PHYSIOLOGY

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Number

9

Subject

Acid-Base Balance

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Date: 00/00/2016

Price:

Notes:

- This sheet was written according to the record of section 3.
- This subject is extremely long, and is thus extremely difficult to discuss it with brevity. I tried my best to summarize things, but it's still long.
- As this topic was explained in one lecture, many concepts were mentioned very quickly by the doctor, so I tried my best to explain them. In this place, thanks to Arthur Guyton and Linda Costanzo who made my task way easier.
- I apologize for the long sheet. I explained the main concepts many times, and this is what actually made it extremely long. So, don't panic, and just read it.
- This lecture, unlike the previous ones, was more Guytonoid than Costanzoid. Therefore, I strongly recommend reading Guyton quickly if you have time (385-395).
- At the end of the sheet, there are some questions on this topic. Please, don't skip them, they are more important than the whole sheet. You can find the answers in BRS physiology, by Linda Costanzo, 6th edition, at the end of chapter 5.

Good Luck

Introduction

- Our body is continuously under the threat of acidosis because acids are taken with food, produced by catabolism of phospholipids and proteins (sulfuric acid and phosphoric acids are produced, respectively) as well as cellular metabolism (produces CO_2).
  → There must be body defenses to prevent the occurrence of acidosis.
- Two types of acid are produced in the body:
  1- Volatile acid:
  - CO_2 (CO_2 by itself is not an acid, but it has the potential to generate H^+ after hydration with H_2O).
  - CO_2 is volatile (i.e. can be expired) → It's not a problem to the body and has no impact on acid-base balance.

  2- Nonvolatile acid:
  - Sulfuric acid (produced by catabolism of proteins), phosphoric acid (produced by catabolism of phospholipids), and others like ketoacids, lactic acid (produced in diseases states) and salicylic acid (produced if someone ingests aspirin tablets).
- These are nonvolatile (i.e. cannot be expired) → It's a problem to the body, and this is what we need acid-base balance for.
- The human body makes 80mM of these acids daily.

- There are three lines of defense against acids:
  1- Buffer 2- Respiratory Mechanisms 3- Renal Mechanisms

Example: [This was not mentioned in the lecture, but it explains why do we have three lines of defense].

- ECF concentration of HCO_3^- is 24 mmole/L.

- If 12 mmol/L of HCl is added to ECF, HCl will completely dissociate in water, giving 12 mmol/L of H+. These 12 mmol/L of added H+ combines with 12 mmol/L of HCO_3^- to form 12 mmol/L of H_2CO_3, which is converted to 12 mmol/L of CO_2 in the presence of carbonic anhydrase.

Now, what happens to the concentrations of CO_2 and HCO_3^-?

After this buffering reaction occurs, the new HCO_3^- concentration will be 12 mmol/L instead of the original 24 mmol/L. The new CO_2 concentration will be the original concentration of 1.2 mmol/L (i.e., 40 mm Hg × 0.03) plus the 12 mmol/L that is generated in the buffering reaction.

Are the buffers enough to get rid of acids?
No. we need the respiratory system to expire the additional CO2. Let's see why?

Assuming for a moment that the additional CO_2 generated cannot be expired by the lungs, the *new* pH will be

$$\text{pH} = 6.1 + \log\frac{12\ \text{mmol/L}}{1.2\ \text{mmol/L} + 12\ \text{mmol/L}}$$
$$= 6.1 + \log\frac{12\ \text{mmol/L}}{13.2\ \text{mmol/L}}$$
$$= 6.06$$

→ Without respiration, pH will be 6.06 (fatal pH).
→ Respiratory compensation by expiring CO2 lowers CO2 concentration and prevents large decrease in pH (see explanation below). This occurs by hyperventilation.

Clearly, a pH this low (6.06) would be fatal! There is, however, a second protective mechanism, respiratory compensation, which prevents the pH from falling to this fatally low value. Acidemia stimulates chemoreceptors in the carotid bodies that produce an immediate increase in the ventilation rate (hyperventilation): All of the excess CO2, plus more, is expired by the lungs. This response, called respiratory compensation, drives the PCO2 down to lower than normal values (e.g., to 24 mm Hg). Substituting these values in the Henderson-Hasselbalch equation, another pH can be calculated:

$$\text{pH} = 6.1 + \log\frac{12\ \text{mmol/L}}{0.03 \times 24\ \text{mm Hg}}$$
$$= 6.1 + \log\frac{12\ \text{mmol/L}}{0.72}$$
$$= 7.32$$

- The combination of buffering by $HCO3^-$ and respiratory compensation (i.e.,hyperventilation) results in an almost normal pH (normal = 7.4). Although both the $HCO3^-$ concentration and the P_{CO2} are severely reduced, the pH is nearly normal.

- Full restoration of acid-base balance depends on the kidneys.

Renal Mechanisms in Acid-Base Balance

- Chemical buffers are the first-line of defense against acidosis.
- The most important extracellular buffer is HCO_3-/CO2 buffer. Any buffer contains HA portion (which will react with any added bases) and A- portion (which will react with any added acids).
- Addition of acids to the fluid consumes the A- portion, necessitating replenishing of A- stores (i.e. if we add HCl to a solution, it will be buffered by HCO_3-, consuming it).
- Every day, the body produces volatile acids (expired and need no buffering), and nonvolatile acids that should be buffered. Mechanisms of expiration of CO2 were covered in hematology and respiratory courses and will not be repeated here and our main focus will be on nonvolatile acids.

- **Under normal conditions the kidneys excrete an amount of acid equal to the production of nonvolatile acids and in so doing replenish the HCO_3- that is lost by neutralization of the nonvolatile acids.**

[The body produces 80 mEq/ day of nonvolatile acids. These acids should be buffered by HCO_3-/ CO2 buffer, consuming HCO_3- → We have to replenish HCO_3- stores by synthesis of new HCO_3- by the kidneys].

- HCO_3- is very precious as it's the most important extracellular buffer → We don't want to lose any HCO_3- in urine + We want to generate new HCO_3- to replenish HCO_3- lost by neutralization of nonvolatile acids.
- The kidney has **two** important **functions**:

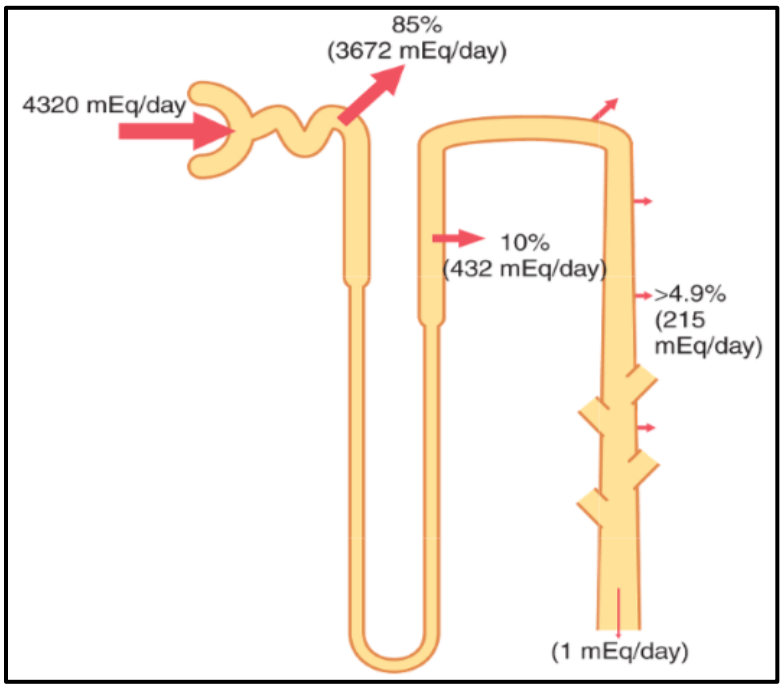
1- Reabsorption of filtered HCO_3- (Reabsoption of 4320 mEq/day of HCO_3-).
2- Excretion of H^+ and formation of new HCO_3- (i.e. HCO_3- gain). We have to excrete 4400 mEq/day of H^+ (4320 mEq/day associated with reabsorption of filtered HCO_3- and 80 mEq/day to synthesize new HCO_3- to replenish HCO_3- stores).

- **Which one is more important, to reabsorb filtered HCO_3- or to produce new HCO_3-?**

Reabsorption of filtered HCO_3- is quantitatively more important because the filtered load of HCO_3- is approximately 4320 mEq/day (24 mEq/L × 180 L/day = 4320 mEq/day), as compared with only 50 to 100 mEq/day needed to balance nonvolatile acid production.

Reabsorption of HCO_3- and Excretion of H^+

- 99.9 % of filtered HCO_3- is reabsorbed.
- Filtered load of HCO_3- = 180 L x 24 mEq/ L = 4320 mEq/ day. Excretion rate of HCO_3- = 1-2 mEq/ day → 99.9 % is reabsorbed and only 0.1 % is excreted.
- This proves that HCO_3- is very precious to the extent that we don't want only to reabsorb most of it but also to synthesize new HCO_3-.
- Most filtered HCO_3- is reabsorbed in the proximal tubule.

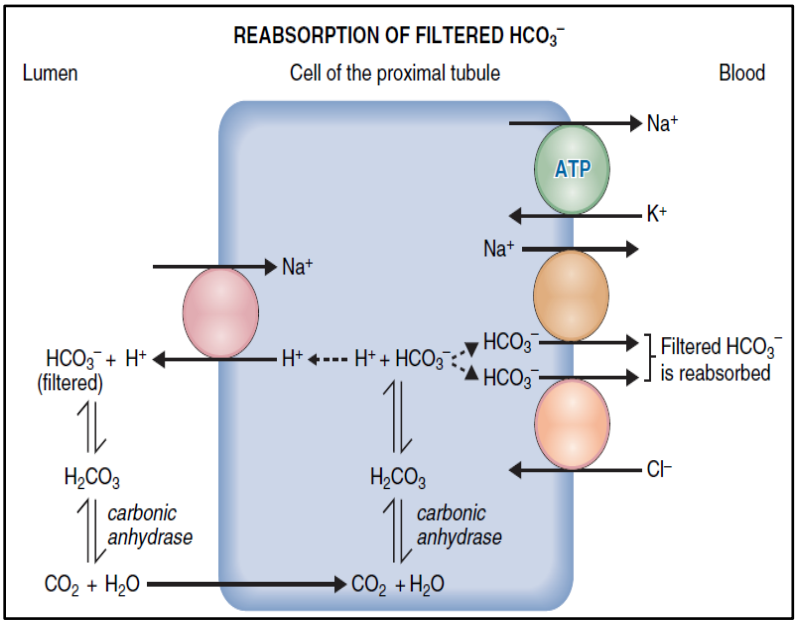


- 85 % of HCO_3- is reabsorbed in the proximal tubule. 10 % in the thick ascending limb of loop of Henle and early DCTs.
  5 % of HCO_3- is reabsorbed in the late DCTs and collecting ducts.
  ** For the sake of the exam, Dr. Yanal has divided them simply to: 85% in proximal tubules, 10% in distal tubules and 5% in the collecting ducts, and mentioned in section 1 that loop of Henle has no role here.
- <u>Keep in mind that for each HCO_3– reabsorbed, an H^+ must be secreted</u>.
- Reabsorption of filtered HCO_3- is completed in the proximal tubule and loop of Henle. So, HCO_3- reabsorbed in the late DCTs and collecting ducts is not filtered HCO_3- (its source is not from filtered plasma) but is newly synthesized in renal tubular cells and then given to the blood.
  Further explanation:
- Keeping in mind that for each HCO_3- reabsorbed, an H^+ is secreted → as long as there's HCO_3- in the TF, each H^+ secreted will be buffered by HCO_3-, forming $H2CO_3$. This $H2CO_3$ will decompose to CO2 and H2O that will diffuse into tubular cells to reform HCO_3- and H^+. This HCO_3- will be reabsorbed into the blood [The detailed mechanism is explained later, so just understand the principle now].
- When all filtered HCO_3- is reabsorbed (i.e. there's no HCO_3- in TF), secreted H^+ will not combine with HCO_3- and HCO_3- synthesized in tubular cells will go into the blood (this is **new** HCO_3- not filtered HCO_3-).

- **<u>Rule:</u> H^+ secretion is coupled to HCO_3- reabsorption. When there's HCO_3- in TF (in early tubular segments from PCTs to early DCTs), H^+ secretion will be coupled to reabsorption of filtered HCO_3-. When there's no HCO_3- in TF (from late DCTs to the end of the nephron), H^+ secretion is coupled to reabsorption of new HCO_3- (HCO_3- synthesized in tubular cells).**

- The mechanism by which HCO_3– is reabsorbed also involves tubular secretion of H^+, but different tubular segments accomplish this task differently. Now, we will discuss how the kidney reabsorbs filtered HCO_3-, and how it forms new HCO_3-.

Reabsorption of Filtered HCO_3- (<u>H^+ secretion by secondary active transport in early tubular segments</u>)



- Reabsorption of filtered HCO_3- takes place in the PCTs, thick ascending limb of loop of Henle and early DCTs.
- The cellular mechanism in all these tubular regions is the same and is explained below.

- **<u>Mechanism of HCO_3- Reabsorption:</u>**
  Note:
  HCO_3- is a charged big molecule (i.e. cannot penetrate the cell membrane). It has no carrier in the apical side (lumen side) of the cell, but has one in the basolateral side. So, the wisest way to get it from the lumen into cells and then into the blood is to combine it with H^+ in the lumen, convert it into CO2, that will diffuse into the cell and get converted back to HCO_3- inside. And this is what actually happens. (see next page)

1- At the apical membrane, Na+ moves in and H+ moves out through Na+-H+ exchanger (countertransport).
2- The H^+ secreted into the lumen combines with filtered HCO_3- to form $H2CO_3$. $H2CO_3$ then decomposes into CO2 and H2O catalyzed by a **brush-border carbonic anhydrase**. The CO2 and H2O that are formed in this reaction readily cross the luminal membrane and enter the cell.
3- Inside the cell, the reactions occur in reverse. CO2 and H2O recombine to form $H2CO_3$, catalyzed by **intracellular carbonic anhydrase**. $H2CO_3$ is converted back into H^+ and HCO_3-.
4- Then, H^+ goes back into the lumen through Na^+-H^+ exchanger to aid in reabsorption of another filtered HCO_3-. HCO_3- is transported across the basolateral membrane into the blood (i.e., the HCO_3- is reabsorbed) by two mechanisms: Na^+-HCO_3- cotransport and Cl–-HCO_3- exchange.
5- So, here we are reabsorbing filtered HCO_3- but not excreting H^+, because the same H^+ is pumped back into the lumen (i.e. there's net reabsorption of HCO_3- but there's no net secretion of H^+).
6- 4320 molecules of bicarbonate can be reabsorbed by only one proton (H^+), there is no net secretion of hydrogen ions so far. (H^+ recycle again and again).
7- In the proximal tubules, H^+ concentration can be increased only about threefold to fourfold and the tubular fluid pH can be reduced to only about 6.7, although large amounts of H^+ are secreted by this nephron segment (because most of secreted H^+ are buffered by filtered HCO_3-).
8- Briefly, in early tubular segments, filtered HCO_3- is reabsorbed and H^+ is secreted through Na^+-H^+ exchanger but with no net secretion of H^+.

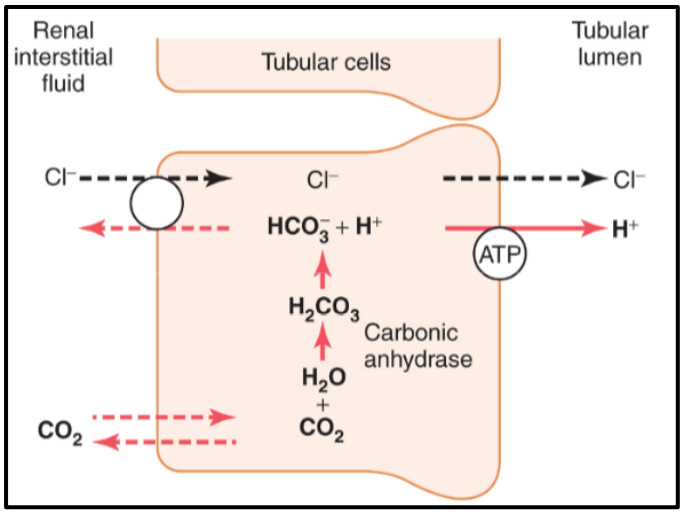
Formation of New HCO_3- (Secretion of H^+ by primary active transport in distal tubular segments)

Now, we've reabsorbed **all** filtered HCO_3-. The second important function of the kidney is to synthesize new HCO_3-. This is accomplished by secreting H^+ and reabsorbing HCO_3- (new HCO_3-).

- This occurs in the intercalated cells of late DCTs and collecting ducts.
- The cellular mechanism of H^+ secretion and HCO_3- reabsorption here is similar to the proximal tubules but the main difference is that H^+ moves across the luminal membrane by an active H^+ pump instead of by counter-transport, as occurs in the early parts of the nephron.

Mechanism of H^+ Secretion in intercalated cells:

Hydrogen ion secretion in these cells is accomplished in two steps: (1) the dissolved CO2 in this cell combines with H2O to form H_2CO_3, and (2) the H_2CO_3 then dissociates into HCO_3–, which is reabsorbed into the blood, plus H^+, which is secreted into the tubule by means of the **hydrogen-ATPase mechanism**.



- These H^+ pumps have a capacity, that if we go beyond it, there would be no secretion of H^+ (H^+ pumps can concentrate H^+ in the collecting tubules up to 900-fold). So, there must be a way by which we can get rid of secreted H^+ to allow for further secretion. This is what urinary buffers do.

- To understand this principle, bear these two rules in mind:

1- The minimum urinary pH is 4.5.

2- After completion of filtered HCO_3- reabsorption, the most important function of the kidney is to synthesize new HCO_3-. For each HCO_3- to be gained, an H^+ must be secreted.

→ Without urinary buffers, the first few H^+ ions secreted will lower the pH to 4.5, and H^+ secretion will stop. To maintain H^+ secretion and HCO_3- gain, we need urinary buffers that will neutralize secreted H^+.

- ❖ To understand this principle better, read the following paragraph from Guyton:

When H+ is secreted in excess of the HCO3– filtered into the tubular fluid, only a small part of the excess H+ can be excreted in the ionic form (H+) in the urine. The reason for this is that the minimal urine pH is about 4.5, corresponding to an H+ concentration of $10^{-4.5}$ mEq/L, or 0.03 mEq/L. Thus, for each liter of urine formed, a maximum of only about 0.03 mEq of free H+ can be excreted. To excrete the 80 mEq of nonvolatile acid formed by metabolism each day, about 2667 liters of urine would have to be excreted if the H+ remained free in solution.

The excretion of large amounts of H+ (on occasion as much as 500 mEq/day) in the urine is accomplished primarily by combining the H+ with buffers in the tubular fluid. The most important buffers are phosphate buffer and ammonia buffer. Other weak buffer systems, such as urate and citrate, are much less important.

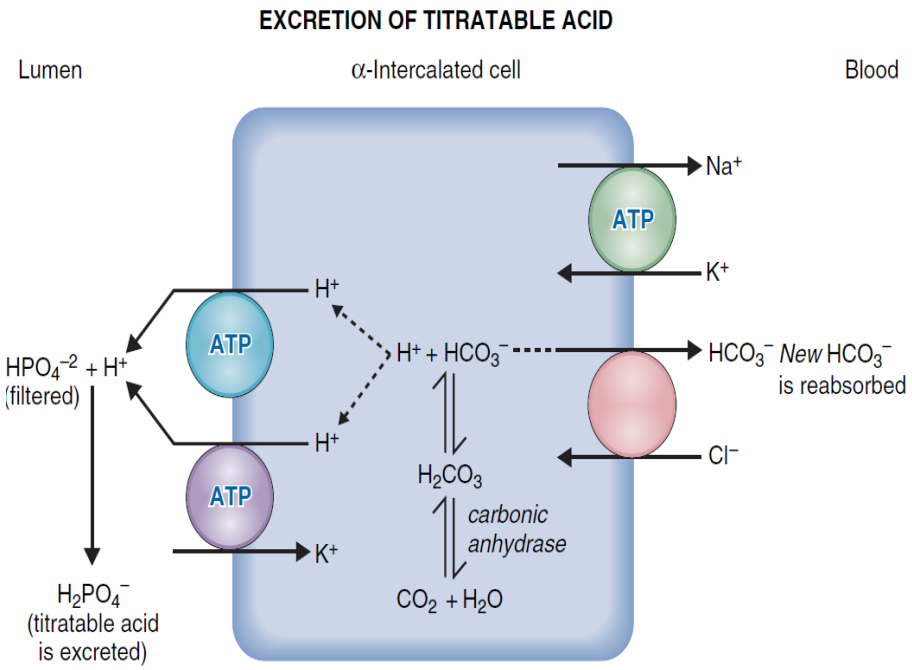
❖ **H^+ is excreted in two ways:**
Either by: **1- Excretion of H^+ as a titratable acid** (combining H^+ with phosphate buffer).
2- Excretion of H^+ as $NH4^+$.

- We said that if secreted H^+ finds HCO_3- in the lumen (i.e. filtered HCO_3- is still not completely reabsorbed), filtered HCO_3- will be reabsorbed in the above-mentioned way. However, when we reach late DCTs, all filtered HCO_3- is now reabsorbed, and each H^+ secreted will be coupled to reabsorption of new HCO_3-.

<u>How does that happen?</u>
Tubular cells metabolism produces CO2 and H2O, and then CA enzyme, $H2CO_3$ forms and dissociated into H^+ and HCO_3-. H^+ will be secreted (and won't combine with HCO_3- now), and HCO_3- will be reabsorbed.

Excretion of H^+ as Titratable Acid

- Titratable acid is H^+ excreted with urinary buffers.
- The most important urinary buffer is inorganic phosphate.
- 90% of the filtered phosphate is reabsorbed; only 10% of the filtered phosphate is left to be excreted as titratable acid in urine.
- Phosphate is present in the plasma in two forms: HPO4-2 and H2PO4-. The form we need for buffering is HPO4-2 because it can more easily combine with H^+.



- The mechanism of excretion of H^+ as titratable acid involves secretion of H^+ through H^+ pump in the apical membrane and reabsorption of new HCO_3- at the basolateral membrane (follow the figure above).
- The main purpose of H^+ secretion here is to reabsorb new HCO_3-. We need 80 mEq/ day of HCO_3- to satisfy body needs, so the question here "Do we have enough phosphate in urine?"

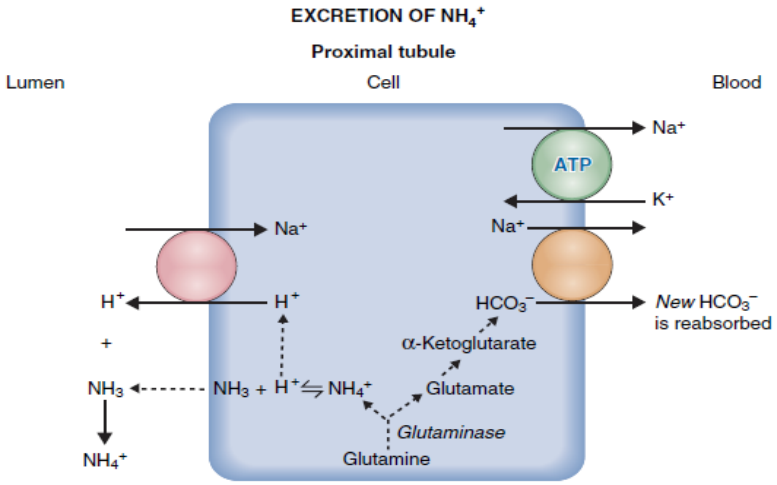
Phosphate concentration in the plasma is 1.25 mEq → Filtered load of phosphate = 1.25 x 180 = 225 mEq/ day. 90 % of filtered phosphate is reabsorbed and only 10 % are excreted in urine (i.e. available for buffering excreted H^+).

0.10 x 225 = 22.5 mEq/ day of phosphate are available for buffering.

- Every day, we want to excrete 80 mmol of nonvolatile H^+ and gain 80 mmol of HCO_3-, and apparently we don't have 80 mEq of phosphate for buffering 80 mmol of H^+.

Conclusion: Under normal conditions, much of the filtered phosphate is reabsorbed, and only about 20 mEq/day are available for buffering H^+. Therefore, much of the buffering of excess H^+ in the tubular fluid in acidosis does not occur through the phosphate buffer system but rather through ammonia buffer system.

Excretion of H^+ as $NH4^+$



- Ammonia buffer system is composed of ammonia (NH_3) and the ammonium ion ($NH4^+$) and is quantitatively more important than the phosphate buffer system.

- Ammonium ion is synthesized from glutamine, which comes mainly from the metabolism of amino acids in the liver. The glutamine delivered to the kidneys is transported into the epithelial cells of the proximal tubules, thick ascending limb of the loop of Henle, and distal tubules.

- Once inside the cell, each molecule of glutamine is metabolized in a series of reactions to ultimately form two $NH4^+$ and two HCO_3–.

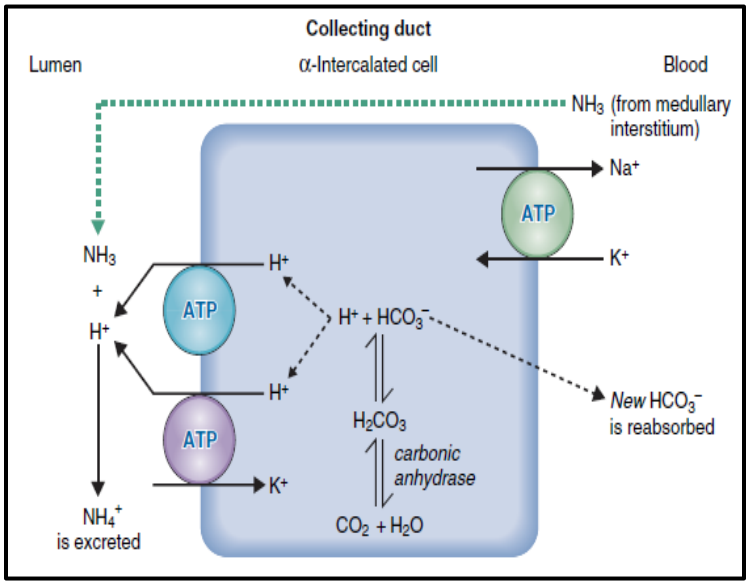
- The mechanism of H^+ excretion is different between the PCTs and the collecting ducts.

- **In the proximal tubule**, $NH4^+$ is in equilibrium with $NH_3 + H^+$. NH_3 diffuses into the lumen, H^+ secreted by Na^+-H^+ exchanger, and HCO_3- is reabsorbed. Thus, for each molecule of glutamine metabolized in the proximal tubules, two $NH4^+$ are secreted into the urine and two HCO_3- are reabsorbed into the blood. The HCO_3- generated by this process constitutes new bicarbonate.

- Some of the secreted $NH4^+$ is excreted, and others are delivered to the loop of Henle.

- Some of the secreted $NH4^+$ is reabsorbed in the thick ascending limb of loop of Henle. Consequently, $NH4^+$ becomes concentrated in the interstitial fluid of the inner medulla and papilla of the kidney.

- **In the collecting duct**, H^+ is secreted by H^+-K^+ ATPase in intercalated cells, and NH_3 diffuses from the medullary interstitum (around the thick ascending limb) into the lumen. There, it combines with H^+ forming $NH4^+$ that's charged and is thus not reabsorbed back.



- So, H^+ (that comes from the pump) combines with NH_3 (that diffuses from the medullary interstitium into the lumen) forming charged, non-reabsorbable $NH4^+$. And, because the diffusible NH_3^+ becomes trapped in the lumen, this is called **Diffusion Trapping of Ammonia**.

Chronic Acidosis Increases $NH4^+$ Excretion

- On a daily basis, H^+ is excreted as both titratable acid and $NH4^+$ so that normally all of the fixed H^+ produced from protein and phospholipid catabolism is eliminated from the body (and all of the HCO_3- used to buffer that fixed H^+ is replaced).
- The amount of H^+ excreted as titratable acid depends on the amount of urinary buffers present, but these are somehow limited. Therefore, to eliminate excess acids in cases of chronic acidosis, we depend more on excretion of H^+ as $NH4^+$.

- If the excess acids were introduced to the body chronically (ex: diabetic ketoacidosis), the kidney can get rid of the excess acid by activating glutaminase enzyme in proximal tubular cells and thus increase H^+ excreted and HCO_3- gained.
- This way of adaptation occurs if the acids were introduced chronically (i.e. slowly over a relatively long period of time). However, if someone ingests a large dose of aspirin (acute salicylate toxicity), the kidney cannot adapt and the patient ends up with acidosis.

Conclusion: The kidney is very efficient, but it's slow (it needs hours to start functioning and days to give you complete function).

Mechanism of this adaptation:
- In normal persons eating a relatively high protein diet, approximately 80 mEq of fixed H^+ is produced daily. The kidneys excrete all (100%) of the fixed acid that is produced: 40% is excreted as titratable acid (32 mEq/day) and 60% as $NH4^+$ (48 mEq/day).

- In persons with diabetic ketoacidosis, fixed acid production may be increased to 500 mEq/day, instead of the normal 80 mEq/day. To excrete this additional acid load, excretion of $NH4^+$ is increased.

- $NH4^+$ excretion is increased because acidosis induces the enzymes involved in glutamine metabolism, thereby increasing NH_3 synthesis. As more NH_3 is produced by the renal cells, more H^+ is excreted as $NH4^+$.

- Excretion of titratable acid, although less significantly, also increases.

- With chronic acidosis, the rate of $NH4^+$ excretion can increase to as much as 500 mEq/day. Therefore, **with chronic acidosis, the dominant mechanism by which acid is eliminated is excretion of $NH4^+$.** This also provides the most important mechanism for generating new bicarbonate during chronic acidosis.

Quantifying Renal Acid-Base Excretion

1- To know HCO_3- excretion, we multiply urinary flow rate by urinary HCO_3- concentration.

2- To know how much HCO_3- is **gained**, we calculate how much H^+ is excreted. As mentioned above, every H^+ excreted in urine has a new HCO_3- that was gained, and this H^+ was buffered as titratable acid/$NH4^+$. So:
Net HCO_3- gain= $NH4^+$ excretion $^+$ Urinary titratable acid – HCO_3- excretion

How can we know the amount of titratable acid in urine?
By titrating the urine with a strong base (NaOH) to a pH of 7.4, the pH of normal plasma, and the pH of the glomerular filtrate. This titration reverses the events that occurred in the tubular lumen when the tubular fluid was titrated by secreted H+. Therefore, the number of milliequivalents of NaOH required to return the urinary pH to 7.4 equals the number of milliequivalents of H+ added to the tubular fluid that combined with phosphate and other organic buffers.

- The titratable acid measurement does not include H+ in association with NH4+ because the pK of the ammonia-ammonium reaction is 9.2, and titration of urine (PH=4.5) with NaOH to a pH of 7.4 does not remove the H+ from NH4+.
*Note 1: according to the equation PH=Pk+log(base/acid), if the PH was 7.4 which is the physiological PH, that leads us to find that the acidic form [Nh4+] conc. in blood is much larger than the basic form [NH3].
*Note 2: The pK of ammonia is 9.2, so the buffering range for it is 8.2-10.2. Adding a *very little* amount of NaOH to the 4.5 PH ammonium solution will make the PH rise quickly to 7.4 since it's far from the buffering range of it, and this little amount of NaOH doesn't affect the *total concentration of ammonium*, that's why we can't use NaOH to meausre ammonium concetration.
- NH4+ excretion is known by measuring NH4+ in urine.

- The reason we subtract HCO_3– excretion is that the loss of HCO_3– is the same as the addition of H^+ to the blood .
- Total H^+ secretion = 4400 mmol/day = HCO_3- reabsorption (4320 mmol/d) + titratable acid ($NaHPO_4$-) ($_3$0 mmol/d) + NH_4^+ excretion (50 mmol/d).
- Net H^+ excretion = 79 mmol/day = titratable acid ($_3$0 mmol/d) $^+$ $NH4^+$ excretion (50 mmol/d) - HCO_3- excretion (1 mmol/d)
- IsoHydric principle: it states that if you know $\frac{HPo4}{H2po4}$ or $\frac{NH3}{NH4}$ etc. you can know the PH of the blood since H^+ is distributed to all of them.

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)

Henderson-Hasselbalch equation:
$pH = pK^{+} \log [A^-]/ [HA]$

Acidosis:	Alkalosis:
- Acidosis means pH below 7.35. - This decrease in pH occurs in one of two situations: 1- Decrease in HCO_3- → Metabolic Acidosis 2- Increase in CO2 → Respiratory Acidosis	Alkalosis means pH above 7.45. - This increase in pH occurs in one of two situations: 1- Increase in HCO_3- → Metabolic Alkalosis 2- Decrease in CO2 → Respiratory Alkalosis

- Acid-base disturbances are either due to HCO_3- disturbance, or CO2 disturbance. Disturbances in HCO_3- are metabolic, and disturbances in CO2 are respiratory.

- Metabolic Acidosis: results from decrease in HCO_3-, due to increased production of acid (diabetic ketoacidosis).
- Respiratory Acidosis: results from increase in CO2, due to hypoventilation.
- Metabolic Alkalosis: results from increase in HCO_3-, due to either loss of acid in urine, or gain of HCO_3-.
- Respiratory Alkalosis: results from hyperventilation.

The rest of the lecture was not explained well (so it will be unwise to write the recording as it is). So, I recommend reading pages 316-327 in Costanzo.

In this sheet, I will try, as much as I can, to fill the gap.

We have four main simple acid-base disturbances:
Simple acid-base disturbance: means acidosis or alkalosis that's either metabolic or respiratory and has only one cause.

1- Metabolic acidosis

- Overproduction or ingestion of fixed acid or loss of base produces a decrease in arterial [HCO_3-]. This decrease is the primary disturbance in metabolic acidosis.
- Overproduction of fixed acid → Diabetic ketoacidosis
  Loss of base → Renal tubular acidosis

Renal tubular acidosis is accumulation of acids in the body, due to failure of the kidney to either reabsorb filtered HCO3- (Proximal: type II RTA) or to secrete H+ (Distal: type I RTA).

- Type I RTA is more severe because it's more distal. In proximal RTA, there's still a chance to correct the disturbance in distal segments of the nephron.
- Decreased HCO_3– concentration causes a decrease in blood pH (acidemia).
- Acidemia causes hyperventilation (Kussmaul breathing), which is the respiratory compensation for metabolic acidosis.
- Correction of metabolic acidosis consists of increased excretion of the excess fixed H^+ as titratable acid and $NH4^+$, and increased reabsorption of "new" HCO_3–, which replenishes the blood HCO_3– concentration.
- The use of carbonic anhydrase enzyme inhibitors (Acetazolamide/Diamox) inhibit reabsorption of HCO3-, causing metabolic acidosis. Acetazolamide was used as a diuretic (not anymore - only used for glaucoma) since it inhibits the formation of H^+ and thereby inhibits its countertransport with Na^+ .
- In chronic metabolic acidosis, an adaptive increase in NH_3 synthesis aids in the excretion of excess H^+.

2. Metabolic alkalosis

- Loss of fixed H^+ or gain of base produces an increase in arterial [HCO_3-]. This increase is the primary disturbance in metabolic alkalosis.
- For example, in vomiting, H^+ is lost from the stomach, HCO_3– remains behind in the blood, and the [HCO_3–] increases.
- Increased HCO_3– concentration causes an increase in blood pH (alkalemia).
- Alkalemia causes hypoventilation, which is the respiratory compensation for metabolic alkalosis.

- Correction of metabolic alkalosis consists of increased excretion of HCO_3– because the filtered load of HCO_3– exceeds the ability of the renal tubule to reabsorb it.
- If metabolic alkalosis is accompanied by ECF volume contraction (e.g., vomiting), the reabsorption of HCO_3– increases (secondary to ECF volume contraction and activation of the renin–angiotensin II–aldosterone system), worsening the metabolic alkalosis (i.e., contraction alkalosis).

3- Respiratory acidosis

- Is caused by decreased alveolar ventilation and retention of CO2.
- Increased arterial Pco2, which is the primary disturbance, causes an increase in [H^+] and [HCO_3-] by mass action.
- There is no respiratory compensation for respiratory acidosis.
- Renal compensation consists of increased excretion of H^+ as titratable acid and $NH4^+$ and increased reabsorption of "new" HCO_3-. This process is aided by the increased Pco2, which supplies more H^+ to the renal cells for secretion. The resulting increase in serum [HCO_3-] helps to normalize the pH.
- In acute respiratory acidosis, renal compensation has not yet occurred.
- In chronic respiratory acidosis, renal compensation (increased HCO_3- reabsorption) has occurred. Thus, arterial pH is increased toward normal (i.e., a compensation).

4. Respiratory alkalosis

- Is caused by increased alveolar ventilation and loss of CO2.
- Decreased arterial Pco2, which is the primary disturbance, causes a decrease in [H^+] and [HCO_3-] by mass action.
- There is no respiratory compensation for respiratory alkalosis.
- Renal compensation consists of decreased excretion of H^+ as titratable acid and $NH4^+$ and decreased reabsorption of "new" HCO_3–. This process is aided by the decreased Pco2, which causes a deficit of H^+ in the renal cells for secretion. The resulting decrease in serum [HCO_3–] helps to normalize the pH.
- In acute respiratory alkalosis, renal compensation has not yet occurred.
- In chronic respiratory alkalosis, renal compensation (decreased HCO_3– reabsorption) has occurred. Thus, arterial pH is decreased toward normal (i.e., a compensation).
- Symptoms of hypocalcemia (e.g., tingling, numbness, muscle spasms) may occur because H^+ and $Ca2^+$ compete for binding sites on plasma proteins. Decreased [H^+] causes increased protein binding of $Ca2^+$ and decreased free ionized $Ca2^+$.

Clinical Measurements and Analysis of Acid-Base Disorders

Appropriate therapy of acid-base disorders requires proper diagnosis. The simple acid-base disorders described previously can be diagnosed by analyzing three measurements from an arterial blood sample: pH, plasma HCO_3– concentration, and PCO2.

- The diagnosis of simple acid-base disorders involves several steps.

1- We examine the pH:
By examining the pH, one can determine whether the disorder is acidosis or alkalosis. A pH less than 7.35 indicates acidosis, whereas a pH greater than 7.45 indicates alkalosis.

2- **To look at HCO_3- and CO2 to know whether the disturbance is metabolic or respiratory:**
The normal value for PCO2 is about 40 mm Hg, and for HCO_3–, it is 24 mEq/L.

- If there's a disturbance in HCO_3-, then it's metabolic. Increased HCO_3- means metabolic alkalosis and decreased HCO_3- means metabolic acidosis.

- If there's a disturbance in CO2, then it's respiratory. Increased CO2 means respiratory acidosis and decreased CO2 means respiratory alkalosis.

3- We look at CO2 and HCO_3- again to see whether there's renal and respiratory compensation or not.

- In metabolic disturbances, there's respiratory compensation:
a- In metabolic acidosis, there's decrease in HCO_3-. The respiratory system tries to compensate by lowering CO2, by hyperventilation (acidosis activates chemoreceptors in the carotid bodies to increase the respiratory rate, to wash out CO2).

b- In metabolic alkalosis, there's increase in HCO_3-. The respiratory system tries to compensate by increasing CO2, by hypoventilation.

- In respiratory disturbances, there's metabolic compensation:
a- In respiratory acidosis, there's increase in CO2. The kidney tries to compensate by excreting the excess acid as titratable acid and as $NH4^+$, both of which are associated with **HCO_3- gain**.

b- In respiratory alkalosis, there's decrease in CO2. The kidney tries to compensate by decreasing excretion of acid and **decreasing the formation of new, gained HCO_3-.**

It's noteworthy to mention that renal compensation is slow. So, if there's an acute respiratory disturbance, renal compensation will be minimal (for each 10 mmHg increase in CO2, there's only 1 mEq/L increase in HCO_3-). On the other hand, if there's a chronic respiratory disturbance, renal compensation will be considerable and will normalize the pH (for each 10 mmHg increase in CO2, there's 4 mEq/L increase in HCO_3-) - *Don't memorize the numbers*.

- For each increase/decrease in CO2, there's a compensatory increase/decrease in HCO_3-. This is accomplished by renal compensation.
- For each increase/decrease in HCO_3-, there's a compensatory increase/decrease in CO2. This is accomplished by respiratory compensation.
- These compensatory increases or decreases are predictable, based on the numbers shown in the table below (it's important to read them and understand the concept, but don't memorize them).

Table 7–3 Renal Rules for Predicting Compensatory Responses in Simple Acid-Base Disorders

Acid-Base Disturbance	Primary Disturbance	Compensation	Predicted Compensatory Response
Metabolic Acidosis	↓ [HCO_3^-]	↓ Pco_2	1 mEq/L decrease in HCO_3^- → 1.3 mm Hg decrease in Pco_2
Metabolic Alkalosis	↑ [HCO_3^-]	↑ Pco_2	1 mEq/L increase in HCO_3^- → 0.7 mm Hg increase in Pco_2
Respiratory Acidosis			
Acute	↑ Pco_2	↑ [HCO_3^-]	1 mm Hg increase in Pco_2→ 0.1 mEq/L increase in HCO_3^-
Chronic	↑ Pco_2	↑ [HCO_3^-]	1 mm Hg increase in Pco_2→ 0.4 mEq/L increase in HCO_3^-
Respiratory Alkalosis			
Acute	↓ Pco_2	↓ [HCO_3^-]	1 mm Hg decrease in Pco_2→ 0.2 mEq/L decrease in HCO_3^-
Chronic	↓ Pco_2	↓ [HCO_3^-]	1 mm Hg decrease in Pco_2→ 0.4 mEq/L decrease in HCO_3^-

- For each 1 mEq/L decrease in HCO_3-, there's 1.3 mmHg (1 for the sake of the exam) decrease in Pco2, whereas for each 1 mEq/L increase in HCO_3-, there's 0.7 mmHg increase in Pco2 - *You should memorize these numbers only*. So, respiratory compensation of metabolic alkalosis is less efficient than that of metabolic acidosis. Why? [Just understand the concept].
- Hyperventilation decreases Pco2 and increases Po2. Hypoventilation does the opposite.

→ When acidosis causes hyperventilation, we get rid of CO2 and increase O2. The increase in O2 is neither good nor bad (if PaO2 becomes 130 for example, nothing will occur).
On the other hand, when alkalosis causes hypoventilation, we increase Pco2 and decrease Po2. The body cannot tolerate decrease in Po2 a lot (the minimum tolerable value of Po2 is 60 mmHg), so CO2 retention (in case of hypoventilation) will not be as large as CO2 washout (in case of hyperventilation).

- If lab values are consistent with this table, then the acid-base disturbanceis simple (i.e. it's either metabolic or respiratory and has only one cause).

- If lab values are inconsistent with this table, then the acid-base disturbance is mixed (i.e. the patient has mixed respiratory and metabolic problem, or even two metabolic disturbances at the same time).

- If a patient has metabolic acidosis, respiratory compensation should get rid of 1.3 mmHg of CO2 for each 1 mEq/L of HCO_3-. If the decrease is more than that, there must be another cause of hyperventilation, causing a huge decrease in Pco2. This is called mixed acid-base disturbance (because it has metabolic and respiratory causes).

- Is it possible to see a patient having mixed metabolic disturbance?

Yes. If he/she is producing excess fixed acids due to diabetic ketoacidosis, and losing gastric H^+ due to vomiting, he/she will have mixed metabolic acid-base disturbance (metabolic acidosis and alkalosis at the same time).
- Also, if someone has hyperaldosteronism and is vomiting, there would be mixed metabolic alkalosis.
- If someone has diabetic ketoacidosis and ingests an overdose of aspirin, there would be mixed metabolic acidosis.

- Is it possible to see a patient having mixed respiratory disturbance?

No. Because, unlike metabolism, respiration has only one player which is the lung. The lung can only hyperventilate or hypoventilate but it never does them both at the same time.

Table 7–2 Summary of Acid-Base Disorders

Disorder	$CO_2 + H_2O$	↔	H^+	+	HCO_3^-	Respiratory Compensation	Renal Compensation or Correction
Metabolic Acidosis	↓		↑		**↓**	Hyperventilation	↑ HCO_3^- reabsorption (correction)
Metabolic Alkalosis	↑		↓		**↑**	Hypoventilation	↑ HCO_3^- excretion (correction)
Respiratory Acidosis	**↑**		↑		↑	None	↑ HCO_3^- reabsorption (compensation)
Respiratory Alkalosis	**↓**		↓		↓	None	↓ HCO_3^- reabsorption (compensation)

Bold arrows indicate initial disturbance.

Examples: (These examples are mentioned in the slides, and they are very helpful, but you can skip them if you want).

1- Maha is a 45-year-old female admitted to the E.R with a severe asthma attack. She has been experiencing increasing shortness of breath since admission three hours ago. Her arterial blood gas result is as follows:

pH = 7.22, PaCO2 = 55, HCO_3- = 25

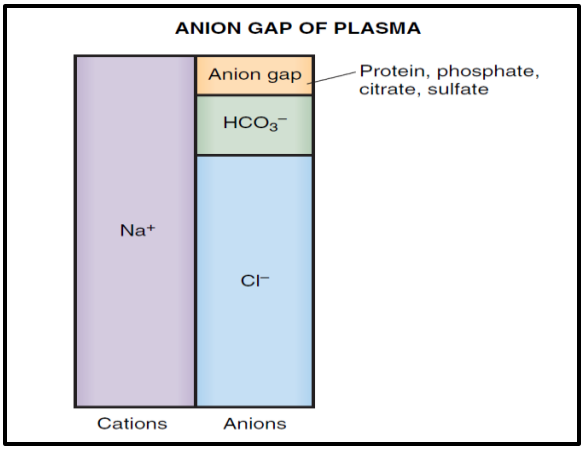
- pH is below 7.35 → Acidosis
- PaCO2 is high → Respiratory Acidosis
- HCO_3- is normal → Slight renal compensation (because it's an acute respiratory disturbance).

2- Maher is a 55-year-old male admitted to E.R with a recurring bowel obstruction. He has been experiencing intractable vomiting for the last several hours despite the use of antiemetics. Here is his arterial blood gas result:
pH = 7.50, PaCO2 = 42, HCO_3- = 33

- pH is above 7.45 → Alkalosis
- PaCO2 is normal.
- HCO_3- is high → Metabolic alkalosis

- These two patients are uncompensated. Patient in example 1 has respiratory acidosis with minimal renal compensation. Patient in example 2 has metabolic alkalosis with no respiratory compensation.

Anion Gap of Plasma



- The plasma is always electroneutral (i.e. cations are equal to anions).
- The major cation in the plasma is Na^+.
- The major anions in the plasma are Cl- and HCO_3-.
- Na^+ concentration in the plasma is greater than the sum of Cl- and HCO_3-, which means that there must be unmeasured anions, because electroneutrality in the plasma is never violated. These unmeasured anions include plasma proteins, phosphate, citrate, sulfate … etc. HCO_3-

-The anion gap of plasma is calculated as follows:
-Plasma anion gap = $[Na^+]-([HCO_3-]^+[Cl-])$
where
Plasma anion gap = Unmeasured anions (mEq/L)
$[Na^+]$ = Measured cation (mEq/L)
$[HCO_3-]$ and [Cl–] = Measured anions (mEq/L)

-The range of normal values for the plasma anion gap is 8 to 16 mEq/L.

-The plasma anion gap is useful primarily in the differential diagnosis of metabolic acidosis. How?
Metabolic acidosis is associated with decrease in HCO_3- (which is a measured anion). Assuming that Na^+ is unchanged, if this anion was replaced by another measured anion (Cl-) to maintain electroneutrality, the anion gap will be normal (because one measured anion is replaced by another measure anion). On the other hand, if this anion is replaced by an unmeasured anion, there would be increased anion gap.
-If metabolic acidosis results from production of fixed acid (diabetic ketoacidosis, lactic acidosis, salicylate poisoning), the excess acid will accumulate in the plasma (unmeasured acid), and HCO_3- will decrease. The result is increased anion gap.
-If metabolic acidosis results from loss of HCO_3- (renal tubular acidosis, diarrhea), the excess acid will be replaced by Cl- (measured anion). So, although HCO_3- decreases, Cl- increases, and anion gap remains normal.
-This type of metabolic acidosis is called hyperchloremic metabolic acidosis with a normal anion gap.

A 45-year-old woman develops severe diarrhea while on vacation. She has the following arterial blood values:

pH = 7.25
Pco_2 = 24 mm Hg
$[HCO_3^-]$ = 10 mEq/L
Venous blood samples show decreased blood $[K^+]$ and a normal anion gap.

3. The correct diagnosis for this patient is

(A) metabolic acidosis
(B) metabolic alkalosis
(C) respiratory acidosis
(D) respiratory alkalosis
(E) normal acid–base status

4. Which of the following statements about this patient is correct?

(A) She is hypoventilating
(B) The decreased arterial $[HCO_3^-]$ is a result of buffering of excess H^+ by HCO_3^-
(C) The decreased blood $[K^+]$ is a result of exchange of intracellular H^+ for extracellular K^+
(D) The decreased blood $[K^+]$ is a result of increased circulating levels of aldosterone
(E) The decreased blood $[K^+]$ is a result of decreased circulating levels of antidiuretic hormone (ADH)

6. The reabsorption of filtered HCO_3^-

(A) results in reabsorption of less than 50% of the filtered load when the plasma concentration of HCO_3^- is 24 mEq/L
(B) acidifies tubular fluid to a pH of 4.4
(C) is directly linked to excretion of H^+ as NH_4^+
(D) is inhibited by decreases in arterial Pco_2
(E) can proceed normally in the presence of a renal carbonic anhydrase inhibitor

8. To maintain normal H^+ balance, total daily excretion of H^+ should equal the daily

(A) fixed acid production plus fixed acid ingestion
(B) HCO_3^- excretion
(C) HCO_3^- filtered load
(D) titratable acid excretion
(E) filtered load of H^+

18. A patient has the following arterial blood values:

pH = 7.52
Pco_2 = 20 mm Hg
$[HCO_3^-]$ = 16 mEq/L
Which of the following statements about this patient is most likely to be correct?

(A) He is hypoventilating
(B) He has decreased ionized $[Ca^{2+}]$ in blood
(C) He has almost complete respiratory compensation
(D) He has an acid–base disorder caused by overproduction of fixed acid
(E) Appropriate renal compensation would cause his arterial $[HCO_3^-]$ to increase

19. Which of the following would best distinguish an otherwise healthy person with severe water deprivation from a person with the syndrome of inappropriate antidiuretic hormone (SIADH)?

(A) Free-water clearance (C_{H_2O})
(B) Urine osmolarity
(C) Plasma osmolarity
(D) Circulating levels of antidiuretic hormone (ADH)
(E) Corticopapillary osmotic gradient

21. A patient arrives at the emergency room with low arterial pressure, reduced tissue turgor, and the following arterial blood values:

pH = 7.69
$[HCO_3^-]$ = 57 mEq/L
Pco_2 = 48 mm Hg

Which of the following responses would also be expected to occur in this patient?

(A) Hyperventilation
(B) Decreased K^+ secretion by the distal tubules
(C) Increased ratio of $H_2PO_4^-$ to HPO_4^{-2} in urine
(D) Exchange of intracellular H^+ for extracellular K^+

30. Which set of arterial blood values describes a heavy smoker with a history of emphysema and chronic bronchitis who is becoming increasingly somnolent?

	pH	HCO_3^- (mEq/L)	Pco_2 (mm Hg)
(A)	7.65	48	45
(B)	7.50	15	20
(C)	7.40	24	40
(D)	7.32	30	60
(E)	7.31	16	33

31. Which set of arterial blood values describes a patient with partially compensated respiratory alkalosis after 1 month on a mechanical ventilator?

	pH	HCO_3^- (mEq/L)	Pco_2 (mm Hg)
(A)	7.65	48	45
(B)	7.50	15	20
(C)	7.40	24	40
(D)	7.32	30	60
(E)	7.31	16	33

32. Which set of arterial blood values describes a patient with chronic renal failure (eating a normal protein diet) and decreased urinary excretion of NH_4^+?

	pH	HCO_3^- (mEq/L)	Pco_2 (mm Hg)
(A)	7.65	48	45
(B)	7.50	15	20
(C)	7.40	24	40
(D)	7.32	30	60
(E)	7.31	16	33

33. Which set of arterial blood values describes a patient with untreated diabetes mellitus and increased urinary excretion of NH_4^+?

	pH	HCO_3^- (mEq/L)	Pco_2 (mm Hg)
(A)	7.65	48	45
(B)	7.50	15	20
(C)	7.40	24	40
(D)	7.32	30	60
(E)	7.31	16	33

34. Which set of arterial blood values describes a patient with a 5-day history of vomiting?

	pH	HCO_3^- (mEq/L)	Pco_2 (mm Hg)
(A)	7.65	48	45
(B)	7.50	15	20
(C)	7.40	24	40
(D)	7.32	30	60
(E)	7.31	16	33