CLINICAL CONNECTIONS

Water Intoxication

On January 12, 2007, 28-year-old Jennifer Strange died of water intoxication after participating in a radio contest, called "Hold Your Wee for a Wii." Contestants were instructed to drink a bottle of water every 15 minutes, with the volume of water in the bottles increasing over time. Whoever lasted the longest without urinating would win the Wii game console. Jennifer won second place, tickets to a Justin Timberlake concert, by drinking nearly two gallons of water in three hours. She complained of a headache after being interviewed, but then went home—where she subsequently passed out and died of water intoxication. The winner of the contest, Lucy Davidson, collapsed 15 minutes after leaving the station, and although feeling ill afterward, recovered fully.

It's difficult for many people to believe that water can be toxic. In fact, consumption of extreme volumes of water alters the osmolarity of the plasma, causing a shift of water from plasma to interstitial fluid and then into cells. Thus body cells swell, including brain cells that are held in a fixed space by the cranium. A minor amount of swelling of the brain cells can cause headaches and nausea, but severe swelling can interfere with brain function, resulting in death.

In October 2009, a jury found the radio station negligent in the death of Jennifer Strange and awarded her husband, Billy Strange, $16.5 million in damages.

Critical Thinking Questions

1. What effect does extreme water intake have on blood osmolarity?
2. What is the biggest health danger posed from the swelling of body cells?
3. What is the cause of death due to extreme water intake?

In the renal tubules, water reabsorption is passive and is coupled to the active reabsorption of solutes. Solute transport creates an osmotic gradient across the tubule epithelium. The precise mechanism responsible for creating the osmotic gradient varies in the different segments of the renal tubules. In the next sections we see that in the proximal and distal tubules, reabsorption of solute increases the osmolarity of the peritubular fluid (which drives reabsorption of water by osmosis), whereas in the collecting ducts, the *medullary osmotic gradient* drives reabsorption of water.

Water Reabsorption in the Proximal Tubule

Because the primary solute in extracellular fluid is sodium and most of the filtered sodium is reabsorbed in the proximal tubule, sodium is the primary solute responsible for producing the osmotic gradient that drives water reabsorption. Although the exact mechanism varies in different segments of the renal tubules, sodium reabsorption always involves the active transport of sodium across the basolateral membrane from the epithelial cell of the tubule into the peritubular fluid, where it can diffuse into the plasma of peritubular capillaries (**Figure 19.4**). Sodium crosses the apical membrane by a variety of mechanisms, including secondary active transport during which the movement of sodium is coupled to the movement of another molecule (such as glucose).

Water is reabsorbed by osmosis, as illustrated in **Figure 19.5**. Active reabsorption of sodium and other solutes in the proximal tubule creates an osmotic gradient, and therefore water follows the solutes. Thus fluid in the proximal tubule is iso-osmotic with the interstitial fluid of the renal cortex, with both fluids being at 300 mOsm. Because reabsorption of water creates a concentration gradient for permeating solutes to move from tubular fluid to the plasma in peritubular capillaries, the movement of permeating solutes follows water reabsorption.

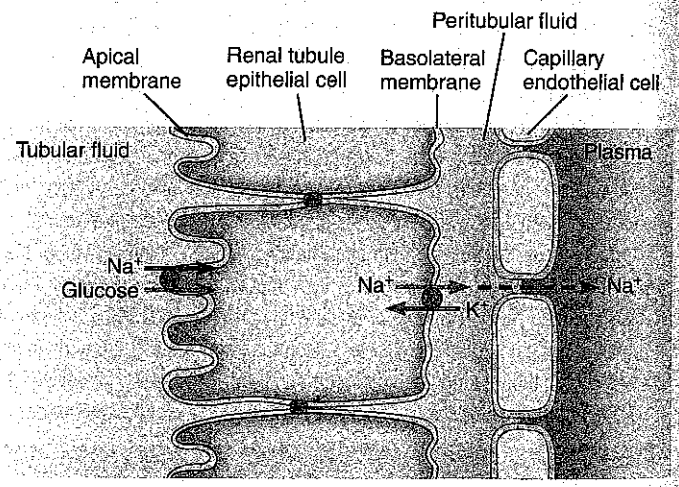
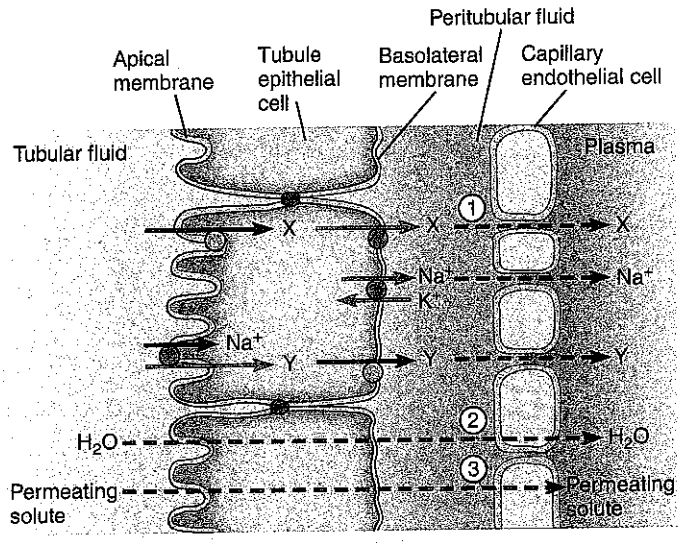


Figure 19.4 Mechanism of sodium reabsorption in the proximal tubule. Sodium is actively transported across the basolateral membrane into the peritubular fluid by the Na^+/K^+ pump. Sodium moves from the tubular fluid into the epithelial cell through sodium channels or via cotransport with other molecules, such as glucose.

Establishment of the Medullary Osmotic Gradient

Within the interstitial fluid of the renal medulla is the **medullary osmotic gradient;** the outer regions of the medulla have a lower osmolarity than the inner regions (**Figure 19.6**). The osmolarity



Steps for water and urea reabsorption:

① Solutes (Na^+, X, Y) are actively reabsorbed, increasing the osmolarity of peritubular fluid and plasma.

② Water is reabsorbed by osmosis.

③ Urea (permeating solute) is reabsorbed passively.

Figure 19.5 Mechanism of water reabsorption. When solutes, such as sodium ions or molecule X, are actively reabsorbed, the osmolarity of the peritubular fluid and plasma increases, such that water moves from the lumen of the renal tubules first into the peritubular fluid and then into plasma by osmosis. Permeating solutes follow water reabsorption.

varies from 300 mOsm at the cortical edge of the medulla to approximately 1200–1400 mOsm at the innermost portion of the medulla near the renal pelvis. This gradient, which is necessary for water reabsorption from the collecting duct, exists because of a mechanism known as the countercurrent multiplier and because of the facilitated diffusion of urea from the lumen of the collecting duct into the medullary interstitial fluid.

Countercurrent Multiplier

The properties of different portions of the loops of Henle of juxtamedullary nephrons are critical to the countercurrent multiplier and establishment of the medullary osmotic gradient. The descending limb is permeable to water, so water diffuses when an osmotic gradient exists. The thick ascending limb, by contrast, is impermeable to water; thus water does not diffuse even if an osmotic gradient exists. In addition, the thick ascending limb has sodium/potassium/chloride active transporters that the descending limb lacks. These transporters pump all three ions into the interstitial fluid, thereby increasing its osmolarity. The term *countercurrent* refers to the fact that fluid flowing through the descending and ascending limbs, which parallel each other, moves in opposite directions (see Figure 19.6).

Figure 19.7 illustrates how the countercurrent multiplier creates the medullary osmotic gradient. ① The figure starts with no osmotic gradient along the tubules or within the medullary interstitial fluid. The fluid that enters the descending limb from the proximal tubule is iso-osmotic with the interstitial fluid, at 300 mOsm. The fluid in the proximal tubule is iso-osmotic because water freely crosses the wall of the tubule and, therefore, is reabsorbed along with solutes. As fluid moves down the descending limb, there is no net movement of water across the tubule wall because there is no osmotic gradient. As the fluid begins to travel up the ascending limb of the loop of Henle, sodium, chloride, and potassium are actively transported from the tubule into the medullary interstitial fluid, ② increasing the osmolarity of the interstitial fluid from 300 mOsm to 400 mOsm and lowering the osmolarity of fluid in the ascending limb to 200 mOsm. When the osmolarity of the peritubular fluid increases, water moves out of the descending limb and into the peritubular fluid until ③ the two are iso-osmotic again at 400 mOsm. This creates a difference in osmolarity between the fluid in the descending limb and the fluid in the ascending limb, with the latter at a lower osmolarity (200 mOsm versus 400 mOsm). ④ As more fluid at 300 mOsm enters the loop of Henle from the proximal tubule, this fluid pushes the fluid ahead of it through the tubule, thereby pushing the higher-osmolarity fluid deeper into the medulla. ⑤ Active transport of sodium, chloride, and potassium in the ascending limb raises the osmolarity of deeper medullary interstitial fluid from 400 mOsm to 500 mOsm, which causes water movement into the medullary interstitial fluid from the descending limb. ⑥ The descending limb is now iso-osmotic with the medullary interstitial fluid. More fluid at 300 mOsm enters the loop of Henle from the proximal tubule, pushing the higher-osmolarity fluid toward the tip of the loop of Henle. ⑦ The process continues until the medullary osmotic gradient is created and the system is in a steady state.

At steady state, the fluid entering the loop of Henle from the proximal tubule is iso-osmotic to extracellular fluid, at 300 mOsm; however, the osmolarity of the tubular fluid within both limbs of the loop of Henle is greater in the deeper portions of the renal medulla. At the tip of the loop of Henle, the osmolarity of the tubular fluid is approximately 1200–1400 mOsm.

Note that at any given level in the medulla, the osmolarity of the fluid in the ascending limb is always lower than the osmolarity of fluid in the descending limb, because the ascending limb actively transports solutes out of the tubular fluid but prevents water from following them. As the tubular fluid leaves the loop of Henle and enters the distal tubule, it is hypo-osmotic to extracellular fluid at approximately 100–200 mOsm.

Role of Urea in the Medullary Osmotic Gradient

The countercurrent multiplier establishes the osmotic gradient, but additional solute is needed to maintain the gradient. That additional solute is **urea**, a waste product generated by the liver during catabolism of proteins, and the primary form by which nitrogen is eliminated from the body. In an average Western diet, urea makes up 40% of the solutes in the glomerular filtrate; consequently, it has profound effects on water movement across the renal tubules. As we will see, only approximately 40% of the filtered urea stays in the tubules, which is critical in preventing massive water loss through the osmotic effect of urea on water. Urea also decreases water loss in other ways, including strengthening the medullary osmotic gradient.

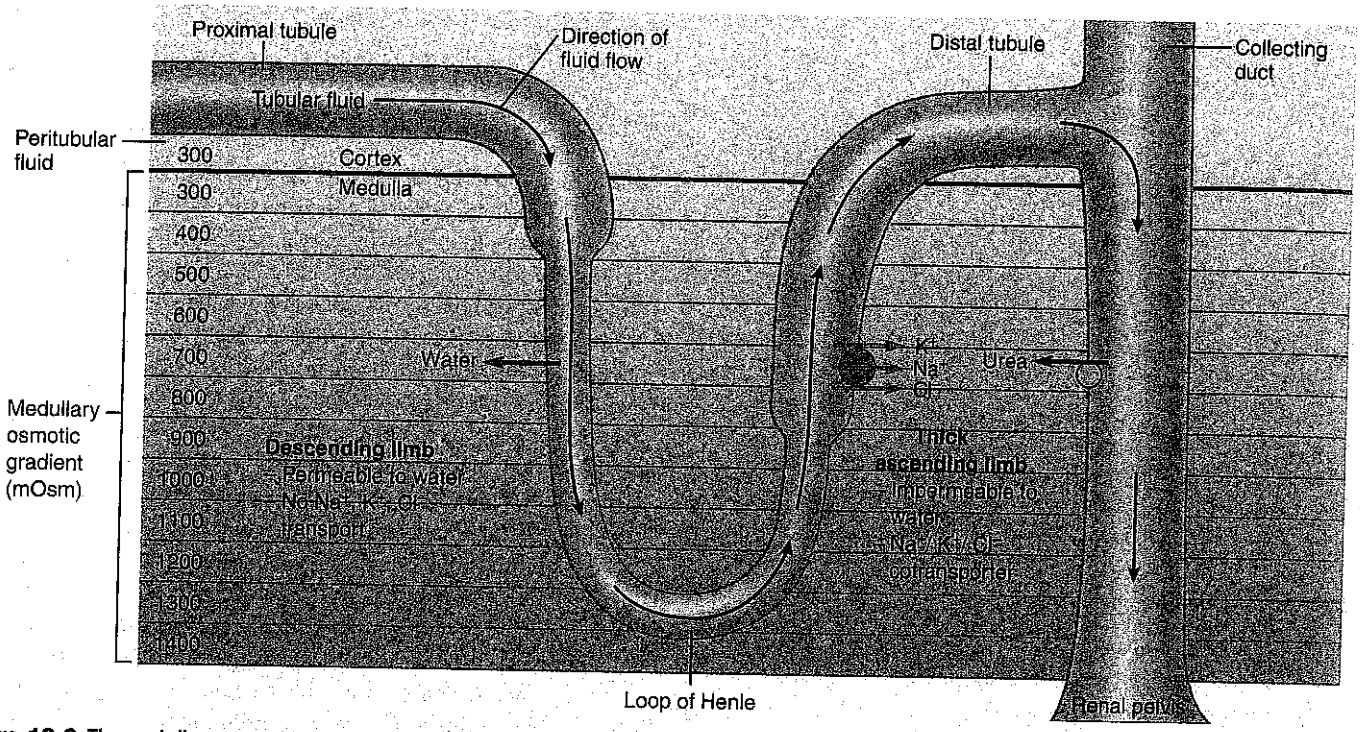


Figure 19.6 **The medullary osmotic gradient.** The descending limb of the loop of Henle is permeable to water, whereas the thick ascending limb is impermeable to water and contains transporters for Na^+, Cl^-, and K^+. Thus, differences in the transport of materials establish an osmotic gradient in the medullary interstitial fluid. The osmolarity of medullary interstitial fluid is 300 mOsm near the cortex, and increases continuously to a maximum of approximately 1400 mOsm near the renal pelvis.

Q Which of the two types of nephrons in the body is depicted in this figure?

Urea is highly water soluble and unable to permeate cell membranes in the absence of urea transporters. Such transporters are located in a number of cell types, including UT-B transporters in the endothelial cells of the descending limb of the vasa recta (discussed in the next subsection), and UT-A transporters of various types found in epithelial cells lining the renal tubules (**Figure 19.8**). In the portion of the collecting duct deep in the renal medulla, the epithelial cells contain UT-A_1 and UT-A_3 transporters that allow facilitated diffusion of urea from filtrate to the peritubular fluid, thereby contributing approximately 40% of the osmolarity of the medullary osmotic gradient (see Figure 19.6). Due to water reabsorption in the proximal tubule, some interstitial urea travels through UT-C transporters into the proximal tubule and can be used again to contribute to the medullary osmotic gradient when it reaches the collecting duct, thereby recycling the urea. (We will see later that active transporters for urea in the collecting duct are also critical in regulating water reabsorption.)

Role of the Vasa Recta in Preventing Dissipation of the Medullary Osmotic Gradient

As blood flows into the renal medulla to supply it with nutrients and oxygen, water tends to diffuse out of capillaries, and solutes tend to diffuse into them. However, the anatomical arrangement of the vasa recta capillaries, which accompany the loops of Henle as they dip into the medulla and return to the cortex (see Figure 18.1b), prevents the diffusion of water and solutes from dissipating the medullary osmotic gradient (**Figure 19.9**). Like the loop of Henle, the vasa recta can be described as having descending and ascending limbs based on the direction of fluid flow. As the descending limb of the vasa recta enters the renal medulla, the plasma has an osmolarity of 300 mOsm. As the descending limbs reach deeper into regions of the medulla with higher osmolarity, water leaves the capillaries by osmosis, and solutes enter the plasma by diffusion. This process, which would tend to reduce the osmolarity of the interstitial fluid if left unchecked, continues to the tip of the vasa recta because of the increasing osmolarity of the medullary interstitial fluid. However, as the blood flows back toward the cortex in the ascending limb, the direction of the osmotic gradient across the capillary walls reverses, so that water moves into the plasma and solutes move into the interstitial fluid. This movement tends to raise the osmolarity of the interstitial fluid. As a result, the osmolarity of the interstitial fluid stays relatively constant, and the osmolarity of plasma leaving the renal medulla in the vasa recta capillaries is just slightly hyperosmotic (325 mOsm) to that of the plasma entering the renal medulla.

Recall that the descending limb of the vasa recta has transporters for urea and that urea is concentrated deep in the medulla. Thus urea enters the descending limb increasing the osmolarity of the plasma, which would draw water into the descending limb, except that the medullary gradient is much stronger. More significant is

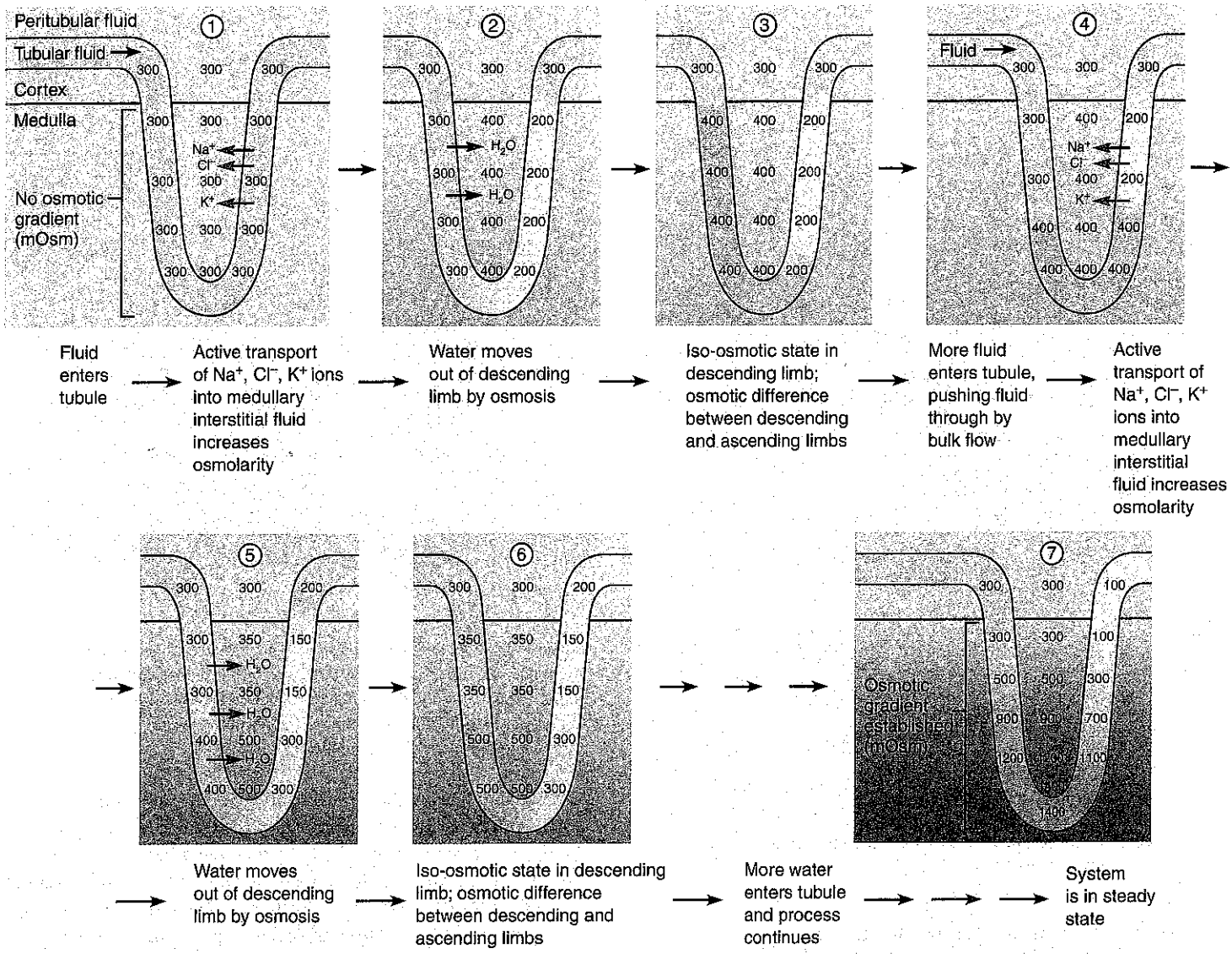


Figure 19.7 How the countercurrent multiplier establishes the medullary osmotic gradient. ① Initially all fluids are iso-osmotic at 300 mOsm. Active transport of solutes (Na^+, Cl^-, K^+) from the ascending limb of the loop of Henle into the medullary interstitial fluid increases the osmolarity of the interstitial fluid and decreases the osmolarity of the tubular fluid in the ascending limb. ② The increased osmolarity of the medullary interstitial fluid draws water from the lumen of the descending limb of the loop of Henle into the interstitial fluid, ③ increasing the osmolarity of the tubular fluid in the descending limb. ④ More tubular fluid then enters the loop of Henle, pushing the fluid farther into the renal tubules. The process of solute transport from the ascending limb ⑤ followed by water movement from the descending limb, ⑥ increasing the osmolarity of the tubular fluid in the descending limb, followed by more tubular fluid entering the loop of Henle, repeats until ⑦ the medullary osmotic gradient is established.

that the ascending limb of the vasa recta does not have urea transporters. Thus urea stays in the plasma (has been reabsorbed), contributing to the high osmolarity of plasma leaving the renal medulla.

Role of the Medullary Osmotic Gradient in Water Reabsorption in the Distal Tubule and Collecting Duct

Recall that 70% of the water filtered from plasma at the renal corpuscle is reabsorbed in the proximal tubule. Approximately 20% of the filtered water is reabsorbed in the distal tubule, and most of the remaining 10% is reabsorbed in the collecting ducts. In the initial portion of the distal tubule, the lumenal fluid (100–200 mOsm) is hypo-osmotic to the peritubular fluid (300 mOsm). As fluid moves down the collecting duct, the osmolarity of the lumenal fluid is always less than the increasing osmolarity of the medullary interstitial fluid, thereby increasing the osmotic force for water to move from the renal tubule into the interstitial fluid as tubular fluid moves down the collecting duct toward the renal pelvis. Thus, when water can permeate the wall of the collecting duct, it is reabsorbed.

Aquaporins and Water Permeability

The epithelial cells lining the late distal tubule and collecting duct are connected by tight junctions such that water cannot pass