis.**
2. **If acidosis, decide what is the primary cause:**
   - **a) Increased PCO_2 ⟶ Respiratory acidosis**
   - **b) Decreased HCO_3 ⟶ Metabolic acidosis**

3. **If alkalosis, decide what is the primary cause**
   - **a) Decreased PCO_2 ⟶ Respiratory alkalosis**
   - **b) Increased HCO_3 ⟶ Metabolic alkalosis.**

4. **Having decided on the primary acid-base disorder, look to see if there is compensation. There will be a change in the other component (the one which was not used to determine the primary disorder) in the direction which compensates for the primary disorder.**



Case # 1

- **A 60-year-old man was admitted to hospital with severe abdominal that had begun 2.5 h earlier. He was not taking any drugs. On examination, he was shocked and had a distended, rigid abdomen; neither femoral pulse was palpable**

Test	Result	Reference values
pH	7.05	7.35 – 7.45
PCO_2	26.3 mmHg	35 – 46 mmHg
Serum HCO_3	7 mmol/L	22 – 30 mmol/L

- **pH is low** ⟶ **acidosis**
- **Bicarbonate is low** ⟶ **metabolic acidosis**
- **PCO_2 is low** ⟶ **compensated metabolic acidosis (hyperventilation)**

TUMOR MARKERS

• Definition of tumor markers:

- Tumor markers are macromolecules mostly proteins whose appearance or changes in concentration in blood or other body fluids is indicative to the presence, extent or progress of a malignant tumor.

- Tumor markers may be tumor antigens, hormones or enzymes.

- Alterations of serum enzymes in malignancy may be due to:

1. Production of increased amounts of enzymes by tumor cells.

2. Release of intracellular enzymes due to cell damage.

• Enzymes used as tumor markers:

1. Alkaline phosphatase (ALP). It increases in bone metastasis.

2. Creatine kinase (CK): The isoenzyme fraction of the brain (CKBB) diagnose breast tumors, prostatic carcinoma, colonic cancer, and transitional cell carcinoma of bladder.

3. Lactic dehydrogenase (LDH). It is generally increased in malignancy.