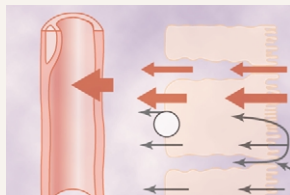# Urine Formation by the Kidneys: II. Tubular Processing of the Glomerular Filtrate

Reabsorption and Secretion by the Renal Tubules

As the glomerular filtrate enters the renal tubules, it flows sequentially through the successive parts of the tubule—the *proximal tubule*, the *loop of Henle*, the *distal tubule*, the *collecting tubule*, and, finally, the *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—as follows:

> Urinary excretion = Glomerular filtration – Tubular reabsorption
> + Tubular secretion

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

Tubular Reabsorption Is Selective and Quantitatively Large

Table 27–1 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

> Filtration = Glomerular filtration rate × 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 27–1, two things are immediately apparent. First, the processes of glomerular filtration and tubular reabsorption are quantitatively very large relative to urinary excretion for many substances. This means that a small change in glomerular filtration or tubular reabsorption can potentially cause a relatively large change in urinary excretion. For example, a 10 per cent 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, however, 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 (that is, 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

Table 27–1

Filtration, Reabsorption, and Excretion Rates of Different Substances by the Kidneys

	Amount Filtered	Amount Reabsorbed	Amount Excreted	% of Filtered Load Reabsorbed
Glucose (g/day)	180	180	0	100
Bicarbonate (mEq/day)	4,320	4,318	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

from the tubules, so that the urinary excretion rate is essentially zero. Many of the 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. Certain waste products, such as urea and creatinine, conversely, are poorly reabsorbed from the tubules and excreted in relatively large amounts.

Therefore, by controlling the rate at which they reabsorb different substances, the kidneys regulate the excretion of solutes independently of one another, a capability that is essential for precise control of the composition of body fluids. 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 27–1). 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 way of the same basic mechanisms discussed in Chapter 4 for transport across other membranes of the body. For instance, water and solutes can be transported either through the cell membranes themselves (*transcellular route*) or through the junctional spaces between the cells (*paracellular route*). Then, after absorption across the tubular epithelial cells into the interstitial fluid, water and solutes are transported the rest of the way 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 very much 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.
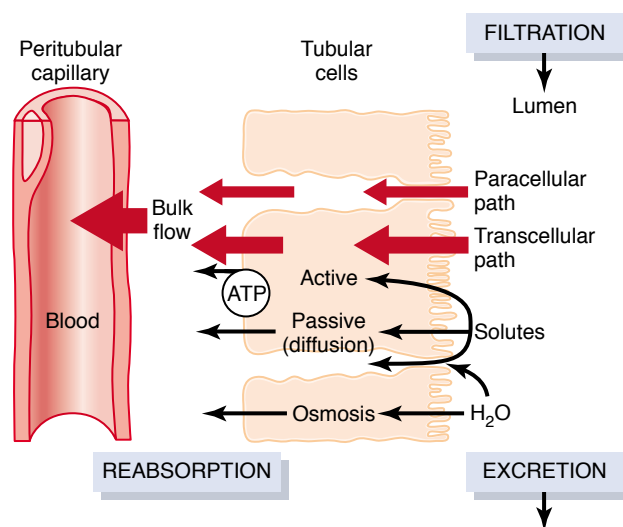

Figure 27–1

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 route) by passive diffusion or active transport, or between the cells (paracellular route) 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).

Active Transport

Active transport can move a solute against an electrochemical gradient and 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*. A good example of this is the sodium-potassium 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 by a passive

(nonactive) physical mechanism called *osmosis*, which means water diffusion from a region of low solute concentration (high water concentration) to one of high solute concentration (low water concentration).

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 by way of the *transcellular pathway* or between the cells by moving across the tight junctions and intercellular spaces by way of 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 Is Linked to Hydrolysis of ATP. *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; the ATPase is also a component of the carrier mechanism that binds and moves solutes across the cell membranes. The primary active transporters that are known include *sodium-potassium 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 27–2. On the basolateral sides of the tubular epithelial cell, the cell membrane has an extensive sodium-potassium 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 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 intracellular sodium concentration is low (12 mEq/L) and tubular fluid sodium concentration is high (140 mEq/L). (2) The negative, −70-millivolt, intracellular potential attracts the positive sodium ions from the tubular lumen into the cell.

Active reabsorption of sodium by sodium-potassium ATPase occurs in most parts of the tubule. In certain parts of the nephron, there are additional provisions for moving large amounts of sodium into the cell. In the proximal tubule, there is an extensive
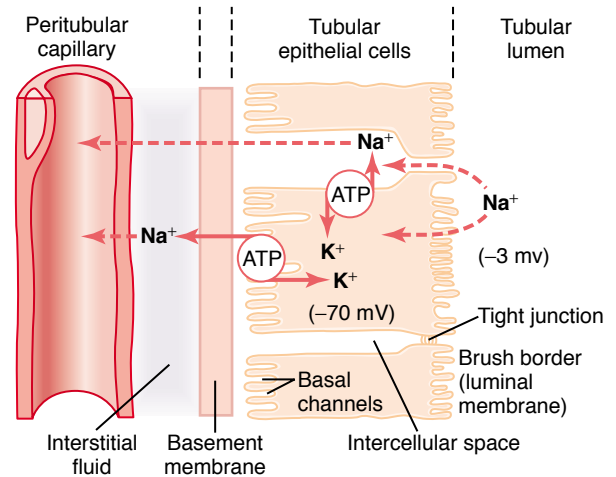

Figure 27–2

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 the negative electrical potential cause sodium ions to diffuse from the tubular lumen into the cell through the brush border.

brush border on the luminal side of the membrane (the side that faces the tubular lumen) that multiplies the surface area about 20-fold. There are also sodium 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 sodium-potassium ATPase pump on the basolateral side of the membrane.
2. Sodium is transported across the basolateral membrane against an electrochemical gradient by the sodium-potassium 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 (for instance, sodium) diffuses down its electrochemical gradient, the energy released is used to drive another substance
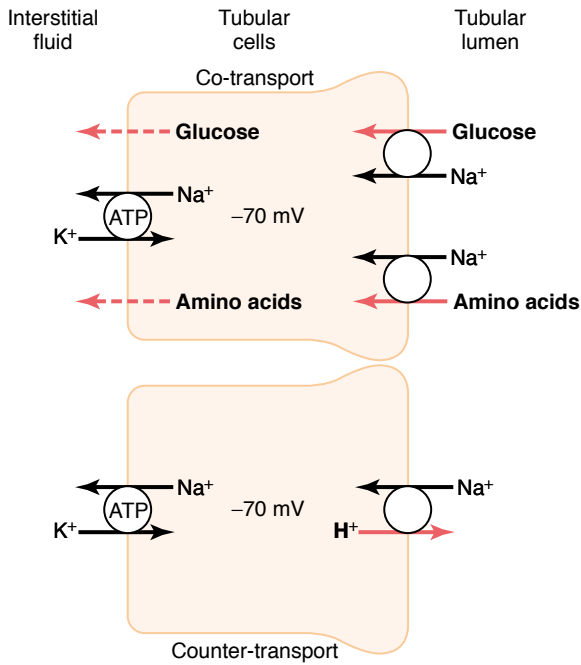
Interstitial fluid   Tubular cells   Tubular lumen

Co-transport

Glucose ← ← ← Glucose

Na+   −70 mV

K+ (ATP) Na+

Na+

Amino acids ← ← ← Amino acids

Na+ (ATP) −70 mV Na+

K+   H+

Counter-transport

Figure 27–3

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.

(for instance, 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 27–3 shows secondary active transport of glucose and amino acids in the proximal tubule. In both instances, a specific carrier protein in the brush border combines 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 facilitated diffusion, driven by the high glucose and amino acid concentrations in the cell.

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 sodium-potassium ATPase pump in the basolateral membrane. Because of the activity of this pump, an electrochemical gradient for 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. This 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 (for example, sodium ions) enables uphill movement of a second substance in the opposite direction.

One example of counter-transport, shown in Figure 27–3, 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 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 additional detail in Chapter 4.

Pinocytosis—An Active Transport Mechanism for Reabsorption of Proteins. Some parts of the tubule, especially the proximal tubule, reabsorb large molecules such as proteins by *pinocytosis*. 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, 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 *tubular load*) exceeds the capacity of the carrier proteins and specific enzymes involved in the transport process.
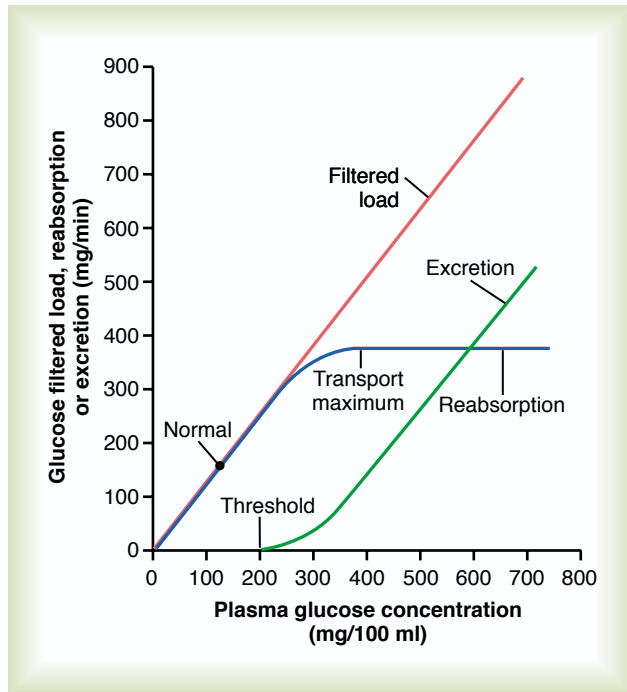
Figure 27–4

Relations among the filtered load of glucose, the rate of glucose reabsorption by the renal tubules, and the 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.

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 27–4 shows the relation 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 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 threshold and transport maximum is that not all

nephrons have the same transport maximum for glucose, and some of the nephrons 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 excretion of glucose in the urine, even after eating a meal. However, in uncontrolled *diabetes mellitus,* plasma glucose 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 mM/min
Sulfate	0.06 mM/min
Amino acids	1.5 mM/min
Urate	15 mg/min
Lactate	75 mg/min
Plasma protein	30 mg/min

Transport Maximums for Substances That Are Actively Secreted. 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. *Substances that are passively reabsorbed do not demonstrate a transport maximum* because their rate of transport is determined by other factors, such as (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.

Some actively transported substances also have characteristics of gradient-time transport. An example is sodium reabsorption in the proximal tubule. The main reason that sodium transport in the proximal tubule does not exhibit a transport maximum is that other factors limit the reabsorption rate besides the maximum rate of active transport. For example, in the proximal tubules, the maximum transport capacity of the basolateral sodium-potassium ATPase pump is usually far greater than the actual rate of net sodium

reabsorption. One of the reasons for this is that a significant amount of sodium transported out of the cell leaks back into the tubular lumen through the epithelial tight junctions. The rate at which this back-leak occurs depends on several factors, including (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 means that the greater the concentration of sodium in the proximal tubules, the greater 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 in response to certain hormones, such as *aldosterone*.

Passive Water Reabsorption by Osmosis Is Coupled Mainly to Sodium Reabsorption

When solutes are transported out of the tubule by either primary or secondary active transport, their concentrations tend to decrease inside the tubule while increasing in the renal interstitium. This 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 occurs through the so-called *tight junctions* between the epithelial cells as well as through the cells themselves. The reason for this, as already discussed, is that the junctions between the cells are not as tight as their name would imply, and they allow significant diffusion of water and small ions. This 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.

As water moves across the tight junctions by osmosis, it can also carry with it some of the solutes, a process referred to as *solvent drag*. And 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 tubular membrane by osmosis. However, antidiuretic hormone (ADH) greatly increases the water permeability in the distal and collecting tubules, as discussed later.

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, the water permeability is always high, and water is reabsorbed as rapidly as the solutes. In the ascending loop of Henle, water permeability is always low, so that 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—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. This causes chloride ions 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 27–5). Thus, the active reabsorption of sodium is closely coupled to the passive reabsorption of chloride by way of an electrical potential and a chloride concentration gradient.
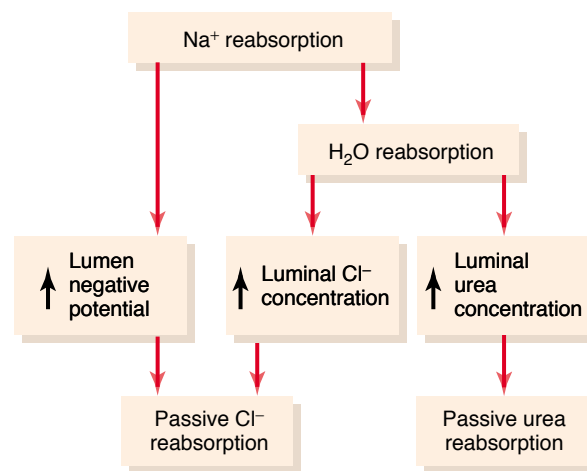
Figure 27–5

Mechanisms by which water, chloride, and urea reabsorption are coupled with sodium reabsorption.

Chloride ions can also be reabsorbed by secondary active transport. The most important of the secondary active transport processes for chloride reabsorption involves 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 27–5). This creates a concentration gradient favoring the 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 one half of the urea that is filtered by the glomerular capillaries is reabsorbed from the tubules. The remainder of the urea passes into the urine, allowing the kidneys to excrete large amounts of this waste product of metabolism.

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 that virtually all the creatinine filtered by the glomerulus is excreted in the urine.

Reabsorption and Secretion Along Different Parts of the Nephron

In the previous sections, we discussed the basic principles by which 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 excretory functions. Only the tubular transport functions that are quantitatively most important are discussed, especially as they relate to the reabsorption of sodium, chloride, and water. In subsequent chapters, we discuss the reabsorption and secretion of other specific substances in different parts of the tubular system.

Proximal Tubular Reabsorption

Normally, about 65 per cent 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 physiologic conditions, as discussed later.

Proximal Tubules Have a 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 27–6. The proximal tubule epithelial cells are highly metabolic and have large numbers of mitochondria to support potent active transport processes. In addition, the proximal
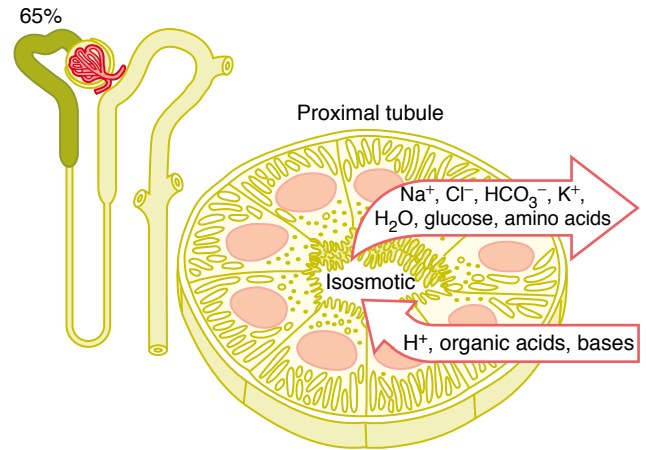

65%

Proximal tubule

Na^+, Cl^-, HCO_3^-, K^+, H_2O, glucose, amino acids

Isosmotic

H^+, organic acids, bases

Figure 27–6

Cellular ultrastructure and primary transport characteristics of the proximal tubule. The proximal tubules reabsorb about 65 per cent 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.

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 by way of the *co-transport* mechanism with multiple organic nutrients such as amino acids and glucose. The remainder of the sodium is transported from the tubular lumen into the cell by *counter-transport* mechanisms, which reabsorb sodium while secreting other substances into the tubular lumen, especially hydrogen ions. As discussed in Chapter 30, the 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 sodium-potassium ATPase pump provides the major force for reabsorption of sodium, chloride, and water throughout the proximal tubule, there are some differences in the mechanisms by which 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. But in the second half of the proximal tubule, little glucose and 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 (around 140 mEq/L) compared with the early
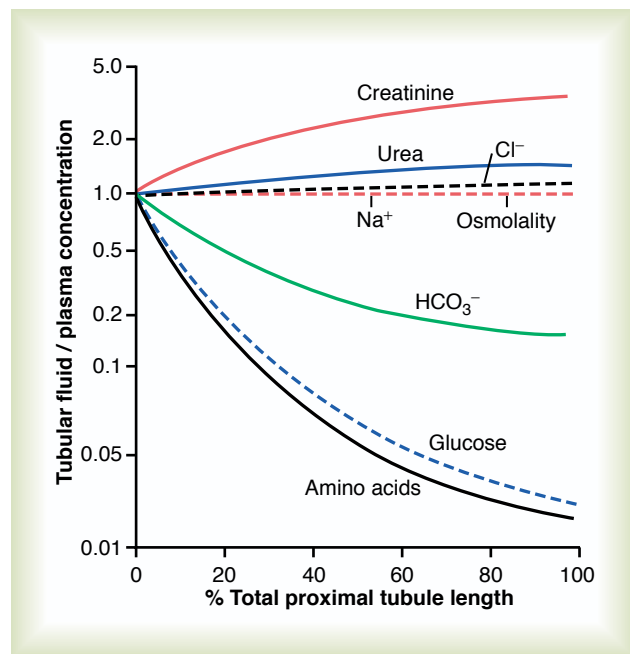
Figure 27–7

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 in the 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.

proximal tubule (about 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 the diffusion of this ion from the tubule lumen through the intercellular junctions into the renal interstitial fluid.

Concentrations of Solutes Along the Proximal Tubule. Figure 27–7 summarizes the changes in concentrations of various solutes along the proximal tubule. Although the *amount* of sodium in the tubular fluid decreases markedly along the proximal tubule, the *concentration* of sodium (and the 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, so that 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.

Secretion of Organic Acids and Bases by the Proximal Tubule. 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 the 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 directly through the tubular cells 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 problem 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 per cent 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, as discussed later.

Solute and Water Transport in the Loop of Henle

The loop of Henle consists of three functionally distinct segments: the *thin descending segment*, the *thin ascending segment*, and the *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 27–8).

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 per cent 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 the 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 27–8). About 25 per cent 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 ascending loop of Henle. The thin segment of the ascending limb has a much lower reabsorptive capacity than the thick segment,
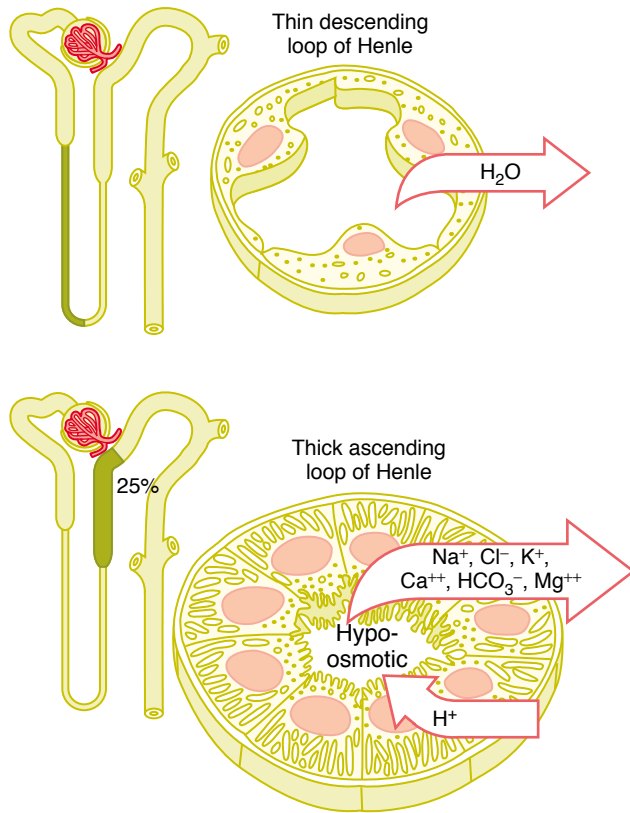
Figure 27–8

Cellular ultrastructure and transport characteristics of the thin descending loop of Henle (*top*) and the 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 per cent 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.

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 sodium-potassium 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 sodium-potassium 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 co-transporter* (Figure 27–9). This co-transport protein carrier 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.
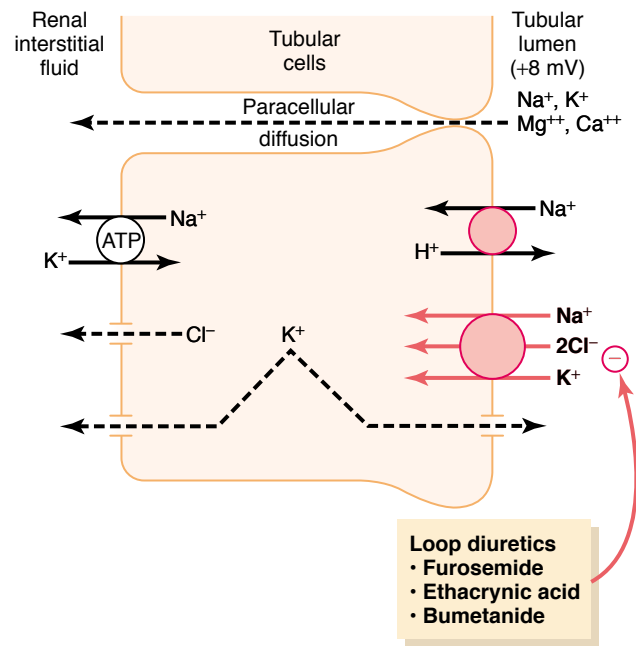

Figure 27–9

Mechanisms of sodium, chloride, and potassium transport in the thick ascending loop of Henle. The sodium-potassium 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 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^{++} and Ca^{++} to diffuse from the lumen to the interstitial fluid via the paracellular pathway.

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 sodium 2-chloride, potassium co-transporter. These diuretics are discussed in Chapter 31.

There is also significant paracellular reabsorption of cations, such as Mg^{++}, Ca^{++}, Na^+, and K^+, in the thick ascending limb owing to the slight positive charge of the tubular lumen relative to the interstitial fluid. Although the 1-sodium, 2-chloride, 1-potassium 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^{++} and Ca^{++} to diffuse from the tubular lumen through the paracellular space and into the interstitial fluid.

The thick ascending limb also has a sodium-hydrogen counter-transport mechanism in its luminal cell membrane that mediates sodium reabsorption and hydrogen secretion in this segment.

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 we discuss much more fully in Chapter 28.

Distal Tubule

The thick segment of the ascending limb of the loop of Henle empties into the *distal tubule*. The very first portion of the distal tubule forms part of the *juxtaglomerular complex* that provides feedback control of 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 percent 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 sodium-potassium ATPase pump transports sodium out of the cell across the basolateral membrane (Figure 27–10). Chloride diffuses out of the 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.
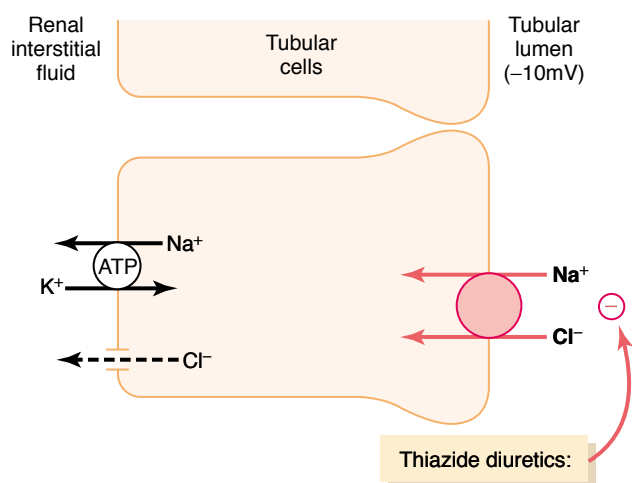
Late Distal Tubule and Cortical Collecting Tubule

The second half of the distal tubule and the subsequent cortical collecting tubule have similar functional characteristics. Anatomically, they are composed of two distinct cell types, the *principal cells and the intercalated cells* (Figure 27–11). The principal cells reabsorb sodium and water from the lumen and secrete potassium ions into the lumen. The 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 sodium-potassium ATPase pump in each cell's basolateral membrane (Figure 27–12). This pump maintains a low sodium concentration inside the cell and, therefore, favors sodium diffusion into the cell through special
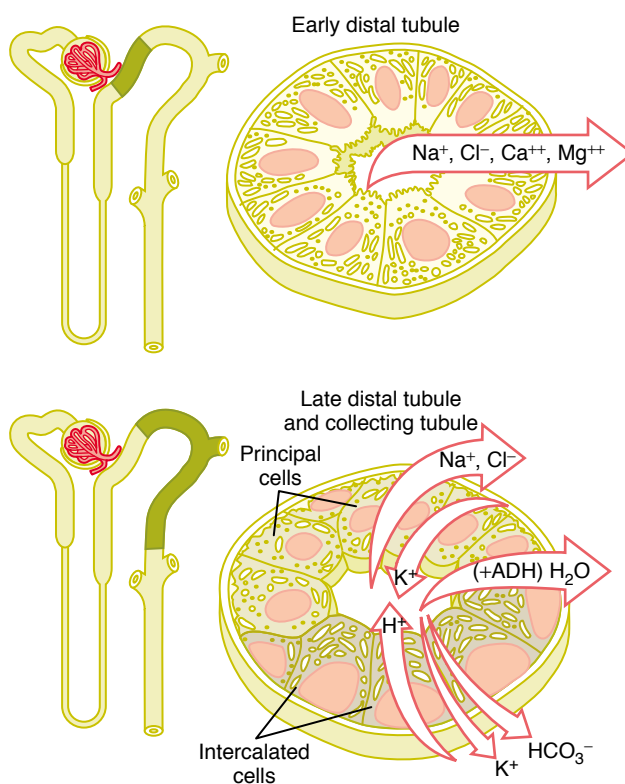

Figure 27–11

Cellular ultrastructure and transport characteristics of the early distal tubule and the 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 the *intercalated cells*. The principal cells reabsorb sodium from the lumen and secrete potassium ions into the lumen. The 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*.

Figure 27–10

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 sodium-potassium ATPase and chloride diffuses into the interstitial fluid via chloride channels.
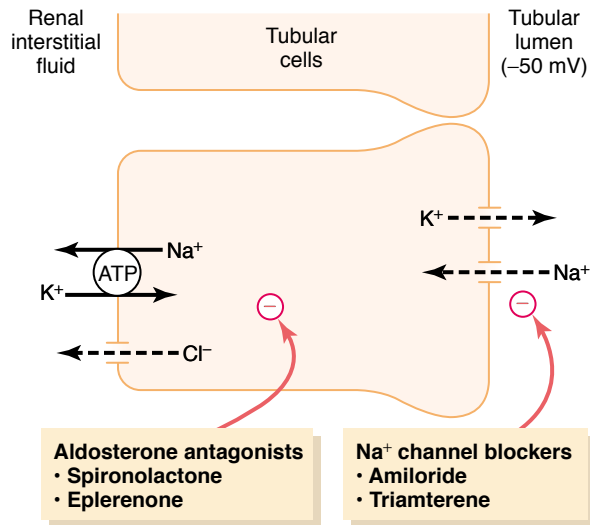
Figure 27–12

Mechanism of sodium chloride reabsorption and potassium secretion in the late distal tubules and cortical collecting tubules. Sodium enters the cell through special channels and is transported out of the cell by the sodium-potassium 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.

channels. The secretion of potassium by these cells from the blood into the tubular lumen involves two steps: (1) Potassium enters the cell because of the sodium-potassium ATPase pump, which maintains a high intracellular potassium concentration, and then (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. Aldosterone antagonists compete with aldosterone for receptor sites in the principal cells and therefore inhibit the stimulatory effects of aldosterone on sodium reabsorption and potassium secretion. Sodium channel blockers 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 sodium-potassium ATPase pump. This, in turn, decreases transport of potassium into the cells and ultimately reduces potassium secretion into the tubular fluid. For this reason the sodium channel blockers as well as the aldosterone antagonists decrease urinary excretion of potassium and act as potassium-sparing diuretics.

Intercalated Cells Avidly Secrete Hydrogen and Reabsorb Bicarbonate and Potassium Ions. Hydrogen ion secretion by the intercalated cells is mediated by a hydrogen-ATPase transport mechanism. 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. A more detailed discussion of this mechanism is presented in Chapter 30. The intercalated cells can also reabsorb potassium ions.

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 the 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 by other factors such as the concentration of potassium ions in the body fluids.
3. The *intercalated cells* of these nephron segments avidly secrete hydrogen ions by an active hydrogen-ATPase mechanism. 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. 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 Duct

Although the medullary collecting ducts reabsorb less than 10 per cent of the filtered water and sodium, they are the final site for processing the urine and, therefore, play an extremely important 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
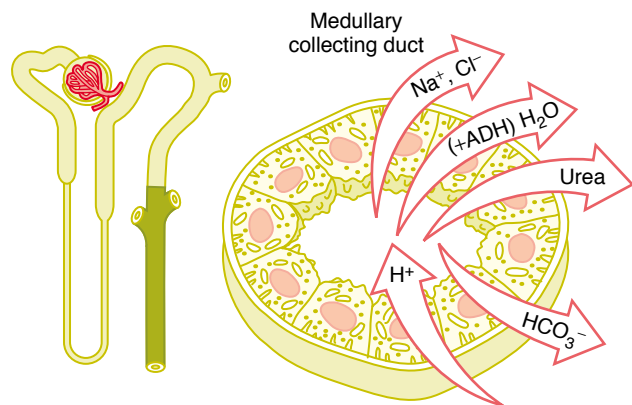
Figure 27–13

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.

few mitochondria (Figure 27–13). 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. Therefore, some of the tubular urea is reabsorbed into the medullary interstitium, helping to raise the osmolality in this region of the kidneys and contributing to the kidneys' overall ability to form a concentrated urine.
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.

Summary of Concentrations of Different Solutes in the 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 27–14 shows the degree of concentration of several substances in the different tubular segments. All the values in this figure represent the tubular fluid concentration divided by the plasma concentration of
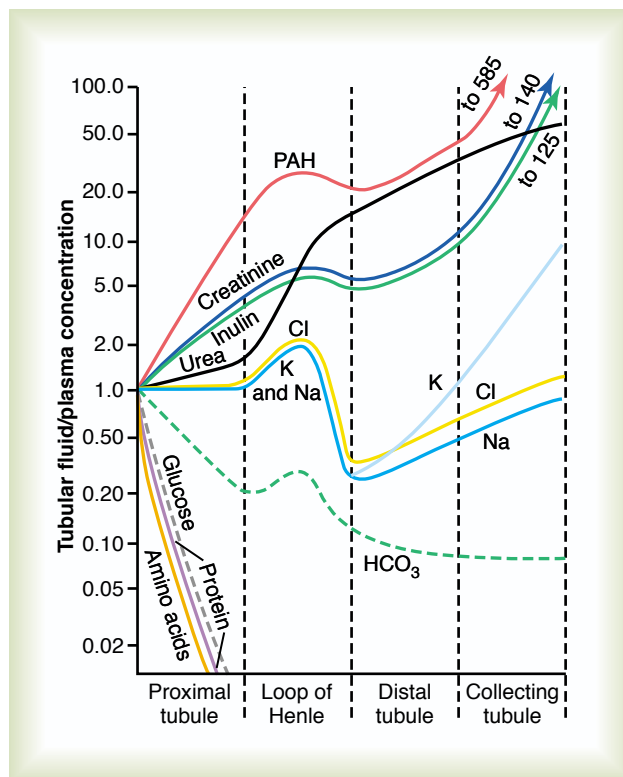

Figure 27–14

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 in the 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.

a substance. If plasma concentration of the substance is assumed to be constant, any change in the ratio of tubular fluid/plasma concentration rate reflects changes in tubular fluid concentration.

As the filtrate moves along the tubular system, the concentration rises to progressively greater 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 27–14, 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 especially great quantities into the urine. Conversely, the substances represented toward 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 Measure Water Reabsorption by the Renal Tubules. Inulin, a polysaccharide used to measure 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 3 times greater than in the plasma and in the glomerular filtrate. Since 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 27–14), 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—The Ability of the Tubules to Increase Reabsorption Rate 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 GFR is increased from 125 ml/min to 150 ml/min, the absolute rate of proximal tubular reabsorption also increases from about 81 ml/min (65 per cent of GFR) to about 97.5 ml/min (65 per cent 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 per cent.

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.

The importance of glomerulotubular balance is that it helps to prevent overloading of the distal tubular segments when GFR increases. Glomerulotubular balance acts as a second line of defense to buffer the effects of spontaneous changes in GFR on urine output. (The first line of defense, discussed earlier, includes the renal autoregulatory mechanisms, especially tubuloglomerular feedback, which help prevent 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 wreak havoc with the maintenance of 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 these physical forces 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 per cent 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

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

The net reabsorptive force represents the sum of the hydrostatic and colloid osmotic forces that either favor or oppose reabsorption across the peritubular capillaries. These forces include (1) hydrostatic pressure inside the peritubular capillaries (peritubular hydrostatic pressure $[P_c]$), which opposes reabsorption; (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 27–15 shows the approximate normal forces that favor and oppose peritubular reabsorption.
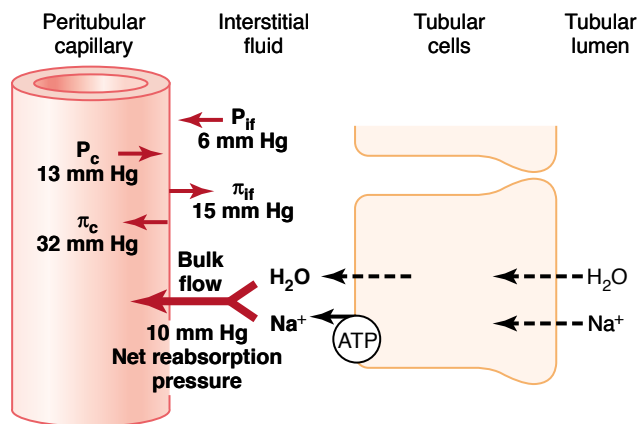
Figure 27–15

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.

Because the normal peritubular capillary pressure averages about 13 mm Hg and 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 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 is a high value, 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/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*. (1) Increases in arterial pressure tend to raise peritubular capillary hydrostatic pressure and decrease 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) Increase in resistance of either the afferent or the 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* (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/renal plasma flow, increased filtration fraction can occur as a result of increased GFR or decreased renal plasma flow. Some renal vasoconstrictors, such as angiotensin II, increase peritubular capillary reabsorption by decreasing renal plasma flow 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 physiologic conditions. Table 27–2 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 either increased peritubular capillary hydrostatic pressure or decreased peritubular capillary colloid osmotic pressure, reduces the uptake of fluid and solutes from the interstitium into the peritubular capillaries. This 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.

Table 27–2

Factors That Can Influence Peritubular Capillary Reabsorption

$\uparrow P_c \rightarrow \downarrow$ Reabsorption
- $\downarrow R_A \rightarrow \uparrow P_c$
- $\downarrow R_E \rightarrow \uparrow P_c$
- $\uparrow$ Arterial Pressure $\rightarrow \uparrow P_c$

$\uparrow \pi_c \rightarrow \uparrow$ Reabsorption
- $\uparrow \pi_A \rightarrow \uparrow \pi_c$
- $\uparrow FF \rightarrow \uparrow \pi_c$

$\uparrow K_f \rightarrow \uparrow$ Reabsorption

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

The mechanisms by which 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 27–16). 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. And once the water and solutes are in the interstitial spaces, they can either 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 that 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 backleak into the tubular lumen, thereby reducing the rate of net reabsorption (refer again to Figure 27–16).

The opposite is true when there is increased peritubular capillary reabsorption 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 of 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 increases.

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 matched to the net reabsorption of water and solutes from the tubular lumen into the interstitium. Therefore, 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.*
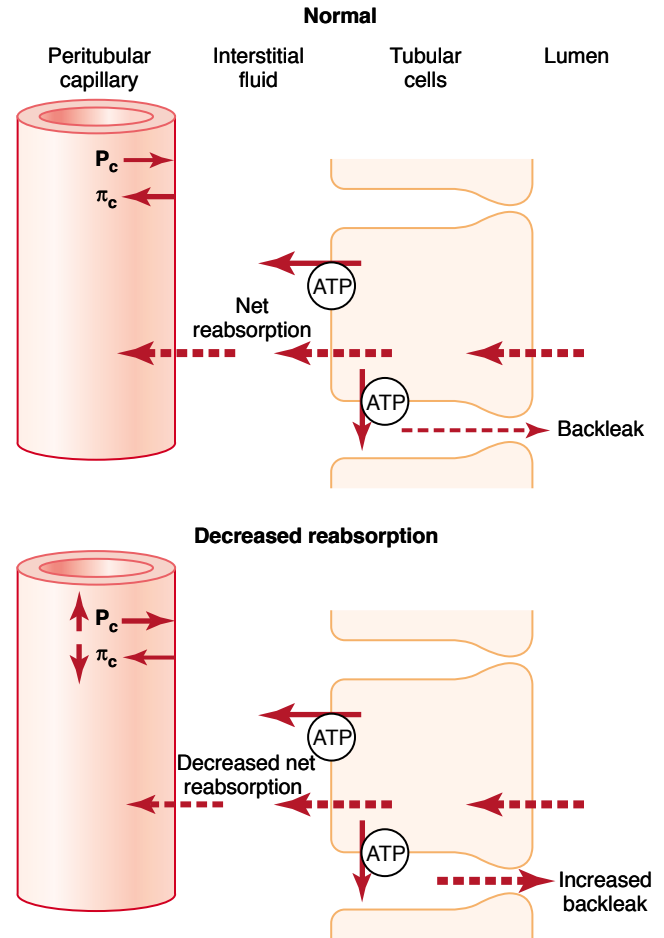

Figure 27–16

Proximal tubular and peritubular capillary reabsorption under normal conditions (*top*) and during decreased peritubular capillary reabsorption (*bottom*) caused by either 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.

Effect of Arterial Pressure on Urine Output—The Pressure-Natriuresis and Pressure-Diuresis Mechanisms

Even small increases in arterial pressure often cause marked increases in urinary excretion of sodium and water, phenomena that are referred to as *pressure natriuresis* and *pressure diuresis.* Because of the autoregulatory mechanisms described in Chapter 26, 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 cause much larger increases in GFR.

A second effect of increased renal arterial pressure that raises urine output is that it decreases the percentage of the filtered load of sodium and water that is reabsorbed by the tubules. The mechanisms responsible for this effect include 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 the pressure-natriuresis and pressure-diuresis mechanisms is reduced angiotensin II formation. Angiotensin II itself increases sodium reabsorption by the tubules; it also 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.

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 appropriately adjust urinary sodium excretion 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 27–3 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 28 and 29, but we briefly review their renal tubular actions in the next few paragraphs.

Aldosterone Increases Sodium Reabsorption and Increases Potassium Secretion. Aldosterone, secreted by the zona glomerulosa cells of the adrenal cortex, is an important regulator of sodium reabsorption and potassium secretion by the renal tubules. *The primary site of aldosterone action is on the principal cells of the cortical collecting tubule.* The mechanism by which aldosterone increases sodium reabsorption while at the same time increasing potassium secretion is by stimulating the sodium-potassium 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. The cellular mechanisms of aldosterone action are discussed in Chapter 77.

In the absence of aldosterone, as occurs with adrenal destruction or malfunction (*Addison's disease*), there is marked loss of sodium from the body and accumulation of potassium. Conversely, excess aldosterone secretion, as occurs in patients with adrenal tumors (*Conn's syndrome*) is associated with sodium retention and potassium depletion. Although day-to-day regulation of sodium balance can be maintained as long as minimal levels of aldosterone are present, the inability to appropriately adjust aldosterone secretion 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 it is for sodium concentration.

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. The increased formation of angiotensin II helps to 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 raise sodium and water

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Table 27–3

Hormones That Regulate Tubular Reabsorption

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

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 the colloid osmotic pressure in the peritubular capillaries; this 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 sodium-potassium 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. Thus, angiotensin II stimulates sodium transport across both the luminal and the basolateral surfaces of the epithelial cell membrane in the tubules.

These multiple actions of angiotensin II cause marked sodium retention by the kidneys when angiotensin II levels are increased.

ADH 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 to 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. 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 28 and 75.

ADH binds to specific V_2 *receptors* in the late distal tubules, collecting tubules, and collecting ducts, increasing the formation of cyclic AMP and activating protein kinases. This, in turn, stimulates the 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 rapidly exit the cells, although these are not believed to be 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.

Atrial Natriuretic Peptide Decreases Sodium and Water Reabsorption. Specific cells of the cardiac atria, when distended because of plasma volume expansion, secrete a peptide called *atrial natriuretic peptide*. Increased levels of this peptide in turn inhibit the reabsorption of sodium and water by the renal tubules, especially in the collecting ducts. This decreased sodium and water reabsorption increases urinary excretion, which helps to return blood volume back toward normal.

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 perhaps also in the loops of Henle. 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 29.

Sympathetic Nervous System Activation Increases Sodium Reabsorption

Activation of the sympathetic nervous system can decrease sodium and water excretion by constricting the renal arterioles, thereby reducing GFR. Sympathetic activation also increases 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. And finally, sympathetic nervous system stimulation 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 27–4). 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 time*. This concept is somewhat abstract because there is no single volume of plasma that is *completely* cleared of a substance. However, renal clearance provides a useful way of quantifying the excretory function of the kidneys and, as discussed later, can be used to quantify the rate at which blood flows through the kidneys as well as the basic functions of the kidneys: glomerular filtration, 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. Thus,

Table 27–4

Use of Clearance to Quantify Kidney Function

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

S, a substance; U, urine concentration; V, urine flow rate; P, plasma concentration; PAH, para-aminohippuric acid; P_{PAH}, renal arterial PAH concentration; E_{PAH}, PAH extraction ratio; V_{PAH}, renal venous PAH concentration.

clearance refers to the volume of plasma that would be necessary to supply the amount of substance excreted in the urine per unit 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 GFR

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 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:

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

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 27–17 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 GFR. Other substances that have been used clinically to estimate GFR include *radioactive iothalamate* and *creatinine*.

Creatinine Clearance and Plasma Creatinine Concentration Can Be Used to Estimate GFR

Creatinine is a by-product of muscle metabolism and is cleared from the body fluids almost entirely by glomerular filtration. Therefore, the clearance of creatinine 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 that the amount of creatinine excreted slightly exceeds the amount filtered. There is normally a slight error in measuring plasma creatinine that leads to an overestimate of the plasma creatinine
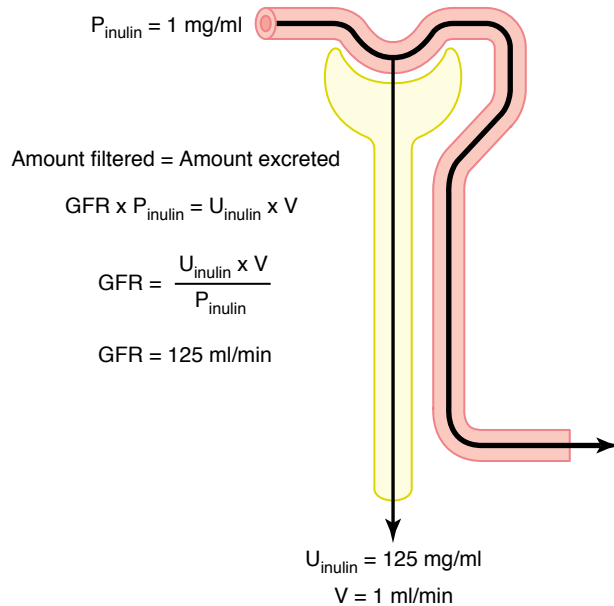
P_{inulin} = 1 mg/ml

Amount filtered = Amount excreted

$$GFR \times P_{inulin} = U_{inulin} \times V$$

$$GFR = \frac{U_{inulin} \times V}{P_{inulin}}$$

GFR = 125 ml/min

U_{inulin} = 125 mg/ml

V = 1 ml/min

Figure 27–17

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; V, urine flow rate.

concentration, and 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 plasma creatinine concentration (P_{Cr}), which is inversely proportional to GFR:

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

If GFR suddenly decreases by 50%, the kidneys will transiently filter and excrete only half as much creatinine, causing accumulation of creatinine in the body fluids and raising plasma concentration. Plasma concentration of creatinine will continue to rise until the filtered load of creatinine ($P_{Cr} \times GFR$) and creatinine excretion ($U_{Cr} \times V$) return to normal and a balance between creatinine production and creatinine excretion is reestablished. This will occur when plasma creatinine increases to approximately twice normal, as shown in Figure 27–18. If GFR falls to one-fourth normal, plasma creatinine would increase to about 4 times normal, and a decrease of GFR to one-eighth normal would raise plasma creatinine to 8 times normal. Thus, under steady-state conditions, the 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 elevated plasma creatinine concentration, as shown in Figure 27–19.

PAH 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
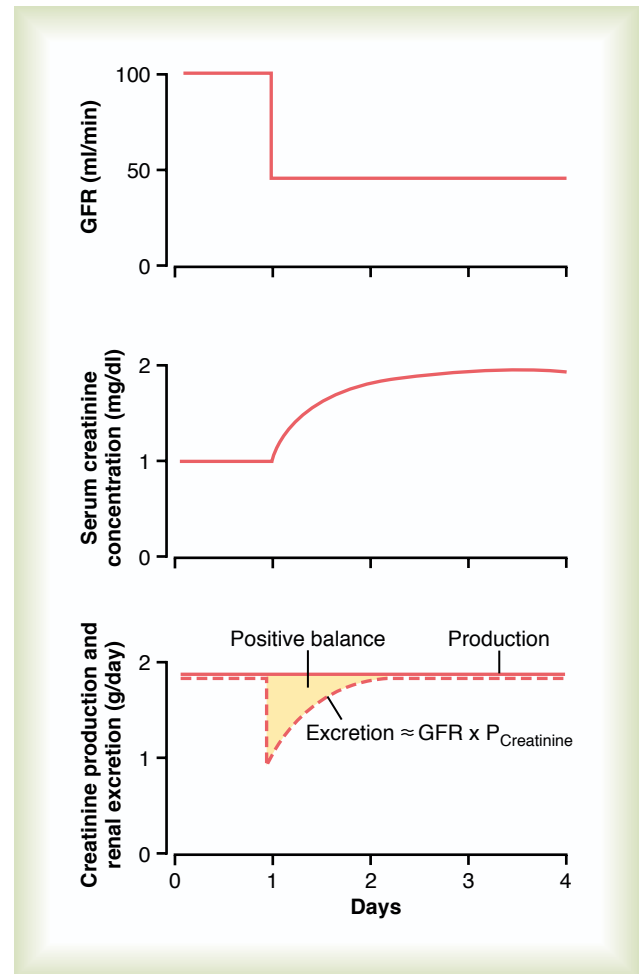

Figure 27–18

Effect of reducing glomerular filtration rate (GRF) by 50 per cent on serum creatinine concentration and on creatinine excretion rate when the production rate of creatinine remains constant. $P_{Creatinine}$, plasma creatinine concentration.

to the total renal plasma flow. In other words, the amount of the substance delivered to the kidneys in the blood (renal plasma flow $\times P_s$) would be equal to the amount excreted in the urine ($U_s \times V$). Thus, renal plasma flow (RPF) could be calculated as

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

Because the GFR is only about 20 per cent of the total plasma flow, a substance that is completely cleared from the plasma must be excreted by tubular secretion as well as glomerular filtration (Figure 27–20). There is no known substance that is *completely* cleared by the kidneys. One substance, however, PAH, is about 90 per cent cleared from the plasma. Therefore, the clearance of PAH can be used as an approximation of renal plasma flow. 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 per cent in normal kidneys. In diseased kidneys, this extraction ratio may be reduced
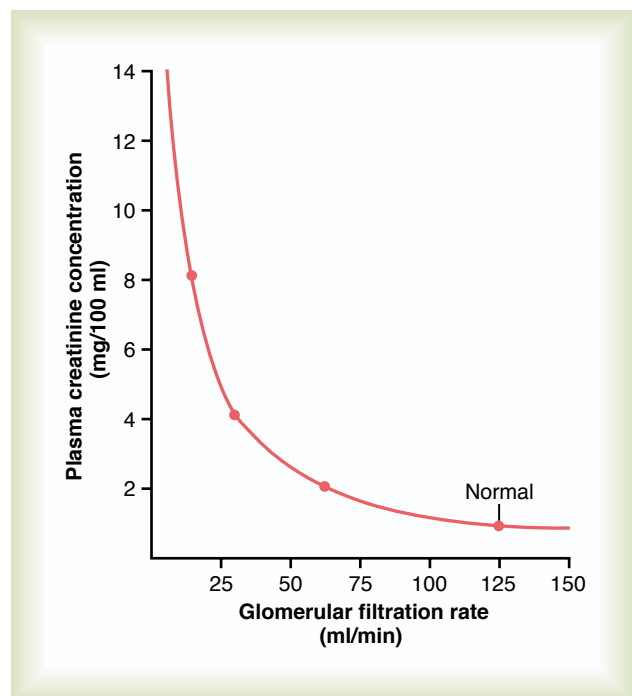
Figure 27–19

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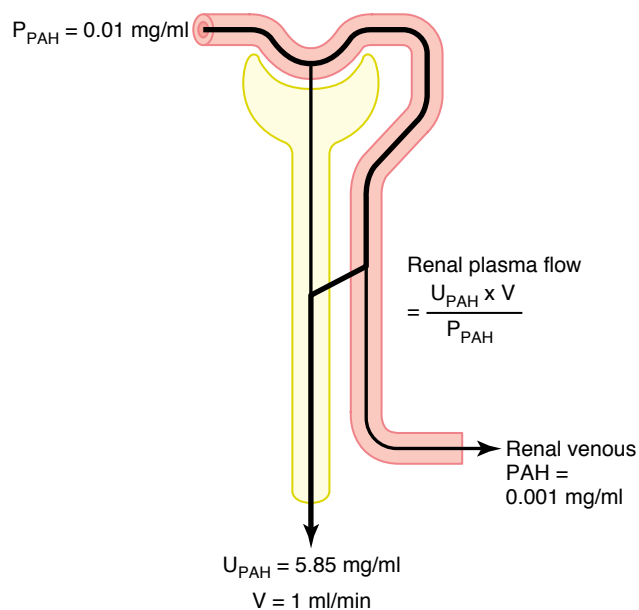

Figure 27–20

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 (C_{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; V, urine flow rate.

because of 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, clearance of PAH calculates to be 585 ml/min.

If the extraction ratio for PAH is 90 per cent, the actual renal plasma flow can be calculated by dividing 585 ml/min by 0.9, yielding a value of 650 ml/min. Thus, total renal plasma flow can be calculated as

Total renal plasma flow =
    Clearance of PAH/Extraction ratio of PAH

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 renal plasma flow and hematocrit (the percentage of red blood cells in the blood). If the hematocrit is 0.45 and the total renal plasma flow 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 Renal Plasma Flow

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

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

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 a net secretion of that substance by the renal tubules. For example, if the rate of excretion of the substance ($U_s \times V$) is less than the filtered load of the substance ($GFR \times P_s$), 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, a measure of 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

References

Aronson PS: Ion exchangers mediating NaCl transport in the renal proximal tubule. Cell Biochem Biophys 36:147, 2002.

Benos DJ, Fuller CM, Shlyonsky VG, et al: Amiloride-sensitive Na$^+$ channels: insights and outlooks. News Physiol Sci 12:55, 1997.

Féraille E, Doucet A: Sodium-potassium-adenosine-triphosphatase–dependent sodium transport in the kidney: Hormonal control. Physiol Rev 81:345, 2001.

Granger JP, Alexander BT, Llinas M: Mechanisms of pressure natriuresis. Curr Hypertens Rep 4:152, 2002.

Hall JE, Brands MW: The renin-angiotensin-aldosterone system: renal mechanisms and circulatory homeostasis. In Seldin DW, Giebisch G (eds): The Kidney—Physiology and Pathophysiology, 3rd ed. New York: Raven Press, 2000.

Humphreys MH, Valentin J-P: Natriuretic hormonal agents. In Seldin DW, Giebisch G (eds): The Kidney—Physiology and Pathophysiology, 3rd ed. New York: Raven Press, 2000.

Kellenberger S, Schild L: Epithelial sodium channel/degenerin family of ion channels: A variety of functions for a shared structure. Physiol Rev 82:735, 2002.

Nielsen S, Frøkiær J, Marples D, et al: Aquaporins in the kidney: from molecules to medicine. Physiol Rev 82:205, 2002.

Palmer LG, Frindt G: Aldosterone and potassium secretion by the cortical collecting duct. Kidney Int 57:1324, 2000.

Rahn KH, Heidenreich S, Bruckner D: How to assess glomerular function and damage in humans. J Hypertens 17:309, 1999.

Reeves WB, Andreoli TE: Sodium chloride transport in the loop of Henle, distal convoluted tubule and collecting duct. In Seldin DW, Giebisch G (eds): The Kidney—Physiology and Pathophysiology, 3rd ed. New York: Raven Press, 2000.

Reilly RF, Ellison DH: Mammalian distal tubule: physiology, pathophysiology, and molecular anatomy. Physiol Rev 80:277, 2000.

Rossier BC, Praderv S, Schild L, Hummler E: Epithelial sodium channel and the control of sodium balance: interaction between genetic and environmental factors. Annu Rev Physiol 64:877, 2002.

Russell JM: Sodium-potassium-chloride cotransport. Physiol Rev 80:211, 2000.

Schafer JA: Abnormal regulation of ENaC: syndromes of salt retention and salt wasting by the collecting duct. Am J Physiol Renal Physiol 283:F221, 2002.

Weinstein AM: Mathematical models of renal fluid and electrolyte transport: acknowledging our uncertainty. Am J Physiol Renal Physiol 284:F871, 2003.

Wright EM: Renal Na(+)-glucose cotransporters. Am J Physiol Renal Physiol 280:F10, 2001.