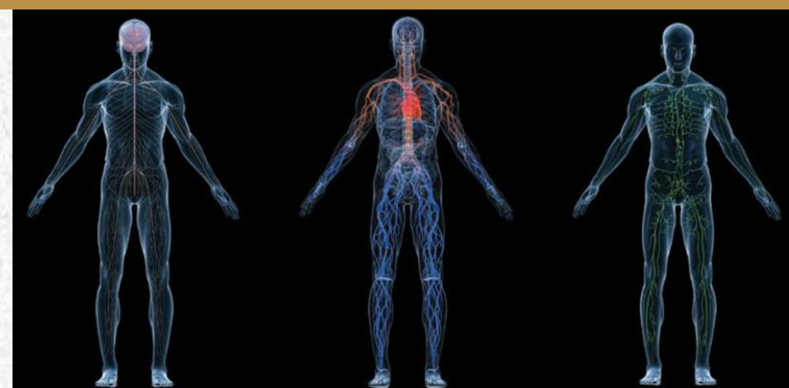
UNIT V

GUYTON AND HALL *Textbook of*

Medical Physiology

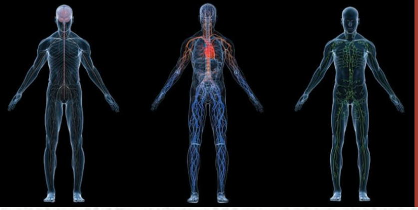
TWELFTH EDITION



Chapter 30:

Acid-Base Regulation in the Kidney

Chapter 30



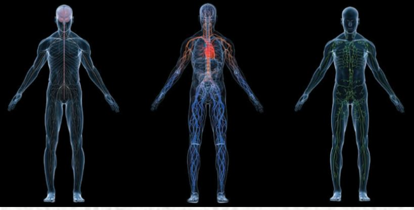
Mechanisms of Hydrogen Ion Regulation

$[H^+]$ is precisely regulated at 3-5 x 10^{-8} moles/L
(pH range 7.2 -7.4)

1. Body fluid chemical buffers (rapid but temporary)
   - bicarbonate - ammonia
   - proteins - phosphate

2. Lungs (rapid, eliminates CO_2)
   $\uparrow [H^+] \longrightarrow \uparrow$ ventilation $\longrightarrow \uparrow CO_2$ loss

3. Kidneys (slow, powerful); eliminates non-volatile acids
   - secretes H^+
   - reabsorbs HCO_3^-
   - generates new HCO_3^-



Buffer Systems in the Body

Bicarbonate : most important ECF buffer

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

Phosphate : important renal tubular buffer

$$HPO_4^{--} + H^+ \longleftrightarrow H_2PO_4^-$$

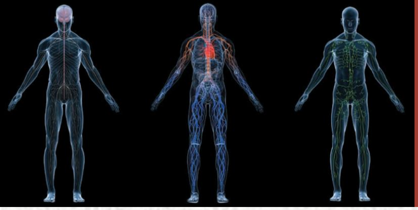
Ammonia : important renal tubular buffer

$$NH_3 + H^+ \longleftrightarrow NH_4^+$$

Proteins : important intracellular buffers

$$H^+ + Hb \longleftrightarrow HHb$$

(60-70% of buffering is in the cells)



Importance of Buffer Systems

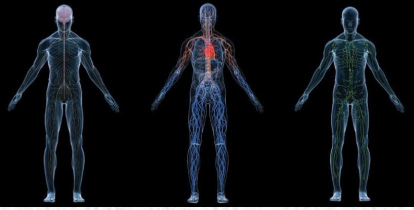
Normal H^+ concentration = 0.00004 mmol/L

Amount of non-volatile acid produced
~ 60-80 mmol/day

80 mmol /42 L = 1.9 mmol/L

= 47,500 times > normal H^+ concentration

PH ----6.8-8 lives for hours



Bicarbonate Buffer System

$$H_2O + CO_2 \overset{\text{carbonic anhydrase}}{\longleftrightarrow} H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

$$pH = pK + \log \frac{HCO_3^-}{\alpha \ pCO_2}$$

$\alpha = 0.03$

$pK = 6.1$

Effectiveness of buffer system depends on:

- concentration of reactants
- pK of system and pH of body fluids

Titration curve for bicarbonate buffer system.

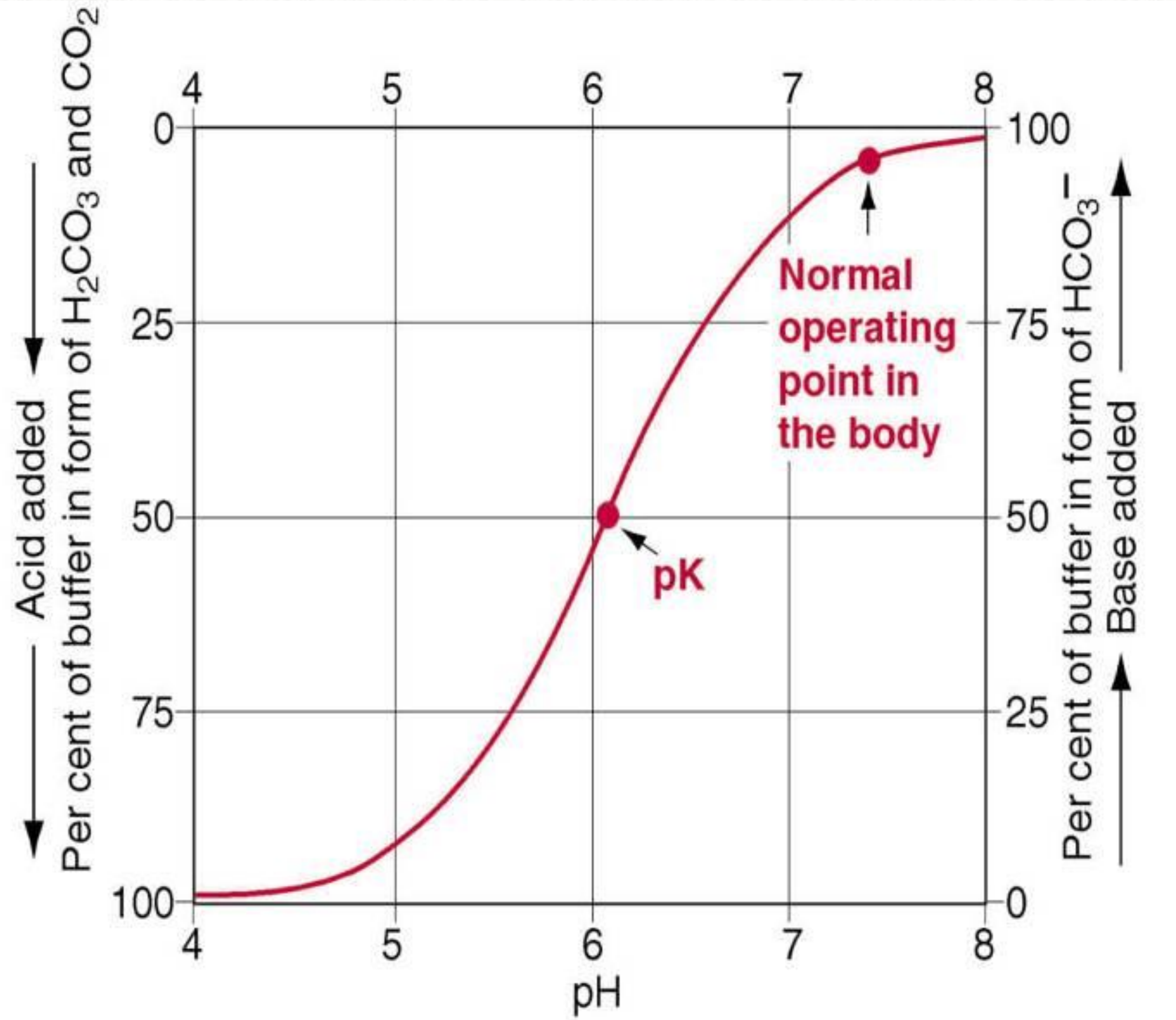
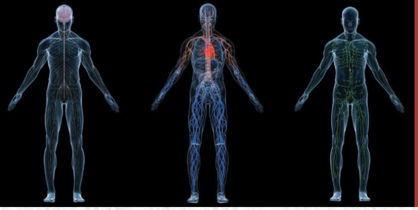


Figure 30-1.

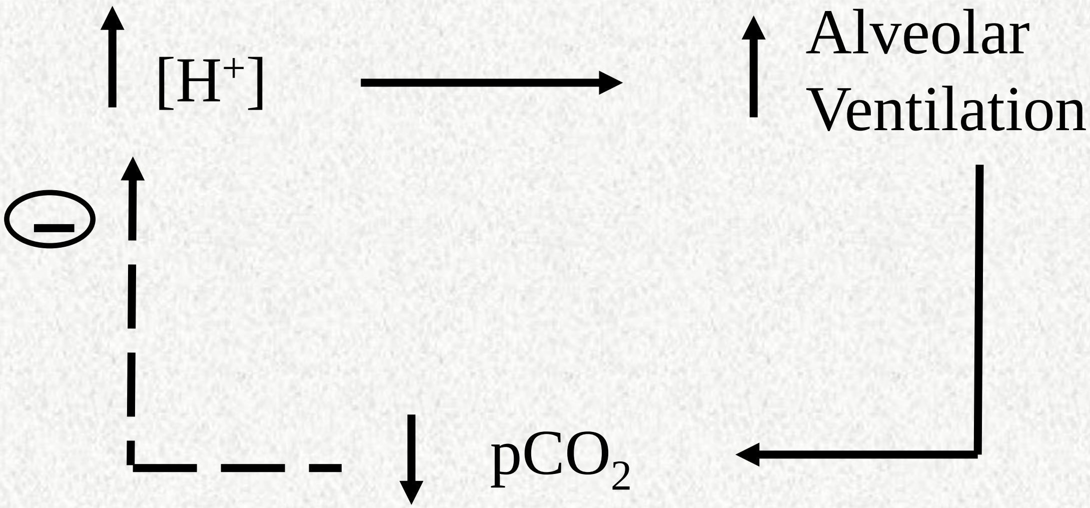
Bicarbonate Buffer System

Is the most important buffer in extracellular fluid even though the concentration of the components are low and pK of the system is 6.1, which is not very close to normal extracellular fluid pH (7.4).

Reason: the components of the system (CO_2 and HCO_3^-) are closely regulated by the lungs and the kidneys



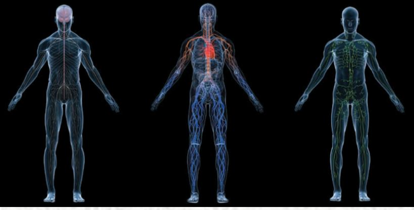
Respiratory Regulation of Acid-Base Balance



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

Feedback Gain = 1.0 to 3.0

(corrects 50 to 75 %)

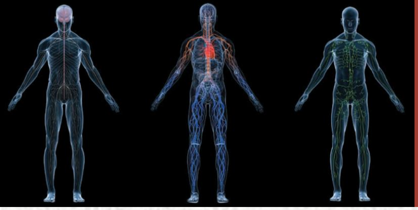
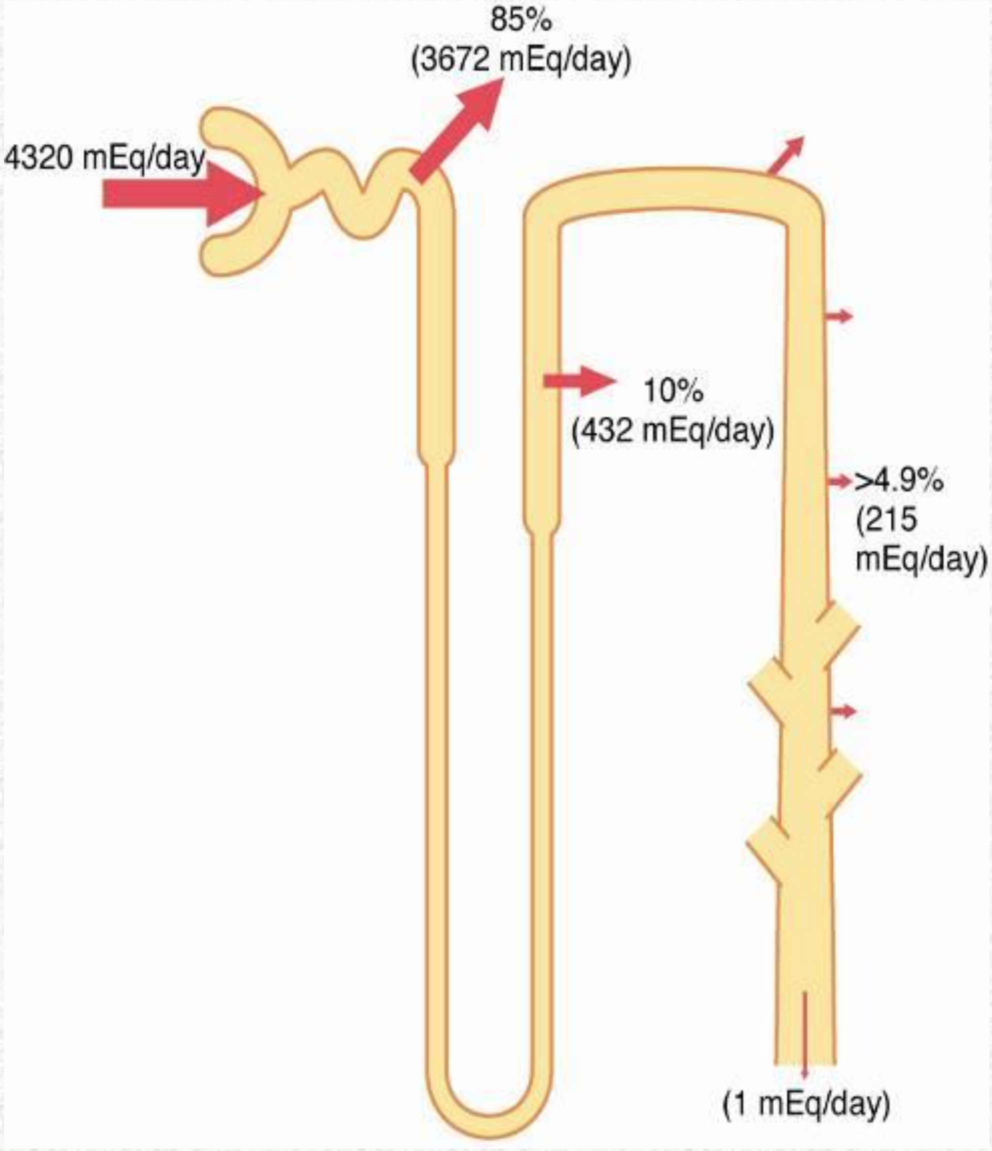


Renal Regulation of Acid-Base Balance

- Kidneys eliminate non-volatile acids (H_2SO_4, H_3PO_4) (~ 80 mmol/day)
- Filtration of HCO_3^- (~ 4320 mmol/day)
- Secretion of H^+ (~ 4400 mmol/day)
- Reabsorption of HCO_3^- (~ 4319 mmol/day)
- Production of new HCO_3^- (~ 80 mmol/day)
- Excretion of HCO_3^- (1 mmol/day)

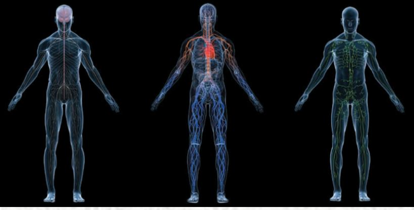
Kidneys conserve HCO_3^- and excrete acidic or basic urine depending on body needs

Reabsorption of bicarbonate (and H^+ secretion) in different segments of renal tubule.

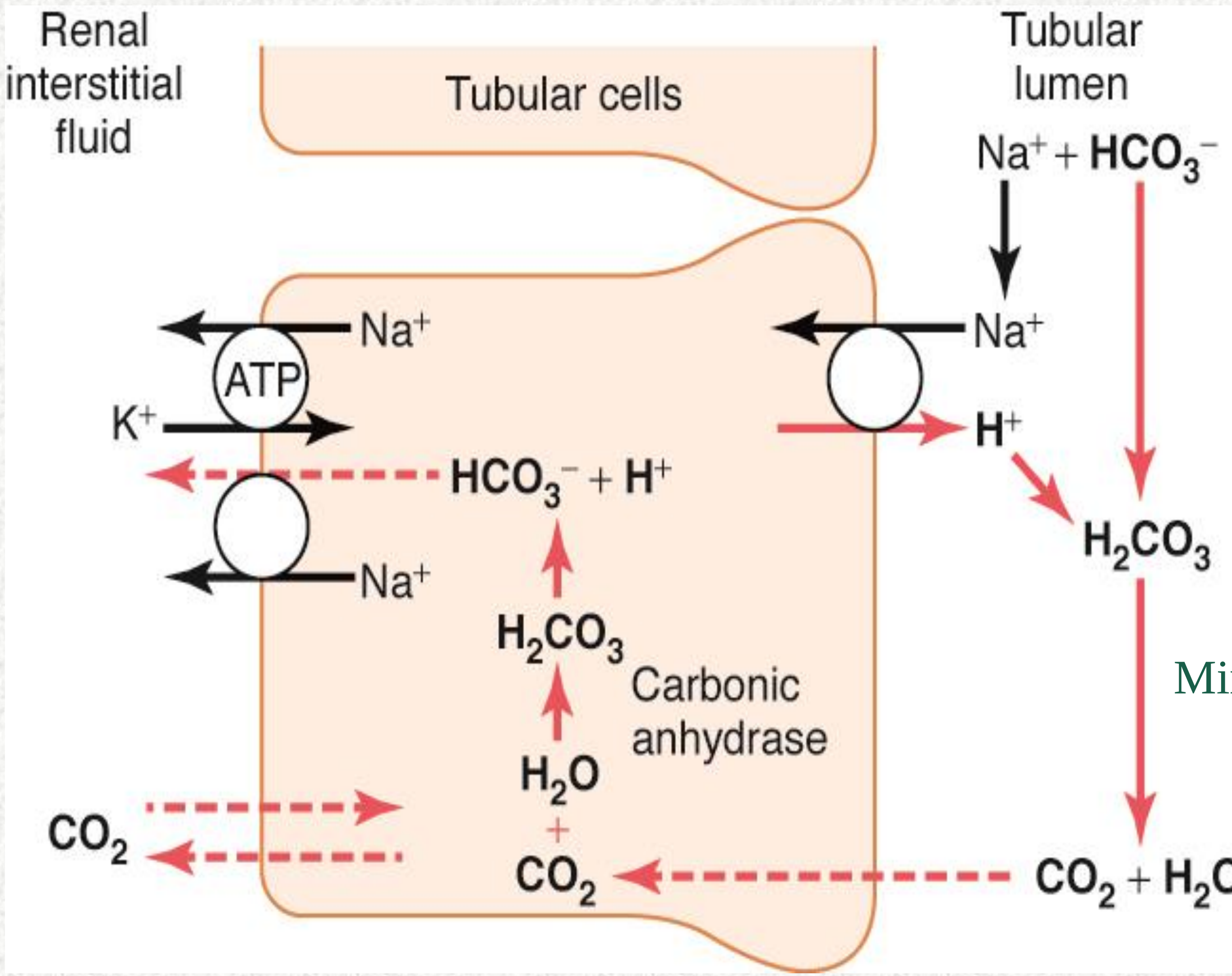



Key point:
For each HCO_3^- reabsorbed, there must be a H^+ secreted

Figure 30-4.



Mechanisms for HCO_3^- reabsorption and Na^+ - H^+ exchange in proximal tubule and thick loop of Henle



Minimal pH
~ 6.7

Figure 30-5.

HCO_3^- reabsorption and H^+ secretion in intercalated cells of late distal and collecting tubules

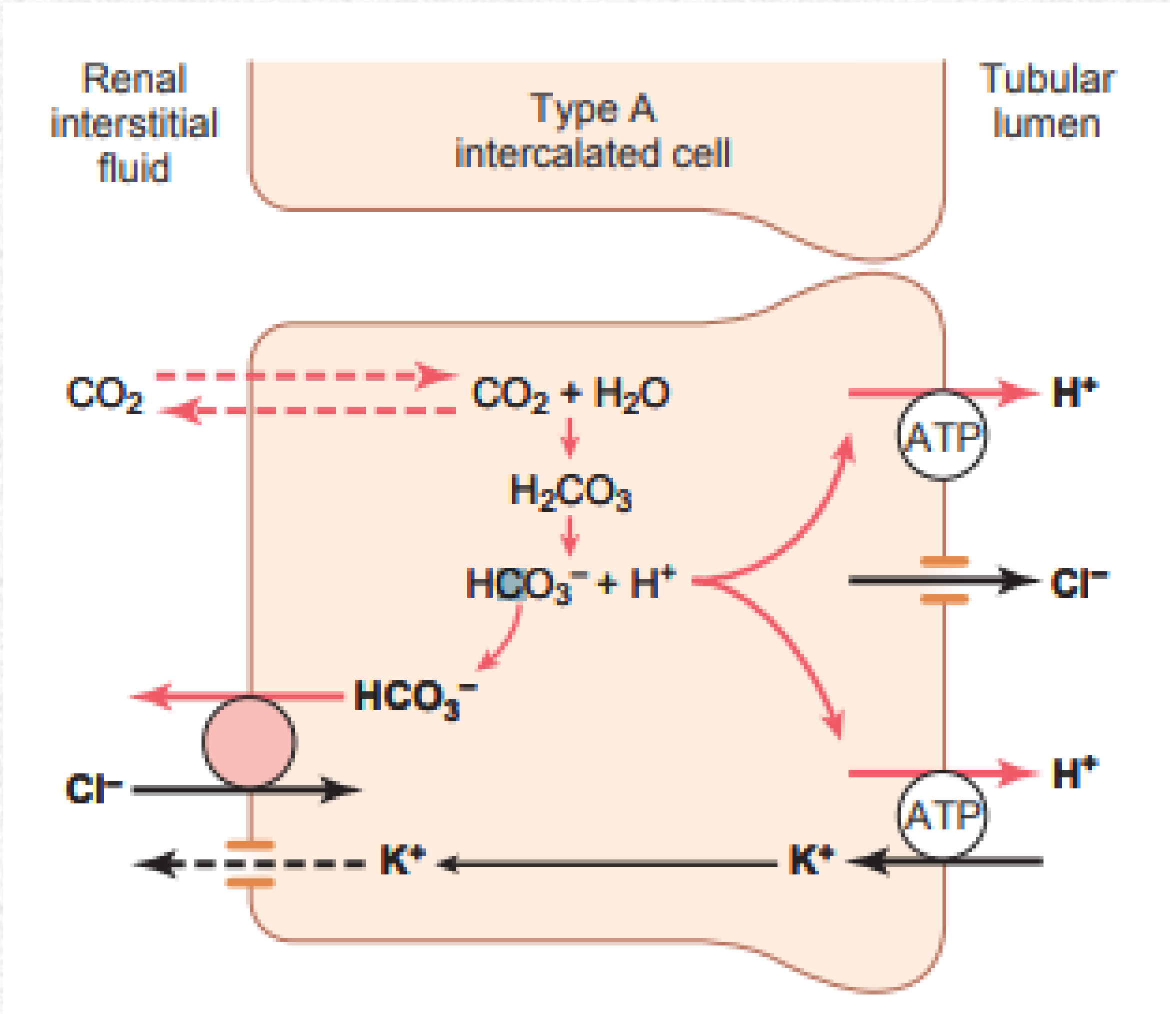
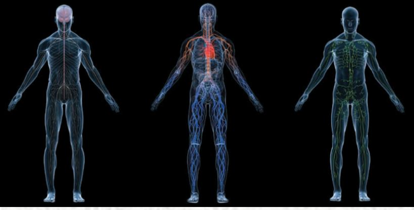


Figure 30-6.

Minimal pH ~4.5



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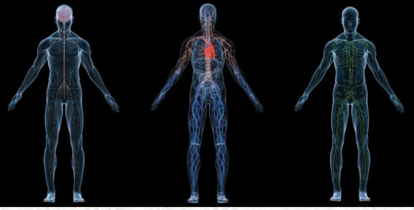


Regulation of H^+ secretion

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

$$pH = pK + \log \frac{HCO_3^-}{\alpha \; pCO_2}$$

- Increased pCO_2 increases H^+ secretion

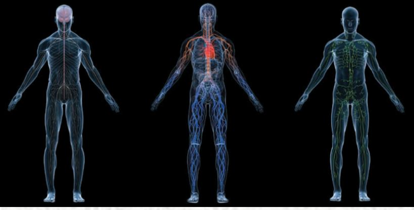
  i.e. respiratory acidosis

- Increased extracellular H^+ increases H^+ secretion

  i.e. metabolic or respiratory acidosis

- Increased tubular fluid buffers increases H^+ secretion

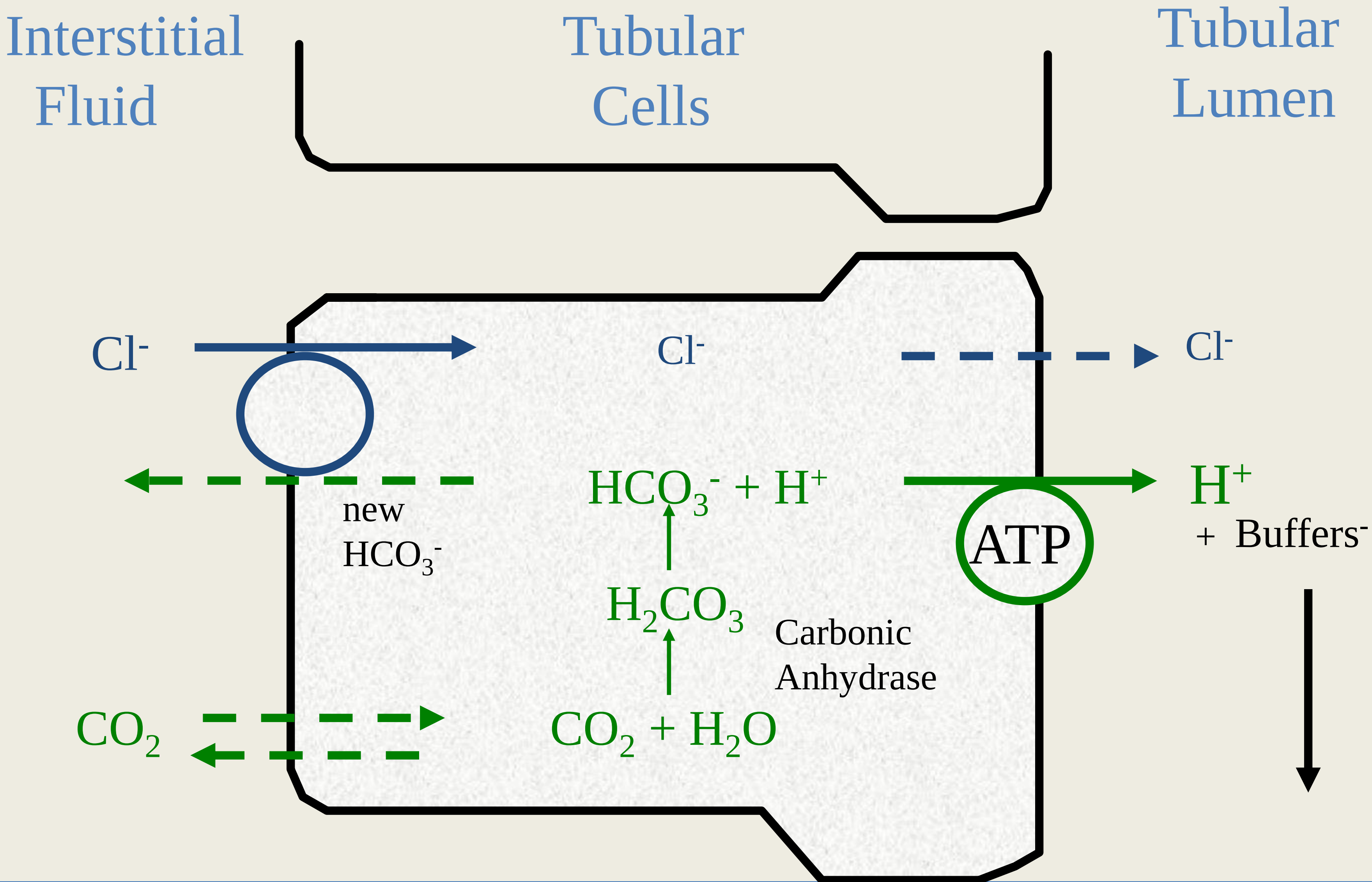
  i.e. metabolic or respiratory acidosis



Renal Compensations for Acid-Base Disorders

- Acidosis:
  - increased H^+ secretion
  - increased HCO_3^- reabsorption
  - production of new HCO_3^-
- Alkalosis:
  - decreased H^+ secretion
  - decreased HCO_3^- reabsorption
  - loss of HCO_3^- in urine

In acidosis all HCO_3^- is titrated and excess H^+ in tubule is buffered



Importance of Renal Tubular Buffers

Minimum urine pH = 4.5

$= 10^{-4.5}$

$= 3 \times 10^{-5}$ moles/L

i.e. the maximal $[H^+]$ of urine is 0.03 mmol/L

Yet, the kidneys must excrete, under normal conditions, at least 60 mmol non-volatile acids each day. To excrete this as free H^+ would require :

$$\frac{60 \text{ mmol}}{.03 \text{mmol/L}} = 2000 \text{ L per day !!!}$$

Buffering of secreted H^+ by filtered phosphate ($NaHPO_4^-$) and generation of "new" HCO_3^-

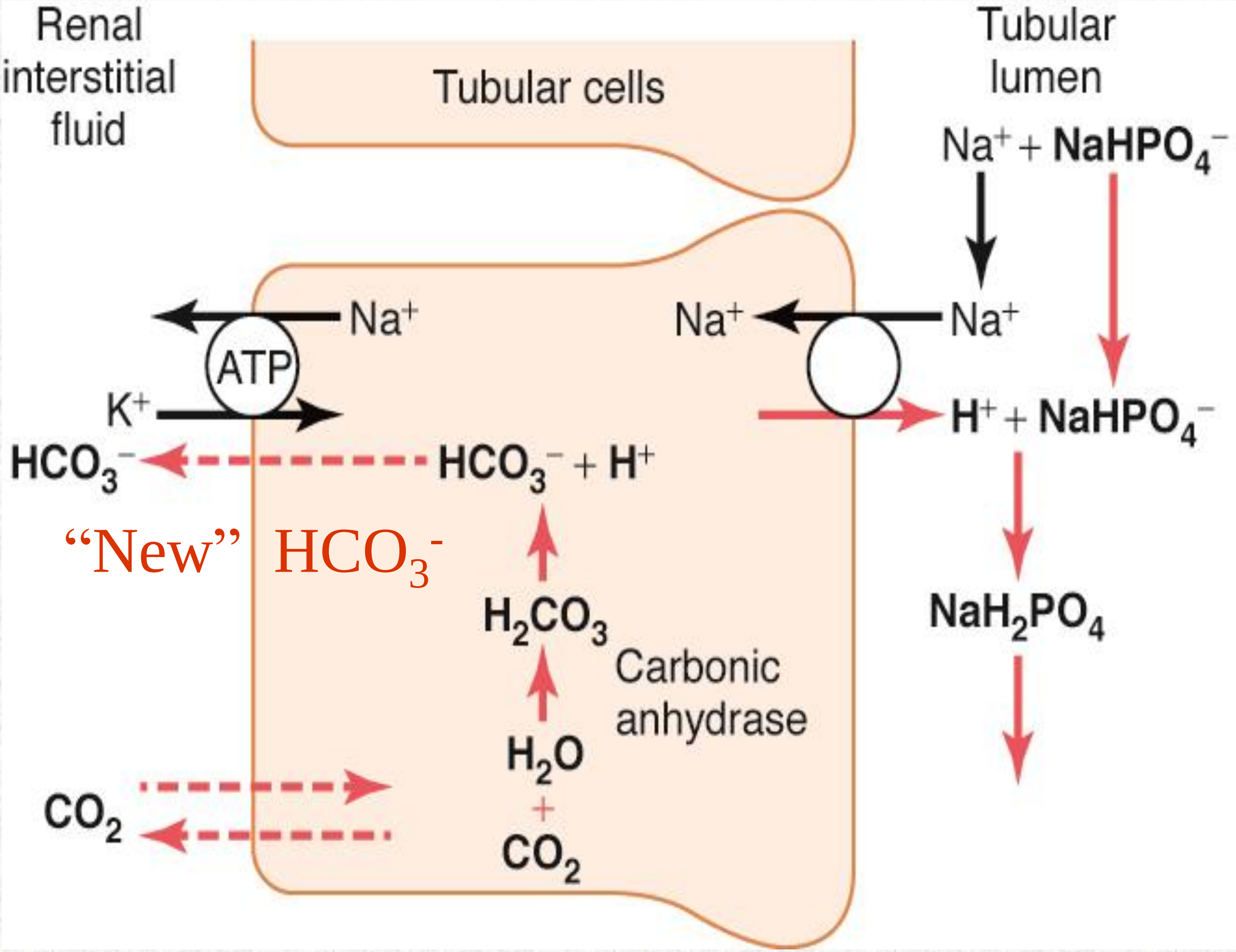
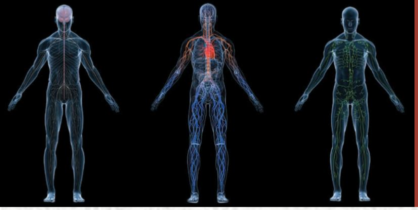


Figure 30-7.



Phosphate as a Tubular Fluid Buffer

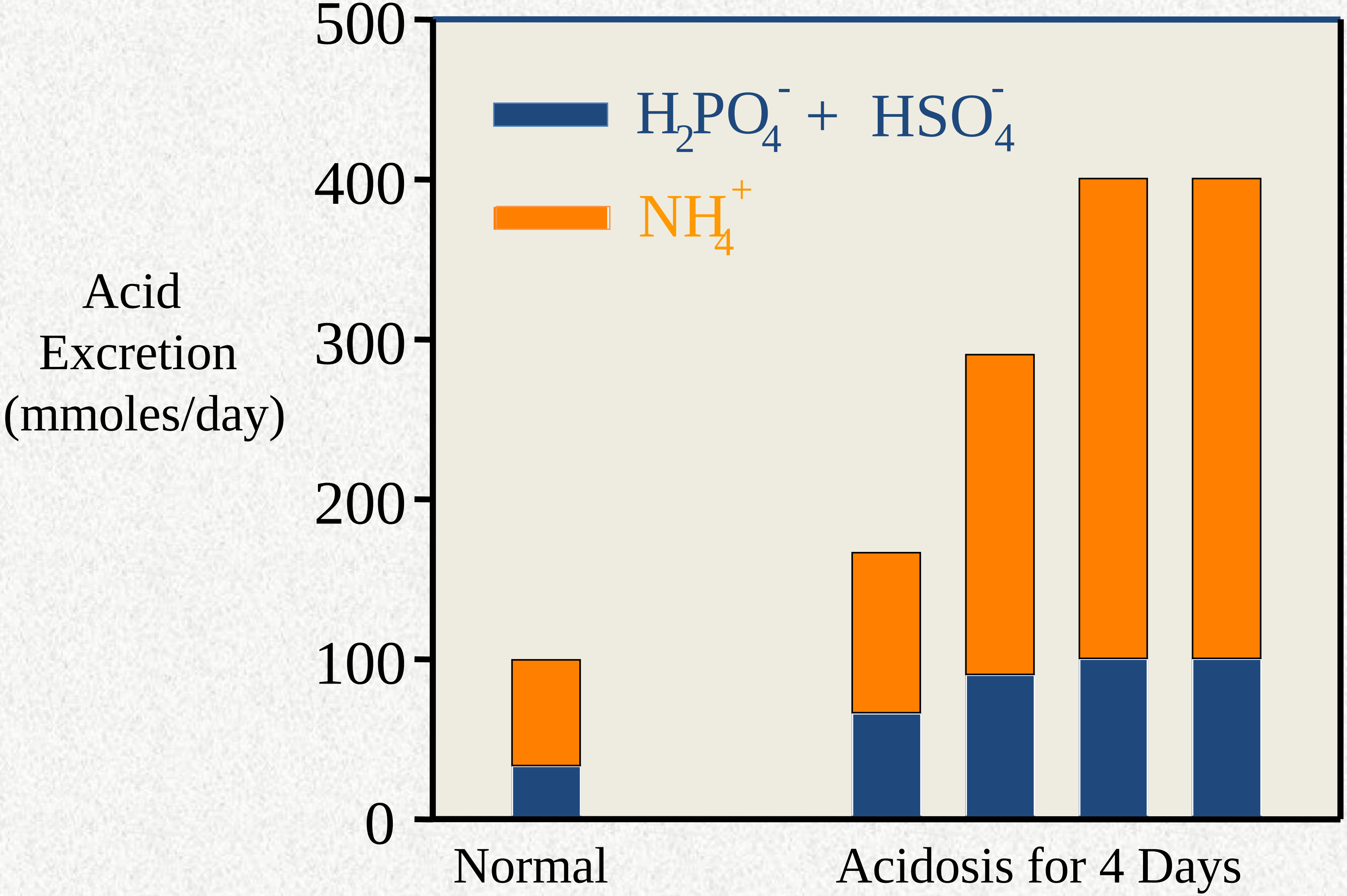
There is a high concentration of phosphate in the tubular fluid; pK = 6.8

Phosphate normally buffers about 30 mmol/day H^+ (about 100 mmol/day phosphate is filtered but 70 % is reabsorbed)

Phosphate buffering capacity does not change much with acid-base disturbances (phosphate is not the major tubular buffer in chronic acidosis

$$NaHPO_4^- + H^+ \longrightarrow NaH_2PO_4$$

Phosphate and Ammonium Buffering In Chronic Acidosis



Production and secretion of NH_4^+ and HCO_3^- by proximal, thick loop of Henle, and distal tubules

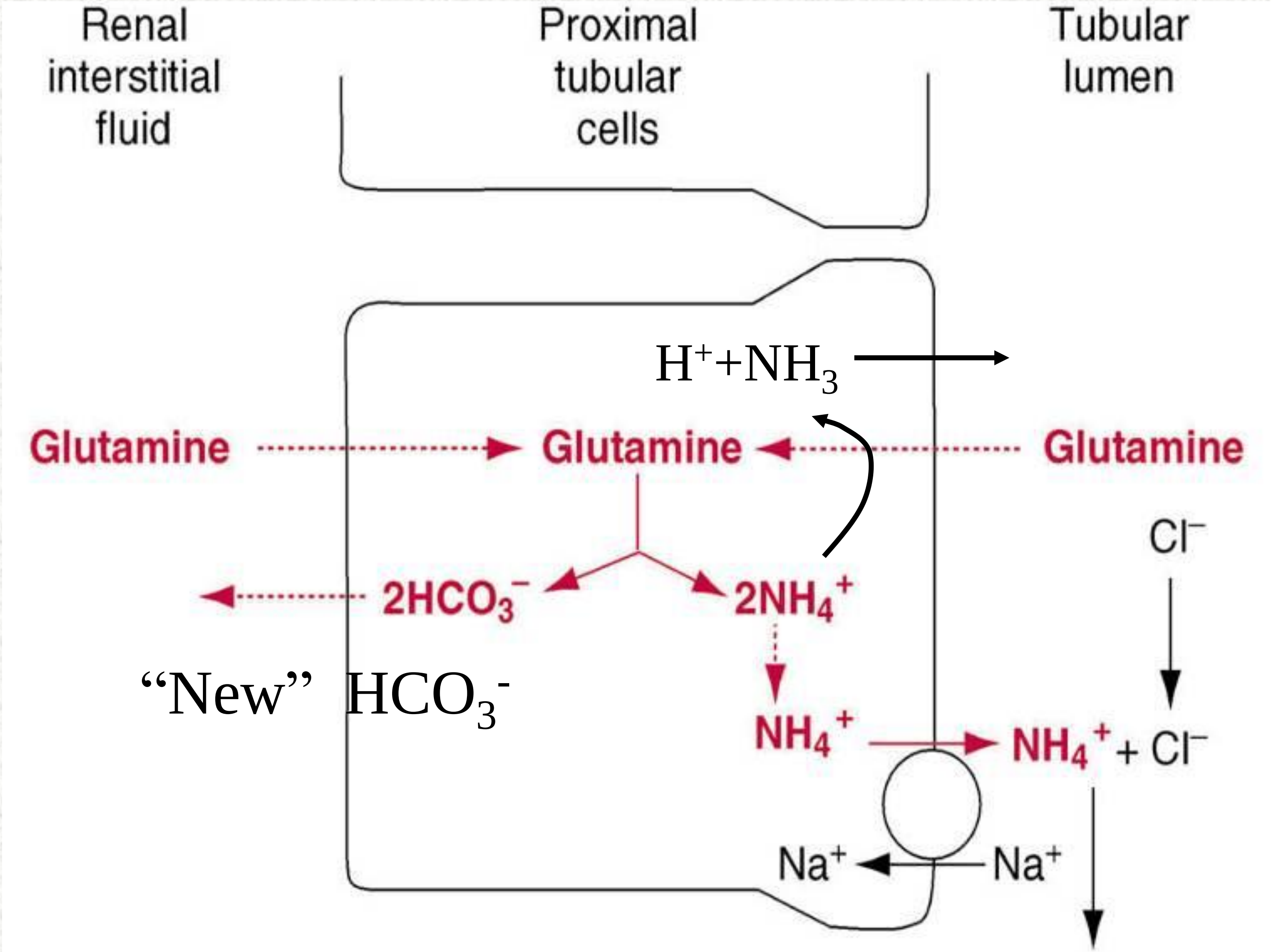


Figure 30-8.

Buffering of hydrogen ion secretion by ammonia (NH_3) in the collecting tubules.

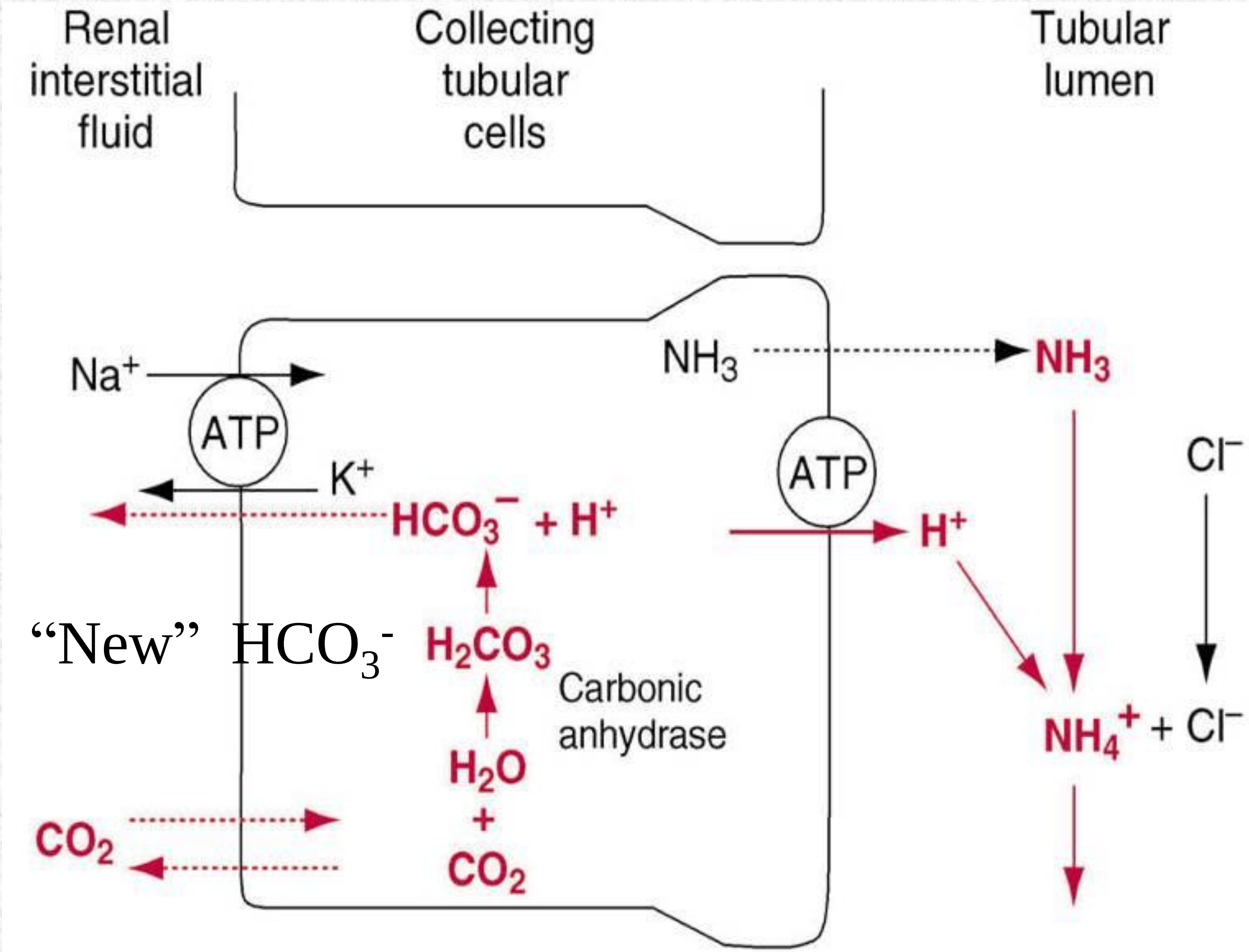
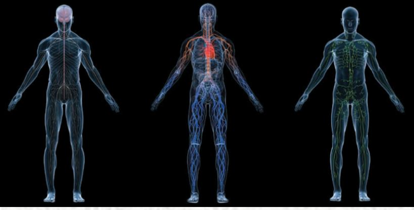


Figure 30-9.



Quantification of Normal Renal Acid-Base Regulation

Total H^+ secretion

= 4320 mEq of H+ secreted (HCO3)+ 60 mEq of H+ non-volatile= 4380

Total H^+ secretion = 4380 mmol/day

= HCO_3^- reabsorption (4320 mmol/d)

+ titratable acid ($NaHPO_4^-$) (30 mmol/d)

+ NH_4^+ excretion (30 mmol/d)

Net H+ excretion=

H+ excreted by buffers not bicarbonate(=new bicarb) - newH+ added to blood(=HCO3- excreted)

Net H^+ excretion = 59 mmol/day

= titratable acid (30 mmol/d)

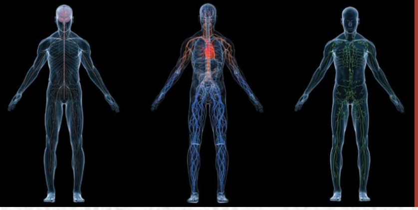
+ NH_4^+ excretion (30 mmol/d)

- HCO_3^- excretion (1 mmol/d)(or new H to blood)

Normal Renal Acid-Base Regulation

Net addition of HCO_3^- to body
(i.e. net loss of H^+)

Titratable acid	= 30 mmol/day
+ NH_4^+ excretion	= 30 mmol/day
- HCO_3^- excretion	= 1 mmol/day
Total	= 59 mmol/day



Renal Compensation for Acidosis

Increased addition of HCO_3^- to body by kidneys
(increased H^+ loss by kidneys)

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

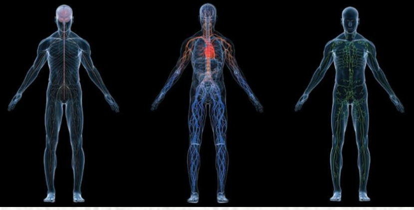
This can increase to as high as 500 mmol/day

Renal Compensation for Alkalosis

Net loss of HCO_3^- from body
(i.e. decreased H^+ loss by kidneys)

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



Classification of Acid-Base Disorders from plasma pH, pCO_2, and HCO_3^-

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

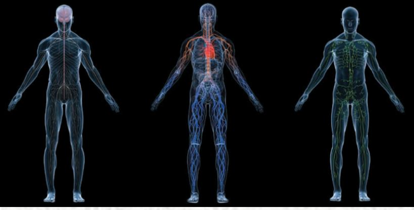
$$pH = pK + \log \frac{HCO_3^-}{\alpha \; pCO_2}$$

Acidosis : pH < 7.4

- metabolic : ↓ HCO_3^-
- respiratory : ↑ pCO_2

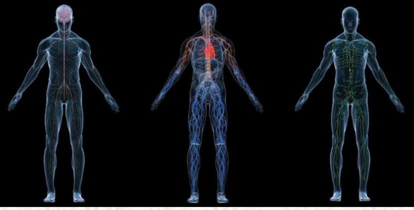
Alkalosis : pH > 7.4

- metabolic : ↑ HCO_3^-
- respiratory : ↓ pCO_2



Renal Compensations for Acid-Base Disorders

- Acidosis:
  - increased H^+ excretion
  - increased HCO_3^- reabsorption
  - production of new HCO_3^-
- Alkalosis:
  - decreased H^+ excretion
  - decreased HCO_3^- reabsorption
  - loss of HCO_3^- in urine



Renal Responses to Respiratory Acidosis

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

Respiratory acidosis : ↓ pH ↑ pCO_2 ↑ HCO_3^-

↑ PCO_2 → ↑ H^+ secretion → complete HCO_3^- reabs.

+

excess tubular H^+

↓

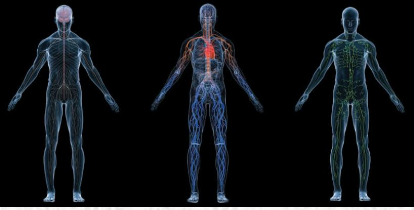
↓ pH

Buffers (NH_4^+, $NaHPO_4^-$) → ↑ H^+ Buffers $^-$

+

↑ new HCO_3^-

(⊖ feedback to ↓ pH)



Renal Responses to Metabolic Acidosis

Metabolic acidosis : ↓ pH ↓ pCO_2 ↓ HCO_3^-

↓ HCO_3^- ⟶ ↓ HCO_3^- filtration ⟶ complete HCO_3^- reabs.

+

excess tubular H^+

↓ pH

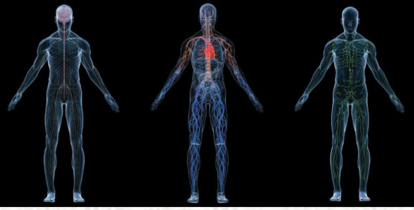
Buffers $(NH_4^+, NaHPO_4^-)$ ⟶

⊖

↑ H^+ Buffers $^-$

+

↑ new HCO_3^-



Renal Responses to Respiratory Alkalosis

Respiratory alkalosis : ↑ pH ↓ pCO_2 ↓ HCO_3^-

↓ PCO_2 ⟶ ↓ H^+ secretion ⟶ ↓ HCO_3^- reabs.

↓

+

↑ pH

excess tubular HCO_3^-

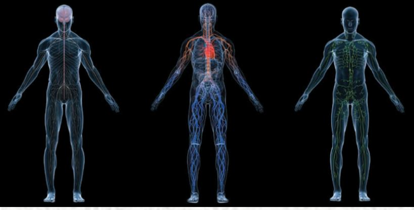
↓

⊖

↑ HCO_3^- excretion

+

↓ H^+ excretion



Renal Responses to Metabolic Alkalosis

Metabolic alkalosis : ↑ pH ↑ pCO_2 ↑ HCO_3^-

↑ HCO_3^- → ↑ HCO_3^- filtration → excess tubular HCO_3^-

↓

↓ HCO_3^- reabs.

↓

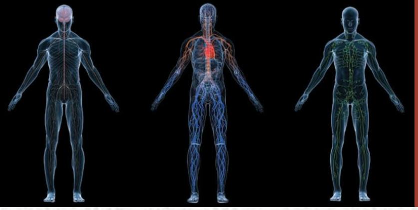
↑ HCO_3^- excretion

+

↓ H^+ excretion

↑ HCO_3^- → ↑ pH

(⊖ feedback from ↑ HCO_3^- excretion to ↑ pH)

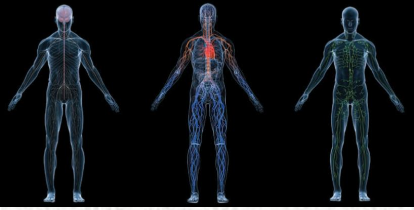


Question

The following data were taken from a patient:

urine volume = 1.0 liter/day
urine HCO_3^- concentration = 2 mmol/liter
urine NH_4^+ concentration = 15 mmol/liter
urine titratable acid = 10 mmol/liter

- What is the daily net acid excretion in this patient ?
- What is the daily net rate of HCO_3^- addition to the extracellular fluids ?



Answer

The following data were taken from a patient:

urine volume = 1.0 liter/day

urine HCO_3^- concentration = 2 mmol/liter

urine NH_4^+ concentration = 15 mmol/liter

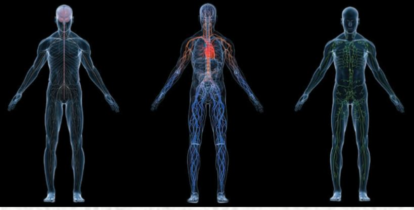
urine titratable acid = 10 mmol/liter

net acid excretion = Titr. Acid + NH_4^+ excret - HCO_3^-

= (10 x 1) + (15 x 1) - (1 x 2)

= 23 mmol/day

net rate of HCO_3^- addition to body = 23 mmol/day



Classification of Acid-Base Disorders from plasma pH, pCO_2, and HCO_3^-

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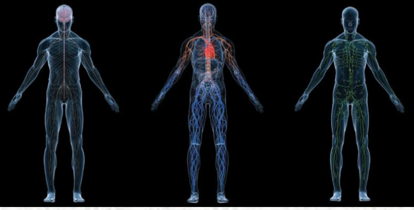
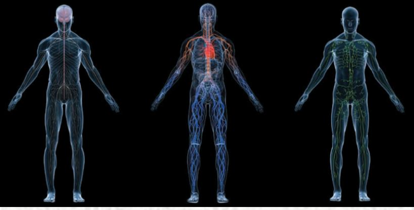
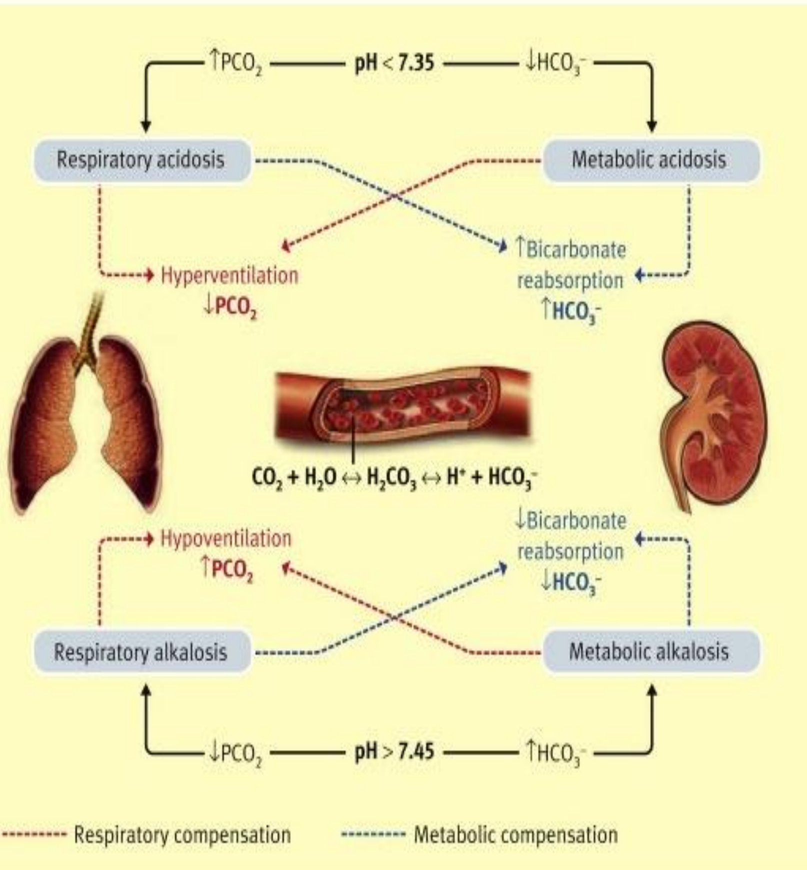


Classification of Acid-Base Disturbances

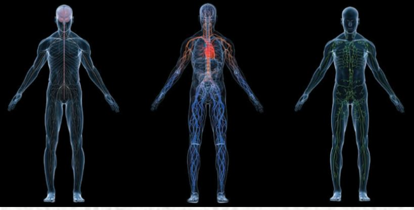
Disturbance	Plasma			Compensation
	pH	HCO_3^-	pCO_2	
metabolic acidosis	↓	↓	↓	↑ ventilation ↑ renal HCO_3 production
respiratory acidosis	↓	↑	↑	↑ renal HCO_3 production
metabolic alkalosis	↑	↑	↑	↓ ventilation ↑ renal HCO_3 excretion
respiratory alkalosis	↑	↓	↓	↑ renal HCO_3 excretion





	pH	HCO_3-	CO_2
Metabolic acidosis	↓	↓	Normal
Metabolic alkalosis	↑	↑	Normal
Metabolic acidosis with respiratory compensation	↓	↓	↓
Metabolic alkalosis with respiratory compensation	↑	↑	↑

Test	Normal	Decrease Value	Increase Value
pH	7.35-7.45	Acidosis	Alkalosis
PaCO2	35-45	Alkalosis	Acidosis
HCO3	22-26	Acidosis	Alkalosis
PaO2	80-100	Hypoxemia	O2 therapy
SaO2	95-100%	Hypoxemia	------------------- -



Question

A plasma sample revealed the following values in a patient: norm for PCO2 35-45, HCO3 22-26

pH = 7.12

PCO_2 = 50

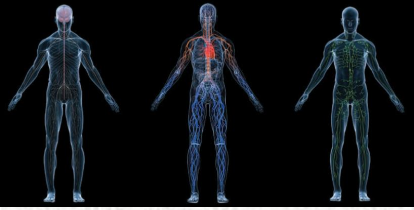
HCO_3^- = 18

diagnose this patient's acid-base status :

acidotic or alkalotic ? Acidotic

respiratory, metabolic, or both ? Both

<u>Mixed acidosis:</u> metabolic and respiratory acidosis



Mixed Acid-Base Disturbances

Two or more underlying causes of acid-base disorder.

pH= 7.60

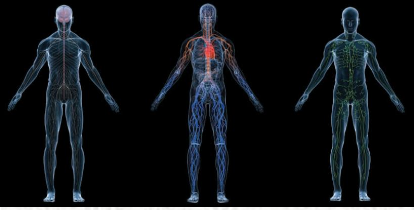
pCO_2 = 30 mmHg

plasma HCO_3^- = 29 mmol/L

What is the diagnosis?

<u>Mixed Alkalosis</u>

- Metabolic alkalosis : increased HCO_3^-
- Respiratory alkalosis : decreased pCO_2



Question

A patient presents in the emergency room and the following data are obtained from the clinical labs:

plasma pH= 7.15, HCO_3^- = 8 mmol/L, pCO_2= 24 mmHg

This patient is in a state of:

1. metabolic alkalosis with partial respiratory compensation
2. respiratory alkalosis with partial renal compensation
3. metabolic acidosis with partial respiratory compensation
4. respiratory acidosis with partial renal compensation

Acid-Base Disturbances

- Metabolic Acidosis : $\downarrow HCO_3^- / pCO2$ in plasma

  ($\downarrow$ pH, $\downarrow HCO_3^-$)

  - aspirin poisoning ($\uparrow H^+$ intake)
  - diabetes mellitus ($\uparrow H^+$ production)
  - diarrhea (HCO_3^- loss)
  - renal tubular acidosis ($\downarrow H^+$ secretion, $\downarrow HCO_3^-$ reabs.)
  - carbonic anhydrase inhibitors ($\downarrow H^+$ secretion)

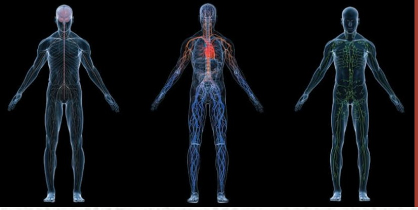
$$H_2O + CO_2 \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

$$\downarrow pH = pK + \log \frac{HCO_3^-}{\alpha \; pCO_2}$$

Anion Gap as a Diagnostic Tool

In body fluids: total cations = total anions

Cations (mEq/L)		Anions (mEq/L)	
Na^+	(142)	Cl^-	(108)
		HCO_3^-	(24)
Unmeasured			
K^+	(4)	Proteins	(17)
Ca^{++}	(5)	Phosphate,	
Mg^{++}	(2)	Sulfate,	
		lactate, etc	(4)
Total	(153)		(153)



Anion Gap as a Diagnostic Tool

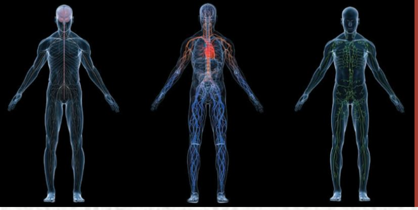
In body fluids: total cations = total anions

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

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

$= 142 \ - 108 - \ 24 \qquad = 10$ mEq/L

Normal anion gap = 8 - 16 mEq / L



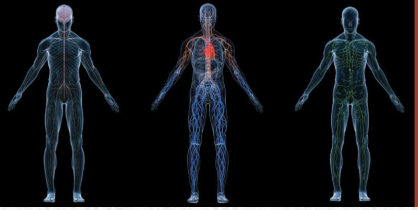
Anion Gap in Metabolic Acidosis

- loss of HCO_3^- = normal anion gap

$\leftrightarrow$ anion gap = Na^+ - $\uparrow Cl^-$ - $\downarrow HCO_3^-$
hyperchloremic metabolic acidosis

- $\uparrow$ unmeasured anions = $\uparrow$ anion gap

$\uparrow$ anion gap = Na^+ - $\leftrightarrow$ Cl^- - $\downarrow HCO_3^-$
normochloremic metabolic acidosis
i.e. diabetic ketoacidosis, lactic acidosis, salicylic acid, etc.



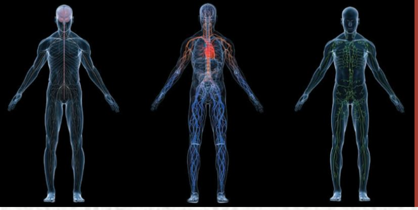
Use of "Anion Gap" as a Diagnostic Tool for Metabolic Acidosis

Increased Anion Gap (normal Cl^-)

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

Normal Anion Gap (increased Cl^-, hyperchloremia)

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



Laboratory values for an uncontrolled diabetic patient include the following:

arterial pH = 7.25

Plasma HCO_3^- = 12

Plasma P_{CO_2} = 28

Plasma Cl^- = 102

Plasma Na^+ = 142

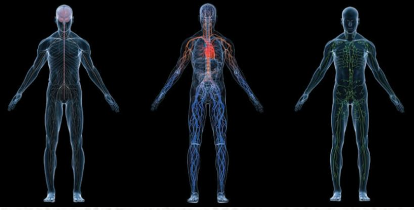
Metabolic Acidosis

Respiratory Compensation

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

What is his anion gap ?

Anion gap = 142 - 102 -12 = 28



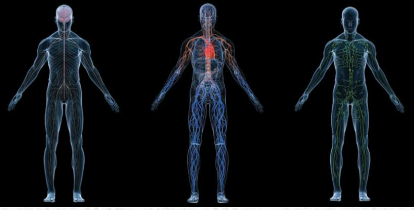
Which of the following are the most likely causes of his acid-base disorder?

a. diarrhea

b. diabetes mellitus

c. Renal tubular acidosis

d. primary aldosteronism



Acid-Base Disturbances

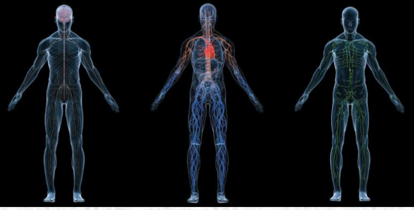
- Respiratory Acidosis : ↓ HCO_3^- / pCO2 in plasma

  (↓ pH, ↑ pCO_2)

  - brain damage
  - pneumonia
  - emphysema
  - other lung disorders

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

$$\downarrow pH = pK + \log \frac{HCO_3^-}{\alpha \ pCO_2}$$



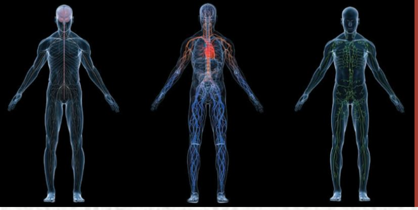
Acid-Base Disturbances

- Metabolic Alkalosis : $\uparrow HCO_3^- / pCO_2$ in plasma
  ($\uparrow$ pH, $\uparrow HCO_3^-$)

  - increased base intake (e.g. $NaHCO_3$)
  - vomiting gastric acid
  - mineralocorticoid excess
  - overuse of diuretics (except carbonic anhydrase inhibitors)

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

$$\uparrow pH = pK + \log \frac{HCO_3^-}{\alpha \ pCO_2}$$



↑ Aldosterone

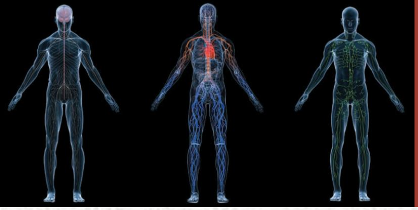
↑ tubular K^+ secretion

K^+ depletion

↑ H^+ secretion ⊕ (from ↑ Aldosterone)

↑ HCO_3 reabsorption
+ ↑ new HCO_3 Production

Metabolic Alkalosis



Overuse of Diuretics

↓ extracellular. volume

↓

↑ angiotensin II

↓

↑ aldosterone

K^+ depletion

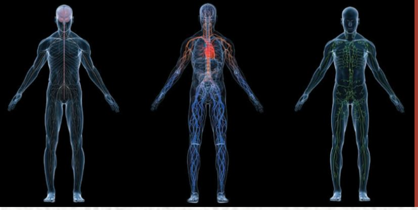
↑ tubular H^+ secretion

↓

↑ HCO_3 reabsorption
+ ↑ new HCO_3 Production

↓

Metabolic Alkalosis



Acid-Base Disturbances

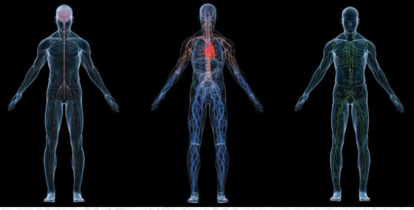
- Respiratory Alkalosis : $\uparrow HCO_3^- / pCO2$ in plasma

  ($\uparrow$ pH, $\downarrow pCO_2$)

  - high altitude
  - psychic (fear, pain, etc)

$$H_2O + CO_2 \longleftrightarrow H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$

$$\uparrow \; pH = pK + \log \frac{HCO_3^-}{\alpha \; pCO_2}$$



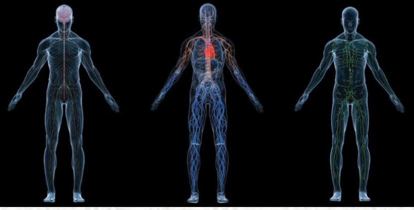
Laboratory values for a patient include the following:

arterial pH = 7.34
Plasma HCO_3^- = 15
Plasma P_{CO_2} = 29
Plasma Cl^- = 118
Plasma Na^+ = 142

Metabolic Acidosis
Respiratory Compensation

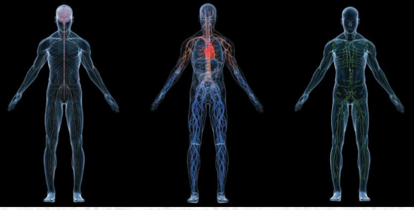
What type of acid-base disorder does this patient have?
What is his anion gap ?

Anion gap = 142 - 118 - 15 = 9 (normal)



Which of the following are the most likely causes of his acid-base disorder?

a. diarrhea
b. diabetes mellitus
c. aspirin poisoning
d. primary aldosteronism



Indicate the Acid -Base Disorders in Each of the Following Patients

pH	HCO_3^-	PCO_2	Acid-Base Disorder ?
7.34	15	29	Metabolic acidosis
7.49	35	48	Metabolic alkalosis
7.34	31	60	Respiratory acidosis
7.62	20	20	Respiratory alkalosis
7.09	15	50	Acidosis: respiratory + metabolic