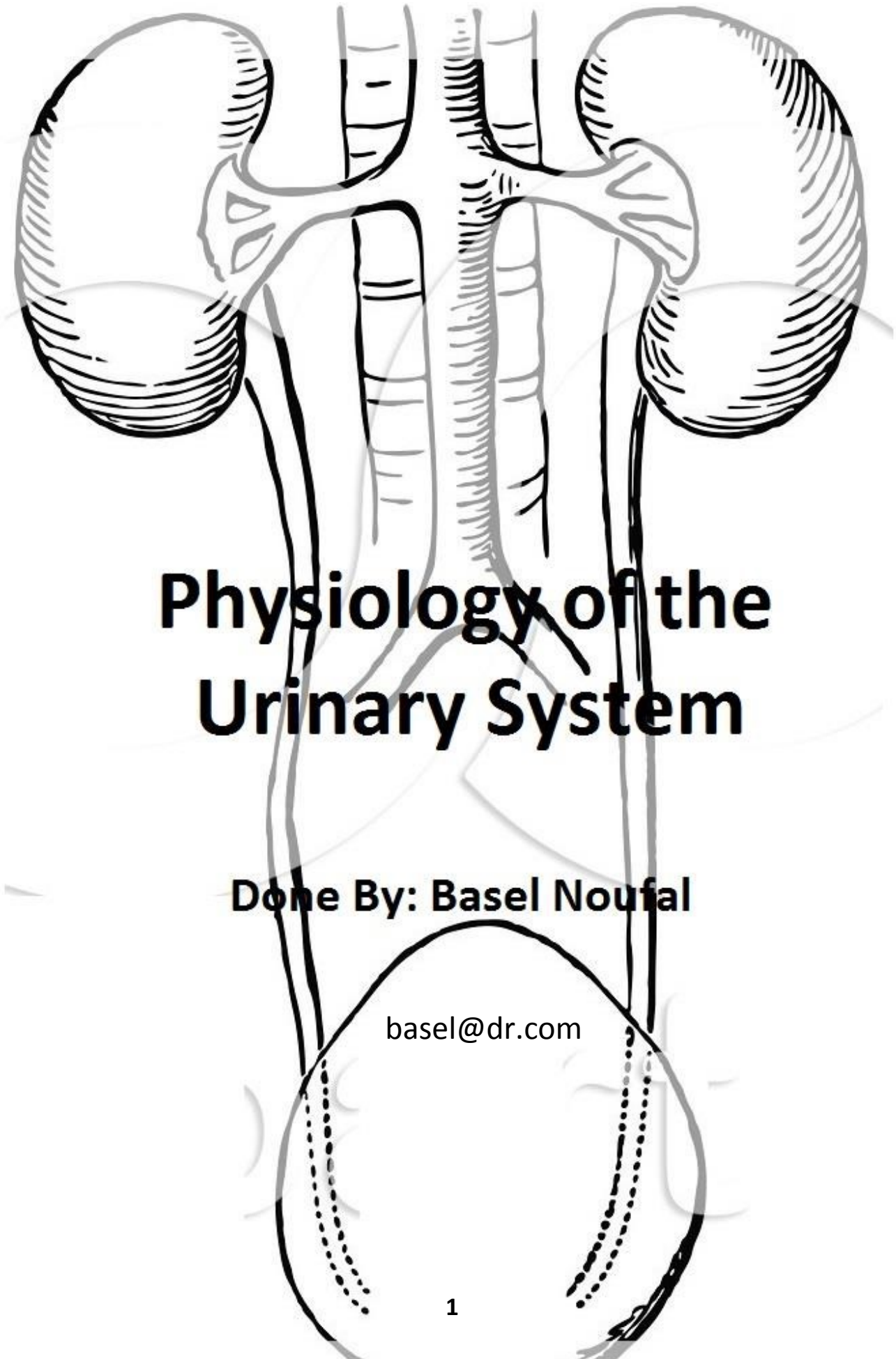


Physiology of the Urinary System

Done By: Basel Noufal

basel@dr.com

Corrected and modified by Yanal A. Shafagoj MD. PhD

Textbook of medical physiology, by A.C. Guyton and John E, Hall•

If you prefer to study from textbook, I'II send you the outline

Acid- Base Balance

Lecture (9)

INTRODUCTION:

An acid is a proton donor, while a base is a proton acceptor.

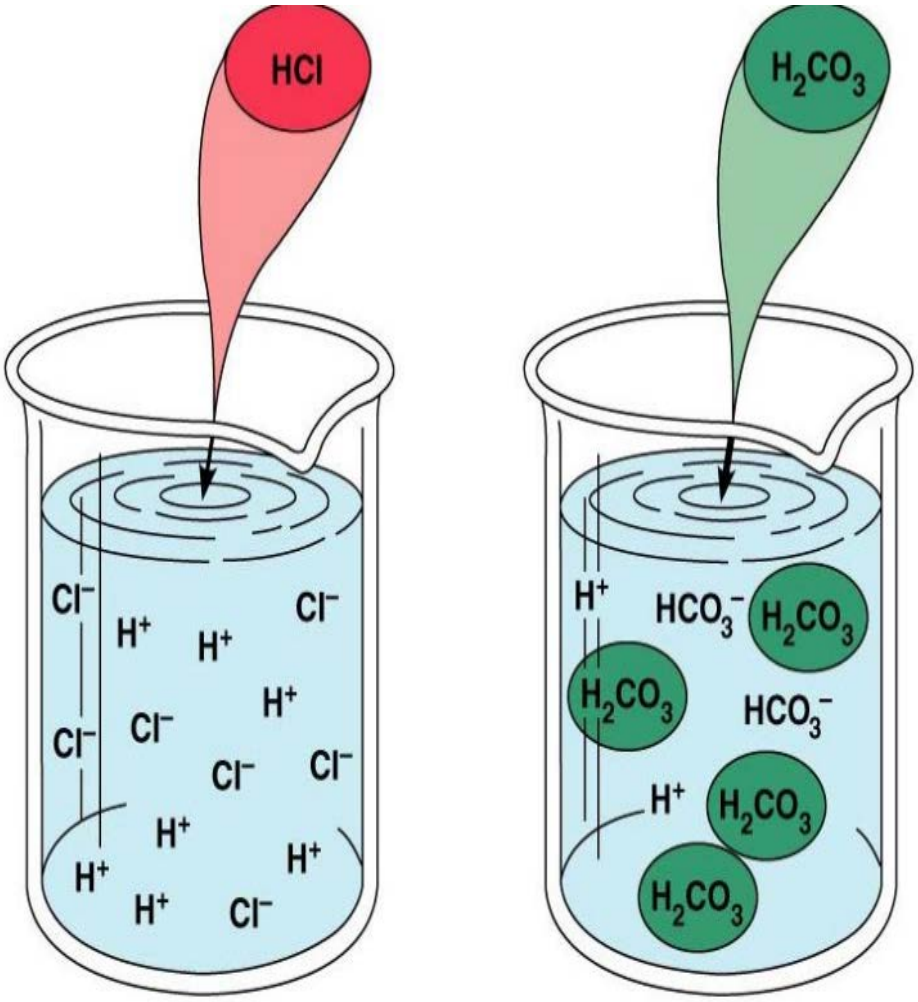
Strong acids or bases dissociate (ionize) completely in solution such as HCl and NaOH.

Weak acids ionizes only partially in a solution: such as H2CO3.

Weak bases also partially ionize such as NaHCO3- or HPO_4^{-2}.

Most of our body acids and bases are weak acids and weak bases

(Note : Hemoglobin and other body proteins are of the most important body bases).



Normally the [H+] in the body fluids is kept at a low level, its concentration in the extracellular fluid is about 40nM/L (ranges from 4 times less (10 nM/L) to 4 times more than normal (160 nM/L) (16 times difference). The body can tolerate a greater increase of H+ from 40 to 160nM/L (120 nM difference) than a decrease from 40 to 10nM/L in the [H+] (30 nM difference). Our body defense mechanisms are ready to deal with attacking acids more than with attacking alkali!!!!

Compare plasma [H+] to [Na+]: [Na+] = 145 mM/L

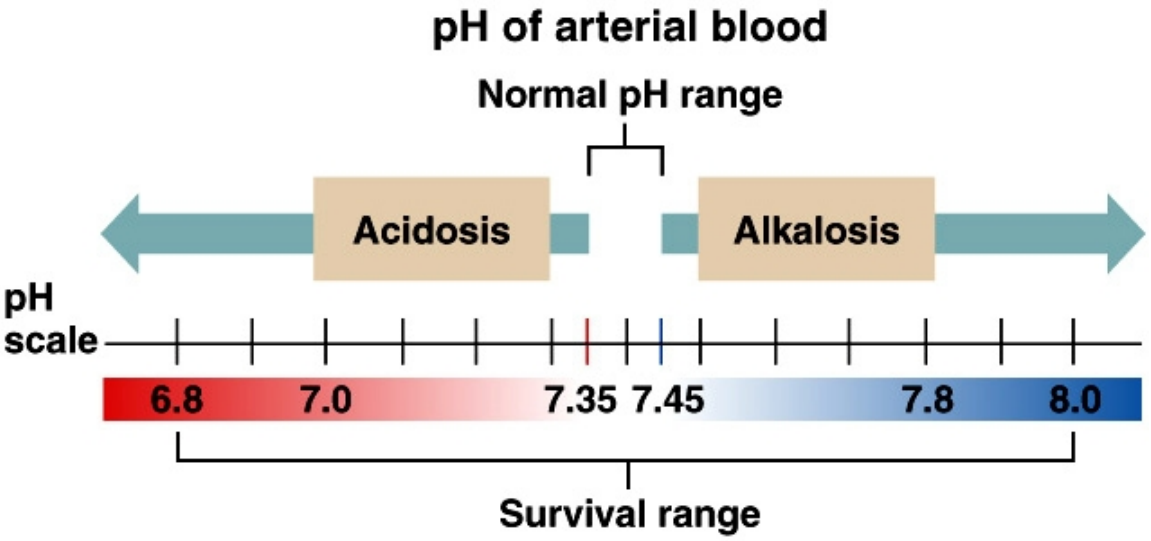
[H+] = 40 nM/L

[Na+] is 3.5 million times more than [H+]. So small in concentration, but still we need 2-3 lectures to discuss it.

[H+] : the only ion that can vary widely from 10-160 nM (16X). For example, if [K+] increases twice its normal concentration, it might stop the heart.

- Normal arterial plasma pH ranges from 7.35-to-7.45

- Venous blood and interstitial fluid pH = 7.35 due to excess CO2
- Intracellular pH ranges from 6.0 – 7.4 (In general 7.0 is the average).
- Urine pH ranges from 4.5 – 8. Usually (avg, 5.5), so urine is acidic
- Below 7.35 is acidosis, and above 7.45 is alkalosis
- pH range compatible with life is between 6.8 - 8.0, below 6.8 or above 8.0 means death.



- However acidosis and alkalosis (between 6.8-8) can produce major disturbances and have dramatic effects on normal cell function

1. Influences enzyme activity. Most enzymes function properly at their optimal pH.

Acidosis → suppression of CNS enzymes → coma → death.

alkalosis → convulsions of the respiratory muscle → death.

2. Affects hormones.

3. Affects electrolyte balance (Na+, K+, Cl-, Ca++).

4. Changes in excitability of nerve and muscle cells.

FACTS

Due to our normal metabolism, our body has tendency towards acidosis rather than alkalosis. We make more acids, normally.

- Acids taken with foods.
- Acids produced by metabolism of lipids, carbohydrates and proteins.
- Cellular metabolism produces CO_2.

$CO_2 + H_20 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$

Defense against changes in hydrogen ion concentration:

Our body is at a constant threat of becoming acidic, so how does it deal with these acids?

1. First Line of defense: Chemical acid-base buffer system (Very Fast…instantaneous)
2. Second Line: The respiratory center (by removing or retaining CO2: intermediate speed, few minutes to start reacting and few hours to reach its maximum and full response)
3. Third Line: The kidneys (the most powerful regulatory system), a slow system that takes a few hours to start working and 3-5 days to reach full response.

So, in acute acidosis, the kidney might not be able help, it needs time to be able to help.

Acids in our body are of two types: volatile acids and Non-volatile acids.

1. Volatile Acids:

The volatile acids are in the form of H_2CO_3 (CO2), removed through the lung. Normally we exhale 300 L of CO_2/D, which corresponds to daily production of 10 M H^+ **(huge amounts), but usually it does not cause problems because it is always getting engaged in this pathway:**

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

CA: carbonic anhydrase enzyme fits here.

- * If more H+ is produced in your body: reaction shifts to left and CO2 will be eliminated by the lungs. Therefore, acidosis is corrected.

* If [H+] is less than normal, reaction shifts to the right; respiration is depressed and more CO2 is retained → forming H+ to correct alkalosis

Note: "CO2 is considered as masked H+"

2. The Non-volatile acids (Fixed Acids):

Those acids are fixed since we cannot remove through the lung.

- Such as phosphoric acid from oxidation of phosphoproteins, phospholipids, and nucleic acid.
- Sulphoric acid → oxidation of methionine and cysteine
- Others: lactic acid, pyrovic acid, beta-OH butyric acid, acetoacetic acids, and Krebs cycle acids.

All these acids are not in the form of CO2 (non volatile…cannot be removed by the lungs.

What threat our body is facing each day?

- Our body produces around 1 mmol/kg/day of fixed acids.
- So, 80 mmol/day are being produced in a 80 kg body weight person. This is large amount of acids and can shift our body pH to very low level (incompatible with life). Let me explain this: we have 14 lit as ECF volume. If 80 mM are distributed in 14 lit (ECF volume), the final concentration would be 5.5 mM/l ($5.5*10^{-3}$ M/l correspond to pH less than 3…is this low pH compatible with life?)

Yet, those 80 mmole shift our body pH just slightly. How come? We have two ways to handle this problem:

- First: can the kidney secrete the 80 mM of H+ in its free form in the urine?

- The minimal urine concentration of H^+ that can be achieved by the collecting ducts is only 0.03 mEq/L (i.e., minimal urine pH = -log (3×10^{-5}) = 4.5). Thus, for a person to excrete all the 80 mEq of H+, 2667 liters of urine must be excreted per day! This mechanism does not work…let us see the second one.

- Second: By buffering the H+ with buffers such as bicarbonate (HCO_3-)

  The second option is to add 80 mmole of HCO3- from the ECF and convert it to CO2, and let the lung take care of it.

  - CO2+ H2O ↔ H2CO3 ↔ 80 mM H+ + 80 mM HCO3-

If we add 80 mM of bicarbonate, you end up with 80 mM HCO_3^- which dissociate to 80 mM of CO2, and lungs this CO2. It seems like this scenario works. However, the price we paid is: we lost 80 mM of bicarb (HCO_3^-) from our body. The question comes now; How much bicarb reserve we have in our body?. ECF [HCO_3^-] = 24 mEq/l. Since we have 14 lit as ECF volume…let us make the calculation:

14*24=336. This amount is enough to buffer fixed acids (H+) for 5-6 days only. In the seventh day, ECF pH shifts dramatically. The truth is: pH does not shift. The reason is the kidneys supply our body with 80 mmole of new bicarbonate each day and the

problem has been solved… we get rid of these acids by converting them to CO2. **In AKI (Acute kidney injury): Acidosis occurs because Kidneys fail to produce new bicarbonate.**

<u>The three means by which pH is strictly regulated are:</u>

1. Body fluid chemical buffers such as bicarbonate, ammonia, proteins, and phosphate

2. Lungs (by controlling blood PCO_2)

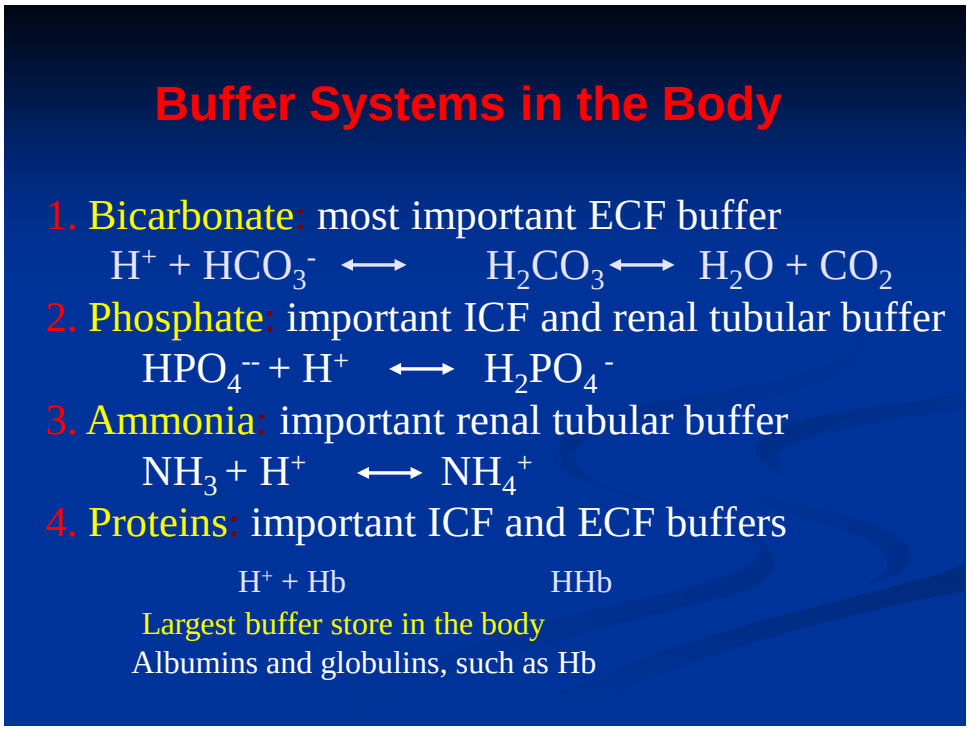
3. Kidneys (powerful) by doing the following:

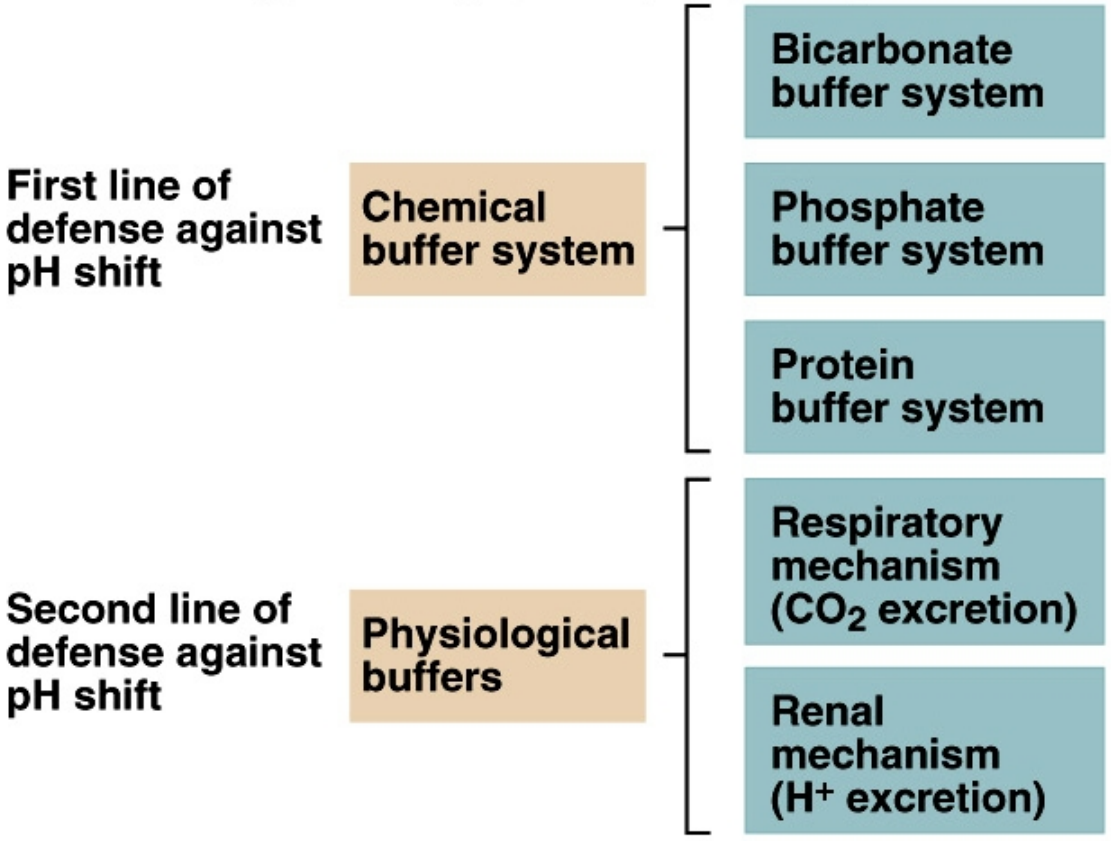
-A. eliminates non-volatile acids

- B. secretes H+

- C. Reabsorbs the entire filtered HCO3-

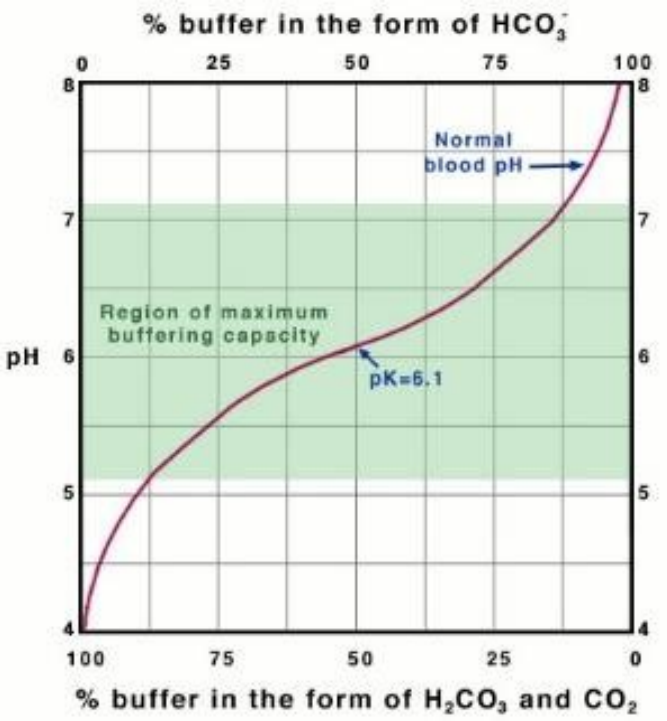
- D. generates new HCO3- (the bicarbonate gain)





- **We will start with the role of the buffer system:**
  - Buffers React within a fraction of a second

- By definition: Buffer is a substance that releases or binds H+ reversibly to resist marked pH changes and keep it compatible with life. Buffers don't eliminate or add H+ but keep it tied up until balance can be reached.
- All chemicals can buffer up to 1000 mM H+ before there is any significant shift in pH.
- What determine the strength of any buffer? Three factors:
- 1. The pK of the buffer
- 2. Th absolute concentration of the buffer

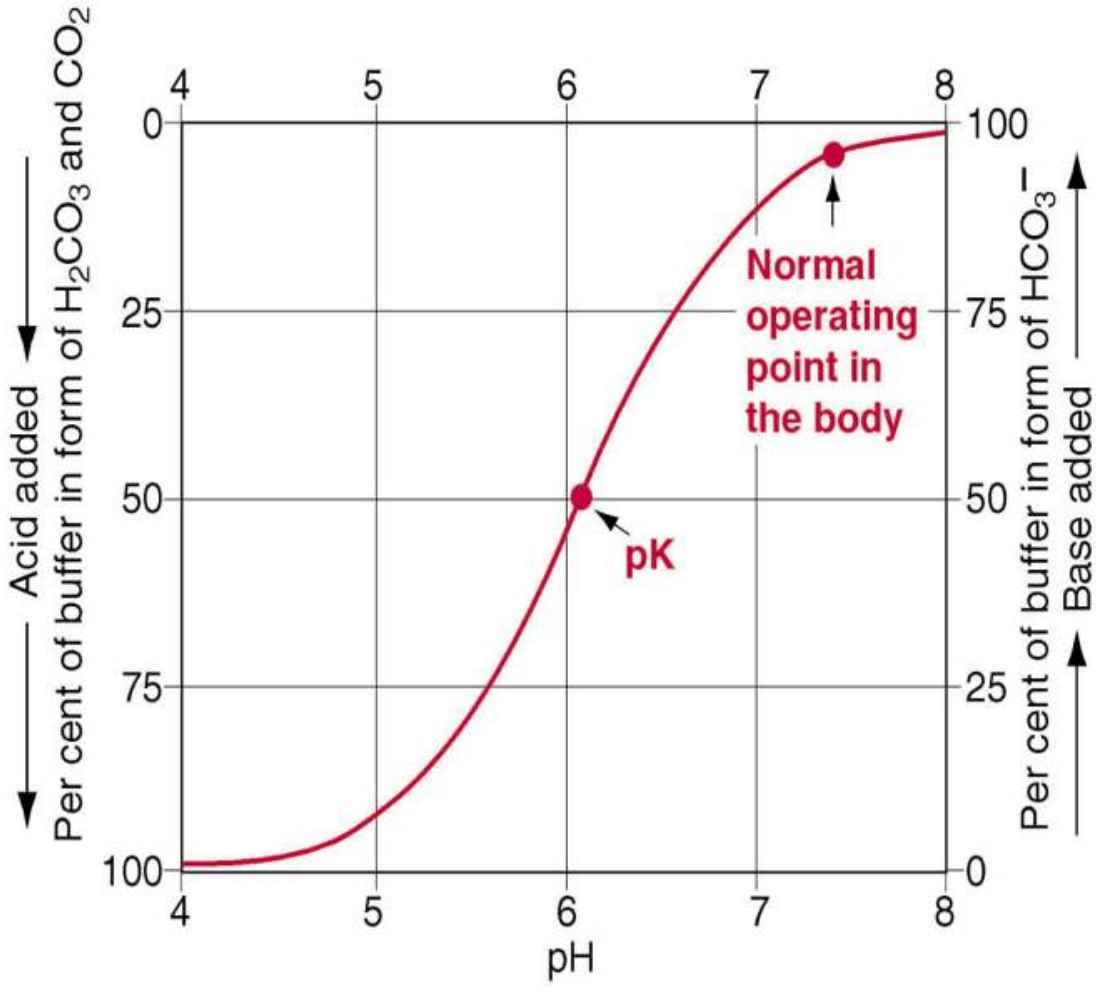


- 3. The buffer renewal ability...which is considered as the most important factor.

• By applying these three criteria to the bicarbonate buffer system

(the most important extracellular buffer), we find that:

• It is a weak buffer in terms of pK (because plasma pH is 7.4, which is outside its most effective area) and in terms of concentration, it is an intermediate buffer having a concentration of 24mEq/L. The bicarbonate buffer has a good renewal capacity which makes it the most important extracellular buffer. Bicarbonate concentration is regulated by the kidney. And PCO_2 is controlled by the rate of respiration.



- The pK of the buffer: The pK of the buffer system is is the pH of solution when each of the components (A-=base=HCO_3^- and AH=acid= CO_2) are equal (each constitutes 50% of the total

concentration of the buffer system. Log (1) = zero, so when the concentration of the salt form (HCO_3^-), equals the concentration of the acid form (CO_2), then the pH = pK. In other words, pK is the pH of a solution when the salt form is equal to the acid form. (Here pK=6.1

- The closer the pK of the buffer to the surrounding pH, the stronger the buffer. This means that the change in pH for any given amount of acid or base added to the system is least when the pH is near the pK of the system The buffer system is most effective in the central part of the curve, where the pH of the solution is ± one unit of its pk (i.e the linear portion of the curve abov**e**). For bicarbonate carbonic acid system 6.1 ±1; for HPO4/H2PO4 system is 6.8±1). For the bicarbonate buffer system it extends from a pH of about 5.1 to 7.1 units. This means that this system operates on the portion of the buffering curve where the slope is low and the buffering power is poor. For the phosphate buffer system it extends from a pH of about 5.8 to 7.8 units. Looking at this aspect only, phosphate is much better buffer than bicarbonate; its pk is closer to our ECF pH (7.4). Beyond these limits, the buffering power rapidly diminishes.

The absolute concentration of the buffers is also an important factor in determining the buffering power of a system. With low concentrations of the buffers, only a small amount of acid or base added to the solution changes the pH considerably.

Also, the concentrations of the two elements of the bicarbonate system, CO_2 and HCO_3, are not great.

- Nevertheless, the bicarbonate buffer system is the most powerful extracellular buffer in the body. This apparent paradox is due mainly to the fact that HCO_3^- and CO_2, are regulated, respectively, by the kidneys and the lungs, as discussed later.

✦

The intracellular pH is around 7.0 (i.e., H^+ is more concentrated inside the cells than in the ECF). Since the pK of Phosphate is 6.8, phosphate buffer is also effective in maintaining intracellular pH of 7.0. Plus phosphate is more concentrated inside the cells and in the TF (99% of water is reabsorped while only 90% of the filtered phosphate is reabsorbed, that makes TF phosphate 10xX concentrated). In addition the pH of the proximal TF is 6.5 which is very close to the phosphate pK.

Proteins are much more concentrated inside the cells, pK of most proteins is around 7.0, however, movement of H+ across cell membrane is slow. Therefore, proteins and phosphate inside the cells do not participate in buffering excess H^+ in the ECF

. •The **Bicarbonate Buffer System:**

- Consists of carbonic acid (**H_2CO_3**) and bicarbonate (**HCO_3^-**)
- **H_2CO_3** is a weak acid formed by a reaction between CO_2 and H_2O catalyzed by carbonic anhydrase.

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

- When a strong acid such as HCl is added, the increased H^+ released from the acid is buffered by HCO_3^- to form the very weak acid H_2CO_3.

  As a result, more H_2CO_3 is formed, causing increased CO_2 and H_2O production. This excess CO2 greatly stimulates respiration, which eliminates it from the ECF.

- When a strong base, such as NaOH, is added, the OH^- released from the NaOH combines with H_2CO_3 to form additional HCO_3^-. Thus, the weak base $HCO3^-$ replaces the strong base NaOH.
- As a result, the concentration of H_2CO_3 decreases (because it reacts with NaOH), causing more CO2 to combine with H2O to replace the H2CO3. This decreases CO2 levels in the blood which inhibits respiration and decreases the rate of CO2 expiration. Also, the rise in blood HCO_3^- is compensated for by increased renal excretion of HCO_3^-.
- Henderson-Hasselbalch equation
  -

In case of bicarbonate buffer system: $pH = pK_a + \log\frac{[A^-]}{[HA]}$ $\quad pH = 6.1 + \log\frac{HCO_3^-}{0.03 \times Pco_2}$

- **Example:** calculate the pH of a solution containing 24 mM of HCO_3^- and 1.2 mM of CO_2.
  pH = 6.1 + log (24/1.2) = 7.4
- **Example:** calculate the pH of a solution containing 0.25 mM of $H_2PO_4^-$ for each 1 mM of HPO_4^-.
  pH = 6.8 + log (1/0.25) = 7.4
- These values are true for the buffer systems in our bodies, why pH calculated to be 7.4,

the normal extracellular pH

- Henderson-Hasselbalch equation: $$pH = pK_a + \log\frac{[A^-]}{[HA]}$$
- In case of the bicarbonate buffer solution: $$pH = pK + \log\frac{[HCO_3^-]}{[H_2CO_3]}$$
- Since H_2CO_3 concentration in the plasma is difficult to measure, and since CO_2 concentration is proportional to it: $$pH = pK_a + \log\frac{[HCO_3^-]}{[CO_2]}$$
-
- Most clinical laboratories measure the blood CO_2 tension (Pco_2). Since plasma concentration of CO_2 = Pco_2 x solubility coefficient, and since the pK for HCO_3^- is 6.1: $$pH = 6.1 + \log\frac{HCO_3^-}{0.03 \times Pco_2}$$

pH = pK + log [Salt/Acid]

We can calculate the pH of any buffer solution by using the above equation if we know the buffer pK and the concentration of the buffer in its salt and acidic forms.

Ex: pK for phosphate buffer = 6.8

pH = 6.8 + log [1.0mmol / 0.25]

= 6.8 + 0.6= 7.4

Ex: ammonia/ammonium ion system (pK = 9.2):

(Note: its not one of the buffer systems mentioned above)

pH = 9.2 + log [NH_3 / NH_4^+] **the result is also 7.4**

The Isohydric principle:

States that all buffers in a common solution are in equilibrium with the same hydrogen ion concentration

Therefore, whenever there is a change in the ECF H^+ concentration, the balance of all other buffer systems changes at the same time.

→ changing the balance of one buffer system changes the others because the systems actually buffer each other.

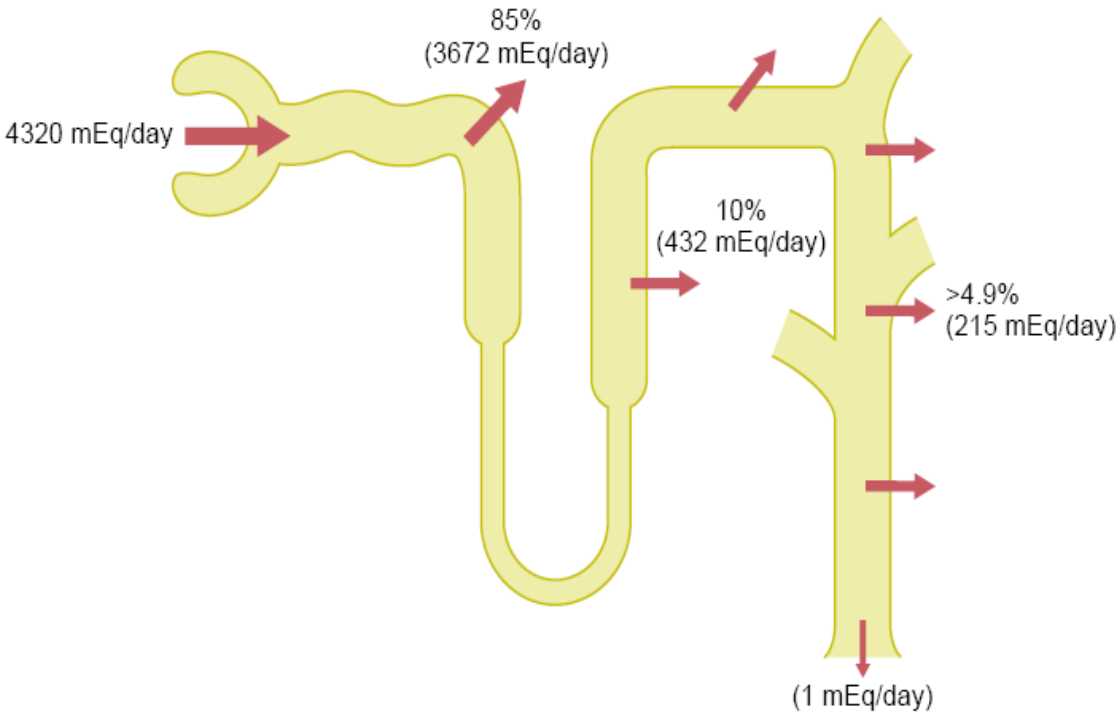
With good understanding of the effects of [HCO_3^-] and Pco_2 on blood pH, it is apparent that acidosis can be due to either decrease in plasma [HCO_3^-] or increase in Pco_2. Alkalosis, on the other hand, can be due to increased plasma [HCO_3^-] or decreased Pco_2.

•Renal Control of Acid-Base Balance

- The kidneys regulate extracellular pH by excreting acidic urine or basic urine.
- Large numbers of HCO_3^- are filtered continuously into the tubules, and if they are excreted into the urine this removes base from the blood.
- The remainder of the discussion will show, in details, how H^+ is secreted and how HCO_3^- is filtered and reabsorbed.

•H^+ secretion and HCO_3^- reabsorption

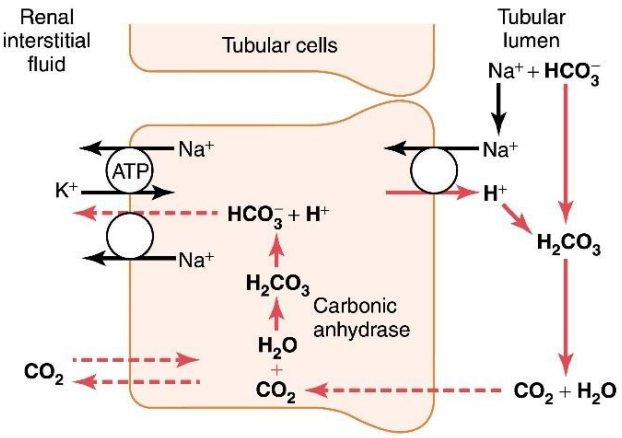
- The filtered load of HCO_3^- is 180 L/day x 24 mEq/L, or 4320mEq/day. All bicarbonate filtered must be reabsorbed…we cannot tolerate loosing bicarb in the urine…it is very precious substance. Theoretically, one proton is enough to reabsorb the entire filtered bicarb, meaning no net H+ secretion. However, after the filtered amount of bicarb has been reabsorbed, any addition H+ secretion is net secretion, and is accompanied by bicarbonate gain.
  - Let me stress on this point again. In any part of the tubule, *for each HCO_3^- reabsorbed from the tubules, H^+ must be secreted into the tubules. However, this is not Net H+ secretion. Because H+ recycle again and reabsorbed (reenter) by the tubules in form of CO2.*
  - 85% of bicarbonate reabsorption occurs in the proximal tubule; 10% in the thick ascending limb of the loop of Henle; about 5% in the distal tubule and collecting duct. Less than 1 mEq of H+ is secreted in the urine each day (free form of H+)



-
  - Reabsorption of HCO_3^- and secretion of H^+ does not occur in the descending and ascending thin limbs of the loop of Henle.

✦ **H^+ secretion in the proximal tubule, thick ascending loop of Henle, and the early distal tubule.**

- CO_2 either diffuses into the tubular cells or is formed by metabolism in the tubular epithelial cells.



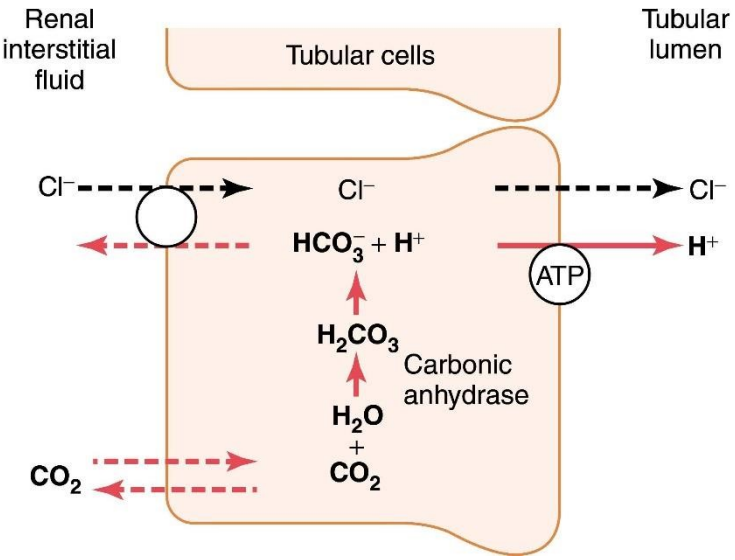
- CO_2, under the influence of the enzyme carbonic anhydrase, combines with H_2O to form H_2CO_3, which dissociates into HCO_3^- and H^+.

- The H^+ is secreted from the cell into the tubular lumen by Na^+/H^+ counter-transporter which uses the energy released by transporting Na^+ downhill to secrete H^+ uphill (i.e., secondary active transport). Because this is not H+ pump, it make [H+] gradient only 5-6 time more in the TF. Therefore, pH of the proximal TF drops only to 6.5
- At the same time, the formed HCO_3^- moves downhill across the basolateral membrane and is reabsorbed by the peritubular capillaries. Note that HCO_3^- which enters the blood is not the same HCO_3^- filtered.

- Drugs that inhibit carbonic anhydrase (e.g., some diuretic) decrease H^+ secretion and HCO_3^- reabsorption, thereby increasing the risk of acidosis.

✦ **H^+ secretion in the Late distal and collecting tubules**

✦ HCO_3^- and H^+ are formed by the same reactions.



- At the luminal membrane of the Intercalated cells of these segments, H^+ is secreted by H^+ ATPase, which uses the energy released by the breakdown of an ATP molecule to transport H^+ uphill (i.e., primary active transport…900X gradient…not more).

- **Note:** also at the luminal membrane, H^+/K^+ ATPase secretes H^+ and reabsorb K^+, both uphill. (refer to K^+ reabsorption section)

  Therefore, the pH of the inner medullary TF is 900 more concentrated than inside the cells. This is the maximum capacity of the pump. Hence, pH of TF (and urine) does not go below 4.5 ($-\log (10^{-7.0} \times 900) = 4.5$)

- Tubular acidosis is of 4 types; type 1 results from decreased activity of this H^+/K^+ ATPase or H^+-ATPase (i.e., decreased secretion of H^+ from the distal and collecting tubules); type 2 results from decreased activity of the proximal Na^+/H^+ counter-transporter.

- With type 1, H^+ gradient can only change pH from 7.4 to, minimally, 5.2. Therefore, type 2 is less dangerous than type 1.

- **Reabsorption of Filtered HCO_3^-**

- HCO_3^- does not permeate the luminal membrane (charged molecule). HCO_3^- in the tubular fluid combines with H^+ to form H_2CO_3 which dissociates into CO_2 and H_2O. CO_2 easily crosses the luminal membrane to enter the cell, where it recombines with H_2O to form H_2CO_3 which dissociates into HCO_3^- and H^+. (Remember: CO2 can cross any biological membrane as if the membrane does not exists)

- o HCO_3^- transport at the basolateral membrane is facilitated by Na^+/HCO_3^- co-transporter in the proximal tubule and Cl^-/HCO_3^- counter-transporter in the late distal tubule, thick ascending loop of Henle and in the collecting tubules and ducts

- **HCO_3^- and H^+ titrate each other in the tubules**

- **O** H^+ secreted into the tubules is buffered by HCO_3^-, keeping tubular pH with slight change. After reabsorption of the 4320 milliequivalents of HCO_3^-, other buffers in the tubules bind to the excess H^+, as discussed later.

  - o When there is an excess of HCO_3^-, as occurs in metabolic alkalosis, the excess HCO_3^- cannot be reabsorbed; therefore, the excess HCO_3^- is left in the tubules and eventually excreted into the urine, which helps correct the metabolic alkalosis. Obviously, the kidney does not make new bicarb.

  - o Reabsorbing 4320 mEq of HCO_3^- (the filtered load of HCO_3^-), is not enough. We expect more from the kidney. We need additional 80 mmole of HCO_3^- (HCO_3^- gain). Summating these numbers, 4400 mEq of HCO_3^- return to the circulation each day. **In quantitative aspect: The reabsorption is more important than the production since its amount (4320 mEq) versus 80 mEq gain.**
  - o How the 80 mmole of HCO_3^- are formed, this is explained next.

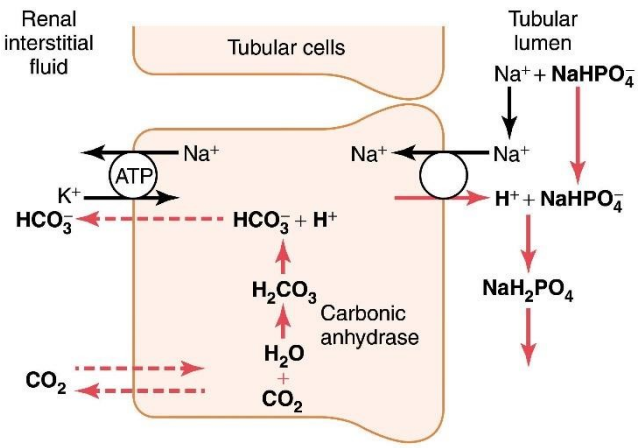
- **New HCO_3^- Generation**

	Reabsorption of HCO3-	Gaining of HCO3-
Proximal parts	**80-85%**	**55 mM**
Distal parts	**15-20%**	**15 mM**

- The minimal urine concentration of H^+ that can be achieved by the previously discussed mechanisms is 0.03 mEq/L (i.e., minimal urine pH = -log (3×10^{-5}) = 4.5). Thus, for a person to excrete all the 80 mEq, 2667 liters of urine must be excreted per day!
- Since CO_2 and H_2O are abundant in the epithelial cells, what limits urine pH? The reader, at this level, is expected to be able to answer this question easily. The answer is that the active transporters in the luminal membrane (coll. ducts) cannot achieve higher concentration gradient of H^+ between the inside of the cell and the tubular fluid (maximum is 900 times).
- Excess H^+ in the tubules which does not react with HCO_3^- combines with tubular buffers, of which the most important are phosphate buffers.

•Phosphate Buffer

- Do we have 80 mMole of phosphate to be excrted in the urine? If yes, then we can gain 80 mMole/D of HCO_3^- → → → The problem is solved!!! We don't need to worry about the 80 mMole of fixed acids anymore.



- Unfortunately, we excrete less than 30 mMole of phosphate
- We still need additional 50 mMole of new HCO_3^- through other source→ By **ammonium production**.
- From the diagram, H^+ reacts with HPO_4^{2-} in the tubule to form $H_2PO_4^-$ which is excreted in the urine.
- Note that this produces new HCO_3^- in the cell to be formed. This will eventually enter the blood.
- Therefore, it is apparent that whenever H^+ in the tubular fluid combines with a buffer other than HCO_3^-, a new HCO_3^- is added to the blood. This is a mechanism by which the kidneys can replenish (only partially) the extracellular fluid stores of HCO_3^-.
- The pK of phosphate buffer is 6.8 (close of the proximal pH=6.5. Therefore, in the tubules, the phosphate buffer system functions at its most effective range of pH.
- The filtered load of phosphate is 180 x 1.5, or 270 mg/day.
- Normally, about 90% of the filtered phosphate is reabsorbed; only 30 mEq/day are available for buffering H^+, and only 30 mEq of bicarb are being gained. There must be other way to make the additional 50 mEq of bicarb.

•Ammonia-ammonium Buffer system

Ammonium production

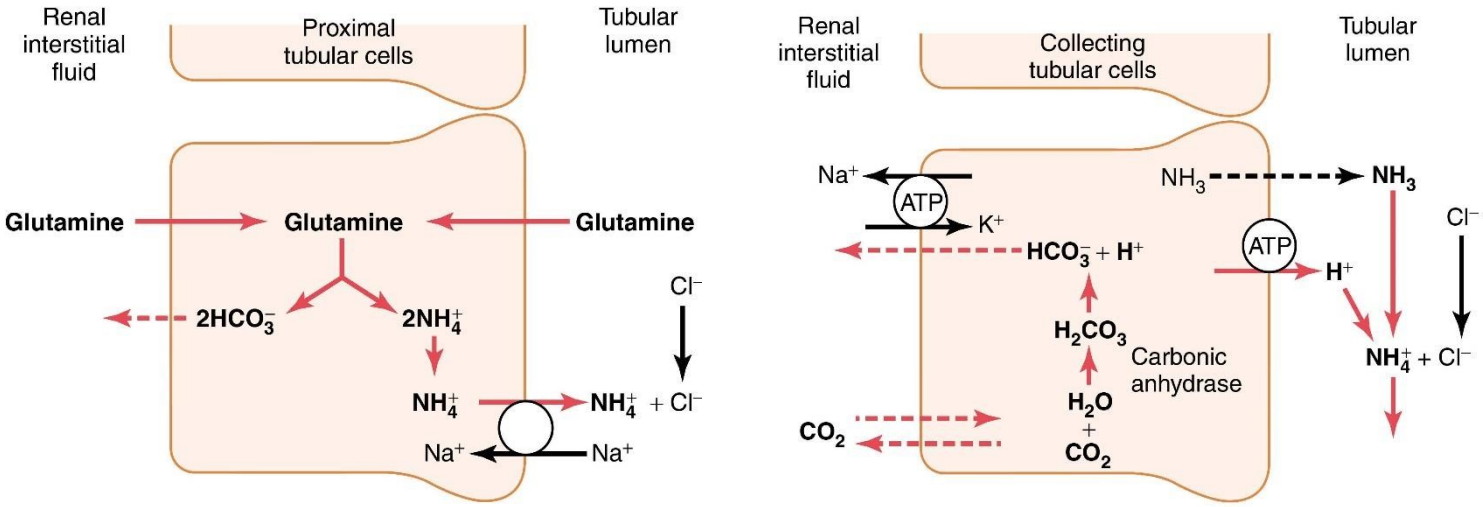
Don't confuse ammonium $NH4^+$ with ammonia NH_3 ,. ammonium is an ion; ammonia is not).

Glutamine from blood or TF enters the proximal cells where it is converted to glutamate then to alpha keto-glutamate which forms 2 NH_4^+ +2HCO_3^-

- Ammonia is secreted into the lumen by counter-transport mechanism in exchange with sodium in proximal tubules, thick ascending loop of Henley and distal tubules.
- In collecting tubules: H+ is secreted into the lumen where it combines with NH_3(ammonia) to form NH^{4+} (ammonium).

→ Collecting tubules membrane is much less permeable for ammonium than ammonia, thus NH_4^+ is trapped in the lumen, this is called → ammonia trapping.

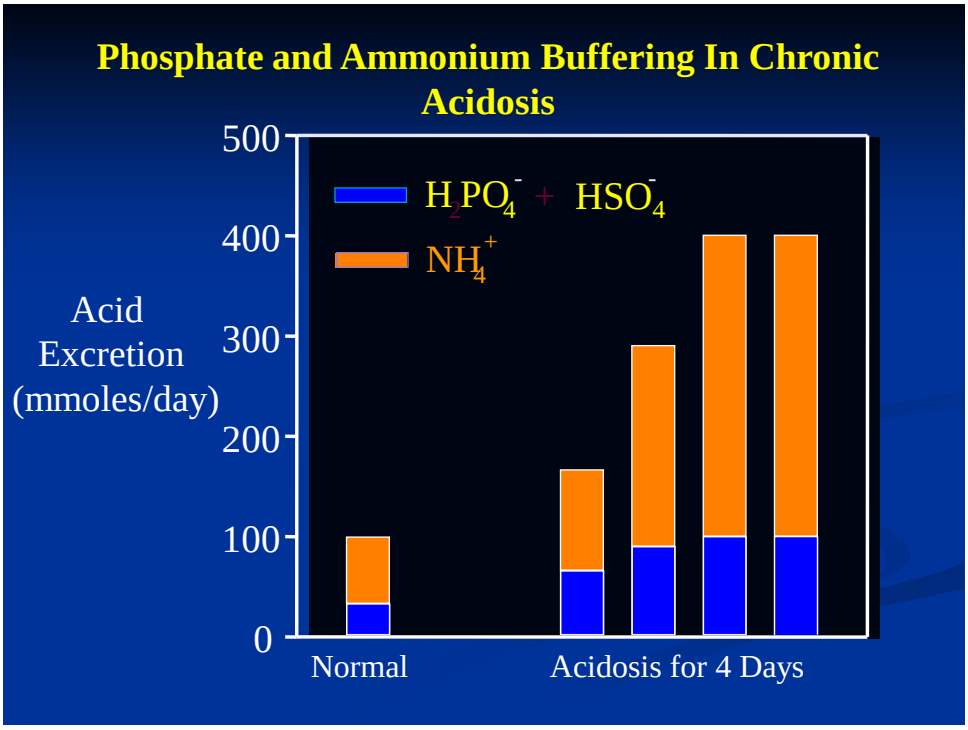
- Ammonium production can be induced unlike phosphate buffer system which is fixed (limited).
- Whenever a hydrogen ion secreted into the tubular lumen combines with a buffer other than bicarbonate, the net effect is the addition of new bicarbonate ion to the **blood.**



- Glutamine enters the epithelial cells of the proximal tubules, thick ascending loop of Henle, and distal tubules.
- In the cell, each molecule of glutamine is metabolized to ultimately form two NH_4^+ and two HCO_3^-. The $2NH_4^+$ are secreted into the lumen by a counter-transport mechanism in exchange for Na^+, which is reabsorbed. The $2HCO_3^-$ are considered new and are transported across the basolateral membrane, along with the reabsorbed Na^+.
- **Note:** In the collecting tubules, the addition of NH_4^+ to the tubular fluids occurs through a different mechanism. Here, H^+ is secreted by the tubular membrane into the lumen, where it combines with NH_3 to form NH_4^+, which is then excreted (this is called ammonia trapping).
- The collecting ducts are permeable to NH_3, which can easily diffuse into the tubular lumen.
  However, the luminal membrane of this part of the tubules is much less permeable to NH_4^+; therefore, once the H^+ has reacted with NH_3 to form NH_4^+, the NH_4^+ is trapped in the tubular lumen and eliminated in the urine. For each NH_4^+ excreted, a new HCO_3^- is generated and added to the blood.

- One of the most important features of the renal ammonia buffer system is that it is subject to physiologic control as follows: An increase in extracellular fluid H^+ concentration stimulates renal glutamine metabolism and, therefore, increases the formation of NH_4^+ and new HCO_3^- to be used in H^+ buffering; a decrease in H+ concentration has the opposite effect.
- Normally, the amount of H^+ eliminated by the ammonia buffer system accounts for about 50% of the acid excreted and HCO_3^- generated by the kidneys.
- With chronic acidosis, glutaminase is stimulated more and the rate of NH_4^+ excretion can increase to as much as 500 mEq/day increasing H^+ excretion and bicarbonate generation. This is the dominant mechanism which helps to correct chronic acidosis. The capacity of the buffers is limited. Low blood pH induces glutaminase enzyme to produce HCO3- and NH4+, so the urine is full of ammonium which is secreted in the from of NH4Cl

- **Net H^+ Excretion (or Net HCO_3^- Gain)**
- **Net H^+ excretion = Net HCO_3^- Gain = NH_4^+ excretion + urinary titratable acid - HCO_3^- excretion**
- Net H^+ excretion = 79 mmol/day = titratable acid (30 mmol/d) + NH_4^+ excretion (50 mmol/d) - HCO_3^- excretion (1 mmol/d).
- HCO_3^- excretion is calculated by multiplying urine flow rate by its urinary concentration.
  - To measure the amount of **HCO_3^-** gained through the ammonia-ammonium system, by multiplying the urinary flow rate by NH_4^+ urinary concentration.
  - To measure the amount of **HCO_3^-** gained through the different buffers (phosphate and other less important buffers, such as citrate and urate, etc), titratable acid value is determined by titrating the urine with a strong base (NaOH) to a pH of 7.4, which is the normal pH of both the plasma and the glomerular filtrate.
  - The number of milliequivalents required to return the pH to 7.4 equals the number of milliequivalents of H^+ added to the tubular fluid and combined with tubular buffers other than ammonia, why other than ammonia? Because pK of the reaction, $NH_3 + H^+ = NH4^+$, is 9.2. Thus, titration to a pH of 7.4 doesn't remove an H^+ from NH_4^+ (i.e., at this pH, most of the NH_3 is still bound to H^+).



- **Regulation of Renal tubular acid secretion**

- If the kidney cannot absorb HCO3- or cannot secrete H+ then there is acidosis, this acidosis is called: renal tubular acidosis

- In alkalosis, secretion of H^+ is reduced to a level that is too low to achieve complete HCO_3^- reabsorption, enabling the kidneys to increase HCO_3^- excretion. Titratable acid and ammonia are not excreted because there is no excess H^+ available to combine with nonbicarbonate buffers; therefore, there is no new HCO_3^- added to the blood in alkalosis.
- In acidosis, the tubular H^+ secretion is increased sufficiently to reabsorb all the filtered HCO_3^- with enough H^+left over to excrete large amounts of NH_4^+ and titratable acid, thereby contributing large amounts of new HCO_3^- to the total body extracellular fluid.

- Aldosterone stimulates the secretion of H^+ by the intercalated cells of the collecting duct. Therefore, excessive secretion of aldosterone, as occurs in Conn's syndrome, can increase secretion of H^+ into the tubular fluid and, consequently, increase the amount of HCO_3^- added back to the blood. This usually causes alkalosis in patients with excessive aldosterone secretion. The tubular cells usually respond to a decrease in H^+ concentration (alkalosis) by reducing H+ secretion.

- H^+ secretion is coupled to Na^+ reabsorption by the Na^+/H^+exchanger in the proximal tubule and thick ascending loop of Henle. Therefore, factors that stimulate Na^+ reabsorption, such as decreased extracellular fluid volume, may also secondarily increase H^+ secretion.
- Angiotensin II directly stimulates the activity of the Na^+/H^+ exchanger, increasing H^+ excretion.
- Hypokalemia stimulates and hyperkalemia inhibits H^+ secretion in the proximal tubule.

Acid-Base Imbalances

Lecture (10)

•Acid-Base Disorders

- **Acidosis**
  - A condition in which the blood has too much acid (or too little base), resulting in a decrease in blood pH (< 7.35)
- **Alkalosis**

A condition in which the blood has too much base (or too little acid), resulting in an increase in blood pH (> 7.45)

- **o** Always look at the ratio HCO_3^-/H^+ in extracellular fluids (plasma) and use Henderson-Hasselbalch equation

$$pH = 6.1 + \log \frac{HCO_3^-}{0.03 \times Pco_2}$$

- Acidosis ↓ in the ratio
  - Due to a fall in HCO_3^- (*metabolic acidosis)*
  - Due to an increase in PCO2 (*respiratory acidosis)*
  - Both (mixed acidosis)
- Alkalosis ↑ in the ratio
  - Due to an increase in HCO_3^- (*metabolic alkalosis)*
  - Due to a fall in PCO2 (*respiratory alkalosis)*
  - Both (mixed alkalosis)

General Notes:

- In clinical practice, acidosis is more common than alkalosis.
- Metabolic acidosis is more common than respiratory acidosis.

Main cause of metabolic acidosis is not diabetes mellitus because diabetes mellitus type 1 is not common.

→ The most common cause of M.acidosis in third world countries is diarrhea.

* When you treat diarrhea: rehydrate the patient, correct both electrolyte and pH

pH disturbance

Metabolic → it is the HCO3- shift
Respiratory → lit is the PCO2 shift

	pH	P_aCO_2	HCO_3^-
M. Acidosis	↓	↓	↓
M. Alkalosis	↑	↑	↑
R. Acidosis	↓	↑	↑
R. alkalosis	↑	↓	↓

To know the type of disorder:
First we look for pH if it increased or decrease, second we look for the cause: is it the HCO3- (metabolic) or the CO2 (respiratory). Third we look for compensation.

To know the type of disorder and as it shows in the box: you have to do three steps:**:**

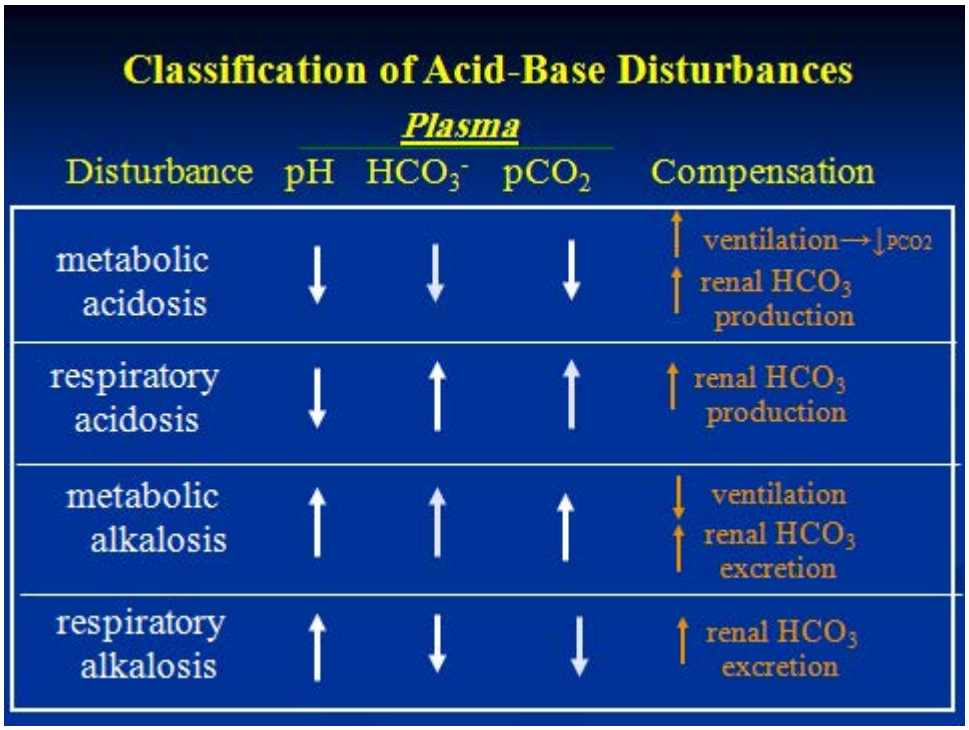
First take a look at the pH; increased (alkalosis) or decreased (acidosis), **second** search for the cause: is it the HCO3- who is causing this shift (metabolic) or the CO2 (respiratory). **Third** look to see if there is compensation from the other element. In compensation, always the two elements move in the same direction to make the shift in pH minimum.

In Metabolic acidosis pH < 7.35 and HCO_3^- is <24 mEq/

In Respiratory acidosis pH < 7.35 and P_aCO_2 > 40 mmHg

In Metabolic alkalosis pH > 7.45 and HCO_3^- is >24 mEq/

In Respiratory acidosis pH > 7.35 and P_aCO_2 < 40 mmHg



Metabolic acidosis

Non-respiratory acidosis is much better term, but metabolic acidosis is most commonly used. Four major causes

1. Decrease H+ secretion and HCO_3^- reabsorption. Renal tubular acidosis.

2. ↑ HCO_3^- loss: diarrhea, deep vomiting with the pancreatic secretions which full of bicarb. (Gastric vomiting as in pyloric stenosis causes metabolic alkalosis, bcs of excessive HCl loss from the stomach).

3. ↑ H+ production: as in D.M (ketoacidosis)

4. ↑ H+ intake: ingestion of Aspirin to escape CORONA time.

In M. Acidosis, respiratory center is stimulated causing hyperventilation→ washing out CO_2 as a compensatory mechanism . ALWAYS use this equation:

$$pH = 6.1 + \log \frac{HCO_3^-}{0.03 \times Pco_2}$$

- Whenever HCO_3^- drops, PCO2 drops in the same direction to make pH shift minimal and thus compatible with life, otherwise pH may go below 6.8 threatening patient's life. The lung help us to cross this crisis until we manage to treat the underlying cause responsible for M. acidosis. Lungs can only bring back pH to 75% normal. Accourding to the values of PCO_2 shift, we can claim: full, partial, or no respiratory compensation? I will give these

numbers, but you don't have to recall any of them, just understand the principles. They are difficult to remember and might be confusing.

- Acute metabolic acidosis (not for long period of time) is not accompanied with respiratory compensation. Respiratory compensation starts to act after minutes, full effect after hours.
- ***<u>In M. Acidosis</u>. For every ↓ 1 mEq HCO_3^- → 1.2 mm Hg PCO_2 ↓ too (means full respiratory compensation)**
- *** if PCO2 ↓ more than expected→ superimposed R. alkalosis too (mixed)**
- *** if PCO2 ↓ less than expected→ superimposed R. acidosis too.**

Renal Compensation for Acidosis

Titratable acid	= 35 mmol/day (small increase)
NH_4^+ excretion	= 165 mmol/day (significantly increased)
HCO_3^- excretion	= 0 mmol/day (decreased)
Total	= 200 mmol/day

The concept of Anion Gap as a Diagnostic Tool in metabolic acidosis (briefly).

Fact: In each of the three compartment (plasma, interstitial, and intracellular): total cations = total anions achieving electroneutrality. Whatever the disturbance in electrolyte concentrations in plasma, the plasma remains electro-neutral, that means anions = cations

$Na^+ = Cl^- + HCO_3^-$ + unmeasured anions

- Definition for the anion gap: Difference between calculated serum cations and anions
- The simplest one: the difference between [Na^+] and the sum of [HCO_3^-] and [Cl^-].
  - **[Na^+] – ([$HC0_3^-$] + [Cl^-]) =** 142 - (24 + 108) = 10
    - Normal range = 12<u>+</u>2: as unmeasured anions or the so called anion gap).

If cation >>> anions → increase anion gap (above 16 mEq): the conclusion is the presence of excess unmeasured anions (α-ketegluteric acid, acetacetats…we don't usually measure them). This scenario is expected in D.M (diabetic ketoacidosis)

<u>In diarrhea however,</u> patient lose Na+ and HCO_3^- at the same time, and therefore he develops M.acidosis but with normal anion gap.

- Clinicians use the anion gap to identify the cause of metabolic acidosis.

Use of "Anion Gap" as a Diagnostic Tool for Metabolic Acidosis

Increased Anion Gap (normal Cl^-)

- diabetes mellitus (ketoacidosis)
- lactic acidosis
- aspirin (acetysalicylic acid) poisoning
- methanol poisoning
- starvation
- Renal Failure

Normal Anion Gap (increased Cl^-, hyperchloremia)

- diarrhea
- renal tubular acidosis
- Addison' disease
- carbonic anhydrase inhibitors

The most common causes of increased Anion Gap in Metabolic Acidosis

- Salicylates raise the gap to 20.
- Renal failure raises gap to 25.
- Diabetic ketoacidosis raises the gap to 35-40.
- Lactic acidosis raises the gap to > 50.
- Largest gaps are caused by ketoacidosis and lactic acidosis.

M Suliman: 2009

0

Let me give a practice question:

Laboratory values for an uncontrolled diabetic patient include the following:
arterial pH = 7.25
Plasma HCO_3^- = 12
Plasma PCO_2 = 28
Plasma Cl^- = 102
Plasma Na^+ = 142

Metabolic Acidosis with Respiratory Compensation

What type of acid-base disorder does this patient have?

What is his anion gap ?

Anion gap = 142 - 102 -12 = 28

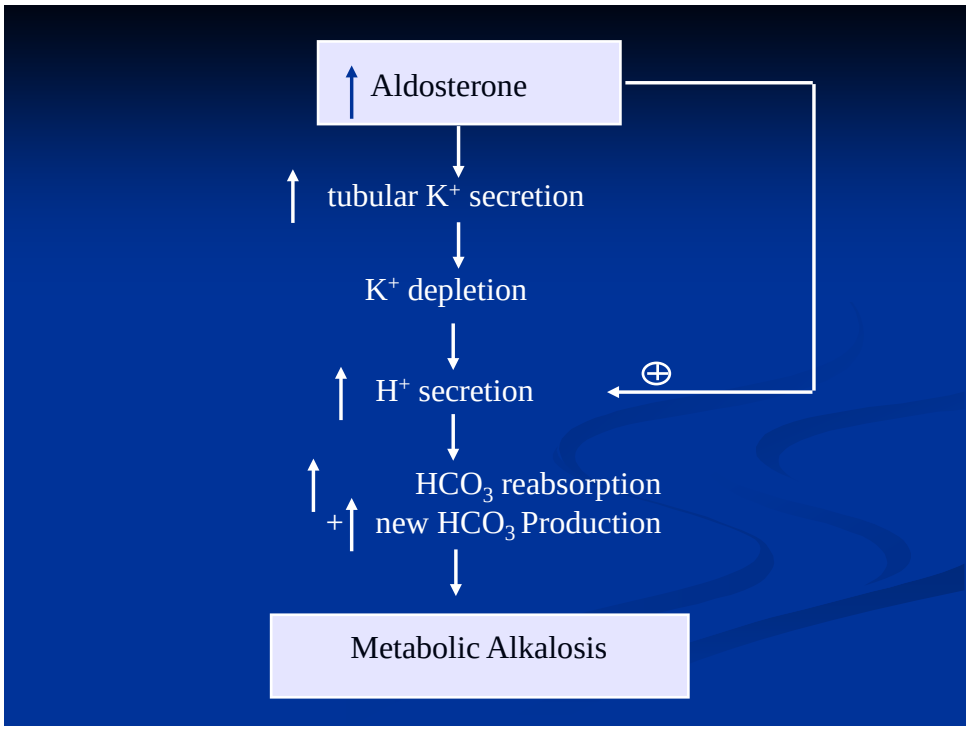
Answer

A. diarrhea
B. diabetes mellitus
C. Renal tubular acidosis
D. primary aldosteronism

- **Metabolic Alkalosis:** "not common"

- Metabolic Alkalosis : ↑(HCO_3^- / PCO_2 in plasma) (↑ pH, ↑ HCO_3^-)

- 1. Diuretics with the exception of C.A inhibitors:↑ flow → ↑ TF flow rate → ↑ H+ secretion→↑ H+ loss in the urine → M.alkalosis

- 2. ↑ aldostrerone secerion.
- 3. Vomiting of gastric content only (Pyloric stenosis)
- 4. Administration of $NaHCO_3$.
- 

****M. Alkalosis** **For every 1 mEq↑ in HCO3-⟶ 0.7 mmHg ↑ in PCO2**

- **** if PCO2 ↑ more than expected⟶ superimposed R. acidosis too.**
- **** if PCO2 ↑ less than expected⟶ superimposed R. alkalosis too.**
- **Notice the increase for PCO2 is only 0.7 (not 1.2 as in M.acidosis), because suppressing ventilation by M.alklosis is opposed by hypoxia.**
- **Renal Compensation for Alkalosis**
- Titratable acid = 0 mmol/day (decreased)
- NH_4^+ excretion = 0 mmol/day (decreased)
- HCO_3^- excretion = 80 mmol/day (increased)
- Total = 80 mmol/day
- HCO_3^- excretion can increase markedly in alkalosis

✦ **Respiratory acidosis**

- Respiratory Acidosis :↓(HCO_3^- / PCO_2 in plasma)

(↓pH, and↑ PCO_2): Elevated extracellular fluid Pco_2

which stimulates H+ formation

- ***Causes:***

1. **Gas exchange (↓ Ability of the lung to eliminate CO2 such as): pneumomia , lack of lung tissue, airway obstruction (COPD), ↓ surface area.**
2. **CNS Damage to the respiratory CNTR. trauma , tumors.**
3. **Respiratory muscles: phrenic paralysis, diaphragmatic fatigue**

- *****R. Acidosis (the kidneys take days to compensate.** In respiratory acidosis and alkalosis, on the other hand, the compensation by the kidneys takes longer time to take place; for example,

- Acute: For every 10 mmHg ↑ in PCO2 → 1 mEq ↑ in HCO3-
- Chronic For every 10 mmHg ↑ in PCO2 →3.5 mEq↑ in HCO3-

*** if HCO3 ↑ more than expected→ superimposed M. alkalosis too.

*** if HCO3 ↑ less than expected→ superimposed M. acidosis too

Respiratory Alkalosis

- Respiratory Acidosis : ↑ (HCO_3^- / PCO_2 in plasma)

(↑pH, and↓ PCO_2):

Causes

- Psychoneurosis. psychic (fear, pain, etc)
- high altitude
- ******R. Alkalosis**
- Acute For every 10 mmHg ↓ PCO2 → 2 mEq ↓ HCO3-
- Chronic For every 10 mmHg ↓ PCO2 → 5 mEq ↓ HCO3-
- **** if HCO3 ↓ more than expected→ superimposed M. acidosis too.
- **** if HCO3 ↓ less than expected→ superimposed M. alkalosis too.

Disorder	$CO_2 + H_2O$	↔	H^+	HCO_3^-	Respiratory Compensation	Renal Compensati
Metabolic acidosis	↓ (respiratory compensation)		↑	**↓**	Hyperventilation	
Metabolic alkalosis	↑ (respiratory compensation)		↓	**↑**	Hypoventilation	
Respiratory acidosis	**↑**		↑	↑	None	↑ H^+ excretion ↑ HCO_3^- reabsorpt
Respiratory alkalosis	**↓**		↓	↓	None	↓ H^+ excretion ↓ HCO_3^- reabsorpt

Heavy arrows indicate *primary* disturbance.

o

✦