33

Elements of Renal Function

LEARNING OBJECTIVES

Upon completion of this chapter the student should be able to answer the following questions:

1. Which structures in the glomerulus are filtration barriers to plasma proteins?
2. What is the physiological significance of the juxtaglomerular apparatus?
3. What blood vessels supply the kidneys?
4. What nerves innervate the kidneys?
5. What is the location of the kidneys, and what are their gross anatomical features?
6. What are the different parts of the nephron, and what is their locations within the cortex and medulla?
7. What are the major components of the glomerulus, and what are the cell types located in each component?
8. How can the concepts of mass balance be used to measure the glomerular filtration rate (GFR)?
9. Why can inulin clearance and creatinine clearance be used to measure GFR?
10. Why is plasma creatinine concentration used clinically to monitor GFR?
11. What are elements of the glomerular filtration barrier, and how do they determine how much protein enters Bowman's space?
12. What Starling forces are involved in formation of the glomerular ultrafiltrate, and how do changes in each force affect GFR?
13. What is autoregulation of renal blood flow and GFR, and which factors and hormones are responsible for autoregulation?
14. Which hormones regulate renal blood flow?
15. Why do hormones influence renal blood flow despite autoregulation?

Overview of Renal Function

The kidney presents in the highest degree the phenomenon of sensibility, the power of reacting to various stimuli in a direction, which is appropriate for the survival of the organism; a power of adaptation which almost gives one the idea that its component parts must be endowed with intelligence.

E. STARLING—1909

Certainly, mental integrity is a sine qua non of the free and independent life. But let the composition of our internal environment suffer change, let our kidneys fail for even a short time to fulfill their tasks, and our mental integrity, or personality is destroyed.

HOMER W. SMITH—1939

As both Starling and Smith recognized, the kidneys are more appropriately considered regulatory rather than excretory organs. The kidneys regulate (1) body fluid osmolality and volumes, (2) electrolyte balance, and (3) acid-base balance. In addition the kidneys excrete metabolic products and foreign substances and produce and secrete hormones.

Control of body fluid osmolality is important for maintenance of normal cell volume in all tissues of the body. Control of body fluid volume is necessary for normal function of the cardiovascular system. The kidneys are also essential in regulating the amount of several important inorganic ions in the body, including Na^+, K^+, Cl^-, bicarbonate (HCO_3^-), hydrogen (H^+), Ca^{++}, and inorganic phosphate (P_i). Excretion of these electrolytes must be equal to daily intake to maintain appropriate total body balance. If intake of an electrolyte exceeds its excretion, the amount of this electrolyte in the body increases and the individual is in *positive balance* for that electrolyte. Conversely, if excretion of an electrolyte exceeds its intake, its amount in the body decreases and the individual is in *negative balance* for that electrolyte. For many electrolytes the kidneys are the sole or principal route for excretion from the body.

Another important function of the kidneys is regulation of acid-base balance. Many metabolic functions of the body are exquisitely sensitive to pH. Thus the pH of body fluids must be maintained within narrow limits. Normal pH is maintained by buffers within body fluids and by the coordinated action of the lungs, liver, and kidneys.

The kidneys excrete a number of the end products of metabolism. These waste products include urea (from amino acids), uric acid (from nucleic acids), creatinine (from muscle creatine), end products of hemoglobin metabolism, and metabolites of hormones. The kidneys eliminate these substances from the body at a rate that matches their production. Thus the kidneys regulate hormone concentrations within body fluids. The kidneys also

represent an important route for elimination of foreign substances such as drugs, toxins (e.g., pesticides), and other chemicals from the body.

Finally, the kidneys are important endocrine organs that produce and secrete renin, calcitriol, and erythropoietin. Renin is not a hormone but an enzyme that activates the renin-angiotensin-aldosterone system, which helps regulate blood pressure and Na^+ and K^+ balance. Calcitriol, a metabolite of vitamin D_3, is necessary for normal absorption of Ca^{++} by the gastrointestinal tract and for its deposition in bone (see Chapter 36). In patients with renal disease the kidneys' ability to produce calcitriol is impaired and levels of this hormone are reduced. As a result, Ca^{++} absorption by the intestine is decreased, which over time contributes to abnormalities in the bone formation and remodeling seen in patients with chronic renal disease. Another consequence of many kidney diseases is a reduction in erythropoietin production and secretion. Erythropoietin stimulates red blood cell formation by bone marrow. Decreased erythrocyte production contributes to the anemia that occurs in **chronic kidney disease (CKD),** a progressive loss in kidney function over a period of months or years.

A variety of conditions impair kidney function. Reduced renal function can be transient or permanent and may progress over time. Patients in whom the **glomerular filtration rate (GFR)** is less than 10% of normal are said to have **kidney failure, also called end-stage kidney disease (ESKD)** and must receive renal replacement therapy (RRT) in the form of either dialysis, hemofiltration or kidney transplantation to survive.

To understand the mechanisms that contribute to renal disease, it is first necessary to understand the normal physiology of renal function. Thus in the following chapters in this section of the book, various aspects of renal function are considered.

Functional Anatomy of the Kidneys

Structure and function are closely linked in the kidneys. Consequently an appreciation of the gross anatomical and histological features of the kidneys is a prerequisite for understanding their functions.

Gross Anatomy

The kidneys are paired organs that lie on the posterior wall of the abdomen behind the peritoneum on either side of the vertebral column. In an adult human, each kidney weighs between 115 and 170 g and is approximately 11 cm long, 6 cm wide, and 3 cm thick.

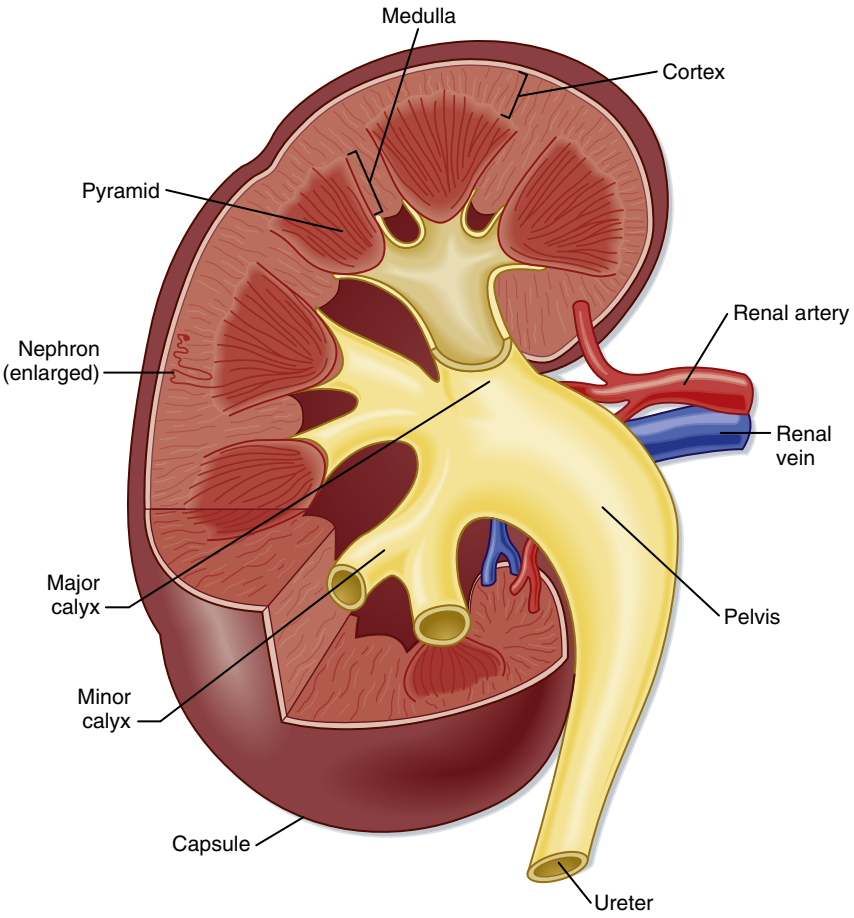
The gross anatomical features of the human kidney are illustrated in Fig. 33.1. The medial side of each kidney contains an indentation through which pass the renal artery and vein, nerves, and pelvis. If a kidney were cut in half, two regions would be evident: an outer region called the **cortex** and an inner region called the **medulla.** The cortex and

IN THE CLINIC

Kidney disease is a major health problem worldwide. In the United States alone:

- Kidney disease affects over 37 million people—that is 1 out of 7 or 15% of the adult population.
- Chronic kidney disease (CKD) is the most under-recognized public health crisis. Approximately 90% of people who have CKD are not even aware of it and 50% of people with very low kidney function, and who are not on dialysis, do not know they have CKD.
- CKD is the eight leading cause of death accounting for more than 100,000 deaths annually.
- The health care cost for CKD in Medicare patients alone exceeds $70 billion per year, and in those patients with end-stage kidney disease (ESKD) it exceeds an additional $50 billion.
- Over 786,000 people are living with **ESKD** with 71% on dialysis and 29% with a kidney transplant.
- Diabetes and hypertension are the leading causes of ESKD.
- More than 23,000 kidney transplants are performed each year. Unfortunately, in excess of 90,000 patients are awaiting kidney transplants.

Individuals with ESKD must undergo RRT, which includes peritoneal dialysis, hemodialysis, hemofiltration, and kidney transplantation. Both peritoneal dialysis and hemodialysis, as their names suggest, rely on the ability to remove small dialyzable molecules from the blood—including metabolic waste products normally removed by intact kidneys—via diffusion across a selectively permeable membrane into a solution lacking these substances, thereby mitigating both their accumulation and associated adverse health effects. In addition, dialysis helps reestablish both fluid and electrolyte balance via removal of excess fluid, correction of acid-base changes, and normalization of plasma electrolyte concentrations). In **peritoneal dialysis,** the peritoneal membrane lining the abdominal cavity acts as a dialyzing membrane. Several liters of a defined dialysis solution are typically introduced into the abdominal cavity, and small molecules in blood diffuse across the peritoneal membrane into the solution, which can then be iteratively removed, discarded, and replaced. In **hemodialysis,** a patient's blood is pumped through an extracorporeal artificial kidney in which blood is separated from a defined dialysis solution by an artificial semipermeable membrane that allows small molecules to diffuse from the blood down their concentration gradient into the dialysis solution, thereby removing small molecules associated with adverse health effects if allowed to accumulate in patients without functioning kidneys. **Hemofiltration** is a form of RRT based on convection, a process during which solutes (metabolic waste products and other small molecules normally cleared by functioning kidneys) and solvent (water) move according to the pressure gradient. In hemofiltration, patient's blood is pumped through an extracorporeal artificial kidney in which solutes are transported across an artificial semipermeable membrane along with movement of solvent (ultrafiltration) that occurs in response to positive transmembrane pressure gradient. Ultrapure replacement fluid is then reinfused into the patient to keep the volume and electrolyte homeostasis. Hemofiltration is used only as a form of continuous RRT in acutely ill, hospitalized patients. Hemodialysis and peritoneal dialysis can also be used in hospitalized patients or as a form of chronic RRT. Patients who are candidates for RRT are often treated with dialysis until an appropriate donor kidney can be procured. Although anemia has historically been a significant problem in ESKD patients owing to severely reduced endogenous erythropoietin production, this problem can now be easily corrected in patients undergoing chronic dialysis via administration of erythropoiesis-stimulating agents (e.g., recombinant human erythropoietin).



• **Fig. 33.1** Structure of a human kidney, cut open to show the internal structures. (Modified from Boron WF, Boulpaep EL. *Medical Physiology.* 2nd ed. Philadelphia: Saunders Elsevier; 2009.)

medulla are composed of **nephrons** (the functional units of the kidney), blood vessels, lymphatics, and nerves. The medulla in the human kidney is divided into conical masses called **renal pyramids**. The base of each pyramid originates at the corticomedullary border, and the apex terminates in a **papilla**, which lies within a **minor calyx**. Minor calyces collect urine from each papilla. The numerous minor calyces expand into two or three open-ended pouches, the **major calyces**. The major calyces in turn feed into the **pelvis**. The pelvis represents the upper expanded region of the **ureter**, which carries urine from the pelvis to the urinary bladder. The walls of the calyces, pelvis, and ureters contain smooth muscle that contracts to propel the urine toward the **urinary bladder**.

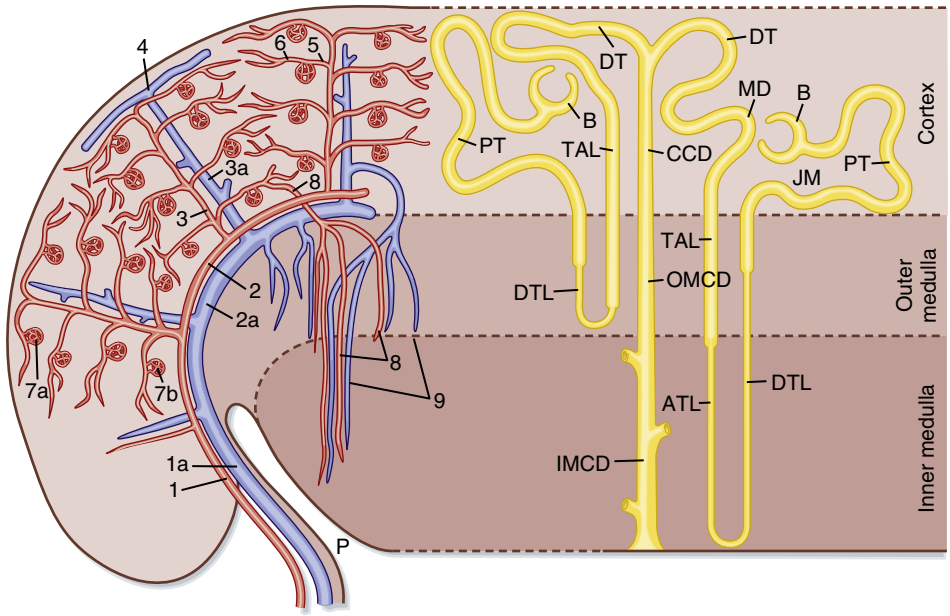
Blood flow to the two kidneys is equivalent to about 25% (1.25 L/minute) of the cardiac output in resting individuals. However, the kidneys constitute less than 0.5% of total body weight. As illustrated in Fig. 33.2 *(left),* the **renal artery** branches progressively to form the **interlobar artery**, the **arcuate artery**, the **interlobular artery,** and the **afferent arteriole**, which leads into the **glomerular capillaries**. The glomerular capillaries come together to form the **efferent arteriole**, which leads into a second capillary network, the **peritubular capillaries**, which supply blood to the nephron. The vessels of the venous system run parallel to the arterial vessels and progressively form the **interlobular vein, arcuate vein, interlobar vein**, and **renal vein**, which courses beside the ureter.

Ultrastructure of the Nephron

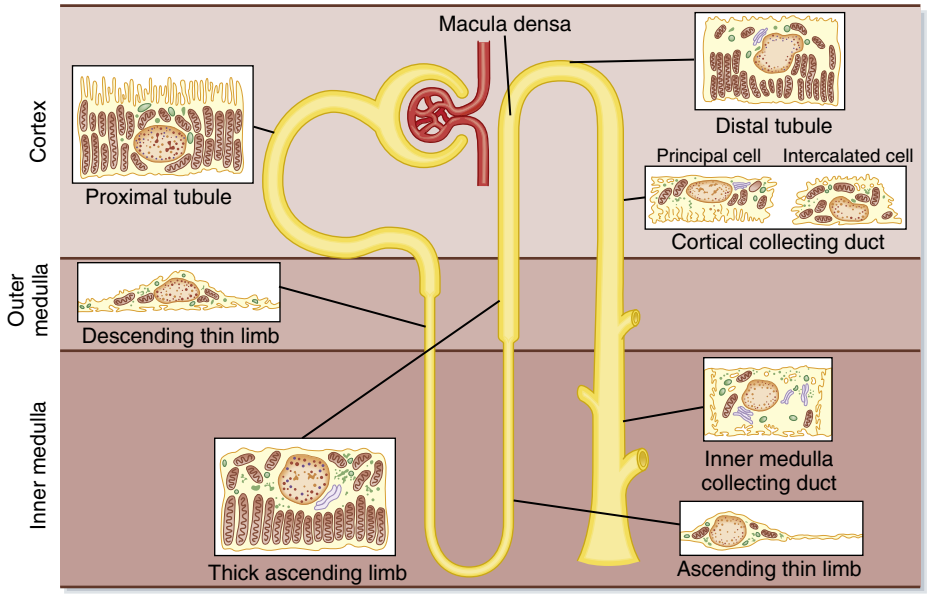
The functional unit of the kidneys is the nephron. Each human kidney contains approximately 1.2 million nephrons, which are essentially hollow tubes composed of a single epithelial cell layer. The nephron consists of a **renal corpuscle, proximal tubule, loop of Henle, distal tubule,** and **collecting duct system**[a] (Fig. 33.3; also see Fig. 33.2). The renal corpuscle[b] consists of glomerular capillaries enclosed within **Bowman's capsule**. The proximal tubule exits this structure and initially forms several coils, followed by a straight piece that descends toward the medulla. The

[a]The organization of the nephron is actually more complicated than presented here. However, for simplicity and clarity of presentation in subsequent chapters, the nephron is divided into five segments. The collecting duct system is not actually part of the nephron. However, again for simplicity, we consider the collecting duct system part of the nephron.

[b]Although the renal corpuscle is composed of glomerular capillaries and Bowman's capsule, the term *glomerulus* is commonly used to described the renal corpuscle.



• **Fig. 33.2** *Left,* Organization of the vascular system of the human kidney. *1,* Interlobar arteries; *1a,* interlobar vein; *2,* arcuate arteries; *2a,* arcuate veins; *3,* interlobular arteries; *3a,* interlobular veins; *4,* stellate vein; *5,* afferent arterioles; *6,* efferent arterioles; *7a, 7b,* glomerular capillary networks; *8,* descending vasa recta; *9,* ascending vasa recta. *Right,* Organization of the human nephron. A superficial nephron is illustrated on the left and a juxtamedullary *(JM)* nephron is illustrated on the right. The loop of Henle includes the straight portion of the proximal tubule *(PT)*, descending thin limb *(DTL)*, ascending thin limb *(ATL)*, and thick ascending limb *(TAL)*. *B,* Bowman's capsule; *CCD,* cortical collecting duct; *DT,* distal tubule; *IMCD,* inner medullary collecting duct; *MD,* macula densa; *OMCD,* outer medullary collecting duct; *P,* pelvis. (Modified from Kriz W, Bankir LA. *Am J Physiol*. 1988;254:F1; and Koushanpour E, Kriz W. *Renal Physiology: Principles, Structure, and Function.* 2nd ed. New York: Springer-Verlag; 1986.)



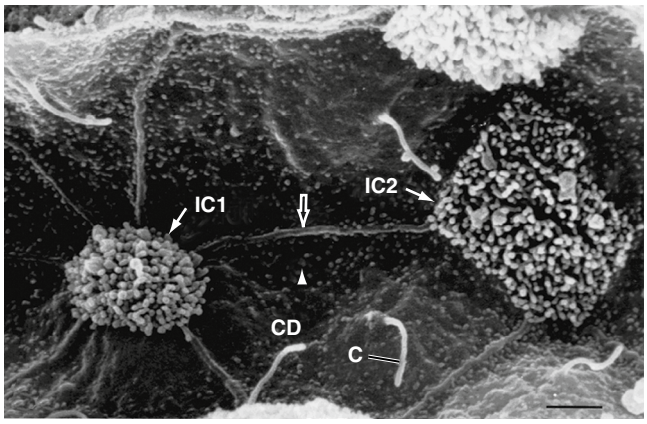
• **Fig. 33.3** Diagram of a nephron including cellular ultrastructure.

next segment is the loop of Henle, which is composed of the straight part of the proximal tubule, the descending thin limb (which ends in a hairpin turn), the ascending thin limb (only in nephrons with long loops of Henle), and the thick ascending limb. Near the end of the thick ascending limb, the nephron passes between the afferent and efferent arterioles of the same nephron. This short segment of the thick ascending limb abutting the glomerulus is called the **macula densa** (see Figs. 33.2 and 33.3). The distal tubule begins a short distance beyond the macula densa and extends to the point in the cortex where two or more nephrons join to form a cortical collecting duct. The **cortical collecting duct** enters the medulla and becomes the outer **medullary collecting duct** and then the **inner medullary collecting duct**.

Each nephron segment is made up of cells that are uniquely suited to perform specific transport functions (see Fig. 33.3). Proximal tubule cells have an extensively amplified apical membrane (the ultrafiltrate or urine side of the cell) called the **brush border**, which is present only in the proximal tubule. The basolateral membrane (the interstitial or blood side of the cell) is highly invaginated. These invaginations contain many mitochondria. In contrast, the descending and ascending thin limbs of the loop of Henle have poorly developed apical and basolateral surfaces and few mitochondria. The cells of the thick ascending limb and the distal tubule have abundant mitochondria and extensive infoldings of the basolateral membrane.

The collecting duct is composed of two cell types: principal cells and intercalated cells. **Principal cells** have a moderately invaginated basolateral membrane and contain few mitochondria (see Fig. 33.3). Principal cells play an important role in reabsorption of NaCl (see Chapters 34 and 35) and secretion of K^+ (see Chapter 36). **Intercalated cells**, which play an important role in regulating acid-base balance, have a high density of mitochondria (see Fig. 33.3). One population of intercalated cells secretes H^+ (i.e., reabsorbs HCO_3^-), and a second population secretes HCO_3^- and can also reabsorb NaCl (see Chapter 37). The final segment of the nephron, the inner medullary collecting duct, is composed of inner medullary collecting duct cells, which have poorly developed apical and basolateral surfaces and few mitochondria.

All cells in the nephron except intercalated cells have in their apical plasma membrane a single nonmotile primary cilium that protrudes into the tubule fluid (Fig. 33.4). Primary cilia are mechanosensors (i.e., they sense changes in the rate of flow of tubule fluid) and chemosensors (i.e., they sense or respond to compounds in the surrounding fluid), and they initiate Ca^{++}-dependent signaling pathways, including those that control kidney cell function, proliferation, differentiation, and apoptosis (i.e., programmed cell death).



• **Fig. 33.4** Scanning electron micrograph illustrating primary cilia (*C*, ≈2–30 µm long and 0.5 µm in diameter) in the apical plasma membrane of principal cells in the cortical collecting duct. Note that intercalated cells (IC1 and IC2) do not have cilia but have numerous microvilli. *CD,* Collecting duct principal cells with short microvilli *(arrowhead);* straight ridges *(open arrow)* represent the cell borders between principal cells; *IC1 and IC2,* intercalated cells with numerous long microvilli in the apical membrane. (From Kriz W, Kaissling B. Structural organization of the mammalian kidney. In: Seldin DW, Giebisch G, eds. *The Kidney: Physiology and Pathophysiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2000.)

AT THE CELLULAR LEVEL

Polycystin 1 (encoded by the *PKD1* gene) and **polycystin 2** (encoded by the *PKD2* gene) are expressed in the membrane of primary cilia and mediate entry of Ca^{++} into cells. PKD1 and PKD2 are thought to play an important role in flow-dependent K^+ secretion by principal cells of the collecting duct. As described in more detail in Chapter 36, increased flow of tubule fluid in the collecting duct is a strong stimulus for secretion of K^+. Increased flow bends the primary cilium in principal cells, which activates the PKD1/PKD2 Ca^{++}-conducting channel complex and allows Ca^{++} to enter the cell and increase intracellular [Ca^{++}]. The increase in [Ca^{++}] activates K^+ channels in the apical plasma membrane, which enhances secretion of K^+ from the cell into the tubule fluid.

IN THE CLINIC

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, occurring in about 1 in 1000 people. More than 12.5 million people worldwide have ADPKD, which is caused primarily by mutations in *PKD1* (85%–90% of cases) or *PKD2* (≈15% of cases). The major phenotype of ADPKD is enlargement of the kidneys due to the presence of hundreds or thousands of fluid-filled renal cysts that can grow to the size of 20 cm in diameter. Cysts are also seen in the liver and other organs in this condition. About 50% of patients with ADPKD progress to ESKD by the age of 60. Although it is not clear how mutations in *PKD1* and *PKD2* cause ADPKD, renal cyst formation may result from defects in Ca^{++} uptake that alter Ca^{++}-dependent signaling pathways, including those controlling kidney cell proliferation, differentiation, and apoptosis.

Nephrons may be subdivided into superficial and juxtamedullary types (see Fig. 33.2), with approximately 10 superficial nephrons for each juxtamedullary nephron. The glomerulus of each superficial nephron is located in the outer region of the cortex. The corresponding loops of Henle are short, and associated efferent arterioles branch into peritubular capillaries that surround its associated nephron segments as well as adjacent nephrons. This capillary network conveys oxygen and important nutrients to the nephron segments in the cortex, delivers substances to individual nephron segments for secretion (i.e., movement of a substance from blood into tubular fluid), and serves as a pathway for return of reabsorbed water and solutes to the circulatory system. A few species, including humans, also possess very short superficial nephrons whose loops of Henle never enter the medulla.

The glomerulus of each **juxtamedullary nephron** is located in the region of the cortex adjacent to the medulla (see Fig. 33.2, *right*). When compared with superficial nephrons, juxtamedullary nephrons differ anatomically in two important ways: the loop of Henle is longer and extends deeper into the medulla, and the efferent arteriole forms not

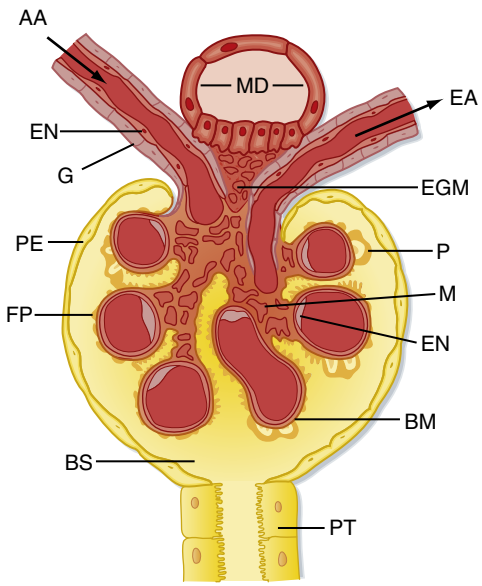
only a network of peritubular capillaries but also a series of accompanying vascular loops called the **vasa recta.**

As shown in Fig. 33.2 *(left),* the vasa recta descend into the medulla, where they form capillary networks that surround the collecting ducts and ascending limbs of the loop of Henle. The blood returns to the cortex via the ascending vasa recta. Although less than 0.7% of the renal blood flow (RBF) enters the vasa recta, these vessels serve important functions in the renal medulla that include (1) conveying oxygen and important metabolic substrates to support nephron function, (2) delivering substances to the nephron for secretion, (3) serving as a pathway for return of reabsorbed water and solutes to the circulatory system, and (4) concentrating and diluting urine (urine concentration and dilution are discussed in more detail in Chapter 35).

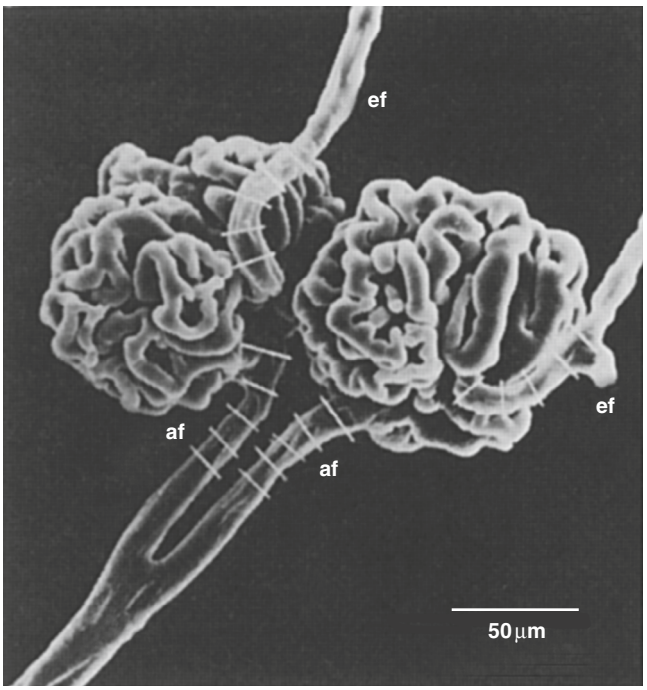
Ultrastructure of the Glomerulus

The first step in urine formation begins with passive movement of a plasma ultrafiltrate from the glomerular capillaries (i.e., glomerulus) into **Bowman's space**. The term *ultrafiltration* refers to this passive movement of fluid—similar in composition to plasma, except for the fact that the ultrafiltrate protein concentration is much lower than that in the plasma—from the glomerular capillaries into Bowman's space. To appreciate this process, one must understand the anatomy of the glomerulus, which consists of a network of capillaries supplied by the afferent arteriole and drained by the efferent arteriole (Figs. 33.5 and 33.6). During embryological development, the glomerular capillaries press into the closed end of the proximal tubule, forming Bowman's capsule. As the epithelial cells thin on the outside circumference of Bowman's capsule, they form the parietal epithelium (see Fig. 33.5). The epithelial cells in contact with the capillaries thicken and develop into **podocytes**, which form the **visceral layer** of Bowman's capsule (Figs. 33.7–33.9). The visceral cells face outward at the vascular pole (i.e., where afferent and efferent arterioles enter and exit Bowman's capsule) to form the parietal layer of Bowman's capsule. The space between the visceral layer and the parietal layer is Bowman's space, which at the urinary pole (i.e., where the proximal tubule joins Bowman's capsule) of the glomerulus becomes the lumen of the proximal tubule.

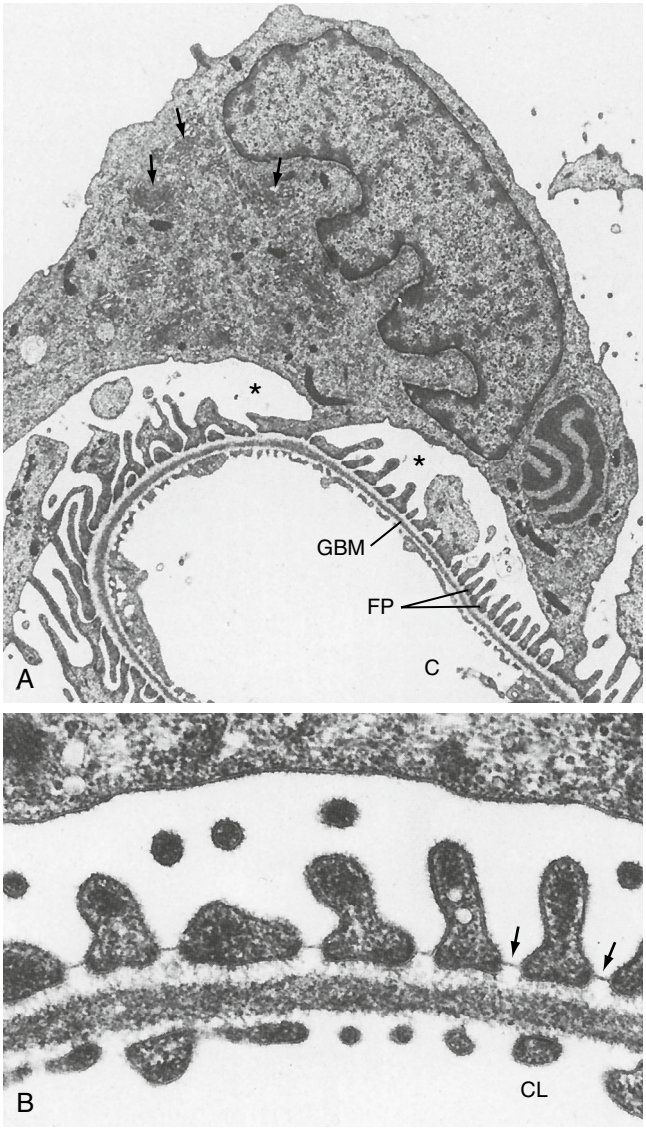
The endothelial cells of glomerular capillaries are covered by a basement membrane surrounded by **podocytes**. The capillary endothelium, basement membrane, and foot processes of podocytes form the so-called **filtration barrier** (see Figs. 33.5 and 33.7–33.9). The endothelium is fenestrated (i.e., contains 700-Å holes, where 1 Å = 10^{-10} m) and freely permeable to water, small solutes (e.g., Na^+, urea, glucose), and most proteins but is not permeable to red blood cells, white blood cells, or platelets. Because endothelial cells express negatively charged glycoproteins on their surface, they minimize the filtration into Bowman's space of albumin, the most abundant plasma protein, and most other plasma proteins. In addition to their role as a barrier to filtration, the endothelial cells synthesize a number of vasoactive substances (e.g., nitric oxide [NO],



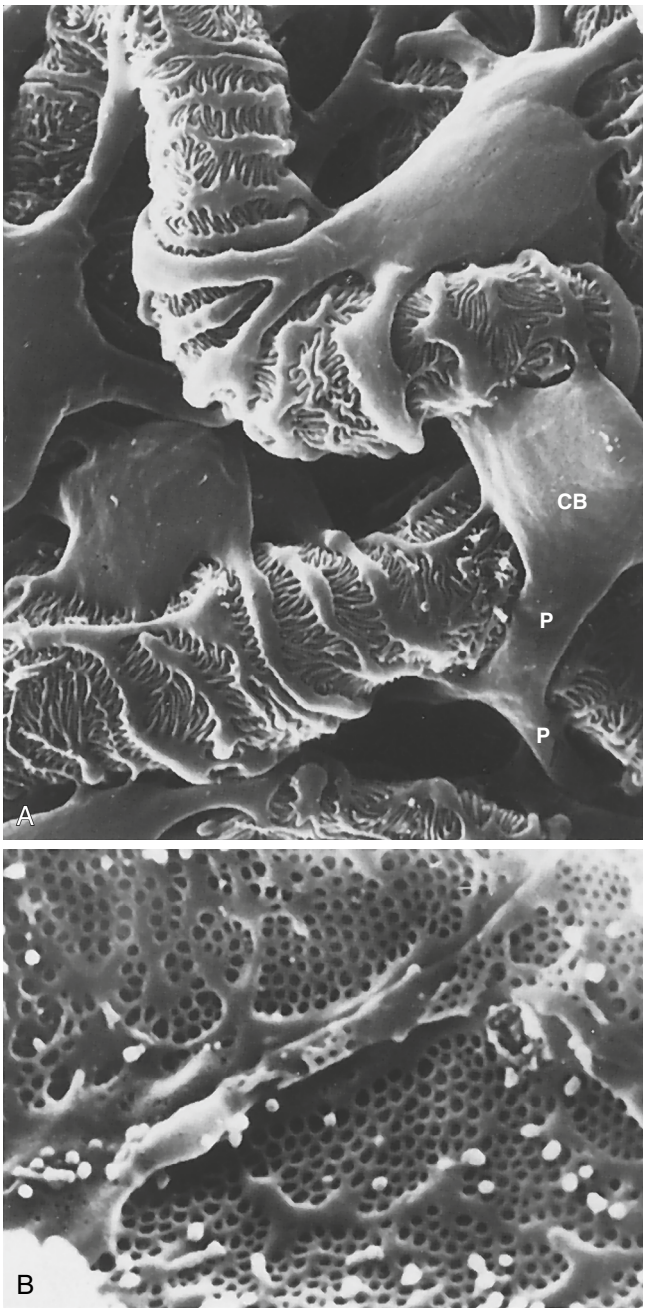
• **Fig. 33.5** Anatomy of the glomerulus and juxtaglomerular apparatus. The juxtaglomerular apparatus is composed of the macula densa *(MD)* of the thick ascending limb, extraglomerular mesangial cells *(EGM)*, and renin- and angiotensin II–producing granular cells *(G)* of the afferent arterioles *(AA)*. *BM,* Basement membrane; *BS,* Bowman's space; *EA,* efferent arteriole; *EN,* endothelial cell; *FP,* foot processes of the podocyte; *M,* mesangial cells between capillaries; *P,* podocyte cell body (visceral cell layer); *PE,* parietal epithelium; *PT,* proximal tubule cell. (Modified from Kriz W, Kaissling B. Structural organization of the mammalian kidney. In: Alpern RJ, Moe OW, Caplan M, eds. *Seldin and Giebisch's The Kidney*. 5th ed. London: Elsevier; 2013. Figure in that source based on Kriz W, Sakai T, et al. Morphological aspects of glomerular function. In: Davison AM, ed. *"Nephrology," Vol. 1, Proceedings of the 10th International Congress of Nephrology*. Bailliere Tindall: London; 1988: 323.)



• **Fig. 33.6** Scanning electron micrograph of the interlobular artery, afferent arteriole *(af)*, efferent arteriole *(ef)*, and glomerulus. The *white bars* on the afferent and efferent arterioles indicate that they are about 15 to 20 μm in diameter. (From Kimura K et al. *Am J Physiol*. 1990;259:F936.)



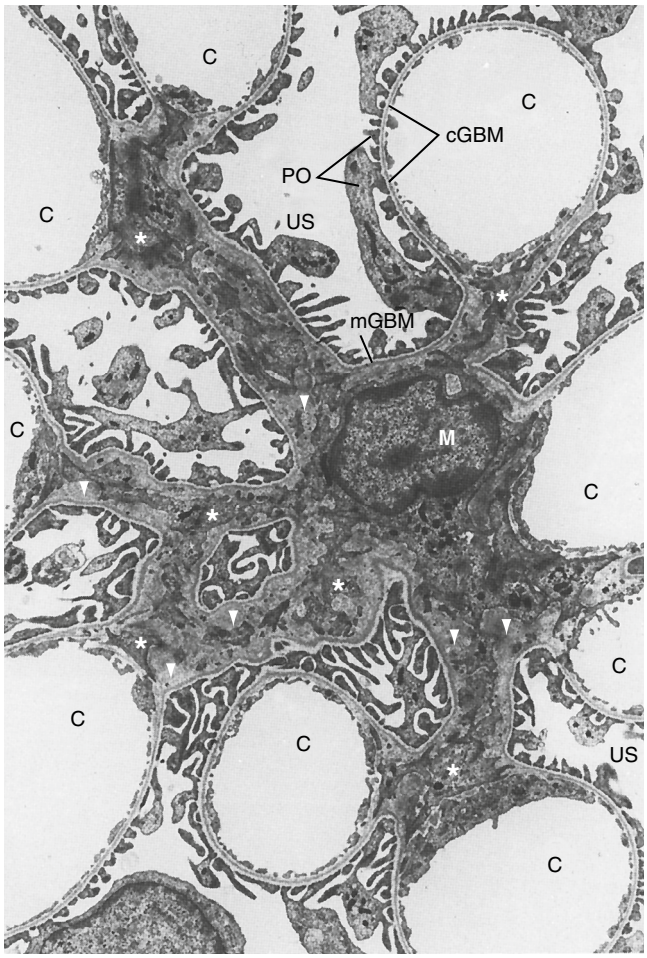
• **Fig. 33.7 A,** Electron micrograph of a podocyte surrounding a glomerular capillary. The cell body of the podocyte contains a large nucleus with three indentations. Cell processes of the podocyte form the interdigitating foot processes *(FP)*. The *arrows* in the cytoplasm of the podocyte indicate the well-developed Golgi apparatus, and the *asterisks* indicate Bowman's space. *C,* Capillary lumen; *GBM,* glomerular basement membrane. **B,** Electron micrograph of the filtration barrier of a glomerular capillary. The filtration barrier is composed of three layers: the endothelium, basement membrane, and foot processes of the podocytes. Note the filtration slit diaphragm bridging the floor of the filtration slits *(arrows). CL,* Capillary lumen. (From Kriz W, Kaissling B. Structural organization of the mammalian kidney. In: Alpern RJ, Moe OW, Caplan M, eds. *Seldin and Giebisch's The Kidney*. 5th ed. London: Elsevier; 2013.)



• **Fig. 33.8 A,** Scanning electron micrograph showing the outer surface of glomerular capillaries. This is the view that would be seen from Bowman's space. Processes *(P)* of podocytes run from the cell body *(CB)* toward the capillaries, where they ultimately split into foot processes. Interdigitation of the foot processes creates the filtration slits. **B,** Scanning electron micrograph of the inner surface (blood side) of a glomerular capillary. This view would be seen from the lumen of the capillary. The fenestrations of the endothelial cells are seen as small 700-Å holes. (From Kriz W, Kaissling B. Structural organization of the mammalian kidney. In: Alpern RJ, Moe OW, Caplan M, eds. *Seldin and Giebisch's The Kidney*. 5th ed. London: Elsevier; 2013.)

a vasodilator, and endothelin 1 [ET-1], a vasoconstrictor) that are important in controlling **renal plasma flow (RPF)**. The basement membrane, which is a porous matrix of negatively charged proteins (type IV collagen, laminin, the proteoglycans agrin and perlecan, and fibronectin), is an important filtration barrier to plasma proteins. The basement membrane is thought to function primarily as a charge-selective filter in which the ability of proteins to cross the filter is based on charge.

The podocytes, which are endocytic, have long finger-like processes that completely encircle the outer surface of the capillaries (see Figs. 33.7 and 33.8A). The processes of the podocytes interdigitate to cover the basement membrane and are separated by apparent gaps called **filtration slits** (see Figs. 33.7 and 33.8A). Each filtration slit is bridged by a thin diaphragm that contains pores with a dimension of



• **Fig. 33.9** Electron micrograph of the mesangium, the area between the glomerular capillaries containing mesangial cells. *C,* Glomerular capillaries; cGBM, capillary glomerular basement membrane surrounded by foot processes of podocytes *(PO)* and endothelial cells; *M,* mesangial cell that gives rise to several processes, some marked by *stars*; *mGBM,* mesangial glomerular basement membrane surrounded by foot processes of podocytes and mesangial cells; *US,* urinary space. Note the extensive extracellular matrix surrounded by mesangial cells *(triangles)* (× 4100). (From Kriz W, Kaissling B. Structural organization of the mammalian kidney. In: Alpern RJ, Moe OW, Caplan M, eds. *Seldin and Giebisch's The Kidney*. 5th ed. London: Elsevier; 2013.)

40 × 140 Å. The **filtration slit diaphragm**, which appears as a continuous structure when viewed by electron microscopy (see Fig. 33.7B), is composed of several proteins, including **nephrin (NPHS1)**, **NEPH-1**, and **podocin (NPHS2)**, and intracellular proteins that associate with the slit diaphragm, including **α-actinin-4 (ACTN4)** and **CD2-AP** (Figs. 33.10 and 33.11). Filtration slits, which function primarily as a size-selective filter, minimize the filtration of proteins and macromolecules that cross the basement membrane from entering Bowman's space. Because both the basement membrane and filtration slits contain negatively charged glycoproteins, some proteins are held back (i.e., not filtered into Bowman's space) on the basis of size and charge. For molecules with an effective molecular radius between 18 and 42 Å, cationic molecules are filtered more readily than anionic molecules.

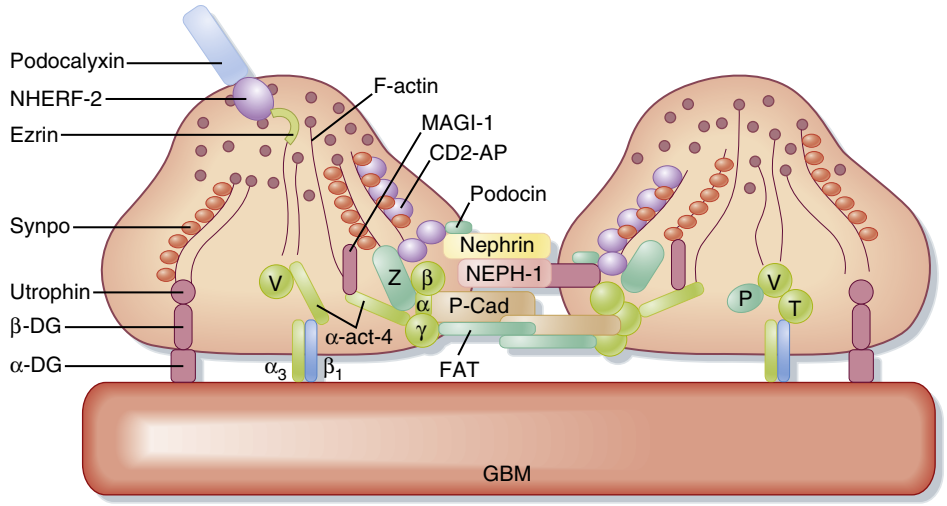
Another important component of the renal corpuscle is the **mesangium,** which consists of **mesangial cells** and the **mesangial matrix** (see Fig. 33.9). Mesangial cells, which possess many properties of smooth muscle cells, provide structural support for the glomerular capillaries, secrete extracellular matrix, exhibit phagocytic activity by removing macromolecules from the mesangium, and secrete prostaglandins and proinflammatory cytokines. Because they also contract and are adjacent to glomerular capillaries, mesangial cells may influence GFR by regulating blood flow through the glomerular capillaries or by altering the capillary surface area. Mesangial cells located outside the glomerulus (between the afferent and efferent arterioles) are called **extraglomerular mesangial cells**.

IN THE CLINIC

The loss of normal podocyte structure affects the integrity of filtration barrier and increases permeability of the glomerular capillaries to proteins. The augmented permeability to proteins results in increased urinary protein excretion **(proteinuria)**. Thus the appearance of proteins in urine can indicate kidney disease. Urinary loss of large quantities of protein leads to hypoalbuminemia and may cause generalized edema. The triad, characterizing a condition called **nephrotic syndrome**, can result from mutations of genes encoding proteins essential to the integrity of filtration barrier. Nephrotic syndrome can also be caused by an infection-triggered dysregulation of the immune system that ultimately affects the filtration barrier. Mutations in several genes encoding either slit diaphragm proteins (see Figs. 33.10 and 33.11), including **nephrin**, **NEPH-1**, and **podocin**, or intracellular proteins that functionally interact with slit diaphragm proteins, such as **CD2-AP** and **α-actinin 4** (ACTN4), result in proteinuria and kidney disease. For example, mutations in the nephrin gene *(NPHS1)* in congenital nephrotic syndrome lead to abnormal slit diaphragms, causing massive proteinuria and renal failure. In addition, mutations in the podocin gene *(NPHS2)* cause nephrotic syndrome.

IN THE CLINIC

Alport syndrome is characterized by structural abnormalities and dysfunction in the glomerular basement membrane type IV collagen leading to hematuria (i.e., blood in the urine), proteinuria, and progressive loss of kidney function, and it accounts for 3% of CKD in children and 0.2% of adults with ESKD in the United States. Alport syndrome is caused by mutations in the *COL4A3, COL4A4, or COL4A5* genes causing defects in the type IV collagen alpha-3, alpha-4, and alpha-5 chains, respectively. The prevailing view is that Alport syndrome is transmitted in an X-linked manner in most cases and results from mutations in the *COL4A5* gene. Mutations in the *COL4A3* or *COL4A4* genes are transmitted in an autosomal manner and account for only a small number of Alport syndrome cases. Our understanding of the genetics of Alport syndrome has evolved in recent years. The new sequencing technologies suggest that the prevalence of all *COL4A4* gene mutations, including those leading to autosomal Alport syndrome in the population, may be much higher than previously anticipated.



• **Fig. 33.10** Anatomy of podocyte foot processes. This figure illustrates the proteins that make up the slit diaphragm between two adjacent foot processes. Nephrin and NEPH1 are membrane-spanning proteins that have large extracellular domains that interact. Podocin, also a membrane-spanning protein, organizes nephrin and NEPH1 in specific microdomains in the plasma membrane, which is important for signaling events that determine the structural integrity of podocyte foot processes. Many of the proteins that compose the slit diaphragm interact with adapter proteins inside the cell, including CD2-AP. The adapter proteins bind to the filamentous actin *(F-actin)* cytoskeleton, which in turn binds either directly or indirectly to proteins such as $\alpha_3\beta_1$ and MAGI-1 that interact with proteins expressed by the glomerular basement membrane *(GBM)*. *α-act-4,* α-Actinin 4; $\alpha_3\beta_1$, $\alpha_3\beta_1$ integrin; *α-DG,* α-dystroglycan; *CD2-AP,* an adapter protein that links nephrin and podocin to intracellular proteins; *FAT,* a protocadherin that organizes actin polymerization; *MAGI-1,* a membrane-associated guanylate kinase protein; *NHERF-2,* Na^+-H^+ exchanger regulatory factor 2; *P,* paxillin; *P-Cad,* P-cadherin; *Synpo,* synaptopodin; *T,* talin; *V,* vinculin; *Z,* zona occludens. (Adapted from Mundel P, Shankland SJ. *J Am Soc Nephrol*. 2002;13:3005.)

Ultrastructure of the Juxtaglomerular Apparatus

The **juxtaglomerular apparatus** is one component of an important feedback mechanism, the tubuloglomerular feedback mechanism, described later in this chapter. Structures that make up the juxtaglomerular apparatus (see Fig. 33.5) include:

1. the **macula densa** of the thick ascending limb
2. extraglomerular mesangial cells
3. renin- and angiotensin II–producing **granular cells** of the afferent arteriole

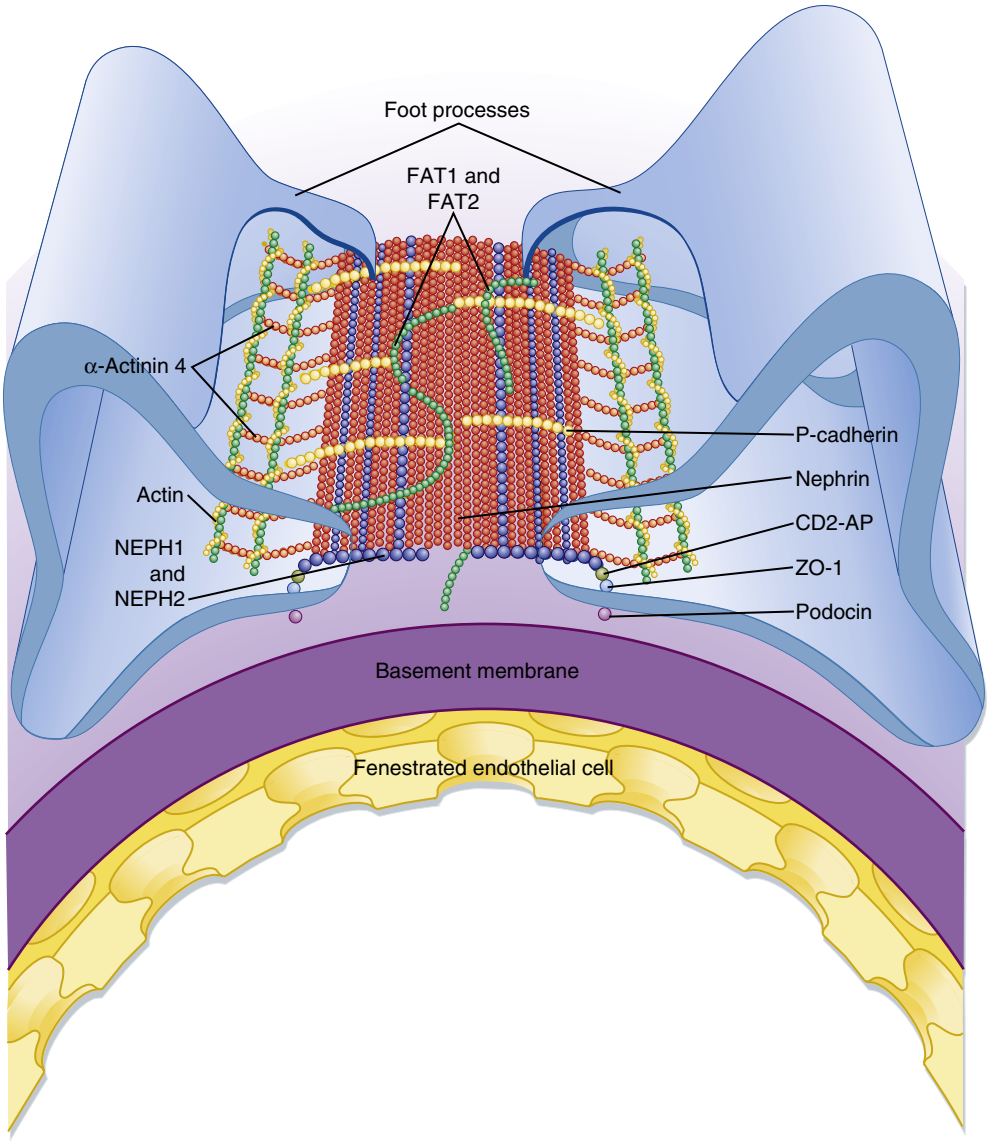
The cells of the macula densa represent a morphologically distinct region of the thick ascending limb. This region passes through the angle formed by the afferent and efferent arterioles of the same nephron. The cells of the macula densa contact the extraglomerular mesangial cells and the granular cells of the afferent arterioles. The granular cells of the afferent arterioles contain smooth muscle myofilaments and—importantly—manufacture, store, and release **renin** in response to signals associated with decreased effective circulating volume and reduced renal perfusion. Renin is involved in proteolytic generation of **angiotensin II** and ultimately in secretion of **aldosterone** (see Chapter 35). The juxtaglomerular apparatus is one component of the tubuloglomerular feedback mechanism involved in autoregulation of RBF and GFR.

Innervation of the Kidneys

Renal nerves regulate RBF, GFR, and salt and water reabsorption by the nephron. The nerve supply to the kidneys consists of sympathetic nerve fibers that originate in the celiac plexus. There is no corresponding parasympathetic innervation. Adrenergic fibers innervating the kidneys release norepinephrine and lie adjacent to the smooth muscle cells of the major branches of the renal artery (interlobar, arcuate, and interlobular arteries) as well as the afferent and efferent arterioles. In addition, sympathetic nerves innervate the renin-producing granular cells of the afferent arterioles. Renin secretion is stimulated by increased sympathetic activity. Nerve fibers also innervate the proximal tubule, loop of Henle, distal tubule, and collecting duct; activation of these nerves enhances Na^+ reabsorption by these nephron segments.

Assessment of Renal Function

The coordinated actions of the nephron's various segments determine the final amount of a substance that appears in urine. This represents three general processes: (1) glomerular filtration, (2) reabsorption of the substance from tubular fluid back into blood, and (3) (in some cases) secretion of the substance from blood into tubule fluid. The first step in urine formation by the kidneys is production of an ultrafiltrate of plasma across the glomerulus. The process of glomerular filtration and regulation of GFR and RBF are



• **Fig. 33.11** Overview of the major proteins that form the slit diaphragm. Nephrins *(red)* from opposite foot processes interdigitate in the center of the slit. In the slit, nephrin interacts with NEPH1 and NEPH2 *(blue),* FAT1 and FAT2 *(green),* and P-cadherin. The intracellular domains of nephrin, NEPH1, and NEPH2 interact with podocin and CD2-AP, which connect these slit diaphragm proteins with ZO-1, α-actinin 4, and actin. (Modified from Tryggvason K et al. *N Engl J Med*. 2006;354:1387.)

discussed later in this chapter. The concept of renal clearance, which is the theoretical basis for measurement of GFR and RBF, is presented in the following section. Reabsorption and secretion are discussed in subsequent chapters.

Renal Clearance

The concept of **renal clearance** is based on the Fick principle (i.e., mass balance or conservation of mass). Fig. 33.12 illustrates the various factors required to describe the mass balance relationships of a kidney. The renal artery is the single input source to the kidney for substances not synthesized by this organ, whereas the renal vein and ureter constitute the two principal output routes. In other words, a nonmetabolized substance entering the renal circulation via the renal artery may only exit this circulation via the renal vein (i.e., the unfiltered fraction plus any filtered amount subsequently reabsorbed back into blood) or the ureter (the combined filtered and secreted fractions less any tubular reabsorption). The following equation defines the mass balance relationship:

Equation 33.1

$$P_x^a \times RPF^a = \left(P_x^v \times RPF^v\right) + \left(U_x \times \dot{V}\right)$$

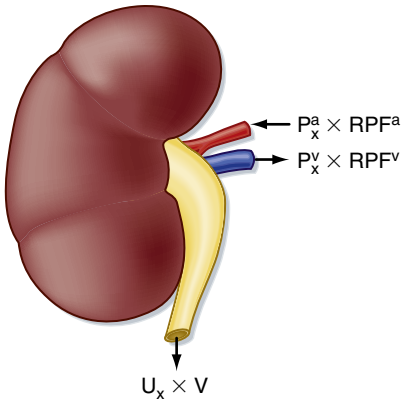
where

P_x^a and P_x^v are the concentrations of substance x in the renal artery and renal vein plasma, respectively

RPF^a and RPF^v are **renal plasma flow** rates in the artery and vein, respectively

U_x is the concentration of substance x in urine

$\dot{V}$ is the urine flow rate



• **Fig. 33.12** Mass balance relationships for the kidney. See text for definition of symbols.

This relationship permits quantification of the amount of substance x excreted in urine versus the amount returned to the systemic circulation in renal venous blood. Thus for any substance that is neither synthesized nor metabolized, the amount that enters the kidneys is equal to the amount that leaves the kidneys in urine plus the amount that leaves the kidneys in renal venous blood.

The principle of renal clearance emphasizes the excretory function of the kidneys; it considers only the rate at which a substance is excreted into urine and not its rate of return to the systemic circulation in the renal vein. Therefore in terms of mass balance (Eq. 33.1) the urinary excretion rate of substance x ($U_x \times \dot{V}$) is proportional to the plasma concentration of substance x (P_x^a):

Equation 33.2

$$P_x^a \propto U_x \times \dot{V}$$

To equate the urinary excretion rate of substance x to its renal arterial plasma concentration, it is necessary to determine the rate at which it is removed from plasma by the kidneys. This removal rate is the clearance (C_x):

Equation 33.3

$$P_x^a \times C_x = U_x \times \dot{V}$$

If Eq. 33.3 is rearranged and the concentration of substance x in renal artery plasma (P_x^a) is assumed to be identical to its concentration in a plasma sample from any peripheral blood vessel (P_x), the following relationship is obtained:

Equation 33.4

$$C_x = \frac{U_x \times \dot{V}}{P_x}$$

Clearance has the dimensions of volume/time, and it represents a volume of plasma from which all the substance has been removed and excreted into urine per unit time. This last point is best illustrated by considering the following example. If a substance is present in urine at a concentration of 100 mg/mL and the urine flow rate is 1 mL/minute, the excretion rate for this substance is calculated as follows:

Equation 33.5

$$\text{Excretion rate} = U_x \times \dot{V} = 100 \text{ mg/mL} \times 1 \text{ mL/minute} = 100 \text{ mg/minute}$$

If this substance is present in plasma at a concentration of 1 mg/mL, its clearance according to Eq. 33.4 is as follows:

Equation 33.6

$$C_x = \frac{U_x \times \dot{V}}{P_x} = \frac{100 \text{ mg/minute}}{1 \text{ mg/mL}} = 100 \text{ mL/minute}$$

In other words, 100 mL of plasma will be completely cleared of substance x each minute. The definition of *clearance* as a volume of plasma from which all the substance has been removed and excreted into urine per unit time is somewhat misleading because it is not a real volume of plasma; rather it is a virtual volume.[c] The concept of clearance is important because it can be used to measure GFR and RPF and determine whether a substance is reabsorbed or secreted along the nephron.

Glomerular Filtration Rate

The GFR is equal to the sum of the filtration rates of all functioning nephrons. Thus it is an aggregate index of kidney function. A fall in GFR generally means the kidney disease is progressing, whereas recovery generally suggests recuperation. Thus serial assessment of a patient's GFR is essential to evaluate the severity and course of kidney disease.

Creatinine is a byproduct of normal skeletal muscle creatine metabolism and is freely filtered across the glomerulus into Bowman's space. It is normally generated by the body at a fairly constant rate, and—to a first approximation—it is not appreciably reabsorbed, secreted, or metabolized by the cells of the nephron after its filtration. Accordingly the amount of creatinine excreted in urine per minute is fairly constant at steady state (i.e., when [creatinine] is constant) and equals the amount of creatinine filtered at the glomerulus each minute (Fig. 33.13):

Equation 33.7

$$\text{Amount filtered} = \text{Amount excreted}$$

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

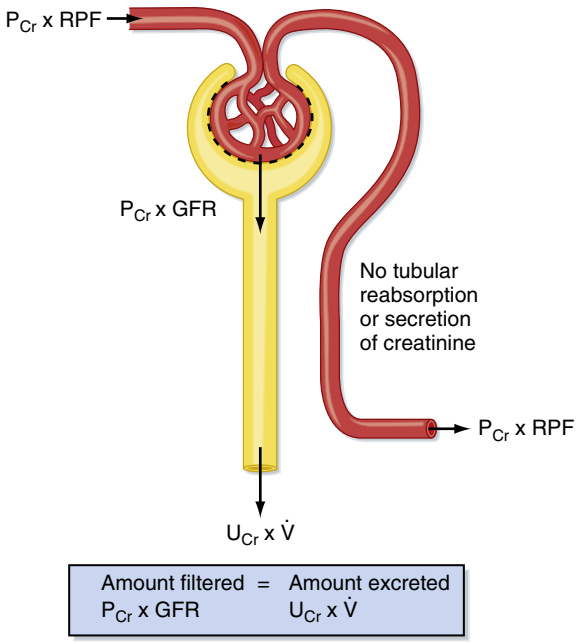
where
P_{Cr} = plasma concentration of creatinine
U_{Cr} = urine concentration of creatinine
$\dot{V}$ = urine flow

If Eq. 33.7 is solved for GFR:

Equation 33.8

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

[c]For most substances cleared from plasma by the kidneys, only a portion is actually removed and excreted in a single pass through the kidneys.



• **Fig. 33.13** Renal handling of creatinine. Creatinine is freely filtered across the glomerulus and is, to a first approximation, not reabsorbed, secreted, or metabolized by the nephron. Note that all the creatinine coming to the kidney in the renal artery does not get filtered at the glomerulus (normally, 15%–20% of plasma creatinine is filtered). The portion that is not filtered is returned to the systemic circulation in the renal vein. P_{Cr}, Plasma creatinine concentration; *RPF,* renal plasma flow; U_{Cr}, urinary concentration of creatinine; *V*, urine flow rate.

This equation is the same form as that for clearance (see Eq. 33.4). Thus measured creatinine clearance (CrCl) can be used clinically to determine GFR at steady state. Clearance has the dimensions of volume/time, and it represents an equivalent volume of plasma from which all of the substance has been removed and excreted into urine per unit time.

Creatinine is not the only substance that can be used to measure GFR; any substance that meets the following criteria can serve as an appropriate marker. The substance must:

1. achieve a stable plasma concentration
2. be freely filtered across the glomerulus into Bowman's space
3. not be reabsorbed or secreted by the nephron
4. not be metabolized or produced by the kidney
5. not alter GFR

Not all creatinine (or other substances used to measure GFR) that enters the kidney in renal arterial plasma is filtered at the glomerulus. Likewise not all plasma coming into the kidneys is filtered. Although nearly all plasma that enters the kidneys in the renal artery passes through the glomerulus, approximately 10% does not. The *portion of filtered plasma* is termed the **filtration fraction** and is determined as:

Equation 33.9

$$\text{Filtration fraction} = \frac{\text{GFR}}{\text{RPF}}$$

Under normal conditions the filtration fraction averages 0.15 to 0.20, which means that only 15% to 20% of the plasma that enters the glomerulus is actually filtered. The remaining 80% to 85% continues on through the glomerular capillaries and into the efferent arterioles and peritubular capillaries before finally returning to the systemic circulation via the renal vein.

IN THE CLINIC

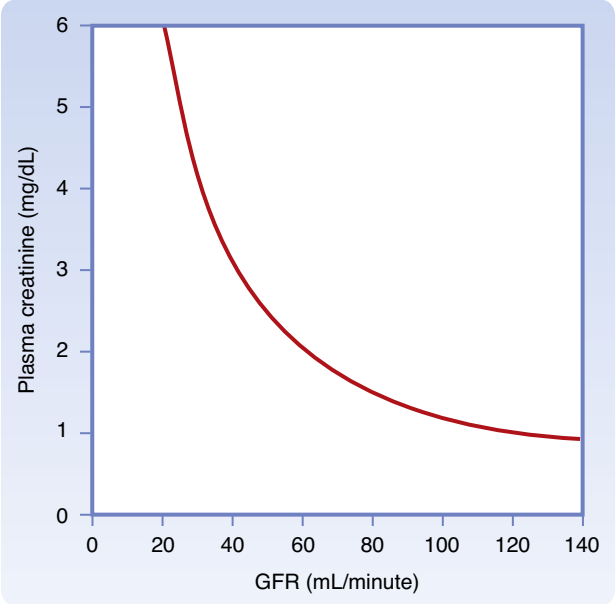
Creatinine clearance (CrCl) can be used to estimate GFR in clinical practice. It is synthesized at a relatively constant rate, and the amount produced is proportional to the total muscle mass. However, creatinine is not a perfect substance for measuring GFR because it is secreted to a small extent by the organic cation secretory system in the proximal tubule (see Chapter 34). The error introduced by this secretory component is approximately 10%. Thus the amount of creatinine excreted in urine exceeds the amount expected from filtration alone by 10%. However, the method used to measure the plasma creatinine concentration (P_{Cr}) overestimates the true value by 10%. Consequently the two errors cancel each other, and in most clinical situations, CrCl provides a reasonably accurate measure of GFR.

Although the creatinine clearance is used to measure the GFR, in most clinical settings the GFR is estimated (eGFR) from the serum [creatinine], and sometimes other serum constituents (e.g., Cystatin C), and takes into account the patients age and sex. When a patient's serum [creatinine] is measured the clinical chemistry laboratory normally calculates and reports the patients' eGFR. An eGFR > 60 mL/minute is considered normal. Values < 60 mL/minute may indicate impaired kidney function.

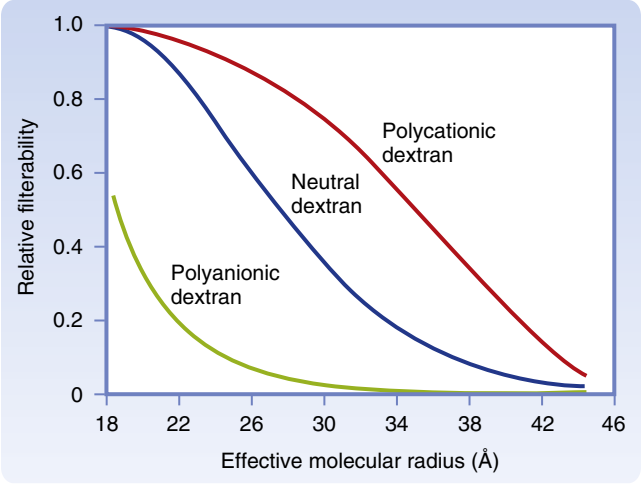
It is important to note that a fall in GFR may be the first and only clinical sign of kidney disease. Thus determining the GFR is important when kidney disease is suspected. However, a 50% loss of functioning nephrons reduces GFR only by about 25%. The decline in GFR is not 50% because the remaining nephrons compensate. Kidney function is usually assessed by measuring the plasma concentration of creatinine (P_{Cr}), which is inversely related to GFR (Fig. 33.14). However, as Fig. 33.14 shows, GFR must decline substantially before an increase in P_{Cr} can be detected. For example, a fall in GFR from 120 to 100 mL/minute is accompanied by an increase in P_{Cr} from 1.0 to 1.2 mg/dL. This does not appear to be a significant change in P_{Cr}, but GFR has actually fallen by almost 20%.

Glomerular Filtration

The first step in the formation of urine is ultrafiltration of plasma by the glomerulus. In normal adults, GFR ranges from 90 to 140 mL/minute in males and from 80 to 125 mL/minute in females. Thus in 24 hours as much as 180 L of plasma is filtered by the glomeruli. The plasma ultrafiltrate is devoid of cellular elements (i.e., red and white blood cells and platelets) and is essentially protein free. The concentration of salts and organic molecules (e.g., glucose, amino acids) is similar in plasma and the



• **Fig. 33.14** Relationship between GFR and plasma [creatinine] (P_{cr}). The amount of creatinine filtered is equal to the amount excreted; thus GFR × P_{Cr} = U_{Cr} × $\dot{V}$. Because the production of creatinine is constant, excretion must be constant to maintain creatinine balance. Therefore if GFR falls from 120 to 60 mL/minute, P_{Cr} must increase from 1 to 2 mg/dL to keep filtration of creatinine and its excretion equal to the production rate. *GFR,* Glomerular filtration rate.



• **Fig. 33.15** Influence of the size and electric charge of dextran on its filterability. A value of 1 indicates that it is filtered freely, whereas a value of zero indicates that it is not filtered. The filterability of dextrans between approximately 18 and 42 Å depends on charge. Dextrans larger than 42 Å are not filtered regardless of charge, and polycationic dextrans and neutral dextrans smaller than 18 Å are freely filtered. The major proteins in plasma are albumin and immunoglobulins. Because the effective molecular radii of immunoglobulin (Ig)G (53 Å) and IgM (>100 Å) are greater than 42 Å, they are not filtered. Although the effective molecular radius of albumin is 35 Å, it is a polyanionic protein, so it does not cross the filtration barrier to a significant degree.

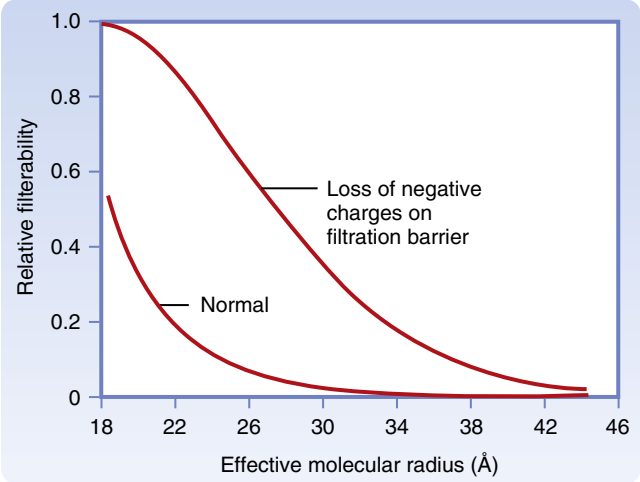
ultrafiltrate. Starling forces drive ultrafiltration across the glomerular capillaries, and changes in these forces alter GFR. GFR and RPF are normally held within very narrow ranges by a phenomenon called *autoregulation.* The next sections of this chapter review the composition of the glomerular filtrate, the dynamics of its formation, and the relationship between RPF and GFR. In addition, factors that contribute to autoregulation and regulation of GFR and RBF are discussed.

Determinants of Ultrafiltrate Composition

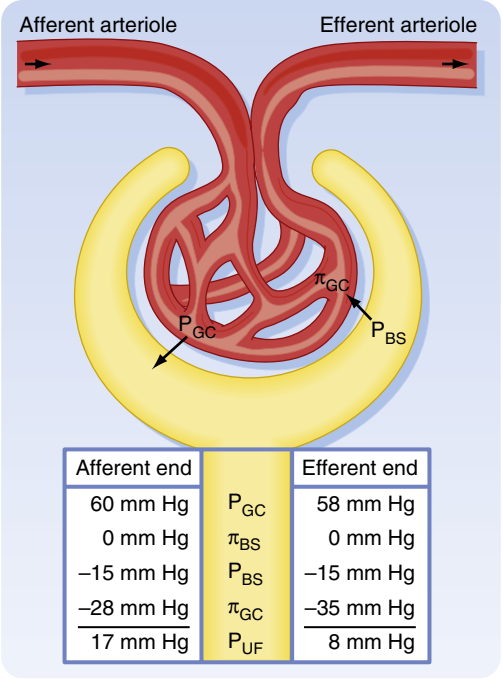
The glomerular filtration barrier determines the composition of the plasma ultrafiltrate. It restricts filtration of molecules on the basis of both size and electric charge (Fig. 33.15). In general, neutral molecules with a radius smaller than about 18 Å are freely filtered, molecules larger than about 42 Å are not filtered, and molecules between about 18 and 42 Å are filtered to varying degrees. Fig. 33.15 shows how electric charge affects filtration of macromolecules (e.g., dextrans) by the glomerulus. Dextrans are a family of exogenous polysaccharides manufactured in various molecular weights. They can be electrically neutral or have either negative (polyanionic) or positive (polycationic) charges. As the size (i.e., effective molecular radius) of a dextran molecule increases, the rate at which it is filtered decreases. For any given molecular radius, cationic molecules are more readily filtered than anionic molecules. The reduced filtration rate for anionic molecules is explained by the presence of negatively charged glycoproteins on the surface of all components of the glomerular filtration barrier. These charged glycoproteins repel similarly charged molecules. Because most plasma proteins are negatively charged, the negative charge on the filtration barrier restricts filtration of anionic proteins more than the filtration of neutral and polyanionic proteins with a molecular radius between approximately 18 to 42 Å. For example, serum albumin, an anionic protein that has an effective molecular radius of 35.5 Å, is poorly filtered. Because the small amount of filtered albumin is normally reabsorbed avidly by the proximal tubule, almost no albumin appears in urine.

IN THE CLINIC

The importance of the negative charges on the filtration barrier in restricting filtration of plasma proteins is shown in Figs. 33.15 and 33.16. Removal of the negative charges from the filtration barrier causes proteins to be filtered solely on the basis of their effective molecular radius (Fig. 33.16). Hence at any molecular radius between approximately 18 and 42 Å, filtration of polyanionic proteins will exceed the filtration that prevails in the normal state (in which the filtration barrier has anionic charges). In a number of glomerular diseases the negative charges on the filtration barrier are reduced because of immunological damage and inflammation. As a result, filtration of anionic proteins between approximately 18 and 42 Å in radius is increased. When the filtered proteins exceed the ability of the proximal tubule to reabsorb and catabolize them, anionic proteins begin to appear in urine **(proteinuria)**, which is a marker of kidney disease.



• **Fig. 33.16** Reduction of the negative charges on the glomerular wall results in filtration of proteins on the basis of size only. In this situation the relative filterability of proteins depends only on the molecular radius. Accordingly, excretion of polyanionic proteins (18–42 Å) in urine increases because more proteins of this size are filtered.



• **Fig. 33.17** Idealized glomerular capillary and the Starling forces across it. The reflection coefficient (σ) for protein across the glomerular capillary is approximately 1. P_{BS}, Hydraulic pressure in Bowman's space; P_{GC}, hydraulic pressure in the glomerular capillary; P_{UF}, net ultrafiltration pressure; π_{BS}, oncotic pressure in Bowman's space; π_{GC}, oncotic pressure in the glomerular capillary. The negative signs for P_{BS} and π_{GC} indicate that these forces oppose formation of the glomerular filtrate.

Dynamics of Ultrafiltration

The forces responsible for glomerular filtration of plasma are the same as those in other capillary beds. Ultrafiltration occurs because the Starling forces (i.e., hydrostatic and oncotic pressures) combine to drive fluid from the lumen of glomerular capillaries across the filtration barrier and into Bowman's space (Fig. 33.17). The hydrostatic pressure inside the glomerular capillary (P_{GC}) is oriented to promote movement of fluid from the glomerular capillary into Bowman's space. Because the glomerular ultrafiltrate is essentially protein free under normal conditions, owing in large part to the paucity of proteins in serum smaller than 18 Å in radius that can be effectively filtered, the reflection coefficient (σ) for proteins across the glomerular capillary is essentially 1. Thus the oncotic pressure in Bowman's space (π_{BS}) is near zero. Therefore P_{GC} is the principal force favoring filtration. In contrast, the hydrostatic pressure in Bowman's space (P_{BS}) and the oncotic pressure in the glomerular capillary (π_{GC}) both oppose filtration.

As shown in Fig. 33.17, a net ultrafiltration pressure (P_{UF}) of 17 mm Hg exists at the afferent end of the glomerulus, whereas at the efferent end it is 8 mm Hg (where $P_{UF} = P_{GC} - P_{BS} - \pi_{GC}$). Two additional points concerning Starling forces and this pressure change are important to note. First, P_{GC} decreases slightly along the length of the capillary because of the resistance to flow along the length of the capillary. Second, π_{GC} increases as plasma is filtered while protein is retained within the glomerular capillary, thereby progressively increasing the protein concentration along the length of the capillary. GFR is proportional to the sum of the Starling forces that exist across the capillaries $[(P_{GC} - P_{BS}) - \sigma(\pi_{GC} - \pi_{BS})]$ multiplied by the ultrafiltration coefficient (K_f) of the capillary. That is,

Equation 33.10

$$GFR = K_f\left[\left(P_{GC} - P_{BS}\right) - \sigma\left(\pi_{GC} - \pi_{BS}\right)\right]$$

K_f is the product of the intrinsic permeability of the glomerular capillary and the glomerular surface area available for filtration. The rate of glomerular filtration is considerably greater in glomerular capillaries than in systemic capillaries, mainly because K_f is approximately 100 times greater in glomerular capillaries. Furthermore P_{GC} is approximately twice as great as the hydrostatic pressure in systemic capillaries.

GFR can be altered by changing K_f or by changing any of the Starling forces. In normal individuals, GFR is regulated by alterations in P_{GC} that are mediated mainly by changes in afferent or efferent arteriolar resistance. P_{GC} is affected in three ways:

1. Changes in afferent arteriolar resistance: A decrease in resistance increases P_{GC} and GFR, whereas an increase in resistance decreases P_{GC} and GFR.
2. Changes in efferent arteriolar resistance: A decrease in resistance reduces P_{GC} and GFR, whereas an increase in resistance elevates P_{GC} and GFR.
3. Changes in renal arteriolar pressure: An increase in blood pressure transiently increases P_{GC} (which enhances GFR), whereas a decrease in blood pressure transiently decreases P_{GC} (which reduces GFR).

IN THE CLINIC

A reduction in GFR in disease states is most often due to decreases in K_f because of the loss of filtration surface area. GFR also changes in pathophysiological conditions because of changes in P_{GC}, π_{GC}, and P_{BS}.

1. Changes in K_f: Increased K_f enhances GFR, whereas decreased K_f reduces GFR. Some kidney diseases reduce K_f by decreasing the number of filtering glomeruli (i.e., diminished surface area). Some drugs and hormones that dilate the glomerular arterioles also increase K_f. Similarly, drugs and hormones that constrict the glomerular arterioles also decrease K_f.
2. Changes in P_{GC}: With decreased renal perfusion, GFR declines because P_{GC} falls. As previously discussed, a reduction in P_{GC} is caused by a decline in renal arterial pressure, an increase in afferent arteriolar resistance, or a decrease in efferent arteriolar resistance.
3. Changes in π_{GC}: An inverse relationship exists between π_{GC} and GFR. Alterations in π_{GC} result from changes in protein synthesis outside the kidneys. In addition the protein loss in urine caused by some renal diseases can lead to a decrease in the plasma protein concentration and thus in π_{GC}.
4. Changes in P_{BS}: Increased P_{BS} reduces GFR, whereas decreased P_{BS} enhances GFR. Acute obstruction of the urinary tract (e.g., a kidney stone occluding the ureter) increases P_{BS}.

Renal Blood Flow

Blood flow through the kidneys serves several important functions:

1. indirectly determines GFR
2. modifies the rate of solute and water reabsorption by the proximal tubule
3. participates in concentration and dilution of urine
4. delivers O_2, nutrients, and hormones to cells along the nephron and returns CO_2, reabsorbed fluid, and solutes to the general circulation
5. delivers substrates for excretion in urine

Blood flow through any organ may be represented by the following equation:

Equation 33.11

$$Q = \frac{\Delta P}{R}$$

where

Q = blood flow

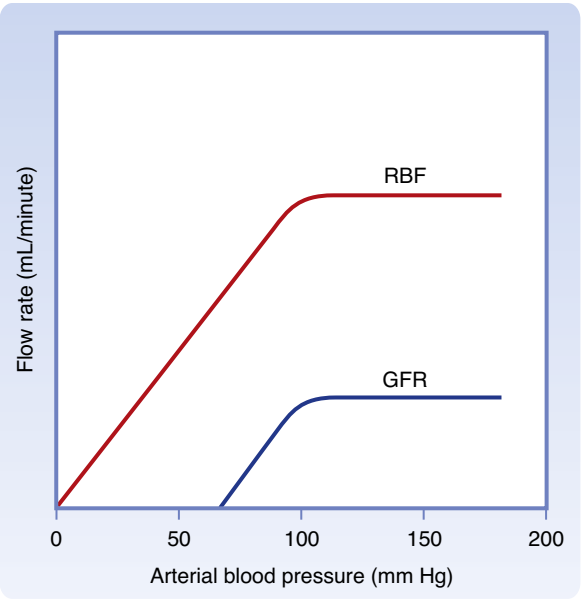
ΔP = mean arterial pressure minus venous pressure for that organ

R = resistance to flow through that organ

Accordingly, RBF is equal to the pressure difference between the renal artery and the renal vein divided by renal vascular resistance:

Equation 33.12

$$RBF = \frac{\text{Aortic pressure} - \text{Renal venous pressure}}{\text{Renal vascular resistance}}$$

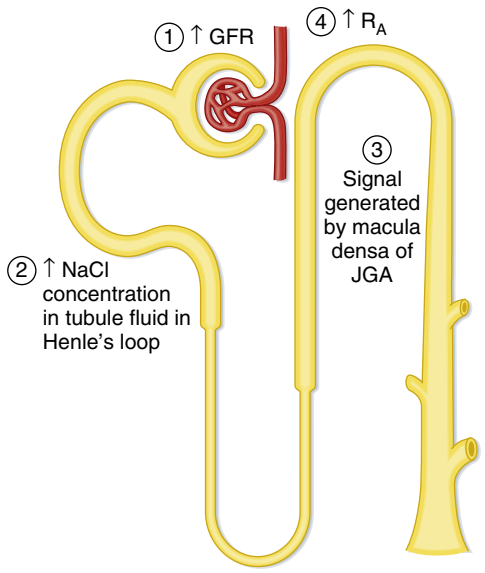


• **Fig. 33.18** Relationship between arterial blood pressure and RBF and between arterial blood pressure and GFR. Autoregulation maintains GFR and RBF relatively constant as blood pressure changes from 90 to 180 mm Hg. *GFR,* Glomerular filtration rate; *RBF,* renal blood flow.

The afferent arteriole, efferent arteriole, and interlobular arteries are the major resistance vessels in the kidneys and thereby determine renal vascular resistance. Like most other organs, the kidneys regulate their blood flow by adjusting vascular resistance in response to changes in arterial pressure. As shown in Fig. 33.18 these adjustments are so precise that blood flow remains relatively constant as arterial blood pressure changes between 90 and 180 mm Hg. GFR is also regulated over the same range of arterial pressures. The phenomenon whereby RBF and GFR are maintained relatively constant between blood pressures of 90 and 180 mm Hg, namely **autoregulation**, is achieved by changes in vascular resistance, mainly through the afferent arterioles of the kidneys. Because both RBF and GFR are regulated over the same range of pressures and because RBF is an important determinant of GFR, it is not surprising that the same mechanisms regulate both flows.

Two mechanisms are responsible for autoregulation of RBF and GFR: one mechanism that responds to changes in arterial pressure and another that responds to changes in [NaCl] in tubular fluid. Both regulate the tone of the afferent arteriole. The pressure-sensitive mechanism, the so-called **myogenic mechanism**, is related to an intrinsic property of vascular smooth muscle: the tendency to contract when stretched. Accordingly, when arterial pressure rises and the renal afferent arteriole is stretched, the smooth muscle contracts in response. Because the increase in resistance of the arteriole offsets the increase in pressure, RBF, and therefore GFR, remains constant. (That is, RBF is constant if ΔP/R is kept constant [see Eq. 33.11].)

The second mechanism responsible for autoregulation of GFR and RBF is the [NaCl]-dependent mechanism



• **Fig. 33.19** Tubuloglomerular feedback. An increase in glomerular filtration rate *(GFR) (1)* increases [NaCl] in tubule fluid in the loop of Henle *(2)*. The increase in [NaCl] is sensed by the macula densa and converted to a signal *(3)* that increases the resistance of the afferent arteriole *(R_A) (4)*, which decreases GFR. A decrease in GFR has the opposite effects. *JGA*, juxtaglomerular apparatus. (Modified from Cogan MG. *Fluid and Electrolytes: Physiology and Pathophysiology.* Norwalk, CT: Appleton & Lange; 1991.)

known as **tubuloglomerular feedback**. This mechanism involves a feedback loop in which a change in GFR leads to alteration in the concentration of NaCl in tubular fluid, which is sensed by the macula densa of the **juxtaglomerular apparatus** and converted into signals that affect afferent arteriolar resistance and thus the GFR (Fig. 33.19). For example, when the GFR increases and causes [NaCl] in tubular fluid in the loop of Henle to rise, more NaCl enters the macula densa cells in this segment (Fig. 33.20). This leads to an increase in formation and release of adenosine triphosphate (ATP) and adenosine (a metabolite of ATP) by macula densa cells, which causes vasoconstriction of the afferent arteriole and normalization of GFR. In contrast, when GFR and [NaCl] in tubule fluid decrease, less NaCl enters the macula densa cells, and both ATP and adenosine production and release decline. The fall in [ATP] and [adenosine] results in afferent arteriolar vasodilation, which returns GFR to normal. NO, a vasodilator produced by the macula densa, attenuates tubuloglomerular feedback, whereas angiotensin II enhances tubuloglomerular feedback. Thus the macula densa may release both vasoconstrictors (e.g., ATP and adenosine) and a vasodilator (e.g., NO) that oppose each other's action at the level of the afferent arteriole. Production plus release of either vasoconstrictors or vasodilators ensures exquisite control over tubuloglomerular feedback.

Fig. 33.20 also illustrates the role of the macula densa in controlling renin secretion by granular cells of the afferent arteriole. This aspect of function of the juxtaglomerular apparatus is considered in detail in Chapter 35.

Because animals engage in many activities that can change arterial blood pressure, mechanisms that maintain RBF and GFR relatively constant despite changes in arterial pressure are highly desirable. If GFR and RBF were to rise or fall suddenly in proportion to changes in blood pressure, urinary excretion of fluid and solute would also change suddenly. Such changes in excretion of water and solutes without comparable changes in intake would alter fluid and electrolyte balance (the reason for which is discussed in Chapter 35). Accordingly, autoregulation of GFR and RBF provides an effective means for uncoupling renal function from arterial pressure, and it ensures that fluid and solute excretion remain relatively constant.

Three points concerning autoregulation should be noted:

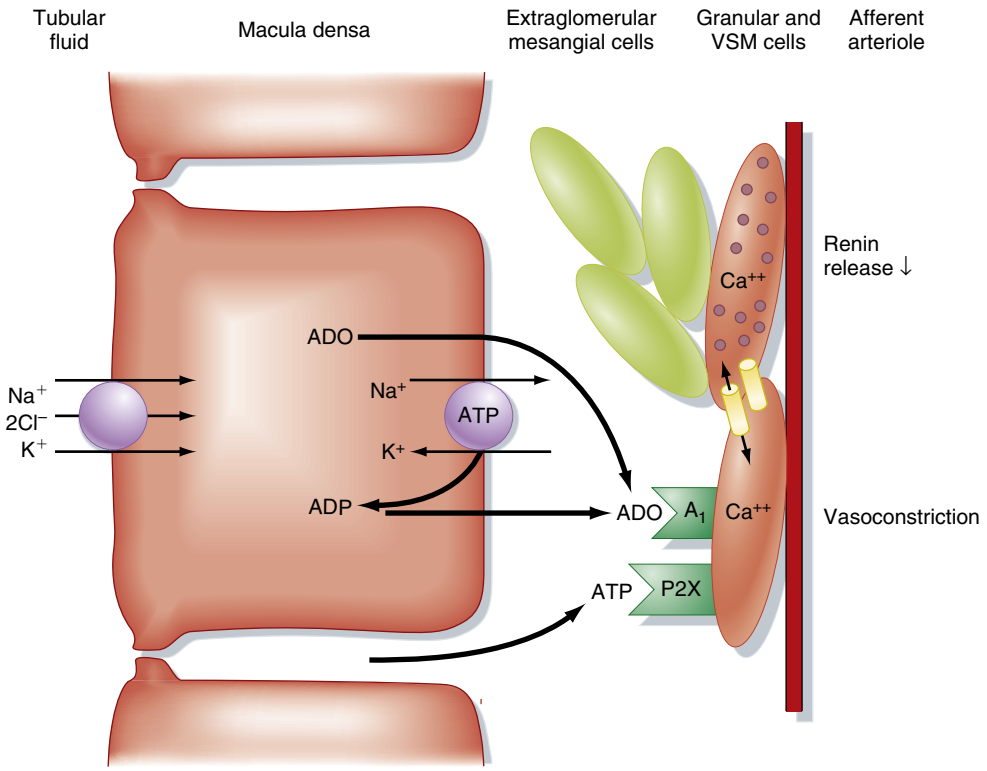
1. Autoregulation is absent when arterial pressure is less than 90 mm Hg.
2. Autoregulation is not perfect; RBF and GFR do change slightly as arterial blood pressure varies.
3. Despite autoregulation, RBF and GFR can be changed by several hormones and by alterations in sympathetic nerve activity that change in response to alterations in the extracellular fluid volume (ECFV) (Table 33.1).

AT THE CELLULAR LEVEL

Tubuloglomerular feedback (TGF) is absent in mice that do not express the adenosine receptor (A_1). This underscores the importance of adenosine signaling in TGF. Studies have shown that when GFR increases and causes the concentration of NaCl in tubular fluid at the macula densa to rise, more NaCl enters cells via the $1Na^+$-$1K^+$-$2Cl^-$ symporter (NKCC2) located in the apical plasma membrane (see Fig. 33.20). Increased intracellular [NaCl] in turn stimulates release of ATP via ATP-conducting ion channels located in the basolateral membrane of macula densa cells. In addition, adenosine production is also enhanced. Adenosine binds to A_1 receptors and ATP binds to P2X receptors located on the plasma membrane of smooth muscle cells in the afferent arteriole. Both hormones increase intracellular [Ca^{++}], which causes vasoconstriction of the afferent artery and therefore a fall in GFR. Although adenosine is a vasodilator in most other vascular beds, it constricts the afferent arteriole in the kidney.

Regulation of Renal Blood Flow and Glomerular Filtration Rate

Several factors and hormones affect both RBF and GFR (see Table 33.1). As already discussed, the myogenic mechanism and tubuloglomerular feedback play key roles in maintaining RBF and GFR constant when blood pressure is greater than 90 mm Hg and ECFV is in the normal range. However, when the ECFV changes sympathetic nerves, angiotensin II, prostaglandins, NO, endothelin, bradykinin, ATP, and adenosine exert major control over RBF and GFR. Fig. 33.21 shows how changes in efferent and afferent arteriolar resistance, mediated by changes in the hormones listed in Table 33.1, modulate both RBF and GFR.

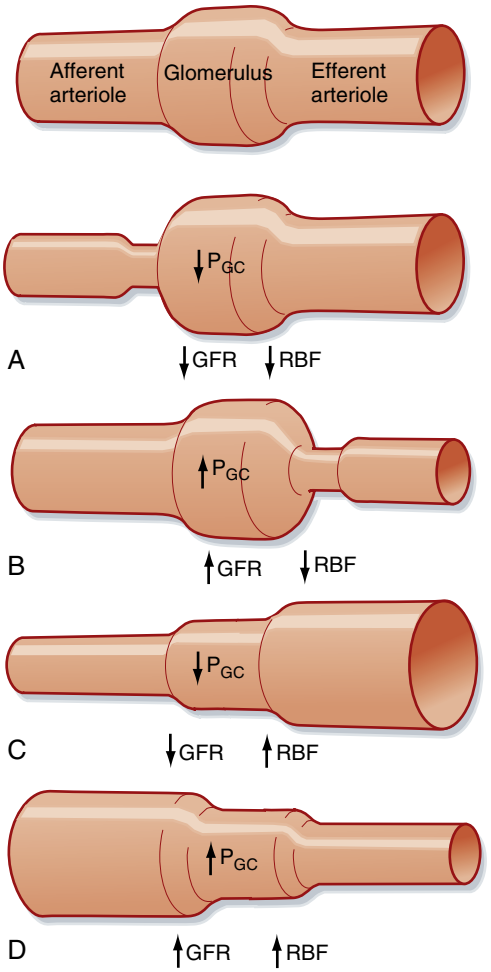


• **Fig. 33.20** Cellular mechanism whereby an increase in delivery of NaCl to the macula densa causes vasoconstriction of the afferent arteriole of the same nephron (i.e., tubuloglomerular feedback). An increase in GFR elevates [NaCl] in tubule fluid at the macula densa. This in turn enhances uptake of NaCl across the apical cell membrane of macula densa cells via the $1Na^+$-$1K^+$-$2Cl^-$ (NKCC2) symporter, which leads to an increase in [ATP] and [adenosine] *(ADO)* release. ATP binds to P2X receptors and adenosine binds to adenosine A_1 receptors in the plasma membrane of smooth muscle cells surrounding the afferent arteriole, both of which increase intracellular [Ca^{++}]. The rise in [Ca^{++}] induces vasoconstriction of the afferent arteriole, thereby returning GFR to normal levels. Note that ATP and adenosine also inhibit renin release by granular cells in the afferent arteriole. This too results from an increase in intracellular [Ca^{++}] as a reflection of electrical coupling of the granular and vascular smooth muscle *(VSM)* cells. When GFR is reduced, [NaCl] in tubule fluid falls, as does uptake of NaCl into macula densa cells. This in turn decreases release of ATP and adenosine by the macula densa, which decreases intracellular [Ca^{++}] in smooth muscle cells and thereby increases GFR and stimulates renin release by granular cells. In addition a decrease in entry of NaCl into macula densa cells enhances production of PGE_2, which also stimulates renin secretion by granular cells. As discussed in detail in Chapter 34, renin increases plasma [angiotensin II], a hormone that enhances NaCl and water retention by the kidneys. (Modified from Persson AEG et al. *Acta Physiol Scand*. 2004;181:471.)

TABLE 33.1 Major Hormones That Influence Glomerular Filtration Rate and Renal Blood Flow

	Stimulus	Effect on GFR	Effect on RBF
Vasoconstrictors			
Sympathetic nerves	↓ ECFV	↓	↓
Angiotensin II	↓ ECFV	↓	↓
Endothelin	↑ Stretch, A-II, bradykinin, epinephrine; ↓ ECFV	↓	↓
Vasodilators			
Prostaglandins (PGE_1, PGE_2, PGI_2)	↓ ECFV; ↑ shear stress, A-II	No change/↑	↑
Nitric oxide (NO)	↑ Shear stress, acetylcholine, histamine, bradykinin, ATP	↑	↑
Bradykinin	↑ Prostaglandins, ↓ ACE	↑	↑
Natriuretic peptides (ANP, BNP)	↑ ECFV	↑	No change

A-II, Angiotensin II; *ACE,* angiotensin-converting enzyme; *ECFV,* extracellular fluid volume.



• **Fig. 33.21** Relationship between selective changes in resistance of either the afferent arteriole or the efferent arteriole on RBF and GFR. Constriction of either the afferent or efferent arteriole increases resistance, and according to Eq. 33.11 ($Q = \Delta P/R$), an increase in resistance (R) decreases flow (Q) (i.e., RBF). Dilation of either the afferent or afferent arteriole increases flow (i.e., RBF). Constriction of the afferent arteriole (A) decreases P_{GC} because less of the arterial pressure is transmitted to the glomerulus, thereby reducing GFR. In contrast, constriction of the efferent arteriole (B) elevates P_{GC} and thus increases GFR. Dilation of the efferent arteriole (C) decreases P_{GC} and thus decreases GFR. Dilation of the afferent arteriole (D) increases P_{GC} because more of the arterial pressure is transmitted to the glomerulus, thereby increasing GFR. *GFR,* Glomerular filtration rate; *RBF,* renal blood flow. (Modified from Rose BD, Rennke KG. *Renal Pathophysiology: The Essentials.* Baltimore: Williams & Wilkins; 1994.)

Sympathetic Nerves

The afferent and efferent arterioles are innervated by sympathetic neurons; however, sympathetic tone is minimal when ECFV is normal (see Chapter 35). When ECFV is reduced, sympathetic nerves release norepinephrine and dopamine, and circulating epinephrine (a catecholamine-like norepinephrine and dopamine) is secreted by the adrenal medulla. Norepinephrine and epinephrine cause vasoconstriction by binding to α_1-adrenoceptors, which are located mainly in afferent arterioles. Activation of α_1-adrenoceptors decreases RBF and GFR. Dehydration or strong emotional stimuli (e.g., fear, pain) also activate sympathetic nerves and reduce RBF and GFR.

IN THE CLINIC

Individuals with **renal artery stenosis** (narrowing of the lumen of the artery) caused by atherosclerosis, for example, often have elevated systemic arterial blood pressure mediated by the renin-angiotensin system. Pressure in the renal artery proximal to the stenosis is increased, but pressure distal to the stenosis is normal or reduced. Autoregulation is important in maintaining RBF, P_{GC}, and GFR in the presence of this stenosis. Administration of drugs to lower systemic blood pressure also lowers the pressure distal to the stenosis; accordingly, RBF, P_{GC}, and GFR fall.

IN THE CLINIC

Significant **hemorrhage** decreases ECF volume and arterial blood pressure and therefore activates sympathetic innervation of the kidneys via the baroreceptor reflex (Fig. 33.22). Norepinephrine causes intense vasoconstriction of the afferent and efferent glomerular arterioles and thereby decreases both RBF and GFR. The rise in sympathetic activity also increases release of epinephrine and angiotensin II, which cause further vasoconstriction and a fall in RBF. The rise in vascular resistance of the kidneys and other vascular beds increases total peripheral resistance. The resulting tendency for blood pressure to increase (blood pressure = cardiac output × total peripheral resistance) offsets the tendency of blood pressure to decrease in response to hemorrhage. Hence this system works to preserve arterial pressure at the expense of maintaining normal RBF and GFR.

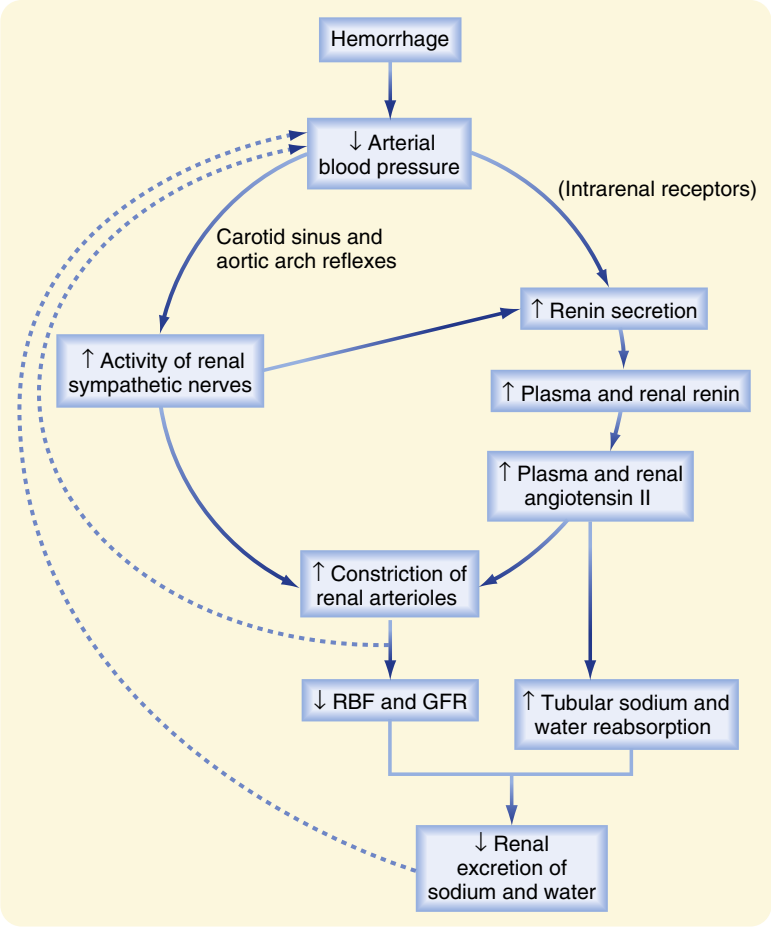
Angiotensin II

Angiotensin II is produced systemically as well as locally within the kidneys. It constricts the afferent and efferent arterioles[d] and decreases both RBF and GFR. Fig. 33.22 shows how norepinephrine, epinephrine, and angiotensin II act together to decrease RBF and GFR and thereby increase blood pressure and ECF volume (e.g., as would occur with hemorrhage).

Prostaglandins

Prostaglandins do not play a major role in regulating RBF in healthy resting individuals. However, during pathophysiological conditions such as hemorrhage and reduced ECFV, prostaglandins (PGI_2, PGE_1, and PGE_2) are produced locally within the kidneys and serve to increase RBF without changing GFR. Prostaglandins increase RBF by dampening

[d]The efferent arteriole is more sensitive than the afferent arteriole to angiotensin II. Therefore with low concentrations of angiotensin II, constriction of the efferent arteriole predominates, and GFR increases and RBF decreases. However, with high concentrations of angiotensin II, constriction of both afferent and efferent arterioles occurs, and GFR and RBF both decrease (see Fig. 33.21).



• **Fig. 33.22** Pathway by which hemorrhage activates renal sympathetic nerve activity and stimulates production of angiotensin II. *GFR,* Glomerular filtration rate; *RBF,* renal blood flow. (Modified from Vander AJ. *Renal Physiology.* 2nd ed. New York: McGraw-Hill; 1980.)

the vasoconstrictor effects of both sympathetic activation and angiotensin II. These effects are important because they prevent severe and potentially harmful vasoconstriction and renal ischemia. Synthesis of prostaglandins is stimulated by ECFV depletion and stress (e.g., surgery, anesthesia), angiotensin II, and sympathetic nerves. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen, potently inhibit prostaglandin synthesis. Thus administration of these drugs during renal ischemia and hemorrhagic shock is contraindicated because, by blocking the production of prostaglandins, they decrease RBF and increase renal ischemia. Prostaglandins also play an increasingly important role in maintaining RBF and GFR as individuals age. Accordingly, NSAIDs can significantly reduce RBF and GFR in the elderly.

Nitric Oxide

NO, an endothelium-derived relaxing factor, is an important vasodilator under basal conditions, and it counteracts the vasoconstriction produced by angiotensin II and catecholamines. When blood flow increases, greater shear force acts on endothelial cells in the arterioles and increases production of NO. In addition a number of vasoactive hormones, including acetylcholine, histamine, bradykinin, and ATP, facilitate release of NO from endothelial cells. Increased production of NO causes dilation of the afferent and efferent arterioles in the kidneys. Whereas increased levels of NO decrease total peripheral resistance, inhibition of NO production increases total peripheral resistance.

IN THE CLINIC

Abnormal production of NO is observed in individuals with **diabetes mellitus** and **hypertension**. Excess renal NO production in diabetes may be responsible for glomerular hyperfiltration (i.e., increased GFR) and damage to the glomerulus, problems characteristic of this disease. Elevated NO levels increase glomerular capillary pressure secondary to a fall in resistance of the afferent arteriole. The ensuing hyperfiltration is thought to cause glomerular damage. The normal response to an increase in dietary salt intake includes stimulation of renal NO production, which prevents an increase in blood pressure. In some individuals, however, NO production may not increase appropriately in response to an elevation in salt intake, so blood pressure rises.

Endothelin

Endothelin is a potent vasoconstrictor secreted by endothelial cells of the renal vessels, mesangial cells, and distal tubular cells in response to angiotensin II, bradykinin, epinephrine, and endothelial shear stress. Endothelin causes profound vasoconstriction of the afferent and efferent arterioles and decreases GFR and RBF. Although this potent vasoconstrictor may not influence GFR and RBF in resting subjects, production of endothelin is elevated in a number of glomerular disease states (e.g., renal disease associated with diabetes mellitus).

Bradykinin

Kallikrein is a proteolytic enzyme produced in the kidneys. Kallikrein cleaves circulating kininogen to bradykinin, which is a vasodilator that acts by stimulating the release of NO and prostaglandins. Bradykinin increases RBF and GFR.

Adenosine

Adenosine is produced within the kidneys and causes vasoconstriction of the afferent arteriole, thereby reducing RBF and GFR. As previously mentioned, adenosine plays an important role in tubuloglomerular feedback.

Natriuretic Peptides

Secretion of atrial natriuretic peptide (ANP) by the cardiac atria and brain natriuretic peptide (BNP) by the cardiac ventricle increases when ECFV is expanded and myocardial wall tension is increased. Both ANP and BNP dilate the afferent arteriole and constrict the efferent arteriole. Therefore ANP and BNP produce a modest increase in GFR with little change in RBF.

Adenosine Triphosphate

Cells release ATP into the renal interstitial fluid. ATP can have bidirectional effects on both RBF and GFR. Under some conditions, ATP constricts the afferent arteriole, reduces RBF and GFR, and may play a role in tubuloglomerular feedback. Under other conditions, ATP may stimulate NO production and have directionally opposite effects, increasing both RBF and GFR.

Glucocorticoids

Administration of therapeutic doses of glucocorticoids increases GFR and RBF.

Histamine

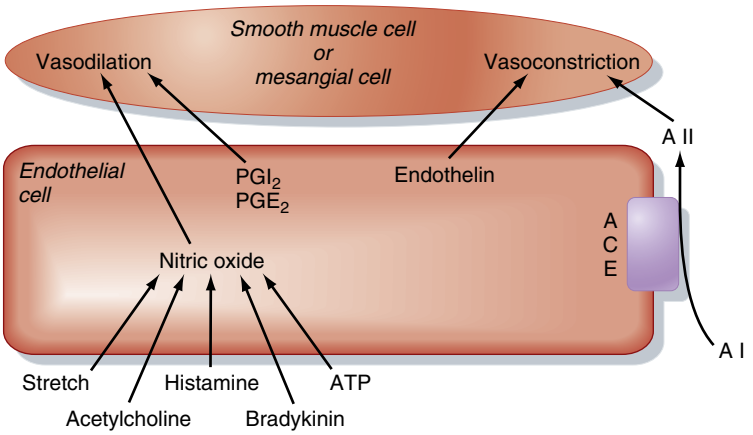
Local release of histamine modulates RBF during the resting state and during inflammation and injury. Histamine decreases the resistance of the afferent and efferent arterioles and thereby increases RBF without elevating GFR.

Dopamine

The proximal tubule produces the vasodilator substance dopamine. Dopamine has several actions within the kidney, such as increasing RBF and inhibiting renin secretion.

Hormones

Finally, as illustrated in Fig. 33.23, endothelial cells play an important role in regulating the resistance of the renal



• **Fig. 33.23** Examples of the interactions of endothelial cells with smooth muscle and mesangial cells. *ACE,* Angiotensin-converting enzyme; *AI,* angiotensin I; *AII,* angiotensin II. (Modified from Navar LG et al. *Physiol Rev*. 1996;76:425.)

afferent and efferent arterioles by producing a number of paracrine hormones, including NO, prostacyclin (PGI_2), endothelin, and angiotensin II. These hormones regulate contraction or relaxation of smooth muscle cells in afferent and efferent arterioles and mesangial cells. Shear stress, acetylcholine, histamine, bradykinin, and ATP stimulate production of NO, which increases GFR and RBF. **Angiotensin-converting enzyme (ACE)**, located on the surface of endothelial cells lining the afferent arteriole and glomerular capillaries, converts angiotensin I to angiotensin II, which decreases GFR and RBF. Angiotensin II is also produced locally by granular cells in the afferent arteriole and by proximal tubular cells. PGI_2 and PGE_2 release by endothelial cells is stimulated by both sympathetic nerve activity and angiotensin II, resulting in increased GFR and RBF. Finally, endothelin release from endothelial cells decreases both RBF and GFR.

IN THE CLINIC

ACE proteolytically inactivates the vasodilatory hormone bradykinin and converts angiotensin I, an inactive hormone, to angiotensin II, an active vasoconstrictive hormone. Thus ACE increases angiotensin II levels and decreases bradykinin levels. **ACE inhibitors** (e.g., lisinopril, enalapril, and captopril) are used clinically to reduce systemic blood pressure in patients with hypertension by decreasing angiotensin II levels and elevating bradykinin levels. Both effects lower systemic vascular resistance, reduce blood pressure, and decrease renal vascular resistance, thereby increasing GFR and RBF. **Angiotensin II receptor antagonists** (e.g., losartan) are also used to treat hypertension. As their name suggests, they block the binding of angiotensin II to the angiotensin II receptor (AT_1). These antagonists block the vasoconstrictor effects of angiotensin II on the afferent arteriole; thus they increase RBF and GFR. In contrast to ACE inhibitors, angiotensin II receptor antagonists do not inhibit kinin metabolism (e.g., bradykinin).

Key Points

1. The first step in urine formation is passive movement of a plasma ultrafiltrate from the glomerular capillaries into Bowman's space. The term *ultrafiltration* refers to passive movement of a plasma-like fluid that has a very low concentration of proteins from the glomerular capillaries into Bowman's space. The endothelial cells of glomerular capillaries are covered by a basement membrane that is surrounded by podocytes. The capillary endothelium, basement membrane, and foot processes of podocytes form the so-called filtration barrier.
2. The juxtaglomerular apparatus is one component of an important feedback mechanism (i.e., tubuloglomerular feedback) that regulates RBF and GFR. The structures that make up the juxtaglomerular apparatus include the macula densa, extraglomerular mesangial cells, and renin- and angiotensin II–producing granular cells.
3. Clinically, GFR is frequently estimated using measures of plasma [creatinine] or by the renal clearance of creatinine.
4. Autoregulation allows GFR and RBF to remain constant despite changes in arterial blood pressure between 90 and 180 mm Hg. When ECFV is altered, sympathetic nerves, catecholamines, angiotensin II, prostaglandins, NO, endothelin, natriuretic peptides, bradykinin, and adenosine exert substantial control over GFR and RBF.