**The Urinary System: Functional Anatomy**

**and Urine Formation by the Kidneys**

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 electrolyte 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

• Regulation of erythrocyte production

• Secretion, metabolism, and excretion of hormones

• Gluconeogenesis

**Excretion of Metabolic Waste Products, Foreign Chemicals, Drugs, and Hormone Metabolites.**

Thekidneys are the primary means for eliminating wasteproducts of metabolism that are no longer needed by thebody. These products include *urea* (from the metabolismof 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. Although temporary (or cyclic) imbalances of water and electrolytes may occur in various physiological and pathophysiological conditions associated with altered intake or renal

excretion, the maintenance of life depends on restoration of water and electrolyte balance.

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 highlevel of 300 mEq/day. Within 2 to 3 he sodium intake, renal excretion also increases to about 300 mEq/day so that a balance between intake and output is rapidly 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 phenomenon 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.**

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 33. 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. 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.

PHYSIOLOGICAL 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 . 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 the bladder is 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*.

**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 formation. 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. These arterioles 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.

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 UNITOF THE KIDNEY**

Each human kidney contains about 800,000 to 1,000,000 *nephrons,* each of which is capable of forming urine. The kidney cannot regenerate new nephrons. Therefore, with renal injury, disease, or normal aging, the number of nephrons gradually decreases. After age 40 years, the number of functioning nephrons usually decreases about 10 percent every 10 years; thus, at age 80 years, many people have 40 percent fewer functioning nephrons

than they did at age 40 years. 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. 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 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. 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. The distal tubule 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 nephronhas all the components described earlier, there aresome differences, depending on how deep the nephronlies within the kidney mass. The nephrons that have

glomeruli located in the outer cortex are called *cortical nephrons;* they have short loops of Henle that penetrateonly a short distance into the medulla .About 20 to 30 percent of the nephrons have glomerulithat lie deep in the renal cortex near the medullaand are called *juxtamedullary nephrons.* These nephronshave long loops of Henle that dip deeply into the medulla,in some cases all the way to the tips of the renalpapillae.The vascular structures supplying the juxtamedullarynephrons also differ from those supplying the corticalnephrons. For the cortical nephrons, the entire tubularsystem is surrounded by an extensive network of peritubularcapillaries. For the juxtamedullary nephrons, longefferent arterioles extend from the glomeruli down intothe outer medulla and then divide into specialized peritubularcapillaries called *vasa recta* that extend downwardinto the medulla, lying side by side with the loopsof Henle. Like the loops of Henle, the vasa recta returntoward the cortex and empty into the cortical veins. Thisspecialized network of capillaries in the medulla plays anessential role in the formation of a concentrated urine .

MICTURITION

Micturition is the process by which the urinary bladder empties when it becomes filled. This process involves two main steps: First, the bladder fills progressively until the tension in its walls rises above a threshold level. This tension 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.

**PHYSIOLOGICAL ANATOMY OF THE BLADDER**

The urinary bladder, shown in, 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. 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. 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 fibers 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 fibers 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. 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, and thus 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, it 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 nervefibers. When a ureter becomes blocked (e.g., by a ureteralstone), intense reflex constriction occurs, which is associatedwith severe pain. Also, the pain impulses cause asympathetic reflex back to the kidney to constrict therenal arterioles, thereby decreasing urine output from thekidney. This effect is called the *ureterorenal reflex* and isimportant for preventing excessive flow of fluid into thepelvis of a kidney with a blocked ureter.

**Filling of the Bladder and Bladder Wall Tone; the Cystometrogram**

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. 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 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, 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 selfregenerative 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 micturitionas 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 action 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 Destructionof Sensory Nerve Fibers.** Micturition reflex contractioncannot 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 occurrence is called *overflow incontinence.* A common cause of atonic bladder is crush injury to thesacral 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 damagedabove 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. Duringthe first few days to several weeks after the damage to thecord has occurred, the micturition reflexes are suppressedbecause of the state of “spinal shock” caused by the suddenloss of facilitative impulses from the brain stem and cerebrum.However, if the bladder is emptied periodically bycatheterization to prevent bladder injury caused by overstretchingof the bladder, the excitability of the micturitionreflex gradually increases until typical micturition reflexesreturn; then, periodic (but unannounced) bladder emptyingoccurs.Some patients can still control urination in this conditionby stimulating the skin (scratching or tickling) in thegenital region, which sometimes elicits a micturition reflex.

**Uninhibited Neurogenic Bladder Caused by Lack of Inhibitory Signals from the Brain.**

Another abnormalityof micturition is the so-called *uninhibited neurogenic**bladder,* which results in frequent and relatively uncontrolledmicturition. This condition derives from partialdamage in the spinal cord or the brain stem that interruptsmost of the inhibitory signals. Therefore, facilitativeimpulses 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: (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 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. 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 pattern 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

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.



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 usually 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, even slight changes 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**

The first step in urine formation is the filtration of large amounts of fluid through the glomerular capillaries into Bowman’s capsule—almost 180 liters each day. Most of

this filtrate is reabsorbed, leaving only about 1 liter of fluid to be excreted each day, although the renal fluid excretion rate may be highly variable depending on fluid intake. The high rate of glomerular filtration depends on a high rate of kidney blood flow, as well as the special properties of the glomerular capillary membranes. In this chapter we discuss the physical forces that determine the glomerular filtration rate (GFR), as well as the physiological mechanisms that regulate GFR and renal blood flow.

**COMPOSITION OF THE GLOMERULAR FILTRATE**

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 RENAL PLASMA FLOW**

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 (Kf),

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 Kf. 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, which 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:

Filtration fraction = GFR/Renalplasma 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. 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 smaller than the fenestrae of the liver. Although the fenestrations are relatively

large, endothelial cell proteins 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. 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.



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).

**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 27-1 lists the effect of molecular size on filterability of different molecules.

Table (27-1) 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 |

A filterability of 1.0 means that the substance is filtered as freely as water, whereas 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 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 27-3** 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 are negatively charged molecules. Neutral dextrans are also filtered more readily than are 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.* The cause for this loss of negative charges is still unclear but is believed to be related to an immunological response with abnormal T-cell secretion of cytokines that reduce anions in the glomerular capillary or podocyte proteins. 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 in the urine, a condition known as *proteinuria* or *albuminuria.* Minimal change nephropathy is most common in young children but can also occur in adults, especially in those who have autoimmune disorders.

 **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 Kf. Expressed mathematically, the GFR equals the product of Kf and the net filtration pressure:



the proteins in Bowman’s capsule (πB), 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


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** **27-4**). These forces include (1) hydrostatic pressure inside the glomerular capillaries (glomerular hydrostatic pressure, PG), which promotes filtration; (2) the hydrostatic pressure in Bowman’s capsule (PB) outside the capillaries, which opposes filtration; (3) the colloid osmotic pressure of the glomerular capillary plasma proteins (πG), which the proteins in Bowman’s capsule (πB), which promotes filtration.opposes filtration; and (4) the colloid osmotic pressure of the proteins in Bowman’s capsule (πB), which promotes filtration.



**Figure (27-4) Summary of forces causing filtration by the glomerular capillaries. The values shown are estimates for healthy humans**