



PHYSIOLOGY

Sheet

Slide

Handout

Number

8

Subject

Acid - Base Balance

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**** This sheet was written -mainly- according to the recording that belongs to section 1. However, few points were added from the lecture in section 3. Please pay attention that the order of ideas in this sheet is different from that in the recording.**

❖ **Topics of this lecture:**

- *Revision for some basics regarding acids and bases.
 - *Normal (physiologic) pH and related conditions (Acidosis/Alkalosis).
 - *Types of acids produced in the body.
 - *The kidneys and bicarbonate (HCO_3^-).
 - *How does the body deal with acidity? (Three Lines of Defense)
-

❖ **Revision for some basics**

I. **What do we mean by acid-base balance?**

Acid- Base balance (التوازن الحمضي - القاعدي) → maintaining the concentration of hydrogen ions (H^+) in the Extracellular Fluid within the normal range.

A concentration that is higher than the normal causes “Acidosis”, while a concentration lower than the normal results in “Alkalosis”.

Note: In physiology, we are more concerned with changes in $[\text{H}^+]$, not $[\text{OH}^-]$.

II. **pH**

Since the values of H^+ concentration in our bodies (physiological values) are small, H^+ concentration is usually expressed as a logarithmic function called pH:

$$\text{pH} = - \log [\text{H}^+]$$

$[\text{H}^+]$: the concentration of H^+ (mole/L)

→ The higher the concentration of H^+ , the smaller the pH.

For example:

If $[\text{H}^+]$ in plasma = 40 nM, calculate the pH of plasma.

nM = nano-Molar = nanomole/L

Answer:

$$[H^+] = 40 \text{ nanomole/L} = 40 * 10^{-9} \text{ mole/L} = 4 * 10^{-8} \text{ mole/L}$$

$$\text{pH} = - \log (4 * 10^{-8})$$

$$= - \{ \log 4 + \log 10^{-8} \}$$

$$= - \{ 0.6 + -8 \}$$

$$= - \{ -7.4 \}$$

$$= 7.4$$

Don't forget:

$$\log (A * B) = \log A + \log B$$

$$-\log (A * B) = - \{ \log A + \log B \}$$

$$= - \log A - \log B$$

***don't forget the brackets when they are necessary, and be pay attention to the minus sign.*

Note: in the last lecture, Dr. Yanal mentioned that we will probably not be allowed to use our calculators in the exam. In case you are interested, the following piece of advice might be helpful, otherwise, you can skip it and move to the next page.

Additional:

In calculations, it is better to deal with logarithms using the abbreviation (**SLA**):

Values to memorize:

$$\text{Log } 1 = \text{zero}$$

$$\text{Log } 10 = 1 \text{ ,, , Log } 100 = 2 \text{ ,, ,}$$

$$((\text{Log } 10^x = X))$$

$$\text{Log } 2 = 0.3$$

$$\text{Log } 4 = 0.6$$

$$\text{Log } 20 = 1.3$$

➤ Simplification

Whatever the number you have, write it in the scientific notation $\rightarrow X.Y * 10^Z$

$$\text{Example: } \log 800 = \log (8.0 * 10^2)$$

$$= \log 8 + \log 10^2$$

➤ Use Logic and Approximation

Example: since log 1 = zero, and log 10 = 1:

Logic ... We expect log 8 to be between zero and one (closer to the 1 to be more accurate)

Approximation ... let's assume that $\log 8 = 0.7$ (or 0.8 or 0.9)

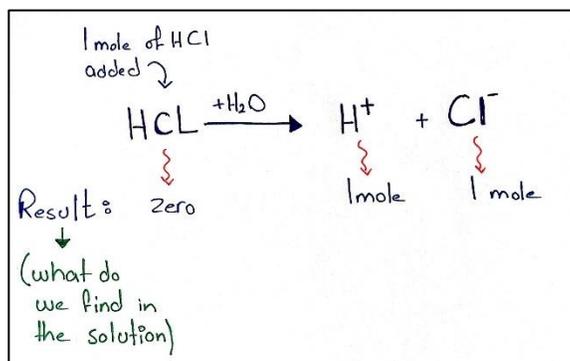
$$\rightarrow \log 800 = \log 8 + \log 10^2 = 0.7 + 2 = 2.7$$

2.7 is not far from the true accurate value of log 800 according to the calculator, which is 2.9. The previous steps give you an idea about the predicted values (not 100% accurate, but useful somehow), and they get easier with practice.

III. Strong and weak acids

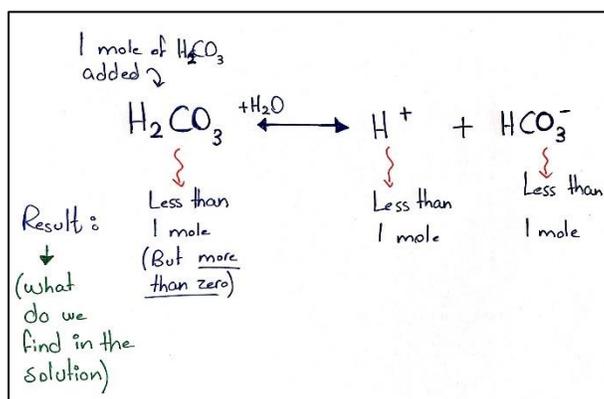
- Strong acid → dissociates completely in water.

For example, one mole of HCL (a strong acid) dissociates completely in water to give 1 mole of H⁺ and one mole of Cl⁻.



- Weak acid → dissociates partially in water.

For example, one mole of H₂CO₃ (a weak acid) does not dissociate completely in water. Thus, at equilibrium, both; the acid and the conjugate base (HCO₃⁻) are present in the solution.



Note: most acids and bases in the human body are weak.

IV. Buffers (المحاليل المُنظِّمة/الدَّارئة)

- From the book: “A buffer is a mixture of a weak acid (HA) and its conjugate base (A⁻), OR a weak base (B) and its conjugate acid (BH⁺).”

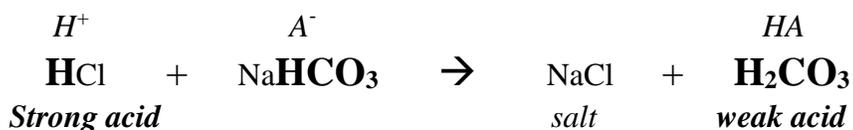
Examples:

- HA/A⁻: H₂CO₃/HCO₃⁻, H₂PO₄⁻/HPO₄⁻²
- B/BH⁺: NH₃/NH₄⁺

- “A buffered solution resists a change in pH. Thus, H⁺ can be added or removed from a buffered solution, but the pH of that solution will change only minimally.”

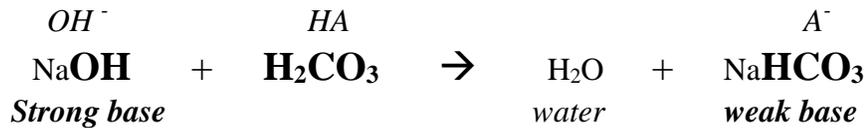
For example (the buffer pair in this example is H₂CO₃/HCO₃⁻):

- When H⁺ is added to a buffered solution containing a weak acid, it combines with the A⁻ form of the buffer and converts it to the HA form.



- ➔ We converted the strong acid into a weak acid. As a result, the effect on pH (decrease) will be minimal (in comparison to the effect when no buffer is used, and the same amount of HCL is added to water).

- Conversely, when H^+ is removed from a buffered solution (or OH^- is added), H^+ is released from the buffer, converting it to the A^- form.



- ➔ We converted the strong base into a weak base. As a result, the effect on pH (increase) will be minimal.

V. Henderson-Hasselbalch Equation

“used to calculate the pH of a buffered solution”

$$pH = pK + \text{Log} ([\text{Base}]/[\text{Acid}]) \rightarrow \boxed{pH = pK + \log \frac{[A^-]}{[HA]}}$$

Don't forget:

$p \rightarrow -\log$

 $pH \rightarrow -\log [H^+]$

$pK \rightarrow -\log K$

Example: for a solution containing the buffer pair (H_2CO_3/HCO_3^-), and knowing that pK for the bicarbonate buffer system is 6.1:

$$pH = 6.1 + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

❖ Normal (physiologic) pH, and related conditions (Acidosis/Alkalosis)

- The normal concentration of H^+ in plasma is 40 nM ($= 4 \times 10^{-8}$ M).
 The normal concentration of Na^+ in plasma is 140 mM ($= 14 \times 10^{-2}$ M).
 ➔ Note that $[Na^+]$ is much higher than $[H^+]$ (*the concentration of Na^+ is almost 3.5 million times the concentration of H^+*). However, $[H^+]$ is extremely important because it affects the activities of all enzymes (*every enzyme has its optimal pH*), hormones and receptors. It also affects ions and the three-dimensional structures of different proteins.

Mentioned in section 3:

[H⁺] in plasma affects other ions. For example, increased [H⁺] in plasma results in an increase in the free Ca⁺⁺ in plasma (*if you want to know why, you can read what's written in the box to the right*).

Another example is K⁺. “The concentration of K⁺ is expected to be affected by the concentration of H⁺ since H⁺-K⁺ exchange occurs at the apical membrane of intercalated cells of the distal part of the uriniferous tubule.”

- The normal [H⁺] in plasma is 40 nM → corresponds to pH of 7.4
As a range, the **normal** pH of plasma is **7.35 - 7.45**.
 - Below 7.35 : Acidosis
 - Above 7.45 : Alkalosis
- We can tolerate an increase in [H⁺] up to four times the normal concentration (up to 160 nM → which corresponds to pH that is equal to 6.8).

The difference in this case is 160 - 40 = 120 nM

- We can tolerate a decrease in [H⁺] down to one fourth the normal concentration (down to 10 nM → Which corresponds to pH that is equal to 8)

The difference in this case is 40 - 10 = 30 nM

- It seems like we can tolerate more acidosis than alkalosis (we can tolerate “excess H⁺” more than we can tolerate “less H⁺”).
→ Our bodies are built to efficiently take care of the extra H⁺ added. On the other hand, when alkaline is added to the body, it might not be handled very well.

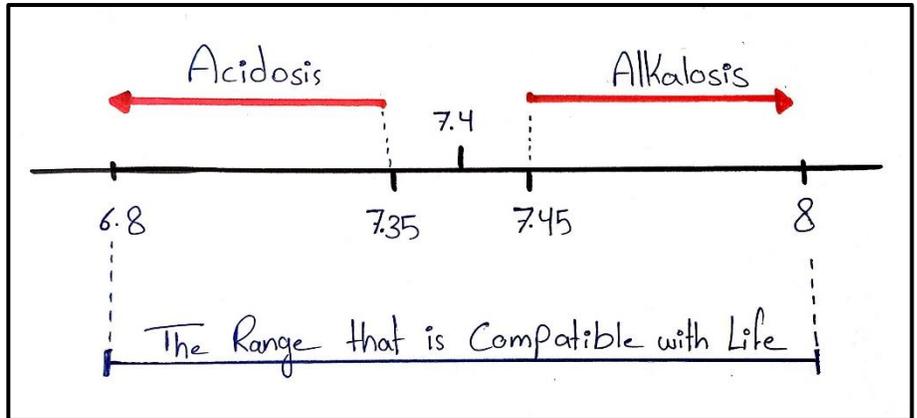
Additional (from the book):

A relationship exists between plasma proteins, H⁺, and calcium (Ca²⁺), which results in changes in ionized Ca²⁺ concentration when there is an acid-base disturbance. (See Chapter 9, Fig. 9-34.) The mechanism is as follows: Negatively charged groups on plasma proteins (e.g., albumin) can bind either H⁺ or Ca²⁺. (Protein-binding of Ca²⁺ is extensive and accounts for 40% of total Ca²⁺.) In **acidemia**, there is an excess of H⁺ in blood. Because more H⁺ is bound to plasma proteins, less Ca²⁺ is bound, producing an increase in free Ca²⁺ concentration. In **alkalemia**, there is a deficit of H⁺ in blood. Because less H⁺ is bound to plasma proteins, more Ca²⁺ is bound, producing a decrease in free Ca²⁺ concentration (hypocalcemia).

Additional pieces of information:

- [H⁺] in plasma is 40 nanomoles/L, or we can say 40 nEq/L.
- an *equivalent* is the number of moles of an ion in a solution, multiplied by the valence of that ion (التكافؤ). If 1 mol of NaCl and 1 mol of CaCl₂ dissolve in a solution, there is 1 Eq Na, 2 Eq Ca, and 3 Eq Cl in that solution. (The valence of calcium is 2, so for that ion you have 1 mole and 2 equivalents).
- A certain amount of univalent ions provides the same amount of equivalents while the same amount of divalent ions provides twice the amount of equivalents. For example, 1 mmol of Na⁺ is equal 1 mEq, while 1 mmol of Ca⁺⁺ is equal 2 mEq.

- The range of pH that is **compatible with** life is between **6.8 and 8**. However, this does not mean that values in this range that are near to 6.8 and 8 are normal. For example, plasma pH of 7 is considered a life-threatening state of acidosis (fatal if not fixed).



- Note: there's no substance in the body that can be handled when its concentration increases up to 4 times its normal concentration, except for H^+ .
For example, we can't tolerate a 4-time increase in $[Na^+]$ or $[K^+]$.

Acidosis and Alkalosis

- The most important buffer in plasma is the Carbonic acid/Bicarbonate buffer (H_2CO_3/HCO_3^-)
***by the end of the lecture, you will be able to justify why we said "MOST IMPORTANT".*
- According to Handerson-Hasselbalch Equation:

$$pH = 6.1 + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

Because H_2CO_3 in the body is present in equilibrium with CO_2 , we can replace $[H_2CO_3]$ in the equation by $[CO_2]$.

$$pH = 6.1 + \log \frac{[HCO_3^-]}{[CO_2]}$$

Mentioned in section 3:

- The plasma contains cations and anions
 - Cations (positively charged ions).
include: Na^+ , K^+ , Mg^{+2} , Ca^{+2} , H^+
 - Anions (negatively charged ions).
- The normal osmolarity of plasma is around 300 mOsmol/L.
 - Cations contribute to 150 mOsmoles.
(Na^+ alone contributes to 140 of these 150 mOsmoles)
 - Anions contribute to 150 mOsmoles.

Quick reminders (additional)

- the **osmole (Osm or osmol)** is a unit of measurement that defines the number of moles of solute that contribute to the osmotic pressure of a solution.
For example, a solution of 1 mol/L NaCl corresponds to an osmolarity of 2 osmol/L. The NaCl salt particle dissociates fully in water to become two separate particles: an Na^+ ion and a Cl^- ion. Therefore, each mole of NaCl becomes two osmoles in solution, one mole of Na^+ and one mole of Cl^- . Similarly, a solution of 1 mol/L $CaCl_2$, gives a solution of 3 osmol/L (Ca^{2+} and 2 Cl^-).
- Osmolarity is defined as the number of osmoles (or mOsmol) per liter of solvent.



Usually, CO₂ is reported as partial pressure (P_{CO2}). But we can't divide a concentration (mmol/L) by a pressure (mmHg). Thus, we use a conversion factor which is (0.03) → [CO₂] = P_{CO2} * 0.03

The final equation is:

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{\text{P}_{\text{CO}_2} * 0.03}$$

- Knowing that the normal [HCO₃⁻] in plasma = 24 mmole/L, and the partial pressure of arterial CO₂ is 40 mmHg :

$$\begin{aligned} \text{pH} &= 6.1 + \log \frac{24}{40 * 0.03} \\ &= 6.1 + \log 20 \\ &= 6.1 + 1.3 \\ &= 7.4 \end{aligned}$$

Values to memorize:

pK for the bicarbonate buffer system is 6.1

Normal [HCO₃⁻] in plasma = 24 mmole/L.

Normal partial pressure of arterial CO₂ = 40 mmHg.

- From this equation, can you predict the conditions (regarding the concentration of HCO₃⁻, and the P_{CO2}) that would cause a decrease in the pH?

1. A decrease in [HCO₃⁻] → causes “**Metabolic Acidosis**”

For example, let's assume that [HCO₃⁻] became 12 instead of 24, and P_{CO2} remained the same as normal:

$$\text{pH} = 6.1 + \log (12/1.2) = 6.1 + 1 = 7.1 \dots\dots \text{“Acidosis”}$$

OR

2. An increase in P_{CO2} → causes “**Respiratory Acidosis**”

For example, let's assume that P_{CO2} became 80 instead of 40, and [HCO₃⁻] remained the same as normal:

$$\text{pH} = 6.1 + \log (24/ (80*0.03)) = 6.1 + 1 = 7.1 \dots\dots \text{“Acidosis”}$$

Important note: the effect on the pH is determined by the RATIO of the base to the acid, not the absolute concentrations. For example, if both values; [HCO₃⁻] and P_{CO2} decreased to the half, the ratio of the base to the acid will stay the same. Thus, pH will remain the same (7.4):

$$\text{pH} = 6.1 + \log (\underline{12}/ (\underline{20}*0.3)) = 6.1 + \log 20 = 6.1 + 1.3 = 7.4$$

- By the same principle used in the previous point, can you predict the conditions (regarding the concentration of HCO₃⁻, and the P_{CO2}) that would cause an increase in the pH?

1. An increase in [HCO₃⁻] → causes “**Metabolic Alkalosis**”

2. A decrease in P_{CO2} → causes “**Respiratory Alkalosis**”

❖ Types of acids produced in the human body

Acids produced in the human body are of two types:

(1) Volatile acid (CO₂)

- From the book: “CO₂, or volatile acid, is the end product of aerobic metabolism in the cells. CO₂ itself is not an acid. However, when it reacts with water (H₂O), it is converted to the weak acid (H₂CO₃).”



→ If you add too much CO₂, the reaction will shift to the right resulting in the production of more H⁺ (tendency for acidosis).

- Everyday, the body generates about 10 moles (10,000 millimoles) of CO₂. We do not worry about these 10,000 millimoles because they get removed through the lungs (during expiration).

(2) Non-volatile (non- CO₂ acids) → also called (Fixed acids)

- Examples:
 - Sulfuric acid (H₂SO₄), which can be generated from the metabolism of proteins with the sulfur-containing amino acids (e.g., methionine, cysteine, cystine).
 - Phosphoric acid (H₂PO₄⁻), which can be generated from phospholipids.
 - Acetoacetic acid.
 - β-Hydroxybutyric acid
 - Lactic acid
- Fixed acids are produced in an amount that approximately equals 1 millimole per Kg body weight per day (1 mmol/Kg/D)
 - In an 80-kg individual, 80 millimoles of fixed acids are produced every day.

Additional (from the book):

Fixed Acid

Catabolism of proteins and phospholipids results in the production of approximately 50 mmol/day of fixed acid. Proteins with the sulfur-containing amino acids (e.g., methionine, cysteine, cystine) generate **sulfuric acid** when they are metabolized, and phospholipids generate **phosphoric acid**. In contrast with CO₂, which is volatile and will be expired by the lungs, sulfuric acid and phosphoric acid are *not* volatile. Therefore, fixed acids first must be buffered in the body fluids until they can be excreted by the kidneys.

In addition to sulfuric and phosphoric acids, which are produced from *normal* catabolic processes, in certain pathophysiologic states, fixed acids can be produced in excessive quantities. These fixed acids include **β-hydroxybutyric acid** and **acetoacetic acid**, both ketoacids that are generated in untreated diabetes mellitus, and **lactic acid**, which may be generated during strenuous exercise or when the tissues are hypoxic. In addition, other fixed acids may be ingested, such as **salicylic acid** (from aspirin overdose), **formic acid** (from methanol ingestion), and **glycolic** and **oxalic acids** (from ethylene glycol ingestion). Overproduction or ingestion of fixed acids causes metabolic acidosis, as discussed later in the chapter.

“In contrast with CO₂, which is volatile and will be expired by the lungs, fixed acids are not volatile. Therefore, they first must be buffered in the body fluids until they can be excreted by the kidneys.”

details later, but keep this sentence in your mind please

- By the end of the day, the amount of acid generated:
 - 10,000 mmole, in form of CO₂ → easily removed (by the lungs)
 - 80 mmole, in the form of fixed acids → very difficult to remove

Note: in the remaining part of this lecture, and in the next lecture, we are concerned with the removal of these 80 mmoles.

❖ The kidneys and bicarbonate (HCO₃⁻)

I. Why do we need the bicarbonate?

- The problem we are facing is that: everyday, 80 millimoles of H⁺ (from fixed acids) are added to the ECF and these need to be removed. Why?
 - In the body, we have 14 L as the Extracellular Fluid Volume (ECFV).
 - (80 mmol/14 L) → approximately 5.5 mmol/L, is the concentration of H⁺.
 - 5.5 mmol/L of H⁺ corresponds to a pH that is around 2.5, which is not compatible with life.
 - The previous means that everyday, the body faces a life-threatening situation of acidity that -if not fixed- would shift the pH to a very low value that is not compatible with life.
- We will mention the mechanisms by which the body deals with these 80 millimoles in the following section (the three lines of defense), but first, keep the following principle in your mind during the rest of the lecture.
 - Since the problem is having 80 millimoles of H⁺/day. What do you expect to happen if we also have 80 millimoles of HCO₃⁻ ?
$$80 (1 \text{ mmol H}^+ + 1 \text{ mmol HCO}_3^-) \rightarrow 80 (1 \text{ mmol H}_2\text{CO}_3)$$
$$\rightarrow 80 (1 \text{ mmol CO}_2 + 1 \text{ mmol H}_2\text{O})$$

CO₂ can be washed out by the lungs.
 - It seems like adding 80 mmoles of HCO₃⁻ can solve the problem
(in fact, solving the problem is not that simple. It requires the three lines of defense we'll discuss later, but as I said, just keep this principle in your mind).

$$[\text{H}^+] = 5.5 \text{ mmol/L} = 5.5 * 10^{-3}$$

$$\text{pH} = - \log (5.5 * 10^{-3})$$

$$= - \{ \log 5.5 + \log 10^{-3} \}$$

By logic and approximation:

$$= - \{ 0.5 + -3 \}$$

$$= 2.5$$

- We solved the problem of H^+ , and ended up having another problem: Do we have enough HCO_3^- ? In other words, what is the bicarbonate reserve (“bank”) in the body?

$[HCO_3^-]$ in plasma = 24 mmol / L

ECFV = 14 L

You should memorize the previous two values.

➔ $24 * 14 = 336$ mmole of HCO_3^- (for simplicity, consider it 340)

We said that we need 80 millimoles per day, this means that this amount of bicarbonate is enough only for 4-5 days ($340/80 = 4.25$ days).

** The amount of HCO_3^- in the ECF is limited and is enough only for 4-5 days. What should we do after these 4-5 days?!

➔ We need a better solution. This solution is : synthesis of NEW 80 millimoles of HCO_3^- everyday. (and the 340 in the ECF remain as a reservoir).

This function is carried out by the Kidneys. ***details later***

II. Functions of the kidneys when it comes to acid-base balance

(1) Reabsorption of the bicarbonate that gets filtered (*most important*)

- Bicarbonate is freely filtered in the kidney:

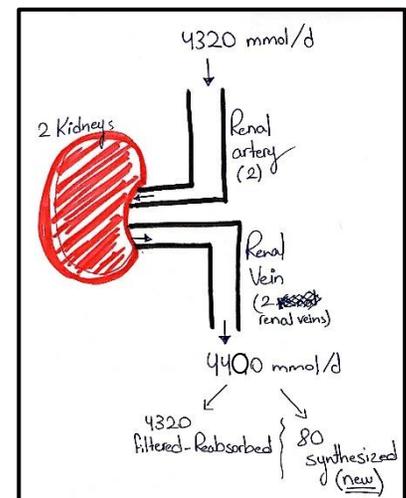
$$\begin{aligned} \text{Filtered Load of } HCO_3^- &= \text{GFR} * [HCO_3^-] \text{ in plasma} \\ &= 180 \text{ L/Day} * 24 \text{ mmol/L} \\ &= 4320 \text{ mmol/Day} \end{aligned}$$

- HCO_3^- is important for the body, so we expect the kidneys to reabsorb (retain) these 4320 mmol/day.

(2) Make new HCO_3^- (gain)

So if 4320 mmoles enter the kidneys everyday through the renal arteries, we need 4400 mmoles ($4320 + 80$) to leave the kidneys everyday through the renal veins.

Note: although 80 mmoles is a small value compared to the 4320 mmoles, these 80 mmoles are very important, because as we said earlier, if the kidneys can make 80 mmoles NEW bicarbonate, then we can fight the 80 mmoles of acid.



(3) Eliminating H^+ from the body by certain mechanisms. (*but not as free H^+*)

➔ How does the kidney accomplish functions (2) and (3)? ➔ *the topic of the next lecture.*

III. ليش الغلابة؟

- The problem we are facing is the 80 mmoles of H^+ . You might ask yourself: "Why not excrete these 80mmoles of H^+ in the urine (as free H^+)?"

ليش نصنع بايكربونات تعادل أيونات الهيدروجين و بعدها نتخلص من ثاني أكسيد الكربون؟
ليش ما من البداية نطلع أيونات الهيدروجين من الجسم زي ما هي من خلال الكلية؟

The answer is simply: "because the kidneys CANNOT do that" (cannot excrete the 80 mmoles of H^+ (in the free form) in the urine).

Justification

- Two parts of the uriniferous tubule play a role in Excretion of H^+ (as H^+):
 - The proximal part
In this part, secretion of H^+ occurs in exchange with Na^+ (**secondary** active transport).

Secondary active transport does not utilize ATP directly. Therefore, it can result in making the concentration gradient of H^+ across the luminal membrane 5-6 times only.

(5 times higher in the lumen compared to the inside of the cell).

- **pH intracellularly = 7 (not 7.4)**
- pH = 7 corresponds to $[H^+] = 10^{-7}$ (intracellularly)
- 5 times higher concentration of H^+ in the lumen of the proximal part means that $[H^+]$ in the lumen = $5 * 10^{-7}$
- $[H^+] = 5 * 10^{-7}$ corresponds to pH that is approximately 6.5

Extra:

(you can skip it because I'm not sure if it's 100% accurate)

Since the process is **secondary** active, it is dependent on the potential energy released by the downhill movement of Na^+ from the lumen to the cell. (not dependent directly on ATP)

- ➔ As a result, the final gradient of H^+ that will result is small (less than 10 times) compared to the gradient that can be generated when the process is **primary** active (driven by ATP), as the case in the distal part.

لو العملية بتعتمد عال ATP، بنقدر نستعمل كميات كبيرة (و لكن إلى حد معين) من ال ATP لضخ أيون الهيدروجين، وبالنهاية ينتج فرق كبير في تركيز أيون الهيدروجين.

أما إذا العملية محكومة ب "فرق التركيز للصوديوم"، فالفرق في تركيز الصوديوم هو اللي رح يحدد أقصى فرق في تركيز أيون الهيدروجين ممكن نحصل عليه، و سيكون أقل من الحالة السابقة، لأنه حنوصل لمرحلة معينة توقف عندها حركة الصوديوم و بالتالي توقف حركة أيون الهيدروجين بالاتجاه المعاكس.

Note: since the proximal part does not affect the pH by a considerable amount, and since the last modification of the tubular fluid occurs in the distal part (collecting duct), we will focus on the changes that occur in the distal part only (see the next page).

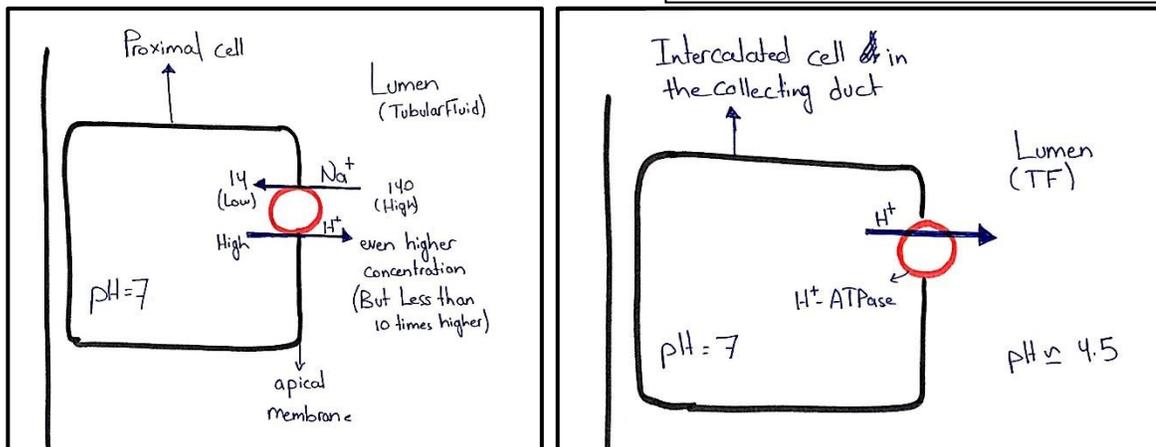
➤ The distal part (collecting duct)

The intercalated cells of this part secrete H^+ actively. The process is **primary** active transport.

Because the process is primary active, it can result in making the $[H^+]$ in the tubular fluid of the collecting duct 900 times higher than the intracellular $[H^+]$.

→ pH of the tubular fluid at this level is 4.5.

- pH intracellularly = 7
- pH = 7 corresponds to $[H^+] = 10^{-7}$ (intracellularly)
- 900 times higher concentration of H^+ in the lumen of the proximal part means that $[H^+]$ in the lumen = $900 * 10^{-7} = 9 * 10^{-5}$
- $[H^+] = 9 * 10^{-5}$ corresponds to pH that is approximately 4.5



- pH of the urine never goes below 4.5 because the capacity (strength) of the hydrogen pump at the luminal side of the intercalated cells of the distal part of the tubule can only make the H^+ concentration gradient 900 times higher in the tubular fluid than intracellular $[H^+]$, but not more than 900 times.
900 times gradient across the membrane corresponds to pH that is near 4.5 in the tubular fluid.
- **Since the lowest possible pH of the urine is 4.5:**
 - pH = 4.5 corresponds to $[H^+] = 9 * 10^{-5}$ mole/L
= $9 * 10^{-2}$ mmole/L
= 0.09 mmole/L (less than 0.1 mmole/L)
 - Let's consider it 0.1 mmole/L. *Let's assume that an individual excretes 1 L of urine in the day*, this means that only 0.1 millimoles of H^+ could be excreted in the urine as H^+ in the day.
Remember, we are facing a bigger problem (80 mmoles), so we still have 79.9 mmoles that need to be removed.
 - That's why we said "the kidneys cannot excrete the 80 mmoles of H^+ (in the free form) in the urine".
- **Conclusion:** we need to deal with the 80 mmoles of H^+ by another practical way.
(In brief, we should attach the H^+ to "something", until the kidneys or the lungs continue the job).

❖ How does the body deal with acidity? (Three Lines of Defense)

**Recall (from the CVS): blood pressure regulation involves three lines of defense. See table (1).

	Type	Speed	Function
First Line	<u>Neural</u> (Baroreceptors)	Fast (fractions of a second)	The function of the first line is to “absorb the shock” (ياكل الضربة). For example: in a patient who has undergone bleeding that resulted in hypotension, the baroreceptors will respond within fractions of a second. Baroreceptors -through the autonomic nervous system, particularly, the sympathetic outflow- will cause vasoconstriction. Thus, the unstressed volume gets less, leading to an increase in the blood pressure. However, they do not replace one single drop of plasma, nor one single RBC. <i>Note: in case you want to refresh your memory, you can read pages 178-179 from Costanzo.</i>
Second Line	<u>Hormonal</u> (Renin-Ang.-Ald. system)	Intermediate speed	Aldosterone causes retention of more Na ⁺ , thus, more water is reabsorbed. (this line replaces some fluid (plasma), but not RBCs).
Third Line	<u>Renal</u> (Release of Erythropoietin “EPO” from the kidneys)	Very slow, but the most important (it is the line that can win the war).	EPO stimulates erythropoiesis resulting in increased number of RBCs.

** A similar principle applies here in our topic. There are three lines of defense against acid or alkaline, but we are more concerned with dealing with acidosis than alkalosis. See table (2).

Note: it is easier for the body to fight/manage acidosis than alkalosis.

	Type	Speed	Function
First Line <i>(discussed in the next few pages)</i>	<u>Buffers</u>	Very Fast (start working within fractions of a second, and give the full response in less than a minute).	Buffers do not eliminate H ⁺ from the body, not even one H ⁺ . They only tighten H ⁺ (mask it) temporarily, until other mechanisms (respiratory/renal) remove the H ⁺ from the body.
Second Line	<u>Respiratory System</u>	Intermediate speed (starts working in few minutes, and gives the full response in few {1 or 2} hours).	Eliminates some of the H ⁺ , but not completely.
Third Line <i>(will be discussed in the next lecture)</i>	<u>Renal</u>	Very slow, (it takes hours to start working, and 5 days to give you the full (maximum) response). But it is the most important line (it is the line that we depend on for returning pH to the normal range).	Eliminates H ⁺ and corrects the whole situation. <i>**Don't forget the functions of the kidneys when it comes to acid-base balance (page 10).</i>

The role of Buffers as the first line of defense

- Let's assume for example, that a certain individual generates too much acids (280 mmols instead of 80 mmols) due to a specific cause like diabetic ketoacidosis or ingestion of several tablets of aspirin (*source of salicylic acid*). Who is going to take care of such high amounts of acid?
- **The first step** is always to prevent a marked shift of the pH of the blood to a level which is not compatible with life, when acid is added. (we must prevent pH from going down below 6.8).

Mentioned in section 3:

If a marked shift of pH occurs (whether an increase or decrease), enzymes of the body will be affected, most importantly, enzymes of the CNS.

For example, too much acid causes suppression of certain enzymes in the CNS, leading to coma and possibly, death.

This is the function of **BUFFERS** → they will **tighten** the H^+ , thus, prevent a marked change in the pH of plasma. However, they **will NOT eliminate** H^+ from the body.

- For the following discussion, we are concerned with three main buffers:
 - Proteins
 - Dibasic/Monobasic phosphate ($HPO_4^{-2}/H_2PO_4^-$)
 - Bicarbonate/Carbonic acid (HCO_3^-/H_2CO_3)
- There are three criteria that determine which of the previous is the strongest buffer in plasma (the buffer that plays the major role in the buffering action in the plasma); the absolute concentration, pK of the buffer, and the renewal ability.

Additional (from the book)

“Intracellular proteins serve as buffers because they contain a large number of acidic or basic groups such as $-COOH/-COO^-$ or $-NH_3^+/-NH_2$.”

(1) The absolute concentration

Proteins are more concentrated than the other two, especially, intracellularly.

→ Thus, in terms of concentration, proteins are the most important, followed by bicarbonate ($[HCO_3^-]$ in plasma = 24 mmol/L) followed by phosphate (the concentration of phosphate (HPO_4^{-2}) in plasma is 1.2 mmol/L).

(2) pK

- What is pK?

When $[Acid] = [Base] \rightarrow pH = pK + \log 1 \rightarrow pH = pK$

$$pH = pK + \log \frac{[A^-]}{[HA]}$$

pK is the pH of the solution when the concentration of the acidic form of the buffer is equal to the concentration of the basic form. ($[Acid] = [Base]$).

- The figure to the right shows the “Titration Curve” of the Bicarbonate/Carbonic acid buffer.

➤
$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{[\text{CO}_2]}$$

- (A): At $\text{pH} = \text{pK} = 6.1$:
 → $[\text{Acid}] = [\text{Base}] = 50\%$

(B): The more the added base (HCO_3^-), the higher the pH {more alkaline}.

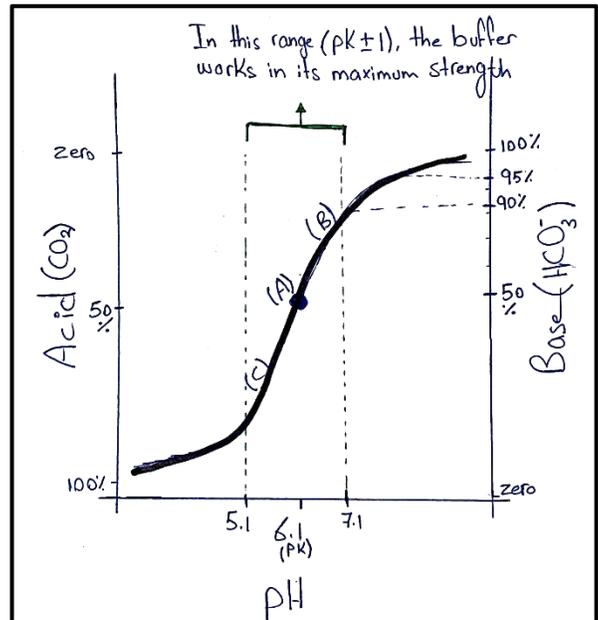
(C): The more the added acid (CO_2), the less the pH {more acidic}.

- Note that the relation is sigmoidal.
 As a result, in the range of pH that is between 5.1 ($\text{pK} - 1$) and 7.1 ($\text{pK} + 1$), the strength of the buffer is the maximum.

For example, if you are at point (A) where $[\text{Acid}] = [\text{Base}] = 50\%$, and you added too much base, up to 90%, the shift in the pH will be minimal (the new pH will be 7.1, which is still near to the pK).

However, beyond this point (7.1), any additional amount of the base -even if minimal- will cause a marked shift in the pH. For example, if the concentration of the base was 90%, and you increased it only to 95%, a considerable shift in the pH will occur (from 7.1 to 10)

***The previous numbers in the example, and the drawn figure are not necessarily accurate. Just focus on the principle.*



From the book:

A striking feature of the titration curve is its sigmoidal shape. In the **linear portion of the curve**, only small changes in pH occur when H^+ is added or removed; the most effective buffering occurs in this range. The linear range of the curve extends 1.0 pH unit above and below the pK ($\text{pK} \pm 1.0$). Therefore, the most effective physiologic buffers will have a pK within 1.0 pH unit of 7.4 (7.4 ± 1.0). Outside the effective buffering range, pH changes drastically when small amounts of H^+ are added or removed.

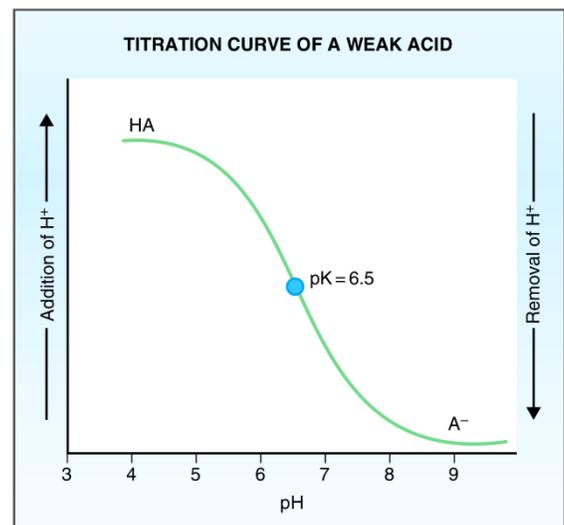


Figure 7-2 Titration curve of a weak acid (HA) and its conjugate base (A^-). When pH equals pK, there are equal concentrations of HA and A^- .

- The strength of the buffer (ability to fight added acids and bases) is the maximum when the pH of the surrounding solution is close to the pK of that buffer (pH range : pK-1 → pK+1).

In other words, **in terms of pK, the best buffer is that which has a pK value that is close to the pH of the surrounding solution.**

- We conclude from the previous discussion that: if we want to have a buffer in the plasma, it is better to be a buffer with a pK that is near to the physiologic pH (7.4). If the pK is 7.4, then we can add considerable amounts of acid or base and the shift in pH will be minimal.

- In terms of pK:

- **Proteins** → pK is around 7 (very close to the intracellular pH). Thus, proteins are good intracellular buffers.

- **Phosphate buffer** → pK = 6.8 (very close to the intracellular pH).

Note: Proteins and phosphate are more concentrated intracellularly and they are very good intracellular buffers (can buffer H⁺ if it enters). However, entry of H⁺ to the cells is difficult because it's charged. That's why we are more interested in ECF buffers.

- **Bicarbonate buffer** → pK = 6.1 (away from the physiologic pH of the ECF).

***In terms of pK, the phosphate buffer is better than the bicarbonate buffer.*

- In section 3, Dr. Yanal said that we can say that the second criterion is “The **Relative Concentrations**” ([Base]/[Acid]).

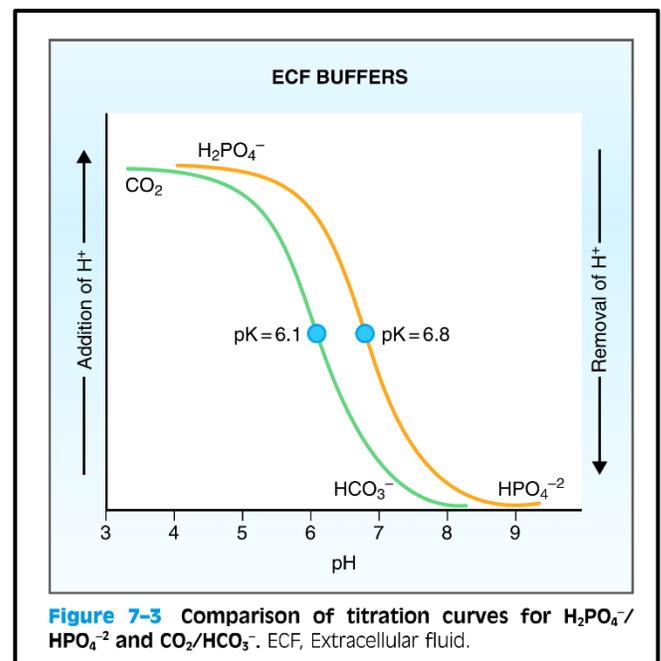
Extra:

I think he considered the relative concentration to be representative of the pK, because according to Handerson-Hasselbalch equation, the pK of the buffer affects its relative concentration ([Base]/[Acid]) in plasma. Not sure though).

$$pH = pK + \text{Log} ([\text{Base}]/[\text{Acid}])$$

$$7.4 = pK + \text{Log} ([\text{Base}]/[\text{Acid}])$$

$$\text{Log} ([\text{Base}]/[\text{Acid}]) = 7.4 - pK$$



(3) **Renewal ability** (*the most important factor determining the strength of any buffer*).

- If we consume **phosphate** in the “buffering function”, we will need more phosphate. Getting more phosphate is difficult because phosphate is ingested (we can't renew phosphate for buffering by breaking down the bone for example). In fact, the buffering function of phosphate is a peripheral (not central) function.
- A Similar principle applies to the **proteins**: The buffering action of proteins is a peripheral function.
- What about the **bicarbonate**??
Bicarbonate is present specifically for the purpose of buffering (مخلوقة لهالشغلة).
If you need more HCO_3^- (new 80 millimoles) instead of the consumed, the kidney will give you what you wish for :D.
In fact, the kidneys can provide up to 500 millimoles of new bicarbonate per day, not only 80 millimoles.
➔ No matter what you eat, drink, or exercise (source of lactic acid), you should not develop acidosis -if you are healthy-.

Bicarbonate Buffer is the most important buffer in plasma.

Phosphate Buffer

- Not a good buffer in plasma (although its pK is closer to 7.4 compared to the bicarbonate). Why?
 - Its absolute concentration in plasma is low (approximately 1 mmol/L)
 - If it is consumed in buffering, it will not be renewed -by breaking bones for example- to compensate what has been used.
- The phosphate buffer is important (is a good buffer) in two locations:
 - Intracellularly
 - In the tubular fluid in the kidney. Why?
 1. pH of the tubular fluid is 6.5 (*remember when we talked about pH in the proximal part*). 6.5 is very close to the pK (6.8).
 2. 90% of the phosphate gets reabsorbed, while 99% of the water gets reabsorbed → this means that phosphate concentration increases 10 times in the tubular fluid.

Note (mentioned in section 3): how can you tell -by the clinical presentation- if a patient has acidosis? The patient would be **hyperventilating**.

A small correction (in sheet 1): in page 9, point (B), the last line. *It is mentioned that $[\text{Na}^+]$ in plasma is 145 mmol/L.* → it should be 140 mmol/L, so correct it please, and sorry for any other mistakes.

At the end of the lecture, Dr. Yanal summarized the lecture by the following key points:

- The major threat the body faces during the day is the addition of **80 millimoles of non-volatile acids**. (*our bodies have tendency towards acidosis*).
- The solution for this problem is to tighten them, then eliminate them.
- We need bicarbonate to counterbalance these acids.
The problem is that we do not have enough bicarbonate reserve in the body. However, one of the functions of the kidney is to make new bicarbonate.
- For fighting the acids added to the body, we need three lines of defense:
 - Buffers (the fastest)
 - Respiratory system (intermediate speed).
 - Renal system (the slowest) → will determine the final result (will the problem be solved eventually or not?)
- Three criteria determine the best buffer; absolute concentration, relative concentration (or pK) and the renewal ability.
→ We concluded that the most important buffer in plasma is the bicarbonate.
- The final outcome (acidosis/no acidosis) depends also on the type of the cause (acute or chronic), because the kidney needs days to give the full response. For example, if a person ingests too much aspirin, he might die because the acidosis may occur very fast, before the kidneys get the chance to try to fix the problem.
- If a person develops ketoacidosis for example, this means that
 - Either his body is forming too much acids, beyond the capacity of the kidneys.
 - Or, the acidosis occurred very fast, before the kidneys got the chance to compensate.

أفخم دفعة بالحياة ..

شكراً على كل كلمة طيبة، كل جملة حلوة، و كل موقف لا يُنسى..

شكراً لكم جميعاً على كل شيء..

و أخص بالذكر: جود المجالي، ندى حجاج، بيان نضال، هيا يانس، سجي الخليلة، أسماء الكيلاني، دانا رضا، رغد بطاينة، وسن الشراعية، دعاء الهلالات، سارة الرفايعة، دانية الحاج ياسين، زين القضاة، مريانا نصير، و تالا العبدللات،

اللي بفضل الله و بسببهم، كانت سنين البيسك أحلى ما يكون ♥

This is probably my last sheet to write in the basic years.

I apologize for any mistake I made.

Wish you all best of luck :D