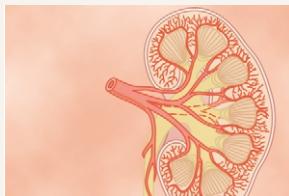


Urine Formation by the Kidneys:

I. Glomerular Filtration, Renal Blood Flow, and Their Control



Multiple Functions of the Kidneys in Homeostasis

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 in large part by the kidneys. This regulatory function of the kidneys maintains the stable environment of the cells necessary for them 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, it is important to recognize that the kidneys serve multiple 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 intake 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

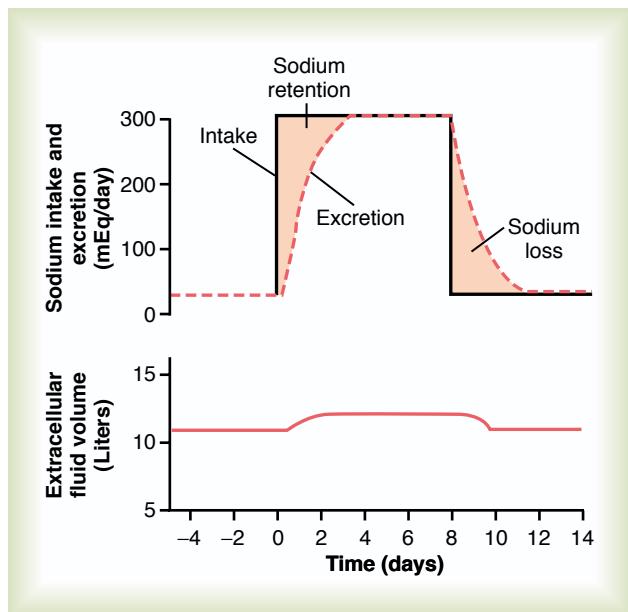


Figure 26-1

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.

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.

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 vasoactive factors or substances, such as *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, 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 D₃ Production. The kidneys produce the active form of vitamin D, 1,25-dihydroxyvitamin D₃ (*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.

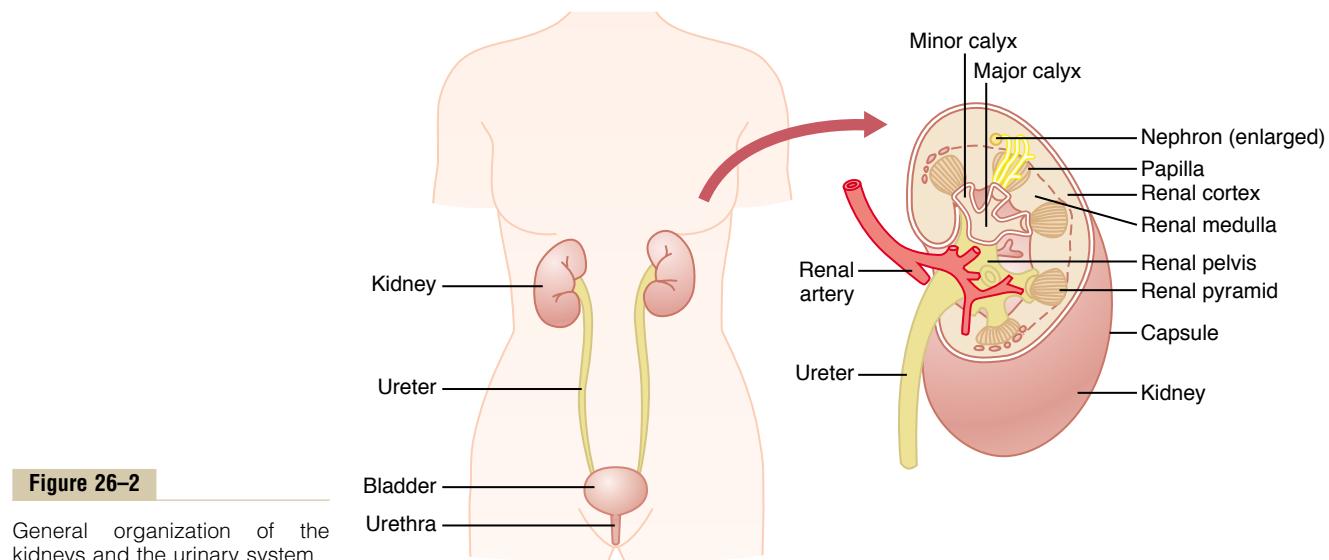


Figure 26-2

General organization of the kidneys and the urinary system.

If the kidney is bisected from top to bottom, the two major regions that can be visualized are the outer *cortex* and the inner region referred to as the *medulla*. The medulla is divided into multiple 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 in later in this chapter.

Renal Blood Supply

Blood flow to the two kidneys is normally about 22 per cent 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 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 that it has 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

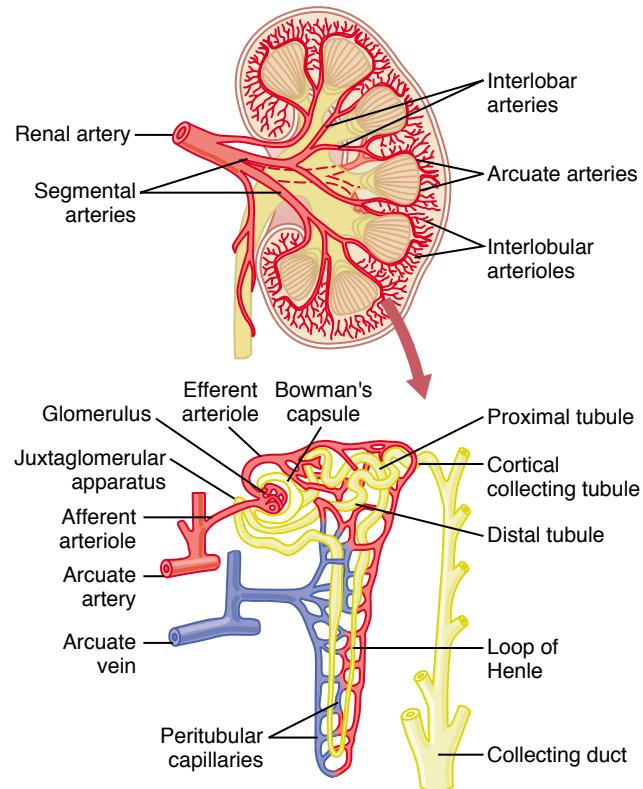


Figure 26-3

Section of the human kidney showing the major vessels that supply the blood flow to the kidney and schematic of the micro-circulation of each nephron.

glomerular filtration, tubular reabsorption, or both in response to body homeostatic demands.

The peritubular capillaries empty into the vessels of the venous system, which run parallel to the arteriolar vessels and 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 1 million *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 per cent every 10 years; thus, at age 80, many people have 40 per cent 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 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 has returned 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, which is actually a plaque in its wall, known as the *macula densa*. As we discuss 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

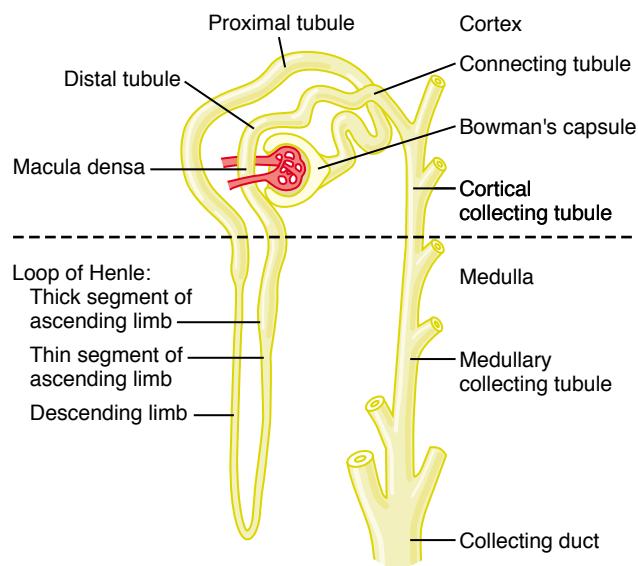


Figure 26-4

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

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).

About 20 to 30 per cent 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.

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.

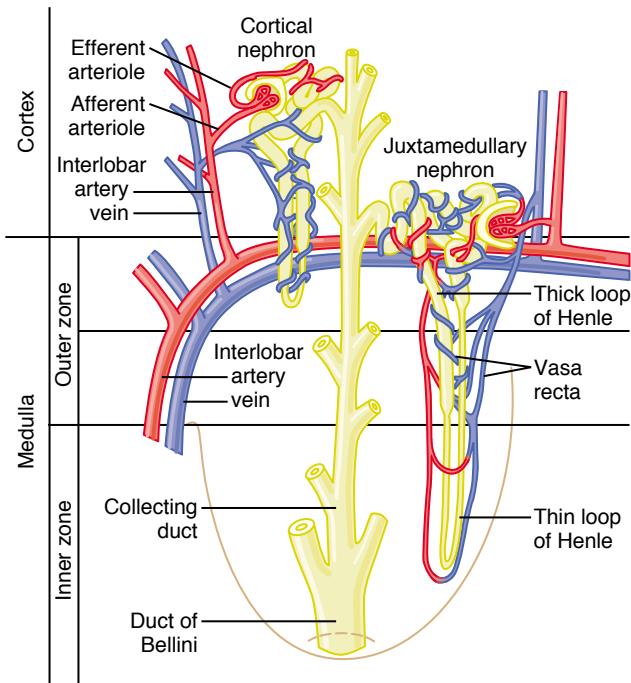


Figure 26-5

Schematic of relations between blood vessels and tubular structures and differences between cortical and juxtamedullary nephrons.

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 and Nervous Connections 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 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.

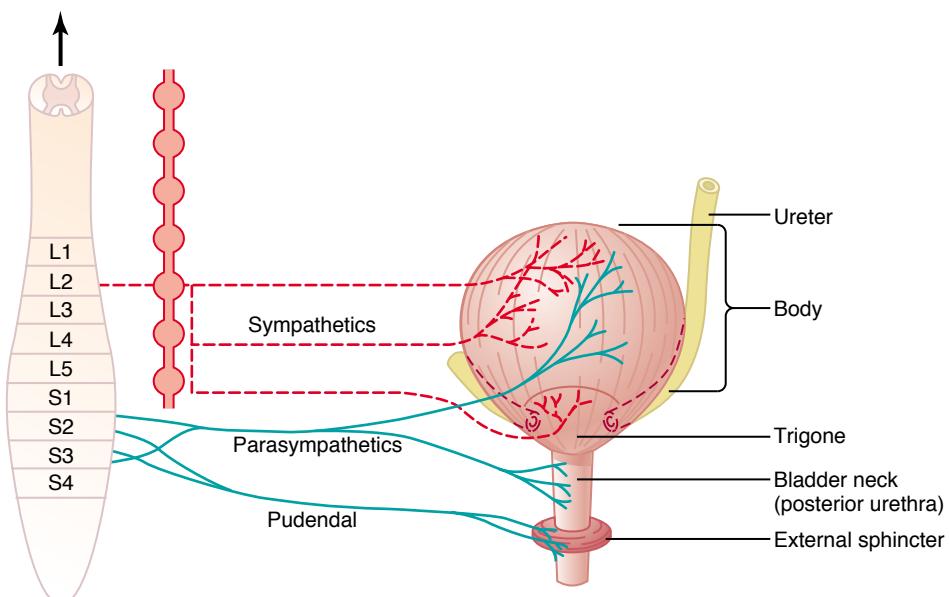


Figure 26-6

Urinary bladder and its innervation.

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 S-2 and S-3. 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 L-2 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. 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 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 that 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 26–7 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 has 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.

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

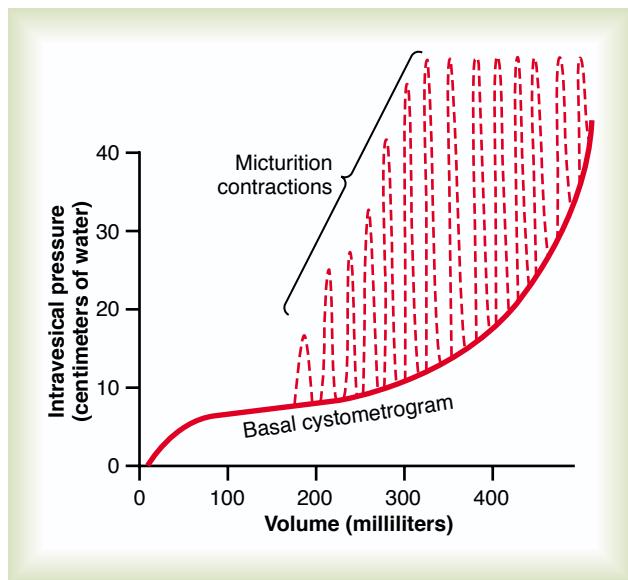


Figure 26-7

Normal cystometrogram, showing also acute pressure waves (dashed spikes) caused by micturition reflexes.

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 26-7, 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 to 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 a completely 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 continual 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 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 26–8: (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,

$$\text{Urinary excretion rate} = \text{Filtration rate} - \text{Reabsorption rate} + \text{Secretion rate}$$

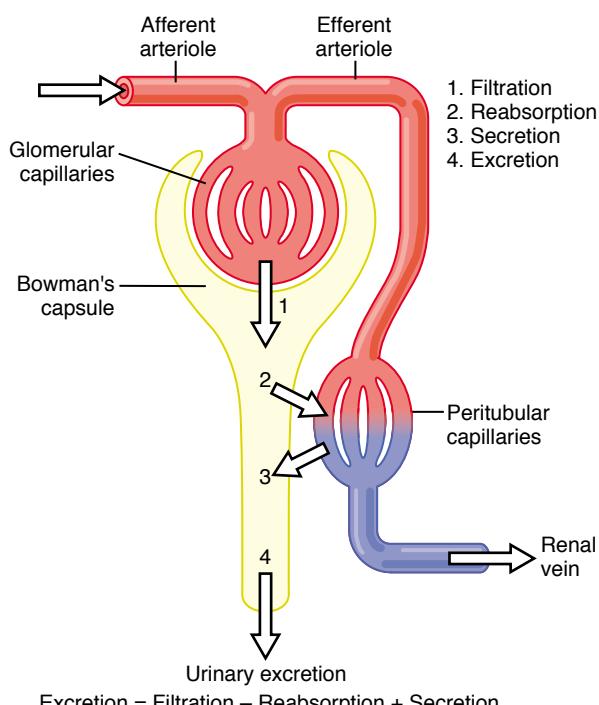


Figure 26–8

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.

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 that 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 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 26–9 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.

In panel C, the substance is freely filtered at the glomerular capillaries but is not excreted into the

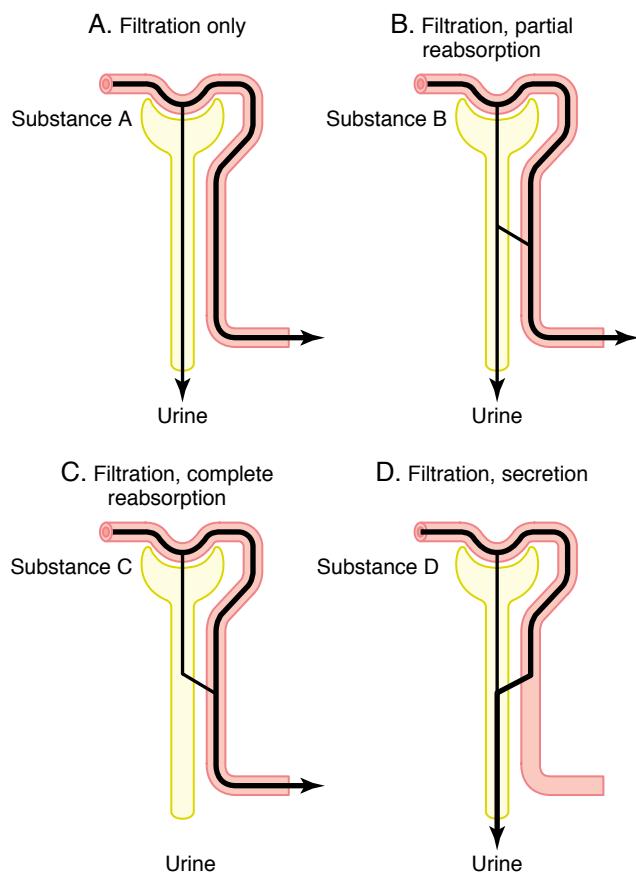


Figure 26-9

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.

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 that their excretion rates are high. Conversely, electrolytes, such as sodium ions, chloride ions, and bicarbonate ions, are highly reabsorbed, so that 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, resulting in 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 per cent (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 primarily 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 kidney 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 that 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. 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 Per Cent 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 per cent 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 26–10). 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.

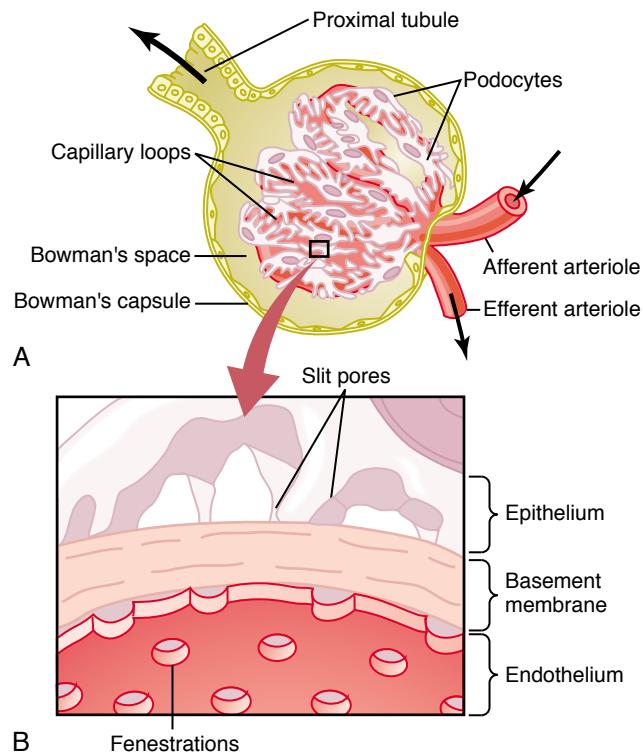


Figure 26–10

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).

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 of the capillaries (see Figure 26–10). 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.

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

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.

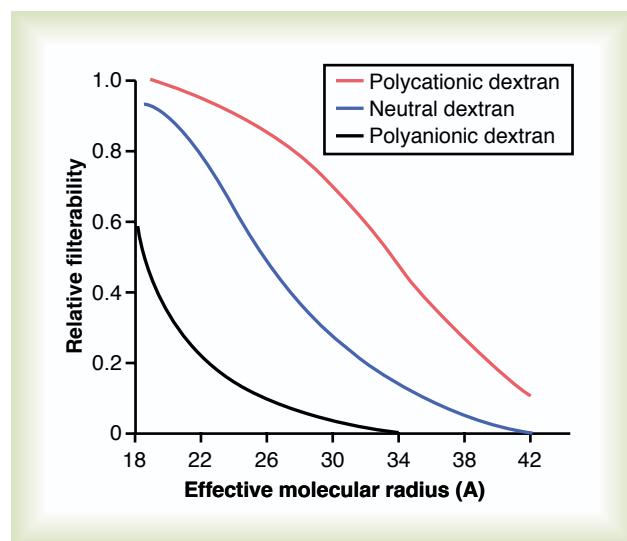
Table 26-1 lists the effect of molecular size on filterability of different molecules. A filterability of 1.0 means that the substance is filtered as freely as water; a filterability of 0.75 means that the substance is filtered only 75 per cent as rapidly as water. Note that electrolytes such as sodium 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 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 26-11 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 of the lower-molecular-weight proteins, especially albumin, are filtered and appear

**Figure 26-11**

Effect of size 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.

in the urine, a condition known as *proteinuria* or *albuminuria*.

Determinants of the GFR

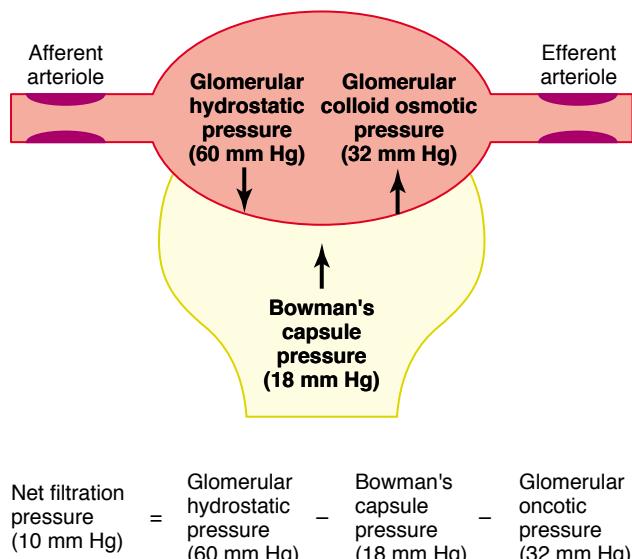
The GFR is determined by (1) the sum of the hydrostatic and colloid osmotic forces across the glomerular membrane, which gives the *net filtration pressure*, and (2) the glomerular capillary filtration coefficient, K_f . Expressed mathematically, the GFR equals the product of K_f and the net filtration 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 26-12). 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

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

**Figure 26-12**

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

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 26-12):

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

$$\text{Net filtration pressure} = 60 - 18 - 32 = +10 \text{ mm Hg}$$

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

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:

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

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 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 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 per cent (Figure 26-13). 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

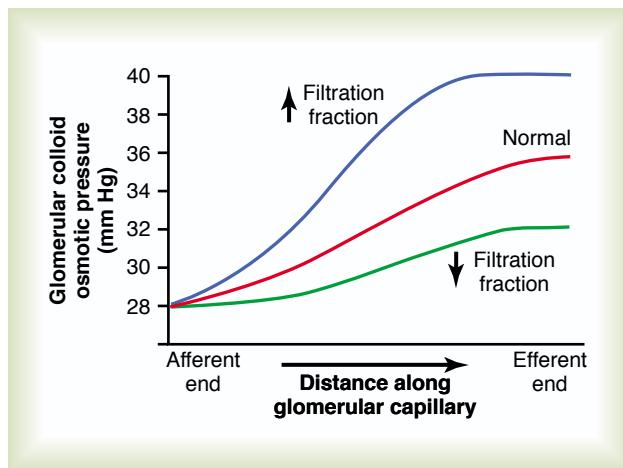


Figure 26-13

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.

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.

Increasing the filtration fraction also concentrates the plasma proteins and raises the glomerular colloid osmotic pressure (see Figure 26-13). 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.*

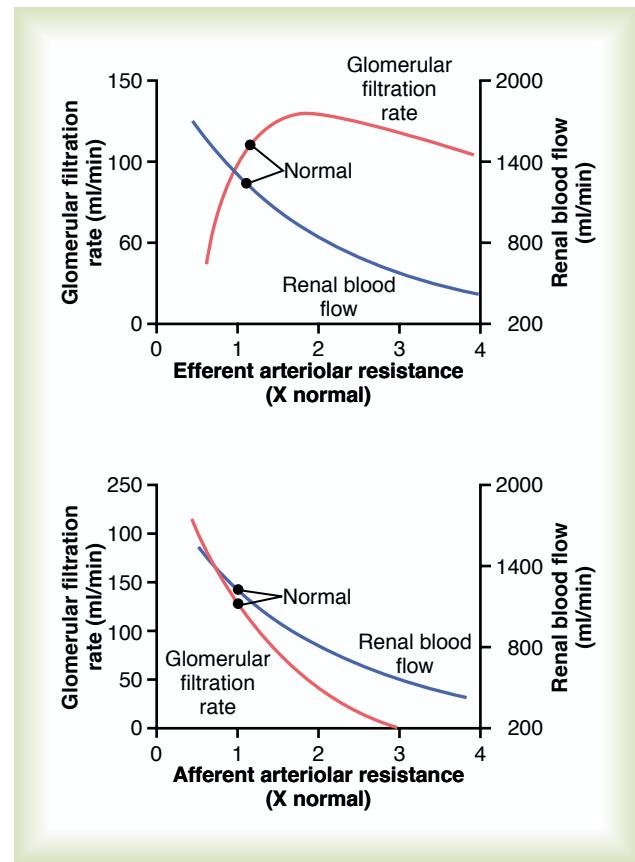


Figure 26-14

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

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 26-14).

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 26–14). 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.

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, non-linear 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.

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.

Renal Blood Flow

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

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 26–15). 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.

Determinants of Renal Blood Flow

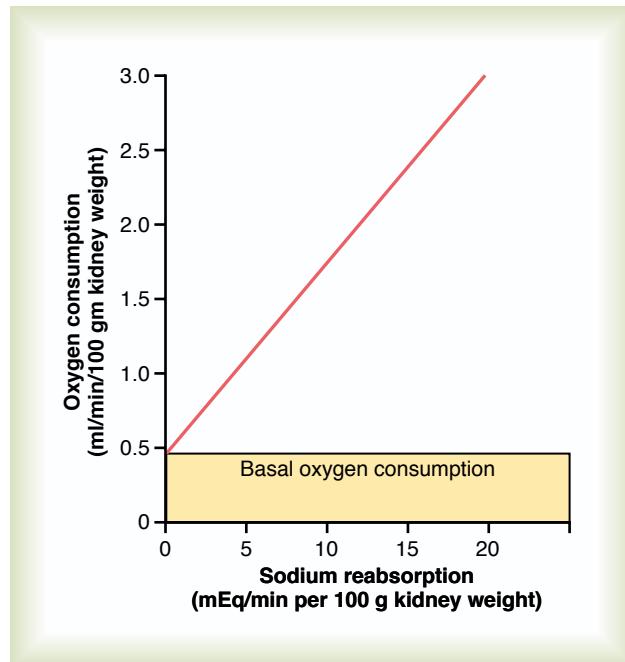
Renal blood flow is determined by the pressure gradient across the renal vasculature (the difference between renal artery and renal vein hydrostatic pressures), divided by the total renal vascular resistance:

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

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).

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

Vessel	Pressure in Vessel (mm Hg)		Per Cent 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

**Figure 26-15**

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.)

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.

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 per cent 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 a 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

There are several hormones and autacoids that 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 also are 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.

Angiotensin II Constricts Efferent Arterioles. 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 as well as in the systemic circulation. Because angiotensin II preferentially constricts efferent arterioles, 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 preserve GFR and maintain 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 this normal formation of nitric oxide increases renal vascular resistance and decreases GFR and urinary sodium excretion, eventually causing high blood pressure. In some hypertensive patients, impaired nitric oxide production could be the cause of increased renal vasoconstriction and increased 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 (PGE₂ and PGI₂) 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

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	↑

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 26–16).

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.

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 changes GFR only a few percentage points. 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

The autoregulatory mechanisms of the kidney are not 100 per cent perfect, but 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 per cent 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.

But in reality, such a change in arterial pressure exerts 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 allow 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.

Role of Tubuloglomerular Feedback in 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

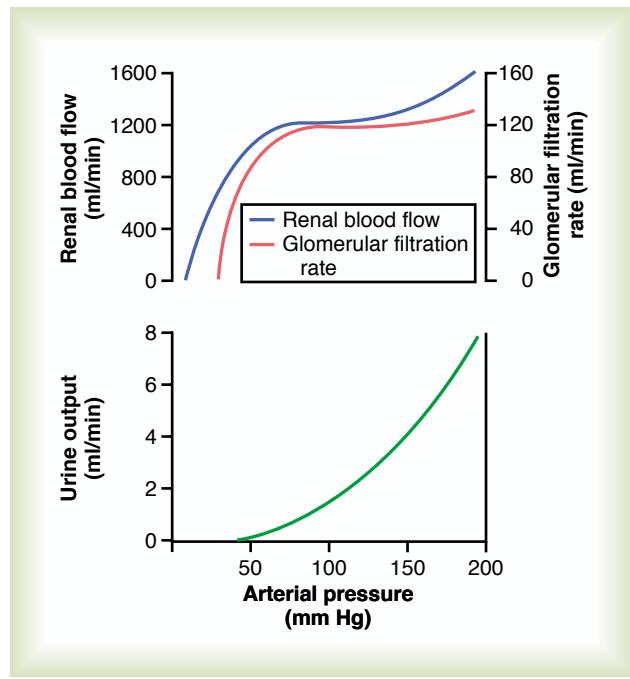


Figure 26–16

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

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 26–17).

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

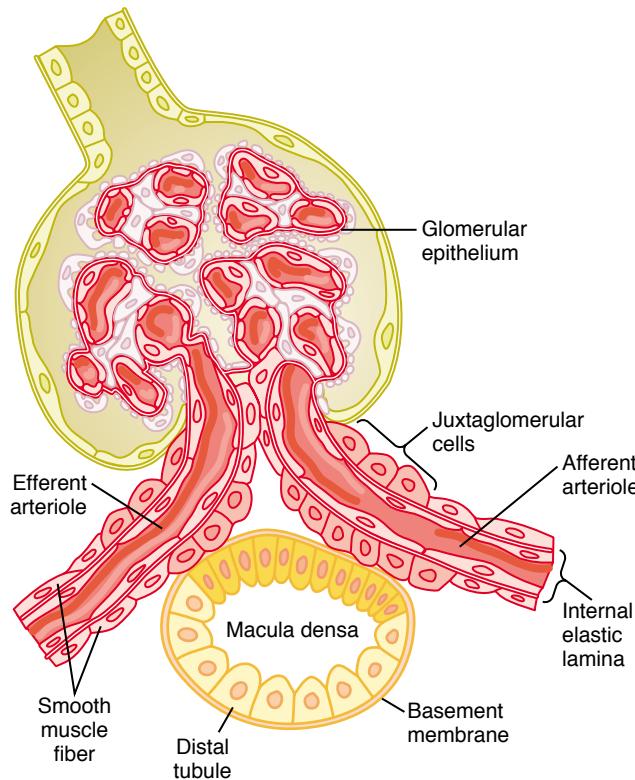


Figure 26–17

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

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 26–18): (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 returning 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.

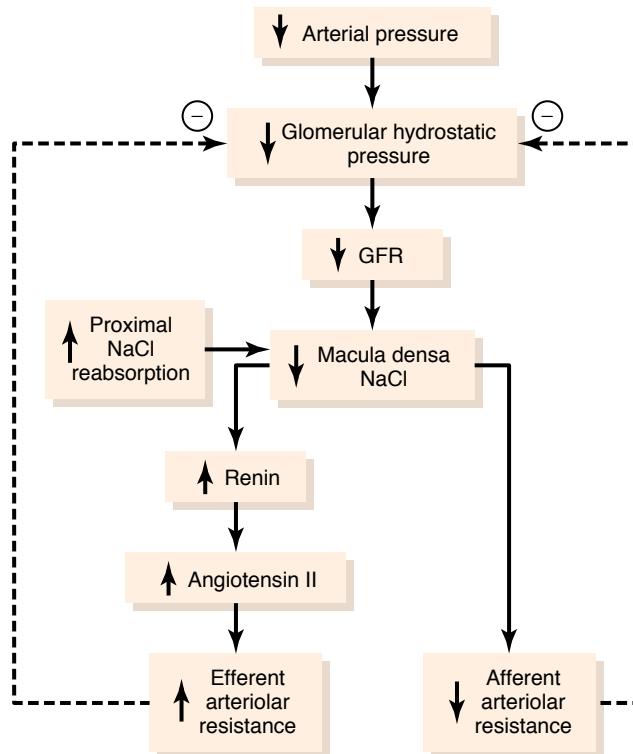


Figure 26–18

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

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 the formation of angiotensin II (angiotensin-converting enzyme inhibitors) or that block the action of angiotensin II (angiotensin II 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 overdistention 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.

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 per cent within 1 or 2 hours after a person eats a high-protein meal.

The exact mechanisms by which this occurs are still not completely understood, but one possible explanation 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, 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 26-18).

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.

References

- Beeuwkes R III: The vascular organization of the kidney. Annu Rev Physiol 42:531, 1980.
- Bell PD, Lapointe JY, Peti-Peterdi J: Macula densa cell signaling. Annu Rev Physiol 65:481, 2003.

Blantz RC, Deng A, Lortie M, et al: The complex role of nitric oxide in the regulation of glomerular ultrafiltration. *Kidney Int* 61:782, 2002.

Cowley AW Jr, Mori T, Mattson D, Zou AP: Role of renal NO production in the regulation of medullary blood flow. *Am J Physiol Regul Integr Comp Physiol* 284:R1355, 2003.

Davis MJ, Hill MA: Signaling mechanisms underlying the vascular myogenic response. *Physiol Rev* 79:387, 1999.

Deen WM, Lazzara MJ, Myers BD: Structural determinants of glomerular permeability. *Am J Physiol Renal Physiol* 281:F579, 2001.

DiBona GF: Neural control of the kidney: past, present, and future. *Hypertension* 41:621, 2003.

Hall JE: Angiotensin II and long-term arterial pressure regulation: the overriding dominance of the kidney. *J Am Soc Nephrol* 10 (Suppl 12):s258, 1999.

Hall JE, Brands MW: The renin-angiotensin-aldosterone system: renal mechanisms and circulatory homeostasis. In Seldin DW, Giebisch G (eds): *The Kidney—Physiology and Pathophysiology*, 3rd ed. New York: Raven Press, 2000, pp 1009-1046.

Haraldsson B, Sörensson J: Why do we not all have proteinuria? An update of our current understanding of the glomerular barrier. *News Physiol Sci* 19:7, 2004.

Kriz W, Kaissling B: Structural organization of the mammalian kidney. In Seldin DW, Giebisch G (eds): *The Kidney—Physiology and Pathophysiology*, 3rd ed. New York: Raven Press, 2000, pp 587-654.

Navar LG, Kobori H, Prieto-Carrasquero M: Intrarenal angiotensin II and hypertension. *Curr Hypertens Rep* 5:135, 2003.

Pallone TL, Zhang Z, Rhinehart K: Physiology of the renal medullary microcirculation. *Am J Physiol Renal Physiol* 284:F253, 2003.

Roman RJ: P-450 metabolites of arachidonic acid in the control of cardiovascular function. *Physiol Rev* 82:131, 2002.

Schnermann J, Levine DZ: Paracrine factors in tubuloglomerular feedback: adenosine, ATP, and nitric oxide. *Annu Rev Physiol* 65:501, 2003.

Whelton A: Renal aspects of treatment with conventional nonsteroidal anti-inflammatory drugs versus cyclooxygenase-2-specific inhibitors. *Am J Med* 110 (Suppl 3A):33S, 2001.