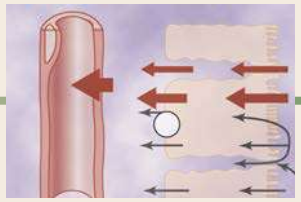

CHAPTER 28

UNIT V

Renal Tubular Reabsorption and Secretion

As the glomerular filtrate enters the renal tubules, it flows sequentially through the successive parts of the tubule—the *proximal tubule, loop of Henle, distal tubule, collecting tubule,* and *collecting duct*—before it is excreted as urine. Along this course, some substances are selectively reabsorbed from the tubules back into the blood, whereas others are secreted from the blood into the tubular lumen. Eventually, the urine that is formed and all the substances in the urine represent the sum of three basic renal processes—glomerular filtration, tubular reabsorption, and tubular secretion:

$$\text{Urinary excretion} = \text{Glomerular filtration} - \text{Tubular reabsorption} + \text{Tubular secretion}$$

For many substances, tubular reabsorption plays a much more important role than secretion in determining the final urinary excretion rate. However, tubular secretion accounts for significant amounts of potassium ions, hydrogen ions, and a few other substances that appear in the urine.

TUBULAR REABSORPTION IS QUANTITATIVELY LARGE AND HIGHLY SELECTIVE

Table 28-1 shows the renal handling of several substances that are all freely filtered in the kidneys and reabsorbed at variable rates. The rate at which each of these substances is filtered is calculated as follows:

$$\text{Filtration} = \text{Glomerular filtration rate} \times \text{Plasma concentration}$$

This calculation assumes that the substance is freely filtered and not bound to plasma proteins. For example, if plasma glucose concentration is 1 g/L, the amount of glucose filtered each day is about 180 L/day × 1 g/L, or 180 g/day. Because virtually none of the filtered glucose is normally excreted, the rate of glucose reabsorption is also 180 g/day.

From Table 28-1, two things are immediately apparent. First, the processes of glomerular filtration and tubular reabsorption are quantitatively large relative to urinary excretion for many substances. Thus, a small change in glomerular filtration or tubular reabsorption can potentially cause a relatively large change in urinary excretion. For example, a 10% decrease in tubular reabsorption, from 178.5 to 160.7 L/day, would increase urine volume from 1.5 to 19.3 L/day (almost a 13-fold increase) if the glomerular filtration rate (GFR) remained constant. In reality, changes in tubular reabsorption and glomerular filtration are closely coordinated so that large fluctuations in urinary excretion are avoided.

Second, unlike glomerular filtration, which is relatively nonselective (essentially all solutes in the plasma are filtered except the plasma proteins or substances bound to them), *tubular reabsorption is highly selective*. Some substances, such as glucose and amino acids, are almost completely reabsorbed from the tubules, so the urinary excretion rate is essentially zero. Many ions in the plasma, such as sodium, chloride, and bicarbonate, are also highly reabsorbed, but their rates of reabsorption and urinary excretion are variable, depending on the needs of the body. Waste products, such as urea and creatinine, conversely, are poorly reabsorbed from the tubules and are excreted in relatively large amounts.

Therefore, by controlling their reabsorption of different substances, the kidneys regulate excretion of solutes independently of one another, a capability that is essential for precise control of the body fluid composition. In this chapter, we discuss the mechanisms that allow the kidneys to selectively reabsorb or secrete different substances at variable rates.

TUBULAR REABSORPTION INCLUDES PASSIVE AND ACTIVE MECHANISMS

For a substance to be reabsorbed, it must first be transported (1) across the tubular epithelial membranes into the renal interstitial fluid and then (2) through the peritubular capillary membrane back into the blood (Figure 28-1). Thus, reabsorption of water and solutes includes a series of transport steps. Reabsorption across the tubular epithelium into the interstitial fluid includes active or passive transport by the same basic mechanisms discussed

Table 28-1 Filtration, Reabsorption, and Excretion Rates of Different Substances by the Kidneys

Substance	Amount Filtered	Amount Reabsorbed	Amount Excreted	% of Filtered Load Reabsorbed
Glucose (g/day)	180	180	0	100
Bicarbonate (mEq/day)	4320	4318	2	>99.9
Sodium (mEq/day)	25,560	25,410	150	99.4
Chloride (mEq/day)	19,440	19,260	180	99.1
Potassium (mEq/day)	756	664	92	87.8
Urea (g/day)	46.8	23.4	23.4	50
Creatinine (g/day)	1.8	0	1.8	0

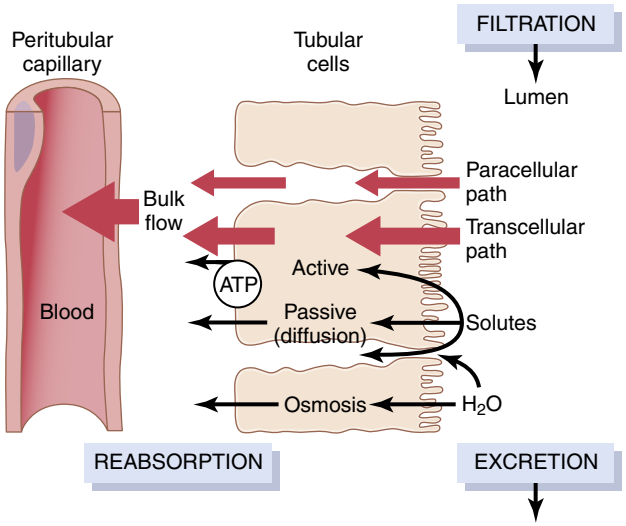

Figure 28-1 Reabsorption of filtered water and solutes from the tubular lumen across the tubular epithelial cells, through the renal interstitium, and back into the blood. Solutes are transported through the cells (*transcellular path*) by passive diffusion or active transport, or between the cells (*paracellular path*) by diffusion. Water is transported through the cells and between the tubular cells by osmosis. Transport of water and solutes from the interstitial fluid into the peritubular capillaries occurs by ultrafiltration (*bulk flow*).

in Chapter 4 for transport across other cell membranes of the body. For example, water and solutes can be transported through the cell membranes *(transcellular route)* or through the spaces between the cell junctions *(paracellular route)*. Then, after absorption across the tubular epithelial cells into the interstitial fluid, water and solutes are transported through the peritubular capillary walls into the blood by *ultrafiltration (bulk flow)* that is mediated by hydrostatic and colloid osmotic forces. The peritubular capillaries behave like the venous ends of most other capillaries because there is a net reabsorptive force that moves the fluid and solutes from the interstitium into the blood.

ACTIVE TRANSPORT

Active transport can move a solute against an electrochemical gradient; this requires energy derived from metabolism. Transport that is coupled directly to an energy source, such as the hydrolysis of adenosine triphosphate (ATP), is termed *primary active transport*. An example of this mechanism is the sodium-potassium adenosine triphosphatase (ATPase) pump (Na^+-K^+ ATPase pump) that functions throughout most parts of the renal tubule. Transport that is coupled *indirectly* to an energy source, such as that due to an ion gradient, is referred to as *secondary active transport*. Reabsorption of glucose by the renal tubule is an example of secondary active transport. Although solutes can be reabsorbed by active and/or passive mechanisms by the tubule, water is always reabsorbed passively across the tubular epithelial membrane by the process of *osmosis*.

Solutes Can Be Transported Through Epithelial Cells or Between Cells. Renal tubular cells, like other epithelial cells, are held together by *tight junctions*. Lateral intercellular spaces lie behind the tight junctions and separate the epithelial cells of the tubule. Solutes can be reabsorbed or secreted across the cells through the *transcellular pathway* or between the cells by moving across the tight junctions and intercellular spaces via the *paracellular pathway*. Sodium is a substance that moves through both routes, although most of the sodium is transported through the transcellular pathway. In some nephron segments, especially the proximal tubule, water is also reabsorbed across the paracellular pathway, and substances dissolved in the water, especially potassium, magnesium, and chloride ions, are carried with the reabsorbed fluid between the cells.

Primary Active Transport Through the Tubular Membrane Linked to Hydrolysis of Adenosine Triphosphatase. *The special importance of primary active transport is that it can move solutes against an electrochemical gradient.* The energy for this active transport comes from the hydrolysis of ATP by way of membrane-bound ATPase, which is also a component of the carrier mechanism that binds and moves solutes across the cell membranes. The primary active transporters in the kidneys that are known include *Na^+-K^+ ATPase, hydrogen ATPase, hydrogen-potassium ATPase,* and *calcium ATPase.*

A good example of a primary active transport system is the reabsorption of sodium ions across the proximal tubular membrane, as shown in **Figure 28-2**. On the

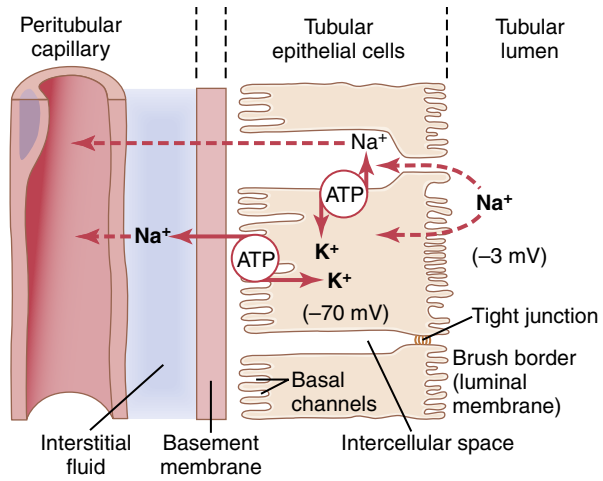

Figure 28-2 Basic mechanism for active transport of sodium through the tubular epithelial cell. The sodium-potassium pump transports sodium from the interior of the cell across the basolateral membrane, creating a low intracellular sodium concentration and a negative intracellular electrical potential. The low intracellular sodium concentration and negative electrical potential cause sodium ions to diffuse from the tubular lumen into the cell through the brush border.

basolateral sides of the tubular epithelial cell, the cell membrane has an extensive Na^+-K^+ ATPase system that hydrolyzes ATP and uses the released energy to transport sodium ions out of the cell into the interstitium. At the same time, potassium is transported from the interstitium to the inside of the cell. The operation of this ion pump maintains low intracellular sodium and high intracellular potassium concentrations and creates a net negative charge of about –70 millivolts within the cell. This active pumping of sodium out of the cell across the *basolateral* membrane of the cell favors passive diffusion of sodium across the *luminal* membrane of the cell, from the tubular lumen into the cell, for two reasons: (1) there is a concentration gradient favoring sodium diffusion into the cell because the intracellular sodium concentration is low (12 mEq/L) and tubular fluid sodium concentration is high (140 mEq/L); and (2) the negative, –70-millivolt, intracellular potential attracts the positive sodium ions from the tubular lumen into the cell.

Active reabsorption of sodium by Na^+-K^+ ATPase occurs in most parts of the tubule. In certain parts of the nephron, there are also additional provisions for moving large amounts of sodium into the cell. In the proximal tubule, there is an extensive brush border on the luminal side of the membrane (the side that faces the tubular lumen) that multiplies the surface area by about 20-fold. There are also carrier proteins that bind sodium ions on the luminal surface of the membrane and release them inside the cell, providing *facilitated diffusion* of sodium through the membrane into the cell. These sodium carrier proteins are also important for secondary active transport of other substances, such as glucose and amino acids, as discussed later.

Thus, the net reabsorption of sodium ions from the tubular lumen back into the blood involves at least three steps:

1. Sodium diffuses across the luminal membrane (also called the *apical membrane*) into the cell down an electrochemical gradient established by the Na^+-K^+ ATPase pump on the basolateral side of the membrane.
2. Sodium is transported across the basolateral membrane against an electrochemical gradient by the Na^+-K^+ ATPase pump.
3. Sodium, water, and other substances are reabsorbed from the interstitial fluid into the peritubular capillaries by ultrafiltration, a passive process driven by the hydrostatic and colloid osmotic pressure gradients.

Secondary Active Reabsorption Through the Tubular Membrane. In secondary active transport, two or more substances interact with a specific membrane protein (a carrier molecule) and are transported together across the membrane. As one of the substances (e.g., sodium) diffuses down its electrochemical gradient, the energy released is used to drive another substance (e.g., glucose) against its electrochemical gradient. Thus, secondary active transport does not require energy directly from ATP or from other high-energy phosphate sources. Rather, the direct source of the energy is that liberated by the simultaneous facilitated diffusion of another transported substance down its own electrochemical gradient.

Figure 28-3 shows secondary active transport of glucose and amino acids in the proximal tubule. In both cases, specific carrier proteins in the brush border combine with a sodium ion and an amino acid or a glucose molecule at the same time. These transport mechanisms are so efficient that they remove virtually all the glucose and amino acids from the tubular lumen. After entry into the cell, glucose and amino acids exit across the basolateral membranes by diffusion, driven by the high glucose and amino acid concentrations in the cell facilitated by specific transport proteins.

Sodium glucose co-transporters (SGLT2 and *SGLT1)* are located on the brush border of proximal tubular cells and carry glucose into the cell cytoplasm against a concentration gradient, as described previously. Approximately 90% of the filtered glucose is reabsorbed by SGLT2 in the early part of the proximal tubule (S1 segment), and the residual 10% is transported by SGLT1 in the latter segments of the proximal tubule. On the basolateral side of the membrane, glucose diffuses out of the cell into the interstitial spaces with the help of *glucose transporters—GLUT2* in the S1 segment and *GLUT1* in the latter part (S3 segment) of the proximal tubule.

Although transport of glucose against a chemical gradient does not directly use ATP, the reabsorption of glucose depends on energy expended by the primary active Na^+-K^+ ATPase pump in the basolateral membrane. Because of the activity of this pump, an electrochemical gradient for

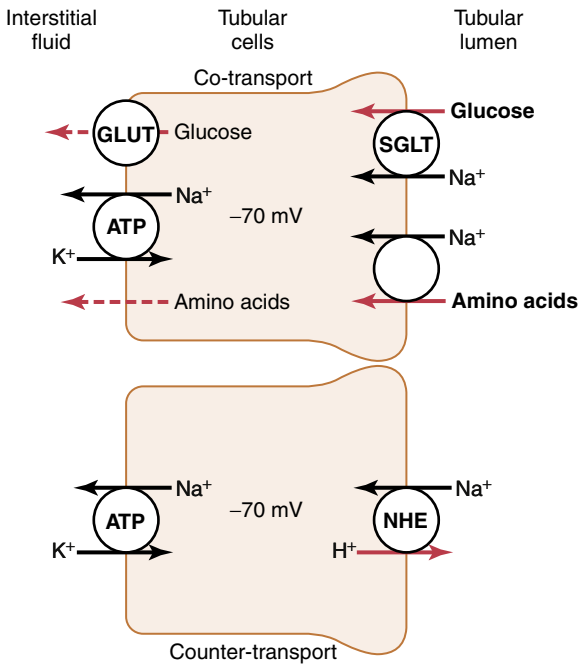

Figure 28-3 Mechanisms of secondary active transport. The upper cell shows the *co-transport* of glucose and amino acids along with sodium ions through the apical side of the tubular epithelial cells, followed by facilitated diffusion through the basolateral membranes. The lower cell shows the *counter-transport* of hydrogen ions from the interior of the cell across the apical membrane and into the tubular lumen; movement of sodium ions into the cell, down an electrochemical gradient established by the sodium-potassium pump on the basolateral membrane, provides the energy for transport of the hydrogen ions from inside the cell into the tubular lumen. ATP, Adenosine triphosphate; GLUT, glucose transporter; NHE, sodium-hydrogen exchanger; SGLT, sodium-glucose co-transporter.

facilitated diffusion of sodium across the luminal membrane is maintained, and it is this downhill diffusion of sodium to the interior of the cell that provides the energy for the simultaneous uphill transport of glucose across the luminal membrane. Thus, this reabsorption of glucose is referred to as *secondary active transport* because glucose itself is reabsorbed uphill against a chemical gradient, but it is secondary to primary active transport of sodium.

Another important point is that a substance is said to undergo active transport when at least one of the steps in the reabsorption involves primary or secondary active transport, even though other steps in the reabsorption process may be passive. For glucose reabsorption, secondary active transport occurs at the luminal membrane, but passive facilitated diffusion occurs at the basolateral membrane, and passive uptake by bulk flow occurs at the peritubular capillaries.

Secondary Active Secretion Into the Tubules. Some substances are secreted into the tubules by secondary active transport, which often involves *counter-transport* of the substance with sodium ions. In counter-transport, the energy liberated from the downhill movement of one of the substances (e.g., sodium ions) enables the uphill movement of a second substance in the opposite direction.

One example of counter-transport, shown in **Figure 28-3**, is the active secretion of hydrogen ions coupled to sodium reabsorption in the luminal membrane of the proximal tubule. In this case, sodium entry into the cell is coupled with hydrogen extrusion from the cell by sodium-hydrogen counter-transport. This transport is mediated by a specific protein *(sodium-hydrogen exchanger)* in the brush border of the luminal membrane. As sodium is carried to the interior of the cell, hydrogen ions are forced outward in the opposite direction into the tubular lumen. The basic principles of primary and secondary active transport are discussed in Chapter 4.

Pinocytosis Is an Active Transport Mechanism for Reabsorption of Proteins. Some parts of the tubule, especially the proximal tubule, reabsorb large molecules such as proteins via *pinocytosis*, a type of *endocytosis*. In this process, the protein attaches to the brush border of the luminal membrane, and this portion of the membrane then invaginates to the interior of the cell until it is completely pinched off and a vesicle is formed containing the protein. Once inside the cell, the protein is digested into its constituent amino acids, which are reabsorbed through the basolateral membrane into the interstitial fluid. Because pinocytosis requires energy, it is considered a form of active transport.

Transport Maximum for Substances That Are Actively Reabsorbed. For most substances that are actively reabsorbed or secreted, there is a limit to the rate at which the solute can be transported, which is often referred to as the *transport maximum*. This limit is due to saturation of the specific transport systems involved when the amount of solute delivered to the tubule (referred to as the *tubular load*) exceeds the capacity of the carrier proteins and specific enzymes involved in the transport process.

The glucose transport system in the proximal tubule is a good example. Normally, measurable glucose does not appear in the urine because essentially all the filtered glucose is reabsorbed in the proximal tubule. However, when the filtered load exceeds the capability of the tubules to reabsorb glucose, urinary excretion of glucose does occur.

In the adult human, the transport maximum for glucose averages about 375 mg/min, whereas the filtered load of glucose is only about 125 mg/min (GFR × plasma glucose = 125 ml/min × 1 mg/ml). With large increases in GFR and/or plasma glucose concentration that increase the filtered load of glucose above 375 mg/min, the excess glucose filtered is not reabsorbed and passes into the urine.

Figure 28-4 shows the relationship between plasma concentration of glucose, filtered load of glucose, tubular transport maximum for glucose, and rate of glucose loss in the urine. Note that when the plasma glucose concentration is 100 mg/100 ml and the filtered load is at its normal level (125 mg/min), there is no loss of glucose in the urine. However, when the plasma concentration of glucose rises above about 200 mg/100 ml, increasing the filtered load to about 250 mg/min, a small amount of glucose begins to appear in the urine. This point is termed the *threshold* for

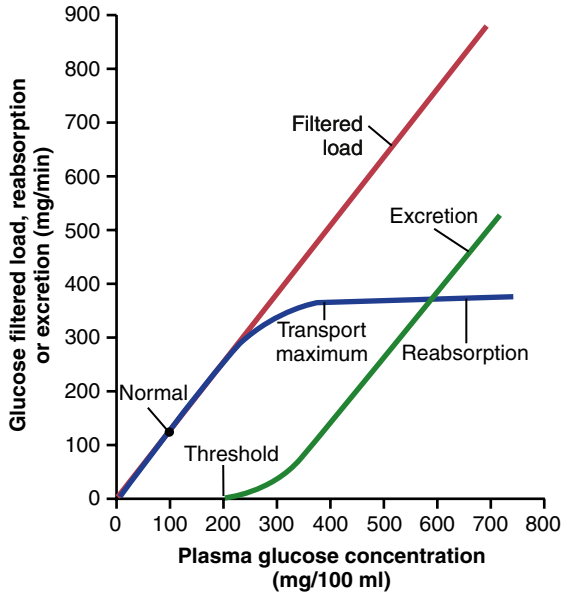

Figure 28-4 Relationships among the filtered load of glucose, rate of glucose reabsorption by the renal tubules, and rate of glucose excretion in the urine. The *transport maximum* is the maximum rate at which glucose can be reabsorbed from the tubules. The *threshold* for glucose refers to the filtered load of glucose at which glucose first begins to be excreted in the urine.

glucose. *Note that this appearance of glucose in the urine (at the threshold) occurs before the transport maximum is reached*. One reason for the difference between the threshold and transport maximum is that not all nephrons have the same transport maximum for glucose, and some of the nephrons therefore begin to excrete glucose before others have reached their transport maximum. *The overall transport maximum for the kidneys, which is normally about 375 mg/min, is reached when all nephrons have reached their maximal capacity to reabsorb glucose.*

The plasma glucose of a healthy person almost never becomes high enough to cause glucose excretion in the urine, even after eating a meal. However, in uncontrolled *diabetes mellitus*, plasma glucose concentration may rise to high levels, causing the filtered load of glucose to exceed the transport maximum and resulting in urinary glucose excretion. Some of the important transport maximums for substances *actively reabsorbed* by the tubules are as follows:

Substance	Transport Maximum
Glucose	375 mg/min
Phosphate	0.10 mmol/min
Sulfate	0.06 mmol/min
Amino acids	1.5 mmol/min
Urate	15 mg/min
Lactate	75 mg/min
Plasma protein	30 mg/min

Transport Maximums for Actively Secreted Substances. Substances that are *actively secreted* also exhibit transport maximums, as follows:

Substance	Transport Maximum
Creatinine	16 mg/min
Para-aminohippuric acid	80 mg/min

Substances That Are Actively Transported but Do Not Exhibit a Transport Maximum. The reason that actively transported solutes often exhibit a transport maximum is that the transport carrier system becomes saturated as the tubular load increases. *Some substances that are actively reabsorbed do not demonstrate a transport maximum* because their rate of transport is determined by other factors, such as the following: (1) the electrochemical gradient for diffusion of the substance across the membrane; (2) the permeability of the membrane for the substance; and (3) the time that the fluid containing the substance remains within the tubule. Transport of this type is referred to as *gradient-time transport* because the rate of transport depends on the electrochemical gradient and the time that the substance is in the tubule, which in turn depends on the tubular flow rate.

An example of gradient-time transport is sodium reabsorption in the proximal tubule, where the maximum transport capacity of the basolateral Na^+-K^+ ATPase pump is usually far greater than the actual rate of net sodium reabsorption because a significant amount of sodium transported out of the cell leaks back into the tubular lumen through junctions of the epithelial cells. The rate at which this backleak occurs depends on (1) the permeability of the tight junctions; and (2) the interstitial physical forces, which determine the rate of bulk flow reabsorption from the interstitial fluid into the peritubular capillaries. Therefore, sodium transport in the proximal tubules obeys mainly gradient-time transport principles rather than tubular maximum transport characteristics. This observation means that the higher the concentration of sodium in the proximal tubules, the higher is its reabsorption rate. Also, the slower the flow rate of tubular fluid, the greater the percentage of sodium that can be reabsorbed from the proximal tubules.

In the more distal parts of the nephron, the epithelial cells have much tighter junctions and transport much smaller amounts of sodium. In these segments, sodium reabsorption exhibits a transport maximum similar to that for other actively transported substances. Furthermore, this transport maximum can be increased by certain hormones, such as *aldosterone*.

PASSIVE WATER REABSORPTION BY OSMOSIS COUPLED MAINLY TO SODIUM REABSORPTION

When solutes are transported out of the tubule by primary or secondary active transport, their concentrations tend to decrease inside the tubule while increasing in the renal interstitium. This phenomenon creates a concentration difference that causes osmosis of water in the

same direction that the solutes are transported, from the tubular lumen to the renal interstitium. Some parts of the renal tubule, especially the proximal tubule, are highly permeable to water, and water reabsorption occurs so rapidly that there is only a small concentration gradient for solutes across the tubular membrane.

A large part of the osmotic flow of water in the proximal tubules occurs through water channels *(aquaporins)* in the cell membranes, as well as through the *tight junctions* between the epithelial cells. As noted previously, the junctions between the cells are not as tight as their name would imply and permit significant diffusion of water and small ions. This condition is especially true in the proximal tubules, which have a high permeability for water and a smaller but significant permeability to most ions, such as sodium, chloride, potassium, calcium, and magnesium.

Water moving across the tight junctions by osmosis also carries with it some of the solutes, a process referred to as *solvent drag*. In addition, because the reabsorption of water, organic solutes, and ions is coupled to sodium reabsorption, changes in sodium reabsorption significantly influence the reabsorption of water and many other solutes.

In the more distal parts of the nephron, beginning in the loop of Henle and extending through the collecting tubule, the tight junctions become far less permeable to water and solutes, and the epithelial cells also have a greatly decreased membrane surface area. Therefore, water cannot move easily across the tight junctions of the tubular membrane by osmosis. However, antidiuretic hormone (ADH) greatly increases the water permeability in the distal and collecting tubules.

Thus, water movement across the tubular epithelium can occur only if the membrane is permeable to water, no matter how large the osmotic gradient. In the proximal tubule and descending loop of Henle, water permeability is always high, and water is rapidly reabsorbed to reach osmotic equilibrium with the surrounding interstitial fluid. This high permeability is due to abundant expression of the water channel *aquaporin-1* (AQP-1) in the luminal and basolateral membranes. In the ascending loop of Henle, water permeability is always low, so almost no water is reabsorbed, despite a large osmotic gradient. Water permeability in the last parts of the tubules—the distal tubules, collecting tubules, and collecting ducts—occurs through aquaporins and can be high or low, depending on the presence or absence of ADH.

REABSORPTION OF CHLORIDE, UREA, AND OTHER SOLUTES BY PASSIVE DIFFUSION

When sodium is reabsorbed through the tubular epithelial cell, negative ions such as chloride are transported along with sodium because of electrical potentials. That is, transport of positively charged sodium ions out of the lumen leaves the inside of the lumen negatively charged, compared with the interstitial fluid causing chloride ions

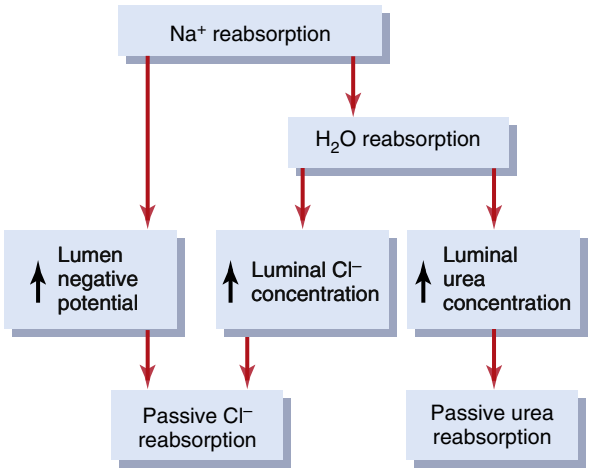

Figure 28-5 Mechanisms whereby water, chloride, and urea reabsorption are coupled with sodium reabsorption.

to diffuse *passively* through the *paracellular pathway*. Additional reabsorption of chloride ions occurs because of a chloride concentration gradient that develops when water is reabsorbed from the tubule by osmosis, thereby concentrating the chloride ions in the tubular lumen (**Figure 28-5**). Thus, active reabsorption of sodium is closely coupled to passive reabsorption of chloride by way of an electrical potential and a chloride concentration gradient.

Chloride ions can also be reabsorbed by secondary active transport. The most important of the secondary active transport processes for chloride reabsorption involves the co-transport of chloride with sodium across the luminal membrane.

Urea is also passively reabsorbed from the tubule, but to a much lesser extent than chloride ions. As water is reabsorbed from the tubules (by osmosis coupled to sodium reabsorption), urea concentration in the tubular lumen increases (see **Figure 28-5**). This increase creates a concentration gradient favoring reabsorption of urea. However, urea does not permeate the tubule as readily as water. In some parts of the nephron, especially the inner medullary collecting duct, passive urea reabsorption is facilitated by specific *urea transporters*. Yet, only about half of the urea that is filtered by the glomerular capillaries is reabsorbed from the tubules. The remaining urea passes into the urine, allowing the kidneys to excrete large amounts of this waste product of metabolism. In mammals, more than 90% of waste nitrogen, mainly generated in the liver as a product of protein metabolism, is normally excreted by the kidneys as urea.

Another waste product of metabolism, creatinine, is an even larger molecule than urea and is essentially impermeant to the tubular membrane. Therefore, almost none of the creatinine that is filtered is reabsorbed, so virtually all the creatinine filtered by the glomerulus is excreted in the urine.

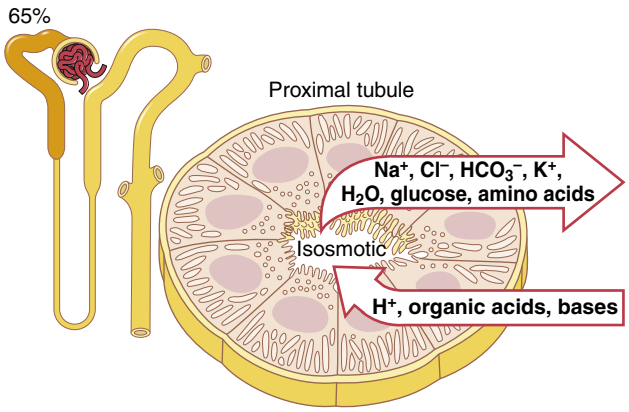

Figure 28-6 Cellular ultrastructure and primary transport characteristics of the proximal tubule. The proximal tubules reabsorb about 65% of the filtered sodium, chloride, bicarbonate, and potassium and essentially all the filtered glucose and amino acids. The proximal tubules also secrete organic acids, bases, and hydrogen ions into the tubular lumen.

REABSORPTION AND SECRETION ALONG DIFFERENT PARTS OF THE NEPHRON

In the previous sections, we discussed the basic principles whereby water and solutes are transported across the tubular membrane. With these generalizations in mind, we can now discuss the different characteristics of the individual tubular segments that enable them to perform their specific functions. Only the tubular transport functions that are quantitatively most important will be discussed, especially as they relate to the reabsorption of sodium, chloride, and water. In subsequent chapters, we discuss the reabsorption and secretion of other substances in different parts of the tubular system.

PROXIMAL TUBULAR REABSORPTION

Normally, about 65% of the filtered load of sodium and water and a slightly lower percentage of filtered chloride are reabsorbed by the proximal tubule before the filtrate reaches the loops of Henle. These percentages can be increased or decreased in different physiological conditions, as discussed later.

Proximal Tubules Have High Capacity for Active and Passive Reabsorption. The high capacity of the proximal tubule for reabsorption results from its special cellular characteristics, as shown in **Figure 28-6**. The proximal tubule epithelial cells are highly metabolic and have large numbers of mitochondria to support powerful active transport processes. In addition, the proximal tubular cells have an extensive brush border on the luminal (apical) side of the membrane, as well as an extensive labyrinth of intercellular and basal channels, all of which together provide an extensive membrane surface area on the luminal and basolateral sides of the epithelium for rapid transport of sodium ions and other substances.

The extensive membrane surface of the epithelial brush border is also loaded with protein carrier molecules that transport a large fraction of the sodium ions across the luminal membrane linked via the *co-transport* mechanism with multiple organic nutrients such as amino acids and glucose. Additional sodium is transported from the tubular lumen into the cell by *counter-transport* mechanisms that reabsorb sodium while secreting other substances into the tubular lumen, especially hydrogen ions. As discussed in Chapter 31, secretion of hydrogen ions into the tubular lumen is an important step in the removal of bicarbonate ions from the tubule (by combining H^+ with the HCO_3^- to form H_2CO_3, which then dissociates into H_2O and CO_2).

Although the Na^+-K^+ ATPase pump provides the major force for the reabsorption of sodium, chloride, and water throughout proximal tubule, there are some differences in the mechanisms whereby sodium and chloride are transported through the luminal side of the early and late portions of the proximal tubular membrane.

In the first half of the proximal tubule, sodium is reabsorbed by co-transport along with glucose, amino acids, and other solutes. However, in the second half of the proximal tubule, little glucose and few amino acids remain to be reabsorbed. Instead, sodium is now reabsorbed, mainly with chloride ions. The second half of the proximal tubule has a relatively high concentration of chloride (≈140 mEq/L) compared with the early proximal tubule (≈105 mEq/L) because when sodium is reabsorbed, it preferentially carries with it glucose, bicarbonate, and organic ions in the early proximal tubule, leaving behind a solution that has a higher concentration of chloride. In the second half of the proximal tubule, the higher chloride concentration favors diffusion of this ion from the tubule lumen through the intercellular junctions into the renal interstitial fluid. Smaller amounts of chloride may also be reabsorbed through specific chloride channels in the proximal tubular cell membrane.

Concentrations of Solutes Along Proximal Tubules. **Figure 28-7** summarizes the changes in concentration of various solutes along the proximal tubule. Although the *amount* of sodium in the tubular fluid decreases markedly along the proximal tubule, sodium *concentration* (and total osmolarity) remains relatively constant because water permeability of the proximal tubules is so great that water reabsorption keeps pace with sodium reabsorption. Certain organic solutes, such as glucose, amino acids, and bicarbonate, are much more avidly reabsorbed than water, and their concentrations decrease markedly along the length of the proximal tubule. Other organic solutes that are less permeant and not actively reabsorbed, such as creatinine, increase their concentration along the proximal tubule. The total solute concentration, as reflected by osmolarity, remains essentially the same all along the proximal tubule because of the extremely high permeability of this part of the nephron to water.

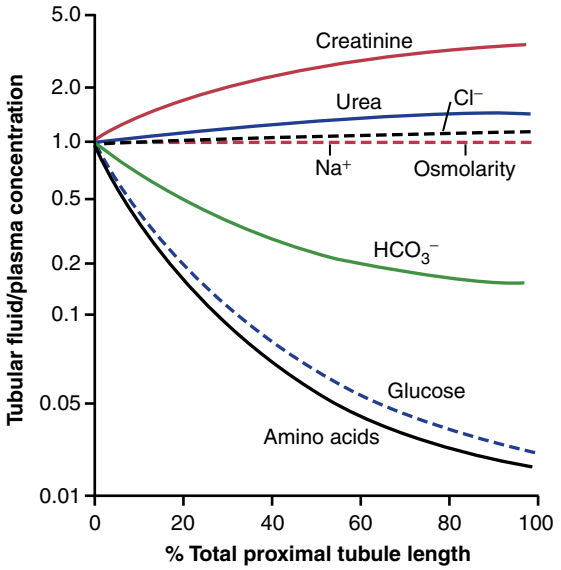

Figure 28-7 Changes in concentrations of different substances in tubular fluid along the proximal convoluted tubule relative to the concentrations of these substances in the plasma and glomerular filtrate. A value of 1.0 indicates that the concentration of the substance in the tubular fluid is the same as the concentration in the plasma. Values below 1.0 indicate that the substance is reabsorbed more avidly than water, whereas values above 1.0 indicate that the substance is reabsorbed to a lesser extent than water or is secreted into the tubules.

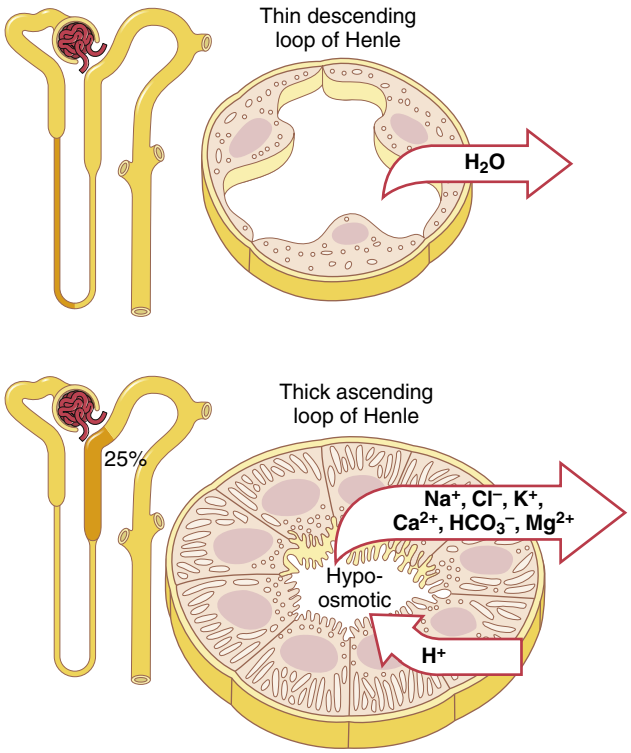

Figure 28-8 Cellular ultrastructure and transport characteristics of the thin descending loop of Henle (*top*) and thick ascending segment of the loop of Henle (*bottom*). The descending part of the thin segment of the loop of Henle is highly permeable to water and moderately permeable to most solutes but has few mitochondria and little or no active reabsorption. The thick ascending limb of the loop of Henle reabsorbs about 25% of the filtered loads of sodium, chloride, and potassium, as well as large amounts of calcium, bicarbonate, and magnesium. This segment also secretes hydrogen ions into the tubular lumen.

Secretion of Organic Acids and Bases by Proximal Tubules. The proximal tubule is also an important site for secretion of organic acids and bases such as *bile salts*, *oxalate*, *urate*, and *catecholamines*. Many of these substances are the end products of metabolism and must be rapidly removed from the body. The *secretion* of these substances into the proximal tubule plus *filtration* into the proximal tubule by the glomerular capillaries and almost total lack of reabsorption by the tubules, all combined, contribute to rapid excretion in the urine.

In addition to the waste products of metabolism, the kidneys secrete many potentially harmful drugs or toxins into the tubules and rapidly clear these substances from the blood. In the case of certain drugs, such as penicillin and salicylates, the rapid clearance by the kidneys creates a challenge in maintaining a therapeutically effective drug concentration.

Another compound that is rapidly secreted by the proximal tubule is para-aminohippuric acid (PAH). PAH is secreted so rapidly that the average person can clear about 90% of the PAH from the plasma flowing through the kidneys and excrete it in the urine. For this reason, the rate of PAH clearance can be used to estimate the renal plasma flow (RPF), as discussed later.

SOLUTE AND WATER TRANSPORT IN LOOPS OF HENLE

The loop of Henle consists of three functionally distinct segments—the *thin descending segment, thin ascending segment,* and *thick ascending segment.* The thin descending and thin ascending segments, as their names imply, have thin epithelial membranes with no brush borders, few mitochondria, and minimal levels of metabolic activity (Figure 28-8).

The descending part of the thin segment is highly permeable to water and moderately permeable to most solutes, including urea and sodium. The function of this nephron segment is mainly to allow simple diffusion of substances through its walls. About 20% of the filtered water is reabsorbed in the loop of Henle, and almost all of this occurs in the thin descending limb. The ascending limb, including both the thin and thick portions, is virtually impermeable to water, a characteristic that is important for concentrating the urine.

The thick segment of the loop of Henle, which begins about halfway up the ascending limb, has thick epithelial cells that have high metabolic activity and are capable of active reabsorption of sodium, chloride, and potassium (see Figure 28-8). About 25% of the filtered loads of sodium, chloride, and potassium are reabsorbed in the loop of Henle, mostly in the thick ascending limb. Considerable amounts of other ions, such as calcium, bicarbonate, and magnesium, are also reabsorbed in the thick

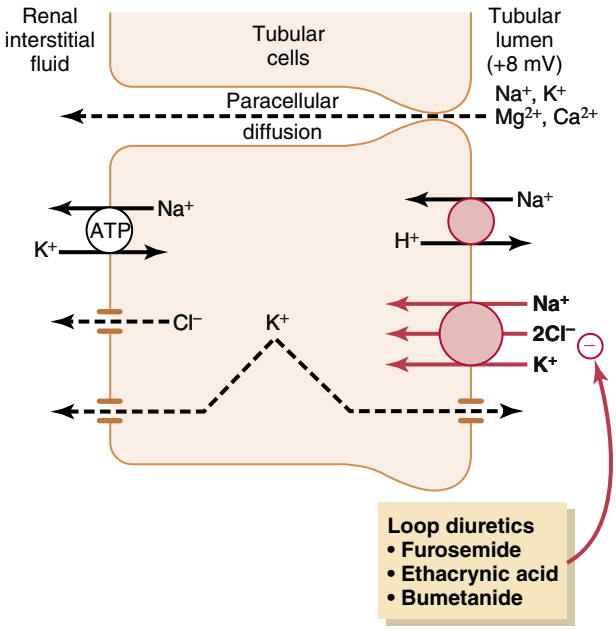

Figure 28-9 Mechanisms of sodium, chloride, and potassium transport in the thick ascending loop of Henle. The Na^+-K^+ ATPase pump in the basolateral cell membrane maintains a low intracellular sodium concentration and a negative electrical potential in the cell. The 1-sodium, 2-chloride, 1-potassium co-transporter in the luminal membrane transports these three ions from the tubular lumen into the cells, using the potential energy released by the diffusion of sodium down an electrochemical gradient into the cells. Sodium is also transported into the tubular cell by sodium-hydrogen counter-transport. The positive charge (+8 mV) of the tubular lumen relative to the interstitial fluid forces cations such as Mg^{2+} and Ca^{2+} to diffuse from the lumen to the interstitial fluid via the paracellular pathway.

ascending loop of Henle. The thin segment of the ascending limb has a much lower reabsorptive capacity than the thick segment, and the thin descending limb does not reabsorb significant amounts of any of these solutes.

An important component of solute reabsorption in the thick ascending limb is the Na^+-K^+ ATPase pump in the epithelial cell basolateral membranes. As in the proximal tubule, the reabsorption of other solutes in the thick segment of the ascending loop of Henle is closely linked to the reabsorptive capability of the Na^+-K^+ ATPase pump, which maintains a low intracellular sodium concentration. The low intracellular sodium concentration in turn provides a favorable gradient for movement of sodium from the tubular fluid into the cell. *In the thick ascending loop, movement of sodium across the luminal membrane is mediated primarily by a 1-sodium, 2-chloride, 1-potassium cotransporter* (NKCC2) (**Figure 28-9**). This co-transport protein in the luminal membrane uses the potential energy released by downhill diffusion of sodium into the cell to drive the reabsorption of potassium into the cell against a concentration gradient.

The thick ascending limb of the loop of Henle is the site of action of the powerful *loop diuretics furosemide, ethacrynic acid,* and *bumetanide,* all of which inhibit the action of the NKCC2 co-transporter. These diuretics are discussed in Chapter 32. The thick ascending limb also has a sodium-hydrogen counter-transport mechanism in its luminal cell membrane that mediates sodium reabsorption and hydrogen secretion (see **Figure 28-9**).

There is also significant paracellular reabsorption of cations, such as Mg^{2+}, Ca^{2+}, Na^+, and K^+, in the thick ascending limb as a result of the slight positive charge of the tubular lumen relative to the interstitial fluid. Although the NKCC2 co-transporter moves equal amounts of cations and anions into the cell, there is a slight backleak of potassium ions into the lumen, creating a positive charge of about +8 millivolts in the tubular lumen. This positive charge forces cations such as Mg^{2+} and Ca^{2+} to diffuse from the tubular lumen through the paracellular space and into the interstitial fluid.

The thick segment of the ascending loop of Henle is virtually impermeable to water. Therefore, most of the water delivered to this segment remains in the tubule, despite reabsorption of large amounts of solute. The tubular fluid in the ascending limb becomes very dilute as it flows toward the distal tubule, a feature that is important in allowing the kidneys to dilute or concentrate the urine under different conditions, as discussed in more detail in Chapter 29.

DISTAL TUBULES

The thick segment of the ascending limb of the loop of Henle empties into the *distal tubule*. The first portion of the distal tubule forms the *macula densa*, a group of closely packed epithelial cells that is part of the *juxtaglomerular complex* and provides feedback control of the GFR and blood flow in this same nephron.

The next part of the distal tubule is highly convoluted and has many of the same reabsorptive characteristics of the thick segment of the ascending limb of the loop of Henle. That is, it avidly reabsorbs most of the ions, including sodium, potassium, and chloride, but is virtually impermeable to water and urea. For this reason, it is referred to as the *diluting segment* because it also dilutes the tubular fluid.

Approximately 5% of the filtered load of sodium chloride is reabsorbed in the early distal tubule. The *sodium-chloride co-transporter* moves sodium chloride from the tubular lumen into the cell, and the Na^+-K^+ ATPase pump transports sodium out of the cell across the basolateral membrane (**Figure 28-10**). Chloride diffuses out of cell into the renal interstitial fluid through chloride channels in the basolateral membrane.

The *thiazide diuretics*, which are widely used to treat disorders such as hypertension and heart failure, inhibit the sodium-chloride co-transporter.

LATE DISTAL TUBULES AND CORTICAL COLLECTING TUBULES

The second half of the distal tubule and subsequent cortical collecting tubule have similar functional characteristics. Anatomically, they are composed of two distinct cell types, the *principal cells* and *intercalated cells*

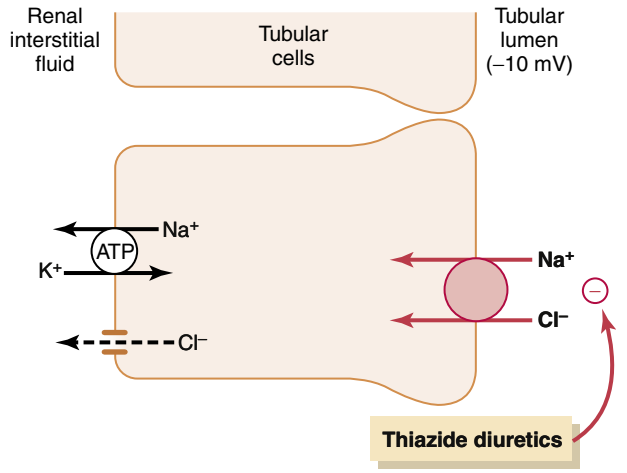

Figure 28-10 Mechanism of sodium chloride transport in the early distal tubule. Sodium and chloride are transported from the tubular lumen into the cell by a co-transporter that is inhibited by thiazide diuretics. Sodium is pumped out of the cell by Na^+-K^+ ATPase adenosine triphosphatase, and chloride diffuses into the interstitial fluid via chloride channels.

(Figure 28-11). The principal cells reabsorb sodium and water from the lumen and secrete potassium ions into the lumen. The type A intercalated cells reabsorb potassium ions and secrete hydrogen ions into the tubular lumen.

Principal Cells Reabsorb Sodium and Secrete Potassium. Sodium *reabsorption* and potassium *secretion* by the principal cells depend on the activity of a Na^+-K^+ ATPase pump in each cell's basolateral membrane (Figure 28-12). This pump maintains a low sodium concentration inside the cell and, therefore, favors sodium diffusion into the cell through special channels. Secretion of potassium by these cells from the blood into the tubular lumen involves two steps: (1) potassium enters the cell because of the Na^+-K^+ ATPase pump, which maintains a high intracellular potassium concentration; and (2) once in the cell, potassium diffuses down its concentration gradient across the luminal membrane into the tubular fluid.

The principal cells are the primary sites of action of the *potassium-sparing diuretics*, including spironolactone, eplerenone, amiloride, and triamterene. *Spironolactone* and *eplerenone* are *mineralocorticoid receptor antagonists* that compete with aldosterone for receptor sites in the principal cells and therefore inhibit the stimulatory effects of aldosterone on sodium reabsorption and potassium secretion. *Amiloride* and *triamterene* are *sodium channel blockers* that directly inhibit the entry of sodium into the sodium channels of the luminal membranes and therefore reduce the amount of sodium that can be transported across the basolateral membranes by the Na^+-K^+ ATPase pump. This, in turn, decreases transport of potassium into the cells and ultimately reduces potassium secretion into the tubular fluid. For this reason, sodium channel blockers, as well as aldosterone antagonists, decrease urinary excretion of potassium and act as *potassium-sparing diuretics*.

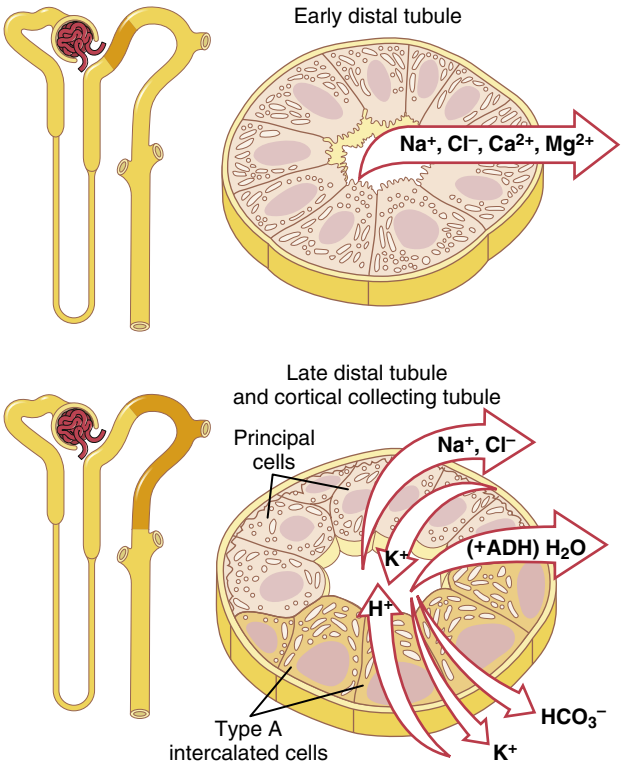

Figure 28-11 Cellular ultrastructure and transport characteristics of the early distal tubule and late distal tubule and collecting tubule. The early distal tubule has many of the same characteristics as the thick ascending loop of Henle and reabsorbs sodium, chloride, calcium, and magnesium but is virtually impermeable to water and urea. The late distal tubules and cortical collecting tubules are composed of two distinct cell types, the *principal cells* and *intercalated cells*. The principal cells reabsorb sodium from the lumen and secrete potassium ions into the lumen. Type A intercalated cells reabsorb potassium and bicarbonate ions from the lumen and secrete hydrogen ions into the lumen. The reabsorption of water from this tubular segment is controlled by the concentration of *antidiuretic hormone*.

Intercalated Cells Can Secrete or Reabsorb Hydrogen, Bicarbonate, and Potassium Ions. Intercalated cells play a major role in acid–base regulation and constitute 30% to 40% of the cells in the collecting tubules and collecting ducts. There are two types of intercalated cells, type A and type B (Figure 28-13). Type A intercalated cells secrete hydrogen ions by a hydrogen-ATPase transporter and by a hydrogen-potassium-ATPase transporter. Hydrogen is generated in this cell by the action of carbonic anhydrase on water and carbon dioxide to form carbonic acid, which then dissociates into hydrogen ions and bicarbonate ions. The hydrogen ions are then secreted into the tubular lumen and, for each hydrogen ion secreted, a bicarbonate ion becomes available for reabsorption across the basolateral membrane. Type A intercalated cells are especially important in eliminating hydrogen ions while reabsorbing bicarbonate in acidosis.

Type B intercalated cells have functions opposite to those of type A cells and secrete bicarbonate into the tubular lumen while reabsorbing hydrogen ions in alkalosis. Type B intercalated cells have hydrogen and bicarbonate

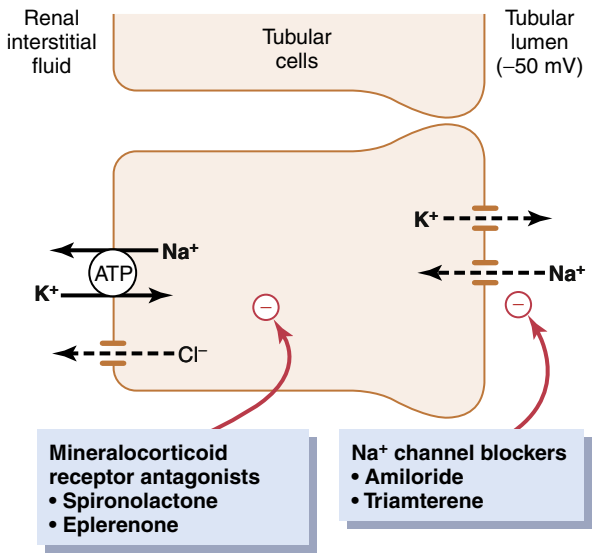

Figure 28-12 Mechanism of sodium-chloride reabsorption and potassium secretion in the principal cells of the late distal tubules and cortical collecting tubules. Sodium enters the cell through special channels and is transported out of the cell by the Na^+-K^+ ATPase pump. Aldosterone antagonists compete with aldosterone for binding sites in the cell and therefore inhibit the effects of aldosterone to stimulate sodium reabsorption and potassium secretion. Sodium channel blockers directly inhibit the entry of sodium into the sodium channels.

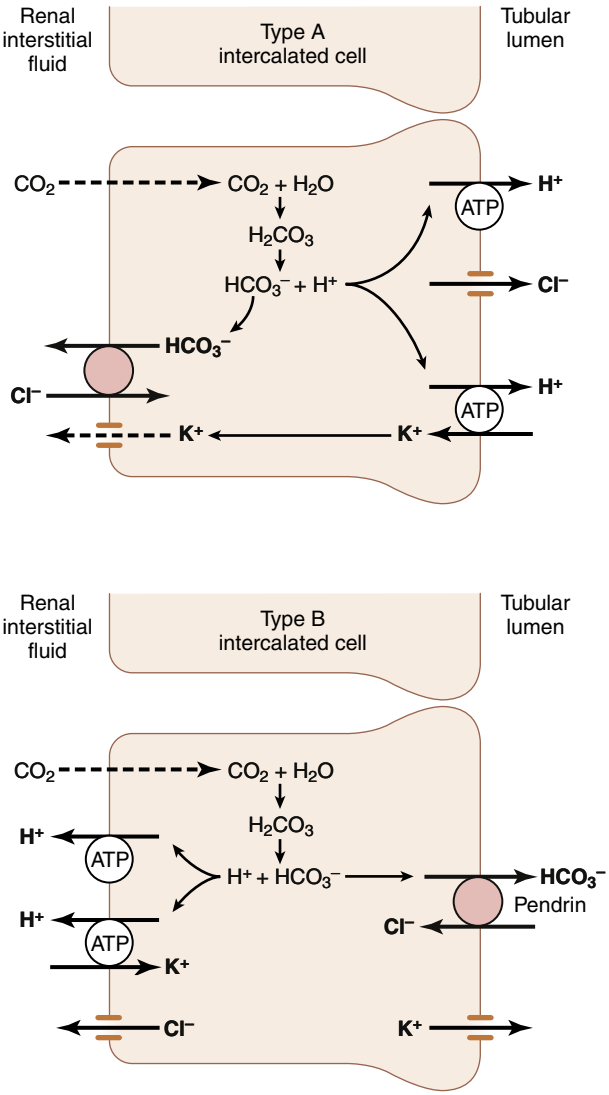

Figure 28-13 Type A and type B intercalated cells of the collecting tubule. Type A cells contain hydrogen-ATPase and hydrogen-potassium-ATPase in the luminal membrane and secrete hydrogen ions while reabsorbing bicarbonate and potassium ions in acidosis. In type B cells, the hydrogen-ATPase and hydrogen-potassium-ATPase transporters are located in the basolateral membrane and reabsorb hydrogen ions while secreting bicarbonate and potassium ions in alkalosis. The chloride-bicarbonate counter-transporter on the apical membrane of type B cells is called *pendrin* and is different than the chloride-bicarbonate transporter of type A intercalated cells.

transporters on opposite sides of the cell membrane compared with type A cells. The chloride-bicarbonate counter-transporter on the apical membrane of type B cells is called *pendrin* and is different than the chloride-bicarbonate transporter of type A cells. Hydrogen ions are actively transported out of the type B intercalated cell on the basolateral side of the cell membrane by hydrogen-ATPase, and bicarbonate is secreted into the lumen, thus eliminating excess plasma bicarbonate in alkalosis. Induction of chronic metabolic alkalosis increases the number of type B intercalated cells, which contribute to increased excretion of bicarbonate, whereas acidosis increases the number of type A cells.

A more detailed discussion of this mechanism is presented in Chapter 31. The intercalated cells can also reabsorb or secrete potassium ions, as shown in **Figure 28-13**.

The functional characteristics of the *late distal tubule* and *cortical collecting tubule* can be summarized as follows:

1. The tubular membranes of both segments are almost completely impermeable to urea, similar to the diluting segment of the early distal tubule. Thus, almost all the urea that enters these segments passes on through and into the collecting duct to be excreted in the urine, although some reabsorption of urea occurs in the medullary collecting ducts.
2. Both the late distal tubule and cortical collecting tubule segments reabsorb sodium ions, and the rate of reabsorption is controlled by hormones, especially aldosterone. At the same time, these segments secrete potassium ions from the peritubular capillary blood into the tubular lumen, a process that is also controlled by aldosterone and other factors, such as the concentration of potassium ions in the body fluids.
3. The type A intercalated cells of these nephron segments can avidly secrete hydrogen ions by an active hydrogen-ATPase mechanism in acidosis. This process is different from the secondary active secretion of hydrogen ions by the proximal tubule because it is capable of secreting hydrogen ions against a large concentration gradient, as much as 1000 to 1. This is in contrast to the relatively small gradient (4- to 10-fold) for hydrogen ions that can be achieved by secondary active secretion in the proximal tubule.

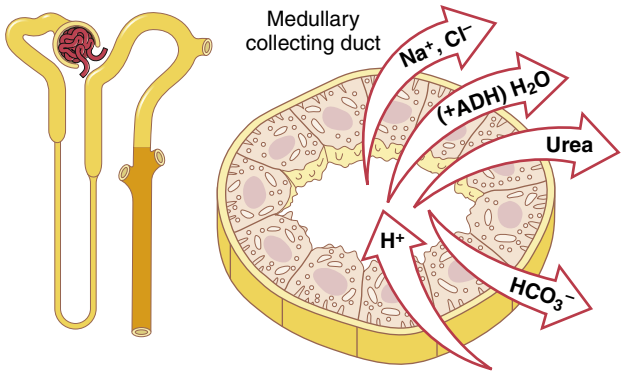

Figure 28-14 Cellular ultrastructure and transport characteristics of the medullary collecting duct. The medullary collecting ducts actively reabsorb sodium and secrete hydrogen ions and are permeable to urea, which is reabsorbed in these tubular segments. The reabsorption of water in medullary collecting ducts is controlled by the concentration of antidiuretic hormone.

In alkalosis, the type B intercalated cells secrete bicarbonate and actively reabsorb hydrogen ions. Thus, the intercalated cells play a key role in acid–base regulation of the body fluids.

4. The permeability of the late distal tubule and cortical collecting duct to water is controlled by the concentration of ADH, which is also called *vasopressin.* With high levels of ADH, these tubular segments are permeable to water but, in the absence of ADH, they are virtually impermeable to water. This special characteristic provides an important mechanism for controlling the degree of dilution or concentration of the urine.

MEDULLARY COLLECTING DUCTS

Although the medullary collecting ducts usually reabsorb less than 5% of the filtered water and sodium, they are the final site for processing the urine and, therefore, play a critical role in determining the final urine output of water and solutes.

The epithelial cells of the collecting ducts are nearly cuboidal in shape, with smooth surfaces and relatively few mitochondria (**Figure 28-14**). Special characteristics of this tubular segment are as follows:

1. The permeability of the medullary collecting duct to water is controlled by the level of ADH. With high levels of ADH, water is avidly reabsorbed into the medullary interstitium, thereby reducing the urine volume and concentrating most of the solutes in the urine.
2. Unlike the cortical collecting tubule, the medullary collecting duct is permeable to urea, and there are special *urea transporters* that facilitate urea diffusion across the luminal and basolateral membranes. Therefore, some of the tubular urea is reabsorbed into the medullary interstitium, helping raise the osmolality in this region of the kidneys and contributing to the kidneys' overall ability to form concentrated urine. This topic is discussed in Chapter 29.
3. The medullary collecting duct is capable of secreting hydrogen ions against a large concentration gradient, as also occurs in the cortical collecting tubule. Thus, the medullary collecting duct also plays a key role in regulating acid-base balance.

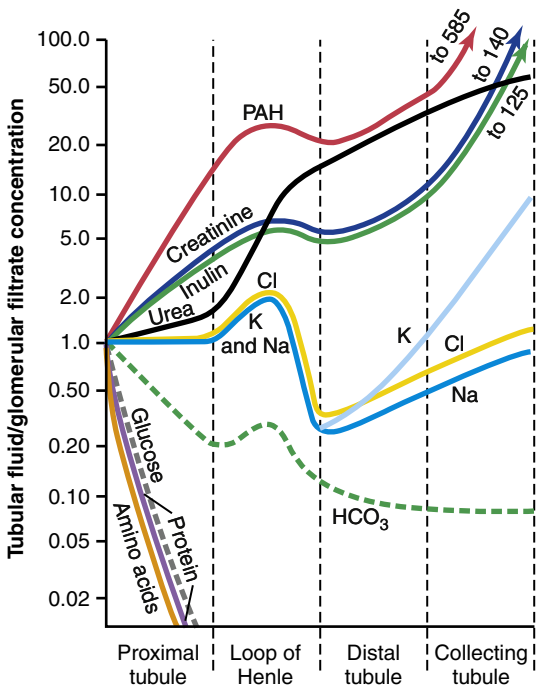

Figure 28-15 Changes in average concentrations of different substances at different points in the tubular system relative to the concentration of that substance in the plasma and glomerular filtrate. A value of 1.0 indicates that the concentration of the substance in the tubular fluid is the same as the concentration of that substance in the plasma. Values below 1.0 indicate that the substance is reabsorbed more avidly than water, whereas values above 1.0 indicate that the substance is reabsorbed to a lesser extent than water or is secreted into the tubules. PAH, Para-aminohippuric acid.

SUMMARY OF CONCENTRATIONS OF DIFFERENT SOLUTES IN DIFFERENT TUBULAR SEGMENTS

Whether a solute will become concentrated in the tubular fluid is determined by the relative degree of reabsorption of that solute versus the reabsorption of water. If a greater percentage of water is reabsorbed, the substance becomes more concentrated. If a greater percentage of the solute is reabsorbed, the substance becomes more diluted.

Figure 28-15 shows the degree of concentration of several substances in different tubular segments. All the values in this figure represent the tubular fluid concentration divided by the plasma concentration of a substance. If plasma concentration of the substance is assumed to be constant, any change in the tubular fluid/plasma concentration ratio reflects changes in tubular fluid concentration.

As the filtrate moves along the tubular system, the concentration rises progressively to higher than 1.0 if more water is reabsorbed than solute, or if there has been a net secretion of the solute into the tubular fluid. If the concentration ratio becomes progressively less than 1.0, this

means that relatively more solute has been reabsorbed than water.

The substances represented at the top of Figure 28-15, such as creatinine, become highly concentrated in the urine. In general, these substances are not needed by the body, and the kidneys have become adapted to reabsorb them only slightly or not at all or even to secrete them into the tubules, thereby excreting large quantities into the urine. Conversely, the substances represented at the bottom of the figure, such as glucose and amino acids, are all strongly reabsorbed. These are all substances that the body needs to conserve, and almost none of them are lost in the urine.

Tubular Fluid/Plasma Inulin Concentration Ratio Can Be Used to Assess Water Reabsorption by Renal Tubules. Inulin, a polysaccharide used to measure the GFR, is not reabsorbed or secreted by the renal tubules. Changes in inulin concentration at different points along the renal tubule, therefore, reflect changes in the amount of water present in the tubular fluid.

For example, the tubular fluid/plasma concentration ratio for inulin rises to about 3.0 at the end of the proximal tubules, indicating that inulin concentration in the tubular fluid is three times greater than in the plasma and glomerular filtrate. Because inulin is not secreted or reabsorbed from the tubules, a tubular fluid/plasma concentration ratio of 3.0 means that only one-third of the water that was filtered remains in the renal tubule and that two-thirds of the filtered water has been reabsorbed as the fluid passes through the proximal tubule. At the end of the collecting ducts, the tubular fluid/plasma inulin concentration ratio rises to about 125 (see Figure 28-15), indicating that only 1/125 of the filtered water remains in the tubule and that more than 99% has been reabsorbed.

REGULATION OF TUBULAR REABSORPTION

Because it is essential to maintain a precise balance between tubular reabsorption and glomerular filtration, there are multiple nervous, hormonal, and local control mechanisms that regulate tubular reabsorption, just as there are for control of glomerular filtration. An important feature of tubular reabsorption is that reabsorption of some solutes can be regulated independently of others, especially through hormonal control mechanisms.

GLOMERULOTUBULAR BALANCE—REABSORPTION RATE INCREASES IN RESPONSE TO INCREASED TUBULAR LOAD

One of the most basic mechanisms for controlling tubular reabsorption is the intrinsic ability of the tubules to increase their reabsorption rate in response to increased tubular load (increased tubular inflow). This phenomenon is referred to as *glomerulotubular balance*. For example, if the GFR increases from 125 to 150 ml/min, the absolute rate of proximal tubular reabsorption also increases from about 81 ml/min (65% of GFR) to about 97.5 ml/min (65% of GFR). Thus, glomerulotubular balance refers to the fact that the total rate of reabsorption increases as the filtered load increases, even though the percentage of GFR reabsorbed in the proximal tubule remains relatively constant, at about 65%.

Some degree of glomerulotubular balance also occurs in other tubular segments, especially the loop of Henle. The precise mechanisms responsible for this are not fully understood but may be due partly to changes in physical forces in the tubule and surrounding renal interstitium, as discussed later. It is clear that the mechanisms for glomerulotubular balance can occur independently of hormones and can be demonstrated in completely isolated kidneys or even in completely isolated proximal tubular segments.

Glomerulotubular balance helps prevent overloading of the distal tubular segments when GFR increases. Glomerulotubular balance acts as another line of defense to buffer the effects of spontaneous changes in the GFR on urine output. (The other line of defense, discussed earlier, includes the renal autoregulatory mechanisms, especially tubuloglomerular feedback, which help prevent large changes in GFR.) Working together, the autoregulatory and glomerulotubular balance mechanisms prevent large changes in fluid flow in the distal tubules when the arterial pressure changes or when there are other disturbances that would otherwise upset sodium and volume homeostasis.

PERITUBULAR CAPILLARY AND RENAL INTERSTITIAL FLUID PHYSICAL FORCES

Hydrostatic and colloid osmotic forces govern the rate of reabsorption across the peritubular capillaries, just as they control filtration in the glomerular capillaries. Changes in peritubular capillary reabsorption can in turn influence the hydrostatic and colloid osmotic pressures of the renal interstitium and, ultimately, reabsorption of water and solutes from the renal tubules.

Normal Values for Physical Forces and Reabsorption Rate. As the glomerular filtrate passes through the renal tubules, more than 99% of the water and most of the solutes are normally reabsorbed. Fluid and electrolytes are reabsorbed from the tubules into the renal interstitium and from there into the peritubular capillaries. The normal rate of peritubular capillary reabsorption is about 124 ml/min.

Reabsorption across the peritubular capillaries can be calculated as follows:

$$\text{Reabsorption} = K_f \times \text{Net reabsorptive force}$$

The net reabsorptive force represents the sum of the hydrostatic and colloid osmotic forces that favor or oppose reabsorption across the peritubular capillaries. These forces include the following: (1) hydrostatic pressure inside the peritubular capillaries (peritubular hydrostatic pressure [P_c]), which opposes reabsorption;

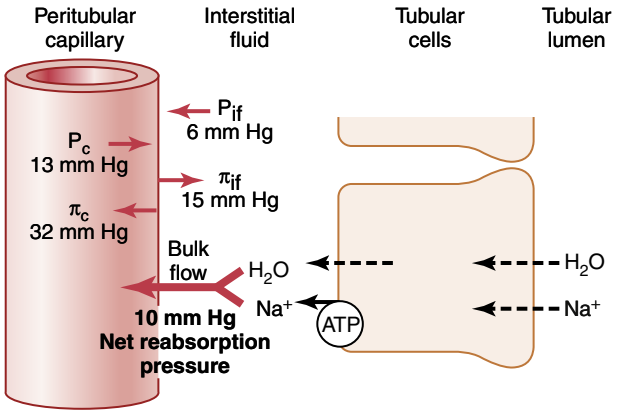

Figure 28-16 Summary of the hydrostatic and colloid osmotic forces that determine fluid reabsorption by the peritubular capillaries. The numerical values shown are estimates of the normal values for humans. The net reabsorptive pressure is normally about 10 mm Hg, causing fluid and solutes to be reabsorbed into the peritubular capillaries as they are transported across the renal tubular cells. ATP, Adenosine triphosphate; P_c, peritubular capillary hydrostatic pressure; P_{if}, interstitial fluid hydrostatic pressure; π_c, peritubular capillary colloid osmotic pressure; π_{if}, interstitial fluid colloid osmotic pressure.

(2) hydrostatic pressure in the renal interstitium (P_{if}) outside the capillaries, which favors reabsorption; (3) colloid osmotic pressure of the peritubular capillary plasma proteins (π_c), which favors reabsorption; and (4) colloid osmotic pressure of the proteins in the renal interstitium (π_{if}), which opposes reabsorption.

Figure 28-16 shows the approximate normal forces that favor and oppose peritubular reabsorption. Because the normal peritubular capillary pressure averages about 13 mm Hg and the renal interstitial fluid hydrostatic pressure averages 6 mm Hg, there is a positive hydrostatic pressure gradient from the peritubular capillary to the interstitial fluid of about 7 mm Hg, which opposes fluid reabsorption. This opposition to fluid reabsorption is more than counterbalanced by the colloid osmotic pressures that favor reabsorption. The plasma colloid osmotic pressure, which favors reabsorption, is about 32 mm Hg, and the colloid osmotic pressure of the interstitium, which opposes reabsorption, is 15 mm Hg, causing a net colloid osmotic force of about 17 mm Hg, favoring reabsorption. Therefore, subtracting the net hydrostatic forces that oppose reabsorption (7 mm Hg) from the net colloid osmotic forces that favor reabsorption (17 mm Hg) gives a net reabsorptive force of about 10 mm Hg. This value is high, similar to that found in the glomerular capillaries, but in the opposite direction.

The other factor that contributes to the high rate of fluid reabsorption in the peritubular capillaries is a large filtration coefficient (K_f) because of the high hydraulic conductivity and large surface area of the capillaries. Because the reabsorption rate is normally about 124 ml/min and net reabsorption pressure is 10 mm Hg, K_f normally is about 12.4 ml/min per mm Hg.

Regulation of Peritubular Capillary Physical Forces. The two determinants of peritubular capillary reabsorption that are directly influenced by renal hemodynamic changes are the hydrostatic and colloid osmotic pressures of the peritubular capillaries. The *peritubular capillary hydrostatic pressure is influenced by the arterial pressure and resistances of the afferent and efferent arterioles* as follows:

1. Increases in arterial pressure tend to raise peritubular capillary hydrostatic pressure and decrease the reabsorption rate. This effect is buffered to some extent by autoregulatory mechanisms that maintain relatively constant renal blood flow, as well as relatively constant hydrostatic pressures in the renal blood vessels.
2. An increase in resistance of the afferent or efferent arterioles reduces peritubular capillary hydrostatic pressure and tends to increase reabsorption rate. Although constriction of the efferent arterioles increases glomerular capillary hydrostatic pressure, it lowers peritubular capillary hydrostatic pressure.

The second major determinant of peritubular capillary reabsorption is the *colloid osmotic pressure* of the plasma in these capillaries; raising the colloid osmotic pressure increases peritubular capillary reabsorption. *The colloid osmotic pressure of peritubular capillaries is determined by* the following: (1) the *systemic plasma colloid osmotic pressure* (increasing the plasma protein concentration of systemic blood tends to raise peritubular capillary colloid osmotic pressure, thereby increasing reabsorption); and (2) *the filtration fraction*—the higher the filtration fraction, the greater the fraction of plasma filtered through the glomerulus and, consequently, the more concentrated the protein becomes in the plasma that remains behind. Thus, increasing the filtration fraction also tends to increase the peritubular capillary reabsorption rate. Because filtration fraction is defined as the ratio of GFR/RPF, an increased filtration fraction can occur as a result of increased GFR or decreased RPF. Some renal vasoconstrictors, such as angiotensin II, increase peritubular capillary reabsorption by decreasing RPF and increasing filtration fraction, as discussed later.

Changes in the peritubular capillary K_f can also influence the reabsorption rate because K_f is a measure of the permeability and surface area of the capillaries. Increases in K_f raise reabsorption, whereas decreases in K_f lower peritubular capillary reabsorption. K_f remains relatively constant in most physiological conditions. Table 28-2 summarizes the factors that can influence the peritubular capillary reabsorption rate.

Renal Interstitial Hydrostatic and Colloid Osmotic Pressures. Ultimately, changes in peritubular capillary physical forces influence tubular reabsorption by changing the physical forces in the renal interstitium surrounding the tubules. For example, a decrease in the reabsorptive force across the peritubular capillary membranes, caused by increased peritubular capillary hydrostatic pressure or decreased peritubular capillary colloid osmotic pressure, reduces the uptake of fluid and solutes from the

Table 28-2 Factors That Can Influence Peritubular Capillary Reabsorption

↑ P_c → ↓ Reabsorption
• ↓ R_A → ↑ P_c
• ↓ R_E → ↑ P_c
• ↑ Arterial pressure → ↑ P_c
↑ π_c → ↑ Reabsorption
• ↑ π_A → ↑ π_c
• ↑ FF → ↑ π_c
↑ K_f → ↑ Reabsorption

FF, Filtration fraction; K_f, peritubular capillary filtration coefficient; P_c, peritubular capillary hydrostatic pressure; π_A, arterial plasma colloid osmotic pressure; π_c, peritubular capillary colloid osmotic pressure; R_A and R_E, afferent and efferent arteriolar resistances, respectively.

interstitium into the peritubular capillaries. This action in turn raises renal interstitial fluid hydrostatic pressure and decreases interstitial fluid colloid osmotic pressure because of dilution of the proteins in the renal interstitium. These changes then decrease the net reabsorption of fluid from the renal tubules into the interstitium, especially in the proximal tubules.

The mechanisms whereby changes in interstitial fluid hydrostatic and colloid osmotic pressures influence tubular reabsorption can be understood by examining the pathways through which solute and water are reabsorbed (**Figure 28-17**). Once the solutes enter the intercellular channels or renal interstitium by active transport or passive diffusion, water is drawn from the tubular lumen into the interstitium by osmosis. Furthermore, once the water and solutes are in the interstitial spaces, they can be swept up into the peritubular capillaries or diffuse back through the epithelial junctions into the tubular lumen. The so-called tight junctions between the epithelial cells of the proximal tubule are actually leaky, so considerable amounts of sodium can diffuse in both directions through these junctions. With the normal high rate of peritubular capillary reabsorption, the net movement of water and solutes is into the peritubular capillaries, with little backleak into the lumen of the tubule. However, when peritubular capillary reabsorption is reduced, there is increased interstitial fluid hydrostatic pressure and a tendency for greater amounts of solute and water to leak back into the tubular lumen, thereby reducing the rate of net reabsorption (see **Figure 28-17**).

The opposite is true when peritubular capillary reabsorption increases above the normal level. An initial increase in reabsorption by the peritubular capillaries tends to reduce interstitial fluid hydrostatic pressure and raise interstitial fluid colloid osmotic pressure. Both these forces favor movement of fluid and solutes out of the tubular lumen and into the interstitium; therefore, backleak of water and solutes into the tubular lumen is reduced, and net tubular reabsorption is increased.

Thus, through changes in the hydrostatic and colloid osmotic pressures of the renal interstitium, the uptake of water and solutes by the peritubular capillaries is closely

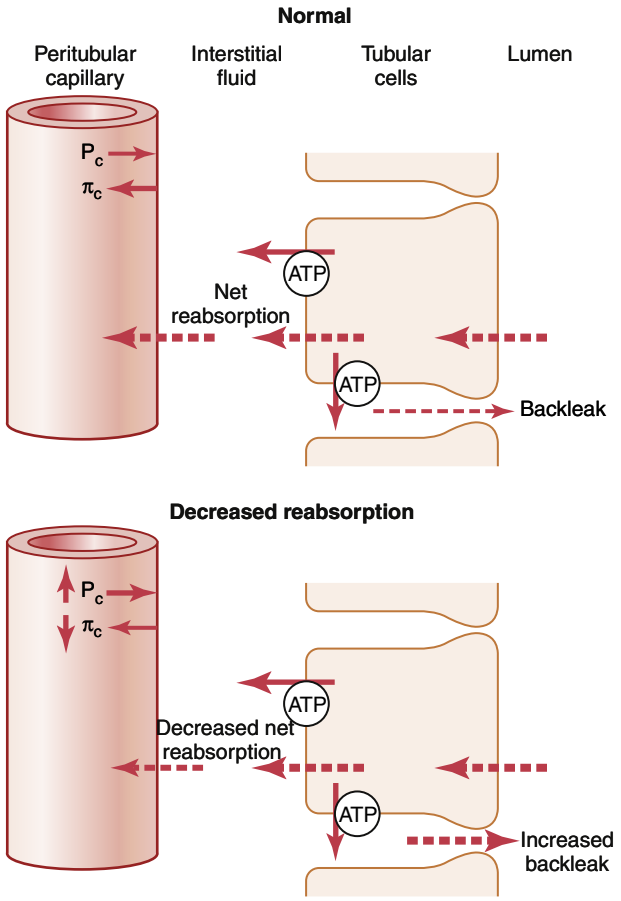

Figure 28-17 Proximal tubular and peritubular capillary reabsorption under normal conditions (*top*) and during decreased peritubular capillary reabsorption (*bottom*) caused by increasing peritubular capillary hydrostatic pressure (P_c) or decreasing peritubular capillary colloid osmotic pressure (π_c). Reduced peritubular capillary reabsorption, in turn, decreases the net reabsorption of solutes and water by increasing the amounts of solutes and water that leak back into the tubular lumen through the tight junctions of the tubular epithelial cells, especially in the proximal tubule.

matched to the net reabsorption of water and solutes from the tubular lumen into the interstitium. In general, *forces that increase peritubular capillary reabsorption also increase reabsorption from the renal tubules. Conversely, hemodynamic changes that inhibit peritubular capillary reabsorption also inhibit tubular reabsorption of water and solutes.*

EFFECT OF ARTERIAL PRESSURE ON URINE OUTPUT—PRESSURE NATRIURESIS AND PRESSURE DIURESIS

Even small increases in arterial pressure can cause marked increases in urinary excretion of sodium and water, phenomena referred to as *pressure natriuresis* and *pressure diuresis*. Because of the autoregulatory mechanisms described in Chapter 27, increasing the arterial pressure between the limits of 75 and 160 mm Hg usually has only a small effect on renal blood flow and GFR. The slight increase in GFR that does occur contributes in part to

the effect of increased arterial pressure on urine output. When GFR autoregulation is impaired, as often occurs in kidney disease, increases in arterial pressure can cause much larger increases in the GFR.

A second effect of increased renal arterial pressure that raises urine output is that it decreases the percentages of the filtered loads of sodium and water that are reabsorbed by the tubules. Although the mechanisms responsible for this effect are not fully understood, they include a cascade of physical factors, as well as paracrine and hormonal effects. Increased arterial pressure causes a slight increase in peritubular capillary hydrostatic pressure, especially in the vasa recta of the renal medulla, and a subsequent *increase in the renal interstitial fluid hydrostatic pressure*. As discussed earlier, an increase in the renal interstitial fluid hydrostatic pressure enhances backleak of sodium into the tubular lumen, thereby reducing the net reabsorption of sodium and water and further increasing the rate of urine output when renal arterial pressure rises.

A third factor that contributes to pressure natriuresis and pressure diuresis is *reduced angiotensin II formation*. Angiotensin II itself increases sodium reabsorption by the tubules and stimulates aldosterone secretion, which further increases sodium reabsorption. Therefore, decreased angiotensin II formation contributes to the decreased tubular sodium reabsorption that occurs when arterial pressure is increased.

A fourth factor that may contribute to pressure natriuresis is *internalization of sodium transporter proteins* from the apical membranes to the cytoplasm of the renal tubules, thereby reducing the amount of sodium that can be transported across the cell membranes. This effect of increased arterial pressure may be mediated, in part, by decreased angiotensin II formation and other autacoid or paracrine signals.

HORMONAL CONTROL OF TUBULAR REABSORPTION

Precise regulation of body fluid volumes and solute concentrations requires the kidneys to excrete different solutes and water at variable rates, sometimes independently of one another. For example, when potassium intake is increased, the kidneys must excrete more potassium while maintaining normal excretion of sodium and other electrolytes. Likewise, when sodium intake is changed, the kidneys must adjust urinary sodium excretion appropriately without major changes in excretion of other electrolytes. Several hormones in the body provide this specificity of tubular reabsorption for different electrolytes and water. **Table 28-3** summarizes some of the most important hormones for regulating tubular reabsorption, their principal sites of action on the renal tubule, and their effects on solute and water excretion. Some of these hormones are discussed in more detail in Chapters 29 and 30, but here we briefly review their renal tubular actions.

Aldosterone Stimulates Renal Sodium Reabsorption and Potassium Secretion. Aldosterone, secreted by the zona glomerulosa cells of the adrenal cortex, is an important regulator of sodium reabsorption and secretion of potassium and hydrogen ions by the renal tubules. *A major renal tubular site of aldosterone action is on the principal cells of the cortical collecting tubule*. The mechanism whereby aldosterone increases sodium reabsorption and potassium secretion is by stimulating the Na^+-K^+ ATPase pump on the basolateral side of the cortical collecting tubule membrane. Aldosterone also increases the sodium permeability of the luminal side of the membrane by the insertion of epithelial sodium channels. The cellular mechanisms of aldosterone action are discussed in Chapter 78.

The most important stimuli for aldosterone are the following: (1) increased extracellular potassium concentration; and (2) increased angiotensin II levels, which typically occur in conditions associated with sodium and volume depletion or low blood pressure. Increased secretion of aldosterone associated with these conditions causes renal sodium and water retention, helping restore extracellular fluid volume and blood pressure toward normal.

When there is a deficit of aldosterone, as occurs with adrenal destruction or malfunction *(Addison disease)*, there is marked sodium loss from the body and accumulation of potassium. Conversely, excess aldosterone secretion, as occurs in patients with adrenal tumors *(Conn syndrome)*, is associated with sodium retention and decreased plasma potassium concentration due, in part, to excessive potassium secretion by the kidneys. Although daily regulation of sodium balance can be maintained as long as minimal levels of aldosterone are present, the

Table 28-3 Hormones That Regulate Tubular Reabsorption

Hormone	Site of Action	Effects
Aldosterone	Collecting tubule and duct	↑NaCl, H_2O reabsorption; ↑K^+ secretion; ↑H^+ secretion
Angiotensin II	Proximal tubule, thick ascending loop of Henle, distal tubule, collecting tubule	↑NaCl, H_2O reabsorption; ↑H^+ secretion
Antidiuretic hormone	Distal tubule/collecting tubule and duct	↑H_2O reabsorption
Atrial natriuretic peptide	Distal tubule/collecting tubule and duct	↓NaCl reabsorption
Parathyroid hormone	Proximal tubule, thick ascending loop of Henle, distal tubule	↓PO_4^- reabsorption; ↑Ca^{2+} reabsorption

inability to adjust aldosterone secretion appropriately greatly impairs the regulation of renal potassium excretion and potassium concentration of the body fluids. Thus, aldosterone is even more important as a regulator of potassium concentration than for sodium concentration, as discussed in Chapter 30.

Angiotensin II Increases Sodium and Water Reabsorption. Angiotensin II is perhaps the body's most powerful sodium-retaining hormone. As discussed in Chapter 19, angiotensin II formation increases in circumstances associated with low blood pressure and/or low extracellular fluid volume, such as during hemorrhage or loss of salt and water from the body fluids by excessive sweating or severe diarrhea. Increased formation of angiotensin II helps return blood pressure and extracellular volume toward normal by increasing sodium and water reabsorption from the renal tubules through three main effects:

1. *Angiotensin II stimulates aldosterone secretion*, which in turn increases sodium reabsorption.
2. *Angiotensin II constricts the efferent arterioles,* which has two effects on peritubular capillary dynamics that increase sodium and water reabsorption. First, efferent arteriolar constriction reduces peritubular capillary hydrostatic pressure, which increases net tubular reabsorption, especially from the proximal tubules. Second, efferent arteriolar constriction, by reducing renal blood flow, raises filtration fraction in the glomerulus and increases the concentration of proteins and colloid osmotic pressure in the peritubular capillaries. This mechanism also increases the reabsorptive force at the peritubular capillaries and raises tubular reabsorption of sodium and water.
3. *Angiotensin II directly stimulates sodium reabsorption in the proximal tubules, the loops of Henle, the distal tubules, and the collecting tubules.* One of the direct effects of angiotensin II is to stimulate the Na^+-K^+ ATPase pump on the tubular epithelial cell basolateral membrane. A second effect is to stimulate sodium-hydrogen exchange in the luminal membrane, especially in the proximal tubule. A third effect of angiotensin II is to stimulate sodium-bicarbonate co-transport in the basolateral membrane (**Figure 28-18**).

Thus, angiotensin II stimulates sodium transport across both the luminal and basolateral surfaces of the epithelial cell membrane in most renal tubular segments. These multiple actions of angiotensin II cause marked sodium and water retention by the kidneys when angiotensin II levels are increased and play a critical role in permitting the body to adapt to wide variations in sodium intake without large changes in extracellular fluid volume and blood pressure, as discussed in Chapter 30.

At the same time that angiotensin II increases renal tubular sodium reabsorption, its vasoconstrictor effect on efferent arterioles also aids in the maintenance of normal excretion of metabolic waste products such as urea and creatinine that depend mainly on an adequate GFR for their excretion. Thus, increased formation of angiotensin II permits the kidneys to retain sodium and water without causing retention of metabolic waste products.

Antidiuretic Hormone Increases Water Reabsorption. The most important renal action of ADH is to increase the water permeability of the distal tubule, collecting tubule, and collecting duct epithelia. This effect helps the body conserve water in circumstances such as dehydration. In the absence of ADH, the permeability of the distal tubules and collecting ducts to water is low, causing the kidneys to excrete large amounts of dilute urine, a condition called *diabetes insipidus*. Thus, the actions of ADH play a key role in controlling the degree of dilution or concentration of the urine, as discussed further in Chapters 29 and 76.

ADH binds to specific V_2 *receptors* in the late distal tubules, collecting tubules, and collecting ducts, increasing the formation of cyclic adenosine monophosphate and activating protein kinases (**Figure 28-19**). This action, in turn, stimulates movement of an intracellular protein, called *aquaporin-2* (AQP-2), to the luminal side of the cell membranes. The molecules of AQP-2 cluster together and fuse with the cell membrane by exocytosis to form *water channels* that permit rapid diffusion of water through the cells. There are other aquaporins, AQP-3 and AQP-4, in the basolateral side of the cell membrane that provide a path for water to exit the cells rapidly, although these aquaporins are not regulated by ADH. Chronic increases in ADH levels also increase the formation of AQP-2 protein in the renal tubular cells by stimulating AQP-2 gene transcription. When the concentration of ADH decreases, the molecules of AQP-2 are shuttled back to the cell cytoplasm, thereby removing the water channels from the luminal membrane and reducing water permeability. These actions of ADH are discussed further in Chapters 29 and 76.

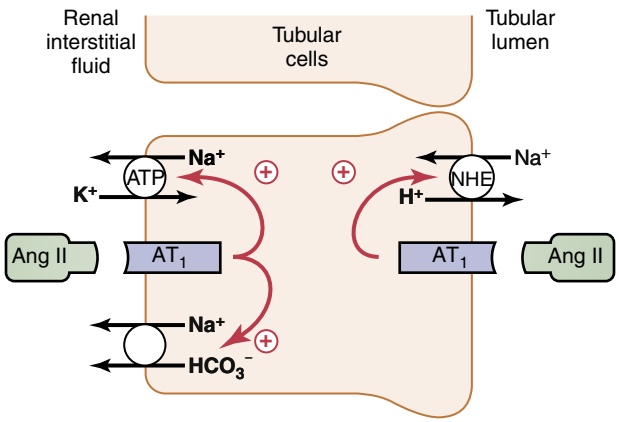

Figure 28-18 Direct effects of angiotensin II (*Ang II*) to increase proximal tubular sodium reabsorption. Ang II stimulates sodium-hydrogen exchange (*NHE*) on the luminal membrane and Na^+-K^+ ATPase transporter as well as sodium-bicarbonate co-transport on the basolateral membrane. These same effects of Ang II likely occur in several other parts of the renal tubule, including the loop of Henle, distal tubule, and collecting tubule. AT_1, Angiotensin II type I receptor.

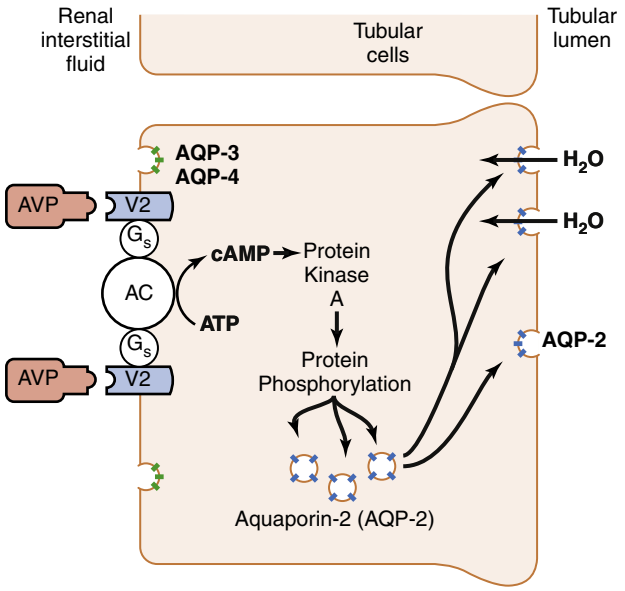

Figure 28-19 Mechanism of action of arginine vasopressin (*AVP*) on the epithelial cells of the late distal tubules, collecting tubules, and collecting ducts. AVP binds to its V_2 receptors, which are coupled with stimulatory G proteins (G_s) that activate adenylate cyclase (*AC*) and stimulate formation of cyclic adenosine monophosphate (*cAMP*). This, in turn, activates protein kinase A and phosphorylation of intracellular proteins, causing movement of aquaporin-2 (*AQP-2*) to the luminal side of the cell membrane. The molecules of *AQP-2* fuse together to form water channels. On the basolateral side of the cell membrane are other aquaporins, *AQP-3* and *AQP-4*, that permit water to flow out of the cell, although these aquaporins do not appear to be regulated by AVP.

Atrial Natriuretic Peptide Decreases Sodium and Water Reabsorption. When specific cells of the cardiac atria are stretched because of plasma volume expansion and increased atrial blood pressure, they secrete a peptide called *atrial natriuretic peptide* (ANP). Increased levels of this peptide in turn directly inhibit reabsorption of sodium and water by the renal tubules, especially in the collecting ducts. ANP also inhibits renin secretion and therefore angiotensin II formation, which in turn reduces renal tubular reabsorption. This decreased sodium and water reabsorption increases urinary excretion, which helps return the blood volume back toward normal.

ANP levels are greatly elevated in congestive heart failure when the cardiac atria are stretched because of impaired pumping of the ventricles. The increased ANP level helps attenuate sodium and water retention in heart failure.

Parathyroid Hormone Increases Calcium Reabsorption. Parathyroid hormone is one of the most important calcium-regulating hormones in the body. Its principal action in the kidneys is to increase tubular reabsorption of calcium, especially in the *distal tubules* and *connecting tubules*, a tubular segment that connects the distal tubules with the cortical collecting duct. Parathyroid hormone also has other actions, including inhibition of phosphate reabsorption by the proximal tubule and stimulation of magnesium reabsorption by the loop of Henle, as discussed in Chapter 30.

SYMPATHETIC NERVOUS SYSTEM ACTIVATION INCREASES SODIUM REABSORPTION

Activation of the sympathetic nervous system, if severe, can decrease sodium and water excretion by constricting the renal arterioles, thereby reducing the GFR. Even low levels of sympathetic activation, however, decrease sodium and water excretion by increasing sodium reabsorption in the proximal tubule, the thick ascending limb of the loop of Henle, and perhaps in more distal parts of the renal tubule. This occurs by activation of α-adrenergic receptors on the renal tubular epithelial cells.

Sympathetic nervous system stimulation also increases renin release and angiotensin II formation, which adds to the overall effect to increase tubular reabsorption and decrease renal excretion of sodium.

USE OF CLEARANCE METHODS TO QUANTIFY KIDNEY FUNCTION

The rates at which different substances are cleared from the plasma provide a useful way of quantitating the effectiveness with which the kidneys excrete various substances (Table 28-4). By definition, the renal clearance of a substance is the volume of plasma that is completely cleared of *the substance by the kidneys per unit of time*.

Although there is no single volume of plasma that is *completely* cleared of a substance, renal clearance provides a useful way of quantifying excretory function of the kidneys. We can use renal clearance to quantify renal blood flow, GFR, tubular reabsorption, and tubular secretion.

To illustrate the clearance principle, consider the following example. If the plasma passing through the kidneys contains 1 milligram of a substance in each milliliter, and if 1 milligram of this substance is also excreted into the urine each minute, then 1 ml/min of the plasma is cleared of the substance. Clearance refers to the volume of plasma that would be necessary to supply the amount of substance excreted in the urine per unit of time. Stated mathematically:

$$C_s \times P_s = U_s \times V$$

where C_s is the clearance rate of a substance s, P_s is the plasma concentration of the substance, U_s is the urine concentration of that substance, and V is the urine flow rate. Rearranging this equation, clearance can be expressed as:

$$C_s = \frac{U_s \times V}{P_s}$$

Thus, renal clearance of a substance is calculated from the urinary excretion rate ($U_s \times V$) of that substance divided by its plasma concentration.

INULIN CLEARANCE CAN BE USED TO ESTIMATE GLOMERULAR FILTRATION RATE

If a substance is freely filtered (filtered as freely as water) and is not reabsorbed or secreted by the renal tubules, then the rate at which that substance is excreted in the

Table 28-4 Use of Clearance to Quantify Kidney Function

Term	Equation	Units
Clearance rate	$C_s = \frac{U_s \times \dot{V}}{P_s}$	ml/min
Glomerular filtration rate	$GFR = \frac{U_{inulin} \times \dot{V}}{P_{inulin}}$	
Clearance ratio	$\text{Clearance ratio} = \frac{C_s}{C_{inulin}}$	None
Effective renal plasma flow	$ERPF = C_{PAH} = \frac{U_{PAH} \times \dot{V}}{P_{PAH}}$	ml/min
Renal plasma flow	$RPF = \frac{C_{PAH}}{E_{PAH}} = \frac{\left(U_{PAH} \times \dot{V}/P_{PAH}\right)}{(P_{PAH} - V_{PAH})/P_{PAH}} = \frac{U_{PAH} \times \dot{V}}{P_{PAH} - V_{PAH}}$	ml/min
Renal blood flow	$RBF = \frac{RPF}{1 - \text{Hematocrit}}$	ml/min
Excretion rate	$\text{Excretion rate} = U_s \times \dot{V}$	mg/min, mmol/min, or mEq/min
Reabsorption rate	$\text{Reabsorption rate} = \text{Filtered load} - \text{Excretion rate} = (GFR \times P_s) - \left(\dot{U} \times V\right)$	mg/min, mmol/min, or mEq/min
Secretion rate	$\text{Secretion rate} = \text{Excretion rate} - \text{Filtered load}$	mg/min, mmol/min, or mEq/min

C_s, Clearance rate of substance s; E_{PAH}, PAH extraction ratio; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; P, plasma concentration; PAH, para-aminohippuric acid; P_{PAH}, renal arterial PAH concentration; RBF, renal blood flow; RPF, renal plasma flow; S, a substance; U, urine concentration; $\dot{V}$, urine flow rate; V_{PAH}, renal venous PAH concentration.

urine ($U_s \times V$) is equal to the filtration rate of the substance by the kidneys ($GFR \times P_s$). Thus:

$$GFR \times P_s = U_s \times V$$

The GFR, therefore, can be calculated as the clearance of the substance as follows:

$$GFR = \frac{U_s \times V}{P_s} = C_2$$

A substance that fits these criteria is *inulin*, a polysaccharide molecule with a molecular weight of about 5200. Inulin, which is not produced in the body, is found in the roots of certain plants and must be administered intravenously to a patient to measure GFR.

Figure 28-20 shows the renal handling of inulin. In this example, the plasma concentration is 1 mg/ml, urine concentration is 125 mg/ml, and urine flow rate is 1 ml/min. Therefore, 125 mg/min of inulin passes into the urine. Then, inulin clearance is calculated as the urine excretion rate of inulin divided by the plasma concentration, which yields a value of 125 ml/min. Thus, 125 milliliters of plasma flowing through the kidneys must be filtered to deliver the inulin that appears in the urine.

Inulin is not the only substance that can be used for determining the GFR. Other substances that have been used clinically to estimate the GFR include *iothalamate, chromium ethylenediaminetetraacetic acid* (EDTA), *cystatin C,* and *creatinine.*

CREATININE CLEARANCE AND PLASMA CREATININE CONCENTRATION CAN BE USED TO ESTIMATE GLOMERULAR FILTRATION RATE

Creatinine is a by-product of muscle metabolism and is cleared from the body fluids almost entirely by glomerular filtration. Therefore, creatinine clearance can also be used to assess GFR. Because measurement of creatinine clearance does not require intravenous infusion into the patient, this method is much more widely used than inulin clearance for estimating GFR clinically. However, creatinine clearance is not a perfect marker of GFR because a small amount of it is secreted by the tubules, so the amount of creatinine excreted slightly exceeds the amount filtered. There is normally a slight error in measuring plasma creatinine that leads to an overestimation of the plasma creatinine concentration; fortuitously, these two errors tend to cancel each other. Therefore, creatinine clearance provides a reasonable estimate of GFR.

In some cases, it may not be practical to collect urine in a patient for measuring creatinine clearance (C_{Cr}). An approximation of *changes* in GFR, however, can be obtained by simply measuring the plasma creatinine concentration (P_{Cr}), which is inversely proportional to the GFR:

$$GFR \approx C_{Cr} = \frac{U_{Cr} \times \dot{V}}{P_{Cr}}$$

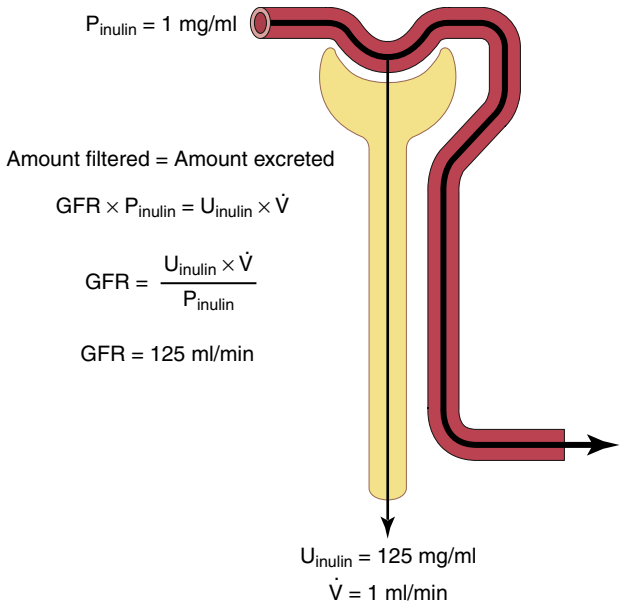

Figure 28-20 Measurement of glomerular filtration rate (*GFR*) from the renal clearance of inulin. Inulin is freely filtered by the glomerular capillaries but is not reabsorbed by the renal tubules. P_{inulin}, Plasma inulin concentration; U_{inulin}, urine inulin concentration; $\dot{V}$, urine flow rate.

If GFR suddenly decreases by 50%, the kidneys will transiently filter and excrete only half as much creatinine, causing the accumulation of creatinine in the body fluids and raising plasma concentration. The plasma concentration of creatinine will continue to rise until the filtered load of creatinine ($P_{Cr} \times GFR$) and creatinine excretion ($U_{Cr} \times \dot{V}$) return to normal, and a balance between creatinine production and creatinine excretion is re-established. This response will occur when the plasma creatinine level increases to approximately twice normal, as shown in **Figure 28-21**.

If GFR falls to one-fourth normal, plasma creatinine level would increase to about four times normal, and a decrease of GFR to one-eighth normal would raise plasma creatinine level to eight times normal. Thus, under steady-state conditions, creatinine excretion rate equals the rate of creatinine production, despite reductions in GFR. However, this normal rate of creatinine excretion occurs at the expense of an elevated plasma creatinine concentration, as shown in **Figure 28-22**.

PARA-AMINOHIPPURIC ACID CLEARANCE CAN BE USED TO ESTIMATE RENAL PLASMA FLOW

Theoretically, if a substance is *completely* cleared from the plasma, the clearance rate of that substance is equal to the total RPF. In other words, the amount of the substance delivered to the kidneys in the blood ($RPF \times P_s$) would be equal to the amount excreted in the urine ($U_s \times \dot{V}$). Thus, RPF could be calculated as follows:

$$RPF = \frac{U_s \times \dot{V}}{P_s} = C_s$$

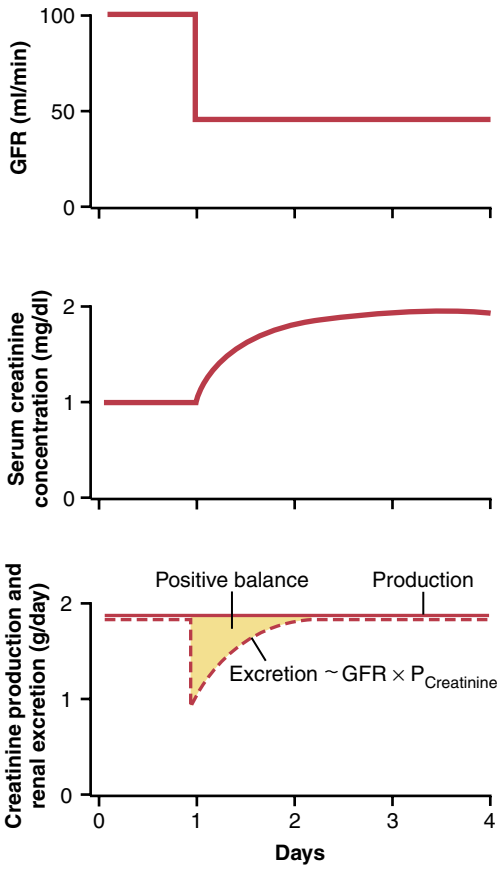

Figure 28-21 Effect of reducing glomerular filtration rate (*GFR*) by 50% on the serum creatinine concentration and on creatinine excretion rate when the production rate of creatinine remains constant. $P_{Creatinine}$, Plasma creatinine concentration.

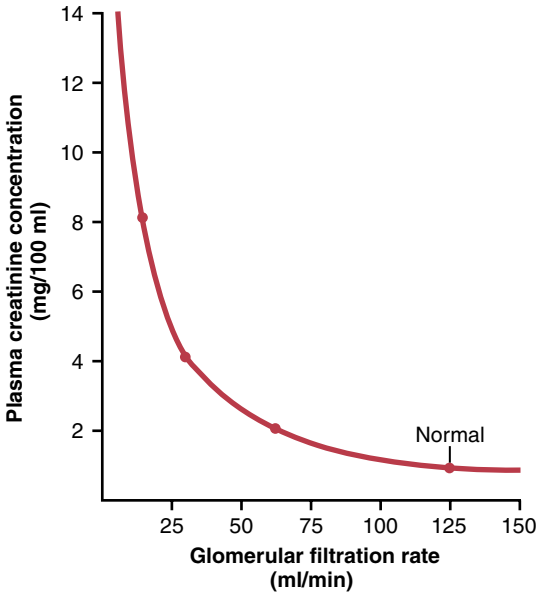

Figure 28-22 Approximate relationship between glomerular filtration rate (*GFR*) and plasma creatinine concentration under steady-state conditions. Decreasing GFR by 50% will increase plasma creatinine level to twice normal if creatinine production by the body remains constant.

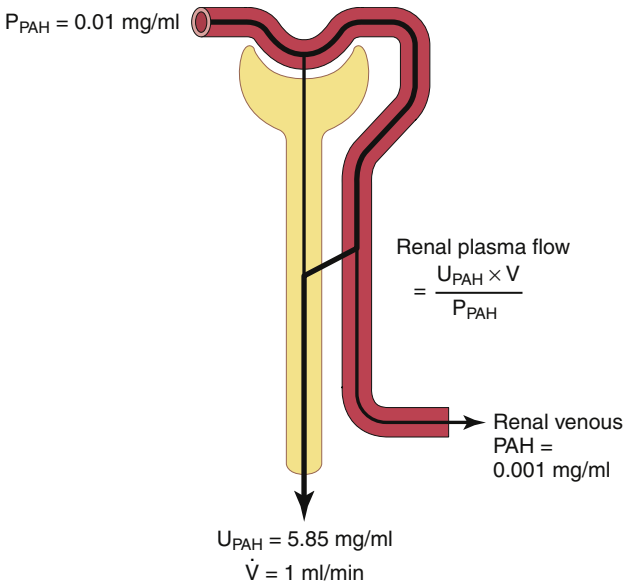

Figure 28-23 Measurement of renal plasma flow from the renal clearance of para-aminohippuric acid (*PAH*). PAH is freely filtered by the glomerular capillaries and is also secreted from the peritubular capillary blood into the tubular lumen. The amount of PAH in the plasma of the renal artery is about equal to the amount of PAH excreted in the urine. Therefore, the renal plasma flow can be calculated from the clearance of PAH. To be more accurate, one can correct for the percentage of PAH that is still in the blood when it leaves the kidneys. P_{PAH}, Arterial plasma PAH concentration; U_{PAH}, urine PAH concentration; $\dot{V}$, urine flow rate.

Because the GFR is only about 20% of the total plasma flow, a substance that is completely cleared from the plasma must be excreted by tubular secretion, as well as by glomerular filtration (**Figure 28-23**). There is no known substance that is *completely* cleared by the kidneys. One substance, PAH, is about 90% cleared from the plasma. Therefore, clearance of PAH can be used to approximate RPF. To be more accurate, one can correct for the percentage of PAH that is still in the blood when it leaves the kidneys. The percentage of PAH removed from the blood is known as the *extraction ratio of PAH* and averages about 90% in normal kidneys. In diseased kidneys, this extraction ratio may be reduced because of the inability of damaged tubules to secrete PAH into the tubular fluid.

The calculation of RPF can be demonstrated by the following example. Assume that the plasma concentration of PAH is 0.01 mg/ml, urine concentration is 5.85 mg/ml, and urine flow rate is 1 ml/min. PAH clearance can be calculated from the rate of urinary PAH excretion (5.85 [mg/ml] × 1 [ml/min]) divided by the plasma PAH concentration (0.01 mg/ml). Thus, the clearance of PAH is calculated to be 585 ml/min.

If the extraction ratio for PAH is 90%, the actual RPF can be calculated by dividing 585 ml/min by 0.9, yielding a value of 650 ml/min. Thus, total RPF can be calculated as follows:

$$\text{Total renal plasma flow} = \frac{\text{PAH clearance}}{\text{PAH extraction ratio}}$$

The extraction ratio (E_{PAH}) is calculated as the difference between the renal arterial PAH (P_{PAH}) and renal venous PAH (V_{PAH}) concentrations, divided by the renal arterial PAH concentration:

$$E_{PAH} = \frac{P_{PAH} - V_{PAH}}{P_{PAH}}$$

One can calculate the total blood flow through the kidneys from the total RPF and hematocrit (the percentage of red blood cells in the blood). If the hematocrit is 0.45 and the total RPF is 650 ml/min, the total blood flow through both kidneys is 650/(1 – 0.45), or 1182 ml/min.

FILTRATION FRACTION IS CALCULATED FROM GFR DIVIDED BY RPF

To calculate the filtration fraction, which is the fraction of plasma that filters through the glomerular membrane, one must first know the RPF (PAH clearance) and the GFR (inulin clearance). If the RPF is 650 ml/min and the GFR is 125 ml/min, the filtration fraction (FF) is calculated as follows:

$$FF = GFR/RPF = 125/650 = 0.19$$

CALCULATION OF TUBULAR REABSORPTION OR SECRETION FROM RENAL CLEARANCES

If the rates of glomerular filtration and renal excretion of a substance are known, one can calculate whether there is a net reabsorption or net secretion of that substance by the renal tubules. For example, if the rate of excretion of the substance ($U_s \times \dot{V}$) is less than the filtered load of the substance (GFR × P_s), then some of the substance must have been reabsorbed from the renal tubules. Conversely, if the excretion rate of the substance is greater than its filtered load, then the rate at which it appears in the urine represents the sum of the rate of glomerular filtration plus tubular secretion.

The following example demonstrates the calculation of tubular reabsorption. Assume the following laboratory values for a patient were obtained:

- Urine flow rate = 1 ml/min
- Urine concentration of sodium (U_{Na}) = 70 mEq/L = 70 μEq/ml
- Plasma sodium concentration = 140 mEq/L = 140 μEq/ml
- GFR (inulin clearance) = 100 ml/min

In this example, the filtered sodium load is GFR × P_{Na}, or 100 ml/min × 140 μEq/ml = 14,000 μEq/min. Urinary sodium excretion (U_{Na} × urine flow rate) is 70 μEq/min. Therefore, tubular reabsorption of sodium is the difference between the filtered load and urinary excretion, or 14,000 μEq/min – 70 μEq/min = 13,930 μEq/min.

Comparisons of Inulin Clearance with Clearances of Different Solutes. The following generalizations can be made by comparing the clearance of a substance with the clearance of inulin, the gold standard for measuring GFR: (1) if the clearance rate of the substance equals that of inulin, the substance is only filtered and not reabsorbed or secreted; (2) if the clearance rate of a substance is less than inulin clearance, the substance must have been reabsorbed by the nephron tubules; and (3) if the clearance rate of a substance is greater than that of inulin, the substance must be secreted by the nephron tubules. Listed below are the approximate clearance rates for some of the substances normally handled by the kidneys:

Substance	Clearance Rate (ml/min)
Glucose	0
Sodium	0.9
Chloride	1.3
Potassium	12.0
Phosphate	25.0
Inulin	125.0
Creatinine	140.0

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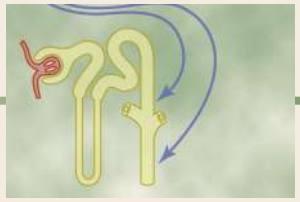

CHAPTER 29

UNIT V

Urine Concentration and Dilution; Regulation of Extracellular Fluid Osmolarity and Sodium Concentration

For the cells of the body to function properly, they must be bathed in extracellular fluid with a relatively constant concentration of electrolytes. The *total concentration* of solutes in the extracellular fluid—and therefore the osmolarity—must also be precisely regulated to prevent the cells from shrinking or swelling. The osmolarity is determined by the amount of solute (mainly sodium chloride) divided by the volume of the extracellular fluid. Thus, to a large extent, extracellular fluid osmolarity and sodium chloride concentration are regulated by the amount of extracellular water. The total body water is controlled by (1) fluid intake, which is regulated by factors that determine thirst; and (2) renal water excretion, which is controlled by multiple factors that influence glomerular filtration and tubular reabsorption.

In this chapter, we discuss the following: (1) mechanisms that cause the kidneys to eliminate excess water by excreting a dilute urine; (2) mechanisms that cause the kidneys to conserve water by excreting a concentrated urine; (3) renal feedback mechanisms that control the extracellular fluid sodium concentration and osmolarity; and (4) thirst and salt appetite mechanisms that determine the intakes of water and salt, which also help control extracellular fluid volume, osmolarity, and sodium concentration.

KIDNEYS EXCRETE EXCESS WATER BY FORMING DILUTE URINE

Normal kidneys have a tremendous capability to vary the relative proportions of solutes and water in the urine in response to various challenges. When there is excess water in the body, and body fluid osmolarity is reduced, the kidneys can excrete urine with an osmolarity as low as 50 mOsm/L, a concentration that is only about one-sixth the osmolarity of normal extracellular fluid. Conversely, when there is a deficit of water in the body, and extracellular fluid osmolarity is high, the kidneys can excrete highly concentrated urine with an osmolarity of 1200 to 1400 mOsm/L. Equally important, the kidneys can excrete a large volume of dilute urine or a small volume of concentrated urine without major changes in rates of excretion of solutes such as sodium and potassium. This ability to regulate water excretion independently of solute excretion is necessary for survival, especially when fluid intake is limited.

ANTIDIURETIC HORMONE CONTROLS URINE CONCENTRATION

The body has a powerful feedback system for regulating plasma osmolarity and sodium concentration that operates by altering renal excretion of water independently of solute excretion rate. A primary effector of this feedback is *antidiuretic hormone* (ADH), also called *vasopressin*.

When osmolarity of the body fluids increases above normal (i.e., the solutes in the body fluids become too concentrated), the posterior pituitary gland secretes more ADH, which increases the permeability of the distal tubules and collecting ducts to water, as discussed in Chapter 28. This mechanism increases water reabsorption and decreases urine volume but does not markedly alter the rate of renal excretion of the solutes.

When there is excess water in the body, and extracellular fluid osmolarity is reduced, secretion of ADH by the posterior pituitary decreases, thereby reducing the permeability of the distal tubule and collecting ducts to water, which causes increased amounts of more dilute urine to be excreted. Thus, the rate of ADH secretion determines, to a large extent, whether the kidney excretes dilute or concentrated urine.

RENAL MECHANISMS FOR EXCRETING DILUTE URINE

When there is a large excess of water in the body, the kidney can excrete as much as 20 L/day of dilute urine, with a concentration as low as 50 mOsm/L. The kidney performs this impressive feat by continuing to reabsorb solutes without reabsorbing large amounts of water in the distal parts of the nephron, including the late distal tubule and collecting ducts.

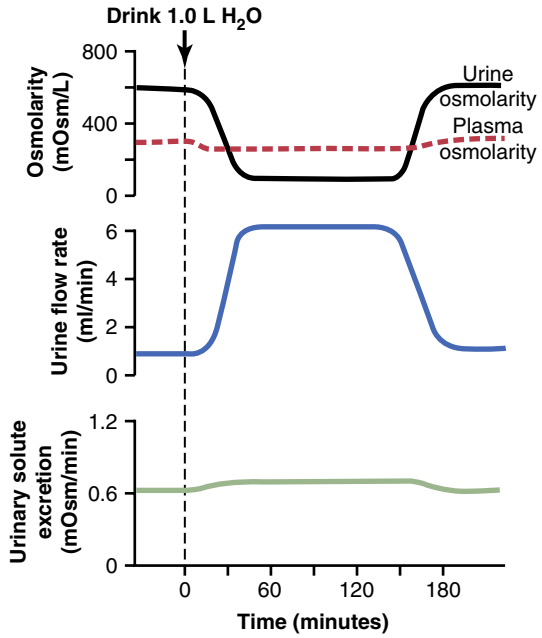

Figure 29-1. Water diuresis in a person after ingestion of 1 liter of water. Note that after water ingestion, urine volume increases and urine osmolarity decreases, causing excretion of a large volume of dilute urine; however, the total amount of solute excreted by the kidneys remains relatively constant. These responses of the kidneys prevent plasma osmolarity from decreasing markedly during excess water ingestion.

Figure 29-1 shows the approximate renal responses in a human after ingestion of 1 liter of water. Note that urine volume increased to about six times normal within 45 minutes after the water had been ingested. However, the total amount of solute excreted remained relatively constant because the urine formed became dilute, and urine osmolarity decreased from 600 to about 100 mOsm/L. Thus, after ingestion of excess water, the kidney rids the body of the excess water but does not excrete excess amounts of solutes.

When the glomerular filtrate is initially formed, its osmolarity is about the same as that of plasma (300 mOsm/L). To excrete excess water, the filtrate is diluted as it passes along the tubule by reabsorbing solutes to a greater extent than water, as shown in Figure 29-2. This dilution, however, occurs only in certain segments of the tubular system, as described in the following sections.

Tubular Fluid Remains Isosmotic in Proximal Tubules. As fluid flows through the proximal tubule, solutes and water are reabsorbed in equal proportions, so little change in osmolarity occurs. Thus, the proximal tubule fluid remains isosmotic to the plasma, with an osmolarity of about 300 mOsm/L. As fluid passes down the descending loop of Henle, water is reabsorbed by osmosis, and the tubular fluid reaches equilibrium with the surrounding interstitial fluid of the renal medulla, which is very hypertonic—about two to four times the osmolarity of the original glomerular filtrate. Therefore, the tubular fluid becomes more concentrated as it flows into the inner medulla.

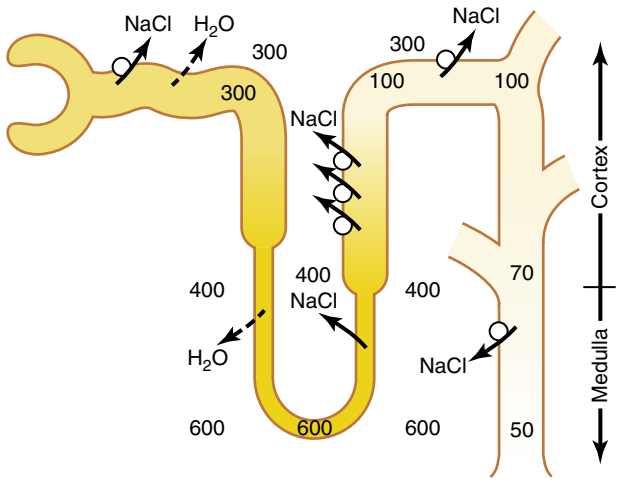

Figure 29-2. Formation of dilute urine when antidiuretic hormone (ADH) levels are very low. Note that in the ascending loop of Henle, the tubular fluid becomes very dilute. In the distal tubules and collecting tubules, the tubular fluid is further diluted by the reabsorption of sodium chloride and the failure to reabsorb water when ADH levels are very low. The failure to reabsorb water and continued reabsorption of solutes lead to a large volume of dilute urine. (Numerical values are in milliosmoles per liter.)

Tubular Fluid Is Diluted in the Ascending Loop of Henle. In the ascending limb of the loop of Henle, especially in the thick segment, sodium, potassium, and chloride are avidly reabsorbed. However, this portion of the tubular segment is impermeable to water, even in the presence of large amounts of ADH. Therefore, the tubular fluid becomes more dilute as it flows up the ascending loop of Henle into the early distal tubule, with the osmolarity decreasing progressively to about 100 mOsm/L by the time the fluid enters the early distal tubular segment. *Thus, regardless of whether ADH is present or absent, fluid leaving the early distal tubular segment is hypo-osmotic, with an osmolarity of only about one-third the osmolarity of plasma.*

Tubular Fluid in Distal and Collecting Tubules Is Further Diluted in Absence of ADH. As the dilute fluid in the early distal tubule passes into the late distal convoluted tubule, cortical collecting duct, and medullary collecting duct, there is additional reabsorption of sodium chloride. In the absence of ADH, this portion of the tubule is also impermeable to water, and the additional reabsorption of solutes causes the tubular fluid to become even more dilute, decreasing its osmolarity to as low as 50 mOsm/L. The failure to reabsorb water and continued reabsorption of solutes lead to a large volume of dilute urine.

To summarize, the mechanism for forming dilute urine is to continue reabsorbing solutes from the distal segments of the tubular system while reducing water reabsorption. In healthy kidneys, fluid leaving the ascending loop of Henle and early distal tubule is always dilute, regardless of the level of ADH. In the absence of ADH, the urine is further diluted in the late distal tubule and collecting ducts, and a large volume of dilute urine is excreted.

KIDNEYS CONSERVE WATER BY EXCRETING CONCENTRATED URINE

The ability of the kidney to form concentrated urine is essential for survival of mammals that live on land, including humans. Water is continuously lost from the body through various routes, including the lungs by evaporation into the expired air, the gastrointestinal tract by way of the feces, the skin through evaporation and perspiration, and the kidneys through excretion of urine. Fluid intake is required to match this loss, but the ability of the kidneys to form a small volume of concentrated urine minimizes the fluid intake required to maintain homeostasis, a function that is especially important when water is in short supply.

When there is a water deficit in the body, the kidneys form concentrated urine by continuing to excrete solutes while increasing water reabsorption and decreasing the urine volume. The human kidney can produce a maximal urine concentration of 1200 to 1400 mOsm/L, four to five times the osmolarity of plasma.

Some desert animals, such as the Australian hopping mouse, can concentrate urine to as high as 10,000 mOsm/L. This ability allows the mouse to survive in the desert without drinking water; sufficient water can be obtained through the ingested food and water produced in the body by metabolism of the food. Animals adapted to freshwater environments usually have minimal urine-concentrating ability. Beavers, for example, can concentrate the urine only to about 500 mOsm/L.

Obligatory Urine Volume

The maximal concentrating ability of the kidney dictates how much urine volume must be excreted each day to rid the body of metabolic waste products and electrolytes that are ingested. A normal 70-kg person must excrete about 600 milliosmoles of solute each day. If the maximal urine concentrating ability is 1200 mOsm/L, the *minimal* volume of urine that must be excreted, called the *obligatory urine volume,* can be calculated as follows:

$$\frac{600 \text{ mOsm/day}}{1200 \text{ mOsm/L}} = 0.5 \text{ L/day}$$

This minimal loss of volume in the urine contributes to dehydration, along with water loss from the skin, respiratory tract, and gastrointestinal tract, when water is not available to drink.

The limited ability of the human kidney to concentrate the urine to only about 1200 mOsm/L explains why severe dehydration occurs if one attempts to drink seawater. Sodium chloride concentration in the ocean averages about 3.0% to 3.5%, with an osmolarity between about 1000 and 1200 mOsm/L. Drinking 1 liter of seawater with a concentration of 1200 mOsm/L would provide a total sodium chloride intake of 1200 milliosmoles. If the maximal urine concentrating ability is 1200 mOsm/L, the amount of urine volume needed to excrete 1200 milliosmoles would be 1.0 liter. Why then does drinking seawater cause dehydration? The answer is that the kidney must also excrete other solutes, especially urea, which contribute about 600 mOsm/L when the urine is maximally concentrated. Therefore, the maximum concentration of sodium chloride that can be excreted by the kidneys is about 600 mOsm/L. Thus, for every liter of seawater ingested, 1.5 liters of urine volume would be required to rid the body of 1200 milliosmoles of sodium chloride ingested in addition to 600 milliosmoles of other solutes, such as urea. This would result in a net fluid loss of 0.5 liter for every liter of seawater, explaining the rapid dehydration that occurs in shipwreck victims who drink seawater. However, a shipwreck victim's pet Australian hopping mouse could drink seawater with impunity.

Urine Specific Gravity

Urine *specific gravity* is often used in clinical settings to provide a rapid estimate of urine solute concentration. The more concentrated the urine, the higher the urine specific gravity. In most cases, urine specific gravity increases linearly with increasing urine osmolarity (**Figure 29-3**). Urine specific gravity, however, is a measure of the weight of solutes in a given volume of urine and is therefore determined by the number and size of the solute molecules. In contrast, osmolarity is determined only by the number of solute molecules in a given volume.

Urine specific gravity is generally expressed in grams per milliliter (g/ml) and, in humans, normally ranges from 1.002 to 1.028 g/ml, rising by 0.001 for every 35- to 40-mOsm/L increase in urine osmolarity. This relationship between specific gravity and osmolarity is altered when there are significant amounts of large molecules in the urine, such as glucose, radiocontrast media used for diagnostic purposes, or some antibiotics. In these cases, urine specific gravity measurements may falsely suggest a highly concentrated urine, despite a normal urine osmolality.

Dipsticks are available that measure approximate urine specific gravity, but most laboratories measure specific gravity with a *refractometer*.

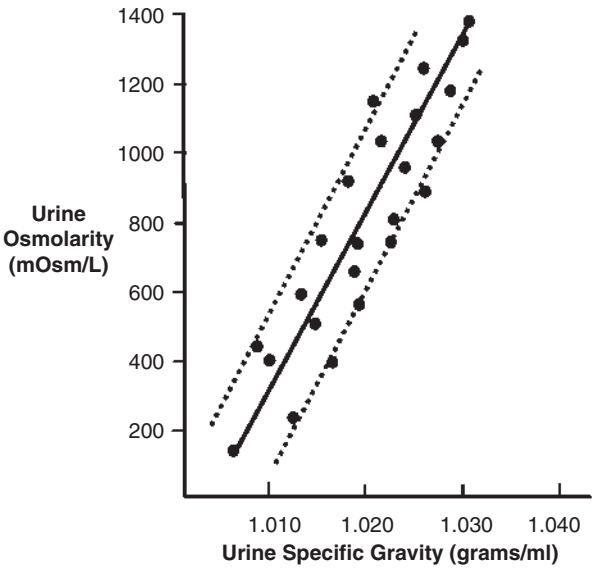

Figure 29-3. Relationship between specific gravity and osmolarity of the urine.

EXCRETING CONCENTRATED URINE REQUIRES HIGH ADH LEVELS AND HYPEROSMOTIC RENAL MEDULLA

The basic requirements for forming a concentrated urine are (1) a *high level of ADH*, which increases the permeability of the distal tubules and collecting ducts to water, thereby allowing these tubular segments to avidly reabsorb water; and (2) *a high osmolarity of the renal medullary interstitial fluid*, which provides the osmotic gradient necessary for water reabsorption to occur in the presence of high levels of ADH.

The renal medullary interstitium surrounding the collecting ducts is normally hyperosmotic, so when ADH levels are high, water moves through the tubular membrane by osmosis into the renal interstitium; from there it is carried away by the vasa recta back into the blood. Thus, the urine-concentrating ability is limited by the level of ADH and by the degree of hyperosmolarity of the renal medulla. We discuss the factors that control ADH secretion later, but for now, what is the process whereby renal medullary interstitial fluid becomes hyperosmotic? This process involves the operation of the *countercurrent multiplier mechanism*.

The countercurrent multiplier mechanism depends on the special anatomical arrangement of the loops of Henle and vasa recta, the specialized peritubular capillaries of the renal medulla. In humans, about 25% of the nephrons are *juxtamedullary nephrons*, with loops of Henle and vasa recta that go deeply into the medulla before returning to the cortex. Some of the loops of Henle dip all the way to the tips of the renal papillae that project from the medulla into the renal pelvis. Paralleling the long loops of Henle are the vasa recta, which also loop down into the medulla before returning to the renal cortex. And finally, the collecting ducts, which carry urine through the hyperosmotic renal medulla before it is excreted, also play a critical role in the countercurrent mechanism.

COUNTERCURRENT MULTIPLIER MECHANISM PRODUCES HYPEROSMOTIC RENAL MEDULLARY INTERSTITIUM

The osmolarity of interstitial fluid in almost all parts of the body is about 300 mOsm/L, which is similar to the plasma osmolarity. (As discussed in Chapter 25, the *corrected osmolar activity,* which accounts for intermolecular attraction, is about 282 mOsm/L.) The osmolarity of the interstitial fluid in the medulla of the kidney is much higher and may increase progressively to about 1200 to 1400 mOsm/L in the pelvic tip of the medulla. This means that the renal medullary interstitium has accumulated solutes in great excess of water. Once the high solute concentration in the medulla is achieved, it is maintained by a balanced inflow and outflow of solutes and water in the medulla.

The major factors that contribute to the buildup of solute concentration into the renal medulla are as follows:

1. Active transport of sodium ions and co-transport of potassium, chloride, and other ions out of the thick portion of the ascending limb of the loop of Henle into the medullary interstitium
2. Active transport of ions from the collecting ducts into the medullary interstitium
3. Facilitated diffusion of urea from the inner medullary collecting ducts into the medullary interstitium
4. Diffusion of only small amounts of water from the medullary tubules into the medullary interstitium—far less than the reabsorption of solutes into the medullary interstitium

LOOP OF HENLE CHARACTERISTICS THAT CAUSE SOLUTES TO BE TRAPPED IN THE RENAL MEDULLA

The transport characteristics of the loops of Henle are summarized in **Table 29-1**, along with the properties of the proximal tubules, distal tubules, cortical collecting tubules, and inner medullary collecting ducts.

A major reason for the high medullary osmolarity is active transport of sodium and co-transport of potassium, chloride, and other ions from the thick ascending loop of Henle into the interstitium. This pump is capable of establishing about a 200-mOsm/L concentration gradient between the tubular lumen and interstitial fluid. Because the thick ascending limb is virtually impermeable to water, the solutes pumped out are not followed by osmotic flow of water into the interstitium. Thus, the active transport of sodium and other ions out of the thick ascending loop adds solutes in excess of water to the renal

Table 29-1 Summary of Tubule Characteristics—Urine Concentration

Structure	Active NaCl Transport	*Permeability*		
		H_2O	NaCl	Urea
Proximal tubule	++	++	+	+
Thin descending limb	0	++	+	+
Thin ascending limb	0	0	+	+
Thick ascending limb	++	0	0	0
Distal tubule	+	+ADH	0	0
Cortical collecting tubule	+	+ADH	0	0
Inner medullary collecting duct	+	+ADH	0	+ADH

ADH, Antidiuretic hormone; NaCl, sodium chloride; 0, minimal level of active transport or permeability; +, moderate level of active transport or permeability; ++, high level of active transport or permeability; +ADH, permeability to water or urea is increased by ADH.

medullary interstitium. There is some passive reabsorption of sodium chloride from the thin ascending limb of Henle's loop, which is also essentially impermeable to water, adding further to the high solute concentration of the renal medullary interstitium.

The descending limb of Henle's loop, in contrast to the ascending limb, is very permeable to water, and the tubular fluid osmolarity quickly becomes equal to the renal medullary osmolarity. Therefore, water diffuses out of the descending limb of Henle's loop into the interstitium, and the tubular fluid osmolarity gradually rises as it flows toward the tip of the loop of Henle.

Steps Involved in Causing Hyperosmotic Renal Medullary Interstitium. Keeping in mind these characteristics of the loop of Henle, let us now discuss how the renal medulla becomes hyperosmotic (Video 29-1). First, assume that the loop of Henle is filled with fluid having a concentration of 300 mOsm/L, the same as that leaving the proximal tubule (**Figure 29-4**, step 1). Next, the active ion pump of the *thick ascending limb* on the loop of Henle reduces the concentration inside the tubule and raises the interstitial concentration; this pump establishes a 200-mOsm/L concentration gradient between the tubular fluid and interstitial fluid (**Figure 29-4**, step 2). The limit to the gradient is about 200 mOsm/L because paracellular diffusion of ions back into the tubule eventually counterbalances the transport of ions out of the lumen when the 200-mOsm/L concentration gradient is achieved.

Step 3 is that the tubular fluid in the *descending limb of the loop of Henle* and interstitial fluid quickly reaches osmotic equilibrium due to osmosis of water out of the descending limb. The interstitial osmolarity is maintained at 400 mOsm/L because of continued transport of ions out of the thick ascending loop of Henle. Thus, by itself, active transport of sodium chloride out of the thick ascending limb is capable of establishing only a 200-mOsm/L concentration gradient, which is much less than that achieved by the countercurrent multiplier system.

Step 4 is the additional flow of fluid into the loop of Henle from the proximal tubule, which causes the hyperosmotic fluid previously formed in the descending limb to flow into the ascending limb. Once this fluid is in the ascending limb, additional ions are pumped into the interstitium and water remains in the tubular fluid until a 200-mOsm/L osmotic gradient is established, and the interstitial fluid osmolarity rises to 500 mOsm/L (step 5). Then, once again, fluid in the descending limb reaches equilibrium with the hyperosmotic medullary interstitial fluid (step 6) and, as the hyperosmotic tubular fluid from the descending limb of the loop of Henle flows into the ascending limb, still more solute is continuously pumped out of the tubules and deposited into the medullary interstitium.

These steps are repeated over and over, with the net effect of adding more and more solute to the medulla in excess of water. With sufficient time, *this process gradually traps solutes in the medulla and multiplies the concentration gradient established by the active pumping of ions out of the thick ascending loop of Henle, eventually raising the interstitial fluid osmolarity to 1200 to 1400 mOsm/L, as shown in step 7.*

Thus, the repetitive reabsorption of sodium chloride by the thick ascending loop of Henle and continued inflow of new sodium chloride from the proximal tubule into the loop of Henle is called the *countercurrent multiplier*. The sodium chloride reabsorbed from the ascending loop of Henle keeps adding to the newly arrived sodium chloride, thus "multiplying" its concentration in the medullary interstitium.

ROLE OF DISTAL TUBULE AND COLLECTING DUCTS IN EXCRETING CONCENTRATED URINE

When the tubular fluid leaves the loop of Henle and flows into the distal convoluted tubule in the renal cortex, the fluid is dilute, with an osmolarity of only about 100 to

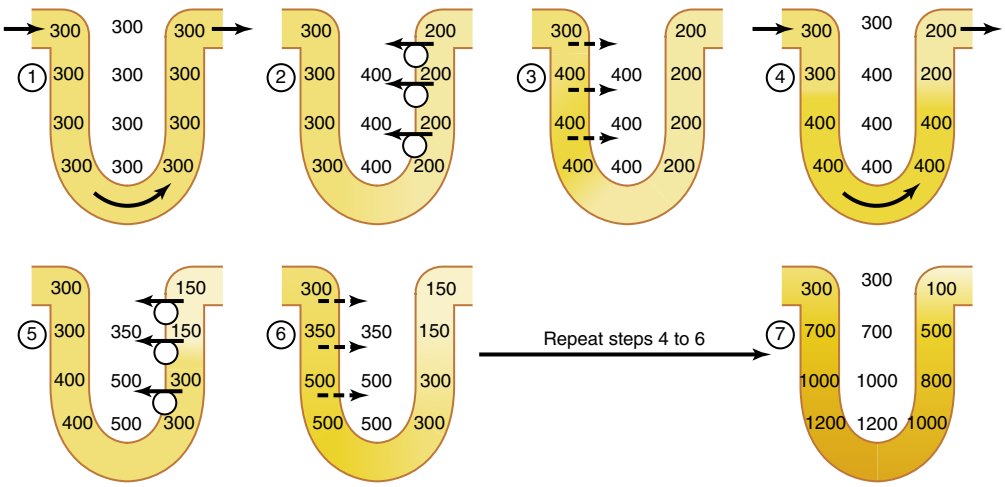

Figure 29-4. Countercurrent multiplier system in the loop of Henle for producing a hyperosmotic renal medulla. (Numerical values are in milliosmoles per liter.)

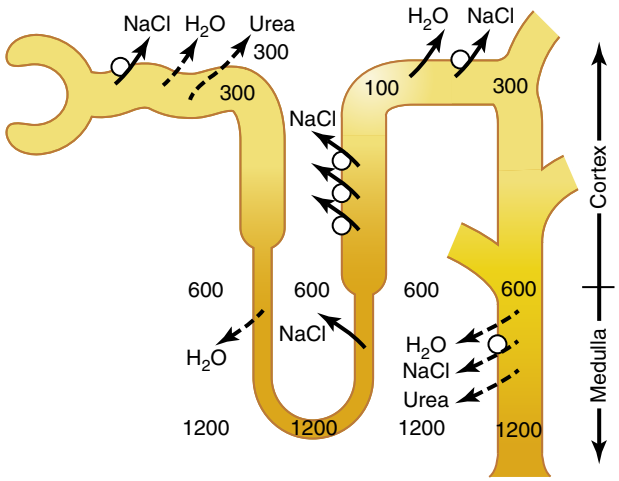

Figure 29-5. Formation of a concentrated urine when antidiuretic hormone (ADH) levels are high. Note that the fluid leaving the loop of Henle is dilute but becomes concentrated as water is absorbed from the distal tubules and collecting tubules. With high ADH levels, the osmolarity of the urine is about the same as the osmolarity of the renal medullary interstitial fluid in the papilla, which is about 1200 mOsm/L. (Numerical values are in milliosmoles per liter.)

140 mOsm/L (**Figure 29-5**). The early distal tubule further dilutes the tubular fluid because this segment, like the ascending loop of Henle, actively transports sodium chloride out of the tubule but is relatively impermeable to water.

As fluid flows into the cortical collecting tubule, the amount of water reabsorbed is critically dependent on the plasma concentration of ADH. In the absence of ADH, this segment is almost impermeable to water and fails to reabsorb water but continues to reabsorb solutes and further dilutes the urine. When there is a high concentration of ADH, the cortical collecting tubule becomes highly permeable to water, so large amounts of water are now reabsorbed from the tubule into the cortex interstitium, where it is swept away by the rapidly flowing peritubular capillaries. *Because large amounts of water are reabsorbed into the cortex, rather than into the renal medulla, this helps preserve the high medullary interstitial fluid osmolarity.*

As the tubular fluid flows along the medullary collecting ducts, there is further water reabsorption from the tubular fluid into the interstitium, but the total amount of water is relatively small compared with that added to the cortex interstitium. The reabsorbed water is carried away by the vasa recta into the venous blood. When high levels of ADH are present, the collecting ducts become permeable to water, so the fluid at the end of the collecting ducts has essentially the same osmolarity as the interstitial fluid of the renal medulla—about 1200 mOsm/L (see **Figure 29-4**). Thus, by reabsorbing as much water as possible, the kidneys form highly concentrated urine, excreting normal amounts of solutes in the urine while adding water back to the extracellular fluid and compensating for deficits of body water.

UREA CONTRIBUTES TO HYPEROSMOTIC RENAL MEDULLARY INTERSTITIUM AND FORMATION OF CONCENTRATED URINE

Urea contributes about 40% to 50% of the osmolarity (500–600 mOsm/L) of the renal medullary interstitium when the kidney is forming a maximally concentrated urine. Unlike sodium chloride, urea is passively reabsorbed from the tubule. When there is a water deficit and blood concentration of ADH is high, large amounts of urea are passively reabsorbed from the inner medullary collecting ducts into the interstitium.

The mechanism for reabsorption of urea into the renal medulla is as follows. As water flows up the ascending loop of Henle and into the distal and cortical collecting tubules, little urea is reabsorbed because these segments are impermeable to urea (see **Table 29-1**). In the presence of high concentrations of ADH, water is reabsorbed rapidly from the cortical collecting tubule, and the urea concentration increases rapidly because urea is not very permeant in this part of the tubule.

As the tubular fluid flows into the inner medullary collecting ducts, still more water reabsorption takes place, resulting in an even higher concentration of urea in the fluid. This high concentration of urea in the tubular fluid of the inner medullary collecting duct causes urea to diffuse out of the tubule into the renal interstitial fluid. This diffusion is greatly facilitated by specific *urea transporters, UT-A1* and *UT-A3*. These urea transporters are activated by ADH, increasing transport of urea out of the inner medullary collecting duct even more when ADH levels are elevated. The simultaneous movement of water and urea out of the inner medullary collecting ducts maintains a high concentration of urea in the tubular fluid and, eventually, in the urine, even though urea is being reabsorbed.

The fundamental role of urea in contributing to urine-concentrating ability is evidenced by the fact that people who ingest a high-protein diet, yielding large amounts of urea as a nitrogenous waste product, can concentrate their urine much better than people whose protein intake and urea production are low. Malnutrition is associated with a low urea concentration in the medullary interstitium and considerable impairment of urine-concentrating ability.

Recirculation of Urea from Collecting Duct to Loop of Henle Contributes to Hyperosmotic Renal Medulla. A healthy person usually excretes about 20% to 60% of the filtered load of urea, depending on urine flow rate and state of hydration. In general, the rate of urea excretion is determined mainly by the following: (1) concentration of urea in the plasma; (2) glomerular filtration rate (GFR); and (3) renal tubular urea reabsorption. In patients with renal disease who have large reductions in GFR, the plasma urea concentration increases markedly, returning the filtered urea load and urea excretion rate to the normal level (equal to the rate of urea production), despite the reduced GFR.

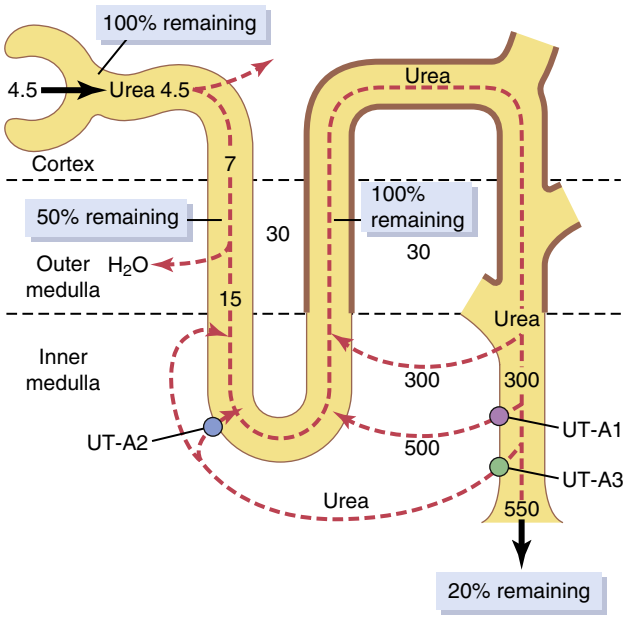

Figure 29-6. Recirculation of urea absorbed from the medullary collecting duct into the interstitial fluid. This urea diffuses into the thin loop of Henle, then passes through the distal tubules, and finally passes back into the collecting duct. The recirculation of urea helps trap urea in the renal medulla and contributes to the hyperosmolarity of the renal medulla. The *heavy lines,* from the thick ascending loop of Henle to the medullary collecting ducts, indicate that these segments are not very permeable to urea. The urea transporters UT-A1 and UT-A3 facilitate diffusion of urea out of the medullary collecting ducts while UT-A2 facilitates urea diffusion into the thin descending loop of Henle. (Numerical values are in milliosmoles per liter of urea during antidiuresis, when large amounts of antidiuretic hormone are present. Percentages of the filtered load of urea that remain in the tubules are indicated in the boxes.)

In the proximal tubule, 40% to 50% of the filtered urea is reabsorbed but, even so, the tubular fluid urea concentration increases because urea is not nearly as permeant as water. The concentration of urea continues to rise as the tubular fluid flows into the thin segments of the loop of Henle, partly because of water reabsorption out of the descending loop of Henle but also because of some *secretion* of urea into the thin loop of Henle from the medullary interstitium (**Figure 29-6**). The passive secretion of urea into the thin loops of Henle is facilitated by the *urea transporter UT-A2.*

The thick limb of the loop of Henle, distal tubule, and cortical collecting tubule are all less permeable to urea, and only small amounts of urea reabsorption normally occur in these tubular segments. When the kidney is forming concentrated urine, and high levels of ADH are present, reabsorption of water from the distal tubule and cortical collecting tubule further raises the tubular fluid concentration of urea. As this urea flows into the inner medullary collecting duct, the high tubular fluid concentration of urea and urea transporters UT-A1 and UT-A3 cause urea to diffuse into the medullary interstitium. A moderate share of the urea that moves into the medullary interstitium eventually diffuses into the thin loop of Henle and then passes upward through the ascending loop of Henle, distal tubule, and cortical collecting tubule and back down into the medullary collecting duct again. In this way, urea can recirculate through these terminal parts of the tubular system several times before it is excreted. Each time around the circuit contributes to a higher concentration of urea.

This urea recirculation provides an additional mechanism for forming a hyperosmotic renal medulla. Because urea is one of the most abundant waste products that must be excreted by the kidneys, this mechanism for concentrating urea before it is excreted is essential to the economy of the body fluid when water is in short supply.

When there is excess water in the body, urine flow rate increases, and therefore the concentration of urea in the inner medullary collecting ducts decreases, causing less diffusion of urea into the renal medullary interstitium. ADH levels are also reduced when there is excess body water, and this reduction, in turn, decreases the permeability of the inner medullary collecting ducts to both water and urea, and more urea is excreted in the urine.

COUNTERCURRENT EXCHANGE IN VASA RECTA PRESERVES HYPEROSMOLARITY OF RENAL MEDULLA

Blood flow must be provided to the renal medulla to supply the metabolic needs of the cells in this part of the kidney. Without a special medullary blood flow system, the solutes pumped into the renal medulla by the countercurrent multiplier system would be rapidly dissipated.

Two special features of the renal medullary blood flow contribute to the preservation of the high solute concentrations:

1. The medullary blood flow is low, accounting for less than 5% of the total renal blood flow. This sluggish blood flow is sufficient to supply the metabolic needs of the tissues but helps minimize solute loss from the medullary interstitium.
2. The vasa recta serve as *countercurrent exchangers,* minimizing the washout of solutes from the medullary interstitium.

The countercurrent exchange mechanism operates as follows (**Figure 29-7**). Blood enters and leaves the medulla via the vasa recta at the boundary of the cortex and renal medulla. The vasa recta, like other capillaries, are highly permeable to solutes in the blood, except for the plasma proteins. As blood descends into the medulla toward the papillae, it becomes progressively more concentrated, partly by solute entry from the interstitium and partly by loss of water into the interstitium. By the time the blood reaches the tips of the vasa recta, it has a concentration of about 1200 mOsm/L, the same as that of the medullary interstitium. As blood ascends back toward the cortex, it becomes progressively less concentrated as solutes diffuse back out into the medullary interstitium and as water moves into the vasa recta.

Although large amounts of fluid and solute are exchanged across the vasa recta, there is little net dilution of the concentration of the interstitial fluid at each level of the renal medulla because of the U shape of the vasa recta capillaries, which act as countercurrent exchangers. *Thus, the vasa recta do not create the medullary hyperosmolarity, but they do prevent it from being dissipated.*

The U-shaped structure of the vessels minimizes loss of solute from the interstitium but does not prevent bulk flow of fluid and solutes into the blood through the usual colloid osmotic and hydrostatic pressures that favor reabsorption in these capillaries. Under steady-state conditions, the vasa recta carry away only as much solute and water as is absorbed from the medullary tubules, and the high concentration of solutes established by the countercurrent mechanism is preserved.

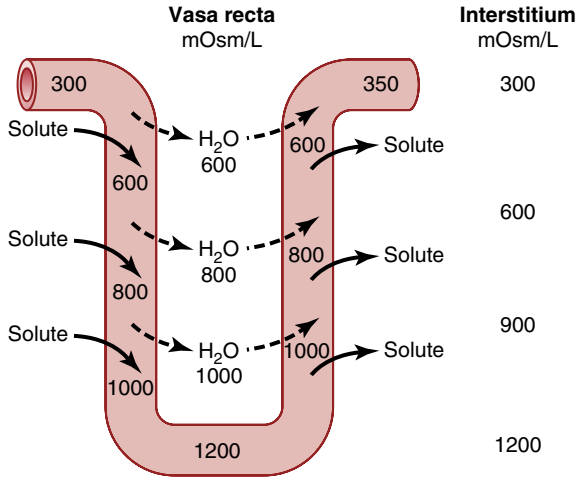

Figure 29-7. Countercurrent exchange in the vasa recta. Plasma flowing down the descending limb of the vasa recta becomes more hyperosmotic because of diffusion of water out of the blood and diffusion of solutes from the renal interstitial fluid into the blood. In the ascending limb of the vasa recta, solutes diffuse back into the interstitial fluid, and water diffuses back into the vasa recta. Large amounts of solutes would be lost from the renal medulla without the U shape of the vasa recta capillaries. (Numerical values are in milliosmoles per liter.)

Increased Medullary Blood Flow Reduces Urine-Concentrating Ability. Certain vasodilators can markedly increase renal medullary blood flow, thereby washing out some of the solutes from the renal medulla and reducing the maximum urine-concentrating ability. Large increases in arterial pressure may also increase the blood flow of the renal medulla to a greater extent than in other regions of the kidney and tend to wash out the hyperosmotic interstitium, thereby reducing urine-concentrating ability. As discussed earlier, maximum concentrating ability of the kidney is determined not only by the level of ADH but also by the osmolarity of the renal medulla interstitial fluid. Even with maximal ADH levels, the urine-concentrating ability will be reduced if medullary blood flow increases enough to reduce the hyperosmolarity in the renal medulla.

SUMMARY OF URINE-CONCENTRATING MECHANISM AND CHANGES IN OSMOLARITY IN DIFFERENT TUBULAR SEGMENTS

The changes in osmolarity and volume of the tubular fluid as it passes through the different parts of the nephron are shown in **Figure 29-8**.

Proximal Tubule. About 65% of most filtered electrolytes is reabsorbed in the proximal tubule. However, the proximal tubular membranes are highly permeable to water so, whenever solutes are reabsorbed, water also diffuses through the tubular membrane by osmosis. Water diffusion across the proximal tubular epithelium is aided by the water channel *aquaporin 1* (AQP-1). Therefore, the osmolarity of the fluid remains about the same as the glomerular filtrate—300 mOsm/L.

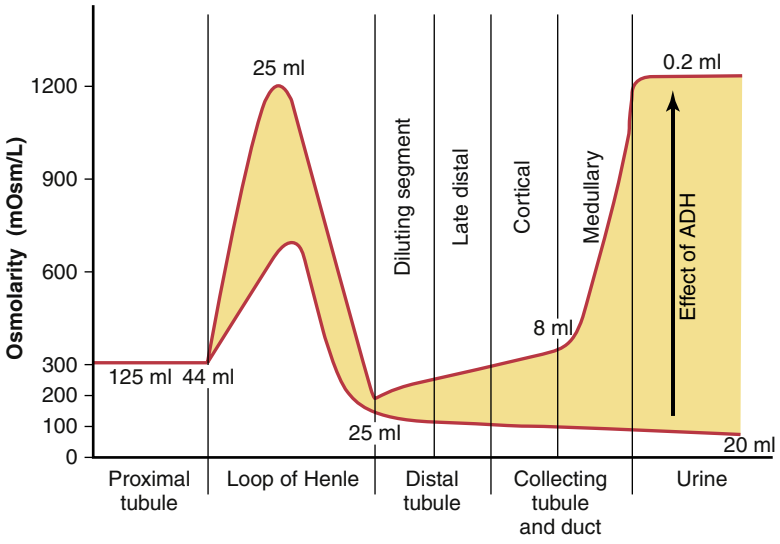

Figure 29-8. Changes in osmolarity of the tubular fluid as it passes through the different tubular segments in the presence of high levels of antidiuretic hormone (*ADH*) and absence of ADH. (Numerical values indicate the approximate volumes in milliliters per minute or in osmolarities in milliosmoles per liter of fluid flowing along the different tubular segments.)

Descending Loop of Henle. As fluid flows down the descending loop of Henle, water is absorbed into the medulla. The descending limb also contains AQP-1 and is highly permeable to water but much less permeable to sodium chloride and urea. Therefore, the osmolarity of the fluid flowing through the descending loop gradually increases until it is nearly equal to that of the surrounding interstitial fluid, which is about 1200 mOsm/L when the blood concentration of ADH is high.

When dilute urine is being formed, as a result of low ADH concentrations, the medullary interstitial osmolarity is less than 1200 mOsm/L; consequently, the descending loop tubular fluid osmolarity also becomes less concentrated. This decrease in concentration is due partly to the fact that less urea is absorbed into the medullary interstitium from the collecting ducts when ADH levels are low, and the kidney is forming a large volume of dilute urine.

Thin Ascending Loop of Henle. The thin ascending limb is essentially impermeable to water but reabsorbs some sodium chloride. Because of the high concentration of sodium chloride in the tubular fluid as a result of water removal from the descending loop of Henle, there is some passive diffusion of sodium chloride from the thin ascending limb into the medullary interstitium. Thus, the tubular fluid becomes more dilute as the sodium chloride diffuses out of the tubule and water remains in the tubule.

Some of the urea absorbed into the medullary interstitium from the collecting ducts also diffuses into the ascending limb, thereby returning the urea to the tubular system and helping prevent its washout from the renal medulla. This *urea recycling* is an additional mechanism that contributes to the hyperosmotic renal medulla.

Thick Ascending Loop of Henle. The thick part of the ascending loop of Henle is also virtually impermeable to water, but large amounts of sodium, chloride, potassium, and other ions are actively transported from the tubule into the medullary interstitium. Therefore, fluid in the thick ascending limb of the loop of Henle becomes very dilute, falling to a concentration of about 140 mOsm/L.

Early Distal Tubule. The early distal tubule has properties similar to those of the thick ascending loop of Henle, so further dilution of the tubular fluid to about 100 mOsm/L occurs as solutes are reabsorbed while water remains in the tubule.

Late Distal Tubule and Cortical Collecting Tubules. In the late distal tubule and cortical collecting tubules, the osmolarity of the fluid depends on the level of ADH. With high ADH levels, these tubules are highly permeable to water, and significant amounts of water are reabsorbed. Urea, however, is not very permeant in this part of the nephron, resulting in increased urea concentration as water is reabsorbed. This process allows most of the urea delivered to the distal tubule and collecting tubule to pass into the inner medullary collecting ducts, from which it is eventually reabsorbed or excreted in the urine. In the absence of ADH, little water is reabsorbed in the late distal tubule and cortical collecting tubule; therefore, osmolarity decreases even further because of continued active reabsorption of ions from these segments.

Inner Medullary Collecting Ducts. The concentration of fluid in the inner medullary collecting ducts also depends on the following: (1) ADH; and (2) the surrounding medullary interstitium osmolarity established by the countercurrent mechanism. In the presence of large amounts of ADH, these ducts are highly permeable to water, and water diffuses from the tubule into the interstitial fluid until osmotic equilibrium is reached, with the tubular fluid having about the same concentration as the renal medullary interstitium (1200–1400 mOsm/L). Thus, a small volume of concentrated urine is produced when ADH levels are high. Because water reabsorption increases urea concentration in the tubular fluid, and because the inner medullary collecting ducts have specific urea transporters that greatly facilitate diffusion, much of the highly concentrated urea in the ducts diffuses out of the tubular lumen into the medullary interstitium. This absorption of the urea into the renal medulla contributes to the high osmolarity of the medullary interstitium and high concentrating ability of the kidney.

Several important points to consider may not be obvious from this discussion. First, although sodium chloride is one of the principal solutes that contribute to the hyperosmolarity of the medullary interstitium, *the kidney can, when needed, excrete a highly concentrated urine that contains little sodium chloride.* The hyperosmolarity of the urine in these circumstances is due to high concentrations of other solutes, especially of waste products such as urea. One condition in which this occurs is dehydration accompanied by low sodium intake. As discussed in Chapter 30, a low sodium intake stimulates formation of the hormones angiotensin II and aldosterone, which together cause avid sodium reabsorption from the tubules while leaving the urea and other solutes to maintain the highly concentrated urine.

Second, *large quantities of dilute urine can be excreted without increasing sodium excretion*. This feat is accomplished by decreasing ADH secretion, which reduces water reabsorption in the more distal tubular segments without significantly altering sodium reabsorption.

Finally, there is an *obligatory urine volume* dictated by the maximum concentrating ability of the kidney and amount of solute that must be excreted. Therefore, if large amounts of solute must be excreted, they must be accompanied by the minimal amount of water necessary to excrete them. For example, if 600 milliosmoles of solute must be excreted each day, this requires *at least* 0.5 liter of urine if the maximal urine concentrating ability is 1200 mOsm/L.

Quantifying Renal Urine Concentration and Dilution: Free Water and Osmolar Clearances

The process of concentrating or diluting the urine requires the kidneys to excrete water and solutes somewhat independently. When the urine is dilute, water is excreted in excess of solutes. Conversely, when the urine is concentrated, solutes are excreted in excess of water.

The total clearance of solutes from the blood can be expressed as the *osmolar clearance* (C_{osm}). This is the volume of plasma cleared of solutes each minute, in the same way that clearance of a single substance is calculated:

$$C_{osm} = \frac{U_{osm} \times \dot{V}}{P_{osm}}$$

where U_{osm} is the urine osmolarity, $\dot{V}$ is the urine flow rate, and P_{osm} is plasma osmolarity. For example, if the plasma osmolarity is 300 mOsm/L, urine osmolarity is 600 mOsm/L, and urine flow rate is 1 ml/min (0.001 L/min), the rate of osmolar excretion is 0.6 mOsm/min (600 mOsm/L × 0.001 L/min), and osmolar clearance is 0.6 mOsm/min divided by 300 mOsm/L, or 0.002 L/min (2.0 ml/min). This means that 2 milliliters of plasma are being cleared of solute each minute.

Free Water Clearance—Relative Rates at Which Solutes and Water Are Excreted

Free water clearance (C_{H2O}) is calculated as the difference between water excretion (urine flow rate) and osmolar clearance:

$$C_{H_2O} = V - C_{osm} = V - \frac{(U_{osm} \times \dot{V})}{P_{osm}}$$

Thus, the rate of free water clearance represents the rate at which solute-free water is excreted by the kidneys. When free water clearance is positive, excess water is being excreted by the kidneys; when free water clearance is negative, excess solutes are being removed from the blood by the kidneys, and water is being conserved.

Using the example discussed earlier, if urine flow rate is 1 ml/min and osmolar clearance is 2 ml/min, free water clearance would be –1 ml/min. This means that instead of water being cleared from the kidneys in excess of solutes, the kidneys are actually returning water to the systemic circulation, as occurs during water deficits. *Thus, whenever urine osmolarity is greater than plasma osmolarity, free water clearance is negative, indicating water conservation.*

When the kidneys are forming a dilute urine (i.e., urine osmolarity < plasma osmolarity), free water clearance will be a positive value, denoting that water is being removed from the plasma by the kidneys in excess of solutes. Thus, water free of solutes, called *free water*, is being lost from the body, and the plasma is being concentrated when free water clearance is positive.

Disorders of Urinary Concentrating Ability

Impairment in the ability of the kidneys to concentrate or dilute the urine appropriately can occur with one or more of the following abnormalities:

1. *Inappropriate secretion of ADH.* Either too much or too little ADH secretion results in abnormal water excretion by the kidneys.
2. *Impairment of the countercurrent mechanism.* A hyperosmotic medullary interstitium is required for maximal urine-concentrating ability. No matter how much ADH is present, maximal urine concentration is limited by the degree of hyperosmolarity of the medullary interstitium.
3. *Inability of the distal tubules, collecting tubules, and collecting ducts to respond to ADH.*

Failure to Produce ADH: Central Diabetes Insipidus. An inability to produce or release ADH from the posterior pituitary can be caused by head injuries or infections, or it can be congenital. Because the distal tubular segments cannot reabsorb water in the absence of ADH, this condition, called *central diabetes insipidus*, results in the formation of a large volume of dilute urine, with urine volumes that can exceed 15 L/day. The thirst mechanisms, discussed later in this chapter, are activated when excessive water is lost from the body; therefore, as long as the person drinks enough water, large decreases in body fluid water do not occur. The primary abnormality observed clinically in people with this condition is the large volume of dilute urine. However, if water intake is restricted, as can occur in a hospital setting when fluid intake is restricted or the patient is unconscious (e.g., because of a head injury), severe dehydration can rapidly occur.

The treatment for central diabetes insipidus is administration of a synthetic analogue of ADH, *desmopressin*, which acts selectively on V_2 receptors to increase water permeability in the late distal and collecting tubules. Desmopressin can be given by injection, as a nasal spray, or orally, and it rapidly restores urine output toward normal.

Inability of Kidneys to Respond to ADH: Nephrogenic Diabetes Insipidus. In some circumstances, normal or elevated levels of ADH are present but the renal tubular segments cannot respond appropriately. This condition is referred to as *nephrogenic diabetes insipidus* because the abnormality resides in the kidneys. This abnormality can be due to failure of the countercurrent mechanism to form a hyperosmotic renal medullary interstitium or failure of the distal and collecting tubules and collecting ducts to respond to ADH. In either case, large volumes of dilute urine are formed, which causes dehydration unless fluid intake is increased by the same amount as urine volume is increased.

Many types of renal diseases can impair the concentrating mechanism, especially those that damage the renal medulla (see Chapter 32 for further discussion). Also, impairment of the function of the loop of Henle, as occurs with diuretics that inhibit electrolyte reabsorption by this segment, such as furosemide, can compromise urine-concentrating ability. Furthermore, certain drugs such as lithium (used to treat manic-depressive disorders) and tetracyclines (used as antibiotics) can impair the ability of the distal nephron segments to respond to ADH.

Nephrogenic diabetes insipidus can be distinguished from central diabetes insipidus by administration of desmopressin, the synthetic analogue of ADH. Lack of a prompt decrease in urine volume and an increase in urine osmolarity within 2 hours after injection of desmopressin is strongly suggestive of nephrogenic diabetes insipidus. The appropriate treatment for nephrogenic diabetes insipidus is to correct, if possible, the underlying renal disorder. The hypernatremia can also be attenuated by a low-sodium diet and administration of a diuretic that enhances renal sodium excretion, such as a thiazide diuretic.

CONTROL OF EXTRACELLULAR FLUID OSMOLARITY AND SODIUM CONCENTRATION

Regulation of extracellular fluid osmolarity and sodium concentration are closely linked because sodium is the most abundant ion in the extracellular compartment. Plasma sodium concentration is normally regulated within close limits of 140 to 145 mEq/L, with an average concentration of about 142 mEq/L. Osmolarity averages about 300 mOsm/L (≈282 mOsm/L when corrected for interionic attraction) and seldom changes more than ±2% to 3%. As discussed in Chapter 25, these variables must be precisely controlled because they determine the distribution of fluid between the intracellular and extracellular compartments.

Estimating Plasma Osmolarity From Plasma Sodium Concentration

In most clinical laboratories, plasma osmolarity is not routinely measured. However, because sodium and its associated anions account for about 94% of the solute in the extracellular compartment, plasma osmolarity (P_{osm}) can be roughly estimated from the plasma sodium concentration (P_{Na^+}) as follows:

$$P_{osm} = 2.1 \times P_{Na^+} (mmol/L)$$

For example, with a plasma sodium concentration of 142 mEq/L, the plasma osmolarity would be estimated from this formula to be about 298 mOsm/L. To be more exact, especially in conditions associated with renal disease, the contribution of the plasma concentrations (in units of mmol/L) of two other solutes, glucose and urea, are usually included:

$$P_{osm} = 2 \times [P_{Na^+}, mmol/L] + [P_{glucose}, mmol/L] + [P_{urea}, mmol/L]$$

Such estimates of plasma osmolarity are usually accurate within a few percentage points of those measured directly.

Normally, sodium ions and associated anions (primarily bicarbonate and chloride) represent about 94% of the extracellular osmoles, with glucose and urea contributing about 3% to 5% of the total osmoles. However, because urea easily permeates most cell membranes, it exerts little *effective* osmotic pressure under steady-state conditions. Therefore, the sodium ions in the extracellular fluid and associated anions are the principal determinants of fluid movement across the cell membrane. Consequently, we can discuss the control of osmolarity and control of sodium ion concentration at the same time.

Although multiple mechanisms control the *amount* of sodium and water excretion by the kidneys, two primary systems are especially involved in regulating the *concentration* of sodium and osmolarity of extracellular fluid: (1) the osmoreceptor-ADH system; and (2) the thirst mechanism.

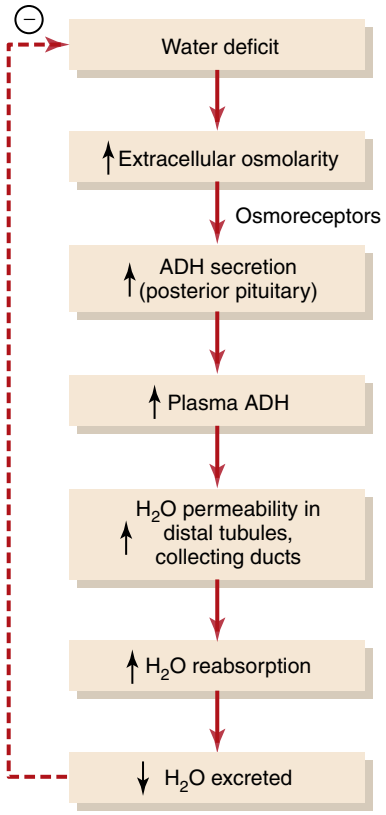

Figure 29-9. Osmoreceptor-antidiuretic hormone (*ADH*) feedback mechanism for regulating extracellular fluid osmolarity in response to a water deficit.

OSMORECEPTOR-ADH FEEDBACK SYSTEM

Figure 29-9 shows the basic components of the osmoreceptor-ADH feedback system for control of extracellular fluid sodium concentration and osmolarity. When osmolarity increases above normal because of water deficit, for example, this feedback system operates as follows:

1. An increase in extracellular fluid osmolarity (which in practical terms means an increase in plasma sodium concentration) causes the special nerve cells called *osmoreceptor cells*, located in the *anterior hypothalamus* near the supraoptic nuclei, to shrink.
2. Shrinkage of the osmoreceptor cells causes them to fire, sending nerve signals to additional nerve cells in the supraoptic nuclei, which then relay these signals down the stalk of the pituitary gland to the posterior pituitary.
3. These action potentials conducted to the posterior pituitary stimulate release of ADH, which is stored in secretory granules (or vesicles) in the nerve endings.
4. ADH enters the blood stream and is transported to the kidneys, where it increases the water permeability of the late distal tubules, cortical collecting tubules, and medullary collecting ducts.

5. The increased water permeability in the distal nephron segments causes increased water reabsorption and excretion of a small volume of concentrated urine.

Thus, water is conserved while sodium and other solutes continue to be excreted in the urine. This causes dilution of the solutes in the extracellular fluid, thereby correcting the initial excessively concentrated extracellular fluid.

The opposite sequence of events occurs when the extracellular fluid becomes too dilute (hypo-osmotic). For example, with excess water ingestion and a decrease in extracellular fluid osmolarity, less ADH is formed, the renal tubules decrease their permeability for water, less water is reabsorbed, and a large volume of dilute urine is formed. This in turn concentrates the body fluids and returns plasma osmolarity toward normal.

ADH SYNTHESIS IN SUPRAOPTIC AND PARAVENTRICULAR NUCLEI OF HYPOTHALAMUS AND ADH RELEASE FROM POSTERIOR PITUITARY

Figure 29-10 shows the neuroanatomy of the hypothalamus and the pituitary gland, where ADH is synthesized and released. The hypothalamus contains two types of *magnocellular* (large) *neurons that synthesize ADH in the supraoptic and paraventricular nuclei of the hypothalamus*, about five-sixths in the supraoptic nuclei and about one-sixth in the paraventricular nuclei. Both of these nuclei have axonal extensions to the posterior pituitary. Once ADH is synthesized, it is transported down the axons of the neurons to their tips, terminating in the posterior pituitary gland. When the supraoptic and paraventricular nuclei are stimulated by increased osmolarity or other factors, nerve impulses pass down these nerve endings, changing their membrane permeability and increasing calcium entry. ADH stored in the secretory granules (also called *vesicles*) of the nerve endings is released in response to increased calcium entry. The released ADH is then carried away in the capillary blood of the posterior pituitary into the systemic circulation. The secretion of ADH in response to an osmotic stimulus is rapid, so plasma ADH levels can increase several-fold within minutes, thereby providing a rapid means for altering renal excretion of water.

A second neuronal area important in controlling osmolarity and ADH secretion is located along the *anteroventral region of the third ventricle,* called the *AV3V region.* At the upper part of this region is a structure called the *subfornical organ* and, at the inferior part, is another structure called the *organum vasculosum* of the *lamina terminalis.* Between these two organs is the *median preoptic nucleus*, which has multiple nerve connections with the two organs, as well as with the supraoptic nuclei and blood pressure control centers in the medulla of the brain. Lesions of the AV3V region cause multiple deficits in the control of ADH secretion, thirst, sodium appetite, and blood pressure. Electrical stimulation of this region or stimulation by angiotensin II can increase ADH secretion, thirst, and sodium appetite.

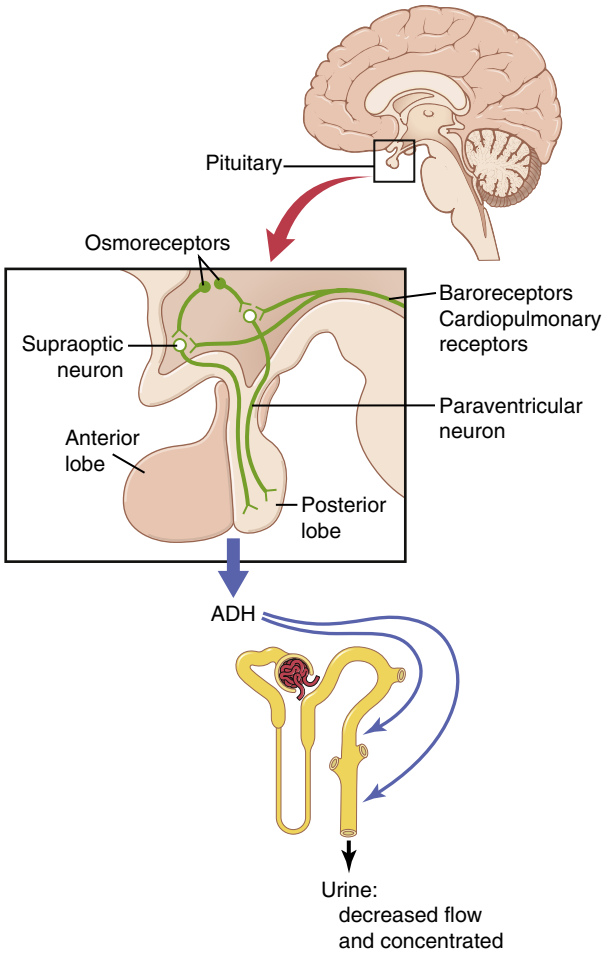

Figure 29-10. Neuroanatomy of the hypothalamus, where antidiuretic hormone (*ADH*) is synthesized, and the posterior pituitary gland, where ADH is released.

In the vicinity of the AV3V region and supraoptic nuclei are neuronal cells that are excited by small increases in extracellular fluid osmolarity—hence, the term *osmoreceptors* has been used to describe these neurons. These cells send nerve signals to the supraoptic nuclei to control their firing and secretion of ADH. It is also likely that they induce thirst in response to increased extracellular fluid osmolarity.

Both the subfornical organ and organum vasculosum of the lamina terminalis have vascular supplies that lack the typical blood–brain barrier that impedes the diffusion of most ions from the blood into brain tissue. This characteristic makes it possible for ions and other solutes to cross between the blood and local interstitial fluid in this region. As a result, the osmoreceptors rapidly respond to changes in osmolarity of the extracellular fluid, exerting powerful control over the secretion of ADH and over thirst, as discussed later.

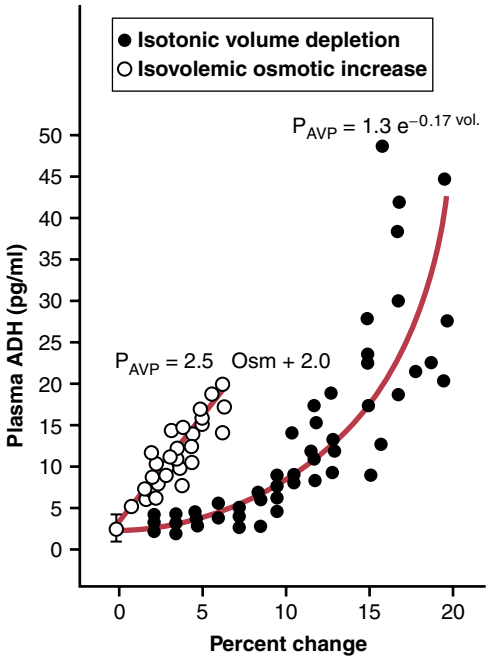

Figure 29-11. Effect of increased plasma osmolarity or decreased blood volume on the level of plasma (*P*) antidiuretic hormone (*ADH*), also called *arginine vasopressin* (*AVP*). *(Modified from Dunn FL, Brennan TJ, Nelson AE, et al: The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 52[12]:3212, 1973.)*

STIMULATION OF ADH RELEASE BY DECREASED ARTERIAL PRESSURE AND/OR DECREASED BLOOD VOLUME

ADH release is also controlled by cardiovascular reflexes that respond to decreases in blood pressure and/or blood volume, including the following: (1) the *arterial baroreceptor reflexes*; and (2) *the cardiopulmonary reflexes*, both of which are discussed in Chapter 18. These reflex pathways originate in high-pressure regions of the circulation, such as the aortic arch and carotid sinus, and in low-pressure regions, especially in the cardiac atria. Afferent stimuli are carried by the vagus and glossopharyngeal nerves, with synapses in the nuclei of the tractus solitarius. Projections from these nuclei relay signals to the hypothalamic nuclei that control ADH synthesis and secretion.

Thus, in addition to increased osmolarity, two other stimuli increase ADH secretion: (1) decreased arterial pressure; and (2) decreased blood volume. Whenever blood pressure and blood volume are reduced, such as during hemorrhage, increased ADH secretion causes increased fluid reabsorption by the kidneys, helping restore blood pressure and blood volume toward normal.

Quantitative Importance of Osmolarity and Cardiovascular Reflexes in Stimulating ADH Secretion

As shown in **Figure 29-11**, a decrease in effective blood volume or an increase in extracellular fluid osmolarity stimulates ADH secretion. However, ADH is considerably more sensitive to small changes in osmolarity than to similar percentage changes in blood volume. For example, a change in plasma osmolarity of only 1% is sufficient to increase ADH levels. By contrast, after blood loss, plasma ADH levels do not change appreciably until blood volume is reduced by about 10%. With further decreases in blood volume, ADH levels rapidly increase. Thus, with severe decreases in blood volume, the cardiovascular reflexes play a major role in stimulating ADH secretion. The usual daily regulation of ADH secretion during simple dehydration is effected mainly by changes in plasma osmolarity. Decreases in blood volume and blood pressure, however, greatly enhance the ADH response to increased osmolarity.

Table 29-2 Control of Antidiuretic Hormone Secretion

Increase ADH	Decrease ADH
↑ Plasma osmolarity	↓ Plasma osmolarity
↓ Blood volume	↑ Blood volume
↓ Blood pressure	↑ Blood pressure
Nausea	
Hypoxia	
Drugs	Drugs
Morphine	Alcohol
Nicotine	Clonidine (antihypertensive)
Cyclophosphamide	Haloperidol (dopamine blocker)

OTHER STIMULI FOR ADH SECRETION

ADH secretion can also be increased or decreased by other stimuli to the central nervous system, as well as by various drugs and hormones, as shown in **Table 29-2**. For example, *nausea* is a potent stimulus for ADH release, which may increase to as much as 100 times normal after vomiting. Also, drugs such as *nicotine* and *morphine* stimulate ADH release, whereas some drugs, such as *alcohol*, inhibit ADH release. The marked diuresis that occurs after ingestion of alcohol is due in part to the inhibition of ADH release.

IMPORTANCE OF THIRST IN CONTROLLING EXTRACELLULAR FLUID OSMOLARITY AND SODIUM CONCENTRATION

The kidneys minimize fluid loss during water deficits through the osmoreceptor-ADH feedback system. Adequate fluid intake, however, is necessary to counterbalance whatever fluid loss does occur through sweating and breathing and through the gastrointestinal tract. Fluid intake is regulated by the thirst mechanism, which, together with the osmoreceptor-ADH mechanism, maintains precise control of extracellular fluid osmolarity and sodium concentration.

Table 29-3 Control of Thirst

Increase Thirst	Decrease Thirst
↑ Plasma osmolarity	↓ Plasma osmolarity
↓ Blood volume	↑ Blood volume
↓ Blood pressure	↑ Blood pressure
↑ Angiotensin II	↓ Angiotensin II
Dry mouth	Gastric distention

Many of the same factors that stimulate ADH secretion also increase thirst, which is defined as the conscious desire for water.

CENTRAL NERVOUS SYSTEM CENTERS FOR THIRST

Referring again to **Figure 29-10**, the same area along the anteroventral wall of the third ventricle that promotes ADH release also stimulates thirst. Located anterolaterally in the preoptic nucleus is another small area that when stimulated electrically, causes immediate drinking that continues as long as the stimulation lasts. All these areas together are called the *thirst center*.

The neurons of the thirst center respond to injections of hypertonic salt solutions by stimulating drinking behavior. These cells almost certainly function as osmoreceptors to activate the thirst mechanism in the same way that the osmoreceptors stimulate ADH release.

Increased osmolarity of the cerebrospinal fluid in the third ventricle has essentially the same effect to promote drinking. It is likely that the *organum vasculosum of the lamina terminalis*, which lies immediately beneath the ventricular surface at the inferior end of the AV3V region, is intimately involved in mediating this response.

STIMULI FOR THIRST

Table 29-3 summarizes some of the known stimuli for thirst.

1. *One of the most important is increased extracellular fluid osmolarity, which causes intracellular dehydration in the thirst centers,* thereby stimulating the sensation of thirst.

The value of this response is obvious: it helps dilute extracellular fluids and returns osmolarity toward normal.

2. *Decreases in extracellular fluid volume and arterial pressure also stimulate thirst* by a pathway that is independent of the one stimulated by increased plasma osmolarity.

Thus, blood volume loss by hemorrhage stimulates thirst, even though there might be no change in plasma osmolarity. This stimulation probably occurs because of neural input from cardiopulmonary and systemic arterial baroreceptors in the circulation.

3. *A third important stimulus for thirst is angiotensin II.*

Studies in animals have shown that angiotensin II acts on the subfornical organ and on the organum vasculosum of the lamina terminalis. These regions are outside the blood–brain barrier, and peptides such as angiotensin II diffuse into the tissues. Because angiotensin II is also stimulated by factors associated with hypovolemia and low blood pressure, its effect on thirst helps restore blood volume and blood pressure toward normal along with the other actions of angiotensin II on the kidneys to decrease fluid excretion.

4. *Dryness of the mouth and mucous membranes of the esophagus can elicit the sensation of thirst.*

As a result, a thirsty person may receive relief from thirst almost immediately after drinking water, even though the water has not been absorbed from the gastrointestinal tract and has not yet had an effect on extracellular fluid osmolarity.

5. *Gastrointestinal and pharyngeal stimuli influence thirst.*

In animals that have an esophageal opening to the exterior so that water is never absorbed into the blood, partial relief of thirst occurs after drinking, although the relief is only temporary. Also, gastrointestinal distention may partially alleviate thirst; For example, simple inflation of a balloon in the stomach can relieve thirst. However, relief of thirst sensations through gastrointestinal or pharyngeal mechanisms is short-lived; the desire to drink is completely satisfied only when plasma osmolarity and/or blood volume returns to normal.

The ability of animals and humans to "meter" fluid intake is important because it prevents overhydration. After a person drinks water, 30 to 60 minutes may be required for the water to be reabsorbed and distributed throughout the body. If the thirst sensation were not temporarily relieved after drinking water, the person would continue to drink more and more, eventually leading to overhydration and excess dilution of the body fluids. Experimental studies have repeatedly shown that animals drink almost exactly the amount necessary to return plasma osmolarity and volume to normal.

THRESHOLD FOR OSMOLAR STIMULUS OF DRINKING

The kidneys must continually excrete an obligatory amount of water, even in a dehydrated person, to rid the body of excess solutes that are ingested or produced by metabolism. Water is also lost by evaporation from the lungs and the gastrointestinal tract and by evaporation and sweating from the skin. Therefore, there is always a tendency for dehydration, with resultant increased extracellular fluid sodium concentration and osmolarity.

When the sodium concentration increases only about 2 mEq/L above normal, the thirst mechanism is activated, causing a desire to drink water. This is called the *threshold for drinking*. Thus, even small increases in plasma osmolarity are normally followed by water intake, which restores extracellular fluid osmolarity and volume toward

normal. In this way, the extracellular fluid osmolarity and sodium concentration are precisely controlled.

Disorders of Thirst and Water Intake. As discussed previously, increased thirst occurs in various medical disorders associated with increased urine volume and reductions in extracellular fluid volume, such as poorly controlled diabetes mellitus or diabetes insipidus. In these cases, increased water intake serves as a compensatory response for increased plasma osmolarity and/or extracellular fluid volume depletion. *Polydipsia*, or excessive thirst, occasionally occurs in the absence of known physiological stimuli for thirst. *Psychogenic polydipsia*, for example, may be caused by mental illnesses such as schizophrenia or obsessive-compulsive disorders and can lead to significant *hyponatremia*. In contrast, *adipsia*, the absence of thirst even in the presence of hypernatremia or volume depletion, is rare but usually results from lesions to the hypothalamic thirst centers caused by trauma, infection, or surgery. Partial deficiency of the thirst mechanism, causing inadequate water intake (*hypodipsia*), or an inability to access fluid may occur in patients who have suffered stroke, in older patients with dementia, or in critically ill patients. In the absence of adequate water intake, dehydration and hypernatremia occur, despite large increases in ADH levels.

INTEGRATED RESPONSES OF OSMORECEPTOR-ADH AND THIRST MECHANISMS

In a healthy person, the osmoreceptor-ADH and thirst mechanisms work in parallel to regulate extracellular fluid osmolarity and sodium concentration precisely, despite the constant challenges of dehydration. Even with additional challenges, such as high salt intake, these feedback systems are usually able to keep plasma osmolarity reasonably constant. **Figure 29-12** shows that an increase in sodium intake to as high as six times normal has only a small effect on plasma sodium concentration as long as the ADH and thirst mechanisms are both functioning normally.

When the ADH or thirst mechanism fails, ordinarily the other can still control extracellular osmolarity and sodium concentration with reasonable effectiveness as long as there is enough fluid intake to balance the daily obligatory urine volume and water losses caused by respiration, sweating, or gastrointestinal losses. However, if both the ADH and thirst mechanisms fail simultaneously, plasma sodium concentration and osmolarity are poorly controlled. Thus, when sodium intake is increased after blocking the total ADH-thirst system, relatively large changes in plasma sodium concentration occur. In the absence of the ADH-thirst mechanisms, no other feedback mechanism is capable of adequately regulating plasma sodium concentration and osmolarity.

Role of Angiotensin II and Aldosterone in Controlling Extracellular Fluid Osmolarity and Sodium Concentration

As discussed in Chapter 28, both angiotensin II and aldosterone play an important role in regulating sodium reabsorption by the renal tubules. When sodium intake is low, increased levels of these hormones stimulate sodium reabsorption by the kidneys and prevent large sodium losses, even though sodium intake may be reduced to as low as 10% of normal. Conversely, with high sodium intake, decreased formation of these hormones permits the kidneys to excrete large amounts of sodium.

Because of the importance of angiotensin II and aldosterone in regulating sodium excretion by the kidneys, one might mistakenly infer that they also play a major role in regulating extracellular fluid sodium concentration. Although these hormones increase the *amount* of sodium in the extracellular fluid, they also increase the extracellular fluid volume by increasing reabsorption of water along with the sodium. Therefore, *angiotensin II and aldosterone have little effect on sodium concentration, except under extreme conditions.*

This relative unimportance of aldosterone in regulating extracellular fluid sodium concentration is shown by the experiment depicted in **Figure 29-13**. This figure shows the effect on plasma sodium concentration of changing sodium intake more than sixfold under two conditions: (1) under normal conditions; and (2) after the aldosterone feedback system was blocked by removing the adrenal glands and infusing the animals with aldosterone at a constant rate so that plasma levels could not increase or decrease. Note that when sodium intake was increased sixfold, plasma concentration changed only about 1% to 2% in either case. This finding indicates that even without a functional aldosterone feedback system, plasma sodium concentration can be well regulated. The same type of experiment has been conducted after blocking angiotensin II formation, with the same result.

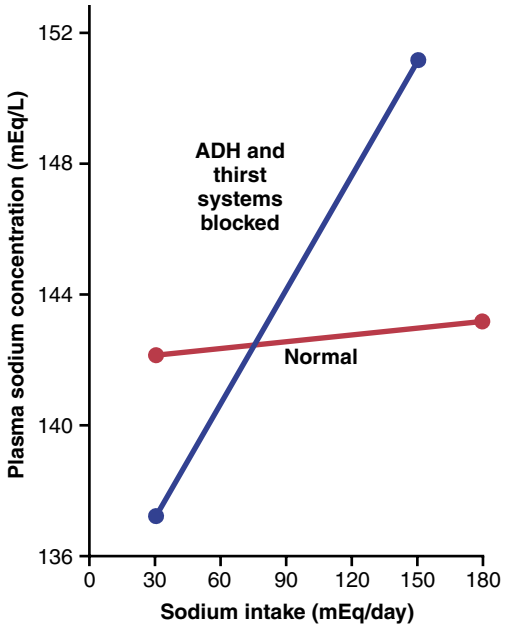

Figure 29-12. Effect of large changes in sodium intake on extracellular fluid sodium concentration in dogs under normal conditions (*red line*) and after the antidiuretic hormone (*ADH*) and thirst feedback systems were blocked (*blue line*). Note that control of extracellular fluid sodium concentration was poor in the absence of these feedback systems. *(Courtesy Dr. David B. Young.)*

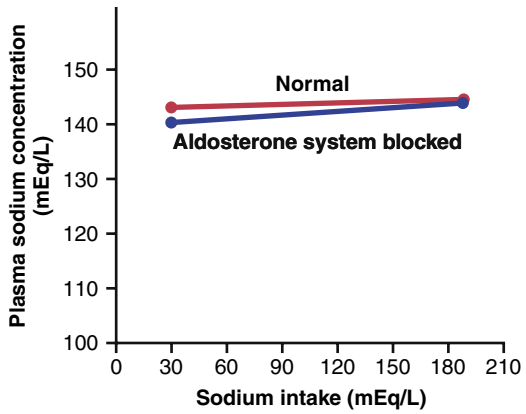

Figure 29-13. Effect of large changes in sodium intake on extracellular fluid sodium concentration in dogs under normal conditions (*red line*) and after the aldosterone feedback system was blocked (*blue line*). Note that the sodium concentration was maintained relatively constant over this wide range of sodium intakes, with or without aldosterone feedback control. *(Courtesy Dr. David B. Young.)*

There are two primary reasons why changes in angiotensin II and aldosterone do not have a major effect on plasma sodium concentration. First, as discussed earlier, angiotensin II and aldosterone increase both sodium and water reabsorption by the renal tubules, leading to increases in extracellular fluid volume and sodium *quantity* but little change in sodium *concentration*. Second, as long as the ADH-thirst mechanism is functional, any tendency toward increased plasma sodium concentration is compensated for by increased water intake or increased plasma ADH secretion, which tends to dilute the extracellular fluid back toward normal. The ADH-thirst system far overshadows the angiotensin II and aldosterone systems for regulating sodium concentration under normal conditions. Even in patients with *primary aldosteronism*, who have extremely high levels of aldosterone, the plasma sodium concentration usually increases only about 3 to 5 mEq/L above normal.

Under extreme conditions caused by complete loss of aldosterone secretion as a result of adrenalectomy or in patients with Addison disease (severely impaired secretion or total lack of aldosterone), there is tremendous loss of sodium by the kidneys, which can lead to a marked reduction in plasma sodium concentration. One reason for this is that large losses of sodium eventually cause severe volume depletion and decreased blood pressure, which can activate the thirst mechanism through the cardiovascular reflexes. This activation leads to a further dilution of the plasma sodium concentration, even though the increased water intake helps minimize the decrease in body fluid volumes under these conditions.

Thus, there are extreme situations in which the plasma sodium concentration may change significantly, even with a functional ADH-thirst mechanism. Even so, the ADH-thirst mechanism is the most powerful feedback system in the body for controlling extracellular fluid osmolarity and sodium concentration.

Salt-Appetite Mechanism for Controlling Extracellular Fluid Sodium Concentration and Volume

The maintenance of a normal extracellular fluid volume and sodium concentration requires a balance between sodium excretion and sodium intake. Currently, sodium intake is almost always greater than necessary for homeostasis. In fact, the average sodium intake for persons in industrialized cultures who eat processed foods usually ranges between 100 and 200 mEq/day, even though humans can survive and function normally while ingesting only 10 to 20 mEq/day. Thus, most people eat far more sodium than is necessary for homeostasis, and evidence indicates that our usual high sodium intake may contribute to cardiovascular disorders such as hypertension.

Salt appetite is due in part to the fact that animals and humans like salt and eat it, regardless of whether they are salt-deficient. Salt appetite also has a regulatory component in which there is a behavioral drive to obtain salt when a sodium deficiency exists in the body. This behavioral drive is particularly important in herbivores, which naturally eat a low-sodium diet, but salt craving may also be important in humans, especially in those who have an extreme deficiency of sodium, such as occurs in Addison disease. In this case, there is a deficiency of aldosterone secretion, which causes excessive loss of sodium in the urine and leads to decreased extracellular fluid volume and decreased sodium concentration; both of these changes elicit the desire for salt.

In general, the primary stimuli that increase salt appetite are those associated with sodium deficits and decreased blood volume or decreased blood pressure associated with circulatory insufficiency.

The neuronal mechanism for salt appetite is analogous to that of the thirst mechanism. Some of the same neuronal centers in the AV3V region of the brain seem to be involved because lesions in this region frequently affect both thirst and salt appetite simultaneously in animals. Also, circulatory reflexes elicited by low blood pressure or decreased blood volume affect both thirst and salt appetite at the same time.

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