TUBULAR SECRETION

Like tubular reabsorption, tubular secretion involves transepithelial transport, but now the steps are reversed. By providing a second route of entry into the tubules for selected substances, *tubular secretion*, the discrete transfer of substances from the peritubular capillaries into the tubular lumen, is a supplemental mechanism that hastens elimination of these compounds from the body. Anything that gains entry to the tubular fluid, whether by glomerular filtration or tubular secretion, and fails to be reabsorbed is eliminated in the urine. The most important substances secreted by the tubules are *hydrogen* ion *(H^+), potassium (K^+),* and *organic anions and cations,* many of which are compounds foreign to the body.

Hydrogen ion secretion is important in acid-base balance

Renal H+ secretion is extremely important in regulating acid-base balance in the body.

Potassium secretion is controlled by aldosterone

Potassium ion is selectively moved in opposite directions in different parts of the tubule; it is actively reabsorbed in the proximal tubule and actively secreted in the distal and collecting tubules. Early in the tubule potassium is reabsorbed in a constant, unregulated fashion, whereas K^+ secretion later in the tubule is variable and subject to regulation.

During K^+ depletion, K^+ secretion in the distal parts of the nephron is reduced to a minimum, so only the small percentage of filtered K^+ that escapes reabsorption in the proximal tubule is excreted in the urine. In this way, K^+ that normally would have been lost in urine is conserved for the body. Conversely, when plasma K^+ levels are elevated, K^+ secretion is adjusted so that just enough K^+ is added to the filtrate for elimination to reduce the plasma K^+ concentration to normal. Thus K^+ secretion, not the filtration or reabsorption of K^+, is varied in a controlled fashion to regulate the rate of K^+ excretion and maintain the desired plasma K^+ concentration.

MECHANISM OF K^+ SECRETION

Potassium secretion in the distal and collecting tubules is coupled to Na^+ reabsorption by the energy-dependent basolateral Na^+-K^+ pump **(**Figure 13-14**)**. This pump not only moves Na^+ out of the cell into the lateral space but also transports K^+ from the lateral space into the tubular cells. The resulting high intracellular K^+ concentration favors net diffusion of K^+ from the cells into the tubular lumen. Movement across the luminal membrane occurs passively through the large number of K^+ channels in this barrier in the distal and collecting tubules. By keeping the interstitial fluid concentration of K^+ low as it transports

K^+ into the tubular cells from the surrounding interstitial fluid, the basolateral pump encourages passive diffusion of K^+ out of the peritubular capillary plasma into the interstitial fluid. Potassium leaving the plasma in this manner is later pumped into the cells, from which it diffuses into the lumen. In this way, the basolateral pump actively induces the net secretion of K^+ from the peritubular capillary plasma into the tubular lumen.

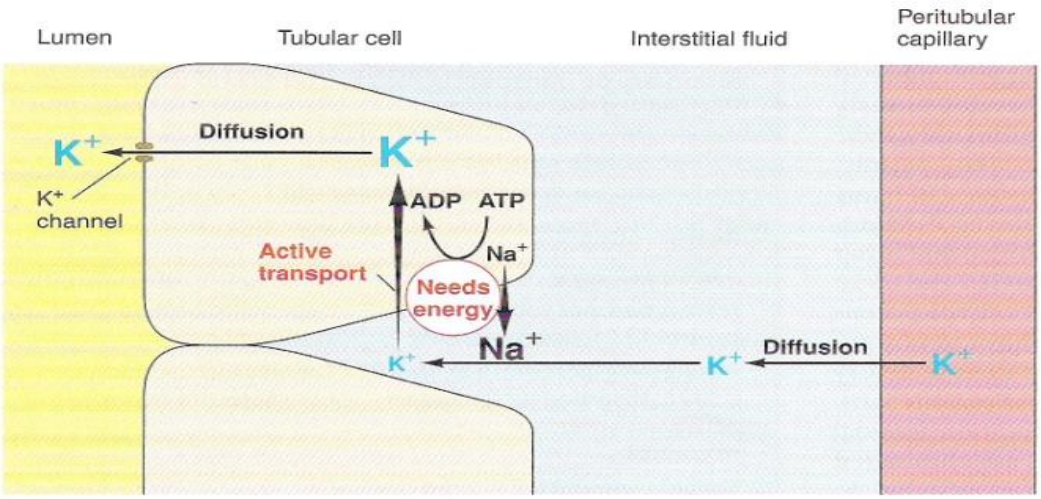


FIGURE 13-14

Potassium secretion. The basolateral pump simultaneously transports Na^+ into the lateral space and K^+ into the tubular cell. In the parts of the tubule that secrete K^+, this ion leaves the cell through channels located in the luminal border, thus being secreted. (In the parts of the tubule that do not secrete K^+, the K^+ pumped into the cell during Na^+ reabsorption leaves the cell through channels located in the basolateral border, thus being retained in the body.)

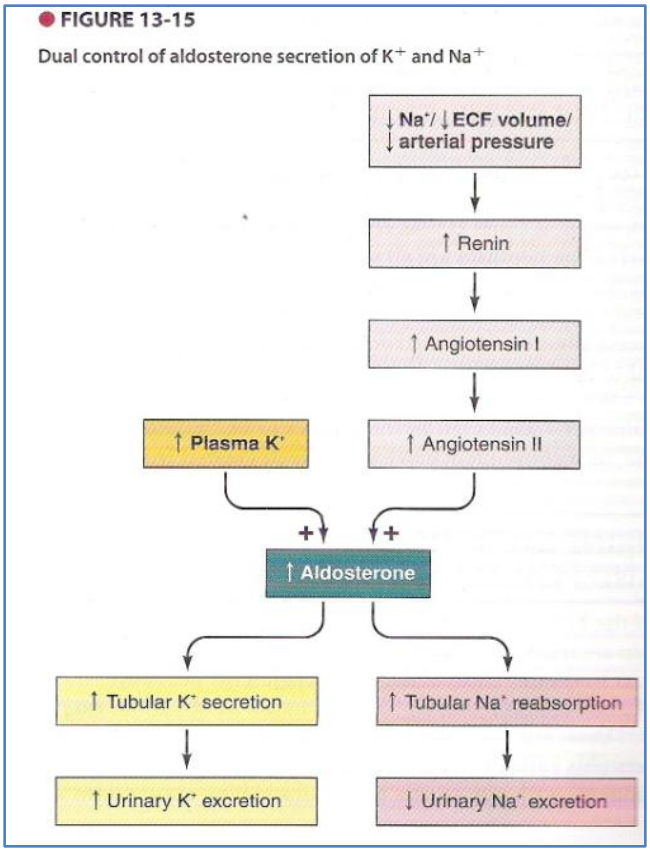
In the distal and collecting tubules, the K^+ channels are concentrated in the luminal membrane, providing a route for K^+ pumped into the cell to exit into the lumen, thus being secreted. In the other tubular segments, the K^+ channels are located primarily in the basolateral membrane. As a result, K^+ pumped into the cell from the lateral space by the Na^+ -K^+ pump simply diffuses back out into the lateral space through these channels. This K^+ recycling permits the ongoing operation of the Na^+-K^+ pump to accomplish Na^+ reabsorption with no local net effect on K^+ .

CONTROL OF K^+ SECRETION

Several factors can alter the rate of K^+ secretion, the most important being aldosterone. This hormone stimulates K^+ secretion by the tubular cells late in the nephron simultaneous to enhancing these cells' reabsorption of Na^+. A rise in plasma K^+ concentration directly stimulates the adrenal cortex to increase its output of aldosterone, which in turn promotes the secretion and ultimate urinary excretion and elimination of excess K^+.

Note that a rise in plasma K^+ concentration directly stimulates aldosterone secretion by the adrenal cortex, whereas a fall in plasma Na^+ concentration stimulates aldosterone secretion by means of the complex RAAS pathway. Thus aldosterone secretion can be stimulated by two separate pathways (Figure 13-15).

The kidneys usually exert a fine degree of control over plasma K^+ concentration. This is extremely important, because even minor fluctuations in plasma K^+ concentration can detrimentally influence the membrane electrical activity of excitable tissues, adversely affecting their performance. For example, a rise in ECF K^+ concentration causes cardiac overexcitability, which can lead to a rapid heart rate and even fatal cardiac arrhythmias.



Organic anion and cation secretion helps efficiently eliminate foreign compounds from the body. The proximal tubule contains two distinct types of secretory carriers, one for the secretion of organic anions and a separate system for secretion of organic cations.

URINE EXCRETION AND PLASMA CLEARANCE

Of the 125 ml of plasma filtered per minute, typically 124 ml/min are reabsorbed, so the final quantity of urine formed averages 1 ml/min. Thus, of the 180 liters filtered per day, 1.5 liters of urine are excreted.

The kidneys can excrete urine of varying concentrations depending on the body's state of hydration

Having considered how the kidneys deal with a variety of solutes in the plasma, we will now concentrate on renal handling of plasma H_2O. The ECF osmolarity (solute concentration) depends on the relative amount of H_2O compared to solute. At normal fluid balance and solute concentration, the body fluids are isotonic at an osmolarity of 300 milliosmols/liter (rnosm/liter). If too much H_2O is present relative to the solute load, the

body fluids are hypotonic, which means they are too dilute at an osmolarity less than 300 mosm/liter. However, if a H_20 deficit exists relative to the solute load, the body fluids are too concentrated or are hypertonic, having an osmolarity greater than 300 mosm/liter.

Knowing that the driving force for H_2O reabsorption throughout the entire length of the tubules is an osmotic gradient between the tubular lumen and surrounding interstitial fluid, you would expect, given osmotic considerations, that the kidneys could not excrete urine more or less concentrated than the body fluids. Indeed, this would be the case if the interstitial fluid surrounding the tubules in the kidneys were identical in osmolarity to the remaining body fluids. Water reabsorption would proceed only until the tubular fluid equilibrated osmotically with the interstitial fluid, and the body would have no way to eliminate excess H_2O when the body fluids were hypotonic, or to conserve H_2O in the presence of hypertonicity.

Fortunately, a large vertical osmotic gradient is uniquely maintained in the interstitial fluid of the medulla of each kidney. The concentration of the interstitial fluid progressively increases from the cortical boundary down through the depth of the renal medulla until it reaches a maximum of 1200 *mosml/*liter in humans at the junction with the renal pelvis **(**Figure 13-17).

By a mechanism described shortly, this gradient enables the kidneys to produce urine that ranges in concentration from 100 to 1200 mosm/liter, depending on the body's state of hydration. When the body is in ideal fluid balance, 1 ml/min of isotonic urine is formed. When the body is overhydrated (too much H_2O), the kidneys can produce a large volume of dilute urine (up to 25 ml/min and hypotonic at 100 mosm/liter), eliminating the excess H_2O in the urine. Conversely, the kidneys can put out a small volume of concentrated urine (down to 0.3 ml/min and hypertonic at 1200 mosm/liter) when the body is dehydrated (too little H_2O), conserving H_2O for the body.

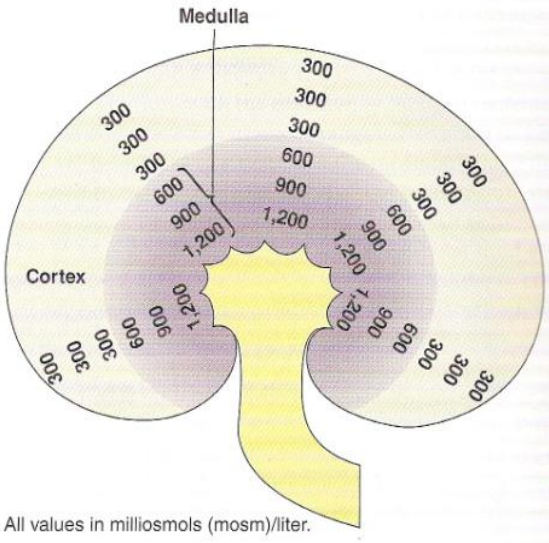


FIGURE 13-17

Vertical osmotic gradient in the renal medulla. Schematic representation of the kidney rotated 90° from its normal position in an upright person for better visualization of the vertical osmotic gradient in the renal medulla. The osmolarity of the interstitial fluid throughout the renal cortex is isotonic at 300 mosm/liter, but the osmolarity of the interstitial fluid in the renal medulla increases progressively from 300 mosm/liter at the boundary with the cortex to a maximum of 1200 mosm/liter at the junction with the renal pelvis.

In most nephrons the hairpin loop of Henle dips only slightly into the medulla,

but in about 20% of nephrons the loop plunges through the entire depth of the medulla so that the tip of the loop lies near the renal pelvis (Figure 13-18). Flow in the long loops of Henle is considered countercurrent, because the flow in the two adjacent limbs of the loop moves in opposite directions. Also running through the medulla in the descending direction only, on their way to the renal pelvis, are the collecting ducts that serve both types of nephrons. This arrangement, coupled with the permeability and transport characteristics of these tubular segments, plays a key role in the kidneys' ability to produce urine of varying concentrations, depending on the body's needs for water conservation or elimination. Briefly, the long loops of Henle *establish* the vertical osmotic gradient and the collecting ducts of all nephrons *use* the gradient, in conjunction with the hormone vasopressin, to produce urine of varying concentrations. Collectively, this entire functional organization is known as the medullary countercurrent system.

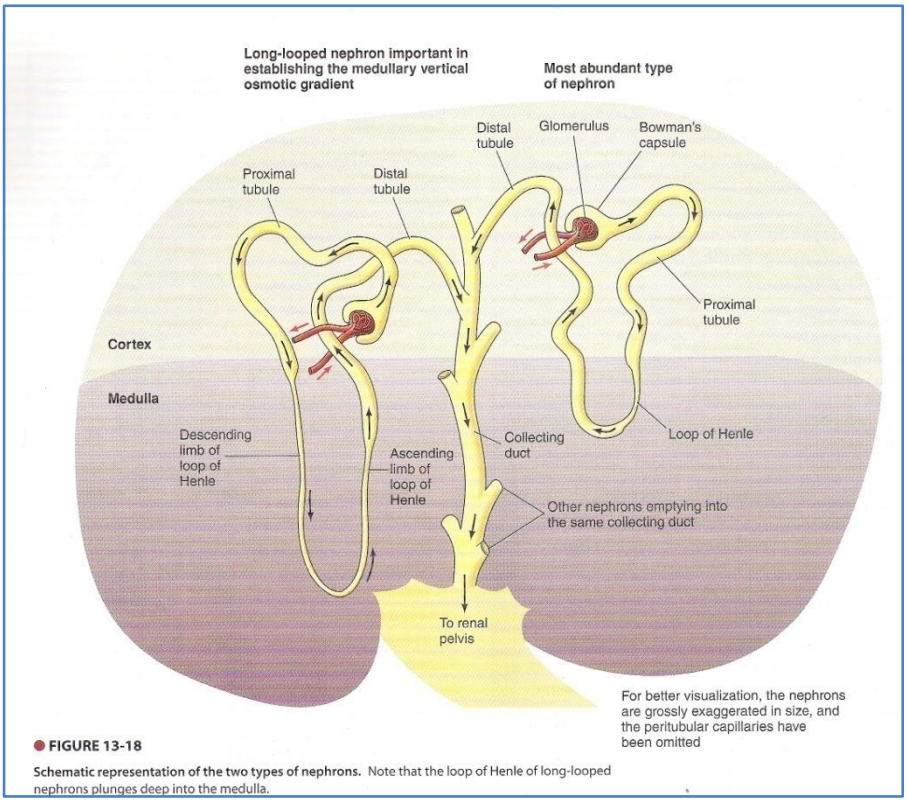


FIGURE 13-18

Schematic representation of the two types of nephrons. Note that the loop of Henle of long-looped nephrons plunges deep into the medulla.

The medullary vertical osmotic gradient is established by countercurrent multiplication

Immediately after the filtrate is formed, uncontrolled osmotic reabsorption of filtered H_2O occurs in the proximal tubule secondary to active Na^+ reabsorption. As a result, by the end of the proximal tubule about 65% of the filtrate has been reabsorbed, but the 35% remaining in the tubular lumen still has the same osmolarity as the body fluids. Therefore the fluid entering the loop of Henle is still isotonic. An additional 15% of the filtered H_2O is obligatorily reabsorbed from the loop of Henle during the establishment and

maintenance of the vertical osmotic gradient, with the osmolarity of the tubular fluid being altered in the process.

PROPERTIES OF THE DESCENDING AND ASCENDING LIMBS OF A LONG HENLE'S LOOP

The following functional distinctions between the descending limb of a long Henle's loop (which carries fluid from the proximal tubule down into the depths of the medulla) and the ascending limb (which carries fluid up and out of the medulla into the distal tubule) are crucial for establishing the incremental osmotic gradient in the medullary interstitial fluid.

The *descending limb*

1. is highly permeable to H_2O.
2. does not actively extrude Na^+. (That is, it does not reabsorb Na^+. It is the only segment of the entire tubule that does not do so.)

The *ascending limb*

1. actively transports NaCl out of the tubular lumen into the surrounding interstitial fluid.
2. is always impermeable to H_2O, so salt leaves the tubular fluid without H_2O osmotically following along.

MECHANISM OF COUNTERCURRENT MULTIPLICATION

The close proximity and countercurrent flow of the two limbs allow important interactions between them. Even though the flow of fluids is continuous through the loop of Henle,

- *Initial scene* (Figure 13-19a). Before the vertical osmotic gradient is established, the medullary interstitial fluid concentration is uniformly 300 mosm/liter, as is the rest of the body fluids.
- *Step* 1 (Figure 13-19b). The active salt pump in the ascending limb can transport NaCl out of the lumen until the surrounding interstitial fluid is 200 mosm/liter more concentrated than the tubular fluid in this limb. When the ascending limb pump starts actively extruding salt, the medullary interstitial fluid becomes hypertonic. Water cannot follow osmotically from the ascending limb, because this limb is impermeable to H_2O. However, net diffusion of H_2O does occur from the descending limb into the interstitial fluid. The tubular fluid entering the descending limb from the proximal tubule is isotonic. Because the descending limb is highly permeable to H_20, net diffusion of H_2O occurs by osmosis out of the descending limb into the more concentrated interstitial fluid. The passive movement of H_2O out of the descending limb continues until the osmolarities of the fluid in the descending limb and interstitial fluid become equilibrated. Thus the tubular fluid entering the loop of Henle immediately starts to become more concentrated as it loses H_2O. At equilibrium, the osmolarity of the ascending limb fluid

is 200 mosm/liter and the osmolarities of the interstitial fluid and descending limb fluid are equal at 400 mosm/liter.

- *Step* 2 (Figure 13-19c). If we now advance the entire column of fluid in the loop of Henle several frames, a mass of 200-mosmlliter fluid exits from the top of the ascending limb into the distal tubule, and a new mass of isotonic fluid at 300 mosm/liter enters the top of the descending limb from the proximal tubule. At the bottom of the loop, a comparable mass of 400-mosm/liter fluid from the descending limb moves forward around the tip into the ascending limb, placing it opposite a 400-mosm/liter region in the descending limb. Note that the 200-mosm/liter concentration difference has been lost at both the top and the bottom of the loop.
- *Step* 3 (Figure 13-19d). The ascending limb pump again transports NaCl out while H_2O passively leaves the descending limb until a 200-mosm/liter difference is re-established between the ascending limb and both the interstitial fluid and descending limb at each horizontal level. Note, however, that the concentration of tubular fluid is progressively increasing in the descending limb and progressively decreasing in the ascending limb.
- *Step* 4 (Figure 13-1e). As the tubular fluid is advanced still further, the 200-mosm/liter concentration gradient is disrupted once again at all horizontal levels.
- *Step* 5 (Figure 13-19f). Again, active extrusion of NaCl from the ascending limb, coupled with the net diffusion of H_2O out of the descending limb, re-establishes the 200-mosm/ liter gradient at each horizontal level.
- Step 6 and on (Figure 13-19g). As the fluid flows slightly forward again and this stepwise process continues, the fluid in the descending limb becomes progressively more hyper tonic until it reaches a maximum concentration of 1200 mosrn/liter at the bottom of the loop, four times the normal concentration of body fluids. Because the interstitial fluid always achieves equilibrium with the descending limb, an incremental vertical concentration gradient ranging from 300 to 1200 mosm/liter is likewise established in the medullary interstitial fluid. In contrast, the concentration of the tubular fluid progressively decreases in the ascending limb as salt is pumped out but H_20 is unable to follow. In fact, the tubular fluid even becomes hypotonic before leaving the ascending limb to enter the distal tubule at a concentration of 100 mosm/liter, one third the normal concentration of body fluids.

Note that although a gradient of only 200 mosm/liter exists between the ascending limb and the surrounding fluids at each medullary horizontal level, a much larger vertical gradient exists from the top to the bottom of the medulla. Even though the ascending limb pump can generate a gradient of only 200 mosm/liter, this effect is multiplied into a large vertical gradient because of the countercurrent flow within the loop. This concentrating mechanism accomplished by the loop of Henle is known as countercurrent multiplication.

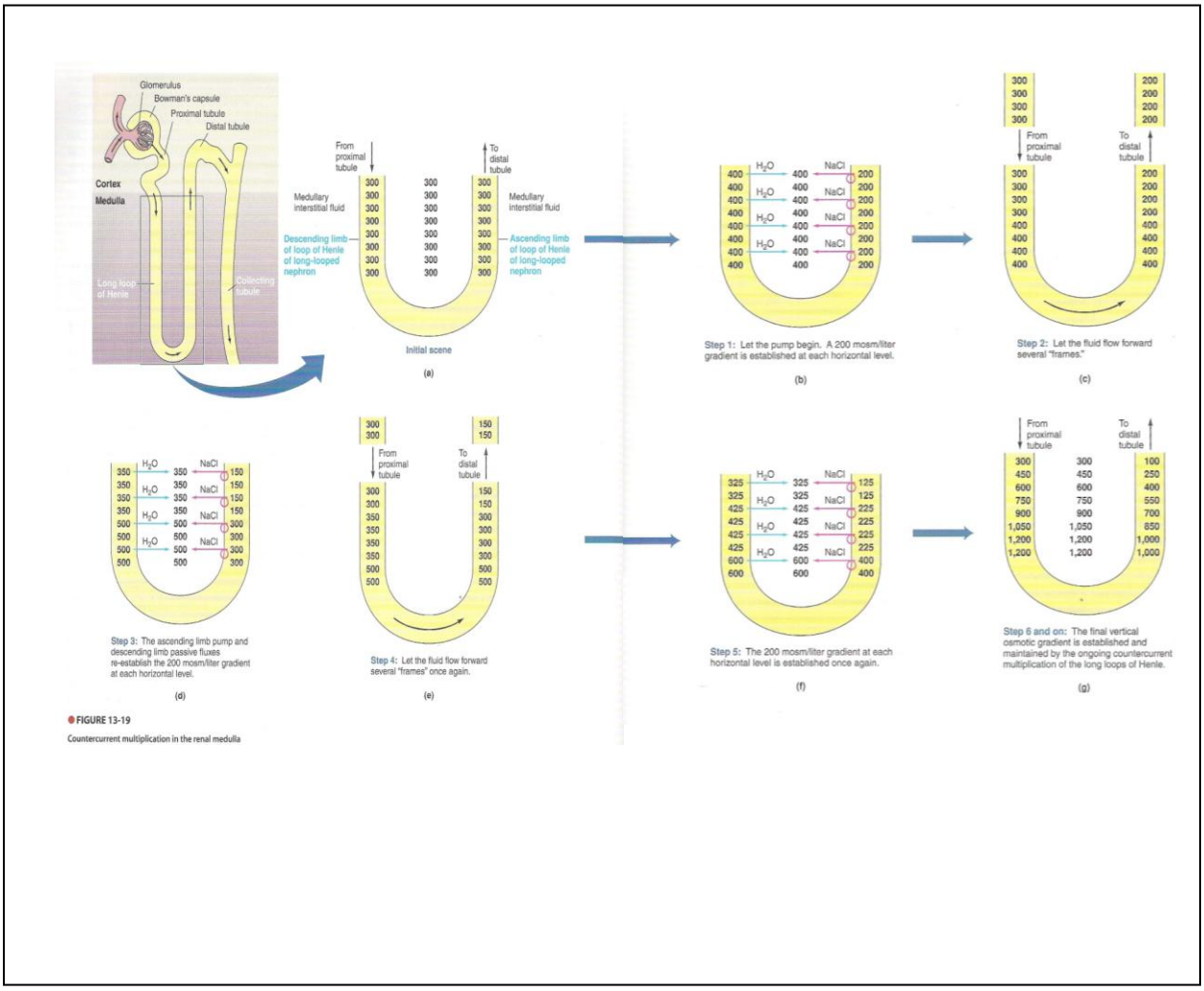


FIGURE 13-19
Countercurrent multiplication in the renal medulla

BENEFITS OF COUNTERCURRENT MULTIPLICATION

If you consider only what happens to the tubular fluid as it flows through the loop of Henle, the whole process seems an exercise in futility. The isotonic fluid that enters the loop becomes progressively more concentrated as it flows down the descending limb, achieving a maximum concentration of 1200 mosm/liter, only to become progressively more dilute as it flows up the ascending limb, finally leaving the loop at a minimum concentration of 100 mosm/liter. What is the point of concentrating the fluid fourfold and then turning around and diluting it until it leaves at one third the concentration at which it entered? Such a mechanism offers two benefits. First, it establishes a vertical osmotic gradient in the medullary interstitial fluid. This gradient, in turn, is used by the collecting ducts to concentrate the tubular fluid so that a urine *more concentrated* than normal body fluids can be excreted. Second, the fact that the fluid is hypotonic as it enters the distal parts of the tubule enables the kidneys to excrete a urine *more dilute* than normal body fluids.

Vasopressin-controlled, variable H_2O reabsorption occurs in the final tubular segments

After obligatory H_2O reabsorption from the proximal tubule (65% of the filtered H_20) and loop of Henle (15% of the filtered H_2O), 20% of the filtered H_20 remains in the lumen to enter the distal and collecting tubules for variable reabsorption that is under hormonal control. This is still a large volume of filtered H_2O subject to regulated reabsorption; 20% X GFR (180 liters/day) = 36 liters per day to be reabsorbed to varying extents, depending on the body's state of hydration.

The fluid leaving the loop of Henle enters the distal tubule at 100 mosm/liter, so it is hypotonic to the surrounding isotonic (300 mosm/liter) interstitial fluid of the renal cortex through which the distal tubule passes. The distal tubule then empties into the collecting duct, which is bathed by progressively increasing concentrations (300 to 1200 mosm/liter) of surrounding interstitial fluid as it descends through the medulla.

ROLE OF VASOPRESSIN

For H_2O absorption to occur across a segment of the tubule, two criteria must be met: (1) An osmotic gradient must exist across the tubule, and (2) the tubular segment must be permeable to H_2O. The distal and collecting tubules are *impermeable* to H_2O except in the presence of vasopressin, also known as antidiuretic hormone *(anti* means "against"; *diuretic* means "increased urine output"), which increases their permeability to H_2O. Vasopressin is produced by several specific neuronal cell bodies in the *hypothalamus,* part of the brain, then stored in the *posterior pituitary gland,* which is attached to the hypothalamus by a thin stalk. The hypothalamus controls release of vasopressin from the posterior pituitary into me blood. In negative-feedback fashion, vasopressin secretion is stimulated by a H_2O deficit, when the ECF is too concentrated (that is, hypertonic) and H_2O must be conserved for the body, and inhibited by a H_2O excess, when the ECF is too dilute (that is, hypotonic) and surplus H_2O must be eliminated in urine.

Vasopressin reaches the basolateral membrane of the tubular cells lining the distal and collecting tubules through the circulatory system. Here it binds with receptors specific for it. This binding activates the cyclic AMP (cAMP) second-messenger system within the tubular cells, which ultimately increases permeability of the opposite luminal membrane to H_2O by promoting insertion of aquaporins in this membrane. Without these aquaporins, the luminal membrane is impermeable to H_2O. Once H_2O enters the tubular cells from the filtrate through these vasopressin-regulated luminal water channels, it passively leaves the cells down the osmotic gradient across the cells' basolateral membrane (which is always permeable to H_2O) to enter the interstitial fluid.

Vasopressin influences H_2O permeability only in the distal part of the nephron, especially

the collecting ducts. When vasopressin secretion increases in response to a H_2O deficit and the permeability of the distal and collecting tubules to H_2O accordingly increases, the hypotonic tubular fluid entering the distal part of the nephron can lose progressively more H_2O by osmosis into the interstitial fluid as the tubular fluid first flows through the isotonic cortex and then is exposed to the ever-increasing osmolarity of the medullary interstitial fluid as it plunges toward the renal pelvis (Figure 13-20a). As the 100 mosm/liter tubular fluid enters the distal tubule and is exposed to a surrounding interstitial fluid of 300 mosm/ liter, H_2O leaves the tubular fluid by osmosis across the now permeable tubular cells until the tubular fluid reaches a maximum concentration of 300 mosm/liter by the end of the distal tubule. As this 300-mosm/liter tubular fluid progresses farther into the collecting duct, it is exposed to even higher osmolarity in the surrounding medullary interstitial fluid. Consequently, the tubular fluid loses more H_2O by osmosis and be. comes further concentrated, only to move farther forward and be exposed to an even higher interstitial fluid osmolarity and lose even more H_2O, and so on.

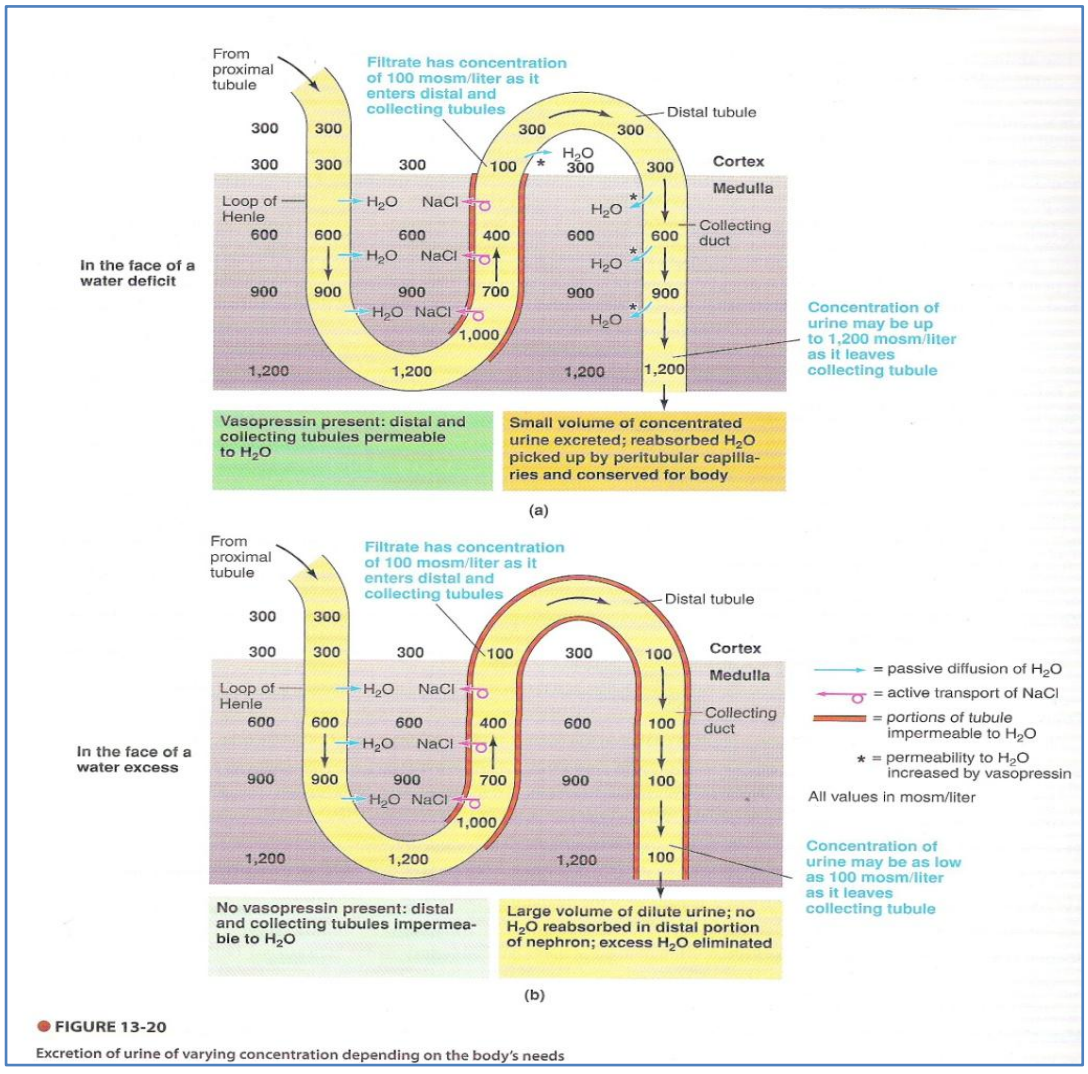


FIGURE 13-20
Excretion of urine of varying concentration depending on the body's needs

Under the influence of maximum levels of vasopressin, it is possible to concentrate the tubular fluid up to 1200 mosm/ liter by the end of the collecting ducts. No further modification of the tubular fluid occurs beyond the collecting duct, so what remains in the tubules at this point is urine. As a result of this extensive vasopressin-promoted reabsorption of H_2O in the late segments of the tubule, a small volume of urine concentrated up to 1200 mosm/liter can be excreted. As little as 0.3 ml of urine may be formed each minute, less than one third the normal urine flow rate of 1 ml/min. The reabsorbed H_2O entering the medullary interstitial fluid is picked up by the peritubular capillaries and returned to the general circulation, thus being conserved for the body.

Thus, under maximal vasopressin influence, 99.7% of the 180 liters of plasma H_2O filtered per day is returned to the blood, with an obligatory H_20 loss of half a liter. The kidneys' ability to tremendously concentrate urine to minimize H_20 loss when necessary is possible only because of the presence of the vertical osmotic gradient in the medulla. If this gradient did not exist, the kidneys could not produce a urine more concentrated than the body fluids no matter how much vasopressin was secreted, because the only driving force for H_2O reabsorption is a concentration differential between the tubular fluid and the interstitial fluid.

REGULATION OF H_2O REABSORPTION IN RESPONSE TO A H_2O EXCESS

Conversely, when a person consumes large quantities of H_2O, the excess H_2O must be removed from the body without simultaneously losing solutes that are critical for maintaining homeostasis. Under these circumstances, no vasopressin is secreted, so the distal and collecting tubules remain impermeable to H_2O. The tubular fluid entering the distal tubule is hypotonic (l00 mosm/liter), having lost salt without an accompanying loss of H_2O in the ascending limb of Henle's loop. As this hypotonic fluid passes through the distal and collecting tubules **(**Figure 13-20b), the medullary osmotic gradient cannot exert any influence because of the late tubular segment's impermeability to H_2O. In other words, none of the H_2O remaining in the tubules can leave the lumen to be reabsorbed, even though the tubular fluid is less concentrated than the surrounding interstitial fluid. Thus in the absence of vasopressin, the 20% of the filtered fluid that reaches the distal tubule is not reabsorbed. Meanwhile, excretion of wastes and other urinary solutes remains constant. The net result is a large volume of dilute urine, which helps rid the body of excess H_2O. Urine osmolarity may be as low as 100 mosm/liter; the same as in the fluid entering the distal tubule. Urine may be increased up to 25 ml/min in the absence of vasopressin, compared to the normal urine production of 1 m/min.

The ability to produce urine less concentrated than the body fluids depends on the fact that the tubular fluid is hyporonic as it enters the distal part of the nephron. This dilution is accomplished in the ascending limb as NaCl is actively extruded but H_2O cannot follow.

Therefore, the loop of Henle, by simultaneously establishing the medullary osmotic gradient and diluting the tubular fluid before it enters the distal segments, plays a key role in allowing the kidneys to excrete urine that ranges in concentration from 100 to 1200 *mosm/liter.*

Excessive water diuresis follows alcohol ingestion. Because alcohol inhibits vasopressin secretion, the kidneys inappropriately lose too much H_2O. Typically, more fluid is lost in the urine than is consumed in the alcoholic beverage, so the body becomes dehydrated despite substantial fluid ingestion.

Renal failure has wide-ranging consequences

Urine excretion and the resulting clearance of wastes and excess electrolytes from the plasma are crucial for maintaining homeostasis. When the functions of both kidneys are so disrupted that they cannot perform their regulatory and excretory functions sufficiently to maintain homeostasis, renal failure has set in. Renal failure can manifest itself either as *acute renal failure,* characterized by a sudden onset with rapidly reduced urine formation until less than the essential minimum of around 500 ml of urine is being produced per day, or *chronic renal failure,* characterized by slow, progressive, insidious loss of renal function. A person may die from acute renal failure, or the condition may be reversible and lead to full recovery Chronic renal failure, in contrast, is not reversible. Gradual, permanent destruction of renal tissue eventually proves fatal. Chronic renal failure is insidious, because up to 75% of the kidney tissue can be destroyed before the loss of kidney function is even noticeable. Because of the abundant reserve of kidney function, only 25% of the kidney tissue is needed to adequately maintain all the essential renal excretory and regulatory functions. With less than 25% of functional kidney tissue remaining, however, renal insufficiency becomes apparent. *End-stage renal failure* ensues when 90% of kidney function has been lost.

We will not sort out the different stages and symptoms associated with various renal disorders, but Table 13-4, which summarizes the potential consequences of renal failure, gives you an idea of the broad effects that kidney impairment can have. The extent of these effects should not be surprising, considering the central role the kidneys play in maintaining homeostasis. When the kidneys cannot maintain a normal internal environment, widespread disruption of cell activities can bring about abnormal function in other organ systems, as well. By the time end-stage renal failure occurs, literally every body system has become impaired to some extent. Because chronic renal failure is irreversible and eventually fatal, treatment is aimed at maintaining renal function by alternative methods, such as dialysis and kidney transplant.

TABLE 13-4

Potential Ramifications of Renal Failure

Uremic toxicity caused by retention of waste products
- Nausea, vomiting, diarrhea, and ulcers caused by a toxic effect on the digestive system
- Bleeding tendency arising from a toxic effect on platelet function
- Mental changes—such as reduced alertness, insomnia, and shortened attention span, progressing to convulsions and coma—caused by toxic effects on the central nervous system
- Abnormal sensory and motor activity caused by a toxic effect on the peripheral nerves

Metabolic acidosis* caused by the inability of the kidneys to adequately secrete H^+ that is continually being added to the body fluids as a result of metabolic activity
- Altered enzyme activity caused by the action of too much acid on enzymes
- Depression of the central nervous system caused by the action of too much acid interfering with neuronal excitability

Potassium retention* resulting from inadequate tubular secretion of K^+
- Altered cardiac and neural excitability as a result of changing the resting membrane potential of excitable cells

Sodium imbalances caused by the inability of the kidneys to adjust Na^+ excretion to balance the changes in Na^+ consumption
- Elevated blood pressure, generalized edema, and congestive heart failure if too much Na^+ is consumed
- Hypotension and, if severe enough, circulatory shock if too little Na^+ is consumed

Phosphate and calcium imbalances arising from impaired reabsorption of these electrolytes
- Disturbances in skeletal structures caused by abnormalities in deposition of calcium phosphate crystals, which harden bone

Loss of plasma proteins as a result of increased "leakiness" of the glomerular membrane
- Edema caused by a reduction in plasma-colloid osmotic pressure

Inability to vary urine concentration as a result of impairment of the countercurrent system
- Hypotonicity of body fluids if too much H_2O is ingested
- Hypertonicity of body fluids if too little H_2O is ingested

Hypertension arising from the combined effects of salt and fluid retention and vasoconstrictor action of excess angiotensin II

Anemia caused by inadequate erythropoietin production

Depression of the immune system, most likely caused by toxic levels of wastes and acids
- Increased susceptibility to infections

*Among the most life-threatening consequences of renal failure.

Urine is temporarily stored in the bladder, from which it is emptied by micturition

Once urine has been formed by the kidneys, it is transmitted through the ureters to the urinary bladder. Urine does not flow through the ureters by gravitational pull alone. Peristaltic contractions of the smooth muscle within the ureteral wall propel the urine forward from the kidneys to the bladder. The ureters penetrate the wall of the bladder obliquely, coursing through the wall several centimeters before they open into the bladder cavity. This anatomic arrangement prevents backflow of urine from the bladder to the kidneys when pressure builds up in the bladder. As the bladder fills, the ureteral ends within its wall are compressed closed. Urine can still enter, however, because ureteral contractions generate enough pressure to overcome the resistance and push urine through the occluded ends.

ROLE OF THE BLADDER

The bladder can accommodate large fluctuations in urine volume. The bladder wall consists of smooth muscle, which can stretch tremendously without building up bladder wall tension. In addition, the highly folded bladder wall flattens out during filling to increase bladder storage capacity. Because the kidneys are continuously forming urine, the bladder must have enough storage capacity to preclude the need to continually get rid of the urine.

The bladder smooth muscle is richly supplied by parasympathetic fibers, stimulation of which causes bladder contraction. If the passageway through the urethra to the outside is open, bladder contraction empties urine from the bladder. The exit from the bladder, however, is guarded by two sphincters, the *internal urethral sphincter* and the *external urethral sphincter*.

ROLE OF THE URETHRAL SPHINCTERS

A sphincter is a ring of muscle that, when contracted, closes off passage through an opening. The internal urethral sphincter-which is smooth muscle and, accordingly, is under involuntary control-is not really a separate muscle but instead consists of the last part of the bladder. Although it is not a true sphincter, it performs the same function as a sphincter. When the bladder is relaxed, the anatomic arrangement of the internal urethral sphincter region closes the outlet of the bladder.

Farther down the passageway, the urethra is encircled by a layer of skeletal muscle, the external urethral sphincter. This sphincter is reinforced by the entire pelvic diaphragm, a skeletal muscle sheet that forms the floor of the pelvis and helps support the pelvic organs. The motor neurons that supply the external sphincter and pelvic diaphragm fire continuously at a moderate rate unless they are inhibited, keeping these muscles tonically contracted so they prevent urine from escaping through the urethra.