Chapter 24
Lecture Outline

See separate PowerPoint slides for all figures and tables pre-inserted into PowerPoint without notes.
Introduction

- Cellular function requires a **fluid medium** with a carefully controlled composition

- **Three types of homeostatic balance**
  - Water balance
  - Electrolyte balance
  - Acid–base balance

- Balances maintained by collective action of urinary, respiratory, digestive, integumentary, endocrine, nervous, cardiovascular, and lymphatic systems
Water Balance

• Expected Learning Outcomes
  – Name the major fluid compartments and explain how water moves from one to another.
  – List the body’s sources of water and routes of water loss.
  – Describe the mechanisms of regulating water intake and output.
  – Describe some conditions in which the body has a deficiency or excess of water or an improper distribution of water among the fluid compartments.
Water Balance

- Newborn baby’s body weight is about 75% water
- Young men average 55% to 60% water
- Women average slightly less
- Obese and elderly people as little as 45% by weight
- Total body water (TBW) of a 70 kg (150 lb) young male is about 40 L
Fluid Compartments

• Major fluid compartments of the body
  - 65% intracellular fluid (ICF)
  - 35% extracellular fluid (ECF)
    • 25% tissue (interstitial) fluid
    • 8% blood plasma and lymphatic fluid
    • 2% transcellular fluid “catch-all” category
      – Cerebrospinal, synovial, peritoneal, pleural, and pericardial fluids
      – Vitreous and aqueous humors of the eye
      – Bile, and fluids of the digestive, urinary, and reproductive tracts
Fluid Compartments

- Fluid continually exchanged between compartments
- Water moves by osmosis
- Because water moves so easily through membranes, osmotic gradients never last long
- If imbalance arises, osmosis restores balance within seconds, so the intracellular and extracellular osmolarity are equal
  - If osmolarity of the tissue fluid rises, water moves out of the cell
  - If it falls, water moves in
Fluid Compartments

• Osmosis from one fluid compartment to another is determined by the relative concentrations of solutes in each compartment
  – **Electrolytes**: the most abundant solute particles, by far
  – **Sodium salts** in ECF
  – **Potassium salts** in ICF

• **Electrolytes** play the principal role in governing the body’s water distribution and total water content
The Movement of Water Between the Major Fluid Compartments
Water Gain and Loss

- **Fluid balance**—when daily gains and losses are equal (about 2,500 mL/day)

- **Gains** come from two sources
  - **Preformed water** (2,300 mL/day)
    - Ingested in food (700 mL/day) and drink (1,600 mL/day)
  - **Metabolic water** (200 mL/day)
    - By-product of aerobic metabolism and dehydration synthesis
      \[ \text{C}_6\text{H}_{12}\text{O}_6 + 6 \text{O}_2 \rightarrow 6 \text{CO}_2 + 6 \text{H}_2\text{O} \]
Water Gain and Loss

• **Sensible water loss** is observable
  – 1,500 mL/day is in urine
  – 200 mL/day is in feces
  – 100 mL/day is sweat in resting adult

• **Insensible water loss** is unnoticed
  – 300 mL/day in expired breath
  – 400 mL/day is cutaneous transpiration
    • Diffuses through epidermis and evaporates
      – Does not come from sweat glands
    – Loss varies greatly with environment and activity
Water Gain and Loss

• **Obligatory water loss**—output that is relatively unavoidable
  – Expired air, cutaneous transpiration, sweat, fecal moisture, and minimum urine output (400 mL/day)
Typical Water Intake and Output

Gains
2,500 mL/day

Metabolic water
200 mL

Food
700 mL

Drink
1,600 mL

Losses
2,500 mL/day

Feces
200 mL

Expired air
300 mL

Cutaneous transpiration
400 mL

Sweat
100 mL

Urine
1,500 mL

Figure 24.2
Regulation of Intake

- **Thirst** mainly governs fluid intake

- **Dehydration**
  - Reduces blood volume and blood pressure
  - Increases blood osmolarity

- **Osmoreceptors** in hypothalamus
  - Respond to *angiotensin II* produced when BP drops and also respond to rise in osmolarity of ECF
  - Osmoreceptors communicate with other hypothalamic neurons and with cerebral cortex
Regulation of Intake

(Continued)

– **Hypothalamus** produces **antidiuretic hormone**
  • Promotes water conservation

– **Cerebral cortex** produces conscious **sense of thirst**
  • **Intense sense of thirst** with 2% to 3% increase in plasma osmolarity or 10% to 15% blood loss

– **Salivation** is inhibited with thirst
  • Sympathetic signals from thirst center to salivary glands
Regulation of Intake

• Long-term inhibition of thirst
  – Absorption of water from small intestine reduces osmolarity of blood
    • Stops the osmoreceptor response, promotes capillary filtration, and makes saliva more abundant and watery
    • Changes require 30 minutes or longer to take effect
Regulation of Intake

• Short-term inhibition of thirst
  – Cooling and moistening of mouth quenches thirst
  – Distension of stomach and small intestine
  – 30 to 45 minutes of satisfaction
    • Must be followed by water being absorbed into the bloodstream or thirst returns
  – Short-term response designed to prevent overdrinking
Dehydration, Thirst, and Rehydration

Figure 24.3
Regulation of Output

• Only way to control water output significantly is through variation in urine volume
  – Kidneys cannot replace water or electrolytes
  – Can only slow rate of water and electrolyte loss until water and electrolytes can be ingested

• Control mechanisms of water output
  – Changes in urine volume linked to adjustments in Na\(^+\) reabsorption
    • As Na\(^+\) is reabsorbed or excreted, water follows
Regulation of Output

Control mechanisms of water output (Continued)

– Water output is slowed through **action of ADH**
  
  • ADH secretion is triggered by hypothalamic osmoreceptors in response to dehydration
  
  • **Aquaporins** are synthesized in response to ADH
    
    – Membrane proteins in renal collecting ducts that are channels allowing water to diffuse back into renal medulla
    
    – Na⁺ is still excreted, so urine’s osmolarity (concentration) increases

  • ADH system is example of **negative feedback**
    
    – If osmolarity rises and/or blood volume falls, more ADH is secreted, and it slows these trends
    
    – If osmolarity falls and/or blood volume rises, ADH release is inhibited, so tubules reabsorb less water, urine output increases, and these trends are reversed
The Action of Antidiuretic Hormone

Dehydration

$\uparrow$ H$_2$O  ↓ H$_2$O  $\uparrow$ Na$^+$  ↓ Na$^+$

Elevates blood osmolarity

Stimulates hypothalamic osmoreceptors

Stimulates posterior pituitary to release antidiuretic hormone (ADH)

Stimulates distal convoluted tubule and collecting duct

Increases water reabsorption

Reduces urine volume

Increases ratio of Na$^+$: H$_2$O in urine

Figure 24.4
Disorders of Water Balance

• The body is in a state of **fluid imbalance** if there is an abnormality of total **volume, concentration, or distribution** of fluid among the compartments

• **Fluid deficiency**: fluid output exceeds intake over long period of time
  – Most serious effects
    • Circulatory shock due to loss of blood volume, neurological dysfunction due to dehydration of brain cells, infant mortality from diarrhea
  – Two types of deficiency: volume depletion and dehydration
Disorders of Water Balance

• Volume depletion (hypovolemicia)
  – Occurs when proportionate amounts of water and sodium are lost without replacement
  – Total body water declines, but osmolarity remains normal
  – Hemorrhage, severe burns, chronic vomiting, diarrhea, or Addison disease
Disorders of Water Balance

• Dehydration (negative water balance)
  – Body eliminates significantly more water than sodium, so ECF osmolarity rises
  – Lack of drinking water, diabetes, ADH hyposecretion (diabetes insipidus), profuse sweating, overuse of diuretics
  – Infants more vulnerable to dehydration than adults due to high metabolic rate that demands high urine excretion, immature kidneys cannot concentrate urine effectively, greater ratio of body surface to volume (more evaporation)
  – Affects all fluid compartments (ICF, blood, and tissue fluid)
Dehydration from Excessive Sweating

- Water loss from sweating
- Sweat produced by capillary filtration
- Blood volume and pressure drop, osmolarity rises
- Blood absorbs tissue fluid to replace loss
- Tissue fluid pulled from ICF
- Blood, ICF and tissue fluid all lose water
- For 1 L of sweat:
  - 300 mL from tissue fluid, and
  - 700 mL from ICF
Fluid Balance in Cold Weather

• In cold, skin blood vessels are constricted
  – Raises blood pressure which inhibits ADH secretion and increases secretion of atrial natriuretic peptide
  – Urine output is increased and blood volume reduced

• Cold air is drier and increases respiratory water loss also reducing blood volume

• Cold weather respiratory and urinary loses cause a state of reduced blood volume (hypovolemia)
  – Exercise will dilate vessels in skeletal muscles
  – Insufficient blood for rest of the body can bring on weakness, fatigue, or fainting (hypovolemic shock)
Fluid Excess

- **Fluid excess**—less common than fluid deficiency because kidneys are highly effective in compensating for excessive intake by excreting more urine
  - Renal failure can lead to fluid retention
The Relationship of Blood Volume to Fluid Intake

- Kidneys compensate very well for excessive fluid intake, but not for inadequate fluid intake.
Fluid Excess

- **Two types of fluid excesses**
  - **Volume excess**
    - Both Na\(^+\) and water retained
    - ECF remains isotonic
    - Caused by aldosterone hypersecretion or renal failure
  - **Hypotonic hydration (water intoxication or positive water balance)**
    - More water than Na\(^+\) retained or ingested
    - ECF becomes hypotonic
      - Can cause cellular swelling
- **Most severe effects:** pulmonary and cerebral edema and death
Fluid Sequestration

- **Fluid sequestration**—excess fluid accumulates in a particular location

- Total body water may be normal, but circulating blood volume may drop to a point causing **circulatory shock**

- Most common form: **edema**—abnormal accumulation of fluid in interstitial spaces, causing swelling of tissues

- **Hemorrhage**: another cause of fluid sequestration
  - Blood that pools in the tissues is lost to circulation

- **Pleural effusion**: several liters of fluid can accumulate in the pleural cavity
  - Caused by some lung infections
### Disorders of Water Balance

**TABLE 24.1** Forms of Fluid Imbalance

<table>
<thead>
<tr>
<th>Form</th>
<th>Total Body Water</th>
<th>Osmolarity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluid deficiency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume depletion (hypovolemia)</td>
<td>Reduced</td>
<td>Isotonic (normal)</td>
</tr>
<tr>
<td>Dehydration (negative water balance)</td>
<td>Reduced</td>
<td>Hypertonic (elevated)</td>
</tr>
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<td><strong>Fluid excess</strong></td>
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<td>Volume excess</td>
<td>Elevated</td>
<td>Isotonic (normal)</td>
</tr>
<tr>
<td>Hypotonic hydration (positive water balance, water intoxication)</td>
<td>Elevated</td>
<td>Hypotonic (reduced)</td>
</tr>
</tbody>
</table>
Electrolyte Balance

• **Expected Learning Outcomes**
  – Describe the physiological roles of sodium, potassium, calcium, chloride, and phosphate.
  – Describe the hormonal and renal mechanisms that regulate the concentrations of these electrolytes.
  – State the term for an excess or deficiency of each electrolyte and describe the consequences of these imbalances.
Electrolyte Balance

• Physiological functions of electrolytes
  – Chemically reactive and participate in metabolism
  – Determine electrical potential (charge difference) across cell membranes
  – Strongly affect osmolarity of body fluids
  – Affect body’s water content and distribution

• Major cations
  – Na\(^+\), K\(^+\), Ca\(^{2+}\), Mg\(^{2+}\), and H\(^+\)

• Major anions
  – Cl\(^-\), HCO\(_3\)^- (bicarbonate), and PO\(_4\)^{3-}\)
Electrolyte Balance

• Great differences between electrolyte concentrations of blood plasma and intracellular fluid (ICF)
  – Have the same osmolarity (300 mOsm/L)

• Concentrations in tissue fluid (ECF) differ only slightly from those in the plasma
Electrolyte Concentrations

Figure 24.7

(a) Blood plasma

- Na\(^+\): 145 mEq/L
- K\(^+\): 4 mEq/L
- Cl\(^-\): 103 mEq/L
- Ca\(^{2+}\): 5 mEq/L
- Pi: 4 mEq/L
- Osmolarity: 300 mOsm/L

(b) Intracellular fluid

- Na\(^+\): 150 mEq/L
- K\(^+\): 4 mEq/L
- Cl\(^-\): < 1 mEq/L
- Ca\(^{2+}\): 75 mEq/L
- Pi: 300 mOsm/L
- Osmolarity: 300 mOsm/L
Sodium

- **Functions of Na\(^+\)**—one of the principal ions responsible for the resting membrane potential
  - Inflow of sodium through membrane gates is an essential event in depolarizations that underlie nerve and muscle function

- **Principal cation in ECF**
  - Sodium salts account for 90% to 95% of osmolarity of ECF
  - Most significant solute in determining total body water and distribution of water among fluid compartments
Sodium

- Na\(^+\) gradient is a source of potential energy for cotransport of other solutes such as glucose, potassium, and calcium

- Na\(^+\)–K\(^+\) pump
  - Important means of generating body heat

- NaHCO\(_3\) has major role in buffering pH in ECF
Sodium

• Homeostasis
  – Adult needs about 0.5 g of sodium per day
  – Typical American diet contains 3 to 7 g/day

• Primary concern: excretion of excess dietary sodium

• Sodium concentration coordinated by:
  – Aldosterone: “salt-retaining hormone”
    • Primary role in adjusting sodium excretion
    • Hyponatremia and hyperkalemia directly stimulate the adrenal cortex to secrete aldosterone
    • Hypotension stimulates its secretion by way of the renin–angiotensin–aldosterone mechanism
Sodium

(Continued)

- Aldosterone receptors in ascending limb of nephron loop, the distal convoluted tubule, and cortical part of collecting duct

- Aldosterone, a steroid, binds to nuclear receptors
  - Activates transcription of a gene for the \( \text{Na}^+–\text{K}^+ \) pumps
  - In 10 to 30 minutes, enough \( \text{Na}^+–\text{K}^+ \) pumps are inserted in the plasma membrane to make a noticeable effect
  - Tubules reabsorb more sodium and secrete more hydrogen and potassium
  - Water and chloride passively follow sodium

- Primary effects of aldosterone are that urine contains less NaCl, but more potassium and a lower pH
The Action of Aldosterone

Figure 24.8
Sodium

• Elevated blood pressure inhibits renin–angiotensin–aldosterone mechanism
  – Kidneys reabsorb almost no sodium
  – Urine contains up to 30 g sodium per day instead of normal 5 g

• ADH—modifies water excretion independently of sodium excretion
  – High sodium concentration in the blood stimulates the posterior lobe of the pituitary to release ADH
  – Kidneys reabsorb more water
  – Slows further increase in blood sodium concentration
  – But if sodium levels drop, ADH release is inhibited, more water is excreted, and sodium concentrations in blood will rise
Sodium

• **Natriuretic peptides** inhibit sodium reabsorption
  – Thus they inhibit water reabsorption
  – They also inhibit secretion of renin and ADH
  – Kidneys eliminate more Na\(^+\) and water, lowering BP

• **Other hormones**
  – **Estrogen** mimics aldosterone: Na\(^+\) and water retained
  – **Progesterone** reduces Na\(^+\) reabsorption and has a diuretic effect
  – **Glucocorticoids** promote Na\(^+\) reabsorption and edema

• **Sodium homeostasis achieved by regulating salt intake**
  – Salt cravings in humans and other animals
Sodium

- **Imbalances** are relatively rare

- **Hypernatremia**
  - Plasma sodium concentration greater than 145 mEq/L
    - From administration of IV saline
    - Water retention, hypertension, and edema

- **Hyponatremia**
  - Plasma sodium concentration less than 130 mEq/L
    - Person loses large volumes of sweat or urine, replacing it with drinking plain water
    - Result of excess body water, quickly corrected by excretion of excess water
Potassium

• **Functions of K⁺**
  – Produces (with sodium) the resting membrane potentials and action potentials of nerve and muscle cells
  – Most abundant cation of ICF
  – Greatest determinant of intracellular osmolarity and cell volume

• **Na⁺–K⁺ pump**
  – Important for thermogenesis

• **Essential cofactor for protein synthesis and other metabolic processes**
Potassium

• **Homeostasis**—potassium homeostasis is closely linked to that of sodium

• 90% of K⁺ in glomerular filtrate is reabsorbed by the PCT
  – Rest excreted in urine

• DCT and cortical portion of collecting duct secrete varying amount of K⁺ in response to blood levels

• Aldosterone stimulates renal secretion of K⁺
Potassium

- **Potassium imbalances**
  - Most dangerous types of electrolyte imbalances

- **Hyperkalemia**—effects depend on whether the potassium concentration rises quickly or slowly
  - Greater than 5.5 mEq/L
  - If concentration rises quickly (crush injury), the sudden increase in extracellular K\(^+\) makes nerve and muscle cells abnormally excitable
    - Can produce cardiac arrest
  - Slow onset, inactivates voltage-regulated Na\(^+\) channels, nerve and muscle cells become less excitable
Potassium

- **Hypokalemia**
  - Less than 3.5 mEq/L
  - Rarely results from dietary deficiency
  - From sweating, chronic vomiting, diarrhea, excessive laxative use, aldosterone hypersecretion, or alkalosis
  - Nerve and muscle cells less excitable
    - Muscle weakness, loss of muscle tone, decreased reflexes, and arrhythmias from irregular electrical activity in the heart
Effects of Potassium Imbalances on Membrane Potentials

(a) Normokalemia
- K⁺ concentrations in equilibrium
- Equal diffusion into and out of cell
- Normal resting membrane potential (RMP)

(b) Hyperkalemia
- Elevated extracellular K⁺ concentration
- Less diffusion of K⁺ out of cell
- Elevated RMP (cells partially depolarized)
- Cells more excitable

(c) Hypokalemia
- Reduced extracellular K⁺ concentration
- Greater diffusion of K⁺ out of cell
- Reduced RMP (cells hyperpolarized)
- Cells less excitable

Figure 24.9
Chloride

• **Functions of Cl**$^{-}$
  – Most abundant anion in ECF
  – Major contribution to ECF osmolarity
  – Required for the formation of stomach acid (HCl)
  – **Chloride shift** that accompanies CO$_2$ loading and unloading in RBCs
  – Major role in regulating body pH
Chloride

• Homeostasis
  – Primary homeostasis achieved as an effect of Na\(^+\) homeostasis
  – Strong attraction to Na\(^+\), K\(^+\), and Ca\(^{2+}\), which chloride passively follows
  – As sodium is retained, chloride ions passively follow
Chloride

- Chloride imbalances disturb acid-base balance
  - And vice-versa

- Hyperchloremia
  - Result of dietary excess or administration of IV saline

- Hypochloremia
  - Side effect of hyponatremia
  - Sometimes from hyperkalemia or acidosis
Calcium

• **Functions of Ca\(^{2+}\)**
  – Lends strength to skeleton
  – Activates sliding filament mechanism of muscle contraction
  – Serves as a second messenger for some hormones and neurotransmitters
  – Activates exocytosis of neurotransmitters and other cellular secretions
  – Essential factor in blood clotting
Calcium

• **Cells maintain very low intracellular Ca\(^{2+}\) levels**
  – To prevent calcium phosphate crystal precipitation
    • Phosphate levels are high in the ICF
  – Cells must pump Ca\(^{2+}\) out
  – Keep intracellular concentration low, or sequester Ca\(^{2+}\) in smooth ER and release it when needed
  – **Calsequestrin**: protein that binds Ca\(^{2+}\) and keeps it unreactive

• **Homeostasis** is chiefly regulated by PTH, calcitriol (vitamin D), and calcitonin (in children)
  – These hormones affect bone deposition and resorption
  – Intestinal absorption and urinary excretion
Calcium

• **Imbalances**
  - **Hypercalcemia**: greater than 5.8 mEq/L
    - Causes: alkalosis, hyperparathyroidism, hypothyroidism
    - Reduces membrane Na\(^+\) permeability, inhibits depolarization of nerve and muscle cells
    - Concentrations greater than 12 mEq/L cause muscular weakness, depressed reflexes, cardiac arrhythmias
(Continued)

- **Hypocalcemia:** less than 4.5 mEq/L
  - Causes: vitamin D deficiency, diarrhea, pregnancy, acidosis, lactation, hypoparathyroidism, hyperthyroidism
  - Increases membrane Na\(^+\) permeability, causing nervous and muscular systems to be abnormally excitable
  - Very low levels result in tetany, laryngospasm, death
Magnesium

• **Functions of Mg\(^{2+}\)**
  - About 54% of Mg\(^{2+}\) is in bone; about 45% in intracellular fluid
  - Most intracellular Mg\(^{2+}\) is complexed with ATP
  - Mg\(^{2+}\) serves as a cofactor for enzymes, transporters, and nucleic acids

• **Homeostasis**
  - Blood levels of Mg\(^{2+}\): 1.5 – 2.0 mEq/L
  - Intestinal absorption from food is regulated by vitamin D
  - Mg\(^{2+}\) is lost in feces and urine
    - Ascending limb of nephron loop can reabsorb Mg\(^{2+}\) and mainly determines the extent of retention or loss
    - Parathyroid hormone governs the rate of reabsorption
Magnesium

• **Imbalances of Mg\(^{2+}\)**
  
  – **Hypomagnesemia** – plasma deficiency of Mg\(^{2+}\)
    
    • Usually due to excessive loss rather than dietary deficiency
    
    • Causes: vomiting, diarrhea, renal disease, intestinal malabsorption
    
    • Effects: hyperirritability of nervous and muscular systems; tremors, spasms, tetanus, hypertension, tachycardia, heart arrhythmia
  
  – **Hypermagnesemia** – excess of Mg\(^{2+}\) in blood
    
    • Rare condition except in renal insufficiency
    
    • Effects: lethargy, weakness, weak reflexes, respiratory depression, hypotension, and flaccid, diastolic cardiac arrest
Phosphates

• Functions of $P_i$
  – Relatively concentrated in ICF due to hydrolysis of ATP and other phosphate compounds

• Inorganic phosphates ($P_i$) of the body fluids are an equilibrium mixture of phosphate ($PO_4^{3-}$), monohydrogen phosphate ($HPO_4^{2-}$), and dihydrogen phosphate ($H_2PO_4^{-}$)
Phosphates

• **Components of:**
  – Nucleic acids, phospholipids, ATP, GTP, cAMP, and creatine phosphate

• **Activates many metabolic pathways by phosphorylating enzymes and substrates such as glucose**

• **Buffers that help stabilize the pH of body fluids**
Phosphates

• **Homeostasis**
  – Normally, phosphate is continually lost by glomerular filtration
  – If plasma concentration drops, renal tubules reabsorb all filtered phosphate

• **Parathyroid hormone**
  – Increases excretion of phosphate which increases concentration of free calcium in the ECF
  – Lowering the ECF concentration of phosphate minimizes the formation of calcium phosphate and helps support plasma calcium concentration

• **Imbalances** not as critical
  – Body can tolerate broad variations in phosphate levels
Acid–Base Balance

• Expected Learning Outcomes
  – Define buffer and write chemical equations for the bicarbonate, phosphate, and protein buffer systems.
  – Discuss the relationship between pulmonary ventilation, pH of the extracellular fluids, and the bicarbonate buffer system.
  – Explain how the kidneys secrete hydrogen ions and how these ions are buffered in the tubular fluid.
  – Identify some types and causes of acidosis and alkalosis, and describe the effects of these pH imbalances.
  – Explain how the respiratory and urinary systems correct acidosis and alkalosis, and compare their effectiveness and limitations.
Acids, Bases, and Buffers

• One of the most important aspects of homeostasis
  – Metabolism depends on enzymes, and enzymes are sensitive to pH
  – Slight deviation from the normal pH can shut down entire metabolic pathways
  – Slight deviation from normal pH can alter the structure and function of macromolecules
Acids, Bases, and Buffers

• pH of a solution is determined solely by its hydrogen ions (H\(^+\))

• Acids—any chemical that releases H\(^+\) in solution
  – A **strong acid** such as hydrochloric acid (HCl) ionizes freely
    • Gives up most of its H\(^+\)
    • Markedly lowers pH of a solution
  – A **weak acid** such as carbonic acid (H\(_2\)CO\(_3\)) ionizes only slightly
    • Keeps most H\(^+\) chemically bound
    • Does not affect pH much
Acids, Bases, and Buffers

• **Bases**—any chemical that accepts $\text{H}^+$
  
  – **Strong bases**, such as the hydroxide ion (OH$^-$), have a strong tendency to bind $\text{H}^+$, markedly raising pH
  
  – **Weak bases**, such as the bicarbonate ion ($\text{HCO}_3^-$), bind less of the available $\text{H}^+$ and have less effect on pH
Acids, Bases, and Buffers

• 7.35 to 7.45 is the normal pH range of blood and tissue fluid

• Challenges to acid–base balance
  – Metabolism constantly produces acid
    • Lactic acids from anaerobic fermentation
    • Phosphoric acid from nucleic acid catabolism
    • Fatty acids and ketones from fat catabolism
    • Carbonic acid from carbon dioxide
Acids, Bases, and Buffers

• **Buffer**—any mechanism that resists changes in pH
  – Convert strong acids or bases to weak ones

• **Physiological buffer**—system that controls output of acids, bases, or CO\textsubscript{2}
  – **Urinary system** buffers greatest quantity of acid or base
    • Takes several hours to days to exert its effect
  – **Respiratory system** buffers within minutes
    • Cannot alter pH as much as the urinary system
Acids, Bases, and Buffers

• **Chemical buffer**—a substance that binds H\(^+\) and removes it from solution as its concentration begins to rise, or releases H\(^+\) into solution as its concentration falls
  - Restores normal pH in fractions of a second
  - **Buffer systems** are mixtures composed of weak acids and weak bases
  - **Three major chemical buffers:** bicarbonate, phosphate, and protein systems
    - Amount of acid or base neutralized depends on the concentration of the buffers and the pH of the working environment
The Bicarbonate Buffer System

- **Bicarbonate buffer system**—a solution of carbonic acid and bicarbonate ions
  
  - **Carbonic acid and bicarbonate ions** participate in a reversible reaction
    - \[ \text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+ \]
    
  - The direction of the reaction determines whether it raises or lowers pH
    - \[ \text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{HCO}_3^- + \text{H}^+ \]
      - Lowers pH by releasing H^+
    - \[ \text{CO}_2 + \text{H}_2\text{O} \leftarrow \text{H}_2\text{CO}_3 \leftarrow \text{HCO}_3^- + \text{H}^+ \]
      - Raises pH by binding H^+
The Bicarbonate Buffer System

- The bicarbonate buffer system coordinates with the lungs and kidneys to help control pH and CO$_2$
  - To lower pH, kidneys excrete HCO$_3^-$
  - To raise pH, kidneys excrete H$^+$ and lungs excrete CO$_2$
The Phosphate Buffer System

• Phosphate buffer system—a solution of $\text{HPO}_4^{2-}$ and $\text{H}_2\text{PO}_4^-$

• $\text{H}_2\text{PO}_4^- \leftrightarrow \text{HPO}_4^{2-} + \text{H}^+$
  – As in the bicarbonate system, reactions that proceed to the right liberate $\text{H}^+$ and decrease pH, and those to the left increase pH

• Important buffering in the ICF and renal tubules
  – In these places, phosphates are more concentrated and the buffer can function closer to its optimum pH of 6.8
    • Constant production of metabolic acids creates pH values from 4.5 to 7.4 in the ICF, avg. 7.0
The Protein Buffer System

- **Proteins** are more concentrated than bicarbonate or phosphate systems, especially in the ICF.

- **Protein buffer system** accounts for about three-quarters of all chemical buffering in the body fluids.

- Proteins’ buffering ability is due to certain side groups of their amino acid residues:
  - Carboxyl (−COOH) side groups release H⁺ when pH begins to rise.
  - Others have amino (−NH₂) side groups that bind H⁺ when pH gets too low.
Respiratory Control of pH

• The bicarbonate buffer system is the basis for the strong buffering capacity of the respiratory system
  – The addition of CO$_2$ to the body fluids raises the H$^+$ concentration and lowers pH
  – The removal of CO$_2$ has the opposite effects

• Neutralizes two or three times as much acid as the chemical buffers can
Respiratory Control of pH

- CO₂ is constantly produced by aerobic metabolism
  - Normally eliminated by the lungs at an equivalent rate
  - CO₂ (from metabolism) + H₂O → H₂CO₃ → HCO₃⁻ + H⁺
    - Lowers pH by releasing H⁺
  - CO₂ (expired) + H₂O ← H₂CO₃ ← HCO₃⁻ + H⁺
    - Raises pH by binding H⁺

- Increased CO₂ and decreased pH stimulate pulmonary ventilation, while an increased pH inhibits pulmonary ventilation
Renal Control of pH

- The kidneys can neutralize more acid or base than either the respiratory system or chemical buffers.

- Renal tubules secrete $H^+$ into the tubular fluid:
  - Most bind to bicarbonate, ammonia, and phosphate buffers.
  - Bound and free $H^+$ are excreted in the urine actually expelling $H^+$ from the body.
  - Other buffer systems only reduce its concentration by binding it to other chemicals.
Secretion and Neutralization of Hydrogen Ions in the Kidney

1. H⁺ in blood reacts with HCO₃⁻ to form H₂CO₃.
2. H₂CO₃ decomposes into H₂O and CO₂, which enter the tubule cell.
3. Tubule cells acquire CO₂ from blood, tubular fluid, and their own aerobic respiration.
4. Carbonic anhydrase (CAH) combines H₂O and CO₂ to re-form H₂CO₃.
5. H₂CO₃ ionizes to form HCO₃⁻ (which returns to the blood) and H⁺.
7. NaHCO₃ from glomerular filtrate decomposes into Na⁺ and HCO₃⁻. Na⁺ is pumped into tubule cell.
8. Na⁺ is removed by Na⁺–K⁺ pump at the base of the cell.
9. HCO₃⁻ reacts with H⁺ from tubule cell to form H₂CO₃.
10. CAH on brush border decomposes H₂CO₃ to H₂O and CO₂ again.
11. CO₂ enters the tubular cell and H₂O passes in the urine (carrying the H⁺ that was originally in the blood).

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Renal Control of pH

• Tubular secretion of $H^+$ (step 6)
  – Continues only with a steep concentration gradient of $H^+$ between tubule cells and tubular fluid
  – If $H^+$ concentration increases in tubular fluid, (to pH of 4.5), secretion of $H^+$ stops, limiting pH for secretion

• This is prevented by buffers in tubular fluid
  – Bicarbonate system: all bicarbonate ions in tubular fluid are consumed, neutralizing $H^+$
    • So there is no $HCO_3^-$ in the urine
    • The more acid the kidneys secrete, the less sodium is in the urine
Renal Control of pH

Tubular buffers (Continued)

- **Phosphate system**: dibasic sodium phosphate is contained in glomerular filtrate
  - Reacts with some of the $\text{H}^+$ replacing a $\text{Na}^+$ in the buffer which passes into the urine
  - $\text{Na}_2\text{HPO}_4 + \text{H}^+ \rightarrow \text{NaH}_2\text{PO}_4 + \text{Na}^+$
- **Ammonia** ($\text{NH}_3$): from amino acid catabolism acts as a base to neutralize acid
  - $\text{NH}_3 + \text{H}^+$ and $\text{Cl}^-$ $\rightarrow$ $\text{NH}_4\text{Cl}$ (ammonium chloride: weak acid)
Acid Buffering in the Urine

Figure 24.11

Key:
- Antiport
- Diffusion through a membrane channel
- Diffusion through the membrane lipid
The Relationship of Bicarbonate–Carbonic Acid Ratio to pH

Figure 24.12

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Disorders of Acid–Base Balance

- **Acidosis**—pH of ECF below 7.35
  - $H^+$ diffuses into cells and drives out $K^+$, elevating $K^+$ concentration in ECF
    - $H^+$ buffered by protein in ICF, so net result is cation loss
    - This causes membrane hyperpolarization, nerve and muscle cells are hard to stimulate; CNS depression may lead to confusion, disorientation, coma, and possibly death

![Figure 24.13](image)
Disorders of Acid–Base Balance

• **Alkalosis** – pH above 7.45
  – H⁺ diffuses out of cells and K⁺ diffuses in, membranes depolarized, nerves overstimulated, muscles causing spasms, tetany, convulsions, respiratory paralysis
  – A person cannot live for more than a few hours if the blood pH is below 7.0 or above 7.7

Figure 24.13
Disorders of Acid–Base Balance

• Acid–base imbalances fall into two categories
  – Respiratory and metabolic

• Respiratory acidosis
  – Occurs when rate of alveolar ventilation fails to keep pace with the body’s rate of CO₂ production
  – Carbon dioxide accumulates in the ECF and lowers its pH
  – Occurs in emphysema where there is a severe reduction of functional alveoli

• Respiratory alkalosis
  – Results from hyperventilation
  – CO₂ eliminated faster than it is produced
Disorders of Acid–Base Balance

• Metabolic acidosis
  – Increased production of organic acids such as lactic acid in anaerobic fermentation, and ketone bodies seen in alcoholism, and diabetes mellitus
  – Ingestion of acidic drugs (aspirin)
  – Loss of base due to chronic diarrhea, laxative overuse

• Metabolic alkalosis
  – Rare, but can result from:
    • Overuse of bicarbonates (antacids and IV bicarbonate solutions)
    • Loss of stomach acid (chronic vomiting)
Compensation for Acid–Base Imbalances

• **Compensated** acidosis or alkalosis
  – Either the *kidneys* compensate for pH imbalances of respiratory origin, or
  – The *respiratory system* compensates for pH imbalances of *metabolic origin*

• **Uncompensated** acidosis or alkalosis
  – A pH imbalance that the body cannot correct without clinical intervention
Compensation for Acid–Base Imbalances

• Respiratory compensation—changes in pulmonary ventilation to correct changes in pH of body fluids by expelling or retaining CO₂
  – If there is hypercapnia, (excess CO₂) it stimulates pulmonary ventilation eliminating CO₂ and allowing pH to rise
  – If there is hypocapnia, (deficiency of CO₂) ventilation is reduced to allow CO₂ to accumulate and thereby lowering pH
Compensation for Acid–Base Imbalances

- Renal compensation—adjustment of pH by changing rate of H\(^+\) secretion by renal tubules
  - Slow, but better at restoring a fully normal pH
  - In **acidosis**, urine pH may drop to 4.5 due to excess H\(^+\)
    - Renal tubules increase rate of H\(^+\) secretion (and ammonia to buffer it) elevating pH in the body
  - In **alkalosis** urine pH as high as 8.2 due to excess HCO\(_3^-\)
    - Renal tubules decrease rate of H\(^+\) secretion, and allow neutralization of bicarbonate, lowering pH in body
- Kidneys cannot act quickly enough to compensate for short-term pH imbalances
- Effective at compensating for pH imbalances that last for a few days or longer
# Acid–Base Imbalances in Relation to Electrolyte and Water Imbalances

<table>
<thead>
<tr>
<th>Cause</th>
<th>Potential Effect</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidosis</td>
<td>Hyperkalemia</td>
<td>$H^+$ diffuses into cells and displaces $K^+$ (see fig. 24.13a). As $K^+$ leaves the ICF, $K^+$ concentration in the ECF rises.</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Acidosis</td>
<td>Opposite from the above; high $K^+$ concentration in the ECF causes less $K^+$ to diffuse out of the cells than normally. $H^+$ diffuses out to compensate, and this lowers the extracellular pH.</td>
</tr>
<tr>
<td>Alkalosis</td>
<td>Hypokalemia</td>
<td>$H^+$ diffuses from ICF to ECF. More $K^+$ remains in the ICF to compensate for the $H^+$ loss, causing a drop in ECF $K^+$ concentration (see fig. 24.13b).</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Alkalosis</td>
<td>Opposite from the above; low $K^+$ concentration in the ECF causes $K^+$ to diffuse out of cells. $H^+$ diffuses in to replace $K^+$, lowering the $H^+$ concentration of the ECF and raising its pH.</td>
</tr>
<tr>
<td>Acidosis</td>
<td>Hypochloremia</td>
<td>More $Cl^-$ is excreted as $NH_4Cl$ to buffer the excess acid in the renal tubules, leaving less $Cl^-$ in the ECF.</td>
</tr>
<tr>
<td>Alkalosis</td>
<td>Hyperchloremia</td>
<td>More $Cl^-$ is reabsorbed from the renal tubules, so ingested $Cl^-$ accumulates in the ECF rather than being excreted.</td>
</tr>
<tr>
<td>Hyperchloremia</td>
<td>Acidosis</td>
<td>More $H^+$ is retained in the blood to balance the excess $Cl^-$, causing hyperchloremic acidosis.</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>Alkalosis</td>
<td>More $Na^+$ is reabsorbed by the kidney. $Na^+$ reabsorption is coupled to $H^+$ secretion (see fig. 24.10), so more $H^+$ is secreted and pH of the ECF rises.</td>
</tr>
<tr>
<td>Hypervolemia</td>
<td>Acidosis</td>
<td>Less $Na^+$ is reabsorbed, so less $H^+$ is secreted into the renal tubules. $H^+$ retained in the ECF causes acidosis.</td>
</tr>
<tr>
<td>Acidosis</td>
<td>Hypocalcemia</td>
<td>Acidosis causes more $Ca^{2+}$ to bind to plasma protein and citrate ions, lowering the concentration of free, ionized $Ca^{2+}$ and causing symptoms of hypocalcemia.</td>
</tr>
<tr>
<td>Alkalosis</td>
<td>Hypercalcemia</td>
<td>Alkalosis causes more $Ca^{2+}$ to dissociate from plasma protein and citrate ions, raising the concentration of free $Ca^{2+}$.</td>
</tr>
</tbody>
</table>
Fluid Replacement Therapy

• Restoring and maintaining proper fluid volume, composition, and distribution is a significant problem in the treatment of seriously ill patients.

• **Fluids may be administered to:**
  – Replenish total body water
  – Restore blood volume and pressure
  – Shift water from one fluid compartment to another
  – Restore and maintain electrolyte and acid–base balance
Fluid Replacement Therapy

• **Drinking water is the simplest method**
  – But water alone does not replace electrolytes

• **Patients who cannot take fluids by mouth**
  – **Enema**: fluid absorbed through the colon
  – **Parenteral routes**: fluid administration other than digestive tract
    • **Intravenous (I.V.) route** is the most common
    • **Subcutaneous (sub-Q) route**
    • **Intramuscular (I.M.) route**
    • Other parenteral routes
Fluid Replacement Therapy

- Excessive blood loss is sometimes countered by quickly giving normal saline (isotonic, 0.9% NaCl)
  - Raises blood volume while maintaining normal osmolarity
    - Requires a very large volume be given, because much of the saline escapes blood and enters interstitial fluid compartment
    - Can induce hypernatremia or hyperchloremia

- Correct pH imbalances
  - Acidosis treated with Ringer’s lactate
  - Alkalosis treated with potassium chloride
Fluid Replacement Therapy

- **Plasma volume expanders**—hypertonic solutions or colloids that are retained in the bloodstream and draw interstitial water into it by osmosis
  - Used to combat hypotonic hydration by drawing water out of swollen cells
  - Can draw several liters of water out of the intracellular compartment within a few minutes
Fluid Replacement Therapy

• **Patients who cannot eat**
  – Isotonic 5% dextrose (glucose) solution
  – Has **protein-sparing effect**: fasting patients lose as much as 70 to 85 g of protein per day
    • I.V. glucose reduces this by half

• **Patients with renal insufficiency**
  – Given slowly through I.V. drip since kidneys might not excrete water fast enough (avoids hypotonic hydration)