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Plasma undergoes modification to urine in the nephron.
— Arthur Grollman, in Clinical Physiology: The Functional Pathology of Disease, 1957

Background Basics
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A bout c.e. 100, Aretaeus the Cappadocian wrote, “Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine. . . . The patients never stop making water [urinating], but the flow is incessant, as if from the opening of aqueducts.” Physicians have known since ancient times that urine, the fluid waste produced by the kidneys, reflects the functioning of the body. To aid them in their diagnosis of illness, they even carried special flasks for the collection and inspection of patients’ urine.

The first step in examining a urine sample is to determine its color. Is it dark yellow (concentrated), pale straw (dilute), red (indicating the presence of blood), or black (indicating the presence of hemoglobin metabolites)? One form of malaria was called blackwater fever because metabolized hemoglobin from the abnormal breakdown of red blood cells turned victims’ urine black or dark red.

Physicians also inspected urine samples for clarity, froth (indicating abnormal presence of proteins), smell, and even taste. Physicians who did not want to taste the urine themselves would allow their students the “privilege” of tasting it for them. A physician without students might expose insects to the urine and study their reaction.

Probably the most famous example of using urine for diagnosis was the taste test for diabetes mellitus, historically known as the honey-urine disease. Diabetes is an endocrine disorder characterized by the presence of glucose in the urine. The urine of diabetics tasted sweet and attracted insects, making the diagnosis clear.

Today we have much more sophisticated tests for glucose in the urine, but the first step of a urinalysis is still to examine the color, clarity, and odor of the urine. In this chapter you will learn why we can tell so much about how the body is functioning by what is present in the urine.

### Functions of the Kidneys

If you ask people on the street, “What is the most important function of the kidney?” they are likely to say, “The removal of wastes.” Actually, the most important function of the kidney is the homeostatic regulation of the water and ion content of the blood, also called salt and water balance or fluid and electrolyte balance. Waste removal is important, but disturbances in blood volume or ion levels cause serious medical problems before the accumulation of metabolic wastes reaches toxic levels.

The kidneys maintain normal blood concentrations of ions and water by balancing intake of those substances with their excretion in the urine, obeying the principle of mass balance. We can divide kidney function into six general areas:

1. **Regulation of extracellular fluid volume and blood pressure.** When extracellular fluid volume decreases, blood pressure also decreases. If ECF volume and blood pressure fall too low, the body cannot maintain adequate blood flow to the brain and other essential organs. The kidneys work in an integrated fashion with the cardiovascular system to ensure that blood pressure and tissue perfusion remain within an acceptable range.
2. **Regulation of osmolality.** The body integrates kidney function with behavioral drives, such as thirst, to maintain blood osmolality at a value close to 290 mOsM. We examine the reflex pathways for regulation of ECF volume and osmolality later.
3. **Maintenance of ion balance.** The kidneys keep concentrations of key ions within a normal range by balancing dietary intake with urinary loss. Sodium (Na⁺) is the major ion involved in the regulation of extracellular fluid volume and osmolality. Potassium (K⁺) and calcium (Ca²⁺) concentrations are also closely regulated.
4. **Homeostatic regulation of pH.** The pH of plasma is normally kept within a narrow range. If extracellular fluid becomes too acidic, the kidneys remove H⁺ and conserve bicarbonate ions (HCO₃⁻), which act as a buffer. Conversely, when extracellular fluid becomes too alkaline, the kidneys remove HCO₃⁻ and conserve H⁺. The kidneys play a significant role in pH homeostasis, but they do not correct pH disturbances as rapidly as the lungs do.
5. **Excretion of wastes.** The kidneys remove metabolic waste products and foreign substances, such as drugs and environmental toxins. Metabolic wastes include creatinine from muscle metabolism and the nitrogenous wastes urea and uric acid. A metabolite of hemoglobin called urobilinogen gives urine its characteristic yellow color. Hormones are another endogenous substance the kidneys clear from the blood. Examples of foreign substances that the kidneys actively remove include the artificial sweetener saccharin and the anion benzoate, part of
Although the kidneys are not endocrine glands, they play important roles in three endocrine pathways. Kidney cells synthesize erythropoietin, the cytokine/hormone that regulates red blood cell synthesis. They also release renin, an enzyme that regulates the production of hormones involved in sodium balance and blood pressure homeostasis. Renal enzymes help convert vitamin D3 into a hormone that regulates calcium balance.

The kidneys, like many other organs in the body, have a tremendous reserve capacity. By most estimates, you must lose nearly three-fourths of your kidney function before homeostasis begins to be affected. Many people function perfectly normally with only one kidney, including the one person in 1000 born with only one kidney (the other fails to develop during gestation) or those people who donate a kidney for transplantation.

Anatomy of the Urinary System

The urinary system is composed of the kidneys and accessory structures (Fig. 19.1a). The study of kidney function is called renal physiology, from the Latin word renes, meaning “kidneys.”

The Urinary System Consists of Kidneys, Ureters, Bladder, and Urethra

Let’s begin by following the route a drop of water takes on its way from plasma to excretion in the urine. In the first step of urine production, water and solutes move from plasma into the hollow tubules (nephrons) that make up the bulk of the paired kidneys. These tubules modify the composition of the fluid as it passes through. The modified fluid leaves the kidney and passes into a hollow tube called a ureter. There are two ureters, one leading from each kidney to the urinary bladder. The bladder expands and fills with urine until, by reflex action, it contracts and expels urine through a single tube, the urethra.

The urethra in males exits the body through the shaft of the penis. In females, the urethral opening is found anterior to the openings of the vagina and anus. Micturition, or urination, is the process by which urine is excreted.

The kidneys are the site of urine formation. They lie on either side of the spine at the level of the eleventh and twelfth ribs, just above the waist (Fig. 19.1b). Although they are below the diaphragm, they are technically outside the abdominal cavity, sandwiched between the membranous peritoneum, which lines the abdomen, and the bones and muscles of the back. Because of their location behind the peritoneal cavity, the kidneys are sometimes described as being retroperitoneal (retro-, behind).

The concave surface of each kidney faces the spine. The renal blood vessels, nerves, lymphatics, and ureters all emerge from this surface. Renal arteries, which branch off the abdominal aorta, supply blood to the kidneys. Renal veins carry blood from the kidneys to the inferior vena cava.

At any given time, the kidneys receive 20–25% of the cardiac output, even though they constitute only 0.4% of total body weight (4.5–6 ounces each). This high rate of blood flow through the kidneys is critical to renal function.

The Nephron Is the Functional Unit of the Kidney

A cross section through a kidney shows that the interior is arranged in two layers: an outer cortex and inner medulla (Fig. 19.1c). The layers are formed by the organized arrangement of microscopic tubules called nephrons. About 80% of the nephrons in a kidney are almost completely contained within the cortex (cortical nephrons), but the other 20%—called juxtamedullary nephrons (juxta-, beside)—dip down into the medulla (Fig. 19.1f, h).

The nephron is the functional unit of the kidney. (A functional unit is the smallest structure that can perform all the functions of an organ.) Each of the 1 million nephrons in a kidney is
The Kidneys

divided into sections (Fig. 19.1i), and each section is closely associated with specialized blood vessels (Fig. 19.1g, h).

**Vascular Elements of the Kidney** Blood enters the kidney through the renal artery before flowing into smaller arteries and then into arterioles in the cortex (Fig. 19.1d, e). At this point, the arrangement of blood vessels turns into a portal system, one of three in the body. Blood flows from the afferent arteriole into a ball-like network of capillaries known as the glomerulus (glomerulus [glomerus, a ball-shaped mass; plural glomeruli] (Fig. 19.1g, j)).

Blood leaving the glomerulus flows into an efferent arteriole, then into a second set of capillaries, the peritubular capillaries (peri-, around) that surround the tubule (Fig. 19.1g). In juxtamedullary nephrons, the long peritubular capillaries that dip into the medulla are called the vasa recta (Fig. 19.1h). Finally, renal capillaries join to form venules and small veins, conducting blood out of the kidney through the renal vein.

The function of the renal portal system is first to filter fluid out of the blood and into the lumen of the nephron at the glomerular capillaries, then to reabsorb fluid from the tubule back into the blood at the peritubular capillaries. The forces behind fluid movement in the renal portal system are similar to those that govern filtration of water and molecules out of systemic capillaries in other tissues.

### Concept Check

<table>
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<tr>
<th>Answers: End of Chapter</th>
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<tr>
<td>3. If net filtration out of glomerular capillaries occurs, then you know that capillary hydrostatic pressure must be (greater than/less than/equal to) capillary colloid osmotic pressure.</td>
</tr>
<tr>
<td>4. If net reabsorption into peritubular capillaries occurs, then capillary hydrostatic pressure must be (greater than/less than/equal to) the capillary colloid osmotic pressure.</td>
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**Tubular Elements of the Kidney** The nephron begins with a hollow, ball-like structure called Bowman’s capsule that surrounds the glomerulus (Fig. 19.1i). The endothelium of the glomerulus is fused to the epithelium of Bowman’s capsule so that fluid filtering out of the capillaries passes directly into the lumen of the tubule. The combination of glomerulus and Bowman’s capsule is called the renal corpuscle.

From Bowman’s capsule, filtered fluid flows into the proximal tubule (proximal, close or near), then into the loop of Henle, a hairpin-shaped segment that dips down toward the medulla and then back up. The loop of Henle is divided into two limbs, a thin descending limb and an ascending limb with thin and thick segments. The fluid then passes into the distal tubule (distal, distant or far). The distal tubules of up to eight nephrons drain into a single larger tube called the collecting duct. (The distal tubule and its collecting duct together form the distal nephron.) Collecting ducts pass from the cortex through the medulla and drain into the renal pelvis (Fig. 19.1c). From the renal pelvis, the filtered and modified fluid, now called urine, flows into the ureter on its way to excretion.

Notice in Figure 19.1g how the nephron twists and folds back on itself so that the final part of the ascending limb of the loop of Henle passes between the afferent and efferent arterioles. This region is known as the juxtaglomerular apparatus. The proximity of the ascending limb and the arterioles allows paracrine communication between the two structures, a key feature of kidney autoregulation. Because the twisted configuration of the nephron makes it difficult to follow fluid flow, we unfold the nephron in many of the remaining figures in this chapter so that fluid flows from left to right across the figure, as in Figure 19.1i.

### Overview of Kidney Function

Imagine drinking a 12-ounce soft drink every three minutes around the clock: by the end of 24 hours, you would have consumed the equivalent of 90 two-liter bottles. The thought of putting 180 liters of liquid into your intestinal tract is staggering, but that is how much plasma moves into the nephrons every day! But because the average volume of urine leaving the kidneys is only 1.5 L/day, more than 99% of the fluid that enters nephrons must find its way back into the blood, or the body would rapidly dehydrate.

**Kidneys Filter, Reabsorb, and Secrete**

Three basic processes take place in the nephron: filtration, reabsorption, and secretion (Fig. 19.2). Filtration is the movement of fluid from blood into the lumen of the nephron. Filtration takes place only in the renal corpuscle, where the walls of glomerular capillaries and Bowman’s capsule are modified to allow bulk flow of fluid.

**RUNNING PROBLEM**

Gout is a metabolic disease characterized by high blood concentrations of uric acid (hyperuricemia). If uric acid concentrations reach a critical level (7.5–8 mg/dL), monosodium urate precipitates out of solution and forms crystals in peripheral joints, particularly in the feet, ankles, and knees. These crystals trigger an inflammatory reaction and cause periodic attacks of excruciating pain. Uric acid crystals may also form kidney stones in the renal pelvis.

**Q1.** Trace the route followed by these kidney stones when they are excreted.

**Q2.** Name the anion formed when uric acid dissociates.
The Urinary System

(a) The urinary system

(b) The kidneys are located retroperitoneally at the level of the lower ribs.

Structure of the Kidney

(c) In cross section, the kidney is divided into an outer cortex and an inner medulla. Urine leaving the nephrons flows into the renal pelvis prior to passing through the ureter into the bladder.

(d) Renal arteries take blood to the cortex.

(e) Afferent arterioles and glomeruli are all found in the cortex.
Structure of the Nephron

(f) Some nephrons dip deep into the medulla.

(g) One nephron has two arterioles and two sets of capillaries that form a portal system.

(h) Juxtamedullary nephron with vasa recta

Parts of a nephron. In this view the nephron has been untwisted so that flow goes left to right. Compare with the nephrons in (f).

(j) The capillaries of the glomerulus form a ball-like mass.

The cortex contains all Bowman’s capsules, proximal and distal tubules.

The medulla contains loops of Henle and collecting ducts.

Bowman’s capsule
Proximal tubule
Distal tubule

Efferent arteriole
Juxtaglomerular apparatus
Afferent arteriole
Glomerulus (capillaries)

Peritubular capillaries

Peritubular capillaries
Glomerulus

Vasa recta
Collecting duct
Loop of Henle

Glomerulus
Cut edge of nephron tubule

To bladder
Nephron Function

The four processes of the nephron are:

- **F**: Filtration: movement from blood to lumen
- **R**: Reabsorption: from lumen to blood
- **S**: Secretion: from blood to lumen
- **E**: Excretion: from lumen to outside the body

This model nephron has been untwisted so that fluid flows left to right.

**Tubular Elements**

- Bowman’s capsule
- Proximal tubule
- Loop of Henle
- Distal tubule
- Collecting duct

**Vascular Elements**

- Efferent arteriole
- Glomerulus
- Afferent arteriole
- Peritubular capillaries
- Vasa recta

**FIGURE QUESTIONS**

1. In which segments of the nephron do the following processes take place:
   (a) filtration
   (b) reabsorption
   (c) secretion
   (d) excretion

2. Calculate the percentage of filtered volume that leaves
   (a) the loop of Henle
   (b) the collecting duct
Once the filtered fluid, called filtrate, passes into the lumen of the nephron, it becomes part of the body’s external environment, just as substances in the lumen of the intestinal tract are part of the external environment. For this reason, anything that filters into the nephron is destined for excretion, removal in the urine, unless it is reabsorbed into the body.

After filtrate leaves Bowman’s capsule, it is modified by reabsorption and secretion. Reabsorption is the process of moving substances in the filtrate from the lumen of the tubule back into the blood flowing through peritubular capillaries. Secretion removes selected molecules from the blood and adds them to the filtrate in the tubule lumen. Although secretion and glomerular filtration both move substances from blood into the tubule, secretion is a more selective process that usually uses membrane proteins to move molecules across the tubule epithelium.

The Kidneys

The Nephron Modifies Fluid Volume and Osmolarity

Now let’s follow some filtrate through the nephron to learn what happens to it in the various segments (Fig. 19.2). The 180 liters of fluid that filters into Bowman’s capsule each day are almost identical in composition to plasma and nearly isosmotic—about 300 mOsM. As this filtrate flows through the proximal tubule, about 70% of its volume is reabsorbed, leaving 54 liters in the lumen.

Reabsorption occurs when proximal tubule cells transport solutes out of the lumen, and water follows by osmosis. Filtrate leaving the proximal tubule has the same osmolarity as filtrate that entered. For this reason, we say that the primary function of the proximal tubule is the reabsorption of isosmotic fluid.

Filtrate leaving the proximal tubule passes into the loop of Henle, the primary site for creating dilute urine. As filtrate passes through the loop, proportionately more solute is reabsorbed than water, and the filtrate becomes hypotonic relative to the plasma. By the time filtrate flows out of the loop, it averages 100 mOsM, and its volume has fallen from 54 L/day to about 18 L/day. Most of the volume originally filtered into Bowman’s capsule has been reabsorbed into the capillaries.

From the loop of Henle, filtrate passes into the distal tubule and the collecting duct. In these two segments, the fine regulation of salt and water balance takes place under the control of several hormones. Reabsorption and (to a lesser extent) secretion determine the final composition of the filtrate. By the end of the collecting duct, the filtrate has a volume of 1.5 L/day and an osmolarity that can range from 50 mOsM to 1200 mOsM. The final volume and osmolarity of urine depend on the body’s need to conserve or excrete water and solute.

A word of caution here: it is very easy to confuse secretion with excretion. Try to remember the origins of the two prefixes. Se- means apart, as in to separate something from its source. In the nephron, secreted solutes are moved from plasma to tubule lumen. Ex- means out, or away, as in out of or away from the body. Excretion refers to the removal of a substance from the body. Besides the kidneys, other organs that carry out excretory processes include the lungs (CO₂) and intestines (undigested food, bilirubin).

Figure 19.2 summarizes filtration, reabsorption, secretion, and excretion. Filtration takes place in the renal corpuscle as fluid moves from the capillaries of the glomerulus into Bowman’s capsule. Reabsorption and secretion occur along the remainder of the tubule, transferring materials between the lumen and the peritubular capillaries. The quantity and composition of the substances being reabsorbed and secreted vary in different segments of the nephron. Filtrate that remains in the lumen at the end of the nephron is excreted as urine.

The amount of any substance excreted in the urine reflects how that substance was handled during its passage through the nephron (Fig. 19.3). The amount excreted is equal to the amount filtered into the tubule, minus the amount reabsorbed into the blood, plus the amount secreted into the tubule lumen:

\[
\text{Amount filtered} - \text{amount reabsorbed} + \text{amount secreted} = \text{amount excreted}
\]

This equation is a useful way to think about renal handling of solutes. In the following sections, we look in more detail at the important processes of filtration, reabsorption, secretion, and excretion.

The urinary excretion of a substance depends on its filtration, reabsorption, and secretion.

A person filters 720 millimoles of K⁺ in a day and secretes 43 millimoles. She excretes 79 millimoles in her urine. What happened to the rest of the K⁺ and how much was it?
The Kidneys

The Renal Corpuscle Contains Filtration Barriers

Filtration takes place in the renal corpuscle (Fig. 19.5), which consists of the glomerular capillaries surrounded by Bowman’s capsule. Substances leaving the plasma must pass through three filtration barriers before entering the tubule lumen: the glomerular capillary endothelium, a basal lamina ( basement membrane ), and the epithelium of Bowman’s capsule (Fig. 19.5d). The details of how these filtration barriers function are still under investigation.

The first barrier is the capillary endothelium. Glomerular capillaries are fenestrated capillaries with large pores that allow most components of the plasma to filter through the endothelium. The pores are small enough, however, to prevent blood cells from leaving the capillary. The negatively charged proteins on the pore surfaces also help repel negatively charged plasma proteins.

Glomerular mesangial cells lie between and around the glomerular capillaries (Fig. 19.5c). Mesangial cells have cytoplasmic bundles of actin-like filaments that enable them to contract and alter blood flow through the capillaries. In addition, mesangial cells secrete cytokines associated with immune and inflammatory processes. Disruptions of mesangial cell function have been linked to several disease processes in the kidney.

The second filtration barrier is the basal lamina, an acellular layer of extracellular matrix that separates the capillary endothelium from the epithelial lining of Bowman’s capsule (Fig. 19.5d). The basal lamina consists of negatively charged glycoproteins, collagen, and other proteins. The lamina acts like a coarse sieve, excluding most plasma proteins from the fluid that filters through it.

**Filtration**

The filtration of plasma into the kidney tubule is the first step in urine formation. This relatively nonspecific process creates a filtrate whose composition is like that of plasma minus most of the plasma proteins. Under normal conditions, blood cells remain in the capillary, so that the filtrate is composed of water and dissolved solutes.

When you visualize plasma filtering out of the glomerular capillaries, it is easy to imagine that all the plasma in the capillary moves into Bowman’s capsule. However, filtration of all the plasma would leave behind a sludge of blood cells and proteins that could not flow out of the glomerulus. Instead, only about one-fifth of the plasma that flows through the kidneys filters into the nephrons. The remaining four-fifths of the plasma, along with most plasma proteins and blood cells, flows into the peritubular capillaries (Fig. 19.4). The percentage of total plasma volume that filters into the tubule is called the filtration fraction.

**THE FILTRATION FRACTION**

Only 20% of the plasma that passes through the glomerulus is filtered. Less than 1% of filtered fluid is eventually excreted.

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**Concept Check**

5. Name one way in which filtration and secretion are alike. Name one way in which they differ.

6. A water molecule enters the renal corpuscle from the blood and ends up in the urine. Name all the anatomical structures that the molecule passes through on its trip to the outside world.

7. What would happen to the body if filtration continued at a normal rate but reabsorption dropped to half the normal rate?

---

**FIGURE QUESTION**

If 120 mL of plasma filter each minute and the filtration fraction is 20%, what is the daily renal plasma flow?
The third filtration barrier is the epithelium of Bowman’s capsule. The portion of the capsule epithelium that surrounds each glomerular capillary consists of specialized cells called podocytes (podos, foot) (Fig. 19.5c). Podocytes have long cytoplasmic extensions called foot processes that extend from the main cell body (Fig. 19.5a, b).

Foot processes wrap around the glomerular capillaries and interlace with one another, leaving narrow filtration slits closed by a semiporous membrane. The filtration slit membrane contains several unique proteins, including nephrin and podocin. These proteins were discovered by investigators looking for the gene mutations responsible for two congenital kidney diseases.
In these diseases, where nephrin or podocin are absent or abnormal, proteins leak across the glomerular filtration barrier into the urine.

The Kidneys

Capillary Pressure Causes Filtration

What drives filtration across the walls of the glomerular capillaries? The process is similar in many ways to filtration of fluid out of systemic capillaries. The three pressures that influence glomerular filtration—capillary blood pressure, capillary colloid osmotic pressure, and capsule fluid pressure—are summarized in Figure 19.6a.

1. The hydrostatic pressure \( (P_H) \) of blood flowing through the glomerular capillaries forces fluid through the leaky endothelium. Capillary blood pressure averages 55 mm Hg and favors filtration into Bowman’s capsule. Although pressure declines along the length of the capillaries, it remains higher than the opposing pressures. Consequently, filtration takes place along nearly the entire length of the glomerular capillaries.

2. The colloid osmotic pressure \( (\pi) \) inside glomerular capillaries is higher than that of the fluid in Bowman’s capsule. This pressure gradient is due to the presence of proteins in the plasma. The osmotic pressure gradient averages 30 mm Hg and favors fluid movement back into the capillaries.

3. Bowman’s capsule is an enclosed space (unlike the interstitial fluid), and so the presence of fluid in the capsule creates a hydrostatic fluid pressure \( (P_{fluid}) \) that opposes fluid movement into the capsule. Fluid filtering out of the capillaries must displace the fluid already in the capsule lumen. Hydrostatic fluid pressure in the capsule averages 15 mm Hg, opposing filtration.

The net driving force is 10 mm Hg in the direction favoring filtration. Although this pressure may not seem very high, when combined with the very leaky nature of the fenestrated capillaries, it results in rapid fluid filtration into the tubules.

The volume of fluid that filters into Bowman’s capsule per unit time is the **glomerular filtration rate** (GFR). Average GFR is 125 mL/min, or 180 L/day, an incredible rate considering that the kidneys filter the entire plasma volume 60 times a day, or 2.5 times every hour. If most of the filtrate were not reabsorbed during its passage through the nephron, we would run out of plasma in only 24 minutes of filtration!

GFR is influenced by two factors: the net filtration pressure just described and the filtration coefficient. Filtration pressure is determined primarily by renal blood flow and blood pressure. The filtration coefficient has two components: the surface area of the glomerular capillaries available for filtration and the permeability of interface between the capillary and Bowman’s capsule. In this respect, glomerular filtration is similar to gas exchange at the alveoli, where the rate of gas exchange depends on partial pressure differences, the surface area of the alveoli, and the permeability of the alveolar-capillary diffusion barrier.

GFR Is Relatively Constant

Blood pressure provides the hydrostatic pressure that drives glomerular filtration. Therefore, it might seem reasonable to assume that if blood pressure increased, GFR would increase, and if blood pressure fell, GFR would decrease. That is not usually the case, however. Instead, GFR is remarkably constant over a wide range of blood pressures. As long as mean arterial blood pressure remains between 80 mm Hg and 180 mm Hg, GFR averages 180 L/day (Fig. 19.6b).

GFR is controlled primarily by regulation of blood flow through the renal arterioles. If the overall resistance of the renal arterioles increases, renal blood flow decreases, and blood is diverted to other organs. The effect of increased resistance on GFR, however, depends on where the resistance change takes place.

If resistance increases in the **afferent** arteriole (Fig. 19.6d), hydrostatic pressure decreases on the glomerular side of the constriction. This translates into a decrease in GFR. If resistance increases in the **efferent** arteriole, blood “dams up” in front of the constriction, and hydrostatic pressure in the glomerular capillaries increases (Fig. 19.8e). Increased glomerular pressure increases GFR. The opposite changes occur with decreased resistance in the afferent or efferent arterioles. Most regulation occurs at the afferent arteriole.

Concept Check

Answers: End of Chapter

8. Why is the osmotic pressure of plasma in efferent arterioles higher than that in afferent arterioles?

9. If a hypertensive person’s blood pressure is 143/107 mm Hg and mean arterial pressure is diastolic pressure + 1/3 the pulse pressure, what is this person’s mean arterial pressure? What is this person’s GFR according to Figure 19.6b?

GFR Is Subject to Autoregulation

Autoregulation of glomerular filtration rate is a local control process in which the kidney maintains a relatively constant GFR in the face of normal fluctuations in blood pressure. One important function of GFR autoregulation is to protect the filtration barriers from high blood pressures that might damage them. We do not completely understand the autoregulation process, but several mechanisms are at work. The **myogenic response** is the intrinsic ability of vascular smooth muscle to respond to pressure changes. **Tubuloglomerular feedback** is a paracrine signaling mechanism through which changes in fluid flow through the loop of Henle influence GFR.
Glomerular Filtration Rate

Filtration out of glomerular capillaries is similar to filtration in other systemic capillaries. Filtration pressure depends on hydrostatic pressure, and is opposed by colloid osmotic pressure and capsule fluid pressure.

(a) Calculating glomerular filtration pressure

\[ P_H - \pi - P_{\text{fluid}} = \text{net filtration pressure} \]

\[ \begin{align*}
55 - 30 - 15 &= 10 \text{ mm Hg}
\end{align*} \]

(b) Autoregulation of glomerular filtration rate takes place over a wide range of blood pressures.

Autoregulation maintains a nearly constant GFR when mean arterial blood pressure is between 80 and 180 mm Hg.

(c) Resistance changes in renal arterioles alter renal blood flow and GFR.

(d) Vasoconstriction of the afferent arteriole increases resistance and decreases renal blood flow, capillary blood pressure \( (P_H) \), and GFR.

(e) Increased resistance of efferent arteriole decreases renal blood flow but increases \( P_H \) and GFR.

Q

FIGURE QUESTION

What happens to capillary blood pressure, GFR, and RBF when the afferent arteriole dilates?
Myogenic Response  The myogenic response of afferent arterioles is similar to autoregulation in other systemic arterioles. When smooth muscle in the arteriole wall stretches because of increased blood pressure, stretch-sensitive ion channels open, and the muscle cells depolarize. Depolarization opens voltage-gated Ca²⁺ channels, and the vascular smooth muscle contracts. Vasoconstriction increases resistance to flow, and so blood flow through the arteriole diminishes. The decrease in blood flow decreases filtration pressure in the glomerulus.

If blood pressure decreases, the tonic level of arteriolar constriction disappears, and the arteriole becomes maximally dilated. However, vasodilation is not as effective at maintaining GFR as vasoconstriction because normally the afferent arteriole is fairly relaxed. Consequently, when mean blood pressure drops below 80 mm Hg, GFR decreases. This decrease is adaptive in the sense that if less plasma is filtered, the potential for fluid loss in the urine is decreased. In other words, a decrease in GFR helps the body conserve fluid volume.

Tubuloglomerular Feedback  Tubuloglomerular feedback is a local control pathway in which fluid flow through the tubule influences GFR. The twisted configuration of the nephron, as shown in Figure 19.7a, causes the final portion of the ascending limb of the loop of Henle to pass between the afferent and efferent arterioles. The tubule and arteriolar walls are modified in the regions where they contact each other and together form the juxtaglomerular apparatus.

The modified portion of the tubule epithelium is a plaque of cells called the macula densa (Fig. 19.7b). The adjacent wall of the afferent arteriole has specialized smooth muscle cells called granular cells (also known as juxtaglomerular cells or JG cells). The granular cells secrete renin, an enzyme involved in salt and water balance. When NaCl delivery past the macula densa increases as a result of increased GFR, the macula densa cells send a paracrine message to the neighboring afferent arteriole (Fig. 19.7c). The afferent arteriole constricts, increasing resistance and decreasing GFR.

Experimental evidence indicates that the macula densa cells transport NaCl, and that increases in salt transport initiate tubuloglomerular feedback. The paracrine signaling between the macula densa and the afferent arteriole is complex, and the details are still being worked out. Experiments show that multiple paracrine signals, including ATP, adenosine, and nitric oxide, pass from the macula densa to the arteriole.

Hormones and Autonomic Neurons Also Influence GFR

Although local mechanisms within the kidney attempt to maintain a constant GFR, the importance of the kidneys in systemic blood pressure homeostasis means that integrating centers outside the kidney can override local controls. Hormones and the autonomic nervous system alter glomerular filtration rate two ways: by changing resistance in the arterioles and by altering the filtration coefficient.

Neural control of GFR is mediated by sympathetic neurons that innervate both the afferent and efferent arterioles. Sympathetic innervation of α-receptors on vascular smooth muscle causes vasoconstriction. If sympathetic activity is moderate, there is little effect on GFR. If systemic blood pressure drops sharply, however, as occurs with hemorrhage or severe dehydration, sympathetically induced vasoconstriction of the arterioles decreases GFR and renal blood flow. This is an adaptive response that helps conserve fluid volume.

A variety of hormones also influence arteriolar resistance. Among the most important are angiotensin II, a potent vasoconstrictor, and prostaglandins, which act as vasodilators. These same hormones may affect the filtration coefficient by acting on podocytes or mesangial cells. Podocytes change the size of the glomerular filtration slits. If the slits widen, more surface area is available for filtration, and GFR increases. Constriction of mesangial cells apparently changes the glomerular capillary surface area available for filtration. We still have much to learn about these processes, and physiologists are actively investigating them.

Concept Check

10. If systemic blood pressure remains constant but the afferent arteriole of a nephron constricts, what happens to renal blood flow and GFR in that nephron?

11. A person with cirrhosis of the liver has lower-than-normal levels of plasma proteins and consequently a higher-than-normal GFR. Explain why a decrease in plasma protein concentration causes an increase in GFR.

EMERGING CONCEPTS: DIABETES

Diabetic Nephropathy

End-stage renal failure, in which kidney function has deteriorated beyond recovery, is a life-threatening complication in 30–40% of people with type 1 diabetes and in 10–20% of those with type 2 diabetes. As with many other complications of diabetes, the exact causes of renal failure are not clear. Diabetic nephropathy usually begins with an increase in glomerular filtration. This is followed by the appearance of proteins in the urine (proteinuria), an indication that the normal filtration barrier has been altered. In later stages, filtration rates decline. This stage is associated with thickening of the glomerular basal lamina and changes in both podocytes and mesangial cells. Abnormal growth of mesangial cells compresses the glomerular capillaries and impedes blood flow, contributing to the decrease in glomerular filtration. At this point, patients must have their kidney function supplemented by dialysis, and eventually they may need a kidney transplant.
Granular cells secrete renin, an enzyme involved in salt and water balance.

(a) The nephron loops back on itself so that the ascending limb of the loop of Henle passes between the afferent and efferent arterioles.

(b) The macula densa cells sense distal tubule flow and release paracrines that affect afferent arteriole diameter.

(c) Tubuloglomerular feedback helps GFR autoregulation.

1. GFR increases.
2. Flow through tubule increases.
3. Flow past macula densa increases.
4. Paracrine from macula densa to afferent arteriole
5. Afferent arteriole constricts.

- Resistance in afferent arteriole increases.
- Hydrostatic pressure in glomerulus decreases.
- GFR decreases.
Reabsorption

Each day, 180 liters of filtered fluid pass from the glomerular capillaries into the tubules, yet only about 1.5 liters are excreted in the urine. Thus more than 99% of the fluid entering the tubules must be reabsorbed into the blood as filtrate moves through the nephrons. Most of this reabsorption takes place in the proximal tubule, with a smaller amount of reabsorption in the distal segments of the nephrons. Regulated reabsorption in the distal nephron allows the kidneys to return ions and water to the plasma selectively—as needed to maintain homeostasis.

One question you might be asking is, “Why bother to filter 180 L/day and then reabsorb 99% of it? Why not simply filter and excrete the 1% that needs to be eliminated?” There are two reasons. First, many foreign substances are filtered into the tubule but not reabsorbed into the blood. The high daily filtration rate helps clear such substances from the plasma very rapidly.

Once a substance filters into the lumen of Bowman’s capsule, it is no longer part of the body’s internal environment. The lumen of the nephron is external environment, and anything in the filtrate is destined to leave the body in the urine if there is a tubule mechanism for reclaiming it. Many small nutrients, such as glucose and citric acid cycle intermediates, are filtered, but the proximal tubule very efficiently reabsorbs them.

Second, filtering ions and water into the tubule simplifies their regulation. If a portion of filtrate that reaches the distal nephron is not needed to maintain homeostasis, it passes into the urine. With a high GFR, this excretion can occur quite rapidly. However, if the ions and water are needed, they are reabsorbed.

Reabsorption May Be Active or Passive

Reabsorption of water and solutes from the tubule lumen to the extracellular fluid depends on active transport. The filtrate flowing out of Bowman’s capsule into the proximal tubule has the same solute concentrations as extracellular fluid. To move solute out of the lumen, the tubule cells must therefore use active transport to create concentration or electrochemical gradients. Water osmotically follows solutes as they are reabsorbed.

Figure 19.8a is an overview of renal reabsorption. Active transport of Na⁺ from the tubule lumen to the extracellular fluid creates a transepithelial electrical gradient in which the lumen is more negative than the ECF. Anions then follow the positively charged Na⁺ out of the lumen. The removal of Na⁺ and anions from lumen to ECF dilutes the luminal fluid and increases the concentration of the ECF, so water leaves the tubule by osmosis.

The loss of volume from the lumen increases the concentration of solutes (including K⁺, Ca²⁺, and urea) left behind in the filtrate: the same amount of solute in a smaller volume equals higher solute concentration. Once luminal solute concentrations are higher than solute concentrations in the extracellular fluid, the solutes diffuse out of the lumen if the epithelium of the tubule is permeable to them.

Reabsorption involves both epithelial transport and paracellular transport. In epithelial transport (also called transcellular transport), substances cross the apical and basolateral membranes of the tubule epithelial cell to reach the interstitial fluid. In the paracellular pathway, substances pass through the cell-cell junction between two adjacent cells. Which route a solute takes depends on the permeability of the epithelial junctions and on the electrochemical gradient for the solute.

For solutes that move by epithelial transport, their concentration or electrochemical gradients determine their transport mechanisms. Solutes moving down their gradient use open leak channels or facilitated diffusion carriers to cross the cell membrane. Molecules that need to be pushed against their gradient are moved by either primary or indirect (usually secondary) active transport. Sodium is directly or indirectly involved in many instances of both passive and active transport.

Active Transport of Sodium

The active reabsorption of Na⁺ is the primary driving force for most renal reabsorption. As noted earlier, filtrate entering the proximal tubule is similar in ion composition to plasma, with a higher Na⁺ concentration than is found in cells. Thus Na⁺ in the filtrate can enter tubule cells passively by moving down its electrochemical gradient (Fig. 19.8b). Apical movement of Na⁺ uses a variety of symport and antiport transport proteins or open leak channels. In the proximal tubule, the Na⁺-H⁺ exchanger (NHE) plays a major role in Na⁺ reabsorption, as does the apical epithelial Na⁺ channel (ENaC, pronounced ee-knack). Once inside a tubule cell, Na⁺ is actively transported out across the basolateral membrane in exchange for K⁺ by the Na⁺-K⁺-ATPase. A basolateral K⁺ leak channel prevents K⁺ from accumulating in the cell. The end result is Na⁺ reabsorption across the tubule epithelium.

Secondary Active Transport: Symport with Sodium

Sodium-linked secondary active transport in the nephron is responsible for the reabsorption of many substances, including glucose, amino acids, ions, and various organic metabolites. Figure 19.8c shows one example: Na⁺-dependent glucose reabsorption across the proximal tubule epithelium. The apical membrane contains the Na⁺-glucose cotransporter (SGLT) that brings glucose into the cytoplasm against its concentration gradient by harnessing the energy of Na⁺ moving down its electrochemical gradient. On the basolateral side of the cell, Na⁺ is pumped out by the Na⁺-K⁺-ATPase, while glucose diffuses out with the aid of a facilitated diffusion GLUT transporter.
Some solutes and water move into and then out of epithelial cells (transcellular or epithelial transport); other solutes move through junctions between epithelial cells (the paracellular pathway). Membrane transporters are not shown in this illustration.

This figure shows the epithelial Na\(^+\) channel, ENaC.

Na\(^+\) enters cell through various membrane proteins, moving down its electrochemical gradient.

Na\(^+\) is pumped out the basolateral side of cell by the Na\(^+\)-K\(^+\)-ATPase.

1. Na\(^+\) is reabsorbed by active transport.
2. Electrochemical gradient drives anion reabsorption.
3. Water moves by osmosis, following solute reabsorption. Concentrations of other solutes increase as fluid volume in lumen decreases.
4. Permeable solutes are reabsorbed by diffusion through membrane transporters or by the paracellular pathway.
The same basic pattern holds for many other molecules absorbed by Na\(^+\)-dependent transport: an apical symport protein and a basolateral facilitated diffusion carrier or ion exchanger. Other molecules that are reabsorbed by similar mechanisms include amino acids, lactate, citric acid cycle intermediates such as citrate and \(\alpha\)-ketoglutarate (\(\alpha\)KG), and ions such as phosphate and sulfate. A few of the apical transporters use H\(^+\) in place of Na\(^+\).

**Passive Reabsorption: Urea**  
The nitrogenous waste product urea has no active transporters in the proximal tubule but can move across the epithelium by diffusion if there is a urea concentration gradient. Initially, urea concentrations in the filtrate and extracellular fluid are equal. However, the active transport of Na\(^+\) and other solutes in the proximal tubule creates a urea concentration gradient by the following process. When Na\(^+\) and other solutes are reabsorbed from the proximal tubule, the transfer of osmotically active particles makes the extracellular fluid more concentrated than the filtrate remaining in the lumen (see Fig. 19.8a). In response to the osmotic gradient, water moves by osmosis across the epithelium. Up to this point, no urea molecules have moved out of the lumen because there has been no urea concentration gradient.

When water is reabsorbed, the concentration of urea in the lumen increases—the same amount of urea is contained in a smaller volume. Once a concentration gradient for urea exists, urea moves out of the lumen into the extracellular fluid by transport through the cells or by the paracellular pathway.

**Endocytosis: Plasma Proteins**  
Filtration of plasma at the glomerulus normally leaves most plasma proteins in the blood, but some smaller proteins and peptides can pass through the filtration barrier. Most filtered proteins are reabsorbed in the proximal tubule, with the result that normally only trace amounts of protein appear in urine. Small as they are, filtered proteins are too large to be reabsorbed by carriers or through channels. Instead they enter proximal tubule cells by receptor-mediated endocytosis at the apical membrane. Once in the cells, the proteins are digested in lysosomes and released as amino acids.

Recently scientists have discovered a membrane-bound receptor protein in coated pits on the surface of proximal tubule cells and some other tissues in the body. The protein is a member of the LDL-receptor family and has been named *megalin*. Megalin appears to be responsible for reabsorption of filtered protein and may also play a role in cellular uptake of carrier-bound steroid hormones and lipid-soluble vitamins.

**Renal Transport Can Reach Saturation**

Most transport in the nephron uses membrane proteins and exhibits the three characteristics of mediated transport: saturation, specificity, and competition.

**Saturation** refers to the maximum rate of transport that occurs when all available carriers are occupied by (are saturated...
The Kidneys

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train, some people will not find seats. And because the sidewalk is moving people past the train toward an exit, they cannot wait for the next train. Instead, they end up being transported out the exit.

Glucose molecules entering Bowman’s capsule in the filtrate are like passengers stepping onto the moving sidewalk. To be reabsorbed, each glucose molecule must bind to a transporter as the filtrate flows through the proximal tubule. If only a few glucose molecules enter the tubule at a time, each one can find a free transporter and be reabsorbed, just as a small number of people on the moving sidewalk all find seats on the train. However, if glucose molecules filter into the tubule faster than the glucose carriers can transport them, some glucose remains in the lumen and is excreted in the urine.

Figure 19.10 is a graphic representation of glucose handling by the kidney. Figure 19.10a shows that the filtration rate of glucose from plasma into Bowman’s capsule is proportional to the plasma concentration of glucose. Because filtration does not exhibit saturation, the graph continues infinitely in a straight line: the filtrate glucose concentration is always equal to the plasma glucose concentration.

Figure 19.10b plots the reabsorption rate of glucose in the proximal tubule against the plasma concentration of glucose. Reabsorption exhibits a maximum transport rate ($T_m$) when the carriers reach saturation. Notice that normal plasma glucose concentrations are well below the saturation point.

Figure 19.10c plots the excretion rate of glucose in relation to the plasma concentration of glucose. Remember that excretion equals filtration minus reabsorption ($E = F - R$). When plasma glucose concentrations are low enough that 100% of the filtered glucose is reabsorbed, no glucose is excreted. Once the carriers reach saturation, glucose excretion begins. The plasma concentration at which glucose first appears in the urine is called the renal threshold for glucose.

Figure 19.10d is a composite graph that compares filtration, reabsorption, and excretion of glucose. Recall from our earlier discussion that

$$\text{Amount excreted} = \text{amount filtered} - \text{amount reabsorbed} + \text{amount secreted}$$

For glucose, which is not secreted, the equation can be rewritten as

$$\text{Glucose excreted} = \text{glucose filtered} - \text{glucose reabsorbed}$$

Under normal conditions, all filtered glucose is reabsorbed. In other words, filtration is equal to reabsorption.

Notice in Figure 19.10d that the lines representing filtration and reabsorption are identical up to the plasma glucose concentration that equals the renal threshold. If filtration equals reabsorption, the algebraic difference between the two is zero, and there is no excretion. Once the renal threshold is reached, filtration begins to exceed reabsorption. Notice on the graph
The Kidneys

entire length of the peritubular capillaries is less than the colloid osmotic pressure, so the net pressure gradient favors reabsorption (Fig. 19.11). The peritubular capillaries have an average hydrostatic pressure of 10 mm Hg (in contrast to the glomerular capillaries, where hydrostatic pressure averages 55 mm Hg). Colloid osmotic pressure, which favors movement of fluid into the capillaries, is 30 mm Hg. As a result, the pressure gradient in peritubular capillaries is 20 mm Hg, favoring the absorption of fluid into the capillaries. Fluid that is reabsorbed passes from the peritubular capillaries to the venous circulation and returns to the heart.

Secretion

Secretion is the transfer of molecules from extracellular fluid into the lumen of the nephron (see Fig. 19.2). Secretion, like reabsorption, depends mostly on membrane transport systems. The secretion of K⁺ and H⁺ by the distal nephron is important in the homeostatic regulation of those ions. In addition, many organic compounds are secreted. These compounds include

Peritubular Capillary Pressures Favor Reabsorption

The reabsorption we have just discussed refers to the movement of solutes and water from the tubule lumen to the interstitial fluid. How does that reabsorbed fluid then get into the capillary? The answer is that the hydrostatic pressure that exists along the entire length of the peritubular capillaries is less than the colloid osmotic pressure, so the net pressure gradient favors reabsorption (Fig. 19.11). The peritubular capillaries have an average hydrostatic pressure of 10 mm Hg (in contrast to the glomerular capillaries, where hydrostatic pressure averages 55 mm Hg). Colloid osmotic pressure, which favors movement of fluid into the capillaries, is 30 mm Hg. As a result, the pressure gradient in peritubular capillaries is 20 mm Hg, favoring the absorption of fluid into the capillaries. Fluid that is reabsorbed passes from the peritubular capillaries to the venous circulation and returns to the heart.

that the filtration and reabsorption lines diverge at this point. The difference between the filtration line and the reabsorption line represents the excretion rate:

$$\text{Excretion} = \text{filtration} - \text{reabsorption}$$

Excretion of glucose in the urine is called glucosuria or glycosuria [-uria, in the urine] and usually indicates an elevated blood glucose concentration. Rarely, glucose appears in the urine even though the blood glucose concentrations are normal. This situation is due to a genetic disorder in which the nephron does not make enough carriers.

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Secretion enables the nephron to enhance excretion of a substance. If a substance is filtered and not reabsorbed, it is excreted very efficiently. If, however, the substance is filtered into the tubule, not reabsorbed, and then more of it is secreted into the tubule from the peritubular capillaries, excretion is even more efficient.

Secretion is an active process because it requires moving substrates against their concentration gradients. Most organic compounds are secreted across the proximal tubule epithelium into the lumen by indirect active transport. Let's look at how the tubule handles the secretion of organic anions (Fig. 19.12).

The transporters responsible for organic solute excretion have broad specificity. For example, the organic anion transporter (OAT) family, shown in this figure, is able to transport a wide variety of endogenous and exogenous anions, ranging from bile salts to benzoate used as a preservative in soft drinks, salicylate from aspirin, and the artificial sweetener saccharine. Secretion of organic anions on the OAT is an example of tertiary active transport, where the use of energy from ATP is two steps removed from the OAT. Let's see how this works.

In the first step of the process, which is direct active transport, the proximal tubule cell uses ATP to maintain the low intracellular concentration of Na\(^{+}\). In the second step, the Na\(^{+}\) gradient is then used to concentrate a dicarboxylate inside the tubule cell, using a Na\(^{+}\)-dicarboxylate cotransporter called the NaDC. The NaDC is found on both apical and basolateral membranes in the proximal tubule.

Dicarboxylates are the anion form of dicarboxylic acids, which have two carboxyl (–COOH) groups. Most of the citric acid cycle intermediates, such as citrate, oxaloacetate, and...
α-ketoglutarate (αKG), are dicarboxylates. Figure 19.12 shows αKG as the dicarboxylate.

The concentration of dicarboxylate inside the tubule cell drives the third step of organic anion secretion. The OAT is an indirect active transporter that uses the dicarboxylate moving out of the cell down its concentration gradient to move an organic anion against its gradient into the cell. In the final step, once the organic anion is concentrated inside the tubule cell, it can use facilitated diffusion to enter the lumen. The apical transporters have not been identified but appear to be anion exchangers.

**Competition Decreases Penicillin Secretion**

The broad specificity of the organic anion transporters means that different substrates must compete for the transporter binding sites. An interesting and important example of an organic molecule secreted by the OAT is the antibiotic *penicillin*. Many people today take antibiotics for granted, but until the early decades of the twentieth century, infections were a leading cause of death.

In 1928, Alexander Fleming discovered a substance in the bread mold *Penicillium* that retarded the growth of bacteria. But the antibiotic was difficult to isolate, so it did not become available for clinical use until the late 1930s. During World War II, penicillin made a major difference in the number of deaths and amputations caused by infected wounds. The only means of producing penicillin, however, was to isolate it from bread mold, and supplies were limited.

Demand for the drug was heightened by the fact that kidney tubules secrete penicillin. Renal secretion is so efficient at clearing foreign molecules from the blood that within three to four hours after a dose of penicillin has been administered, about 80% has been excreted in the urine. During the war, the drug was in such short supply that it was common procedure to collect the urine from patients being treated with penicillin so that the antibiotic could be isolated and reused.

This solution was not satisfactory, however, and so researchers looked for a way to slow penicillin secretion. They hoped to find a molecule that could compete with penicillin for the organic anion transporter responsible for secretion. That way, when presented with both drugs, the OAT carrier would bind preferentially to the competitor and secrete it, leaving penicillin behind in the blood.

A synthetic compound named *probenecid* was the answer. When probenecid is administered concurrently with penicillin, the transporter removes probenecid preferentially, prolonging the activity of penicillin in the body. Once mass-produced synthetic penicillin became available and supply was no longer a problem, the medical use of probenecid declined.

**Excretion**

Urine output is the result of all the processes that take place in the kidney. By the time fluid reaches the end of the nephron, it bears little resemblance to the filtrate that started in Bowman’s capsule. Glucose, amino acids, and useful metabolites are gone, having been reabsorbed into the blood, and organic wastes are more concentrated. The concentrations of ions and water in the urine are highly variable, depending on the state of the body.

Although excretion tells us what the body is eliminating, excretion by itself cannot tell us the details of renal function. Recall that for any substance,

\[
\text{Excretion} = \text{filtration} - \text{reabsorption} + \text{secretion}
\]

Simply looking at the excretion rate of a substance tells us nothing about how the kidney handled that substance. The excretion rate of a substance depends on (1) the filtration rate of the substance and (2) whether the substance is reabsorbed, secreted, or both, as it passes through the tubule.

Renal handling of a substance and GFR are often of clinical interest. For example, clinicians use information about a person’s glomerular filtration rate as an indicator of overall kidney function. And pharmaceutical companies developing drugs must provide the Food and Drug Administration with complete information on how the human kidney handles each new compound.

But how can investigators dealing with living humans assess filtration, reabsorption, and secretion at the level of the

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**RUNNING PROBLEM**

Michael found it amazing that a metabolic problem could lead to pain in his big toe. “How do we treat gout?” he asked. Dr. García explained that the treatment includes anti-inflammatory agents, lots of water, and avoidance of alcohol, which can trigger gout attacks. “In addition, I would like to put you on a uricosuric agent, like probenecid, which will enhance renal excretion of urate,” replied Dr. García. “By enhancing excretion, we can reduce uric acid levels in your blood and thus provide relief.” Michael agreed to try these measures.

**Q5.** Urate is reabsorbed by some proximal tubule cells and secreted by others using membrane transporters, one on the apical membrane and one on the basolateral membrane. Could the same transporters be used by cells that reabsorb urate and cells that secrete it? Defend your reasoning.

**Q6.** Uricosuric agents, like urate, are organic acids. Given this fact, explain how uricosuric agents might enhance excretion of urate.
individual nephron? They have no way to do this directly because the kidneys are not easily accessible and the nephrons are microscopic. Scientists therefore had to develop a technique that would allow them to assess renal function using only analysis of the urine and blood. To do this, they apply the concept of clearance.

**Clearance Is a Noninvasive Way to Measure GFR**

*Clearance* of a solute is the rate at which that solute disappears from the body by excretion or by metabolism. The general equation for clearance is:

\[
\text{Clearance of } X = \frac{\text{excretion rate of } X \text{ (mg/min)}}{[X]_{\text{plasma}} \text{ (mg/mL plasma)}}
\]

where clearance is mL plasma cleared of X per minute. Notice that the units for clearance are mL plasma and time. Substance X does not appear anywhere in the clearance units.

For any solute that is cleared only by renal excretion, clearance is expressed as the volume of plasma passing through the kidneys that has been totally cleared of that solute in a given period of time. Because this is such an indirect way to think of excretion (how much blood has been cleared of X rather than how much X has been excreted), clearance is often a very difficult concept to grasp.

Before we jump into the mathematical expression of clearance, let’s look at an example that shows how clearance relates to kidney function. For our example, we use inulin, a polysaccharide isolated from the tuberous roots of a variety of plants. (Inulin is not the same as insulin, the protein hormone that regulates glucose metabolism.) Scientists discovered from experiments with isolated nephrons that inulin injected into the plasma filters freely into the nephron. As it passes through the kidney tubule, inulin is neither reabsorbed nor secreted. In other words, 100% of the inulin that filters into the tubule is excreted.

How does this relate to clearance? To answer this question, take a look at Figure 19.13, which assumes that 100% of a filtered volume of plasma is reabsorbed. (This is not too far off the actual value, which is more than 99%.) In Figure 19.13a, inulin has been injected so that its plasma concentration is 4 inulin molecules per 100 mL plasma. If GFR is 100 mL plasma filtered per minute, we can calculate the filtration rate, or *filtered load*, of inulin using the equation

\[
\text{Filtered load of } X = [X]_{\text{plasma}} \times \text{GFR}
\]

As the filtered inulin and the filtered plasma pass along the nephron, all the plasma is reabsorbed, but all the inulin remains in the tubule. The reabsorbed plasma contains no inulin, so we say it has been totally *cleared* of inulin. The *inulin clearance* therefore is 100 mL of plasma cleared/min. At the same time, the excretion rate of inulin is 4 inulin molecules excreted per minute.

What good is this information? For one thing, we can use it to calculate the glomerular filtration rate. Notice from Figure 19.13a that inulin clearance (100 mL plasma cleared/min) is equal to the GFR (100 mL plasma filtered/min). Thus, for any substance that is freely filtered but neither reabsorbed nor secreted, its clearance is equal to GFR.

Now let’s show mathematically that inulin clearance is equal to GFR. We already know that

\[
\text{Filtered load of } X = [X]_{\text{plasma}} \times \text{GFR}
\]

We also know that 100% of the inulin that filters into the tubule is excreted. In other words:

\[
\text{Filtered load of inulin} = \text{excretion rate of inulin}
\]

Because of this equality, we can substitute excretion rate for filtered load in equation (1) by using algebra (if \( A = B \) and \( A = C \), then \( B = C \)):

\[
\text{Excretion rate of inulin} = [\text{inulin}]_{\text{plasma}} \times \text{GFR}
\]

This equation can be rearranged to read

\[
\text{GFR} = \frac{\text{excretion rate of inulin}}{[\text{inulin}]_{\text{plasma}}}
\]

It turns out that the right side of this equation is identical to the clearance equation for inulin. Thus the general equation for the clearance of any substance X (mL plasma cleared/min) is

\[
\text{Clearance of } X = \frac{\text{excretion rate of } X \text{ (mg/min)}}{[X]_{\text{plasma}} \text{ (mg/mL plasma)}}
\]

For inulin:

\[
\text{Inulin clearance} = \frac{\text{excretion rate of inulin}}{[\text{inulin}]_{\text{plasma}}}
\]

The right sides of equations (4) and (6) are identical, so by using algebra again, we can say that:

\[
\text{GFR} = \text{inulin clearance}
\]

So why is this important? For one thing, you have just learned how we can measure GFR in a living human by taking only blood and urine samples. Try the example in Concept Check 12 to see if you understand the preceding discussion. Table 19.1 is a summary table of equations you will find useful for renal physiology.
Renal Clearance

These figures show the relationship between clearance and excretion. Each figure represents the events taking place in one minute. For simplicity, 100% of the filtered volume is assumed to be reabsorbed.

(a) Inulin clearance is equal to GFR.

(b) Glucose clearance: Normally all glucose that filters is reabsorbed.

(c) Urea clearance is an example of net reabsorption. If filtration is greater than excretion, there is net reabsorption.

(d) Penicillin clearance is an example of net secretion. If excretion is greater than filtration, there is net secretion.
Inulin is not practical for routine clinical applications because it does not occur naturally in the body and must be administered by continuous intravenous infusion. As a result, inulin use is restricted to research. Unfortunately, no substance that occurs naturally in the human body is handled by the kidney exactly the way inulin is handled.

In clinical settings, physicians use creatinine to estimate GFR. Creatinine is a breakdown product of phosphocreatine, an energy-storage compound found primarily in muscles. It is constantly produced by the body and need not be administered. Normally, the production and breakdown rates of phosphocreatine are relatively constant, and the plasma concentration of creatinine does not vary much.

Although creatinine is always present in the plasma and is easy to measure, it is not the perfect molecule for estimating GFR because a small amount is secreted into the urine. However, the amount secreted is small enough that, in most people, creatinine clearance is routinely used to estimate GFR.

### Useful Equations in Renal Physiology

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excretion = Filtration – Reabsorption + Secretion</td>
<td></td>
</tr>
<tr>
<td>Filtration of X = [X]_{plasma} \times GFR</td>
<td></td>
</tr>
<tr>
<td>Clearance of X = \frac{\text{excretion rate of } X (\text{mg/min})}{[X]_{plasma} (\text{mg/mL plasma})}</td>
<td></td>
</tr>
<tr>
<td>When [X]_{plasma} = \text{renal threshold for } X, \text{ then reabsorption of } X = \text{transport maximum for } X.</td>
<td></td>
</tr>
</tbody>
</table>

### Table 19.1

<table>
<thead>
<tr>
<th>Substance</th>
<th>Filtrated</th>
<th>Reabsorbed</th>
<th>Secreted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>125 mL</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Creatinine</td>
<td>180 mL</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

### Concept Check

12. If plasma creatinine = 1.8 mg/100 mL plasma, urine creatinine = 1.5 mg/mL urine, and urine volume is 1100 mL in 24 hours, what is the creatinine clearance? What is GFR?

### Clearance Helps Us Determine Renal Handling

Once we know a person’s GFR, we can determine how the kidney handles any solute by measuring the solute’s plasma concentration and its excretion rate. If we assume that the solute is freely filtered at the glomerulus, we know from equation (1) that

\[ \text{Filtered load of } X = [X]_{plasma} \times GFR \]

By comparing the filtered load of the solute with its excretion rate, we can tell how the nephron handled that substance (Fig. 19.13). For example, if less of the substance appears in the urine than was filtered, net reabsorption occurred (excreted = filtered – reabsorbed). If more of the substance appears in the urine than was filtered, there must have been net secretion of the substance into the lumen (excreted = filtered + secreted). If the same amount of the substance is filtered and excreted, then the substance is handled like inulin—neither reabsorbed nor secreted. Let’s look at some examples.

Suppose that glucose is present in the plasma at 100 mg glucose/dL plasma, and GFR and FFR is calculated from creatinine clearance to be 125 mL plasma/min. For these values, equation (1) tells us that

\[ \text{Filtered load of glucose} = (100 \text{ mg glucose/100 mL plasma}) \times 125 \text{ mL plasma/min} \]

There is no glucose in this person’s urine, however: glucose excretion is zero. Because glucose was filtered at a rate of 125 mg/min but excreted at a rate of 0 mg/min, it must have been totally reabsorbed.

Clearance values can also be used to determine how the nephron handles a filtered solute. In this method, researchers calculate creatinine or inulin clearance, then compare the clearance of the solute being investigated with the creatinine or inulin clearance. If clearance of the solute is less than the inulin clearance, the solute has been reabsorbed. If the clearance of the solute is higher than the inulin clearance, additional solute has been secreted into the urine. More plasma was cleared of the solute than was filtered, so the additional solute must have been removed from the plasma by secretion.

Figure 19.13 shows filtration, excretion, and clearance of three molecules: glucose, urea, and penicillin. All solutes have the same concentration in the blood entering the glomerulus: 4 molecules/100 mL plasma. GFR is 100 mL/min, and we assume for simplicity that the entire 100 mL of plasma filtered into the tubule is reabsorbed.

For any solute, its clearance reflects how the kidney tubule handles it. For example, 100% of the glucose that filters is reabsorbed, and glucose clearance is zero (Fig. 19.13b). On the other hand, urea is partially reabsorbed; four molecules filter, but two are reabsorbed and two are excreted (Fig. 19.13c). Consequently, urea clearance is 50 mL plasma per minute. Urea and glucose clearance are both less than the inulin clearance of 100 mL/min, which tells you that urea and glucose have been reabsorbed.

As you learned earlier, penicillin is filtered, not reabsorbed, and additional penicillin molecules are secreted from plasma in the peritubular capillaries. In Figure 19.13d, four penicillin are filtered, but six are excreted. An extra 50 mL of plasma have been cleared of penicillin in addition to the original 100 mL that were filtered. The penicillin clearance therefore is 150 mL plasma cleared per minute. Penicillin clearance is greater than the inulin clearance of 100 mL/min, which tells you that net secretion of penicillin occurs.
The Kidneys

Note that a comparison of clearance values tells you only the net handling of the solute. It does not tell you if a molecule is both reabsorbed and secreted. For example, nearly all K\(^+\) filtered is reabsorbed in the proximal tubule and loop of Henle, and then a small amount is secreted back into the tubule lumen at the distal nephron. On the basis of K\(^+\) clearance, it appears that only reabsorption occurred.

Clearance calculations are relatively simple because all you need to know are the urine excretion rates and the plasma concentrations for any solute of interest, and both values are easily obtained. If you also know either inulin or creatinine clearance, then you can determine the renal handling of any compound.

**Micturition**

Once filtrate leaves the collecting ducts, it can no longer be modified, and its composition does not change. The filtrate, now called urine, flows into the renal pelvis and then down the ureter to the bladder with the help of rhythmic smooth muscle contractions. The bladder is a hollow organ whose walls contain well-developed layers of smooth muscle. In the bladder, urine is stored until released in the process known as urination, voiding, or more formally, **micturition** \(\text{micturire, to desire to urinate}\).

The bladder can expand to hold a volume of about 500 mL. The neck of the bladder is continuous with the urethra, a single tube through which urine passes to reach the external environment. The opening between the bladder and urethra is closed by two rings of muscle called sphincters (Fig. 19.14a).

The **internal sphincter** is a continuation of the bladder wall and consists of smooth muscle. Its normal tone keeps it contracted. The **external sphincter** is a ring of skeletal muscle controlled by somatic motor neurons. Tonic stimulation from the central nervous system maintains contraction of the external sphincter except during urination.

Micturition is a simple spinal reflex that is subject to both conscious and unconscious control from higher brain centers. As the bladder fills with urine and its walls expand, stretch receptors send signals via sensory neurons to the spinal cord (Fig. 19.14b). There the information is integrated and

---

**Fig. 19.14**

**Micturition**

Micturition is a spinal reflex subject to higher brain control.

(a) Bladder at rest

(b) Micturition

1. Stretch receptors fire.
2. Parasympathetic neurons fire. Motor neurons stop firing.
transferred to two sets of neurons. The stimulus of a full bladder excites parasympathetic neurons leading to the smooth muscle in the bladder wall. The smooth muscle contracts, increasing the pressure on the bladder contents. Simultaneously, somatic motor neurons leading to the external sphincter are inhibited.

Contraction of the bladder occurs in a wave that pushes urine downward toward the urethra. Pressure exerted by the urine forces the internal sphincter open while the external sphincter relaxes. Urine passes into the urethra and out of the body, aided by gravity.

This simple micturition reflex occurs primarily in infants who have not yet been toilet trained. A person who has been toilet trained acquires a learned reflex that keeps the micturition reflex inhibited until she or he consciously desires to urinate. The learned reflex involves additional sensory fibers in the bladder that signal the degree of fullness. Centers in the brain stem and cerebral cortex receive that information and override the basic micturition reflex by directly inhibiting the parasympathetic fibers and by reinforcing contraction of the external sphincter. When an appropriate time to urinate arrives, those same centers remove the inhibition and facilitate the reflex by inhibiting contraction of the external sphincter.

In addition to conscious control of urination, various subconscious factors can affect the micturition reflex. “Bashful bladder” is a condition in which a person is unable to urinate in the presence of other people despite the conscious intent to do so. The sound of running water facilitates micturition and is often used to help patients urinate if the urethra is irritated from insertion of a catheter, a tube inserted into the bladder to drain it passively.

### RUNNING PROBLEM CONCLUSION

#### Gout

In this running problem, you learned that gout, which often presents as a debilitating pain in the big toe, is a metabolic problem whose cause and treatment can be linked to kidney function. Urate handling by the kidney is a complex process because urate is both secreted and reabsorbed in different segments of the proximal tubule. Scientists have now identified three different but related transport proteins that are involved in the process: the organic anion transporter (OAT), which exchanges two anions in an electrically neutral exchange; urate transporter 1 (URAT1), which is also an anion exchanger but with high specificity for urate; and urate transporter (UAT), an electrogenic uniport urate transporter. The arrangement of these transport proteins on the polarized cell membrane determines whether the cell reabsorbs or secretes urate.

Gout is one of the oldest known diseases and for many years was considered a “rich man’s” disease caused by too much rich food and drink. Thomas Jefferson and Benjamin Franklin both suffered from gout. To learn more about its causes, symptoms, and treatments, go to the Mayo Clinic’s health information pages (www.mayoclinic.com) and search for gout. Check your understanding of this running problem by comparing your answers against the information in the summary table.

<table>
<thead>
<tr>
<th>Question</th>
<th>Facts</th>
<th>Integration and Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Trace the route followed by kidney stones when they are excreted.</td>
<td>Kidney stones often form in the renal pelvis.</td>
<td>From the renal pelvis, a stone passes down the ureter, into the urinary bladder, then into the urethra and out of the body.</td>
</tr>
<tr>
<td>2. Name the anion formed when uric acid dissociates.</td>
<td>The suffix –ate is used to identify the anion of organic acids.</td>
<td>The anion of uric acid is urate.</td>
</tr>
</tbody>
</table>
### The Kidneys

The urinary system, like the lungs, uses the principle of mass balance to maintain homeostasis. The components of urine are constantly changing and reflect the kidney's functions of regulating ions and water and removing wastes. One of the body's three portal systems—each of which includes two capillary beds—is found in the kidney. Filtration occurs in the first capillary bed and reabsorption in the second. The pressure-flow-resistance relationship you encountered in the cardiovascular and pulmonary systems also plays a role in glomerular filtration and urinary excretion. Compartmentation is illustrated by the movement of water and solutes between the internal and external environments as filtrate is modified along the nephron. Reabsorption and secretion of solutes depend on molecular interactions and on the movement of molecules across membranes of the tubule cells.

### Chapter Summary

The urinary system, like the lungs, uses the principle of mass balance to maintain homeostasis. The components of urine are constantly changing and reflect the kidney's functions of regulating ions and water and removing wastes. One of the body's three portal systems—each of which includes two capillary beds—is found in the kidney. Filtration occurs in the first capillary bed and reabsorption in the second. The pressure-flow-resistance relationship you encountered in the cardiovascular and pulmonary systems also plays a role in glomerular filtration and urinary excretion. Compartmentation is illustrated by the movement of water and solutes between the internal and external environments as filtrate is modified along the nephron. Reabsorption and secretion of solutes depend on molecular interactions and on the movement of molecules across membranes of the tubule cells.

### RUNNING PROBLEM CONCLUSION (continued)

<table>
<thead>
<tr>
<th>Question</th>
<th>Facts</th>
<th>Integration and Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Purines are part of which category of biomolecules? Using that information, explain why uric acid levels in the blood go up when cell breakdown increases.</td>
<td>Purines include adenine and guanine, which are components of DNA, RNA, and ATP. When a cell dies, nuclear DNA and other chemical components are broken down.</td>
<td>Degradation of the cell's DNA, RNA, and ATP increases purine production, which in turn increases uric acid production.</td>
</tr>
<tr>
<td>4. Based on what you have learned about uric acid and urate, predict two ways a person may develop hyperuricemia.</td>
<td>Hyperuricemia is a disturbance of mass balance. Uric acid is made from purines. Urate is filtered by the kidneys with net secretion.</td>
<td>Hyperuricemia results either from overproduction of uric acid or from a defect in the renal excretion of urate.</td>
</tr>
<tr>
<td>5. Could the same transporters be used by cells that reabsorb urate and cells that secrete it? Defend your reasoning.</td>
<td>Some transporters move substrates in one direction only but others are reversible. Assume one urate transporter brings urate into the cell and another takes it out.</td>
<td>You could use the same two transporters if you reverse their positions on the apical and basolateral membranes. Cells reabsorbing urate would bring it in on the apical side and move it out on the basolateral. Cells secreting urate would reverse this pattern.</td>
</tr>
<tr>
<td>6. Uricosuric agents, like urate, are organic acids. With that information, explain how uricosuric agents might enhance excretion of urate.</td>
<td>Mediated transport exhibits competition, in which related molecules compete for one transporter. Usually, one molecule binds preferentially and therefore inhibits transport of the second molecule.</td>
<td>Uricosuric agents are organic anions, so they may compete with urate for the proximal tubule organic anion transporter. Preferential binding of the uricosuric agents would block urate access to the OAT, leaving urate in the lumen and increasing its excretion.</td>
</tr>
<tr>
<td>7. Explain why not drinking enough water while taking uricosuric agents may cause uric acid stones to form in the urinary tract.</td>
<td>Uric acid stones form when uric acid concentrations exceed a critical level and crystals precipitate.</td>
<td>If a person drinks large volumes of water, the excess water will be excreted by the kidneys. Large amounts of water dilute the urine, thereby preventing the high concentrations of uric acid needed for stone formation.</td>
</tr>
</tbody>
</table>

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Functions of the Kidneys

1. The kidneys regulate extracellular fluid volume, blood pressure, and osmolality; maintain ion balance; regulate pH; excrete wastes and foreign substances; and participate in endocrine pathways.

Anatomy of the Urinary System

Urinary System: Glomerular Filtration

2. The urinary system is composed of two kidneys, two ureters, a bladder, and a urethra. (Fig. 19.1a)
3. Each kidney has about 1 million microscopic nephrons. In cross section, a kidney is arranged into an outer cortex and inner medulla. (Fig. 19.1c)
4. Renal blood flow goes from afferent arteriole to glomerulus to efferent arteriole to peritubular capillaries. The vasa recta capillaries dip into the medulla. (Fig. 19.1g, h, i)
5. Fluid filters from the glomerulus into Bowman’s capsule. From there, it flows through the proximal tubule, loop of Henle, distal tubule, and collecting duct, then drains into the renal pelvis. Urine flows through the ureter to the urinary bladder. (Fig. 19.1b, c, i)

Overview of Kidney Function

6. Filtration is the movement of fluid from plasma into Bowman’s capsule. Reabsorption is the movement of filtered materials from tubule to blood. Secretion is the movement of selected molecules from blood to tubule. (Fig. 19.2)
7. Average urine volume is 1.5 L/day. Osmolarity varies between 50 and 1200 mOsM. (Fig. 19.2)
8. The amount of a solute excreted equals the amount filtered minus the amount reabsorbed plus the amount secreted. (Fig. 19.3)

Filtration

Urinary System: Glomerular Filtration

9. One-fifth of renal plasma flow filters into the tubule lumen. The percentage of total plasma volume that filters is called the filtration fraction. (Fig. 19.4)
10. Bowman’s capsule epithelium has specialized cells called podocytes that wrap around the glomerular capillaries and create filtration slits. Mesangial cells are associated with the glomerular capillaries. (Fig. 19.5a, c)
11. Filtered solutes must pass first through glomerular capillary endothelium, then through a basal lamina, and finally through Bowman’s capsule epithelium before reaching the lumen of Bowman’s capsule. (Fig. 19.5d)
12. Filtration allows most components of plasma to enter the tubule but excludes blood cells and most plasma proteins.
13. Hydrostatic pressure in glomerular capillaries averages 55 mm Hg, favoring filtration. Opposing filtration are colloid osmotic pressure of 30 mm Hg and hydrostatic capsule fluid pressure averaging 15 mm Hg. The net driving force is 10 mm Hg, favoring filtration. (Fig. 19.6)
14. The glomerular filtration rate (GFR) is the amount of fluid that filters into Bowman’s capsule per unit time. Average GFR is 125 mL/min, or 180 L/day.
15. Hydrostatic pressure in glomerular capillaries can be altered by changing resistance in the afferent and efferent arterioles. (Fig. 19.6c)

Autoregulation of glomerular filtration is accomplished by a myogenic response of vascular smooth muscle in response to pressure changes and by tubuloglomerular feedback. When fluid flow through the distal tubule increases, the macula densa cells send a paracrine signal to the afferent arteriole, which constricts. (Fig. 19.7c)

Reflex control of GFR is mediated through systemic signals, such as hormones, and through the autonomic nervous system.

Reabsorption

Urinary System: Early Filtrate Processing

18. Most reabsorption takes place in the proximal tubule. Finely regulated reabsorption takes place in the more distal segments of the nephron.
19. The active transport of Na+ and other solutes creates concentration gradients for passive reabsorption of urea and other solutes. (Fig. 19.8a)
20. Most reabsorption involves transepithelial transport, but some solutes and water are reabsorbed by the paracellular pathway.
21. Glucose, amino acids, ions, and various organic metabolites are reabsorbed by Na+-linked secondary active transport. (Fig. 19.8c)
22. Most renal transport is mediated by membrane proteins and exhibits saturation, specificity, and competition. The transport maximum Tm is the transport rate at saturation. (Fig. 19.9)
23. The renal threshold is the plasma concentration at which a substance first appears in the urine. (Fig. 19.9)
24. Peritubular capillaries reabsorb fluid along their entire length. (Fig. 19.11)

Secretion

25. Secretion enhances excretion by removing solutes from the peritubular capillaries. K+, H+, and a variety of organic compounds are secreted. (Fig. 19.12)
26. Molecules that compete for renal carriers slow the secretion of a molecule.

Excretion

27. The excretion rate of a solute depends on (1) its filtered load and (2) whether it is reabsorbed or secreted as it passes through the nephron.
28. Clearance describes how many milliliters of plasma passing through the kidneys have been totally cleared of a solute in a given period of time.
29. Inulin clearance is equal to GFR. In clinical settings, creatinine is used to measure GFR. (Fig. 19.13)
30. Clearance can be used to determine how the nephron handles a solute filtered into it. (Fig. 19.13)

Micturition

31. The external sphincter of the bladder is skeletal muscle that is tonically contracted except during urination. (Fig. 19.14)
32. Micturition is a simple spinal reflex subject to conscious and unconscious control.
33. Parasympathetic neurons cause contraction of the smooth muscle in the bladder wall. Somatic motor neurons leading to the external sphincter are simultaneously inhibited.
Questions

**Level One  Reviewing Facts and Terms**

1. List and explain the significance of the five characteristics of urine that can be found by physical examination.
2. List and explain the six major kidney functions.
3. At any given time, what percentage of cardiac output goes to the kidneys?
4. List the major structures of the urinary system in their anatomical sequence, from the kidneys to the urine leaving the body. Describe the function of each structure.
5. Arrange the following structures in the order that a drop of water entering the nephron would encounter them:
   (a) afferent arteriole
   (b) Bowman’s capsule
   (c) collecting duct
   (d) distal tubule
   (e) glomerulus
   (f) loop of Henle
   (g) proximal tubule
   (h) renal pelvis
6. Name the three filtration barriers that solutes must cross as they move from plasma to the lumen of Bowman’s capsule. What components of blood are usually excluded by these layers?
7. What force(s) promote(s) glomerular filtration? What force(s) oppose(s) it? What is meant by the term net driving force?
8. What does the abbreviation GFR stand for? What is a typical numerical value for GFR in milliliters per minute? In liters per day?
9. Identify the following structures, then explain their significance in renal physiology:
   (a) juxtaglomerular apparatus
   (b) macula densa
   (c) mesangial cells
   (d) podocytes
   (e) sphincters in the bladder
   (f) renal cortex
10. In which segment of the nephron does most reabsorption take place? When a molecule or ion is reabsorbed from the lumen of the nephron, where does it go? If a solute is filtered and not reabsorbed from the tubule, where does it go?
11. Match each of the following substances with its mode(s) of transport in proximal tubule reabsorption.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Mode(s) of Transport</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na(^+)</td>
<td>1. simple diffusion</td>
</tr>
<tr>
<td>glucose</td>
<td>2. primary active transport</td>
</tr>
<tr>
<td>urea</td>
<td>3. indirect active transport</td>
</tr>
<tr>
<td>plasma proteins</td>
<td>4. facilitated diffusion</td>
</tr>
<tr>
<td>water</td>
<td>5. movement through open channels</td>
</tr>
<tr>
<td></td>
<td>6. endocytosis</td>
</tr>
<tr>
<td></td>
<td>7. paracellular movement</td>
</tr>
</tbody>
</table>
12. List three solutes secreted into the tubule lumen.
13. What solute that is normally present in the body is used to estimate GFR in humans?
14. What is micturition?

**Level Two  Reviewing Concepts**

15. Map the following terms. You may add terms if you like.
   - filtration
   - reabsorption
   - secretion
   - filtration rate
   - plasma concentration of inulin
   - excretion
   - GFR
16. Define, compare, and contrast the items in the following sets of terms:
   (a) filtration, secretion, and excretion
   (b) saturation, transport maximum, and renal threshold
   (c) probenecid, creatinine, inulin, and penicillin
   (d) clearance, excretion, and glomerular filtration rate
17. What are the advantages of a kidney that filters a large volume of fluid and then reabsorbs 99% of it?
18. If the afferent arteriole of a nephron constricts, what happens to GFR in that nephron? If the efferent arteriole of a nephron constricts, what happens to GFR in that nephron? Assume that no autoregulation takes place.
19. Diagram the micturition reflex. How is this reflex altered by toilet training? How do higher brain centers influence micturition?
20. Antimuscarinic drugs are the accepted treatment for an overactive bladder. Explain why they work for this condition.

**Level Three  Problem Solving**

21. You have been asked to study kidney function in a new species of rodent found in the Amazonian jungle. You isolate some nephrons and expose them to inulin. The following graph shows the results of your studies. (a) How is the rodent nephron handling inulin? Is inulin filtered? Is it excreted? Is there net inulin reabsorption? Is there net secretion? (b) On the graph, accurately draw a line indicating the net reabsorption or secretion. (Hint: excretion = filtration - reabsorption - secretion)
The Kidneys

22. Draw a section of renal tubule epithelium showing three cells joined by cell junctions. Label the apical and basolateral membranes, the tubule lumen, and the extracellular fluid. Use the following written description of proximal tubule processes to draw a model cell. The proximal tubule cells contain carbonic anhydrase, which promotes the conversion of CO$_2$ and water to carbonic acid. Carbonic acid then dissociates to H$^+$ and HCO$_3^-$; sodium is reabsorbed by an apical Na$^+$-H$^+$ antiporter and a basolateral Na$^+$-K$^+$-ATPase. Chloride is passively reabsorbed by movement through the paracellular pathway. Bicarbonate produced in the cytoplasm leaves the cell on a basolateral Na$^+$-HCO$_3^-$ symporter.

23. Read the box on hemodialysis and see if you can create a model system that would work for dialysis. Draw two compartments (one to represent blood and one to represent dialysis fluid) separated by a semipermeable membrane. In the blood compartment, list normal extracellular fluid solutes and their concentrations. What will happen to the concentrations of these solutes during kidney failure? Which of these solutes should you put in the dialysis fluid, and what should their concentrations be? (Hint: Do you want diffusion into the dialysis fluid, out of the dialysis fluid, or no net movement?) How would you change the dialysis fluid if the patient was retaining too much water?

Level Four Quantitative Problems

24. Darlene weighs 50 kg. Assume that her total blood volume is 8% of her body weight, that her heart pumps her total blood volume once a minute, and that her renal blood flow is 25% of her cardiac output. Calculate the volume of blood that flows through Darlene’s kidneys each minute.

25. Dwight was competing for a spot on the Olympic equestrian team. As his horse, Nitro, cleared a jump, the footing gave way, causing the horse to somersault, landing on Dwight and crushing him. The doctors feared kidney damage and ran several tests. Dwight’s serum creatinine level was 2 mg/100 mL. His 24-hour urine specimen had a volume of 1 L and a creatinine concentration of 20 mg/mL. A second specimen taken over the next 24 hours had the same serum creatinine value and urine volume, but a urine creatinine concentration of 4 mg/mL. How many milligrams of creatinine are in each specimen? What is Dwight’s creatinine clearance in each test? What is his GFR? Evaluate these results and comment on Dwight’s kidney function.

26. You are a physiologist taking part in an archeological expedition to search for Atlantis. One of the deep-sea submersibles has come back with a mermaid, and you are taking a series of samples from her. You have determined that her GFR is 250 mL/min and that her kidneys reabsorb glucose with a transport maximum of 50 mg/min. What is her renal threshold for glucose? When her plasma concentration of glucose is 15 mg/mL, what is its glucose clearance?

27. If 140 liters of plasma are filtered in a day, and the filtration fraction is 20%:

(a) What is the renal plasma flow?
(b) If this person has a hematocrit of 30%, what is the renal blood flow?
(c) If renal blood flow is 20% of this person’s cardiac output, what is her cardiac output in L/min?

8. Osmotic pressure is higher in efferent arterioles because fluid volume is decreased there, leaving the same amount of protein in a smaller volume.

9. This person’s mean arterial pressure is 119 mm Hg. This person’s GFR is 180 L/day.

10. If the afferent arteriole constricts, the resistance in that arteriole increases, and blood flow through that arteriole is diverted to lower-resistance arterioles. GFR decreases in the nephron whose arteriole constricted.

11. The primary driving force for GFR is blood pressure opposed by fluid pressure in Bowman’s capsule and colloid osmotic pressure due to plasma proteins (Fig. 19.6). With fewer plasma proteins, the plasma has lower-than-normal colloid osmotic pressure. With less colloid osmotic pressure opposing GFR, GFR increases.

12. Creatinine clearance = creatinine excretion rate/[creatinine]$_{\text{plasma}}$ = (1.5 mg creatinine/mL urine × 1.1 L urine/day)/1.8 mg creatinine/100 mL plasma. Creatinine clearance is about 92 L/day, and GFR is equal to creatinine clearance.
The Kidneys

Answers to Figure and Graph Questions

Figure 19.2: 1. (a) Bowman’s capsule, (b) proximal tubule, loop of Henle, distal tubule, collecting duct, (c) proximal tubule, distal tubule, collecting duct, (d) collecting duct. 2. (a) 18/180 = 10%, 1.5/180 = 0.8%

Figure 19.3: E = F – R + S. 79 mmol/day = 720 – R + 43. R = 684 nmol reabsorbed per day.

Figure 19.4: 120 mL/min × 1440 min/day = 172,800 mL/day filtered = 172.8 L. 172.8 L = 20% of plasma flow. Plasma flow = 864 L/day.

Answers to Review Questions

Level One Reviewing Facts and Terms
1. Color (concentration), odor (infection or excreted substances), clarity (presence of cells), taste (presence of glucose), and froth (presence of proteins)
2. Regulation of extracellular fluid volume (to maintain adequate blood pressure), regulation of osmolality, maintenance of ion balance (neuron function), regulation of pH (proteins denature if pH not maintained), excretion of wastes and foreign substances (to prevent toxic effects), and production of hormones (that regulate RBC synthesis, Ca²⁺ and Na⁺ balance).
3. 20–25%
4. Nephrons through ureters to urinary bladder (storage), leaving through the urethra
5. (a), (e), (b), (g), (f), (d), (c), (h)
6. Glomerular capillary endothelium, basal lamina, and epithelium of Bowman’s capsule. Blood cells and most plasma proteins are excluded.
7. Capillary hydrostatic pressure promotes filtration. Fluid pressure in Bowman’s capsule and colloid osmotic (oncotic) pressure of plasma oppose it. Net driving force is the sum of these pressures.
8. GFR—glomerular filtration rate. 125 mL/min or 180 L/day.
9. (a) Found where distal tubule passes between afferent and efferent arterioles. Composed of macula densa cells in the distal tubule and granular cells in arteriole wall. (b) Macula densa paracrine signals control autoregulation of GFR and renin secretion. (c) Alter the size of filtration slits. (d) Specialized epithelial cells that surround glomerular capillaries. Changes in slit size alter GFR. (e) An internal smooth muscle sphincter that is passively contracted and an external skeletal muscle sphincter that is tonically (actively) contracted. (f) Outer layer of the kidney that contains renal corpuscles, proximal and distal tubules, and parts of the loop of Henle and collecting ducts.
10. 70% occurs in the proximal tubule. Reabsorbed molecules go into the peritubular capillaries and the systemic venous circulation. If filtered and not reabsorbed, a molecule is excised in the urine.
11. (a) 2, 3; (b) 3, 4; (c) 4, 7; (d) 6; (e) 5, 7
12. penicillin, K⁺, and H⁺
13. creatinine
14. urination

Level Two Reviewing Concepts
15. Use Figures 19.5, 19.6, and 19.7.
16. (a) Filtration and secretion both move material from blood to tubule lumen, but filtration is a bulk flow process while secretion is a selective process. Excretion is also bulk flow but involves movement from the kidney lumen to the outside world. (b) Saturation—all transporter binding sites are occupied by ligand. Transport maximum—the maximum rate at which carriers are saturated by substrate. Renal threshold—plasma concentration at which saturation occurs. (c) Creatinine and inulin—compounds used to determine GFR. Penicillin and probenecid—xenobiotics that are secreted. (d) Clearance—rate at which plasma is cleared of a substance (mL plasma cleared of substance X/min). GFR—filtration rate of plasma (mL plasma filtered/min). Excretion—removal of urine, mL urine/min.
17. Allows rapid removal of foreign substances that are filtered but not reabsorbed.
19. See Figure 19.14. Toilet training allows higher brain centers to inhibit the reflex until an appropriate time. Higher brain centers can also initiate the reflex.
20. Bladder smooth muscle contracts under parasympathetic control, so blocking muscarinic receptors decreases bladder contraction.

Level Three Problem Solving
21. (a) Inulin is filtered, secreted, and excreted. No evidence for reabsorption is presented. (b) The line indicating net secretion will be close to the filtration line until the slope changes, after which the secretion line is horizontal (no further increase in rate due to saturation).
22. See Figure 19.8. Place transporters as described. CJ⁻ moves between the cells.
23. Dialysis fluid should resemble plasma without waste substances, such as urea. This will allow diffusion of solutes and water from the blood into the dialysis fluid, but diffusion will stop at the desired concentration. To remove excess water from the loop, you can make the dialysis fluid more concentrated than plasma.

Level Four Quantitative Problems
24. 1 L/min
25. First specimen clearance = 1000 L plasma/day. Normally creatinine clearance = GFR. However, this value is not at all realistic for GFR (normal average is 180 L/day). The repeat test has 4000 mg of creatinine and gives a clearance of 200 L/day, which is within normal limits. The abnormal values on the first test were probably a laboratory error. Dwight’s kidney function is normal.
26. For any solute that filters: plasma concentration × GFR = filtration rate. At the transport maximum: filtration rate = reabsorption rate of Tᵢᵣ. By substitution: plasma concentration × GFR = Tᵢᵣ. The renal threshold represents...
the plasma concentration at which the transporters are working at their maximum ($T_m$). By substitution: renal threshold $\times$ GFR = $T_m$. Mermaid’s GFR is 250 mL/min and $T_m$ is 50 mg/min, so renal threshold is 0.2 mg glucose/mL plasma. Clearance = excretion rate/plasma concentration. At 15 mg glucose/mL plasma, 3750 mg/min filter and 50 mg/min reabsorb, so 3700 mg/min are excreted.

27. (a) 140 L/day is 20% of renal plasma flow (RBF), so plasma flow is 700 L/day. (b) Hematocrit is percent of blood occupied by packed red blood cells; the remainder (70%) is plasma. 700 L/day is 70% of RBF, so RBF is 1000 L/day. (c) If RBF is 20% of cardiac output (CO), then CO = 5000 L/day or 3.47 L/min.

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