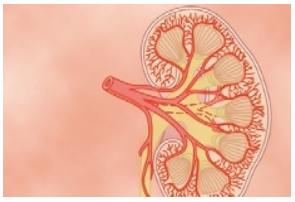
Urine Formation by the Kidneys: I. Glomerular Filtration, Renal Blood Flow, and Their Control



Multiple Functions of the Kidneys

Most people are familiar with one important function of the kidneys—to rid the body of waste materials that are either ingested or produced by metabolism. A second function that is especially critical is to control the volume and composition of the body fluids. For water and virtually all electrolytes in the body, the balance between intake (due to ingestion or metabolic production) and output (due to excretion or metabolic consumption) is maintained largely by the kidneys. This regulatory function of the kidneys maintains the stable internal environment necessary for the cells to perform their various activities.

The kidneys perform their most important functions by filtering the plasma and removing substances from the filtrate at variable rates, depending on the needs of the body. Ultimately, the kidneys "clear" unwanted substances from the filtrate (and therefore from the blood) by excreting them in the urine while returning substances that are needed back to the blood.

Although this chapter and the next few chapters focus mainly on the control of renal excretion of water, electrolytes, and metabolic waste products, the kidneys serve many important homeostatic functions, including the following:

- Excretion of metabolic waste products and foreign chemicals
- Regulation of water and electrolyte balances
- Regulation of body fluid osmolality and electrolyte concentrations
- Regulation of arterial pressure
- Regulation of acid-base balance
- Secretion, metabolism, and excretion of hormones
- Gluconeogenesis

Excretion of Metabolic Waste Products, Foreign Chemicals, Drugs, and Hormone Metabolites. The kidneys are the primary means for eliminating waste products of metabolism that are no longer needed by the body. These products include *urea* (from the metabolism of amino acids), *creatinine* (from muscle creatine), *uric acid* (from nucleic acids), *end products of hemoglobin breakdown* (such as bilirubin), and *metabolites of various hormones.* These waste products must be eliminated from the body as rapidly as they are produced. The kidneys also eliminate most toxins and other foreign substances that are either produced by the body or ingested, such as pesticides, drugs, and food additives.

Regulation of Water and Electrolyte Balances. For maintenance of homeostasis, excretion of water and electrolytes must precisely match intake. If intake exceeds excretion, the amount of that substance in the body will increase. If intake is less than excretion, the amount of that substance in the body will decrease.

Intake of water and many electrolytes is governed mainly by a person's eating and drinking habits, requiring the kidneys to adjust their excretion rates to match the intakes of various substances. Figure 26-1 shows the response of the kidneys to a sudden 10-fold increase in sodium intake from a low level of 30 mEq/day to a high level of 300 mEq/day. Within 2 to 3 days after raising the sodium intake, renal excretion also increases to about 300 mEq/day so that a balance between intake and output is re-established. However, during the 2 to 3 days of renal adaptation to the high sodium intake, there is a modest accumulation of sodium that raises extracellular fluid volume slightly and triggers hormonal changes and other compensatory responses that signal the kidneys to increase their sodium excretion.

The capacity of the kidneys to alter sodium excretion in response to changes in sodium intake is enormous. Experimental studies have shown that in many people, sodium intake can be increased to 1500 mEq/day (more than 10 times normal) or decreased to 10 mEq/day (less than one-tenth normal) with relatively small changes in extracellular fluid volume or plasma sodium concentration. This is also true for water and for most other electrolytes, such as chloride, potassium, calcium, hydrogen, magnesium, and phosphate ions. In the next few chapters, we discuss the specific mechanisms that permit the kidneys to perform these amazing feats of homeostasis.

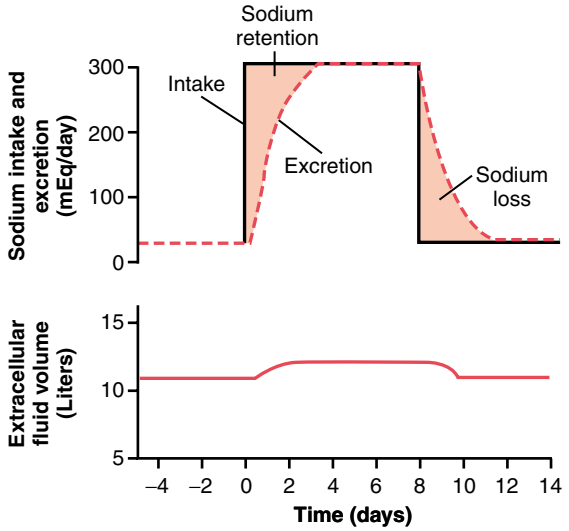


Figure 26-1 Effect of increasing sodium intake 10-fold (from 30 to 300 mEq/day) on urinary sodium excretion and extracellular fluid volume. The shaded areas represent the net sodium retention or the net sodium loss, determined from the difference between sodium intake and sodium excretion.

Regulation of Arterial Pressure. As discussed in Chapter 19, the kidneys play a dominant role in long-term regulation of arterial pressure by excreting variable amounts of sodium and water. The kidneys also contribute to short-term arterial pressure regulation by secreting hormones and vasoactive factors or substances (e.g., *renin*) that lead to the formation of vasoactive products (e.g., angiotensin II).

Regulation of Acid-Base Balance. The kidneys contribute to acid-base regulation, along with the lungs and body fluid buffers, by excreting acids and by regulating the body fluid buffer stores. The kidneys are the only means of eliminating from the body certain types of acids, such as sulfuric acid and phosphoric acid, generated by the metabolism of proteins.

Regulation of Erythrocyte Production. The kidneys secrete *erythropoietin,* which stimulates the production of red blood cells by *hematopoietic stem cells* in the bone marrow, as discussed in Chapter 32. One important stimulus for erythropoietin secretion by the kidneys is *hypoxia.* The kidneys normally account for almost all the erythropoietin secreted into the circulation. In people with severe kidney disease or who have had their kidneys removed and have been placed on hemodialysis, severe anemia develops as a result of decreased erythropoietin production.

Regulation of 1,25-Dihydroxyvitamin D_3 Production. The kidneys produce the active form of vitamin D, 1,25-dihydroxyvitamin D_3 (*calcitriol*), by hydroxylating this vitamin at the "number 1" position. Calcitriol is essential for normal calcium deposition in bone and calcium reabsorption by the gastrointestinal tract. As discussed in Chapter 79, calcitriol plays an important role in calcium and phosphate regulation.

Glucose Synthesis. The kidneys synthesize glucose from amino acids and other precursors during prolonged fasting, a process referred to as *gluconeogenesis.* The kidneys' capacity to add glucose to the blood during prolonged periods of fasting rivals that of the liver.

With chronic kidney disease or acute failure of the kidneys, these homeostatic functions are disrupted and severe abnormalities of body fluid volumes and composition rapidly occur. With complete renal failure, enough potassium, acids, fluid, and other substances accumulate in the body to cause death within a few days, unless clinical interventions such as hemodialysis are initiated to restore, at least partially, the body fluid and electrolyte balances.

Physiologic Anatomy of the Kidneys

General Organization of the Kidneys and Urinary Tract

The two kidneys lie on the posterior wall of the abdomen, outside the peritoneal cavity (Figure 26-2). Each kidney of the adult human weighs about 150 grams and is about the size of a clenched fist. The medial side of each kidney contains an indented region called the *hilum* through which pass the renal artery and vein, lymphatics, nerve supply, and ureter, which carries the final urine from the kidney to the bladder, where it is stored until emptied. The kidney is surrounded by a tough, fibrous *capsule* that protects its delicate inner structures.

If the kidney is bisected from top to bottom, the two major regions that can be visualized are the outer *cortex* and the inner *medulla* regions. The medulla is divided into 8 to 10 cone-shaped masses of tissue called *renal pyramids.* The base of each pyramid originates at the border between the cortex and medulla and terminates in the *papilla,* which projects into the space of the *renal pelvis,* a funnel-shaped continuation of the upper end of the ureter. The outer border of the pelvis is divided into open-ended pouches called *major calyces* that extend downward and divide into *minor calyces,* which collect urine from the tubules of each papilla. The walls of the calyces, pelvis, and ureter contain contractile elements that propel the urine toward the *bladder,* where urine is stored until it is emptied by *micturition,* discussed later in this chapter.

Renal Blood Supply

Blood flow to the two kidneys is normally about 22 percent of the cardiac output, or 1100 ml/min. The renal artery enters the kidney through the hilum and then branches progressively to form the *interlobar arteries, arcuate arteries, interlobular arteries* (also called *radial arteries*) and *afferent arterioles,* which lead to the *glomerular capillaries,* where large amounts of fluid and solutes (except the plasma proteins) are filtered to begin urine

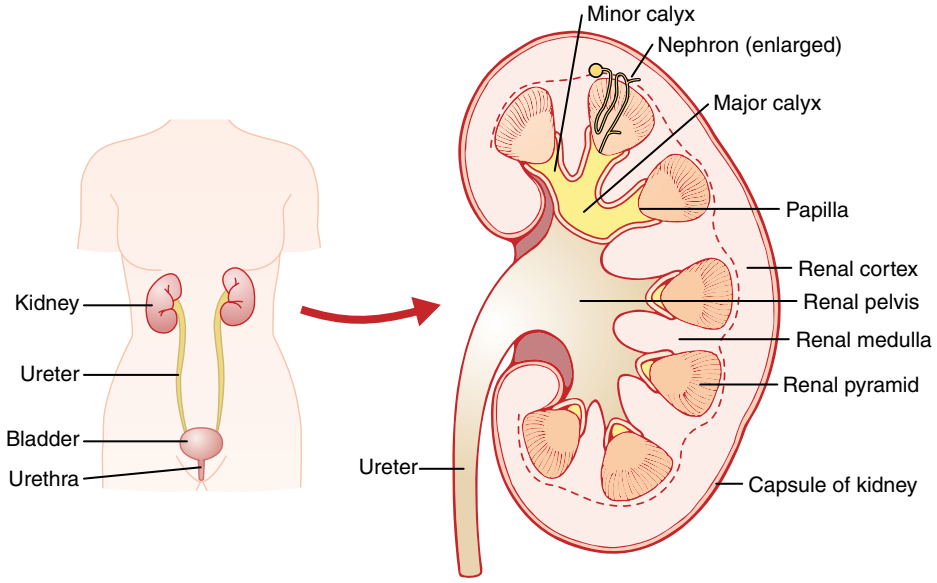


Figure 26-2 General organization of the kidneys and the urinary system.

formation (Figure 26-3). The distal ends of the capillaries of each glomerulus coalesce to form the *efferent arteriole,* which leads to a second capillary network, the *peritubular capillaries,* that surrounds the renal tubules.

The renal circulation is unique in having two capillary beds, the glomerular and peritubular capillaries, which are arranged in series and separated by the efferent arterioles, which help regulate the hydrostatic pressure in both sets of capillaries. High hydrostatic pressure in the glomerular capillaries (about 60 mm Hg) causes rapid fluid filtration, whereas a much lower hydrostatic pressure in the peritubular capillaries (about 13 mm Hg) permits rapid fluid reabsorption. By adjusting the resistance of the afferent and efferent arterioles, the kidneys can regulate the hydrostatic pressure in both the glomerular and the peritubular capillaries, thereby changing the rate of glomerular filtration, tubular reabsorption, or both in response to body homeostatic demands.

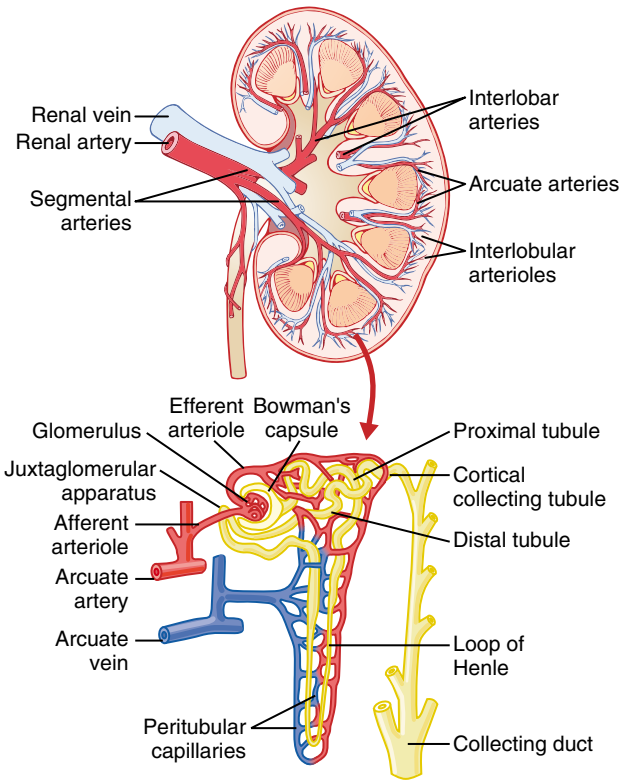


Figure 26-3 Section of the human kidney showing the major vessels that supply the blood flow to the kidney and schematic of the microcirculation of each nephron.

The peritubular capillaries empty into the vessels of the venous system, which run parallel to the arteriolar vessels. The blood vessels of the venous system progressively form the *interlobular vein, arcuate vein, interlobar vein,* and *renal vein,* which leaves the kidney beside the renal artery and ureter.

The Nephron Is the Functional Unit of the Kidney

Each kidney in the human contains about 800,000 to 1,000,000 *nephrons,* each capable of forming urine. The kidney cannot regenerate new nephrons. Therefore, with renal injury, disease, or normal aging, there is a gradual decrease in nephron number. After age 40, the number of functioning nephrons usually decreases about 10 percent every 10 years; thus, at age 80, many people have 40 percent fewer functioning nephrons than they did at age 40. This loss is not life threatening because adaptive changes in the remaining nephrons allow them to excrete the proper amounts of water, electrolytes, and waste products, as discussed in Chapter 31.

Each nephron contains (1) a tuft of glomerular capillaries called the *glomerulus,* through which large amounts of fluid are filtered from the blood, and (2) a long *tubule* in which the filtered fluid is converted into urine on its way to the pelvis of the kidney (see Figure 26-3).

The glomerulus contains a network of branching and anastomosing glomerular capillaries that, compared with other capillaries, have high hydrostatic pressure (about

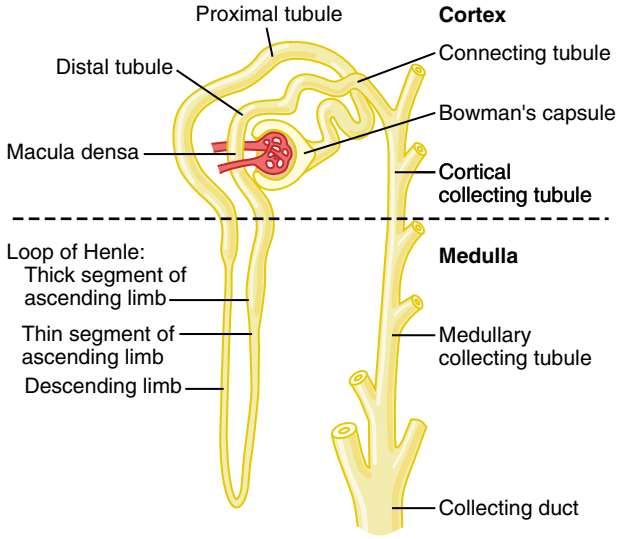


Figure 26-4 Basic tubular segments of the nephron. The relative lengths of the different tubular segments are not drawn to scale.

60 mm Hg). The glomerular capillaries are covered by epithelial cells, and the total glomerulus is encased in *Bowman's capsule.*

Fluid filtered from the glomerular capillaries flows into Bowman's capsule and then into the *proximal tubule,* which lies in the cortex of the kidney (Figure 26-4). From the proximal tubule, fluid flows into the *loop of Henle,* which dips into the renal medulla. Each loop consists of a *descending* and an *ascending limb.* The walls of the descending limb and the lower end of the ascending limb are very thin and therefore are called the *thin segment of the loop of Henle.* After the ascending limb of the loop returns partway back to the cortex, its wall becomes much thicker, and it is referred to as the *thick segment of the ascending limb.*

At the end of the thick ascending limb is a short segment that has in its wall a plaque of specialized epithelial cells, known as the *macula densa.* As discussed later, the macula densa plays an important role in controlling nephron function. Beyond the macula densa, fluid enters the *distal tubule,* which, like the proximal tubule, lies in the renal cortex. This is followed by the *connecting tubule* and the *cortical collecting tubule,* which lead to the *cortical collecting duct.* The initial parts of 8 to 10 cortical collecting ducts join to form a single larger collecting duct that runs downward into the medulla and becomes the *medullary collecting duct.* The collecting ducts merge to form progressively larger ducts that eventually empty into the renal pelvis through the tips of the *renal papillae.* In each kidney, there are about 250 of the very large collecting ducts, each of which collects urine from about 4000 nephrons.

Regional Differences in Nephron Structure: Cortical and Juxtamedullary Nephrons. Although each nephron has all the components described earlier, there are some differences, depending on how deep the nephron lies within the kidney mass. Those nephrons that have glomeruli located in the outer cortex are called *cortical nephrons;* they have short loops of Henle that penetrate only a short distance into the medulla (Figure 26-5).

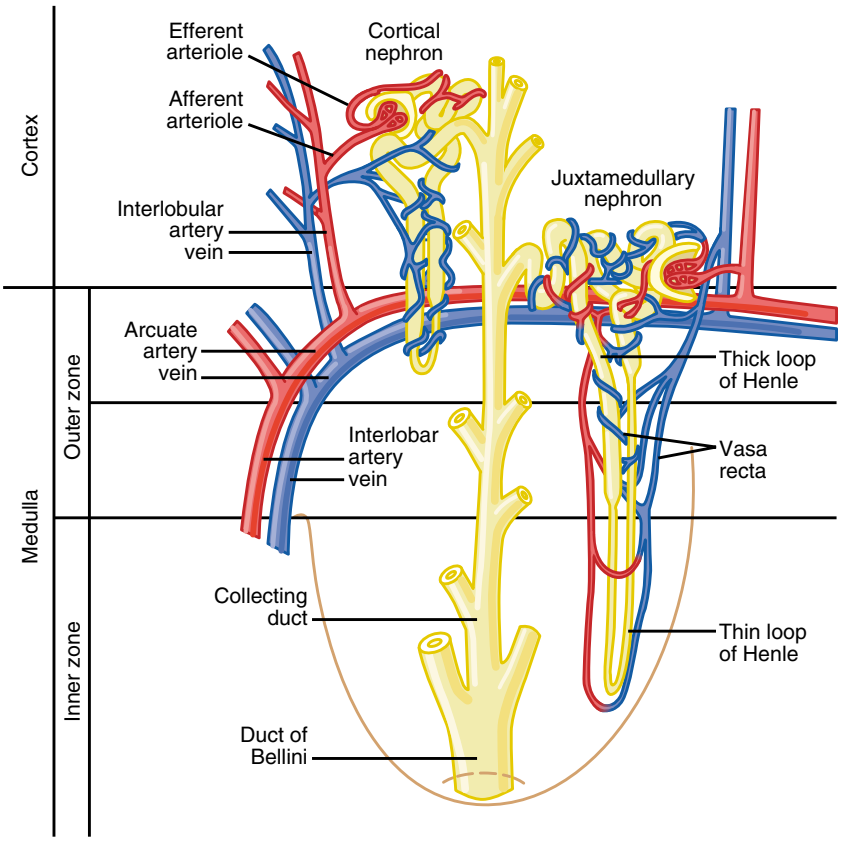


Figure 26-5 Schematic of relations between blood vessels and tubular structures and differences between cortical and juxtamedullary nephrons.

About 20 to 30 percent of the nephrons have glomeruli that lie deep in the renal cortex near the medulla and are called *juxtamedullary nephrons.* These nephrons have long loops of Henle that dip deeply into the medulla, in some cases all the way to the tips of the renal papillae.

The vascular structures supplying the juxtamedullary nephrons also differ from those supplying the cortical nephrons. For the cortical nephrons, the entire tubular system is surrounded by an extensive network of peritubular capillaries. For the juxtamedullary nephrons, long efferent arterioles extend from the glomeruli down into the outer medulla and then divide into specialized peritubular capillaries called *vasa recta* that extend downward into the medulla, lying side by side with the loops of Henle. Like the loops of Henle, the vasa recta return toward the cortex and empty into the cortical veins. This specialized network of capillaries in the medulla plays an essential role in the formation of a concentrated urine and is discussed in Chapter 28.

Micturition

Micturition is the process by which the urinary bladder empties when it becomes filled. This involves two main steps: First, the bladder fills progressively until the tension in its walls rises above a threshold level; this elicits the second step, which is a nervous reflex called the *micturition reflex* that empties the bladder or, if this fails, at least causes a conscious desire to urinate. Although the micturition reflex is an autonomic spinal cord reflex, it can also be inhibited or facilitated by centers in the cerebral cortex or brain stem.

Physiologic Anatomy of the Bladder

The urinary bladder, shown in Figure 26-6, is a smooth muscle chamber composed of two main parts: (1) the *body,* which is the major part of the bladder in which urine collects, and (2) the *neck,* which is a funnel-shaped extension of the body, passing inferiorly and anteriorly into the urogenital triangle and connecting with the urethra. The lower part of the bladder neck is also called the *posterior urethra* because of its relation to the urethra.

The smooth muscle of the bladder is called the *detrusor muscle.* Its muscle fibers extend in all directions and, when contracted, can increase the pressure in the bladder to 40 to 60 mm Hg. Thus, *contraction of the detrusor muscle is a major step in emptying the bladder*. Smooth muscle cells of the detrusor muscle fuse with one another so that low-resistance electrical pathways exist from one muscle

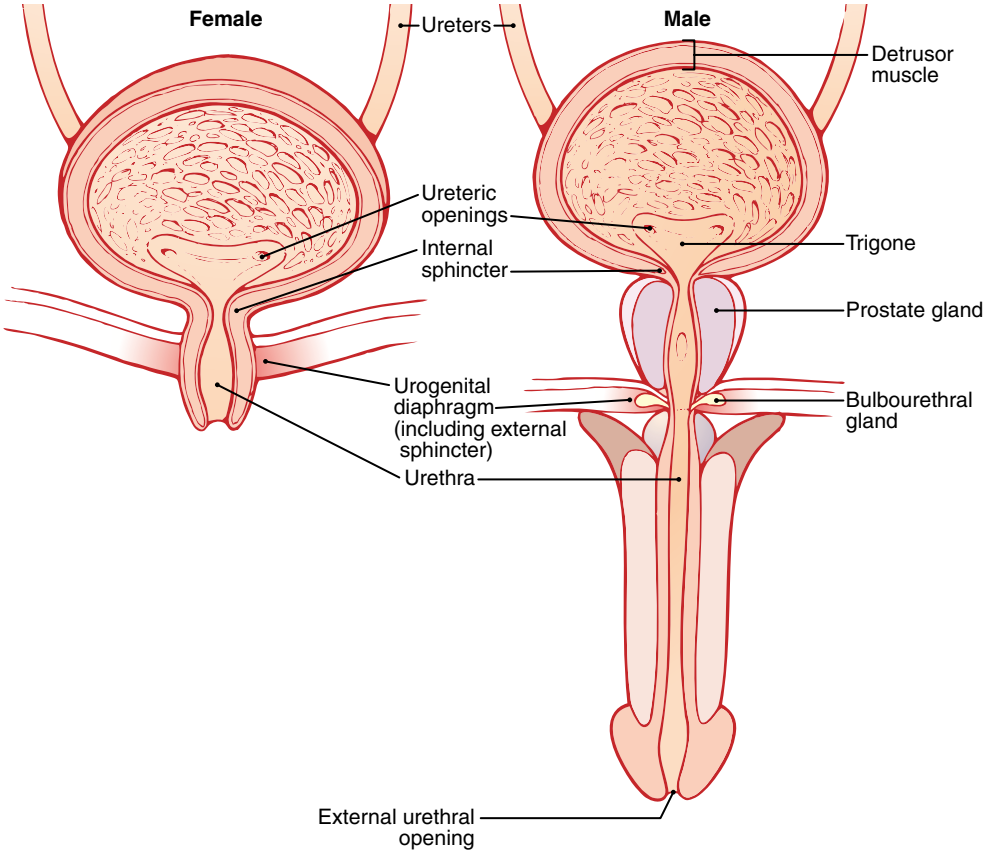


Figure 26-6 Anatomy of the urinary bladder in males and females.

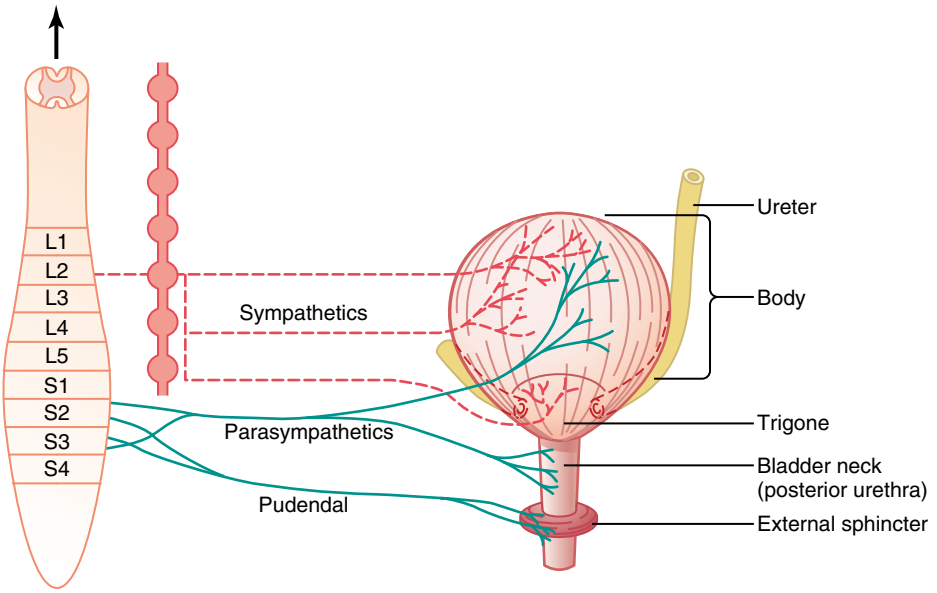


Figure 26-7 Innervation of the urinary bladder.

cell to the other. Therefore, an action potential can spread throughout the detrusor muscle, from one muscle cell to the next, to cause contraction of the entire bladder at once.

On the posterior wall of the bladder, lying immediately above the bladder neck, is a small triangular area called the *trigone.* At the lowermost apex of the trigone, the bladder neck opens into the *posterior urethra* and the two ureters enter the bladder at the uppermost angles of the trigone. The trigone can be identified by the fact that its *mucosa,* the inner lining of the bladder, is smooth, in contrast to the remaining bladder mucosa, which is folded to form *rugae.*

Each ureter, as it enters the bladder, courses obliquely through the detrusor muscle and then passes another 1 to 2 centimeters beneath the bladder mucosa before emptying into the bladder.

The bladder neck (posterior urethra) is 2 to 3 centimeters long, and its wall is composed of detrusor muscle interlaced with a large amount of elastic tissue. The muscle in this area is called the *internal sphincter.* Its natural tone normally keeps the bladder neck and posterior urethra empty of urine and, therefore, prevents emptying of the bladder until the pressure in the main part of the bladder rises above a critical threshold.

Beyond the posterior urethra, the urethra passes through the *urogenital diaphragm,* which contains a layer of muscle called the *external sphincter* of the bladder. This muscle is a voluntary skeletal muscle, in contrast to the muscle of the bladder body and bladder neck, which is entirely smooth muscle. The external sphincter muscle is under voluntary control of the nervous system and can be used to consciously prevent urination even when involuntary controls are attempting to empty the bladder.

Innervation of the Bladder

The principal nerve supply of the bladder is by way of the *pelvic nerves,* which connect with the spinal cord through the *sacral plexus,* mainly connecting with cord segments S2 and S3 (Figure 26-7). Coursing through the pelvic nerves are both *sensory nerve fibers* and *motor nerve fibers.* The sensory fibers detect the degree of stretch in the bladder wall. Stretch signals from the posterior urethra are especially strong and are mainly responsible for initiating the reflexes that cause bladder emptying.

The motor nerves transmitted in the pelvic nerves are *parasympathetic fibers.* These terminate on ganglion cells located in the wall of the bladder. Short postganglionic nerves then innervate the detrusor muscle.

In addition to the pelvic nerves, two other types of innervation are important in bladder function. Most important are the *skeletal motor fibers* transmitted through the *pudendal nerve* to the external bladder sphincter. These are *somatic nerve fibers* that innervate and control the voluntary skeletal muscle of the sphincter. Also, the bladder receives *sympathetic innervation* from the sympathetic chain through the *hypogastric nerves,* connecting mainly with the L2 segment of the spinal cord. These sympathetic fibers stimulate mainly the blood vessels and have little to do with bladder contraction. Some sensory nerve fibers also pass by way of the sympathetic nerves and may be important in the sensation of fullness and, in some instances, pain.

Transport of Urine from the Kidney Through the Ureters and into the Bladder

Urine that is expelled from the bladder has essentially the same composition as fluid flowing out of the collecting ducts; there are no significant changes in the composition of urine as it flows through the renal calyces and ureters to the bladder.

Urine flowing from the collecting ducts into the renal calyces stretches the calyces and increases their inherent

pacemaker activity, which in turn initiates peristaltic contractions that spread to the renal pelvis and then downward along the length of the ureter, thereby forcing urine from the renal pelvis toward the bladder. In adults, the ureters are normally 25 to 35 centimeters (10 to 14 inches) long.

The walls of the ureters contain smooth muscle and are innervated by both sympathetic and parasympathetic nerves, as well as by an intramural plexus of neurons and nerve fibers that extends along the entire length of the ureters. As with other visceral smooth muscle, *peristaltic contractions in the ureter are enhanced by parasympathetic stimulation and inhibited by sympathetic stimulation.*

The ureters enter the bladder through the *detrusor muscle* in the trigone region of the bladder, as shown in Figure 26-6. Normally, the ureters course obliquely for several centimeters through the bladder wall. The normal tone of the detrusor muscle in the bladder wall tends to compress the ureter, thereby preventing backflow (reflux) of urine from the bladder when pressure builds up in the bladder during micturition or bladder compression. Each peristaltic wave along the ureter increases the pressure within the ureter so that the region passing through the bladder wall opens and allows urine to flow into the bladder.

In some people, the distance that the ureter courses through the bladder wall is less than normal, so contraction of the bladder during micturition does not always lead to complete occlusion of the ureter. As a result, some of the urine in the bladder is propelled backward into the ureter, a condition called *vesicoureteral reflux.* Such reflux can lead to enlargement of the ureters and, if severe, can increase the pressure in the renal calyces and structures of the renal medulla, causing damage to these regions.

Pain Sensation in the Ureters, and the Ureterorenal Reflex. The ureters are well supplied with pain nerve fibers. When a ureter becomes blocked (e.g., by a ureteral stone), intense reflex constriction occurs, associated with severe pain. Also, the pain impulses cause a sympathetic reflex back to the kidney to constrict the renal arterioles, thereby decreasing urine output from the kidney. This effect is called the *ureterorenal reflex* and is important for preventing excessive flow of fluid into the pelvis of a kidney with a blocked ureter.

Filling of the Bladder and Bladder Wall Tone; the Cystometrogram

Figure 26-8 shows the approximate changes in intravesicular pressure as the bladder fills with urine. When there is no urine in the bladder, the intravesicular pressure is about 0, but by the time 30 to 50 milliliters of urine have collected, the pressure rises to 5 to 10 centimeters of water. Additional urine—200 to 300 milliliters—can collect with only a small additional rise in pressure; this constant level of pressure is caused by intrinsic tone of the bladder wall itself. Beyond 300 to 400 milliliters, collection of more urine in the bladder causes the pressure to rise rapidly.

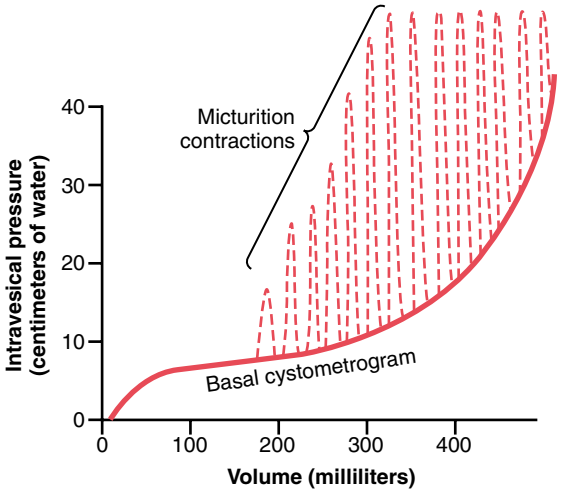


Figure 26-8 Normal cystometrogram, showing also acute pressure waves (*dashed spikes*) caused by micturition reflexes.

Superimposed on the tonic pressure changes during filling of the bladder are periodic acute increases in pressure that last from a few seconds to more than a minute. The pressure peaks may rise only a few centimeters of water or may rise to more than 100 centimeters of water. These pressure peaks are called *micturition waves* in the cystometrogram and are caused by the micturition reflex.

Micturition Reflex

Referring again to Figure 26-8, one can see that as the bladder fills, many superimposed *micturition contractions* begin to appear, as shown by the dashed spikes. They are the result of a stretch reflex initiated by *sensory stretch receptors* in the bladder wall, especially by the receptors in the posterior urethra when this area begins to fill with urine at the higher bladder pressures. Sensory signals from the bladder stretch receptors are conducted to the sacral segments of the cord through the *pelvic nerves* and then reflexively back again to the bladder through the *parasympathetic nerve fibers* by way of these same nerves.

When the bladder is only partially filled, these micturition contractions usually relax spontaneously after a fraction of a minute, the detrusor muscles stop contracting, and pressure falls back to the baseline. As the bladder continues to fill, the micturition reflexes become more frequent and cause greater contractions of the detrusor muscle.

Once a micturition reflex begins, it is "self-regenerative." That is, initial contraction of the bladder activates the stretch receptors to cause a greater increase in sensory impulses from the bladder and posterior urethra, which causes a further increase in reflex contraction of the bladder; thus, the cycle is repeated again and again until the bladder has reached a strong degree of contraction. Then, after a few seconds to more than a minute, the self-regenerative reflex begins to fatigue and the regenerative cycle of the micturition reflex ceases, permitting the bladder to relax.

Thus, the micturition reflex is a single complete cycle of (1) progressive and rapid increase of pressure, (2) a

period of sustained pressure, and (3) return of the pressure to the basal tone of the bladder. Once a micturition reflex has occurred but has not succeeded in emptying the bladder, the nervous elements of this reflex usually remain in an inhibited state for a few minutes to 1 hour or more before another micturition reflex occurs. As the bladder becomes more and more filled, micturition reflexes occur more and more often and more and more powerfully.

Once the micturition reflex becomes powerful enough, it causes another reflex, which passes through the *pudendal nerves* to the *external sphincter* to inhibit it. If this inhibition is more potent in the brain than the voluntary constrictor signals to the external sphincter, urination will occur. If not, urination will not occur until the bladder fills still further and the micturition reflex becomes more powerful.

Facilitation or Inhibition of Micturition by the Brain

The micturition reflex is an autonomic spinal cord reflex, but it can be inhibited or facilitated by centers in the brain. These centers include (1) strong *facilitative* and *inhibitory centers in the brain stem, located mainly in the pons,* and (2) several *centers located in the cerebral cortex* that are mainly inhibitory but can become excitatory.

The micturition reflex is the basic cause of micturition, but the higher centers normally exert final control of micturition as follows:

1. The higher centers keep the micturition reflex partially inhibited, except when micturition is desired.
2. The higher centers can prevent micturition, even if the micturition reflex occurs, by tonic contraction of the external bladder sphincter until a convenient time presents itself.
3. When it is time to urinate, the cortical centers can facilitate the sacral micturition centers to help initiate a micturition reflex and at the same time inhibit the external urinary sphincter so that urination can occur.

Voluntary urination is usually initiated in the following way: First, a person voluntarily contracts his or her abdominal muscles, which increases the pressure in the bladder and allows extra urine to enter the bladder neck and posterior urethra under pressure, thus stretching their walls. This stimulates the stretch receptors, which excites the micturition reflex and simultaneously inhibits the external urethral sphincter. Ordinarily, all the urine will be emptied, with rarely more than 5 to 10 milliliters left in the bladder.

Abnormalities of Micturition

Atonic Bladder and Incontinence Caused by Destruction of Sensory Nerve Fibers. Micturition reflex contraction cannot occur if the sensory nerve fibers from the bladder to the spinal cord are destroyed, thereby preventing transmission of stretch signals from the bladder. When this happens, a person loses bladder control, despite intact efferent fibers from the cord to the bladder and despite intact neurogenic connections within the brain. Instead of emptying periodically, the bladder fills to capacity and overflows a few drops at a time through the urethra. This is called *overflow incontinence.*

A common cause of atonic bladder is crush injury to the sacral region of the spinal cord. Certain diseases can also cause damage to the dorsal root nerve fibers that enter the spinal cord. For example, syphilis can cause constrictive fibrosis around the dorsal root nerve fibers, destroying them. This condition is called *tabes dorsalis,* and the resulting bladder condition is called *tabetic bladder.*

Automatic Bladder Caused by Spinal Cord Damage Above the Sacral Region. If the spinal cord is damaged above the sacral region but the sacral cord segments are still intact, typical micturition reflexes can still occur. However, they are no longer controlled by the brain. During the first few days to several weeks after the damage to the cord has occurred, the micturition reflexes are suppressed because of the state of "spinal shock" caused by the sudden loss of facilitative impulses from the brain stem and cerebrum. However, if the bladder is emptied periodically by catheterization to prevent bladder injury caused by overstretching of the bladder, the excitability of the micturition reflex gradually increases until typical micturition reflexes return; then, periodic (but unannounced) bladder emptying occurs.

Some patients can still control urination in this condition by stimulating the skin (scratching or tickling) in the genital region, which sometimes elicits a micturition reflex.

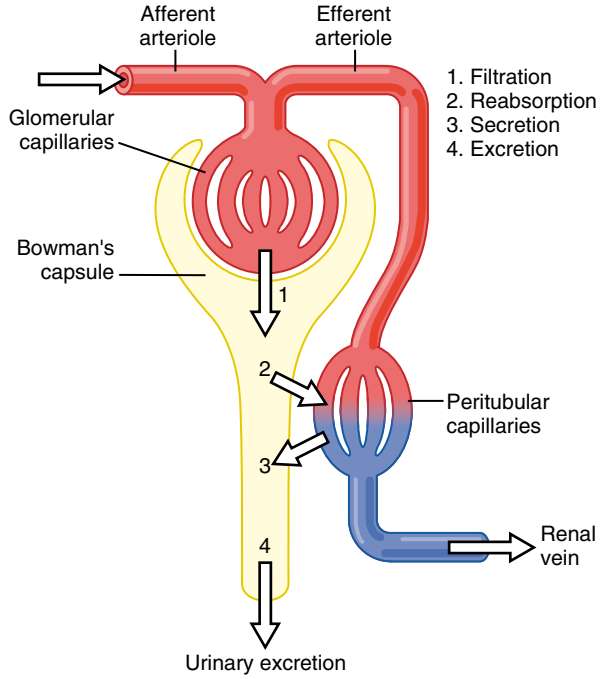
Uninhibited Neurogenic Bladder Caused by Lack of Inhibitory Signals from the Brain. Another abnormality of micturition is the so-called uninhibited neurogenic bladder, which results in frequent and relatively uncontrolled micturition. This condition derives from partial damage in the spinal cord or the brain stem that interrupts most of the inhibitory signals. Therefore, facilitative impulses passing continually down the cord keep the sacral centers so excitable that even a small quantity of urine elicits an uncontrollable micturition reflex, thereby promoting frequent urination.

Urine Formation Results from Glomerular Filtration, Tubular Reabsorption, and Tubular Secretion

The rates at which different substances are excreted in the urine represent the sum of three renal processes, shown in Figure 26-9: (1) glomerular filtration, (2) reabsorption of substances from the renal tubules into the blood, and (3) secretion of substances from the blood into the renal tubules. Expressed mathematically,

Urinary excretion rate =
Filtration rate − Reabsorption rate + Secretion rate

Urine formation begins when a large amount of fluid that is virtually free of protein is filtered from the glomerular capillaries into Bowman's capsule. Most substances in the plasma, except for proteins, are freely filtered, so their concentration in the glomerular filtrate in Bowman's capsule is almost the same as in the plasma. As filtered fluid leaves Bowman's capsule and passes through



Excretion = Filtration – Reabsorption + Secretion

Figure 26-9 Basic kidney processes that determine the composition of the urine. Urinary excretion rate of a substance is equal to the rate at which the substance is filtered minus its reabsorption rate plus the rate at which it is secreted from the peritubular capillary blood into the tubules.

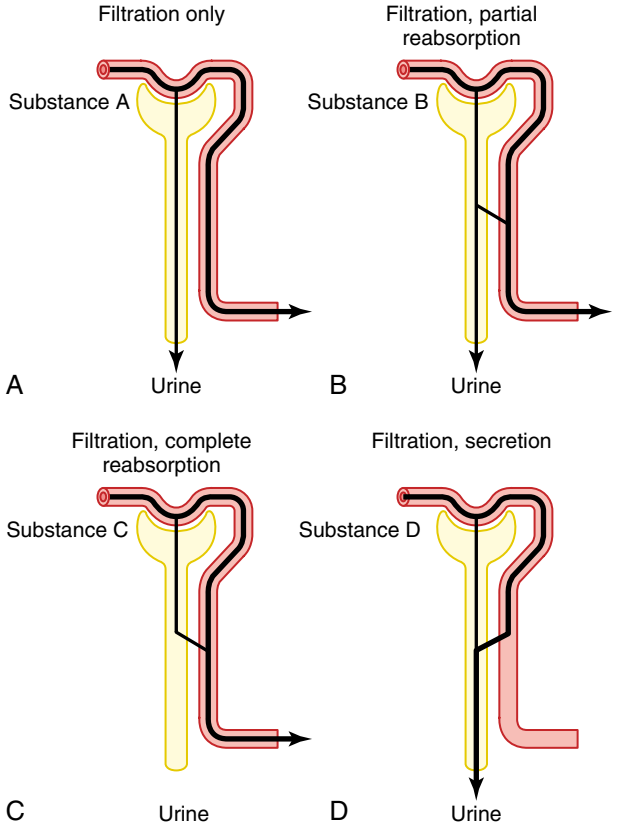


Figure 26-10 Renal handling of four hypothetical substances. *A,* The substance is freely filtered but not reabsorbed. *B,* The substance is freely filtered, but part of the filtered load is reabsorbed back in the blood. *C,* The substance is freely filtered but is not excreted in the urine because all the filtered substance is reabsorbed from the tubules into the blood. *D,* The substance is freely filtered and is not reabsorbed but is secreted from the peritubular capillary blood into the renal tubules.

the tubules, it is modified by reabsorption of water and specific solutes back into the blood or by secretion of other substances from the peritubular capillaries into the tubules.

Figure 26-10 shows the renal handling of four hypothetical substances. The substance shown in panel A is freely filtered by the glomerular capillaries but is neither reabsorbed nor secreted. Therefore, its excretion rate is equal to the rate at which it was filtered. Certain waste products in the body, such as creatinine, are handled by the kidneys in this manner, allowing excretion of essentially all that is filtered.

In panel B, the substance is freely filtered but is also partly reabsorbed from the tubules back into the blood. Therefore, the rate of urinary excretion is less than the rate of filtration at the glomerular capillaries. In this case, the excretion rate is calculated as the filtration rate minus the reabsorption rate. This is typical for many of the electrolytes of the body such as sodium and chloride ions.

In panel C, the substance is freely filtered at the glomerular capillaries but is not excreted into the urine because all the filtered substance is reabsorbed from the tubules back into the blood. This pattern occurs for some of the nutritional substances in the blood, such as amino acids and glucose, allowing them to be conserved in the body fluids.

The substance in panel D is freely filtered at the glomerular capillaries and is not reabsorbed, but additional quantities of this substance are secreted from the peritubular capillary blood into the renal tubules. This pattern often occurs for organic acids and bases, permitting them to be rapidly cleared from the blood and excreted in large amounts in the urine. The excretion rate in this case is calculated as filtration rate plus tubular secretion rate.

For each substance in the plasma, a particular combination of filtration, reabsorption, and secretion occurs. The rate at which the substance is excreted in the urine depends on the relative rates of these three basic renal processes.

Filtration, Reabsorption, and Secretion of Different Substances

In general, tubular reabsorption is quantitatively more important than tubular secretion in the formation of urine, but secretion plays an important role in determining the amounts of potassium and hydrogen ions and a few other substances that are excreted in the urine. Most substances that must be cleared from the blood, especially the end products of metabolism such as urea, creatinine, uric acid, and urates, are poorly reabsorbed and are therefore excreted in large amounts in the urine. Certain foreign substances and drugs are also poorly reabsorbed but, in addition, are secreted from the blood into the tubules, so their excretion rates are high.

Conversely, electrolytes, such as sodium ions, chloride ions, and bicarbonate ions, are highly reabsorbed, so only small amounts appear in the urine. Certain nutritional substances, such as amino acids and glucose, are completely reabsorbed from the tubules and do not appear in the urine even though large amounts are filtered by the glomerular capillaries.

Each of the processes—glomerular filtration, tubular reabsorption, and tubular secretion—is regulated according to the needs of the body. For example, when there is excess sodium in the body, the rate at which sodium is filtered increases and a smaller fraction of the filtered sodium is reabsorbed, causing increased urinary excretion of sodium.

For most substances, the rates of filtration and reabsorption are extremely large relative to the rates of excretion. Therefore, subtle adjustments of filtration or reabsorption can lead to relatively large changes in renal excretion. For example, an increase in glomerular filtration rate (GFR) of only 10 percent (from 180 to 198 L/day) would raise urine volume 13-fold (from 1.5 to 19.5 L/day) if tubular reabsorption remained constant. In reality, changes in glomerular filtration and tubular reabsorption usually act in a coordinated manner to produce the necessary changes in renal excretion.

Why Are Large Amounts of Solutes Filtered and Then Reabsorbed by the Kidneys? One might question the wisdom of filtering such large amounts of water and solutes and then reabsorbing most of these substances. One advantage of a high GFR is that it allows the kidneys to rapidly remove waste products from the body that depend mainly on glomerular filtration for their excretion. Most waste products are poorly reabsorbed by the tubules and, therefore, depend on a high GFR for effective removal from the body.

A second advantage of a high GFR is that it allows all the body fluids to be filtered and processed by the kidneys many times each day. Because the entire plasma volume is only about 3 liters, whereas the GFR is about 180 L/day, the entire plasma can be filtered and processed about 60 times each day. This high GFR allows the kidneys to precisely and rapidly control the volume and composition of the body fluids.

Glomerular Filtration—the First Step in Urine Formation

Composition of the Glomerular Filtrate

Urine formation begins with filtration of large amounts of fluid through the glomerular capillaries into Bowman's capsule. Like most capillaries, the glomerular capillaries are relatively impermeable to proteins, so the filtered fluid (called the *glomerular filtrate*) is essentially protein free and devoid of cellular elements, including red blood cells.

The concentrations of other constituents of the glomerular filtrate, including most salts and organic molecules, are similar to the concentrations in the plasma. Exceptions to this generalization include a few low-molecular-weight substances, such as calcium and fatty acids, that are not freely filtered because they are partially bound to the plasma proteins. For example, almost one half of the plasma calcium and most of the plasma fatty acids are bound to proteins and these bound portions are not filtered through the glomerular capillaries.

GFR Is About 20 Percent of the Renal Plasma Flow

As in other capillaries, the GFR is determined by (1) the balance of hydrostatic and colloid osmotic forces acting across the capillary membrane and (2) the capillary filtration coefficient (K_f), the product of the permeability and filtering surface area of the capillaries. The glomerular capillaries have a much higher rate of filtration than most other capillaries because of a high glomerular hydrostatic pressure and a large K_f. In the average adult human, the GFR is about 125 ml/min, or 180 L/day. The fraction of the renal plasma flow that is filtered (the filtration fraction) averages about 0.2; this means that about 20 percent of the plasma flowing through the kidney is filtered through the glomerular capillaries. The filtration fraction is calculated as follows:

$$\text{Filtration fraction} = \text{GFR}/\text{Renal plasma flow}$$

Glomerular Capillary Membrane

The glomerular capillary membrane is similar to that of other capillaries, except that it has three (instead of the usual two) major layers: (1) the *endothelium* of the capillary, (2) a *basement membrane,* and (3) a layer of *epithelial cells (podocytes)* surrounding the outer surface of the capillary basement membrane (Figure 26-11). Together, these layers make up the filtration barrier, which, despite the three layers, filters several hundred times as much water and solutes as the usual capillary membrane. Even with this high rate of filtration, the glomerular capillary membrane normally prevents filtration of plasma proteins.

The high filtration rate across the glomerular capillary membrane is due partly to its special characteristics. The capillary *endothelium* is perforated by thousands of small holes called *fenestrae,* similar to the fenestrated capillaries found in the liver. Although the fenestrations are relatively large, endothelial cells are richly endowed with fixed negative charges that hinder the passage of plasma proteins.

Surrounding the endothelium is the *basement membrane,* which consists of a meshwork of collagen and proteoglycan fibrillae that have large spaces through which large amounts of water and small solutes can filter. The basement membrane effectively prevents filtration of plasma proteins, in part because of strong negative electrical charges associated with the proteoglycans.

The final part of the glomerular membrane is a layer of epithelial cells that line the outer surface of the glomerulus. These cells are not continuous but have long footlike processes (podocytes) that encircle the outer surface

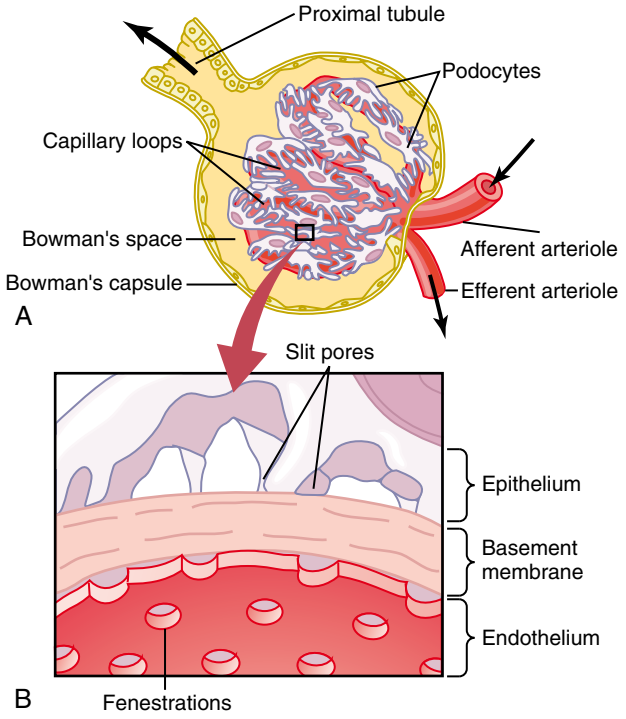


Figure 26-11 *A,* Basic ultrastructure of the glomerular capillaries. *B,* Cross section of the glomerular capillary membrane and its major components: capillary endothelium, basement membrane, and epithelium (podocytes).

of the capillaries (see Figure 26-11). The foot processes are separated by gaps called *slit pores* through which the glomerular filtrate moves. The epithelial cells, which also have negative charges, provide additional restriction to filtration of plasma proteins. Thus, all layers of the glomerular capillary wall provide a barrier to filtration of plasma proteins.

Filterability of Solutes Is Inversely Related to Their Size. The glomerular capillary membrane is thicker than most other capillaries, but it is also much more porous and therefore filters fluid at a high rate. Despite the high filtration rate, the glomerular filtration barrier is selective in determining which molecules will filter, based on their size and electrical charge.

Table 26-1 lists the effect of molecular size on filterability of different molecules. A filterability of 1.0 means that the substance is filtered as freely as water; a filterability of 0.75 means that the substance is filtered only 75 percent as rapidly as water. Note that electrolytes such as sodium and small organic compounds such as glucose are freely filtered. As the molecular weight of the molecule approaches that of albumin, the filterability rapidly decreases, approaching zero.

Negatively Charged Large Molecules Are Filtered Less Easily Than Positively Charged Molecules of Equal Molecular Size. The molecular diameter of the plasma protein albumin is only about 6 nanometers, whereas the pores of the glomerular membrane are thought to be about

Table 26-1 Filterability of Substances by Glomerular Capillaries Based on Molecular Weight

Substance	Molecular Weight	Filterability
Water	18	1.0
Sodium	23	1.0
Glucose	180	1.0
Inulin	5,500	1.0
Myoglobin	17,000	0.75
Albumin	69,000	0.005

8 nanometers (80 angstroms). Albumin is restricted from filtration, however, because of its negative charge and the electrostatic repulsion exerted by negative charges of the glomerular capillary wall proteoglycans.

Figure 26-12 shows how electrical charge affects the filtration of different molecular weight dextrans by the glomerulus. Dextrans are polysaccharides that can be manufactured as neutral molecules or with negative or positive charges. Note that for any given molecular radius, positively charged molecules are filtered much more readily than negatively charged molecules. Neutral dextrans are also filtered more readily than negatively charged dextrans of equal molecular weight. The reason for these differences in filterability is that the negative charges of the basement membrane and the podocytes provide an important means for restricting large negatively charged molecules, including the plasma proteins.

In certain kidney diseases, the negative charges on the basement membrane are lost even before there are noticeable changes in kidney histology, a condition referred to as *minimal change nephropathy.* As a result of this loss of negative charges on the basement membranes, some

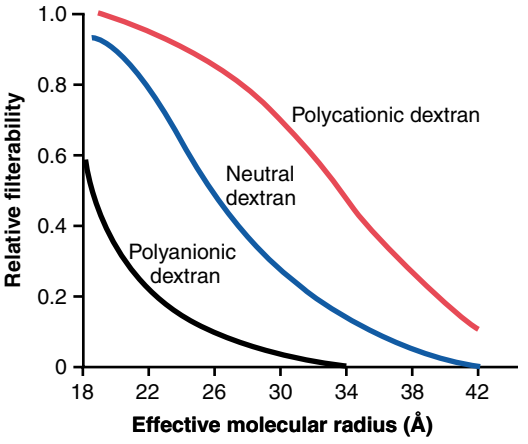


Figure 26-12 Effect of molecular radius and electrical charge of dextran on its filterability by the glomerular capillaries. A value of 1.0 indicates that the substance is filtered as freely as water, whereas a value of 0 indicates that it is not filtered. Dextrans are polysaccharides that can be manufactured as neutral molecules or with negative or positive charges and with varying molecular weights.

of the lower-molecular-weight proteins, especially albumin, are filtered and appear in the urine, a condition known as *proteinuria* or *albuminuria.*

Determinants of the GFR

The GFR is determined by (1) the sum of the hydrostatic and colloid osmotic forces across the glomerular membrane, which gives the *net filtration pressure,* and (2) the glomerular capillary filtration coefficient, K_f. Expressed mathematically, the GFR equals the product of K_f and the net filtration pressure:

$$GFR = K_f \times \text{Net filtration pressure}$$

The net filtration pressure represents the sum of the hydrostatic and colloid osmotic forces that either favor or oppose filtration across the glomerular capillaries (Figure 26-13). These forces include (1) hydrostatic pressure inside the glomerular capillaries (glomerular hydrostatic pressure, P_G), which promotes filtration; (2) the hydrostatic pressure in Bowman's capsule (P_B) outside the capillaries, which opposes filtration; (3) the colloid osmotic pressure of the glomerular capillary plasma proteins (π_G), which opposes filtration; and (4) the colloid osmotic pressure of the proteins in Bowman's capsule (π_B), which promotes filtration. (Under normal conditions, the concentration of protein in the glomerular filtrate is so low that the colloid osmotic pressure of the Bowman's capsule fluid is considered to be zero.)

The GFR can therefore be expressed as

$$GFR = K_f \times (P_G - P_B - \pi_G + \pi_B)$$

Although the normal values for the determinants of GFR have not been measured directly in humans, they have been estimated in animals such as dogs and rats. Based on the results in animals, the approximate normal forces favoring and opposing glomerular filtration in humans are believed to be as follows (see Figure 26-13):

Forces Favoring Filtration (mm Hg)	
Glomerular hydrostatic pressure	60
Bowman's capsule colloid osmotic pressure	0
Forces Opposing Filtration (mm Hg)	
Bowman's capsule hydrostatic pressure	18
Glomerular capillary colloid osmotic pressure	32

Net filtration pressure = 60 − 18 − 32 = +10 mm Hg

Some of these values can change markedly under different physiologic conditions, whereas others are altered mainly in disease states, as discussed later.

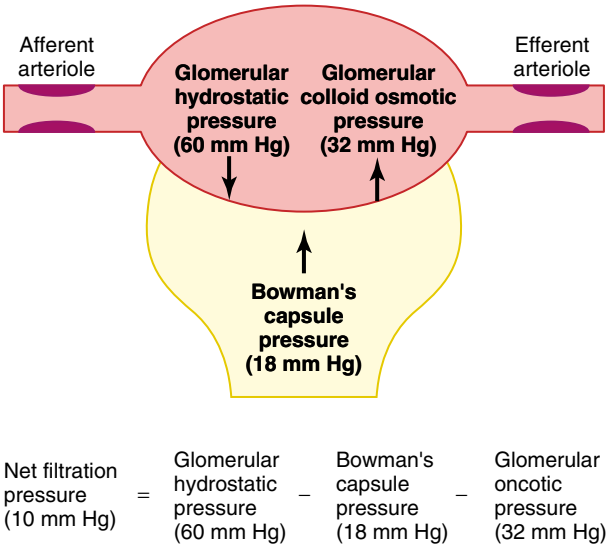


Figure 26-13 Summary of forces causing filtration by the glomerular capillaries. The values shown are estimates for healthy humans.

Increased Glomerular Capillary Filtration Coefficient Increases GFR

The K_f is a measure of the product of the hydraulic conductivity and surface area of the glomerular capillaries. The K_f cannot be measured directly, but it is estimated experimentally by dividing the rate of glomerular filtration by net filtration pressure:

$$K_f = GFR/\text{Net filtration pressure}$$

Because total GFR for both kidneys is about 125 ml/min and the net filtration pressure is 10 mm Hg, the normal K_f is calculated to be about 12.5 ml/min/mm Hg of filtration pressure. When K_f is expressed per 100 grams of kidney weight, it averages about 4.2 ml/min/mm Hg, a value about 400 times as high as the K_f of most other capillary systems of the body; the average K_f of many other tissues in the body is only about 0.01 ml/min/mm Hg per 100 grams. This high K_f for the glomerular capillaries contributes tremendously to their rapid rate of fluid filtration.

Although increased K_f raises GFR and decreased K_f reduces GFR, changes in K_f probably do not provide a primary mechanism for the normal day-to-day regulation of GFR. Some diseases, however, lower K_f by reducing the number of functional glomerular capillaries (thereby reducing the surface area for filtration) or by increasing the thickness of the glomerular capillary membrane and reducing its hydraulic conductivity. For example, chronic, uncontrolled hypertension and diabetes mellitus gradually reduce K_f by increasing the thickness of the glomerular capillary basement membrane and, eventually, by damaging the capillaries so severely that there is loss of capillary function.

Increased Bowman's Capsule Hydrostatic Pressure Decreases GFR

Direct measurements, using micropipettes, of hydrostatic pressure in Bowman's capsule and at different points in the proximal tubule in experimental animals suggest that a reasonable estimate for Bowman's capsule pressure in humans is about 18 mm Hg under normal conditions. Increasing the hydrostatic pressure in Bowman's capsule

reduces GFR, whereas decreasing this pressure raises GFR. However, changes in Bowman's capsule pressure normally do not serve as a primary means for regulating GFR.

In certain pathological states associated with obstruction of the urinary tract, Bowman's capsule pressure can increase markedly, causing serious reduction of GFR. For example, precipitation of calcium or of uric acid may lead to "stones" that lodge in the urinary tract, often in the ureter, thereby obstructing outflow of the urinary tract and raising Bowman's capsule pressure. This reduces GFR and eventually can cause *hydronephrosis* (distention and dilation of the renal pelvis and calyces) and can damage or even destroy the kidney unless the obstruction is relieved.

Increased Glomerular Capillary Colloid Osmotic Pressure Decreases GFR

As blood passes from the afferent arteriole through the glomerular capillaries to the efferent arterioles, the plasma protein concentration increases about 20 percent (Figure 26-14). The reason for this is that about one fifth of the fluid in the capillaries filters into Bowman's capsule, thereby concentrating the glomerular plasma proteins that are not filtered. Assuming that the normal colloid osmotic pressure of plasma entering the glomerular capillaries is 28 mm Hg, this value usually rises to about 36 mm Hg by the time the blood reaches the efferent end of the capillaries. Therefore, the average colloid osmotic pressure of the glomerular capillary plasma proteins is midway between 28 and 36 mm Hg, or about 32 mm Hg.

Thus, two factors that influence the glomerular capillary colloid osmotic pressure are (1) the arterial plasma colloid osmotic pressure and (2) the fraction of plasma filtered by the glomerular capillaries (filtration fraction). Increasing the arterial plasma colloid osmotic pressure raises the glomerular capillary colloid osmotic pressure, which in turn decreases GFR.

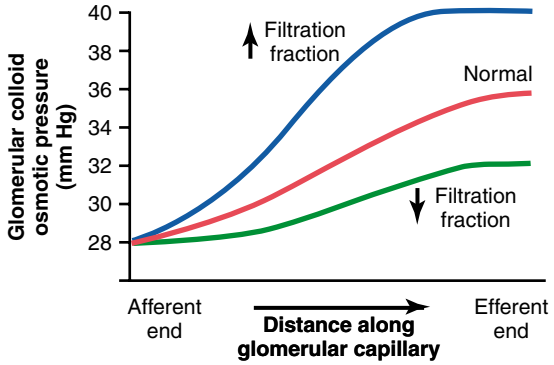


Figure 26-14 Increase in colloid osmotic pressure in plasma flowing through the glomerular capillary. Normally, about one fifth of the fluid in the glomerular capillaries filters into Bowman's capsule, thereby concentrating the plasma proteins that are not filtered. Increases in the filtration fraction (glomerular filtration rate/renal plasma flow) increase the rate at which the plasma colloid osmotic pressure rises along the glomerular capillary; decreases in the filtration fraction have the opposite effect.

Increasing the filtration fraction also concentrates the plasma proteins and raises the glomerular colloid osmotic pressure (see Figure 26-14). Because the filtration fraction is defined as GFR/renal plasma flow, the filtration fraction can be increased either by raising GFR or by reducing renal plasma flow. For example, a reduction in renal plasma flow with no initial change in GFR would tend to increase the filtration fraction, which would raise the glomerular capillary colloid osmotic pressure and tend to reduce GFR. For this reason, changes in renal blood flow can influence GFR independently of changes in glomerular hydrostatic pressure.

With increasing renal blood flow, a lower fraction of the plasma is initially filtered out of the glomerular capillaries, causing a slower rise in the glomerular capillary colloid osmotic pressure and less inhibitory effect on GFR. *Consequently, even with a constant glomerular hydrostatic pressure, a greater rate of blood flow into the glomerulus tends to increase GFR and a lower rate of blood flow into the glomerulus tends to decrease GFR.*

Increased Glomerular Capillary Hydrostatic Pressure Increases GFR

The glomerular capillary hydrostatic pressure has been estimated to be about 60 mm Hg under normal conditions. Changes in glomerular hydrostatic pressure serve as the primary means for physiologic regulation of GFR. Increases in glomerular hydrostatic pressure raise GFR, whereas decreases in glomerular hydrostatic pressure reduce GFR.

Glomerular hydrostatic pressure is determined by three variables, each of which is under physiologic control: (1) *arterial pressure,* (2) *afferent arteriolar resistance,* and (3) *efferent arteriolar resistance.*

Increased arterial pressure tends to raise glomerular hydrostatic pressure and, therefore, to increase GFR. (However, as discussed later, this effect is buffered by autoregulatory mechanisms that maintain a relatively constant glomerular pressure as blood pressure fluctuates.)

Increased resistance of afferent arterioles reduces glomerular hydrostatic pressure and decreases GFR. Conversely, dilation of the afferent arterioles increases both glomerular hydrostatic pressure and GFR (Figure 26-15).

Constriction of the efferent arterioles increases the resistance to outflow from the glomerular capillaries. This raises the glomerular hydrostatic pressure, and as long as the increase in efferent resistance does not reduce renal blood flow too much, GFR increases slightly (see Figure 26-15). However, because efferent arteriolar constriction also reduces renal blood flow, the filtration fraction and glomerular colloid osmotic pressure increase as efferent arteriolar resistance increases. Therefore, if the constriction of efferent arterioles is severe (more than about a threefold increase in efferent arteriolar resistance), the rise in colloid osmotic pressure exceeds the increase in glomerular capillary hydrostatic pressure caused by efferent arteriolar constriction. When this occurs, the *net force* for filtration actually decreases, causing a reduction in GFR.

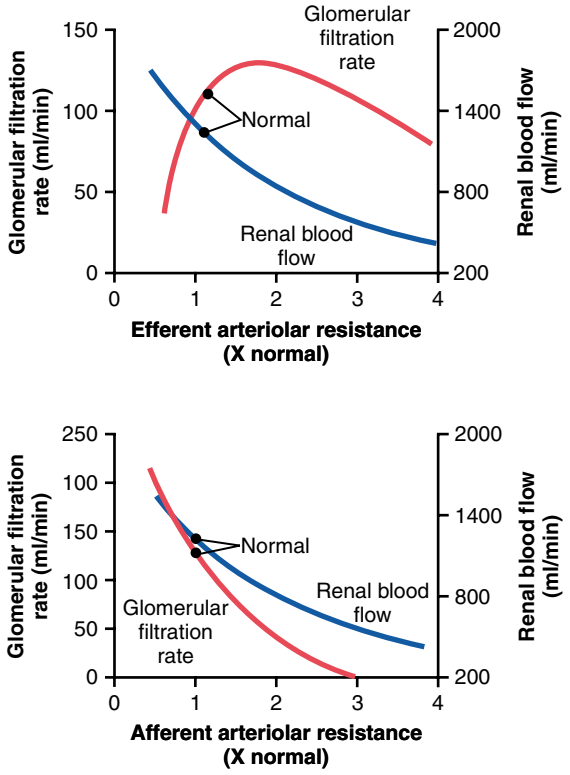


Figure 26-15 Effect of change in afferent arteriolar resistance or efferent arteriolar resistance on glomerular filtration rate and renal blood flow.

Thus, efferent arteriolar constriction has a biphasic effect on GFR. At moderate levels of constriction, there is a slight increase in GFR, but with severe constriction, there is a decrease in GFR. The primary cause of the eventual decrease in GFR is as follows: As efferent constriction becomes severe and as plasma protein concentration increases, there is a rapid, nonlinear increase in colloid osmotic pressure caused by the Donnan effect; the higher the protein concentration, the more rapidly the colloid osmotic pressure rises because of the interaction of ions bound to the plasma proteins, which also exert an osmotic effect, as discussed in Chapter 16.

To summarize, constriction of afferent arterioles reduces GFR. However, the effect of efferent arteriolar constriction depends on the severity of the constriction; modest efferent constriction raises GFR, but severe efferent constriction (more than a threefold increase in resistance) tends to reduce GFR.

Table 26-2 summarizes the factors that can decrease GFR.

Renal Blood Flow

In an average 70-kilogram man, the combined blood flow through both kidneys is about 1100 ml/min, or about 22 percent of the cardiac output. Considering that the two kidneys constitute only about 0.4 percent of the total body weight, one can readily see that they receive an extremely high blood flow compared with other organs.

Table 26-2 Factors That Can Decrease the Glomerular Filtration Rate (GFR)

Physical Determinants*	Physiologic/Pathophysiologic Causes
$\downarrow K_f \rightarrow \downarrow$ GFR	Renal disease, diabetes mellitus, hypertension
$\uparrow P_B \rightarrow \downarrow$ GFR	Urinary tract obstruction (e.g., kidney stones)
$\uparrow \pi_G \rightarrow \downarrow$ GFR	$\downarrow$ Renal blood flow, increased plasma proteins
$\downarrow P_G \rightarrow \downarrow$ GFR	
$\downarrow A_P \rightarrow \downarrow P_G$	$\downarrow$ Arterial pressure (has only small effect due to autoregulation)
$\downarrow R_E \rightarrow \downarrow P_G$	$\downarrow$ Angiotensin II (drugs that block angiotensin II formation)
$\uparrow R_A \rightarrow \downarrow P_G$	$\uparrow$ Sympathetic activity, vasoconstrictor hormones (e.g., norepinephrine, endothelin)

*Opposite changes in the determinants usually increase GFR.
K_f, glomerular filtration coefficient; P_B, Bowman's capsule hydrostatic pressure; π_G, glomerular capillary colloid osmotic pressure; P_G, glomerular capillary hydrostatic pressure; A_P, systemic arterial pressure; R_E, efferent arteriolar resistance; R_A, afferent arteriolar resistance.

As with other tissues, blood flow supplies the kidneys with nutrients and removes waste products. However, the high flow to the kidneys greatly exceeds this need. The purpose of this additional flow is to supply enough plasma for the high rates of glomerular filtration that are necessary for precise regulation of body fluid volumes and solute concentrations. As might be expected, the mechanisms that regulate renal blood flow are closely linked to the control of GFR and the excretory functions of the kidneys.

Renal Blood Flow and Oxygen Consumption

On a per-gram-weight basis, the kidneys normally consume oxygen at twice the rate of the brain but have almost seven times the blood flow of the brain. Thus, the oxygen delivered to the kidneys far exceeds their metabolic needs, and the arterial-venous extraction of oxygen is relatively low compared with that of most other tissues.

A large fraction of the oxygen consumed by the kidneys is related to the high rate of active sodium reabsorption by the renal tubules. If renal blood flow and GFR are reduced and less sodium is filtered, less sodium is reabsorbed and less oxygen is consumed. Therefore, renal oxygen consumption varies in proportion to renal tubular sodium reabsorption, which in turn is closely related to GFR and the rate of sodium filtered (Figure 26-16). If glomerular filtration completely ceases, renal sodium reabsorption also ceases and oxygen consumption decreases to about one-fourth normal. This residual oxygen consumption reflects the basic metabolic needs of the renal cells.

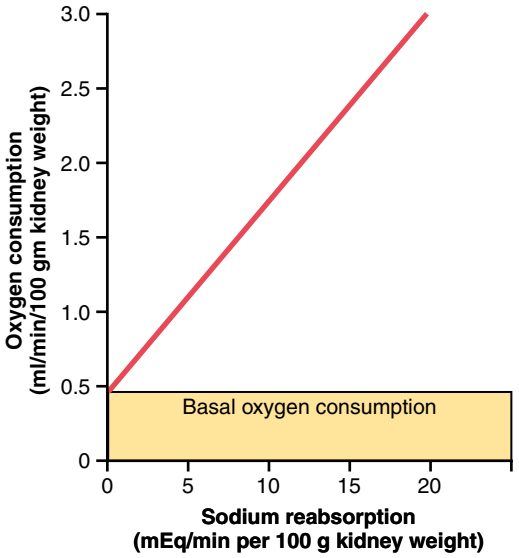


Figure 26-16 Relationship between oxygen consumption and sodium reabsorption in dog kidneys. (Kramer K, Deetjen P: Relation of renal oxygen consumption to blood supply and glomerular filtration during variations of blood pressure. Pflugers Arch Physiol 271:782, 1960.)

Determinants of Renal Blood Flow

Renal blood flow is determined by the pressure gradient across the renal vasculature (the difference between renal artery and renal vein hydrostatic pressures), divided by the total renal vascular resistance:

$$\frac{\text{(Renal artery pressure}-\text{Renal vein pressure)}}{\text{Total renal vascular resistance}}$$

Renal artery pressure is about equal to systemic arterial pressure, and renal vein pressure averages about 3 to 4 mm Hg under most conditions. As in other vascular beds, the total vascular resistance through the kidneys is determined by the sum of the resistances in the individual vasculature segments, including the arteries, arterioles, capillaries, and veins (Table 26-3).

Most of the renal vascular resistance resides in three major segments: interlobular arteries, afferent arterioles, and efferent arterioles. Resistance of these vessels is controlled by the sympathetic nervous system, various hormones, and local internal renal control mechanisms, as discussed later. An increase in the resistance of any of the vascular segments of the kidneys tends to reduce the renal blood flow, whereas a decrease in vascular resistance increases renal blood flow if renal artery and renal vein pressures remain constant.

Although changes in arterial pressure have some influence on renal blood flow, the kidneys have effective mechanisms for maintaining renal blood flow and GFR relatively constant over an arterial pressure range between 80 and 170 mm Hg, a process called *autoregulation.* This capacity for autoregulation occurs through mechanisms that are completely intrinsic to the kidneys, as discussed later in this chapter.

Table 26-3 Approximate Pressures and Vascular Resistances in the Circulation of a Normal Kidney

Vessel	Pressure in Vessel (mm Hg)		Percent of Total Renal Vascular Resistance
	Beginning	*End*	
Renal artery	100	100	≈0
Interlobar, arcuate, and interlobular arteries	≈100	85	≈16
Afferent arteriole	85	60	≈26
Glomerular capillaries	60	59	≈1
Efferent arteriole	59	18	≈43
Peritubular capillaries	18	8	≈10
Interlobar, interlobular, and arcuate veins	8	4	≈4
Renal vein	4	≈4	≈0

Blood Flow in the Vasa Recta of the Renal Medulla Is Very Low Compared with Flow in the Renal Cortex

The outer part of the kidney, the renal cortex, receives most of the kidney's blood flow. Blood flow in the renal medulla accounts for only 1 to 2 percent of the total renal blood flow. Flow to the renal medulla is supplied by a specialized portion of the peritubular capillary system called the *vasa recta.* These vessels descend into the medulla in parallel with the loops of Henle and then loop back along with the loops of Henle and return to the cortex before emptying into the venous system. As discussed in Chapter 28, the vasa recta play an important role in allowing the kidneys to form concentrated urine.

Physiologic Control of Glomerular Filtration and Renal Blood Flow

The determinants of GFR that are most variable and subject to physiologic control include the glomerular hydrostatic pressure and the glomerular capillary colloid osmotic pressure. These variables, in turn, are influenced by the sympathetic nervous system, hormones and autacoids (vasoactive substances that are released in the kidneys and act locally), and other feedback controls that are intrinsic to the kidneys.

Sympathetic Nervous System Activation Decreases GFR

Essentially all the blood vessels of the kidneys, including the afferent and the efferent arterioles, are richly innervated

by sympathetic nerve fibers. Strong activation of the renal sympathetic nerves can constrict the renal arterioles and decrease renal blood flow and GFR. Moderate or mild sympathetic stimulation has little influence on renal blood flow and GFR. For example, reflex activation of the sympathetic nervous system resulting from moderate decreases in pressure at the carotid sinus baroreceptors or cardiopulmonary receptors has little influence on renal blood flow or GFR.

The renal sympathetic nerves seem to be most important in reducing GFR during severe, acute disturbances lasting for a few minutes to a few hours, such as those elicited by the defense reaction, brain ischemia, or severe hemorrhage. In the healthy resting person, sympathetic tone appears to have little influence on renal blood flow.

Hormonal and Autacoid Control of Renal Circulation

Several hormones and autacoids can influence GFR and renal blood flow, as summarized in Table 26-4.

Norepinephrine, Epinephrine, and Endothelin Constrict Renal Blood Vessels and Decrease GFR. Hormones that constrict afferent and efferent arterioles, causing reductions in GFR and renal blood flow, include *norepinephrine* and *epinephrine* released from the adrenal medulla. In general, blood levels of these hormones parallel the activity of the sympathetic nervous system; thus, norepinephrine and epinephrine have little influence on renal hemodynamics except under extreme conditions, such as severe hemorrhage.

Another vasoconstrictor, *endothelin,* is a peptide that can be released by damaged vascular endothelial cells of the kidneys, as well as by other tissues. The physiologic role of this autacoid is not completely understood. However, endothelin may contribute to hemostasis (minimizing blood loss) when a blood vessel is severed, which damages the endothelium and releases this powerful vasoconstrictor. Plasma endothelin levels are also increased in certain disease states associated with vascular injury, such as toxemia of pregnancy, acute renal failure, and chronic uremia, and may contribute to renal vasoconstriction and decreased GFR in some of these pathophysiologic conditions.

Table 26-4 Hormones and Autacoids That Influence Glomerular Filtration Rate (GFR)

Hormone or Autacoid	Effect on GFR
Norepinephrine	↓
Epinephrine	↓
Endothelin	↓
Angiotensin II	↔ (prevents ↓)
Endothelial-derived nitric oxide	↑
Prostaglandins	↑

Angiotensin II Preferentially Constricts Efferent Arterioles in Most Physiologic Conditions. A powerful renal vasoconstrictor, *angiotensin II,* can be considered a circulating hormone, as well as a locally produced autacoid because it is formed in the kidneys and in the systemic circulation. Receptors for angiotensin II are present in virtually all blood vessels of the kidneys. However, the preglomerular blood vessels, especially the afferent arterioles, appear to be relatively protected from angiotensin II–mediated constriction in most physiologic conditions associated with activation of the renin-angiotensin system such as during a low-sodium diet or reduced renal perfusion pressure due to renal artery stenosis. This protection is due to release of vasodilators, especially *nitric oxide* and *prostaglandins,* which counteract the vasoconstrictor effects of angiotensin II in these blood vessels.

The efferent arterioles, however, are highly sensitive to angiotensin II. Because angiotensin II preferentially constricts efferent arterioles in most physiologic conditions, increased angiotensin II levels raise glomerular hydrostatic pressure while reducing renal blood flow. It should be kept in mind that increased angiotensin II formation usually occurs in circumstances associated with decreased arterial pressure or volume depletion, which tend to decrease GFR. In these circumstances, the increased level of angiotensin II, by constricting efferent arterioles, helps *prevent* decreases in glomerular hydrostatic pressure and GFR; at the same time, though, the reduction in renal blood flow caused by efferent arteriolar constriction contributes to decreased flow through the peritubular capillaries, which in turn increases reabsorption of sodium and water, as discussed in Chapter 27.

Thus, increased angiotensin II levels that occur with a low-sodium diet or volume depletion help maintain GFR and normal excretion of metabolic waste products such as urea and creatinine that depend on glomerular filtration for their excretion; at the same time, the angiotensin II-induced constriction of efferent arterioles increases tubular reabsorption of sodium and water, which helps restore blood volume and blood pressure. This effect of angiotensin II in helping to "autoregulate" GFR is discussed in more detail later in this chapter.

Endothelial-Derived Nitric Oxide Decreases Renal Vascular Resistance and Increases GFR. An autacoid that decreases renal vascular resistance and is released by the vascular endothelium throughout the body is *endothelial-derived nitric oxide.* A basal level of nitric oxide production appears to be important for maintaining vasodilation of the kidneys. This allows the kidneys to excrete normal amounts of sodium and water. Therefore, administration of drugs that inhibit formation of nitric oxide increases renal vascular resistance and decreases GFR and urinary sodium excretion, eventually causing high blood pressure. In some hypertensive patients or in patients with atherosclerosis, damage of the vascular endothelium and impaired nitric oxide production may contribute to increased renal vasoconstriction and elevated blood pressure.

Prostaglandins and Bradykinin Tend to Increase GFR. Hormones and autacoids that cause vasodilation and increased renal blood flow and GFR include the prostaglandins (PGE_2 and PGI_2) and bradykinin. These substances are discussed in Chapter 17. Although these vasodilators do not appear to be of major importance in regulating renal blood flow or GFR in normal conditions, they may dampen the renal vasoconstrictor effects of the sympathetic nerves or angiotensin II, especially their effects to constrict the afferent arterioles.

By opposing vasoconstriction of afferent arterioles, the prostaglandins may help prevent excessive reductions in GFR and renal blood flow. Under stressful conditions, such as volume depletion or after surgery, the administration of nonsteroidal anti-inflammatory agents, such as aspirin, that inhibit prostaglandin synthesis may cause significant reductions in GFR.

Autoregulation of GFR and Renal Blood Flow

Feedback mechanisms intrinsic to the kidneys normally keep the renal blood flow and GFR relatively constant, despite marked changes in arterial blood pressure. These mechanisms still function in blood-perfused kidneys that have been removed from the body, independent of systemic influences. This relative constancy of GFR and renal blood flow is referred to as *autoregulation* (Figure 26-17).

The primary function of blood flow autoregulation in most tissues other than the kidneys is to maintain the delivery of oxygen and nutrients at a normal level and to remove the waste products of metabolism, despite changes in the arterial pressure. In the kidneys, the normal blood flow is much higher than that required for these functions. The major function of autoregulation in the kidneys is to maintain a relatively constant GFR and to allow precise control of renal excretion of water and solutes.

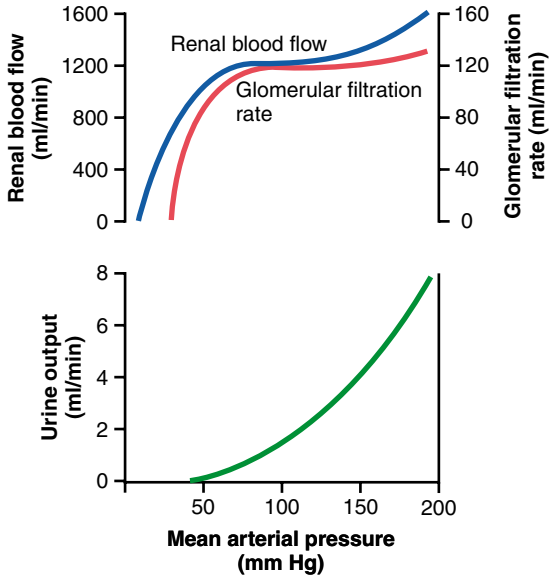


Figure 26-17 Autoregulation of renal blood flow and glomerular filtration rate but lack of autoregulation of urine flow during changes in renal arterial pressure.

The GFR normally remains autoregulated (that is, remains relatively constant), despite considerable arterial pressure fluctuations that occur during a person's usual activities. For instance, a decrease in arterial pressure to as low as 75 mm Hg or an increase to as high as 160 mm Hg usually changes GFR less than 10 percent. In general, renal blood flow is autoregulated in parallel with GFR, but GFR is more efficiently autoregulated under certain conditions.

Importance of GFR Autoregulation in Preventing Extreme Changes in Renal Excretion

Although the renal autoregulatory mechanisms are not perfect, they do prevent potentially large changes in GFR and renal excretion of water and solutes that would otherwise occur with changes in blood pressure. One can understand the quantitative importance of autoregulation by considering the relative magnitudes of glomerular filtration, tubular reabsorption, and renal excretion and the changes in renal excretion that would occur without autoregulatory mechanisms.

Normally, GFR is about 180 L/day and tubular reabsorption is 178.5 L/day, leaving 1.5 L/day of fluid to be excreted in the urine. In the absence of autoregulation, a relatively small increase in blood pressure (from 100 to 125 mm Hg) would cause a similar 25 percent increase in GFR (from about 180 to 225 L/day). If tubular reabsorption remained constant at 178.5 L/day, this would increase the urine flow to 46.5 L/day (the difference between GFR and tubular reabsorption)—a total increase in urine of more than 30-fold. Because the total plasma volume is only about 3 liters, such a change would quickly deplete the blood volume.

In reality, changes in arterial pressure usually exert much less of an effect on urine volume for two reasons: (1) renal autoregulation prevents large changes in GFR that would otherwise occur, and (2) there are additional adaptive mechanisms in the renal tubules that cause them to increase their reabsorption rate when GFR rises, a phenomenon referred to as *glomerulotubular balance* (discussed in Chapter 27). Even with these special control mechanisms, changes in arterial pressure still have significant effects on renal excretion of water and sodium; this is referred to as *pressure diuresis* or *pressure natriuresis,* and it is crucial in the regulation of body fluid volumes and arterial pressure, as discussed in Chapters 19 and 29.

Tubuloglomerular Feedback and Autoregulation of GFR

To perform the function of autoregulation, the kidneys have a feedback mechanism that links changes in sodium chloride concentration at the macula densa with the control of renal arteriolar resistance. This feedback helps ensure a relatively constant delivery of sodium chloride to the distal tubule and helps prevent spurious fluctuations in renal excretion that would otherwise occur. In many circumstances, this feedback autoregulates renal blood

flow and GFR in parallel. However, because this mechanism is specifically directed toward stabilizing sodium chloride delivery to the distal tubule, there are instances when GFR is autoregulated at the expense of changes in renal blood flow, as discussed later.

The tubuloglomerular feedback mechanism has two components that act together to control GFR: (1) an afferent arteriolar feedback mechanism and (2) an efferent arteriolar feedback mechanism. These feedback mechanisms depend on special anatomical arrangements of the *juxtaglomerular complex* (Figure 26-18).

The juxtaglomerular complex consists of *macula densa cells* in the initial portion of the distal tubule and *juxtaglomerular cells* in the walls of the afferent and efferent arterioles. The macula densa is a specialized group of epithelial cells in the distal tubules that comes in close contact with the afferent and efferent arterioles. The macula densa cells contain Golgi apparatus, which are intracellular secretory organelles directed toward the arterioles, suggesting that these cells may be secreting a substance toward the arterioles.

Decreased Macula Densa Sodium Chloride Causes Dilation of Afferent Arterioles and Increased Renin Release. The macula densa cells sense changes in volume delivery to the distal tubule by way of signals that are not completely understood. Experimental studies suggest that decreased GFR slows the flow rate in the loop of Henle, causing increased reabsorption of sodium and chloride ions in the ascending loop of Henle, thereby reducing the concentration of sodium chloride at the macula densa cells. This decrease in sodium chloride concentration initiates a signal from the macula densa that has two effects (Figure 26-19): (1) It decreases resistance to blood flow in the afferent arterioles, which raises glomerular hydrostatic pressure and helps return GFR toward normal, and (2) it increases renin release from the juxtaglomerular cells of the afferent and efferent arterioles, which are the major storage sites for renin. Renin released from these cells then functions as an enzyme to increase the formation of angiotensin I, which is converted to angiotensin II. Finally, the angiotensin II constricts the efferent arterioles, thereby increasing glomerular hydrostatic pressure and helping to return GFR toward normal.

These two components of the tubuloglomerular feedback mechanism, operating together by way of the special anatomical structure of the juxtaglomerular apparatus, provide feedback signals to both the afferent and the efferent arterioles for efficient autoregulation of GFR during changes in arterial pressure. When both of these mechanisms are functioning together, the GFR changes only a few percentage points, even with large fluctuations in arterial pressure between the limits of 75 and 160 mm Hg.

Blockade of Angiotensin II Formation Further Reduces GFR During Renal Hypoperfusion. As discussed earlier, a preferential constrictor action of angiotensin II on efferent arterioles helps prevent serious reductions in glomerular hydrostatic pressure and GFR when renal perfusion pressure falls below normal. The administration of drugs that block

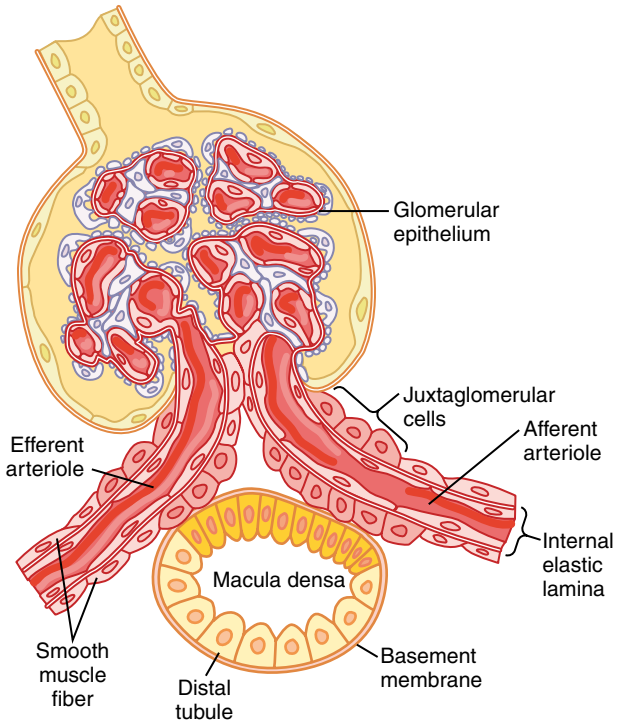


Figure 26-18 Structure of the juxtaglomerular apparatus, demonstrating its possible feedback role in the control of nephron function.

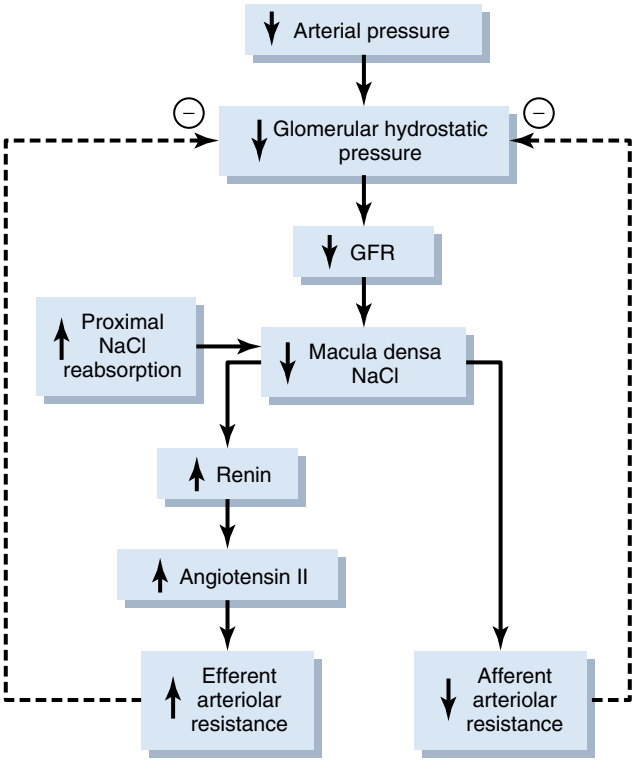


Figure 26-19 Macula densa feedback mechanism for autoregulation of glomerular hydrostatic pressure and glomerular filtration rate (GFR) during decreased renal arterial pressure.

the formation of angiotensin II (angiotensin-converting enzyme inhibitors) or that block the action of angiotensin II (angiotensin II receptor antagonists) causes greater reductions in GFR than usual when the renal arterial pressure falls below normal. Therefore, an important complication of using these drugs to treat patients who have hypertension because of renal artery stenosis (partial blockage of the renal artery) is a severe decrease in GFR that can, in some cases, cause acute renal failure. Nevertheless, angiotensin II–blocking drugs can be useful therapeutic agents in many patients with hypertension, congestive heart failure, and other conditions, as long as they are monitored to ensure that severe decreases in GFR do not occur.

Myogenic Autoregulation of Renal Blood Flow and GFR

Another mechanism that contributes to the maintenance of a relatively constant renal blood flow and GFR is the ability of individual blood vessels to resist stretching during increased arterial pressure, a phenomenon referred to as the *myogenic mechanism.* Studies of individual blood vessels (especially small arterioles) throughout the body have shown that they respond to increased wall tension or wall stretch by contraction of the vascular smooth muscle. Stretch of the vascular wall allows increased movement of calcium ions from the extracellular fluid into the cells, causing them to contract through the mechanisms discussed in Chapter 8. This contraction prevents excessive stretch of the vessel and at the same time, by raising vascular resistance, helps prevent excessive increases in renal blood flow and GFR when arterial pressure increases.

Although the myogenic mechanism probably operates in most arterioles throughout the body, its importance in renal blood flow and GFR autoregulation has been questioned by some physiologists because this pressure-sensitive mechanism has no means of directly detecting changes in renal blood flow or GFR per se. On the other hand, this mechanism may be more important in protecting the kidney from hypertension-induced injury. In response to sudden increases in blood pressure, the myogenic constrictor response in afferent arterioles occurs within seconds and therefore attenuates transmission of increased arterial pressure to the glomerular capillaries.

Other Factors That Increase Renal Blood Flow and GFR: High Protein Intake and Increased Blood Glucose

Although renal blood flow and GFR are relatively stable under most conditions, there are circumstances in which these variables change significantly. For example, *a high protein intake is known to increase both renal blood flow and GFR.* With a chronic high-protein diet, such as one that contains large amounts of meat, the increases in GFR and renal blood flow are due partly to growth of the kidneys. However, GFR and renal blood flow increase 20 to 30 percent within 1 or 2 hours after a person eats a high-protein meal.

One likely explanation for the increased GFR is the following: A high-protein meal increases the release of amino acids into the blood, which are reabsorbed in the proximal tubule. Because amino acids and sodium are reabsorbed together by the proximal tubules, increased amino acid reabsorption also stimulates sodium reabsorption in the proximal tubules. This decreases sodium delivery to the macula densa (see Figure 26-19), which elicits a tubuloglomerular feedback–mediated decrease in resistance of the afferent arterioles, as discussed earlier. The decreased afferent arteriolar resistance then raises renal blood flow and GFR. This increased GFR allows sodium excretion to be maintained at a nearly normal level while increasing the excretion of the waste products of protein metabolism, such as urea.

A similar mechanism may also explain the marked increases in renal blood flow and GFR that occur with large increases in blood glucose levels in uncontrolled diabetes mellitus. Because glucose, like some of the amino acids, is also reabsorbed along with sodium in the proximal tubule, increased glucose delivery to the tubules causes them to reabsorb excess sodium along with glucose. This, in turn, decreases delivery of sodium chloride to the macula densa, activating a tubuloglomerular feedback-mediated dilation of the afferent arterioles and subsequent increases in renal blood flow and GFR.

These examples demonstrate that renal blood flow and GFR per se are not the primary variables controlled by the tubuloglomerular feedback mechanism. The main purpose of this feedback is to ensure a constant delivery of sodium chloride to the distal tubule, where final processing of the urine takes place. Thus, disturbances that tend to increase reabsorption of sodium chloride at tubular sites before the macula densa tend to elicit increased renal blood flow and GFR, which helps return distal sodium chloride delivery toward normal so that normal rates of sodium and water excretion can be maintained (see Figure 26-19).

An opposite sequence of events occurs when proximal tubular reabsorption is reduced. For example, when the proximal tubules are damaged (which can occur as a result of poisoning by heavy metals, such as mercury, or large doses of drugs, such as tetracyclines), their ability to reabsorb sodium chloride is decreased. As a consequence, large amounts of sodium chloride are delivered to the distal tubule and, without appropriate compensations, would quickly cause excessive volume depletion. One of the important compensatory responses appears to be a tubuloglomerular feedback–mediated renal vasoconstriction that occurs in response to the increased sodium chloride delivery to the macula densa in these circumstances. These examples again demonstrate the importance of this feedback mechanism in ensuring that the distal tubule receives the proper rate of delivery of sodium chloride, other tubular fluid solutes, and tubular fluid volume so that appropriate amounts of these substances are excreted in the urine.

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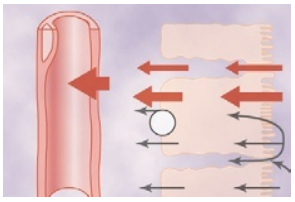
Urine Formation by the Kidneys: II. Tubular Reabsorption and Secretion



Renal Tubular Reabsorption and Secretion

As the glomerular filtrate enters the renal tubules, it flows sequentially through the successive parts of the tubule—the *proximal tubule,* 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:

Urinary excretion = Glomerular filtration – Tubular reabsorption + Tubular secretion

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

Tubular Reabsorption Is Quantitatively Large and Highly Selective

Table 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 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 percent 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 (essentially all solutes in the plasma are filtered except the plasma proteins or substances bound to them), *tubular reabsorption is highly selective.* Some substances, such as glucose and amino acids, are almost completely reabsorbed from the tubules, so the urinary excretion rate is essentially zero. Many 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. 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 body fluid composition. In this chapter, we discuss the mechanisms that allow the kidneys to selectively reabsorb or secrete different substances at variable rates.

Tubular Reabsorption Includes Passive and Active Mechanisms

For a substance to be reabsorbed, it must first be transported (1) across the tubular epithelial membranes into the renal interstitial fluid and then (2) through the peritubular capillary membrane back into the blood (Figure 27-1).

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

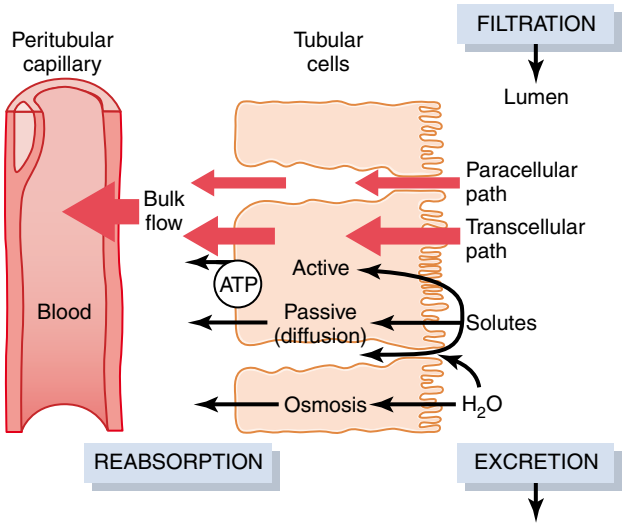


Figure 27-1 Reabsorption of filtered water and solutes from the tubular lumen across the tubular epithelial cells, through the renal interstitium, and back into the blood. Solutes are transported through the cells (*transcellular path)* by passive diffusion or active transport, or between the cells (*paracellular path*) by diffusion. Water is transported through the cells and between the tubular cells by osmosis. Transport of water and solutes from the interstitial fluid into the peritubular capillaries occurs by ultrafiltration (*bulk flow*).

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

Active Transport

Active transport can move a solute against an electrochemical gradient 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 through 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

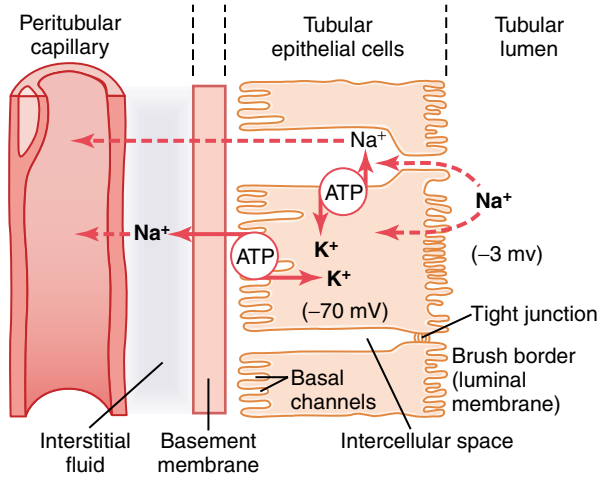


Figure 27-2 Basic mechanism for active transport of sodium through the tubular epithelial cell. The sodium-potassium pump transports sodium from the interior of the cell across the basolateral membrane, creating a low intracellular sodium concentration and a negative intracellular electrical potential. 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.

a component of the carrier mechanism that binds and moves solutes across the cell membranes. The primary active transporters in the kidneys that are known include *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 active pumping of sodium out of the cell across the *basolateral* membrane of the cell favors passive diffusion of sodium across the *luminal* membrane of the cell, from the tubular lumen into the cell, for two reasons: (1) There is a concentration gradient favoring sodium diffusion into the cell because intracellular sodium concentration is low (12 mEq/L) and tubular fluid sodium concentration is high (140 mEq/L) and (2) the negative, –70-millivolt, intracellular potential attracts the positive sodium ions from the tubular lumen into the cell.

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

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

1. Sodium diffuses across the luminal membrane (also called the *apical membrane*) into the cell down an electrochemical gradient established by the 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 (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, specific carrier proteins in the brush border combine with a sodium ion and an amino acid or a glucose molecule at the same time. These transport mechanisms are so efficient that they remove virtually all the glucose and amino acids from the tubular lumen. After entry into the cell, glucose and amino acids exit across the basolateral membranes by diffusion, driven by the high glucose and amino acid concentrations in the cell facilitated by specific transport proteins.

Sodium glucose co-transporters (SGLT2 and SGLT1) are located on the brush border of proximal tubular cells and carry glucose into the cell cytoplasm against a concentration gradient, as described previously. Approximately 90 percent of the filtered glucose is reabsorbed by SGLT2 in the early part of the proximal tubule (S1 segment) and the residual 10 percent is transported by SGLT1 in the latter segments of the proximal tubule. On the basolateral

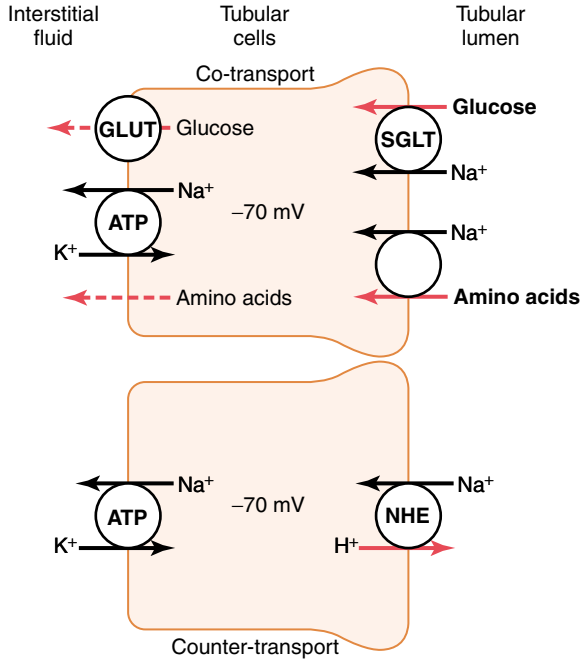


Figure 27-3 Mechanisms of secondary active transport. The upper cell shows the *co-transport* of glucose and amino acids along with sodium ions through the apical side of the tubular epithelial cells, followed by facilitated diffusion through the basolateral membranes. The lower cell shows the *counter-transport* 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. GLUT, glucose transporter; NHE, sodium-hydrogen exchanger; SGLT, sodium-glucose co-transporter.

side of the membrane, glucose diffuses out of the cell into the interstitial spaces with the help of *glucose transporters -GLUT2,* in the S1 segment and *GLUT1* in the latter part (S3 segment) of the proximal tubule.

Although transport of glucose against a chemical gradient does not directly use ATP, the reabsorption of glucose depends on energy expended by the primary active 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 (e.g., 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 (*sodium-hydrogen exchanger*) in the brush border of the luminal membrane. As sodium is carried to the interior of the cell, hydrogen ions are forced outward in the opposite direction into the tubular lumen. The basic principles of primary and secondary active transport are discussed in 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.

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

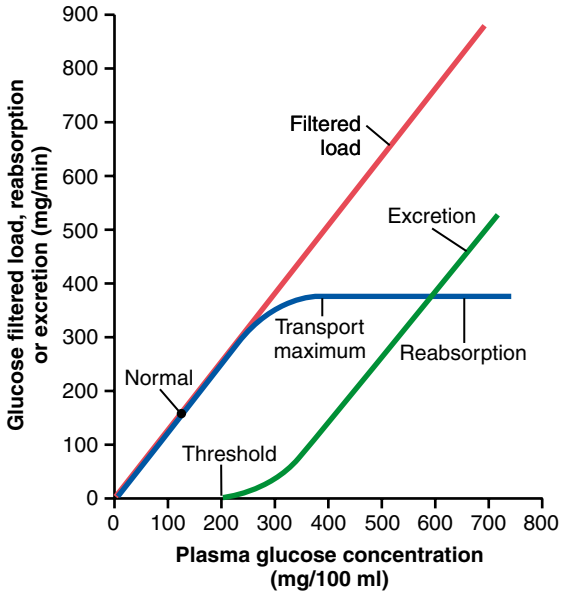


Figure 27-4 Relations among the filtered load of glucose, the rate of glucose reabsorption by the renal tubules, and the rate of glucose excretion in the urine. The *transport maximum* is the maximum rate at which glucose can be reabsorbed from the tubules. The *threshold* for glucose refers to the filtered load of glucose at which glucose first begins to be excreted in the urine.

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 therefore begin to excrete glucose before others have reached their transport maximum. *The overall transport maximum for the kidneys, which is normally about 375 mg/min, is reached when all nephrons have reached their maximal capacity to reabsorb glucose.*

The plasma glucose of a healthy person almost never becomes high enough to cause glucose excretion in the urine, even after eating a meal. However, in uncontrolled *diabetes mellitus,* plasma glucose 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. *Some 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 backleak 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 by 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 in the proximal tubules 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 permit 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 tight junctions of 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 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.

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

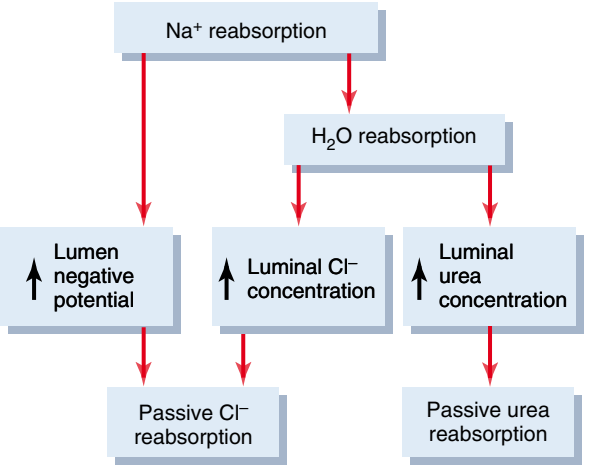


Figure 27-5 Mechanisms by which water, chloride, and urea reabsorption are coupled with sodium reabsorption.

amounts of this waste product of metabolism. In mammals, greater than 90 percent of waste nitrogen, mainly generated in the liver as a product of protein metabolism, is normally excreted by the kidneys as urea.

Another waste product of metabolism, creatinine, is an even larger molecule than urea and is essentially impermeant to the tubular membrane. Therefore, almost none of the creatinine that is filtered is reabsorbed, so 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 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 percent 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 powerful active transport processes. In addition, the proximal tubular cells have an extensive brush border on the luminal (apical) side of the membrane, as well as an extensive labyrinth of intercellular and basal channels, all of which together provide an extensive membrane surface area on the luminal and basolateral sides of the epithelium for rapid transport of sodium ions and other substances.

The extensive membrane surface of the epithelial brush border is also loaded with protein carrier molecules that transport a large fraction of the sodium ions across the luminal membrane linked by way of the *co-transport* mechanism with multiple organic nutrients such as amino acids and glucose. Additional sodium is transported from the tubular lumen into the cell by *counter-transport* mechanisms that reabsorb sodium while secreting other substances into the tubular lumen, especially hydrogen

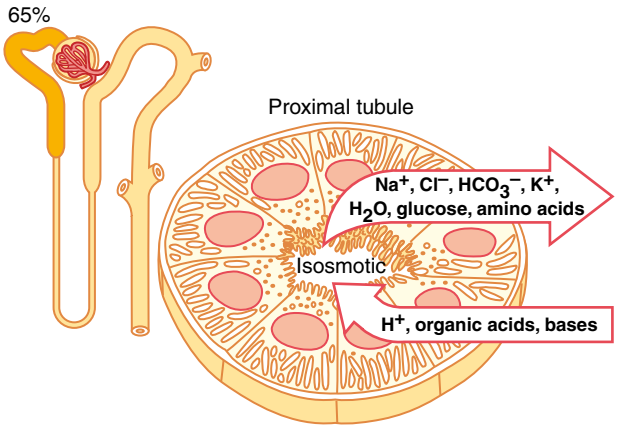


Figure 27-6 Cellular ultrastructure and primary transport characteristics of the proximal tubule. The proximal tubules reabsorb about 65 percent of the filtered sodium, chloride, bicarbonate, and potassium and essentially all the filtered glucose and amino acids. The proximal tubules also secrete organic acids, bases, and hydrogen ions into the tubular lumen.

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 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. Smaller amounts of chloride may also be reabsorbed through specific chloride channels in the proximal tubular cell membrane.

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

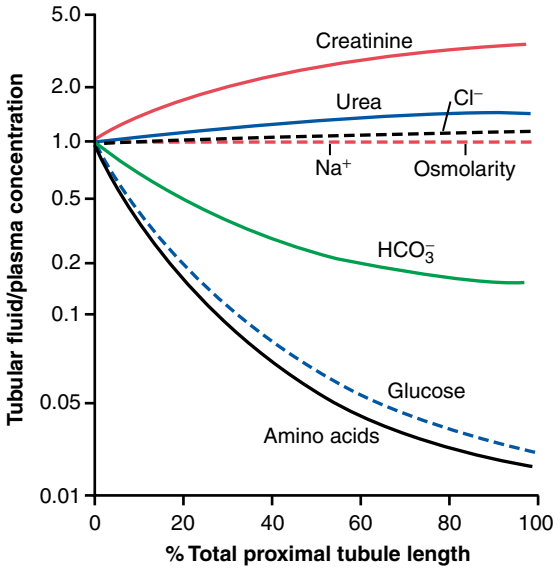


Figure 27-7 Changes in concentrations of different substances in tubular fluid along the proximal convoluted tubule relative to the concentrations of these substances in the plasma and in the glomerular filtrate. A value of 1.0 indicates that the concentration of the substance in the tubular fluid is 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 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 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 percent 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 percent of the filtered water is reabsorbed in the loop of Henle, and almost

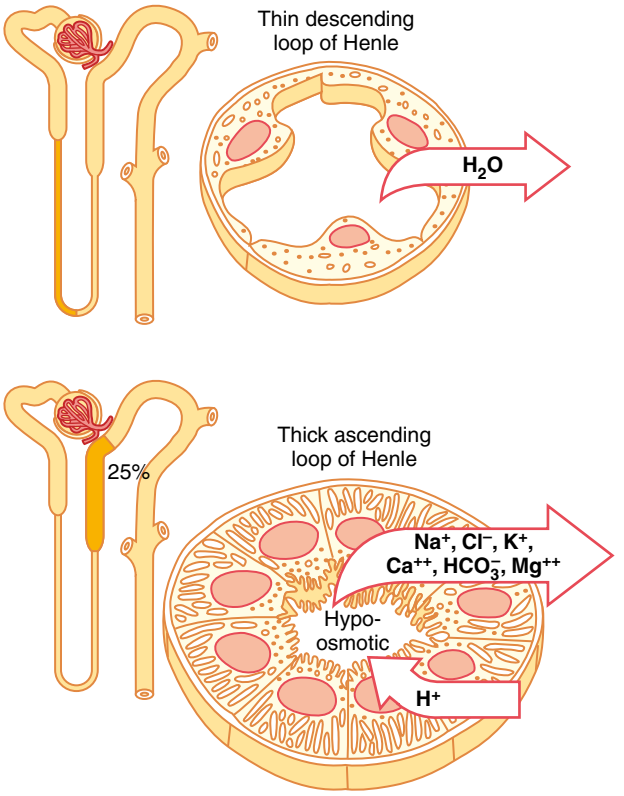


Figure 27-8 Cellular ultrastructure and transport characteristics of the thin descending loop of Henle (*top*) and the thick ascending segment of the loop of Henle (*bottom*). The descending part of the thin segment of the loop of Henle is highly permeable to water and moderately permeable to most solutes but has few mitochondria and little or no active reabsorption. The thick ascending limb of the loop of Henle reabsorbs about 25 percent 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.

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 percent 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, 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.

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.

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 (see Figure 27-9).

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 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

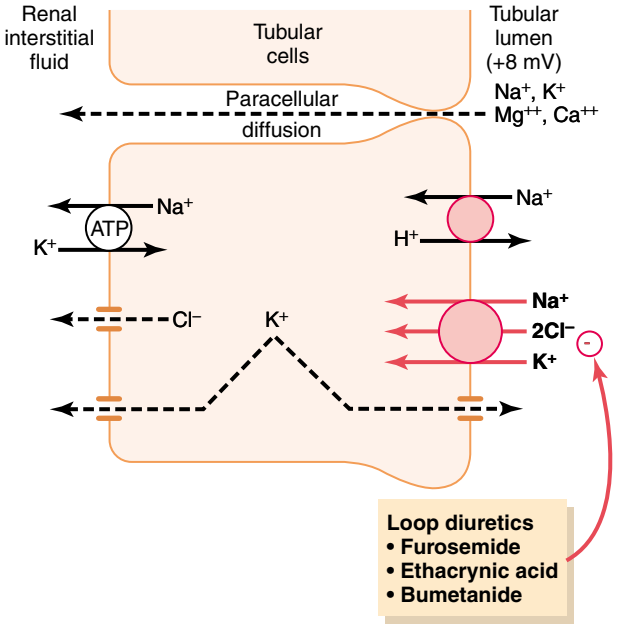


Figure 27-9 Mechanisms of sodium, chloride, and potassium transport in the thick ascending loop of Henle. The sodium-potassium ATPase pump in the basolateral cell membrane maintains a low intracellular sodium concentration and a negative electrical potential in the cell. The 1-sodium, 2-chloride, 1-potassium 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.

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 first portion of the distal tubule forms the *macula densa,* a group of closely packed epithelial cells that is part of the *juxtaglomerular complex* and provides feedback control of 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

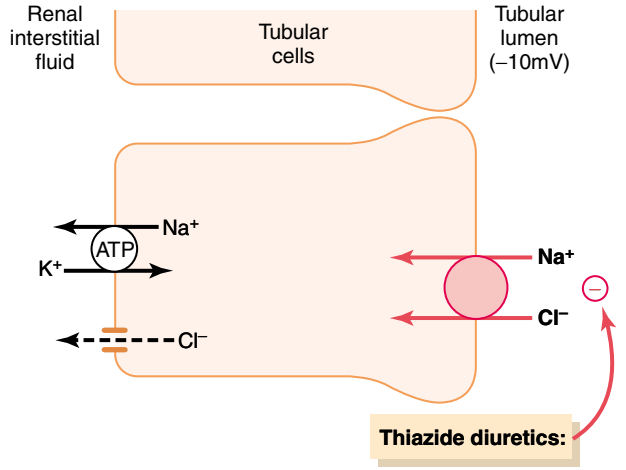


Figure 27-10 Mechanism of sodium chloride transport in the early distal tubule. Sodium and chloride are transported from the tubular lumen into the cell by a co-transporter that is inhibited by thiazide diuretics. Sodium is pumped out of the cell by sodium-potassium ATPase and chloride diffuses into the interstitial fluid via chloride channels.

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 *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 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. *Spironolactone*

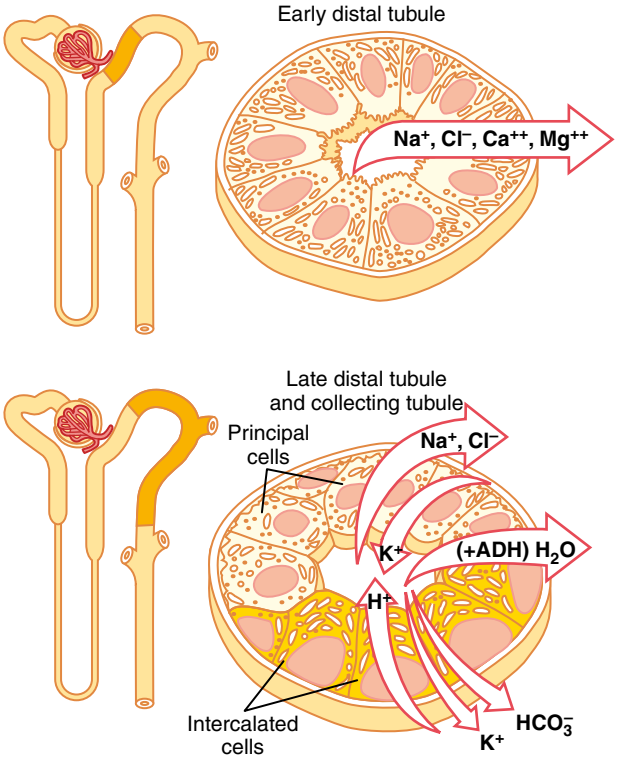


Figure 27-11 Cellular ultrastructure and transport characteristics of the early distal tubule and the late distal tubule and collecting tubule. The early distal tubule has many of the same characteristics as the thick ascending loop of Henle and reabsorbs sodium, chloride, calcium, and magnesium but 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*.

and *eplerenone* are mineralocorticoid receptor antagonists that compete with aldosterone for receptor sites in the principal cells and therefore inhibit the stimulatory effects of aldosterone on sodium reabsorption and potassium secretion. *Amiloride* and *triamterene* are sodium channel blockers that directly inhibit the entry of sodium into the sodium channels of the luminal membranes and therefore reduce the amount of sodium that can be transported across the basolateral membranes by the 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 Secrete Hydrogen and Reabsorb Bicarbonate and Potassium Ions. Hydrogen ion secretion by the intercalated cells is mediated by a hydrogen-ATPase transporter. Hydrogen is generated in this cell by the action of carbonic anhydrase on water and carbon

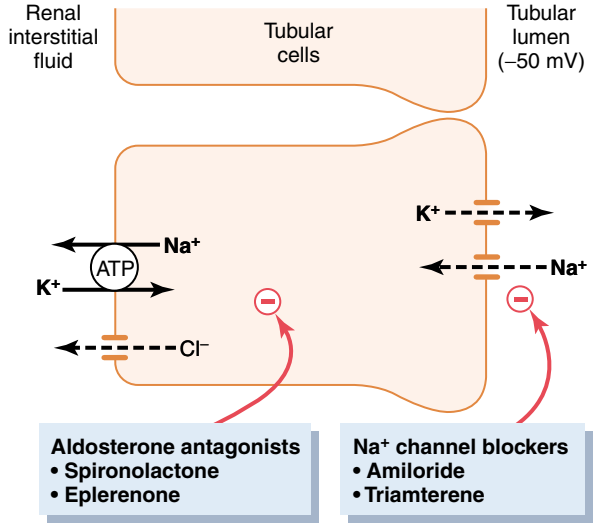


Figure 27-12 Mechanism of sodium chloride reabsorption and potassium secretion in the late distal tubules and cortical collecting tubules. Sodium enters the cell through special channels and is transported out of the cell by the sodium-potassium ATPase pump. Aldosterone antagonists compete with aldosterone 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.

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 percent 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 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 and there are special *urea transporters* that facilitate urea diffusion across the luminal and basolateral membranes. Therefore, some of the tubular urea is reabsorbed into the medullary interstitium, helping to raise the osmolality in this

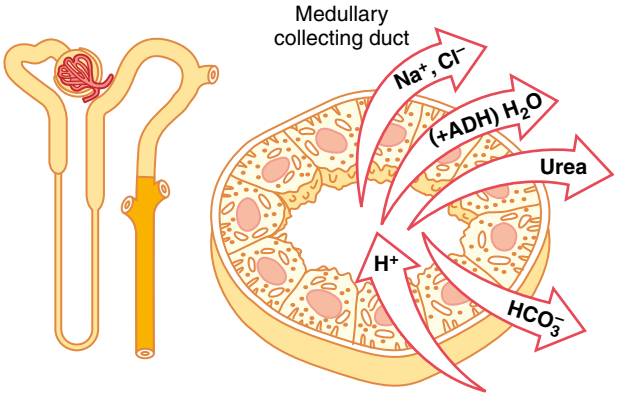


Figure 27-13 Cellular ultrastructure and transport characteristics of the medullary collecting duct. The medullary collecting ducts actively reabsorb sodium and secrete hydrogen ions and are permeable to urea, which is reabsorbed in these tubular segments. The reabsorption of water in medullary collecting ducts is controlled by the concentration of antidiuretic hormone.

region of the kidneys and contributing to the kidneys' overall ability to form concentrated urine. This is discussed in Chapter 28.

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 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.

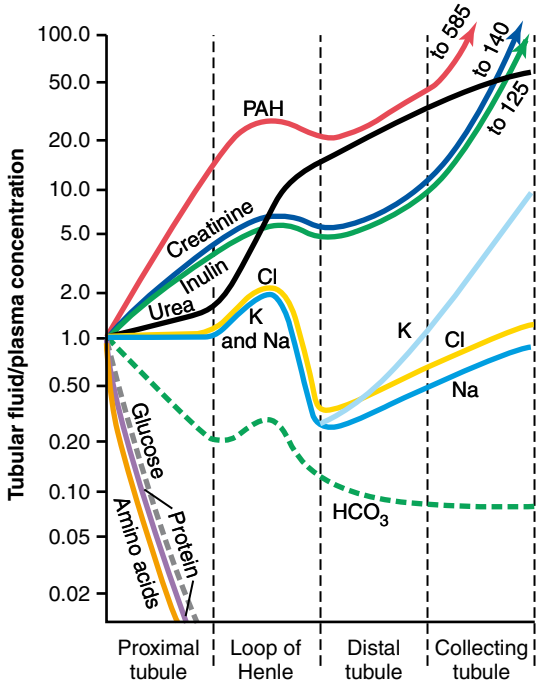


Figure 27-14 Changes in average concentrations of different substances at different points in the tubular system relative to the concentration of that substance in the plasma and in the glomerular filtrate. A value of 1.0 indicates that the concentration of the substance in the tubular fluid is the same 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.

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 three times greater than in the plasma and in the glomerular filtrate. Because inulin is not secreted or reabsorbed from the tubules, a tubular fluid/plasma concentration ratio of 3.0 means that only one third of the water that was filtered remains in the renal tubule and that two thirds of the filtered water has been reabsorbed as the fluid passes through the proximal tubule. At the end of the collecting ducts, the tubular fluid/plasma inulin concentration ratio rises to about 125 (see Figure 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 percent of GFR) to about 97.5 ml/min (65 percent 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 percent.

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

Glomerulotubular balance helps 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 upset sodium and volume homeostasis.

Peritubular Capillary and Renal Interstitial Fluid Physical Forces

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

Normal Values for Physical Forces and Reabsorption Rate. As the glomerular filtrate passes through the renal tubules, more than 99 percent 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. 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.

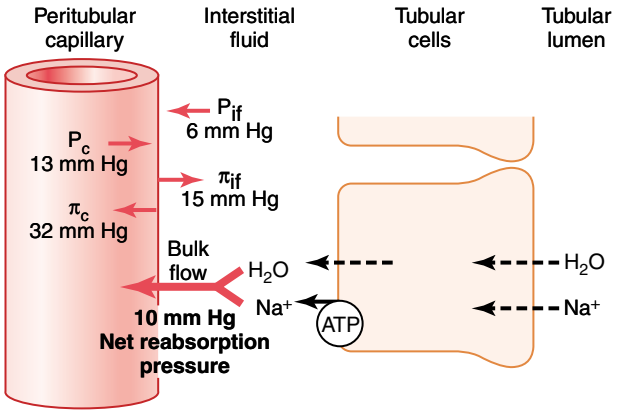


Figure 27-15 Summary of the hydrostatic and colloid osmotic forces that determine fluid reabsorption by the peritubular capillaries. The numerical values shown are estimates of the normal values for humans. The net reabsorptive pressure is normally about 10 mm Hg, causing fluid and solutes to be reabsorbed 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.

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 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

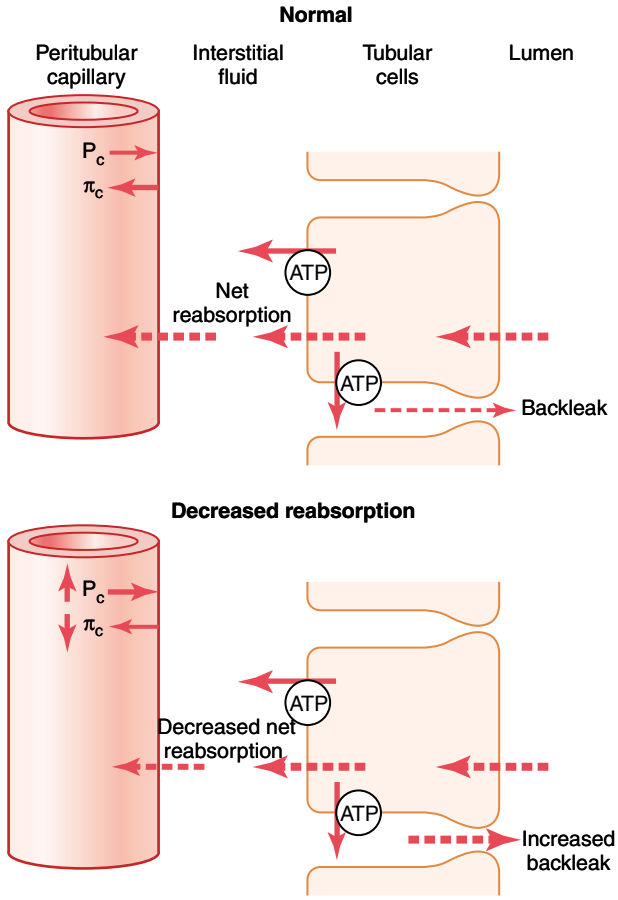


Figure 27-16 Proximal tubular and peritubular capillary reabsorption under normal conditions (*top*) and during decreased peritubular capillary reabsorption (*bottom*) caused by either increasing peritubular capillary hydrostatic pressure (P_c) or decreasing peritubular capillary colloid osmotic pressure (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.

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.*

Effect of Arterial Pressure on Urine Output—Pressure Natriuresis and Pressure Diuresis

Even small increases in arterial pressure can cause marked increases in urinary excretion of sodium and water, phenomena 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 Stimulates 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. *A major renal tubular 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.

Table 27-3 Hormones That Regulate Tubular Reabsorption

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

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

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 decreased plasma potassium concentration due, in part, to excessive potassium secretion by the kidneys. 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 by excessive sweating or severe diarrhea. 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 increase sodium and water reabsorption. First, efferent arteriolar constriction reduces peritubular capillary hydrostatic pressure, which increases net tubular reabsorption, especially from the proximal tubules. Second, efferent arteriolar constriction, by reducing renal blood flow, raises filtration fraction in the glomerulus and increases the concentration of proteins and 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. A third effect of angiotensin II is to stimulate sodium-bicarbonate co-transport in the basolateral membrane (Figure 27-17).

Thus, angiotensin II stimulates sodium transport across both the luminal and the basolateral surfaces of the epithelial cell membrane in most renal tubular segments. These multiple actions of angiotensin II cause marked sodium and water retention by the kidneys when angiotensin II levels are increased and play a critical role in

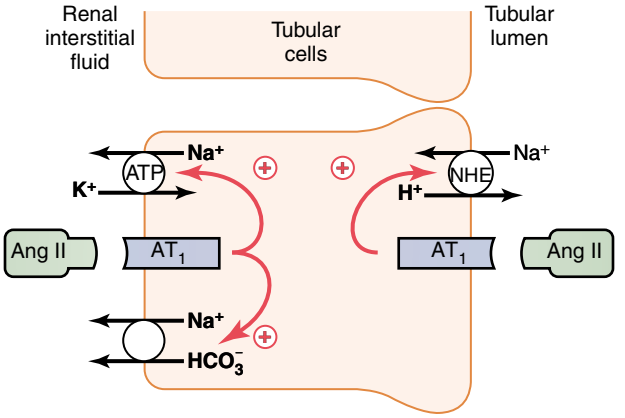


Figure 27-17 Direct effects of angiotensin II (*Ang II*) to increase proximal tubular sodium reabsorption. Ang II stimulates sodium sodium-hydrogen exchange (*NHE*) on the luminal membrane and the sodium-potassium ATPase transporter as well as sodium-bicarbonate co-transport on the basolateral membrane. These same effects of Ang II likely occur in several other parts of the renal tubule, including the loop of Henle, distal tubule, and collecting tubule.

permitting the body to adapt to wide variations in sodium intake without large changes in extracellular fluid volume and blood pressure, as discussed in Chapter 29.

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

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 (Figure 27-18). 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. These cellular actions of ADH are discussed further in Chapter 75.

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 (ANP).* Increased levels of this peptide in turn directly inhibit the reabsorption of sodium and water by the renal tubules, especially in the collecting ducts. ANP also inhibits renin secretion and therefore angiotensin II formation, which in turn reduces renal tubular reabsorption. This decreased sodium and water reabsorption increases urinary excretion, which helps to return blood volume back toward normal.

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

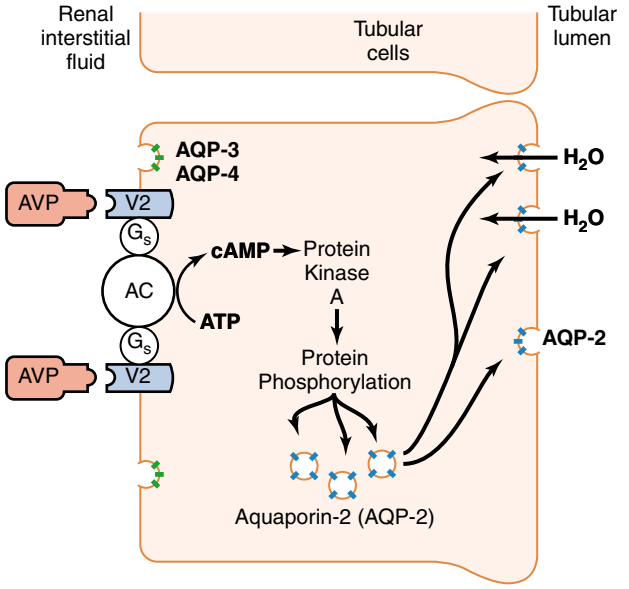


Figure 27-18 Mechanism of action of arginine vasopressin (*AVP*) on the epithelial cells of the late distal tubules, collecting tubules and collecting ducts. AVP binds to its V_2 receptors, which are coupled with stimulatory G proteins (G_s) that activate adenylate cyclase (*AC*) and stimulate formation of cyclic adenosine monophosphate (*cAMP*). This, in turn, activates protein kinase A and phosphorylation of intracellular proteins, causing movement of aquaporin-2 (*AQP-2*) to the luminal side of the cell membrane. The molecules of AQP-2 fuse together to form water channels. On the basolateral side of the cell membrane are other aquaporins, *AQP-3* and *AQP-4,* that permit water to flow out of the cell, although these aquaporins do not appear to be regulated by AVP.

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

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

Use of Clearance Methods to Quantify Kidney Function

The rates at which different substances are "cleared" from the plasma provide a useful way of quantitating the effectiveness with which the kidneys excrete various substances (Table 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, 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 27-19 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

Table 27-4 Use of Clearance to Quantify Kidney Function

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

S, a substance; U, urine concentration; $\dot{V}$, 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.

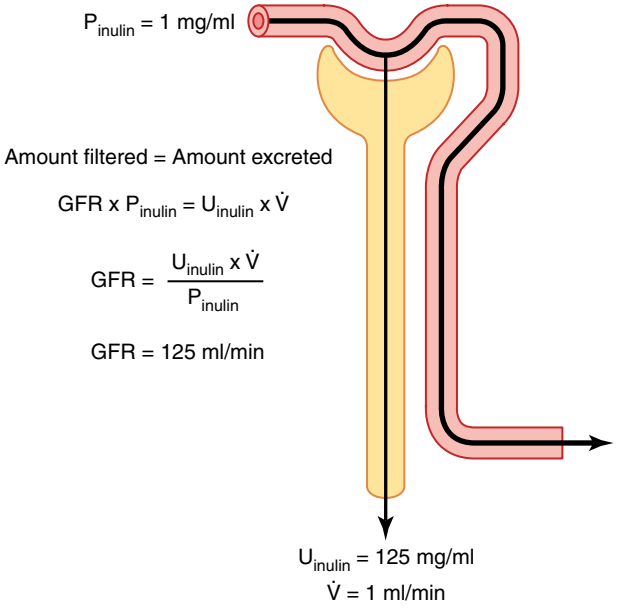


Figure 27-19 Measurement of glomerular filtration rate (*GFR*) from the renal clearance of inulin. Inulin is freely filtered by the glomerular capillaries but is not reabsorbed by the renal tubules. P_{inulin}, plasma inulin concentration; U_{inulin}, urine inulin concentration; $\dot{V}$, urine flow rate.

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 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 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:

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

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} × GFR) and creatinine excretion (U_{Cr} × $\dot{V}$) return to normal and a balance between creatinine production and creatinine excretion is re-established. This will occur when plasma creatinine increases to approximately twice normal, as shown in Figure 27-20.

If GFR falls to one-fourth normal, plasma creatinine would increase to about four times normal and a decrease of GFR to one-eighth normal would raise plasma creatinine to eight 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 27-21.

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

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

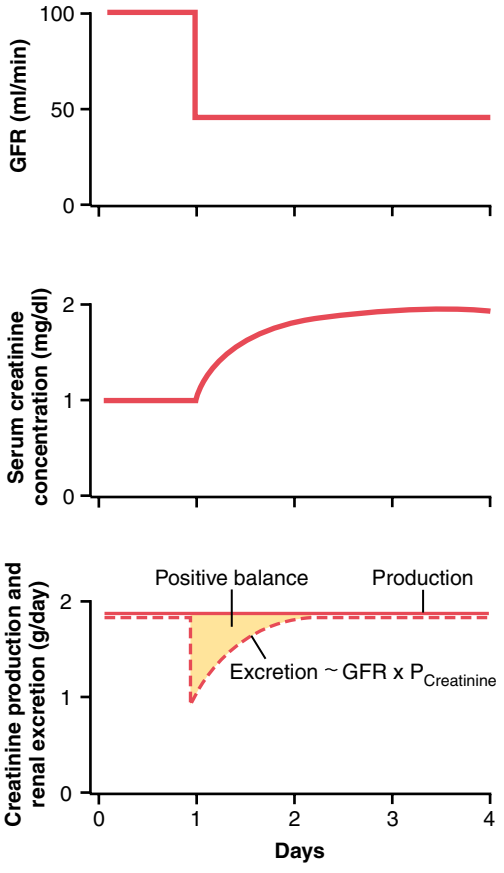


Figure 27-20 Effect of reducing glomerular filtration rate (*GRF*) by 50 percent on serum creatinine concentration and on creatinine excretion rate when the production rate of creatinine remains constant. $P_{Creatinine}$, plasma creatinine concentration.

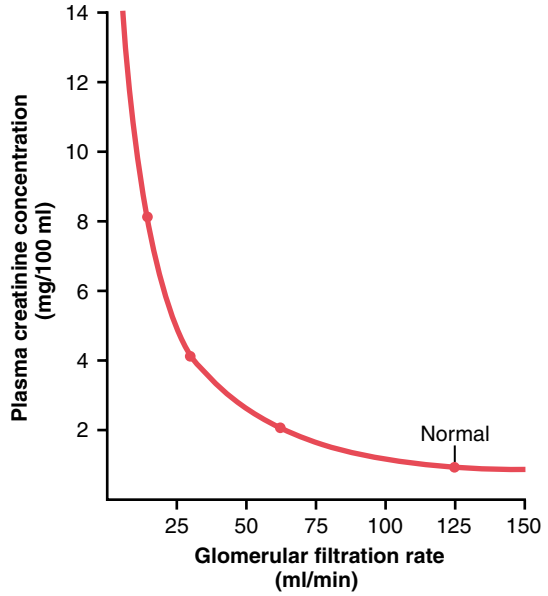


Figure 27-21 Approximate relationship between glomerular filtration rate (GFR) and plasma creatinine concentration under steady-state conditions. Decreasing GFR by 50 percent will increase plasma creatinine to twice normal if creatinine production by the body remains constant.

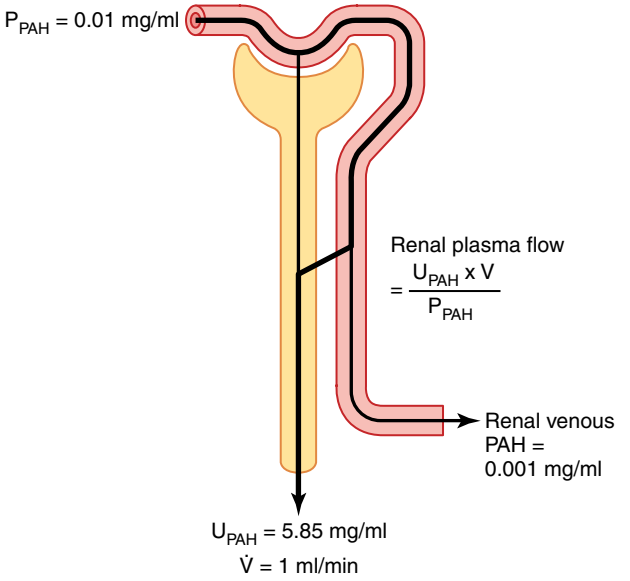


Figure 27-22 Measurement of renal plasma flow from the renal clearance of para-aminohippuric acid (*PAH*). PAH is freely filtered by the glomerular capillaries and is also secreted from the peritubular capillary blood into the tubular lumen. The amount of PAH in the plasma of the renal artery is about 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; $\dot{V}$, urine flow rate.

Because the GFR is only about 20 percent 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 27-22). There is no known substance that is *completely* cleared by the kidneys. One substance, however, PAH, is about 90 percent 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 percent in normal kidneys. In diseased kidneys, this extraction ratio may be reduced 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 percent, 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

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

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

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

One can calculate the total blood flow through the kidneys from the total 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 to 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

$$\text{FF} = \text{GFR}/\text{RPF} = 125/650 = 0.19$$

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 ($U_s \times \dot{V}$) 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

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CHAPTER 28

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

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

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

Kidneys Excrete Excess Water by Forming Dilute Urine

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

Antidiuretic Hormone Controls Urine Concentration

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

When osmolarity of the body fluids increases above normal (i.e., the solutes in the body fluids become too concentrated), the posterior pituitary gland secretes more ADH, which increases the permeability of the distal tubules and collecting ducts to water, as discussed in Chapter 27. This permits large amounts of water to be reabsorbed and decreases urine volume but does not markedly alter the rate of renal excretion of the solutes.

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

Renal Mechanisms for Excreting Dilute Urine

When there is a large excess of water in the body, the kidney can excrete as much as 20 L/day of dilute urine, with a concentration as low as 50 mOsm/L. The kidney performs this impressive feat by continuing to reabsorb solutes while failing to reabsorb large amounts of water in the distal parts of the nephron, including the late distal tubule and the collecting ducts.

Figure 28-1 shows the approximate renal responses in a human after ingestion of 1 liter of water. Note that urine volume increases to about six times normal within 45 minutes after the water has been drunk. However, the total amount of solute excreted remains relatively constant because the urine formed becomes very dilute and urine osmolarity decreases from 600 to about 100 mOsm/L.

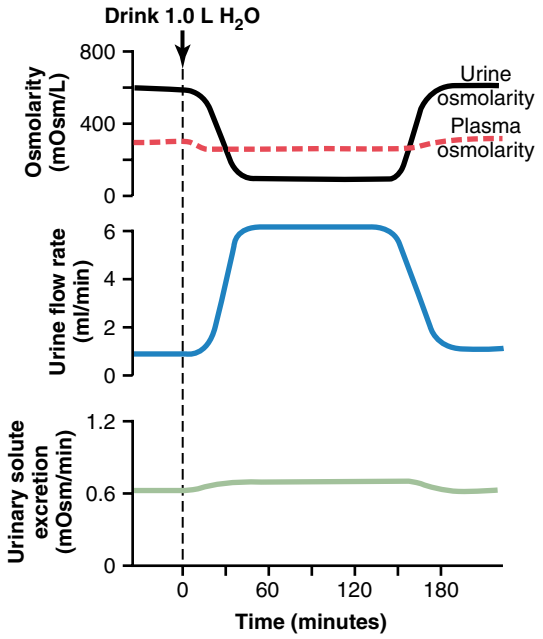

Figure 28-1 Water diuresis in a human after ingestion of 1 liter of water. Note that after water ingestion, urine volume increases and urine osmolarity decreases, causing the excretion of a large volume of dilute urine; however, the total amount of solute excreted by the kidneys remains relatively constant. These responses of the kidneys prevent plasma osmolarity from decreasing markedly during excess water ingestion.

Thus, after ingestion of excess water, the kidney rids the body of the excess water but does not excrete excess amounts of solutes.

When the glomerular filtrate is initially formed, its osmolarity is about the same as that of plasma (300 mOsm/L). To excrete excess water, it is necessary to dilute the filtrate as it passes along the tubule. This is achieved by reabsorbing solutes to a greater extent than water, as shown in Figure 28-2, but this occurs only in certain segments of the tubular system as follows.

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

Tubular Fluid Is Diluted in the Ascending Loop of Henle. In the ascending limb of the loop of Henle, especially in the thick segment, sodium, potassium, and chloride are avidly reabsorbed. However, this portion of the tubular segment is impermeable to water, even in the presence of large amounts of ADH. Therefore, the tubular fluid becomes more dilute as it flows up the ascending loop of Henle into

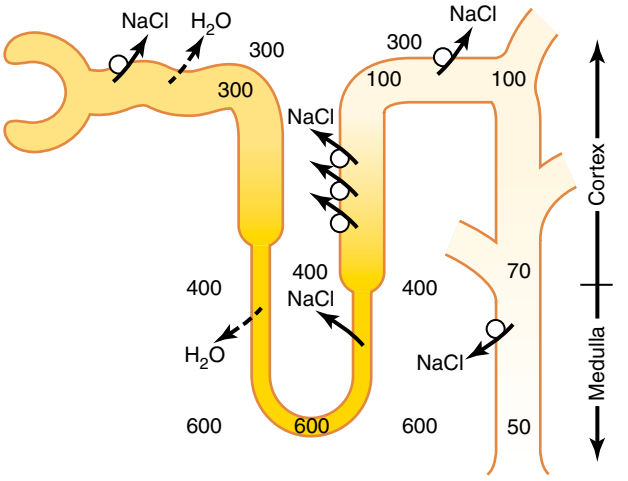

Figure 28-2 Formation of dilute urine when antidiuretic hormone (ADH) levels are very low. Note that in the ascending loop of Henle, the tubular fluid becomes very dilute. In the distal tubules and collecting tubules, the tubular fluid is further diluted by the reabsorption of sodium chloride and the failure to reabsorb water when ADH levels are very low. The failure to reabsorb water and continued reabsorption of solutes lead to a large volume of dilute urine. (Numerical values are in milliosmoles per liter.)

the early distal tubule, with the osmolarity decreasing progressively to about 100 mOsm/L by the time the fluid enters the early distal tubular segment. *Thus, regardless of whether ADH is present or absent, fluid leaving the early distal tubular segment is hypo-osmotic, with an osmolarity of only about one-third the osmolarity of plasma.*

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

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

Kidneys Conserve Water by Excreting Concentrated Urine

The ability of the kidney to form urine that is more concentrated than plasma is essential for survival of mammals that live on land, including humans. Water is continuously lost from the body through various routes, including the

lungs by evaporation into the expired air, the gastrointestinal tract by way of the feces, the skin through evaporation and perspiration, and the kidneys through the excretion of urine. Fluid intake is required to match this loss, but the ability of the kidney to form a small volume of concentrated urine minimizes the intake of fluid required to maintain homeostasis, a function that is especially important when water is in short supply.

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

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

Obligatory Urine Volume

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

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

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

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

Urine Specific Gravity

Urine *specific gravity* is often used in clinical settings to provide a rapid estimate of urine solute concentration. The more concentrated the urine, the higher the urine specific gravity. In most cases, urine specific gravity increases linearly with increasing urine osmolarity (Figure 28-3). Urine specific gravity, however, is a measure of the weight of solutes in a given volume of urine and is therefore determined by the number and size of the solute molecules. This contrasts with osmolarity, which is determined only by the number of solute molecules in a given volume.

Urine specific gravity is generally expressed in grams/ml and, in humans, normally ranges from 1.002 to 1.028 g/ml, rising by .001 for every 35 to 40 mOsmol/L increase in urine osmolarity. This relationship between specific gravity and osmolarity is altered when there are significant amounts of large molecules in the urine, such as glucose, radiocontrast media used for diagnostic purposes, or some antibiotics. In these cases, urine specific gravity measurements may falsely suggest a very concentrated urine, despite a normal urine osmolality.

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

Requirements for Excreting a Concentrated Urine—High ADH Levels and Hyperosmotic Renal Medulla

The basic requirements for forming a concentrated urine are (1) a *high level of ADH,* which increases the permeability of the distal tubules and collecting ducts to water,

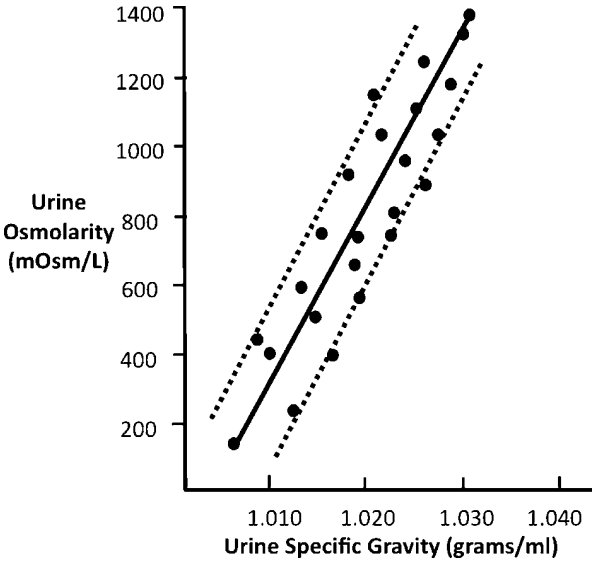

Figure 28-3 Relationship between specific gravity (grams/ml) and osmolarity of the urine.

thereby allowing these tubular segments to avidly reabsorb water, and (2) *a high osmolarity of the renal medullary interstitial fluid,* which provides the osmotic gradient necessary for water reabsorption to occur in the presence of high levels of ADH.

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

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

Countercurrent Mechanism Produces a Hyperosmotic Renal Medullary Interstitium

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

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

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

Special Characteristics of Loop of Henle That Cause Solutes to Be Trapped in the Renal Medulla. The transport characteristics of the loops of Henle are summarized in Table 28-1, along with the properties of the proximal tubules, distal tubules, cortical collecting tubules, and inner medullary collecting ducts.

The most important cause of the high medullary osmolarity is active transport of sodium and co-transport of potassium, chloride, and other ions from the thick ascending loop of Henle into the interstitium. This pump is capable of establishing about a 200-milliosmole concentration gradient between the tubular lumen and the interstitial fluid. Because the thick ascending limb is virtually impermeable to water, the solutes pumped out are

Table 28-1 Summary of Tubule Characteristics—Urine Concentration

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

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

not followed by osmotic flow of water into the interstitium. Thus, the active transport of sodium and other ions out of the thick ascending loop adds solutes in excess of water to the renal medullary interstitium. There is some passive reabsorption of sodium chloride from the thin ascending limb of Henle's loop, which is also impermeable to water, adding further to the high solute concentration of the renal medullary interstitium.

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

Steps Involved in Causing Hyperosmotic Renal Medullary Interstitium. Keeping in mind these characteristics of the loop of Henle, let us now discuss how the renal medulla becomes hyperosmotic. First, assume that the loop of Henle is filled with fluid with a concentration of 300 mOsm/L, the same as that leaving the proximal tubule (Figure 28-4, step 1). Next, the active ion pump of the *thick ascending limb* on the loop of Henle reduces the concentration inside the tubule and raises the interstitial concentration; this pump establishes a 200-mOsm/L concentration gradient between the tubular fluid and the interstitial fluid (step 2). The limit to the gradient is about 200 mOsm/L because paracellular diffusion of ions back into the tubule eventually counterbalances transport of ions out of the lumen when the 200-mOsm/L concentration gradient is achieved.

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

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

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

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

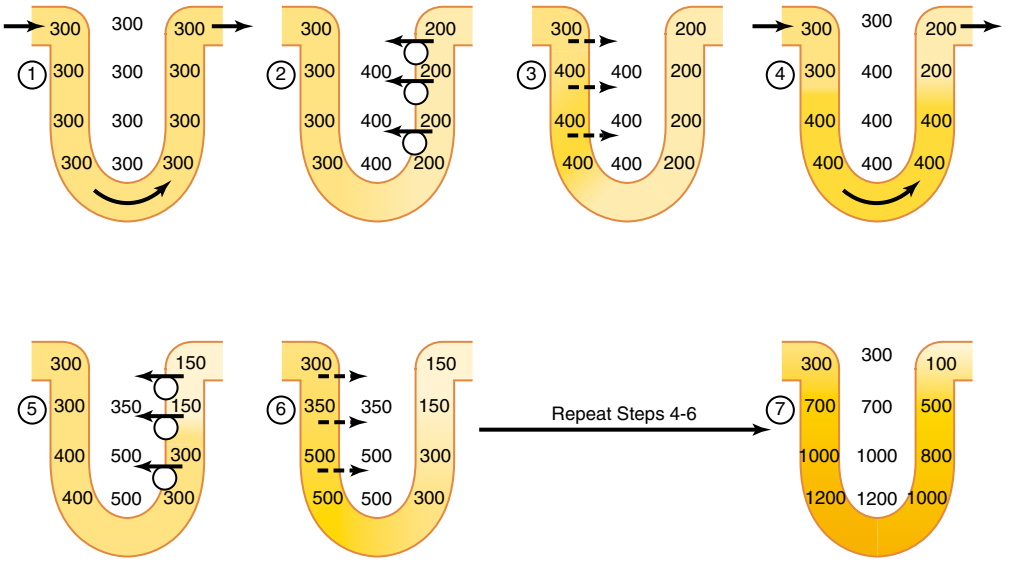

Figure 28-4 Countercurrent multiplier system in the loop of Henle for producing a hyperosmotic renal medulla. (Numerical values are in milliosmoles per liter.)

Role of Distal Tubule and Collecting Ducts in Excreting Concentrated Urine

When the tubular fluid leaves the loop of Henle and flows into the distal convoluted tubule in the renal cortex, the fluid is dilute, with an osmolarity of only about 100 mOsm/L (Figure 28-5). The early distal tubule further dilutes the tubular fluid because this segment, like the ascending loop of Henle, actively transports sodium chloride out of the tubule but is relatively impermeable to water.

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

As the tubular fluid flows along the medullary collecting ducts, there is further water reabsorption from the tubular fluid into the interstitium, but the total amount of water is relatively small compared with that added to the cortex interstitium. The reabsorbed water is quickly carried away by the vasa recta into the venous blood. When high levels of ADH are present, the collecting ducts become permeable to water, so the fluid at the end of the collecting ducts has essentially the same osmolarity as the interstitial fluid of the renal medulla—about 1200 mOsm/L (see Figure 28-4). Thus, by reabsorbing as much water as possible, the kidneys form highly concentrated urine, excreting normal amounts of solutes in the urine while adding water back to the extracellular fluid and compensating for deficits of body water.

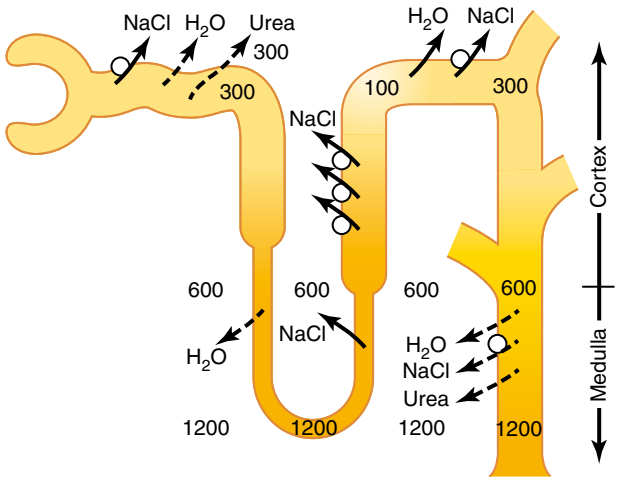

Figure 28-5 Formation of a concentrated urine when antidiuretic hormone (ADH) levels are high. Note that the fluid leaving the loop of Henle is dilute but becomes concentrated as water is absorbed from the distal tubules and collecting tubules. With high ADH levels, the osmolarity of the urine is about the same as the osmolarity of the renal medullary interstitial fluid in the papilla, which is about 1200 mOsm/L. (Numerical values are in milliosmoles per liter.)

Urea Contributes to Hyperosmotic Renal Medullary Interstitium and Formation of Concentrated Urine

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

The mechanism for reabsorption of urea into the renal medulla is as follows: As water flows up the ascending loop of Henle and into the distal and cortical collecting tubules, little urea is reabsorbed because these segments are impermeable to urea (see Table 28-1). In the presence of high concentrations of ADH, water is reabsorbed rapidly from the cortical collecting tubule and the urea concentration increases rapidly because urea is not very permeant in this part of the tubule.

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

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

Recirculation of Urea from Collecting Duct to Loop of Henle Contributes to Hyperosmotic Renal Medulla. A healthy person usually excretes about 20 to 50 percent of the filtered load of urea. In general, the rate of urea excretion is determined mainly by two factors: (1) the concentration of urea in the plasma and

(2) the glomerular filtration rate (GFR). In patients with renal disease who have large reductions of GFR, the plasma urea concentration increases markedly, returning the filtered urea load and urea excretion rate to the normal level (equal to the rate of urea production), despite the reduced GFR.

In the proximal tubule, 40 to 50 percent of the filtered urea is reabsorbed, but even so, the tubular fluid urea concentration increases because urea is not nearly as permeant as water. The concentration of urea continues to rise as the tubular fluid flows into the thin segments of the loop of Henle, partly because of water reabsorption out of the descending loop of Henle but also because of some *secretion* of urea into the thin loop of Henle from the medullary interstitium (Figure 28-6). The passive secretion of urea into the thin loops of Henle is facilitated by the urea transporter *UT-A2*.

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

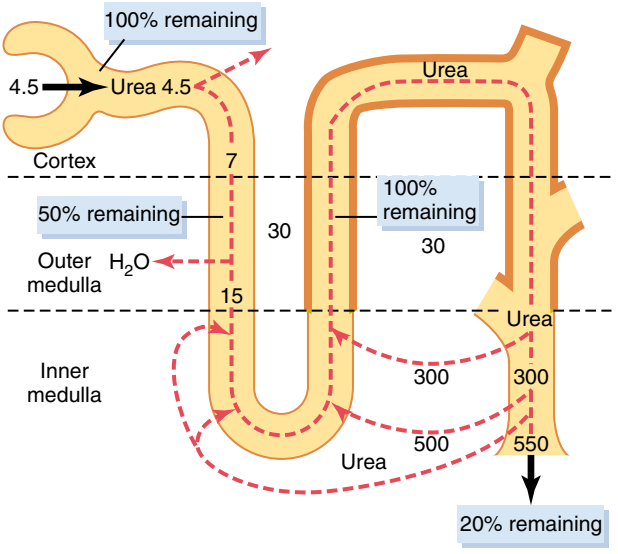

Figure 28-6 Recirculation of urea absorbed from the medullary collecting duct into the interstitial fluid. This urea diffuses into the thin loop of Henle and then passes through the distal tubules, and it finally passes back into the collecting duct. The recirculation of urea helps to trap urea in the renal medulla and contributes to the hyperosmolarity of the renal medulla. The ***heavy tan lines,*** from the thick ascending loop of Henle to the medullary collecting ducts, indicate that these segments are not very permeable to urea. (Numerical values are in milliosmoles per liter of urea during antidiuresis, when large amounts of antidiuretic hormone are present. Percentages of the filtered load of urea that remain in the tubules are indicated in the blue boxes.)

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

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

Countercurrent Exchange in the Vasa Recta Preserves Hyperosmolarity of the Renal Medulla

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

There are two special features of the renal medullary blood flow that contribute to the preservation of the high solute concentrations:

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

The countercurrent exchange mechanism operates as follows (Figure 28-7): Blood enters and leaves the medulla by way of the vasa recta at the boundary of the cortex and renal medulla. The vasa recta, like other capillaries, are highly permeable to solutes in the blood, except for the plasma proteins. As blood descends into the medulla toward the papillae, it becomes progressively more concentrated, partly by solute entry from the interstitium and partly by loss of water into the interstitium. By the time the blood reaches the tips of the vasa recta, it has a concentration of about 1200 mOsm/L, the same as that of the medullary interstitium. As blood ascends back toward the cortex, it becomes progressively less concentrated as solutes diffuse back out into the medullary interstitium and as water moves into the vasa recta.

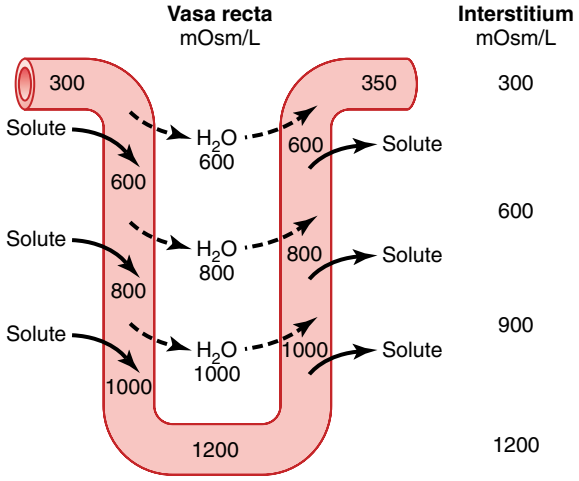

Figure 28-7 Countercurrent exchange in the vasa recta. Plasma flowing down the descending limb of the vasa recta becomes more hyperosmotic because of diffusion of water out of the blood and diffusion of solutes from the renal interstitial fluid into the blood. In the ascending limb of the vasa recta, solutes diffuse back into the interstitial fluid and water diffuses back into the vasa recta. Large amounts of solutes would be lost from the renal medulla without the U shape of the vasa recta capillaries. (Numerical values are in milliosmoles per liter.)

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

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

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

Summary of Urine Concentrating Mechanism and Changes in Osmolarity in Different Segments of the Tubules

The changes in osmolarity and volume of the tubular fluid as it passes through the different parts of the nephron are shown in Figure 28-8.

Proximal Tubule. About 65 percent of the filtered electrolytes is reabsorbed in the proximal tubule. However, the proximal tubular membranes are highly permeable to water, so that whenever solutes are reabsorbed, water also diffuses through the tubular membrane by osmosis. Therefore, the osmolarity of the fluid remains about the same as the glomerular filtrate, 300 mOsm/L.

Descending Loop of Henle. As fluid flows down the descending loop of Henle, water is absorbed into

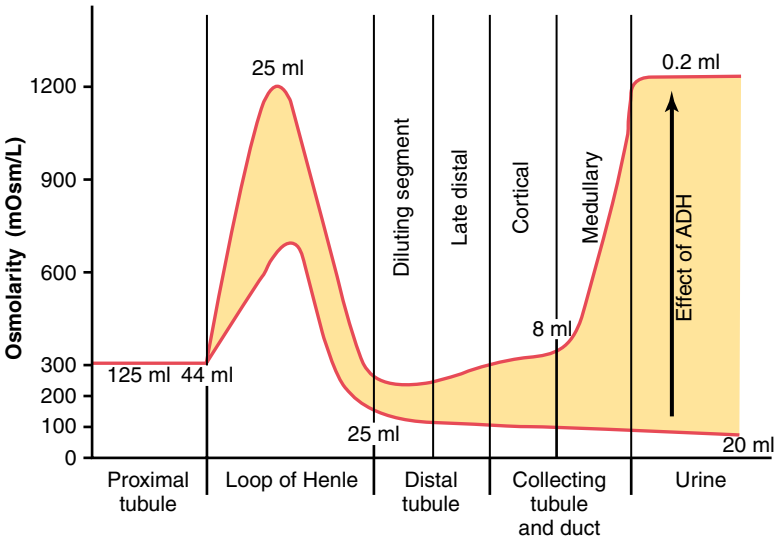

Figure 28-8 Changes in osmolarity of the tubular fluid as it passes through the different tubular segments in the presence of high levels of antidiuretic hormone (ADH) and in the absence of ADH. (Numerical values indicate the approximate volumes in milliliters per minute or in osmolarities in milliosmoles per liter of fluid flowing along the different tubular segments.)

the medulla. The descending limb is highly permeable to water but much less permeable to sodium chloride and urea. Therefore, the osmolarity of the fluid flowing through the descending loop gradually increases until it is nearly equal to that of the surrounding interstitial fluid, which is about 1200 mOsm/L when the blood concentration of ADH is high.

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

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

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

Thick Ascending Loop of Henle. The thick part of the ascending loop of Henle is also virtually impermeable to water, but large amounts of sodium, chloride, potassium, and other ions are actively transported from the tubule into the medullary interstitium. Therefore, fluid in the thick ascending limb of the loop of Henle becomes very dilute, falling to a concentration of about 100 mOsm/L.

Early Distal Tubule. The early distal tubule has properties similar to those of the thick ascending loop of Henle, so further dilution of the tubular fluid to about 50 mOsm/L occurs as solutes are reabsorbed while water remains in the tubule.

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

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

Several important points to consider may not be obvious from this discussion. First, although sodium chloride is one of the principal solutes that contribute to the hyperosmolarity of the medullary interstitium, *the kidney can, when needed, excrete a highly concentrated urine that contains little sodium chloride.* The hyperosmolarity of the urine in these circumstances is due to high concentrations of other solutes, especially of waste products such as urea. One condition in which this occurs is dehydration accompanied by low sodium intake. As discussed in Chapter 29, low sodium intake stimulates formation of the hormones angiotensin II and aldosterone, which together cause avid sodium reabsorption from the tubules while leaving the urea and other solutes to maintain the highly concentrated urine.

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

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

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

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

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

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

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

Relative Rates at Which Solutes and Water Are Excreted Can Be Assessed Using the Concept of "Free-Water Clearance."

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

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

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

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

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

Disorders of Urinary Concentrating Ability

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

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

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

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

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

Many types of renal diseases can impair the concentrating mechanism, especially those that damage the renal medulla (see Chapter 31 for further discussion). Also, impairment of the function of the loop of Henle, as occurs with diuretics that inhibit electrolyte reabsorption by this segment, such as furosemide, can compromise urine concentrating ability. And certain drugs, such as lithium (used to treat manic-depressive disorders) and tetracyclines (used as antibiotics), can impair the ability of the distal nephron segments to respond to ADH.

Nephrogenic diabetes insipidus can be distinguished from central diabetes insipidus by administration of desmopressin, the synthetic analog of ADH. Lack of a prompt decrease in urine volume and an increase in urine osmolarity within

2 hours after injection of desmopressin is strongly suggestive of nephrogenic diabetes insipidus. The treatment for nephrogenic diabetes insipidus is to correct, if possible, the underlying renal disorder. The hypernatremia can also be attenuated by a low-sodium diet and administration of a diuretic that enhances renal sodium excretion, such as a thiazide diuretic.

Control of Extracellular Fluid Osmolarity and Sodium Concentration

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

Estimating Plasma Osmolarity from Plasma Sodium Concentration

In most clinical laboratories, plasma osmolarity is not routinely measured. However, because sodium and its associated anions account for about 94 percent of the solute in the extracellular compartment, plasma osmolarity (P_{osm}) can be roughly approximated as

$$P_{osm} = 2.1 \times \text{Plasma sodium concentration}$$

For instance, with a plasma sodium concentration of 142 mEq/L, the plasma osmolarity would be estimated from this formula to be about 298 mOsm/L. To be more exact, especially in conditions associated with renal disease, the contribution of two other solutes, glucose and urea, should be included. Such estimates of plasma osmolarity are usually accurate within a few percentage points of those measured directly.

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

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

Osmoreceptor-ADH Feedback System

Figure 28-9 shows the basic components of the osmoreceptor-ADH feedback system for control of extracellular fluid sodium concentration and osmolarity. When osmolarity (plasma sodium concentration) increases above normal because of water deficit, for example, this feedback system operates as follows:

1. An increase in extracellular fluid osmolarity (which in practical terms means an increase in plasma sodium concentration) causes the special nerve cells called *osmoreceptor cells,* located in the *anterior hypothalamus* near the supraoptic nuclei, to shrink.
2. Shrinkage of the osmoreceptor cells causes them to fire, sending nerve signals to additional nerve cells in the supraoptic nuclei, which then relay these signals down the stalk of the pituitary gland to the posterior pituitary.
3. These action potentials conducted to the posterior pituitary stimulate the release of ADH, which is stored in secretory granules (or vesicles) in the nerve endings.

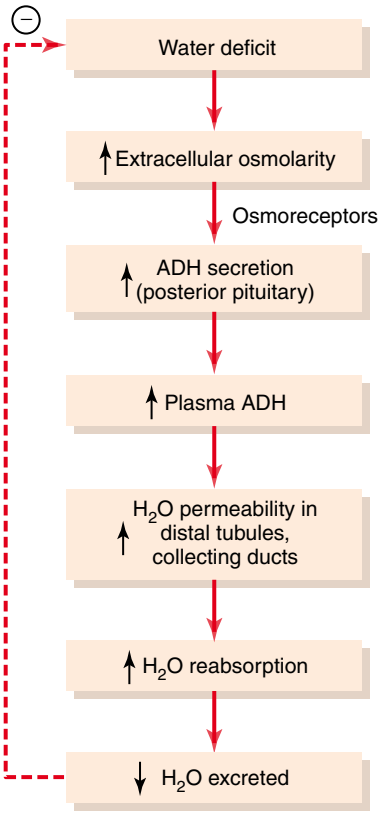

Figure 28-9 Osmoreceptor-antidiuretic hormone (ADH) feedback mechanism for regulating extracellular fluid osmolarity in response to a water deficit.

4. ADH enters the blood stream and is transported to the kidneys, where it increases the water permeability of the late distal tubules, cortical collecting tubules, and medullary collecting ducts.
5. The increased water permeability in the distal nephron segments causes increased water reabsorption and excretion of a small volume of concentrated urine.

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

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

ADH Synthesis in Supraoptic and Paraventricular Nuclei of the Hypothalamus and ADH Release from the Posterior Pituitary

Figure 28-10 shows the neuroanatomy of the hypothalamus and the pituitary gland, where ADH is synthesized and released. The hypothalamus contains two types of *magnocellular (large) neurons that synthesize ADH in the supraoptic and paraventricular nuclei of the hypothalamus,* about five sixths in the supraoptic nuclei and about one sixth in the paraventricular nuclei. Both of these nuclei have axonal extensions to the posterior pituitary. Once ADH is synthesized, it is transported down the axons of the neurons to their tips, terminating in the posterior pituitary gland. When the supraoptic and paraventricular nuclei are stimulated by increased osmolarity or other factors, nerve impulses pass down these nerve endings, changing their membrane permeability and increasing calcium entry. ADH stored in the secretory granules (also called vesicles) of the nerve endings is released in response to increased calcium entry. The released ADH is then carried away in the capillary blood of the posterior pituitary into the systemic circulation.

Secretion of ADH in response to an osmotic stimulus is rapid, so plasma ADH levels can increase severalfold within minutes, thereby providing a rapid means for altering renal excretion of water.

A second neuronal area important in controlling osmolarity and ADH secretion is located along the *anteroventral region of the third ventricle,* called the *AV3V region.* At the upper part of this region is a structure called the *subfornical organ,* and at the inferior part is another structure called the *organum vasculosum* of the *lamina terminalis.* Between these two organs is the *median preoptic nucleus,* which has multiple nerve connections with the two organs, as well as with the supraoptic nuclei and

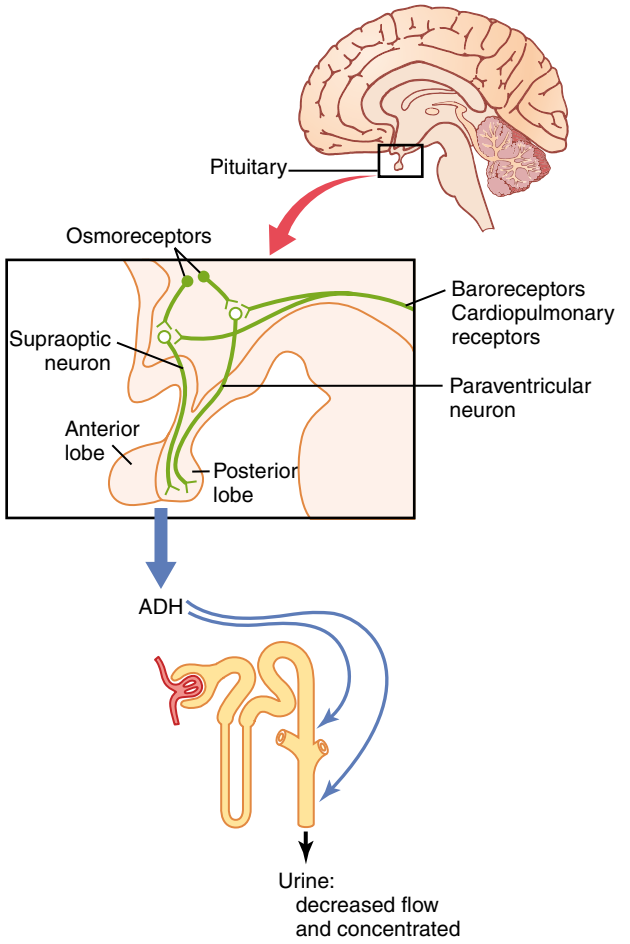

Figure 28-10 Neuroanatomy of the hypothalamus, where antidiuretic hormone (ADH) is synthesized, and the posterior pituitary gland, where ADH is released.

the blood pressure control centers in the medulla of the brain. Lesions of the AV3V region cause multiple deficits in the control of ADH secretion, thirst, sodium appetite, and blood pressure. Electrical stimulation of this region or stimulation by angiotensin II can increase ADH secretion, thirst, and sodium appetite.

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

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

Stimulation of ADH Release by Decreased Arterial Pressure and/or Decreased Blood Volume

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

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

Quantitative Importance of Osmolarity and Cardiovascular Reflexes in Stimulating ADH Secretion

As shown in Figure 28-11, either a decrease in effective blood volume or an increase in extracellular fluid osmolarity stimulates ADH secretion. However, ADH is considerably more sensitive to small changes in osmolarity than to similar percentage changes in blood volume. For example, a change in plasma osmolarity of only 1 percent is sufficient to increase ADH levels. By contrast, after blood loss, plasma ADH levels do not change appreciably until blood volume is reduced by about 10 percent. With further decreases in blood volume, ADH levels rapidly increase. Thus, with severe decreases in blood volume, the cardiovascular reflexes play a major role in stimulating ADH secretion. The usual day-to-day regulation of ADH secretion during simple dehydration is effected mainly by changes in plasma osmolarity. Decreased blood volume, however, greatly enhances the ADH response to increased osmolarity.

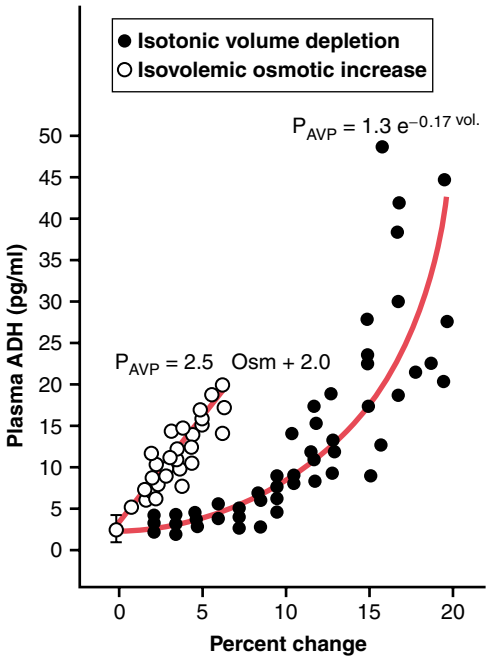

Figure 28-11 The effect of increased plasma osmolarity or decreased blood volume on the level of plasma (P) antidiuretic hormone (ADH), also called *arginine vasopressin* (AVP). (Redrawn from Dunn FL, Brennan TJ, Nelson AE, et al: The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 52(12):3212, 1973. By copyright permission of the American Society of Clinical Investigation.)

Other Stimuli for ADH Secretion

ADH secretion can also be increased or decreased by other stimuli to the central nervous system, as well as by various drugs and hormones, as shown in Table 28-2. For example, *nausea* is a potent stimulus for ADH release, which may increase to as much as 100 times normal after vomiting. Also, drugs such as *nicotine* and *morphine* stimulate ADH release, whereas some drugs, such as *alcohol*, inhibit ADH release. The marked diuresis that occurs after ingestion of alcohol is due in part to inhibition of ADH release.

Importance of Thirst in Controlling Extracellular Fluid Osmolarity and Sodium Concentration

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

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

Table 28-2 Regulation of ADH Secretion

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

Central Nervous System Centers for Thirst

Referring again to Figure 28-10, the same area along the anteroventral wall of the third ventricle that promotes ADH release also stimulates thirst. Located anterolaterally in the preoptic nucleus is another small area that, when stimulated electrically, causes immediate drinking that continues as long as the stimulation lasts. All these areas together are called the *thirst center.*

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

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

Stimuli for Thirst

Table 28-3 summarizes some of the known stimuli for thirst. One of the most important is *increased extracellular fluid osmolarity, which causes intracellular dehydration in the thirst centers,* thereby stimulating the sensation of thirst. The value of this response is obvious: it helps to dilute extracellular fluids and returns osmolarity toward normal.

Decreases in extracellular fluid volume and arterial pressure also stimulate thirst by a pathway that is independent of the one stimulated by increased plasma osmolarity. Thus, blood volume loss by hemorrhage stimulates thirst even though there might be no change in plasma osmolarity. This probably occurs because of neural input from cardiopulmonary and systemic arterial baroreceptors in the circulation.

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

Table 28-3 Control of Thirst

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

Dryness of the mouth and mucous membranes of the esophagus can elicit the sensation of thirst. As a result, a thirsty person may receive relief from thirst almost immediately after drinking water, even though the water has not been absorbed from the gastrointestinal tract and has not yet had an effect on extracellular fluid osmolarity.

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

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

Threshold for Osmolar Stimulus of Drinking

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

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

Integrated Responses of Osmoreceptor-ADH and Thirst Mechanisms in Controlling Extracellular Fluid Osmolarity and Sodium Concentration

In a healthy person, the osmoreceptor-ADH and thirst mechanisms work in parallel to precisely regulate extracellular fluid osmolarity and sodium concentration, despite the constant challenges of dehydration. Even with additional challenges, such as high salt intake, these feedback

systems are able to keep plasma osmolarity reasonably constant. Figure 28-12 shows that an increase in sodium intake to as high as six times normal has only a small effect on plasma sodium concentration as long as the ADH and thirst mechanisms are both functioning normally.

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

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

As discussed in Chapter 27, both angiotensin II and aldosterone play an important role in regulating sodium reabsorption by the renal tubules. When sodium intake is low, increased levels of these hormones stimulate sodium reabsorption by the kidneys and, therefore, prevent large sodium losses, even though sodium intake may be reduced to as low as 10 percent of normal. Conversely, with high sodium intake, decreased formation of these hormones permits the kidneys to excrete large amounts of sodium.

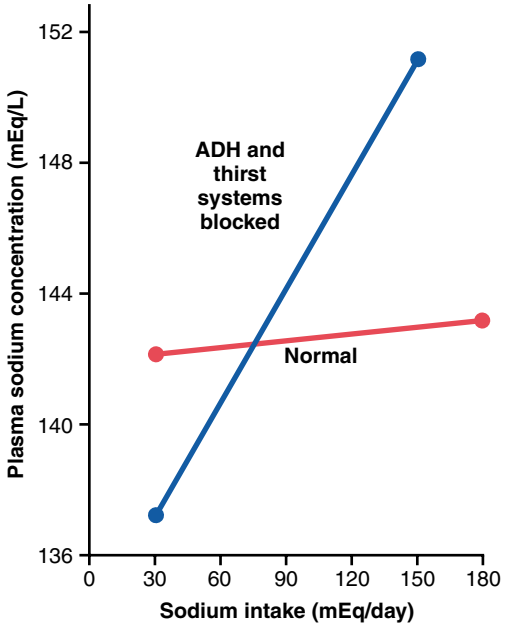

Figure 28-12 Effect of large changes in sodium intake on extracellular fluid sodium concentration in dogs under normal conditions (*red line*) and after the antidiuretic hormone (ADH) and thirst feedback systems had been blocked (*blue line*). Note that control of extracellular fluid sodium concentration is poor in the absence of these feedback systems. (Courtesy Dr. David B. Young.)

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

This relative unimportance of aldosterone in regulating extracellular fluid sodium concentration is shown by the experiment of Figure 28-13. This figure shows the effect on plasma sodium concentration of changing sodium intake more than sixfold under two conditions: (1) under normal conditions and (2) after the aldosterone feedback system was blocked by removing the adrenal glands and infusing the animals with aldosterone at a constant rate so that plasma levels could not change upward or downward. Note that when sodium intake was increased sixfold, plasma concentration changed only about 1 to 2 percent in either case. This indicates that even without a functional aldosterone feedback system, plasma sodium concentration can be well regulated. The same type of experiment has been conducted after blocking angiotensin II formation, with the same result.

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

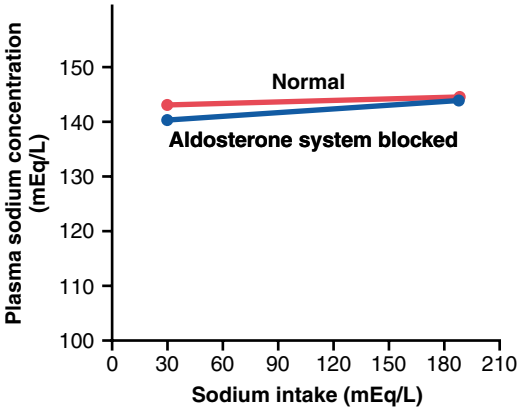

Figure 28-13 Effect of large changes in sodium intake on extracellular fluid sodium concentration in dogs under normal conditions (*red line*) and after the aldosterone feedback system had been blocked (*blue line*). Note that sodium concentration is maintained relatively constant over this wide range of sodium intakes, with or without aldosterone feedback control. (Courtesy Dr. David B. Young.)

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

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

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

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

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

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

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

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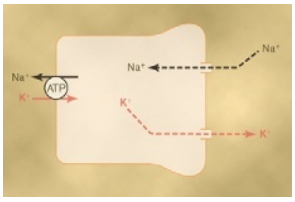
Renal Regulation of Potassium, Calcium, Phosphate, and Magnesium; Integration of Renal Mechanisms for Control of Blood Volume and Extracellular Fluid Volume



Regulation of Extracellular Fluid Potassium Concentration and Potassium Excretion

Extracellular fluid potassium concentration normally is regulated precisely at about 4.2 mEq/L, seldom rising or falling more than ±0.3 mEq/L. This precise control is necessary because many cell functions are very sensitive to changes in extracellular fluid potassium concentration. For instance, an increase in plasma potassium concentration of only 3 to 4 mEq/L can cause cardiac arrhythmias, and higher concentrations can lead to cardiac arrest or fibrillation.

A special difficulty in regulating extracellular potassium concentration is the fact that more than 98 percent of the total body potassium is contained in the cells and only 2 percent in the extracellular fluid (Figure 29-1). For a 70-kilogram adult, who has about 28 liters of intracellular fluid (40 percent of body weight) and 14 liters of extracellular fluid (20 percent of body weight), about 3920 mEq of potassium are inside the cells and only about 59 mEq are in the extracellular fluid. Also, the potassium contained in a single meal is often as high as 50 mEq, and the daily intake usually ranges between 50 and 200 mEq/day; therefore, failure to rapidly rid the extracellular fluid of the ingested potassium could cause life-threatening *hyperkalemia* (increased plasma potassium concentration). Likewise, a small loss of potassium from the extracellular fluid could cause severe *hypokalemia* (low plasma potassium concentration) in the absence of rapid and appropriate compensatory responses.

Maintenance of balance between intake and output of potassium depends primarily on excretion by the kidneys because the amount excreted in the feces is only about 5 to 10 percent of the potassium intake. Thus, the maintenance of normal potassium balance requires the kidneys to adjust their potassium excretion rapidly and precisely in response to wide variations in intake, as is also true for most other electrolytes.

Control of potassium distribution between the extracellular and intracellular compartments also plays an important role in potassium homeostasis. Because more than 98 percent of the total body potassium is contained in the cells, they can serve as an overflow site for excess extracellular fluid potassium during hyperkalemia or as a source of potassium during hypokalemia. Thus, redistribution of potassium between the intracellular and extracellular fluid compartments provides a first line of defense against changes in extracellular fluid potassium concentration.

Regulation of Internal Potassium Distribution

After ingestion of a normal meal, extracellular fluid potassium concentration would rise to a lethal level if the ingested potassium did not rapidly move into the cells. For example, absorption of 40 mEq of potassium (the amount contained in a meal rich in vegetables and fruit) into an extracellular fluid volume of 14 liters would raise plasma potassium concentration by about 2.9 mEq/L if all the potassium remained in the extracellular compartment. Fortunately, most of the ingested potassium rapidly moves into the cells until the kidneys can eliminate the excess. Table 29-1 summarizes some of the factors that can influence the distribution of potassium between the intracellular and extracellular compartments.

Insulin Stimulates Potassium Uptake into Cells. Insulin is important for increasing cell potassium uptake after a meal. In people who have insulin deficiency owing to diabetes mellitus, the rise in plasma potassium concentration after eating a meal is much greater than normal. Injections of insulin, however, can help to correct the hyperkalemia.

Aldosterone Increases Potassium Uptake into Cells. Increased potassium intake also stimulates secretion of aldosterone, which increases cell potassium uptake. Excess aldosterone secretion (Conn's syndrome) is almost invariably associated with hypokalemia, due in part to movement of extracellular potassium into the cells. Conversely, patients with deficient aldosterone production (Addison's disease) often have clinically significant hyperkalemia due to accumulation of potassium in the extracellular space, as well as to renal retention of potassium.

β-Adrenergic Stimulation Increases Cellular Uptake of Potassium. Increased secretion of catecholamines,

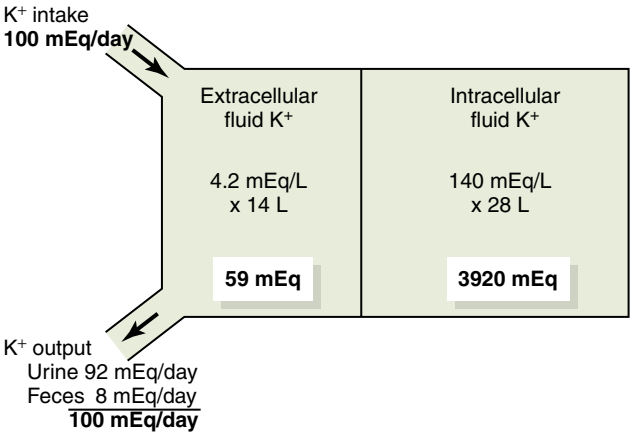


Figure 29-1 Normal potassium intake, distribution of potassium in the body fluids, and potassium output from the body.

Table 29-1 Factors That Can Alter Potassium Distribution Between the Intracellular and Extracellular Fluid

Factors That Shift K^+ into Cells (Decrease Extracellular $[K^+]$)	Factors That Shift K^+ Out of Cells (Increase Extracellular $[K^+]$)
• Insulin • Aldosterone • β-adrenergic stimulation • Alkalosis	• Insulin deficiency (diabetes mellitus) • Aldosterone deficiency (Addison's disease) • β-adrenergic blockade • Acidosis • Cell lysis • Strenuous exercise • Increased extracellular fluid osmolarity

especially epinephrine, can cause movement of potassium from the extracellular to the intracellular fluid, mainly by activation of β_2-adrenergic receptors. Conversely, treatment of hypertension with β-adrenergic receptor blockers, such as propranolol, causes potassium to move out of the cells and creates a tendency toward hyperkalemia.

Acid-Base Abnormalities Can Cause Changes in Potassium Distribution. Metabolic acidosis increases extracellular potassium concentration, in part by causing loss of potassium from the cells, whereas metabolic alkalosis decreases extracellular fluid potassium concentration. Although the mechanisms responsible for the effect of hydrogen ion concentration on potassium internal distribution are not completely understood, one effect of increased hydrogen ion concentration is to reduce the activity of the sodium-potassium adenosine triphosphatase (ATPase) pump. This in turn decreases cellular uptake of potassium and raises extracellular potassium concentration.

Cell Lysis Causes Increased Extracellular Potassium Concentration. As cells are destroyed, the large amounts of potassium contained in the cells are released into the extracellular compartment. This can cause significant hyperkalemia if large amounts of tissue are destroyed, as occurs with severe muscle injury or with red blood cell lysis.

Strenuous Exercise Can Cause Hyperkalemia by Releasing Potassium from Skeletal Muscle. During prolonged exercise, potassium is released from skeletal muscle into the extracellular fluid. Usually the hyperkalemia is mild, but it may be clinically significant after heavy exercise, especially in patients treated with β-adrenergic blockers or in individuals with insulin deficiency. In rare instances, hyperkalemia after exercise may be severe enough to cause cardiac arrhythmias and sudden death.

Increased Extracellular Fluid Osmolarity Causes Redistribution of Potassium from the Cells to Extracellular Fluid. Increased extracellular fluid osmolarity causes osmotic flow of water out of the cells. The cellular dehydration increases intracellular potassium concentration, thereby promoting diffusion of potassium out of the cells and increasing extracellular fluid potassium concentration. Decreased extracellular fluid osmolarity has the opposite effect.

Overview of Renal Potassium Excretion

Renal potassium excretion is determined by the sum of three processes: (1) the rate of potassium filtration (GFR multiplied by the plasma potassium concentration), (2) the rate of potassium reabsorption by the tubules, and (3) the rate of potassium secretion by the tubules. The normal rate of potassium filtration by the glomerular capillaries is about 756 mEq/day (GFR, 180 L/day multiplied by plasma potassium, 4.2 mEq/L); this rate of filtration is relatively constant in healthy persons because of the autoregulatory mechanisms for GFR discussed previously and the precision with which plasma potassium concentration is regulated. Severe decreases in GFR in certain renal diseases, however, can cause serious potassium accumulation and hyperkalemia.

Figure 29-2 summarizes the tubular handling of potassium under normal conditions. About 65 percent of the filtered potassium is reabsorbed in the proximal tubule. Another 25 to 30 percent of the filtered potassium is reabsorbed in the loop of Henle, especially in the thick ascending part where potassium is actively co-transported along with sodium and chloride. In both the proximal tubule and the loop of Henle, a relatively constant fraction of the filtered potassium load is reabsorbed. Changes in potassium reabsorption in these segments can influence potassium excretion, but most of the day-to-day variation of potassium excretion is not due to changes in reabsorption in the proximal tubule or loop of Henle.

Daily Variations in Potassium Excretion Are Caused Mainly by Changes in Potassium Secretion in Distal and Collecting Tubules. The most important sites for regulating potassium excretion are the principal cells

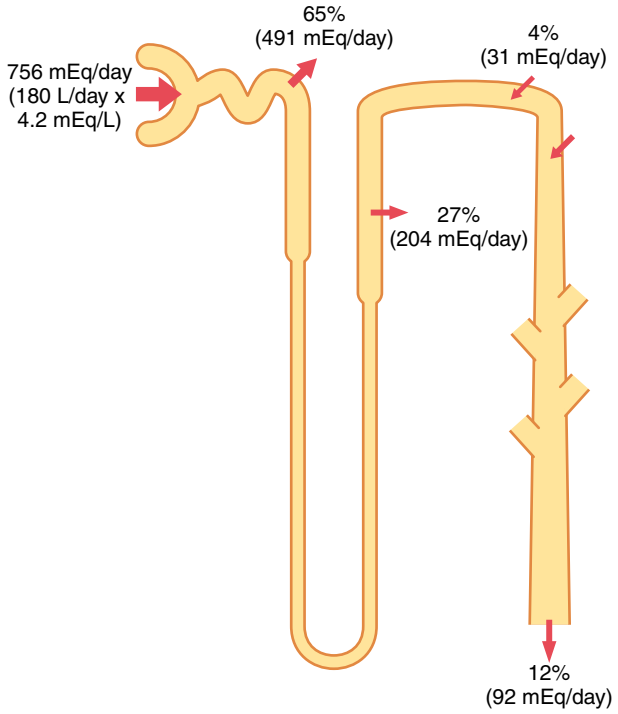


Figure 29-2 Renal tubular sites of potassium reabsorption and secretion. Potassium is reabsorbed in the proximal tubule and in the ascending loop of Henle, so only about 8 percent of the filtered load is delivered to the distal tubule. Secretion of potassium into the late distal tubules and collecting ducts adds to the amount delivered; therefore, the daily excretion is about 12 percent of the potassium filtered at the glomerular capillaries. The percentages indicate how much of the filtered load is reabsorbed or secreted into the different tubular segments.

of the late distal tubules and cortical collecting tubules. In these tubular segments, potassium can at times be reabsorbed or at other times be secreted, depending on the needs of the body. With a normal potassium intake of 100 mEq/day, the kidneys must excrete about 92 mEq/day (the remaining 8 mEq are lost in the feces). About 31 mEq/day of potassium are secreted into the distal and collecting tubules, accounting for about one third of the excreted potassium.

With high potassium intakes, the required extra excretion of potassium is achieved almost entirely by increasing the secretion of potassium into the distal and collecting tubules. In fact, with extremely high potassium diets, the rate of potassium excretion can exceed the amount of potassium in the glomerular filtrate, indicating a powerful mechanism for secreting potassium.

When potassium intake is low, the secretion rate of potassium in the distal and collecting tubules decreases, causing a reduction in urinary potassium secretion. With extreme reductions in potassium intake, there is net reabsorption of potassium in the distal segments of the nephron, and potassium excretion can fall to 1 percent of the potassium in the glomerular filtrate (to <10 mEq/day). With potassium intakes below this level, severe hypokalemia can develop.

Thus, most of the day-to-day regulation of potassium excretion occurs in the late distal and cortical collecting tubules, where potassium can be either reabsorbed or secreted, depending on the needs of the body. In the next section, we consider the basic mechanisms of potassium secretion and the factors that regulate this process.

Potassium Secretion by Principal Cells of Late Distal and Cortical Collecting Tubules

The cells in the late distal and cortical collecting tubules that secrete potassium are called *principal cells* and make up about 90 percent of the epithelial cells in these regions. Figure 29-3 shows the basic cellular mechanisms of potassium secretion by the principal cells.

Secretion of potassium from the blood into the tubular lumen is a two-step process, beginning with uptake from the interstitium into the cell by the sodium-potassium ATPase pump in the basolateral cell membrane; this pump moves sodium out of the cell into the interstitium and at the same time moves potassium to the interior of the cell.

The second step of the process is passive diffusion of potassium from the interior of the cell into the tubular fluid. The sodium-potassium ATPase pump creates a high intracellular potassium concentration, which provides the driving force for passive diffusion of potassium from the cell into the tubular lumen. The luminal membrane of the principal cells is highly permeable to potassium. One reason for this high permeability is that special channels are specifically permeable to potassium ions, thus allowing these ions to rapidly diffuse across the membrane.

Control of Potassium Secretion by Principal Cells.

The primary factors that control potassium secretion by the principal cells of the late distal and cortical collecting tubules are (1) the activity of the sodium-potassium ATPase pump, (2) the electrochemical gradient for potassium secretion from the blood to the tubular lumen,

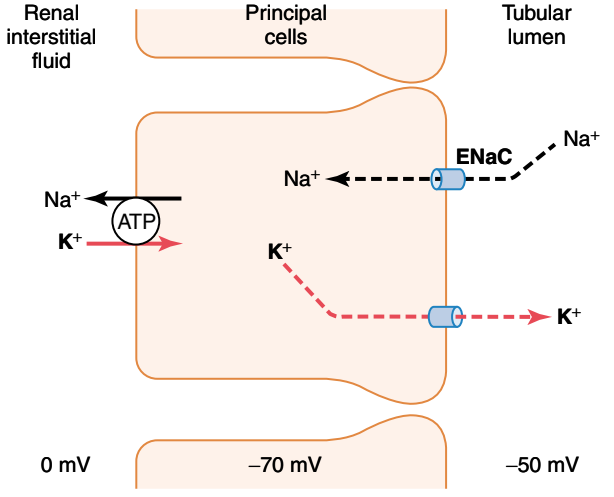


Figure 29-3 Mechanisms of potassium secretion and sodium reabsorption by the principal cells of the late distal and collecting tubules.

and (3) the permeability of the luminal membrane for potassium. These three determinants of potassium secretion are in turn regulated by the factors discussed later.

Intercalated Cells Can Reabsorb Potassium During Potassium Depletion. In circumstances associated with severe potassium depletion, there is a cessation of potassium secretion and actually a net reabsorption of potassium in the late distal and collecting tubules. This reabsorption occurs through the *intercalated cells;* although this reabsorptive process is not completely understood, one mechanism believed to contribute is a *hydrogen-potassium ATPase* transport mechanism located in the luminal membrane. This transporter reabsorbs potassium in exchange for hydrogen ions secreted into the tubular lumen, and the potassium then diffuses through the basolateral membrane of the cell into the blood. This transporter is necessary to allow potassium reabsorption during extracellular fluid potassium depletion, but under normal conditions it plays only a small role in controlling potassium excretion.

Summary of Factors That Regulate Potassium Secretion: Plasma Potassium Concentration, Aldosterone, Tubular Flow Rate, and Hydrogen Ion Concentration

Because normal regulation of potassium excretion occurs mainly as a result of changes in potassium secretion by the principal cells of the late distal and collecting tubules, in this chapter we discuss the primary factors that influence secretion by these cells. The most important factors that *stimulate* potassium secretion by the principal cells include (1) increased extracellular fluid potassium concentration, (2) increased aldosterone, and (3) increased tubular flow rate.

One factor that *decreases* potassium secretion is increased hydrogen ion concentration (acidosis).

Increased Extracellular Fluid Potassium Concentration Stimulates Potassium Secretion. The rate of potassium secretion in the late distal and cortical collecting tubules is directly stimulated by increased extracellular fluid potassium concentration, leading to increases in potassium excretion, as shown in Figure 29-4. This effect is especially pronounced when extracellular fluid potassium concentration rises above about 4.1 mEq/L, slightly less than the normal concentration. Increased plasma potassium concentration, therefore, serves as one of the most important mechanisms for increasing potassium secretion and regulating extracellular fluid potassium ion concentration.

Increased extracellular fluid potassium concentration raises potassium secretion by three mechanisms: (1) Increased extracellular fluid potassium concentration stimulates the sodium-potassium ATPase pump, thereby increasing potassium uptake across the basolateral membrane. This in turn increases intracellular potassium ion concentration, causing potassium to diffuse across the luminal membrane into the tubule. (2) Increased extracellular potassium concentration increases the potassium gradient from the renal interstitial fluid to the interior of the epithelial cell; this reduces back leakage of potassium ions from inside the cells through the basolateral membrane. (3) Increased potassium concentration stimulates aldosterone secretion by the adrenal cortex, which further stimulates potassium secretion, as discussed next.

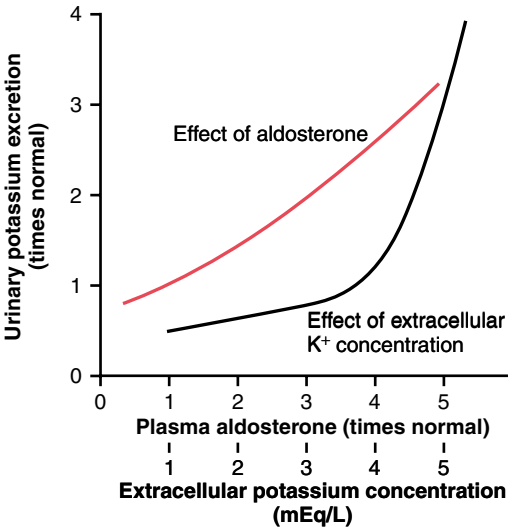


Figure 29-4 Effect of plasma aldosterone concentration (*red line*) and extracellular potassium ion concentration (*black line*) on the rate of urinary potassium excretion. These factors stimulate potassium secretion by the principal cells of the cortical collecting tubules. (Drawn from data in Young DB, Paulsen AW: Interrelated effects of aldosterone and plasma potassium on potassium excretion. Am J Physiol 244:F28, 1983.)

Aldosterone Stimulates Potassium Secretion. Aldosterone stimulates active reabsorption of sodium ions by the principal cells of the late distal tubules and collecting ducts (see Chapter 27). This effect is mediated through a sodium-potassium ATPase pump that transports sodium outward through the basolateral membrane of the cell and into the blood at the same time that it pumps potassium into the cell. Thus, aldosterone also has a powerful effect to control the rate at which the principal cells secrete potassium.

A second effect of aldosterone is to increase the permeability of the luminal membrane for potassium, further adding to the effectiveness of aldosterone in stimulating potassium secretion. Therefore, aldosterone has a powerful effect to increase potassium excretion, as shown in Figure 29-4.

Increased Extracellular Potassium Ion Concentration Stimulates Aldosterone Secretion. In negative feedback control systems, the factor that is controlled usually has a feedback effect on the controller. In the case of the aldosterone-potassium control system, the rate of aldosterone secretion by the adrenal gland is controlled

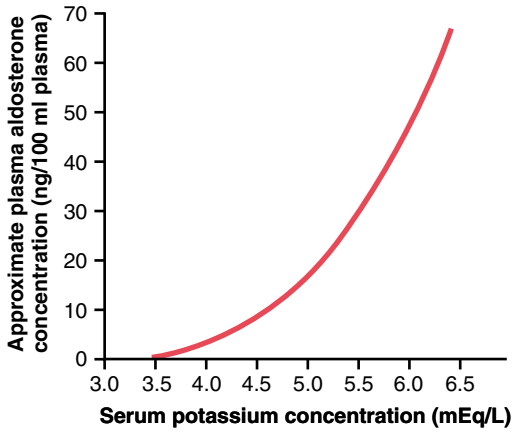


Figure 29-5 Effect of extracellular fluid potassium ion concentration on plasma aldosterone concentration. Note that small changes in potassium concentration cause large changes in aldosterone concentration.

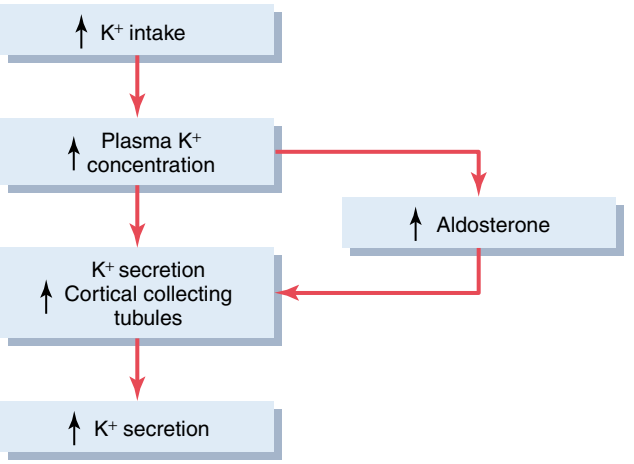


Figure 29-7 Primary mechanisms by which high potassium intake raises potassium excretion. Note that increased plasma potassium concentration directly raises potassium secretion by the cortical collecting tubules and indirectly increases potassium secretion by raising plasma aldosterone concentration.

strongly by extracellular fluid potassium ion concentration. Figure 29-5 shows that an increase in plasma potassium concentration of about 3 mEq/L can increase plasma aldosterone concentration from nearly 0 to as high as 60 ng/100 ml, a concentration almost 10 times normal.

The effect of potassium ion concentration to stimulate aldosterone secretion is part of a powerful feedback system for regulating potassium excretion, as shown in Figure 29-6. In this feedback system, an increase in plasma potassium concentration stimulates aldosterone secretion and, therefore, increases the blood level of aldosterone (block 1). The increase in blood aldosterone then causes a marked increase in potassium excretion by the kidneys (block 2). The increased potassium excretion then reduces the extracellular fluid potassium concentration back toward normal (blocks 3 and 4). Thus, this feedback mechanism acts synergistically with the direct effect of increased extracellular potassium concentration to elevate potassium excretion when potassium intake is raised (Figure 29-7).

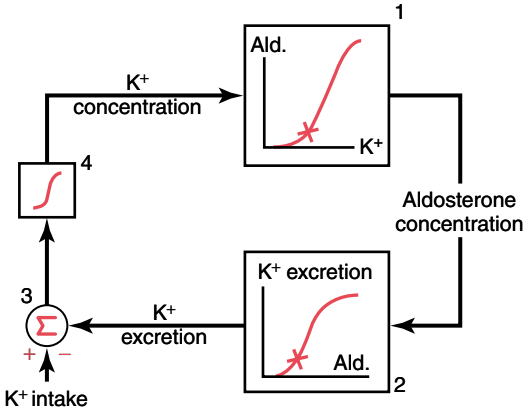


Figure 29-6 Basic feedback mechanism for control of extracellular fluid potassium concentration by aldosterone (*Ald.*).

Blockade of Aldosterone Feedback System Greatly Impairs Control of Potassium Concentration. In the absence of aldosterone secretion, as occurs in patients with Addison's disease, renal secretion of potassium is impaired, thus causing extracellular fluid potassium concentration to rise to dangerously high levels. Conversely, with excess aldosterone secretion (primary aldosteronism), potassium secretion becomes greatly increased, causing potassium loss by the kidneys and thus leading to hypokalemia.

In addition to its stimulatory effect on renal secretion of potassium, aldosterone also increases cellular uptake of potassium, which contributes to the powerful aldosterone-potassium feedback system, as discussed previously.

The special quantitative importance of the aldosterone feedback system in controlling potassium concentration is shown in Figure 29-8. In this experiment, potassium intake was increased almost sevenfold in dogs under two conditions: (1) under normal conditions and (2) after the aldosterone feedback system had been blocked by removing the adrenal glands and placing the animals on a fixed rate of aldosterone infusion so that plasma aldosterone concentration could neither increase nor decrease.

Note that in the normal animals, a sevenfold increase in potassium intake caused only a slight increase in potassium concentration, from 4.2 to 4.3 mEq/L. Thus, when the aldosterone feedback system is functioning normally, potassium concentration is precisely controlled, despite large changes in potassium intake.

When the aldosterone feedback system was blocked, the same increases in potassium intake caused a much larger increase in potassium concentration, from 3.8 to almost 4.7 mEq/L. Thus, control of potassium concentration is greatly impaired when the aldosterone feedback system is blocked. A similar impairment of potassium regulation is observed in humans with poorly functioning aldosterone feedback systems, such as occurs in patients

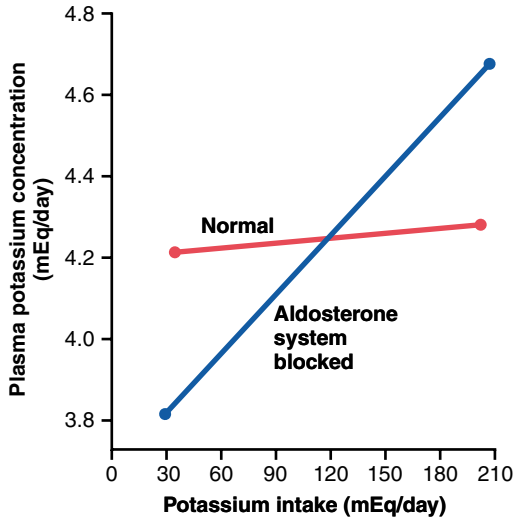


Figure 29-8 Effect of large changes in potassium intake on extracellular fluid potassium concentration under normal conditions (*red line*) and after the aldosterone feedback had been blocked (*blue line*). Note that after blockade of the aldosterone system, regulation of potassium concentration was greatly impaired. (Courtesy Dr. David B. Young.)

with either primary aldosteronism (too much aldosterone) or Addison's disease (too little aldosterone).

Increased Distal Tubular Flow Rate Stimulates Potassium Secretion. A rise in distal tubular flow rate, as occurs with volume expansion, high sodium intake, or treatment with some diuretics, stimulates potassium secretion (Figure 29-9). Conversely, a decrease in distal tubular flow rate, as caused by sodium depletion, reduces potassium secretion.

The effect of tubular flow rate on potassium secretion in the distal and collecting tubules is strongly influenced by potassium intake. When potassium intake is high, increased tubular flow rate has a much greater effect to stimulate potassium secretion than when potassium intake is low (see Figure 29-9).

The mechanism for the effect of high-volume flow rate is as follows: When potassium is secreted into the tubular fluid, the luminal concentration of potassium increases, thereby reducing the driving force for potassium diffusion across the luminal membrane. With increased tubular flow rate, the secreted potassium is continuously flushed down the tubule, so the rise in tubular potassium concentration becomes minimized. Therefore, net potassium secretion is stimulated by increased tubular flow rate.

The effect of increased tubular flow rate is especially important in helping to preserve normal potassium excretion during changes in sodium intake. For example, with a high sodium intake, there is decreased aldosterone secretion, which by itself would tend to decrease the rate of potassium secretion and, therefore, reduce urinary excretion of potassium. However, the high distal tubular flow rate that occurs with a high sodium intake tends to increase potassium secretion (Figure 29-10), as discussed in the previous paragraph. Therefore, the two effects of high sodium intake, decreased aldosterone secretion and

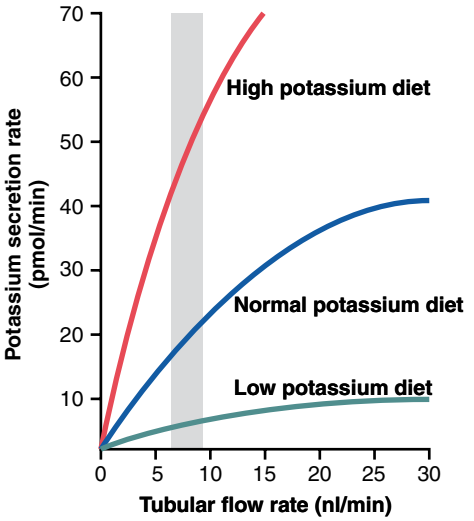


Figure 29-9 Relationship between flow rate in the cortical collecting tubules and potassium secretion and the effect of changes in potassium intake. Note that a high dietary potassium intake greatly enhances the effect of increased tubular flow rate to increase potassium secretion. The *shaded bar* shows the approximate normal tubular flow rate under most physiological conditions. (Data from Malnic G, Berliner RW, Giebisch G. *Am J Physiol* 256:F932, 1989.)

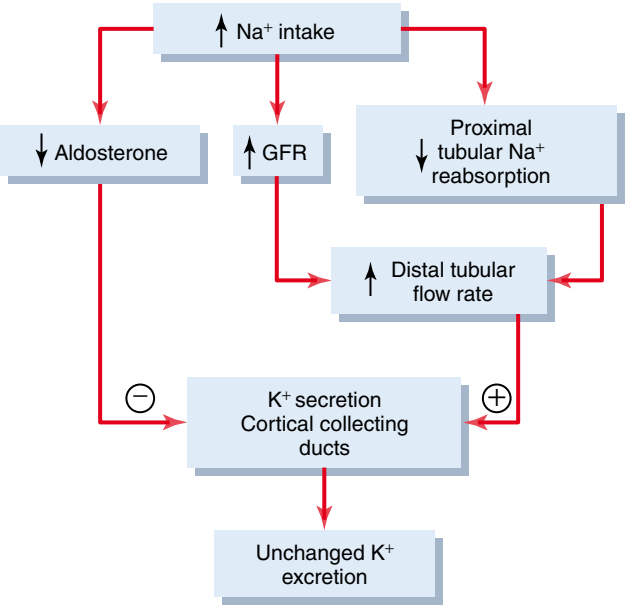


Figure 29-10 Effect of high sodium intake on renal excretion of potassium. Note that a high-sodium diet decreases plasma aldosterone, which tends to decrease potassium secretion by the cortical collecting tubules. However, the high-sodium diet simultaneously increases fluid delivery to the cortical collecting duct, which tends to increase potassium secretion. The opposing effects of a high-sodium diet counterbalance each other, so there is little change in potassium excretion.

the high tubular flow rate, counterbalance each other, so there is little change in potassium excretion. Likewise, with a low sodium intake, there is little change in potassium excretion because of the counterbalancing effects of increased aldosterone secretion and decreased tubular flow rate on potassium secretion.

Acute Acidosis Decreases Potassium Secretion. Acute increases in hydrogen ion concentration of the extracellular fluid (acidosis) reduce potassium secretion, whereas decreased hydrogen ion concentration (alkalosis) increases potassium secretion. The primary mechanism by which increased hydrogen ion concentration inhibits potassium secretion is by reducing the activity of the sodium-potassium ATPase pump. This in turn decreases intracellular potassium concentration and subsequent passive diffusion of potassium across the luminal membrane into the tubule.

With more prolonged acidosis, lasting over a period of several days, there is an increase in urinary potassium excretion. The mechanism for this effect is due in part to an effect of chronic acidosis to inhibit proximal tubular sodium chloride and water reabsorption, which increases distal volume delivery, thereby stimulating the secretion of potassium. This effect overrides the inhibitory effect of hydrogen ions on the sodium-potassium ATPase pump. *Thus, chronic acidosis leads to a loss of potassium, whereas acute acidosis leads to decreased potassium excretion.*

Beneficial Effects of a Diet High in Potassium and Low in Sodium Content. For most of human history, the typical diet has been one that is low in sodium and high in potassium content, compared with the typical modern diet. In isolated populations that have not experienced industrialization, such as the Yanomamo tribe living in the Amazon of Northern Brazil, sodium intake may be as low as 10 to 20 mmol/day while potassium intake may be as high as 200 mmol/day. This is due to their consumption of a diet containing large amounts of fruits and vegetables and no processed foods. Populations consuming this type of diet typically do not experience age-related increases in blood pressure and cardiovascular diseases.

With industrialization and increased consumption of processed foods, which often have high sodium and low potassium content, there have been dramatic increases in sodium intake and decreases in potassium intake. In most industrialized countries potassium consumption averages only 30 to 70 mmol/day while sodium intake averages 140 to 180 mmol/day.

Experimental and clinical studies have shown that the combination of high sodium and low potassium intake increases the risk for hypertension and associated cardiovascular and kidney diseases. A diet rich in potassium, however, seems to protect against the adverse effects of a high-sodium diet, reducing blood pressure and the risk for stroke, coronary artery disease, and kidney disease. The beneficial effects of increasing potassium intake are especially apparent when combined with a low-sodium diet.

Dietary guidelines published by U.S. National Academy of Sciences, the American Heart Association, and other organizations recommend reducing dietary intake sodium chloride to around 65 mmol/day (corresponding to 1.5 g/day of sodium or 3.8 g/day sodium chloride), while increasing potassium intake to 120 mmol/day (4.7 g/day) for healthy adults.

Control of Renal Calcium Excretion and Extracellular Calcium Ion Concentration

The mechanisms for regulating calcium ion concentration are discussed in detail in Chapter 79, along with the endocrinology of the calcium-regulating hormones, parathyroid hormone (PTH), and calcitonin. Therefore, calcium ion regulation is discussed only briefly in this chapter.

Extracellular fluid calcium ion concentration normally remains tightly controlled within a few percentage points of its normal level, 2.4 mEq/L. When calcium ion concentration falls to low levels *(hypocalcemia),* the excitability of nerve and muscle cells increases markedly and can in extreme cases result in *hypocalcemic tetany.* This is characterized by spastic skeletal muscle contractions. *Hypercalcemia* (increased calcium concentration) depresses neuromuscular excitability and can lead to cardiac arrhythmias.

About 50 percent of the total calcium in the plasma (5 mEq/L) exists in the ionized form, which is the form that has biological activity at cell membranes. The remainder is either bound to the plasma proteins (about 40 percent) or complexed in the non-ionized form with anions such as phosphate and citrate (about 10 percent).

Changes in plasma hydrogen ion concentration can influence the degree of calcium binding to plasma proteins. With acidosis, less calcium is bound to the plasma proteins. Conversely, in alkalosis, a greater amount of calcium is bound to the plasma proteins. Therefore, *patients with alkalosis are more susceptible to hypocalcemic tetany.*

As with other substances in the body, the intake of calcium must be balanced with the net loss of calcium over the long term. Unlike ions such as sodium and chloride, however, a large share of calcium excretion occurs in the feces. The usual rate of dietary calcium intake is about 1000 mg/day, with about 900 mg/day of calcium excreted in the feces. Under certain conditions, fecal calcium excretion can exceed calcium ingestion because calcium can also be secreted into the intestinal lumen. Therefore, the gastrointestinal tract and the regulatory mechanisms that influence intestinal calcium absorption and secretion play a major role in calcium homeostasis, as discussed in Chapter 79.

Almost all the calcium in the body (99 percent) is stored in the bone, with only about 0.1 percent in the extracellular fluid and 1.0 percent in the intracellular fluid and cell organelles. The bone, therefore, acts as a large reservoir for storing calcium and as a source of calcium when extracellular fluid calcium concentration tends to decrease.

One of the most important regulators of bone uptake and release of calcium is PTH. When extracellular fluid calcium concentration falls below normal, the parathyroid glands are directly stimulated by the low calcium levels to promote increased secretion of PTH. This hormone then acts directly on the bones to increase the resorption of bone salts (release of salts from the bones) and to release large

amounts of calcium into the extracellular fluid, thereby returning calcium levels back toward normal. When calcium ion concentration is elevated, PTH secretion decreases, so almost no bone resorption occurs; instead, excess calcium is deposited in the bones. Thus, the day-to-day regulation of calcium ion concentration is mediated in large part by the effect of PTH on bone resorption.

The bones, however, do not have an inexhaustible supply of calcium. Therefore, over the long term, the intake of calcium must be balanced with calcium excretion by the gastrointestinal tract and the kidneys. The most important regulator of calcium reabsorption at both of these sites is PTH. *Thus, PTH regulates plasma calcium concentration through three main effects: (1) by stimulating bone resorption; (2) by stimulating activation of vitamin D, which then increases intestinal reabsorption of calcium; and (3) by directly increasing renal tubular calcium reabsorption* (Figure 29-11). The control of gastrointestinal calcium reabsorption and calcium exchange in the bones is discussed elsewhere, and the remainder of this section focuses on the mechanisms that control renal calcium excretion.

Control of Calcium Excretion by the Kidneys

Calcium is both filtered and reabsorbed in the kidneys but not secreted. Therefore, the rate of renal calcium excretion is calculated as

Renal calcium excretion =
Calcium filtered – Calcium reabsorbed

Only about 50 percent of the plasma calcium is ionized, with the remainder being bound to the plasma proteins or complexed with anions such as phosphate. Therefore, only about 50 percent of the plasma calcium can be filtered at the glomerulus. Normally, about 99 percent of the filtered calcium is reabsorbed by the tubules, with only about 1 percent of the filtered calcium being excreted. About 65 percent of the filtered calcium is reabsorbed in the proximal tubule, 25 to 30 percent is reabsorbed in the loop of Henle, and 4 to 9 percent is reabsorbed in the distal and collecting tubules. This pattern of reabsorption is similar to that for sodium.

As is true with the other ions, calcium excretion is adjusted to meet the body's needs. With an increase in calcium intake, there is also increased renal calcium excretion, although much of the increase of calcium intake is eliminated in the feces. With calcium depletion, calcium excretion by the kidneys decreases as a result of enhanced tubular reabsorption.

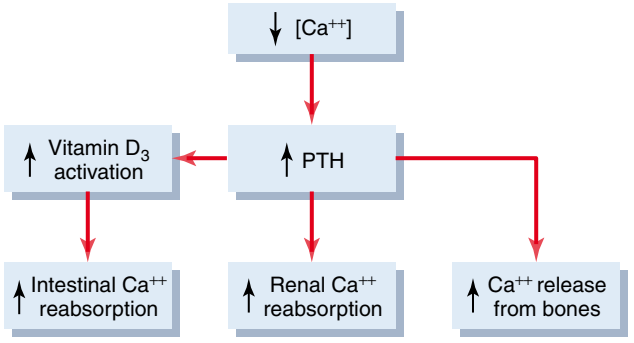


Figure 29-11 Compensatory responses to decreased plasma ionized calcium concentration mediated by parathyroid hormone (PTH) and vitamin D.

Proximal Tubular Calcium Reabsorption. Most of the calcium reabsorption in the proximal tubule occurs through the paracellular pathway, dissolved in water and carried with the reabsorbed fluid as it flows between the cells. Only about 20% of proximal tubular calcium reabsorption occurs through the transcellular pathway in two steps: (1) calcium diffuses from the tubular lumen into the cell down an electrochemical gradient due to the much higher concentration of calcium in the tubular lumen, compared with the epithelial cell cytoplasm, and because the cell interior has a negative relative to the tubular lumen; (2) calcium exits the cell across the basolateral membrane by a calcium-ATPase pump and by sodium-calcium counter-transporter (Figure 29-12).

Loop of Henle and Distal Tubule Calcium Reabsorption. In the loop of Henle, calcium reabsorption is restricted to the thick ascending limb. Approximately 50% of calcium reabsorption in the thick ascending limb occurs through the paracellular route by passive diffusion due to the slight positive charge of the tubular lumen relative to the interstitial fluid. The remaining 50% of calcium reabsorption in the thick ascending limb occurs through the transcellular pathway, a process that is stimulated by PTH.

In the distal tubule, calcium reabsorption occurs almost entirely by active transport through the cell membrane. The mechanism for this active transport is similar to that in the proximal tubule and thick ascending limb and involves diffusion across the luminal membrane through calcium channels and exit across the basolateral membrane by a calcium-ATPase pump, as well as a

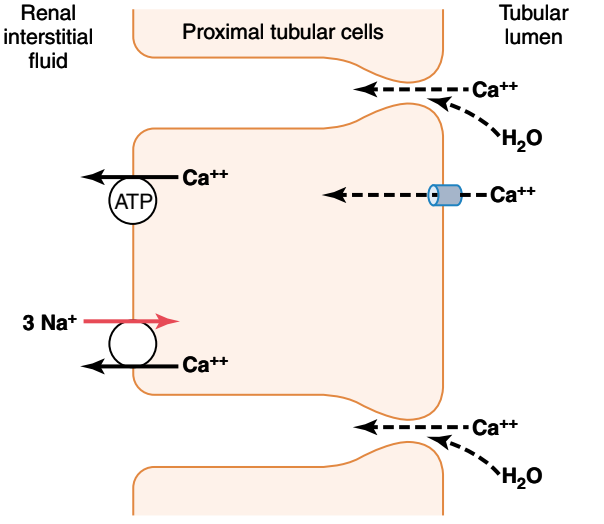


Figure 29-12 Mechanisms of calcium reabsorption by paracellular and transcellular pathways in the proximal tubular cells.

sodium-calcium counter transport mechanism. In this segment, as well as in the loops of Henle, PTH stimulates calcium reabsorption. Vitamin D (Calcitrol) and calcitonin also stimulate calcium reabsorption in the thick ascending limb of Henle's loop and in the distal tubule, although these hormones are not as important quantitatively as PTH in reducing renal calcium excretion.

Factors that Regulate Tubular Calcium Reabsorption. One of the primary controllers of renal tubular calcium reabsorption is PTH. Increased levels of PTH stimulate calcium reabsorption in the thick ascending loops of Henle and distal tubules, which reduces urinary excretion of calcium. Conversely, reduction of PTH promotes calcium excretion by decreasing reabsorption in the loops of Henle and distal tubules.

In the proximal tubule, calcium reabsorption usually parallels sodium and water reabsorption and is independent of PTH. Therefore, in instances of extracellular volume expansion or increased arterial pressure—both of which decrease proximal sodium and water reabsorption—there is also reduction in calcium reabsorption and, consequently, increased urinary excretion of calcium. Conversely, with extracellular volume contraction or decreased blood pressure, calcium excretion decreases primarily because of increased proximal tubular reabsorption.

Another factor that influences calcium reabsorption is the plasma concentration of phosphate. Increased plasma phosphate stimulates PTH, which increases calcium reabsorption by the renal tubules, thereby reducing calcium excretion. The opposite occurs with reduction in plasma phosphate concentration.

Calcium reabsorption is also stimulated by metabolic acidosis and inhibited by metabolic alkalosis. Most of the effect of hydrogen ion concentration on calcium excretion results from changes in calcium reabsorption in the distal tubule.

A summary of the factors that are known to influence calcium excretion by the renal tubules is shown in Table 29-2.

Regulation of Renal Phosphate Excretion

Phosphate excretion by the kidneys is controlled primarily by an overflow mechanism that can be explained as follows: The renal tubules have a normal transport maximum for reabsorbing phosphate of about 0.1 mM/min. When less than this amount of phosphate is present in the glomerular filtrate, essentially *all* the filtered phosphate is reabsorbed. When more than this is present, the *excess* is excreted. Therefore, phosphate normally begins to spill into the urine when its concentration in the extracellular fluid rises above a threshold of about 0.8 mM/L, which gives a tubular load of phosphate of about 0.1 mM/min, assuming a GFR of 125 ml/min. Because most people ingest large quantities of phosphate in milk products and meat, the concentration of phosphate is usually maintained above 1 mM/L, a level at which there is continual excretion of phosphate into the urine.

The proximal tubule normally reabsorbs 75 to 80 percent of the filtered phosphate. The distal tubule reabsorbs about 10 percent of the filtered load, and only very small amounts are reabsorbed in the loop of Henle, collecting tubules, and collecting ducts. Approximately 10 percent of the filtered phosphate is excreted in the urine.

In the proximal tubule, phosphate reabsorption occurs mainly through the transcellular pathway. Phosphate enters the cell from the lumen by a sodium-phosphate co-transporter and exits the cell across the basolateral membrane by a process that is not well understood but may involve a counter transport mechanism in which phosphate is exchanged for an anion.

Changes in tubular phosphate reabsorptive capacity can also occur in different conditions and influence phosphate excretion. For instance, a diet low in phosphate can, over time, increase the reabsorptive transport maximum for phosphate, thereby reducing the tendency for phosphate to spill over into the urine.

PTH can play a significant role in regulating phosphate concentration through two effects: (1) PTH promotes bone resorption, thereby dumping large amounts of phosphate ions into the extracellular fluid from the bone salts, and (2) PTH decreases the transport maximum for phosphate by the renal tubules, so a greater proportion of the tubular phosphate is lost in the urine. *Thus, whenever plasma PTH is increased, tubular phosphate reabsorption is decreased and more phosphate is excreted.* These interrelations among phosphate, PTH, and calcium are discussed in more detail in Chapter 79.

Table 29-2 Factors That Alter Renal Calcium Excretion

↓ Calcium Excretion	↑ Calcium Excretion
↑ Parathyroid hormone (PTH)	↓ PTH
↓ Extracellular fluid volume	↑ Extracellular fluid volume
↓ Blood pressure	↑ Blood pressure
↑ Plasma phosphate	↓ Plasma phosphate
Metabolic acidosis	Metabolic alkalosis
Vitamin D_3	

Control of Renal Magnesium Excretion and Extracellular Magnesium Ion Concentration

More than one half of the body's magnesium is stored in the bones. Most of the rest resides within the cells, with less than 1 percent located in the extracellular fluid. Although the total plasma magnesium concentration is about 1.8 mEq/L, more than one half of this is bound to plasma proteins. Therefore, the free ionized concentration of magnesium is only about 0.8 mEq/L.

The normal daily intake of magnesium is about 250 to 300 mg/day, but only about one half of this intake is absorbed by the gastrointestinal tract. To maintain

magnesium balance, the kidneys must excrete this absorbed magnesium, about one half the daily intake of magnesium, or 125 to 150 mg/day. The kidneys normally excrete about 10 to 15 percent of the magnesium in the glomerular filtrate.

Renal excretion of magnesium can increase markedly during magnesium excess or decrease to almost nil during magnesium depletion. Because magnesium is involved in many biochemical processes in the body, including activation of many enzymes, its concentration must be closely regulated.

Regulation of magnesium excretion is achieved mainly by changing tubular reabsorption. The proximal tubule usually reabsorbs only about 25 percent of the filtered magnesium. The primary site of reabsorption is the loop of Henle, where about 65 percent of the filtered load of magnesium is reabsorbed. Only a small amount (usually <5 percent) of the filtered magnesium is reabsorbed in the distal and collecting tubules.

The mechanisms that regulate magnesium excretion are not well understood, but the following disturbances lead to increased magnesium excretion: (1) increased extracellular fluid magnesium concentration, (2) extracellular volume expansion, and (3) increased extracellular fluid calcium concentration.

Integration of Renal Mechanisms for Control of Extracellular Fluid

Extracellular fluid volume is determined mainly by the balance between intake and output of water and salt. In many instances, salt and fluid intakes are dictated by a person's habits rather than by physiologic control mechanisms. Therefore, the burden of extracellular volume regulation is usually placed on the kidneys, which must adapt their excretion of salt and water to match intake of salt and water under steady-state conditions.

In discussing the regulation of extracellular fluid volume, we consider the factors that regulate the amount of sodium chloride in the extracellular fluid because changes in extracellular fluid sodium chloride content usually cause parallel changes in extracellular fluid volume, provided the antidiuretic hormone (ADH)-thirst mechanisms are operative. When the ADH-thirst mechanisms are functioning normally, a change in the amount of sodium chloride in the extracellular fluid is matched by a similar change in the amount of extracellular water, so osmolality and sodium concentration are maintained relatively constant.

Sodium Intake and Excretion Are Precisely Matched Under Steady-State Conditions

An important consideration in overall control of sodium excretion—or excretion of most electrolytes, for that matter—is that under steady-state conditions, excretion by the kidneys is determined by intake. To maintain life, a person must, over the long term, excrete almost precisely the amount of sodium ingested. Therefore, even with disturbances that cause major changes in kidney function, balance between intake and output of sodium usually is restored within a few days.

If disturbances of kidney function are not too severe, sodium balance may be achieved mainly by intrarenal adjustments with minimal changes in extracellular fluid volume or other systemic adjustments. But when perturbations to the kidneys are severe and intrarenal compensations are exhausted, systemic adjustments must be invoked, such as changes in blood pressure, changes in circulating hormones, and alterations of sympathetic nervous system activity.

These adjustments can be costly in terms of overall homeostasis because they cause other changes throughout the body that may, in the long run, be damaging. For example, impaired kidney function may lead to increased blood pressure that, in turn, helps to maintain normal sodium excretion. Over the long term the high blood pressure may cause injury to the blood vessels, heart, and other organs. These compensations, however, are necessary because a sustained imbalance between fluid and electrolyte intake and excretion would quickly lead to accumulation or loss of electrolytes and fluid, causing cardiovascular collapse within a few days. Thus, one can view the systemic adjustments that occur in response to abnormalities of kidney function as a necessary trade-off that brings electrolyte and fluid excretion back in balance with intake.

Sodium Excretion Is Controlled by Altering Glomerular Filtration or Tubular Sodium Reabsorption Rates

The two variables that influence sodium and water excretion are the rates of glomerular filtration and tubular reabsorption:

Excretion = Glomerular filtration – Tubular reabsorption

GFR normally is about 180 L/day, tubular reabsorption is 178.5 L/day, and urine excretion is 1.5 L/day. Thus, small changes in GFR or tubular reabsorption potentially can cause large changes in renal excretion. For example, a 5 percent increase in GFR (to 189 L/day) would cause a 9 L/day increase in urine volume, if tubular compensations did not occur; this would quickly cause catastrophic changes in body fluid volumes. Similarly, small changes in tubular reabsorption, in the absence of compensatory adjustments of GFR, would also lead to dramatic changes in urine volume and sodium excretion. Tubular reabsorption and GFR usually are regulated precisely, so excretion by the kidneys can be exactly matched to intake of water and electrolytes.

Even with disturbances that alter GFR or tubular reabsorption, changes in urinary excretion are minimized by various buffering mechanisms. For example, if the kidneys become greatly vasodilated and GFR increases (as can occur with certain drugs or high fever), this raises sodium chloride delivery to the tubules, which in turn leads to at least two intrarenal compensations: (1) increased tubular

reabsorption of much of the extra sodium chloride filtered, called *glomerulotubular balance,* and (2) *macula densa feedback,* in which increased sodium chloride delivery to the distal tubule causes afferent arteriolar constriction and return of GFR toward normal. Likewise, abnormalities of tubular reabsorption in the proximal tubule or loop of Henle are partially compensated for by these same intrarenal feedbacks.

Because neither of these two mechanisms operates perfectly to restore distal sodium chloride delivery all the way back to normal, changes in either GFR or tubular reabsorption can lead to significant changes in urine sodium and water excretion. When this happens, other feedback mechanisms come into play, such as changes in blood pressure and changes in various hormones, and eventually return sodium excretion to equal sodium intake. In the next few sections, we review how these mechanisms operate together to control sodium and water balance and in so doing act also to control extracellular fluid volume. All these feedback mechanisms control renal excretion of sodium and water by altering either GFR or tubular reabsorption.

Importance of Pressure Natriuresis and Pressure Diuresis in Maintaining Body Sodium and Fluid Balance

One of the most basic and powerful mechanisms for the maintenance of sodium and fluid balance, as well as for controlling blood volume and extracellular fluid volume, is the effect of blood pressure on sodium and water excretion—called the *pressure natriuresis* and *pressure diuresis* mechanisms, respectively. As discussed in Chapter 19, this feedback between the kidneys and the circulatory system also plays a dominant role in long-term blood pressure regulation.

Pressure diuresis refers to the effect of increased blood pressure to raise urinary volume excretion, whereas pressure natriuresis refers to the rise in sodium excretion that occurs with elevated blood pressure. Because pressure diuresis and natriuresis usually occur in parallel, we refer to these mechanisms simply as "pressure natriuresis" in the following discussion.

Figure 29-13 shows the effect of arterial pressure on urinary sodium output. Note that acute increases in blood pressure of 30 to 50 mm Hg cause a twofold to threefold increase in urinary sodium output. This effect is independent of changes in activity of the sympathetic nervous system or of various hormones, such as angiotensin II, ADH, or aldosterone, because pressure natriuresis can be demonstrated in an isolated kidney that has been removed from the influence of these factors. With chronic increases in blood pressure, the effectiveness of pressure natriuresis is greatly enhanced because the increased blood pressure also, after a short time delay, suppresses renin release and, therefore, decreases formation of angiotensin II and aldosterone. As discussed previously, decreased levels of angiotensin II and aldosterone inhibit renal tubular reabsorption of sodium, thereby amplifying the direct effects of increased blood pressure to raise sodium and water excretion.

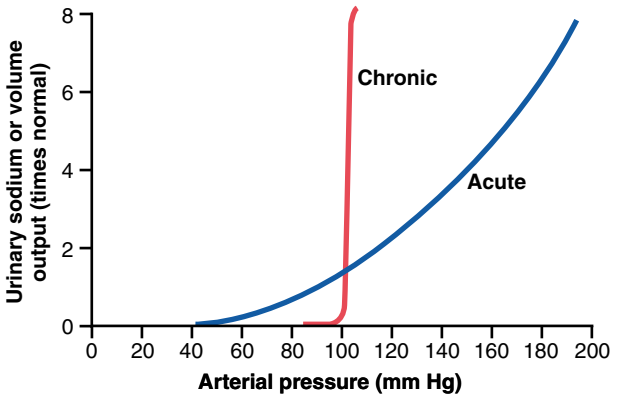


Figure 29-13 Acute and chronic effects of arterial pressure on sodium output by the kidneys (pressure natriuresis). Note that chronic increases in arterial pressure cause much greater increases in sodium output than those measured during acute increases in arterial pressure.

Pressure Natriuresis and Diuresis Are Key Components of a Renal-Body Fluid Feedback for Regulating Body Fluid Volumes and Arterial Pressure

The effect of increased blood pressure to raise urine output is part of a powerful feedback system that operates to maintain balance between fluid intake and output, as shown in Figure 29-14. This is the same mechanism that is discussed in Chapter 19 for arterial pressure control. The extracellular fluid volume, blood volume, cardiac output, arterial pressure, and urine output are all controlled at the same time as separate parts of this basic feedback mechanism.

During changes in sodium and fluid intake, this feedback mechanism helps to maintain fluid balance and to minimize changes in blood volume, extracellular fluid volume, and arterial pressure as follows:

1. An increase in fluid intake (assuming that sodium accompanies the fluid intake) above the level of urine output causes a temporary accumulation of fluid in the body.
2. As long as fluid intake exceeds urine output, fluid accumulates in the blood and interstitial spaces, causing parallel increases in blood volume and extracellular fluid volume. As discussed later, the actual increases in these variables are usually small because of the effectiveness of this feedback.
3. An increase in blood volume raises mean circulatory filling pressure.
4. An increase in mean circulatory filling pressure raises the pressure gradient for venous return.
5. An increased pressure gradient for venous return elevates cardiac output.
6. An increased cardiac output raises arterial pressure.

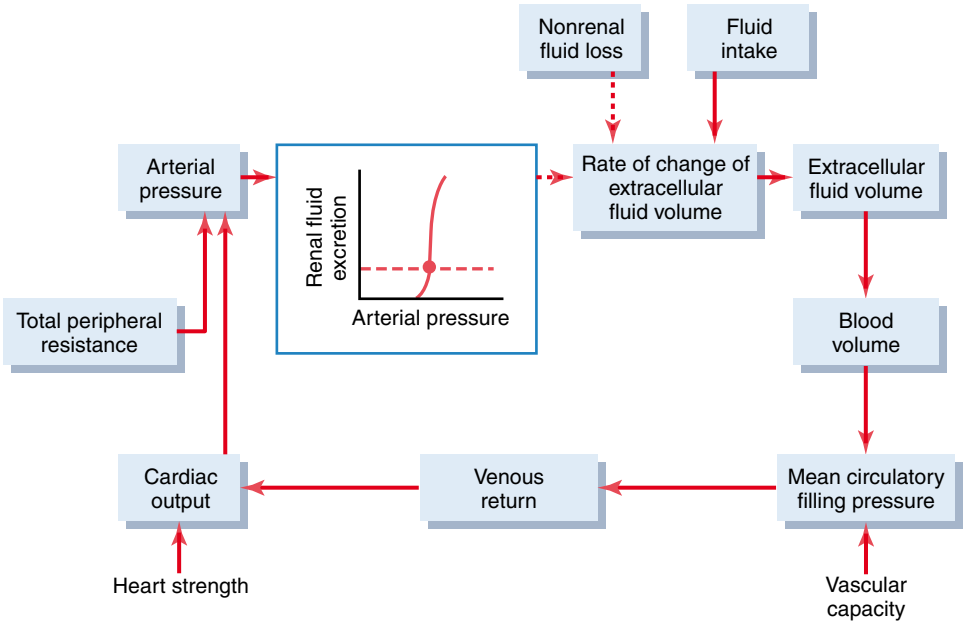


Figure 29-14 Basic renal-body fluid feedback mechanism for control of blood volume, extracellular fluid volume, and arterial pressure. *Solid lines* indicate positive effects, and *dashed lines* indicate negative effects.

7. An increased arterial pressure increases urine output by way of pressure diuresis. The steepness of the normal pressure natriuresis relation indicates that only a slight increase in blood pressure is required to raise urinary excretion severalfold.
8. The increased fluid excretion balances the increased intake, and further accumulation of fluid is prevented.

Thus, the renal-body fluid feedback mechanism operates to prevent continuous accumulation of salt and water in the body during increased salt and water intake. As long as kidney function is normal and the pressure diuresis mechanism is operating effectively, large changes in salt and water intake can be accommodated with only slight changes in blood volume, extracellular fluid volume, cardiac output, and arterial pressure.

The opposite sequence of events occurs when fluid intake falls below normal. In this case, there is a tendency toward decreased blood volume and extracellular fluid volume, as well as reduced arterial pressure. Even a small decrease in blood pressure causes a large decrease in urine output, thereby allowing fluid balance to be maintained with minimal changes in blood pressure, blood volume, or extracellular fluid volume. The effectiveness of this mechanism in preventing large changes in blood volume is demonstrated in Figure 29-15, which shows that changes in blood volume are almost imperceptible despite large variations in daily intake of water and electrolytes, except when intake becomes so low that it is not sufficient to make up for fluid losses caused by evaporation or other inescapable losses.

As discussed later, there are nervous and hormonal systems, in addition to intrarenal mechanisms, that can raise sodium excretion to match increased sodium intake even without measureable increases in arterial pressure

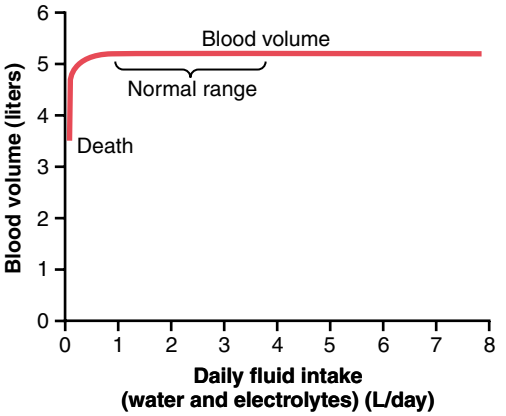


Figure 29-15 Approximate effect of changes in daily fluid intake on blood volume. Note that blood volume remains relatively constant in the normal range of daily fluid intakes.

in many persons. Other individuals who are more "salt sensitive" have significant increases in arterial pressure with even moderate increases in sodium intake. With prolonged high-sodium intake, lasting over several years, high blood pressure may occur even in those persons who are not initially salt sensitive. When blood pressure does rise, pressure natriuresis provides a critical means of maintaining balance between sodium intake and urinary sodium excretion.

Precision of Blood Volume and Extracellular Fluid Volume Regulation

By studying Figure 29-14, one can see why the blood volume remains almost exactly constant despite extreme changes in daily fluid intake. The reason for this is the following: (1) A slight change in blood volume causes a marked change in cardiac output, (2) a slight change in

cardiac output causes a large change in blood pressure, and (3) a slight change in blood pressure causes a large change in urine output. These factors work together to provide effective feedback control of blood volume.

The same control mechanisms operate whenever there is a blood loss because of hemorrhage. In this case, a fall in blood pressure along with nervous and hormonal factors discussed later cause fluid retention by the kidneys. Other parallel processes occur to reconstitute the red blood cells and plasma proteins in the blood. If abnormalities of red blood cell volume remain, such as occurs when there is deficiency of erythropoietin or other factors needed to stimulate red blood cell production, the plasma volume will simply make up the difference, and the overall blood volume will return essentially to normal despite the low red blood cell mass.

Distribution of Extracellular Fluid Between the Interstitial Spaces and Vascular System

From Figure 29-14 it is apparent that blood volume and extracellular fluid volume are usually controlled in parallel with each other. Ingested fluid initially goes into the blood, but it rapidly becomes distributed between the interstitial spaces and the plasma. Therefore, blood volume and extracellular fluid volume usually are controlled simultaneously.

There are circumstances, however, in which the distribution of extracellular fluid between the interstitial spaces and blood can vary greatly. As discussed in Chapter 25, *the principal factors that can cause accumulation of fluid in the interstitial spaces include (1) increased capillary hydrostatic pressure, (2) decreased plasma colloid osmotic pressure, (3) increased permeability of the capillaries, and (4) obstruction of lymphatic vessels.* In all these conditions, an unusually high proportion of the extracellular fluid becomes distributed to the interstitial spaces.

Figure 29-16 shows the normal distribution of fluid between the interstitial spaces and the vascular system and the distribution that occurs in edema states. When small amounts of fluid accumulate in the blood as a result of either too much fluid intake or a decrease in renal output of fluid, about 20 to 30 percent of it stays in the blood and increases the blood volume. The remainder is distributed to the interstitial spaces. When the extracellular fluid volume rises more than 30 to 50 percent above normal, almost all the additional fluid goes into the interstitial spaces and little remains in the blood. This occurs because once the interstitial fluid pressure rises from its normally negative value to become positive, the tissue interstitial spaces become compliant and large amounts of fluid then pour into the tissues without interstitial fluid pressure rising much more. In other words, the safety factor against edema, owing to a rising interstitial fluid pressure that counteracts fluid accumulation in the tissues, is lost once the tissues become highly compliant.

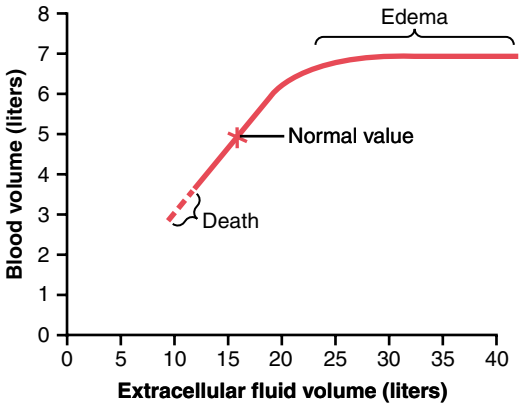


Figure 29-16 Approximate relation between extracellular fluid volume and blood volume, showing a nearly linear relation in the normal range but also showing the failure of blood volume to continue rising when the extracellular fluid volume becomes excessive. When this occurs, the additional extracellular fluid volume resides in the interstitial spaces and edema results.

Thus, under normal conditions, the interstitial spaces act as an "overflow" reservoir for excess fluid, sometimes increasing in volume 10 to 30 liters. This causes edema, as explained in Chapter 25, but it also acts as an important overflow release valve for the circulation, protecting the cardiovascular system against dangerous overload that could lead to pulmonary edema and cardiac failure.

To summarize, extracellular fluid volume and blood volume are controlled simultaneously, but the quantitative amounts of fluid distribution between the interstitium and the blood depend on the physical properties of the circulation and the interstitial spaces, as well as on the dynamics of fluid exchange through the capillary membranes.

Nervous and Hormonal Factors Increase the Effectiveness of Renal-Body Fluid Feedback Control

In Chapter 27, we discuss the nervous and hormonal factors that influence GFR and tubular reabsorption and, therefore, renal excretion of salt and water. These nervous and hormonal mechanisms usually act in concert with the pressure natriuresis and pressure diuresis mechanisms, making them more effective in minimizing the changes in blood volume, extracellular fluid volume, and arterial pressure that occur in response to day-to-day challenges. However, abnormalities of kidney function or of the various nervous and hormonal factors that influence the kidneys can lead to serious changes in blood pressure and body fluid volumes, as discussed later.

Sympathetic Nervous System Control of Renal Excretion: Arterial Baroreceptor and Low-Pressure Stretch Receptor Reflexes

Because the kidneys receive extensive sympathetic innervation, changes in sympathetic activity can alter renal sodium and water excretion, as well as regulation of

extracellular fluid volume under some conditions. For example, when blood volume is reduced by hemorrhage, pressures in the pulmonary blood vessels and other low-pressure regions of the thorax decrease, causing reflex activation of the sympathetic nervous system. This in turn increases renal sympathetic nerve activity, which has several effects to decrease sodium and water excretion: (1) constriction of the renal arterioles, with resultant decreased GFR of the sympathetic activation if severe; (2) increased tubular reabsorption of salt and water; and (3) stimulation of renin release and increased angiotensin II and aldosterone formation, both of which further increase tubular reabsorption. And if the reduction in blood volume is great enough to lower systemic arterial pressure, further activation of the sympathetic nervous system occurs because of decreased stretch of the arterial baroreceptors located in the carotid sinus and aortic arch. All these reflexes together play an important role in the rapid restitution of blood volume that occurs in acute conditions such as hemorrhage. Also, reflex inhibition of renal sympathetic activity may contribute to the rapid elimination of excess fluid in the circulation that occurs after eating a meal that contains large amounts of salt and water.

Role of Angiotensin II in Controlling Renal Excretion

One of the body's most powerful controllers of sodium excretion is angiotensin II. Changes in sodium and fluid intake are associated with reciprocal changes in angiotensin II formation, and this in turn contributes greatly to the maintenance of body sodium and fluid balances. That is, when sodium intake is elevated above normal, renin secretion is decreased, causing decreased angiotensin II formation. Because angiotensin II has several important effects in increasing tubular reabsorption of sodium, as explained in Chapter 27, a reduced level of angiotensin II decreases tubular reabsorption of sodium and water, thus increasing the kidneys' excretion of sodium and water. The net result is to minimize the rise in extracellular fluid volume and arterial pressure that would otherwise occur when sodium intake increases.

Conversely, when sodium intake is reduced below normal, increased levels of angiotensin II cause sodium and water retention and oppose reductions in arterial blood pressure that would otherwise occur. Thus, changes in activity of the renin-angiotensin system act as a powerful amplifier of the pressure natriuresis mechanism for maintaining stable blood pressures and body fluid volumes.

Importance of Changes in Angiotensin II in Altering Pressure Natriuresis. The importance of angiotensin II in making the pressure natriuresis mechanism more effective is shown in Figure 29-17. Note that when the angiotensin control of natriuresis is fully functional, the pressure natriuresis curve is steep (normal curve), indicating that only minor changes in blood pressure are necessary to increase sodium excretion when sodium intake is raised.

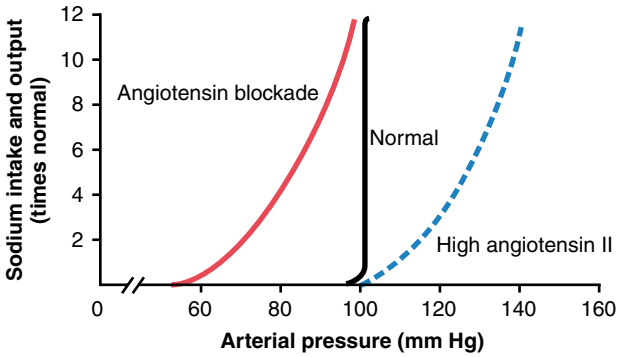


Figure 29-17 Effects of excessive angiotensin II formation and blocking angiotensin II formation on the renal-pressure natriuresis curve. Note that high levels of angiotensin II formation decrease the slope of pressure natriuresis, making blood pressure very sensitive to changes in sodium intake. Blockade of angiotensin II formation shifts pressure natriuresis to lower blood pressures.

In contrast, when angiotensin levels cannot be decreased in response to increased sodium intake (high angiotensin II curve), as occurs in some hypertensive patients who have impaired ability to decrease renin secretion, the pressure natriuresis curve is not nearly as steep. Therefore, when sodium intake is raised, much greater increases in arterial pressure are necessary to increase sodium excretion and maintain sodium balance. For example, in most people, a 10-fold increase in sodium intake causes an increase of only a few millimeters of mercury in arterial pressure, whereas in subjects who cannot suppress angiotensin II formation appropriately in response to excess sodium, the same rise in sodium intake causes blood pressure to rise as much as 50 mm Hg. Thus, the inability to suppress angiotensin II formation when there is excess sodium reduces the slope of pressure natriuresis and makes arterial pressure very salt sensitive, as discussed in Chapter 19.

The use of drugs to block the effects of angiotensin II has proved to be important clinically for improving the kidneys' ability to excrete salt and water. When angiotensin II formation is blocked with an angiotensin-converting enzyme inhibitor (see Figure 29-17) or an angiotensin II receptor antagonist, the renal-pressure natriuresis curve is shifted to lower pressures; this indicates an enhanced ability of the kidneys to excrete sodium because normal levels of sodium excretion can now be maintained at reduced arterial pressures. This shift of pressure natriuresis provides the basis for the chronic blood pressure–lowering effects in hypertensive patients of the angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists.

Excessive Angiotensin II Does Not Usually Cause Large Increases in Extracellular Fluid Volume Because Increased Arterial Pressure Counterbalances Angiotensin-Mediated Sodium Retention. Although angiotensin II is one of the most powerful sodium- and water-retaining hormones in the body, neither a decrease nor an increase in circulating angiotensin II has a large effect on extracellular fluid volume or blood volume as long as heart failure or kidney failure does not occur. The reason

for this is that with large increases in angiotensin II levels, as occurs with a renin-secreting tumor of the kidney, the high angiotensin II levels initially cause sodium and water retention by the kidneys and a small increase in extracellular fluid volume. This also initiates a rise in arterial pressure that quickly increases kidney output of sodium and water, thereby overcoming the sodium- and water-retaining effects of the angiotensin II and re-establishing a balance between intake and output of sodium at a higher blood pressure. Conversely, after blockade of angiotensin II formation, as occurs when an angiotensin-converting enzyme inhibitor is administered, there is initial loss of sodium and water, but the fall in blood pressure offsets this effect and sodium excretion is once again restored to normal.

If the heart is weakened or there is underlying heart disease, cardiac pumping ability may not be great enough to raise arterial pressure enough to overcome the sodium retaining effects of high levels of angiotensin II; in these instances angiotensin II may cause large amounts of sodium and water retention that may progress to *congestive heart failure.* Blockade of angiotensin II formation may, in these cases, relieve some of the sodium and water retention and attenuate the large expansion of extracellular fluid volume associated with heart failure.

Role of Aldosterone in Controlling Renal Excretion

Aldosterone increases sodium reabsorption, especially in the cortical collecting tubules. The increased sodium reabsorption is also associated with increased water reabsorption and potassium secretion. Therefore, the net effect of aldosterone is to make the kidneys retain sodium and water but also to increase potassium excretion in the urine.

The function of aldosterone in regulating sodium balance is closely related to that described for angiotensin II. That is, with reduction in sodium intake, the increased angiotensin II levels that occur stimulate aldosterone secretion, which in turn contributes to the reduction in urinary sodium excretion and, therefore, to the maintenance of sodium balance. Conversely, with high sodium intake, suppression of aldosterone formation decreases tubular reabsorption, allowing the kidneys to excrete larger amounts of sodium. Thus, changes in aldosterone formation also aid the pressure natriuresis mechanism in maintaining sodium balance during variations in salt intake.

During Chronic Oversecretion of Aldosterone, the Kidneys "Escape" from Sodium Retention as Arterial Pressure Rises. Although aldosterone has powerful effects on sodium reabsorption, when there is excessive infusion of aldosterone or excessive formation of aldosterone, as occurs in patients with tumors of the adrenal gland (Conn's syndrome), the increased sodium reabsorption and decreased sodium excretion by the kidneys are transient. After 1 to 3 days of sodium and water retention, the extracellular fluid volume rises by about 10 to 15 percent and there is a simultaneous increase in arterial blood pressure. When the arterial pressure rises sufficiently, the kidneys "escape" from the sodium and water retention and thereafter excrete amounts of sodium equal to the daily intake, despite continued presence of high levels of aldosterone. The primary reason for the escape is the pressure natriuresis and diuresis that occur when the arterial pressure rises.

In patients with adrenal insufficiency who do not secrete enough aldosterone (Addison's disease), there is increased excretion of sodium and water, reduction in extracellular fluid volume, and a tendency toward low blood pressure. In the complete absence of aldosterone, the volume depletion may be severe unless the person is allowed to eat large amounts of salt and drink large amounts of water to balance the increased urine output of salt and water.

Role of ADH in Controlling Renal Water Excretion

As discussed in Chapter 28, ADH plays an important role in allowing the kidneys to form a small volume of concentrated urine while excreting normal amounts of salt. This effect is especially important during water deprivation, which strongly elevates plasma levels of ADH that in turn increase water reabsorption by the kidneys and help to minimize the decreases in extracellular fluid volume and arterial pressure that would otherwise occur. Water deprivation for 24 to 48 hours normally causes only a small decrease in extracellular fluid volume and arterial pressure. However, if the effects of ADH are blocked with a drug that antagonizes the action of ADH to promote water reabsorption in the distal and collecting tubules, the same period of water deprivation causes a substantial fall in both extracellular fluid volume and arterial pressure. Conversely, when there is excess extracellular volume, *decreased* ADH levels reduce reabsorption of water by the kidneys, thus helping to rid the body of the excess volume.

Excess ADH Secretion Usually Causes Only Small Increases in Extracellular Fluid Volume but Large Decreases in Sodium Concentration. Although ADH is important in regulating extracellular fluid volume, excessive levels of ADH seldom cause large increases in arterial pressure or extracellular fluid volume. Infusion of large amounts of ADH into animals initially causes renal retention of water and a 10 to 15 percent increase in extracellular fluid volume. As the arterial pressure rises in response to this increased volume, much of the excess volume is excreted because of the pressure diuresis mechanism. Also, the rise in blood pressure causes pressure natriuresis and loss of sodium from the extracellular fluid. After several days of ADH infusion, the blood volume and extracellular fluid volume are elevated no more than 5 to 10 percent and the arterial pressure is also elevated by less than 10 mm Hg. The same is true for patients with *inappropriate ADH syndrome,* in which ADH levels may be elevated severalfold.

Thus, high levels of ADH do not cause major increases of either body fluid volume or arterial pressure, although *high ADH levels can cause severe reductions in extracellular sodium ion concentration.* The reason for this is that increased water reabsorption by the kidneys dilutes

the extracellular sodium, and at the same time, the small increase in blood pressure that does occur causes loss of sodium from the extracellular fluid in the urine through pressure natriuresis.

In patients who have lost their ability to secrete ADH because of destruction of the supraoptic nuclei, the urine volume may become 5 to 10 times normal. This is almost always compensated for by ingestion of enough water to maintain fluid balance. If free access to water is prevented, the inability to secrete ADH may lead to marked reductions in blood volume and arterial pressure.

Role of Atrial Natriuretic Peptide in Controlling Renal Excretion

Thus far, we have discussed mainly the role of sodium- and water-retaining hormones in controlling extracellular fluid volume. However, several different natriuretic hormones may also contribute to volume regulation. One of the most important of the natriuretic hormones is a peptide referred to as *atrial natriuretic peptide (ANP),* released by the cardiac atrial muscle fibers. The stimulus for release of this peptide appears to be increased stretch of the atria, which can result from excess blood volume. Once released by the cardiac atria, ANP enters the circulation and acts on the kidneys to cause small increases in GFR and decreases in sodium reabsorption by the collecting ducts. These combined actions of ANP lead to increased excretion of salt and water, which helps to compensate for the excess blood volume.

Changes in ANP levels probably help to minimize changes in blood volume during various disturbances, such as increased salt and water intake. However, excessive production of ANP or even complete lack of ANP does not cause major changes in blood volume because these effects can easily be overcome by small changes in blood pressure, acting through pressure natriuresis. For example, infusions of large amounts of ANP initially raise urine output of salt and water and cause slight decreases in blood volume. In less than 24 hours, this effect is overcome by a slight decrease in blood pressure that returns urine output toward normal, despite continued excess of ANP.

Integrated Responses to Changes in Sodium Intake

The integration of the different control systems that regulate sodium and fluid excretion under normal conditions can be summarized by examining the homeostatic responses to progressive increases in dietary sodium intake. As discussed previously, the kidneys have an amazing capability to match their excretion of salt and water to intakes that can range from as low as one tenth of normal to as high as 10 times normal.

High Sodium Intake Suppresses Antinatriuretic Systems and Activates Natriuretic Systems. As sodium intake is increased, sodium output initially lags slightly behind intake. The time delay results in a small increase in the cumulative sodium balance, which causes a slight increase in extracellular fluid volume. It is mainly this small increase in extracellular fluid volume that triggers various mechanisms in the body to increase sodium excretion. These mechanisms include the following:

1. *Activation of low-pressure receptor reflexes* that originate from the stretch receptors of the right atrium and the pulmonary blood vessels. Signals from the stretch receptors go to the brain stem and there inhibit sympathetic nerve activity to the kidneys to decrease tubular sodium reabsorption. This mechanism is most important in the first few hours—or perhaps the first day—after a large increase in salt and water intake.
2. *Suppression of angiotensin II formation,* caused by increased arterial pressure and extracellular fluid volume expansion, decreases tubular sodium reabsorption by eliminating the normal effect of angiotensin II to increase sodium reabsorption. Also, reduced angiotensin II decreases aldosterone secretion, thus further reducing tubular sodium reabsorption.
3. *Stimulation of natriuretic systems,* especially ANP, contributes further to increased sodium excretion. Thus, the combined activation of natriuretic systems and suppression of sodium- and water-retaining systems leads to an increase in sodium excretion when sodium intake is increased. The opposite changes take place when sodium intake is reduced below normal levels.
4. *Small increases in arterial pressure,* caused by volume expansion, may occur with large increases in sodium intake; this raises sodium excretion through pressure natriuresis. As discussed previously, if the nervous, hormonal, and intrarenal mechanisms are operating effectively, measurable increases in blood pressure may not occur even with large increases in sodium intake over several days. However, when high sodium intake is sustained for months or years, the kidneys may become damaged and less effective in excreting sodium, necessitating increased blood pressure to maintain sodium balance through the pressure natriuresis mechanism.

Conditions That Cause Large Increases in Blood Volume and Extracellular Fluid Volume

Despite the powerful regulatory mechanisms that maintain blood volume and extracellular fluid volume reasonably constant, there are abnormal conditions that can cause large increases in both of these variables. Almost all of these conditions result from circulatory abnormalities.

Increased Blood Volume and Extracellular Fluid Volume Caused by Heart Diseases

In congestive heart failure, blood volume may increase 15 to 20 percent and extracellular fluid volume sometimes increases by 200 percent or more. The reason for

this can be understood by re-examination of Figure 29-14. Initially, heart failure reduces cardiac output and, consequently, decreases arterial pressure. This in turn activates multiple sodium-retaining systems, especially the renin-angiotensin, aldosterone, and sympathetic nervous systems. In addition, the low blood pressure itself causes the kidneys to retain salt and water. Therefore, the kidneys retain volume in an attempt to return the arterial pressure and cardiac output toward normal.

If the heart failure is not too severe, the rise in blood volume can often return cardiac output and arterial pressure virtually all the way to normal and sodium excretion will eventually increase back to normal, although there will remain increased extracellular fluid volume and blood volume to keep the weakened heart pumping adequately. However, if the heart is greatly weakened, arterial pressure may not be able to increase enough to restore urine output to normal. When this occurs, the kidneys continue to retain volume until the person develops severe circulatory congestion and may eventually die of pulmonary edema.

In myocardial failure, heart valvular disease, and congenital abnormalities of the heart, increased blood volume serves as an important circulatory compensation, which helps to return cardiac output and blood pressure toward normal. This allows even the weakened heart to maintain a life-sustaining level of cardiac output.

Increased Blood Volume Caused by Increased Capacity of Circulation

Any condition that increases vascular capacity will also cause the blood volume to increase to fill this extra capacity. An increase in vascular capacity initially reduces mean circulatory filling pressure (see Figure 29-14), which leads to decreased cardiac output and decreased arterial pressure. The fall in pressure causes salt and water retention by the kidneys until the blood volume increases sufficiently to fill the extra capacity.

In pregnancy the increased vascular capacity of the uterus, placenta, and other enlarged organs of the woman's body regularly increases the blood volume 15 to 25 percent. Similarly, in patients who have large varicose veins of the legs, which in rare instances may hold up to an extra liter of blood, the blood volume simply increases to fill the extra vascular capacity. In these cases, salt and water are retained by the kidneys until the total vascular bed is filled enough to raise blood pressure to the level required to balance renal output of fluid with daily intake of fluid.

Conditions That Cause Large Increases in Extracellular Fluid Volume but with Normal Blood Volume

In several conditions extracellular fluid volume becomes markedly increased but blood volume remains normal or even slightly reduced. These conditions are usually initiated by leakage of fluid and protein into the interstitium, which tends to decrease the blood volume. The kidneys' response to these conditions is similar to the response after hemorrhage. That is, the kidneys retain salt and water in an attempt to restore blood volume toward normal. Much of the extra fluid, however, leaks into the interstitium, causing further edema.

Nephrotic Syndrome—Loss of Plasma Proteins in Urine and Sodium Retention by the Kidneys

The general mechanisms that lead to extracellular edema are reviewed in Chapter 25. One of the most important clinical causes of edema is the so-called *nephrotic syndrome.* In nephrotic syndrome, the glomerular capillaries leak large amounts of protein into the filtrate and the urine because of increased glomerular capillary permeability. Thirty to 50 grams of plasma protein can be lost in the urine each day, sometimes causing the plasma protein concentration to fall to less than one-third normal. As a consequence of the decreased plasma protein concentration, the plasma colloid osmotic pressure falls to low levels. This causes the capillaries all over the body to filter large amounts of fluid into the various tissues, which in turn causes edema and decreases the plasma volume.

Renal sodium retention in nephrotic syndrome occurs through multiple mechanisms activated by leakage of protein and fluid from the plasma into the interstitial fluid, including stimulation of various sodium-retaining systems such as the renin-angiotensin system, aldosterone, and the sympathetic nervous system. The kidneys continue to retain sodium and water until plasma volume is restored nearly to normal. However, because of the large amount of sodium and water retention, the plasma protein concentration becomes further diluted, causing still more fluid to leak into the tissues of the body. The net result is massive fluid retention by the kidneys until tremendous extracellular edema occurs unless treatment is instituted to restore the plasma proteins.

Liver Cirrhosis—Decreased Synthesis of Plasma Proteins by the Liver and Sodium Retention by the Kidneys

A similar sequence of events occurs in cirrhosis of the liver as in nephrotic syndrome, except that in liver cirrhosis, the reduction in plasma protein concentration results from destruction of liver cells, thus reducing the ability of the liver to synthesize enough plasma proteins. Cirrhosis is also associated with large amounts of fibrous tissue in the liver structure, which greatly impedes the flow of portal blood through the liver. This in turn raises capillary pressure throughout the portal vascular bed, which also contributes to the leakage of fluid and proteins into the peritoneal cavity, a condition called *ascites.*

Once fluid and protein are lost from the circulation, the renal responses are similar to those observed in other conditions associated with decreased plasma volume. That is, the kidneys continue to retain salt and water until plasma volume and arterial pressure are restored

to normal. In some cases, plasma volume may actually increase above normal because of increased vascular capacity in cirrhosis; the high pressures in the portal circulation can greatly distend veins and therefore increase vascular capacity.

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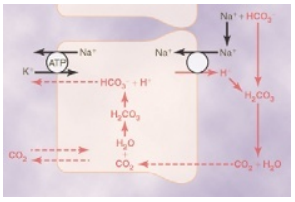
Acid-Base Regulation



Regulation of hydrogen ion (H^+) balance is similar in some ways to the regulation of other ions in the body. For instance, there must be a balance between the intake or production of H^+ and the net removal of H^+ from the body to achieve homeostasis. And, as is true for other ions, the kidneys play a key role in regulating H^+ removal from the body. However, precise control of extracellular fluid H^+ concentration involves much more than simple elimination of H^+ by the kidneys. There are also multiple acid-base buffering mechanisms involving the blood, cells, and lungs that are essential in maintaining normal H^+ concentrations in both the extracellular and intracellular fluid.

In this chapter, the various mechanisms that contribute to the regulation of H^+ concentration are discussed, with special emphasis on the control of renal H^+ secretion and renal reabsorption, production, and excretion of bicarbonate ions (HCO_3^-), one of the key components of acid-base control systems in the body fluids.

H^+ Concentration Is Precisely Regulated

Precise H^+ regulation is essential because the activities of almost all enzyme systems in the body are influenced by H^+ concentration. Therefore, changes in H^+ concentration alter virtually all cell and body functions.

Compared with other ions, the H^+ concentration of the body fluids normally is kept at a low level. For example, the concentration of sodium in extracellular fluid (142 mEq/L) is about 3.5 million times as great as the normal concentration of H^+, which averages only 0.00004 mEq/L. Equally important, the normal variation in H^+ concentration in extracellular fluid is only about one millionth as great as the normal variation in sodium ion (Na^+) concentration. Thus, the precision with which H^+ is regulated emphasizes its importance to the various cell functions.

Acids and Bases—Their Definitions and Meanings

A hydrogen ion is a single free proton released from a hydrogen atom. Molecules containing hydrogen atoms that can release hydrogen ions in solutions are referred to as *acids.* An example is hydrochloric acid (HCl), which ionizes in water to form hydrogen ions (H^+) and chloride ions (Cl^-). Likewise, carbonic acid (H_2CO_3) ionizes in water to form H^+ and bicarbonate ions (HCO_3^-).

A *base* is an ion or a molecule that can accept an H^+. For example, HCO_3^- is a base because it can combine with H^+ to form H_2CO_3. Likewise, $HPO_4^=$ is a base because it can accept an H^+ to form $H_2PO_4^-$. The proteins in the body also function as bases because some of the amino acids that make up proteins have net negative charges that readily accept H^+. The protein hemoglobin in the red blood cells and proteins in the other cells of the body are among the most important of the body's bases.

The terms *base* and *alkali* are often used synonymously. An *alkali* is a molecule formed by the combination of one or more of the alkaline metals—sodium, potassium, lithium, and so forth—with a highly basic ion such as a hydroxyl ion (OH^-). The base portion of these molecules reacts quickly with H^+ to remove it from solution; they are, therefore, typical bases. For similar reasons, the term *alkalosis* refers to excess removal of H^+ from the body fluids, in contrast to the excess addition of H^+, which is referred to as *acidosis.*

Strong and Weak Acids and Bases. A strong acid is one that rapidly dissociates and releases especially large amounts of H^+ in solution. An example is HCl. Weak acids are less likely to dissociate their ions and, therefore, release H^+ with less vigor. An example is H_2CO_3. A strong base is one that reacts rapidly and strongly with H^+ and, therefore, quickly removes these from a solution. A typical example is OH^-, which reacts with H^+ to form water (H_2O). A typical weak base is HCO_3^- because it binds with H^+ much more weakly than does OH^-. Most acids and bases in the extracellular fluid that are involved in normal acid-base regulation are weak acids and bases. The most

important ones that we discuss in detail are H_2CO_3 and HCO_3^- base.

Normal H^+ Concentration and pH of Body Fluids and Changes That Occur in Acidosis and Alkalosis. As discussed earlier, the blood H^+ concentration is normally maintained within tight limits around a normal value of about 0.00004 mEq/L (40 nEq/L). Normal variations are only about 3 to 5 nEq/L, but under extreme conditions, the H^+ concentration can vary from as low as 10 nEq/L to as high as 160 nEq/L without causing death.

Because H^+ concentration normally is low, and because these small numbers are cumbersome, it is customary to express H^+ concentration on a logarithm scale, using pH units. pH is related to the actual H^+ concentration by the following formula (H^+ concentration $[H^+]$ is expressed in *equivalents* per liter):

$$pH = \log \frac{1}{[H^+]} = -\log [H^+]$$

For example, the normal $[H^+]$ is 40 nEq/L (0.00000004 Eq/L). Therefore, the normal pH is

$$pH = -\log [0.00000004]$$
$$pH = 7.4$$

From this formula, one can see that pH is inversely related to the H^+ concentration; therefore, a low pH corresponds to a high H^+ concentration and a high pH corresponds to a low H^+ concentration.

The normal pH of arterial blood is 7.4, whereas the pH of venous blood and interstitial fluids is about 7.35 because of the extra amounts of carbon dioxide (CO_2) released from the tissues to form H_2CO_3 in these fluids (Table 30-1). Because the normal pH of arterial blood is 7.4, a person is considered to have *acidosis* when the pH falls below this value and to have *alkalosis* when the pH rises above 7.4. The lower limit of pH at which a person can live more than a few hours is about 6.8, and the upper limit is about 8.0.

Intracellular pH usually is slightly lower than plasma pH because the metabolism of the cells produces acid, especially H_2CO_3. Depending on the type of cells, the pH of intracellular fluid has been estimated to range between 6.0 and 7.4. Hypoxia of the tissues and poor blood flow to the tissues can cause acid accumulation and decreased intracellular pH.

The pH of urine can range from 4.5 to 8.0, depending on the acid-base status of the extracellular fluid. As discussed later, the kidneys play a major role in correcting abnormalities of extracellular fluid H^+ concentration by excreting acids or bases at variable rates.

An extreme example of an acidic body fluid is the HCl secreted into the stomach by the oxyntic (parietal) cells of the stomach mucosa, as discussed in Chapter 64. The H^+ concentration in these cells is about 4 million times greater than the hydrogen concentration in blood, with a pH of 0.8. In the remainder of this chapter, we discuss the regulation of extracellular fluid H^+ concentration.

Table 30-1 pH and H^+ Concentration of Body Fluids

	H^+ Concentration (mEq/L)	pH
Extracellular fluid		
Arterial blood	4.0×10^{-5}	7.40
Venous blood	4.5×10^{-5}	7.35
Interstitial fluid	4.5×10^{-5}	7.35
Intracellular fluid	1×10^{-3} to 4×10^{-5}	6.0-7.4
Urine	3×10^{-2} to 1×10^{-5}	4.5-8.0
Gastric HCl	160	0.8

Defending Against Changes in H^+ Concentration: Buffers, Lungs, and Kidneys

Three primary systems regulate the H^+ concentration in the body fluids to prevent acidosis or alkalosis: (1) the *chemical acid-base buffer systems of the body fluids,* which immediately combine with acid or base to prevent excessive changes in H^+ concentration; (2) the *respiratory center,* which regulates the removal of CO_2 (and, therefore, H_2CO_3) from the extracellular fluid; and (3) the *kidneys,* which can excrete either acid or alkaline urine, thereby readjusting the extracellular fluid H^+ concentration toward normal during acidosis or alkalosis.

When there is a change in H^+ concentration, the *buffer systems* of the body fluids react within seconds to minimize these changes. Buffer systems do not eliminate H^+ from or add them to the body but only keep them tied up until balance can be re-established.

The second line of defense, the *respiratory system,* acts within a few minutes to eliminate CO_2 and, therefore, H_2CO_3 from the body.

These first two lines of defense keep the H^+ concentration from changing too much until the more slowly responding third line of defense, the *kidneys,* can eliminate the excess acid or base from the body. Although the kidneys are relatively slow to respond compared with the other defenses, over a period of hours to several days, they are by far the most powerful of the acid-base regulatory systems.

Buffering of H^+ in the Body Fluids

A buffer is any substance that can reversibly bind H^+. The general form of the buffering reaction is

$$\text{Buffer} + H^+ \rightleftharpoons \text{H Buffer}$$

In this example, a free H^+ combines with the buffer to form a weak acid (H buffer) that can either remain as an unassociated molecule or dissociate back to buffer and H^+. When the H^+ concentration increases, the reaction is forced to the right and more H^+ binds to the buffer, as

long as buffer is available. Conversely, when the H^+ concentration decreases, the reaction shifts toward the left and H^+ is released from the buffer. In this way, changes in H^+ concentration are minimized.

The importance of the body fluid buffers can be quickly realized if one considers the low concentration of H^+ in the body fluids and the relatively large amounts of acids produced by the body each day. For example, about 80 milliequivalents of H^+ is either ingested or produced each day by metabolism, whereas the H^+ concentration of the body fluids normally is only about 0.00004 mEq/L. Without buffering, the daily production and ingestion of acids would cause huge changes in body fluid H^+ concentration.

The action of acid-base buffers can perhaps best be explained by considering the buffer system that is quantitatively the most important in the extracellular fluid—the bicarbonate buffer system.

Bicarbonate Buffer System

The bicarbonate buffer system consists of a water solution that contains two ingredients: (1) a weak acid, H_2CO_3, and (2) a bicarbonate salt, such as $NaHCO_3$.

H_2CO_3 is formed in the body by the reaction of CO_2 with H_2O.

$$CO_2 + H_2O \underset{}{\overset{\text{carbonic anhydrase}}{\rightleftharpoons}} H_2CO_3$$

This reaction is slow, and exceedingly small amounts of H_2CO_3 are formed unless the enzyme *carbonic anhydrase* is present. This enzyme is especially abundant in the walls of the lung alveoli, where CO_2 is released; carbonic anhydrase is also present in the epithelial cells of the renal tubules, where CO_2 reacts with H_2O to form H_2CO_3.

H_2CO_3 ionizes weakly to form small amounts of H^+ and HCO_3^-.

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

The second component of the system, bicarbonate salt, occurs predominantly as sodium bicarbonate ($NaHCO_3$) in the extracellular fluid. $NaHCO_3$ ionizes almost completely to form HCO_3^- and Na^+, as follows:

$$NaHCO_3 \rightleftharpoons Na^+ + HCO_3^-$$

Now, putting the entire system together, we have the following:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + \underbrace{HCO_3^-}_{+\ Na^+}$$

Because of the weak dissociation of H_2CO_3, the H^+ concentration is extremely small.

When a strong acid such as HCl is added to the bicarbonate buffer solution, the increased H^+ released from the acid ($HCl \rightarrow H^+ + Cl^-$) is buffered by HCO_3^-.

$$\uparrow H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$$

As a result, more H_2CO_3 is formed, causing increased CO_2 and H_2O production. From these reactions, one can see that H^+ from the strong acid HCl reacts with HCO_3^- to form the very weak acid H_2CO_3, which in turn forms CO_2 and H_2O. The excess CO_2 greatly stimulates respiration, which eliminates the CO_2 from the extracellular fluid.

The opposite reactions take place when a strong base, such as sodium hydroxide (NaOH), is added to the bicarbonate buffer solution.

$$NaOH + H_2CO_3 \rightarrow NaHCO_3 + H_2O$$

In this case, the OH^- from the NaOH combines with H_2CO_3 to form additional HCO_3^-. Thus, the weak base $NaHCO_3$ replaces the strong base NaOH. At the same time, the concentration of H_2CO_3 decreases (because it reacts with NaOH), causing more CO_2 to combine with H_2O to replace the H_2CO_3.

$$\underset{}{CO_2 + H_2O} \longrightarrow \underset{+\ NaOH}{H_2CO_3} \longrightarrow \underset{+\ Na}{\uparrow HCO_3^- + H^+}$$

The net result, therefore, is a tendency for the CO_2 levels in the blood to decrease, but the decreased CO_2 in the blood inhibits respiration and decreases the rate of CO_2 expiration. The rise in blood HCO_3^- that occurs is compensated for by increased renal excretion of HCO_3^-.

Quantitative Dynamics of the Bicarbonate Buffer System

All acids, including H_2CO_3, are ionized to some extent. From mass balance considerations, the concentrations of H^+ and HCO_3^- are proportional to the concentration of H_2CO_3.

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

For any acid, the concentration of the acid relative to its dissociated ions is defined by the *dissociation constant K′*.

$$K' = \frac{H^+ \times HCO_3^-}{H_2CO_3} \qquad (1)$$

This equation indicates that in an H_2CO_3 solution, the amount of free H^+ is equal to

$$H^+ = K' \times \frac{H_2CO_3}{HCO_3^-} \qquad (2)$$

The concentration of undissociated H_2CO_3 cannot be measured in solution because it rapidly dissociates into CO_2 and H_2O or to H^+ and HCO_3^-. However, the CO_2 dissolved in the blood is directly proportional to the amount of undissociated H_2CO_3. Therefore, equation 2 can be rewritten as

$$H^+ = K \times \frac{CO_2}{HCO_3^-} \qquad (3)$$

The dissociation constant (K) for equation 3 is only about $^1/_{400}$ of the dissociation constant (K′) of equation 2 because the proportionality ratio between H_2CO_3 and CO_2 is 1:400.

Equation 3 is written in terms of the total amount of CO_2 dissolved in solution. However, most clinical laboratories measure the blood CO_2 tension (P_{CO_2}) rather than the actual amount of CO_2. Fortunately, the amount of CO_2 in the blood

is a linear function of P_{CO_2} multiplied by the solubility coefficient for CO_2; under physiologic conditions, the solubility coefficient for CO_2 is 0.03 mmol/mm Hg at body temperature. This means that 0.03 millimole of H_2CO_3 is present in the blood for each mm Hg P_{CO_2} measured. Therefore, equation 3 can be rewritten as

$$H^+ = K \times \frac{(0.03 \times P_{CO_2})}{HCO_3^-} \quad (4)$$

Henderson-Hasselbalch Equation. As discussed earlier, it is customary to express H^+ concentration in pH units rather than in actual concentrations. Recall that pH is defined as $pH = -\log H^+$.

The dissociation constant can be expressed in a similar manner.

$$pK = -\log K$$

Therefore, we can express the H^+ concentration in equation 4 in pH units by taking the negative logarithm of that equation, which yields

$$-\log H^+ = -\log pK - \log \frac{(0.03 \times P_{CO_2})}{HCO_3^-} \quad (5)$$

Therefore,

$$pH = pK - \log \frac{(0.03 \times P_{CO_2})}{HCO_3^-} \quad (6)$$

Rather than work with a negative logarithm, we can change the sign of the logarithm and invert the numerator and denominator in the last term, using the law of logarithms to yield

$$pH = pK + \log \frac{HCO_3^-}{(0.03 \times P_{CO_2})} \quad (7)$$

For the bicarbonate buffer system, the pK is 6.1, and equation 7 can be written as

$$pH = 6.1 + \log \frac{HCO_3^-}{0.03 \times P_{CO_2}} \quad (8)$$

Equation 8 is the Henderson-Hasselbalch equation, and with it, one can calculate the pH of a solution if the molar concentration of HCO_3^- and the P_{CO_2} are known.

From the Henderson-Hasselbalch equation, it is apparent that an increase in HCO_3^- concentration causes the pH to rise, shifting the acid-base balance toward alkalosis. An increase in P_{CO_2} causes the pH to decrease, shifting the acid-base balance toward acidosis.

The Henderson-Hasselbalch equation, in addition to defining the determinants of normal pH regulation and acid-base balance in the extracellular fluid, provides insight into the physiologic control of acid and base composition of the extracellular fluid. As discussed later, *the HCO_3^- concentration is regulated mainly by the kidneys, whereas the P_{CO_2} in extracellular fluid is controlled by the rate of respiration.* By increasing the rate of respiration, the lungs remove CO_2 from the plasma, and by decreasing respiration, the lungs elevate P_{CO_2}. Normal physiologic acid-base homeostasis results from the coordinated efforts of both of these organs, the lungs and the kidneys, and acid-base disorders occur when one or both of these control mechanisms are impaired, thus altering either the HCO_3^- concentration or the P_{CO_2} of extracellular fluid.

When disturbances of acid-base balance result from a primary change in extracellular fluid HCO_3^- concentration, they are referred to as *metabolic* acid-base disorders. Therefore, acidosis caused by a primary decrease in HCO_3^- concentration is termed *metabolic acidosis,* whereas alkalosis caused by a primary increase in HCO_3^- concentration is called *metabolic alkalosis.* Acidosis caused by an increase in P_{CO_2} is called *respiratory acidosis,* whereas alkalosis caused by a decrease in P_{CO_2} is termed *respiratory alkalosis.*

Bicarbonate Buffer System Titration Curve. Figure 30-1 shows the changes in pH of the extracellular fluid when the ratio of HCO_3^- to CO_2 in extracellular fluid is altered. When the concentrations of these two components are equal, the right-hand portion of equation 8 becomes the log of 1, which is equal to 0. Therefore, when the two components of the buffer system are equal, the pH of the solution is the same as the pK (6.1) of the bicarbonate buffer system. When base is added to the system, part of the dissolved CO_2 is converted into HCO_3^- causing an increase in the ratio of HCO_3^- to CO_2 and increasing the pH, as is evident from the Henderson-Hasselbalch equation. When acid is added, it is buffered by HCO_3^-, which is then converted into dissolved CO_2, decreasing the ratio of HCO_3^- to CO_2 and decreasing the pH of the extracellular fluid.

"Buffer Power" Is Determined by the Amount and Relative Concentrations of the Buffer Components. From the titration curve in Figure 30-1, several points are apparent. First, the pH of the system is the same as the pK when each of the components (HCO_3^- and CO_2) constitutes 50 percent of the total concentration of the buffer system. Second, the buffer system is most effective in the central part of the curve, where the pH is near the pK of the system. This means that the change in pH for any given amount of acid or base added to the system is least when the pH is near the pK of the system. The buffer system is still reasonably effective for 1.0 pH unit on either side of the pK, which for the bicarbonate buffer system extends from a pH of about 5.1 to 7.1 units. Beyond these limits, the buffering power rapidly diminishes. And when all the CO_2 has been converted into HCO_3^- or when all the HCO_3^- has been converted into CO_2, the system has no more buffering power.

The absolute concentration of the buffers is also an important factor in determining the buffer power of a system. With low concentrations of the buffers, only a small amount of acid or base added to the solution changes the pH considerably.

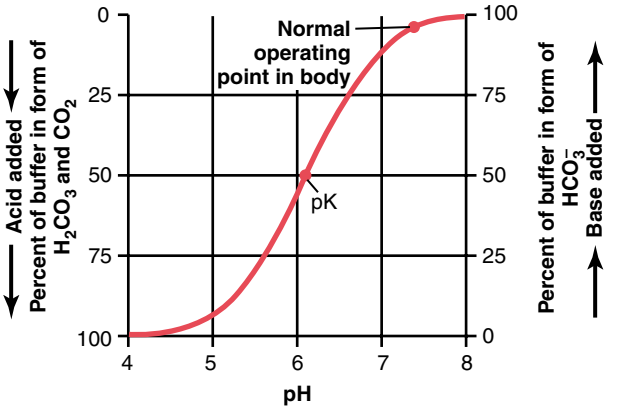


Figure 30-1 Titration curve for bicarbonate buffer system showing the pH of extracellular fluid when the percentages of buffer in the form of HCO_3^- and CO_2 (or H_2CO_3) are altered.

Bicarbonate Buffer System Is the Most Important Extracellular Buffer. From the titration curve shown in Figure 30-1, one would not expect the bicarbonate buffer system to be powerful, for two reasons: First, the pH of the extracellular fluid is about 7.4, whereas the pK of the bicarbonate buffer system is 6.1. This means that there is about 20 times as much of the bicarbonate buffer system in the form of HCO_3^- as in the form of dissolved CO_2. For this reason, this system operates on the portion of the buffering curve where the slope is low and the buffering power is poor. Second, the concentrations of the two elements of the bicarbonate system, CO_2 and HCO_3^-, are not great.

Despite these characteristics, the bicarbonate buffer system is the most powerful extracellular buffer in the body. This apparent paradox is due mainly to the fact that the two elements of the buffer system, HCO_3^- and CO_2, are regulated, respectively, by the kidneys and the lungs, as discussed later. As a result of this regulation, the pH of the extracellular fluid can be precisely controlled by the relative rate of removal and addition of HCO_3^- by the kidneys and the rate of removal of CO_2 by the lungs.

Phosphate Buffer System

Although the phosphate buffer system is not important as an extracellular fluid buffer, it plays a major role in buffering renal tubular fluid and intracellular fluids.

The main elements of the phosphate buffer system are $H_2PO_4^-$ and $HPO_4^=$. When a strong acid such as HCl is added to a mixture of these two substances, the hydrogen is accepted by the base $HPO_4^=$ and converted to $H_2PO_4^-$.

$$HCl + Na_2HPO_4 \rightarrow NaH_2PO_4 + NaCl$$

The result of this reaction is that the strong acid, HCl, is replaced by an additional amount of a weak acid, NaH_2PO_4, and the decrease in pH is minimized.

When a strong base, such as NaOH, is added to the buffer system, the OH^- is buffered by the $H_2PO_4^-$ to form additional amounts of $HPO_4^= + H_2O$.

$$NaOH + NaH_2PO_4 \rightarrow Na_2HPO_4 + H_2O$$

In this case, a strong base, NaOH, is traded for a weak base, NaH_2PO_4, causing only a slight increase in pH.

The phosphate buffer system has a pK of 6.8, which is not far from the normal pH of 7.4 in the body fluids; this allows the system to operate near its maximum buffering power. However, its concentration in the extracellular fluid is low, only about 8 percent of the concentration of the bicarbonate buffer. Therefore, the total buffering power of the phosphate system in the extracellular fluid is much less than that of the bicarbonate buffering system.

In contrast to its rather insignificant role as an extracellular buffer, *the phosphate buffer is especially important in the tubular fluids of the kidneys,* for two reasons: (1) phosphate usually becomes greatly concentrated in the tubules, thereby increasing the buffering power of the phosphate system, and (2) the tubular fluid usually has a considerably lower pH than the extracellular fluid does, bringing the operating range of the buffer closer to the pK (6.8) of the system.

The phosphate buffer system is also important in buffering intracellular fluid because the concentration of phosphate in this fluid is many times that in the extracellular fluid. Also, the pH of intracellular fluid is lower than that of extracellular fluid and therefore is usually closer to the pK of the phosphate buffer system compared with the extracellular fluid.

Proteins Are Important Intracellular Buffers

Proteins are among the most plentiful buffers in the body because of their high concentrations, especially within the cells.

The pH of the cells, although slightly lower than in the extracellular fluid, nevertheless changes approximately in proportion to extracellular fluid pH changes. There is a slight diffusion of H^+ and HCO_3^- through the cell membrane, although these ions require several hours to come to equilibrium with the extracellular fluid, except for rapid equilibrium that occurs in the red blood cells. CO_2, however, can rapidly diffuse through all the cell membranes. *This diffusion of the elements of the bicarbonate buffer system causes the pH in intracellular fluid to change when there are changes in extracellular pH.* For this reason, the buffer systems within the cells help prevent changes in the pH of extracellular fluid but may take several hours to become maximally effective.

In the red blood cell, hemoglobin (Hb) is an important buffer, as follows:

$$H^+ + Hb \rightleftharpoons HHb$$

Approximately 60 to 70 percent of the total chemical buffering of the body fluids is inside the cells, and most of this results from the intracellular proteins. However, except for the red blood cells, the slowness with which H^+ and HCO_3^- move through the cell membranes often delays for several hours the maximum ability of the intracellular proteins to buffer extracellular acid-base abnormalities.

In addition to the high concentration of proteins in the cells, another factor that contributes to their buffering power is the fact that the pKs of many of these protein systems are fairly close to intracellular pH.

Isohydric Principle: All Buffers in a Common Solution Are in Equilibrium with the Same H^+ Concentration

We have been discussing buffer systems as though they operated individually in the body fluids. However, they all work together because H^+ is common to the reactions of all these systems. Therefore, whenever there is a change in H^+ concentration in the extracellular fluid, the balance of all the buffer systems changes at the same time. This phenomenon

is called the *isohydric principle* and is illustrated by the following formula:

$$H^+ = K_1 \times \frac{HA_1}{A_1} = K_2 \times \frac{HA_2}{A_2} = K_3 \times \frac{HA_3}{A_3}$$

K_1, K_2, K_3 are the dissociation constants of three respective acids, HA_1, HA_2, HA_3, and A_1, A_2, A_3 are the concentrations of the free negative ions that constitute the bases of the three buffer systems.

The implication of this principle is that any condition that changes the balance of one of the buffer systems also changes the balance of all the others because the buffer systems actually buffer one another by shifting H^+ back and forth between them.

Respiratory Regulation of Acid-Base Balance

The second line of defense against acid-base disturbances is control of extracellular fluid CO_2 concentration by the lungs. An increase in ventilation eliminates CO_2 from extracellular fluid, which, by mass action, reduces the H^+ concentration. Conversely, decreased ventilation increases CO_2, thus also increasing H^+ concentration in the extracellular fluid.

Pulmonary Expiration of CO_2 Balances Metabolic Formation of CO_2

CO_2 is formed continually in the body by intracellular metabolic processes. After it is formed, it diffuses from the cells into the interstitial fluids and blood and the flowing blood transports it to the lungs, where it diffuses into the alveoli and then is transferred to the atmosphere by pulmonary ventilation. About 1.2 mol/L of dissolved CO_2 normally is in the extracellular fluid, corresponding to a Pco_2 of 40 mm Hg.

If the rate of metabolic formation of CO_2 increases, the Pco_2 of the extracellular fluid is likewise increased. Conversely, a decreased metabolic rate lowers the Pco_2. If the rate of pulmonary ventilation is increased, CO_2 is blown off from the lungs and the Pco_2 in the extracellular fluid decreases. Therefore, changes in either pulmonary ventilation or the rate of CO_2 formation by the tissues can change the extracellular fluid Pco_2.

Increasing Alveolar Ventilation Decreases Extracellular Fluid H^+ Concentration and Raises pH

If the metabolic formation of CO_2 remains constant, the only other factor that affects Pco_2 in extracellular fluid is the rate of alveolar ventilation. The higher the alveolar ventilation, the lower the Pco_2; conversely, the lower the alveolar ventilation rate, the higher the Pco_2. As discussed previously, when CO_2 concentration increases, the H_2CO_3 concentration and H^+ concentration also increase, thereby lowering extracellular fluid pH.

Figure 30-2 shows the approximate changes in blood pH that are caused by increasing or decreasing the rate of alveolar ventilation. Note that increasing alveolar ventilation to about twice normal raises the pH of the extracellular fluid by about 0.23. If the pH of the body fluids is 7.40 with normal alveolar ventilation, doubling the ventilation rate raises the pH to about 7.63. Conversely, a decrease in alveolar ventilation to one fourth normal reduces the pH by 0.45. That is, if the pH is 7.4 at a normal alveolar ventilation, reducing the ventilation to one fourth normal reduces the pH to 6.95. Because the alveolar ventilation rate can change markedly, from as low as 0 to as high as 15 times normal, one can easily understand how much the pH of the body fluids can be changed by the respiratory system.

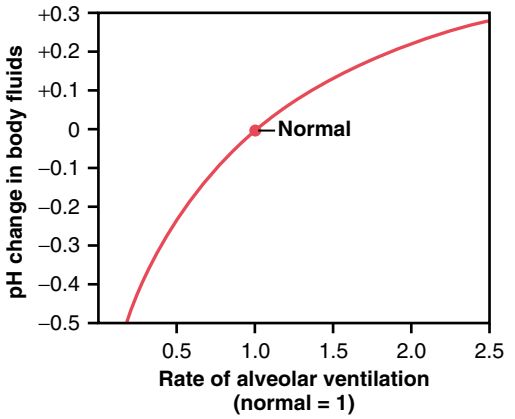


Figure 30-2 Change in extracellular fluid pH caused by increased or decreased rate of alveolar ventilation, expressed as times normal.

Increased H^+ Concentration Stimulates Alveolar Ventilation

Not only does the alveolar ventilation rate influence H^+ concentration by changing the Pco_2 of the body fluids, but the H^+ concentration affects the rate of alveolar ventilation. Thus, Figure 30-3 shows that the alveolar ventilation rate increases four to five times normal as the pH decreases from the normal value of 7.4 to the strongly acidic value of 7.0. Conversely, when plasma pH rises above 7.4, this causes a decrease in the ventilation rate. As one can see from the graph, the change in ventilation rate per unit pH change is much greater at reduced levels

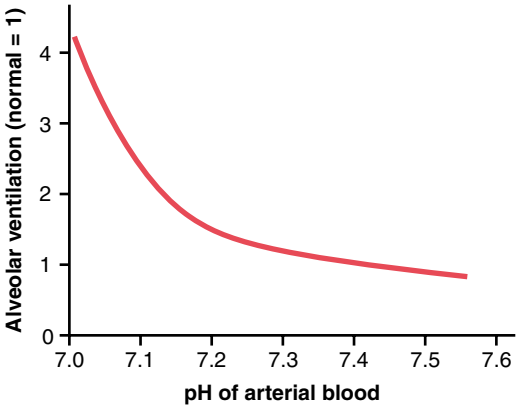
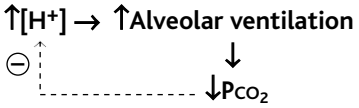


Figure 30-3 Effect of blood pH on the rate of alveolar ventilation.

of pH (corresponding to elevated H^+ concentration) compared with increased levels of pH. The reason for this is that as the alveolar ventilation rate decreases, owing to an increase in pH (decreased H^+ concentration), the amount of oxygen added to the blood decreases and the partial pressure of oxygen (P_{O_2}) in the blood also decreases, which stimulates the ventilation rate. Therefore, the respiratory compensation for an increase in pH is not nearly as effective as the response to a marked reduction in pH.

Feedback Control of H^+ Concentration by the Respiratory System. Because increased H^+ concentration stimulates respiration, and because increased alveolar ventilation decreases the H^+ concentration, the respiratory system acts as a typical negative feedback controller of H^+ concentration.



That is, whenever the H^+ concentration increases above normal, the respiratory system is stimulated and alveolar ventilation increases. This decreases the P_{CO_2} in extracellular fluid and reduces H^+ concentration back toward normal. Conversely, if H^+ concentration falls below normal, the respiratory center becomes depressed, alveolar ventilation decreases, and H^+ concentration increases back toward normal.

Efficiency of Respiratory Control of H^+ Concentration. Respiratory control cannot return the H^+ concentration all the way back to normal when a disturbance outside the respiratory system has altered pH. Ordinarily, the respiratory mechanism for controlling H^+ concentration has an effectiveness between 50 and 75 percent, corresponding to a *feedback gain* of 1 to 3. That is, if the pH is suddenly increased by adding acid to the extracellular fluid and pH falls from 7.4 to 7.0, the respiratory system can return the pH to a value of about 7.2 to 7.3. This response occurs within 3 to 12 minutes.

Buffering Power of the Respiratory System. *Respiratory regulation of acid-base balance is a physiologic type of buffer system* because it acts rapidly and keeps the H^+ concentration from changing too much until the slowly responding kidneys can eliminate the imbalance. In general, the overall buffering power of the respiratory system is one to two times as great as the buffering power of all other chemical buffers in the extracellular fluid combined. That is, one to two times as much acid or base can normally be buffered by this mechanism as by the chemical buffers.

Impairment of Lung Function Can Cause Respiratory Acidosis. We have discussed thus far the role of the *normal* respiratory mechanism as a means of buffering changes in H^+ concentration. However, *abnormalities of respiration* can also cause changes in H^+ concentration. For example, an impairment of lung function, such as severe emphysema, decreases the ability of the lungs to eliminate CO_2; this causes a buildup of CO_2 in the extracellular fluid and a tendency toward *respiratory acidosis.* Also, the ability to respond to metabolic acidosis is impaired because the compensatory reductions in P_{CO_2} that would normally occur by means of increased ventilation are blunted. In these circumstances, the kidneys represent the sole remaining physiologic mechanism for returning pH toward normal after the initial chemical buffering in the extracellular fluid has occurred.

Renal Control of Acid-Base Balance

The kidneys control acid-base balance by excreting either acidic or basic urine. Excreting acidic urine reduces the amount of acid in extracellular fluid, whereas excreting basic urine removes base from the extracellular fluid.

The overall mechanism by which the kidneys excrete acidic or basic urine is as follows: Large numbers of HCO_3^- are filtered continuously into the tubules, and if they are excreted into the urine this removes base from the blood. Large numbers of H^+ are also secreted into the tubular lumen by the tubular epithelial cells, thus removing acid from the blood. If more H^+ is secreted than HCO_3^- is filtered, there will be a net loss of acid from the extracellular fluid. Conversely, if more HCO_3^- is filtered than H^+ is secreted, there will be a net loss of base.

As discussed previously, each day the body produces about 80 mEq of nonvolatile acids, mainly from the metabolism of proteins. These acids are called *nonvolatile* because they are not H_2CO_3 and, therefore, cannot be excreted by the lungs. The primary mechanism for removal of these acids from the body is renal excretion. The kidneys must also prevent the loss of bicarbonate in the urine, a task that is quantitatively more important than the excretion of nonvolatile acids. Each day the kidneys filter about 4320 mEq of bicarbonate (180 L/day × 24 mEq/L); under normal conditions, almost all this is reabsorbed from the tubules, thereby conserving the primary buffer system of the extracellular fluid.

As discussed later, both the reabsorption of bicarbonate and the excretion of H^+ are accomplished through the process of H^+ secretion by the tubules. Because the HCO_3^- must react with a secreted H^+ to form H_2CO_3 before it can be reabsorbed, 4320 mEq of H^+ must be secreted each day just to reabsorb the filtered bicarbonate. Then an additional 80 mEq of H^+ must be secreted to rid the body of the nonvolatile acids produced each day, for a total of 4400 mEq of H^+ secreted into the tubular fluid each day.

When there is a reduction in the extracellular fluid H^+ concentration (alkalosis), the kidneys fail to reabsorb all the filtered HCO_3^-, thereby increasing the excretion of HCO_3^-. Because HCO_3^- normally buffers H^+ in the extracellular fluid, this loss of HCO_3^- is the same as adding an H^+ to the extracellular fluid. Therefore, in alkalosis, the removal of HCO_3^- raises the extracellular fluid H^+ concentration back toward normal.

In acidosis, the kidneys do not excrete HCO_3^- into the urine but reabsorb all the filtered HCO_3^- and produce new HCO_3^-, which is added back to the extracellular fluid. This reduces the extracellular fluid H^+ concentration back toward normal.

Thus, the kidneys regulate extracellular fluid H^+ concentration through three fundamental mechanisms: (1) secretion of H^+, (2) reabsorption of filtered HCO_3^-, and (3) production of new HCO_3^-. All these processes are accomplished through the same basic mechanism, as discussed in the next few sections.

Secretion of H^+ and Reabsorption of HCO_3^- by the Renal Tubules

Hydrogen ion secretion and HCO_3^- reabsorption occur in virtually all parts of the tubules except the descending and ascending thin limbs of the loop of Henle. Figure 30-4 summarizes HCO_3^- reabsorption along the tubule. Keep in mind that for each HCO_3^- reabsorbed, a H^+ must be secreted.

About 80 to 90 percent of the bicarbonate reabsorption (and H^+ secretion) occurs in the proximal tubule, so only a small amount of HCO_3^- flows into the distal tubules and collecting ducts. In the thick ascending loop of Henle, another 10 percent of the filtered HCO_3^- is reabsorbed, and the remainder of the reabsorption takes place in the distal tubule and collecting duct. As discussed previously, the mechanism by which HCO_3^- is reabsorbed also involves tubular secretion of H^+, but different tubular segments accomplish this task differently.

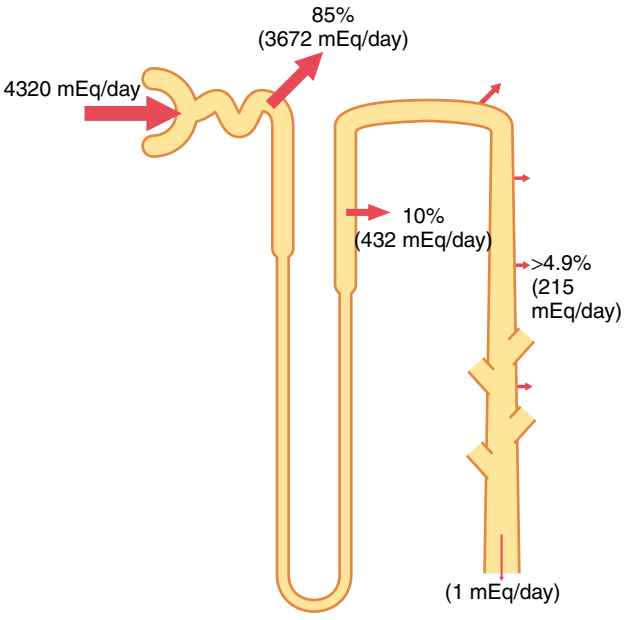


Figure 30-4 Reabsorption of bicarbonate in different segments of the renal tubule. The percentages of the filtered load of HCO_3^- absorbed by the various tubular segments are shown, as well as the number of milliequivalents reabsorbed per day under normal conditions.

H^+ is Secreted by Secondary Active Transport in the Early Tubular Segments

The epithelial cells of the proximal tubule, the thick segment of the ascending loop of Henle, and the early distal tubule all secrete H^+ into the tubular fluid by sodium-hydrogen counter-transport, as shown in Figure 30-5. This secondary active secretion of H^+ is coupled with the transport of Na^+ into the cell at the luminal membrane by the *sodium-hydrogen exchanger* protein, and the energy for H^+ secretion against a concentration gradient is derived from the sodium gradient favoring Na^+ movement into the cell. This gradient is established by the sodium-potassium adenosine triphosphatase (ATPase) pump in the basolateral membrane. About 95 percent of the bicarbonate is reabsorbed in this manner, requiring about 4000 mEq of H^+ to be secreted each day by the tubules. This mechanism, however, does not establish a very high H^+ concentration in the tubular fluid; the tubular fluid becomes very acidic only in the collecting tubules and collecting ducts.

Figure 30-5 shows how the process of H^+ secretion achieves HCO_3^- reabsorption. The secretory process begins when CO_2 either diffuses into the tubular cells or is formed by metabolism in the tubular epithelial cells. CO_2, under the influence of the enzyme *carbonic anhydrase,* combines with H_2O to form H_2CO_3, which dissociates into HCO_3^- and H^+. The H^+ is secreted from the cell into the tubular lumen by sodium-hydrogen counter-transport. That is, when Na^+ moves from the lumen of the tubule to the interior of the cell, it first combines with a carrier protein in the luminal border of the cell membrane; at the same time, an H^+ in the interior of the cells combines with the carrier protein. The Na^+ moves into the cell down a concentration gradient that has been established by the sodium-potassium ATPase pump in the basolateral membrane. The gradient for Na^+ movement into the cell then

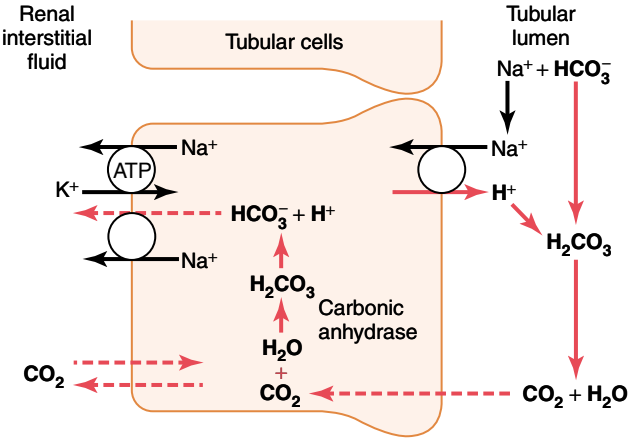


Figure 30-5 Cellular mechanisms for (1) active secretion of H^+ into the renal tubule; (2) tubular reabsorption of HCO_3^- by combination with H^+ to form carbonic acid, which dissociates to form carbon dioxide and water; and (3) sodium ion reabsorption in exchange for H^+ secreted. This pattern of H^+ secretion occurs in the proximal tubule, the thick ascending segment of the loop of Henle, and the early distal tubule.

provides the energy for moving H^+ in the opposite direction from the interior of the cell to the tubular lumen.

The HCO_3^- generated in the cell (when H^+ dissociates from H_2CO_3) then moves downhill across the basolateral membrane into the renal interstitial fluid and the peritubular capillary blood. The net result is that for every H^+ secreted into the tubular lumen, an HCO_3^- enters the blood.

Filtered HCO_3^- is Reabsorbed by Interaction with H^+ in the Tubules

Bicarbonate ions do not readily permeate the luminal membranes of the renal tubular cells; therefore, HCO_3^- that is filtered by the glomerulus cannot be directly reabsorbed. Instead, HCO_3^- is reabsorbed by a special process in which it first combines with H^+ to form H_2CO_3, which eventually becomes CO_2 and H_2O, as shown in Figure 30-5.

This reabsorption of HCO_3^- is initiated by a reaction in the tubules between HCO_3^- filtered at the glomerulus and H^+ secreted by the tubular cells. The H_2CO_3 formed then dissociates into CO_2 and H_2O. The CO_2 can move easily across the tubular membrane; therefore, it instantly diffuses into the tubular cell, where it recombines with H_2O, under the influence of carbonic anhydrase, to generate a new H_2CO_3 molecule. This H_2CO_3 in turn dissociates to form HCO_3^- and H^+; the HCO_3^- then diffuses through the basolateral membrane into the interstitial fluid and is taken up into the peritubular capillary blood. The transport of HCO_3 across the basolateral membrane is facilitated by two mechanisms: (1) Na^+-HCO_3^- co-transport in the proximal tubules and (2) Cl^--HCO_3^- exchange in the late segments of the proximal tubule, the thick ascending loop of Henle, and in the collecting tubules and ducts.

Thus, each time an H^+ is formed in the tubular epithelial cells, an HCO_3^- is also formed and released back into the blood. The net effect of these reactions is "reabsorption" of HCO_3^- from the tubules, although the HCO_3^- that actually enters the extracellular fluid is not the same as that filtered into the tubules. The reabsorption of filtered HCO_3^- does not result in net secretion of H^+ because the secreted H^+ combines with the filtered HCO_3^- and is therefore not excreted.

HCO_3^- is "Titrated" Against H^+ in the Tubules. Under normal conditions, the rate of tubular H^+ secretion is about 4400 mEq/day, and the rate of filtration by HCO_3^- is about 4320 mEq/day. Thus, the quantities of these two ions entering the tubules are almost equal, and they combine with each other to form CO_2 and H_2O. Therefore, it is said that HCO_3^- and H^+ normally "titrate" each other in the tubules.

The titration process is not quite exact because there is usually a slight excess of H^+ in the tubules to be excreted in the urine. This excess H^+ (about 80 mEq/day) rids the body of nonvolatile acids produced by metabolism. As discussed later, most of this H^+ is not excreted as free H^+ but rather in combination with other urinary buffers, especially phosphate and ammonia.

When there is an excess of HCO_3^- over H^+ in the urine, as occurs in metabolic alkalosis, the excess HCO_3^- cannot be reabsorbed; therefore, the excess HCO_3^- is left in the tubules and eventually excreted into the urine, which helps correct the metabolic alkalosis.

In acidosis, there is excess H^+ relative to HCO_3^- causing complete reabsorption of the HCO_3^-; the excess H^+ passes into the urine. The excess H^+ is buffered in the tubules by phosphate and ammonia and eventually excreted as salts. Thus, the basic mechanism by which the kidneys correct either acidosis or alkalosis is incomplete titration of H^+ against HCO_3^-, leaving one or the other to pass into the urine and be removed from the extracellular fluid.

Primary Active Secretion of H^+ in the Intercalated Cells of Late Distal and Collecting Tubules

Beginning in the late distal tubules and continuing through the remainder of the tubular system, the tubular epithelium secretes H^+ by *primary active transport.* The characteristics of this transport are different from those discussed for the proximal tubule, loop of Henle, and early distal tubule.

The mechanism for primary active H^+ secretion is shown in Figure 30-6. It occurs at the luminal membrane of the tubular cell, where H^+ is transported directly by a specific protein, a *hydrogen-transporting ATPase.* The energy required for pumping the H^+ is derived from the breakdown of ATP to adenosine diphosphate.

Primary active secretion of H^+ occurs in special types of cells called the *intercalated cells* of the late distal tubule and in the collecting tubules. Hydrogen ion secretion in these cells is accomplished in two steps: (1) the dissolved CO_2 in this cell combines with H_2O to form H_2CO_3, and (2) the H_2CO_3 then dissociates into HCO_3^-, which is reabsorbed into the blood, plus H^+, which is secreted into the tubule by means of the hydrogen-ATPase mechanism. For each H^+ secreted, an HCO_3^- is reabsorbed, similar to the process in the proximal tubules. The main difference is

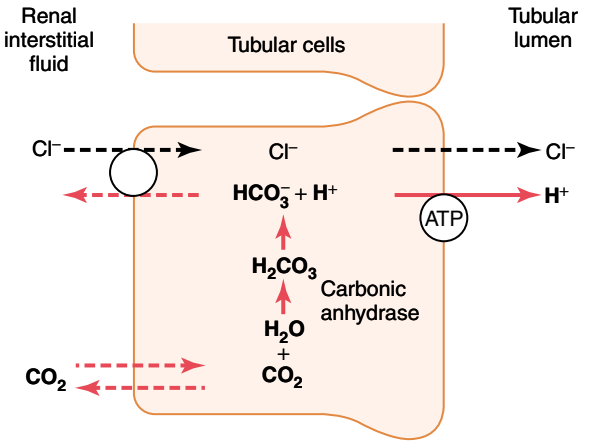


Figure 30-6 Primary active secretion of H^+ through the luminal membrane of the intercalated epithelial cells of the late distal and collecting tubules. Note that one HCO_3^- is absorbed for each H^+ secreted, and a chloride ion is passively secreted along with the H^+.

that H^+ moves across the luminal membrane by an active H^+ pump instead of by counter-transport, as occurs in the early parts of the nephron.

Although the secretion of H^+ in the late distal tubule and collecting tubules accounts for only about 5 percent of the total H^+ secreted, this mechanism is important in forming maximally acidic urine. In the proximal tubules, H^+ concentration can be increased only about threefold to fourfold and the tubular fluid pH can be reduced to only about 6.7, although large *amounts* of H^+ are secreted by this nephron segment. However, H^+ concentration can be increased as much as 900-fold in the collecting tubules. This decreases the pH of the tubular fluid to about 4.5, which is the lower limit of pH that can be achieved in normal kidneys.

Combination of Excess H^+ with Phosphate and Ammonia Buffers in the Tubule Generates "New" HCO_3^-

When H^+ is secreted in excess of the HCO_3^- filtered into the tubular fluid, only a small part of the excess H^+ can be excreted in the ionic form (H^+) in the urine. The reason for this is that the minimal urine pH is about 4.5, corresponding to an H^+ concentration of $10^{-4.5}$ mEq/L, or 0.03 mEq/L. Thus, for each liter of urine formed, a maximum of only about 0.03 mEq of free H^+ can be excreted. To excrete the 80 mEq of nonvolatile acid formed by metabolism each day, about 2667 liters of urine would have to be excreted if the H^+ remained free in solution.

The excretion of large amounts of H^+ (on occasion as much as 500 mEq/day) in the urine is accomplished primarily by combining the H^+ with buffers in the tubular fluid. The most important buffers are phosphate buffer and ammonia buffer. Other weak buffer systems, such as urate and citrate, are much less important.

When H^+ is titrated in the tubular fluid with HCO_3^-, this leads to reabsorption of one HCO_3^- for each H^+ secreted, as discussed earlier. But when there is excess H^+ in the urine, it combines with buffers other than HCO_3^-, and this leads to generation of new HCO_3^- that can also enter the blood. Thus, when there is excess H^+ in the extracellular fluid, the kidneys not only reabsorb all the filtered HCO_3^- but also generate new HCO_3^-, thereby helping to replenish the HCO_3^- lost from the extracellular fluid in acidosis. In the next two sections, we discuss the mechanisms by which phosphate and ammonia buffers contribute to the generation of new HCO_3^-.

Phosphate Buffer System Carries Excess H^+ into the Urine and Generates New HCO_3^-

The phosphate buffer system is composed of $HPO_4^=$ and $H_2PO_4^-$. Both become concentrated in the tubular fluid because water is normally reabsorbed to a greater extent than phosphate by the renal tubules. Therefore, although phosphate is not an important extracellular fluid buffer, it is much more effective as a buffer in the tubular fluid.

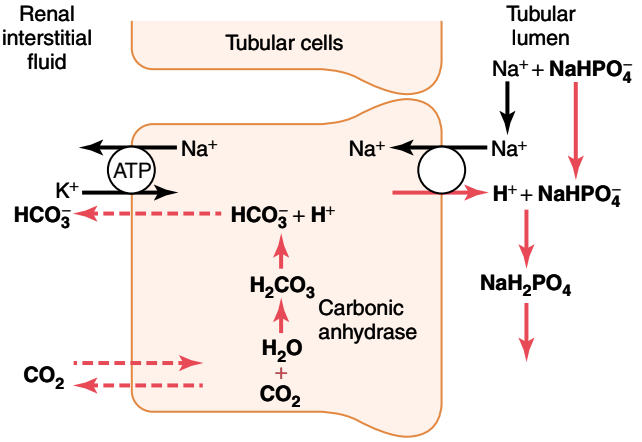


Figure 30-7 Buffering of secreted H^+ by filtered phosphate ($NaHPO_4^-$). Note that a new HCO_3^- is returned to the blood for each $NaHPO_4^-$ that reacts with a secreted H^+.

Another factor that makes phosphate important as a tubular buffer is the fact that the pK of this system is about 6.8. Under normal conditions, the urine is slightly acidic, and the urine pH is near the pK of the phosphate buffer system. Therefore, in the tubules, the phosphate buffer system normally functions near its most effective range of pH.

Figure 30-7 shows the sequence of events by which H^+ is excreted in combination with phosphate buffer and the mechanism by which new HCO_3^- is added to the blood. The process of H^+ secretion into the tubules is the same as described earlier. As long as there is excess HCO_3^- in the tubular fluid, most of the secreted H^+ combines with HCO_3^-. However, once all the HCO_3^- has been reabsorbed and is no longer available to combine with H^+, any excess H^+ can combine with $HPO_4^=$ and other tubular buffers. After the H^+ combines with $HPO_4^=$ to form $H_2PO_4^-$, it can be excreted as a sodium salt (NaH_2PO_4), carrying with it the excess H^+.

There is one important difference in this sequence of H^+ excretion from that discussed previously. In this case, the HCO_3^- that is generated in the tubular cell and enters the peritubular blood represents a net gain of HCO_3^- by the blood, rather than merely a replacement of filtered HCO_3^-. *Therefore, whenever an H^+ secreted into the tubular lumen combines with a buffer other than HCO_3^-, the net effect is addition of a new HCO_3^- to the blood.* This demonstrates one of the mechanisms by which the kidneys are able to replenish the extracellular fluid stores of HCO_3^-.

Under normal conditions, much of the filtered phosphate is reabsorbed, and only about 30 to 40 mEq/day are available for buffering H^+. Therefore, much of the buffering of excess H^+ in the tubular fluid in acidosis occurs through the ammonia buffer system.

Excretion of Excess H^+ and Generation of New HCO_3^- by the Ammonia Buffer System

A second buffer system in the tubular fluid that is even more important quantitatively than the phosphate buffer system is composed of ammonia (NH_3) and the ammonium ion (NH_4^+). Ammonium ion is synthesized

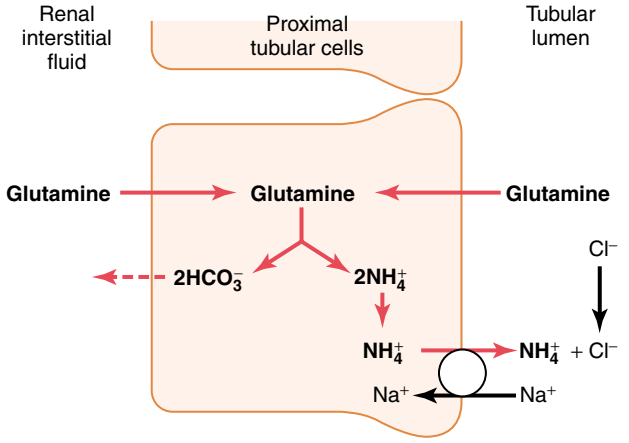


Figure 30-8 Production and secretion of ammonium ion (NH_4^+) by proximal tubular cells. Glutamine is metabolized in the cell, yielding NH_4^+ and bicarbonate. The NH_4^+ is secreted into the lumen by a sodium-NH_4^+ exchanger. For each glutamine molecule metabolized, two NH_4^+ are produced and secreted and two HCO_3^- are returned to the blood.

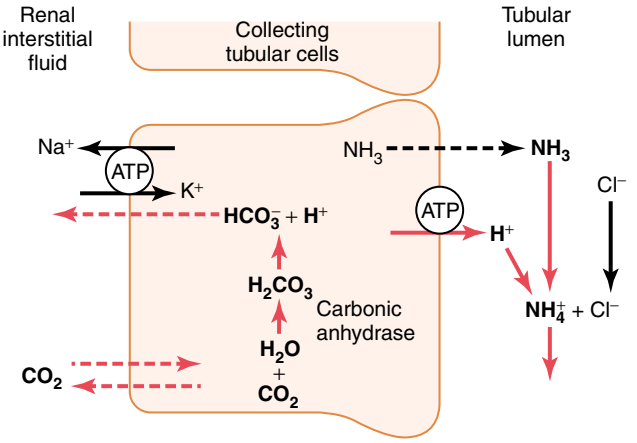


Figure 30-9 Buffering of hydrogen ion secretion by ammonia (NH_3) in the collecting tubules. Ammonia diffuses into the tubular lumen, where it reacts with secreted H^+ to form NH_4^+, which is then excreted. For each NH_4^+ excreted, a new HCO_3^- is formed in the tubular cells and returned to the blood.

from glutamine, which comes mainly from the metabolism of amino acids in the liver. The glutamine delivered to the kidneys is transported into the epithelial cells of the proximal tubules, thick ascending limb of the loop of Henle, and distal tubules (Figure 30-8). Once inside the cell, each molecule of glutamine is metabolized in a series of reactions to ultimately form two NH_4^+ and two HCO_3^-. The NH_4^+ is secreted into the tubular lumen by a countertransport mechanism in exchange for sodium, which is reabsorbed. The HCO_3^- is transported across the basolateral membrane, along with the reabsorbed Na^+, into the interstitial fluid and is taken up by the peritubular capillaries. Thus, for each molecule of glutamine metabolized in the proximal tubules, two NH_4^+ are secreted into the urine and two HCO_3^- are reabsorbed into the blood. *The HCO_3^- generated by this process constitutes new bicarbonate.*

In the collecting tubules, the addition of NH_4^+ to the tubular fluids occurs through a different mechanism (Figure 30-9). Here, H^+ is secreted by the tubular membrane into the lumen, where it combines with NH_3 to form NH_4^+, which is then excreted. The collecting ducts are permeable to NH_3, which can easily diffuse into the tubular lumen. However, the luminal membrane of this part of the tubules is much less permeable to NH_4^+; therefore, once the H^+ has reacted with NH_3 to form NH_4^+, the NH_4^+ is trapped in the tubular lumen and eliminated in the urine. *For each NH_4^+ excreted, a new HCO_3^- is generated and added to the blood.*

Chronic Acidosis Increases NH_4^+ Excretion. One of the most important features of the renal ammonium-ammonia buffer system is that it is subject to physiologic control. An increase in extracellular fluid H^+ concentration stimulates renal glutamine metabolism and, therefore, increases the formation of NH_4^+ and new HCO_3^- to be used in H^+ buffering; a decrease in H^+ concentration has the opposite effect.

Under *normal conditions,* the amount of H^+ eliminated by the ammonia buffer system accounts for about 50 percent of the acid excreted and 50 percent of the new HCO_3^- generated by the kidneys. However, with *chronic acidosis,* the rate of NH_4^+ excretion can increase to as much as 500 mEq/day. *Therefore, with chronic acidosis, the dominant mechanism by which acid is eliminated is excretion of NH_4^+.* This also provides the most important mechanism for generating new bicarbonate during chronic acidosis.

Quantifying Renal Acid-Base Excretion

Based on the principles discussed earlier, we can quantify the kidneys' net excretion of acid or net addition or elimination of HCO_3^- from the blood as follows.

Bicarbonate excretion is calculated as the urine flow rate multiplied by urinary HCO_3^- concentration. This number indicates how rapidly the kidneys are removing HCO_3^- from the blood (which is the same as adding an H^+ to the blood). In alkalosis, the loss of HCO_3^- helps return the plasma pH toward normal.

The amount of new HCO_3^- contributed to the blood at any given time is equal to the amount of H^+ secreted that ends up in the tubular lumen with nonbicarbonate urinary buffers. As discussed previously, the primary sources of nonbicarbonate urinary buffers are NH_4^+ and phosphate. Therefore, the amount of HCO_3^- added to the blood (and H^+ excreted by NH_4^+) is calculated by measuring NH_4^+ excretion (urine flow rate multiplied by urinary NH_4^+ concentration).

The rest of the nonbicarbonate, non-NH_4^+ buffer excreted in the urine is measured by determining a value known as *titratable acid.* The amount of titratable acid in the urine is measured by titrating the urine with a strong base, such as NaOH, to a pH of 7.4, the pH of normal plasma, and the pH of the glomerular filtrate. This titration reverses the events that occurred in the tubular

lumen when the tubular fluid was titrated by secreted H^+. Therefore, the number of milliequivalents of NaOH required to return the urinary pH to 7.4 equals the number of milliequivalents of H^+ added to the tubular fluid that combined with phosphate and other organic buffers. The titratable acid measurement does not include H^+ in association with NH_4^+ because the pK of the ammonia-ammonium reaction is 9.2, and titration with NaOH to a pH of 7.4 does not remove the H^+ from NH_4^+.

Thus, the *net acid excretion* by the kidneys can be assessed as

Net acid excretion = NH_4^+ excretion + Urinary titratable acid − HCO_3^- excretion

The reason we subtract HCO_3^- excretion is that the loss of HCO_3^- is the same as the addition of H^+ to the blood. To maintain acid-base balance, the net acid excretion must equal the nonvolatile acid production in the body. In acidosis, the net acid excretion increases markedly, especially because of increased NH_4^+ excretion, thereby removing acid from the blood. The net acid excretion also equals the rate of net HCO_3^- addition to the blood. *Therefore, in acidosis, there is a net addition of HCO_3^- back to the blood as more NH_4^+ and urinary titratable acid are excreted.*

In alkalosis, titratable acid and NH_4^+ excretion drop to 0, whereas HCO_3^- excretion increases. *Therefore, in alkalosis, there is a negative net acid secretion.* This means that there is a net loss of HCO_3^- from the blood (which is the same as adding H^+ to the blood) and that no new HCO_3^- is generated by the kidneys.

Regulation of Renal Tubular H^+ Secretion

As discussed earlier, H^+ secretion by the tubular epithelium is necessary for both HCO_3^- reabsorption and generation of new HCO_3^- associated with titratable acid formation. Therefore, the rate of H^+ secretion must be carefully regulated if the kidneys are to effectively perform their functions in acid-base homeostasis. Under normal conditions, the kidney tubules must secrete at least enough H^+ to reabsorb almost all the HCO_3^- that is filtered, and there must be enough H^+ left over to be excreted as titratable acid or NH_4^+ to rid the body of the nonvolatile acids produced each day from metabolism.

In alkalosis, tubular secretion of H^+ is reduced to a level that is too low to achieve complete HCO_3^- reabsorption, enabling the kidneys to increase HCO_3^- excretion. In this condition, titratable acid and ammonia are not excreted because there is no excess H^+ available to combine with nonbicarbonate buffers; therefore, there is no new HCO_3^- added to the urine in alkalosis. During acidosis, the tubular H^+ secretion is increased sufficiently to reabsorb all the filtered HCO_3^- with enough H^+ left over to excrete large amounts of NH_4^+ and titratable acid, thereby contributing large amounts of new HCO_3^- to the total body extracellular fluid. *The most important stimuli for increasing H^+ secretion by the tubules in acidosis are (1) an increase in P_{CO_2} of the extracellular fluid in respiratory acidosis and (2) an increase in H^+ concentration of the extracellular fluid (decreased pH) respiratory or metabolic acidosis.*

The tubular cells respond directly to an increase in P_{CO_2} of the blood, as occurs in respiratory acidosis, with an increase in the rate of H^+ secretion as follows: The increased P_{CO_2} raises the P_{CO_2} of the tubular cells, causing increased formation of H^+ in the tubular cells, which in turn stimulates the secretion of H^+. The second factor that stimulates H^+ secretion is an increase in extracellular fluid H^+ concentration (decreased pH).

A special factor that can increase H^+ secretion under some pathophysiologic conditions is excessive aldosterone secretion. Aldosterone stimulates the secretion of H^+ by the intercalated cells of the collecting duct. Therefore, excessive secretion of aldosterone, as occurs in Conn's syndrome, can increase secretion of H^+ into the tubular fluid and, consequently, increase the amount of HCO_3^- added back to the blood. This usually causes alkalosis in patients with excessive aldosterone secretion.

The tubular cells usually respond to a decrease in H^+ concentration (alkalosis) by reducing H^+ secretion. The decreased H^+ secretion results from decreased extracellular P_{CO_2}, as occurs in respiratory alkalosis, or from a decrease in H^+ concentration per se, as occurs in both respiratory and metabolic alkalosis.

Table 30-2 summarizes the major factors that influence H^+ secretion and HCO_3^- reabsorption. Some of these are not directly related to the regulation of acid-base balance. For example, H^+ secretion is coupled to Na^+ reabsorption by the Na^+-H^+ exchanger in the proximal tubule and thick ascending loop of Henle. Therefore, factors that stimulate Na^+ reabsorption, such as decreased extracellular fluid volume, may also secondarily increase H^+ secretion.

Extracellular fluid volume depletion stimulates sodium reabsorption by the renal tubules and increases H^+ secretion and HCO_3^- reabsorption through multiple mechanisms, including (1) increased angiotensin II levels, which directly stimulate the activity of the Na^+-H^+ exchanger in the renal tubules, and (2) increased aldosterone levels, which stimulate H^+ secretion by the intercalated cells of the cortical collecting tubules. Therefore, extracellular fluid volume depletion tends to cause alkalosis due to excess H^+ secretion and HCO_3^- reabsorption.

Table 30-2 Factors That Increase or Decrease H^+ Secretion and HCO_3^- Reabsorption by the Renal Tubules

Increase H^+ Secretion and HCO_3^- Reabsorption	Decrease H^+ Secretion and HCO_3^- Reabsorption
↑ P_{CO_2}	↓ P_{CO_2}
↑ H^+, ↓ HCO_3^-	↓ H^+, ↑ HCO_3^-
↓ Extracellular fluid volume	↑ Extracellular fluid volume
↑ Angiotensin II	↓ Angiotensin II
↑ Aldosterone	↓ Aldosterone
Hypokalemia	Hyperkalemia

Changes in plasma potassium concentration can also influence H^+ secretion, with hypokalemia stimulating and hyperkalemia inhibiting H^+ secretion in the proximal tubule. A decreased plasma potassium concentration tends to increase the H^+ concentration in the renal tubular cells. This, in turn, stimulates H^+ secretion and HCO_3^- reabsorption and leads to alkalosis. Hyperkalemia decreases H^+ secretion and HCO_3^- reabsorption and tends to cause acidosis.

Renal Correction of Acidosis—Increased Excretion of H^+ and Addition of HCO_3^- to the Extracellular Fluid

Now that we have described the mechanisms by which the kidneys secrete H^+ and reabsorb HCO_3^-, we can explain how the kidneys readjust the pH of the extracellular fluid when it becomes abnormal.

Referring to equation 8, the Henderson-Hasselbalch equation, we can see that acidosis occurs when the ratio of HCO_3^- to CO_2 in the extracellular fluid decreases, thereby decreasing pH. If this ratio decreases because of a fall in HCO_3^-, the acidosis is referred to as *metabolic acidosis.* If the pH falls because of an increase in P_{CO_2}, the acidosis is referred to as *respiratory acidosis.*

Acidosis Decreases the Ratio of HCO_3^-/H^+ in Renal Tubular Fluid

Both respiratory and metabolic acidosis cause a decrease in the ratio of HCO_3^- to H^+ in the renal tubular fluid. As a result, there is excess H^+ in the renal tubules, causing complete reabsorption of HCO_3^- and still leaving additional H^+ available to combine with the urinary buffers NH_4^+ and $HPO_4^=$. Thus, in acidosis, the kidneys reabsorb all the filtered HCO_3^- and contribute new HCO_3^- through the formation of NH_4^+ and titratable acid.

In metabolic acidosis, an excess of H^+ over HCO_3^- occurs in the tubular fluid primarily because of decreased filtration of HCO_3^-. This decreased filtration of HCO_3^- is caused mainly by a decrease in the extracellular fluid concentration of HCO_3^-.

In respiratory acidosis, the excess H^+ in the tubular fluid is due mainly to the rise in extracellular fluid P_{CO_2}, which stimulates H^+ secretion.

As discussed previously, with chronic acidosis, regardless of whether it is respiratory or metabolic, there is an increase in the production of NH_4^+, which further contributes to the excretion of H^+ and the addition of new HCO_3^- to the extracellular fluid. With severe chronic acidosis, as much as 500 mEq/day of H^+ can be excreted in the urine, mainly in the form of NH_4^+; this, in turn, contributes up to 500 mEq/day of new HCO_3^- that is added to the blood.

Thus, with chronic acidosis, the increased secretion of H^+ by the tubules helps eliminate excess H^+ from the body and increases the quantity of HCO_3^- in the extracellular fluid. This increases the HCO_3^- part of the bicarbonate buffer system, which, in accordance with the Henderson-Hasselbalch equation, helps raise the extracellular pH and corrects the acidosis. If the acidosis is metabolically mediated, additional compensation by the lungs causes a reduction in P_{CO_2}, also helping to correct the acidosis.

Table 30-3 summarizes the characteristics associated with respiratory and metabolic acidosis, as well as respiratory and metabolic alkalosis, which are discussed in the next section. Note that in *respiratory acidosis,* there is a reduction in pH, an increase in extracellular fluid H^+ concentration, and an increase in P_{CO_2}, which is the initial cause of the acidosis. *The compensatory response is an increase in plasma HCO_3^-, caused by the addition of new HCO_3^- to the extracellular fluid by the kidneys.* The rise in HCO_3^- helps offset the increase in P_{CO_2}, thereby returning the plasma pH toward normal.

In *metabolic acidosis,* there is also a decrease in pH and a rise in extracellular fluid H^+ concentration. However, in this case, the primary abnormality is a decrease in plasma HCO_3^-. *The primary compensations include increased ventilation rate, which reduces P_{CO_2}, and renal compensation, which, by adding new HCO_3^- to the extracellular fluid, helps minimize the initial fall in extracellular HCO_3^- concentration.*

Renal Correction of Alkalosis—Decreased Tubular Secretion of H^+ and Increased Excretion of HCO_3^-

The compensatory responses to alkalosis are basically opposite to those that occur in acidosis. In alkalosis, the ratio of HCO_3^- to CO_2 in the extracellular fluid increases,

Table 30-3 Characteristics of Primary Acid-Base Disturbances

	pH	H^+	P_{CO_2}	HCO_3^-
Normal	7.4	40 mEq/L	40 mm Hg	24 mEq/L
Respiratory acidosis	↓	↑	↑↑	↑
Respiratory alkalosis	↑	↓	↓↓	↓
Metabolic acidosis	↓	↑	↓	↓↓
Metabolic alkalosis	↑	↓	↑	↑↑

The primary event is indicated by the double arrows (↑↑ or ↓↓). Note that respiratory acid-base disorders are initiated by an increase or decrease in P_{CO_2}, whereas metabolic disorders are initiated by an increase or decrease in HCO_3^-.

causing a rise in pH (a decrease in H^+ concentration), as is evident from the Henderson-Hasselbalch equation.

Alkalosis Increases the Ratio of HCO_3^-/H^+ in Renal Tubular Fluid

Regardless of whether the alkalosis is caused by metabolic or respiratory abnormalities, there is still an increase in the ratio of HCO_3^- to H^+ in the renal tubular fluid. The net effect of this is an excess of HCO_3^- that cannot be reabsorbed from the tubules and is, therefore, excreted in the urine. Thus, in alkalosis, HCO_3^- is removed from the extracellular fluid by renal excretion, which has the same effect as adding an H^+ to the extracellular fluid. This helps return the H^+ concentration and pH back toward normal.

Table 30-3 shows the overall characteristics of respiratory and metabolic alkalosis. In *respiratory alkalosis,* there is an increase in extracellular fluid pH and a decrease in H^+ concentration. *The cause of the alkalosis is a decrease in plasma P_{CO_2}, caused by hyperventilation.* The reduction in P_{CO_2} then leads to a decrease in the rate of H^+ secretion by the renal tubules. The decrease in H^+ secretion reduces the amount of H^+ in the renal tubular fluid. Consequently, there is not enough H^+ to react with all the HCO_3^- that is filtered. Therefore, the HCO_3^- that cannot react with H^+ is not reabsorbed and is excreted in the urine. This results in a decrease in plasma HCO_3^- concentration and correction of the alkalosis. *Therefore, the compensatory response to a primary reduction in P_{CO_2} in respiratory alkalosis is a reduction in plasma HCO_3^- concentration, caused by increased renal excretion of HCO_3^-.*

In *metabolic alkalosis,* there is also an increase in plasma pH and a decrease in H^+ concentration. *The cause of metabolic alkalosis, however, is a rise in the extracellular fluid HCO_3^- concentration.* This is partly compensated for by a reduction in the respiration rate, which increases P_{CO_2} and helps return the extracellular fluid pH toward normal. In addition, the increase in HCO_3^- concentration in the extracellular fluid leads to an increase in the filtered load of HCO_3^-, which in turn causes an excess of HCO_3^- over H^+ secreted in the renal tubular fluid. The excess HCO_3^- in the tubular fluid fails to be reabsorbed because there is no H^+ to react with, and it is excreted in the urine. *In metabolic alkalosis, the primary compensations are decreased ventilation, which raises P_{CO_2}, and increased renal HCO_3^- excretion, which helps compensate for the initial rise in extracellular fluid HCO_3^- concentration.*

Clinical Causes of Acid-Base Disorders

Respiratory Acidosis Results from Decreased Ventilation and Increased P_{CO_2}

From the previous discussion, it is obvious that any factor that decreases the rate of pulmonary ventilation also increases the P_{CO_2} of extracellular fluid. This causes an increase in H_2CO_3 and H^+ concentration, thus resulting in acidosis. Because the acidosis is caused by an abnormality in respiration, it is called *respiratory acidosis.*

Respiratory acidosis can occur from pathological conditions that damage the respiratory centers or that decrease the ability of the lungs to eliminate CO_2. For example, damage to the respiratory center in the medulla oblongata can lead to respiratory acidosis. Also, obstruction of the passageways of the respiratory tract, pneumonia, emphysema, or decreased pulmonary membrane surface area, as well as any factor that interferes with the exchange of gases between the blood and the alveolar air, can cause respiratory acidosis.

In respiratory acidosis, the compensatory responses available are (1) the buffers of the body fluids and (2) the kidneys, which require several days to compensate for the disorder.

Respiratory Alkalosis Results from Increased Ventilation and Decreased P_{CO_2}

Respiratory alkalosis is caused by excessive ventilation by the lungs. Rarely does this occur because of physical pathological conditions. However, a psychoneurosis can occasionally increase breathing to the extent that a person becomes alkalotic.

A physiologic type of respiratory alkalosis occurs when a person ascends to high altitude. The low oxygen content of the air stimulates respiration, which causes loss of CO_2 and development of mild respiratory alkalosis. Again, the major means for compensation are the chemical buffers of the body fluids and the ability of the kidneys to increase HCO_3^- excretion.

Metabolic Acidosis Results from Decreased Extracellular Fluid HCO_3^- Concentration

The term *metabolic acidosis* refers to all other types of acidosis besides those caused by excess CO_2 in the body fluids. Metabolic acidosis can result from several general causes: (1) failure of the kidneys to excrete metabolic acids normally formed in the body, (2) formation of excess quantities of metabolic acids in the body, (3) addition of metabolic acids to the body by ingestion or infusion of acids, and (4) loss of base from the body fluids, which has the same effect as adding an acid to the body fluids. Some specific conditions that cause metabolic acidosis are the following.

Renal Tubular Acidosis. This type of acidosis results from a defect in renal secretion of H^+ or in reabsorption of HCO_3^-, or both. These disorders are generally of two types: (1) impairment of renal tubular HCO_3^- reabsorption, causing loss of HCO_3^- in the urine, or (2) inability of the renal tubular H^+ secretory mechanism to establish normal acidic urine, causing the excretion of alkaline urine. In these cases, inadequate amounts of titratable acid and NH_4^+ are excreted, so there is net accumulation of acid in the body fluids. Some causes of renal tubular acidosis include chronic renal failure, insufficient aldosterone secretion (Addison's disease), and several hereditary and acquired disorders that impair tubular function, such as Fanconi's syndrome (see Chapter 31).

Diarrhea. Severe diarrhea is probably the most frequent cause of metabolic acidosis. *The cause of this acidosis is the loss of large amounts of sodium bicarbonate into the feces.* The gastrointestinal secretions normally contain large amounts of bicarbonate, and diarrhea results in the loss of HCO_3^- from the body, which has the same effect as losing large amounts of bicarbonate in the urine. This form of metabolic acidosis can be particularly serious and can cause death, especially in young children.

Vomiting of Intestinal Contents. Vomiting of gastric contents alone would cause loss of acid and a tendency toward alkalosis because the stomach secretions are highly acidic. However, vomiting large amounts from deeper in the gastrointestinal tract, which sometimes occurs, causes loss of bicarbonate and results in metabolic acidosis in the same way that diarrhea causes acidosis.

Diabetes Mellitus. Diabetes mellitus is caused by lack of insulin secretion by the pancreas (type I diabetes) or by insufficient insulin secretion to compensate for decreased sensitivity to the effects of insulin (type II diabetes). In the absence of sufficient insulin, the normal use of glucose for metabolism is prevented. Instead, some of the fats are split into acetoacetic acid, and this is metabolized by the tissues for energy in place of glucose. With severe diabetes mellitus, blood acetoacetic acid levels can rise very high, causing severe metabolic acidosis. In an attempt to compensate for this acidosis, large amounts of acid are excreted in the urine, sometimes as much as 500 mmol/day.

Ingestion of Acids. Rarely are large amounts of acids ingested in normal foods. However, severe metabolic acidosis occasionally results from the ingestion of certain acidic poisons. Some of these include acetylsalicylics (aspirin) and methyl alcohol (which forms formic acid when it is metabolized).

Chronic Renal Failure. When kidney function declines markedly, there is a buildup of the anions of weak acids in the body fluids that are not being excreted by the kidneys. In addition, the decreased glomerular filtration rate reduces the excretion of phosphates and NH_4^+, which reduces the amount of HCO_3^- added back to the body fluids. Thus, chronic renal failure can be associated with severe metabolic acidosis.

Metabolic Alkalosis Results from Increased Extracellular Fluid HCO_3^- Concentration

When there is excess retention of HCO_3^- or loss of H^+ from the body, this causes metabolic alkalosis. Metabolic alkalosis is not nearly as common as metabolic acidosis, but some of the causes of metabolic alkalosis are as follows.

Administration of Diuretics (Except the Carbonic Anhydrase Inhibitors). All diuretics cause increased flow of fluid along the tubules, usually increasing flow in the distal and collecting tubules. This leads to increased reabsorption of Na^+ from these parts of the nephrons. Because the sodium reabsorption here is coupled with H^+ secretion, the enhanced sodium reabsorption also leads to an increase in H^+ secretion and an increase in bicarbonate reabsorption. These changes lead to the development of alkalosis, characterized by increased extracellular fluid bicarbonate concentration.

Excess Aldosterone. When large amounts of aldosterone are secreted by the adrenal glands, a mild metabolic alkalosis develops. As discussed previously, aldosterone promotes extensive reabsorption of Na^+ from the distal and collecting tubules and at the same time stimulates the secretion of H^+ by the intercalated cells of the collecting tubules. This increased secretion of H^+ leads to its increased excretion by the kidneys and, therefore, metabolic alkalosis.

Vomiting of Gastric Contents. Vomiting of the gastric contents alone, without vomiting of the lower gastrointestinal contents, causes loss of the HCl secreted by the stomach mucosa. The net result is a loss of acid from the extracellular fluid and development of metabolic alkalosis. This type of alkalosis occurs especially in neonates who have pyloric obstruction caused by hypertrophied pyloric sphincter muscles.

Ingestion of Alkaline Drugs. A common cause of metabolic alkalosis is ingestion of alkaline drugs, such as sodium bicarbonate, for the treatment of gastritis or peptic ulcer.

Treatment of Acidosis or Alkalosis

The best treatment for acidosis or alkalosis is to correct the condition that caused the abnormality. This is often difficult, especially in chronic diseases that cause impaired lung function or kidney failure. In these circumstances, various agents can be used to neutralize the excess acid or base in the extracellular fluid.

To neutralize excess acid, large amounts of *sodium bicarbonate* can be ingested by mouth. The sodium bicarbonate is absorbed from the gastrointestinal tract into the blood and increases the HCO_3^- portion of the bicarbonate buffer system, thereby increasing pH toward normal. Sodium bicarbonate can also be infused intravenously, but because of the potentially dangerous physiologic effects of such treatment, other substances are often used instead, such as *sodium lactate* and *sodium gluconate.* The lactate and gluconate portions of the molecules are metabolized in the body, leaving the sodium in the extracellular fluid in the form of sodium bicarbonate and thereby increasing the pH of the fluid toward normal.

For the treatment of alkalosis, *ammonium chloride* can be administered by mouth. When the ammonium chloride is absorbed into the blood, the ammonia portion is converted by the liver into urea. This reaction liberates HCl, which immediately reacts with the buffers of the body fluids to shift the H^+ concentration in the acidic direction. Ammonium chloride occasionally is infused intravenously, but NH_4^+ is highly toxic and this procedure can be dangerous. Another substance used occasionally is *lysine monohydrochloride.*

Clinical Measurements and Analysis of Acid-Base Disorders

Appropriate therapy of acid-base disorders requires proper diagnosis. The simple acid-base disorders described previously can be diagnosed by analyzing three measurements from an arterial blood sample: pH, plasma HCO_3^- concentration, and P_{CO_2}.

The diagnosis of simple acid-base disorders involves several steps, as shown in Figure 30-10. By examining the pH, one can determine whether the disorder is acidosis or alkalosis. A pH less than 7.4 indicates acidosis, whereas a pH greater than 7.4 indicates alkalosis.

The second step is to examine the plasma P_{CO_2} and HCO_3^- concentration. The normal value for P_{CO_2} is about 40 mm Hg, and for HCO_3^-, it is 24 mEq/L. If the disorder has been characterized as acidosis and the plasma P_{CO_2} is increased, there must be a respiratory component to the acidosis. After renal compensation, the plasma HCO_3^- concentration in respiratory acidosis would tend to increase above normal. *Therefore, the expected values for a simple respiratory acidosis would be reduced plasma pH, increased* P_{CO_2},

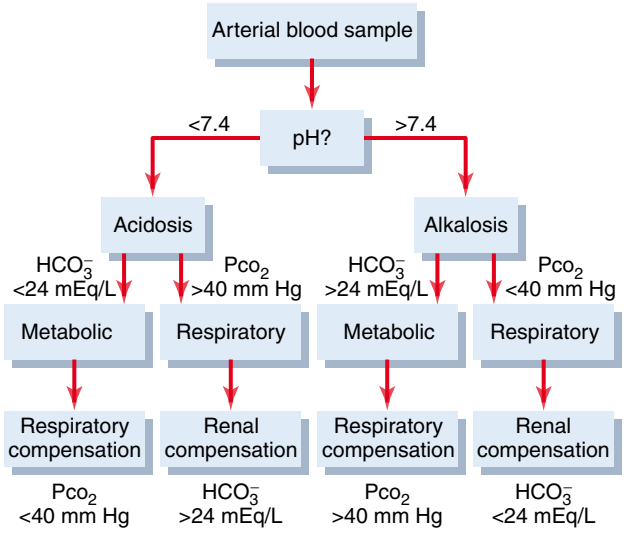


Figure 30-10 Analysis of simple acid-base disorders. If the compensatory responses are markedly different from those shown at the bottom of the figure, one should suspect a mixed acid-base disorder.

and increased plasma HCO_3^- concentration after partial renal compensation.

For metabolic acidosis, there would also be a decrease in plasma pH. However, with metabolic acidosis, the primary abnormality is a decrease in plasma HCO_3^- concentration. Therefore, if a low pH is associated with a low HCO_3^- concentration, there must be a metabolic component to the acidosis. In simple metabolic acidosis, the P_{CO_2} is reduced because of partial respiratory compensation, in contrast to respiratory acidosis, in which P_{CO_2} is increased. *Therefore, in simple metabolic acidosis, one would expect to find a low pH, a low plasma HCO_3^- concentration, and a reduction in P_{CO_2} after partial respiratory compensation.*

The procedures for categorizing the types of alkalosis involve the same basic steps. First, alkalosis implies that there is an increase in plasma pH. If the increase in pH is associated with decreased P_{CO_2}, there must be a respiratory component to the alkalosis. If the rise in pH is associated with increased HCO_3^-, there must be a metabolic component to the alkalosis. *Therefore, in simple respiratory alkalosis, one would expect to find increased pH, decreased P_{CO_2}, and decreased HCO_3^- concentration in the plasma. In simple metabolic alkalosis, one would expect to find increased pH, increased plasma HCO_3^-, and increased P_{CO_2}.*

Complex Acid-Base Disorders and Use of the Acid-Base Nomogram for Diagnosis

In some instances, acid-base disorders are not accompanied by appropriate compensatory responses. When this occurs, the abnormality is referred to as a *mixed acid-base disorder.* This means that there are two or more underlying causes for the acid-base disturbance. For example, a patient with low pH would be categorized as acidotic. If the disorder was metabolically mediated, this would also be accompanied by a low plasma HCO_3^- concentration and, after appropriate respiratory compensation, a low P_{CO_2}. However, if the low plasma pH and low HCO_3^- concentration are associated with elevated P_{CO_2}, one would suspect a respiratory component to the acidosis, as well as a metabolic component. Therefore, this disorder would be categorized as a mixed acidosis. This could occur, for example, in a patient with acute HCO_3^- loss from the gastrointestinal tract because of diarrhea (metabolic acidosis) who also has emphysema (respiratory acidosis).

A convenient way to diagnose acid-base disorders is to use an acid-base nomogram, as shown in Figure 30-11. This

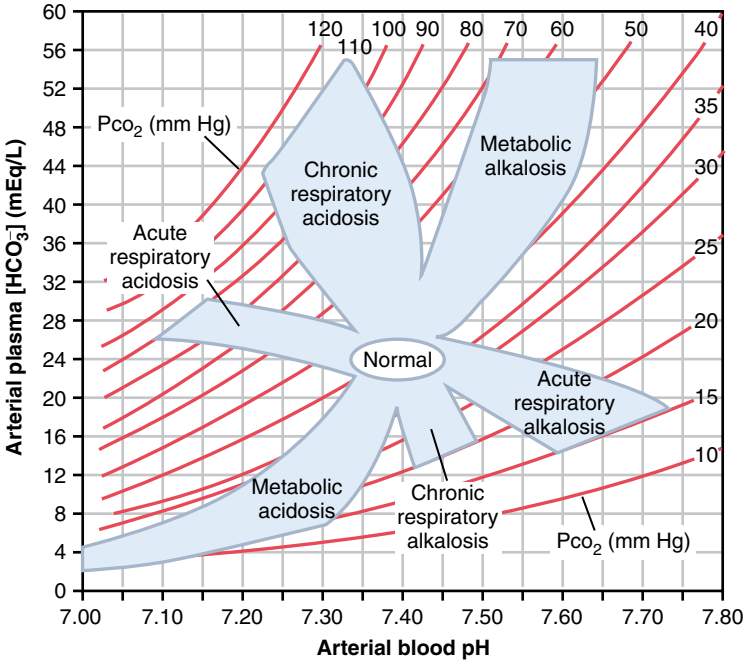


Figure 30-11 Acid-base nomogram showing arterial blood pH, arterial plasma HCO_3^-, and P_{CO_2} values. The central open circle shows the approximate limits for acid-base status in normal people. The shaded areas in the nomogram show the approximate limits for the normal compensations caused by simple metabolic and respiratory disorders. For values lying outside the shaded areas, one should suspect a mixed acid-base disorder. (Adapted from Cogan MG, Rector FC Jr: Acid-Base Disorders in the Kidney, 3rd ed. Philadelphia: WB Saunders, 1986.)

diagram can be used to determine the type of acidosis or alkalosis, as well as its severity. In this acid-base diagram, pH, HCO_3^- concentration, and P_{CO_2} values intersect according to the Henderson-Hasselbalch equation. The central open circle shows normal values and the deviations that can still be considered within the normal range. The shaded areas of the diagram show the 95 percent confidence limits for the normal compensations to simple metabolic and respiratory disorders.

When using this diagram, one must assume that sufficient time has elapsed for a full compensatory response, which is 6 to 12 hours for the ventilatory compensations in primary metabolic disorders and 3 to 5 days for the metabolic compensations in primary respiratory disorders. If a value is within the shaded area, this suggests that there is a simple acid-base disturbance. Conversely, if the values for pH, bicarbonate, or P_{CO_2} lie outside the shaded area, this suggests that there may be a mixed acid-base disorder.

It is important to recognize that an acid-base value within the shaded area does not *always* mean that there is a simple acid-base disorder. With this reservation in mind, the acid-base diagrams can be used as a quick means of determining the specific type and severity of an acid-base disorder.

For example, assume that the arterial plasma from a patient yields the following values: pH 7.30, plasma HCO_3^- concentration 12.0 mEq/L, and plasma P_{CO_2} 25 mm Hg. With these values, one can look at the diagram and find that this represents a simple metabolic acidosis, with appropriate respiratory compensation that reduces the P_{CO_2} from its normal value of 40 mm Hg to 25 mm Hg.

A second example would be a patient with the following values: pH 7.15, plasma HCO_3^- concentration 7 mEq/L, and plasma P_{CO_2} 50 mm Hg. In this example, the patient is acidotic, and there appears to be a metabolic component because the plasma HCO_3^- concentration is lower than the normal value of 24 mEq/L. However, the respiratory compensation that would normally reduce P_{CO_2} is absent and P_{CO_2} is slightly increased above the normal value of 40 mm Hg. This is consistent with a mixed acid-base disturbance consisting of metabolic acidosis, as well as a respiratory component.

The acid-base diagram serves as a quick way to assess the type and severity of disorders that may be contributing to abnormal pH, P_{CO_2}, and plasma bicarbonate concentrations. In a clinical setting, the patient's history and other physical findings also provide important clues concerning causes and treatment of the acid-base disorders.

Use of Anion Gap to Diagnose Acid-Base Disorders

The concentrations of anions and cations in plasma must be equal to maintain electrical neutrality. Therefore, there is no real "anion gap" in the plasma. However, only certain cations and anions are routinely measured in the clinical laboratory. The cation normally measured is Na^+, and the anions are usually Cl^- and HCO_3^-. The "anion gap" (which is only a diagnostic concept) is the difference between unmeasured anions and unmeasured cations and is estimated as

$$\text{Plasma anion gap} = [Na^+] - [HCO_3^-] - [Cl^-]$$
$$= 144 - 24 - 108 = 12 \text{ mEq/L}$$

The anion gap will increase if unmeasured anions rise or if unmeasured cations fall. The most important unmeasured cations include calcium, magnesium, and potassium, and the major unmeasured anions are albumin, phosphate, sulfate, and other organic anions. Usually the unmeasured anions exceed the unmeasured cations, and the anion gap ranges between 8 and 16 mEq/L.

The plasma anion gap is used mainly in diagnosing different causes of metabolic acidosis. In metabolic acidosis, the plasma HCO_3^- is reduced. If the plasma sodium concentration is unchanged, the concentration of anions (either Cl^- or an unmeasured anion) must increase to maintain electroneutrality. If plasma Cl^- increases in proportion to the fall in plasma HCO_3^-, the anion gap will remain normal. This is often referred to as *hyperchloremic metabolic acidosis.*

If the decrease in plasma HCO_3^- is not accompanied by increased Cl^-, there must be increased levels of unmeasured anions and therefore an increase in the calculated anion gap. Metabolic acidosis caused by excess nonvolatile acids (besides HCl), such as lactic acid or ketoacids, is associated with an increased plasma anion gap because the fall in HCO_3^- is not matched by an equal increase in Cl^-. Some examples of metabolic acidosis associated with a normal or increased anion gap are shown in Table 30-4. By calculating the anion gap, one can narrow some of the potential causes of metabolic acidosis.

Table 30-4 Metabolic Acidosis Associated with Normal or Increased Plasma Anion Gap

Increased Anion Gap (Normochloremia)	Normal Anion Gap (Hyperchloremia)
Diabetes mellitus (ketoacidosis)	Diarrhea
Lactic acidosis	Renal tubular acidosis
Chronic renal failure	Carbonic anhydrase inhibitors
Aspirin (acetylsalicylic acid) poisoning	Addison's disease
Methanol poisoning	
Ethylene glycol poisoning	
Starvation	

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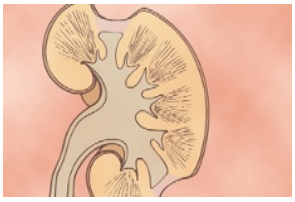
CHAPTER 31

Diuretics, Kidney Diseases



Diuretics and Their Mechanisms of Action

A diuretic is a substance that increases the rate of urine volume output, as the name implies. Most diuretics also increase urinary excretion of solutes, especially sodium and chloride. In fact, most diuretics that are used clinically act by decreasing the rate of sodium reabsorption from the tubules, which causes natriuresis (increased sodium output), which in turn causes diuresis (increased water output). That is, in most cases, increased water output occurs secondary to inhibition of tubular sodium reabsorption because sodium remaining in the tubules acts osmotically to decrease water reabsorption. Because the renal tubular reabsorption of many solutes, such as potassium, chloride, magnesium, and calcium, is also influenced secondarily by sodium reabsorption, many diuretics raise renal output of these solutes as well.

The most common clinical use of diuretics is to reduce extracellular fluid volume, especially in diseases associated with edema and hypertension. As discussed in Chapter 25, loss of sodium from the body mainly decreases extracellular fluid volume; therefore, diuretics are most often administered in clinical conditions in which extracellular fluid volume is expanded.

Some diuretics can increase urine output more than 20-fold within a few minutes after they are administered. However, the effect of most diuretics on renal output of salt and water subsides within a few days (Figure 31-1). This is due to activation of other compensatory mechanisms initiated by decreased extracellular fluid volume. For example, a decrease in extracellular fluid volume may reduce arterial pressure and glomerular filtration rate (GFR) and increase renin secretion and angiotensin II formation; all these responses, together, eventually override the chronic effects of the diuretic on urine output. Thus, in the steady state, urine output becomes equal to intake, but only after reductions in arterial pressure and extracellular fluid volume have occurred, relieving the hypertension or edema that prompted the use of diuretics in the first place.

The many diuretics available for clinical use have different mechanisms of action and, therefore, inhibit tubular reabsorption at different sites along the renal nephron. The general classes of diuretics and their mechanisms of action are shown in Table 31-1.

Osmotic Diuretics Decrease Water Reabsorption by Increasing Osmotic Pressure of Tubular Fluid

Injection into the blood stream of substances that are not easily reabsorbed by the renal tubules, such as urea, mannitol, and sucrose, causes a marked increase in the concentration of osmotically active molecules in the tubules. The osmotic pressure of these solutes then reduces water reabsorption, flushing large amounts of tubular fluid into the urine.

Large volumes of urine are also formed in certain diseases associated with excess solutes that fail to be reabsorbed from the tubular fluid. For example, when the blood glucose concentration rises to high levels in diabetes mellitus, the increased filtered load of glucose into the tubules exceeds their capacity to reabsorb glucose (i.e., exceeds their *transport maximum* for glucose). Above a plasma glucose concentration of about 250 mg/dl, little of the extra glucose is reabsorbed by the tubules; instead, the excess glucose remains in the tubules, acts as an osmotic diuretic, and causes rapid loss of fluid into the urine. In patients with diabetes mellitus, the high urine output is balanced by a high level of fluid intake owing to activation of the thirst mechanism.

"Loop" Diuretics Decrease Active Sodium-Chloride-Potassium Reabsorption in the Thick Ascending Loop of Henle

Furosemide, ethacrynic acid, and *bumetanide* are powerful diuretics that decrease active reabsorption in the thick ascending limb of the loop of Henle by blocking the 1-sodium, 2-chloride, 1-potassium co-transporter located in the luminal membrane of the epithelial cells. These "loop" diuretics are among the most powerful of the clinically used diuretics.

By blocking active sodium-chloride-potassium co-transport in the luminal membrane of the loop of Henle, the loop diuretics raise urine output of sodium, chloride,

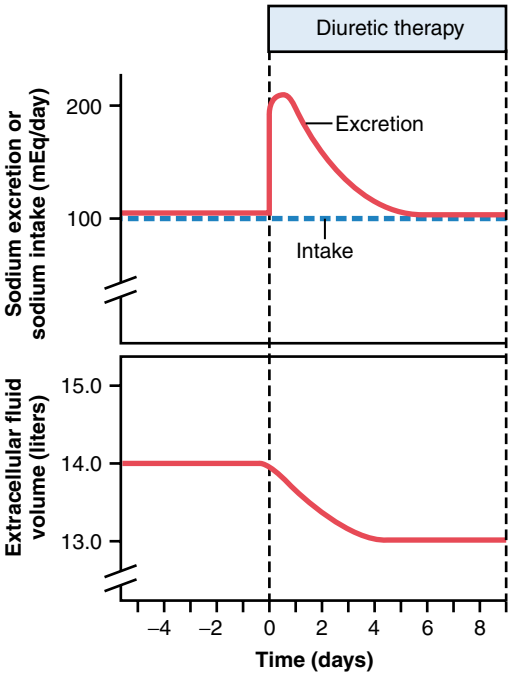


Figure 31-1 Sodium excretion and extracellular fluid volume during diuretic administration. The immediate increase in sodium excretion is accompanied by a decrease in extracellular fluid volume. If sodium intake is held constant, compensatory mechanisms will eventually return sodium excretion to equal sodium intake, thus re-establishing sodium balance.

potassium, and other electrolytes, as well as water, for two reasons: (1) they greatly increase the quantities of solutes delivered to the distal parts of the nephrons, and these act as osmotic agents to prevent water reabsorption as well; and (2) they disrupt the countercurrent multiplier system by decreasing absorption of ions from the loop of Henle into the medullary interstitium, thereby decreasing the osmolarity of the medullary interstitial fluid. Because of this effect, loop diuretics impair the ability of the kidneys to either concentrate or dilute the urine. Urinary dilution is impaired because the inhibition of sodium and chloride reabsorption in the loop of Henle causes more of these ions to be excreted along with increased water excretion. Urinary concentration is impaired because the renal medullary interstitial fluid concentration of these ions, and therefore renal medullary osmolarity, is reduced. Consequently, reabsorption of fluid from the collecting ducts is decreased, so the maximal concentrating ability of the kidneys is also greatly reduced. In addition, decreased renal medullary interstitial fluid osmolarity reduces absorption of water from the descending loop of Henle. Because of these multiple effects, 20 to 30 percent of the glomerular filtrate may be delivered into the urine, causing, under acute conditions, urine output to be as great as 25 times normal for at least a few minutes.

Thiazide Diuretics Inhibit Sodium-Chloride Reabsorption in the Early Distal Tubule

The thiazide derivatives, such as chlorothiazide, act mainly on the early distal tubules to block the sodium-chloride co-transporter in the luminal membrane of the tubular cells. Under favorable conditions, these agents may cause a maximum of 5 to 10 percent of the glomerular filtrate to pass into the urine. This is about the same amount of sodium normally reabsorbed by the distal tubules.

Carbonic Anhydrase Inhibitors Block Sodium Bicarbonate Reabsorption in the Proximal Tubules

Acetazolamide inhibits the enzyme *carbonic anhydrase,* which is critical for the reabsorption of bicarbonate in the proximal tubule, as discussed in Chapter 30. Carbonic anhydrase is abundant in the proximal tubule, the primary site of action of carbonic anhydrase inhibitors. Some carbonic anhydrase is also present in other tubular cells, such as in the intercalated cells of the collecting tubule.

Because H^+ secretion and HCO_3^- reabsorption in the proximal tubules are coupled to sodium reabsorption through the sodium-hydrogen ion counter-transport mechanism in the luminal membrane, decreasing HCO_3^-

Table 31-1 Classes of Diuretics, Their Mechanisms of Action, and Tubular Sites of Action

Class of Diuretic	Mechanism of Action	Tubular Site of Action
Osmotic diuretics (mannitol)	Inhibit water and solute reabsorption by increasing osmolarity of tubular fluid	Mainly proximal tubules
Loop diuretics (furosemide, bumetanide)	Inhibit Na^+-K^+-Cl^- co-transport in luminal membrane	Thick ascending loop of Henle
Thiazide diuretics (hydrochlorothiazide, chlorthalidone)	Inhibit Na^+-Cl^- co-transport in luminal membrane	Early distal tubules
Carbonic anhydrase inhibitors (acetazolamide)	Inhibit H^+ secretion and HCO_3^- reabsorption, which reduces Na^+ reabsorption	Proximal tubules
Aldosterone antagonists (spironolactone, eplerenone)	Inhibit action of aldosterone on tubular receptor, decrease Na^+ reabsorption, and decrease K^+ secretion	Collecting tubules
Sodium channel blockers (triamterene, amiloride)	Block entry of Na^+ into Na^+ channels of luminal membrane, decrease Na^+ reabsorption, and decrease K^+ secretion	Collecting tubules

reabsorption also reduces sodium reabsorption. The blockage of sodium and HCO_3^- reabsorption from the tubular fluid causes these ions to remain in the tubules and act as an osmotic diuretic. Predictably, a disadvantage of the carbonic anhydrase inhibitors is that they cause some degree of acidosis because of the excessive loss of HCO_3^- in the urine.

Competitive Inhibitors of Aldosterone Decrease Sodium Reabsorption from and Potassium Secretion into the Cortical Collecting Tubule

Spironolactone and *eplerenone* are mineralocorticoid receptor antagonists that compete with aldosterone for receptor binding sites in the cortical collecting tubule epithelial cells and, therefore, can decrease the reabsorption of sodium and secretion of potassium in this tubular segment. As a consequence, sodium remains in the tubules and acts as an osmotic diuretic, causing increased excretion of water, as well as sodium. Because these drugs also block the effect of aldosterone to promote potassium secretion in the tubules, they decrease the excretion of potassium. Mineralocorticoid receptor antagonists also cause movement of potassium from the cells to the extracellular fluid. In some instances, this causes extracellular fluid potassium concentration to increase excessively. For this reason, spironolactone and other mineralocorticoid receptor antagonists are referred to as *potassium-sparing diuretics.* Many of the other diuretics cause loss of potassium in the urine, in contrast to the mineralocorticoid receptor antagonists, which "spare" the loss of potassium.

Diuretics That Block Sodium Channels in the Collecting Tubules Decrease Sodium Reabsorption

Amiloride and *triamterene* also inhibit sodium reabsorption and potassium secretion in the collecting tubules, similar to the effects of spironolactone. However, at the cellular level, these drugs act directly to block the entry of sodium into the sodium channels of the luminal membrane of the collecting tubule epithelial cells. Because of this decreased sodium entry into the epithelial cells, there is also decreased sodium transport across the cells' basolateral membranes and, therefore, decreased activity of the sodium-potassium-adenosine triphosphatase pump. This decreased activity reduces the transport of potassium into the cells and ultimately decreases the secretion of potassium into the tubular fluid. For this reason, the sodium channel blockers are also potassium-sparing diuretics and decrease the urinary excretion rate of potassium.

Kidney Diseases

Diseases of the kidneys are among the most important causes of death and disability in many countries throughout the world. For example, in 2009, more than 26 million adults in the United States were estimated to have chronic kidney disease, and many more millions of people have acute renal failure or less severe forms of kidney dysfunction.

Severe kidney diseases can be divided into two main categories: (1) *acute renal failure,* in which the kidneys abruptly stop working entirely or almost entirely but may eventually recover nearly normal function, and (2) *chronic renal failure,* in which there is progressive loss of function of more and more nephrons that gradually decreases overall kidney function. Within these two general categories, there are many specific kidney diseases that can affect the kidney blood vessels, glomeruli, tubules, renal interstitium, and parts of the urinary tract outside the kidney, including the ureters and bladder. In this chapter, we discuss specific physiologic abnormalities that occur in a few of the more important types of kidney diseases.

Acute Renal Failure

The causes of acute renal failure can be divided into three main categories:

1. Acute renal failure resulting from decreased blood supply to the kidneys; this condition is often referred to as *prerenal acute renal failure* to reflect the fact that the abnormality occurs as a result of an abnormality originating outside the kidneys. For example, prerenal acute renal failure can be a consequence of heart failure with reduced cardiac output and low blood pressure or conditions associated with diminished blood volume and low blood pressure, such as severe hemorrhage.
2. *Intrarenal acute renal failure* resulting from abnormalities within the kidney itself, including those that affect the blood vessels, glomeruli, or tubules.
3. *Postrenal acute renal failure,* resulting from obstruction of the urinary collecting system anywhere from the calyces to the outflow from the bladder. The most common causes of obstruction of the urinary tract outside the kidney are kidney stones, caused by precipitation of calcium, urate, or cystine.

Prerenal Acute Renal Failure Caused by Decreased Blood Flow to the Kidney

The kidneys normally receive an abundant blood supply of about 1100 ml/min, or about 20 to 25 percent of the cardiac output. The main purpose of this high blood flow to the kidneys is to provide enough plasma for the high rates of glomerular filtration needed for effective regulation of body fluid volumes and solute concentrations. Therefore, decreased renal blood flow is usually accompanied by decreased GFR and decreased urine output of water and solutes. Consequently, conditions that acutely diminish blood flow to the kidneys usually cause *oliguria,* which refers to diminished urine output below the level of intake of water and solutes. This causes accumulation of water and solutes in the body fluids. If renal blood flow is markedly reduced, total cessation of urine output can occur, a condition referred to as *anuria.*

Table 31-2 Some Causes of Prerenal Acute Renal Failure

Intravascular Volume Depletion
Hemorrhage (trauma, surgery, postpartum, gastrointestinal)
Diarrhea or vomiting
Burns
Cardiac Failure
Myocardial infarction
Valvular damage
Peripheral Vasodilation and Resultant Hypotension
Anaphylactic shock
Anesthesia
Sepsis, severe infections
Primary renal hemodynamic abnormalities
Renal artery stenosis, embolism, or thrombosis of renal artery or vein

Table 31-3 Some Causes of Intrarenal Acute Renal Failure

Small Vessel and /or Glomerular Injury
Vasculitis (polyarteritis nodosa)
Cholesterol emboli
Malignant hypertension
Acute glomerulonephritis
Tubular Epithelial Injury (Tubular Necrosis)
Acute tubular necrosis due to ischemia
Acute tubular necrosis due to toxins (heavy metals, ethylene glycol, insecticides, poison mushrooms, carbon tetrachloride)
Renal Interstitial Inury
Acute pyelonephritis
Acute allergic interstitial nephritis

As long as renal blood flow does not fall below about 20 to 25 percent of normal, acute renal failure can usually be reversed if the cause of the ischemia is corrected before damage to the renal cells has occurred. Unlike some tissues, the kidney can endure a relatively large reduction in blood flow before actual damage to the renal cells occurs. The reason for this is that as renal blood flow is reduced, the GFR and the amount of sodium chloride filtered by the glomeruli (as well as the filtration rate of water and other electrolytes) are reduced. This decreases the amount of sodium chloride that must be reabsorbed by the tubules, which use most of the energy and oxygen consumed by the normal kidney. Therefore, as renal blood flow and GFR fall, the requirement for renal oxygen consumption is also reduced. As the GFR approaches zero, oxygen consumption of the kidney approaches the rate that is required to keep the renal tubular cells alive even when they are not reabsorbing sodium. When blood flow is reduced below this basal requirement, which is usually less than 20 to 25 percent of the normal renal blood flow, the renal cells start to become hypoxic, and further decreases in renal blood flow, if prolonged, will cause damage or even death of the renal cells, especially the tubular epithelial cells.

If the cause of prerenal acute renal failure is not corrected and ischemia of the kidney persists longer than a few hours, this type of renal failure can evolve into intrarenal acute renal failure, as discussed later. Acute reduction of renal blood flow is a common cause of acute renal failure in hospitalized patients, especially those who have suffered severe injuries. Table 31-2 shows some of the common causes of decreased renal blood flow and prerenal acute renal failure.

Intrarenal Acute Renal Failure Caused by Abnormalities Within the Kidney

Abnormalities that originate within the kidney and that abruptly diminish urine output fall into the general category of *intrarenal acute renal failure.* This category of acute renal failure can be further divided into (1) conditions that injure the glomerular capillaries or other small renal vessels, (2) conditions that damage the renal tubular epithelium, and (3) conditions that cause damage to the renal interstitium. This type of classification refers to the primary site of injury, but because the renal vasculature and tubular system are functionally interdependent, damage to the renal blood vessels can lead to tubular damage, and primary tubular damage can lead to damage of the renal blood vessels. Some causes of intrarenal acute renal failure are listed in Table 31-3.

Acute Renal Failure Caused by Glomerulonephritis

Acute glomerulonephritis is a type of *intrarenal* acute renal failure usually caused by an abnormal immune reaction that damages the glomeruli. In about 95 percent of the patients with this disease, damage to the glomeruli occurs 1 to 3 weeks after an infection elsewhere in the body, usually caused by certain types of group A beta streptococci. The infection may have been a streptococcal sore throat, streptococcal tonsillitis, or even streptococcal infection of the skin. It is not the infection itself that damages the kidneys. Instead, over a few weeks, as antibodies develop against the streptococcal antigen, the antibodies and antigen react with each other to form an insoluble immune complex that becomes entrapped in the glomeruli, especially in the basement membrane portion of the glomeruli.

Once the immune complex has deposited in the glomeruli, many of the cells of the glomeruli begin to proliferate, but mainly the mesangial cells that lie between the endothelium and the epithelium. In addition, large numbers of white blood cells become entrapped in the glomeruli. Many of the glomeruli become blocked by this inflammatory reaction, and those that are not blocked usually become excessively permeable, allowing both

protein and red blood cells to leak from the blood of the glomerular capillaries into the glomerular filtrate. In severe cases, either total or almost complete renal shutdown occurs.

The acute inflammation of the glomeruli usually subsides in about 2 weeks and, in most patients, the kidneys return to almost normal function within the next few weeks to few months. Sometimes, however, many of the glomeruli are destroyed beyond repair, and in a small percentage of patients, progressive renal deterioration continues indefinitely, leading to *chronic renal failure,* as described in a subsequent section of this chapter.

Tubular Necrosis as a Cause of Acute Renal Failure

Another cause of intrarenal acute renal failure is *tubular necrosis,* which means destruction of epithelial cells in the tubules. Some common causes of tubular necrosis are (1) severe ischemia and inadequate supply of oxygen and nutrients to the tubular epithelial cells and (2) poisons, toxins, or medications that destroy the tubular epithelial cells.

Acute Tubular Necrosis Caused by Severe Renal Ischemia

Severe ischemia of the kidney can result from circulatory shock or any other disturbance that severely impairs the blood supply to the kidney. If the ischemia is severe enough to seriously impair the delivery of nutrients and oxygen to the renal tubular epithelial cells, and if the insult is prolonged, damage or eventual destruction of the epithelial cells can occur. When this happens, tubular cells "slough off" and plug many of the nephrons, so that there is no urine output from the blocked nephrons; the affected nephrons often fail to excrete urine even when renal blood flow is restored to normal, as long as the tubules remain plugged. The most common causes of ischemic damage to the tubular epithelium are the prerenal causes of acute renal failure associated with circulatory shock, as discussed earlier in this chapter.

Acute Tubular Necrosis Caused by Toxins or Medications

There is a long list of renal poisons and medications that can damage the tubular epithelium and cause acute renal failure. Some of these are *carbon tetrachloride, heavy metals* (such as mercury and lead), *ethylene glycol* (which is a major component in antifreeze), various *insecticides,* some *medications* (such as tetracyclines) used as antibiotics, and *cis-platinum*, which is used in treating certain cancers. Each of these substances has a specific toxic action on the renal tubular epithelial cells, causing death of many of them. As a result, the epithelial cells slough away from the basement membrane and plug the tubules. In some instances, the basement membrane also is destroyed. If the basement membrane remains intact, new tubular epithelial cells can grow along the surface of the membrane, so the tubule may repair itself within 10 to 20 days.

Postrenal Acute Renal Failure Caused by Abnormalities of the Lower Urinary Tract

Multiple abnormalities in the lower urinary tract can block or partially block urine flow and therefore lead to acute renal failure even when the kidneys' blood supply and other functions are initially normal. If the urine output of only one kidney is diminished, no major change in body fluid composition will occur because the contralateral kidney can increase its urine output sufficiently to maintain relatively normal levels of extracellular electrolytes and solutes, as well as normal extracellular fluid volume. With this type of renal failure, normal kidney function can be restored if the basic cause of the problem is corrected within a few hours. But chronic obstruction of the urinary tract, lasting for several days or weeks, can lead to irreversible kidney damage. Some of the causes of postrenal acute failure include (1) bilateral obstruction of the ureters or renal pelvises caused by large stones or blood clots, (2) bladder obstruction, and (3) obstruction of the urethra.

Physiologic Effects of Acute Renal Failure

A major physiologic effect of acute renal failure is retention in the blood and extracellular fluid of water, waste products of metabolism, and electrolytes. This can lead to water and salt overload, which, in turn, can lead to edema and hypertension. Excessive retention of potassium, however, is often a more serious threat to patients with acute renal failure because increases in plasma potassium concentration (hyperkalemia) above 8 mEq/L (only twice normal) can be fatal. Because the kidneys are also unable to excrete sufficient hydrogen ions, patients with acute renal failure develop metabolic acidosis, which in itself can be lethal or can aggravate the hyperkalemia.

In the most severe cases of acute renal failure, complete anuria occurs. The patient will die in 8 to 14 days unless kidney function is restored or unless an artificial kidney is used to rid the body of the excessive retained water, electrolytes, and waste products of metabolism. Other effects of diminished urine output, as well as treatment with an artificial kidney, are discussed in the next section in relation to chronic renal failure.

Chronic Renal Failure: An Irreversible Decrease in the Number of Functional Nephrons

Chronic renal failure results from progressive and irreversible loss of large numbers of functioning nephrons. Serious clinical symptoms often do not occur until the number of functional nephrons falls to at least 70 to 75 percent below normal. In fact, relatively normal blood concentrations of most electrolytes and normal body fluid volumes can still be maintained until the number of functioning nephrons decreases below 20 to 25 percent of normal.

Table 31-4 Some Causes of Chronic Renal Failure

Metablolic Disorders
Diabetes mellitus
Obesity
Amyloidosis
Hypertension
Renal Vascular Disorders
Atherosclerosis
Nephrosclerosis-hypertension
Immunologic Disorders
Glomerulonephritis
Polyarteritis nodosa
Lupus erythernatosus
Infections
Pyelonephritis
Tuberculosis
Primary Tubular Disorders
Nephrotoxins (analgesics, heavy metals)
Urinary Tract Obstruction
Renal calculi
Hypertrophy of prostate
Urethral constriction
Congenital Disorders
Polycystic disease
Congenital absence of kidney tissue (renal hypoplasia)

Table 31-4 gives some of the most important causes of chronic renal failure. In general, chronic renal failure, like acute renal failure, can occur because of disorders of the blood vessels, glomeruli, tubules, renal interstitium, and lower urinary tract. Despite the wide variety of diseases that can lead to chronic renal failure, the end result is essentially the same—a decrease in the number of functional nephrons.

Vicious Cycle of Chronic Renal Failure Leading to End-Stage Renal Disease

In many cases, an initial insult to the kidney leads to progressive deterioration of kidney function and further loss of nephrons to the point where the person must be placed on dialysis treatment or transplanted with a functional kidney to survive. This condition is referred to as *end-stage renal disease (ESRD).*

Studies in laboratory animals have shown that surgical removal of large portions of the kidney initially causes adaptive changes in the remaining nephrons that lead to increased blood flow, increased GFR, and increased urine output in the surviving nephrons. The exact mechanisms responsible for these changes are not well understood but involve hypertrophy (growth of the various structures of the surviving nephrons), as well as functional changes that decrease vascular resistance and tubular reabsorption in the surviving nephrons. These adaptive changes permit a person to excrete normal amounts of water and solutes even when kidney mass is reduced to 20 to 25 percent of normal. Over a period of several years, however, these renal adaptive changes may lead to further injury of the remaining nephrons, particularly to the glomeruli of these nephrons.

The cause of this additional injury is not known, but some investigators believe that it may be related in part to increased pressure or stretch of the remaining glomeruli, which occurs as a result of functional vasodilation or increased blood pressure; the chronic increase in pressure and stretch of the small arterioles and glomeruli are believed to cause injury and sclerosis of these vessels (replacement of normal tissue with connective tissue). These sclerotic lesions can eventually obliterate the glomerulus, leading to further reduction in kidney function, further adaptive changes in the remaining nephrons, and a slowly progressing vicious cycle that eventually terminates in ESRD (Figure 31-2). The only proven method of slowing down this progressive loss of kidney function is to lower arterial pressure and glomerular hydrostatic pressure, especially by using drugs such as angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists.

Table 31-5 gives the most common causes of ESRD. In the early 1980s, *glomerulonephritis* in all its various forms was believed to be the most common initiating cause of

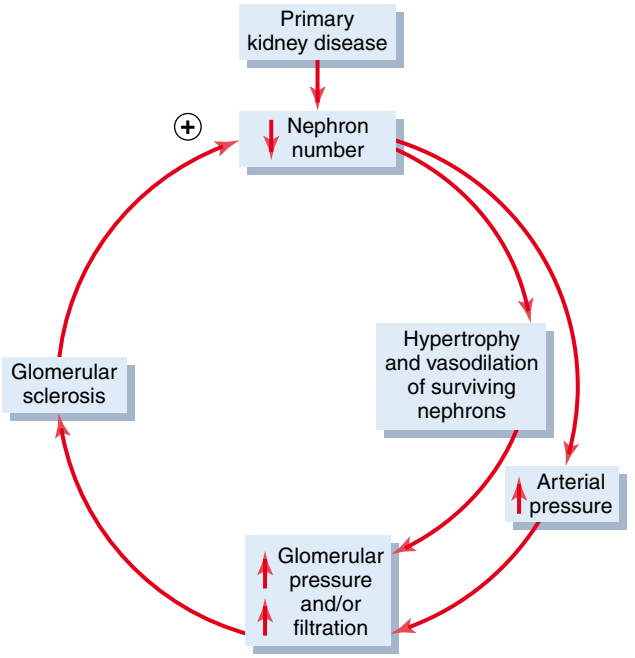


Figure 31-2 Vicious circle that can occur with primary kidney disease. Loss of nephrons because of disease may increase pressure and flow in the surviving glomerular capillaries, which in turn may eventually injure these "normal" capillaries as well, thus causing progressive sclerosis and eventual loss of these glomeruli.

Table 31-5 Most Common Causes of End-Stage Renal Disease (ESRD)

Cause	Percentage of Total ESRD Patients
Diabetes mellitus	45
Hypertension	27
Glomerulonephritis	8
Polycystic kidney disease	2
Other/unknown	18

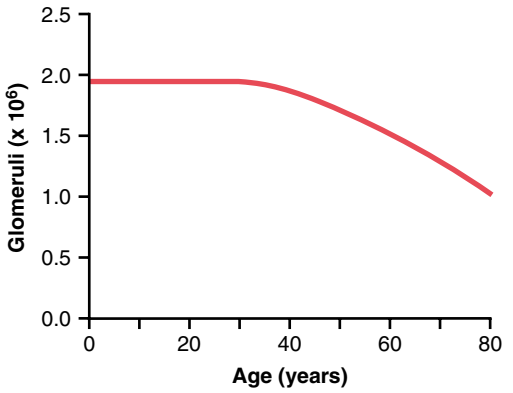


Figure 31-3 Effect of aging on the number of functional glomeruli.

ESRD. In recent years, *diabetes mellitus* and *hypertension* have become recognized as the leading causes of ESRD, together accounting for more than 70 percent of all chronic renal failure.

Excessive weight gain (obesity) appears to be the most important risk factor for the two main causes of ESRD—diabetes and hypertension. As discussed in Chapter 78, type II diabetes, which is closely linked to obesity, accounts for more than 90 percent of all diabetes mellitus. Excess weight gain is also a major cause of essential hypertension, accounting for as much as 65 to 75 percent of the risk for developing hypertension in adults. In addition to causing renal injury through diabetes and hypertension, obesity may have additive or synergistic effects to worsen renal function in patients with preexisting kidney disease.

Injury to the Renal Vasculature as a Cause of Chronic Renal Failure

Many types of vascular lesions can lead to renal ischemia and death of kidney tissue. The most common of these are (1) *atherosclerosis* of the larger renal arteries, with progressive sclerotic constriction of the vessels; (2) *fibromuscular hyperplasia* of one or more of the large arteries, which also causes occlusion of the vessels; and (3) *nephrosclerosis,* caused by sclerotic lesions of the smaller arteries, arterioles, and glomeruli.

Atherosclerotic or hyperplastic lesions of the large arteries frequently affect one kidney more than the other and, therefore, cause unilaterally diminished kidney function. As discussed in Chapter 19, hypertension often occurs when the artery of one kidney is constricted while the artery of the other kidney is still normal, a condition analogous to "two-kidney" Goldblatt hypertension.

Benign nephrosclerosis, the most common form of kidney disease, is seen to at least some extent in about 70 percent of postmortem examinations in people who die after the age of 60. This type of vascular lesion occurs in the smaller interlobular arteries and in the afferent arterioles of the kidney. It is believed to begin with leakage of plasma through the intimal membrane of these vessels. This causes fibrinoid deposits to develop in the medial layers of these vessels, followed by progressive thickening of the vessel wall that eventually constricts the vessels and, in some cases, occludes them. Because there is essentially no collateral circulation among the smaller renal arteries, occlusion of one or more of them causes destruction of a comparable number of nephrons. Therefore, much of the kidney tissue becomes replaced by small amounts of fibrous tissue. When sclerosis occurs in the glomeruli, the injury is referred to as *glomerulosclerosis.*

Nephrosclerosis and glomerulosclerosis occur to some extent in most people after the fourth decade of life, causing about a 10 percent decrease in the number of functional nephrons each 10 years after age 40 (Figure 31-3). This loss of glomeruli and overall nephron function is reflected by a progressive decrease in both renal blood flow and GFR. Even in "normal" people, kidney plasma flow and GFR decrease by 40 to 50 percent by age 80.

The frequency and severity of nephrosclerosis and glomerulosclerosis are greatly increased by concurrent *hypertension* or *diabetes mellitus.* In fact, diabetes mellitus and hypertension are the two most important causes of ESRD, as discussed previously. Thus, benign nephrosclerosis in association with severe hypertension can lead to a rapidly progressing *malignant nephrosclerosis.* The characteristic histological features of malignant nephrosclerosis include large amounts of fibrinoid deposits in the arterioles and progressive thickening of the vessels, with severe ischemia occurring in the affected nephrons. For unknown reasons, the incidence of malignant nephrosclerosis and severe glomerulosclerosis is significantly higher in blacks than in whites of similar ages who have similar degrees of severity of hypertension or diabetes.

Injury to the Glomeruli as a Cause of Chronic Renal Failure—Glomerulonephritis

Chronic glomerulonephritis can be caused by several diseases that cause inflammation and damage to the capillary loops in the glomeruli of the kidneys. In contrast to the acute form of this disease, chronic glomerulonephritis is a slowly progressive disease that often leads to irreversible renal failure. It may be a primary kidney disease, following acute glomerulonephritis, or it may be secondary to systemic diseases, such as *lupus erythematosus.*

In most cases, chronic glomerulonephritis begins with accumulation of precipitated antigen-antibody complexes in the glomerular membrane. In contrast to acute glomerulonephritis, streptococcal infections account for only a small percentage of patients with the chronic form of glomerulonephritis. Accumulation of antigen-antibody complex in the glomerular membranes causes inflammation, progressive thickening of the membranes, and eventual invasion of the glomeruli by fibrous tissue. In the later stages of the disease, the glomerular capillary filtration coefficient becomes greatly reduced because of decreased numbers of filtering

capillaries in the glomerular tufts and because of thickened glomerular membranes. In the final stages of the disease, many glomeruli are replaced by fibrous tissue and are, therefore, unable to filter fluid.

Injury to the Renal Interstitium as a Cause of Chronic Renal Failure—Interstitial Nephritis

Primary or secondary disease of the renal interstitium is referred to as *interstitial nephritis.* In general, this can result from vascular, glomerular, or tubular damage that destroys individual nephrons, or it can involve primary damage to the renal interstitium by poisons, drugs, and bacterial infections.

Renal interstitial injury caused by bacterial infection is called *pyelonephritis.* The infection can result from different types of bacteria but especially from *Escherichia coli* that originate from fecal contamination of the urinary tract. These bacteria reach the kidneys either by way of the blood stream or, more commonly, by ascension from the lower urinary tract by way of the ureters to the kidneys.

Although the normal bladder is able to clear bacteria readily, there are two general clinical conditions that may interfere with the normal flushing of bacteria from the bladder: (1) the inability of the bladder to empty completely, leaving residual urine in the bladder, and (2) the existence of obstruction of urine outflow. With impaired ability to flush bacteria from the bladder, the bacteria multiply and the bladder becomes inflamed, a condition termed *cystitis.* Once cystitis has occurred, it may remain localized without ascending to the kidney, or in some people, bacteria may reach the renal pelvis because of a pathological condition in which urine is propelled up one or both of the ureters during micturition. This condition is called *vesicoureteral reflux* and is due to the failure of the bladder wall to occlude the ureter during micturition; as a result, some of the urine is propelled upward toward the kidney, carrying with it bacteria that can reach the renal pelvis and renal medulla, where they can initiate the infection and inflammation associated with pyelonephritis.

Pyelonephritis begins in the renal medulla and therefore usually affects the function of the medulla more than it affects the cortex, at least in the initial stages. Because one of the primary functions of the medulla is to provide the countercurrent mechanism for concentrating urine, patients with pyelonephritis frequently have markedly impaired ability to concentrate the urine.

With long-standing pyelonephritis, invasion of the kidneys by bacteria not only causes damage to the renal medulla interstitium but also results in progressive damage of renal tubules, glomeruli, and other structures throughout the kidney. Consequently, large parts of functional renal tissue are lost and chronic renal failure can develop.

Nephrotic Syndrome—Excretion of Protein in the Urine Because of Increased Glomerular Permeability

Many patients with kidney disease develop the *nephrotic syndrome,* which is characterized by loss of large quantities of plasma proteins into the urine. In some instances, this occurs without evidence of other major abnormalities of kidney function, but more often it is associated with some degree of renal failure.

The cause of the protein loss in the urine is increased permeability of the glomerular membrane. Therefore, any disease that increases the permeability of this membrane can cause the nephrotic syndrome. Such diseases include (1) *chronic glomerulonephritis,* which affects primarily the glomeruli and often causes greatly increased permeability of the glomerular membrane; (2) *amyloidosis,* which results from deposition of an abnormal proteinoid substance in the walls of the blood vessels and seriously damages the basement membrane of the glomeruli; and (3) *minimal change nephrotic syndrome,* which is associated with no major abnormality in the glomerular capillary membrane that can be detected with light microscopy. As discussed in Chapter 26, minimal change nephropathy has been found to be associated with loss of the negative charges that are normally present in the glomerular capillary basement membrane. Immunologic studies have also shown abnormal immune reactions in some cases, suggesting that the loss of the negative charges may have resulted from antibody attack on the membrane. Loss of normal negative charges in the basement membrane of the glomerular capillaries allows proteins, especially albumin, to pass through the glomerular membrane with ease because the negative charges in the basement membrane normally repel the negatively charged plasma proteins.

Minimal-change nephropathy can occur in adults, but more frequently it occurs in children between the ages of 2 and 6 years. Increased permeability of the glomerular capillary membrane occasionally allows as much as 40 grams of plasma protein loss into the urine each day, which is an extreme amount for a young child. Therefore, the child's plasma protein concentration often falls below 2 g/dl and the colloid osmotic pressure falls from a normal value of 28 to less than 10 mm Hg. As a consequence of this low colloid osmotic pressure in the plasma, large amounts of fluid leak from the capillaries all over the body into most of the tissues, causing severe edema, as discussed in Chapter 25.

Nephron Function in Chronic Renal Failure

Loss of Functional Nephrons Requires the Surviving Nephrons to Excrete More Water and Solutes. It would be reasonable to suspect that decreasing the number of functional nephrons, which reduces the GFR, would also cause major decreases in renal excretion of water and solutes. Yet patients who have lost up to 75 to 80 percent of their nephrons are able to excrete normal amounts of water and electrolytes without serious accumulation of any of these in the body fluids. Further reduction in the number of nephrons, however, leads to electrolyte and fluid retention, and death usually ensues when the number of nephrons falls below 5 to 10 percent of normal.

In contrast to the electrolytes, many of the waste products of metabolism, such as urea and creatinine, accumulate almost in proportion to the number of nephrons that have been destroyed. The reason for this is that substances such as creatinine and urea depend largely on glomerular filtration for their excretion, and they are not reabsorbed as avidly as the electrolytes. Creatinine, for example, is not reabsorbed at all, and the excretion rate is approximately equal to the rate at which it is filtered.

Creatinine filtration rate = GFR × Plasma creatinine concentration = Creatinine excretion rate

Therefore, if GFR decreases, the creatinine excretion rate also transiently decreases, causing accumulation of creatinine in the body fluids and raising plasma concentration until the excretion rate of creatinine returns to normal—the same rate at which creatinine is produced in the body (Figure 31-4). 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 curve A of Figure 31-5.

Some solutes, such as phosphate, urate, and hydrogen ions, are often maintained near the normal range until GFR falls below 20 to 30 percent of normal. Thereafter, the plasma concentrations of these substances rise, but not in proportion to the fall in GFR, as shown in curve B of Figure 31-5. Maintenance of relatively constant plasma concentrations of these solutes as GFR declines is accomplished by excreting progressively larger fractions of the amounts of these solutes that are filtered at the glomerular capillaries; this occurs by decreasing the rate of tubular reabsorption or, in some instances, by increasing tubular secretion rates.

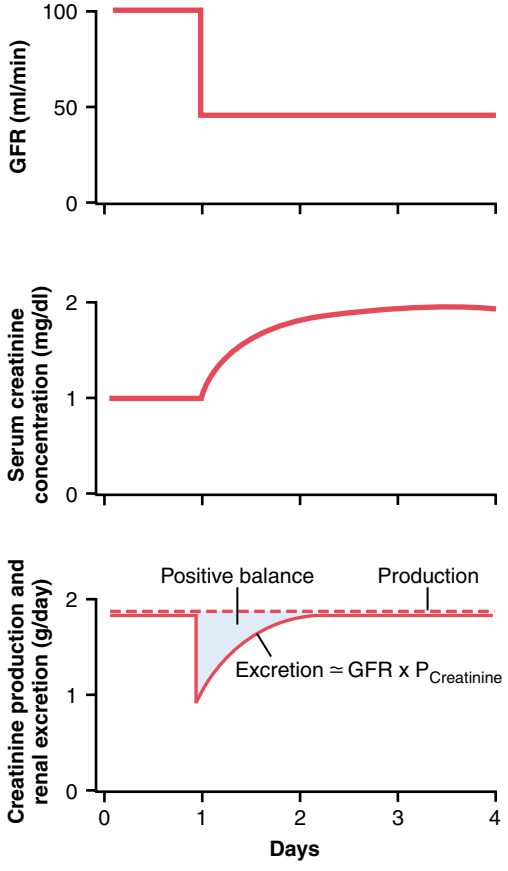


Figure 31-4 Effect of reducing glomerular filtration rate (GFR) by 50 percent on serum creatinine concentration and on creatinine excretion rate when the production rate of creatinine remains constant.

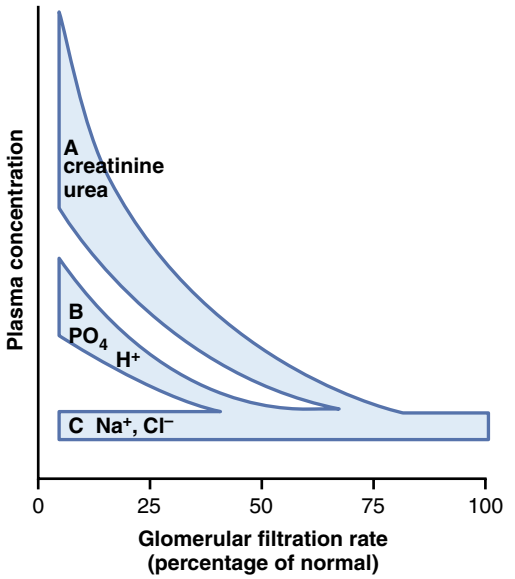


Figure 31-5 Representative patterns of adaptation for different types of solutes in chronic renal failure. Curve A shows the approximate changes in the plasma concentrations of solutes such as creatinine and urea that are filtered and poorly reabsorbed. Curve B shows the approximate concentrations for solutes such as phosphate, urate, and hydrogen ion. Curve C shows the approximate concentrations for solutes such as sodium and chloride.

In the case of sodium and chloride ions, their plasma concentrations are maintained virtually constant even with severe decreases in GFR (see curve C of Figure 31-5). This is accomplished by greatly decreasing tubular reabsorption of these electrolytes.

For example, with a 75 percent loss of functional nephrons, each surviving nephron must excrete four times as much sodium and four times as much volume as under normal conditions (Table 31-6).

Part of this adaptation occurs because of increased blood flow and increased GFR in each of the surviving nephrons, owing to hypertrophy of the blood vessels and glomeruli, as well as functional changes that cause the blood vessels to dilate. Even with large decreases in the total GFR, normal rates of renal excretion can still be maintained by decreasing the rate at which the tubules reabsorb water and solutes.

Table 31-6 Total Kidney Excretion and Excretion per Nephron in Renal Failure

	Normal	75% Loss of Nephrons
Number of nephrons	2,000,000	500,000
Total GFR (ml/min)	125	40
Single nephron GFR (nl/min)	62.5	80
Volume excreted for all nephrons (ml/min)	1.5	1.5
Volume excreted per nephron (nl/min)	0.75	3.0

GFR, glomerular filtration rate.

Isosthenuria—Inability of the Kidney to Concentrate or Dilute the Urine. One important effect of the rapid rate of tubular flow that occurs in the remaining nephrons of diseased kidneys is that the renal tubules lose their ability to fully concentrate or dilute the urine. The concentrating ability of the kidney is impaired mainly because (1) the rapid flow of tubular fluid through the collecting ducts prevents adequate water reabsorption, and (2) the rapid flow through both the loop of Henle and the collecting ducts prevents the countercurrent mechanism from operating effectively to concentrate the medullary interstitial fluid solutes. Therefore, as progressively more nephrons are destroyed, the maximum concentrating ability of the kidney declines and urine osmolarity and specific gravity (a measure of the total solute concentration) approach the osmolarity and specific gravity of the glomerular filtrate, as shown in Figure 31-6.

The diluting mechanism in the kidney is also impaired when the number of nephrons decreases because the rapid flushing of fluid through the loops of Henle and the high load of solutes such as urea cause a relatively high solute concentration in the tubular fluid of this part of the nephron. As a consequence, the diluting capacity of the kidney is impaired and the minimal urine osmolality and specific gravity approach those of the glomerular filtrate. Because the concentrating mechanism becomes impaired to a greater extent than does the diluting mechanism in chronic renal failure, an important clinical test of renal function is to determine how well the kidneys can concentrate urine when a person's water intake is restricted for 12 or more hours.

Effects of Renal Failure on the Body Fluids—Uremia

The effect of renal failure on the body fluids depends on (1) water and food intake and (2) the degree of impairment of renal function. Assuming that a person with complete renal failure continues to ingest the same amounts of water and food, the concentrations of different substances in the extracellular fluid are approximately those shown in Figure 31-7. Important effects include (1) *generalized edema* resulting from water and salt retention; (2) *acidosis* resulting from failure of the kidneys to rid the body of normal acidic products; (3) *high concentration of the nonprotein nitrogens*—especially urea, creatinine, and uric acid—resulting from failure of the body to excrete the metabolic end products of proteins; and (4) *high concentrations of other substances* excreted by the kidney, including *phenols, sulfates, phosphates, potassium,* and *guanidine bases.* This total condition is called *uremia* because of the high concentration of urea in the body fluids.

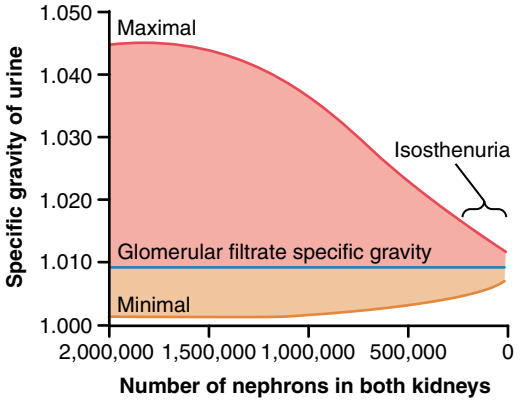


Figure 31-6 Development of isosthenuria in a patient with decreased numbers of functional nephrons.

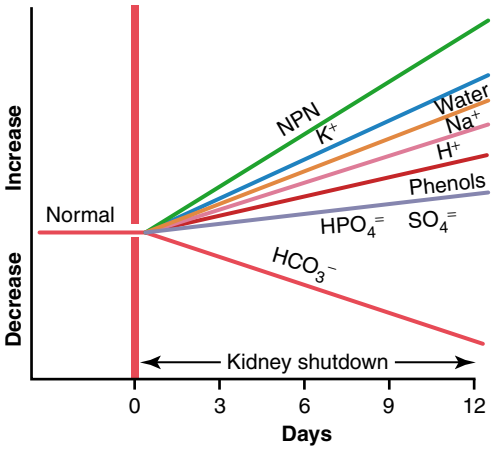


Figure 31-7 Effect of kidney failure on extracellular fluid constituents. NPN, nonprotein nitrogens.

Water Retention and Development of Edema in Renal Failure. If water intake is restricted immediately after acute renal failure begins, the total body fluid content may become only slightly increased. If fluid intake is not limited and the patient drinks in response to the normal thirst mechanisms, the body fluids begin to increase immediately and rapidly.

With chronic partial kidney failure, accumulation of fluid may not be severe, as long as salt and fluid intake are not excessive, until kidney function falls to 25 percent of normal or lower. The reason for this, as discussed previously, is that the surviving nephrons excrete larger amounts of salt and water. Even the small fluid retention that does occur, along with increased secretion of renin and angiotensin II that usually occurs in ischemic kidney disease, often causes severe hypertension in chronic renal failure. Almost all patients with kidney function so reduced as to require dialysis to preserve life develop hypertension. In many of these patients, severe reduction of salt intake or removal of extracellular fluid by dialysis can control the hypertension. The remaining patients continue to have hypertension even after excess sodium has been removed by dialysis. In this group, removal of the ischemic kidneys usually corrects the hypertension (as long as fluid retention is prevented by dialysis) because it removes the source of excessive renin secretion and subsequent increased angiotensin II formation.

Uremia—Increase in Urea and Other Nonprotein Nitrogens (Azotemia). The nonprotein nitrogens include urea, uric acid, creatinine, and a few less important compounds. These, in general, are the end products of protein metabolism and must be removed from the body to ensure continued normal protein metabolism in the cells. The concentrations of these, particularly of urea, can rise to as high as 10 times normal during 1 to 2 weeks of total renal failure. With chronic renal failure, the concentrations rise approximately in proportion to the degree of reduction in functional nephrons. For this reason, measuring the concentrations of

these substances, especially of urea and creatinine, provides an important means for assessing the degree of renal failure.

Acidosis in Renal Failure. Each day the body normally produces about 50 to 80 millimoles more metabolic acid than metabolic alkali. Therefore, when the kidneys fail to function, acid accumulates in the body fluids. The buffers of the body fluids normally can buffer 500 to 1000 millimoles of acid without lethal increases in extracellular fluid H^+ concentration, and the phosphate compounds in the bones can buffer an additional few thousand millimoles of H^+. However, when this buffering power is used up, the blood pH falls drastically and the patient will become comatose and die if the pH falls below about 6.8.

Anemia in Chronic Renal Failure Caused by Decreased Erythropoietin Secretion. Patients with severe chronic renal failure almost always develop *anemia.* The most important cause of this is decreased renal secretion of *erythropoietin,* which stimulates the bone marrow to produce red blood cells. If the kidneys are seriously damaged, they are unable to form adequate quantities of erythropoietin, which leads to diminished red blood cell production and consequent anemia.

The availability since 1989 of recombinant erythropoietin, however, has provided a means of treating anemia in patients with chronic renal failure.

Osteomalacia in Chronic Renal Failure Caused by Decreased Production of Active Vitamin D and by Phosphate Retention by the Kidneys. Prolonged renal failure also causes *osteomalacia,* a condition in which the bones are partially absorbed and, therefore, become greatly weakened. An important cause of this condition is the following: Vitamin D must be converted by a two-stage process, first in the liver and then in the kidneys, into 1,25-dihydroxycholecalciferol before it is able to promote calcium absorption from the intestine. Therefore, serious damage to the kidney greatly reduces the blood concentration of *active* vitamin D, which in turn decreases intestinal absorption of calcium and the availability of calcium to the bones.

Another important cause of demineralization of the skeleton in chronic renal failure is the rise in serum phosphate concentration that occurs as a result of decreased GFR. This rise in serum phosphate increases binding of phosphate with calcium in the plasma, thus decreasing the plasma serum *ionized* calcium concentration, which, in turn, stimulates *parathyroid hormone* secretion. This secondary hyperparathyroidism then stimulates the release of calcium from bones, causing further demineralization of the bones.

Hypertension and Kidney Disease

As discussed earlier in this chapter, hypertension can exacerbate injury to the glomeruli and blood vessels of the kidneys and is a major cause of end-stage renal disease. Abnormalities of kidney function can also cause hypertension, as discussed in detail in Chapter 19. Thus, the relation between hypertension and kidney disease can, in some instances, propagate a vicious cycle: primary kidney damage leads to increased blood pressure, which causes further damage to the kidneys, further increases in blood pressure, and so forth, until end-stage renal disease develops.

Not all types of kidney disease cause hypertension because damage to certain portions of the kidney causes uremia without hypertension. Nevertheless, some types of renal damage are particularly prone to cause hypertension. A classification of kidney disease relative to hypertensive or nonhypertensive effects is the following.

Renal Lesions That Reduce the Ability of the Kidneys to Excrete Sodium and Water Promote Hypertension. Renal lesions that decrease the ability of the kidneys to excrete sodium and water almost invariably cause hypertension. Therefore, lesions that either *decrease GFR* or *increase tubular reabsorption* usually lead to hypertension of varying degrees. Some specific types of renal abnormalities that can cause hypertension are as follows:

1. *Increased renal vascular resistance,* which reduces renal blood flow and GFR. An example is hypertension caused by renal artery stenosis.
2. *Decreased glomerular capillary filtration coefficient, which reduces GFR.* An example of this is chronic glomerulonephritis, which causes inflammation and thickening of the glomerular capillary membranes, thereby reducing the glomerular capillary filtration coefficient.
3. *Excessive tubular sodium reabsorption.* An example is hypertension caused by excessive aldosterone secretion, which increases sodium reabsorption mainly in the cortical collecting tubules.

Once hypertension has developed, renal excretion of sodium and water returns to normal because the high arterial pressure causes pressure natriuresis and pressure diuresis, so intake and output of sodium and water become balanced once again. Even when there are large increases in renal vascular resistance or decreases in the glomerular capillary coefficient, the GFR may still return to nearly normal levels after the arterial blood pressure rises. Likewise, when tubular reabsorption is increased, as occurs with excessive aldosterone secretion, the urinary excretion rate is initially reduced but then returns to normal as arterial pressure rises. Thus, after hypertension develops, there may be no obvious sign of impaired excretion of sodium and water other than the hypertension. As explained in Chapter 19, normal excretion of sodium and water at an elevated arterial pressure means that pressure natriuresis and pressure diuresis have been reset to a higher arterial pressure.

Hypertension Caused by Patchy Renal Damage and Increased Renal Secretion of Renin. If one part of the kidney is ischemic and the remainder is not ischemic, such as occurs when one renal artery is severely constricted, the ischemic renal tissue secretes large quantities of renin. This secretion leads to increased formation of angiotensin II, which can cause hypertension. The most likely sequence of events in causing this hypertension, as discussed in Chapter 19, is (1) the ischemic kidney tissue itself excretes less than normal amounts of water and salt; (2) the renin secreted by the ischemic kidney, as well as the subsequent increased angiotensin II formation, affects the nonischemic kidney tissue, causing it also to retain salt and water; and (3) excess salt and water cause hypertension in the usual manner.

A similar type of hypertension can result when patchy areas of one or both kidneys become ischemic as a result of arteriosclerosis or vascular injury in specific portions of the kidneys. When this occurs, the ischemic nephrons excrete less salt and water but secrete greater amounts of renin, which causes increased angiotensin II formation. The high levels of angiotensin II then impair the ability of the surrounding otherwise normal nephrons to excrete sodium and water. As a result, hypertension develops, which restores the

overall excretion of sodium and water by the kidney, so balance between intake and output of salt and water is maintained, but at the expense of high blood pressure.

Kidney Diseases That Cause Loss of Entire Nephrons Lead to Renal Failure but May Not Cause Hypertension. Loss of large numbers of whole nephrons, such as occurs with the loss of one kidney and part of another kidney, almost always leads to renal failure if the amount of kidney tissue lost is great enough. If the remaining nephrons are normal and the salt intake is not excessive, this condition might not cause clinically significant hypertension because even a slight rise in blood pressure will raise the GFR and decrease tubular sodium reabsorption sufficiently to promote enough water and salt excretion in the urine, even with the few nephrons that remain intact. However, a patient with this type of abnormality may become severely hypertensive if additional stresses are imposed, such as eating a large amount of salt. In this case, the kidneys simply cannot clear adequate quantities of salt at a normal blood pressure with the small number of functioning nephrons that remain. Increased blood pressure restores excretion of salt and water to match intake of salt and water under steady-state conditions.

Effective treatment of hypertension requires that the kidneys' capability to excrete salt and water is increased, either by increasing GFR or by decreasing tubular reabsorption, so that balance between intake and renal excretion of salt and water excretion can be maintained at lower blood pressures. This can be achieved by drugs that block the effects of nervous and hormonal signals that cause the kidneys to retain salt and water (e.g., with β-adrenergic blockers, angiotensin receptor antagonists, or angiotensin-converting enzyme inhibitors) or with diuretic drugs that directly inhibit renal tubular reabsorption of salt and water.

Specific Tubular Disorders

In Chapter 27, we point out that several mechanisms are responsible for transporting different individual substances across the tubular epithelial membranes. In Chapter 3, we also point out that each cellular enzyme and each carrier protein is formed in response to a respective gene in the nucleus. If any required gene happens to be absent or abnormal, the tubules may be deficient in one of the appropriate carrier proteins or one of the enzymes needed for solute transport by the renal tubular epithelial cells. In other instances, too much of the enzyme or carrier protein is produced. Thus, many hereditary tubular disorders occur because of abnormal transport of individual substances or groups of substances through the tubular membrane. In addition, damage to the tubular epithelial membrane by toxins or ischemia can cause important renal tubular disorders.

Renal Glycosuria—Failure of the Kidneys to Reabsorb Glucose. In this condition the blood glucose concentration may be normal, but the transport mechanism for tubular reabsorption of glucose is greatly limited or absent. Consequently, despite a normal blood glucose level, large amounts of glucose pass into the urine each day. Because diabetes mellitus is also associated with the presence of glucose in the urine, renal glycosuria, which is a relatively benign condition, must be ruled out before making the diagnosis of diabetes mellitus.

Aminoaciduria—Failure of the Kidneys to Reabsorb Amino Acids. Some amino acids share mutual transport systems for reabsorption, whereas other amino acids have their own distinct transport systems. Rarely, a condition called *generalized aminoaciduria* results from deficient reabsorption of all amino acids; more frequently, deficiencies of specific carrier systems may result in (1) *essential cystinuria,* in which large amounts of cystine fail to be reabsorbed and often crystallize in the urine to form renal stones; (2) *simple glycinuria,* in which glycine fails to be reabsorbed; or (3) *beta-aminoisobutyricaciduria,* which occurs in about 5 percent of all people but apparently has no major clinical significance.

Renal Hypophosphatemia—Failure of the Kidneys to Reabsorb Phosphate. In renal hypophosphatemia, the renal tubules fail to reabsorb large enough quantities of phosphate ions when the phosphate concentration of the body fluids falls very low. This condition usually does not cause serious immediate abnormalities because the phosphate concentration of the extracellular fluid can vary widely without causing major cellular dysfunction. Over a long period, a low phosphate level causes diminished calcification of the bones, causing the person to develop rickets. This type of rickets is refractory to vitamin D therapy, in contrast to the rapid response of the usual type of rickets, as discussed in Chapter 79.

Renal Tubular Acidosis—Failure of the Tubules to Secrete Hydrogen Ions. In this condition, the renal tubules are unable to secrete adequate amounts of hydrogen ions. As a result, large amounts of sodium bicarbonate are continually lost in the urine. This causes a continued state of metabolic acidosis, as discussed in Chapter 30. This type of renal abnormality can be caused by hereditary disorders, or it can occur as a result of widespread injury to the renal tubules.

Nephrogenic Diabetes Insipidus—Failure of the Kidneys to Respond to Antidiuretic Hormone. Occasionally, the renal tubules do not respond to antidiuretic hormone, causing large quantities of dilute urine to be excreted. As long as the person is supplied with plenty of water, this condition seldom causes severe difficulty. However, when adequate quantities of water are not available, the person rapidly becomes dehydrated.

Fanconi's Syndrome—A Generalized Reabsorptive Defect of the Renal Tubules. Fanconi's syndrome is usually associated with increased urinary excretion of virtually all amino acids, glucose, and phosphate. In severe cases, other manifestations are also observed, such as (1) failure to reabsorb sodium bicarbonate, which results in metabolic acidosis; (2) increased excretion of potassium and sometimes calcium; and (3) nephrogenic diabetes insipidus.

There are multiple causes of Fanconi's syndrome, which results from a generalized inability of the renal tubular cells to transport various substances. Some of these causes include (1) hereditary defects in cell transport mechanisms, (2) toxins or drugs that injure the renal tubular epithelial cells, and (3) injury to the renal tubular cells as a result of ischemia. The proximal tubular cells are especially affected in Fanconi's syndrome caused by tubular injury because these cells reabsorb and secrete many of the drugs and toxins that can cause damage.

Bartter's Syndrome—Decreased Sodium, Chloride, and Potassium Reabsorption in the Loops of Henle. *Bartter's syndrome* is an autosomal recessive disorder caused by impaired function of the 1-sodium, 2-chloride, 1-potassium co-transporter, or by defects in potassium channels in the luminal

membrane or chloride channels in the basolateral membrane of the thick ascending loop of Henle. These disorders result in increased excretion of water, sodium, chloride, potassium, and calcium by the kidneys. The salt and water loss leads to mild volume depletion, resulting in activation of the renin-angiotensin-aldosterone system. The increased aldosterone and high distal tubular flow, due to impaired loop of Henle reabsorption, stimulate potassium and hydrogen secretion in the collecting tubules, leading to hypokalemia and metabolic alkalosis.

Gitelman's Syndrome—Decreased Sodium Chloride Reabsorption in the Distal Tubules. *Gitelman's syndrome* is an autosomal recessive disorder of the thiazide-sensitive sodium-chloride co-transporter in the distal tubules. Patients with Gitelman's syndrome have some of the same characteristics as patients with Bartter's syndrome—salt and water loss, mild water volume depletion, and activation of the renin-angiotensin-aldosterone system—although these abnormalities are usually less severe in Gitelman's syndrome.

Because the tubular defects in Bartter's or Gitelman's syndrome cannot be corrected, treatment is usually focused on replacing the losses of sodium chloride and potassium. Some studies suggest that blockade of prostaglandin synthesis with nonsteroidal anti-inflammatory drugs and administration of aldosterone antagonists, such as spironolactone, may be useful in correcting the hypokalemia.

Liddle's Syndrome—Increased Sodium Reabsorption. *Liddle's syndrome* is a rare autosomal dominant disorder resulting from various mutations in the amiloride-sensitive epithelial sodium channel (ENaC) in the distal and collecting tubules. These mutations cause excessive activity of ENaC, resulting in increased reabsorption of sodium and water, hypertension, and metabolic alkalosis similar to the changes that occur with oversecretion of aldosterone (primary aldosteronism).

Patients with Liddle's syndrome, however, have decreased levels of aldosterone due to sodium retention and compensatory decreases in renin secretion and angiotensin II levels, which, in turn, decrease adrenal secretion of aldosterone. Fortunately, Liddle's syndrome can be treated with the diuretic amiloride, which blocks the excessive ENaC activity.

Treatment of Renal Failure by Transplantation or by Dialysis with an Artificial Kidney

Severe loss of kidney function, either acutely or chronically, is a threat to life and requires removal of toxic waste products and restoration of body fluid volume and composition toward normal. This can be accomplished by kidney transplantation or by dialysis with an artificial kidney. More than 500,000 patients in the United States are currently receiving some form of ESRD therapy.

Successful transplantation of a single donor kidney to a patient with ESRD can restore kidney function to a level that is sufficient to maintain essentially normal homeostasis of body fluids and electrolytes. Approximately 16,000 kidney transplants are performed each year in the United States. Patients who receive kidney transplants typically live longer and have fewer health problems than those who are maintained on dialysis. Maintenance of immunosuppressive therapy is required for almost all patients to help prevent acute rejection and loss of the transplanted kidney. The side effects of drugs that suppress the immune system include increased risk for infections and for some cancers, although the amount of immunosuppressive therapy can usually be reduced over time to greatly reduce these risks.

More than 350,000 people in the United States with irreversible renal failure or total kidney removal are being maintained chronically by dialysis with artificial kidneys. Dialysis is also used in certain types of acute renal failure to tide the patient over until the kidneys resume their function. If the loss of kidney function is irreversible, it is necessary to perform dialysis chronically to maintain life. Because dialysis cannot maintain completely normal body fluid composition and cannot replace all the multiple functions performed by the kidneys, the health of patients maintained on artificial kidneys usually remains significantly impaired.

Basic Principles of Dialysis. The basic principle of the artificial kidney is to pass blood through minute blood channels bounded by a thin membrane. On the other side of the membrane is a *dialyzing fluid* into which unwanted substances in the blood pass by diffusion.

Figure 31-8 shows the components of one type of artificial kidney in which blood flows continually between two thin membranes of cellophane; outside the membrane is a dialyzing fluid. The cellophane is porous enough to allow the constituents of the plasma, except the plasma proteins, to diffuse in both directions—from plasma into the dialyzing fluid or from the dialyzing fluid back into the plasma.

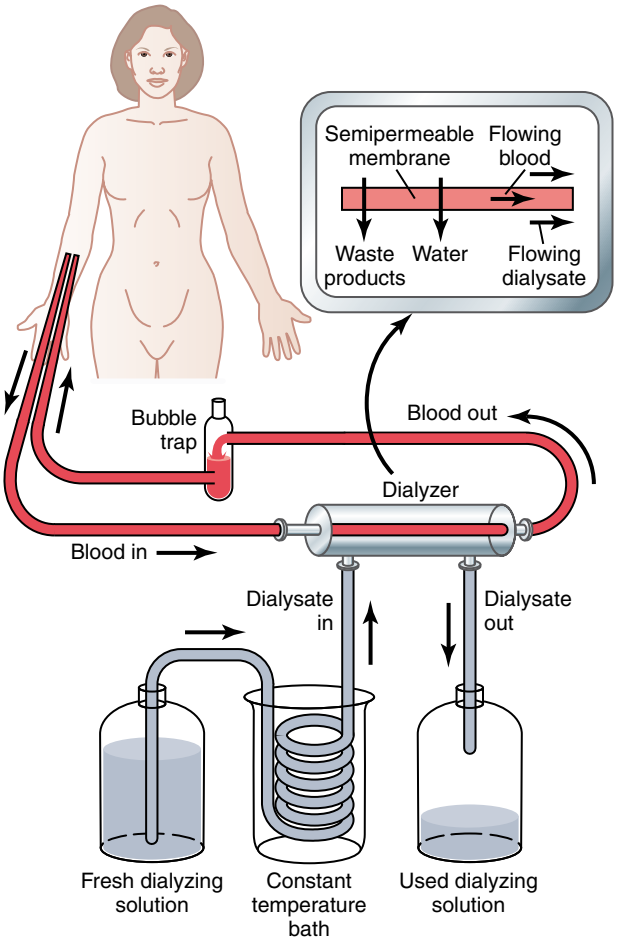


Figure 31-8 Principles of dialysis with an artificial kidney.

If the concentration of a substance is greater in the plasma than in the dialyzing fluid, there will be a net transfer of the substance from the plasma into the dialyzing fluid.

The rate of movement of solute across the dialyzing membrane depends on (1) the concentration gradient of the solute between the two solutions, (2) the permeability of the membrane to the solute, (3) the surface area of the membrane, and (4) the length of time that the blood and fluid remain in contact with the membrane.

Thus, the maximum rate of solute transfer occurs initially when the concentration gradient is greatest (when dialysis is begun) and slows down as the concentration gradient is dissipated. In a flowing system, as is the case with "hemodialysis," in which blood and dialysate fluid flow through the artificial kidney, the dissipation of the concentration gradient can be reduced and diffusion of solute across the membrane can be optimized by increasing the flow rate of the blood, the dialyzing fluid, or both.

In normal operation of the artificial kidney, blood flows continually or intermittently back into the vein. The total amount of blood in the artificial kidney at any one time is usually less than 500 milliliters, the rate of flow may be several hundred milliliters per minute, and the total diffusion surface area is between 0.6 and 2.5 square meters. To prevent coagulation of the blood in the artificial kidney, a small amount of heparin is infused into the blood as it enters the artificial kidney. In addition to diffusion of solutes, mass transfer of solutes and water can be produced by applying a hydrostatic pressure to force the fluid and solutes across the membranes of the dialyzer; such filtration is called *bulk flow.*

Dialyzing Fluid. Table 31-7 compares the constituents in a typical dialyzing fluid with those in normal plasma and uremic plasma. Note that the concentrations of ions and other substances in dialyzing fluid are not the same as the concentrations in normal plasma or in uremic plasma. Instead, they are adjusted to levels that are needed to cause appropriate movement of water and solutes through the membrane during dialysis.

Note that there is no phosphate, urea, urate, sulfate, or creatinine in the dialyzing fluid; however, these are present in high concentrations in the uremic blood. Therefore, when a uremic patient is dialyzed, these substances are lost in large quantities into the dialyzing fluid.

The effectiveness of the artificial kidney can be expressed in terms of the amount of plasma that is cleared of different substances each minute, which, as discussed in Chapter 27, is the primary means for expressing the functional effectiveness of the kidneys themselves to rid the body of unwanted substances. Most artificial kidneys can clear urea from the plasma at a rate of 100 to 225 ml/min, which shows that at least for the excretion of urea, the artificial kidney can function about twice as rapidly as two normal kidneys together, whose urea clearance is only 70 ml/min. Yet the artificial kidney is used for only 4 to 6 hours per day, three times a week. Therefore, the overall plasma clearance is still considerably limited when the artificial kidney replaces the normal kidneys. Also, it is important to keep in mind that the artificial kidney cannot replace some of the other functions of the kidneys, such as secretion of erythropoietin, which is necessary for red blood cell production.

Table 31-7 Comparison of Dialyzing Fluid with Normal and Uremic Plasma

Constituent	Normal Plasma	Dialyzing Fluid	Uremic Plasma
Electrolytes (mEq/L)			
Na^+	142	133	142
K^+	5	1.0	7
Ca^{++}	3	3.0	2
Mg^{++}	1.5	1.5	1.5
Cl^-	107	105	107
HCO_3^-	24	35.7	14
$Lactate^-$	1.2	1.2	1.2
$HPO_4^=$	3	0	9
$Urate^-$	0.3	0	2
$Sulfate^=$	0.5	0	3
Nonelectrolytes			
Glucose	100	125	100
Urea	26	0	200
Creatinine	1	0	6

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