I. BODY FLUIDS

- Total body water (TBW) is approximately 60% of body weight.
- The percentage of TBW is highest in newborns and adult males and lowest in adult females and in adults with a large amount of adipose tissue.

A. Distribution of water (Figure 5-1 and Table 5-1)

1. Intracellular fluid (ICF)
   - is two-thirds of TBW.
   - The major cations of ICF are K⁺ and Mg²⁺.
   - The major anions of ICF are protein and organic phosphates [adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP)].

2. Extracellular fluid (ECF)
   - is one-third of TBW.
   - is composed of interstitial fluid and plasma.
   - The major cation of ECF is Na⁺.
   - The major anions of ECF are Cl⁻ and HCO₃⁻.

   a. Plasma is one-fourth of the ECF. Thus, it is one-twelfth of TBW (1/4 × 1/3).
      - The major plasma proteins are albumin and globulins.

   b. Interstitial fluid is three-fourths of the ECF. Thus, it is one-fourth of TBW (3/4 × 1/3).
      - The composition of interstitial fluid is the same as that of plasma except that it has little protein. Thus, interstitial fluid is an ultrafiltrate of plasma.

3. 60-40-20 rule
   - TBW is 60% of body weight.
   - ICF is 40% of body weight.
   - ECF is 20% of body weight.

B. Measuring the volumes of the fluid compartments (see Table 5-1)

1. Dilution method
   - A known amount of a substance is given whose volume of distribution is the body fluid compartment of interest.

   For example:

   1. Tritiated water is a marker for TBW that distributes wherever water is found.
   2. Mannitol is a marker for ECF because it is a large molecule that cannot cross cell membranes and is therefore excluded from the ICF.
Evans blue is a marker for plasma volume because it is a dye that binds to serum albumin and is therefore confined to the plasma compartment.

b. The substance is allowed to equilibrate.
c. The concentration of the substance is measured in plasma, and the volume of distribution is calculated as follows:

\[
\text{Volume} = \frac{\text{Amount}}{\text{Concentration}}
\]

*where:*

- Volume = volume of distribution, or volume of the body fluid compartment (L)
- Amount = amount of substance present (mg)
- Concentration = concentration in plasma (mg/L)

d. Sample calculation

A patient is injected with 500 mg of mannitol. After a 2-hour equilibration period, the concentration of mannitol in plasma is 3.2 mg/100 mL. During the equilibration period, 10% of the injected mannitol is excreted in urine. What is the patient’s ECF volume?

\[
\begin{align*}
\text{Volume} &= \frac{\text{Amount}}{\text{Concentration}} \quad \text{Amount injected} = 500 \text{ mg} \\
&= \frac{500 \text{ mg} - 50 \text{ mg}}{3.2 \text{ mg/100 mL}} \\
&= 14.1 \text{ L}
\end{align*}
\]

**Table 5-1** Body Water and Body Fluid Compartments

<table>
<thead>
<tr>
<th>Body Fluid Compartment</th>
<th>Fraction of TBW*</th>
<th>Markers Used to Measure Volume</th>
<th>Major Cations</th>
<th>Major Anions</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBW</td>
<td>1.0</td>
<td>Tritiated H₂O, D₂O, Antipyrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECF</td>
<td>1/3</td>
<td>Sulfate, Inulin, Mannitol</td>
<td>Na⁺</td>
<td>Cl⁻, HCO₃⁻</td>
</tr>
<tr>
<td>Plasma</td>
<td>1/12 (1/4 of ECF)</td>
<td>RISA, Evans blue</td>
<td>Na⁺</td>
<td>Cl⁻, HCO₃⁻ Plasma protein</td>
</tr>
<tr>
<td>Interstitial</td>
<td>1/4 (3/4 of ECF)</td>
<td>ECF–plasma volume (indirect)</td>
<td>Na⁺</td>
<td>Cl⁻, HCO₃⁻ Plasma protein</td>
</tr>
<tr>
<td>ICF</td>
<td>2/3</td>
<td>TBW–ECF (indirect)</td>
<td>K⁺</td>
<td>Organic phosphates Protein</td>
</tr>
</tbody>
</table>

*Total body water (TBW) is approximately 60% of total body weight, or 42 L in a 70-kg man. ECF = extracellular fluid, ICF = intracellular fluid, RISA = radioiodinated serum albumin.
2. **Substances used for major fluid compartments** (see Table 5-1)
   a. **TBW**
      - Tritiated water, D₂O, and antipyrene
   b. **ECF**
      - Sulfate, inulin, and mannitol
   c. **Plasma**
      - Radioiodinated serum albumin (RISA) and Evans blue
   d. **Interstitial**
      - Measured indirectly (ECF volume–plasma volume)
   e. **ICF**
      - Measured indirectly (TBW–ECF volume)

C. **Shifts of water between compartments**

1. **Basic principles**
   a. At steady state, **ECF osmolarity and ICF osmolarity are equal.**
   b. To achieve this equality, **water shifts** between the ECF and ICF compartments.
   c. It is assumed that solutes such as NaCl and mannitol do not cross cell membranes and are confined to ECF.

2. **Examples of shifts of water between compartments** (Figure 5-2 and Table 5-2)
   a. **Infusion of isotonic NaCl**—addition of isotonic fluid
      - is also called **isosmotic volume expansion.**

![FIGURE 5-2](image-url)
ECF volume increases, but no change occurs in the osmolarity of ECF or ICF.

Because osmolarity is unchanged, water does not shift between the ECF and ICF compartments.

2. Plasma protein concentration and hematocrit decrease because the addition of fluid to the ECF dilutes the protein and red blood cells (RBCs). Because ECF osmolarity is unchanged, the RBCs will not shrink or swell.

3. Arterial blood pressure increases because ECF volume increases.

b. Diarrhea—loss of isotonic fluid
   - is also called isosmotic volume contraction.

1. ECF volume decreases, but no change occurs in the osmolarity of ECF or ICF. Because osmolarity is unchanged, water does not shift between the ECF and ICF compartments.

2. Plasma protein concentration and hematocrit increase because the loss of ECF concentrates the protein and RBCs. Because ECF osmolarity is unchanged, the RBCs will not shrink or swell.

3. Arterial blood pressure decreases because ECF volume decreases.

c. Excessive NaCl intake—addition of NaCl
   - is also called hyperosmotic volume expansion.

1. The osmolarity of ECF increases because osmoles (NaCl) have been added to the ECF.

2. Water shifts from ICF to ECF As a result of this shift, ICF osmolarity increases until it equals that of ECF.

3. As a result of the shift of water out of the cells, ECF volume increases (volume expansion) and ICF volume decreases.

4. Plasma protein concentration and hematocrit decrease because of the increase in ECF volume.

d. Sweating in a desert—loss of water
   - is also called hyperosmotic volume contraction.

1. The osmolarity of ECF increases because sweat is hyposmotic (relatively more water than salt is lost).

2. ECF volume decreases because of the loss of volume in the sweat. Water shifts out of ICF; as a result of the shift, ICF osmolarity increases until it is equal to ECF osmolarity, and ICF volume decreases.

---

**Table 5-2: Changes in Volume and Osmolarity of Body Fluids**

<table>
<thead>
<tr>
<th>Type</th>
<th>Key Examples</th>
<th>ECF Volume</th>
<th>ICF Volume</th>
<th>ECF Osmolarity</th>
<th>Hct and Serum [Na⁺]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isosmotic volume expansion</td>
<td>Isotonic NaCl infusion</td>
<td>↑</td>
<td>No change</td>
<td>No change</td>
<td>↓ Hct, ↓[Na⁺]</td>
</tr>
<tr>
<td>Isosmotic volume contraction</td>
<td>Diarrhea</td>
<td>↓</td>
<td>No change</td>
<td>No change</td>
<td>↑ Hct, ↑[Na⁺]</td>
</tr>
<tr>
<td>Hyperosmotic volume expansion</td>
<td>High NaCl intake</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓ Hct, ↑[Na⁺]</td>
</tr>
<tr>
<td>Hyperosmotic volume contraction</td>
<td>Sweating</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>−Hct, ↓[Na⁺]</td>
</tr>
<tr>
<td>Hyposmotic volume expansion</td>
<td>SIADH</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>−Hct, ↓[Na⁺]</td>
</tr>
<tr>
<td>Hyposmotic volume contraction</td>
<td>Adrenal insufficiency</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑ Hct, ↑[Na⁺]</td>
</tr>
</tbody>
</table>

- = no change; ECF = extracellular fluid; Hct = hematocrit; ICF = intracellular fluid; SIADH = syndrome of inappropriate antidiuretic hormone.
Plasma protein concentration increases because of the decrease in ECF volume. Although hematocrit might also be expected to increase, it remains unchanged because water shifts out of the RBCs, decreasing their volume and offsetting the concentrating effect of the decreased ECF volume.

e. Syndrome of inappropriate antidiuretic hormone (SIADH)—gain of water

- is also called hyposmotic volume expansion.

1. The osmolarity of ECF decreases because excess water is retained.
2. ECF volume increases because of the water retention. Water shifts into the cells; as a result of this shift, ICF osmolarity decreases until it equals ECF osmolarity, and ICF volume increases.
3. Plasma protein concentration decreases because of the increase in ECF volume. Although hematocrit might also be expected to decrease, it remains unchanged because water shifts into the RBCs, increasing their volume and offsetting the diluting effect of the gain of ECF volume.

f. Adrenocortical insufficiency—loss of NaCl

- is also called hyposmotic volume contraction.

1. The osmolarity of ECF decreases. As a result of the lack of aldosterone in adrenocortical insufficiency, there is decreased NaCl reabsorption, and the kidneys excrete more NaCl than water.
2. ECF volume decreases. Water shifts into the cells; as a result of this shift, ICF osmolarity decreases until it equals ECF osmolarity, and ICF volume increases.
3. Plasma protein concentration decreases because of the decrease in ECF volume. Hematocrit increases because of the decreased ECF volume and because the RBCs swell as a result of water entry.
4. Arterial blood pressure decreases because of the decrease in ECF volume.

II. RENAL CLEARANCE, RENAL BLOOD FLOW (RBF), AND GLOMERULAR FILTRATION RATE (GFR)

A. Clearance equation

- indicates the volume of plasma cleared of a substance per unit time.
- The units of clearance are mL/min and mL/24 hr.

\[ C = \frac{UV}{P} \]

where:
- \( C \) = clearance (mL/min or mL/24 hr)
- \( U \) = urine concentration (mg/mL)
- \( V \) = urine volume/time (mL/min)
- \( P \) = plasma concentration (mg/mL)

Example: If the plasma [Na⁺] is 140 mEq/L, the urine [Na⁺] is 700 mEq/L, and the urine flow rate is 1 mL/min, what is the clearance of Na⁺?

\[ C_{Na^+} = \frac{[U]_{Na^+} \times V}{[P]_{Na^+}} \]
\[ = \frac{700 \text{ mEq/L} \times 1 \text{ mL/min}}{140 \text{ mEq/L}} \]
\[ = 5 \text{ mL/min} \]
B. RBF

- is 25% of the cardiac output.
- is directly proportional to the pressure difference between the renal artery and the renal vein, and is inversely proportional to the resistance of the renal vasculature.
- Vasoconstriction of renal arterioles, which leads to a decrease in RBF, is produced by activation of the sympathetic nervous system and angiotensin II. At low concentrations, angiotensin II preferentially constricts efferent arterioles, thereby “protecting” (increasing) the GFR. Angiotensin-converting enzyme (ACE) inhibitors dilate efferent arterioles and produce a decrease in GFR; these drugs reduce hyperfiltration and the occurrence of diabetic nephropathy in diabetes mellitus.
- Vasodilation of renal arterioles, which leads to an increase in RBF, is produced by prostaglandins E₂ and I₂, bradykinin, nitric oxide, and dopamine.

1. Autoregulation of RBF

- is accomplished by changing renal vascular resistance. If arterial pressure changes, a proportional change occurs in renal vascular resistance to maintain a constant RBF.
- RBF remains constant over the range of arterial pressures from 80 to 200 mm Hg (autoregulation).
- The mechanisms for autoregulation include:
  a. Myogenic mechanism, in which the renal afferent arterioles contract in response to stretch. Thus, increased renal arterial pressure stretches the arterioles, which contract and increase resistance to maintain constant blood flow.
  b. Tubuloglomerular feedback, in which increased renal arterial pressure leads to increased delivery of fluid to the macula densa. The macula densa senses the increased load and causes constriction of the nearby afferent arteriole, increasing resistance to maintain constant blood flow.

2. Measurement of renal plasma flow (RPF)—clearance of para-aminohippuric acid (PAH)

- PAH is filtered and secreted by the renal tubules.
- Clearance of PAH is used to measure RPF.
- Clearance of PAH measures effective RPF and underestimates true RPF by 10%. (Clearance of PAH does not measure renal plasma flow to regions of the kidney that do not filter and secrete PAH.)

\[
RPF = C_{PAH} = \frac{[U]_{PAH} \cdot V}{[P]_{PAH}}
\]

where:
- \( RPF \) = renal plasma flow (mL/min or mL/24 hr)
- \( C_{PAH} \) = clearance of PAH (mL/min or mL/24 hr)
- \([U]_{PAH}\) = urine concentration of PAH (mg/mL)
- \( V \) = urine flow rate (mL/min or mL/24 hr)
- \([P]_{PAH}\) = plasma concentration of PAH (mg/mL)

3. Measurement of RBF

\[
RBF = \frac{RPF}{1 - \text{Hematocrit}}
\]

- Note that the denominator in this equation, 1–hematocrit, is the fraction of blood volume occupied by plasma.
C. GFR

1. Measurement of GFR—clearance of inulin
   - Inulin is filtered, but not reabsorbed or secreted by the renal tubules.
   - The clearance of inulin is used to measure GFR, as shown in the following equation:

   \[ GFR = \frac{[U]_{\text{inulin}} \times V}{[P]_{\text{inulin}}} \]

   where:
   - \( GFR \) = glomerular filtration rate (mL/min or mL/24 hr)
   - \([U]_{\text{inulin}}\) = urine concentration of inulin (mg/mL)
   - \( V \) = urine flow rate (mL/min or mL/24 hr)
   - \([P]_{\text{inulin}}\) = plasma concentration of inulin (mg/mL)

   **Example of calculation of GFR:** Inulin is infused in a patient to achieve a steady-state plasma concentration of 1 mg/mL. A urine sample collected during 1 hour has a volume of 60 mL and an inulin concentration of 120 mg/mL. What is the patient’s GFR?

   \[
   GFR = \frac{[U]_{\text{inulin}} \times V}{[P]_{\text{inulin}}}
   = \frac{120 \text{ mg/mL} \times 60 \text{ mL/hr}}{1 \text{ mg/mL}}
   = \frac{120 \text{ mg/mL} \times 1 \text{ mL/min}}{1 \text{ mg/mL}}
   = 120 \text{ mL/min}
   \]

2. Estimates of GFR with blood urea nitrogen (BUN) and serum [creatinine]
   - Both BUN and serum [creatinine] increase when GFR decreases.
   - In prerenal azotemia (hypovolemia), BUN increases more than serum creatinine and there is an increased BUN/creatinine ratio (>20:1).
   - GFR decreases with age, although serum [creatinine] remains constant because of decreased muscle mass.

3. Filtration fraction
   - is the fraction of RPF filtered across the glomerular capillaries, as shown in the following equation:

   \[ \text{Filtration fraction} = \frac{GFR}{\text{RPF}} \]

   - is normally about 0.20. Thus, 20% of the RPF is filtered. The remaining 80% leaves the glomerular capillaries by the efferent arterioles and becomes the peritubular capillary circulation.
   - Increases in the filtration fraction produce increases in the protein concentration of peritubular capillary blood, which leads to increased reabsorption in the proximal tubule.
   - Decreases in the filtration fraction produce decreases in the protein concentration of peritubular capillary blood and decreased reabsorption in the proximal tubule.

4. Determining GFR—Starling forces (Figure 5-3)
   - The driving force for glomerular filtration is the net ultrafiltration pressure across the glomerular capillaries.
   - Filtration is always favored in glomerular capillaries because the net ultrafiltration pressure always favors the movement of fluid out of the capillary.
GFR can be expressed by the Starling equation:

\[
GFR = K_f \left[ (P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS}) \right]
\]

a. **GFR** is filtration across the glomerular capillaries.

b. **\( K_f \)** is the filtration coefficient of the glomerular capillaries.

- The glomerular barrier consists of the capillary endothelium, basement membrane, and filtration slits of the podocytes.
- Normally, *anionic glycoproteins line the filtration barrier* and restrict the filtration of plasma proteins, which are also negatively charged.
- In **glomerular disease**, the anionic charges on the barrier may be removed, resulting in proteinuria.

c. **\( P_{GC} \)** is glomerular capillary hydrostatic pressure, which is constant along the length of the capillary.

- It is increased by dilation of the afferent arteriole or constriction of the efferent arteriole. Increases in \( P_{GC} \) cause increases in net ultrafiltration pressure and GFR.

d. **\( P_{BS} \)** is Bowman’s space hydrostatic pressure and is analogous to \( P_i \) in systemic capillaries.

- It is increased by constriction of the ureters. Increases in \( P_{BS} \) cause decreases in net ultrafiltration pressure and GFR.

e. **\( \pi_{GC} \)** is glomerular capillary oncotic pressure. It normally increases along the length of the glomerular capillary because filtration of water increases the protein concentration of glomerular capillary blood.

- It is increased by increases in protein concentration. Increases in \( \pi_{GC} \) cause decreases in net ultrafiltration pressure and GFR.

f. **\( \pi_{BS} \)** is Bowman’s space oncotic pressure. It is usually zero, and therefore ignored, because only a small amount of protein is normally filtered.

5. **Sample calculation of ultrafiltration pressure with the Starling equation**

At the afferent arteriolar end of a glomerular capillary, \( P_{GC} \) is 45 mm Hg, \( P_{BS} \) is 10 mm Hg, and \( \pi_{GC} \) is 27 mm Hg. What are the value and direction of the net ultrafiltration pressure?

\[
\text{Net pressure} = (P_{GC} - P_{BS}) - \pi_{GC}
\]

\[
\text{Net pressure} = (45 \text{ mm Hg} - 10 \text{ mm Hg}) - 27 \text{ mm Hg}
\]

\[
= +8 \text{ mm Hg (favoring filtration)}
\]

6. **Changes in Starling forces—effect on GFR and filtration fraction** (Table 5-3)
### Table 5-3
Effect of Changes in Starling Forces on GFR, RPF, and Filtration Fraction

<table>
<thead>
<tr>
<th>Effect on GFR</th>
<th>Effect on RPF</th>
<th>Effect on Filtration Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constriction of afferent arteriole (e.g., sympathetic)</strong></td>
<td>↓ (caused by ↓ $P_{GC}$)</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Constriction of efferent arteriole (e.g., angiotensin II)</strong></td>
<td>↑ (caused by ↑ $P_{GC}$)</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Increased plasma [protein]</strong></td>
<td>↓ (caused by ↑ $π_{GC}$)</td>
<td>No change</td>
</tr>
<tr>
<td><strong>Ureteral stone</strong></td>
<td>↓ (caused by ↑ $P_{BS}$)</td>
<td>No change</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate; RPF = renal plasma flow.

### III. REABSORPTION AND SECRETION (FIGURE 5-4)

#### A. Calculation of reabsorption and secretion rates

- The reabsorption or secretion rate is the difference between the amount filtered across the glomerular capillaries and the amount excreted in urine. It is calculated with the following equations:

  \[
  \begin{align*}
  \text{Filtered load} &= \text{GFR} \times [\text{plasma}] \\
  \text{Excretion rate} &= V \times [\text{urine}] \\
  \text{Reabsorption rate} &= \text{Filtered load} - \text{Excretion rate} \\
  \text{Secretion rate} &= \text{Excretion rate} - \text{Filtered load}
  \end{align*}
  \]

- If the filtered load is greater than the excretion rate, then **net reabsorption** of the substance has occurred. If the filtered load is less than the excretion rate, then **net secretion** of the substance has occurred.

![Figure 5-4](image-url) Processes of filtration, reabsorption, and secretion. The sum of the three processes is excretion.
Example: A woman with untreated diabetes mellitus has a GFR of 120 mL/min, a plasma glucose concentration of 400 mg/dL, a urine glucose concentration of 2500 mg/dL, and a urine flow rate of 4 mL/min. What is the reabsorption rate of glucose?

- Filtered load of glucose
  \[
  \text{Filtered load} = \text{GFR} \times \text{Plasma [glucose]} \\
  = 120 \text{ mL/min} \times 400 \text{ mg/dL} \\
  = 480 \text{ mg/min}
  \]

- Excretion
  \[
  \text{Excretion} = V \times \text{Urine [glucose]} \\
  = 4 \text{ mL/min} \times 2500 \text{ mg/dL} \\
  = 100 \text{ mg/min}
  \]

- Reabsorption
  \[
  \text{Reabsorption} = 480 \text{ mg/min} - 100 \text{ mg/min} \\
  = 380 \text{ mg/min}
  \]

B. Transport maximum (Tm) curve for glucose—a reabsorbed substance (Figure 5-5)

1. Filtered load of glucose
   - increases in direct proportion to the plasma glucose concentration (filtered load of glucose = GFR \times [P_{\text{glucose}}]).

2. Reabsorption of glucose
   a. Na⁺–glucose cotransport in the proximal tubule reabsorbs glucose from tubular fluid into the blood. There are a limited number of Na⁺–glucose carriers.
   b. At plasma glucose concentrations less than 250 mg/dL, all of the filtered glucose can be reabsorbed because plenty of carriers are available; in this range, the line for reabsorption is the same as that for filtration.
   c. At plasma glucose concentrations greater than 350 mg/dL, the carriers are saturated. Therefore, increases in plasma concentration above 350 mg/dL do not result in increased rates of reabsorption. The reabsorptive rate at which the carriers are saturated is the Tm.

3. Excretion of glucose
   a. At plasma concentrations less than 250 mg/dL, all of the filtered glucose is reabsorbed and excretion is zero. Threshold (defined as the plasma concentration at which glucose first appears in the urine) is approximately 250 mg/dL.
   b. At plasma concentrations greater than 350 mg/dL, reabsorption is saturated (Tm). Therefore, as the plasma concentration increases, the additional filtered glucose cannot be reabsorbed and is excreted in the urine.
4. Splay
- is the region of the glucose curves between threshold and $T_m$.
- occurs between plasma glucose concentrations of approximately 250 and 350 mg/dL.
- represents the excretion of glucose in urine before saturation of reabsorption ($T_m$) is fully achieved.
- is explained by the heterogeneity of nephrons and the relatively low affinity of the Na$^+$–glucose carriers.

C. $T_m$ curve for PAH—a secreted substance (Figure 5-6)
1. Filtered load of PAH
- As with glucose, the filtered load of PAH increases in direct proportion to the plasma PAH concentration.

2. Secretion of PAH
   a. Secretion of PAH occurs from peritubular capillary blood into tubular fluid (urine) via carriers in the proximal tubule.
   b. At low plasma concentrations of PAH, the secretion rate increases as the plasma concentration increases.
   c. Once the carriers are saturated, further increases in plasma PAH concentration do not cause further increases in the secretion rate ($T_m$).

3. Excretion of PAH
   a. Excretion of PAH is the sum of filtration across the glomerular capillaries plus secretion from peritubular capillary blood.
   b. The curve for excretion is steepest at low plasma PAH concentrations (lower than at $T_m$). Once the $T_m$ for secretion is exceeded and all of the carriers for secretion are saturated, the excretion curve flattens and becomes parallel to the curve for filtration.
   c. RPF is measured by the clearance of PAH at plasma concentrations of PAH that are lower than at $T_m$.

D. Relative clearances of substances
1. Substances with the highest clearances
- are those that are both filtered across the glomerular capillaries and secreted from the peritubular capillaries into urine (e.g., PAH).

2. Substances with the lowest clearances
- are those that either are not filtered (e.g., protein) or are filtered and subsequently reabsorbed into peritubular capillary blood (e.g., Na$^+$, glucose, amino acids, HCO$_3^-$, Cl$^-$).

FIGURE 5-6 Para-aminohippuric acid (PAH) titration curve. PAH filtration, excretion, and secretion are shown as a function of plasma [PAH]. $T_m$ = transport maximum.
3. **Substances with clearances equal to GFR**
   - are **glomerular markers**.
   - are those that are freely filtered, but not reabsorbed or secreted (e.g., inulin).

4. **Relative clearances**
   - PAH > K⁺ (high-K⁺ diet) > inulin > urea > Na⁺ > glucose, amino acids, and HCO₃⁻.

**E. Nonionic diffusion**

1. **Weak acids**
   - have an HA form and an A⁻ form.
   - The HA form, which is uncharged and lipid-soluble, can “back-diffuse” from urine to blood.
   - The A⁻ form, which is charged and not lipid-soluble, cannot back-diffuse.
   - At **acidic urine pH**, the HA form predominates, there is more back-diffusion, and there is decreased excretion of the weak acid.
   - At **alkaline urine pH**, the A⁻ form predominates, there is less back-diffusion, and there is increased excretion of the weak acid. For example, the excretion of **salicylic acid** can be increased by alkalinizing the urine.

2. **Weak bases**
   - have a BH⁺ form and a B form.
   - The B form, which is uncharged and lipid-soluble, can “back-diffuse” from urine to blood.
   - The BH⁺ form, which is charged and not lipid-soluble, cannot back-diffuse.
   - At **acidic urine pH**, the BH⁺ form predominates, there is less back-diffusion, and there is increased excretion of the weak base.
   - At **alkaline urine pH**, the B form predominates, there is more back-diffusion, and there is decreased excretion of the weak base.

**IV. NaCl REGULATION**

**A. Single nephron terminology**

- **Tubular fluid (TF) is urine** at any point along the nephron.
- **Plasma (P) is systemic plasma.** It is considered to be constant.

1. **TF/Px ratio**
   - compares the concentration of a substance in tubular fluid at any point along the nephron with the concentration in plasma.
   a. **If TF/P = 1.0**, then either there has been no reabsorption of the substance or reabsorption of the substance has been exactly proportional to the reabsorption of water.
      - **For example**, if TF/Pₙa⁺ = 1.0, the [Na⁺] in tubular fluid is identical to the [Na⁺] in plasma.
      - For any freely filtered substance, TF/P = 1.0 in Bowman's space (before any reabsorption or secretion has taken place to modify the tubular fluid).
   b. **If TF/P < 1.0**, then reabsorption of the substance has been greater than the reabsorption of water and the concentration in tubular fluid is less than that in plasma.
      - **For example**, if TF/Pₙa⁺ = 0.8, then the [Na⁺] in tubular fluid is 80% of the [Na⁺] in plasma.
   c. **If TF/P > 1.0**, then either reabsorption of the substance has been less than the reabsorption of water or there has been secretion of the substance.
2. TF/P\textsubscript{inulin}
   - is used as a marker for water reabsorption along the nephron.
   - increases as water is reabsorbed.
   - Because inulin is freely filtered, but not reabsorbed or secreted, its concentration in tubular fluid is determined solely by how much water remains in the tubular fluid.
   - The following equation shows how to calculate the fraction of the filtered water that has been reabsorbed:
     \[
     \text{Fraction of filtered H}_2\text{O reabsorbed} = 1 - \frac{1}{[\text{TF/P}]_{\text{inulin}}}
     \]
   - For example, if 50% of the filtered water has been reabsorbed, the TF/P\textsubscript{inulin} = 2.0. For another example, if TF/P\textsubscript{inulin} = 3.0, then 67% of the filtered water has been reabsorbed (i.e., 1 − 1/3).

3. [TF/P\textsubscript{X}]/[TF/P\textsubscript{inulin}] ratio
   - corrects the TF/P\textsubscript{X} ratio for water reabsorption. This double ratio gives the fraction of the filtered load remaining at any point along the nephron.
   - For example, if [TF/P\textsubscript{K}]/[TF/P\textsubscript{inulin}] = 0.3 at the end of the proximal tubule, then 30% of the filtered K\textsuperscript{+} remains in the tubular fluid and 70% has been reabsorbed into the blood.

B. General information about Na\textsuperscript{+} reabsorption
   - Na\textsuperscript{+} is freely filtered across the glomerular capillaries; therefore, the [Na\textsuperscript{+}] in the tubular fluid of Bowman's space equals that in plasma (i.e., TF/P\textsubscript{Na} = 1.0).
   - Na\textsuperscript{+} is reabsorbed along the entire nephron, and very little is excreted in urine (<1% of the filtered load).

C. Na\textsuperscript{+} reabsorption along the nephron (Figure 5-7)
   1. Proximal tubule
      - reabsorbs two-thirds, or 67%, of the filtered Na\textsuperscript{+} and H\textsubscript{2}O, more than any other part of the nephron.
      - is the site of glomerulotubular balance.
The process is isosmotic. The reabsorption of Na\(^+\) and H\(_2\)O in the proximal tubule is exactly proportional. Therefore, both TF/P\(_{Na^+}\) and TF/P\(_{osm}\) = 1.0.

a. Early proximal tubule—special features (Figure 5-8)

- reabsorbs Na\(^+\) and H\(_2\)O with HCO\(_3^-\), glucose, amino acids, phosphate, and lactate.
- Na\(^+\) is reabsorbed by cotransport with glucose, amino acids, phosphate, and lactate. These cotransport processes account for the reabsorption of all of the filtered glucose and amino acids.
- Na\(^+\) is also reabsorbed by countertransport via Na\(^+\)--H\(^+\) exchange, which is linked directly to the reabsorption of filtered HCO\(_3^-\).
- Carbonic anhydrase inhibitors (e.g., acetazolamide) are diuretics that act in the early proximal tubule by inhibiting the reabsorption of filtered HCO\(_3^-\).

b. Late proximal tubule—special features

- Filtered glucose, amino acids, and HCO\(_3^-\) have already been completely removed from the tubular fluid by reabsorption in the early proximal tubule.
- In the late proximal tubule, Na\(^+\) is reabsorbed with Cl\(^-\).

c. Glomerulotubular balance in the proximal tubule

- maintains constant fractional reabsorption (two-thirds, or 67%) of the filtered Na\(^+\) and H\(_2\)O.

(1) For example, if GFR spontaneously increases, the filtered load of Na\(^+\) also increases. Without a change in reabsorption, this increase in GFR would lead to increased Na\(^+\) excretion. However, glomerulotubular balance functions such that Na\(^+\) reabsorption also will increase, ensuring that a constant fraction is reabsorbed.

(2) The mechanism of glomerulotubular balance is based on Starling forces in the peritubular capillaries, which alter the reabsorption of Na\(^+\) and H\(_2\)O in the proximal tubule (Figure 5-9).

- The route of isosmotic fluid reabsorption is from the lumen, to the proximal tubule cell, to the lateral intercellular space, and then to the peritubular capillary blood.
- Starling forces in the peritubular capillary blood govern how much of this isosmotic fluid will be reabsorbed.
- Fluid reabsorption is increased by increases in \(\pi_c\) of the peritubular capillary blood and decreased by decreases in \(\pi_c\).
- Increases in GFR and filtration fraction cause the protein concentration and \(\pi_c\) of peritubular capillary blood to increase. This increase, in turn, produces an increase in fluid reabsorption. Thus, there is matching of filtration and reabsorption, or glomerulotubular balance.
d. Effects of ECF volume on proximal tubular reabsorption

(1) ECF volume contraction increases reabsorption. Volume contraction increases peritubular capillary protein concentration and $\pi_c$, and decreases peritubular capillary $P_c$. Together, these changes in Starling forces in peritubular capillary blood cause an increase in proximal tubular reabsorption.

(2) ECF volume expansion decreases reabsorption. Volume expansion decreases peritubular capillary protein concentration and $\pi_c$, and increases $P_c$. Together, these changes in Starling forces in peritubular capillary blood cause a decrease in proximal tubular reabsorption.

2. Thick ascending limb of the loop of Henle (Figure 5-10)

- reabsorbs 25% of the filtered Na$^+$.
- contains a Na$^+$–K$^+$–2Cl$^-$ cotransporter in the luminal membrane.
- is the site of action of the loop diuretics (furosemide, ethacrynic acid, bumetanide), which inhibit the Na$^+$–K$^+$–2Cl$^-$ cotransporter.
- is impermeable to water. Thus, NaCl is reabsorbed without water. As a result, tubular fluid [Na$^+$] and tubular fluid osmolarity decrease to less than their concentrations in plasma (i.e., TF/P$_{\text{Na}}$ and TF/P$_{\text{osm}} < 1.0$). This segment, therefore, is called the diluting segment.
- has a lumen-positive potential difference. Although the Na$^+$–K$^+$–2Cl$^-$ cotransporter appears to be electroneutral, some K$^+$ diffuses back into the lumen, making the lumen electrically positive.

3. Distal tubule and collecting duct

- together reabsorb 8% of the filtered Na$^+$.

a. Early distal tubule—special features

- reabsorbs NaCl by a Na$^+$–Cl$^-$ cotransporter.
- is the site of action of thiazide diuretics.
is impermeable to water, as is the thick ascending limb. Thus, reabsorption of NaCl occurs without water, which further dilutes the tubular fluid.

is called the cortical diluting segment.

b. Late distal tubule and collecting duct—special features

have two cell types.

(1) Principal cells

- reabsorb Na⁺ and H₂O.
- secrete K⁺.
- Aldosterone increases Na⁺ reabsorption and increases K⁺ secretion. Like other steroid hormones, the action of aldosterone takes several hours to develop because new protein synthesis of Na⁺ channels (ENaC) is required. About 2% of overall Na⁺ reabsorption is affected by aldosterone.
- Antidiuretic hormone (ADH) increases H₂O permeability by directing the insertion of H₂O channels in the luminal membrane. In the absence of ADH, the principal cells are virtually impermeable to water.
- K⁺-sparing diuretics (spironolactone, triamterene, amiloride) decrease K⁺ secretion.

(2) α-Intercalated cells

- secrete H⁺ by an H⁺-adenosine triphosphatase (ATPase), which is stimulated by aldosterone.
- reabsorb K⁺ by an H⁺,K⁺-ATPase.

V. K⁺ REGULATION

A. Shifts of K⁺ between the ICF and ECF (Figure 5-11 and Table 5-4)

- Most of the body's K⁺ is located in the ICF.
- A shift of K⁺ out of cells causes hyperkalemia.
- A shift of K⁺ into cells causes hypokalemia.

B. Renal regulation of K⁺ balance (Figure 5-12)

- K⁺ is filtered, reabsorbed, and secreted by the nephron.
- K⁺ balance is achieved when urinary excretion of K⁺ exactly equals intake of K⁺ in the diet.
  - K⁺ excretion can vary widely from 1% to 110% of the filtered load, depending on dietary K⁺ intake, aldosterone levels, and acid–base status.

1. Glomerular capillaries

- Filtration occurs freely across the glomerular capillaries. Therefore, TF/Pk⁺ in Bowman’s space is 1.0.

2. Proximal tubule

- reabsorbs 67% of the filtered K⁺ along with Na⁺ and H₂O.
3. Thick ascending limb of the loop of Henle

- **reabsorbs 20%** of the filtered K⁺.
- Reabsorption involves the \( \text{Na}^+\text{–K}^+\text{–2Cl}^- \) cotransporter in the luminal membrane of cells in the thick ascending limb (see Figure 5-10).

4. Distal tubule and collecting duct

- either reabsorb or secrete K⁺, depending on dietary K⁺ intake.

a. Reabsorption of K⁺

- involves an \( \text{H}^+\text{–K}^+\text{–ATPase} \) in the luminal membrane of the α-intercalated cells.
- occurs only on a low-K⁺ diet (K⁺ depletion). Under these conditions, K⁺ excretion can be as low as 1% of the filtered load because the kidney conserves as much K⁺ as possible.
b. Secretion of $K^+$

- occurs in the principal cells.
- is variable and accounts for the wide range of urinary $K^+$ excretion.
- depends on factors such as dietary $K^+$, aldosterone levels, acid–base status, and urine flow rate.

1) **Mechanism of distal $K^+$ secretion** (Figure 5-13)

   a) At the basolateral membrane, $K^+$ is actively transported into the cell by the $Na^+/K^+$ pump. As in all cells, this mechanism maintains a high intracellular $K^+$ concentration.

   b) At the luminal membrane, $K^+$ is passively secreted into the lumen through $K^+$ channels. The magnitude of this passive secretion is determined by the chemical and electrical driving forces on $K^+$ across the luminal membrane.

   - Maneuvers that increase the intracellular $K^+$ concentration or decrease the luminal $K^+$ concentration will increase $K^+$ secretion by increasing the driving force.
   - Maneuvers that decrease the intracellular $K^+$ concentration will decrease $K^+$ secretion by decreasing the driving force.

2) **Factors that change distal $K^+$ secretion** (see Figure 5-13 and Table 5-5)

- Distal $K^+$ secretion by the principal cells is increased when the electrochemical driving force for $K^+$ across the luminal membrane is increased. Secretion is decreased when the electrochemical driving force is decreased.

   a) **Dietary $K^+$**

   - A diet high in $K^+$ increases $K^+$ secretion, and a diet low in $K^+$ decreases $K^+$ secretion.
   - On a **high-$K^+$ diet**, intracellular $K^+$ increases so that the driving force for $K^+$ secretion also increases.

<table>
<thead>
<tr>
<th>Causes of Increased Distal $K^+$ Secretion</th>
<th>Causes of Decreased Distal $K^+$ Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-$K^+$ diet</td>
<td>Low-$K^+$ diet</td>
</tr>
<tr>
<td>Hyperaldosteronism</td>
<td>Hypoaldosteronism</td>
</tr>
<tr>
<td>Alkalosis</td>
<td>Acidosis</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>$K^+$-sparing diuretics</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td></td>
</tr>
<tr>
<td>Luminal anions</td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 5-13** Mechanism of $K^+$ secretion in the principal cell of the distal tubule.
On a low-K+ diet, intracellular K+ decreases so that the driving force for K+ secretion decreases. Also, the α-intercalated cells are stimulated to reabsorb K+ by the H+K+-ATPase.

(b) Aldosterone
- increases K+ secretion.
- The mechanism involves increased Na+ entry into the cells across the luminal membrane and increased pumping of Na+ out of the cells by the Na+-K+ pump. Stimulation of the Na+-K+ pump simultaneously increases K+ uptake into the principal cells, increasing the intracellular K+ concentration and the driving force for K+ secretion. Aldosterone also increases the number of luminal membrane K+ channels.
- Hyperaldosteronism increases K+ secretion and causes hypokalemia.
- Hypoaldosteronism decreases K+ secretion and causes hyperkalemia.

(c) Acid–base
- Effectively, H+ and K+ exchange for each other across the basolateral cell membrane.
- Acidosis decreases K+ secretion. The blood contains excess H+; therefore, H+ enters the cell across the basolateral membrane and K+ leaves the cell. As a result, the intracellular K+ concentration and the driving force for K+ secretion decrease.
- Alkalosis increases K+ secretion. The blood contains too little H+; therefore, H+ leaves the cell across the basolateral membrane and K+ enters the cell. As a result, the intracellular K+ concentration and the driving force for K+ secretion increase.

(d) Thiazide and loop diuretics
- increase K+ secretion.
- Diuretics that increase flow rate through the distal tubule (e.g., thiazide diuretics, loop diuretics) cause dilution of the luminal K+ concentration, increasing the driving force for K+ secretion. Also, as a result of increased K+ secretion, these diuretics cause hypokalemia.

(e) K+–sparing diuretics
- decrease K+ secretion. If used alone, they cause hyperkalemia.
- Spironolactone is an antagonist of aldosterone; triamterene and amiloride act directly on the principal cells.
- The most important use of the K+–sparing diuretics is in combination with thiazide or loop diuretics to offset (reduce) urinary K+ losses.

(f) Luminal anions
- Excess anions (e.g., HCO3–) in the lumen cause an increase in K+ secretion by increasing the negativity of the lumen, which favors K+ secretion.

VI. RENAL REGULATION OF UREA, PHOSPHATE, CALCIUM, AND MAGNESIUM

A. Urea
- Fifty percent of the filtered urea is reabsorbed passively in the proximal tubule.
- The distal tubule, cortical collecting ducts, and outer medullary collecting ducts are impermeable to urea; thus, no urea is reabsorbed by these segments.
- ADH increases the urea permeability of the inner medullary collecting ducts. Urea reabsorption from inner medullary collecting ducts contributes to urea recycling in the inner medulla and to the development of the corticopapillary osmotic gradient.
Urea excretion varies with urine flow rate. At high levels of water reabsorption (low urine flow rate), there is greater urea reabsorption and decreased urea excretion. At low levels of water reabsorption (high urine flow rate), there is less urea reabsorption and increased urea excretion.

B. Phosphate

Eighty-five percent of the filtered phosphate is reabsorbed in the proximal tubule by Na\(^+\)-phosphate cotransport. Because distal segments of the nephron do not reabsorb phosphate, 15% of the filtered load is excreted in urine. Parathyroid hormone (PTH) inhibits phosphate reabsorption in the proximal tubule by activating adenylate cyclase, generating cyclic AMP (cAMP), and inhibiting Na\(^+\)-phosphate cotransport. Therefore, PTH causes phosphaturia and increased urinary cAMP.

Phosphate is a urinary buffer for H\(^+\); excretion of H\(_2\)PO\(_4^–\) is called titratable acid.

C. Calcium (Ca\(^{2+}\))

Sixty percent of the plasma Ca\(^{2+}\) is filtered across the glomerular capillaries. Together, the proximal tubule and thick ascending limb reabsorb more than 90% of the filtered Ca\(^{2+}\) by passive processes that are coupled to Na\(^+\) reabsorption. Loop diuretics (e.g., furosemide) cause increased urinary Ca\(^{2+}\) excretion. Because Ca\(^{2+}\) reabsorption is linked to Na\(^+\) reabsorption in the loop of Henle, inhibiting Na\(^+\) reabsorption with a loop diuretic also inhibits Ca\(^{2+}\) reabsorption. If volume is replaced, loop diuretics can be used in the treatment of hypercalcemia.

Together, the distal tubule and collecting duct reabsorb 8% of the filtered Ca\(^{2+}\) by an active process.

1. PTH increases Ca\(^{2+}\) reabsorption by activating adenylate cyclase in the distal tubule.
2. Thiazide diuretics increase Ca\(^{2+}\) reabsorption in the distal tubule and therefore decrease Ca\(^{2+}\) excretion. For this reason, thiazides are used in the treatment of idiopathic hypercalciuria.

D. Magnesium (Mg\(^{2+}\))

is reabsorbed in the proximal tubule, thick ascending limb of the loop of Henle, and distal tubule.

In the thick ascending limb, Mg\(^{2+}\) and Ca\(^{2+}\) compete for reabsorption; therefore, hypercalcemia causes an increase in Mg\(^{2+}\) excretion (by inhibiting Mg\(^{2+}\) reabsorption). Likewise, hypermagnesemia causes an increase in Ca\(^{2+}\) excretion (by inhibiting Ca\(^{2+}\) reabsorption).

VII. CONCENTRATION AND DILUTION OF URINE

A. Regulation of plasma osmolarity

is accomplished by varying the amount of water excreted relative to the amount of solute excreted (i.e., by varying urine osmolarity).

1. Response to water deprivation (Figure 5-14)
2. Response to water intake (Figure 5-15)

B. Production of concentrated urine (Figure 5-16)

is also called hyperosmotic urine, in which urine osmolarity > blood osmolarity.

is produced when circulating ADH levels are high (e.g., water deprivation, hemorrhage, SIADH).

1. Corticopapillary osmotic gradient—high ADH

is the gradient of osmolarity from the cortex (300 mOsm/L) to the papilla (1200 mOsm/L), and is composed primarily of NaCl and urea.

is established by countercurrent multiplication and urea recycling.

is maintained by countercurrent exchange in the vasa recta.
a. Countercurrent multiplication in the loop of Henle
   - depends on NaCl reabsorption in the thick ascending limb and countercurrent flow in the descending and ascending limbs of the loop of Henle.
   - is augmented by ADH, which stimulates NaCl reabsorption in the thick ascending limb. Therefore, the presence of ADH increases the size of the corticopapillary osmotic gradient.

b. Urea recycling from the inner medullary collecting ducts into the medullary interstitial fluid also is augmented by ADH.

c. Vasa recta are the capillaries that supply the loop of Henle. They maintain the corticopapillary gradient by serving as osmotic exchangers. Vasa recta blood equilibrates osmotically with the interstitial fluid of the medulla and papilla.

2. Proximal tubule—high ADH
   - The osmolarity of the glomerular filtrate is identical to that of plasma (300 mOsm/L).
   - Two-thirds of the filtered H2O is reabsorbed isosmotically (with Na+, Cl−, HCO3−, glucose, amino acids, and so forth) in the proximal tubule.
   - TF/P_{osm} = 1.0 throughout the proximal tubule because H2O is reabsorbed isosmotically with solute.

3. Thick ascending limb of the loop of Henle—high ADH
   - is called the diluting segment.
   - reabsorbs NaCl by the Na+-K+-2Cl- cotransporter.
Water intake

Decreases plasma osmolarity

Inhibits osmoreceptors in anterior hypothalamus

Decreases secretion of ADH from posterior pituitary

Decreases water permeability of late distal tubule and collecting duct

Decreases water reabsorption

Decreases urine osmolarity and increases urine volume

Increases plasma osmolarity toward normal

**FIGURE 5-15** Responses to water intake. ADH = antidiuretic hormone.

**FIGURE 5-16** Mechanisms for producing hyperosmotic (concentrated) urine in the presence of antidiuretic hormone (ADH). Numbers indicate osmolarity. Heavy arrows indicate water reabsorption. The thick outline shows the water-impermeable segments of the nephron. (Adapted with permission from Valtin H. Renal Function. 3rd ed. Boston: Little, Brown; 1995:158.)
is impermeable to H$_2$O. Therefore, H$_2$O is not reabsorbed with NaCl, and the tubular fluid becomes dilute.

The fluid that leaves the thick ascending limb has an osmolarity of 100 mOsm/L and $\text{T}_{\text{F}}/\text{P}_{\text{osm}} < 1.0$ as a result of the dilution process.

4. Early distal tubule—high ADH

is called the cortical diluting segment. Like the thick ascending limb, the early distal tubule reabsorbs NaCl but is impermeable to water. Consequently, tubular fluid is further diluted.

5. Late distal tubule—high ADH

ADH increases the H$_2$O permeability of the principal cells of the late distal tubule. H$_2$O is reabsorbed from the tubule until the osmolarity of distal tubular fluid equals that of the surrounding interstitial fluid in the renal cortex (300 mOsm/L).

$\text{T}_{\text{F}}/\text{P}_{\text{osm}} = 1.0$ at the end of the distal tubule because osmotic equilibration occurs in the presence of ADH.

6. Collecting ducts—high ADH

As in the late distal tubule, ADH increases the H$_2$O permeability of the principal cells of the collecting ducts. As tubular fluid flows through the collecting ducts, it passes through the corticopapillary gradient (regions of increasingly higher osmolarity), which was previously established by countercurrent multiplication and urea recycling. H$_2$O is reabsorbed from the collecting ducts until the osmolarity of tubular fluid equals that of the surrounding interstitial fluid.

The osmolarity of the final urine equals that at the bend of the loop of Henle (1200 mOsm/L).

$\text{T}_{\text{F}}/\text{P}_{\text{osm}} > 1.0$ because osmotic equilibration occurs with the corticopapillary gradient in the presence of ADH.

C. Production of dilute urine (Figure 5-17)

is called hyposmotic urine, in which urine osmolarity < blood osmolarity.

is produced when circulating levels of ADH are low (e.g., water intake, central diabetes insipidus) or when ADH is ineffective (nephrogenic diabetes insipidus).

**FIGURE 5-17** Mechanisms for producing hyposmotic (dilute) urine in the absence of antidiuretic hormone (ADH). Numbers indicate osmolarity. Heavy arrow indicates water reabsorption. The thick outline shows the water-impermeable segments of the nephron. (Adapted with permission from Valtin H. Renal Function. 3rd ed. Boston: Little, Brown; 1995:159.)
1. Corticopapillary osmotic gradient—no ADH
   - is smaller than in the presence of ADH because ADH stimulates both countercurrent multiplication and urea recycling.

2. Proximal tubule—no ADH
   - As in the presence of ADH, two-thirds of the filtered water is reabsorbed isosmotically.
   - $\text{TF/Posm} = 1.0$ throughout the proximal tubule.

3. Thick ascending limb of the loop of Henle—no ADH
   - As in the presence of ADH, NaCl is reabsorbed without water, and the tubular fluid becomes dilute (although not quite as dilute as in the presence of ADH).
   - $\text{TF/Posm} < 1.0$.

4. Early distal tubule—no ADH
   - As in the presence of ADH, NaCl is reabsorbed without $H_2O$ and the tubular fluid is further diluted.
   - $\text{TF/Posm} < 1.0$.

5. Late distal tubule and collecting ducts—no ADH
   - In the absence of ADH, the cells of the late distal tubule and collecting ducts are impermeable to $H_2O$.
   - Thus, even though the tubular fluid flows through the corticopapillary osmotic gradient, osmotic equilibration does not occur.
   - The osmolarity of the final urine will be dilute with an osmolarity as low as 50 mOsm/L.
   - $\text{TF/Posm} < 1.0$.

D. Free-water clearance ($C_{H_2O}$)
   - is used to estimate the ability to concentrate or dilute the urine.
   - Free water, or solute-free water, is produced in the diluting segments of the kidney (i.e., thick ascending limb and early distal tubule), where NaCl is reabsorbed and free water is left behind in the tubular fluid.
   - In the absence of ADH, this solute-free water is excreted and $C_{H_2O}$ is positive.
   - In the presence of ADH, this solute-free water is not excreted, but is reabsorbed by the late distal tubule and collecting ducts, and $C_{H_2O}$ is negative.

1. Calculation of $C_{H_2O}$

   $$C_{H_2O} = V - C_{osm}$$

   where:
   - $C_{H_2O}$ = free-water clearance (mL/min)
   - $V$ = urine flow rate (mL/min)
   - $C_{osm}$ = osmolar clearance ($U_{osm} \cdot V/Posm$) [mL/min]

   Example: If the urine flow rate is 10 mL/min, urine osmolarity is 100 mOsm/L, and plasma osmolarity is 300 mOsm/L, what is the free-water clearance?

   $$C_{H_2O} = V - C_{osm}$$
   $$= 10 \text{ mL/min} - \frac{100 \text{ mOsm/L} \times 10 \text{ mL/min}}{300 \text{ mOsm/L}}$$
   $$= 10 \text{ mL/min} - 3.33 \text{ mL/min}$$
   $$= +6.7 \text{ mL/min}$$
2. Urine that is isosmotic to plasma (isosthenuric)

- \( CH_2O \) is zero.
- is produced during treatment with a loop diuretic, which inhibits NaCl reabsorption in the thick ascending limb, inhibiting both dilution in the thick ascending limb and production of the corticopapillary osmotic gradient. Therefore, the urine cannot be diluted during high water intake (because a diluting segment is inhibited) or concentrated during water deprivation (because the corticopapillary gradient has been abolished).

3. Urine that is hyposmotic to plasma (low ADH)

- \( CH_2O \) is positive.
- is produced with high water intake (in which ADH release from the posterior pituitary is suppressed), central diabetes insipidus (in which pituitary ADH is insufficient), or nephrogenic diabetes insipidus (in which the collecting ducts are unresponsive to ADH).

4. Urine that is hyperosmotic to plasma (high ADH)

- \( CH_2O \) is negative.
- is produced in water deprivation (ADH release from the pituitary is stimulated) or SIADH.

E. Clinical disorders related to the concentration or dilution of urine (Table 5-6)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Serum ADH</th>
<th>Serum Osmolarity/ Serum [Na(^+)]</th>
<th>Urine Osmolarity</th>
<th>Urine Flow Rate</th>
<th>( CH_2O )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary polydipsia</td>
<td>↓</td>
<td>Decreased</td>
<td>Hyposmotic</td>
<td>High</td>
<td>Positive</td>
</tr>
<tr>
<td>Central diabetes insipidus</td>
<td>↓</td>
<td>Increased (because of excretion of too much H(_2)O)</td>
<td>Hyposmotic</td>
<td>High</td>
<td>Positive</td>
</tr>
<tr>
<td>Nephrogenic diabetes insipidus</td>
<td>↑ (because of increased plasma osmolarity)</td>
<td>Increased (because of excretion of too much H(_2)O)</td>
<td>Hyposmotic</td>
<td>High</td>
<td>Positive</td>
</tr>
<tr>
<td>Water deprivation</td>
<td>↑</td>
<td>High-normal</td>
<td>Hyperosmotic</td>
<td>Low</td>
<td>Negative</td>
</tr>
<tr>
<td>SIADH</td>
<td>↑↑</td>
<td>Decreased (because of reabsorption of too much H(_2)O)</td>
<td>Hyperosmotic</td>
<td>Low</td>
<td>Negative</td>
</tr>
</tbody>
</table>

ADH = antidiuretic hormone; \( CH_2O \) = free-water clearance; SIADH = syndrome of inappropriate antidiuretic hormone.

2. Urine that is isosmotic to plasma (isosthenuric)

- \( CH_2O \) is zero.
- is produced during treatment with a loop diuretic, which inhibits NaCl reabsorption in the thick ascending limb, inhibiting both dilution in the thick ascending limb and production of the corticopapillary osmotic gradient. Therefore, the urine cannot be diluted during high water intake (because a diluting segment is inhibited) or concentrated during water deprivation (because the corticopapillary gradient has been abolished).

3. Urine that is hyposmotic to plasma (low ADH)

- \( CH_2O \) is positive.
- is produced with high water intake (in which ADH release from the posterior pituitary is suppressed), central diabetes insipidus (in which pituitary ADH is insufficient), or nephrogenic diabetes insipidus (in which the collecting ducts are unresponsive to ADH).

4. Urine that is hyperosmotic to plasma (high ADH)

- \( CH_2O \) is negative.
- is produced in water deprivation (ADH release from the pituitary is stimulated) or SIADH.

E. Clinical disorders related to the concentration or dilution of urine (Table 5-6)

VIII. RENAL HORMONES

See Table 5-7 for a summary of renal hormones (see Chapter 7 for a discussion of hormones).

IX. ACID–BASE BALANCE

A. Acid production

- Two types of acid are produced in the body: volatile acid and nonvolatile acids.

1. Volatile acid

- is \( CO_2 \).
- is produced from the aerobic metabolism of cells.
- \( CO_2 \) combines with \( H_2O \) to form the weak acid \( H_2CO_3 \), which dissociates into \( H^+ \) and \( HCO_3^- \) by the following reactions:

\[
CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \]
Carbonic anhydrase, which is present in most cells, catalyzes the reversible reaction between CO₂ and H₂O.

2. Nonvolatile acids
- are also called fixed acids.
- include sulfuric acid (a product of protein catabolism) and phosphoric acid (a product of phospholipid catabolism).
- are normally produced at a rate of 40–60 mmoles/day.
- Other fixed acids that may be overproduced in disease or may be ingested include ketoacids, lactic acid, and salicylic acid.

B. Buffers
- prevent a change in pH when H⁺ ions are added to or removed from a solution.
- are most effective within 1.0 pH unit of the pK of the buffer (i.e., in the linear portion of the titration curve).

1. Extracellular buffers
   a. The major extracellular buffer is HCO₃⁻, which is produced from CO₂ and H₂O.
      - The pK of the CO₂/HCO₃⁻ buffer pair is 6.1.
   b. Phosphate is a minor extracellular buffer.
      - The pK of the H₂PO₄⁻/HPO₄²⁻ buffer pair is 6.8.
      - Phosphate is most important as a urinary buffer; excretion of H⁺ as H₂PO₄⁻ is called titratable acid.
2. Intracellular buffers
   a. Organic phosphates [e.g., AMP, ADP, ATP, 2,3-diphosphoglycerate (DPG)]
   b. Proteins
      - Imidazole and α-amino groups on proteins have pKs that are within the physiologic pH range.
      - Hemoglobin is a major intracellular buffer.
      - In the physiologic pH range, deoxyhemoglobin is a better buffer than oxyhemoglobin.

3. Using the Henderson–Hasselbalch equation to calculate pH

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

   where:
   - \( \text{pH} = -\log [\text{H}^+] \) (pH units)
   - \( \text{pK} = -\log K_\text{eq} \) equilibrium constant (pH units)
   - \([\text{A}^-]\) = base form of buffer (mM)
   - \([\text{HA}]\) = acid form of buffer (mM)

   - \( \text{A}^- \), the base form of the buffer, is the \( \text{H}^+ \) acceptor.
   - \( \text{HA} \), the acid form of the buffer, is the \( \text{H}^+ \) donor.
   - When the concentrations of \( \text{A}^- \) and HA are equal, the pH of the solution equals the pK of the buffer, as calculated by the Henderson–Hasselbalch equation.
   - Example: The pK of the \( \text{H}_2\text{PO}_4^-/\text{HPO}_4^{2-} \) buffer pair is 6.8. What are the relative concentrations of \( \text{H}_2\text{PO}_4^- \) and \( \text{HPO}_4^{2-} \) in a urine sample that has a pH of 4.8?

   \[
   \text{pH} = \text{pK} + \log \frac{\text{HPO}_4^{2-}}{\text{H}_2\text{PO}_4^-} \\
   4.8 = 6.8 + \log \frac{\text{HPO}_4^{2-}}{\text{H}_2\text{PO}_4^-} \\
   \log \frac{\text{HPO}_4^{2-}}{\text{H}_2\text{PO}_4^-} = -2.0 \\
   \frac{\text{HPO}_4^{2-}}{\text{H}_2\text{PO}_4^-} = 0.01 \\
   \frac{\text{H}_2\text{PO}_4^-}{\text{HPO}_4^{2-}} = 100
   \]

   For this buffer pair, \( \text{HPO}_4^{2-} \) is \( \text{A}^- \) and \( \text{H}_2\text{PO}_4^- \) is HA. Thus, the Henderson–Hasselbalch equation can be used to calculate that the concentration of \( \text{H}_2\text{PO}_4^- \) is 100 times that of \( \text{HPO}_4^{2-} \) in a urine sample of pH 4.8.

4. Titration curves (Figure 5-18)
   - describe how the pH of a buffered solution changes as \( \text{H}^+ \) ions are added to it or removed from it.
   - As \( \text{H}^+ \) ions are added to the solution, the HA form is produced; as \( \text{H}^+ \) ions are removed, the \( \text{A}^- \) form is produced.
   - A buffer is most effective in the linear portion of the titration curve, where the addition or removal of \( \text{H}^+ \) causes little change in pH.
   - According to the Henderson–Hasselbalch equation, when the pH of the solution equals the pK, the concentrations of HA and \( \text{A}^- \) are equal.

C. Renal acid–base

1. Reabsorption of filtered \( \text{HCO}_3^- \) (Figure 5-19)
   - occurs primarily in the proximal tubule.
a. Key features of reabsorption of filtered HCO₃⁻
(1) H⁺ and HCO₃⁻ are produced in the proximal tubule cells from CO₂ and H₂O. CO₂ and H₂O combine to form H₂CO₃, catalyzed by intracellular carbonic anhydrase; H₂CO₃ dissociates into H⁺ and HCO₃⁻. H⁺ is secreted into the lumen via the Na⁺-H⁺ exchange mechanism in the luminal membrane. The HCO₃⁻ is reabsorbed.
(2) In the lumen, the secreted H⁺ combines with filtered HCO₃⁻ to form H₂CO₃, which dissociates into CO₂ and H₂O, catalyzed by brush border carbonic anhydrase. CO₂ and H₂O diffuse into the cell to start the cycle again.
(3) The process results in net reabsorption of filtered HCO₃⁻. However, it does not result in net secretion of H⁺.

b. Regulation of reabsorption of filtered HCO₃⁻
(1) Filtered load
- Increases in the filtered load of HCO₃⁻ result in increased rates of HCO₃⁻ reabsorption. However, if the plasma HCO₃⁻ concentration becomes very high (e.g., metabolic alkalosis), the filtered load will exceed the reabsorptive capacity, and HCO₃⁻ will be excreted in the urine.

(2) PCO₂
- Increases in PCO₂ result in increased rates of HCO₃⁻ reabsorption because the supply of intracellular H⁺ for secretion is increased. This mechanism is the basis for the renal compensation for respiratory acidosis.
- Decreases in PCO₂ result in decreased rates of HCO₃⁻ reabsorption because the supply of intracellular H⁺ for secretion is decreased. This mechanism is the basis for the renal compensation for respiratory alkalosis.

FIGURE 5-18 Titration curve for a weak acid (HA) and its conjugate base (A⁻).
ECF volume

- **ECF volume expansion** results in decreased HCO\(_3^-\) reabsorption.
- **ECF volume contraction** results in increased HCO\(_3^-\) reabsorption ( contraction alkalosis).

Angiotensin II

- stimulates Na\(^+\)-H\(^+\) exchange and thus increases HCO\(_3^-\) reabsorption, contributing to the contraction alkalosis that occurs secondary to ECF volume contraction.

2. Excretion of fixed H\(^+\)

- Fixed H\(^+\) produced from the catabolism of protein and phospholipid is excreted by two mechanisms, titratable acid and NH\(_4^+\).

  a. **Excretion of H\(^+\) as titratable acid (H\(_2\)PO\(_4^-\))** [Figure 5-20]

  - The amount of H\(^+\) excreted as titratable acid depends on the amount of urinary buffer present (usually HPO\(_4^{2-}\)) and the **pK of the buffer**.
  - H\(^+\) and HCO\(_3^-\) are produced in the cell from CO\(_2\) and H\(_2\)O. The H\(^+\) is secreted into the lumen by an H\(^+\)-ATPase, and the HCO\(_3^-\) is reabsorbed into the blood ("new" HCO\(_3^-\)). In the urine, the secreted H\(^+\) combines with filtered HPO\(_4^{2-}\) to form H\(_2\)PO\(_4^-\), which is excreted as titratable acid. The H\(^+\)-ATPase is increased by aldosterone.
  - This process results in **net secretion of H\(^+\) and net reabsorption of newly synthesized HCO\(_3^-\)**.
  - As a result of H\(^+\) secretion, the pH of urine becomes progressively lower. The **minimum urinary pH** is 4.4.
  - The amount of H\(^+\) excreted as titratable acid is determined by the amount of urinary buffer and the **pK of the buffer**.

  b. **Excretion of H\(^+\) as NH\(_4^+\)** (Figure 5-21)

  - The amount of H\(^+\) excreted as NH\(_4^+\) depends on both the amount of NH\(_3\) synthesized by renal cells and the **urine pH**.
  - NH\(_3\) is produced in renal cells from glutamine. It diffuses down its concentration gradient from the cells into the lumen.
  - H\(^+\) and HCO\(_3^-\) are produced in the cells from CO\(_2\) and H\(_2\)O. The H\(^+\) is secreted into the lumen via an H\(^+\)-ATPase and combines with NH\(_3\) to form NH\(_4^+\), which is excreted (diffusion trapping). The HCO\(_3^-\) is reabsorbed into the blood ("new" HCO\(_3^-\)).
  - The lower the pH of the tubular fluid, the greater the excretion of H\(^+\) as NH\(_4^+\); at low urine pH, there is more NH\(_4^+\) relative to NH\(_3\) in the urine, thus increasing the gradient for NH\(_3\) diffusion.
  - In acidosis, an **adaptive increase in NH\(_3\) synthesis** occurs and aids in the excretion of excess H\(^+\).
Hyperkalemia inhibits NH₃ synthesis, which produces a decrease in H⁺ excretion as NH₄⁺, leading to type 4 renal tubular acidosis (RTA). Conversely, hypokalemia stimulates NH₃ synthesis, which produces an increase in H⁺ excretion.

D. Acid–base disorders (Tables 5-8 and 5-9 and Figure 5-22)

- The expected compensatory responses to simple acid–base disorders can be calculated as shown in Table 5-10. If the actual response equals the calculated (predicted) response, then one acid–base disorder is present. If the actual response differs from the calculated response, then more than one acid–base disorder is present.

1. Metabolic acidosis
   a. Overproduction or ingestion of fixed acid or loss of base produces an increase in arterial [H⁺] (acidemia).
   b. HCO₃⁻ is used to buffer the extra fixed acid. As a result, the arterial [HCO₃⁻] decreases. This decrease is the primary disturbance.
   c. Acidemia causes hyperventilation (Kussmaul breathing), which is the respiratory compensation for metabolic acidosis.
   d. Correction of metabolic acidosis consists of increased excretion of the excess fixed H⁺ as titratable acid and NH₄⁺, and increased reabsorption of “new” HCO₃⁻, which replenishes the HCO₃⁻ used in buffering the added fixed H⁺.
   - In chronic metabolic acidosis, an adaptive increase in NH₃ synthesis aids in the excretion of excess H⁺.
   e. Serum anion gap = [Na⁺] – ([Cl⁻] + [HCO₃⁻]) (Figure 5-23)

   - The serum anion gap represents unmeasured anions in serum. These unmeasured anions include phosphate, citrate, sulfate, and protein.
   - The normal value of the serum anion gap is 12 mEq/L (range, 8–16 mEq/L)

<table>
<thead>
<tr>
<th>Table 5-8 Summary of Acid–Base Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disorder</strong></td>
</tr>
<tr>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
</tr>
</tbody>
</table>

Heavy arrows indicate primary disturbance.
In metabolic acidosis, the serum $[\text{HCO}_3^-]$ decreases as it is depleted in buffering fixed acid. For electroneutrality, the concentration of another anion must increase to replace $\text{HCO}_3^-$. That anion can be $\text{Cl}^-$ or it can be an unmeasured anion.

1. The serum anion gap is increased if the concentration of an unmeasured anion (e.g., phosphate, lactate, $\beta$-hydroxybutyrate, and formate) is increased to replace $\text{HCO}_3^-$. 
2. The serum anion gap is normal if the concentration of $\text{Cl}^-$ is increased to replace $\text{HCO}_3^-$. (hyperchloremic metabolic acidosis).

### Table 5-9: Causes of Acid–Base Disorders

<table>
<thead>
<tr>
<th>Example</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic acidosis</strong></td>
<td></td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>Accumulation of $\beta$-OH-butryric acid and acetoacetic acid ↑ anion gap</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>Accumulation of lactic acid during hypoxia ↑ anion gap</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Failure to excrete $\text{H}^+$ as titratable acid and $\text{NH}_4^+$ ↑ anion gap</td>
</tr>
<tr>
<td>Salicylate intoxication</td>
<td>Also causes respiratory alkalosis ↑ anion gap</td>
</tr>
<tr>
<td>Methanol/formaldehyde intoxication</td>
<td>Produces formic acid ↑ anion gap</td>
</tr>
<tr>
<td>Ethylene glycol intoxication</td>
<td>Produces glycolic and oxalic acids ↑ anion gap</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>GI loss of $\text{HCO}_3^-$ Normal anion gap</td>
</tr>
<tr>
<td>Type 2 RTA</td>
<td>Renal loss of $\text{HCO}_3^-$ Normal anion gap</td>
</tr>
<tr>
<td>Type 1 RTA</td>
<td>Failure to excrete titratable acid and $\text{NH}_4^+$; failure to acidify urine Normal anion gap</td>
</tr>
<tr>
<td>Type 4 RTA</td>
<td>Hypoaldosteronism; failure to excrete $\text{NH}_4^+$ Hyperkalemia caused by lack of aldosterone inhibits $\text{NH}_3$ synthesis Normal anion gap</td>
</tr>
<tr>
<td><strong>Metabolic alkalosis</strong></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>Loss of gastric $\text{H}^+$; leaves $\text{HCO}_3^-$ behind in blood Worsened by volume contraction Hypokalemia May have ↑ anion gap because of production of ketoacids (starvation)</td>
</tr>
<tr>
<td>Hyperaldosteronism</td>
<td>Increased $\text{H}^+$ secretion by distal tubule; increased new $\text{HCO}_3^-$ reabsorption</td>
</tr>
<tr>
<td>Loop or thiazide diuretics</td>
<td>Volume contraction alkalosis</td>
</tr>
<tr>
<td><strong>Respiratory acidosis</strong></td>
<td></td>
</tr>
<tr>
<td>Opiates; sedatives; anesthetics</td>
<td>Inhibition of medullary respiratory center Weakening of respiratory muscles ↓ $\text{CO}_2$ exchange in lungs</td>
</tr>
<tr>
<td>Guillain–Barré syndrome; polio; ALS; multiple sclerosis Airway obstruction Adult respiratory distress syndrome; COPD</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory alkalosis</strong></td>
<td></td>
</tr>
<tr>
<td>Pneumonia; pulmonary embolus</td>
<td></td>
</tr>
<tr>
<td>High altitude</td>
<td></td>
</tr>
<tr>
<td>Psychogenic</td>
<td></td>
</tr>
<tr>
<td>Salicylate intoxication</td>
<td></td>
</tr>
<tr>
<td>Hypoxemia causes ↑ ventilation rate</td>
<td></td>
</tr>
<tr>
<td>Hypoxemia causes ↑ ventilation rate</td>
<td></td>
</tr>
<tr>
<td>Direct stimulation of medullary respiratory center; also causes metabolic acidosis</td>
<td></td>
</tr>
</tbody>
</table>

ALS = amyotrophic lateral sclerosis; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; RTA = renal tubular acidosis.

In metabolic acidosis, the serum $[\text{HCO}_3^-]$ decreases as it is depleted in buffering fixed acid. For electroneutrality, the concentration of another anion must increase to replace $\text{HCO}_3^-$. That anion can be $\text{Cl}^-$ or it can be an unmeasured anion.

1. **The serum anion gap is increased** if the concentration of an unmeasured anion (e.g., phosphate, lactate, $\beta$-hydroxybutyrate, and formate) is increased to replace $\text{HCO}_3^-$. 
2. **The serum anion gap is normal** if the concentration of $\text{Cl}^-$ is increased to replace $\text{HCO}_3^-$. (hyperchloremic metabolic acidosis).

### 2. Metabolic alkalosis

a. Loss of fixed $\text{H}^+$ or gain of base produces a **decrease in arterial $[\text{H}^+]$ (alkalemia)**.

b. As a result, arterial $[\text{HCO}_3^-]$ increases. This increase is the primary disturbance.

For example, in **vomiting**, $\text{H}^+$ is lost from the stomach, $\text{HCO}_3^-$ remains behind in the blood, and the $[\text{HCO}_3^-]$ increases.
c. Alkalemia causes hypoventilation, which is the respiratory compensation for metabolic alkalosis.

d. Correction of metabolic alkalosis consists of increased excretion of $\text{HCO}_3^-$ because the filtered load of $\text{HCO}_3^-$ 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 $\text{HCO}_3^-$ 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 a decrease in respiratory rate and retention of $\text{CO}_2$.

a. Increased arterial $\text{Pco}_2$, which is the primary disturbance, causes an increase in $[\text{H}^+]$ and $[\text{HCO}_3^-]$ by mass action.

b. There is no respiratory compensation for respiratory acidosis.
c. **Renal compensation** consists of increased excretion of H\(^+\) as titratable acid and NH\(_4^+\), and increased reabsorption of “new” HCO\(_3^-\). This process is aided by the increased PCO\(_2\), 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 an increase in respiratory rate** and **loss of CO\(_2\)**.
  a. Decreased arterial PCO\(_2\), which is the primary disturbance, causes a **decrease in [H\(^+\)]** and **[HCO\(_3^-\)]** by mass action.
  b. There is **no respiratory compensation** for respiratory alkalosis.
  c. **Renal compensation** consists of decreased excretion of H\(^+\) as titratable acid and NH\(_4^+\), and decreased reabsorption of “new” HCO\(_3^-\). This process is aided by the decreased

---

**Table 5-10 Calculating Compensatory Responses to Simple Acid–Base Disorders**

<table>
<thead>
<tr>
<th>Acid–Base Disturbance</th>
<th>Primary Disturbance</th>
<th>Compensation</th>
<th>Predicted Compensatory Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>↓ [HCO(_3^-)]</td>
<td>↓ PCO(_2)</td>
<td>1 mEq/L decrease in HCO(_3^-) → 1.3 mm Hg decrease in PCO(_2)</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>↑ [HCO(_3^-)]</td>
<td>↑ PCO(_2)</td>
<td>1 mEq/L increase in HCO(_3^-) → 0.7 mm Hg increase in PCO(_2)</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>Acute</td>
<td>↑ PCO(_2)</td>
<td>↑ [HCO(_3^-)] 1 mm Hg increase in PCO(_2) → 0.1 mEq/L increase in HCO(_3^-)</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>↑ PCO(_2)</td>
<td>↑ [HCO(_3^-)] 1 mm Hg increase in PCO(_2) → 0.4 mEq/L increase in HCO(_3^-)</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>Acute</td>
<td>↓ PCO(_2)</td>
<td>↓ [HCO(_3^-)] 1 mm Hg decrease in PCO(_2) → 0.2 mEq/L decrease in HCO(_3^-)</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>↓ PCO(_2)</td>
<td>↓ [HCO(_3^-)] 1 mm Hg decrease in PCO(_2) → 0.4 mEq/L decrease in HCO(_3^-)</td>
</tr>
</tbody>
</table>

**Diagram:**

- Anion gap
- HCO\(_3^-\)
- Unmeasured anions = protein, phosphate, citrate, sulfate
- Na\(^+\)
- Cl\(^-\)

**Figure 5-23** Serum anion gap.
PCO₂, which causes a deficit of H⁺ in the renal cells for secretion. The resulting decrease in serum [HCO₃⁻] helps to normalize the pH.

- In **acute respiratory alkalosis**, renal compensation has not yet occurred.
- In **chronic respiratory alkalosis**, renal compensation (decreased HCO₃⁻ reabsorption) has occurred. Thus, arterial pH is decreased toward normal (i.e., a compensation).

d. 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⁺.

## X. DIURETICS (TABLE 5-11)

## XI. INTEGRATIVE EXAMPLES

### A. Hypoaldosteronism

1. **Case study**

   - A woman has a history of weakness, weight loss, orthostatic hypotension, increased pulse rate, and increased skin pigmentation. She has decreased serum [Na⁺], decreased serum osmolarity, increased serum [K⁺], and arterial blood gases consistent with metabolic acidosis.

2. **Explanation of hypoaldosteronism**

   a. The **lack of aldosterone** has three direct effects on the kidney: decreased Na⁺ reabsorption, decreased K⁺ secretion, and decreased H⁺ secretion. As a result, there is ECF

### Table 5-11 Effects of Diuretics on the Nephron

<table>
<thead>
<tr>
<th>Class of Diuretic</th>
<th>Site of Action</th>
<th>Mechanism</th>
<th>Major Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonic anhydrase inhibitors (acetazolamide)</td>
<td>Proximal tubule</td>
<td>Inhibition of carbonic anhydrase</td>
<td>↑ HCO₃⁻ excretion</td>
</tr>
<tr>
<td>Loop diuretics (furosemide, ethacrynic acid, bumetanide)</td>
<td>Thick ascending limb of the loop of Henle</td>
<td>Inhibition of Na⁺–K⁺–2Cl⁻ cotransport</td>
<td>↑ NaCl excretion&lt;br&gt;↑ K⁺ excretion (↑ distal tubule flow rate)&lt;br&gt;↑ Ca²⁺ excretion (treat hypercalciemia)&lt;br&gt;↓ ability to concentrate urine (↑ corticopapillary gradient)&lt;br&gt;↓ ability to dilute urine (inhibition of diluting segment)</td>
</tr>
<tr>
<td>Thiazide diuretics (chlorothiazide, hydrochlorothiazide)</td>
<td>Early distal tubule (cortical diluting segment)</td>
<td>Inhibition of Na⁺–Cl⁻ cotransport</td>
<td>↑ NaCl excretion&lt;br&gt;↑ K⁺ excretion (↑ distal tubule flow rate)&lt;br&gt;↓ Ca²⁺ excretion (treatment of idiopathic hypercalciuria)&lt;br&gt;↓ ability to dilute urine (inhibition of cortical diluting segment)&lt;br&gt;No effect on ability to concentrate urine</td>
</tr>
<tr>
<td>K⁺-sparing diuretics (spironolactone, triamterene, amiloride)</td>
<td>Late distal tubule and collecting duct</td>
<td>Inhibition of Na⁺ reabsorption&lt;br&gt;Inhibition of K⁺ secretion&lt;br&gt;Inhibition of H⁺ secretion</td>
<td>↑ Na⁺ excretion (small effect)&lt;br&gt;↓ K⁺ excretion (used in combination with loop or thiazide diuretics)&lt;br&gt;↓ H⁺ excretion</td>
</tr>
</tbody>
</table>
volume contraction (caused by decreased Na\(^+\) reabsorption), hyperkalemia (caused by decreased K\(^+\) secretion), and metabolic acidosis (caused by decreased H\(^+\) secretion).

b. The ECF volume contraction is responsible for this woman’s orthostatic hypotension. The decreased arterial pressure produces an increased pulse rate via the baroreceptor mechanism.

c. ECF volume contraction also stimulates ADH secretion from the posterior pituitary via volume receptors. ADH causes increased water reabsorption from the collecting ducts, which results in decreased serum [Na\(^+\)] (hyponatremia) and decreased serum osmolarity. Thus, ADH released by a volume mechanism is “inappropriate” for the serum osmolarity in this case.

d. Hyperpigmentation is caused by adrenal insufficiency. Decreased levels of cortisol produce increased secretion of adrenocorticotropic hormone (ACTH) by negative feedback. ACTH has pigmenting effects similar to those of melanocyte-stimulating hormone.

B. Vomiting

1. Case study
   - A man is admitted to the hospital for evaluation of severe epigastric pain. He has had persistent nausea and vomiting for 4 days. Upper gastrointestinal (GI) endoscopy shows a pyloric ulcer with partial gastric outlet obstruction. He has orthostatic hypotension, decreased serum [K\(^+\)], decreased serum [Cl\(^-\)], arterial blood gases consistent with metabolic alkalosis, and decreased ventilation rate.

2. Responses to vomiting (Figure 5-24)
   a. Loss of H\(^+\) from the stomach by vomiting causes increased blood [HCO\(_3\)^-] and metabolic alkalosis. Because Cl\(^-\) is lost from the stomach along with H\(^+\), hypochloremia and ECF volume contraction occur.
   b. The decreased ventilation rate is the respiratory compensation for metabolic alkalosis.
   c. ECF volume contraction is associated with decreased blood volume and decreased renal perfusion pressure. As a result, renin secretion is increased, production of angiotensin II is increased, and secretion of aldosterone is increased. Thus, the ECF volume contraction worsens the metabolic alkalosis because angiotensin II increases HCO\(_3\)^- reabsorption in the proximal tubule (contraction alkalosis).
   d. The increased levels of aldosterone (secondary to ECF volume contraction) cause increased distal K\(^+\) secretion and hypokalemia. Increased aldosterone also causes increased distal H\(^+\) secretion, further worsening the metabolic alkalosis.
   e. Treatment consists of NaCl infusion to correct ECF volume contraction (which is maintaining the metabolic alkalosis and causing hypokalemia) and administration of K\(^+\) to replace K\(^+\) lost in the urine.

C. Diarrhea

1. Case study
   - A man returns from a trip abroad with “traveler’s diarrhea.” He has weakness, weight loss, orthostatic hypotension, increased pulse rate, increased breathing rate, pale skin, a serum [Na\(^+\)] of 132 mEq/L, a serum [Cl\(^-\)] of 111 mEq/L, and a serum [K\(^+\)] of 2.3 mEq/L. His arterial blood gases are: pH, 7.25; PCO\(_2\), 24 mm Hg; HCO\(_3\)^-, 10.2 mEq/L.

2. Explanation of responses to diarrhea
   a. Loss of HCO\(_3\)^- from the GI tract causes a decrease in the blood [HCO\(_3\)^-] and, according to the Henderson–Hasselbalch equation, a decrease in blood pH. Thus, this man has metabolic acidosis.
   b. To maintain electroneutrality, the HCO\(_3\)^- lost from the body is replaced by Cl\(^-\), a measured anion; thus, there is a normal anion gap. The serum anion gap = [Na\(^+\)] - ([Cl\(^-\)] + [HCO\(_3\)^-]) = 132 – (111 + 10.2) = 10.8 mEq/L.
   c. The increased breathing rate (hyperventilation) is the respiratory compensation for metabolic acidosis.
As a result of his diarrhea, this man has **ECF volume contraction**, which leads to decreases in blood volume and arterial pressure. The decrease in arterial pressure activates the **baroreceptor reflex**, resulting in increased sympathetic outflow to the heart and blood vessels. The **increased pulse rate** is a consequence of increased sympathetic activity in the sinoatrial (SA) node, and the pale skin is the result of cutaneous vasoconstriction.

**ECF volume contraction** also activates the renin–angiotensin–aldosterone system. Increased levels of aldosterone lead to increased distal K\(^+\) secretion and **hypokalemia**. Loss of K\(^+\) in diarrhea fluid also contributes to hypokalemia.

**Treatment** consists of replacing all fluid and electrolytes lost in diarrhea fluid and urine, including Na\(^+\), HCO\(_3^-\), and K\(^+\).

**FIGURE 5-24** Metabolic alkalosis caused by vomiting. ECF = extracellular fluid.