pH Fighters and acid base disorders

by

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Learning objectives:

You should be able to:

- Discuss PH
- Discuss different types of buffers
- Determine regulation of PH
- Define acidosis and alkalosis and identify their types, causes and compensation
- Describe anion gap

RECOMENDED TEXT BOOKS AND REFERENCES FOR SYSTEM MODULES

- Lecture notes authorized and edited by the Medical Biochemistry and Molecular Biology Department
- Lippincott's Illustrated Biochemistry Reviews (3rd edition), 2009.
- Harper's Illustrated Biochemistry, 29th edition (2009).
- Guyton & Hall, Textbook of Medical Physiology 11th edition, 2006.
- Sherwood L. Human Physiology from Cells to Systems, 5th edition, 2007.

Regulation of pH:

There are 3 lines of defense (pH fighters) which regulates pH:

- The 1st line is blood buffers
- The 2nd line is the respiratory regulation
- The 3rd line is the renal regulation

I. Regulation of blood pH by buffers:

- **Buffers** are solutions which resist any changes in their pH when a moderate amount of an acid or alkali is added to them. **Composed of** mixtures of either:

1. ***Weak acid*** and its salt with a strong base e.g. H_2CO_3 and $NaHCO_3$ (bicarbonate system) or acetic acid and sodium acetate.
2. ***Weak base*** and its salt with a strong acid e.g. ammonium hydroxide and ammonium chloride.

Types of buffers:

1. **Physiological buffer system:** **Bicarbonate**, phosphate and protein systems most important.

a. Bicarbonate system: $BHCO_3/H_2CO_3$

- Normal plasma bicarbonate level is 24 mmol/L, normal carbonic acid is 1.2 mmol/L. Bicarbonate to carbonic acid ratio is 20:1. B is Na^+ if extracellular or K^+ if intracellular.
- Bicarbonate system is 65% of buffering system capacity in plasma and 40% of buffering action in the whole body. Bicarbonate is regulated by kidney (metabolic component) while carbonic acid is regulated by respiration (respiratory component).

$$H^+ + Cl^- + B^+ + HCO_3^- \rightarrow H_2CO_3 + BCl$$

$$Na^+ + OH^- + H^+ + HCO_3^- \rightarrow NaHCO_3 + HOH$$

B. phosphate system:

$$\frac{B_2HPO_4}{BH_2PO_4}$$

$$\frac{dibasic\ monohydrogen\ phosphate}{monobasic\ dihydrogen\ phosphate}$$

$$\frac{basic\ phosphate}{acid\ phosphate}$$

- It is mainly an intracellular buffer. The ratio between phosphates and phosphoric acid is 4. Phosphate buffer system is effective at a wide pH range because it has more than one ionizable group e.g.

$$H_3PO_4 \rightarrow H^+ + H_2PO_4^-$$

$$H_2PO_4^- \rightarrow H^+ + HPO_4^{-2} \left(\frac{Na_2HPO_4}{NaH_2PO_4}\right)$$

$$HPO_4^{-2} \rightarrow H^+ + PO_4^{-3}$$

- HCL is neutralized by basic phosphate:

$$H^+ + Cl^- + B^+ + BHPO_4^- \rightarrow BH_2PO_4 + B^+ + Cl^-$$

- NaOH is neutralized by acid phosphate:

$$Na^+ + OH^- + B^+ + H_2PO_4^- \rightarrow NaH_2PO_4 + B^+ + OH^-$$

$$Na^+ + OH^- + H^+ + BHPO_4^- \rightarrow NaBHPO_4 + H^+ + OH^-$$

C. Protein system: $\frac{proteinate\ salts}{proteinic\ acid}$ $\frac{B-proteinate}{H=proteinate}$

if an acid is added, it is neutralized by proteinate salt:

$$H^+ + Cl^- + B^+ + proteinate^- \rightarrow H.proteinate + B^+ + Cl^-$$

if an alkali is added, it is neutralized by proteinic acid:

$$Na^+ + OH^- + H^+ + proteinate^- \rightarrow Na\ proteinate + H^+ + OH^-$$

II. Blood Buffers:

- Blood buffers include all the physiological buffer system in addition to hemoglobin and oxyhemoglobin the in red blood cells.

A.Hemoglobin buffer: $\frac{KHb}{HHb}$

B. Oxyhemoglobin: $\frac{KHbO_2}{HHbO_2}$

- The 2 systems act together to get rid of CO_2 produced as metabolites from tissues. Blood buffers keep the pH of blood fixed at 7.4 ± 0.05
- So, fatal academia or alkalemia does not occur.

Buffers	Extracellular fluid	Intracellular fluid	Erythrocyte fluid
Bicarbonate system	$NaHCO_3/H_2CO_3$	$KHCO_3/H_2CO_3$	$KHCO_3/H_2CO_3$
Phosphate system	$\frac{Na_2HPO_4}{NaH_2PO_4}$	$\frac{K_2HPO_4}{KH_2PO_4}$	$\frac{K_2HPO_4}{KH_2PO_4}$
Proteinate system	$Na\ albumin/Halbumin$	$\frac{Kproteinate}{H\ proteinate}$	$\frac{KHb}{HHb}$ Hemoglobin system

Although the buffer system can respond immediately to the addition of acid or alkali, this system cannot eliminate them. So, the respiratory and renal regulations are very essential for the final elimination of acids.

Actions of hemoglobin:

At rest, about 200 ml of CO_2 is produced per minute in tissues. The CO_2 is carried by the following 3 ways:

1. Dissolved form: 10%

2. Isohydric transport CO_2: 75% as the dissolved but $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow HCO_3^- + H^+$ is buffered by deoxyHb in tissues & diffuse to plasma H^+ HCO_3^-

3. Carbamino-hemoglobin: 15% as carbaminoHb

R-NH + CO2 → R-NH

Hb generates HCO_3^- **or the alkali reserve by Carbonic anhydrase**

At tissues;

$$CO_2 + H_2O \rightarrow H_2CO_3$$
$$H_2CO_3 \rightarrow HCO_3^- + H^+$$
$$H^+ + Hb^- \rightarrow HHb$$

- When the blood reaches the lung, the reverse occurs. The following steps show how O_2 can combine with hemoglobin and CO_2 is released through the expiration.

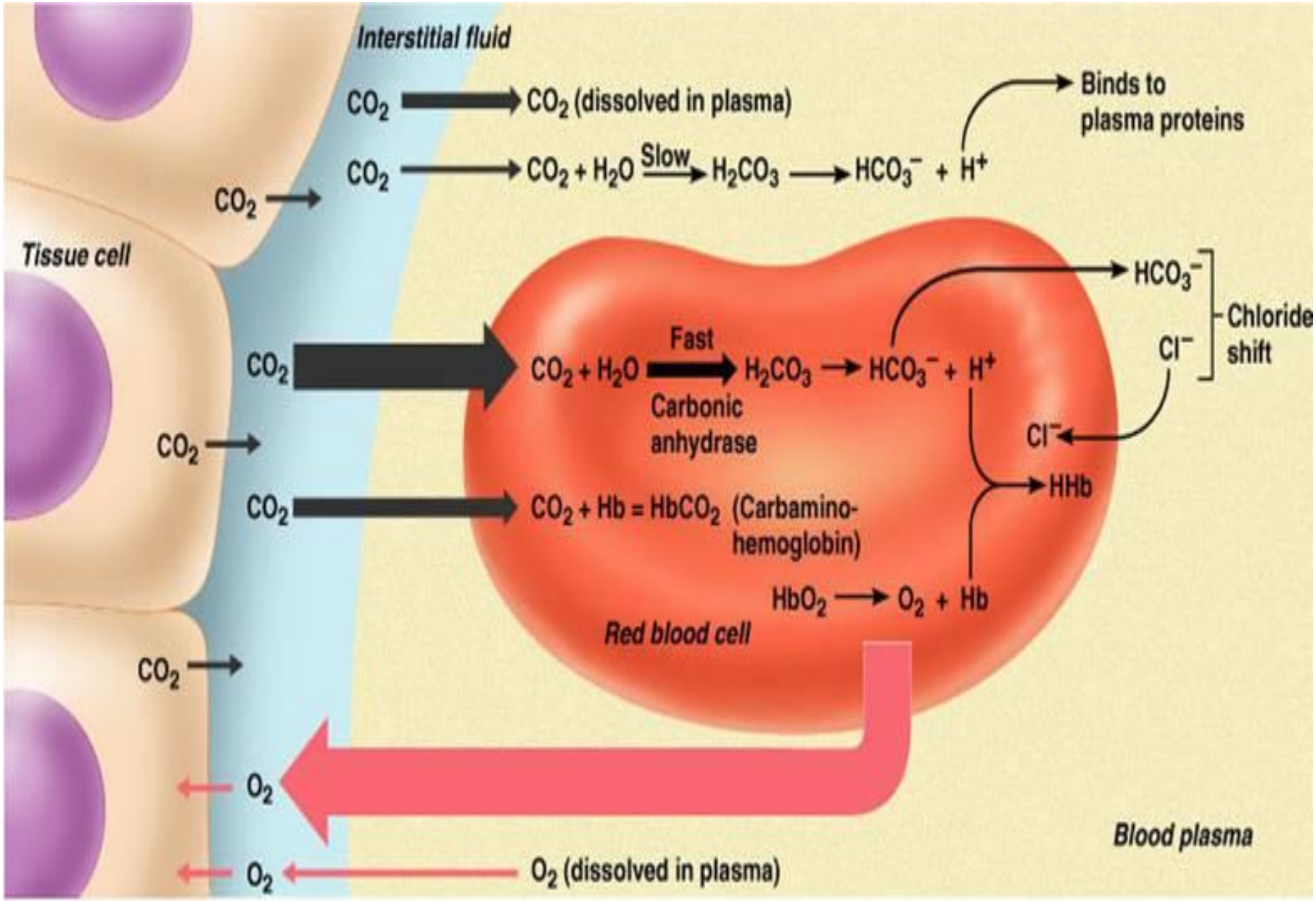
$$HHb + O_2 \rightarrow HbO_2 + H^+$$

$$HCO_3^- + H^+ \rightarrow H_2CO_3$$

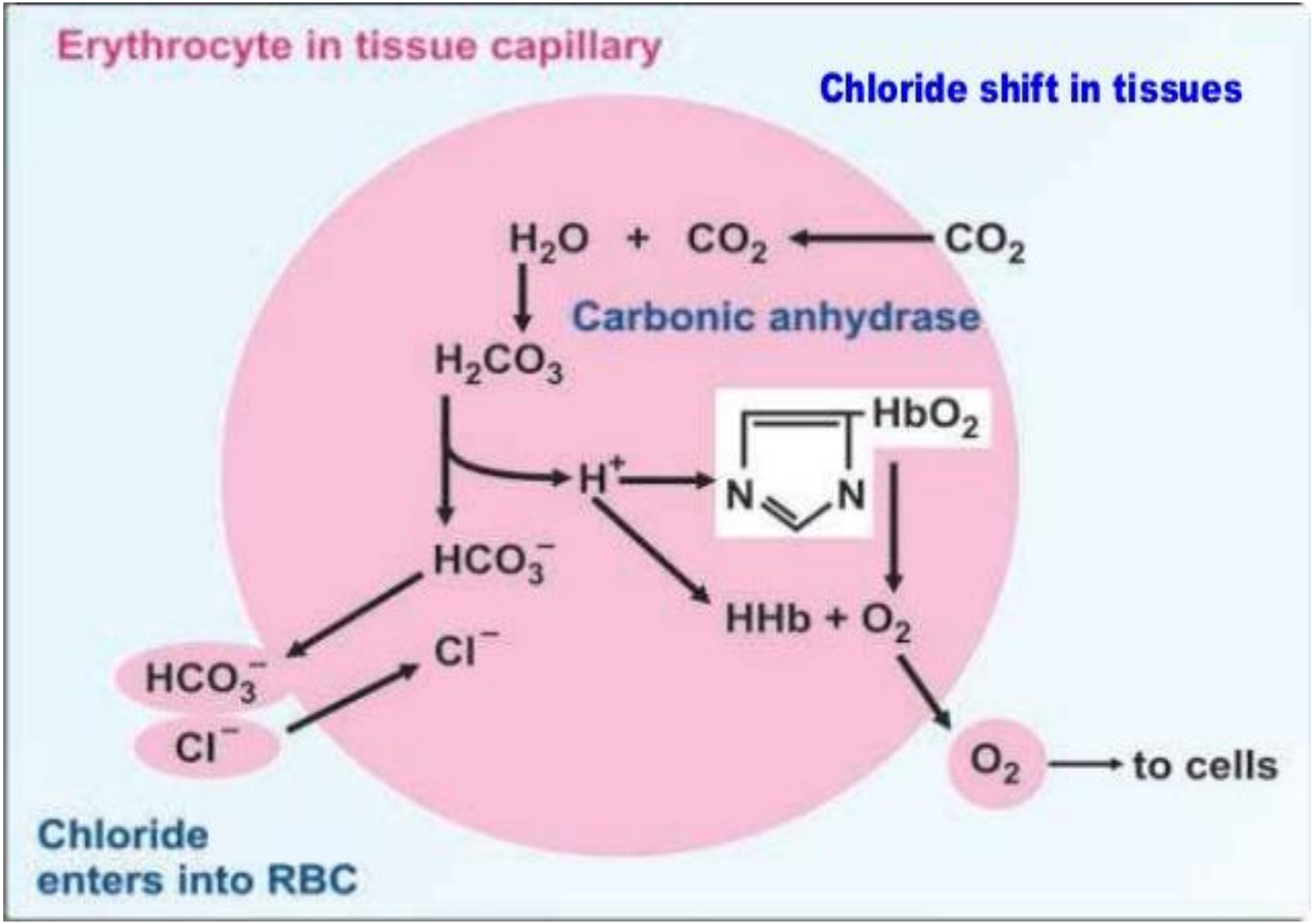
- N.B. the bicarbonate reenters the erythrocytes by reversal of chloride shift

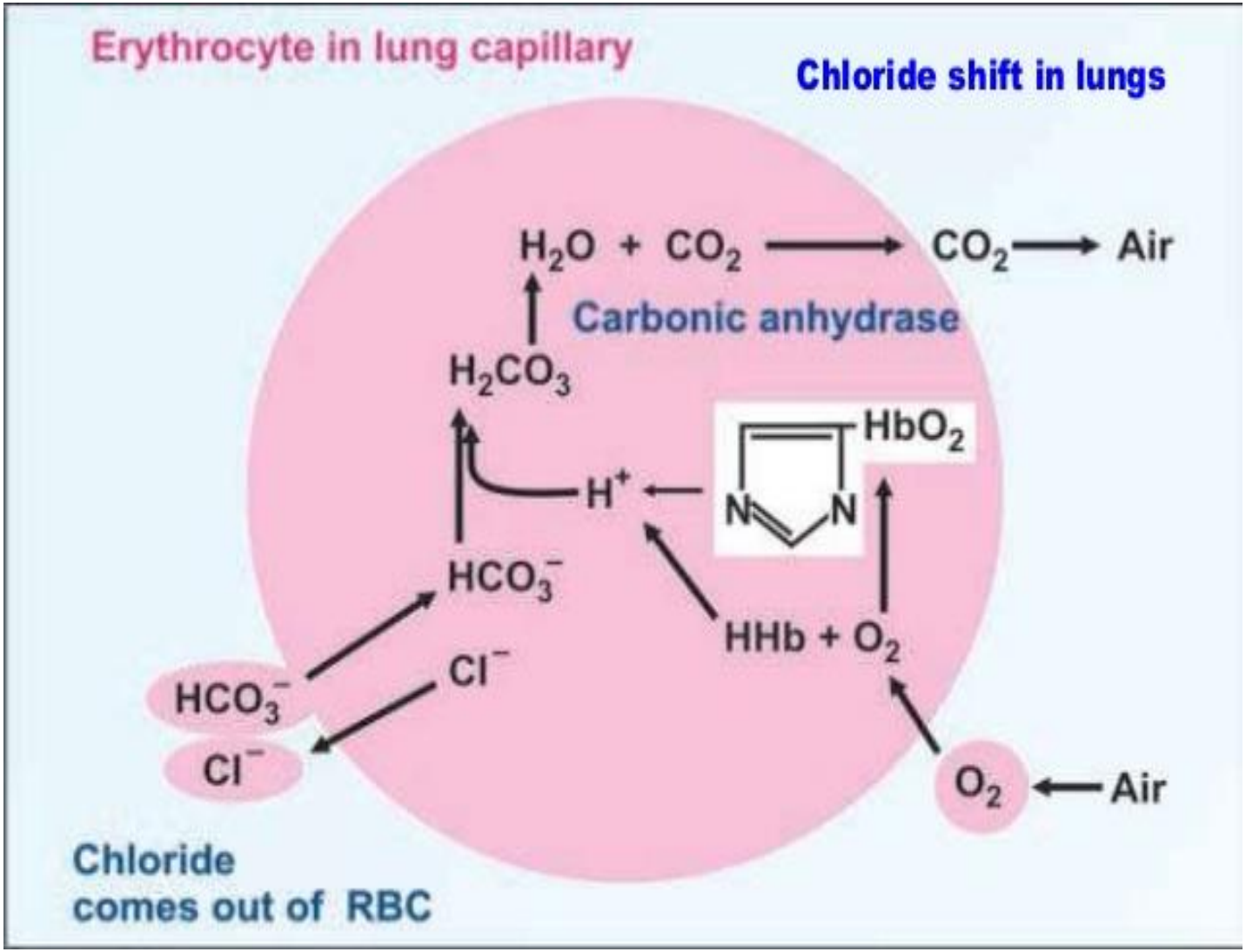
$$H_2CO_3 \rightarrow H_2O + CO_2$$

- Carbonic anhydrase (carbonate dehydratase) activity increases in acidosis and decreases in alkalosis (low hydrogen ion concentration).



(a) Oxygen release and carbon dioxide pickup at the tissues


Erythrocyte in tissue capillary
Chloride shift in tissues
H_2O + CO_2
CO_2
Carbonic anhydrase
H_2CO_3
HbO_2
H^+
N N
HCO_3^-
HHb + O_2
Cl^-
HCO_3^-
Cl^-
O_2 to cells
Chloride
enters into RBC


Erythrocyte in lung capillary
Chloride shift in lungs
$H_2O + CO_2$
CO_2
Air
Carbonic anhydrase
H_2CO_3
HbO_2
H^+
N
N
HCO_3^-
$HHb + O_2$
HCO_3^-
Cl^-
Cl^-
O_2
Air
Chloride
comes out of RBC

II. Respiratory regulation of pH

- This is the 2nd line of defense against the change in pH. When there is fall in pH (acidosis), the chemo receptors in the respiratory center are stimulated resulting in hyperventilation that eliminates more CO_2, thus lowering H_2CO_3 level i.e.

$$\uparrow H_2CO_3 \text{ (acidosis)} \rightarrow \text{stimulates chemoreceptors} \rightarrow \text{hyperventillation}$$

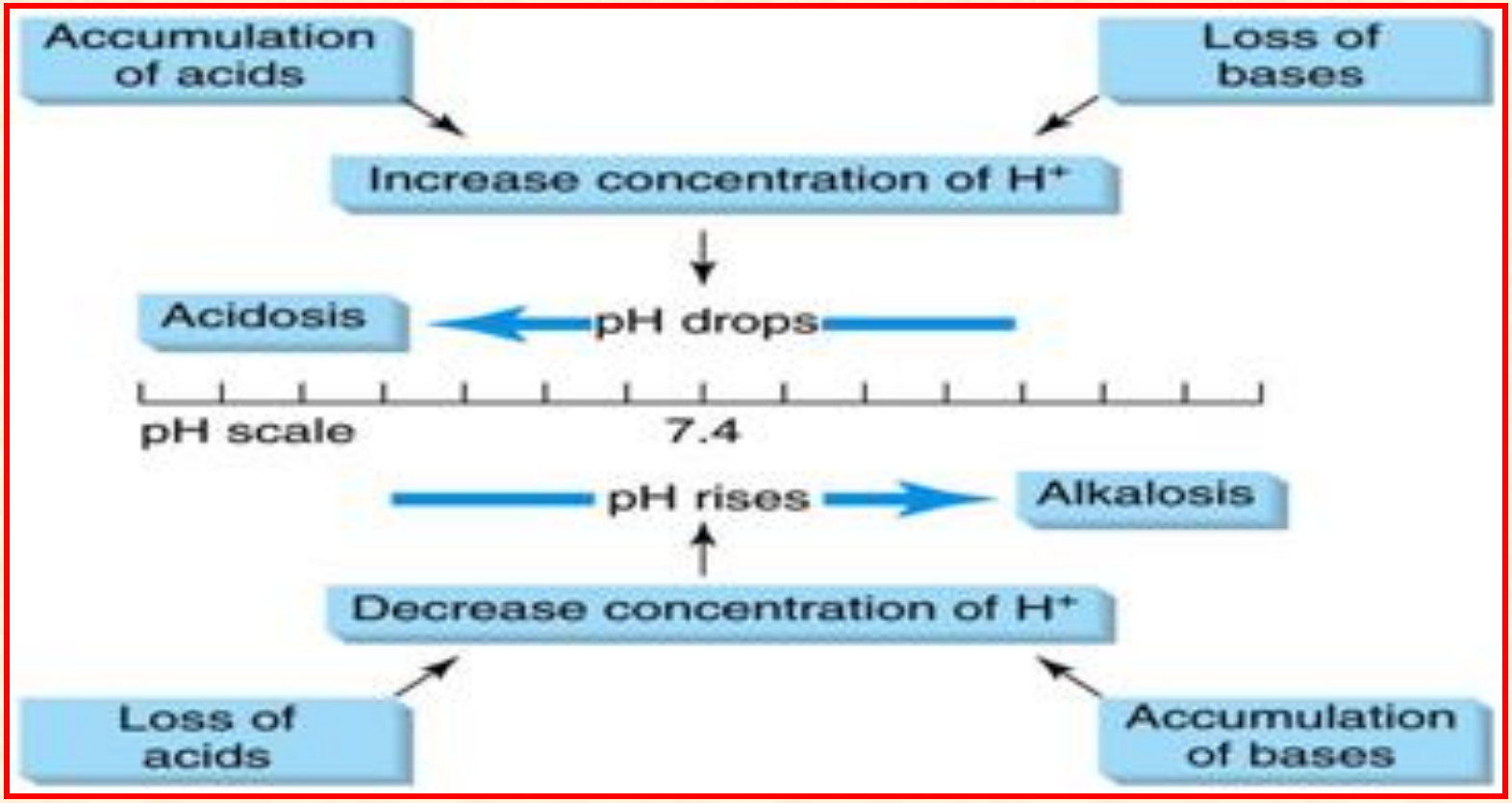
($\uparrow$loss of CO_2)

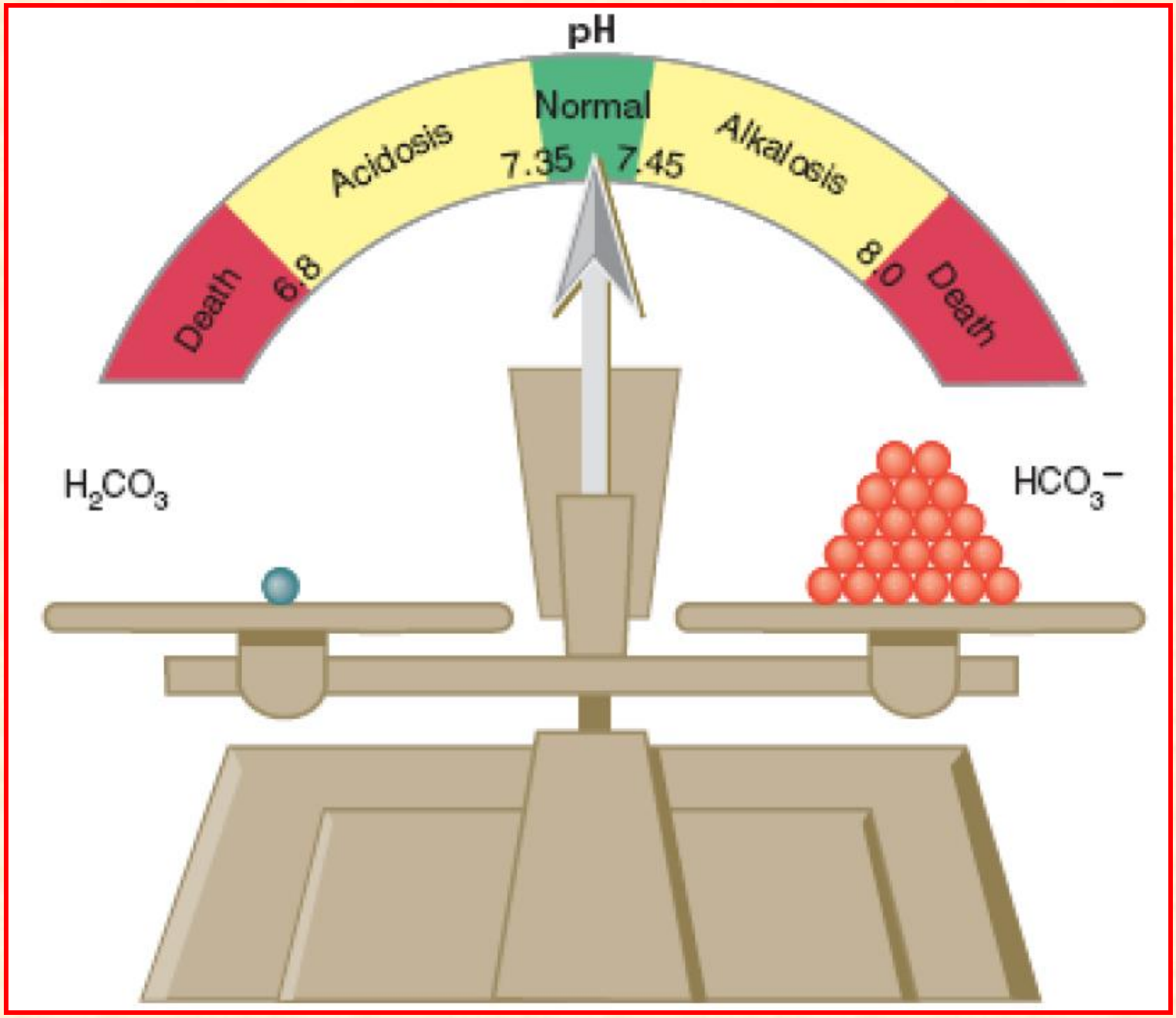
II. Renal regulation of pH

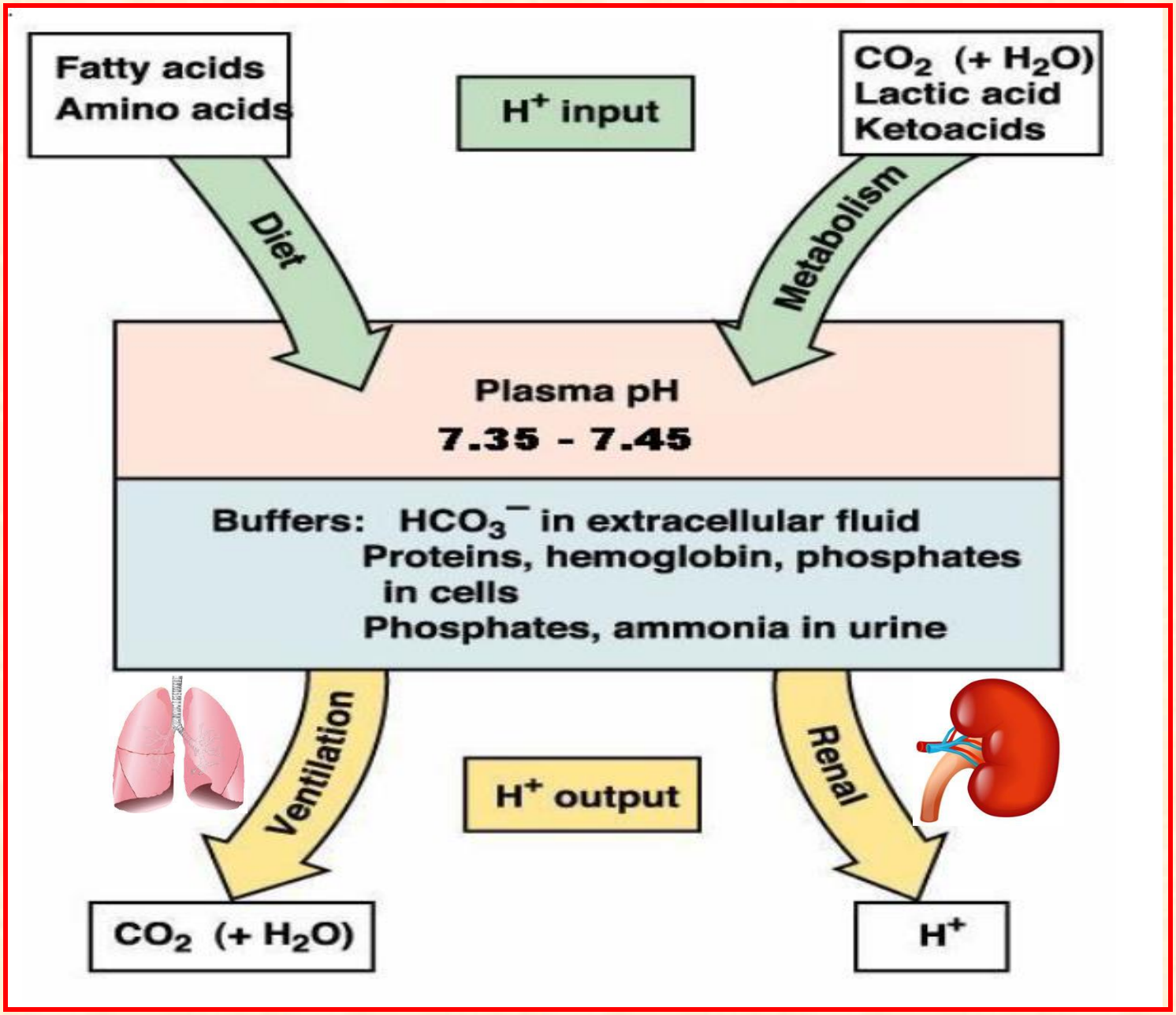
(see the renal module in the third semester)

Normal values;

- Normal pH range 7.35-7.45.
- The normal plasma bicarbonate (HCO_3-) level is 24 mmol/L
- The normal carbonic acid (H_2CO_3) is 1.2 mmol/L.
- The bicarbonate / carbonic acid ratio is equal to 20:1.




pH
Normal
Acidosis
Alkalosis
7.35
7.45
Death
6.8
8.0
Death
H_2CO_3
HCO_3^-


Fatty acids
Amino acids
H+ input
CO2 (+ H2O)
Lactic acid
Ketoacids
Diet
Metabolism
Plasma pH
7.35 - 7.45
Buffers: HCO3− in extracellular fluid
Proteins, hemoglobin, phosphates
in cells
Phosphates, ammonia in urine
Ventilation
H+ output
Renal
CO2 (+ H2O)
H+

Point	Acidosis		Alkalosis	
Def.	The blood pH tends to			
	decrease		increase	
	due to formation of			
	excessive acids		excess alkali	
	at a rate exceeding the capacity of the body to neutralize & eliminate			
Types	**Respiratory**	**Metabolic**	**Respiratory**	**Metabolic**
Causes	**CO_2 retention**	↓ blood HCO_3^-	↑ **CO_2 loss**	↑ blood HCO_3^-

Points		cidosis	kalosis
Causes		**CO2 retention**	**excess CO_2 loss**
		• Bronchial asthma • Chronic bronchitis • Emphysema • Pneumonia • Respiratory center inhibition • Asphyxia	• **F**ever • Ence**ph**alitis • **H**igh altitude • Late stage of salicylate (**a**spirin) poisoning • **H**ysterical hyperventilation
Mechanism	**Uncompensated**	• ↓ HCO_3^-/H_2CO_3 ratio while HCO_3^- remains as it is.→ "uncompensated respiratory acidosis" or "acidemia".	• ↑ HCO_3^-/H_2CO_3 (HCO_3^- remains unchanged) → uncompensated respiratory alkalosis • The alkali reserve is normal (no change in bicarbonate)
	Compensated	The kidney will reabsorb more (HCO_3^-), till the ratio HCO_3^-/H_2CO_3 reaches 20:1 → compensated respiratory acidosis	Renal tubular reabsorption of HCO_3^- is inhibited [↑ K^+ & HCO_3^- excretion of in urine (alkaline)] till HCO_3^-/H_2CO_3 ratio reaches 20:1 → compensated respiratory alkalosis

Points		Respiratory acidosis	Respiratory alkalosis
Uncompensated (disturbed HCO_3^- /H_2CO_3 ratio)	**HCO_3^-**	**Normal**	**Normal**
	H_2CO_3	**Increased**	**Low**
	pH	**Decreased**	**Increased**
Compensated (normal HCO_3^- /H_2CO_3 ratio)	**HCO_3^-**	**Increased**	**Decreased**
	H_2CO_3	**Increased**	**Low**
	pH	**Decreased**	**Increased**

Points	cidosis	kalosis
Causes	↓ blood HCO_3^-	↑ blood HCO_3^-
	1. Increased production of acids: **• Muscular exercise** **• Ketosis** **• Diet producing acids** **• Administration of NH_4Cl** **3. Increased loss of bases:** **•Diarrhea** **•Vomiting** (low intestinal obstruction) **•Hyperkalemia (Addison's disease)** **2. Failure of excretion of acids:** **•Chronic renal failure**	**1. Increased absorption of bases:** **• Intake of high vegetables & fruits** **• Intake of drugs containing citrate and bicarbonate salts** (anti-acids) **2. Increased loss of acids:** **• Prolonged suction of gastric juice** **• Vomiting (high intestinal obstruction)** **•Hypokalemia (Cushing's syndrome) "paradoxical alkalosis" (blood alkaline and urine acidic).**
Mechanism **Uncomp**	**HCO_3^- is decreased** & the **H_2CO_3 remains as it is**, **"uncompensated metabolic acidosis" or "acidemia"**	Increased HCO_3^- & normal H_2CO_3. So, the ratio is increased **"uncompensated metabolic alkalosis"**

Points		Metabolic acidosis	Metabolic alkalosis
Uncompensated (disturbed HCO_3^- /H_2CO_3 ratio)	**HCO_3^-**	Low	**increased**
	H_2CO_3	Normal	**Normal**
	pH	Decreased	**Increased**
Compensated (normal HCO_3^- /H_2CO_3 ratio)	**HCO_3^-**	Low	**Increased**
	H_2CO_3	**Decreased**	**increased**
	pH	Decreased	**Increased**

B. Metabolic acidosis:

Causes: It usually results from decreased blood HCO_3^- as in;

1. Excess production of acids:

- **Muscular exercise**: with production of excess lactic acid.
- **Ketosis:** in diabetes mellitus (DM), ketone bodies will increase in blood; acetoacetic and β-hydroxybuteric acids.
- **Diet:** different foodstuffs yield excessive amount of acids from their metabolism like; pyruvic, lactic, sulfuric, phosphoric and nucleic acids.
- **Administration** NH_4Cl: Cl^- will replace bicarbonate decreasing it while NH_4^+ is transformed into urea.

2. Failure of excretion of acids:

- In chronic renal failure; fatty acid, uric acid and phosphoric acid accumulate. The kidney fails to excrete these acids.

3. Excessive loss of bases:

- **Diarrhea:** intestinal juices are alkaline rich in Na^+ and K^+ bicarbonate
- **Vomiting:** due to low intestinal obstruction.
- **Hyperkalemia (e.g. Addison's disease);**

➢ increased renal tubular reabsorption of Na^+ in exchange with K^+.

➢ Na^+ : H^+ exchange will stop.

➢ Na reabsorption will be in the form of NaCl (not $NaHCO_3$) which will be excreted in the form of **$KHCO_3$ in urine.**

➢ Cl^- will increase in blood leading to hyperchloraemic acidosis

➢ The blood acidity and urine alkalinity is called **"paradoxical acidosis".**

Mechanism of metabolic acidosis:

- The ratio of HCO_3^- / H_2CO_3 20:1 becomes disturbed because **HCO_3^- is decreased** and the **H_2CO_3 remains as it is**, **"uncompensated metabolic acidosis" or "acidemia"** :

  HCO_3^- is low

  H_2CO_3 is normal

  pH is decreased

- After that, **respiration** will be **stimulated** for CO_2 loss through the lung leading to decrease H_2CO_3: HCO_3^- is low

  H_2CO_3 is decreased

  The ratio will return to 20:1 pH reaches 7.4

"compensated metabolic acidosis" will be attained, but the **alkali reserve is decreased.**

- In healthy kidney (not in hyperkalemia), bicarbonate is not excreted through the kidney and Na will be absorbed in the form of $NaHCO_3$ and alkali reserve is being normal.
-

Anion gap

- It is the difference between the total amount of certain measured cations and certain measured anions.
- It is calculated as the difference between **($Na^+ + K^+$)** which represents 95% of total cations and **($HCO_3^- + Cl^-$)** which represents 86% of total anions. The **unmeasured anions constitute the anion gap**.
- As sodium is the main extracellular cation, and chloride and bicarbonate are the main anions.
- Normally, it is about 12 mmol/l
- Anion gap = $(Na^+ + K^+) - (Cl^- + HCO_3^-) = 12$ mmol/l

[Na^+=138 mmol/l, K^+= 4 mmol/l, Cl^- =105 mmol /l, HCO_3^-=25 mmol/l]

Types:

- There are 2 types of anion gap acidosis; normal & high.

High anion gap acidosis:

Causes:

1. **Chronic Renal failure:** this is due to decreased acid excretion (H^+) and decreased HCO_3^- reabsorption. Accumulation of sulfates, phosphates and urate (unmeasured anions).

2. **Diabetic ketoacidosis:** ↑ketone bodies in lipid metabolism (↑unmeasured anions) and ↑increased anion gap. HCO_3^- level decreases to buffer the increased acids. The bicarbonate is consumed by the unmeasured anion (as a buffer) resulting in a high anion gap.

3. **Lactic acidosis:** due to tissue hypoxia, circulatory failure and intake of biguanides (e.g. Cidophage tablets which contain metformin HCl and can cause lactic acidosis by decreasing glucose production by the liver, accumulates lactic acid).

Normal anion gap acidosis:

- When there is loss of both anions and cations, the anion gap is normal but acidosis may prevail.
- The drop in HCO_3^- lost is compensated by Cl^- (hyperchloremic acidosis).

Causes:

1. **Diarrhea:** there is loss of HCO_3^- , Na^+ and K^+.
2. **Hyperchloremic acidosis:** this occurs in;
   - **Renal tubular acidosis**: Renal loss of HCO_3^-
   - **Intake of carbonic anhydrase inhibitor** (acetazolamide)
   - **Ureteric transplantation into large gut** (as in cancer bladder)
3. **Addison's disease:** because of reabsorption of NaCl and excretion of $KHCO_3$

B. Metabolic alkalosis:

It is due to increased blood HCO_3^- which results from:

I. Increased absorption of bases:

- **Intake of high vegetable and fruit** diets containing big amount of citrate and bicarbonate salts. Citrate salts are transformed through Krebs' cycle into bicarbonate salts
- **Intake of drugs containing citrate and bicarbonate salts** (anti-acids for treatment of hyperacidity and peptic ulcer).

II. Increased loss of acids;

- **Prolonged suction of gastric juice**
- **Vomiting due to high intestinal obstruction**
- **Hypokalemia (Cushing's syndrome):**

➢ there is disturbed Na^+ and K^+ exchange in renal tubules.

➢ Instead, there is Na^+ and H^+ exchange.

➢ Na^+ is reabsorbed in the form of $NaHCO_3$ rather than NaCl.

➢ Cl^- will be lost in urine leading to hypochloremia.

➢ $NaHCO_3$ in blood causes metabolic alkalosis while ammonium chloride in urine causes urine to be acidic; **"paradoxical alkalosis" (blood alkaline and urine acidic).**

- **Cushing syndrome:** sodium and water retention and potassium excretion leading to hypokalemia.

Mechanism of metabolic alkalosis:

- There is increase in HCO_3^- while H_2CO_3 is normal. So, the ratio of HCO_3^- / H_2CO_3 (20:1) is increased. This is **"uncompensated metabolic alkalosis"**
- Alkalemia is corrected by **respiratory inhibition**. This leads to CO_2 retention and H_2CO_3 is increased; so the ratio returns 20:1 again but the **alkali reserve is high**.
- The kidneys try to keep alkali reserve normal by increasing Na^+ : K^+ exchange. So, to inhibit Na^+ : H^+ exchange, the kidneys excrete HCO_3^- in the form of $KHCO_3$ and Cl^- will be reabsorbed in the form of NaCl.

- To summarize:
- In **metabolic** acidosis and alkalosis; the disturbance is in the **bicarbonate** level while in **respiratory** acidosis and alkalosis; the disturbance is in the **carbonic acid** level.

- The normal bicarbonate/carbonic acid ratio is 20/1; if disturbed it is **uncompensated** acidosis or alkalosis.

- The bicarbonate level is the alkali reserve. In metabolic acidosis it is decreased and in metabolic alkalosis it is increased.

- Correction of alkaline reserve is strictly renal; if **increased** it is corrected by **increased $KHCO_3$ excretion and increased NaCl reabsorption** and if **decreased** it is corrected by **increased $NaHCO_3$ reabsorption and ammonium chloride excretion.**

Uncompensated acidosis & alkalosis

ABG	pH	$PaCO_2$	HCO_3
Respiratory Acidosis	↓	↑	normal
Respiratory Alkalosis	↑	↓	normal
Metabolic Acidosis	↓	normal	↓
Metabolic Alkalosis	↑	normal	↑

Uncompensated acidosis & alkalosis

ABG	pH	$PaCO_2$	HCO_3
Respiratory Acidosis	↓	↑	↑
Respiratory Alkalosis	↑	↓	↓
Metabolic Acidosis	↓	↓	↓
Metabolic Alkalosis	↑	↑	↑

N.B. ABG: arterial blood gases

Violet arrows are for compensation.